The run-in phase of the prospective WSG-ADAPT HR+/HER2− trial demonstrates the feasibility of a study design combining static and dynamic biomarker assessments for individualized therapy in early breast cancer

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Abstract

Background: Endocrine sensitivity, as determined by response of the proliferation marker Ki-67 to short-term preoperative endocrine therapy (ET), is currently not included in adjuvant treatment decisions in hormone receptor (HR)+/human epidermal growth factor receptor 2 (HER2)− breast cancer (BC).

Methods: The prospective WSG-ADAPT HR+/HER2− trial included patients with N0/N1 early BC who were candidates for adjuvant chemotherapy based on clinical–pathological criteria alone. The trial utilized a genomic assessment [the Recurrence Score (RS)] plus endocrine sensitivity testing to guide treatment. All patients received 3 (±1) weeks of preoperative induction ET. According to protocol, patients with RS 0–11 or RS 12–25 plus endocrine proliferation response (EPR, post-induction Ki-67 ≤ 10%) were to be spared adjuvant chemotherapy.

Results: The ADAPT HR+/HER2− trial run-in phase included 407 patients with baseline RS, of whom 386 (median age: 54 years) had complete data for Ki-67 at both baseline and post-induction. RS distribution: 23.1% RS 0–11, 58.3% RS 12–25, and 18.7% RS 26–100. EPR occurred in 84.3%, 76.0%, and 36.1% of these RS groups, respectively. Differences in EPR proportions (RS 26–100 versus others, RS 0–11 versus others) were significant (both p < 0.001); Ki-67 quotients were higher for RS 26–100 (p = 0.02, Mann–Whitney). In premenopausal women (n = 146, mostly tamoxifen-treated), median quotient of Ki-67 level (post/pre) was significantly higher than in postmenopausal women (n = 222, mostly aromatase-inhibitor treated; 0.67 versus 0.25, p < 0.001). EPR was significantly associated with baseline estrogen-receptor status as determined by immunohistochemistry (p = 0.002) or real-time polymerase chain reaction (p < 0.001). Also, a strong correlation was observed between RS measured pre- and post-ET (R² = 0.7, n = 181).

Conclusions: This phase of the WSG-ADAPT HR+/HER2− trial confirms trial design estimates of RS and EPR. It indicates that the ADAPT concept of combining static and dynamic biomarker assessment for individualized therapy decisions in early BC is feasible using the EPR criterion post-induction Ki-67 ≤ 10%.

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Introduction

Adjuvant endocrine therapy has been the standard of care for women with early hormone receptor (HR)+ breast cancer (BC) for chemotherapy, modern precision medicine strategies are increasingly applied to identify the minority of patients with HR+ human epidermal growth-factor receptor 2 (HER2) — tumors who could benefit from it. For endocrine therapy, its use in the HR+ population is unselective, as there are currently no validated predictive markers for patient selection. Possible predictors for AI sensitivity in the adjuvant setting were identified, and include lobular histology, Ki-67, and high estrogen receptor (ER) expression (determined by immunohistochemistry).

The preoperative/neoadjuvant setting offers a unique opportunity for assessment of sensitivity to specific therapies. For HR disease, Ki-67 is a validated pharmacodynamic predictor for endocrine therapy response. The IMPACT trial, which compared preoperative therapy with tamoxifen, anastrozole, or their combination for 12 weeks in postmenopausal women with HR+ BC demonstrated that higher Ki-67 levels after 2 weeks of endocrine therapy (but not at baseline) were statistically significantly associated with lower recurrence-free survival (RFS).

Methods

Study design

The study design was previously described. In short, the WSG-ADAPT HR+/HER2 trial was a sub-trial under the prospective, multi-center, controlled, non-blinded, randomized, investigator-initiated phase II/III WSG-ADAPT umbrella trial (Figure 1). All patients in the WSG-ADAPT HR+/HER2 trial received endocrine therapy as induction treatment according to menopausal status as per the German Gynecological Oncology Group (AGO) guidelines. Premenopausal patients were recommended to receive tamoxifen (20 mg, daily) and postmenopausal patients were recommended to receive AIs (letrozole, 2.5 mg, daily; anastrozole, 1 mg, daily; or exemestane, 25 mg, daily, at investigator’s choice). Use of luteinizing-hormone releasing hormone (LHRH) agonists in premenopausal patients was optional at investigator’s discretion. Deviations from these recommendations are reported below.

Patients underwent diagnostic core biopsy, followed by induction endocrine therapy for 3 weeks. Analysis of the initial and second biopsy after induction endocrine therapy included Ki-67 evaluation (determined by immunohistochemistry in a central lab) and RS assessment (performed by Genomic Health, Inc., Redwood City, CA). In addition to Ki-67 changes, the run-in phase included immunohistochemical measurements of staining percent for progesterone receptor (PR) and ER post-therapy versus baseline and of

impact, no relapses were recorded for patients with pathological stage 0/1, and a PEPI risk score of 0 [T1/T2, N0, post-treatment ER status of 3–8 (Allred score), and Ki-67 ≤ 2.7%].

The goal of the WSG-ADAPT HR+/HER2 trial was to address individualization of adjuvant therapy in early BC by using a static biomarker [the 21-gene Recurrence Score (RS), a well-validated prognosticator and a predictor of chemotherapy benefit in HR+ HER2– BC patients in combination with an early response predictor (the levels of the proliferation marker Ki-67 before and after induction therapy)]. The aim of the run-in phase of the WSG-ADAPT HR+/HER2 trial was to determine feasibility of the trial concept with EPR defined as post-induction Ki-67 ≤ 10% and to test key assumptions used in trial design.
genomic proliferation response (utilizing a subset of the RS genes). ER, PR mRNA expression levels by reverse transcriptase polymerase chain reaction (RT-PCR) were reported within 21-gene RS assay and analyzed as reported previously. These additional measurements served as auxiliary indicators of response/resistance to endocrine therapy.

Study participants
Eligibility criteria were previously described. In short, the WSG-ADAPT umbrella trial included women with early primary invasive BC aged >18 years with any cT1a–cT4c tumor size and any nodal status. The WSG-ADAPT HR+/HER2− sub-trial included patients with HR+/HER2− early BC and no evidence of metastatic disease who were candidates for (neo)adjuvant chemotherapy by current guidelines. HR and HER2 status for this trial were determined by local pathology. In addition, patients had to be not pregnant (i.e. negative pregnancy test within 7 days prior to induction therapy), had to be able to tolerate treatment, as indicated by normal laboratory values and proper organ function, and without known hypersensitivity reaction to the therapeutic agents. Patients with risk of poor compliance and those not able to consent were excluded.

The run-in phase reported here included N0–N3 patients; patients with N2–N3 disease were considered high risk and were randomized to a chemotherapy arm irrespective of RS and EPR.

According to protocol, the run-in phase, which began in July 2012, continued until a ‘freeze date’ determined by the requirement that 400 patients with valid baseline RS had been registered. The resulting freeze date for the run-in phase was 31 July 2013. Due to measurement and reporting latencies, the run-in patient collective as analyzed in this paper, in fact, included \( n = 407 \) consecutively registered patients with valid baseline RS.

Outcome assessments
In the main trial, patients with RS 0–11 in the initial biopsy were considered low risk and were to receive endocrine therapy only (Figure 1). Patients with RS 12–25 were considered intermediate risk and were to be randomized to a chemotherapy arm, as described. For patients with RS 12–25 (intermediate risk), the goal according to protocol was to verify the feasibility of defining EPR to induction therapy as a 3-week measurement of Ki-67 \( \leq 10\% \) (denoted EPR below); the intention was to utilize EPR as the criterion to allocate the group of patients with RS 12–25 and pN0–1 to low-risk and high-risk treatment groups. In order to verify trial design assumptions, the feasibility study determined...
EPR proportions according to baseline RS category. In addition to EPR defined in this way, other indicators of proliferation response such as changes (3-week versus baseline) in endocrine receptor measurements as well as in genomic variables served as an additional window to the underlying biological processes that motivated splitting the RS 12–25 group in the main trial according to early response. They also served as potential alternative criteria for early response.

Statistical considerations

Descriptive statistics were used to describe patient characteristics and Ki-67 proliferation dynamics. To avoid confusion, it is worth noting that the units of Ki-67 are '%' due to the measurement methodology. A binary variable denoted EPR was coded as one if post-therapy Ki-67 ≤ 10%, otherwise zero. Associations in $2 \times 2$ contingency tables were tested by chi-squared or Fisher’s exact test. Differences in means of continuous variables between two independent subgroups were tested by $t$-test statistics if approximately normally distributed; otherwise (as in the case of Ki-67 ratios post-/pre-treatment), medians were reported and the Mann–Whitney $U$ test was used. In case of continuous variable comparisons among three subgroups (e.g., RS groups 0–11, 12–25, 26–100), pairwise comparisons were considered. Correlation analysis among continuous variables used rank (Spearman) correlation coefficients, denoted $R_S$. Multiple (forward) regression (logistic and linear) models were used to test for potential impacts of additional dynamical variables (such as RS change) on Ki-67 response to therapy. The in-sample area under the curve (AUC) of the receiver operating characteristic (ROC) curve from the logistic regression model was computed to characterize residual variance. No corrections for multiple testing were performed. SPSS version 25 (IBM, Armonk, New York, USA) was used for models and statistical tests. $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

The ADAPT HR+/HER2− trial run-in phase included 407 patients with baseline RS, of whom 386 had complete data for Ki-67 at both baseline and post-induction. Patient characteristics are presented in Table 1. Median age was 54 (range: 28–75) years. Among patients with known nodal status (cN) about 87% were cN0, and less than 1% were considered cN2–3. Approximately 60% had cT1 tumors, 37% had cT2, and less than 3% had larger tumors.

Ki-67 proliferation dynamics and RS

The distribution of the RS was 23.1% RS 0–11, 58.3% RS 12–25, and 18.7% RS 26–100. Baseline Ki-67 was moderately correlated with baseline RS ($R_S = 0.47$, $n = 386$). The median baseline Ki-67 levels were 10%, 15%, and 30% in these RS groups, respectively (Table 2).

Analysis of Ki-67 levels after induction therapy in each RS group demonstrated heterogeneity of the proliferation dynamics, and a strong relationship between the baseline RS group and changes in both EPR and quantitative Ki-67 (Table 2). In the RS 0–11, 12–25, and 26–100 groups, EPR occurred in 84.3%, 76.0%, and 36.1%, while median Ki-67 quotients (post-induction/baseline) were 0.33, 0.40, and 0.60, respectively. These differences in EPR proportions were significant for the comparisons of RS 26–100 versus others and RS 0–11 versus others (both $p < 0.001$); Ki-67 quotients were significantly higher for RS 26–100 than for other RS groups ($p = 0.02$, Mann–Whitney).

Endocrine therapy with AI appeared to be more effective in reducing Ki-67 on treatment than tamoxifen: median post-/pre-treatment Ki-67 quotients were 0.25 (AI) versus 0.67 (tamoxifen) ($p < 0.001$). However, noting that only 2/156
premenopausal women received AI (plus gonado-tropin-releasing hormone analogs), and only 21/230 postmenopausal women received tamoxifen, the same median reduction quotients are found if we compare postmenopausal with premenopausal women (rather than AI with tamoxifen). Among postmenopausal women, the absolute decrease in Ki-67 on AI therapy was 12.9% compared to 7.8% on tamoxifen ($p=0.05$). This difference within postmenopausal women suggests that treatment with AI may in fact be more effective in overcoming endocrine resistance, but more data will be required to separate out the confounded impacts of menopausal status versus AI treatment. The percentage of postmenopausal patients ($n=209$) with EPR was approximately 83% on AI compared with approximately 71% on tamoxifen ($n=21$), but this difference was not significant.

### Impact of additional baseline factors on response to induction therapy

In addition to the association with the RS, EPR was associated with baseline ER levels as determined either by immunohistochemistry ($p=0.003$) or by RT-PCR ($p<0.001$); EPR was also associated with baseline PR levels as determined by RT-PCR ($p=0.003$; all $p$ values by Mann–Whitney $U$ test).

### Alternative measures of proliferation response

An mRNA-based measure of proliferation response (recurrence proliferation score) was available in 176 patients. This mRNA-based proliferation response measure was strongly correlated with the change (post-therapy minus baseline) in Ki-67 ($R_s=0.6$, $n=185$); mRNA-based proliferation response was stronger with AI than with tamoxifen ($p<0.001$).

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**Table 1.** Patient baseline characteristics.

| Characteristic                  | $n=386$ |
|--------------------------------|---------|
| Age, years                     | Median (range) 54 (28–75) |
| Menopausal status*, $n$ (%)     |         |
| Premenopausal                   | 156 (40.4) |
| Postmenopausal                  | 230 (59.6) |
| Nodal status, $n$ (%)           |         |
| cN0                             | 335 (86.8) |
| cN1                             | 46 (11.9) |
| cN2                             | 2 (0.5) |
| cN3                             | 1 (0.3) |
| NA                              | 2 (0.5) |
| Grade, $n$ (%)                  |         |
| G1                              | 25 (6.5) |
| G2                              | 259 (67.1) |
| G3                              | 99 (25.6) |
| NA                              | 3 (0.8) |
| Tumor size, $n$ (%)             |         |
| cT1                             | 232 (60.1) |
| cT2                             | 142 (36.8) |
| cT3                             | 9 (2.3) |
| cT4                             | 2 (0.5) |
| NA                              | 1 (0.3) |
| Therapy, $n$ (%)                |         |
| Tamoxifen                       | 175 (45.3) |
| Aromatase inhibitor             | 208 (53.9) |
| NA                              | 3 (0.8) |
| Recurrence Score result, $n$ (%)|         |
| 0–11                            | 89 (23.1) |
| 12–25                           | 225 (58.3) |
| 26–100                          | 72 (18.7) |
| Ki-67, $n$ (%)                  |         |
| 0–10%                           | 126 (32.6) |
| 11–35%                          | 224 (58.0) |
| $\geq$40%                       | 36 (9.3) |

*Known or assigned, based on therapy. NA, not available/not applicable.
PR change (percent stained cells post-therapy minus baseline) was weakly correlated with both Ki-67 change (Rs = 0.25, n = 386) and with mRNA-based proliferation response (Rs = 0.27, n = 176). PR percent decreased more strongly on AI (−43) than on tamoxifen (−9) (p < 0.001). Finally, PR change had a weak negative correlation with RS change (Rs = −0.39, n = 176).

ER change was not significantly correlated with changes in Ki-67, RS, PR, or with mRNA-based proliferation response among all patients. Among patients receiving AI, ER change had a weak negative correlation with mRNA-based proliferation response (Rs = −0.28, p = 0.007).

Since the RS is hardly subject to interobserver variability, the potential predictive value of RS dynamics (post-therapy versus baseline) to characterize endocrine response was studied by multiple linear multiple regression models for post-treatment Ki-67 (as a continuous variable) and by multiple logistic regression for EPR (as a binary variable). Baseline Ki-67 and both baseline values and changes in ER, PR (immunohistochemistry staining percentages), and RS were entered in both kinds of regression models. In linear regression of post-therapy Ki-67, the resulting predictors were baseline Ki-67, PR, and RS, as well as change in RS. However, in logistic regression for EPR, the predictors in the model were baseline Ki-67, PR, and RS, as well as the change in PR, but not change in RS [ER (baseline or change) did not enter either of the multiple regression models]. The in-sample AUC of the logistic regression model was 0.75, indicating considerable residual variance.

Discussion
The run-in phase of the WSG-ADAPT HR+/HER2− study confirmed feasibility of EPR, defined as Ki-67 ≤ 10%, and trial design estimates with respect to RS distribution and the prevalence of EPR in RS groups (particularly the EPR rate of >70% in the RS 12−25 group). The results thus indicated feasibility of the multicenter prospective ADAPT concept combining static and dynamic biomarker assessment for individualized therapy decisions in early BC.

The WSG-ADAPT trial is the first BC trial in which patients with RS 12–25 (intermediate genomic risk) who are responders by Ki-67 (here according to EPR) receive no chemotherapy. The WSG-ADAPT HR+/HER2− trial tests non-inferiority (for event-free survival) in N0/N1 patients with RS 12–25 and EPR, compared with N0/N1 patients with RS 0–11 (low genomic risk), with both groups receiving endocrine therapy only. If non-inferiority can be demonstrated, it would provide strong support for the WSG-ADAPT strategy, namely using RS and endocrine proliferation response to spare adjuvant chemotherapy in >70% of N0/N1 HR+/HER2− patients who would otherwise be candidates for adjuvant chemotherapy, based on clinical–pathological criteria alone.

The run-in phase demonstrated that proliferation response (by EPR or other measures) was strongly associated with menopausal status and/or therapy group (i.e. AI in postmenopausal women versus tamoxifen in premenopausal women). The main trial could help clarify the relative importance of factors influencing response.

Lastly, the study suggests that measuring the RS at baseline (from the core biopsy) is sufficient, and that there is no need to measure the RS again after the induction therapy. The absence of RS dynamics in the logistic regression model for EPR, as well as the strong correlation of RS pre- and post-endocrine therapy, suggest that post-therapy RS would provide only limited additional value for characterizing response to endocrine therapy. The residual variance (evident from only moderately high in-sample AUC of 0.75, presumably lower out of sample) also indicates that EPR cannot be accurately predicted using baseline values.

Our study has some limitations. Omission of chemotherapy in patients with pN0 and particularly in pN1 BC patients with RS 12–25 and EPR represents an experimental strategy which will be addressed by the results of the fully recruited ADAPT trial. Furthermore, the lower EPR rates observed after tamoxifen alone in premenopausal women compared with those after AI in postmenopausal women may be overcome by use of LHRH agonists, together with an AI in premenopausal patients. This may indeed be a more promising strategy for premenopausal women at high risk for recurrence based on the results of the SOFT/Text trials, which were published after the ADAPT trial had started.

In conclusion, the run-in phase of WSG-ADAPT HR+/HER2− sub-trial was successful. The whole WSG-ADAPT HR+/HER2− sub-trial includes a total of 5625 registered and 4691 randomized (2356 allocated to endocrine treatment, 94 to the
run-in chemotherapy question, and 2241 to the ‘main phase’ chemotherapy question) patients; first outcome results will be available after completing a minimum of 5-year follow up in at least 1740 patients treated with endocrine therapy alone (expected towards the end of 2020 or in 2021).

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Conflict of interest statement
U Nitz has minority non-profit ownership at WSG Study Group; received honoraria from Amgen, AstraZeneca, Genomic Health, Novartis, Pfizer, Pierre Fabre, Roche, Zodiac Pharma; has a consulting/advisory board role at Agenda, AstraZeneca, Celgene, Daiichi Sanyko, Lilly, Merck Sharp & Dohme, Novartis, Odonate Therapeutics, Pfizer, Pierre Fabre, Roche/Genentech, Sandoz, Seattle Genetics, received research funding from Lilly (Inst), Merck Sharp & Dohme (Inst), Novartis (Inst), Pfizer (Inst), Roche/Genentech (Inst), provided expert testimony for Genomic Health; and received travel accommodations/expenses from Roche, Genomic Health, Pfizer, Celgene. O Gluz has minority non-profit ownership at WSG Study Group; received honoraria from Genomic Health, Roche, Celgene, Pfizer, Novartis, NanoString Technologies, AstraZeneca; has a consulting/advisory board role at Amgen, Roche, Daiichi Sanyko, Genomic Health, Merck Sharp & Dohme; received research funding from AstraZeneca, Celgene, Daiichi Sanyko, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, RTI Surgical, Teva; has a consulting/advisory board role at AstraZeneca, Celgene, Genomic Health, GlaxoSmithKline, Medac, Novartis, Pfizer, Roche, RTI Surgical, Teva. K Lüdtke-Heckenkamp has a consulting/advisory board role at Roche, Lilly, Novartis, Celgene; received research funding from Roche (Inst), Lilly (Inst), Novartis (Inst), Pfizer (Inst); and received travel accommodations/expenses from Roche, Celgene, Pfizer, Novartis. B Nuding has a consulting/advisory board role at Roche, Novartis, Pfizer; and received travel accommodations/expenses from Novartis. C Schumacher received research funding from Roche (Inst), Novartis (Inst), Boehringer (Inst); and serves on the Speaker's bureau of Roche. K Krauss has stock/interest at Fresenius (Fam); received honoraria from Roche, Celgene; received research funding from Novartis, Pfizer; and received travel accommodations/expenses from Medtronic. W Malter received honoraria from Nanostring, Celgene, Roche; and has a consulting/advisory board role at Genomic Health, Pfizer, Novartis, Hologic. M Thill received honoraria from Amgen, Art Tempi, AstraZeneca, Celgene, Clovis, Connect Medica, Eisai, Exact Sciences, Daiichi Sanyko, Gedeon Richter, Hexal, I-Med-Institute, Lilly, MCI, Medtronic, MSD, Novartis, onkowissen.de, Omnimed, Pfizer, pfm Medical, Roche, RTI Surgical; has a consulting/advisory board role at Amgen, AstraZeneca, Biom’Up, Celgene, ClearCut, Clovis, Daiichi Sanyko, Eisai, Exact Sciences, Lilly, MSD, Norgine, Neodynamics, Novartis, onkowissen.de, Pfizer, pfm Medical, Pierre-Fabre, Roche, RTI Surgical, Sysmex, Tesaro; received research funding from Exact Sciences; received travel accommodation/expenses from Amgen, Art Tempi, AstraZeneca, Celgene, Clovis, Connect Medica, Daiichi Sanyko, Eisai, Exact Sciences, Hexal, I-Med-Institute, Lilly, MCI, Medtronic, MSD, Norgine, Novartis,
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References
1. Viale G, Giobbie-Hurder A, Regan MM, et al. Prognostic and predictive value of centrally reviewed Ki-67 labeling index in postmenopausal women with endocrine-responsive breast cancer: results from Breast International Group Trial 1-98 comparing adjuvant tamoxifen with letrozole. J Clin Oncol 2008; 26: 5569–5575.
2. Strasser-Weigl K, Sudan G, Ramjesi Singh R, et al. Outcomes in women with invasive ductal or invasive lobular early stage breast cancer treated with anastrozole or exemestane in CCTG (NCIC CTG) MA.27. Eur J Cancer 2018; 90: 19–25.
3. Bartlett JM, Brookes CL, Robson T, et al. Estrogen receptor and progesterone receptor as predictive biomarkers of response to endocrine therapy: a prospectively powered pathology study in the tamoxifen and exemestane adjuvant multination trial. J Clin Oncol 2011; 29: 1531–1538.
4. Kim C, Tang G, Pogue-Geile KL, et al. Estrogen receptor (ESR1) mRNA expression and benefit from tamoxifen in the treatment and prevention of estrogen receptor-positive breast cancer. J Clin Oncol 2011; 29: 4160–4167.
5. Dowsett M, Smith IE, Ebbs SR, et al. Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. J Natl Cancer Inst 2007; 99: 167–170.
6. Ellis MJ, Coop A, Singh B, et al. Letrozole inhibits tumor proliferation more effectively than tamoxifen independent of HER1/2 expression status. Cancer Res 2003; 63: 6523–6531.
7. Ellis MJ and Ma C. Letrozole in the neoadjuvant setting: the P024 trial. Breast Cancer Res Treat 2007; 105 (Suppl. 1): 33–43.
8. Dowsett M, Smith I, Robertson J, et al. Endocrine therapy, new biologicals, and new study designs for presurgical studies in breast cancer. J Natl Cancer Inst Monogr 2011; 2011: 120–123.
9. Bliss JM, Morden J, Evans A, et al. Clinico-pathological relationships with Ki67 in POETIC (CRUK/07/015) – Critical lessons for assessing Ki67 for prognosis and as a pharmacodynamic marker. Presented at San Antonio Breast Cancer Symposium, 6–10 December 2016, San Antonio, TX.
10. Ellis MJ, Tao Y, Luo J, et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. J Natl Cancer Inst 2008; 100: 1380–1388.
11. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004; 351: 2817–2826.
12. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with
node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol* 2006; 24: 3726–3734.

13. Sparano JA, Gray RJ, Makower DF, *et al.* Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med* 2018; 379: 111–121.

14. Hofmann D, Nitz U, Gluz O, *et al.* WSG ADAPT - adjuvant dynamic marker-adjusted personalized therapy trial optimizing risk assessment and therapy response prediction in early breast cancer: study protocol for a prospective, multi-center, controlled, non-blinded, randomized, investigator initiated phase II/III trial. *Trials* 2013; 14: 261.

15. AGO recommendations for the diagnosis and treatment of patients with early breast cancer, http://www.ago-online.de/ (accessed 24 May 2020).

16. Francis PA, Pagani O, Fleming GF, *et al.* Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med* 2018; 379: 122–137.