SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research
DECEMBER 9–12, 2025
HENRY B. GONZALEZ CONVENTION CENTER • SAN ANTONIO, TX

Gene Expression-based Subtyping of Early Triple-Negative Breast Cancer (TNBC) for Prediction of Response to Neoadjuvant Immune-chemotherapy in the NSABP B-59/GBG-96-GeparDouze Trial

Carsten Denkert[1], Sivaramakrishna Rachakonda[2], Thomas Karn[3], Andreas Schneeweiss[4], Christine Solbach[5], Priya Rastogi[6,7], Fernando Moreno[8,9], Tanner Freeman[6,7], Theresa Link[10], Joao Mouta[11], Mattea Reinisch[12], Ralf Meyer[13], Álvaro Rodríguez Lescure[9,14], Vesna Bjelic-Radisic[15,16], Peter Fasching[17], Marija Balic[6,7], Michael Untch[18], Kerstin Rhiem[19], Julia Teply-Szymanski[1], Kerstin Lüdtke-Heckenkamp[20], Jens Huober[21], Serafin Morales[9,22], Isabel Blancas[9,23], Johannes Holtschmidt[2], Valentina Nekljudova[2], Norman Wolmark[6,7], Charles E. Geyer, Jr.[6,7], Sibylle Loibl[2]

1 Institute of Pathology, Philipps-Universität Marburg and University Hospital Marburg, Marburg, Germany; 2 GBG c/o GBG Forschungs GmbH, Neu-Isenburg, Germany; 3 UCT Frankfurt-Marburg, Frankfurt University Hospital, Germany; 4 National Center for Tumor Diseases, University Hospital and German Cancer Research Center, Heidelberg, Germany; 5 Breast Unit, University Medical Center, Goethe-University Frankfurt; 6 NSABP Foundation, Inc., Pittsburgh, PA, USA; 7 University of Pittsburgh School of Medicine, and UPMC Hillman Cancer Center, Pittsburgh, PA, USA; 8 Department of Medical Oncology, Hospital Universitario Clínico San Carlos, Madrid, Spain; 9 GEICAM Spanish Breast Cancer Group, Spain; 10 Department of Gynecology and Obstetrics, Medical Faculty and University Hospital Carl Gustav Carus, Technische Universität Dresden; 11 Roche Farmacêutica Química Lda, Amadora, Portugal; 12 Interdisciplinary Breast Unit, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany; 13 Hämato-Onkologie im Medicum Bremen, Germany ; 14 Hospital General Universitario de Elche, Elche, Spain ; 15 Helios University Clinic Wuppertal, Germany; 16 University Witten/Herdecke, Germany; 17 Department of Gynecology and Obstetrics, University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany; 18 Interdisciplinary Breast Cancer Center, HELIOS Hospital Berlin Buch, Berlin, Germany; 19 Center for Hereditary Breast and Ovarian Cancer, University Hospital Cologne, Germany; 20 Niels-Stensen-clinics, Harderberg, German; 21 HOCH Health Ostschweiz, Brustzentrum Kantonsspital St.Gallen, St. Gallen, Switzerland; 22 Hospital Arnau de Vilanova, Lleida, Spain; 23 Hospital Clinico S Cecilio, Spain

NSABP Foundation, Inc. IDDI PASSION. SCIENCE. EXPERIENCE. GEICAM investigación en cáncer de mama TRIO TRANSLATIONAL RESEARCH IN ONCOLOGY US Oncology Research GBG GERMAN BREAST GROUP

Disclosure Information

Carsten Denkert

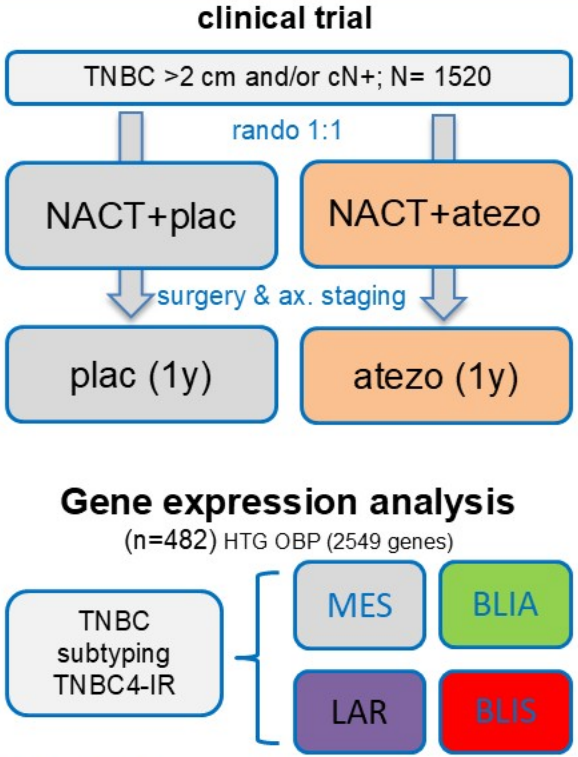
- Advisory Board: MSD Oncology, Daiichi Sankyo, Astra Zeneca, Biontech
- Invited Speaker: Astra Zeneca
- Licencing Fees: VmScope digital pathology software
- Research grants (institutional) Myriad, German Breast Group
- Patents: WO2020109570A1; Patent WO2015114146A1; Patent WO2010076322A1

Background – TILs and immunotherapy

- Tumor-infiltrating lymphocytes (TILs) are prognostic in TNBC[1-5], indicating that a subgroup of TNBC is immunogenic.[6]
- Neoadjuvant immunotherapy in TNBC:
  - **KEYNOTE-522:**[7] neoadjuvant pembrolizumab as standard treatment for TNBC
  - **GeparNuevo:** improved iDFS and OS with neoadjuvant durvalumab[8]; gene signatures (immune, proliferation and stromal signature)[9]
- **NSABP B-59/GeparDouze:** no difference in EFS with neoadjuvant atezolizumab; subgroup analysis for TILs and N+ disease (C. Geyer, SABCS 2024)[10]
- **Research question: Can we use TILs (and molecular TNBC-subtypes) to predict immunotherapy response?**

1. Denkert et al., J Clin Oncol. 2010 PMID: 19917869; 2. Salgado R, Ann Oncol. 2015, PMID: 25214542; 3. Denkert et al. Lancet Oncol. 2018, PMID: 29233559; 4. Loi et al. J Clin Oncol. 2019 PMID: 30650045 5. Leon-Ferre et al. JAMA. 2024, PMID: 38563834; 6. Savas et al., Nat Rev Clin Oncol. 2016, PMID: 26667975. 7. Schmid et al. N Engl J Med. 2024, PMID: 39282906. 8. Loibl et al. Ann Oncol. 2022, PMID: 35961599. 9. Denkert et al., Cell Rep Med. 2024 PMID: 39566464; 10. Geyer el al., SABCS 2024, oral presentation, GS3-05

Aim: Comparison of TILs and TNBC subtypes

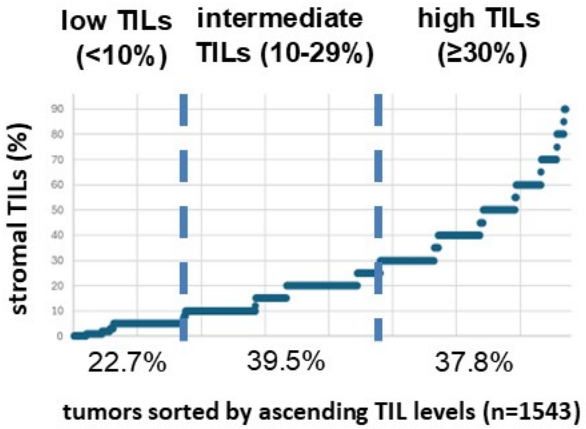


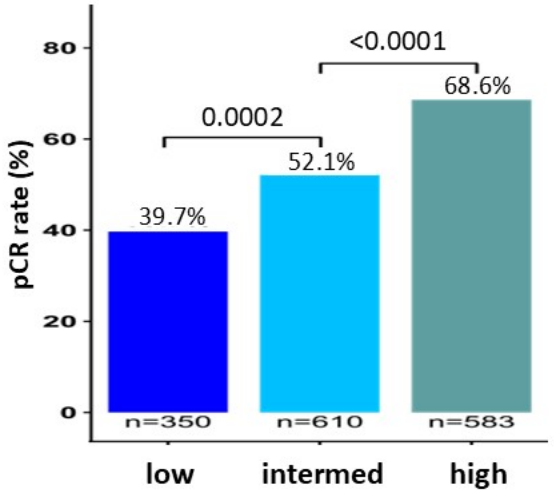
- **TILs in complete trial cohort** (n=1543)
  - 3 stromal TIL groups: low <10%, intermed. 10-29%, high ≥30%
  - pCR, EFS, atezolizumab response
- **TNBC subtypes for immunotherapy response** (TNBC4-IR, n=482)
  - **BLIA:** basal-like immune-activated,
  - **BLIS:** basal-like immunosuppressed,
  - **LAR:** luminal androgen receptor,
  - **MES:** mesenchymal
  - modified subtyping (Burstein et al.[1], Bissanum et al.[2])
- **TNBC6**: BL1, BL2, IM, MES, M, LAR[3] as well as gene expression analysis: will be reported separately

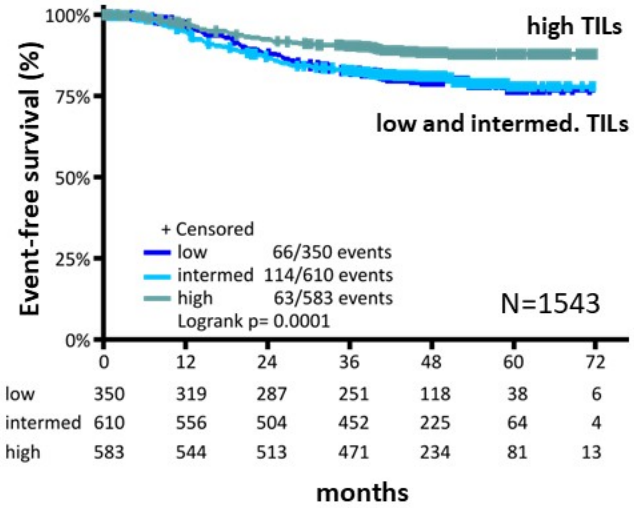
1. Burstein et al. Clin Cancer Res. 2015, PMID: 25208879;
2. Bissanum et al. J Pers Med. 2021 PMID: 34575658;
3. Lehmann et al, J Clin Invest. 2011, PMID: 21633166.

TILs: increased pCR and improved EFS

(complete cohort, n=1543)*



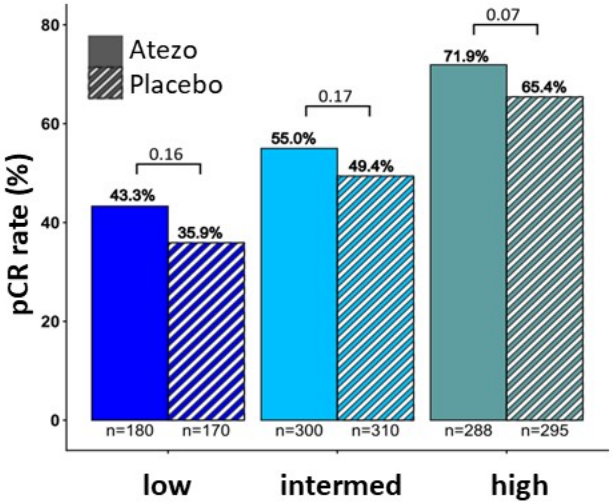


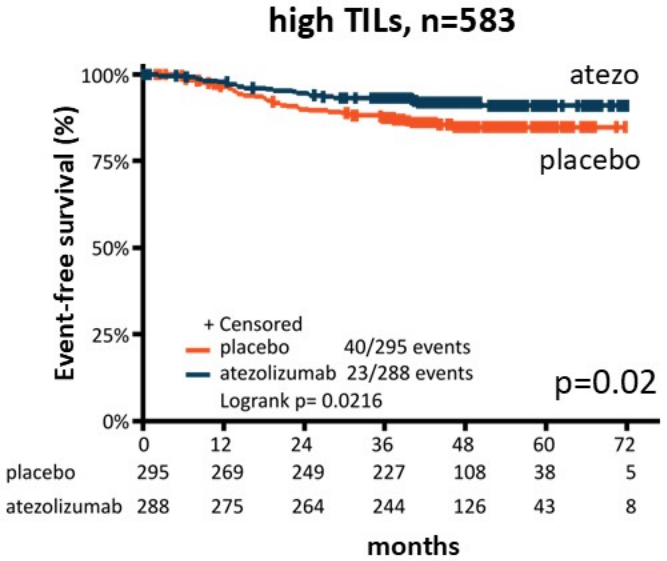


- increased TILs: improved pCR rate (p=0.0002 and p<0.0001)
- high TILs: improved EFS (p=0.0001), no difference for low and intermediate TILs

* no TIL data for 7 patients (core biopsies from lymph node)

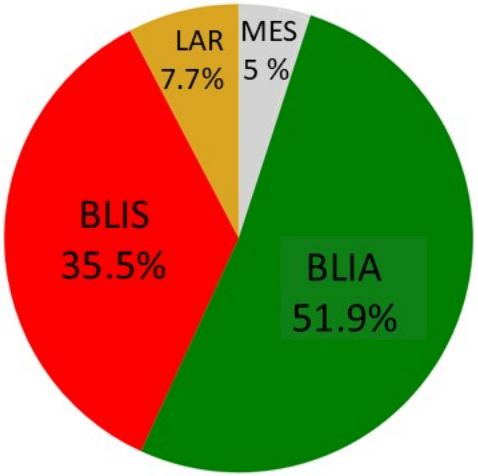
TILs and atezolizumab treatment

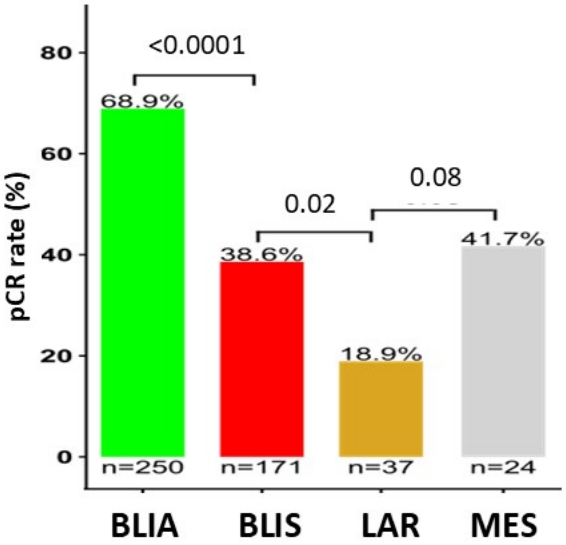


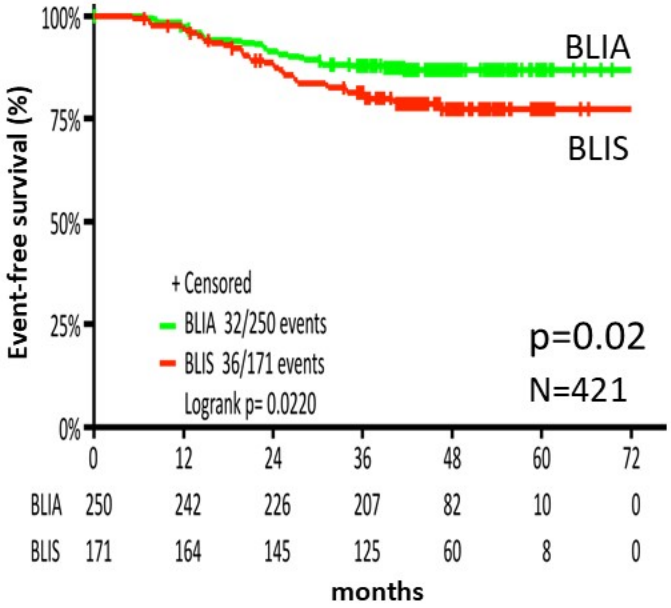


- atezolizumab: numerically increased pCR rate in all 3 TIL groups
- improved EFS with atezolizumab in pts with high TILs (≥30%, p=0.02)
- no significant difference for low & intermediate TILs

BLIA and BLIS as main subtypes



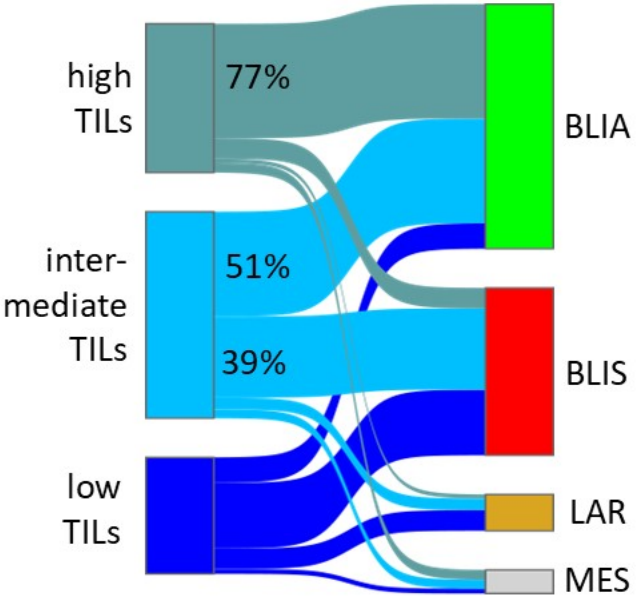


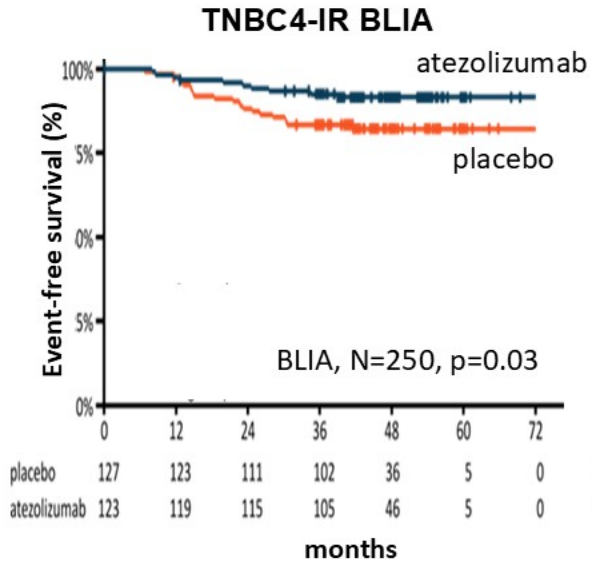


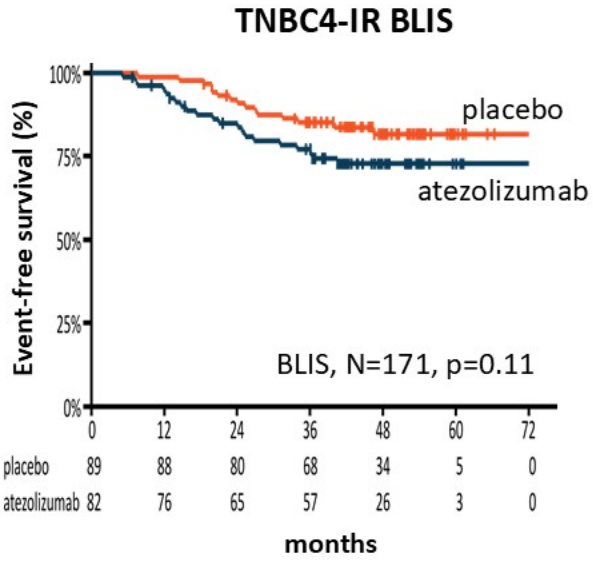
- Highly significant differences in pCR rate for TNBC4-IR, complete cohort
- improved EFS for BLIA compared to BLIS (p=0.02), complete cohort

Comparison of TILs and TNBC-subtypes

heterogeneity of intermediate TILs







- intermed. TILs: heterogeneous mixture of BLIA and BLIS
- improved EFS with atezolizumab only in BLIA tumors

Conclusions: Heterogeneity of TNBC - options for immunotherapy biomarkers

1. positive effect of atezolizumab on EFS in immune-activated tumors
   - defined as either TILs ≥ 30% or BLIA subtype
2. tumors with intermediate TILs are heterogenous (mixed BLIA & BLIS)
   - combination of immune activation & exhaustion
3. TNBC subtyping should be implemented in clinical trials (and diagnostic practice)
   - subtypes are relevant for pCR and EFS in TNBC in both trial arms
4. emerging options for immunotherapy biomarkers:
   - identify tumors with high TILs: most of them are BLIA tumors
   - evaluate BLIA subtype in tumors with intermediate TILs
   - validation in additional clinical trial cohorts is needed (PD-L1 vs. PD1 inhibitors)

Acknowledgements

THANK YOU

To all the patients who participated in this trial and their families.

To the investigators and their research staff of NSABP, GBG, GEICAM, USOR, and TRIO, and the headquarter teams at NSABP, GBG, and IDDI.

To the translational research team at Marburg University and to all pathologist who have contributed tissue samples for translational analysis.

Research funding: Genentech/Roche (clinical trial), European Commission (ONCOBIOME project, translational research) and BMFTR (SATURN3 project, translational research).

Federal Ministry of Research, Technology and Space

Funded by the European Union