Can resistance to trastuzumab be reversed by endocrine therapy?
Combination of trastuzumab and letrozole after resistance to sequential trastuzumab and aromatase inhibitor monotherapies in patients with ER-positive, HER-2 positive, advanced breast cancer: a proof-of-concept trial (SAKK 23/03)

On behalf of the Swiss Group for Clinical Cancer Research (SAKK)

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Abstract (updated)

Introduction: HER-2 is part of a highly interactive signaling network that may impair efficacy of endocrine therapy. A sequential treatment design was chosen in this trial to ensure complete resistance to single agent non-steroidal aromatase inhibitor (AI) and trastuzumab (T) both given as monotherapy before receiving both a non-steroidal AI and T in combination. Clinical activity with combined treatment of AI and T after progression of single agent treatments could indicate restoration of sensitivity as a consequence of cross-talk and networking between both pathways.

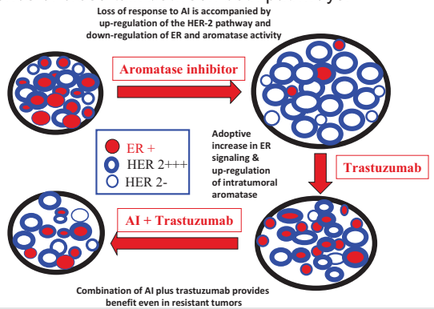
Methods: Key eligibility criteria included postmenopausal patients with advanced, measurable, HER-2 positive [assessed by FISH, ratio (≥2)], hormone receptor (HR) positive disease and progression on prior treatment with a non-steroidal AI, e.g. letrozole or anastrozole, either in the adjuvant or advanced setting. Patients received standard dose T monotherapy in step 1 and upon disease progression, continued T in combination with letrozole in step 2. The primary endpoint was clinical benefit rate (CBR: CR, PR or DS ≥ 6 months) in step 2.

Results: Thirteen patients were enrolled. In step 1, six patients (46%) achieved CBR. Median time to progression (TTP) was 161 days (95% confidence interval (CI): 82-281). CBR was observed in eight out of the eleven evaluable patients (73%) in step 2, including one patient with partial response. Median TTP for all eleven patients was 188 days (95% CI: 77-not reached). Mean time on trial treatment (TTP in step 1 plus TTP in step 2) for patients reaching step 2 was 420 days (range: 174-990).

Conclusion: Results of this proof-of-concept trial suggest that complete resistance to both AI and T can be overcome in a proportion of patients by combined treatment of AI and T, as all patients served as their own control. Our results appear promising for a new treatment strategy which offers a chemotherapy-free option for at least a subset of patients with ER positive, HER-2 positive breast cancer over a clinical relevant time period.

Background & Hypothesis

We hypothesized that the clinical relevance of the upfront combined inhibition of hormonal and growth factor pathways was undefined, and a sequential approach might be advantageous. Thus a sequential treatment design was chosen in this proof-of-concept-trial to ensure complete clinical resistance to single agent therapy before receiving both a non-steroidal AI and T. We speculated, that clinical anti-tumor activity with combined treatment of AI and T after progression of single agent treatments could indicate restoration of sensitivity as a consequence of cross-talk between both pathways.

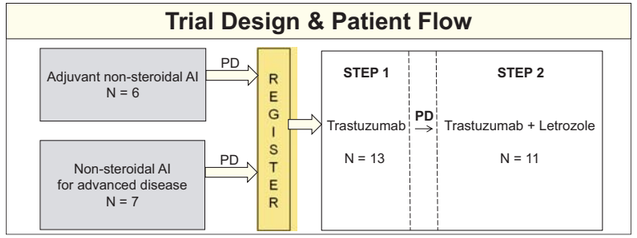


Trial Overview

Key eligibility criteria

- Histologically or cytologically confirmed diagnosis of breast cancer
- ER and/or PgR ≥ 10 fmol/mg cytosol protein; or 10% of the tumor cells positive by immunohistochemical evaluation
- HER-2 amplification (≥ 2) by FISH
- Progression after prior treatment with a non-steroidal AI, e.g. letrozole or anastrozole, either in an adjuvant or an advanced setting

Trial Design & Patient Flow



Treatment Plan

Treatment in step 1 consisted of T monotherapy given as an initial dose of 4 mg/kg iv followed by a weekly dose of 2 mg/kg iv or an initial dose of 8 mg/kg iv followed by a dose of 6 mg/kg iv every 3 weeks (at the discretion of the investigator) until tumor progression. After tumor progression (same key exclusion criteria as at trial entry), T was continued (at the same dose and schedule as in step 1) together with letrozole 2.5 mg daily in patients eligible for step 2.

Sample size calculations deduced that twenty evaluable patients were required for step 2. A CBR of at least 20% in step 2 would have been considered clinically interesting.

Endpoints

Primary endpoint: CBR in step 2

Secondary endpoints: CBR in step 1, TTP, TTF, safety, duration of CB

Results

Baseline Characteristics

Patient	ER* (%)	PgR (%)	High level HER-2†	Centromer ratio ≥ 6 or clustering of HER-2 signal	Prior AI	AI Use	AI Duration (months)**	Metastatic sites
1	20	70	Yes	Yes	A	Adjuvant	4	Bone
2	40	0	Yes	Yes	A	Adjuvant	11	Bone, Lymph nodes
3	40	10	No	No	A	Adjuvant	15	Bone, Lymph nodes, Lung, Liver
4	90	5	Yes	Yes	L	Adjuvant	13	Bone
5	50	50	Yes	Yes	L	Metastatic	13	Bone, Lung
6	90	75	No	No	L	Metastatic	20	Bone, Lymph nodes, Liver, Other
7	90	10	No	No	L	Metastatic	6	Lung, Pleura, Liver
8	99	5	Yes	Yes	A	Metastatic	4	Bone, Primary tumor
9	75	69	Yes	Yes	L	Metastatic	20	Bone, Lymph nodes
10	20	0	Yes	Yes	L	Metastatic	3	Bone, Lymph nodes
11	70	30	Yes	No	A	Adjuvant	36	Bone
12	Bio. pos	Bio. Pos.	No	No	A	Metastatic	35	Lymph nodes, Lung
13	90	0	Yes	Yes	A	Adjuvant	60	Lymph nodes, Lung

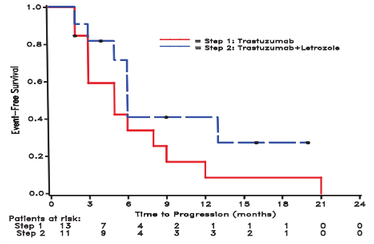
* ER quantitative, † High-level amplified HER-2 tumors: (FISH HER-2 signal : centromer ratio ≥ 4), ** prior to trial entry
AI: Aromatase Inhibitor; A: Anastrozole; L: Letrozole; Bio. Pos.: Biochemical positive

Summary of Main Efficacy Endpoints

Step	No. of Patients with CB n (%)	Duration of CB (days) Median (95% CI)	TTP (days) Median (95% CI)	TTF (days) Median (95% CI)
Step 1 (N=13): Trastuzumab	6 (46%)	267 (161 – 627)	161 (82 – 281)	98 (82 – 168)
Step 2 (N=11): Trastuzumab + Letrozole	**8 (73%) Primary endpoint**	286 (161 – NC)	188 (77 – NC)	184 (77 – NC)

NC = not calculable; CI = Confidence Interval

Kaplan-Meier curves for TTP



Summary & Discussion

This trial was closed early due to slow accrual. However the goal of the trial – proof-of-concept for clinical relevant activity of combination AI plus T in patients with resistant disease to single agent exposure - was achieved with less patients accrued than initially planned (20 patients) due to the surprisingly high CBR in the 13 patients included.

Although the results of this trial must be interpreted with caution because of the small number of patients, it is in concordance with a CBR of 65%, observed in twenty-six patients with ER+/HER+ breast cancers receiving first-line treatment with letrozole and T within a randomized trial (1). Furthermore, this finding is in line with results of the anastrozole plus T arm (CBR 43%) of the randomized TAnDEM trial (2) and of another phase II trial using letrozole and T (CBR 52%) as first or second-line therapy (3).

The results of this trial suggest that complete clinical resistance to both AI and T can be overcome in a proportion of patients by combined treatment, as all patients served as their own control. It also indicates at least partial restoration of sensitivity following this treatment sequence, possibly as a consequence of bidirectional cross-talk and networking between the endocrine and the HER-2 signaling pathways.

In summary, this proof-of-concept trial provides additional clinical evidence for a dynamic interdependence of the ER and HER-2 pathways. It further indicates, that sequential (vertical) blockade of these pathways is feasible without compromising the effectiveness of a combined (horizontal) treatment of targeted therapeutics, thus offering a chemotherapy-free option for at least a subset of patients with ER+/HER-2+ breast cancer.

References:

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