Translationale Forschung - Review of the year 2021

Carsten Denkert
Philipps Universität Marburg
Universitätsklinikum Marburg (UKGM)
10.3.2022

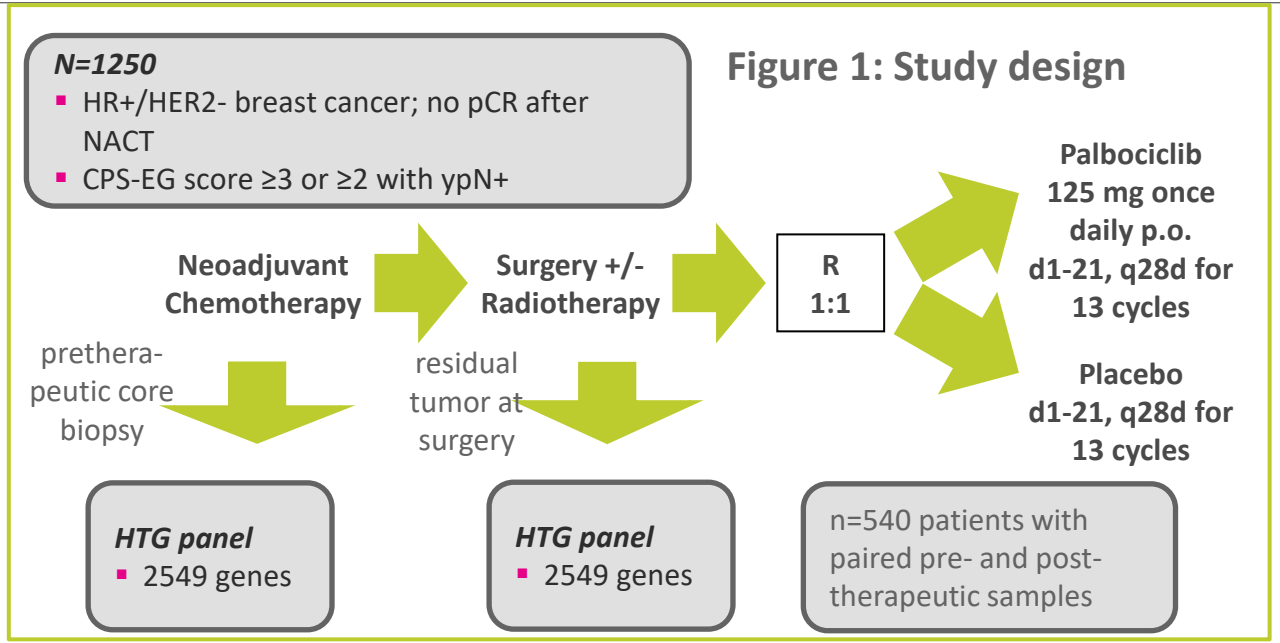
Conflict of Interest

- Advisory board, honoraria: Novartis, Pfizer, Roche, Amgen, MSD, Daiichi Sankyo, Lilly
- Cofounder: Sividon Diagnostics (now Myriad) – Endopredict gene expression assays
- Licensing fees: VMscope digital pathology software
- Research funding: Myriad, Roche

Überblick translationale Forschung 2021

- **Translationale Forschung Penelope**
  - ASCO 2021: Molekulare Subtypen in Stanzbiopsien
  - SABCS 2021: Molekulare Plastizität – Vergleich von Stanzbiopsien und OP Resektaten
- **HRD und genomische Instabilität**
  - ESMO breast cancer: RAD51 und HRD (Kooperation mit Violeta Serra)
- **Neue Biomarker / molekulare Subtypen**
  - Lancet oncology: Her2-low-positive breast cancer
- BigPicture - IMI – digitale Pathologie und machine learning
- Saturn3 – BMBF - Tumorheterogenität
- Immunonkologie (Thomas Karn)

Penelope – translational research

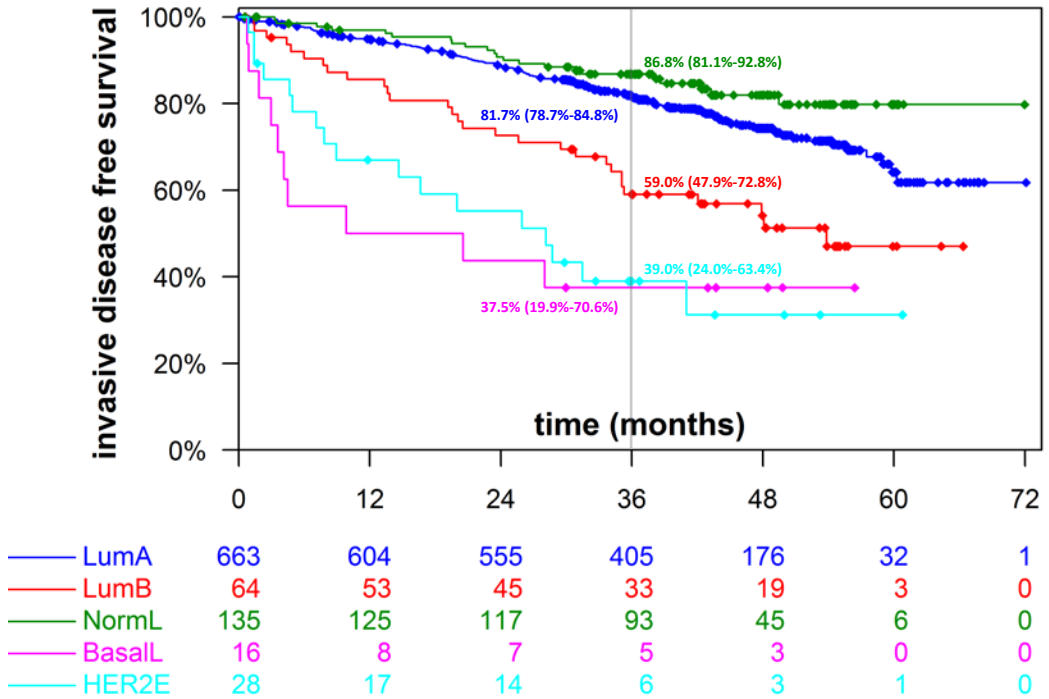


Research questions:

- AIMS subtypes in pre- and post NACT tumors
- Prognostic effect
- Response to palbociclib
- genes involved

- gene expression in 540 paired pre-Tx (n=540) post-NACT residual tumor samples
- HTG EdgeSeq Oncology Biomarker Panel including 2549 genes (HTG Molecular Diagnostics Inc)
- based on 91 genes of this panel, the AIMS subtype was calculated.
- exploratory biomarker analyses

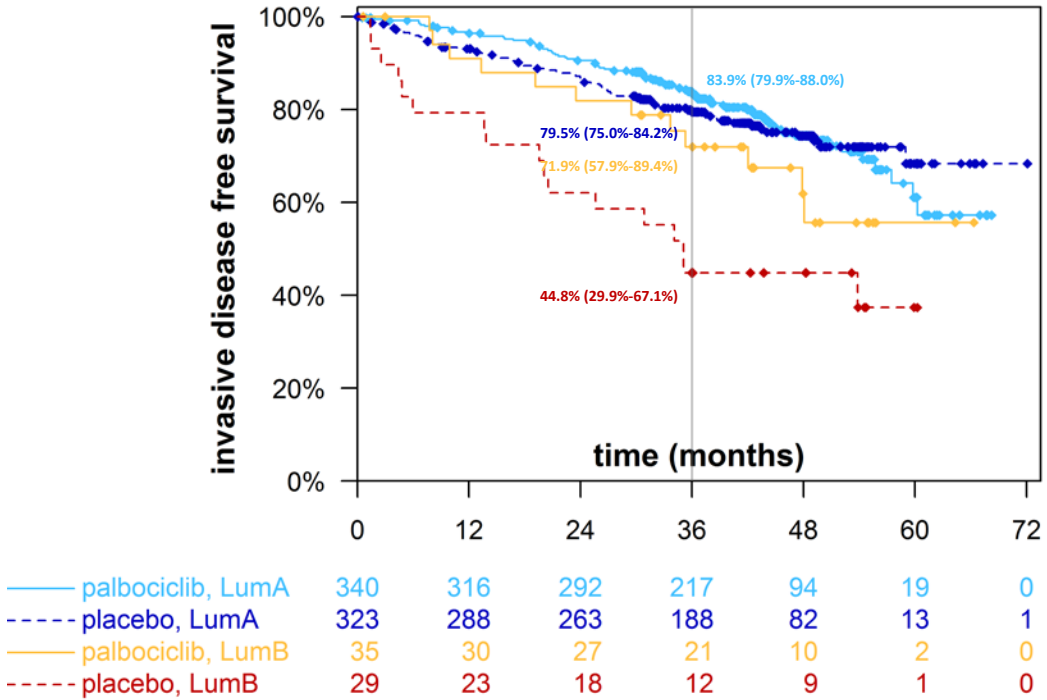
iDFS by AIMS subtype – core biopsy (treatment arms combined)



Gene expression data:
906 of 1250 (72%) pts.

- 663 LumA subtype,
- 64 LumB,
- 135 NormL,
- 16 BasalL and 28 HER2E.

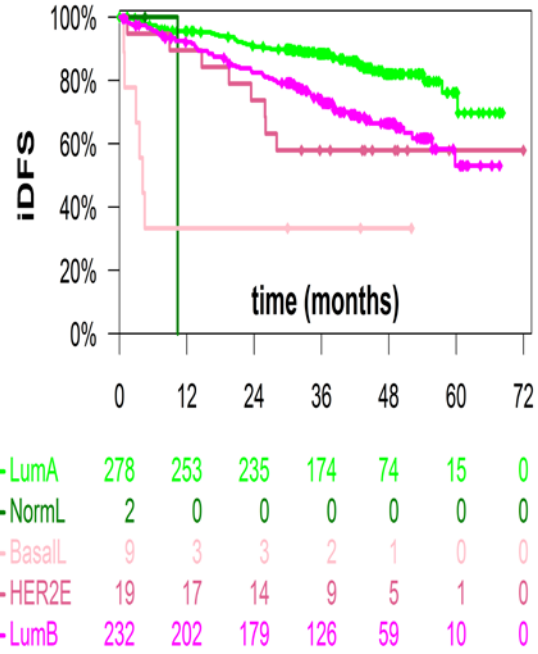
iDFS by AIMS subtype (core biopsy) and treatment in the AIMS-luminal cohort



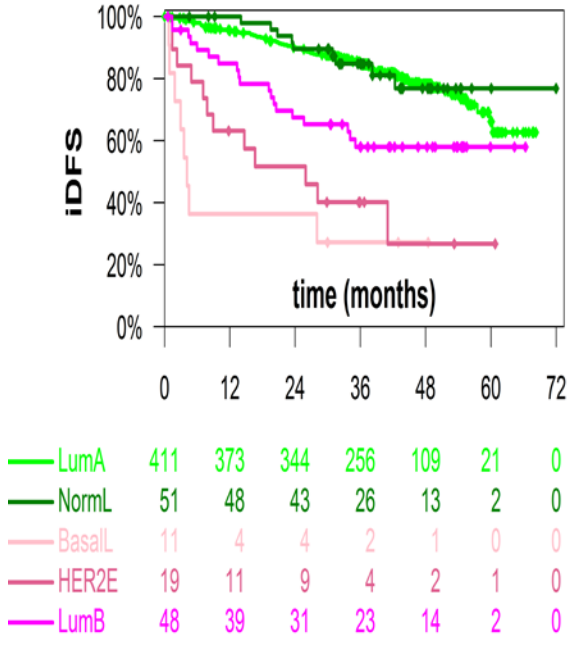
Patients with LumB tumors had an estimated 3-year iDFS of 71.9% (Figure 3) with palbociclib vs 44.8% with placebo; the hazard ratio was 0.50 (0.24-1.05). Due to the small size of the LumB subcohort, the potentially benefit is numerical and not statistically significant.
Outcome was not different between treatment arms in patients with LumA tumors (3-year iDFS 83.9% vs 79.5%, hazard ratio 0.93 (0.68-1.28), interaction p=0.132)

Prognostic role of AIMS subtypes (n=540 paired and post NACT)

AIMS subtypes in pre-therapeutic core biopsies



AIMS subtypes in post-therapeutic residual tumor samples



model	AIMS subtype		
		HR (95% CI)	p
Bivariable n=540	pre-Tx	1.86 (1.26-2.73)	0.002
	post-Tx	2.83 (1.90-4.20)	<0.001
Multi-variable* n=532	pre-Tx	1.90 (1.26-2.86)	0.002
	post-Tx	2.66 (1.68-4.20)	<0.001

*covariables: age, region, cT, ypT, ypN, Ki-67, grade, and risk status

Table 1: Pre-therapeutic and post-therapeutic AIMS subtypes (LumB/BasalL/HER2E vs LumA/NormL) are independent prognostic parameters for iDFS

Presented at: SABCS, 2021

Molecular plasticity – changes in AIMS subtypes in pre-and post-therapy samples

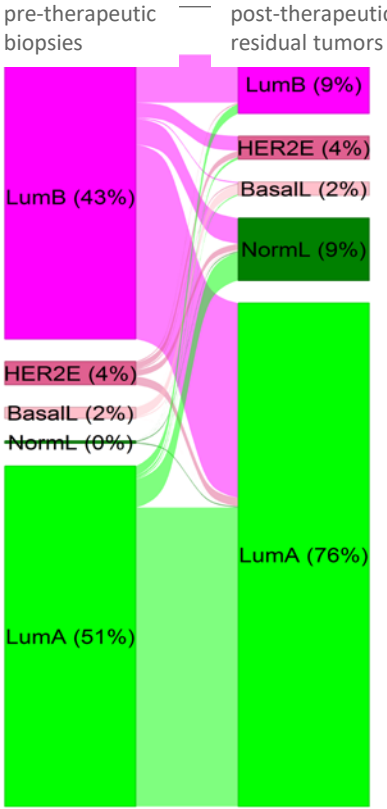
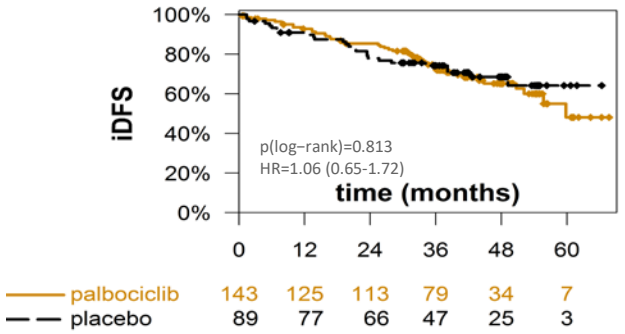
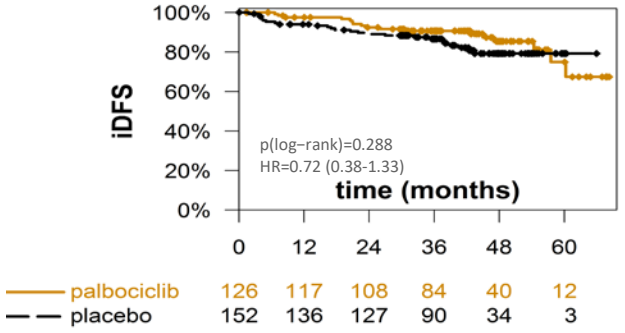


Figure 3

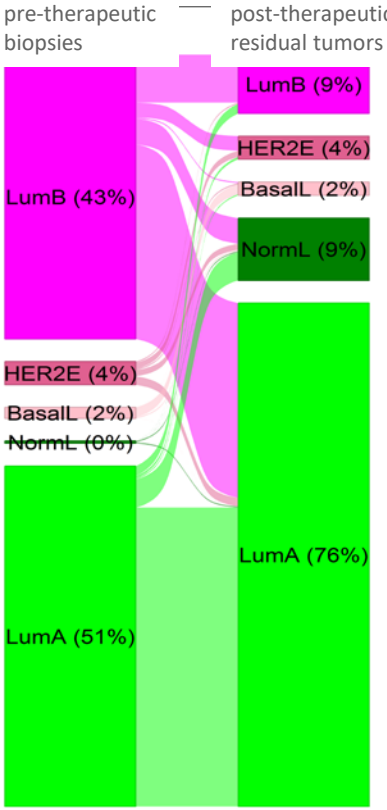
Molecular plasticity – changes in AIMS subtypes in pre-and post-therapy samples

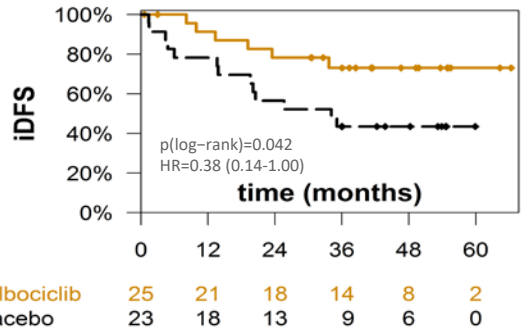


LumB pre-therapeutic – no differences between therapy arms

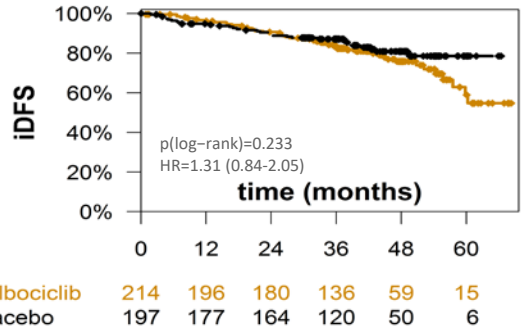


LumA pre-therapeutic – no differences between therapy arms





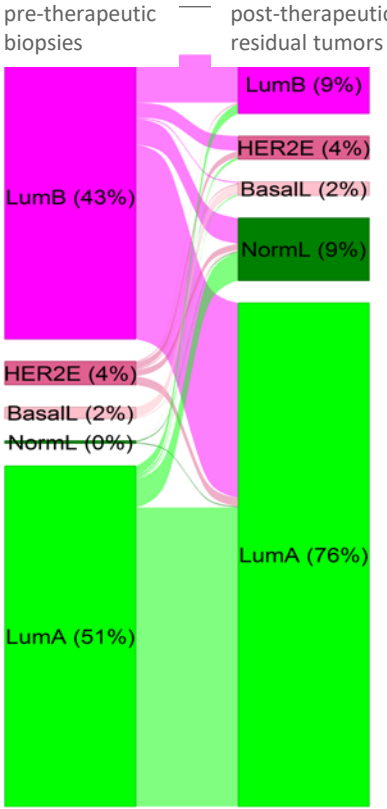
LumB post-Tx: small group of patients with significant differences between therapy arms

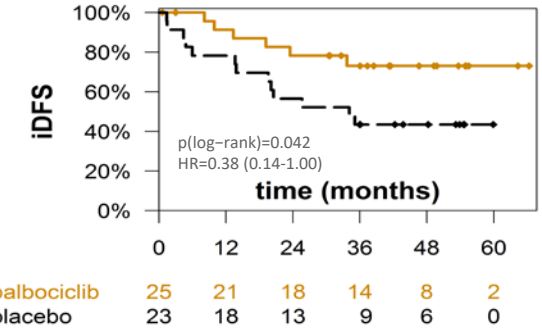


LumA post-therapeutic – no differences between therapy arms

Molecular plasticity – changes in AIMS subtypes in pre-and post-therapy samples

LumB pre-therapeutic – no differences between therapy arms





LumB post-Tx: small group of patients with significant differences between therapy arms

LumA pre-therapeutic – no differences between therapy arms

LumA post-therapeutic – no differences between therapy arms

Translationale Forschung Penelope – aktueller Stand

- **AIMS subtypes sind prognostisch**
  - in Stanzbiopsien
  - im Residualtumor
- **Luminal switch**
  - Luminal B (präTx) zu Luminal A (postTx)
  - Palbo-benefit in luminal B postTx (kleine Gruppe)
- **Offene Fragen**
  - Wie ist der Subtyp im Rezidiv? Bleibt der Switch zu luminal A bestehen?
  - Kann man die Gruppe mit Palbo-Benefit noch besser definieren?

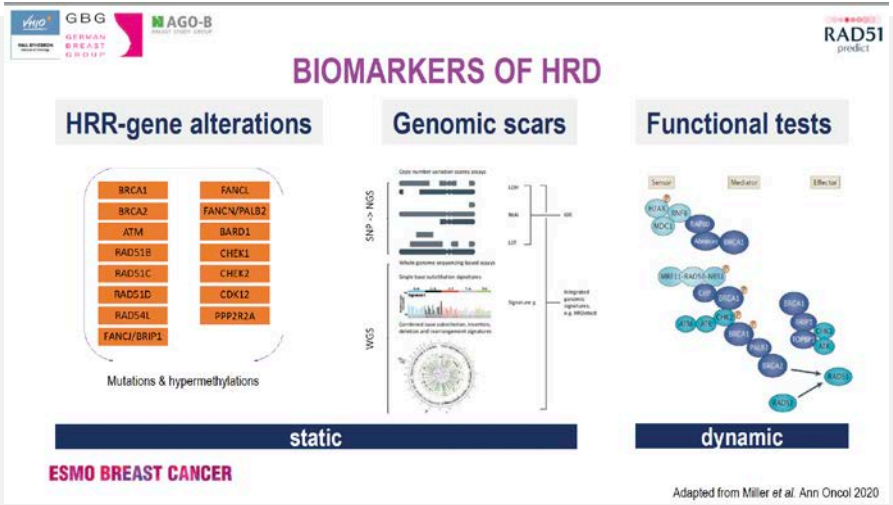
ESMO BREAST CANCER
VIRTUAL CONGRESS

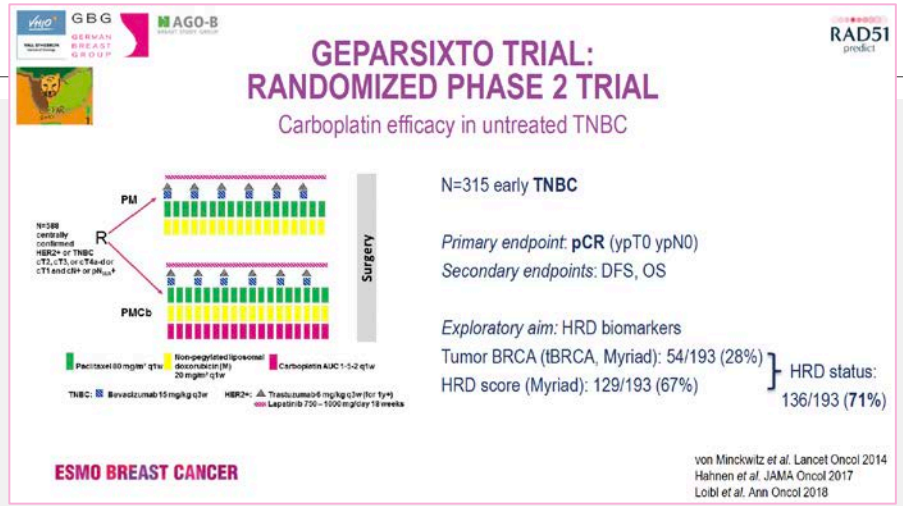
ASSOCIATION OF RAD51 WITH HOMOLOGOUS RECOMBINATION DEFICIENCY (HRD) AND CLINICAL OUTCOMES IN UNTREATED TRIPLE-NEGATIVE BREAST CANCER (TNBC): ANALYSIS OF THE GEPARSIXTO RANDOMIZED CLINICAL TRIAL

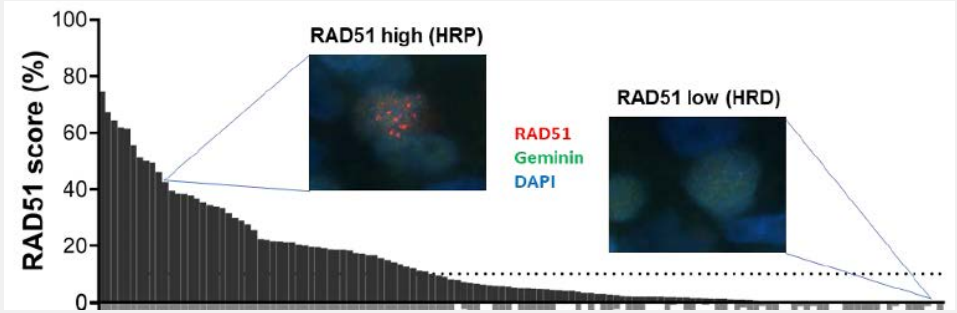
Proffered Paper #321

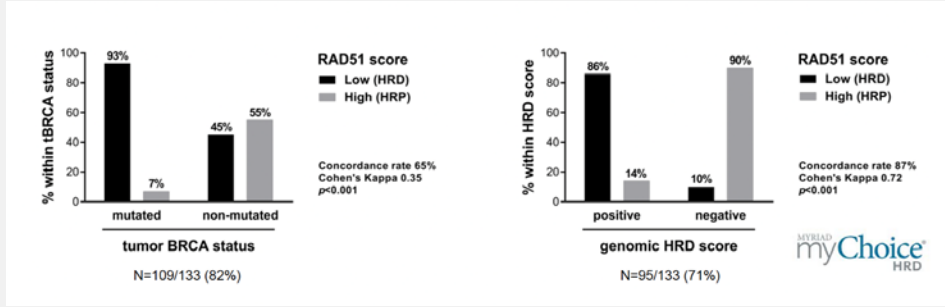
Alba Llop-Guevara, Valentina Vladimirova, Andreas Schneeweiss, Guillermo Villacampa, Thomas Karn, Dirk-Michael Zahm, Andrea Herencia-Ropero, Paul Jank, Marion van Mackelenbergh, Peter A. Fasching, Frederik Marmé, Elmar Stickeler, Christian Schem, Rodrigo Dienstmann, Stefan Florian, Valentina Nekljudova, Sibylle Loibl, Judith Balmaña, Carsten Denkert, Violeta Serra

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
VHIO VALL D'HEBRON Institute of Oncology
GBG GERMAN BREAST GROUP
AGO-B BREAST STUDY GROUP





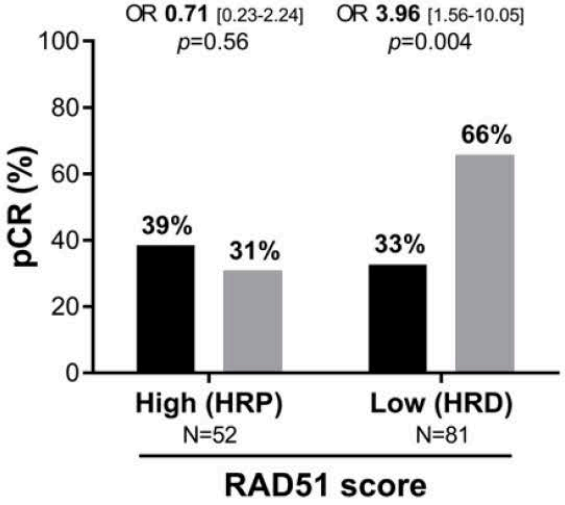




Llop-Guevara A et al, ESMO Breast 2021, Ann. Oncol. Dec 2021

RAD51 AS A PREDICTIVE BIOMARKER

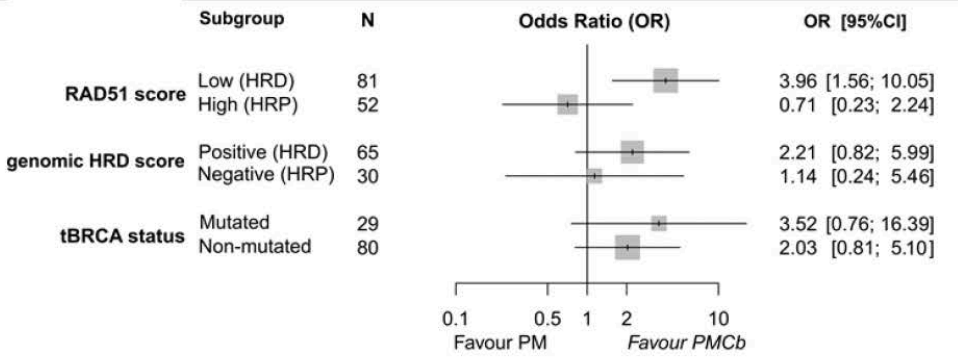
Association of RAD51 with pCR



Treatment arm

- PM
- PMCb

Test of interaction
***p*=0.02**

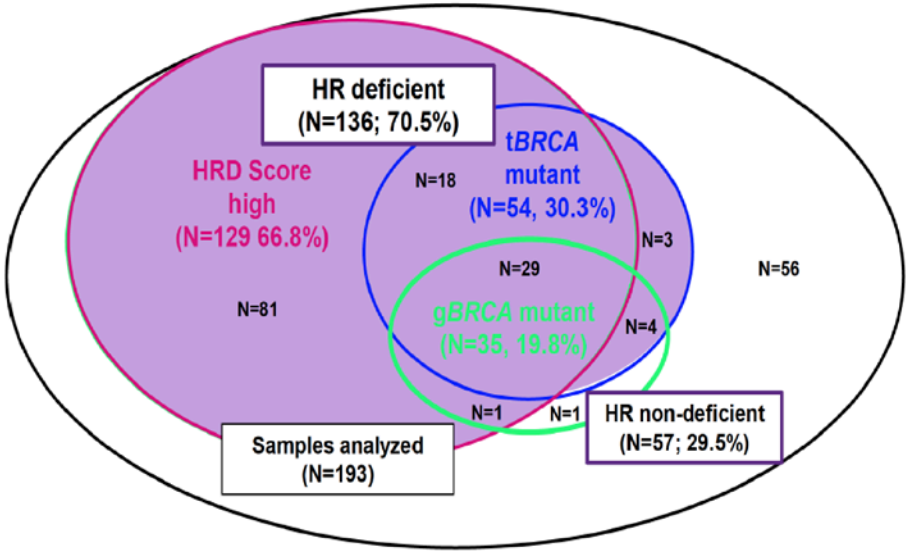


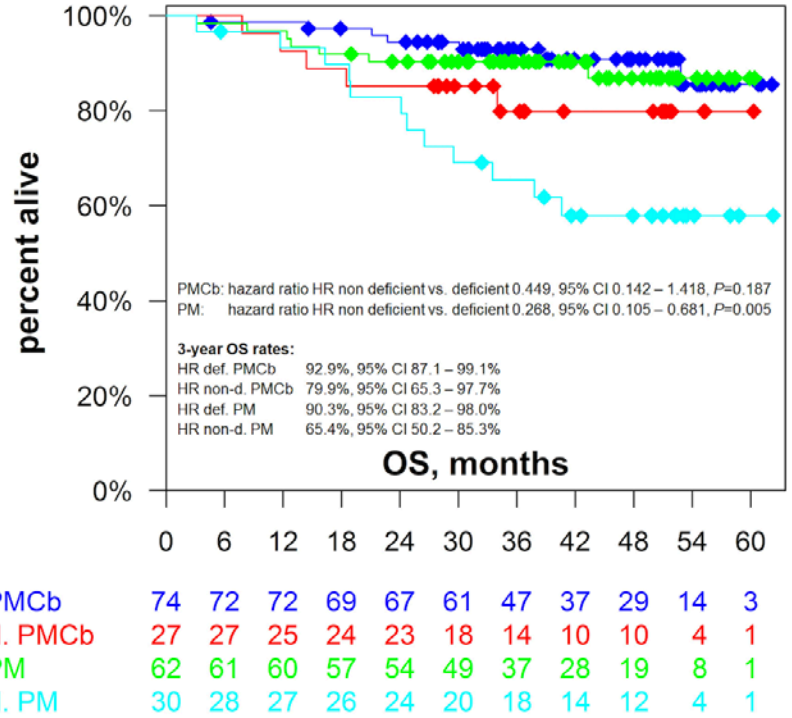
Multivariate analysis:
RAD51 low (HRD) OR=7.52, *p*=0.001
RAD51 high (HRP) OR=0.72, *p*=0.639

ESMO BREAST CANCER

Llop-Guevara A et al, ESMO Breast 2021, Ann. Oncol. Dec 2021

GeparSixto TNBC (n=193) – 20% gBRCA, aber 61-67% HRD positiv





GeparSixto:

- 19.8% gBRCA mutant
- 30.3% tBRCA mutant
- 66.8 % HRD score high
- **61% functional HRD (RAD51-low)**

Philipps Universität Marburg

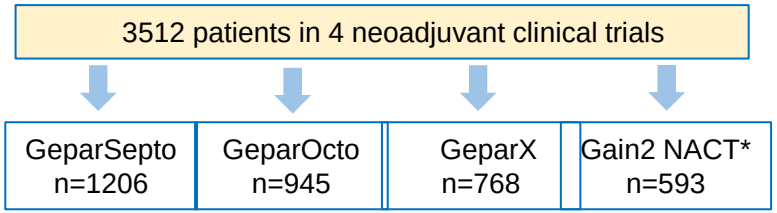
Loibl et al, Ann. Oncol 2018
Llop-Guevara A et al, Ann. Oncol. Dec 2021

Pooled analysis of HER2-low-positive tumors in 4 GBG trials

Lancet oncology 2021

Clinical and molecular characteristics of HER2-low-positive breast cancer: pooled analysis of individual patient data from four prospective, neoadjuvant clinical trials

Carsten Denkert, Fenja Seither, Andreas Schneeweiss, Theresa Link, Jens-Uwe Blohmer, Marianne Just, Pauline Wimberger, Almuth Forberger, Hans Tesch, Christian Jackisch, Sabine Schmatloch, Mattea Reinisch, Erich F Solomayer, Wolfgang D Schmitt, Claus Hanusch, Peter A Fasching, Kristina Lübbe, Christine Solbach, Jens Huober, Kerstin Rhiem, Frederik Marmé, Toralf Reimer, Marcus Schmidt, Bruno V Sinn, Wolfgang Janni, Elmar Stickeler, Laura Michel, Oliver Stötzer, Eric Hahnen, Jenny Furlanetto, Sabine Seiler, Valentina Nekljudova, Michael Untch, Sibylle Loibl



HER2 score	Group
0	HER2-zero
1+ or 2+/ISH negative	HER2-low-positive
3+ or 2+/ISH positive	HER2-positive

Pooled analysis of HER2-low-positive tumors in 4 GBG trials

3512 patients in 4 neoadjuvant clinical trials

GeparSepto	GeparOcto	GeparX	Gain2 NACT*
n=1206	n=945	n=768	n=593

HER2 score	Group
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1+ or 2+/ISH negative	HER2-low-positive
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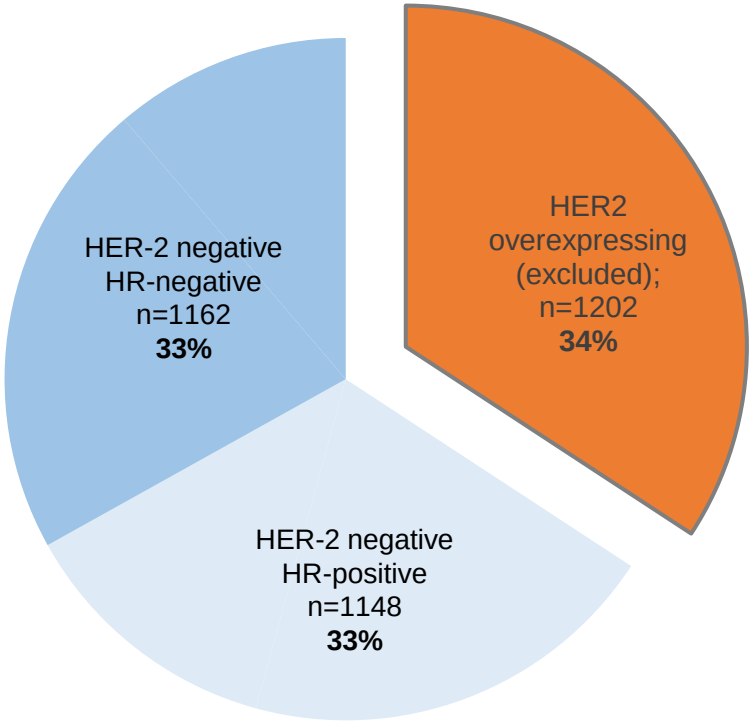

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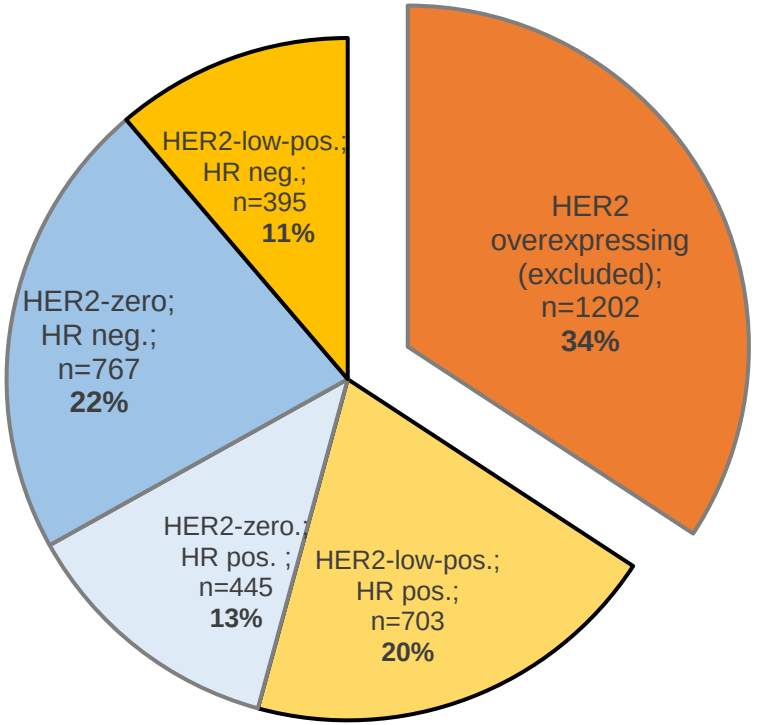
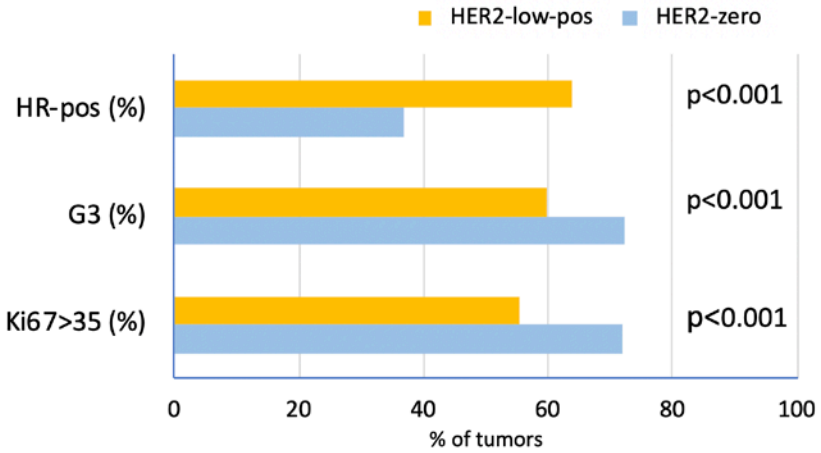
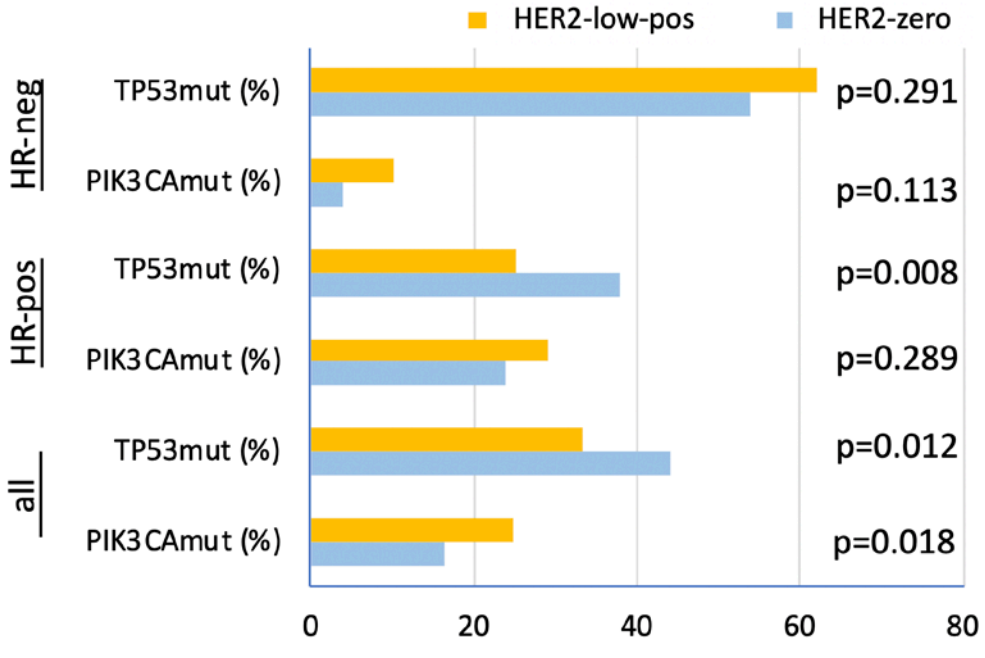


Denkert et al, Lancet oncology 2021

Biological differences of HER2-low-positive tumors

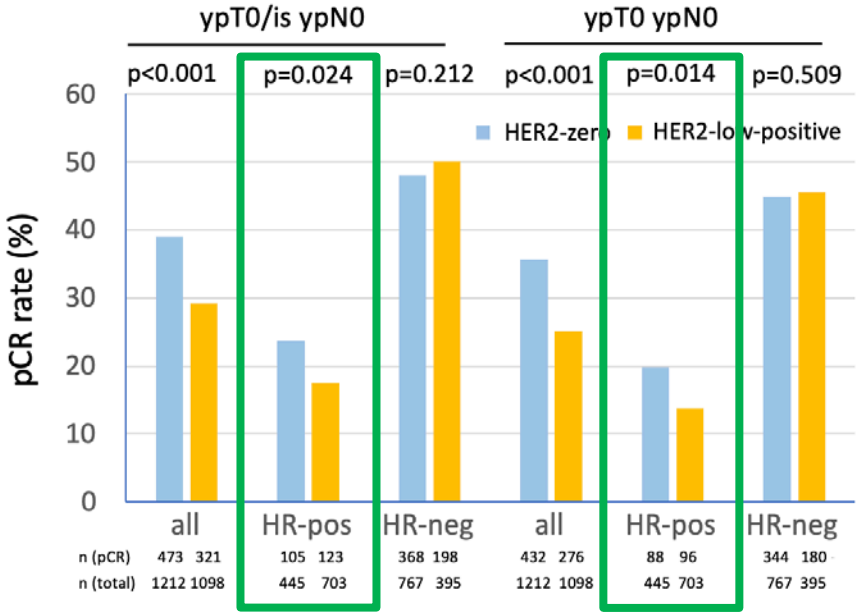


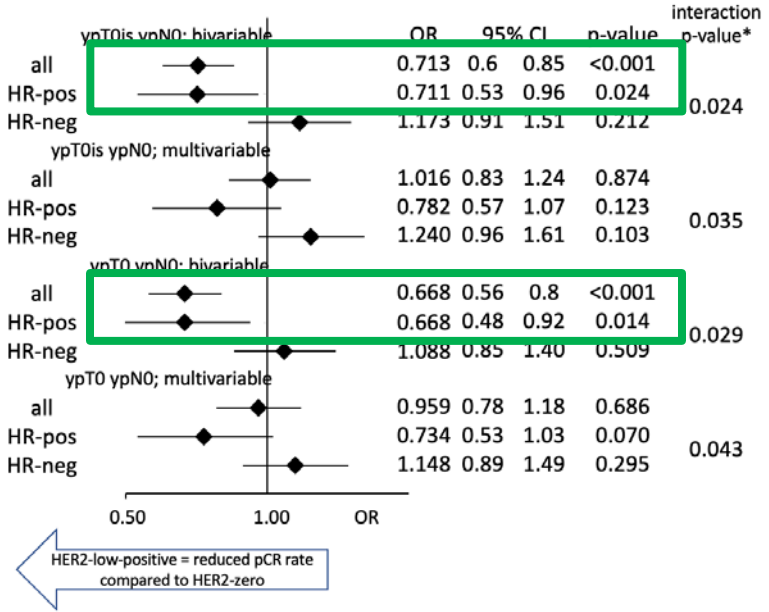


HER2-low-positive: less grade 3 tumors, lower proliferation, less tp53 mutations

Denkert et al, Lancet oncology 2021

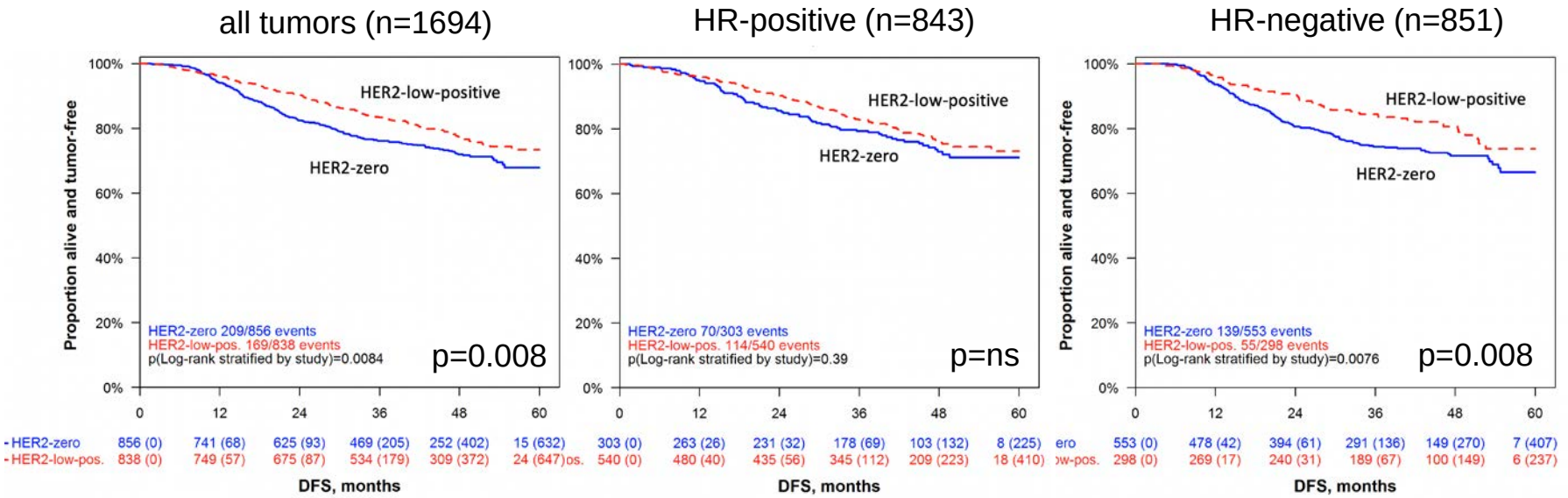
HER2-low-positive tumors have a reduced pCR rate, in particular in the HR-positive subgroup





Denkert et al, Lancet oncology 2021

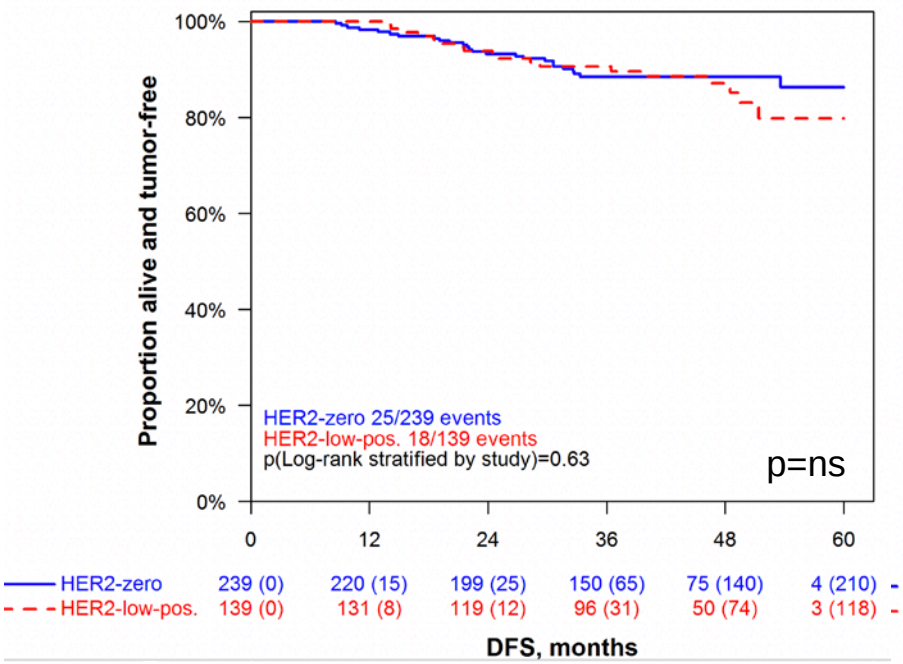
Improved DFS for HER2-low-positive tumors – in particular in the HR-negative subgroup



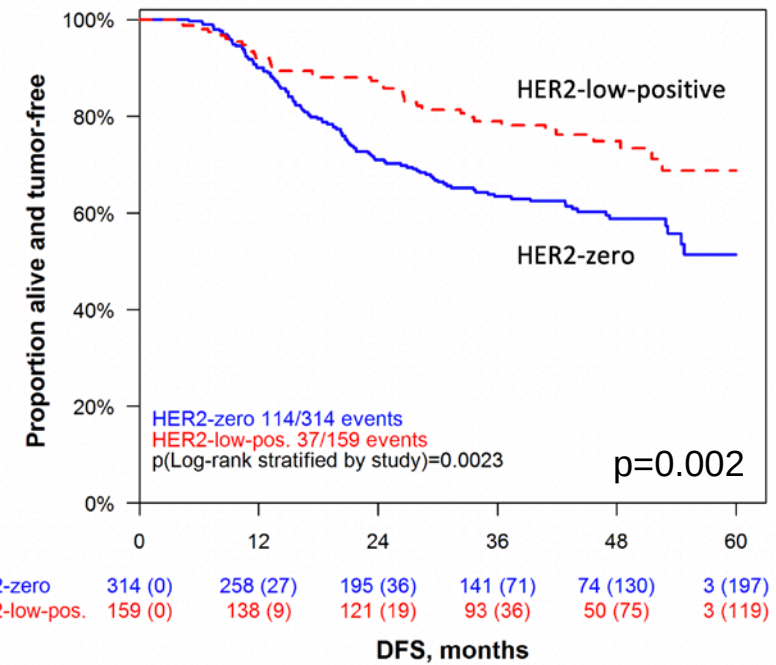
Denkert et al, Lancet oncology 2021

Improved DFS for HER2-low-positive tumors – in HR-negative BC driven by non-pCR subgroup

HR-negative, with pCR (n=378)



HR-negative, with non-pCR (n=473)



Denkert et al, Lancet oncology 2021

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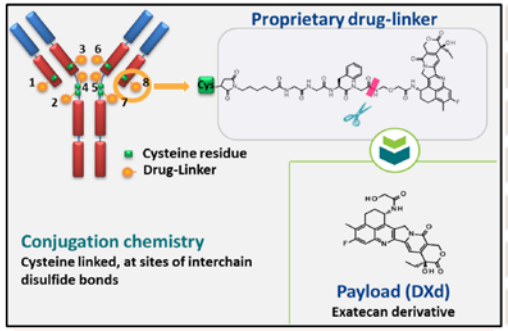
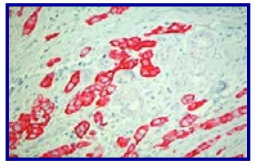
Zeitverlauf:

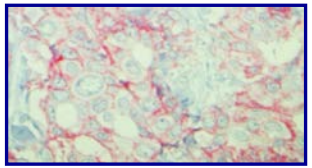
- 22.10.20: Projektidee und erste Version des Statistischen Analyseplan
- 15.1.21: Statistischer Analyseplan fertiggestellt
- 9.2.21: Statistical Report von GBG Statistik Team fertiggestellt
- 3.3.21: Manuskript zu den Koautoren
- 25.3.21: Manuskript 1. Version eingereicht bei Lancet Oncology
- 12.5.21: Manuskript 3. Version eingereicht bei Lancet Oncology
- 14.5.21: Manuskript akzeptiert - Lancet Oncology

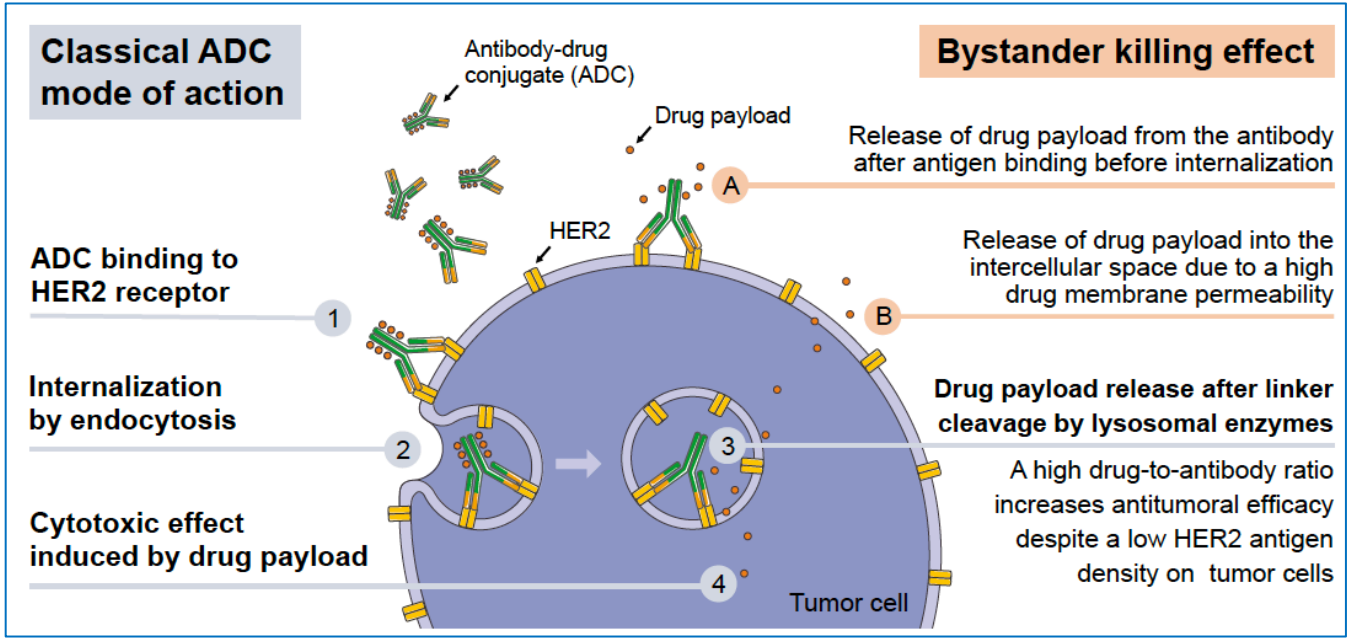
7 Monate
Vielen Dank an alle Beteiligten!



New therapy strategies with antibody-drug conjugates







https://www.daiichisankyo.com/files/investors/library/materials/2017/pdf/Material.pdf

Rinnerthaler et. al., Int. J. Mol. Scie. 2019

DESTINY-Breast03

DESTINY-Breast03: First Randomized Ph3 Study of T-DXd

An open-label, multicenter study (NCT03529110)

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

R 1:1

- **T-DXd** 5.4 mg/kg Q3W (n = 261)
- **T-DM1** 3.6 mg/kg Q3W (n = 263)

Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

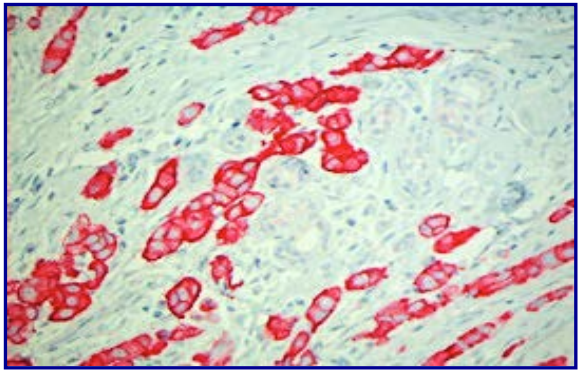
Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Interim analysis for PFS (data cutoff: May 21, 2021)
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

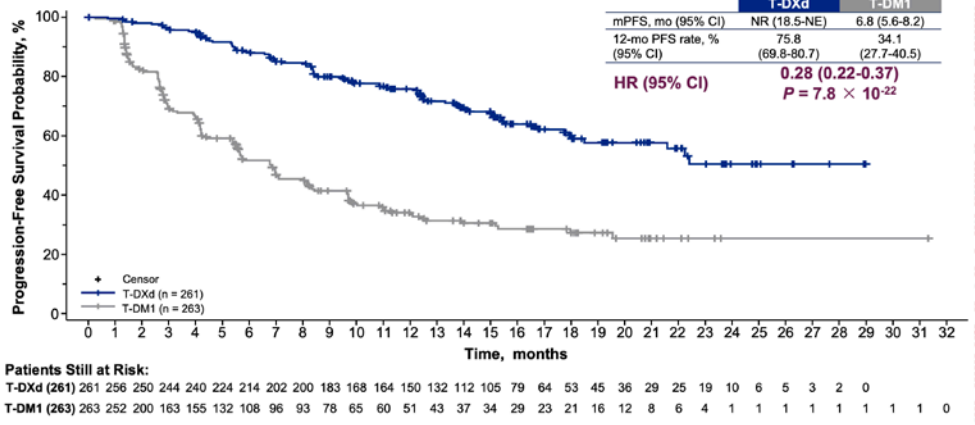
2021 ESMO congress

BICR, blinded independent central review; DOR, duration of response; ORR, objective response rate; OS, ov
Q3W, every 3 weeks.
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after complet



DESTINY-Breast03

Primary Endpoint: PFS by BICR



	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	

Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	0

2021 ESMO congress

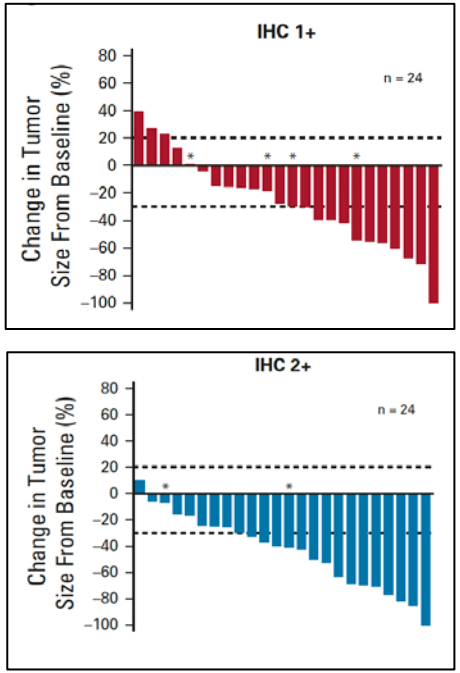
Median PFS follow-up for T-DXd was 15.5 months (range, 15.1-16.6) and for T-DM1 was 13.9 months (range, 11.8-15.1)
HR, hazard ratio; INV, investigator; mo, month; NE, not estimable; NR, not reached.

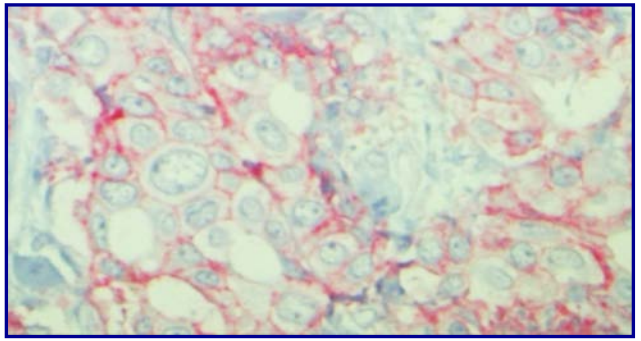
Marburg

Cortés et al. ESMO 2021

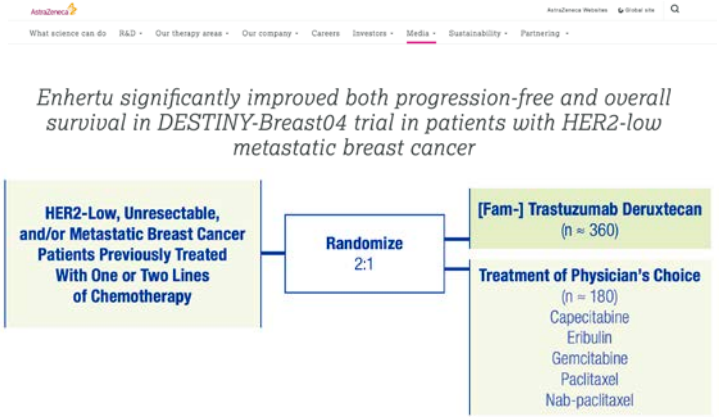
Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients With HER2-Low–Expressing Advanced Breast Cancer: Results From a Phase Ib Study

Shanu Modi, MD[1]; Haeseong Park, MD, MPH[2]; Rashmi K. Murthy, MD, MBE[3]; Hiroji Iwata, PhD, MD[4]; Kenji Tamura, MD, PhD[5]; Junji Tsurutani, MD, PhD[6]; Alvaro Moreno-Aspitia, PhD[7]; Toshihiko Doi, MD, PhD[8]; Yasuaki Sagara, MD[9]; Charles Redfern, MD[10]; Ian E. Krop, MD, PhD[11]; Caleb Lee, MD, PhD[12]; Yoshihiko Fujisaki, MS[13]; Masahiro Sugihara, PhD[13]; Lin Zhang, MD, PhD[12]; Javad Shahidi, MD[12]; and Shunji Takahashi, MD[14]





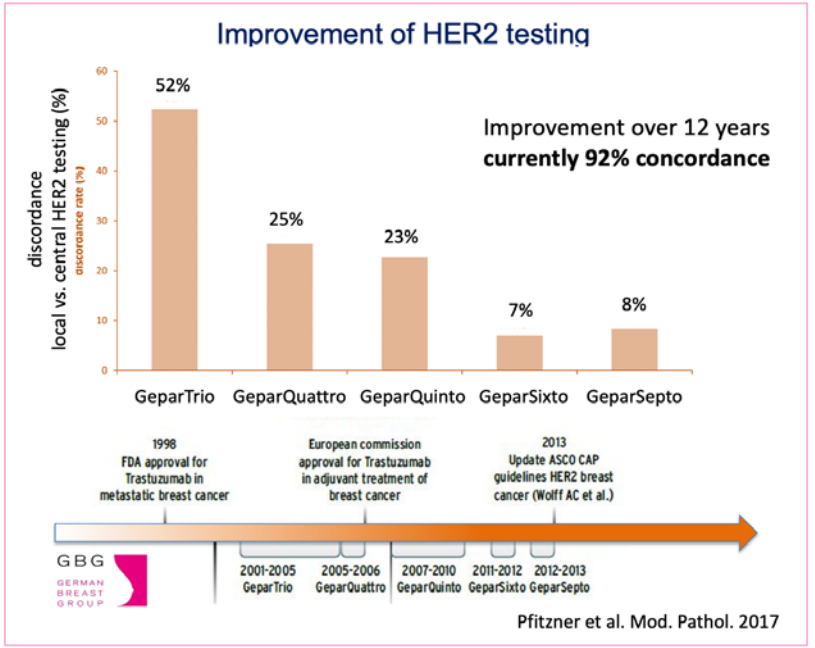
DESTINY-Breast04 press release 21.2.22



Modi et al. JCO 2020

Low-HER2-positive breast cancer – aktueller Stand

- **Destiny Breast 04: neue Therapieoption (?)**
- **GBG Analyse low-HER2-positive BC:**
  1. Es gibt signifikante Unterschiede zwischen low-HER2-positive und HER2-zero Mammakarzinomen.
  2. Die low-HER2-positive Gruppe existiert als biologische Subgruppe.
  3. Die low-HER2-positive Gruppe kann in einer standardisierten Zentralpathologie identifiziert werden.
- **To do: Standardisierung der dezentralen low HER2 Bestimmung!**



HERZLICHEN DANK!

Vielen Dank an alle Patientinnen, Studienzentren und Pathologen, die Gewebeproben zur Verfügung stellen!

Vielen Dank an alle Kooperationspartner!

Vielen Dank an:
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das Team der Zentralpatho der Charité und
das aktuelle Team der Zentralpatho Uni Marburg!

carsten.denkert@uni-marburg.de