Male-GBG54: A prospective, randomised, multi-centre, phase II study evaluating endocrine treatment with either tamoxifen +/- gonadotropin releasing hormone analogue (GnRHa) or an aromatase inhibitor + GnRHa in male breast cancer patients

Mattea Reinisch[1], Sabine Seiler[2,3], Tanja Hauzenberger[4], Sabine Schmatloch[5], Hans-Joachim Strittmatter[6], Dirk-Michael Zahm[7], Christian Thode[8], Christian Jackisch[3], Michael Untch[9], Dominica Strik[10], Volker Moebus[11], Toralf Reimer T[12], Bruno Sinn[13], Elmar Stickeler[14], Frederik Marmé[15], Wolfgang Janni[16], Axel Kamischke[17], Christian Rudlowski[18], Valentina Nekljudova[2], Gunter von Minckwitz[2], Sibylle Loibl[2]

[1]Kliniken Essen-Mitte, Essen, Germany; [2]German Breast Group, Neu-Isenburg, Germany; [3]Sana-Klinikum Offenbach, Germany; [4]Klinikum St. Marien Amberg, Germany; [5]Elisabeth Krankenhaus Kassel, Germany; [6]Rems-Murr-Klinik-Winnenden, Germany; [7]SRH Wald-Klinikum, Gera, Germany; [8]Amedes MVZ Wagnerstibbe für Laboratoriumsmedizin, medizinische Mikrobiologie und Immunologie, Göttingen, Germany; [9]Helios-Kliniken Berlin-Buch, Berlin, Germany; [10]Endokrinologikum Berlin, Germany; [11]Klinikum Frankfurt Höchst , Germany; [12]Universitätsklinikum Rostock, Germany; [13]Institut für Pathologie, Charité Berlin, Germany; [14]Universitätsklinikum Aachen, Germany; [15]Universitätsklinikum Heidelberg, Germany; [16]Universitätsklinikum Ulm, Germany; [17]MVZ Kinderwunschzentrum Münster, Germany; [18] Evangelisches Krankenhaus Bergisch Gladbach, Germany

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Background

Over 90% of male patients (pts) with breast cancer (BC) have a hormone receptor (HR) positive BC. Although tamoxifen is recommended as standard of care, there is a lack of data regarding efficacy and safety of the standard antihormonal therapy and of alternatives. Due to small incidence of male BC, therapy strategies are extrapolated from principles established for the treatment of female BC and no prospectively randomized study in male BC pts has been conducted so far. The Male study is the first prospective, randomized, multicentre trial presenting data on the efficacy and safety of different endocrine treatment options in male BC pts.

Materials and Methods

In the phase II Male trial (NCT01638247), pts were randomized to receive either tamoxifen 20 mg/day per os (p.o.) or tamoxifen 20mg/day p.o. + GnRH analogue (a) subcutaneous (s.c.) q3m or exemestane 25 mg/day p.o. + GnRHa s.c for 6 months as (neo)adjuvant or metastatic therapy (see figure 1). Primary objective was the 17-ß-estradiol (E2) suppression in the 3 treatment arms after 3 months therapy. Secondary objectives were decreased estradiol suppression after 6 months, compliance and safety of the three therapies, the level of different steroidal hormones testosterone (T), dihydrotestosterone (DHT), sexual hormone binding globuline (SHBG), FSH, LH, free Androgen Index in the three arms. Standard values are depicted in table 2. Tissue and blood was collected for translational research. Male BC pts with a Karnofsky Index ≥60%, normal lipids, and no history or evidence of prostate cancer were eligible. The sample size of 48 evaluable pts was calculated for the Kruskal-Wallis test to have 80% power to detect at the 5% significance level a difference in median E2 decrease between 3 therapy groups, based on the following assumptions: the mean E2 level at baseline of 25 ng/L with standard deviation of 8 ng/L, no change with tamoxifen alone after 3 months, 50% decrease with tamoxifen + GnRHa and 80% decrease with exemestan + GnRHa.

Table 2: Reference laboratory values

Hormones	Standard values
FSH	1.5 - 12.4 IU/l
LH	1.7 - 8.6 IU/l
17-β-Estradiol (E2)	27 - 52 ng/l
Testosteron	2.8 - 8.8 µg/l
Sexual Hormone Binding Globuline	10 - 40 nmol/l

Results

Table 1: Baseline characteristics

Parameter n (%)	Category	A (tamoxifen)	B (tamoxifen + GnRHa)	C (exemestane + GnRHa)	Overall	p-value
Age (min-max)	**years**	59 (37-83)	60 (45-82)	67 (45-80)	62 (37-83)	0.235
Setting	**neoadjuvant**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.045
	adjuvant	14 (82.4)	15 (100)	18 (100)	47 (94.0)	
	metastatic	3 (17.6)	0 (0.0)	0 (0.0)	3 (6.0)	
Prior CTX	**no**	11 (64.7)	10 (66.7)	11 (61.1)	32 (64.0)	0.944
	yes	6 (35.3)	5 (33.3)	7 (38.9)	18 (36.0)	
pT	**pT1**	6 (42.9)	2 (15.4)	8 (47.1)	16 (36.4)	0.355
	pT2	6 (42.9)	10 (76.9)	7 (41.2)	23 (52.3)	
	pT3	0 (0.0)	0 (0.0)	1 (5.9)	1 (2.3)	
	pT4	2 (14.3)	1 (7.7)	1 (5.9)	4 (9.1)	
	missing	3	2	1	6	
pN	**pN0**	8 (57.1)	6 (42.9)	9 (52.9)	23 (51.1)	0.356
	pN+	6 (42.9)	8 (57.1)	8 (47.1)	19 (42.2)	
	missing	3	1	1	5	
M	**M0**	15 (88.2)	14 (100)	18 (100)	47 (95.9)	0.141
	M1	2 (11.8)	0 (0.0)	0 (0.0)	2 (4.1)	
	missing	0	1	0	1	
HER2, primary tumor	**negative**	14 (82.4)	12 (80.0)	17 (94.4)	43 (86.0)	0.427
	positive	3 (17.6)	3 (20.0)	1 (5.6)	7 (14.0)	
Grading, primary tumor	**G1**	3 (17.6)	2 (13.3)	2 (11.1)	7 (14.0)	0.907
	G2	9 (52.9)	8 (53.3)	12 (66.7)	29 (58.0)	
	G3	5 (29.4)	5 (33.3)	4 (22.2)	14 (28.0)	

Figure 1: Study design of the Male Study

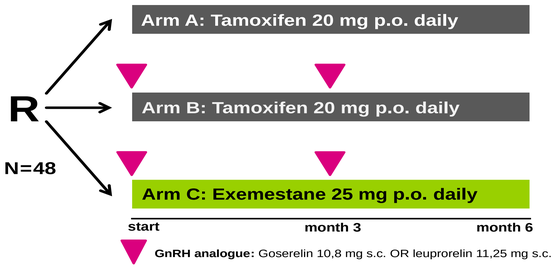
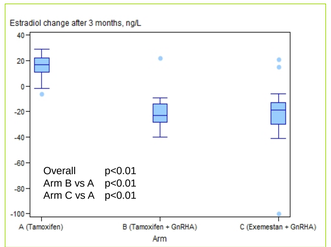


Figure 2: Changes in E2, absolute values between BL + 3 months

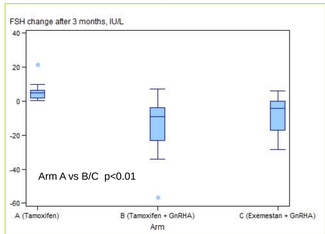


E2 in ng/l (median)	Arm A	B	C
at BL	27.0	33.0	27.5
after 3 months	45.0	5.0	7.5

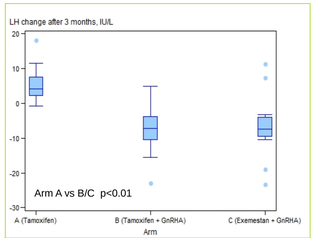
Table 3: Overview of the reported SAEs

Arm A: tamoxifen	Arm B: tamoxifen + GnRHa	Arm C: exemestane + GnRHa
a) global cardiac decompensation CTC grade 3	hyperglycemia CTC grade 4	abscess right groin CTC grade 3
b) visceral arterial ischemia CTC grade 3		

Figure 3+4: Changes in FSH and LH, absolute values between BL + 3 months

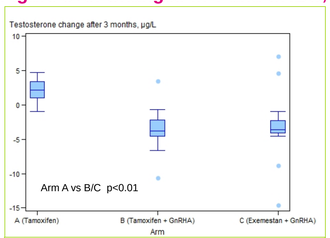


FSH in IU/l (median)	Arm A	B	C
at BL	15.6	9.7	9.5
after 3 months	16.2	1.5	6.0

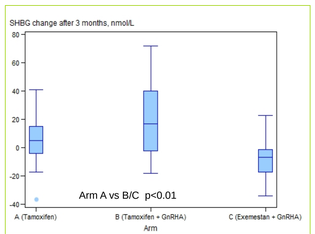


LH in IU/l (median)	Arm A	B	C
at BL	6.3	7.4	7.6
after 3 months	11.3	0.1	0.1

Figure 5+6: Changes in T and SHBG, absolute values between BL + 3 months



T in µg/l (median)	Arm A	B	C
at BL	3.7	3.9	4.0
after 3 months	6.2	0.1	0.25



SHBG in nmol/l (median)	Arm A	B	C
at BL	48.0	52.0	55.0
after 3 months	56.0	58.0	48.0

Between October 2012 and May 2017, 56 pts were randomized within 24 centers in Germany (study design is depicted in figure 1). 50 pts were fully evaluable and comprised the analysis set.
The median age was 62 years (range 37 – 83 years). The baseline (BL) characteristics were well balanced between the 3 treatment groups (Table 1).
The majority had a pT2 (52.3%), pN0 (51.1%) BC. The median BMI was 26.7 kg/m^2 (range 18.6 - 49.4). 4 serious adverse events (SAE) were reported overall, all resolved without sequel, no death was reported. Details see table 3. Figure 2 describes the changes of the E2 levels after 3 months of antihormonal therapy (primary objective). The changes in estradiol level between baseline and month 3 were significantly different between treatment arms, pairwise comparisons of arm B vs A and Arm C vs A were also significant. FSH and LH decrease in pts receiving an GnRHa and it increases in pts receiving tamoxifen (figure 3 +4).
Testosterone, FAI and DHT increase in patients in arm A by about 40% and 30% respectively and significantly decreases in arm B and C. Testosterone and SHGB values under therapy are shown in figure 5+6.

Conclusions

- We describe for the first time hormonal parameters in male BC pts receiving antihormonal therapy in a prospective, randomized setting.
- Overall, the results reflect the expected changes of the hormonal parameters.
- GnRHa + tamoxifen (arm B) or + exemestane (arm C) led to a comparable reduction of E2, FSH and LH. Decrease of LH and FSH leads to a decrease in the aromatization of androgen to estradiol[2].
- Tamoxifen increases plasma estradiol concentrations by interfering with the negative pituitary feedback mechanisms, therefore resulting in an FSH increase[1], which we also observed in our cohort. Dimitrov et al.[2] stated that AI+ GnRH may insufficiently suppress the circulating E2 as it may not have an effect on the testicular secretion of estrogen. In our cohort, the E2 suppression after 3 months in arm C was 72.7%. According to the literature[3], AI alone leads to an E2 suppresion of about 35% only.
- The three different therapy strategies were well tolerated with no safety concerns.
- Validated questioners evaluating the patients side effect have also been collected along the study and will be presented in future meeting as well as data after 6 months of antihormonal treatment.

References

1: Shapiro C et al., N Engl J Med. 2001; 344(26):1997-2008.
2: Dimitrov NV et. al., The Oncologist 2007; 12:798–807
3: Leder BZ et al., Clin Endocrinol Metab, 2004; 89:1174–1180

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