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Concordance and clinical impact of ER, PR, HER2 expression by local and central immunohistochemistry vs RT-PCR in HR+/HER2- early breast cancer (EBC): Results from the ADAPT trial

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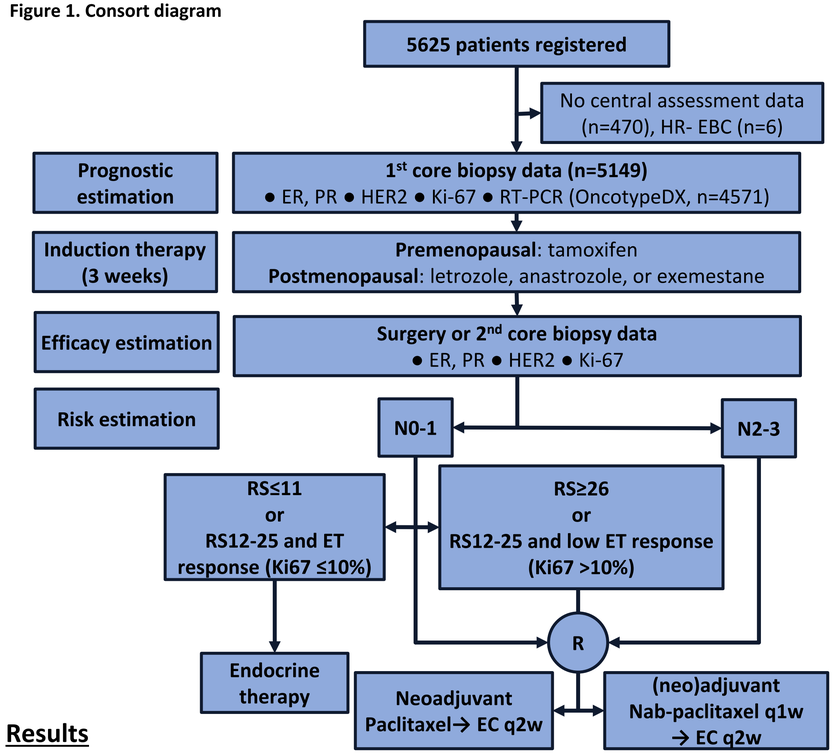
Background

Validity of borderline ER-positivity (1-10%) is clinically important as treatment concepts differ substantially between luminal-like and triple-negative breast cancer (TNBC). Moreover, the HER2-low subgroup gains therapeutical relevance, although there is no standardized test available so far. We evaluated concordance of ER, PR and HER2 status between local, central, and mRNA assessments (RT-PCR) and its clinical impact in the (neo-)adjuvant WSG-ADAPT HR+/HER2- phase III trial (NCT01779206).

Methods

5625 patients were screened from 81 centers in Germany for participation in the ADAPT HR+/HER2- trial. ER/PR/HER2 values were documented in 5149 patients with clinically high-risk ER and/or PR positive (≥1%,) and HER2-negative EBC (by local lab, Figure 1). 4691 patients were allocated to endocrine therapy (n=2356 endocrine therapy, 2335 treated by chemotherapy).

Figure 1. Consort diagram



Results

- Out of 4374 (99.7%) ER+ and/or PR+ tumors by central IHC (Table 1), 4336 (99.1%) were ER+ and/or PR+ by RT-PCR (overall concordance: 99.1%, κ=0.38)
- High concordance for ER status (Table 2)
  - Out of 4512 (99.6%) ER+ tumors ER+ by local IHC, 4484 (99.3%) were ER+ by central IHC (overall concordance: 99.3%, κ=0.45)
  - Out of 4348 (99.4%) ER+ tumors by central IHC, 4309 (99.1%) were ER+ by RT-PCR.
  - Among 60 (1.4%) ER- tumors by RT-PCR, 39 (65.0%) were ER+ by central IHC (overall concordance: 99.0%, κ=0.48)
- Lower concordance for PR status
  - Out of 350 (7.7%) PR- tumors identified by local IHC, 118 (33.7%) were PR+ by central IHC (overall concordance: 93.1%, κ=0.56)
  - Out of 715 (16.3%) PR- tumors by RT-PCR, 365 (51%) were PR+ by central IHC (overall concordance: 90.5%, κ=0.58)
  - Continuous ER and PR expression by all three methods was significantly associated with improved iDFS after 59 months of FU

Conclusions:

- Agreement between local and central IHC and RT-PCR for ER, PR, HER2 assessment is high in HR+/HER2- EBC
- Standardization and quality assurance measures may be needed for determination of HER2-low status (1+ or 2+ but ISH negative)
- Treatment of the heterogeneous ER-low group (1-10%) as TNBC appears reasonable only if ER-low is confirmed by a second assessment and in cases with Ki67>40%
- Assessment of response to preoperative endocrine therapy may be helpful if an endocrine-based therapy concept is intended

Table 1. Baseline characteristics regarding ER, PR, HER2

Local IHC, n (%)	Negative	Positive	Missing
ER and/or PR	1 (0.0)	5148 (100.0)	0
ER	28 (0.5)	5094 (98.9)	27 (0.5)
PR	426 (8.3)	4680 (90.9)	43 (0.8)
HER2	5126 (99.6)	0 (0.0)	23 (0.4)
Central IHC, n (%)	**Negative**	**Positive**	**Missing**
ER and/or PR	24 (0.5)	4541 (88.2)	584 (11.3)
ER	42 (0.8)	4509 (87.6)	598 (11.6)
PR	448 (8.7)	4106 (79.7)	595 (11.6)
HER2	4443 (86.3)	98 (1.9)	608 (11.8)

RT-PCR, n (%)	Negative	Positive	Equivocal	Missing
ER and/or PR	52 (1.0)	4519 (87.8)	-	578 (11.2)
ER	62 (1.2)	4509 (87.6)	-	578 (11.2)
PR	750 (14.6)	3821 (74.2)	-	578 (11.2)
HER2	4464 (86.7)	25 (0.5)	82 (1.6)	578 (11.2)

Table 2. Agreement in ER and PR by three assessments

	ER	PR
Local vs central IHC	99.3% (κ=0.45)	93.1% (κ=0.56)
RT-PCR vs central IHC	99.0% (κ=0.48)	90.5% (κ=0.58)

- Overall, 163 tumors (3.2%, Table 3) were HER2+ (3+ and/or positive ISH) by central assessment, including 98 (60.1%) identified by the 1st and the remaining 65 (39.9%) by the 2nd biopsy
- Out of 75 (1.7%) HER2+ tumors by central IHC with available RT-PCR data, 55 (73.3%) were HER2 negative by RT-PCR (overall concordance: 98.2%, κ=0.20).
- 3078 tumors (68%) with available local and central IHC assessments were HER2-low (1+ or 2+ but ISH negative) by local and/or central IHC on the first biopsy
- Overall, only 53.8% of tumors had a concordant status: HER2-low (1+ or 2+ but ISH negative) or HER2- (HER2=0) in both local and central IHC (κ=0.10)
- We have observed stronger correlation between continuous central HER expression vs. RT-PCR than between local HER2 expression and RT-PCR (r_Spearman = 0.47 versus 0.23)
- There is only 29% concordance (n=998 of 3385 with both available pre- and post-ET samples) in HER2-low status between 1st and 2nd sample both assessed by central lab
- Neither local nor central HER2-low status had an impact on iDFS
- Regarding pCR (ypT0/is, ypN0) after neoadjuvant chemotherapy (n=864): only local (14.1 vs. 20.5%, p=.02), but not central HER2-low (14.1 vs. 16%, n.s.) status (vs.HER2 0) was associated with significantly lower pCR rate

Table 3. Agreement in HER2 status (local/central lab)

Central Local	HER2-	HER2-low	HER2+	Total, n (%)
HER2-	1399 (53.6)	1165 (44.7)	44 (1.7)	2608 (100.0)
HER2-low	826 (43.2)	1035 (54.1)	52 (2.7)	1913 (100.0)
Total, n (%)	2225 (49.2)	2200 (48.7)	96 (2.1)	4521 (100.0)

Table 4. Agreement in ER-low (1-10%) status

Central Local	ER-	ER 1-10%	ER >10%	n miss	Total, n (%)
ER-	13 (46.4)	1 (3.6)	2 (7.1)	12 (42.9)	28 (100.0)
ER 1-10%	8 (9.8)	9 (11.0)	41 (50.0)	24 (29.3)	82 (100.0)
ER >10%	20 (0.4)	26 (0.5)	4408 (88.0)	558 (11.1)	5012 (100.0)
n miss	1 (3.7)	0 (0.0)	22 (81.5)	4 (14.8)	27 (100.0)
Total, n (%)	42 (0.8)	36 (0.7)	4473 (86.9)	598 (11.6)	5149 (100.0)

- 109 (2.1%) were ER-low (1-10%, Table 4) by local and/or central IHC (n=85 with both values available); including 9/109 (8.3%)-with ER-low by both assessments and 8/109 (7.3%) with TNBC by central IHC, 67/109 (61.5%) had ER>10% by one of both assessments.
- Overall concordance: 97.8%, κ=0.34
- 69% of the ER-low group had ER-positivity by RT-PCR (n=53/77)
- Of 17 cases with ER-low (central lab) on 1st biopsy and available pre- and post-ET samples, only 2 (12%) were ER-low at 2nd sample assessment by central lab

- Worse Ki67 response after 3-week induction endocrine therapy in ER-low tumors (36.2% ET-responders vs. ER>10% (59% ET-responders). 42% had RS≤25 (Figure 2)
- All cases with ER-low by both assessments and those with Ki67>40% had RS >25
- Worse iDFS in ER-low (by either local and/or central assessment) vs ER (by both assessments) >10%: HR 1.92 (95%CI 1.05, 3.50; p=0.034)

Figure 2. ET-response and high risk by RS according to ER-low status