Final analysis of the WSG-ADAPT HER2+/HR- phase II trial: Efficacy, safety, and predictive markers for 12-weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab ± weekly paclitaxel in HER2+/HR- early breast cancer (EBC)

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Background

Cure rates in HER2+ eBC have improved substantially over the last decades due to the addition of trastuzumab to chemotherapy. New compounds like lapatinib, neratinib, T-DM1, and pertuzumab and their combinations are now available for therapy of metastatic BC. Pertuzumab is the first new compound available for neoadjuvant treatment in combination with trastuzumab and docetaxel. Results from the NeoSphere trial and a metaanalysis show different response patterns depending on co-expression of hormone receptors. ADAPT HER2+/HR- is the first prospective trial evaluating the value of chemotherapy added to dual blockade in HER+/HR- eBC alone.

Methods

The WSG-ADAPT HER2+/HR- phase 2 trial randomizes patients with HER2+ and HR-negative eBC to 12 weeks of pertuzumab (P) + trastuzumab (T) ± paclitaxel weekly in a neoadjuvant setting.

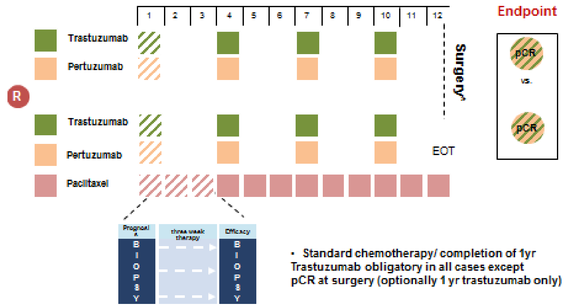


Fig. 1: Trial Design WSG-ADAPT HER2+/HR-

Inclusion criteria: Female patients, age at diagnosis 18 - 75 years, histologically confirmed unilateral primary invasive carcinoma of the breast cT1-4c (participation of patients with tumors >cT2 strongly recommended), all cN, no evidence for distant metastasis by conventional staging (cM0), good Performance Status ECOG ≤1 or KI ≥ 80% with normal organ function and documented LVEF within normal limits of each institution measured by echocardiography and normal ECG (within 42 days prior to induction treatment). Written informed consent prior to beginning specific protocol procedures, including expected cooperation for treatment and follow-up, must be obtained and documented according to local regulatory requirements.

Exclusion criteria: Known hypersensitivity reaction to the compounds or incorporated substances, prior malignancy with DFS < 10 years (except curatively treated basalioma of the skin or pTis of the cervix uteri), non-operable breast cancer including inflammatory breast cancer, previous or concurrent treatment with cytotoxic agents, concurrent treatment with other experimental drugs and participation in another clinical trial. Known polyneuropathy ≥ grade 2, severe and relevant co-morbidity that would interact with the application of cytotoxic agents or the participation in the study .

Pathology (central lab): ER or PR negative if immunostaining in <1% of tumor nuclei. HER2 positive: 3+ immunostaining or HER-2/CEP-17 ratio >2.0 or > 6 ISH signals

Treatment: Eligible patients were randomized to Pertuzumab at a loading dose of 840 mg and then 420 mg every 3 weeks plus trastuzumab at a loading dose of 8 mg/kg and then 6 mg/kg all three weeks (P+T) for four cycles versus the P + T + paclitaxel (P+T+Pac) 80 mg/m2 weekly x 12. Core needle biopsies were taken at the time of diagnosis and at the time of the second neoadjuvant treatment cycle.

Patients had to have surgery or histological confirmation of non-pCR by core needle biopsy (if further downstaging of tumor was intended) within three weeks after the end of neoadjuvant study treatment. After that patients had to receive standard chemotherapy (recommended regimen 4 x EC +/- 12 x Paclitaxel q1w) and anti HER2 therapy (1 year of trastuzumab). Further chemotherapy could be omitted in case of pCR at surgery after 12 weeks of neoadjuvant treatment. Radiotherapy was given according to national standards.

Study endpoints: **Primary objective**: Trial tests non-inferiority of pCR in responders (T+P) vs. (T+P+Pac) with pCR: no invasive carcinoma in breast and nodes (ypT0/is ypN0). Study was planned for n=220 patients (randomization P+T vs. P+T+Pac 2.5:1) following pCR assumption of 60% in P+T+Pac arm,

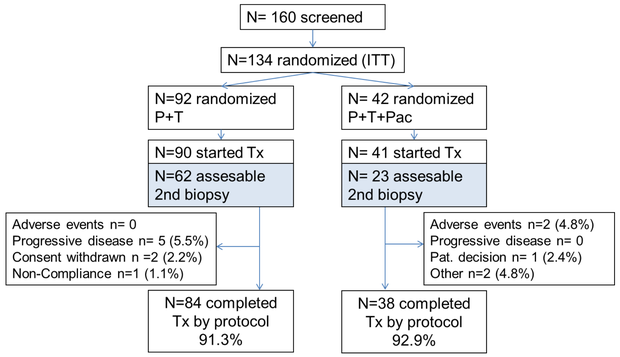
At the pre-planned interim analysis (IA), DSMB recommended 2nd IA for validation of trial assumptions and re-evaluation of responder definition (e.g. Ki67 drop ≥ 30% or <500 invasive tumor cells after 3 weeks of therapy).

Secondary objectives: Evaluation of dynamic testing, EFS, OS, toxicity and safety

Results

From February 2014 to December 2015 160 patients were screened; 134 were randomized (Figure 2).

Fig. 2 CONSORT diagram



Randomization was done on a 2.5: 1 basis . 91.3 % of patients randomized to P+T completed treatment and 92.9% completed P+T+Pac per protocol. Analyses presented refer to the ITT population.

Table 1: patients characteristics

	P + T (n=92)	P + T+ Pac (n=42)
Age median (range)	54 (28-74)	51.5 (30-78)
< 40 years old	8 (8.7%)	2 (4.8%)
cT1	38 (41.3%)	17 (40.5%)
cT2	47 (51.1%)	22 (52.4%)
cT3-4	7 (7.6%)	3 (7.1%)
cN0	50 (54.3%)	26 (61.9%)
G1/2	7 (7.6%)	5 (11.9%)
G3	77 (83.7%)	34 (81.0%)
Ki-67 (median)	50% (15-90)	50%(10-90)

Safety: A total of 10 SAE`s were reported (n=5 T+P , n=5 T+P+Pac). AEs of any grade were reported in 68.9% (n=153) of P+T treated patients and 97.6% (n=269) of P+T+Pac treated patients (Table 2).

Most common toxicities with P+T+Pac were anemia, neutropenia (9.8% of patients), peripheral polyneuropathy (42%), epistaxis (31.7%), most of them being G1-2. No significant differences in G3-4 toxicities were observed between both study arms. A low incidence of 4.9% polyneuropathy G3-4 was observed in the P+T+Pac arm

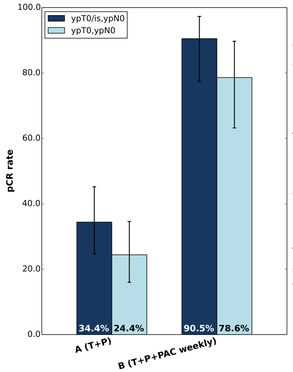
Table 2: Adverse events (all grades) according to treatment arm with corresponding significance

AE	T+P (n=62 Pat.)	%	T+P + Pac (n=40 Pat.)	%	p-value
Anemia	0	0	11	26.8	<0.001
Cardiac disorders	1	1.1	3	7.3	0.09
Ear/labyrinth disorders	1	1.1	3	7.3	0.09
Eye disorders	1	1.1	4	9.8	0.03
GI disorders	33	36.7	25	61.0	0.01
- diarhoea	26	28.9	19	46.3	0.07
- vomiting	2	2.2	1	2.4	1.0
Fatigue	15	16.7	15	36.6	0.01
Infections/infestations	10	11.1	13	31.7	0.01
Decreased appetite	0	0	4	9.8	0.01
Nerveous system disroders	14	15.6	23	56.1	<0.001
Skin disorders	16	17.8	26	63.4	<0.001
Respiratory disorders	8	8.9	16	39.0	<0.001

pCR rates after 12 weeks of neoadjuvant treatment

The observed pCR (ypT0/is, ypN0) rate after P + T alone is 33.7% (n=1 missing) and well within the range expected from prior trials. The pCR rate after 12 weeks of T+P+Pac is 90.5% (p<0.001). This represents a > 2-fold increase with addition of chemotherapy to dual blockade in HER2+/HR- eBC. Total pCR (ypT0, ypN0) rates were 24.4 and 78.6% in the two study arms, respectively (Figure 3).

Fig. 3: pCR rate and total pCR rate according to treatment arm (w/o missing)

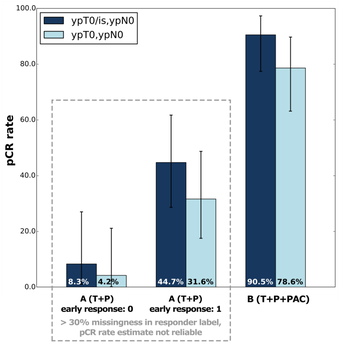


Early response was defined as a proliferation decrease by >30% after 3 weeks of therapy. In addition, if the 2nd measurement of Ki67 could not be performed due to low number of tumor cells (n<500), a patient may be considered as a cellularity responder. Both Ki67 proliferation or cellularity responders define the pre-defined set of early reponders.

Responder determination was not possible in 30 patients from the T+P arm (32.6%). Any statistical analysis of the pCR prevelance in the responder group is thus highly unreliable due to >30% missingness.

In a hypothesis generating analysis, a pCR rate of 44.7% in the responder subgroup vs. only 8.3% in the „non-responder" subgroup of the P+T arm was observed.

Figure 4: pCR rates according to responder status



The pCR rate of 90.5% in the P+T+Pac arm after the extension of the first pre-planned analysis (n=75) recommeded by the DSMB, is substantially higher than the expected 60%.Due to this reason and methodological concerns due to missing data required for the responder determination, a recommendation for premature study termination was made by the DSMB and followed by WSG. This decision was further supported by an ad-hoc Bayesian predictive analysis which suggested an exceedingly low probability of being able to show non-inferiority of pCR rates for early responders to P+T vs. all patients treated by P+T+Pac.

Conclusions

- **WSG ADAPT HER2+/HR- is a unique phase II trial focusing only on HER2+ HR- eBC**
- **90.5% pCR after only twelve weeks of T+P+Pac is substantial**
- **Addition of chemotherapy to dual blockade more than doubles pCR in HER2+/HR- eBC**
- **34.4% pCR after P+T alone is clinically meaningful** (e.g. for frail patients, small tumors)
- **Early response at 3-weeks seems to be positively correlated with pCR, but high percentage of missing data precludes definite clinical conclusions**
- **A low overall toxicity was observed in both study arms, with an excess of G1-2 toxicity in the P+R+Pac arm; no new safety signals were detected**
- **The study was terminated prematurely (after n=134 instead of 220) due to a very low probability of confirming non-inferiority of pCR in responders of the P+T arm vs. those of the P+T+Pac arm.**

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Conflict of interest: ADAPT is an investigator sponsored trial, which is financially supported by (in alphabetical order): Amgen, Celgene, Genomic Health, Roche, Teva.