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CLINICAL TRIAL

A randomized phase II study of weekly paclitaxel with or without pelareorep in patients with metastatic breast cancer: final analysis of Canadian Cancer Trials Group IND.213.

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Abstract

Background Pelareorep, a serotype 3 reovirus, has demonstrated preclinical and early clinical activity in breast cancer and synergistic cytotoxic activity with microtubule targeting agents. This multicentre, randomized, phase II trial was undertaken to evaluate the efficacy and safety of adding pelareorep to paclitaxel for patients with metastatic breast cancer (mBC).

Methods Following a safety run-in of 7 patients, 74 women with previously treated mBC were randomized either to paclitaxel 80 mg/m^2 intravenously on days 1, 8, and 15 every 4 weeks plus pelareorep 3×10^{10} $TCID_{50}$ intravenously on days 1, 2, 8, 9, 15, and 16 every 4 weeks (Arm A) or to paclitaxel alone (Arm B). Primary endpoint was progression-free survival (PFS). Secondary endpoints were objective response rate, overall survival (OS), circulating tumour cell counts, safety, and exploratory correlative analyses. All comparisons used a two-sided test at an alpha level of 20%. Survival analyses were adjusted for prior paclitaxel.

Results Final analysis was performed after a median follow-up of 29.5 months. Pelareorep was well tolerated. Patients in Arm A had more favourable baseline prognostic variables. Median adjusted PFS (Arm A vs B) was 3.78 mo vs 3.38 mo (HR 1.04, 80% CI 0.76–1.43, $P = 0.87$). There was no difference in response rate between arms ($P = 0.87$). Median OS (Arm A vs B) was 17.4 mo vs 10.4 mo (HR 0.65, 80% CI 0.46–0.91, $P = 0.1$).

Conclusions This first, phase II, randomized study of pelareorep and paclitaxel in previously treated mBC did not show a difference in PFS (the primary endpoint) or RR. However, there was a significantly longer OS for the combination. Further exploration of this regimen in mBC may be of interest.

Keywords Breast cancer · Paclitaxel · Oncolytic virus · Reovirus · Phase 2 · Randomized

Introduction

Despite advances in diagnosis and treatment, breast cancer (mBC) remains the second most common cause of female cancer-related death in North America [1]. Pelareorep (Reolysin™) is a live, replication-competent, naturally occurring Dearing strain of reovirus serotype 3, with in vitro and in vivo activity in several tumour types, including breast cancer [2, 3]. Oncolytic viruses may result in direct cytopathic effects or induce immune effects [4,

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5]. Pelareorep is well tolerated, with mild flu-like, respiratory and enteric symptoms; dose-limiting toxicity was not reported. Single-agent activity is limited [6–8] although activity was described in mBC [9–11]. Phase I studies in combination with taxanes and gemcitabine have also reported activity in mBC patients [12–14].

The Canadian Cancer Trials Group (CCTG) designed four randomized phase II studies of pelareorep–chemotherapy. We report here our study (NCT01656538) of pelareorep/paclitaxel compared to paclitaxel in mBC.

Methods

Patients with metastatic breast adenocarcinoma appropriate for systemic treatment with paclitaxel were recruited from eight Canadian cancer centres. All patients gave written informed consent following institutional board approval. Eligibility criteria included: patients with measurable disease (RECIST version 1.1 [15]), Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2, adequate bone marrow and organ function, and those who had received at least one prior palliative chemotherapy regimen (unless had received prior taxanes/anthracycline adjuvant therapy or had relapsed within 6 months

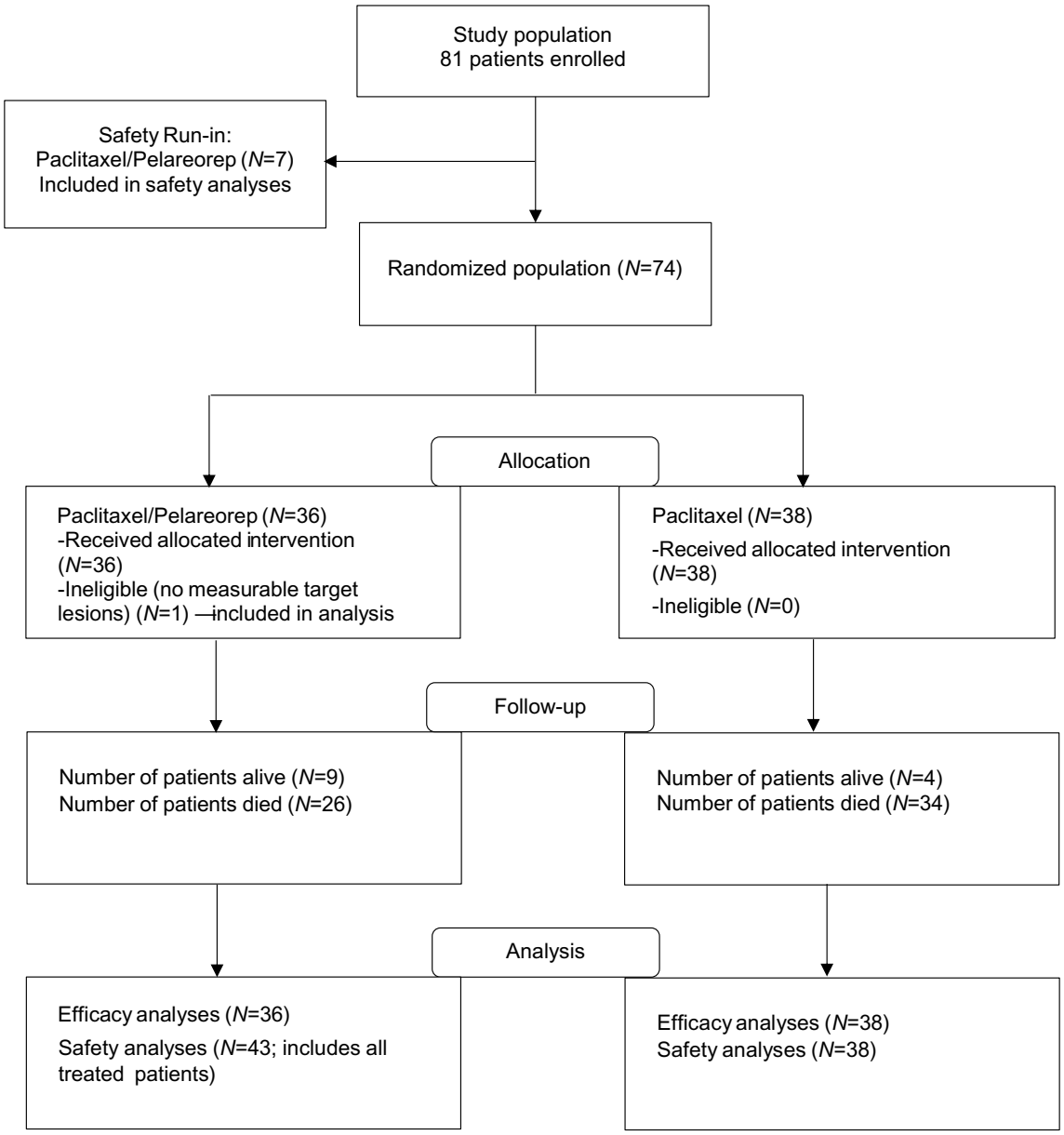


Fig. 1 Patient disposition

Table 1 Baseline characteristics of patients randomized to Arm A or Arm B

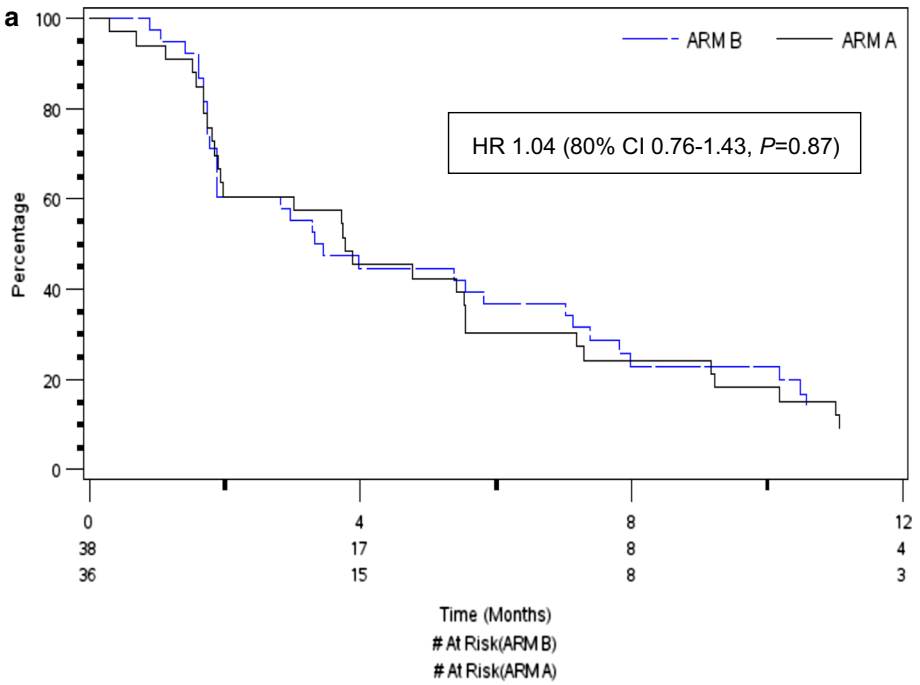
		Arm A Paclitaxel/Pelareorep $N = 36$ (%)	Arm B Paclitaxel $N = 38$ (%)
Age in years	median (range)	61 (44–78)	57 (36–73)
	< 65	27 (75)	32 (84)
ECOG PS	0	17 (47)	13 (34)
	1	17 (47)	20 (53)
	2	2 (6)	5 (13)
Diagnosis to randomization	(months: median (range))	46.4 (10–282)	57.5 (10–208)
First relapse to randomization	(months; median (range))	4.4 (0.7–199)	11.9 (0.2–106)
Histology	Inflammatory	1 (3)	0 (0)
	Ductal	30 (83)	33 (87)
	Lobular	5 (14)	4 (11)
Grade	Low	5 (14)	3 (8)
	Moderate	20 (56)	17 (45)
	High	9 (25)	14 (37)
Visceral metastases	Liver	22 (61)	27(71)
Lung metastases	Lung	16 (44)	15 (40)
Receptor status	positive	29 (81)	29 (76)
	negative	7 (19)	9 (24)
	Her-2 positive	0 (0)	1 (3)
Baseline LDH	Abnormal	19 (53)	23 (63)
Prior radiotherapy	Yes	29 (81)	34 (90)
Prior chemotherapy	Any	36 (100)	38 (100)
	Palliative	23(64)	25(66)
	Paclitaxel	9 (25)	8 (21)
# of prior chemotherapy	1	25 (69)	20 (53)
	2	8 (22)	9 (24)
	3 +	3 (8)	9 (24)
Prior endocrine therapy		23 (64)	28 (74)
# of prior endocrine therapy	1	11 (31)	10 (26)
	2	4 (11)	11 (29)
	3 +	8 (22)	7 (18)
# of target lesions	1	5 (14)	6 (16)
	2	17 (47)	16 (42)
	3 +	13 (36)	16 (42)
Number of disease sites	1	6 (17)	6 (16)
	2	10 (28)	12 (32)
	3+	19 (53)	20 (53)

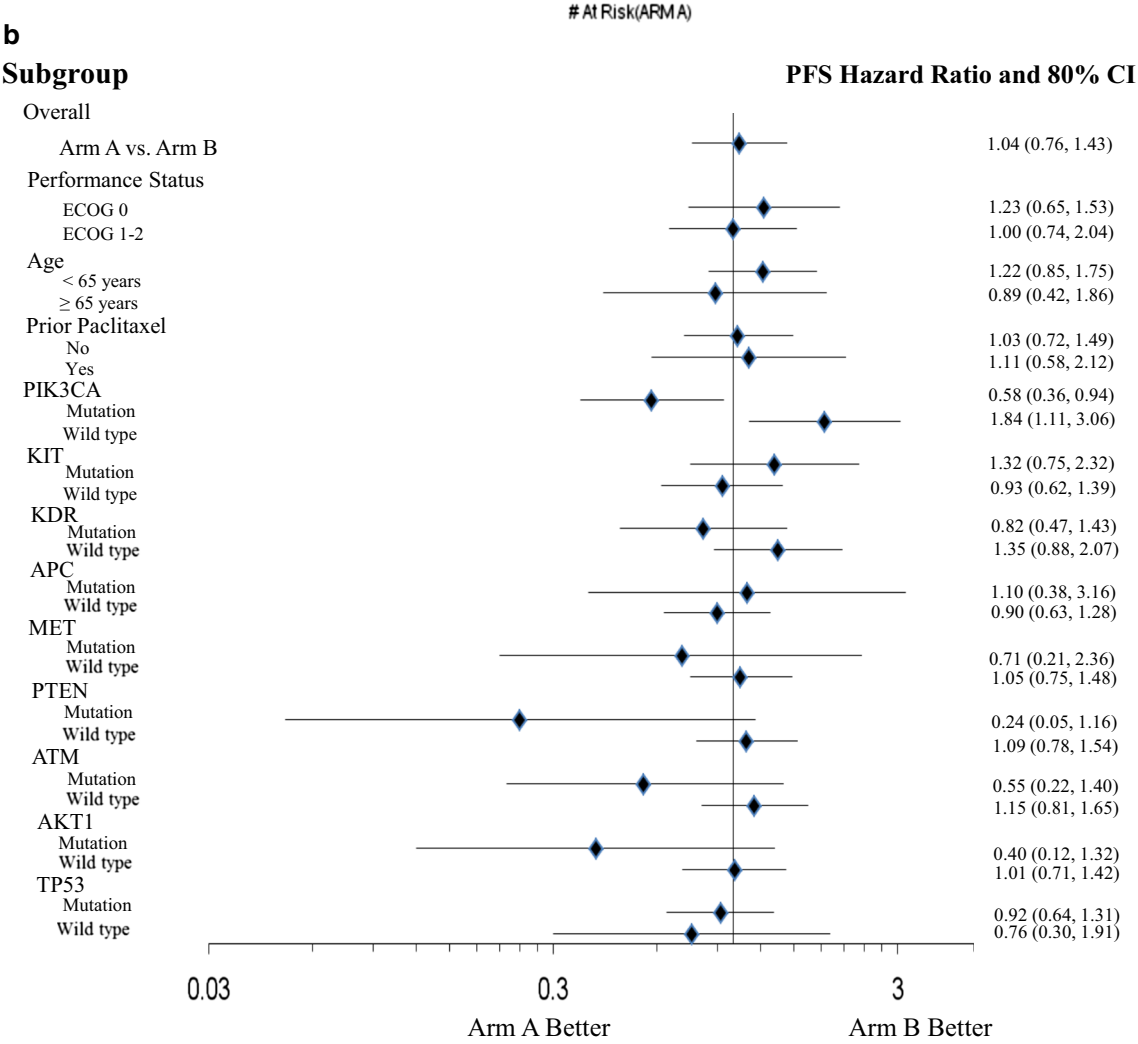
of any adjuvant chemotherapy). Patients with significant pulmonary, cardiac, neurological disease, hepatitis B or C, HIV, other malignancies, central nervous system metastases, uncontrolled infections, or those who required immunosuppression were not eligible.

After a safety run-in with paclitaxel/pelareorep, patients were randomized 1:1 to open-label paclitaxel/pelareorep (Arm A) or paclitaxel alone (Arm B). Randomization was dynamically balanced by prior paclitaxel treatment using a minimization method. Study conduct was overseen by the CCTG Data Safety Monitoring Committee.

Paclitaxel 80 mg/m^2 was given on days 1, 8, and 15 every 28 days, while pelareorep 3×10^{10} $TCID_{50}$ was given over 1 h on days 1, 2, 8, 9, 15, and 16. Doses of paclitaxel were modified for haematologic and other adverse events, with no re-escalation permitted. Pelareorep was held, reduced (to 1×10^{10} $TCID_{50}$), or discontinued for related ≥ grade 3 toxicity. Patients on paclitaxel/pelareorep who discontinued one protocol drug for toxicity related to that therapy could continue the other drug. Crossover was not permitted.

Prior to day 1 haematology (CBC), urinalysis and biochemistry were assessed; CBC was also assessed weekly


a
ARM B
ARM A
HR 1.04 (80% CI 0.76-1.43, P=0.87)
Percentage
100
80
60
40
20
0
0 4 8 12
38 17 8 4
36 15 8 3
Time (Months)
At Risk(ARM B)
At Risk(ARM A)


b
Subgroup
PFS Hazard Ratio and 80% CI
Overall
Arm A vs. Arm B 1.04 (0.76, 1.43)
Performance Status
ECOG 0 1.23 (0.65, 1.53)
ECOG 1-2 1.00 (0.74, 2.04)
Age
< 65 years 1.22 (0.85, 1.75)
≥ 65 years 0.89 (0.42, 1.86)
Prior Paclitaxel
No 1.03 (0.72, 1.49)
Yes 1.11 (0.58, 2.12)
PIK3CA 0.58 (0.36, 0.94)
Mutation 1.84 (1.11, 3.06)
Wild type
KIT
Mutation 1.32 (0.75, 2.32)
Wild type 0.93 (0.62, 1.39)
KDR
Mutation 0.82 (0.47, 1.43)
Wild type 1.35 (0.88, 2.07)
APC
Mutation 1.10 (0.38, 3.16)
Wild type 0.90 (0.63, 1.28)
MET
Mutation 0.71 (0.21, 2.36)
Wild type 1.05 (0.75, 1.48)
PTEN
Mutation 0.24 (0.05, 1.16)
Wild type 1.09 (0.78, 1.54)
ATM
Mutation 0.55 (0.22, 1.40)
Wild type 1.15 (0.81, 1.65)
AKT1
Mutation 0.40 (0.12, 1.32)
Wild type 1.01 (0.71, 1.42)
TP53
Mutation 0.92 (0.64, 1.31)
Wild type 0.76 (0.30, 1.91)
0.03
0.3
3
Arm A Better
Arm B Better

◂**Fig. 2** Progression-free survival. **a** Kaplan–Meier curves by treatment arm and **b** forest plot for hazard ratios of progression-free survival by subgroup

and biochemistry on day 8 of cycles 1 and 2. Imaging was performed at baseline and every 8 weeks until progression. Circulating tumour cells (CTC) and correlative blood samples were collected at baseline, at the end of cycles 2 and 4, and at treatment discontinuation.

Statistical considerations

The primary endpoint was progression-free survival (PFS) defined as the time from randomization until disease progression or death from any cause. The estimated PFS for paclitaxel cohort was 4 months. With 67 PFS events, an increase in PFS from 4 to 7.5 months [i.e., hazard ratio (HR) of 0.5] with 90% power and a two-sided alpha of 0.2 could be detected. Slower than expected accrual and higher than expected event rates allowed protocol amendment and the final analysis to be conducted after 74 patients were accrued rather than the planned 100.

Secondary endpoints were objective response rate (ORR; RECIST 1.1), overall survival (OS), CTC, and the exploratory assessment of potential prognostic or predictive molecular factors (tissue or blood). Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Randomized patients were analysed on an intention-to-treat basis. Safety analyses included patients receiving at least one dose of protocol therapy. PFS and OS were analysed using Kaplan–Meier methods. Primary comparisons used the stratified log-rank test adjusted for prior paclitaxel. Exploratory analyses adjusting for PS, age [< 65 vs. ≥ 65 years], baseline ER, PgR, and HER2 status were planned. All mutations occurring in at least 1 patient in each arm were included irrespective of known clinical relevance. HRs with 80% confidence intervals (CI) were calculated from stratified Cox regression models with treatment group as the single factor. Discrete variables were compared using Fisher's exact test and continuous ordinal categorical variables using the Wilcoxon test. A two-sided P value < 0.2 was considered statistically significant.

Correlative studies

Blood was collected in CellSave Preservation Tubes® and analysed on the CellSearch® System (Janssen Diagnostics). CTC counts were dichotomized at < 5 versus ≥ 5 cells per 7.5 mL [16]. A patient was considered as having a favourable CTC status if counts were < 5 CTC/7.5 mL.

Available archival tumour tissue also underwent targeted hotspot mutational analysis (Online Resource 1).

Role of funding

CCTG, the trial sponsor, was responsible for study design, collection, analysis, and interpretation of data, report writing, and the publication. Oncolytics Biotech Inc provided partial financial support, supplied pelareorep, approved the study design, and provided comments on the manuscript.

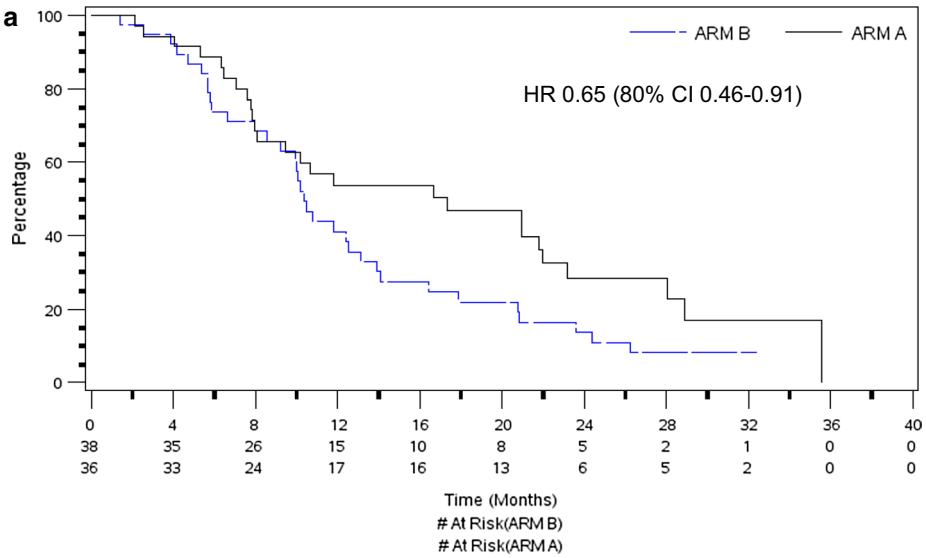
Results

Seven patients were enrolled into the safety cohort, with no major toxicities. Between July 2013 and April 2016, 74 patients were randomized: 36 to Arm A and 38 to Arm B. Data cutoff was November 2016, when all patients had discontinued protocol treatment (Fig. 1). Median duration of follow-up was 30 months. One patient with no target lesions

Table 2 Objective response assessed by RECIST 1.1 for patients randomized to Arm A or Arm B

	Arm A Pelareorep/Paclitaxel $N = 36$ (%)	Arm B Paclitaxel $N = 38$ (%)	
Complete response (CR)	0 (0)	0 (0)	
Partial response (PR)	9 (25)	9 (23.7)	
Stable disease (SD)	11 (30.6)	12 (31.6)	
Progressive disease (PD)	13 (36.1)	14 (36.8)	
Not evaluable	3 (8.3)	3 (7.9)	
Objective response rate (ORR)	9 (25)	9 (23.7)	OR 1.11 (0.51,2.45), p0.86
Median duration of response in months (80% CI)	3.78 (1.87–5.72)	4.47 (1.87–5.75)	$P = 0.93$

OR odds ratio



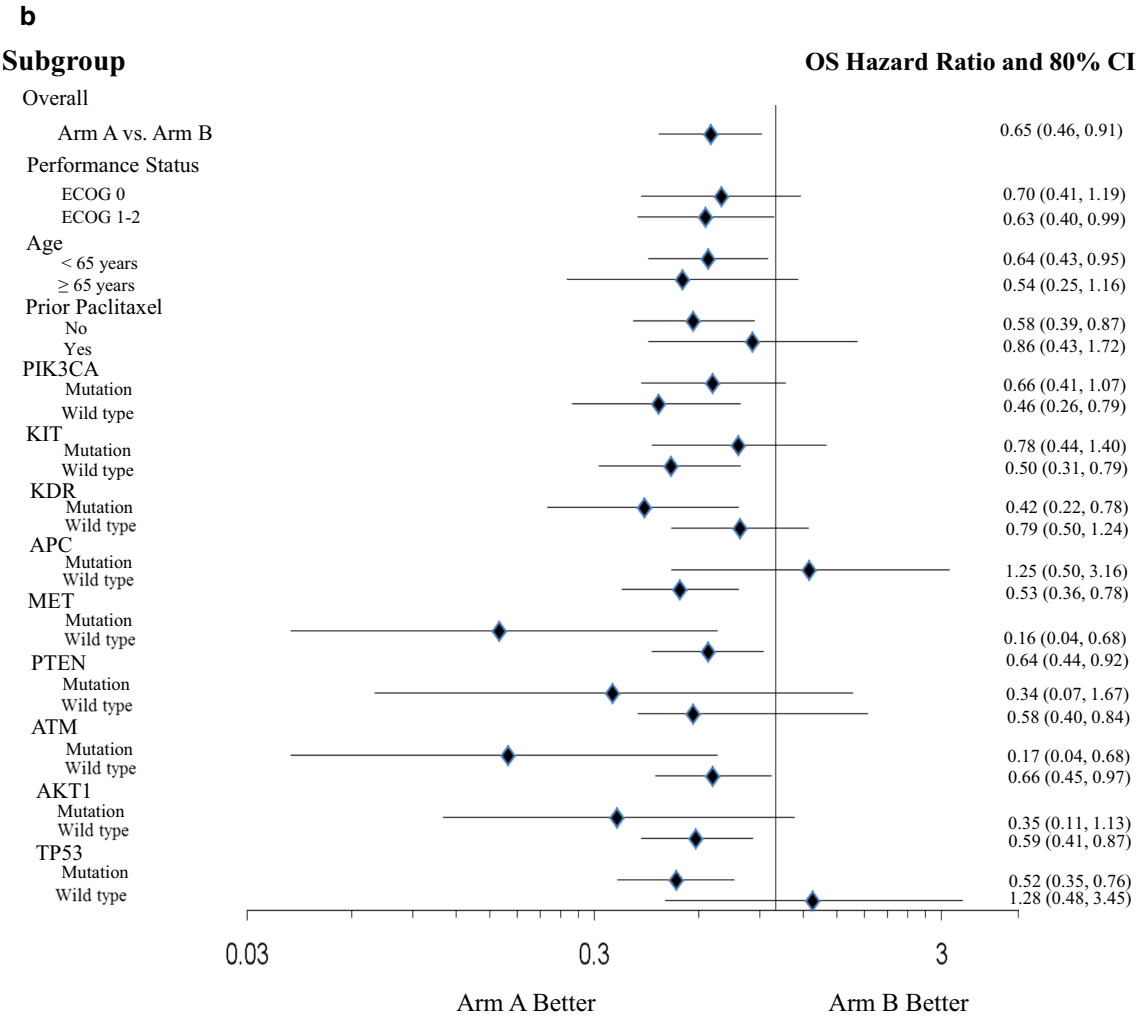


Fig. 3 Overall survival. **a** Kaplan–Meier curves by treatment arm and **b** forest plot for hazard ratios of overall survival by subgroup

Table 3 Adverse events of any causality with a grade ≥ 3 occurring in ≥ 5% of patients in either arm

Adverse Event	Arm A Pelareorep/Paclitaxel $N = 43$ (%)	Arm B Paclitaxel $N = 38$ (%)
Any event	43	47
Fatigue	16	13
Anorexia	7	3
Diarrhoea	0	8
Vomiting	0	8
Nausea	2	8
Pain	2	5
Fall	2	5
mBC related	2	8

was ineligible, and one patient was lost to follow-up, having withdrawn consent.

Baseline characteristics of the randomized cohort are summarized in Table 1. Arm B patients were younger, had worse PS, had higher grade and hormone receptor-negative tumours and higher CTC, more visceral metastases (including hepatic), and abnormal LDH, but had longer time from diagnosis or first relapse to randomization. Age (on a continuous scale), baseline CTC counts, and time from first relapse to randomization were significantly imbalanced between the arms.

Sixty-seven PFS events were observed. Median PFS was 3.78 months for Arm A and 3.38 months for Arm B (HR 1.04, 80% CI 0.76–1.43, $P = 0.87$; Fig. 2a). After adjusting for prespecified factors, the difference remained non-significant (HR 1.11, 80% CI 0.77–1.60, $P = 0.71$). In the exploratory analysis, only 9 biomarkers had ≥ 1 mutation in both groups, and among those only PIK3CA mutations were significant (Fig. 2b).

There were no complete responses (CR). Partial response and duration were similar between arms (odds ratio 1.09, 80% CI 0.54–2.22, $P = 0.87$) (Table 2). There was no difference in the pattern of progression (new lesions versus progression in baseline sites). No significant differences in ORR were seen in any of the preplanned subsets (Online Resource Fig. 1).

Median OS was 17.4 months for Arm A vs 10.4 months for Arm B (HR 0.65, 80% CI 0.46–0.91, $P = 0.10$; Fig. 3a). In adjusted analyses HR was 0.61 (80% CI 0.41–0.91, $P = 0.11$). Differences remained significant when two baseline factors with significant imbalances (age and time from first relapse to randomization) were included (HR 0.58, 80% CI 0.32–1.04, $P = 0.07$), but when baseline CTC were included (when available), OS was no longer significantly different (HR 0.80, 80% CI 0.42–1.55, $P = 0.51$). Subset analyses for mutation status are shown in Fig. 3b. TP53 appeared to select for patients with OS benefit in Arm A (20.93 mo OS in Arm A vs 10.35 mo in Arm B (HR 0.52, 80% CI 0.35–0.76)); when common benign polymorphisms were excluded (for example c.215C > G p.Pro72Arg), the findings were reversed, with patients having tumours without p53 mutations demonstrating longer OS (21 mo versus 10 mo, HR 0.40 CI 0.24, 0.67).

There were no differences in CTC conversion rates between arms (Online Resource Table 1).

Median number of cycles was 5 (1–15) for Arm A and 4 (1–10) for Arm B. The median duration of treatment was 16.1 weeks in both arms. Pelareorep dosing was delayed in 10 patients (statutory holiday being the most common cause), omitted in 24 (statutory holiday, patient request, and neutropenia the most common cause), and reduced in 2. Paclitaxel delays were more common for Arm B (21% vs. 32%; Arm A vs B), while omissions (49% vs. 42%) and reductions (28% vs. 26%) were similar between arms.

Adverse events

The most common pelareorep-related AEs were fever (65%), fatigue (60%), diarrhoea (40%), chills (40%), nausea (35%), and "flu-like" symptoms (33%) (Table 3 and Online Resource Table 2). Hospitalization rates were similar in each arm (21%).

Twenty-seven patients (75%) in Arm A and 29 (76.3%) in Arm B had salvage therapy (Online Resource Table 3). Response rates to these therapies was similar between arms.

Discussion

Our trial is the first randomized phase II trial of pelareorep with chemotherapy in advanced breast cancer. Pelareorep given with weekly paclitaxel was tolerable, although patients did experience more flu-like symptoms, mostly grades 1–2. We were unable to detect any benefit of the addition of pelareorep to paclitaxel when assessed by PFS, ORR, or CTC conversion. However, we found a statistically significant OS benefit. Our study was small and, while randomized, was not powered to detect a difference in OS, and the two arms were imbalanced favouring pelareorep. The OS for the control arm was lower than expected given that 35% of patients had not received prior palliative chemotherapy [17–19]. Also of note is the P value of < 0.2, adequate for a screening phase II endpoint, but not having the same weight as a P value of < 0.05 for a phase III trial.

Discrepancies between response-based endpoints and OS have been previously described. MA.19, a CCTG trial

of doxorubicin ± DPPE in mBC, showed almost identical findings with an improvement in OS but no difference in PFS or RR in phase III testing [20]. Subsequent phase III studies failed to confirm an OS benefit [21]. Agents with a postulated immune mechanism have reported no PFS benefit despite significant OS benefits [22, 23]. Some trials of immune checkpoint inhibitors have shown an OS benefit, with PFS curves that separate late, postulated to be due to 'pseudoprogression' [24–26]. Our study reported almost identical PFS and RR between arms, and we observed no evidence of pseudoprogression or difference in progression patterns, development of new metastases, or response to subsequent therapies.

In our study, KRAS mutations were not identified, and thus we cannot either confirm or refute an impact on outcomes for KRAS status. In subset analyses, we identified OS benefit for PI3KCA WT, APC WT, KDR MT, MET MT, and TP53 MT, but we included all mutations and the results changed significantly when selected 'benign' polymorphisms are reclassified. Why PI3KCA MT effect is disparate and results in better PFS and OS but not RR is unclear. One of the purported mechanisms of action of pelareorep is inducing autophagy of the cancer cell through P13KCA/AKT/mTOR signalling [27].

This study was one of four concurrent randomized phase II CCTG trials that evaluated pelareorep in metastatic solid tumours: colorectal (CRC) (NCT01622543), non-small cell lung cancer (NSCLC) (NCT01708993), and prostate cancer (NCT01619813). The results of the CRC trial have been presented and showed a significant ORR, but also a significantly shorter duration, with no improvement in PFS; female participants had better outcomes [28]. The other trials do not show any benefit in RR, PFS, or OS; indeed, OS was inferior in the prostate cancer trial. Although this suggests a hitherto undescribed impact of gender on outcomes with pelareorep, a randomized phase II trial of weekly paclitaxel ± pelareorep in ovarian cancer (GOG-01086H) showed no significant differences in response rate, decline in Ca-125, or OS from pelareorep [29].

In summary, our trial did not demonstrate a benefit in the primary endpoint of PFS in MBC. While we did demonstrate any improvement in OS, this might have occurred due to imbalances in prognostic factors. These data may support further investigation of this combination.

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Compliance with ethical standards

Conflicts of interest The CCTG (L Seymour) received partial financial support from Oncolytics Biotech to offset the costs of the trial. K Gelmon reports having acted as an advisor to Oncolytics Biotech. All the remaining authors have declared no relevant conflicts of interest.

Ethical standards The experiments in this study comply with the current laws of the country in which they were performed.

Informed consent Informed consent was obtained from all individual participants included in the study.

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