Translationale Forschung - Review of the year 2020

Carsten Denkert
Philipps Universität Marburg
Universitätsklinikum Marburg (UKGM)

25.2.2021

Conflict of Interest

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

Überblick translationale Forschung 2020

Biomarker in klinischen Studien-kohorten

- Expression von RANK in GeparX
- Charakterisierung von Tumoren mit einer lowHR Expression
- Mutational signatures in GeparSepto

Immun-onkologische Projekte (Thomas Karn)

aktuell laufende Projekte

GeparX - GBG 88

Denosumab as add-on to different regimen of nab-paclitaxel-anthracycline based neoadjuvant chemotherapy in early breast cancer: Subgroup analyses by RANK expression and HR status

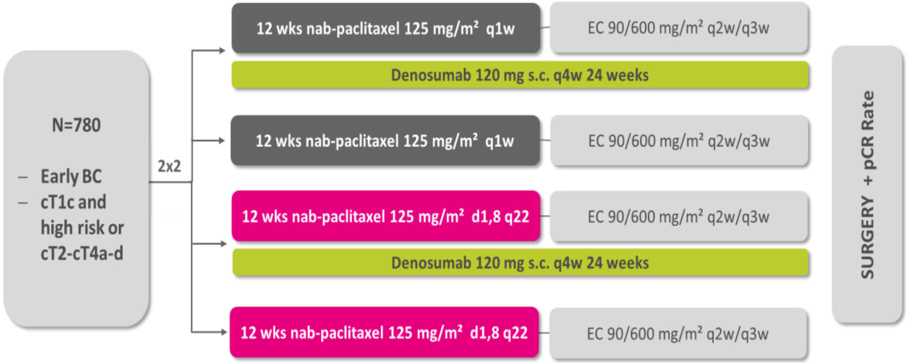
Theresa Link, Jens-Uwe Blohmer, Marianne Just, Michael Untch, Oliver Stötzer, Peter A. Fasching, Andreas Schneeweiss, Pauline Wimberger, Sabine Seiler, Jens Huober, Wolfgang D. Schmitt, Christian Jackisch, Kerstin Rhiem, Claus Hanusch, Carsten Denkert, Bruno Sinn, Knut Engels, Valentina Nekljudova, Sibylle Loibl

-This is a joint study by GBG and AGO-B-

GBG GERMAN BREAST GROUP

VIRTUAL 2020 ESMO congress

GeparX Study: 2x2 Design



N=780

- Early BC
- cT1c and high risk or cT2-cT4a-d

2x2

12 wks nab-paclitaxel 125 mg/m² q1w → EC 90/600 mg/m² q2w/q3w
Denosumab 120 mg s.c. q4w 24 weeks

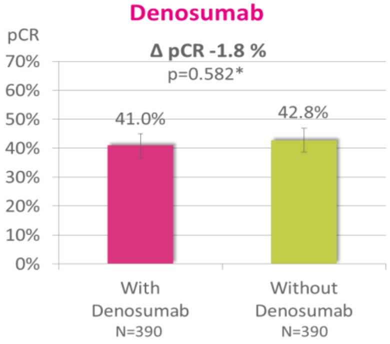
12 wks nab-paclitaxel 125 mg/m² q1w → EC 90/600 mg/m² q2w/q3w

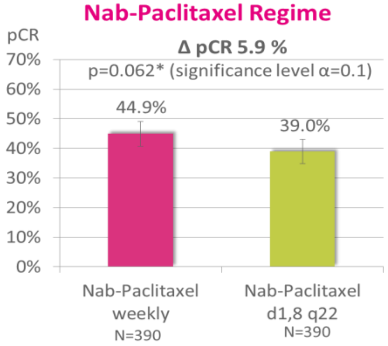
12 wks nab-paclitaxel 125 mg/m² d1,8 q22 → EC 90/600 mg/m² q2w/q3w
Denosumab 120 mg s.c. q4w 24 weeks

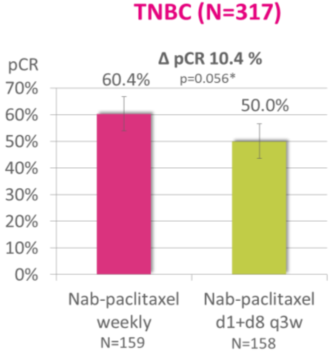
12 wks nab-paclitaxel 125 mg/m² d1,8 q22 → EC 90/600 mg/m² q2w/q3w

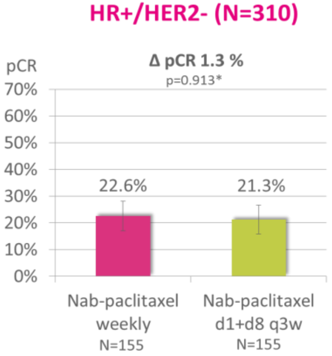
SURGERY + pCR Rate

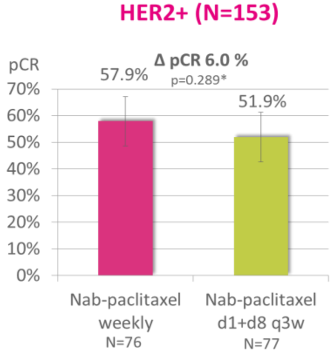
Co-primary efficacy endpoint analysis











*stratified by sTILs, Subtype, EC schedule and denosumab, as applicable

Stratification factors:

- sTILs
- Subtype
- EC schedule
- Denosumab

Treatment backbone:

- HER2+: Trastuzumab (ABP 980)+ Pertuzumab q3w
- TNBC: Carboplatin AUC2 q1w in addition to taxane

Co-primary objektives and endpoints:

- pCR (ypT0 ypN0) rate of:
  - with vs. without denosumab treatment
  - nab-paclitaxel 125mg/m² weekly vs. nab-paclitaxel 125mg/m² day 1,8 q22

Blohmer et al. Cancer Res 2020; 80(4 Suppl): Abstract # GS3-01

Predefined Subgroups: pCR Rates

Subgroup	pCR rates Denosumab (%)		p-value*	pCR rates nab-Paclitaxel (%)		p-value*
	with	without		nP q1w	nP d1, 8 q22	
HR+/HER2-	21.6	22.3	0.961	22.6	21.3	0.913
TNBC	52.5	58.0	0.313	60.4	50.0	0.056
HER2+	55.8	53.9	0.821	57.9	51.9	0.289
EC q2w	40.3	43.3	0.609	46.9	36.7	0.038
EC q3w	41.8	42.3	0.794	42.6	41.5	0.597
>50% sTILs	71.0	61.3	0.528	71.0	61.3	0.135
≤50% sTILs	38.4	41.2	0.453	42.6	37.0	0.126
With Dmab	X	X	X	48.2	33.8	0.027
Without Dmab	X	X	X	41.5	44.1	0.665

* stratified by sTILs, Subtype, EC schedule and denosumab, as applicable

Subgroup Analysis by RANK

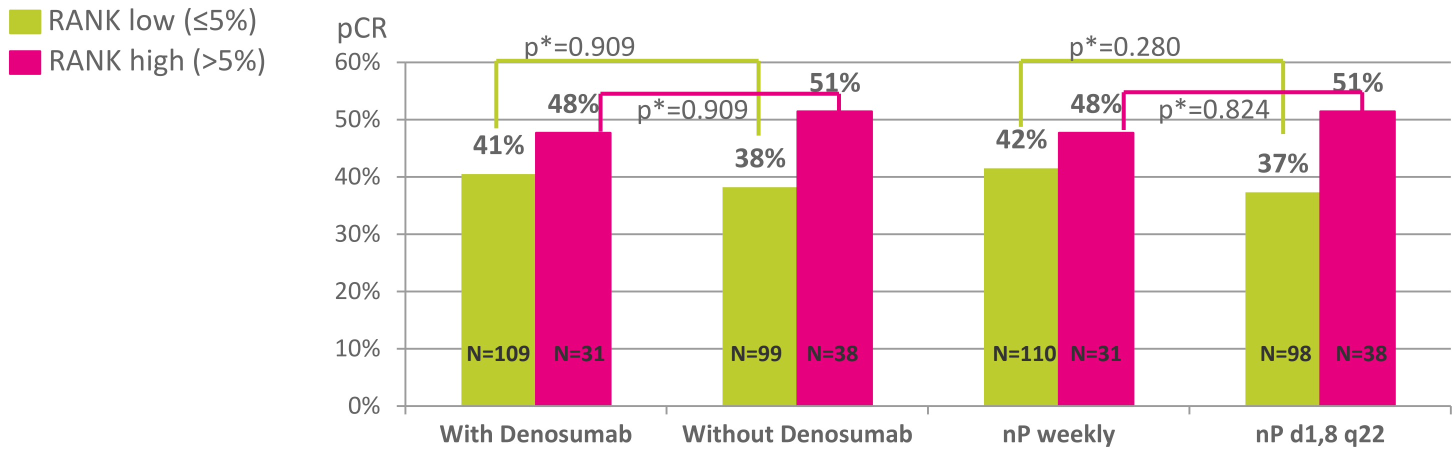
Association of RANK expression with baseline patient and tumor characteristics

Parameter	Category	RANK low (≤5%), N (%)	RANK high (>5%), N (%)	p-value
Age (years)	<40	82 (15.5)	45 (32.4)	<0.001
BC subtype	HR+/HER2-	233 (44.1)	33 (23.7)	<0.001
	TNBC	182 (34.5)	87 (62.6)	
	HER2+	113 (21.4)	19 (13.7)	
Tumor grade	G3	336 (63.6)	104 (74.8)	0.033
Ki-67	>20%	426 (80.7)	127 (91.4)	0.002
sTILs	median (range)	10.0 (0.0-90.0)	20.0 (2.0-90.0)	0.002

- Of the 780 patients included in GeparX study, 667 had evaluable RANK protein values.
- RANK expression was categorized at 75th percentile (Q3) into low (≤5%) or high (>5%).
- A high RANK expression was detected in 139/667 (20.8%) of the patients.

Pfitzner B et al.
Breast Cancer Res Treat. 2014.

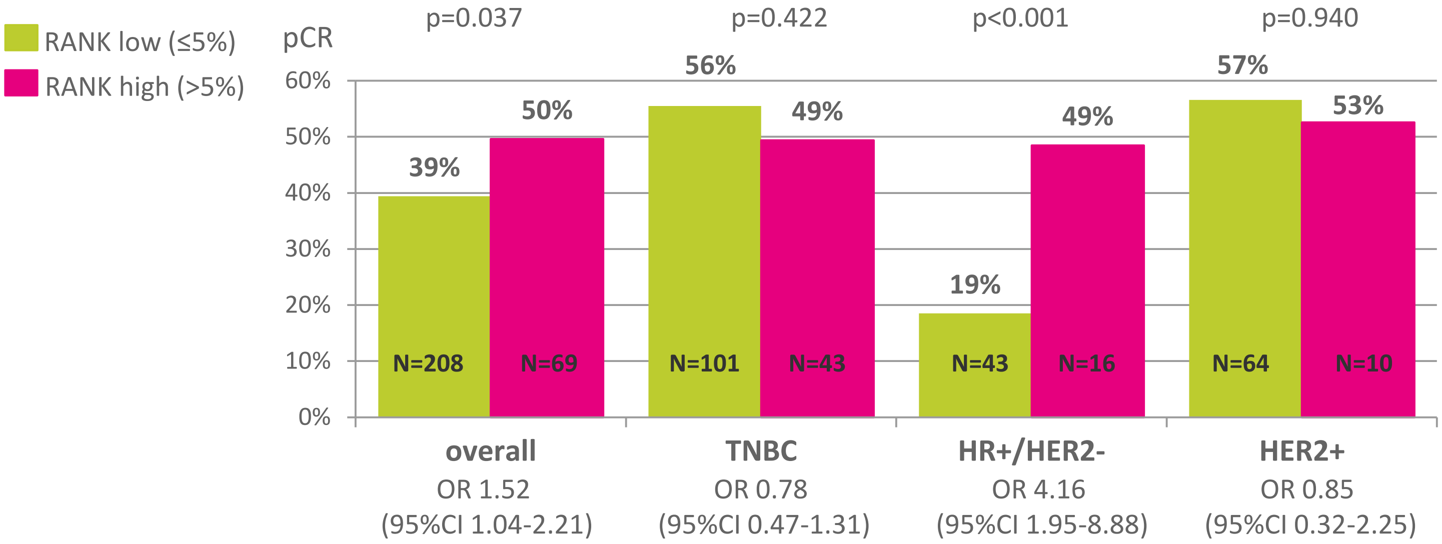
pCR Rates by RANK and Treatment



*stratified by sTILs, subtype, EC schedule and denosumab; nP, nab-paclitaxel

Parameter	Denosumab			Nab-paclitaxel (nP) regime		
	OR (with vs. without) [95% CI]	p-value	interaction p-value	OR (nP weekly vs. nP d1,8 q22) [95% CI]	p-value	interaction p-value
RANK low	1.10 [0.78-1.56]	0.589	0.528	1.19 [0.84-1.69]	0.318	0.833
RANK high	0.86 [0.44-1.68]	0.667		1.30 [0.67-2.52]	0.447	

pCR Rates by RANK and Subtype



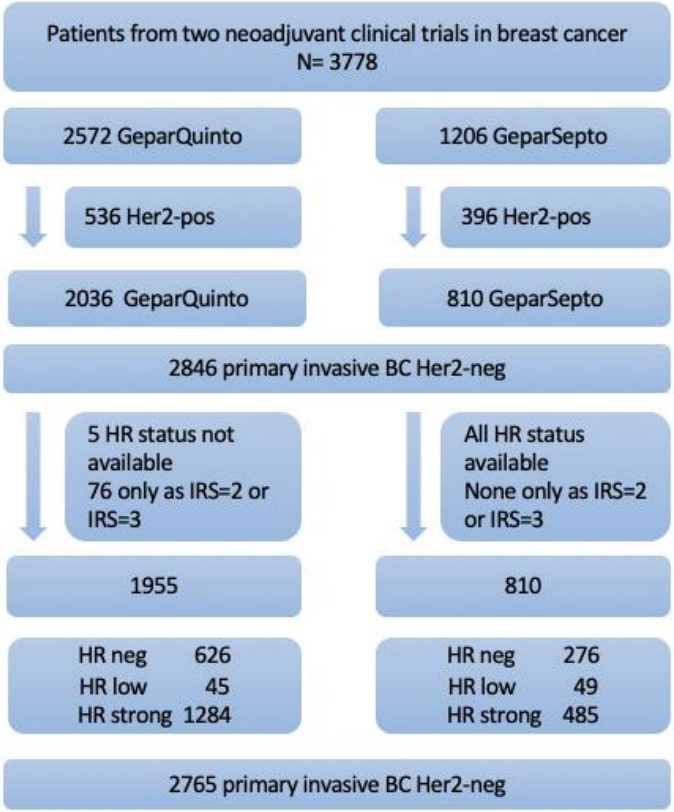
Interaction Test RANK*subtype
(%, high vs low) p=0.0012

- Overall, RANK expression did not add additional predictive value (OR=1.05 [95%CI 0.69-1.60], p=0.823) when adjusted for BC subtype and the continuous variables age, Ki-67 and sTILs in multivariate model.
- In HR+/HER2- RANK expression was an independent significant predictor of pCR (OR=2.98 [95%CI 1.30-6.79], p=0.010) when adjusted for the continuous variables age, Ki-67 and sTILs.

Summary and Conclusion

- A high RANK expression was detected in 20.8% of the patients.
- A high RANK expression was associated with significantly higher pCR rates (49.6% vs. 39.4%; p=0.037).
- This effect was driven by patients with HR+/HER2- BC.
- However, a clinical benefit of denosumab in relation to RANK expression could not be shown. Further explorative analyses are still ongoing.

low HR positive BC (1-9%) – GBG pooled analysis, n=2765



Patients from two neoadjuvant clinical trials in breast cancer
N= 3778

2572 GeparQuinto

536 Her2-pos

2036 GeparQuinto

1206 GeparSepto

396 Her2-pos

810 GeparSepto

2846 primary invasive BC Her2-neg

5 HR status not available
76 only as IRS=2 or IRS=3

1955

HR neg 626
HR low 45
HR strong 1284

All HR status available
None only as IRS=2 or IRS=3

810

HR neg 276
HR low 49
HR strong 485

2765 primary invasive BC Her2-neg

- complete cohort: 2765 patients
- low HR positive (n=94) =**3.4% of all breast cancer patients**

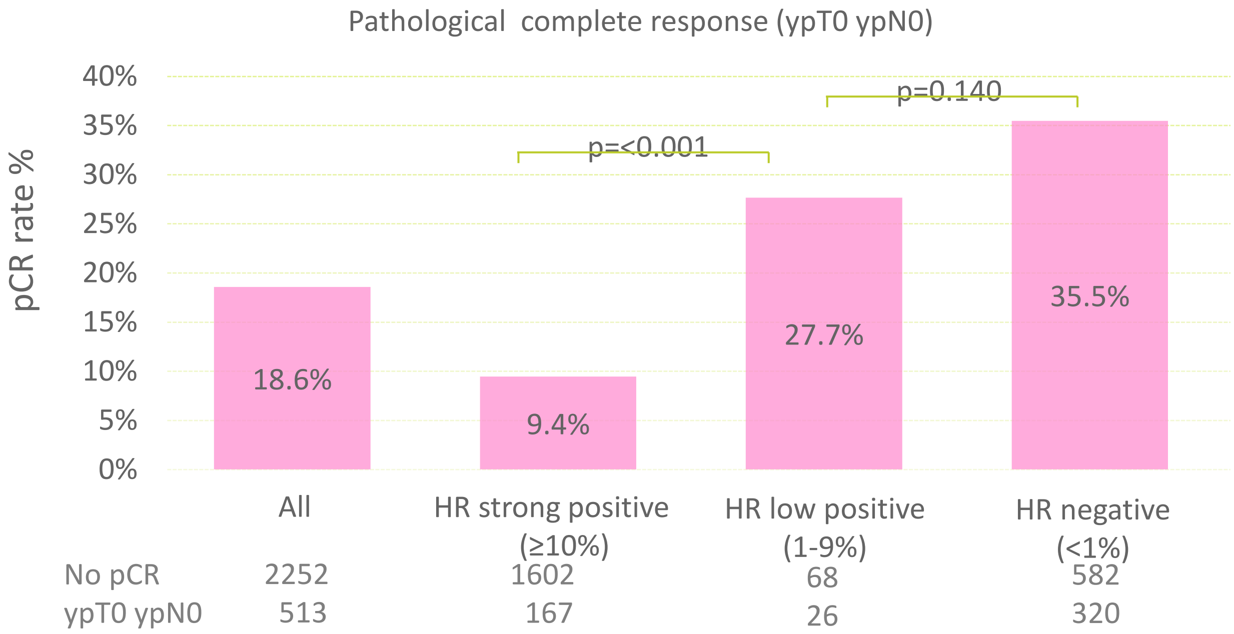
- “HR negative“ tumors: 902
- low HR pos tumor: **10,4% additional tumors (in HR negative cohorts)**

- 10% more patients in neoadjuvant TNBC trials if lowHR patients would be included

Villegas et al. Eur J Cancer, accepted 2021

GBG
GERMAN
BREAST
GROUP

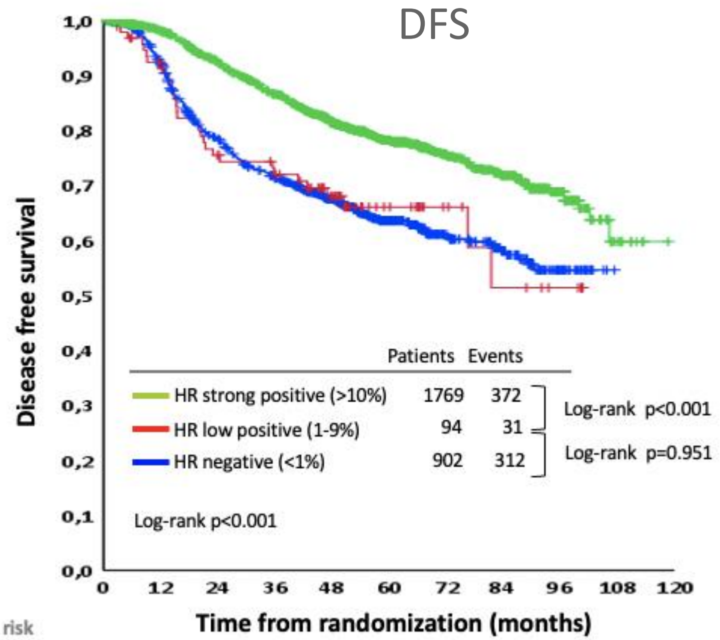
low HR positive breast cancer (1-9%) – pCR rate



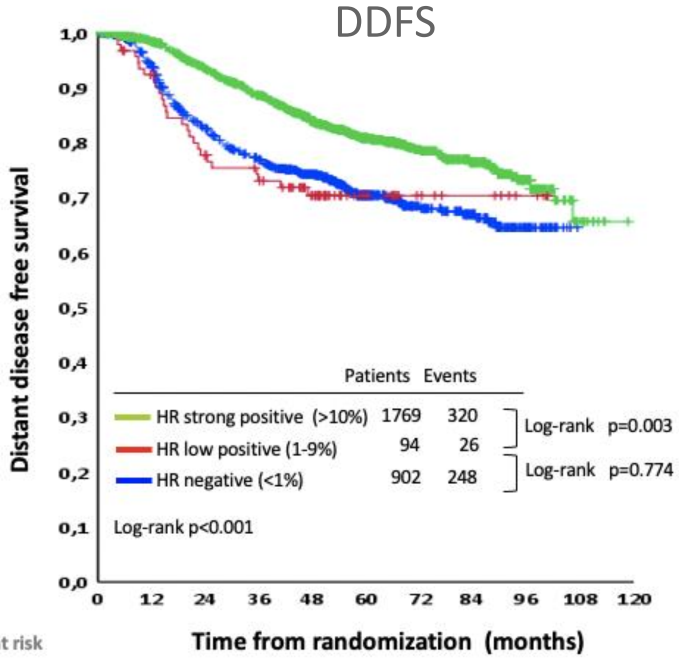
	All	HR strong positive (≥10%)	HR low positive (1-9%)	HR negative (<1%)
No pCR	2252	1602	68	582
ypT0 ypN0	513	167	26	320

Villegas et al. Eur J Cancer, accepted 2021

low HR positive breast cancer (1-9%) – survival analysis



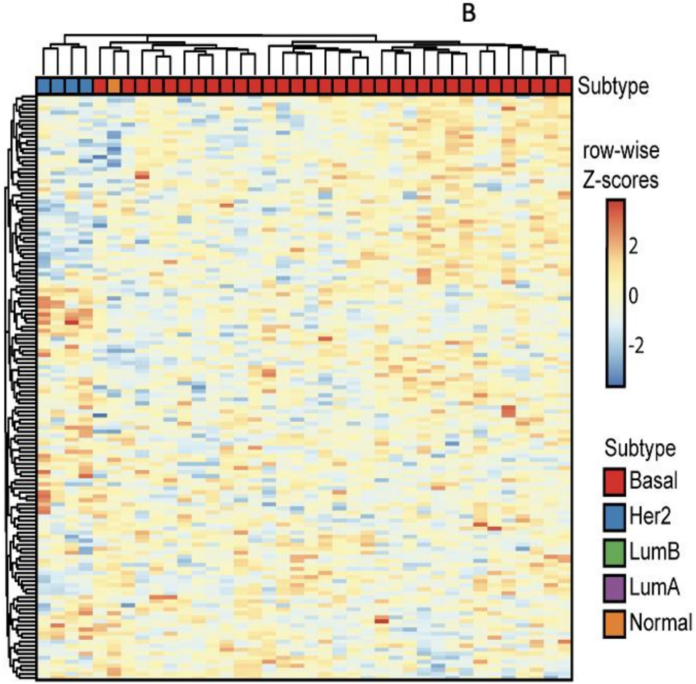
Patients at risk										
HR strong positive	1769	1628	1463	1312	1077	720	377	262	93	11
HR negative	902	796	650	569	467	275	139	91	30	
HR low positive	94	82	66	61	44	21	11	7	4	



Patients at risk										
HR strong positive	1769	1634	1479	1339	1108	740	392	275	97	12
HR negative	902	811	684	608	507	295	155	102	32	
HR low positive	94	83	68	62	46	23	12	9	5	

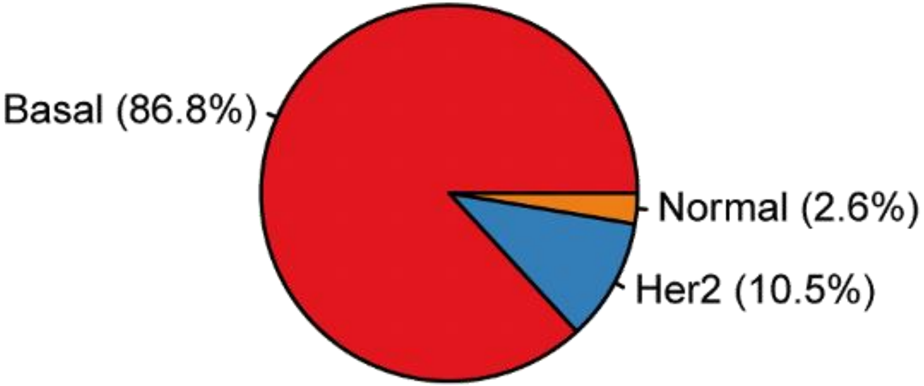
Villegas et al. Eur J Cancer, accepted 2021

RNA profiling of low HR tumors: basal subtype



Conclusion:

- patients with low HR positive tumors (1-9%) should be included in TNBC neoadjuvant trials
- = an additional 10% of patients



Christian Albig, Nicole Pfarr, Wilko Weichert, TU Munich

Villegas et al. Eur J Cancer, accepted 2021

Mutational signatures in breast cancer

Induction of mutations over months/years by different mutational processes

HRD

APOBEC

Age

MMR

tobacco

other/ unkown

Alexandrov et al.
Nature 2013
Nature 2020;
Science 2016;
Science 2015,
Nat.Genet 2015


ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

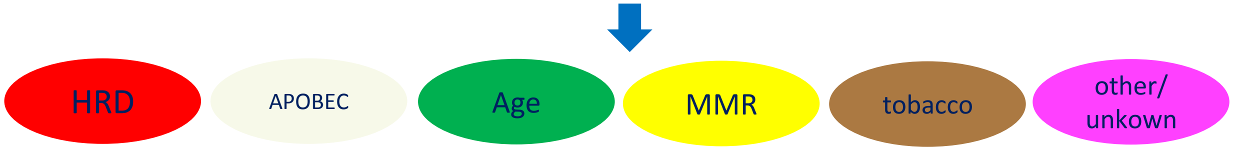
ORIGINAL ARTICLE

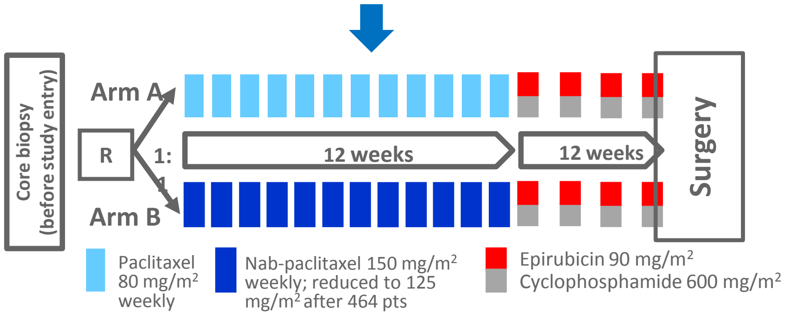
Reconstructing tumor history in breast cancer: signatures of mutational processes and response to neoadjuvant chemotherapy☆

C. Denkert[1,2*†], M. Untch[3†], S. Benz[4], A. Schneeweiss[5], K. E. Weber[6], S. Schmatloch[7], C. Jackisch[8], H. P. Sinn[9,10], J. Golovato[4], T. Karn[11], F. Marmé[12], T. Link[13], J. Budczies[2,9,10], V. Nekljudova[6], W. D. Schmitt[2], E. Stickeler[14], V. Müller[15], P. Jank[1,2], R. Parulkar[4], E. Heinmöller[16], J. Z. Sanborn[4], C. Schem[17], B. V. Sinn[2], P. Soon-Shiong[4], M. van Mackelenbergh[18], P. A. Fasching[19], S. Rabizadeh[4] & S. Loibl[6,20]

Mutational signatures in breast cancer

Induction of mutations over months/years by different mutational processes





GeparSepto neoadjuvant cohort (GBG)

Successfull whole exome sequencing (n=405)
HRneg (=TNBC): n=121; HRpos (=lum/HER2neg): n=284
30 mutational signatures

Mutational signatures in breast cancer

Induction of mutations over months/years by different mutational processes

HRD

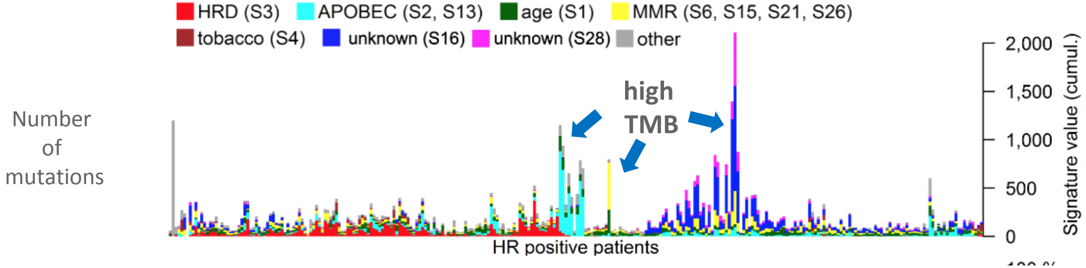
APOBEC

Age

MMR

tobacco

other/ unkown



GeparSepto trial, Luminal Tumors, N=284

Mutational signatures in breast cancer

Induction of mutations over months/years by different mutational processes

HRD

APOBEC

Age

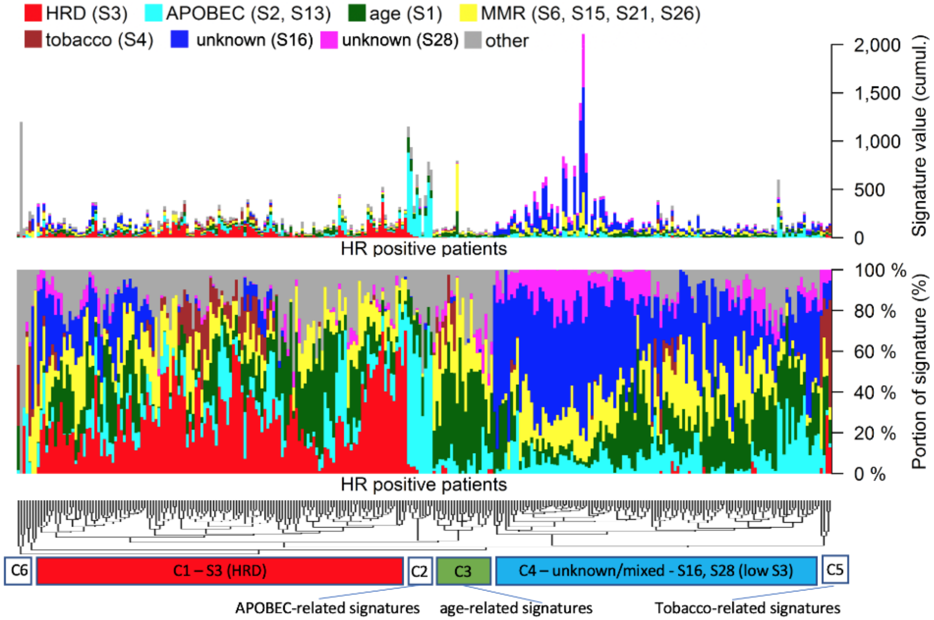
MMR

tobacco

other/
unkown

Number
of
mutations

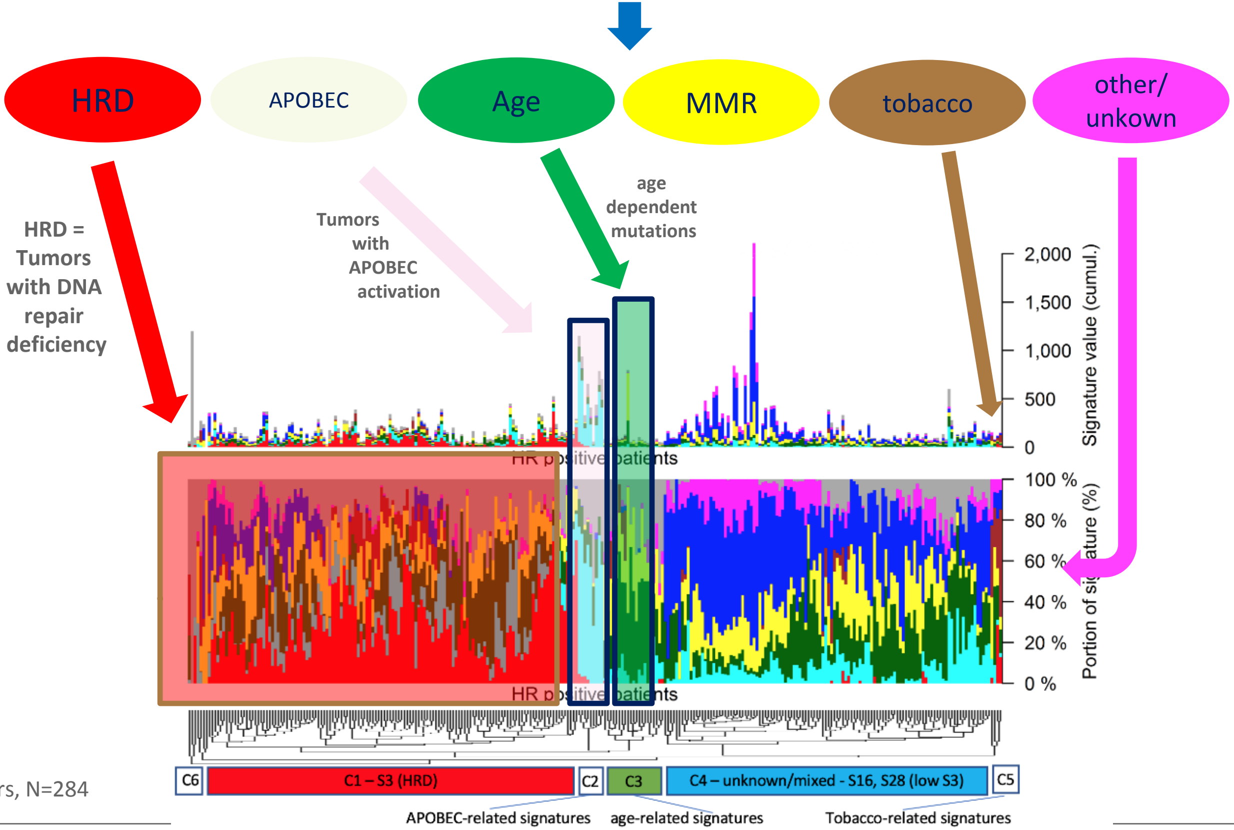
Percentage
of
mutational
signatures



GeparSepto trial, Luminal Tumors, N=284

Mutational signatures in breast cancer

Induction of mutations over months/years by different mutational processes



GeparSepto trial, Luminal Tumors, N=284

Mutational signatures in breast cancer – clinical outcome

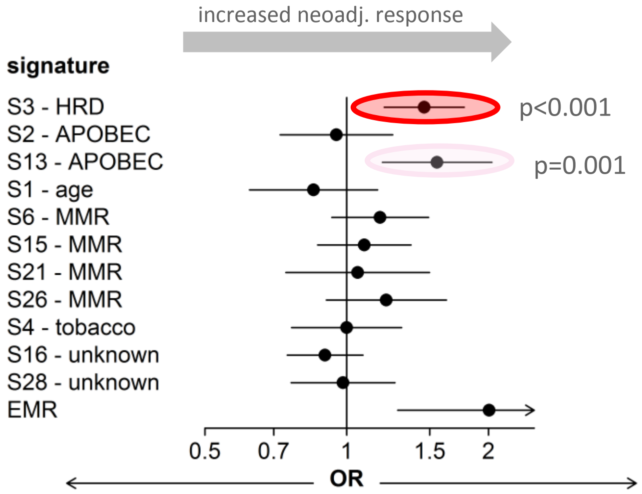
Induction of mutations over months/years by different mutational processes

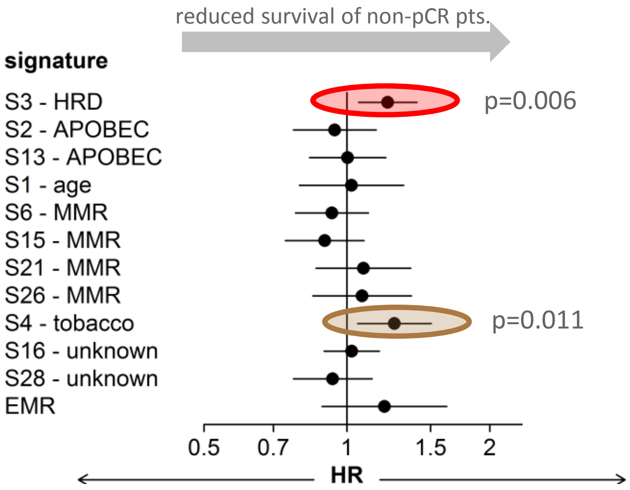
HRD | **APOBEC** | Age | MMR | **tobacco** | other/ unkown

HRD-DNA repair deficiency

APOBEC activation

Tobacco related mutations





GeparSepto trial, Luminal Tumors, N=284

Überblick translationale Forschung 2020

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Expression von RANK in GeparX

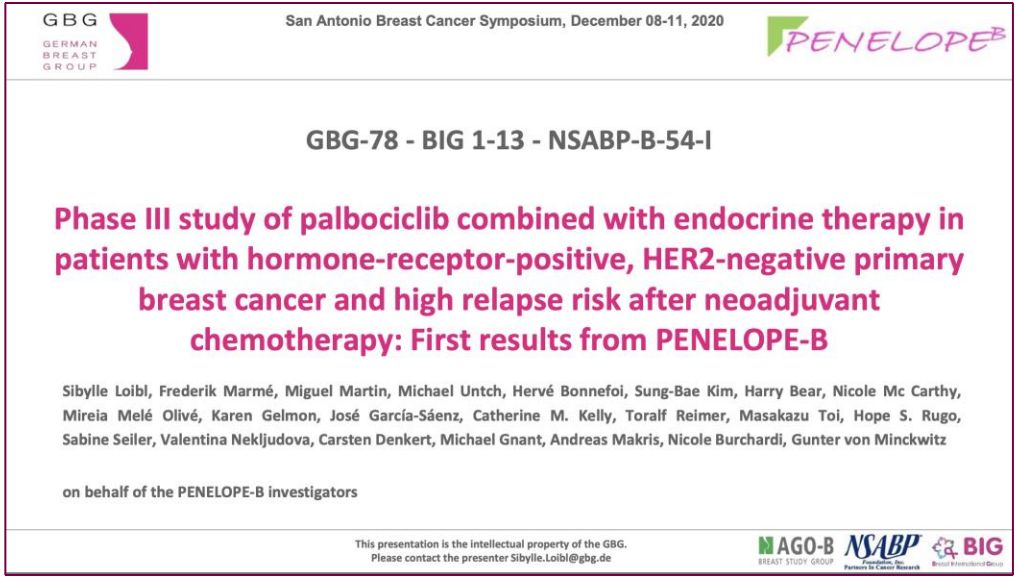
Charakterisierung von Tumoren mit einer lowHR Expression

Mutational signatures in GeparSepto

Immun-onkologische Projekte (Thomas Karn)

aktuell laufende Projekte

Aktuell laufende Projekte



San Antonio Breast Cancer Symposium, December 08-11, 2020

GBG-78 - BIG 1-13 - NSABP-B-54-I

Phase III study of palbociclib combined with endocrine therapy in patients with hormone-receptor-positive, HER2-negative primary breast cancer and high relapse risk after neoadjuvant chemotherapy: First results from PENELOPE-B

Sibylle Loibl, Frederik Marmé, Miguel Martin, Michael Untch, Hervé Bonnefoi, Sung-Bae Kim, Harry Bear, Nicole Mc Carthy, Mireia Melé Olivé, Karen Gelmon, José García-Sáenz, Catherine M. Kelly, Toralf Reimer, Masakazu Toi, Hope S. Rugo, Sabine Seiler, Valentina Nekljudova, Carsten Denkert, Michael Gnant, Andreas Makris, Nicole Burchardi, Gunter von Minckwitz

on behalf of the PENELOPE-B investigators

This presentation is the intellectual property of the GBG.
Please contact the presenter Sibylle.Loibl@gbg.de

mRNA Profiling, N=906

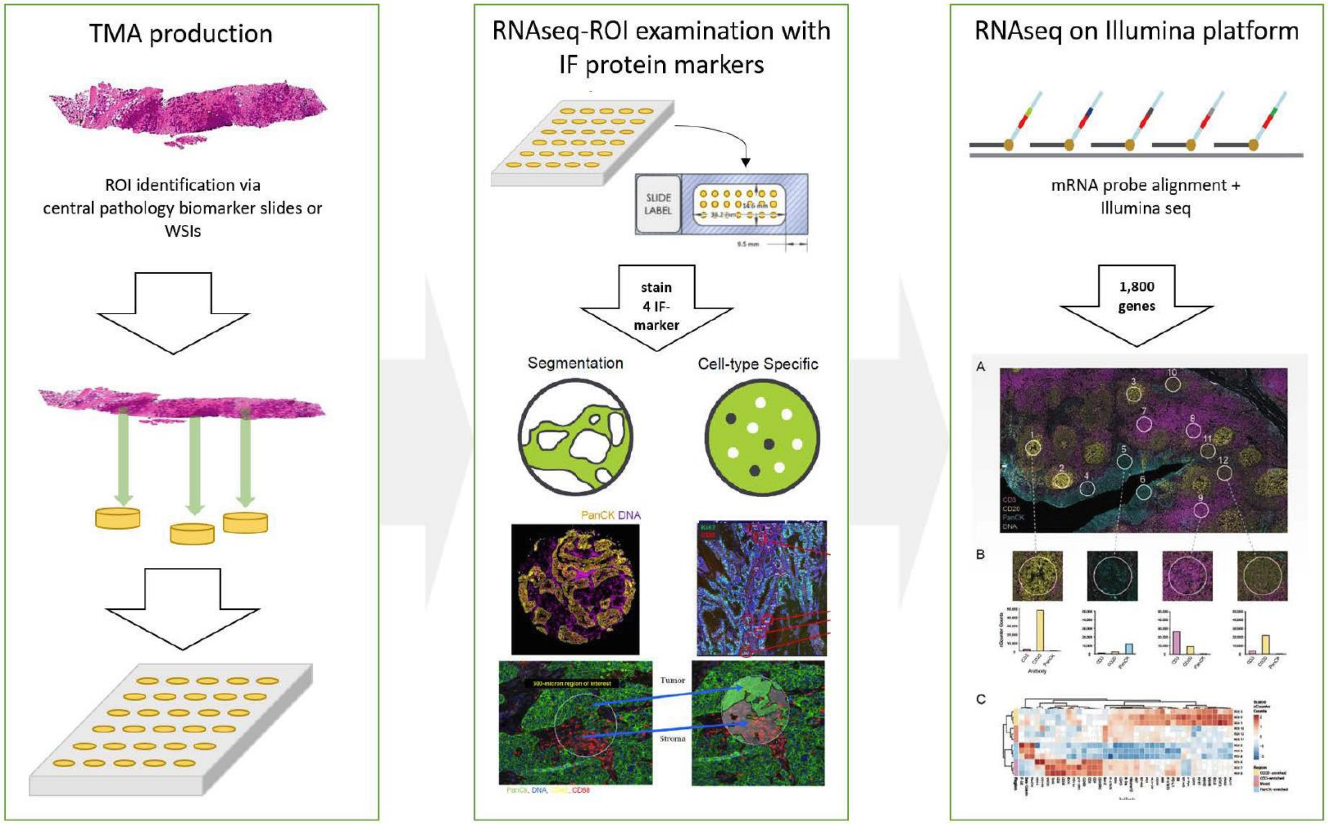
HTGEdgeSeq Methode

2559 Gene

ASCO Abstract 2021

Julia Teply-Szymanski, Pathologie Marburg

Spatial mRNA profiles in clinical trial samples - ongoing



TMA production

ROI identification via central pathology biomarker slides or WSIs

RNAseq-ROI examination with IF protein markers

stain 4 IF-marker

Segmentation

Cell-type Specific

RNAseq on Illumina platform

mRNA probe alignment + Illumina seq

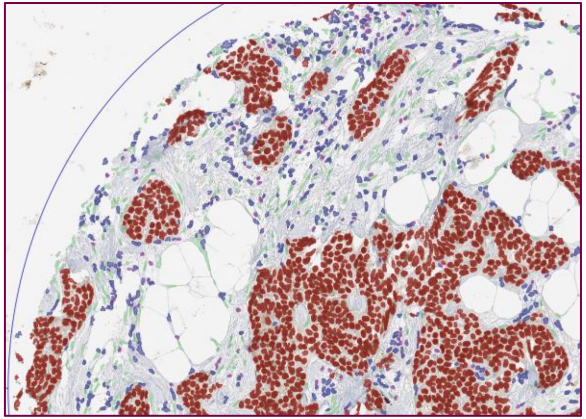
1,800 genes

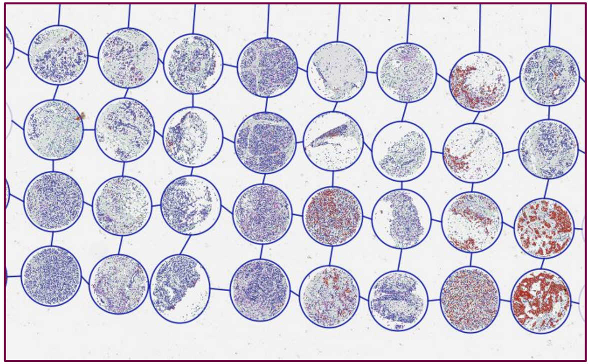
Ziel:

Vergleich von räumlich aufgelösten mRNA Profilen, z.B.

- Immunzellen vs. Tumorzellen
- stromale TILs vs. intratumorale TILs

Aktuell laufende Projekte – digitale Pathologie





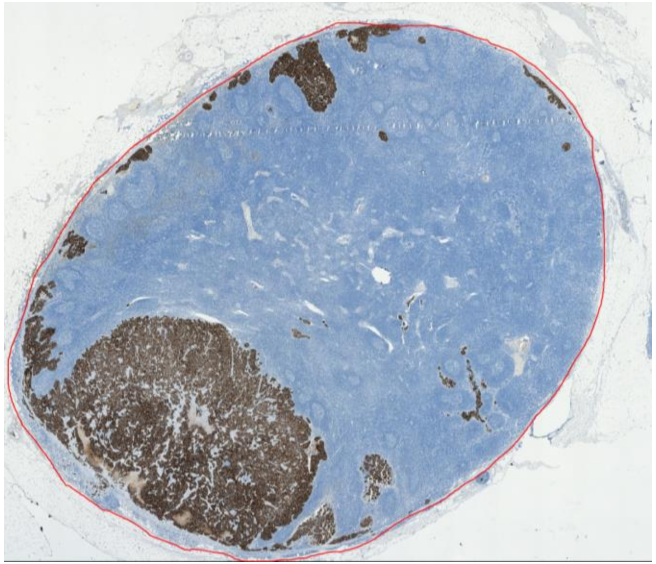
- QuPath – digital imaging – breast cancer in pregnancy (immune marker)
- Gain tissue microarray
- Ziel: standardisierte digitale Auswertung von Immunhisto-Biomarkern

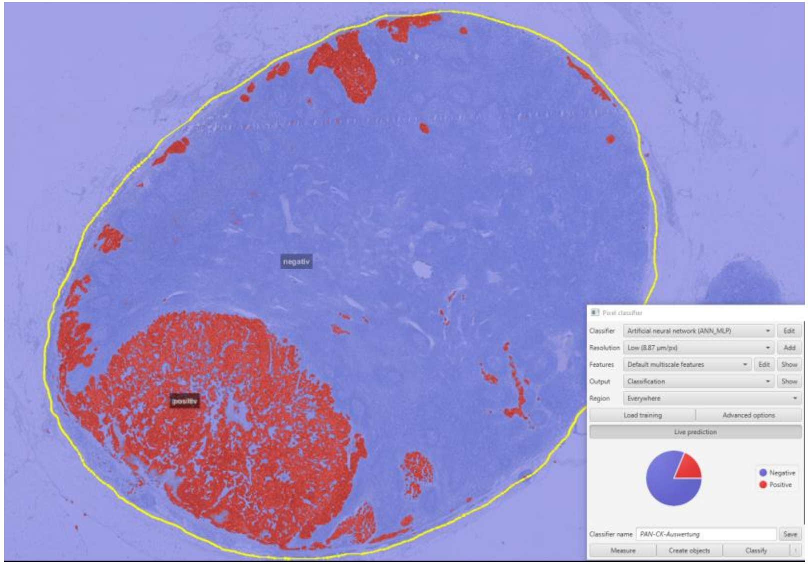
Aktuell laufende Projekte – digitale Pathologie

Regression patterns and immune infiltrate in lymph nodes after neoadjuvant therapy

n=700 from neoadjuvant trials, standardized image analysis

comprehensive dataset of tumor regression in lymph nodes





Classifier: Artificial neural network (ANN_MLP)
Resolution: Low (8.87 µm/px)
Features: Default multiscale features
Output: Classification
Region: Everywhere
Classifier name: PAN-CK-Auswertung

Digitale Pathology and artificial intelligence

innovative medicines initiative

Central repository of digital pathology slides to support the development of artificial intelligence tools

Pierre Moulin, MD, PhD, MBA
14.06.2019• IMI webinar

BIGPICTURE

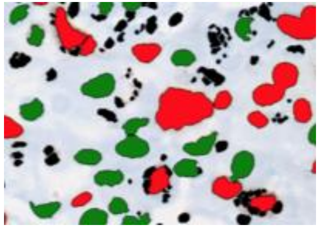
Central Repository for Digital Pathology

- coordinator: Jeroen van der Laak (Radboud University)
- 38 academic Partner und 10 industry partner
- Budget: 32 Mio. Euro
- planned: 3 Mio. digital slides
  - 2 Mio. slides preclinical (Pharma)
  - 1 Mio slides pathology (academia)
- Project start: 03/2021
- GBG und UMR: clinical trial node

innovative medicines initiative

Digitalisierung der GBG Biobank

ca. 100.000
digitale Schnitte
(ca. 100 TB)



Machine learning,
digitales Grading
Responseprädiktion

Digital Revolution in Pathology

Pierre Moulin

GBG Jahrestreffen 2021

HERZLICHEN
DANK!

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

Vielen Dank an alle Kooperationspartner!

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

carsten.denkert@uni-marburg.de