Neues aus der Translationalen Forschung - TILs and beyond

GBG Jahrestreffen 2017, 2.3.2017

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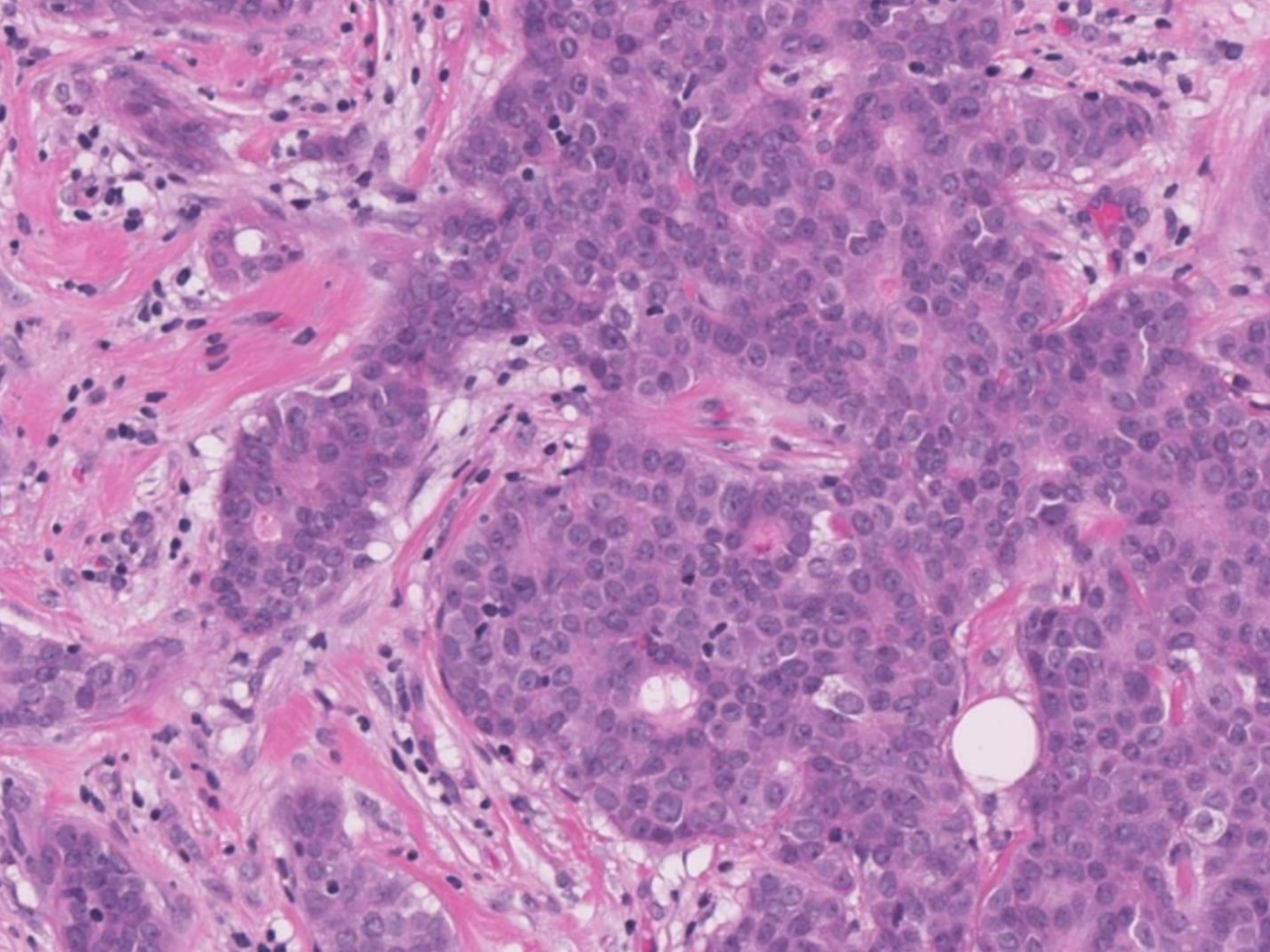
Charité Berlin



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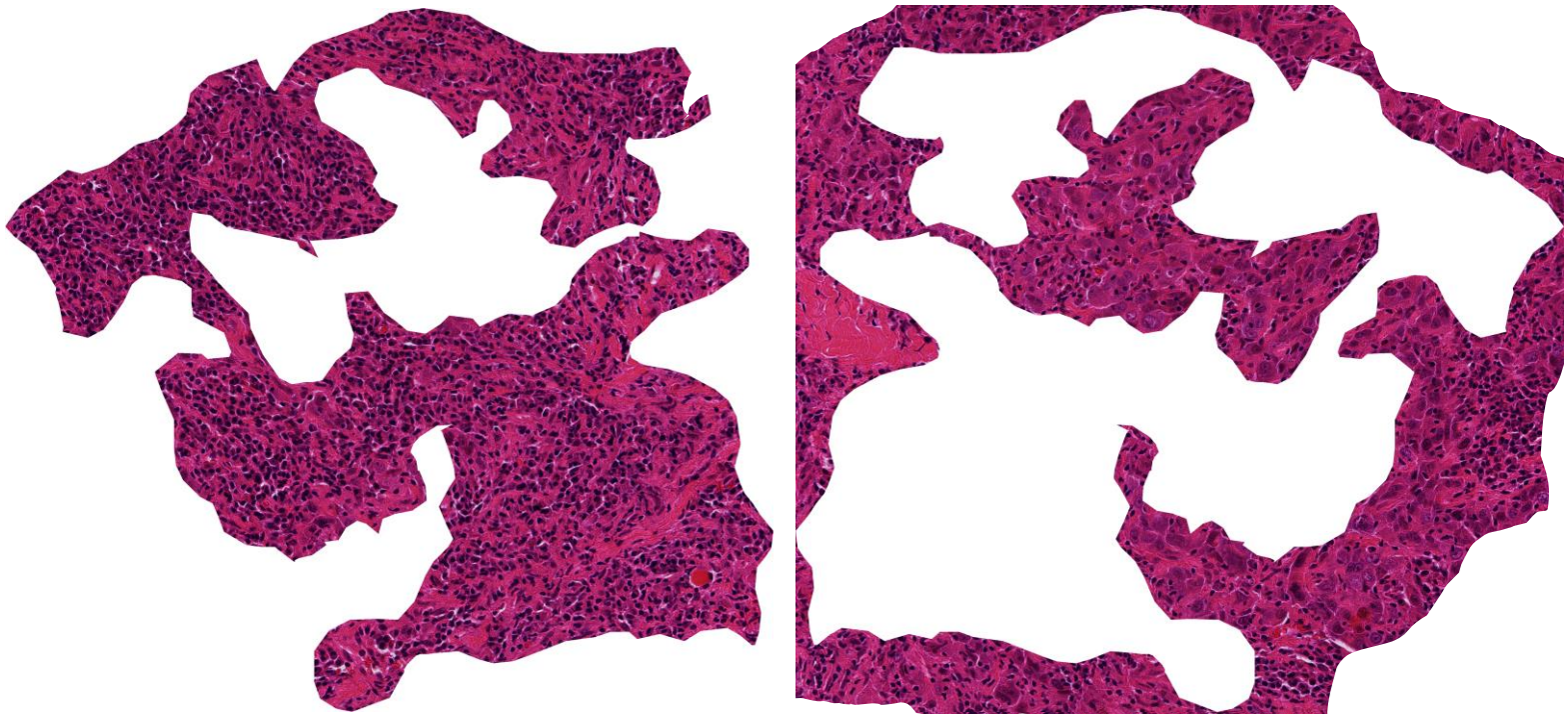
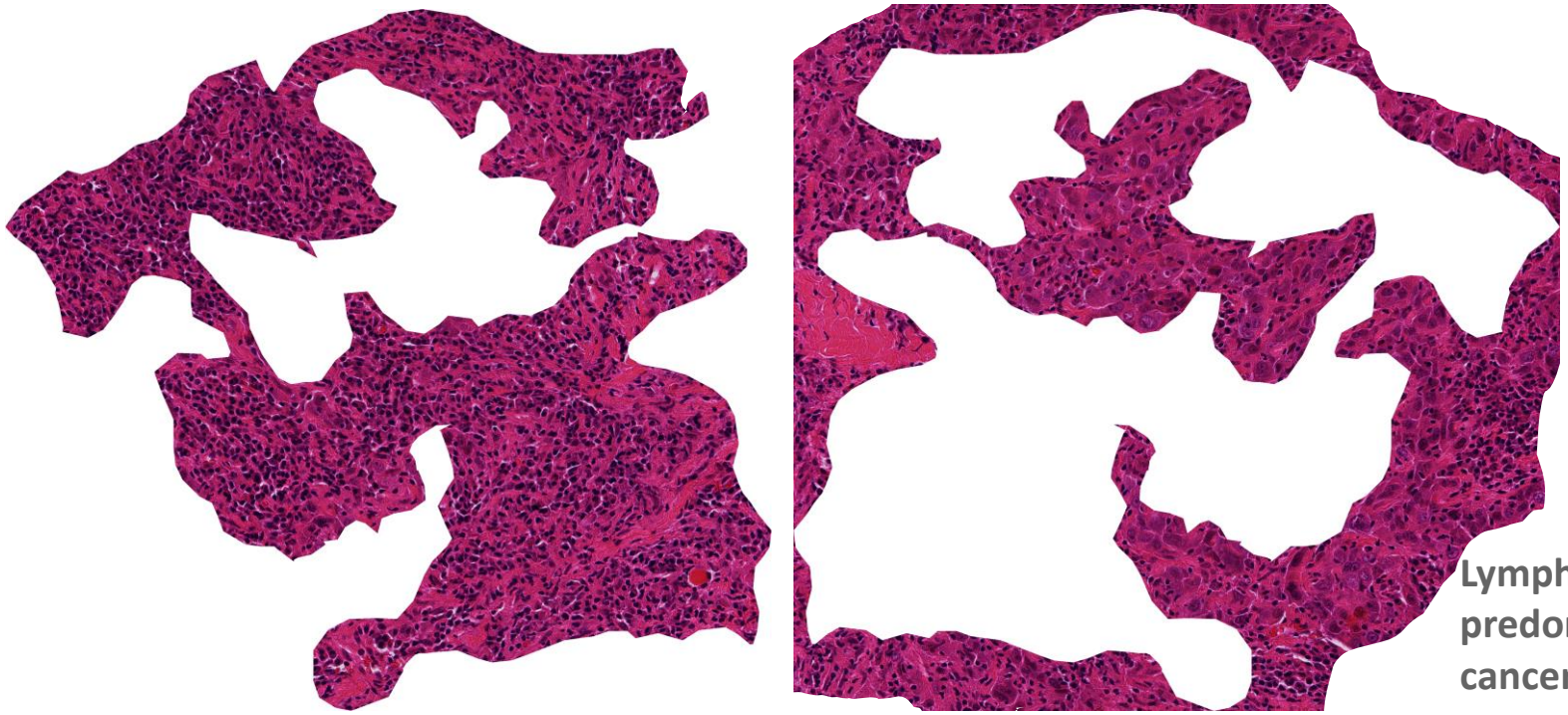
Stromale und intratumorale TILs



Stromale und intratumorale TILs

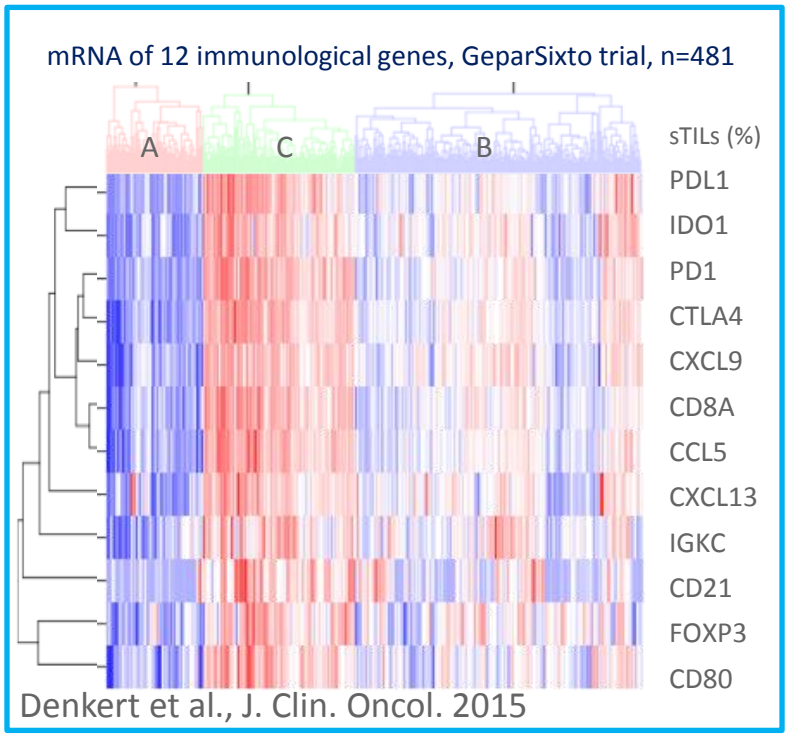
Stromal TILs –
located in the connective tissue within the tumor
majority of TILs in breast cancer
best parameter for evaluation

„intratumoral“TILs –
directly infiltrating the tumor cell nests
additional parameter for evaluation



Lymphocyte predominant breast cancer (LPBC)
„more lymphocytes than tumor cells“
10-25% of BC

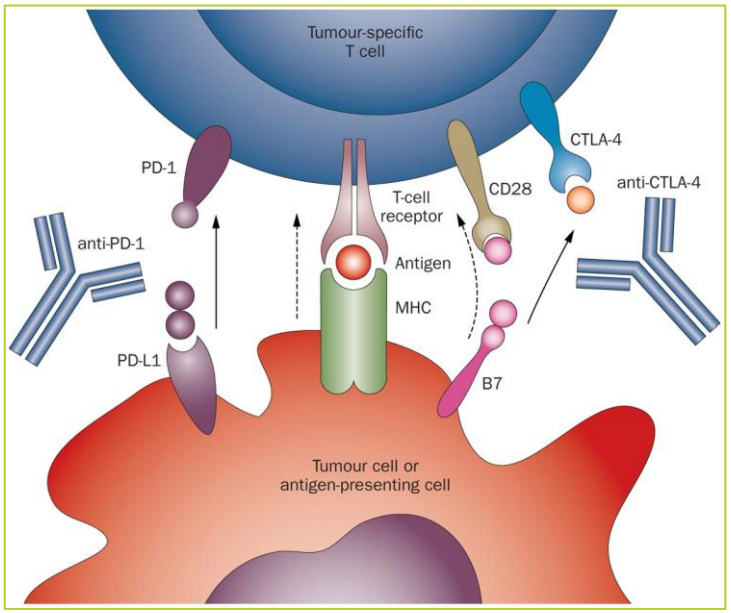
Immun-Gensignaturen und therapeutische Targets



Denkert et al., J. Clin. Oncol. 2015

Therapeutische Ansätze:

- PDL1: atezolizumab, avelumab, durvalumab
- IDO1: epacadostat, indoximod, NLG919
- PD1: nivolumab, pembrolizumab
- CTLA4: ipilimumab



Drake et al., Nat. Rev. Clin. Oncol. 2013

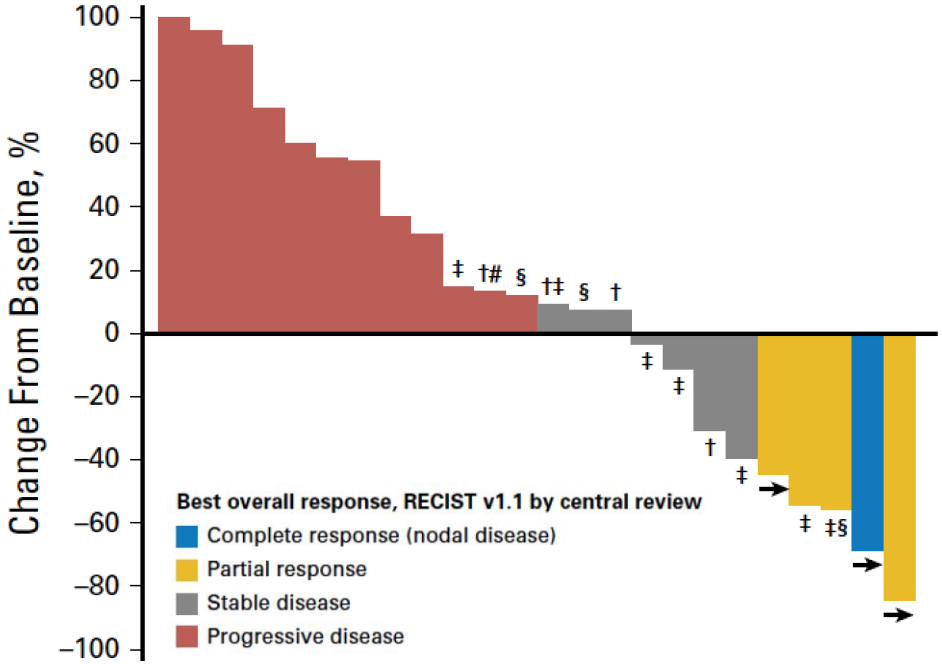
Gepar Nuevo

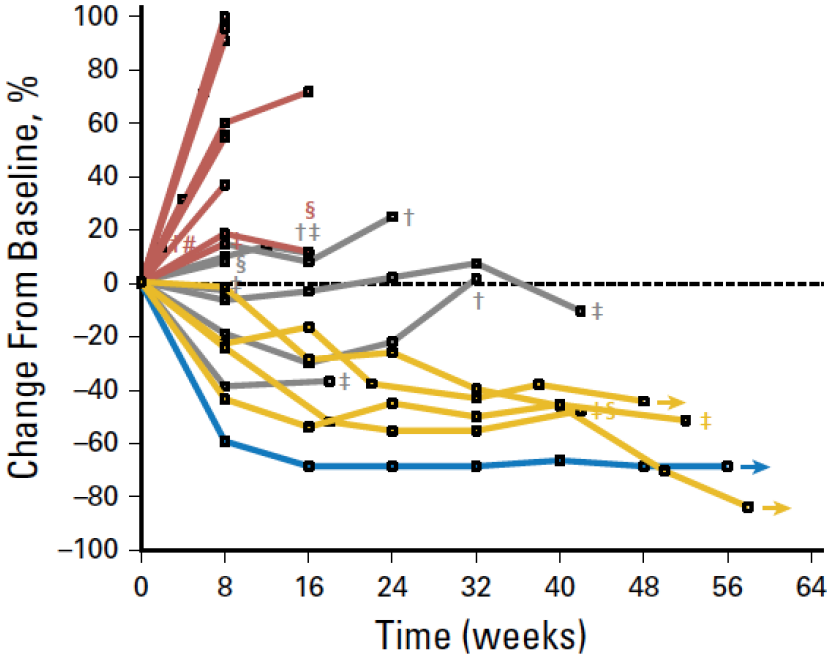
Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study

anti-PD1

Rita Nanda, Laura Q.M. Chow, E. Claire Dees, Raanan Berger, Shilpa Gupta, Ravit Geva, Lajos Pusztai, Kumudu Pathiraja, Gursel Aktan, Jonathan D. Cheng, Vassiliki Karantza, and Laurence Buisseret

JCO, July 20th, 2016





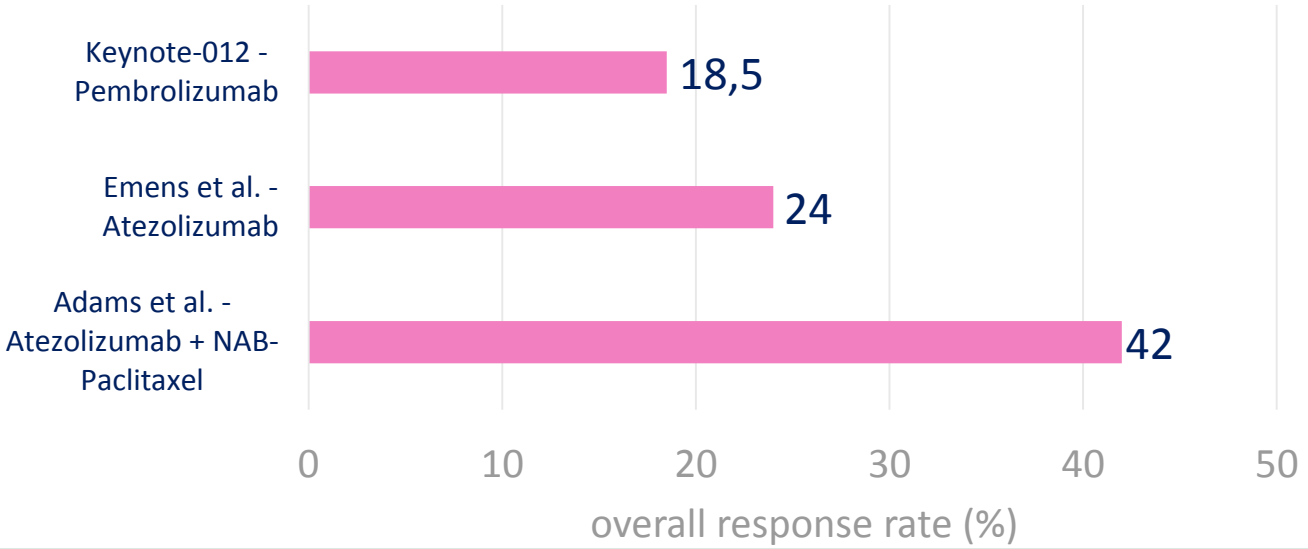
TNBC, n=32

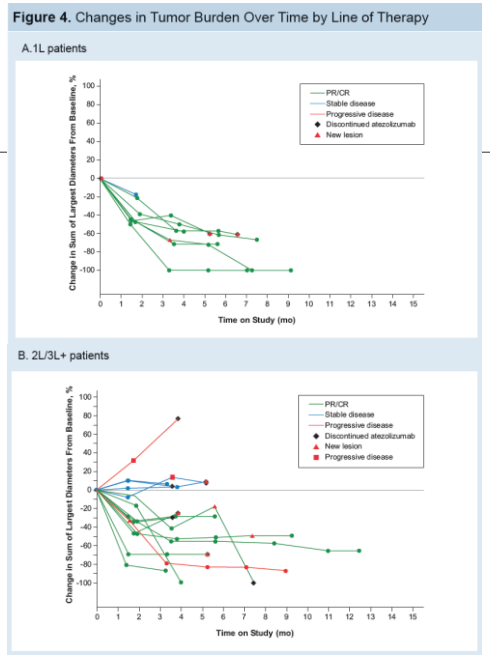
PDL1+ in stroma or in ≥1% of tumor cells (>58% of TNBC screened)

overall response rate 18.5%

ongoing phase 2 study (KEYNOTE-086 trial)

Phase 1 trials – checkpoint inhibitors in TNBC





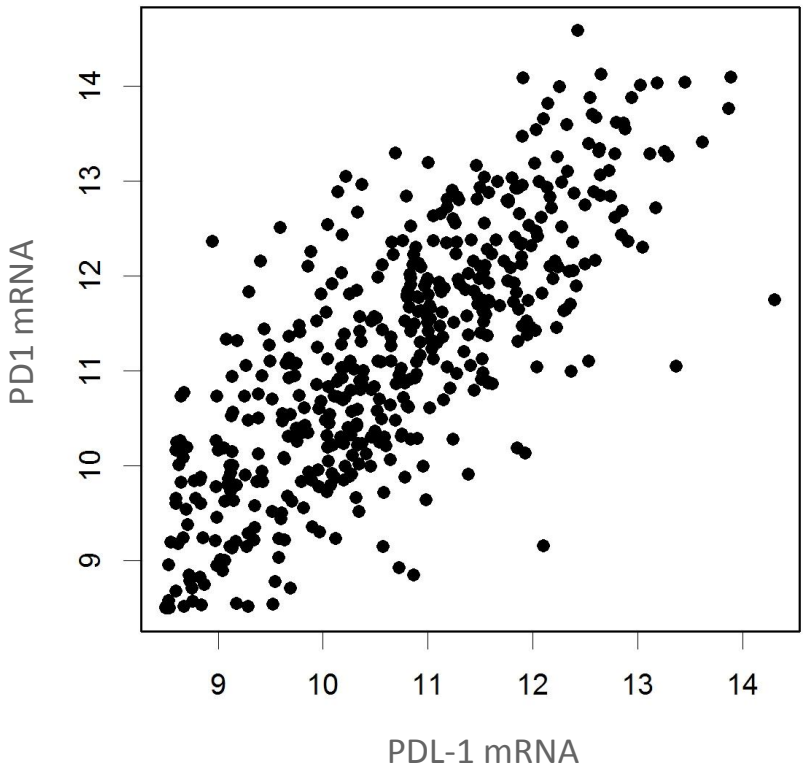
Sylvia Adams, SABCS 2015

	Clinical cohort and therapeutic intervention	Main result
Immune checkpoint inhibitors		
KEYNOTE-012: non-randomised, multicohort, phase Ib study[74] (NCT01848834)	Patients with metastatic PD-L1-positive TNBC (all therapy lines); PD-L1 inhibitor pembrolizumab given intravenously at 10 mg/kg every 2 weeks; 32 patients with TNBC enrolled, 28 patients with evaluable response	Overall response rate 18·5%; median time to response 17·9 weeks; 15·6% incidence of grade 3 to 5 treatment-related adverse events
Multicentre phase Ia study[75] (NCT01375842)	Patients with pretreated metastatic PD-L1-positive TNBC received the PD-L1 inhibitor atezolizumab; n=27	Unconfirmed RECIST overall response rate 24%; grade 3–5 related adverse events in 11% of patients
GP28328: phase Ib multicenter trial[76] (NCT01633970)	Patients with metastatic TNBC treated with ≤3 previous lines of therapy; atezolizumab (800 mg once every two weeks [day 1, 15]) in combination with nab-paclitaxel (125 mg/m^2 once weekly [day 1, 8, 15], for 3 of 4 weeks); n=32	Overall response rates: first-line, 67%; second-line, 25%; third-line, 29%; all patients, 42%; 56% grade 3-4 adverse events

Denkert et al. Lancet 2016

Immun-Gensignaturen und diagnostische Tests

TNBC and HER2+ BC, GeparSixto trial, n=481



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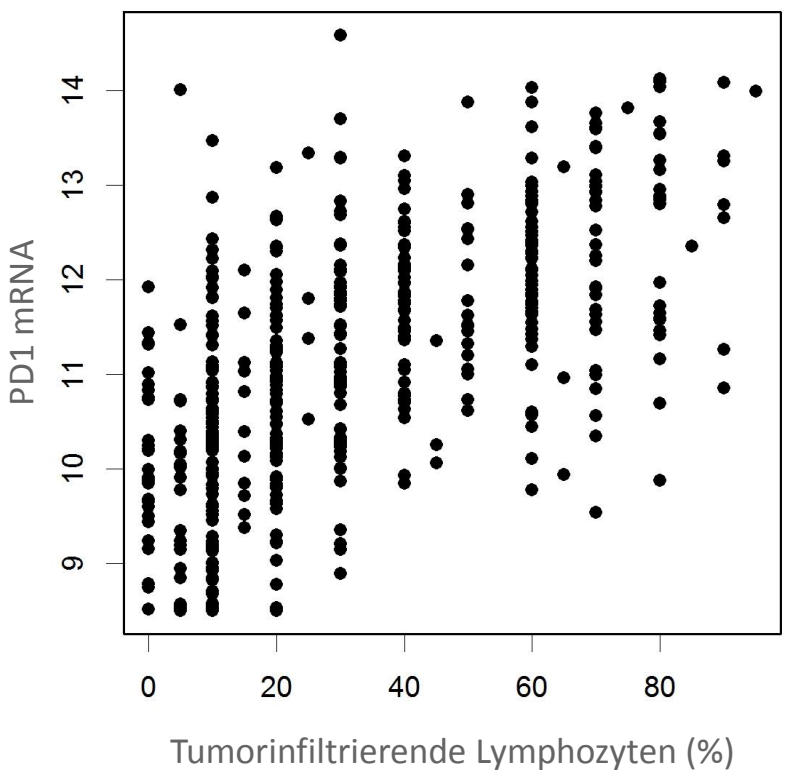
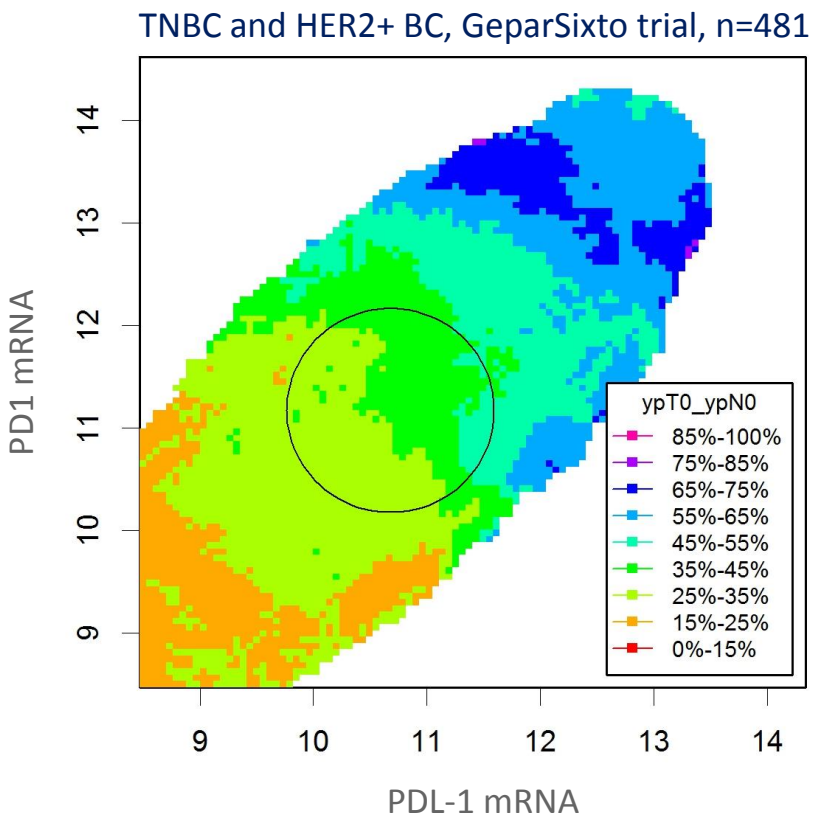
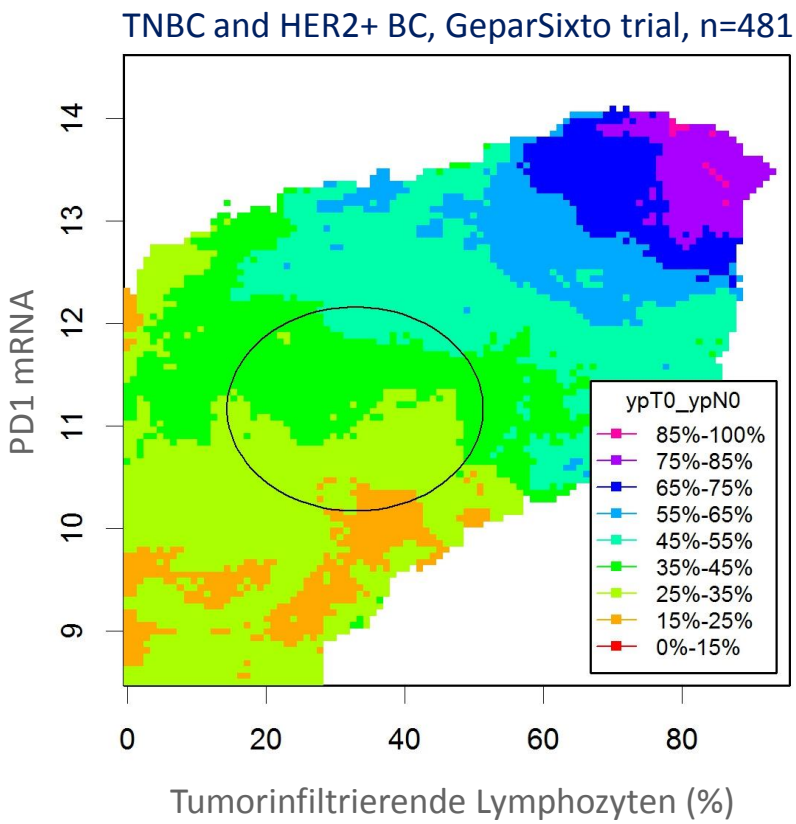
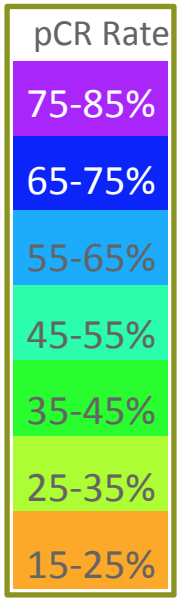


Immun-Gensignaturen und diagnostische Tests







Jan Budczies, 2D STEPP analysis

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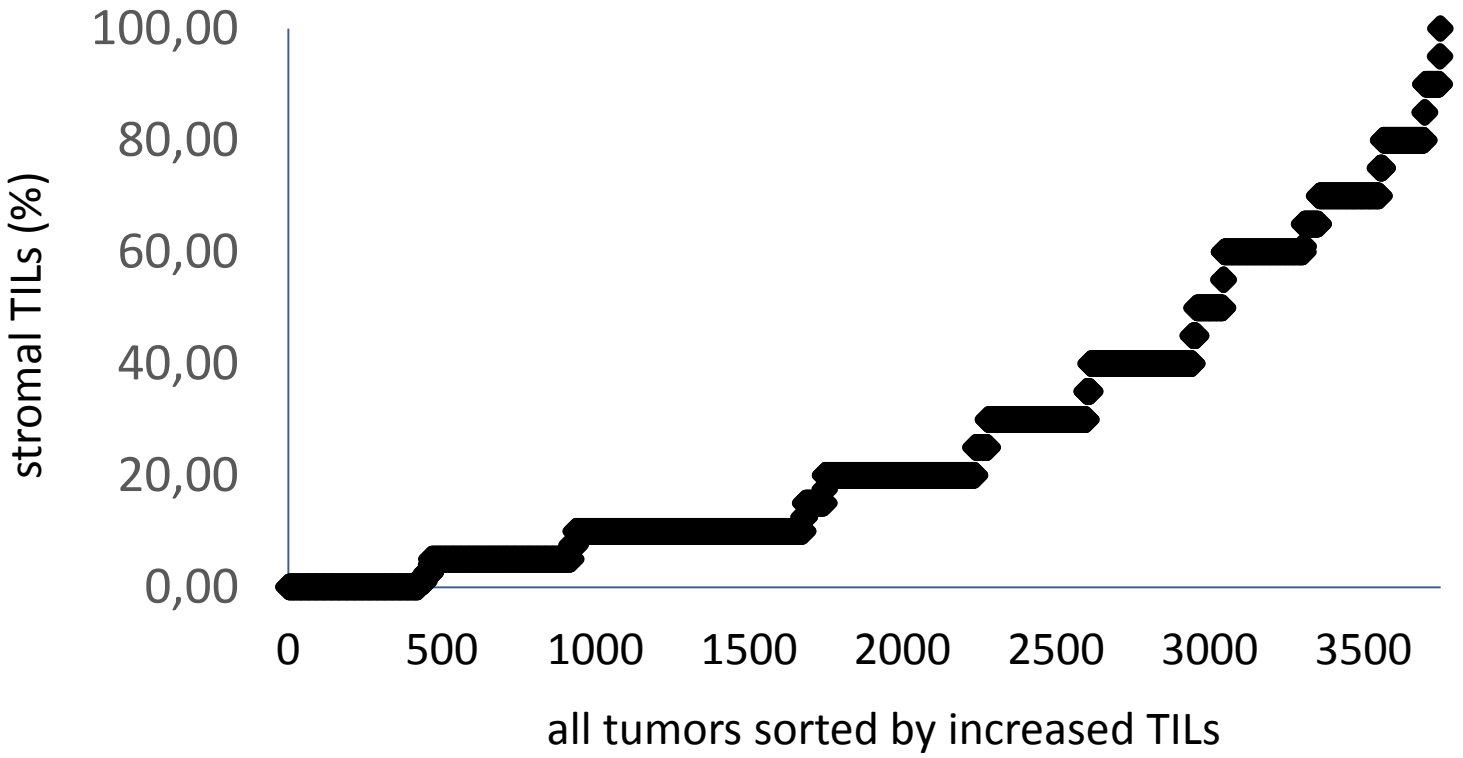
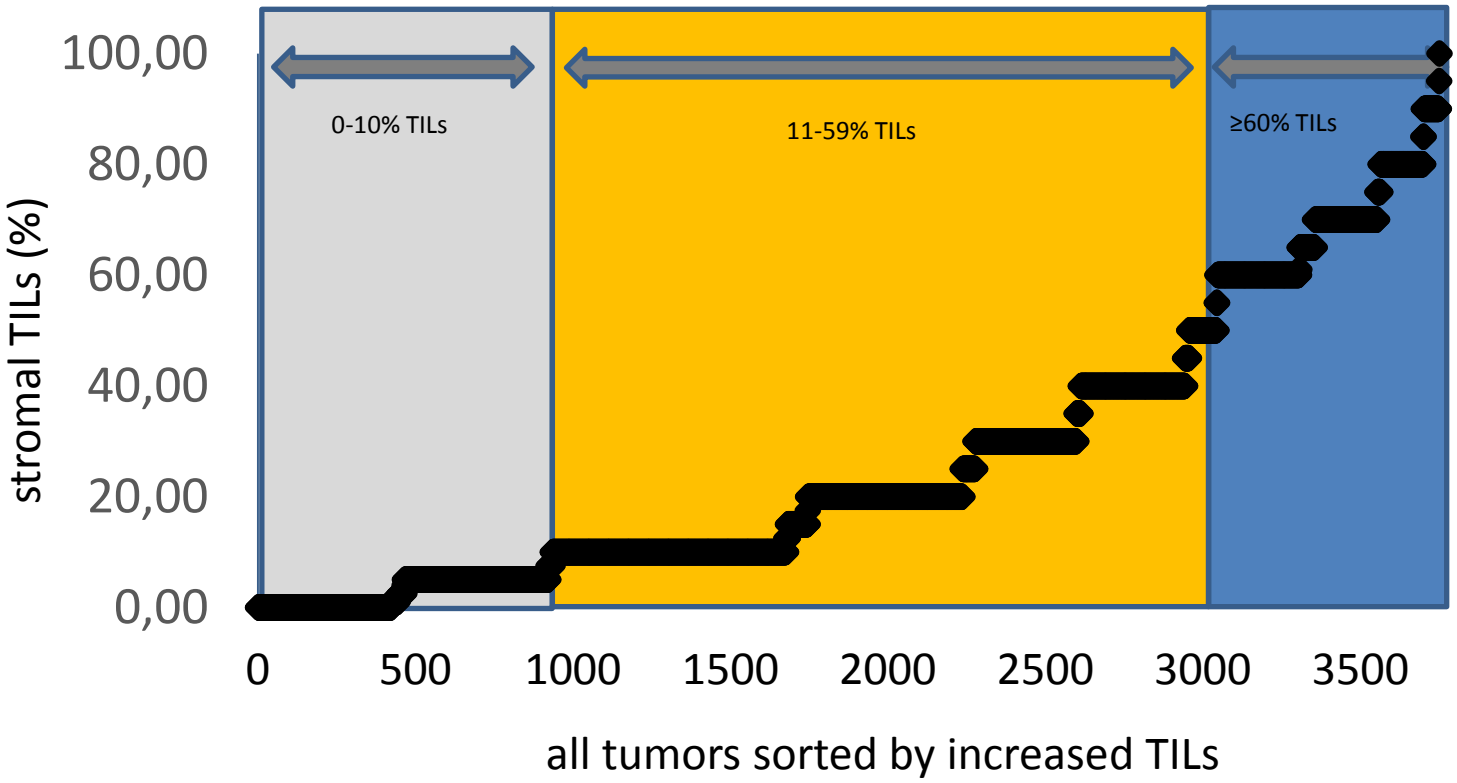
TIL Metaanalyse – Transcan Projekt – 2016-17

- **Vorhandene TIL Daten**
  - GeparDuo, GeparTrio
  - GeparQuattro, GeparQuinto
  - GeparSixto, GeparSepto
- **Zusammenfassende Analyse**
  - pCR und DFS
  - TILs in molekulare Subtypen
  - Unterschiedliche Therapien

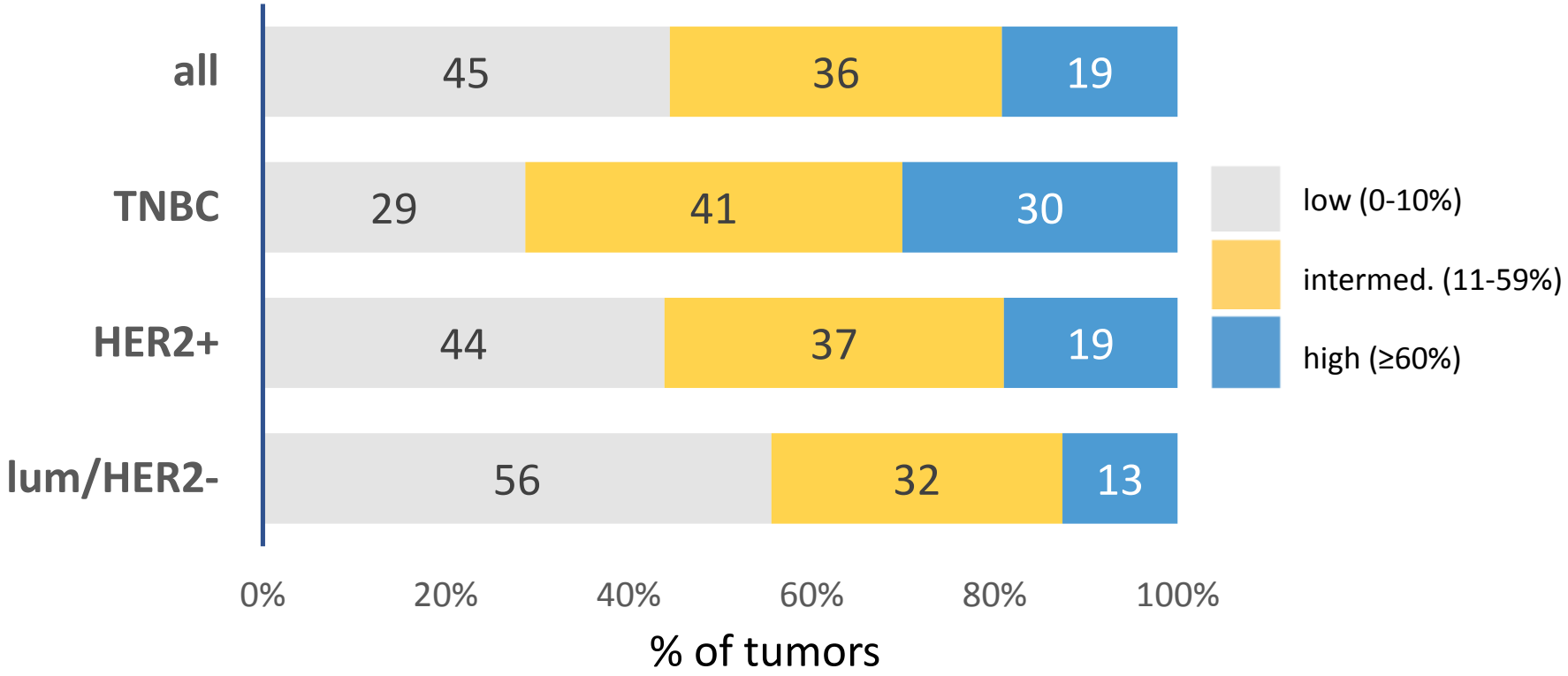
Stromal TILs as a continuous parameter



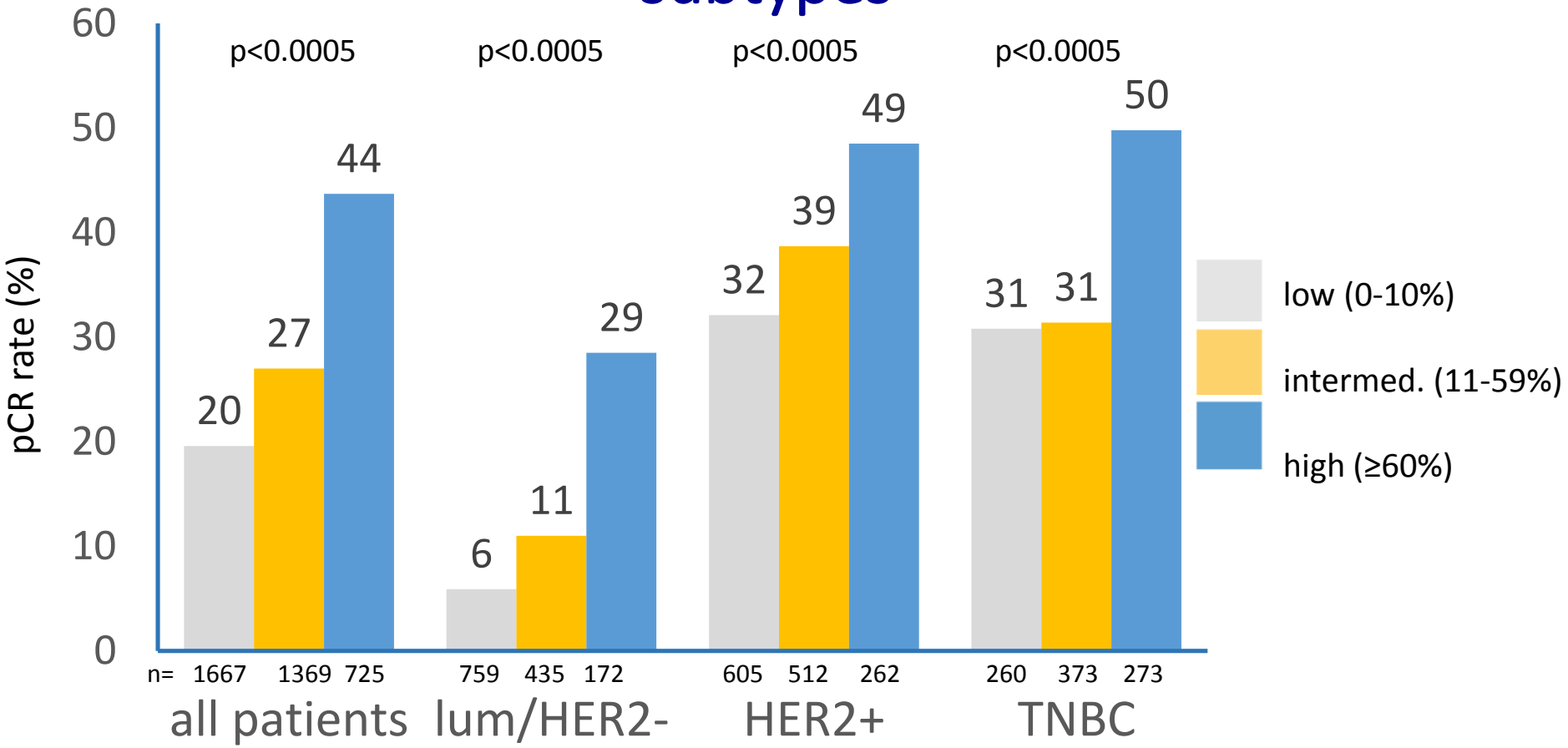
Stromal TILs - predefined subgroups



Distribution of TILs in different breast cancer subtypes

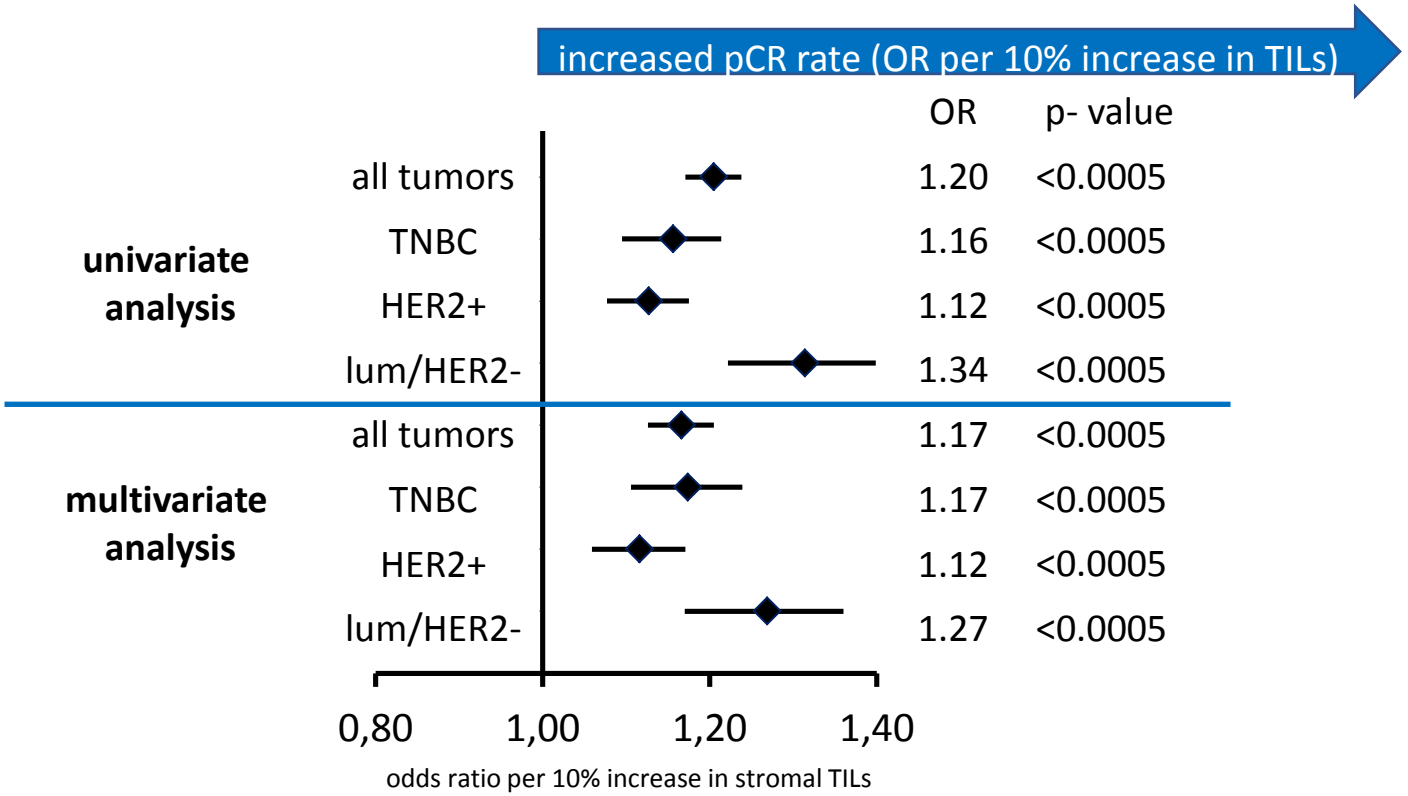


TILs are linked to increased pCR rates in all subtypes

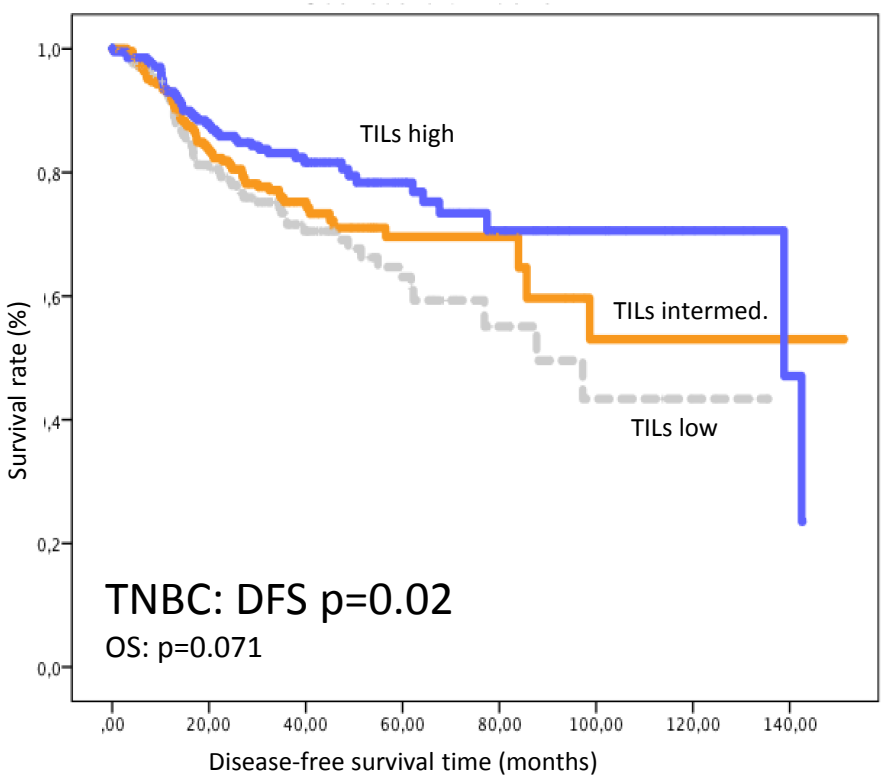


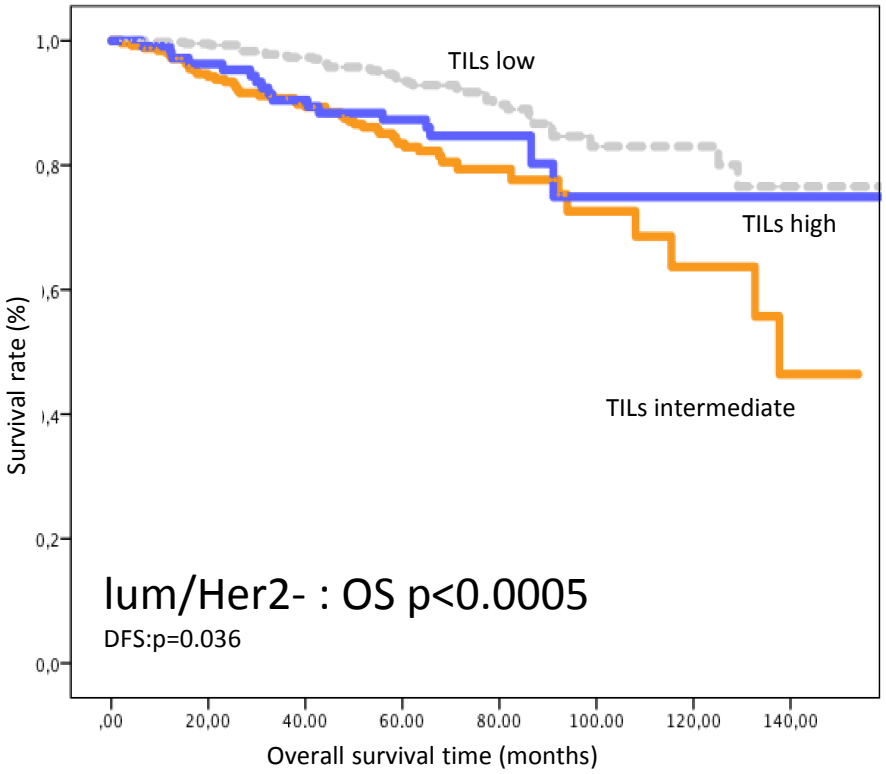
pCR: ypT0ypN0

TILs as continous parameter: increased pCR rates in all subtypes



TILs and prognosis – differences between TNBC and luminal tumors





Prognostic impact of TILs in subtypes – possible interpretation

TNBC and HER2+ tumors

- high TILs ➜ improved survival
- most clearly seen for DFS = early in the therapeutic course
- improved survival can be explained by increased pCR rate
- TILs:
  - positive predictive factor and
  - positive prognostic factor

Prognostic impact of TILs in subtypes – possible interpretation

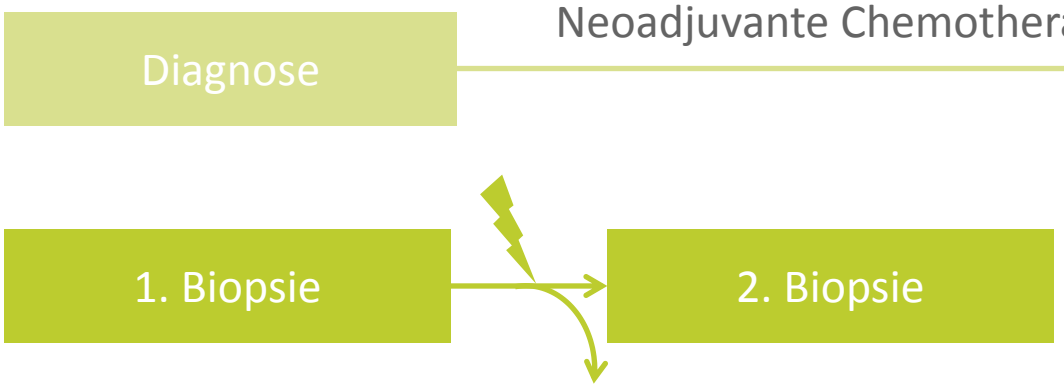
TNBC and HER2+ tumors

- high TILs ➜ improved survival
- most clearly seen for DFS = early in the therapeutic course
- improved survival can be explained by increased pCR rate
- TILs:
  - positive predictive factor and
  - positive prognostic factor

luminal breast cancer

- low TILs ➜ improved survival
- most clearly seen for OS = late in the therapeutic course
- Interpretation / limitations:
  - chance finding (?)
  - no mechanistic data, correlative study
  - high TILs in luminal tumors: more aggressive phenotype
- Hypothesis: TILs may be linked to reduced endocrine response.
- Validation studies are needed!

2017: Untersuchung sequentieller Biopsien G4-G6, n=385



1. Tumorgehalt, Ki67, TILs

2. Molekulare Alterationen

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Quattro	N = 127 Paare
Quinto	N = 181
Sixto	N = 77

Katharina Sychra, Bruno Sinn, BIH

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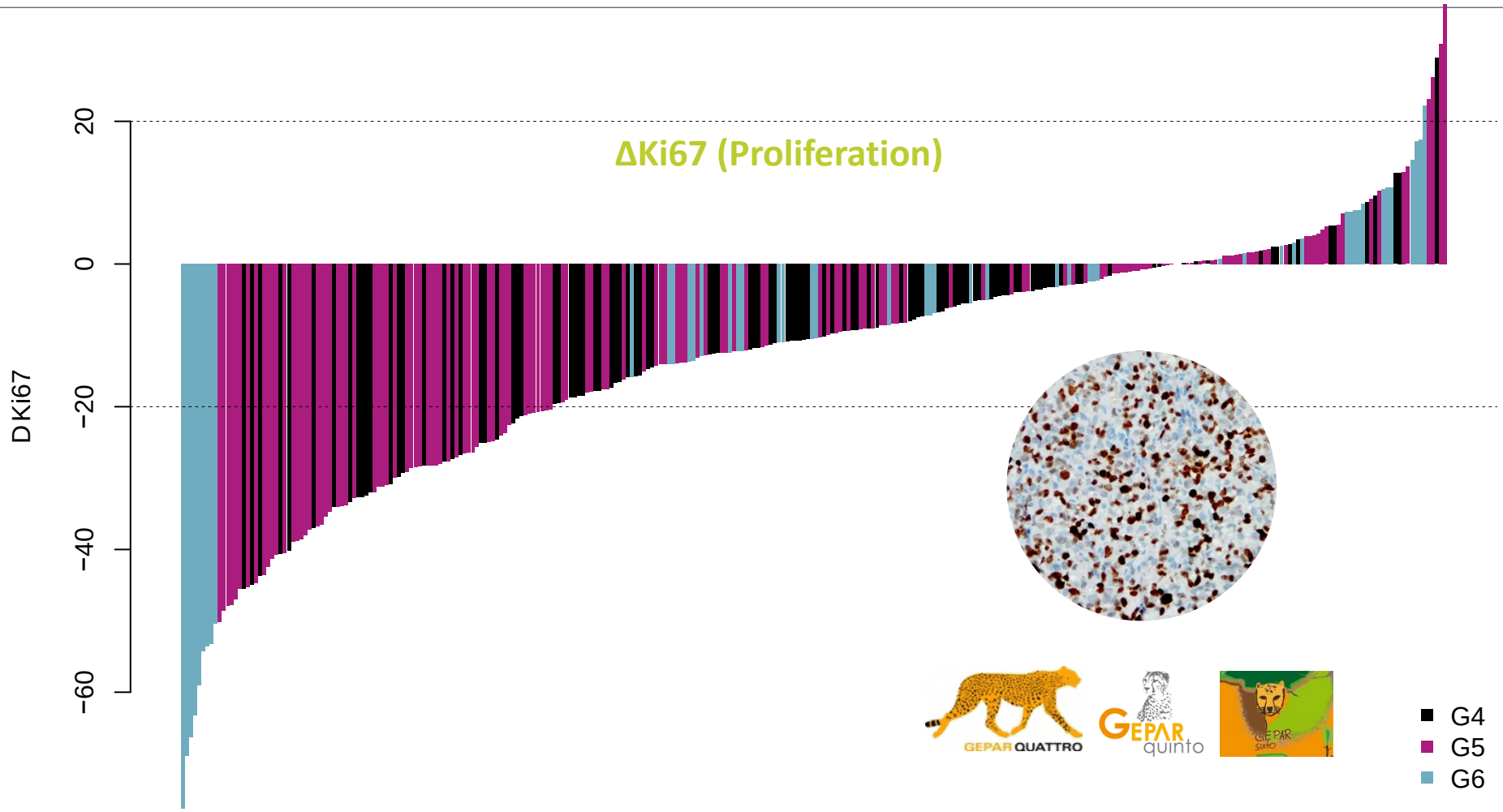
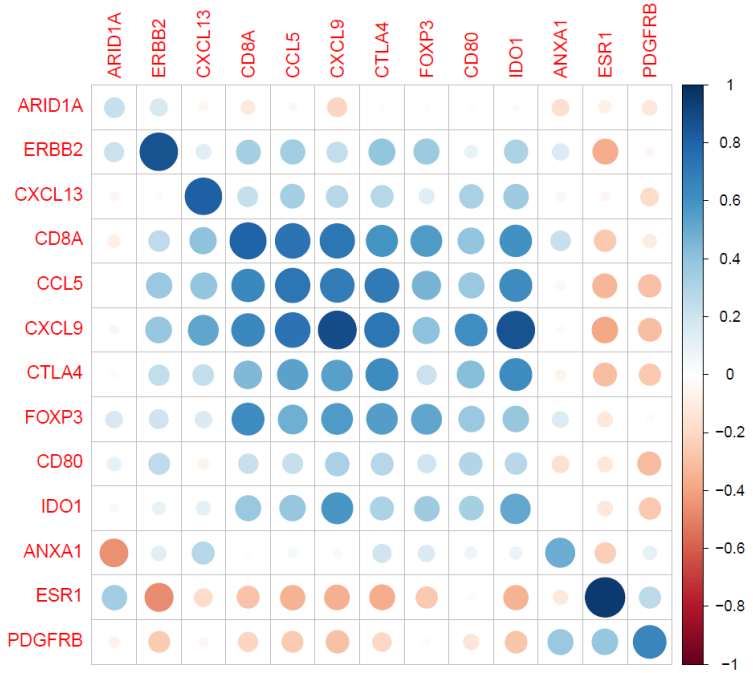
Erste Ergebnisse – Veränderung von Ki67



Katharina Sychra, Bruno Sinn, BIH

Molekulare Untersuchung – RNA Sequencing

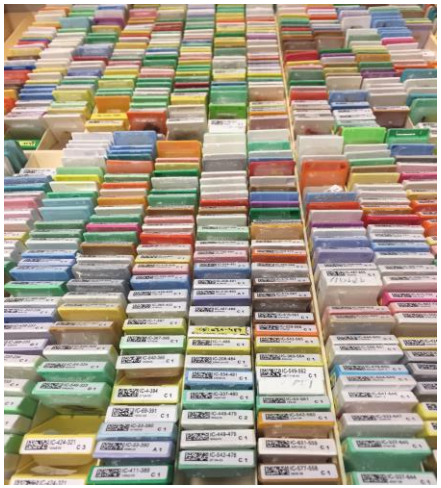
HTG Edge System



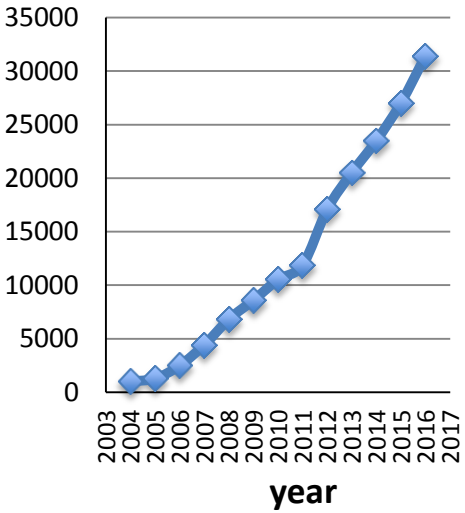
HTG Molecular Oncology Biomarker Panel
Targeted RNASeq (~2,500 Transkripte)
Makrodissektion von FFPE Gewebe, 1,5 mm^2 eines 5 µm Schnitt (1-5 ng)

1. **Untersuchung in sequentiellen Biopsien G4, G5, G6**
2. **Immunsignaturen in GeparNuevo**

GBG Biobank 2017 – Möglichkeiten für zukünftige Projekte



31.1.2017: 31.343 Proben in der GBG Tumorbank



Forschungsanträge an das Translationale Subboard der GBG sind sehr willkommen!

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

We would like to thank all patients, clinicians, and pathologists participating in the clinical studies and the biomaterial collection.

GBG

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Stefanie Lettkemann
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Neoadjuvant Subboard of GBG

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Christos Sotiriou
Fabrice André
Roberto Salgado
TIL working group

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ERA-NET on Translational Cancer Research

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AGO-B BREAST STUDY GROUP

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