No survival benefit of chemotherapy escalation in patients with pCR and "high-immune" triple-negative early breast cancer in the neoadjuvant WSG-ADAPT-TN trial

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ADAPT HR-/HER2-:
Clinical background

- Pathological Complete Response (pCR) is a well-validated surrogate for survival in triple-negative breast cancer (TNBC)[1]
- The optimal chemotherapy regimen remains to be defined
  - Potential key role of pCR in the context of therapy de-escalation
- Nab-paclitaxel was recently reported to be superior to solvent-based paclitaxel (in terms of pCR and survival)[2]
- Carboplatin-containing A-T*-based combination increased pCR in early TNBC; conflicting survival results[3,4]

[1] Liedtke et al. JCO 2018; [2] Schneeweiss et al. SABCS 2017; [3] Loibl et al. Ann Oncol 2018; [4] Sikov et al. SABCS 2015
* Anthracycline-taxane

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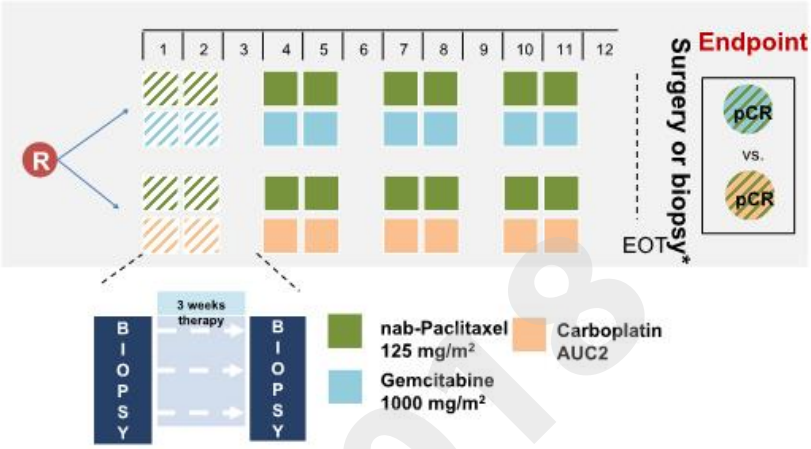
ADAPT HR-/HER2-:
Rationale for translational analyses

- Immune markers and/or stromal Tumor-Infiltrating Lymphocytes (sTILs) are predictive for pCR[1,2]
- Higher baseline sTILs are associated with improved survival in A-T-treated TNBC patients (irrespective of pCR)[2]
- Higher sTIL's in residual cancer burden after NACT are associated with improved survival, but are not predictive for benefit from further chemotherapy[3]
- Prognostic relevance of sTILs in carboplatin- (A-free) treated TNBC is unclear

[1] Denkert et al. JCO 2014; [2] Denkert et al. Lancet Oncol 2018; [3] Dieci et al. Ann Oncol 2014

ADAPT HR-/HER2-:
Trial Design

- Centrally confirmed TNBC (ER/PR<1%)
- cT1c-cT4c or cN+
- M0
- Adequate organ function



Standard chemotherapy (4xEC) recommended after surgery / 12-week biopsy (in case of clinical non-pCR)

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ADAPT HR-/HER2-:
Statistics

- Primary endpoint: ypT0/is ypN0
- Secondary endpoints:
  - Event free (event: invasive relapse, secondary malignancy or death) and overall survival (EFS, OS)
  - First safety survival analysis planned after 36 months follow up
  - Predictive markers/prognostic markers translational research
  - Methods: uni- and multivariable Cox regression analysis, Kaplan-Meier and log rank analysis
    - Scale measurements were coded as continuous variables using fractional ranks

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ADAPT HR-/HER2-:
Translational Research Methods

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- Sufficient tissue for TR in 306/336 patients
  - Tumor bank collective is representative
- Using the nCounter platform*:
  - Expression of 119 breast cancer-related genes and 5 housekeeping genes (ACTB, MRPL19, PSMC4, RPLP0 and SF3A1)
  - Basal and other subtypes by PAM50
  - Scores for Proliferation, HER2, ROR-S, ROR-P**, ER, and hypoxia
- sTILs were evaluated by pathologist (two-observer approach) on digital sections on H&E staining[1]

[1] Salgado et al. Ann Oncol 2014
* Nanostring Technologies, Seattle, WA, US
** Risk of relapse-subtype/proliferation

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ADAPT HR-/HER2-:
Baseline characteristics tumor bank population

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	Arm	
	A (Nab-Pac/Gem)	B (Nab-Pac/Carbo)
	169	137
% of whole population	93%	90%
Pathological complete response (ypT0/is, ypN0)	48 (28.4%)	61 (44.5%)
No additional 4xEC in pCR	25 (52%)	19 (31%)
Age (median)	50 years old	51 years old
Clinical tumor size		
cT1	64 (38%)	54 (39%)
cT2	95 (56%)	72 (53%)
cT3-4	10 (6%)	11 (8%)
Clinical nodal status		
cN0	125 (74%)	102 (74.5%)
cN1	39 (23%)	30 (22%)
cN2-3	5 (3%)	5 (3.5%)
Grade		
G2	10 (5.9%)	12 (8.8%)
G3	159 (94%)	124 (90.5%)
unknown		1 (0.7%)
Ki-67 (median)	75%	75%

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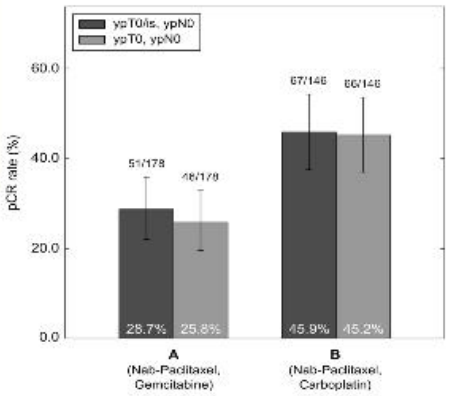
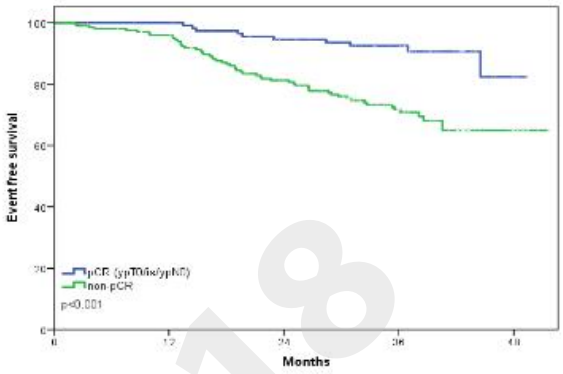
ADAPT HR-/HER2-: Superiority of Nab-Paclitaxel / Carboplatin for pCR and survival impact of pCR



pCR; ypT0/is, ypN0) and total pCR (ypT0/ypN0) by treatment arms

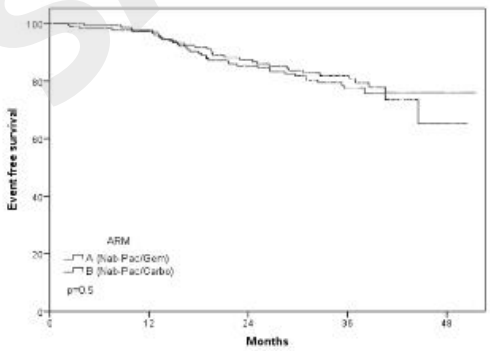


Event-free survival by pCR status

Gluz et al. SABCS 2015 and JNCI 2018; Gluz et al. ASCO 2018

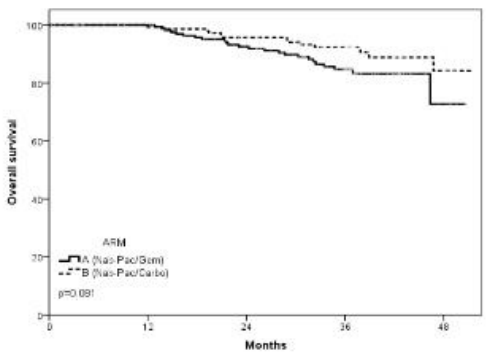
ADAPT HR-/HER2-: Survival impact of Carboplatin vs. Gemcitabine-containing NACT

Event-free survival



n at risk									
A	182	168	162	145	128	112	79	28	5
B	154	147	142	129	118	104	74	39	11

Overall survival



n at risk									
A	182	171	166	155	138	122	82	31	5
B	154	147	145	137	125	114	82	41	11

Gluz et al. ASCO 2018

ADAPT HR-/HER2-: Survival impact of additional 4xEC in patients with pCR after 12 weeks of NACT

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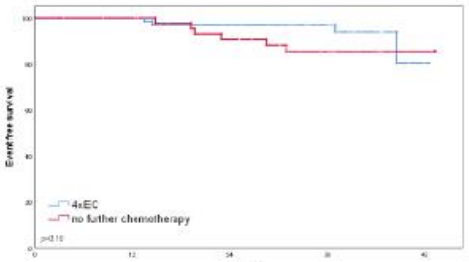
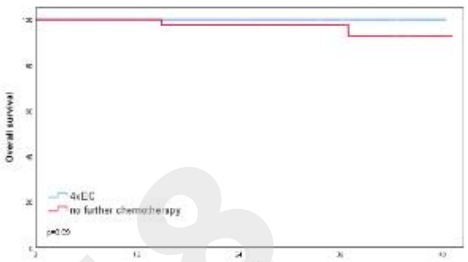
Event-free survival



n at risk									
no adjuvant CT	48	45	44	42	37	33	26	12	2
4xEC	70	69	68	63	37	33	26	12	2

Overall survival



n at risk									
no adjuvant CT	48	45	44	42	39	36	29	13	2
4xEC	70	69	68	64	60	56	40	16	1

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ADAPT HR-/HER2-: Effect of additional 4xEC on EFS in patients with pCR after 12 weeks of NACT, by arm

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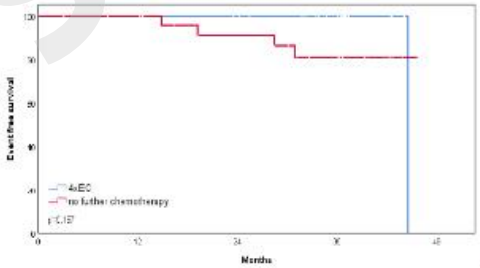
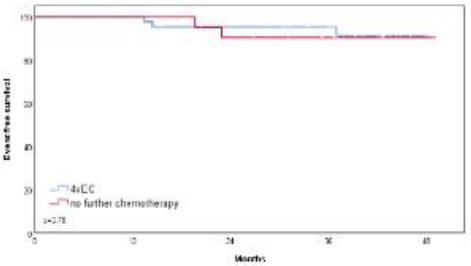
Gemcitabine-containing arm



n at risk									
no adjuvant CT	26	24	23	21	18	16	12	5	0
4xEC	25	24	24	22	21	19	14	2	0

Carboplatin-containing arm



n at risk									
no adjuvant CT	22	20	20	20	18	16	13	6	2
4xEC	45	44	43	40	38	36	25	12	1

ADAPT HR-/HER2-:
Correlation analyses

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- Spearman correlations among CD8, PD1, and PDL1 were strongly positive (about 0.9)
- Their correlations with sTILs were moderately positive (about 0.4 – 0.5)
- sTILs were strongly associated with smaller tumor size, positive lymph node status[1]

[1] Liedtke et al. ASCO 2018

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ADAPT HR-/HER2-:
Predictive markers for pCR

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Marker	OR	LCL	UCL	p
basal subtype (vs. other)	2.45	1.17	5.13	0.015
cN (cN+ vs. cN0)	0.73	0.42	1.26	0.260
cT (cT2-4c vs. cT1)	0.46	0.29	0.75	0.002
sTIL's	1.85	1.21	2.81	0.004
ANGPTL4	0.69	0.46	1.04	0.080
CD8	1.53	1.01	2.31	0.040
CDC20	1.35	0.9	2.04	0.140
CENPF	1.27	0.84	1.9	0.250
EMP3	1.33	0.88	2	0.170
FGFR4	0.73	0.48	1.1	0.130
HER2 Score	0.48	0.31	0.73	0.001
KI-67 (IHC)	2.7	1.72	4.24	<0.001
ROR_P	1.88	1.23	2.88	<0.001
ROR_S	1.92	1.26	2.94	>0.001
TYMS	1.31	0.87	1.97	0.190
VEGFA	0.74	0.5	1.12	0.160

Predictive in the gemcitabine-containing arm

Predictive in the carboplatinum-containing arm

Predictive in both arms

None of them was predictive for EFS benefit for carboplatin vs. gemcitabine-containing arm

ADAPT HR-/HER2-: Prognostic markers for EFS

	Univariable			
	HR	LCL	UCL	p
continuous variables (*)				
sTILs	**0.39**	**0.16**	**0.91**	**.03**
Ki-67 (by IHC)	1.83	0.78	4.30	.17
Proliferation score	1.41	0.55	3.65	.48
ROR_P score	1.01	0.99	1.02	.59
ROR_S score	1.00	0.98	1.03	.75
HER2 score	0.97	0.41	2.31	.95
PD1	**0.36**	**0.15**	**0.86**	**.02**
PDL1	0.50	0.21	1.19	.12
CD8	0.48	0.20	1.15	.10
ANGPTL4	1.11	0.47	2.62	.81
TYMS	1.20	0.78	1.86	.41
binary variables				
cN (cN+ vs. cN0)	**1.77**	**1.29**	**2.42**	**<.001**
cT (cT2-4c vs. cT1)	**1.82**	**1.05**	**3.16**	**.03**
basal subype (vs. other)	1.12	0.61	2.05	.72
pCR	0.24	0.11	0.49	<.001
interaction with pCR				
PD1*pCR				

(*)fractionally ranked: hazard ratios refer to 75th vs. 25th percentile

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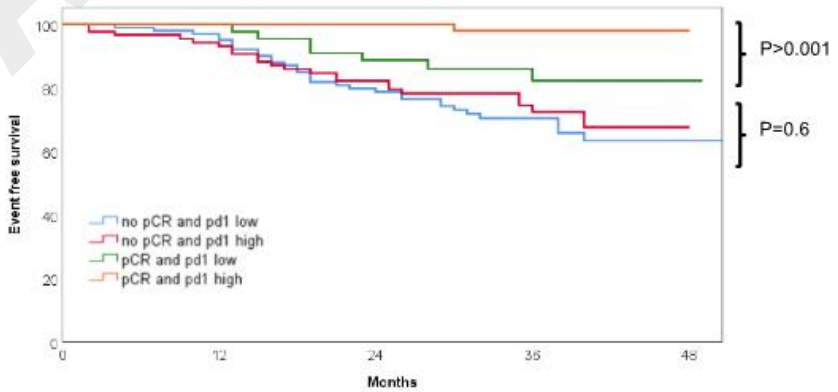
ADAPT HR-/HER2-: Prognostic impact of pCR and PD1 status



n at risk									
no pCR and pd1 low	106	101	98	84	74	63	45	24	8
no pCR and pd1 high	91	84	79	70	63	54	35	10	2
pCR and pd1 low	49	46	45	41	35	31	22	10	3
pCR and pd1 high	60	59	58	57	55	51	38	15	0

ADAPT HR-/HER2-: Effect of additional chemotherapy (4xEC) according to PD1 status in patients with pCR

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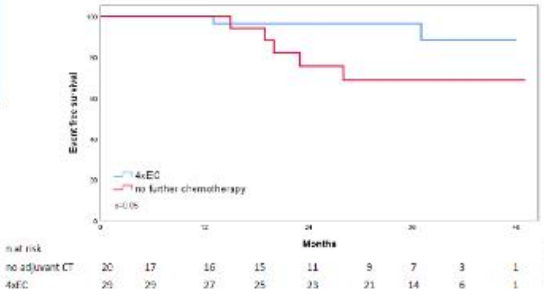
PD1 expression < median



n at risk									
no adjuvant CT	20	17	16	15	11	9	7	3	1
4xEC	29	29	27	25	23	21	14	6	1

PD1 expression ≥ median

n at risk									
no adjuvant CT	24	23	23	22	21	19	14	6	0
4xEC	36	35	34	34	34	31	23	8	0

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ADAPT HR-/HER2-: Conclusions

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- In TNBC, due to an excellent efficacy and safety profile, 12 weeks of nab-paclitaxel/carboplatin seem to be a promising approach for chemotherapy de-escalation
- No predictive markers for survival benefit from carboplatin were identified by our exploratory analyses
- In TNBC, early pCR can be used to adapt further treatment (de-) escalation:
  - Patients with high baseline PD1 (by mRNA) seem to be ideal candidates for further investigation of de-escalated therapy approaches (chemotherapy and/or immunotherapy)
  - In non-pCR, clinical factors (cN, Ki-67) have strong prognostic impact and may thus be suitable for further risk stratification
- Due to the exploratory nature of the analyses and the short follow-up, validation of our results in further studies is needed

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