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Prognostic Markers in Residual Tumors after Neoadjuvant Chemotherapy (NACT) for Early Triple-Negative Breast Cancer (TNBC) – a Pooled Analysis from nine Neoadjuvant GBG/AGO-B Trials

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

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Disclosure Information

Johannes Holtschmidt

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Background

- Residual invasive disease after NACT for early TNBC is associated with higher recurrence rates and impaired overall survival (OS).[1,2,3,4]
- However, dichotomic assessment in pathologic complete response (pCR) vs. non-pCR in early breast cancer is not consistently linked to OS, as many pts without pCR do not experience relapse.[5]
- One possible explanation is, that partial responses or favorable changes in tumor biology during NACT are not factored in this dichotomic risk assessment.
- Therefore, we investigated proliferation (Ki67) and tumor-infiltrating lymphocytes (TILs) in residual invasive breast tumors for improved prediction of outcome.
- Distant disease-free survival (DDFS) as a reliable surrogate endpoint for OS was chosen as primary endpoint.[6]

1. Cortazer P. et al. Lancet 2014; 2. Marmé F. et al. Eur J Cancer 2021; 3. Masuda N. et al. NEJM 2017; 4. Schmid P. et al NEJM 2024
5. Conforti F. & Nekljudova V. et al. JCO 20205; 6. Conforti F. & Holtschmidt J et al. Lancet Oncol 2025

Consort Flow Diagram & Methods

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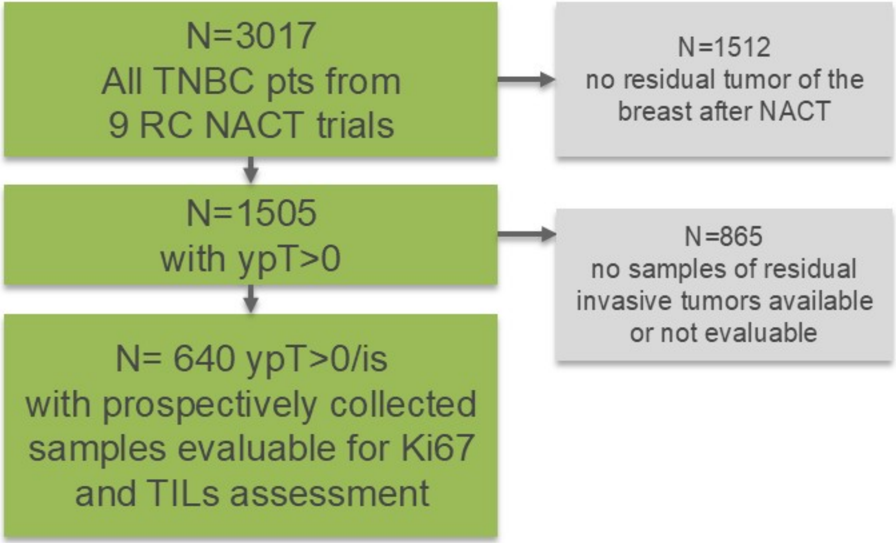
Data from 3017 pts with early TNBC (ER/PR<1%), who were enrolled in nine neoadjuvant randomized controlled (RC) GBG /AGO-B trials (GeparTrio, GeparQuattro, GeparQuinto, GeparSixto, GeparSepto, GeparOcto, GeparNuevo, GeparOla, and GeparX) were included.



- Central assessment for Ki67 and TILs
- Landmark analyses for survival were performed with the landmark set at the time of surgery (Log-rank stratified by study/Cox PH regression with study as random effect)
  - DDFS (Primary endpoint)
  - OS

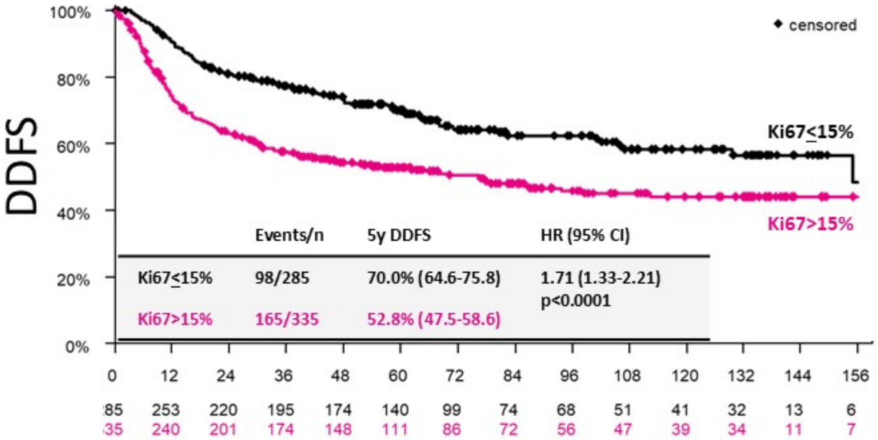
Main Baseline Characteristics

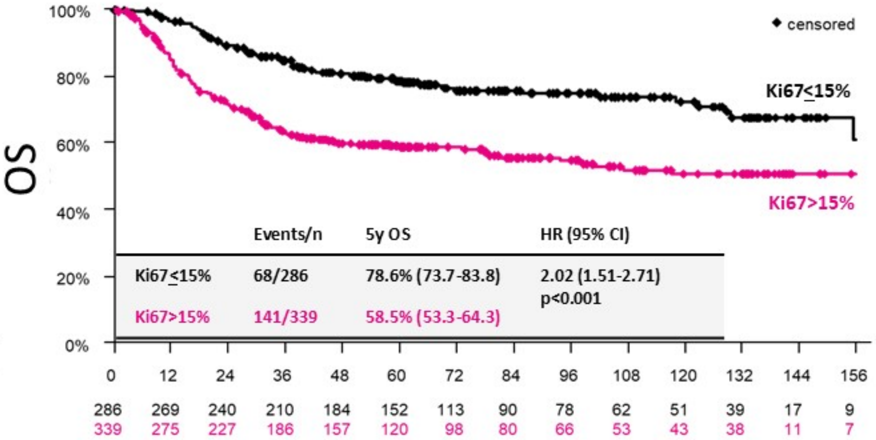
Parameter Difference to overall N is missing	**Residual tumors evaluated cohort N=640**	**Residual tumors overall (TNBC) N=1505**
Median Age (range)	49 (23-80)	49 (23-80)
cT1	135 (21.1%)	290 (19.3%)
cT2	368 (57.6%)	888 (59.1%)
cT3	87 (13.6%)	196 (13.0%)
cT4	49 (7.7%)	129 (8.6%)
cN+	234 (36.9%)	610 (41.0%)
Stage II	393 (61.6%)	947 (63.1%)
G3	445 (69.6%)	1007 (67.4%)
Ki67>15% (baseline)	423 (93.4%)	917 (93.1%)
TILs $\leq$10% (baseline)	175 (43.2%)	366 (43.6%)
Median follow up	77.3 months	71.3 months

Main Baseline Characteristics

Parameter Difference to overall N is missing	**Residual tumors evaluated cohort N=640**	**Residual tumors overall N=1505**
Residual tumor size		
- ypT1	355 (55.5%)	832 (55.3%)
- ypT2	144 (22.5%)	311 (20.7%)
- ypT3-4	46 (7.2%)	116 (7.7%)
- >ypT0 but ypT Stage unknown	95 (14.8%)	246 (16.3%)
Residual nodal burden		
- ypN0	402 (68.4%)	907 (65.7%)
- ypN1	112 (19.0%	276 (20.0%)
- ypN2	43 (7.3%)	124 (9.0%)
- ypN3	31 (5.3%)	74 (5.4%)

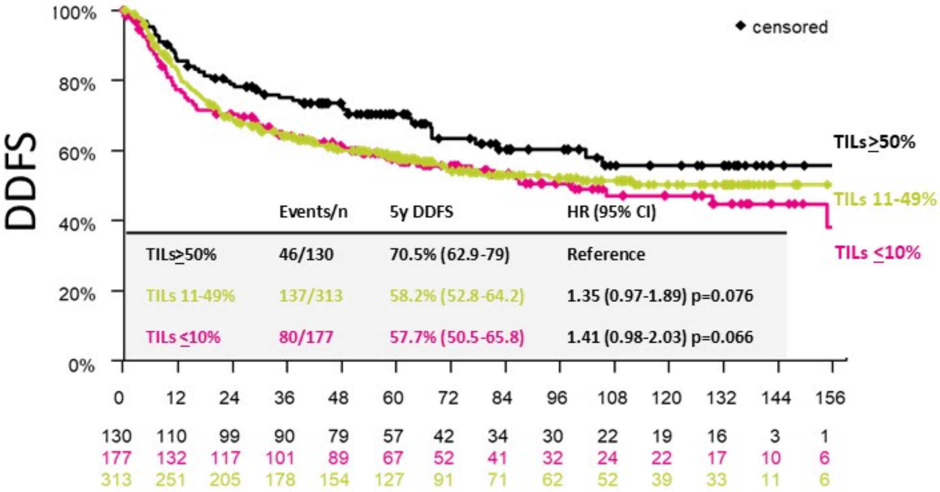
Ki67 >15% vs ≤15% in Residual Tumors



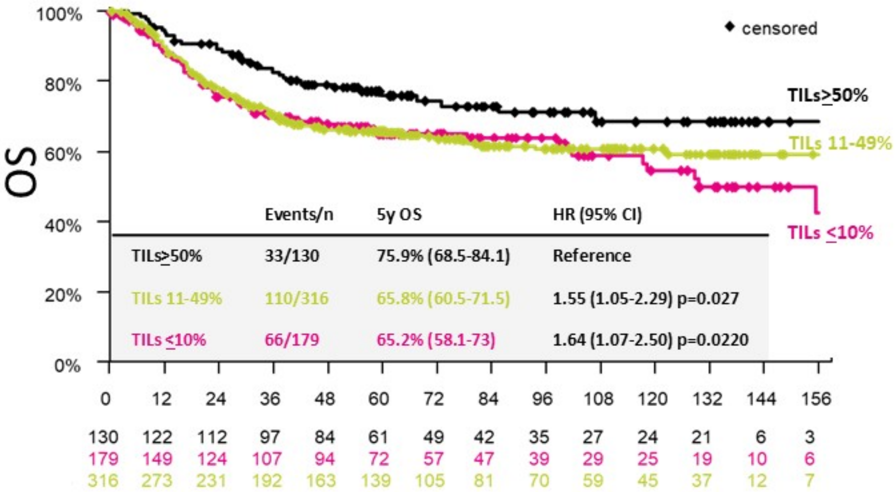


- Ki67 >15% vs ≤15% in residual tumors was associated with significantly worse DDFS and OS
- A significant increase in relative risk (HR) for DDFS/OS events by 9.4%/10.7% for each 10% increase in Ki67 in residual tumors was observed

TILs ≥50% vs 11%-49% vs ≤10% in Residual Tumors



	Events/n	5y DDFS	HR (95% CI)
TILs≥50%	46/130	70.5% (62.9-79)	Reference
TILs 11-49%	137/313	58.2% (52.8-64.2)	1.35 (0.97-1.89) p=0.076
TILs ≤10%	80/177	57.7% (50.5-65.8)	1.41 (0.98-2.03) p=0.066



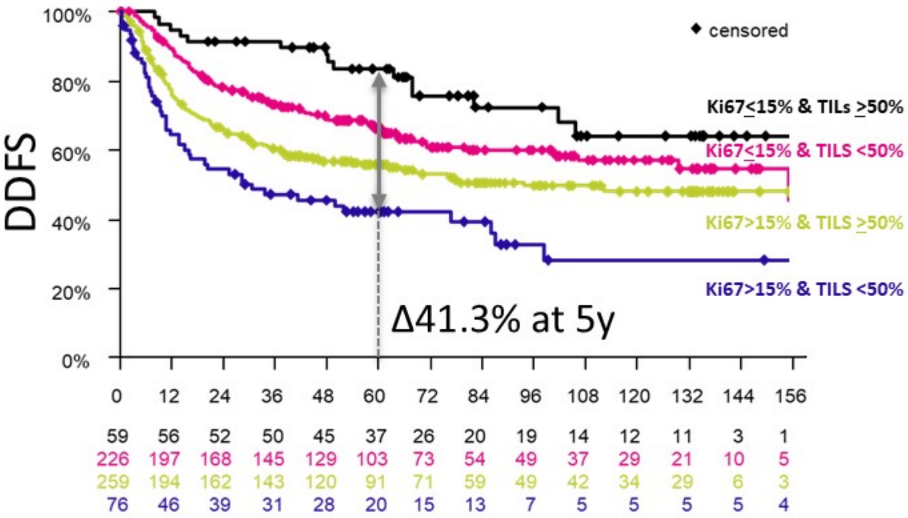
	Events/n	5y OS	HR (95% CI)
TILs≥50%	33/130	75.9% (68.5-84.1)	Reference
TILs 11-49%	110/316	65.8% (60.5-71.5)	1.55 (1.05-2.29) p=0.027
TILs ≤10%	66/179	65.2% (58.1-73)	1.64 (1.07-2.50) p=0.0220

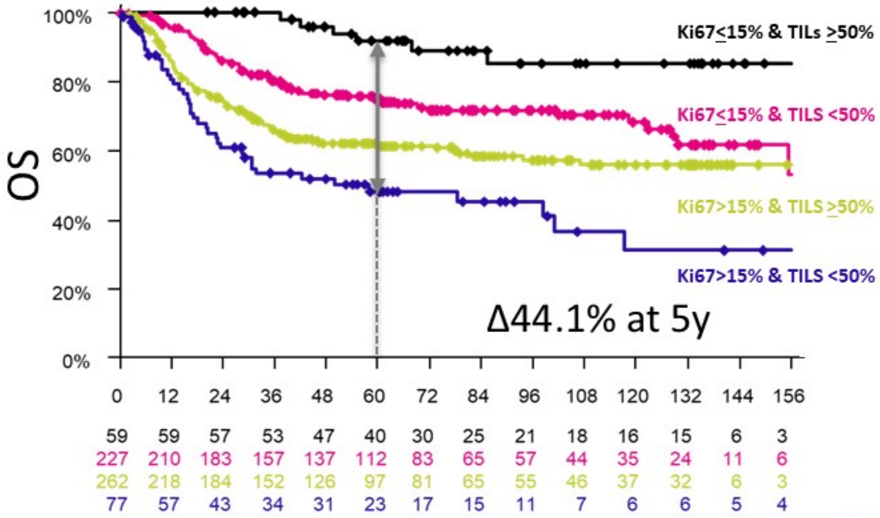
- TILs ≥50% in residual tumors were associated with a significantly improved OS and a clear trend towards improved DDFS
- TILs in residual tumors were associated with a significant relative reduction of 6.3%/8.7% in risk (HR) for DDFS/OS events for each 10% increased TILs level at surgery.

Combined Ki67 & TILs in Residual Tumors

	Events/n	5y DDFS	HR (95% CI)
Ki67≤15% & TILs ≥50%	15/59	83.7% (74.5-94.1)	Reference
Ki67≤15% & TILS <50%	83/226	66.3% (60.1-73.1)	1.66 (0.96-2.89) p=0.07
Ki67>15% & TILS ≥50%	120/259	55.8% (49.9-62.4)	2.35 (1.37-4.03) p=0.002
Ki67>15% & TILS <50%	45/76	42.4% (32.2-55.8)	3.62 (2.00-6.52) p<0.0001

	Events/n	5y OS	HR (95% CI)
Ki67≤15% & TILs ≥50%	6/59	92.1% (84.9-99.9)	Reference
Ki67≤15% & TILS <50%	62/227	75.0% (69.3-81.2)	3.12 (1.35-7.21) p=0.008
Ki67>15% & TILS ≥50%	101/262	61.5% (55.6-67.9)	4.77 (2.09-10.91) p=0.0002
Ki67>15% & TILS <50%	40/77	48.0% (37.4-61.7)	7.57 (3.19-17.94) p<0.0001





Conclusions Residual Tumors in TNBC

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- Low Ki67 in residual tumors was prognostic for superior DDFS and OS especially when combined with high TILs irrespective of extend of residual disease.
- Risk of death was more than 7-fold increased for pts with Ki67>15% & TILs<50% compared to Ki67≤15% & TILs≥50% (abs. Δ of 44.1% for OS at 5y)
- Amongst pts with ypT1, ypN0 those with Ki67≤15% and TILs≥50% had numerically better survival compared to pts with ypT1, ypN0 not meeting these criteria.
  - 5y DDFS rates: 87.5% (76.7-99.9) vs 76.1% (70.3-82.4); HR 1.61 (0.69-3.76) p=0.27
  - 5y OS rates: 96.8% (90.8-100) vs 82.7% (77.3-88.4); HR 2.01 (0.61-6.56) p=0.25
- Our results suggest that the combined assessment of Ki67 and TILs in residual disease after NACT for TNBC can be done in clinical practice to improve individual risk evaluation and to improve personalized selection of post neoadjuvant therapy strategies.

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GBG

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