ARB: Phase II window of opportunity study of short-term preoperative treatment with enzalutamide in ER-positive and Triple-negative breast cancer

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BACKGROUND

- The androgen receptor (AR) is expressed in 60 - 80% of breast cancers (BC), with a higher incidence in ER+ve compared to ER-ve tumours.
- Enzalutamide, a potent 2nd generation anti-androgen, has demonstrated substantial preclinical anti-tumour activity in both TNBC and ER+ve BC.
- ARB was a short-term preoperative window of opportunity study that aimed to assess the anti-tumour effects of enzalutamide in ER+ve BC and TNBC.

PATIENTS AND METHODS

- Investigator-led and Sponsored, window of opportunity phase II trial conducted in the UK, Germany, Spain and the USA (NCT02676986). Recruitment took place from Sep2015 to Nov2017.
- Baseline characteristics were similar between both study arms (Table 2).

Table 2. Patient demographics and disease characteristics at baseline.

	ER+ve Cohort		TNBC, AR+ve Cohort
	Exemestane Alone (N=63)	Enzalutamide + Exemestane (N=129)	Enzalutamide Alone (N=27)
Age (years), median (range)	66 (52 – 86)	65 (49 – 87)	60 (44 - 78)
Race, n (%)			
Asian	0	2 (2)	0
Black (African)	0	1 (1)	0
Black (Caribbean)	1 (2)	0	0
Other	1 (2)	0	0
White	61 (97)	126 (98)	27 (100)
Country, n (%)			
Germany	34 (54)	68 (53)	22 (81)
Spain	7 (11)	17 (13)	N/A
United Kingdom	18 (29)	41 (32)	5 (19)
United States	4 (6)	3 (2)	N/A
Pathological tumour size (mm), median (range)	17 (10 – 60)	17 (1.5 – 130)	19 (11 – 90)
Tumour grade, n (%)			
Grade 1	7 (11)	18 (14)	1 (4)
Grade 2	46 (73)	87 (67)	12 (44)
Grade 3	10 (16)	24 (19)	14 (52)
Tumour lymph node status, n (%)			
N0	55 (87)	114 (88)	20 (74)
N1	5 (8)	13 (10)	4 (15)
N2	0	1 (1)	1 (4)
Nx	2 (3)	1 (1)	1 (4)
Not done	1 (2)	0	1 (4)
ECOG, n (%)			
0	58 (92)	119 (92)	26 (96)
1	5 (8)	10 (8)	1 (4)

SAFETY DATA

- The incidence of related AE's were consistent and as expected for the study drugs.
- Hot flushes were the only treatment related AE reported in more than 10% of the ER+ve cohort.

TNBC, AR+ve COHORT

27 patients with AR+ve, TNBC were recruited (Fig 1) .

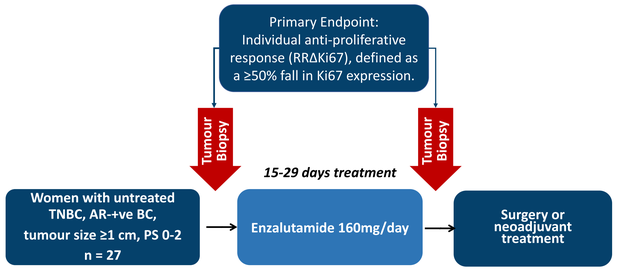

Fig 1: TNBC, AR+ve Cohort Trial Schema.

- AR+ve, TNBC evaluable patients were defined as those who received at least 13 days of treatment and had pre- and post-treatment samples.
- The geometric mean post-treatment % reduction of Ki67 was 8% (95% CI, -8%-21%). Ki67-response was 4.8% *(Fig 2).*

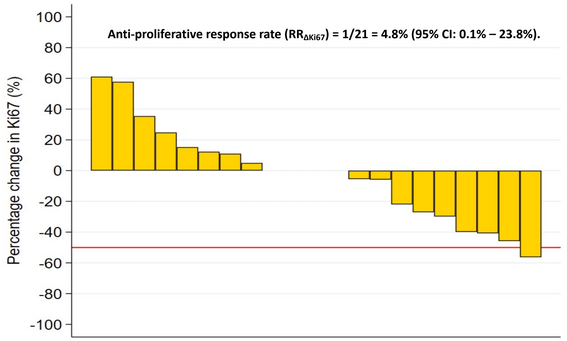

Fig 2. Waterfall plot of individual relative percentage changes in tumour-cell proliferation (Ki67 expression) from baseline to end of treatment. A positive change denotes an increase in Ki67 over time and a negative change denotes a decrease in Ki67 over time. 4 patients had no change in Ki67 over time. A reference line has been added for anti-proliferative response rate (RRΔKi67) i.e. a ≥50% fall in Ki67 expression over the course of study treatment.

ER+ve COHORT

194 patients with newly diagnosed, untreated ER+ve, invasive primary breast cancer were recruited (Fig 3).

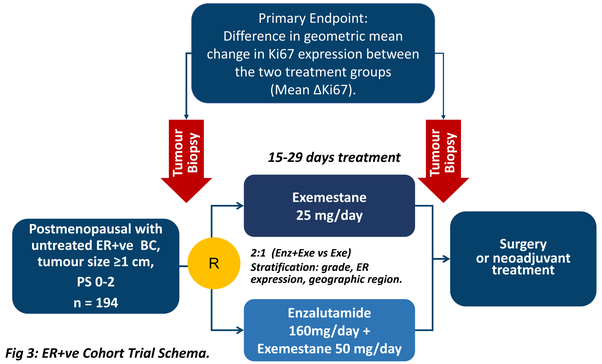

Fig 3: ER+ve Cohort Trial Schema.

- ER+ve evaluable patients were defined as those who received at least 15 days of treatment and had pre- and post-treatment samples.
- The geometric mean post-treatment percentage reduction of Ki67 was 56% (95% CI, 47%-63%) for exe alone and 60% (95% CI, 53%-66%) for enz+exe. Ki67-response was 54.2% for exe alone and 63.4% for enz+exe (one-sided p-value=0.19) *(Fig 4).*

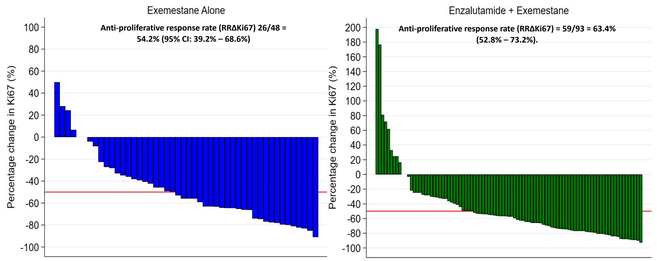

Fig 4. Waterfall plot of individual relative percentage changes in tumour-cell proliferation (Ki67 expression) from baseline to end of treatment. A positive change denotes an increase in Ki67 over time and a negative change denotes a decrease in Ki67 over time. 4 patients (2 in the Exe arm and 2 in the Enz + Exe arm) had no change in Ki67 over time. A reference line has been added for anti-proliferative response rate (RRΔKi67) i.e. a ≥50% fall in Ki67 expression over the course of study treatment.

- Planned sub analyses showed a significant interaction of response to enz+exe with molecular subtype.
- Patients with LumA tumours had a higher Ki67 response with enz+exe compared to exe alone (64% vs 38%, one-sided p-value=0.03) *(Fig. 5a).*
- Ki67 response was similar for both treatments for LumB tumours (enz+exe, 63%; exe alone, 71%, one-sided p-value=0.36) *(Fig. 5b).*

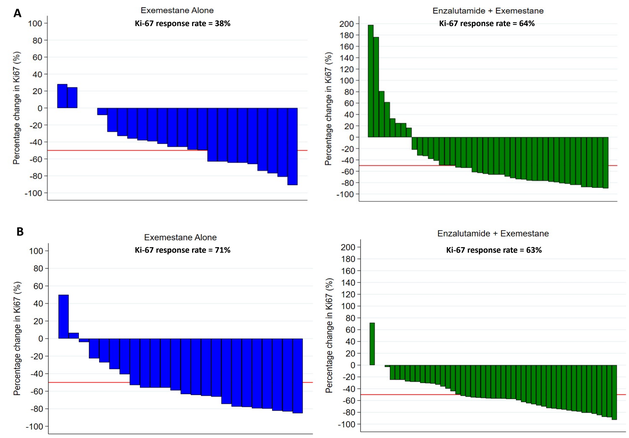

Fig 5. Waterfall plot of individual relative percentage changes in tumour-cell proliferation (Ki67 expression) from baseline to end of treatment ER+ cohort patients with Luminal A disease (3a) and Luminal B disease (3b). Luminal A was defined as ER+ve, HER2 –ve and pre-treatment Ki67 expression <14%. A positive change denotes an increase in Ki67 over time and a negative change denotes a decrease in Ki67 over time. A reference line has been added for anti-proliferative response rate (RRΔKi67) i.e. a ≥50% fall in Ki67 expression over the course of study treatment.

CONCLUSIONS

- No difference was seen overall in the inhibition of Ki67 expression after treatment with enzalutamide.
- Subgroup analysis showed a possible response in Luminal A patients.

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