ISRCTN15621797

PIONEER results summary

15 October 2024

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Trial Identification and Report Information	
Title	Randomised Phase II clinical trial PIONEER- A Pre-operative wIndOw study of letrozole plus PR agonist (Megestrol Acetate) versus letrozole aloNE in post-menopausal patients with ER-positive breast cancer
Final Protocol version:	Version 9.0, 28Mar2022
Date of End of Trial	16th of November 2023
Chief Investigator:	Dr Richard Baird
REC Ref no.:	17/NE/0113
ISRCTN Number:	ISRCTN15621797
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Study design

Introduction:

Around 75% of breast cancers are defined and driven by Oestrogen receptor alpha (ERα) transcriptional activity. A number of established endocrine treatments already exist, including Selective Oestrogen Receptor Modulators (SERMs) such as tamoxifen, Selective Oestrogen Receptor Down regulators (SERDs) such as fulvestrant, and Aromatase inhibitors (AIs) such as Letrozole, anastrozole (both non-steroidal) and exemestane (steroidal). However, clinical outcomes vary considerably, and a proportion of women with early breast cancer driven by ERα transcriptional activity develop drug resistance, and relapse with incurable, metastatic disease. There is an urgent need for better treatment strategies.

Rationale for the trial:

In 2015, the Carroll laboratory (Cambridge Institute, Cancer Research UK) has published preclinical findings exploring ER function in breast cancer, providing new insights into progestogen action and functional 'cross-talk' between ER and PR in breast cancer.

These preclinical discoveries have shown that the progesterone receptor (PR) activity is not simply a passive consequence of a functional oestrogen receptor (ER). PR interacts directly with ER, and modulation of PR function (eg. with a PR agonist) reprograms which DNA sites ER binds to, and consequently changes the ER transcriptional program and overall function. Hence the addition of a PR agonist can modify how breast cancer cells respond to anti-oestrogen therapy, with a potentially beneficial effect; and *In vivo* xenograft experiments shown that the addition of a PR agonist enhanced the anti-proliferative effects of anti-oestrogens.

Therefore, the combination of a PR agonist (eg. megestrol acetate / Megace) with an anti-oestrogen (eg. letrozole) might have better clinical efficacy than letrozole alone.

Furthermore, there are existing clinical data which show that low-dose Megace can help control the side effects from anti-oestrogen therapy, including intolerable hot flashes. This provides a strong second rationale to test this combination in the clinic since at the very least the addition of Megace should improve the quality of life for patients taking adjuvant anti-oestrogens for many years after their breast cancer surgery. The addition of Megace may also help prevent patients from stopping their adjuvant anti-oestrogen therapy prematurely - this in itself might also improve clinical outcomes.

Synopsis:

The PIONEER trial is a three arm, open-label, multicentre, randomised, window of opportunity, phase II trial which evaluates the effects of 15 days (+≤ 4 days) preoperative therapy with Letrozole, or Letrozole plus low dose Megestrol acetate (40mg), or Letrozole plus high dose Megestrol acetate (160mg) in postmenopausal women with newly diagnosed, ER-positive, HER2-negative, invasive primary breast cancer of at least 1 cm size.

Trial Design:

A three-arm, open label, multi-centre randomised phase II pre-surgical window trial.

Sample size:

N = 189 evaluable patients

Procedures and Assessment

- Screening & Enrolment
- Baseline
- Treatment period

Study duration

15 days (+ ≤4 days) of single agent or combined endocrine therapy followed by tumour excision and/or core biopsy.

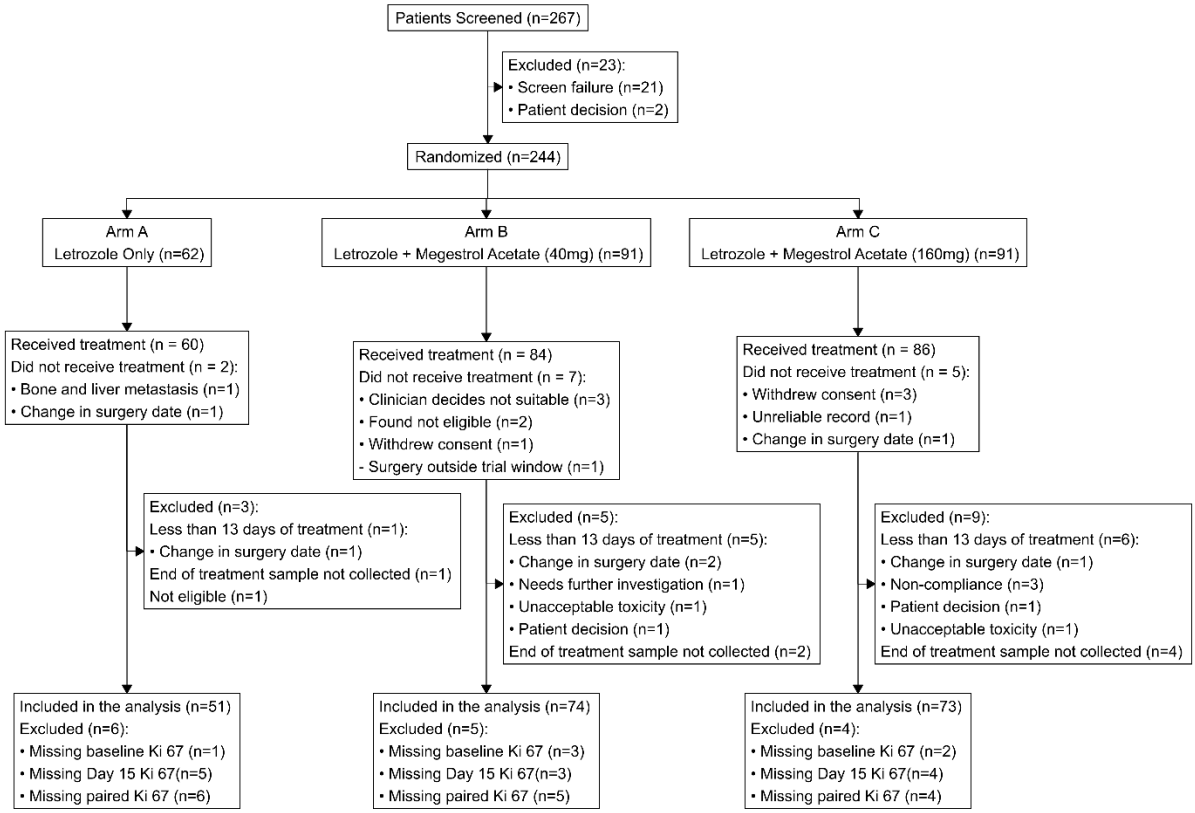
Planned recruitment:

- All patient: 189 evaluable patients
- Patients with PR positive breast cancer: 149

Actual recruitment:

- All patients: 198 evaluable patients
- Patients with PR positive breast cancer: 175

Participant Flow



Baseline Characteristics

Table 1. Baseline characteristics of per-protocol population (n = 198)

	Arm A (N=51)	Arm B (N=74)	Arm C (N=73)	Arm B+C (N=147)
Age, median (IQR)	67.2 (10.3)	67.9 (12.1)	68.4 (11.0)	68.1 (11.9)
ECOG performance status				
0	43 (84%)	66 (89%)	60 (82%)	126 (86%)
1	7 (14%)	7 (9%)	12 (16%)	19 (13%)
2	1 (2%)	1 (1%)	1 (1%)	2 (1%)
Histological grade				
1	5 (10%)	9 (12%)	4 (5%)	13 (9%)
2	32 (63%)	52 (70%)	56 (77%)	108 (73%)
3	14 (27%)	13 (18%)	13 (18%)	26 (18%)
Breast tumour type				
Ductal	38 (75%)	60 (81%)	51 (70%)	111 (76%)
Lobular	10 (20%)	9 (12%)	14 (19%)	23 (16%)
Other	3 (6%)	5 (7%)	8 (11%)	13 (9%)
Estrogen Receptor ALLRED score				
3-6	1 (2%)	1 (1%)	2 (3%)	3 (2%)
7-8	50 (98%)	73 (99%)	71 (97%)	144 (98%)
T stage				
1C	24 (47%)	48 (65%)	46 (63%)	94 (64%)
2	24 (47%)	22 (30%)	26 (36%)	48 (33%)
3	3 (6%)	4 (5%)	1 (1%)	5 (3%)
N stage				

0	45 (88%)	61 (82%)	65 (89%)	126 (86%)
1	4 (8%)	11 (15%)	5 (7%)	16 (11%)
2	1 (2%)	1 (1%)	1 (1%)	2 (1%)
3	-	1 (1%)	1 (1%)	2 (1%)
X	1 (2%)	-	1 (1%)	1 (1%)
Progesterone Receptor ALLRED score*				
0-3	10 (20%)	14 (19%)	20 (28%)	34 (23%)
4-6	11 (22%)	12 (16%)	12 (17%)	24 (17%)
7-8	30 (59%)	47 (64%)	40 (56%)	87 (60%)
PR status				
Negative	7 (14%)	5 (7%)	10 (14%)	15 (10%)
Positive (1%+)	44 (86%)	69 (93%)	63 (86%)	132 (90%)
AR status†				
Negative	1 (2%)		2 (3%)	2 (1%)
Positive (1%+)	48 (98%)	73 (100%)	71 (97%)	144 (99%)
Ki67 status				
< 10%	10 (20%)	5 (7%)	19 (26%)	24 (16%)
10%+	41 (80%)	69 (93%)	54 (74%)	123 (84%)
Adjusted Ki67‡	18.9 (2.0)	20.2 (1.6)	18.1 (2.0)	19.1 (1.8)

* Two patients, 1 in Arm B and 1 in Arm C, had missing PR ALLRED score.

† Three patients, 2 in Arm A and 1 in Arm B, had missing AR status.

‡ Geometric mean and standard deviation were reported.

Outcome Measures

Table 2. Antiproliferative Response to Treatment

	Arm A	Arm B + Arm C	Risk (95% CI)	p
Ki-67 EOT/Baseline	0.29 (0.23, 0.36)	0.20 (0.17, 0.24)	0.71 (0.54, 0.93)	0.013
Ki67 EOT	5.42 (4.10, 7.15)	3.86 (3.23, 4.62)	0.71 (0.51, 0.99)	0.043
AURKA EOT/Baseline	0.11 (0.05, 0.25)	0.01 (0.01, 0.03)	0.13 (0.05, 0.36)	<0.001
EOT Ki67 < 10% †	64.7 (50.1, 77.6)	79.6 (72.2, 85.8)	0.81 (0.64, 0.99)	0.033

NOTE: Ki67/AURKA EOT/baseline are the geometric means of proportional change (EOT/baseline). p-values are based on t-test of the geometric means. 95% CI were reported for the ratio of two geometric means. Ki67 EOT is the geometric mean of EOT Ki67 values, presented on the original scale. † Proportion of patients and 95% CI using Clopper-Pearson method. The ratio of the proportions and its 95% CI based on 1000 bootstrap are reported for the comparison.

Adverse Events

Table 3. AE terms by grade and treatment arm experienced by at least 2 participants (Population: Safety (n = 230))

AECLEANTERM	CTCAE Grade (1-5)	Arm A	Arm B	Arm C
Fatigue	1	6 (10.0%)	16 (19.0%)	12 (14.0%)
Fatigue	2	1 (1.7%)	1 (1.2%)	3 (3.5%)
Hot flashes	1	9 (15.0%)	10 (11.9%)	9 (10.5%)
Hot flashes	2	0 (0%)	1 (1.2%)	2 (2.3%)
Nausea	1	7 (11.7%)	8 (9.5%)	10 (11.6%)
Nausea	2	0 (0%)	1 (1.2%)	1 (1.2%)
Headache	1	6 (10.0%)	6 (7.1%)	6 (7.0%)
Headache	2	1 (1.7%)	1 (1.2%)	0 (0%)
Arthralgia	1	4 (6.7%)	7 (8.3%)	5 (5.8%)
Insomnia	1	3 (5.0%)	7 (8.3%)	3 (3.5%)
Dry mouth	1	0 (0%)	8 (9.5%)	4 (4.7%)
Dizziness	1	2 (3.3%)	4 (4.8%)	5 (5.8%)
Diarrhea	1	2 (3.3%)	2 (2.4%)	5 (5.8%)
Seroma	2	0 (0%)	3 (3.6%)	4 (4.7%)
Breast pain	1	3 (5.0%)	1 (1.2%)	3 (3.5%)
Dyspnea	1	0 (0%)	2 (2.4%)	5 (5.8%)
Constipation	1	1 (1.7%)	2 (2.4%)	2 (2.3%)
Vaginal hemorrhage	1	0 (0%)	3 (3.6%)	1 (1.2%)
Vaginal hemorrhage	2	0 (0%)	0 (0%)	2 (2.3%)
Hyperhidrosis	1	1 (1.7%)	2 (2.4%)	2 (2.3%)
Myalgia	1	1 (1.7%)	2 (2.4%)	1 (1.2%)
Pain in extremity	1	2 (3.3%)	2 (2.4%)	1 (1.2%)
Rash maculo-papular	1	2 (3.3%)	1 (1.2%)	1 (1.2%)
Hypertension	3	0 (0%)	0 (0%)	3 (3.5%)
Bloating	1	3 (5.0%)	0 (0%)	1 (1.2%)
Dysgeusia	1	3 (5.0%)	1 (1.2%)	0 (0%)
Alopecia	1	0 (0%)	2 (2.4%)	2 (2.3%)
Depression	1	0 (0%)	2 (2.4%)	1 (1.2%)
Metabolism and nutrition disorders - other, hyperphagia	1	0 (0%)	3 (3.6%)	1 (1.2%)

AECLEANTERM	CTCAE Grade (1-5)	Arm A	Arm B	Arm C
Urinary tract infection	2	0 (0%)	1 (1.2%)	2 (2.3%)
Back pain	1	2 (3.3%)	0 (0%)	0 (0%)
Cough	1	1 (1.7%)	1 (1.2%)	1 (1.2%)
Edema limbs	1	1 (1.7%)	1 (1.2%)	0 (0%)
Irritability	1	2 (3.3%)	0 (0%)	1 (1.2%)
Oral pain	1	1 (1.7%)	0 (0%)	2 (2.3%)
Pain	1	1 (1.7%)	1 (1.2%)	1 (1.2%)
Paresthesia	1	1 (1.7%)	2 (2.4%)	0 (0%)
Abdominal pain	1	0 (0%)	3 (3.6%)	0 (0%)
Epistaxis	1	0 (0%)	2 (2.4%)	1 (1.2%)
Urinary frequency	1	0 (0%)	1 (1.2%)	2 (2.3%)
Pruritus	1	0 (0%)	0 (0%)	3 (3.5%)
Vaginal dryness	2	1 (1.7%)	1 (1.2%)	0 (0%)
Flatulence	1	1 (1.7%)	0 (0%)	1 (1.2%)
Gastroesophageal reflux disease	1	1 (1.7%)	1 (1.2%)	0 (0%)
Hyperphagia	1	1 (1.7%)	0 (0%)	1 (1.2%)
Lung infection	2	1 (1.7%)	0 (0%)	1 (1.2%)
Wound infection	2	1 (1.7%)	1 (1.2%)	0 (0%)
Dyspepsia	2	0 (0%)	1 (1.2%)	1 (1.2%)
Thromboembolic event	2	0 (0%)	1 (1.2%)	1 (1.2%)