Concept: A randomised multicentre trial of first line chemotherapy comparing three weekly cabazitaxel versus weekly paclitaxel in HER2 negative metastatic breast cancer[☆],[☆☆]

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ABSTRACT

Background: Paclitaxel is commonly used as first-line chemotherapy for HER2-negative metastatic breast cancer (MBC) patients. However, with response rates of 21.5–53.7% and significant risk of peripheral neuropathy, there is need for better chemotherapy.

Patients and methods: This open-label phase II/III trial randomised HER2-negative MBC patients 1:1 to either 6 cycles of three-weekly cabazitaxel (25 mg/m^2), or, weekly paclitaxel (80 mg/m^2) over 18 weeks.

The primary endpoint was progression free survival (PFS). Secondary endpoints included objective response rate (ORR), time to response (TTR), overall survival (OS), safety and tolerability and quality of life (QoL).

Results: 158 patients were recruited. Comparing cabazitaxel to paclitaxel, median PFS was 6.7 vs 5.8 months (HR 0.87; 80%CI 0.70–1.08, P = 0.4). There was no difference in median OS (20.6 vs 18.2 months, HR 1.00; 95%CI 0.69–1.45, P = 0.99), ORR (41.8% vs 36.7%) or TTR (HR 1.09; 95%CI 0.68–1.75, P = 0.7).

Grade ≥3 adverse events occurred in 41.8% on cabazitaxel and 46.8% on paclitaxel; the most common being neutropenia (16.5%) and febrile neutropenia (12.7%) cabazitaxel and neutropenia (8.9%) and lung infection (7.6%) paclitaxel. Peripheral neuropathy of any grade occurred in 54.5% paclitaxel vs 16.5% cabazitaxel. Mean EQ-5D-5L single index utility score (+0.05; 95%CI 0.004–0.09, P = 0.03) and visual analogue scale score (+7.7; 95%CI 3.1–12.3, P = 0.001) were higher in cabazitaxel vs paclitaxel.

Conclusions: Three-weekly cabazitaxel in HER2-negative MBC does not significantly improve PFS compared to weekly paclitaxel, although it has a lower risk of peripheral neuropathy with better patient reported QoL outcomes. It is well tolerated and requires fewer hospital visits.

1. Introduction

More than two million cases of breast cancer were diagnosed worldwide in 2020 making it one of the most prevalent cancers globally [1]. Metastatic breast cancer (MBC) remains an incurable disease and systemic anti-cancer therapy (SACT) has the aim of life-prolongation and palliation.

For MBC patients with Oestrogen receptor (ER) positive disease, endocrine therapy, with or without the addition of targeted agents, is recommended as first line SACT [2,3]. However, for patients with endocrine resistance or significant symptoms from visceral disease, cytotoxic chemotherapy remains first line management. Similarly, MBC patients with triple negative (and PDL-1 negative) disease are recommended to commence sequential, single-agent cytotoxic chemotherapy in the first line setting. Thus, these are the patients most likely to benefit from advances in novel cytotoxic agents.

Anthracyclines or taxanes are frequently used in the first line setting for these patients. Paclitaxel is increasingly used, particularly if anthracyclines or docetaxel have been used in the neo-adjuvant or adjuvant setting [2–4].

The efficacy and tolerability of weekly paclitaxel, 80 mg/m^2, for MBC has been assessed in numerous studies, with response rates between 21.5%–53.7%.[5–14] These response rates are better than response rates seen with the three-weekly dosing regimen [5–8]. However, the weekly regimen has higher incidence of grade 3 peripheral neuropathy and an increased time burden on patients and resources [5].

Observational studies suggest that response rates in patients with taxane re-challenge remain relatively high [15]. However, for patients with a short disease free interval before progression, this may not be the case. Subsequent lines of alternative chemotherapy can lead to prolonged disease response in some patients, although prognosis is significantly poorer in patients with taxane-resistant disease [16–18].

Thus, there is an unmet need for an alternative first line SACT for patients with MBC, particularly for those who have had previous taxane exposure.

Cabazitaxel is a recent taxoid agent which has shown *in vitro* and *in vivo* activity in cell lines and tumours which are resistant to docetaxel and paclitaxel [19]. Cabazitaxel in combination with prednisone or prednisolone is indicated for the treatment of adult patients with metastatic castration resistant prostate cancer previously treated with a docetaxel-containing regimen [20].

Two phase II trials have demonstrated promising results for the use of cabazitaxel in MBC patients previously treated with taxanes, and specifically in patients who had developed taxane resistance [21,22]. Overall response (OR) and stable disease (SD) rates were 13% and 44%, respectively, in a group of 61 taxane resistant patients being treated in the second or third line setting and 22.6% and 31%, respectively, in 81 patients treated in the second line setting who had previous taxane exposure [21,22]. Trials which combined cabazitaxel with other cytotoxic agents have demonstrated intolerable toxicties [23,24].

This randomised, open-label phase II/III study aimed to compare weekly paclitaxel versus three-weekly cabazitaxel in the first line setting for patients with HER 2-negative MBC, where weekly paclitaxel (considered standard of care) would have been first line treatment of choice.

2. Methods

2.1. Patient characteristics

Eligible patients were randomly assigned (1:1) to cabazitaxel or paclitaxel. Patients were stratified according to previous chemotherapy in adjuvant setting (docetaxel vs no docetaxel); in the UK, National Institute for Health and Care excellence (NICE) guidance suggests docetaxel can be given as neoadjuvant or adjuvant chemotherapy (paclitaxel could not be used in this setting) therefore no patients would have had had previous paclitaxel exposure. Patients were also stratified by tumour subtype (ER positive or negative; ER positive defined at biopsy as Allred Score of 5/8, 6/8, 7/8 or 8/8).

The main inclusion criteria were: histologically confirmed HER2-negative MBC, fit to receive first line cytotoxic chemotherapy, ECOG performance status 0 or 1, life expectancy of >6 months, measurable disease as per RECIST 1.1 by CT/MRI scan within 6 weeks of the first dose of chemotherapy, adequate liver, renal and bone marrow function.

Patients were excluded if they had previously received paclitaxel chemotherapy or concurrent palliative radiotherapy to identified target lesions or concurrent palliative radiotherapy given on the same day as chemotherapy. Previous hormone treatment and treatment with CDK4-6 inhibitors in the first line setting was allowed, if received previously in a trial or after NICE approval.

Other exclusion criteria were symptomatic brain metastases, grade ≥2 peripheral motor and/or sensory neuropathy, grade ≥2 oral mucositis or a history of severe hypersensitivity reaction (≥grade 3) to taxanes or to polysorbate 80-containing drugs.

The study was approved by local Research & Development departments, national Research Ethics Committee and the Medicine and Healthcare products Regulatory Agency (MHRA).

2.2. Regimens

Patients on cabazitaxel received a 1 h infusion at 25 mg/m^2 every 21 days (capped at body surface area of 2.25 m [2]). Chlorphenamine 10 mg, dexamethasone 8 mg and ranitidine 50 mg premedication was given 30 min prior to infusion to mitigate allergic reactions. A total of 6 cycles were planned. Primary prophylaxis with Granulocyte Colony Stimulating Factor (G-CSF) was mandatory for all cabazitaxel patients.

Patients assigned to paclitaxel received a 1 h infusion of 80 mg/m^2 on a weekly basis (D1, 8, 15 on each 21 day cycle), receiving up to 18 infusions in total, administered according to standard procedures at each site.

One dose reduction for cabazitaxel (20 mg/m^2) or Paclitaxel (60 mg/m^2) was permitted due to toxicity, unless by special permission from the chief investigator. Treatment delays of up to 3 weeks were allowed, to recover from acute toxicity.

Once trial treatment ended, patients received standard of care and follow-up at site, including resuming hormonal therapies and/or further systemic therapies, as per treating physician's decision.

2.3. Assessments

Response to disease was assessed on CT/MRI scans using RECIST 1.1 criteria. The primary end point was progression free survival (PFS), defined as the time from randomisation to the date of progressive disease (PD) or death from any cause, whichever came first. Patients who did not progress or die were censored at the date of last valid tumour assessment. Secondary end points were clinical benefit rate (CBR), defined as SD rate + partial response (PR) rate + complete response (CR) rate (according to RECIST 1.1 recorded from the start of treatment to completion of 6 cycles); OR rate (defined as CR and PR recorded from the start of treatment to completion of 6 cycles); Time to response (TTR), time from randomisation to the CT scan showing first and best response; Overall survival (OS), time from randomisation to the date of death from any cause; QoL; Time to next cytotoxic chemotherapy treatment or death from any cause.

RECIST response assessments were performed before cycles 3 and 5, or at equivalent times points if the patient stopped treatment early for reasons other than PD, and at the end of treatment (EoT) with further CT scans arranged at each follow-up visit until PD. Radiological assessment was made by investigators at local institutions. Common Terminology Criteria for Adverse Events (CTCAE) v.4.03 was used to grade toxicity.

2.4. QoL

Patients were asked to self-complete the EQ-5D-5L and FACT-B questionnaires during clinic visits at baseline, prior to cycles 3, 5 and at EoT. (EQ-5D-5L is a standardised, validated non-disease specific tool for evaluating health states [25,26]. The FACT-B questionnaire is reliable and validated for MBC patients with a focus on emotional well-being [27]).

2.5. Statistical analyses

Sample size was calculated based on the assumption that there would be an improvement in median PFS from 5.5 months in the paclitaxel arm to 8.5 months in the cabazitaxel arm corresponding to a hazard ratio (HR) of 0.65.127 PFS events were required to detect this difference with 85% power at a one-sided 10% significance level. To achieve this recruitment was set at 160 patients (80 in each arm).

Data were analysed on an intention-to-treat basis. Response rates were compared using chi-squared tests. The Kaplan-Meier method and log-rank test stratified by previous chemotherapy in adjuvant setting (docetaxel vs No docetaxel) and subtype tumour (ER positive or negative) as specified at the time of randomisation were used to analyse survival outcomes. QoL summary measures were assessed across all time points using mixed-effects linear regression models with adjustment for baseline values.

A post-hoc analysis looked at the chemotherapy-free interval from the date of trial treatment end until start of next cytotoxic therapy or death.

3. Results

3.1. Patient characteristics

Between January 2015 and March 2020, 159 patients from 14 UK centres were recruited into the study with 158 included in the final analysis. One patient was registered in error and excluded. Baseline characteristics are shown in Table 1. Median [range] follow-up times for patients in the cabazitaxel and paclitaxel arms were 30.2 [9.4 to 33.9] months and 32.9 [1.4 to 62.4] months, respectively.

Median number of previous lines of treatment is 1 (range 0–6), with cabazitaxel: 1 (0–6) and paclitaxel: 1 (0–6). In ER positive MBC, median lines of endocrine treatment is 0 (range 0–5), with cabazitaxel 0 (0–5) and paclitaxel 0 (0–4) with some endocrine therapies being repeated. In this patient group, 8 patients (4 cabazitaxel and 4 paclitaxel) had previously received exemestane + everolimus whilst 21 (12 cabazitaxel, 9 paclitaxel) are reported to have had exemestane and/or everolimus.

20patients (9 cabazitaxel, 11 paclitaxel) received CDK 4/6 inhibitors prior to the trial.

Table 1
Baseline characteristics.

	Cabazitaxel	Paclitaxel	Total
	N = 79	N = 79	N = 158
Median (range)			
Age, years	56 (34–81)	61 (34–79)	58 (34–81)
BMI, kg/m^2	26 (17–38)	28 (18–43)	27 (17–43)
Number of patients (%)			
ECOG			
0	53 (67.1)	44 (55.7)	97 (61.4)
1	26 (32.9)	35 (44.3)	61 (38.6)
ER status			
Negative	21 (26.6)	20 (25.3)	41 (26.0)
Positive	58 (73.4)	59 (74.7)	117 (74.1)
Previous docetaxel			
No	46 (58.2)	52 (65.8)	98 (62.0)
Yes	33 (41.8)	27 (34.2)	60 (38.0)
Presence of liver metastases (target/non-target hepatic lesion at baseline)			
No	33 (41.8)	34 (43.0)	67 (42.4)
Yes	46 (58.2)	45 (57.0)	91 (57.6)
Previous treatment with CDK 4/6 inhibitors			
No	70 (88.6)	68 (86.0)	138 (87.3)
Yes	9 (11.4)	11 (14.0)	20 (12.7)
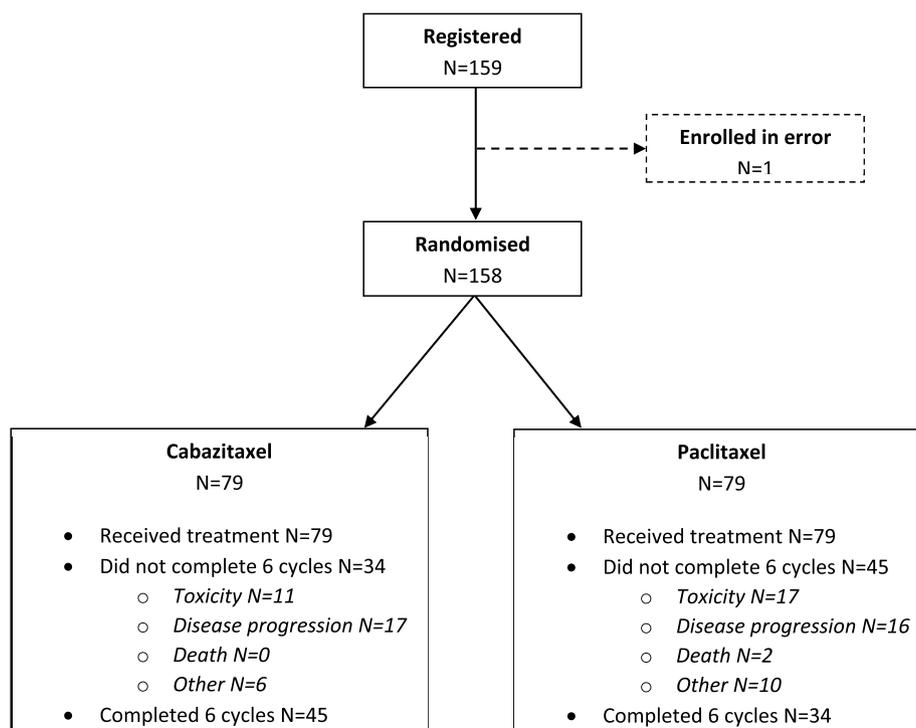
31 patients received no previous lines of treatment suggesting at least this number were de novo MBC.

3.2. Treatment

45 patients (57%) on cabazitaxel completed 6 cycles of SACT compared to 34 (43%) on paclitaxel (p = 0.08). 17 (21.5%) and 16 (20.3%) patients on paclitaxel stopped treatment due to toxicity or PD respectively, compared to 11 (13.9%) and 17 (21.5%) in the cabazitaxel arm.

More patients in the paclitaxel arm required dose modifications, with 29 (36.7%) having a dose reduction due to toxicity, compared to only 17 (21.5%) patients in the cabazitaxel arm.

3.3. Efficacy

3.3.1. Primary endpoint

74 (93.7%) patients in the cabazitaxel arm had a PFS event during the study period, median PFS 6.7 months (95% CI 5.4–7.6), compared to 75 (94.9%) in the paclitaxel arm, median PFS 5.8 months (95% CI 4.6–6.9), HR 0.87 (80% CI 0.70–1.08, p = 0.4) Fig. 1.

3.4. Secondary end-points

3.4.1. Response rates

Response rates were not significantly different between treatment arms. For cabazitaxel, the CR, PR, SD and PD rates were 0%, 41.8%, 36.7% and 21.5%, compared with 2.5%, 34.2%, 46.8% and 12.7% for paclitaxel. In the paclitaxel arm, one patient died before treatment response and 2 patients were not evaluated, as they withdrew from the study after only one cycle of treatment. CBR (CR + PR + SD) was 78.5% (95% CI 67.8–86.9) in the cabazitaxel arm compared to 83.5% (95% CI 73.5–90.9) in the paclitaxel arm (p = 0.4) and ORR (CR + PR) was 41.8% (95% CI 30.8–53.4) and 36.7% (95% CI 26.1–48.3) (p = 0.5) in the cabazitaxel and paclitaxel groups, respectively.

3.5. Time to first response and time to best response

There was no significant difference between time to first response between the two treatment arms, HR 1.09 (95% CI 0.68–1.75, p = 0.7), nor best response HR 1.10 (95% CI 0.68–1.76, p = 0.7). In responders, median time to first response was 2.7 months (95% CI 1.8–3.1) and 1.8 months (95% CI 1.5–3.0) in the cabazitaxel and paclitaxel arms, respectively.

3.6. Overall survival

Median OS was 20.6 months (95% CI 15.8–27.7) and 18.2 months (95% CI 13.1–24.1) in the cabazitaxel and paclitaxel arms, respectively, HR 1.00 (95% CI 0.69–1.45, p = 0.99). (Fig. 2).

55 (69.6%) and 56 (70.9%) patients from the cabazitaxel and paclitaxel groups, respectively, died, 51 (92.7%) and 50 (89.3%) from PD. One patient experienced a death 'probably related' to paclitaxel (death due to non-neutropenic chest sepsis).

3.7. Subgroup analysis

Women aged ≥65 had significant PFS benefit from cabazitaxel compared to paclitaxel, HR = 0.45 (95% CI 0.25–0.80, p < 0.01). However, there was no significant OS benefit for this age group. There also appeared to be an interaction with docetaxel exposure in terms of PFS, with taxane naïve patients tending to perform better on cabazitaxel compared to those with previous exposure (HR 0.70 (95%CI 0.46–1.07) vs HR 1.41 (95% CI 0.83–2.39), interaction p = 0.04, respectively).

Among ER positive patients, those with previous CDK inhibitor use had significantly worse PFS and OS than those who had not, PFS HR = 1.72 (95% CI 1.04–2.86, P = 0.04) and OS HR = 2.35 (95% CI 1.23–4.49, p = 0.01). There was no significant difference between treatment arms.

ER status made no difference to the effect of treatment for either PFS (ER positive HR 0.87 (95% CI 0.59–1.27) vs TNBC HR 1.07 (95% CI 0.57–1.99), interaction p = 0.58) or OS (ER positive HR 0.90 (95% CI 0.58–1.40) vs TNBC HR 1.39 (95% CI 0.69–2.83), interaction p = 0.31). A starting ECOG of 0 or 1 made no difference to treatment effect. Supplemental Fig. 1.

3.8. Time to next cytotoxic treatment or death

In total, 59 (74.7%) patients on cabazitaxel compared to 54 (68.4%) on paclitaxel had second line cytotoxic chemotherapy. 14 (17.7%) and 20 (25.3%) patients from each arm died before starting second line chemotherapy, respectively. Median time to start second line chemotherapy was 5.7 months (95% CI 5.1–7.6) in the cabazitaxel arm compared to 7.2 months (95% CI 5.5–8.1) in the paclitaxel arm, HR 1.10 (95% CI 0.79–1.53, p = 0.6). Capecitabine was the most common subsequent treatment in both arms. Taxane treatment as second line chemotherapy was very low, seen in 4 cabazitaxel (5.06%) and 2 paclitaxel (2.53%) patients. Time to next cytotoxic treatment or death was not significantly different between ER positive and ER negative
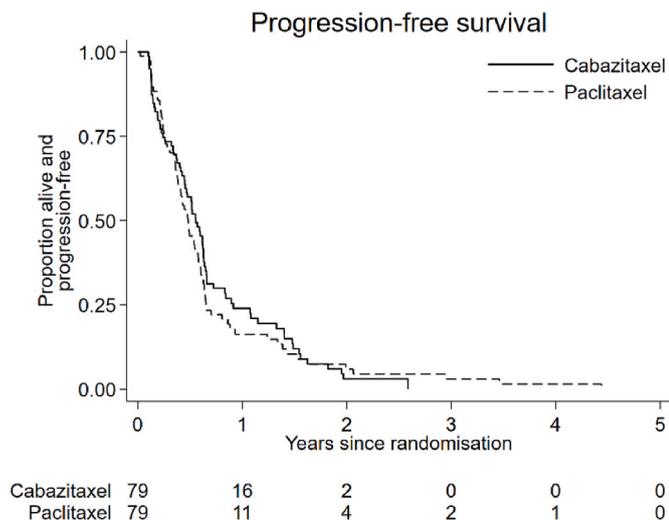
Fig. 1. Progression-free survival curves by treatment arm.

Cabazitaxel	79	16	2	0	0	0
Paclitaxel	79	11	4	2	1	0
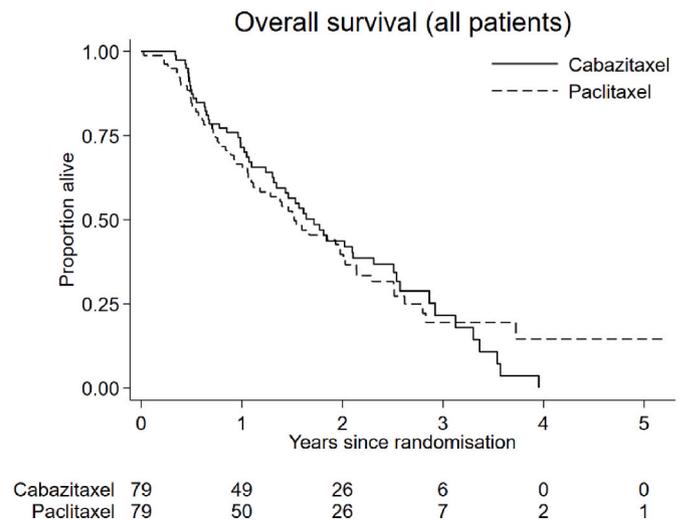
Fig. 2. Overall survival curves by treatment arm for all patients.

Cabazitaxel	79	49	26	6	0	0
Paclitaxel	79	50	26	7	2	1

Table 2

AEs based on the maximum toxicity grade for each patient. All grade ≥3 toxicities are represented, as well as any grade of toxicity occurring in 4 or more patients. All AEs occurred after the subject had started treatment until 30 days after the last dose.

Adverse event	Cabazitaxel (N = 79)		Paclitaxel (N = 79)	
	Grade 1-2	3+	Grade 1-2	3+
Blood and lymphatic system disorders	**16 (20.3)**	**12 (15.2)**	**17 (21.5)**	**3 (3.8)**
Anaemia	19 (24.1)	2 (2.5)	17 (21.5)	2 (2.5)
Febrile neutropenia		10 (12.7)		1 (1.3)
Cardiac disorders	**5 (6.3)**	**1 (1.3)**	**8 (10.1)**	**1 (1.3)**
Acute coronary syndrome				1 (1.3)
Pericardial effusion		1 (1.3)		
Sinus tachycardia	2 (2.5)		6 (7.6)	
Eye disorders	**5 (6.3)**		**7 (8.9)**	
Gastrointestinal disorders	**57 (72.2)**	**16 (20.3)**	**50 (63.3)**	**7 (8.9)**
Abdominal pain	11 (13.9)	1 (1.3)	7 (8.9)	
Constipation	30 (38.0)		23 (29.1)	
Dental caries		1 (1.3)		1 (1.3)
Diarrhoea	42 (53.2)	9 (11.4)	20 (25.3)	1 (1.3)
Dry mouth	8 (10.1)		4 (5.1)	
Dyspepsia	11 (13.9)		15 (19.0)	
Gastroesophageal reflux disease	2 (2.5)		4 (5.1)	
Mucositis oral	19 (24.1)		18 (22.8)	
Nausea	40 (50.6)	7 (8.9)	28 (35.4)	
Oral pain	2 (2.5)		2 (2.5)	1 (1.3)
Other: Diverticulitis		1 (1.3)		
Other: Mouth ulcer	1 (1.3)		1 (1.3)	1 (1.3)
Other: Perforated diverticulum				1 (1.3)
Vomiting	19 (24.1)	6 (7.6)	10 (12.7)	4 (5.1)
General disorders and administration site conditions	**54 (68.4)**	**4 (5.1)**	**61 (77.2)**	**4 (5.1)**
Edema limbs	3 (3.8)		8 (10.1)	1 (1.3)
Fatigue	46 (58.2)	2 (2.5)	46 (58.2)	
Fever	6 (7.6)	1 (1.3)	10 (12.7)	1 (1.3)
Flu like symptoms	2 (2.5)		8 (10.1)	
Infusion related reaction	13 (16.5)		7 (8.9)	
Non-cardiac chest pain			1 (1.3)	1 (1.3)
Pain	11 (13.9)	1 (1.3)	11 (13.9)	1 (1.3)
Hepatobiliary disorders	**2 (2.5)**			**1 (1.3)**
Hepatic pain	1 (1.3)			1 (1.3)
Immune system disorders	**2 (2.5)**		**2 (2.5)**	**1 (1.3)**
Allergic reaction	2 (2.5)		1 (1.3)	1 (1.3)
Infections and infestations	**19 (24.1)**	**9 (11.4)**	**22 (27.8)**	**10 (12.7)**
Device related infection		1 (1.3)		
Lung infection	2 (2.5)	4 (5.1)	4 (5.1)	6 (7.6)
Mucosal infection	1 (1.3)	1 (1.3)		
Other: Cold symptoms	4 (5.1)		1 (1.3)	
Other: Hickman line infection				1 (1.3)
Other: PICC line infection	1 (1.3)	1 (1.3)		
Other: Portacath infection				1 (1.3)
Other: Toe infection				1 (1.3)
Other: Unspecified infection		1 (1.3)		
Sepsis		2 (2.5)		1 (1.3)
Upper respiratory infection	2 (2.5)		3 (3.8)	
Urinary tract infection	8 (10.1)	1 (1.3)	5 (6.3)	
Injury, poisoning and procedural complications	**3 (3.8)**		**4 (5.1)**	**1 (1.3)**
Bruising	2 (2.5)		3 (3.8)	
Fracture				1 (1.3)
Investigations	**12 (15.2)**	**14 (17.7)**	**17 (21.5)**	**10 (12.7)**
Alanine aminotransferase increased	2 (2.5)		7 (8.9)	
Blood bilirubin increased		1 (1.3)	1 (1.3)	2 (2.5)
GGT increased	1 (1.3)	1 (1.3)		
Neutrophil count decreased	2 (2.5)	13 (16.5)	7 (8.9)	7 (8.9)
Other: Neutrophil count increased	1 (1.3)			1 (1.3)
Other: Pancytopenic				1 (1.3)
White blood cell decreased			2 (2.5)	1 (1.3)
Metabolism and nutrition disorders	**30 (38.0)**	**4 (5.1)**	**19 (24.1)**	**1 (1.3)**
Anorexia	21 (26.6)		10 (12.7)	
Hyperkalaemia	2 (2.5)			1 (1.3)
Hypoalbuminaemia	8 (10.1)		4 (5.1)	
Hypocalcaemia	3 (3.8)		5 (6.3)	
Hypokalaemia	3 (3.8)		2 (2.5)	
Hypomagnesemia	3 (3.8)		3 (3.8)	
Hyponatremia		4 (5.1)		
Musculoskeletal and connective tissue disorders	**25 (31.6)**		**28 (35.4)**	**2 (2.5)**
Arthralgia	4 (5.1)		7 (8.9)	
Back pain	11 (13.9)		5 (6.3)	
Bone pain	3 (3.8)		2 (2.5)	
Myalgia	7 (8.9)		9 (11.4)	

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Table 2 (*continued*)

Adverse event	Cabazitaxel (N = 79)		Paclitaxel (N = 79)	
	Grade 1-2	3+	Grade 1-2	3+
Pain in extremity	7 (8.9)		9 (11.4)	2 (2.5)
Nervous system disorders	**40 (50.6)**	**2 (2.5)**	**49 (62.0)**	**7 (8.9)**
Dizziness	3 (3.8)		9 (11.4)	
Dysgeusia	20 (25.3)		17 (21.5)	
Headache	13 (16.5)		16 (20.3)	2 (2.5)
Lethargy	4 (5.1)		2 (2.5)	
Paresthesia	3 (3.8)		7 (8.9)	
Peripheral motor neuropathy	1 (1.3)		2 (2.5)	1 (1.3)
Peripheral sensory neuropathy	13 (16.5)		39 (49.4)	4 (5.1)
Seizure		1 (1.3)		
Vasovagal reaction		1 (1.3)		
Psychiatric disorders	**9 (11.4)**		**14 (17.7)**	**1 (1.3)**
Depression	2 (2.5)		4 (5.1)	
Insomnia	2 (2.5)		11 (13.9)	1 (1.3)
Renal and urinary disorders	**5 (6.3)**	**1 (1.3)**	**4 (5.1)**	
Acute kidney injury	1 (1.3)	1 (1.3)		
Urinary tract obstruction		1 (1.3)		
Respiratory, thoracic and mediastinal disorders	**28 (35.4)**	**2 (2.5)**	**37 (46.8)**	**5 (6.3)**
Cough	11 (13.9)		13 (16.5)	
Dyspnoea	15 (19.0)		13 (16.5)	4 (5.1)
Epistaxis	6 (7.6)	1 (1.3)	22 (27.8)	
Pleural effusion		1 (1.3)		
Pneumonitis				1 (1.3)
Sore throat	6 (7.6)		5 (6.3)	
Skin and subcutaneous tissue disorders	**30 (38.0)**		**43 (54.4)**	**1 (1.3)**
Alopecia	21 (26.6)		33 (41.8)	
Dry skin	2 (2.5)		5 (6.3)	
Nail discolouration			6 (7.6)	
Nail loss	2 (2.5)		3 (3.8)	
Other: Ankle blister				1 (1.3)
Other: Red sore extremity				1 (1.3)
Rash maculo-papular	2 (2.5)		14 (17.7)	
Surgical and medical procedures		**1 (1.3)**	**1 (1.3)**	
Other: Tooth extraction		1 (1.3)		
Vascular disorders	**14 (17.7)**	**2 (2.5)**	**8 (10.1)**	**4 (5.1)**
Flushing	8 (10.1)		1 (1.3)	
Hot flashes	1 (1.3)		4 (5.1)	
Hypotension	2 (2.5)	1 (1.3)	1 (1.3)	1 (1.3)
Other: Jugular vein mass ? tumour thrombus		1 (1.3)		
Thromboembolic event			1 (1.3)	3 (3.8)
Any toxicity (regardless of incidence)	**45 (57.0)**	**33 (41.8)**	**41 (51.9)**	**37 (46.8)**

subgroups (HR 1.02 (95% CI 0.70–1.49, p = 0.9).

In post-hoc analysis, the chemotherapy-free interval shows a median of 2.0 months for the cabazitaxel (95% CI 1.4–3.5) and 3.0 months for the paclitaxel arms (95% CI 2.1–3.9), HR = 1.08 (95% CI 0.78–1.50), p = 0.6. The shorter time on paclitaxel treatment therefore does not significantly outweigh the PFS benefit of cabazitaxel. ER status had no effect on this conclusion ER positive: HR = 1.11 (95% CI 0.76–1.62), p = 0.6; TNBC: HR = 1.10 (95% CI 0.57–2.14), p = 0.8.

3.9. Safety

A summary of grade 1-2 adverse events (AEs) affecting 4 or more participants and all grade ≥3 AEs can be seen in Table 2.

Highest grade toxicity of ≥3 was experienced by 33 (41.8%) patients on cabazitaxel and 37 (46.8%) patients on paclitaxel.

Neutropenia was the most common grade ≥3 toxicity in both treatment arms with rates of 16.5% in patients on cabazitaxel and 8.9% in those on paclitaxel. Febrile neutropenia and diarrhoea were the next most prevalent grade ≥3 toxicities in the cabazitaxel arm, with rates of 12.7% and 11.4%, respectively, compared to 1.3% for both in the paclitaxel arm. In the paclitaxel arm, lung infection and peripheral sensory neuropathy rates were the next most common, with rates of 7.6% and 5.1%, respectively, compared to 5.1% and 0% in the cabazitaxel arm.

Diarrhoea of any grade was reported by 64.6% of patients on cabazitaxel, compared to 26.6% of patients on paclitaxel (P < 0.001). 59.5% of patients on cabazitaxel reported nausea of any grade, compared to 35.4% of patients on paclitaxel (P = 0.002).

Sensory peripheral neuropathy of any grade was reported by 54.5% of patients treated with paclitaxel compared to only 16.5% on cabazitaxel (P < 0.001). 41.8% of patients on paclitaxel experienced all-grade alopecia, compared to 26.6% on cabazitaxel (P = 0.06). Scalp-cooling was allowed.

3.10. QoL

Over the course of treatment, mean single index utility scores (a composite measure of patient responses to the EQ-5D-5L across all five domains) were higher (+0.05 (95% CI -0.00 to 0.09, p = 0.03)), and mean EQ-5D-5L visual analogue scale scores were higher (+7.7 (95% CI 3.1–12.3, p = 0.001)) indicating better QoL in the cabazitaxel arm compared to the paclitaxel arm. **Supplemental Figs. 2G and H.**

For the FACT-B breast cancer subscale, higher scores (indicating better QoL) were reported in the cabazitaxel arm compared with the paclitaxel arm with mean difference 1.8 (95% CI 0.4–3.1, p = 0.01). There was no significant difference between arms within the other FACT-B well-being domains or in the FACT-B total score. Supplemental Figs. 2A–F.

4. Discussion

This is the first randomised control trial to directly compare three-

weekly cabazitaxel to weekly paclitaxel in the first line setting for patients with HER2-negative MBC. Our results demonstrate no significant difference in PFS (HR = 0.87, 80% CI 0.70–1.08) or OS (HR 1.00, 95% CI 0.69–1.45) between the two arms.

Overall, the number and grade of AEs across both treatment arms were similar. However, patients receiving paclitaxel were 3.3 times more likely to experience sensory peripheral neuropathy. Chemotherapy associated sensory neuropathies can be disabling and are associated with a decline in QoL [28], so the use of cabazitaxel in place of paclitaxel could be an advantage for patients. However, the higher incidences of diarrhoea and febrile neutropenia with cabazitaxel needs to be kept in perspective.

G-CSF was mandatory for cabazitaxel, in line with MHRA guidance, as reflected in the Summary of Product Characteristic (SmPC) and American Society of Clinical Oncology guidelines which recommends G-CSF is given alongside cabazitaxel to limit the incidence and severity of neutropenia. In our trial, the incidence of this adverse event was still higher in the cabazitaxel arm, but there was less discontinuation and higher rates of completion of the planned 6 cycles cabazitaxel which may have been due to the mandated G-CSF. Data from the Hellenic Cooperative Oncology Group (HeCOG) Trial [22], using cabazitaxel 25 mg/m^2 which recommended G-CSF (but did not mandate) reported grade 3–4 neutropenia in 22.6% and febrile neutropenia in 6% of the patients, which is comparable to our trial. In addition, on the HeCOG trial (n = 84) there were two fatal events (one febrile neutropenia and one sepsis) reported as being related to study treatment. In our trial, we had zero fatalities within the cabazitaxel arm. This suggests that primary prophylaxis with G-CSF for cabazitaxel 25 mg/m^2 should continue to be indicated.

Throughout treatment, patients on cabazitaxel reported significantly better QoL outcomes on the EQ-5D-5L single index utility scores, EQ-5D-5L visual analogue scores and FACT-B breast cancer subscale, compared to the paclitaxel arm. While significant, the magnitude of the differences observed are lower than minimally important differences described in the literature for each measure, and so are unlikely to represent a clinically meaningful effect [29–31]. It should also be noted that there was no difference in the total FACT-B score or any of the other subscales.

It is however encouraging that cabazitaxel is well tolerated and at least as good as weekly paclitaxel in terms of QoL in this first line MBC setting. Weekly paclitaxel has been generally favoured as first line chemotherapy treatment for MBC in view of efficacy and its favourable QoL profile. Therefore, the QoL data with cabazitaxel is an important consideration, especially as the three-weekly dosing regimen is less demanding on healthcare resources compared to the weekly paclitaxel regimen and less burdensome for patients. Reduced nursing, phlebotomy, pharmacy, administration and chair time have significant costing implications. For patients, reduced travel and treatment times could be hugely advantageous, both during the Covid-19 pandemic and beyond.

Our sub-group analysis suggests that patients over the age of 65 have significantly longer PFS with cabazitaxel than paclitaxel (HR = 0.45, 95% CI 0.25–0.80, p < 0.01). 54.6% of patients over 65 completed 6 cycles of cabazitaxel, compared to only 32.1% completing 6 cycles of paclitaxel. Neuropathy was higher in the paclitaxel arm, 17 patients (61%, 3 with grade ≥3) compared to 5 on the cabazitaxel arm (23%, all grade1-2) and might have influenced early termination of paclitaxel treatment, although this rate is similar to the entire intention-to-treat population. However, when adjusted for the number of cycles received (excluding patients who stopped because of progression or death) the difference in PFS between arms in this sub-group remains significant and the magnitude of the difference increases slightly (HR = 0.36 (95% CI 0.18–0.73), p < 0.01). This was the case when also adjusted for dose reductions (HR = 0.36 (95% CI 0.18–0.72), p < 0.01), suggesting the benefit of cabazitaxel for patients over the age of 65 is independent of the number of cycles or whether they received a reduced dose. This benefit is notable, as clinical practice tends to prefer a weekly paclitaxel regimen in this older cohort, given its tolerability [7,14].

There was a significant interaction between the effect of treatment and previous docetaxel exposure on PFS (p = 0.04) as patients without previous exposure tended to benefit more from cabazitaxel than those with previous exposure. This trend is surprising given the role of cabazitaxel in taxane resistance, and warrants further investigation in a larger study. One of our study limitations is that while data was collected on whether or not the patent received (neo) adjuvant docetaxel, the disease free interval before trial registration was not. This may have been a useful stratification factor, although its utility would be limited as only 38% received previous docetaxel.

Interestingly, patients ≥65 were less likely to have had previous docetaxel exposure (p = 0.002). However, there were too few patients to investigate further.

Previous phase 2 trials which have assessed cabazitaxel in the second or third line setting for patients with HER 2-negative MBC and previous taxane exposure or resistance, found ORR between 14% and 22.6% [21, 22]. These results are superior to eribulin or capecitabine used in a similar setting [32]. However, in the more recent trial, patients who specifically had taxane resistance had worse median OS, 12.7 months compared to 19.4 months for non-resistant patients [22]. So, although cabazitaxel can be efficacious for these patients, it does not seem to completely overcome the issue of taxane resistance.

Cabazitaxel and weekly paclitaxel have been directly compared in the GENEVIEVE study in the neo-adjuvant BC setting in 333 patients with HER 2-negative disease. In this setting, cabazitaxel was not as effective as paclitaxel, with only 1.2% (95% CI 0.0–2.9) CR rate, compared to 10.8% (95% CI 6.1–15.5) in the paclitaxel arm [33]. However, the study concluded that neither agent used as monotherapy was adequate in the neoadjuvant setting.

Our study is the first to directly compare cabazitaxel and paclitaxel in the first line MBC setting.

Results for the paclitaxel arm are consistent with the literature. The ORR of 37% is comparable to previous studies (21.5–53.7%), and the median PFS of 5.8 months and OS of 18 months compares to 4.7–9.7 months and 9.9–35.8 months, respectively, quoted in the literature [5, 7–13].

A study limitation was that this was a relatively small phase II/III study. As a superiority trial, it was powered to detect significant improvement with a PFS HR 0.65. Our PFS HR result (0.87) was in favour of cabazitaxel and a larger trial with a more modest predicted difference between arms would be helpful in establishing whether there is a significant benefit.

Advancements in treatment strategies, including use of CDK 4/6 inhibitors, atezolizumab and pembrolizumab (in triple-negative PD-L1 positive MBC) have been recently recommended and approved after our trial was initiated. Therefore, numbers of patients pre-treated with CDK 4/6 inhibitors was low. There was no approved treatment based on PDL-1 status during the conduct of the trial and PD-L1 status was not routinely requested, therefore this data is not available in our patient group.

In conclusion, this randomised phase II/III trial suggests that three-weekly cabazitaxel does not significantly improve PFS in first line chemotherapy management of HER 2-negative MBC patients compared to weekly paclitaxel. However, PFS and OS were similar between the two arms and cabazitaxel was associated with better patient reported health outcomes and lower rates of peripheral neuropathy. With the additional benefit of a three-weekly regimen, this could be a preferred treatment option for some patients, including older patients, during the Covid-19 pandemic and beyond.

Author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.09.005.

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