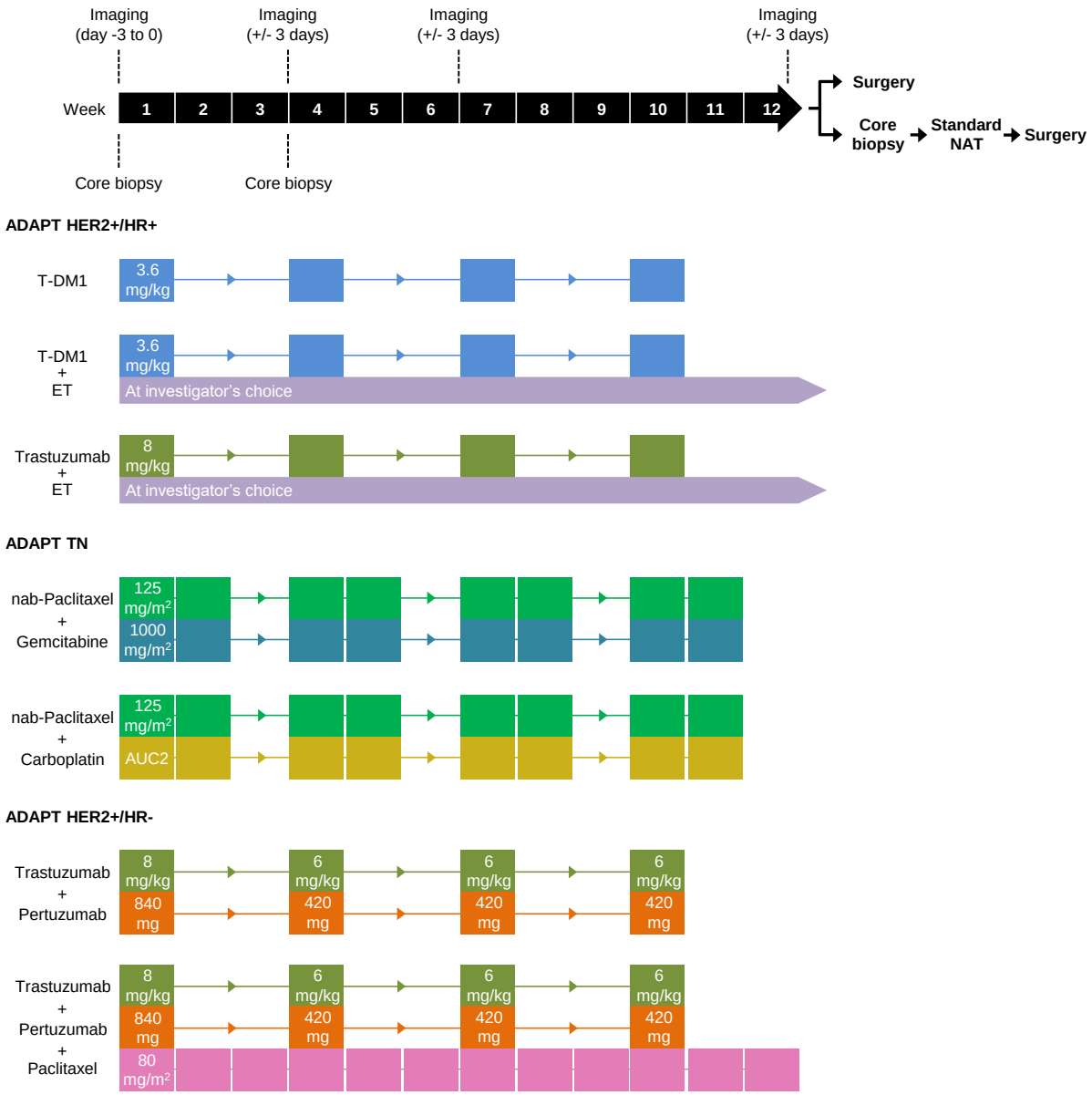
Supplementary Material

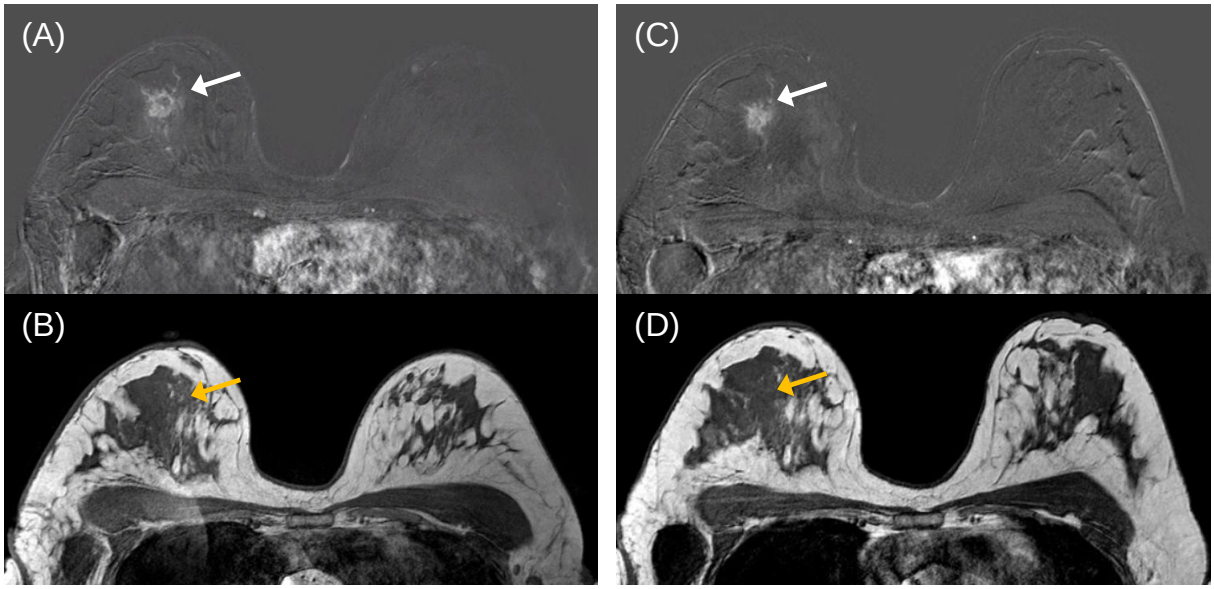
Early Response by MR Imaging and Ultrasound as Predictor of Pathologic Complete Response to 12-Week Neoadjuvant Therapy for Different Early Breast Cancer Subtypes: Combined Analysis from the WSG ADAPT Subtrials.

Monika Graeser[*], Simone Schrading[*], Oleg Gluz, Kevin Strobel, Rachel Würstlein, Sherko Kümmel, Claudia Schumacher, Eva-Maria Grischke, Helmut Forstbauer, Michael Braun, Matthias Christgen, Jascha Adams, Henrik Nitzsche, Marianne Just, Hans Holger Fischer, Bahriye Aktas, Jochem Potenberg, Raquel von Schumann, Cornelia Kolberg-Liedtke, Nadia Harbeck, Christiane K. Kuhl, Ulrike Nitz

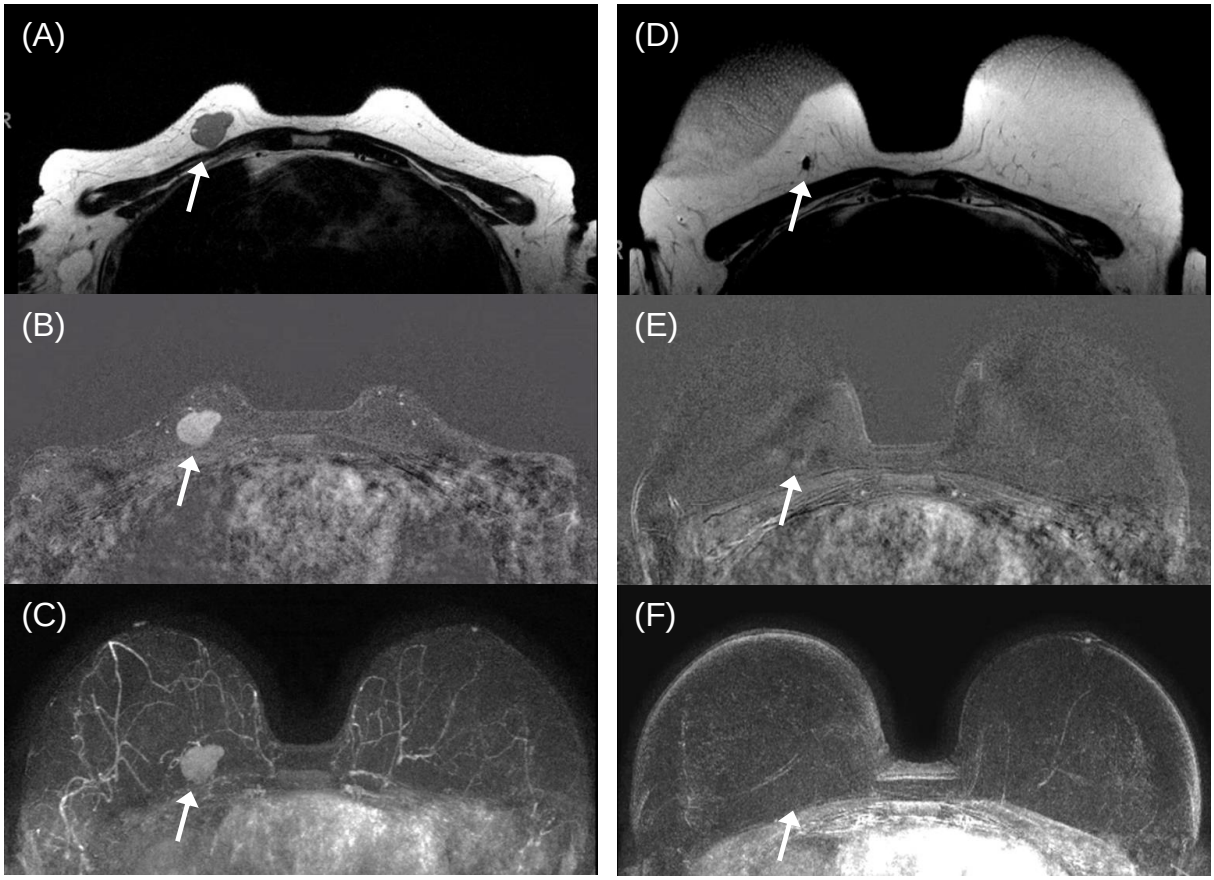
[*]These authors contributed equally to the manuscript.



Supplementary Figure 1: Design of the West German Study Group umbrella trial ADAPT (Adjuvant Dynamic Marker-adjusted Personalized Therapy Trial Optimizing Risk assessment and Therapy Response Prediction in Early Breast Cancer). Treatment details for ADAPT HER2+/HR+, ADAPT TN and ADAPT HER2+/HR- substudies are shown. EOT, end of treatment; ET, endocrine therapy; pCR, pathological complete response; Standard NAT, neoadjuvant therapy according to national guidelines; T-DM1, trastuzumab emtansine.



Supplementary Figure 2: A true-negative case of magnetic resonance imaging (MRI) predicting a pathological complete response (pCR). 54 years old patient with biopsy proven invasive HR-/HER2- cancer (cT2, cN0, cM0, grade 3). (A) and (B) Baseline MRI prior to neoadjuvant chemotherapy showed a round, irregular mass with a strong enhancement and inhomogeneous internal structure in the upper central right breast (arrow). (C) and (D) MRI 3 weeks after start of neoadjuvant nab-paclitaxel + gemcitabine showed an almost a stable lesion with no significant reduction in size and enhancement compared to baseline. Final histology after surgery revealed a non-pCR. (A) and (C) axial subtraction of the first post contrast series; (B) and (D) axial T1 gradient echo before contrast.



Supplementary Figure 3: A true-positive case of magnetic resonance imaging (MRI) predicting a pathological complete response (pCR). 56 years old patient with biopsy proven invasive HR-/HER2- cancer (cT2, cN0, cM0, Grade 2). (A), (B) and (C) baseline MRI prior to neoadjuvant chemotherapy showed a strong enhancing oval mass with smooth border and inhomogeneous internal structure in the upper inner right breast (arrow). Axial T2-weighted turbo spin echo (TSE) sequence showed a relatively hyperintense cancer (A). (D), (E) and (F) MRI 3 weeks after start of neoadjuvant nab-paclitaxel + gemcitabine showed a partial response with a significant reduction of size and enhancement of the invasive cancer in the upper inner quadrant of the right breast (arrow). Also the tumor size in T2-weighted images was significantly reduced compared to the baseline with only a 8 mm hypointense residual at the cancer side (D). Final histology after surgery revealed a pCR. (A) and (D) axial T2-weighted turbo spin echo sequence; (B) and (E) axial early T1 gradient echo sequence after contrast application; (C) and (F) axial maximum intensity projection of the first post contrast subtraction sequence.

Supplementary Table 1: Rates of pCR and Ki-67 response in patients with ECR in the MRI and US group

pCR	MRI		US		Ki-67 response	MRI		US	
	ECR	No ECR	ECR	No ECR		ECR	No ECR	ECR	No ECR
Overall									
pCR*	28	9	20	17	**Ki-67 response***	36	23	25	34
	(43.75)	(20.93)	(52.63)	(24.64)		(56.25)	(53.49)	(65.79)	(49.28)
No pCR*	35	33	17	51	**No Ki-67 response***	12	15	7	20
	(54.69)	(76.74)	(44.74)	(73.91)		(18.75)	(34.88)	(18.42)	(28.99)
Missing*	1	1	1	1	**Missing***	16	5	6	15
	(1.56)	(2.33)	(2.63)	(1.45)		(25.00)	(11.63)	(15.79)	(21.74)
Total†	64	43	38	69	**Total†**	64	43	38	69
	(59.81)	(40.19)	(35.51)	(64.49)		(59.81)	(40.19)	(35.51)	(64.49)
HR+/HER2+									
pCR*	14	9	13	10	**Ki-67 response***	22	20	20	22
	(41.18)	(28.13)	(48.15)	(25.64)		(64.71)	(62.50)	(74.07)	(56.41)
No pCR*	19	23	13	29	**No Ki-67 response***	4	10	4	10
	(55.88)	(71.88)	(48.15)	(74.36)		(11.76)	(31.25)	(14.81)	(25.64)
Missing*	1	0	1	0	**Missing***	8	2	3	7
	(2.94)	-	(3.70)	-		(23.53)	(6.25)	(11.11)	(17.95)
Total†	34	32	27	39	**Total†**	34	32	27	39
	(51.52)	(48.48)	(40.91)	(59.09)		(51.52)	(48.48)	(40.91)	(59.09)
HR-/HER2-									
pCR*	5	0	2	3	**Ki-67 response***	11	2	2	11
	(27.78)	-	(66.67)	(13.64)		(61.11)	(28.57)	(66.67)	(50.00)
No pCR*	13	6	1	18	**No Ki-67 response***	7	4	1	10
	(72.22)	(85.71)	(33.33)	(81.82)		(38.89)	(57.14)	(33.33)	(45.45)
Missing*	0	1	0	1	**Missing***	0	1	0	1
	-	(14.29)	-	(4.55)		-	(14.29)	-	(4.55)
Total†	18	7	3	22	**Total†**	18	7	3	22
	(72.00)	(28.00)	(12.00)	(88.00)		(72.00)	(28.00)	(12.00)	(88.00)
HR-/HER2+									
pCR*	9	0	5	4	**Ki-67 response***	3	1	3	1
	(75.00)	-	(62.50)	(50.00)		(25.00)	(25.00)	(37.50)	(12.50)
No pCR*	3	4	3	4	**No Ki-67 response***	1	1	2	0
	(25.00)	(100.00)	(37.50)	(50.00)		(8.33)	(25.00)	(25.00)	-
Missing*	0	0	0	0	**Missing***	8	2	3	7
	-	-	-	-		(66.67)	(50.00)	(37.50)	(87.50)
Total†	12	4	8	8	**Total†**	12	4	8	8
	(75.00)	(25.00)	(50.00)	(50.00)		(75.00)	(25.00)	(50.00)	(50.00)

*Rates of pCR, no pCR and patients with missing data among the patients with and without imaging response; †Share of patients with and without imaging response.

ECR, early clinical response.

Supplementary Table 2: Area under curve, sensitivity and specificity for combined assessments relative to US

Definition of response		Overall	HR+/HER2+	HR-/HER2-	HR-/HER2+
Ki-67 combined with US					
ECR by both tests	AUC	0.6187	0.5715	0.6783	0.7033
	SENS	0.433	0.3898	0.3750	0.7143
	SPEC	0.8044	0.7532	0.9815	0.6923
ECR by at least one test	AUC	0.6041	0.5746	0.6551	0.6539
	SENS	0.866	0.8644	0.7917	1.0000
	SPEC	0.3422	0.2848	0.5185	0.3077
ECR by US only (reference)	AUC	0.5838	0.5400	0.6320	0.6621
	SENS	0.4742	0.4407	0.3750	0.7857
	SPEC	0.6933	0.6392	0.8889	0.5385
MRI combined with US					
ECR by both tests	AUC	0.6513	0.6144	0.6000	0.6350
	SENS	0.4054	0.3478	0.4000	0.5556
	SPEC	0.8971	0.8810	1.0000	0.7143
ECR by at least one test	AUC	0.6151	0.5916	0.6316	0.7143
	SENS	0.8919	0.8261	1.0000	1.0000
	SPEC	0.3382	0.3571	0.2632	0.4286
ECR by US only (reference)	AUC	0.6453	0.6279	0.6737	0.5635
	SENS	0.5405	0.5652	0.4000	0.5556
	SPEC	0.7500	0.6905	0.9474	0.5714
MRI and Ki-67 combined with US					
ECR by each test	AUC	0.6322	0.5497	0.6000	0.7500
	SENS	0.3333	0.2105	0.4000	1.0000
	SPEC	0.9310	0.8889	1.0000	1.0000
ECR by at least one test	AUC	0.5406	0.5307	0.5790	0.5000
	SENS	0.9259	0.8947	1.0000	1.0000
	SPEC	0.1552	0.1667	0.1579	0.0000
ECR by US only (reference)	AUC	0.6670	0.6228	0.6737	0.6667
	SENS	0.5926	0.5789	0.40000	1.0000
	SPEC	0.7414	0.6667	0.9474	0.3333

SENS, Sensitivity, defined as P(R=1|pCR=1); SPEC, Specificity, defined as P(R=0|pCR=0 where P(A|B) denotes the conditional probability of event A given that event B has occurred and R is a placeholder for ECR or Ki-67 response. AUC, area under the receiver operating characteristic curve; ECR, early clinical response.