CT131: A Randomized (RCT) Phase II Study of Oncolytic Reovirus (Pelareorep) plus Standard Weekly Paclitaxel (P) as Therapy for Metastatic Breast Cancer (mBC)

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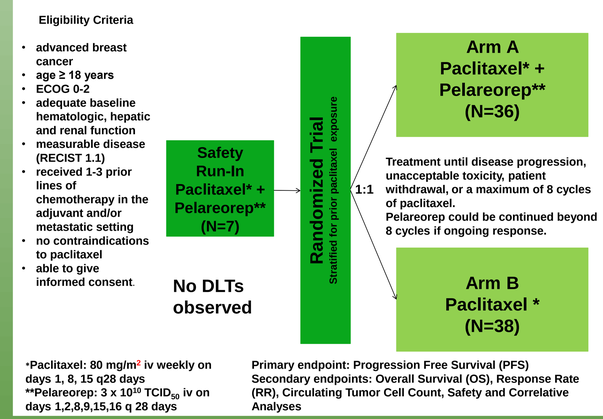
BACKGROUND

- Pelareorep (Reolysin™) is a Dearing strain of reovirus serotype 3.
- Has been shown in vitro to have synergistic cytotoxic activity with microtubule targeting agents.
- Activity reported in six human breast cancer cell lines, and in phase I trials including advanced breast cancer patients, both as single agent and combined with chemotherapy.
- In phase I trials, well tolerated with no observed dose limiting toxicities (DLTs); most common toxicity is flu-like illness.
- This randomized phase II study was designed to determine the efficacy and safety of pelareorep + paclitaxel compared to paclitaxel alone in advanced breast cancer.

TRIAL SCHEMA



*Paclitaxel: 80 mg/m^2 iv weekly on days 1, 8, 15 q28 days
**Pelareorep: 3 x 10^{10} $TCID_{50}$ iv on days 1,2,8,9,15,16 q 28 days

Primary endpoint: Progression Free Survival (PFS)
Secondary endpoints: Overall Survival (OS), Response Rate (RR), Circulating Tumor Cell Count, Safety and Correlative Analyses

METHODS

- Primary endpoint was progression free survival (PFS); expected median PFS was 4 months.
- Analysis was planned after 67 PFS events, for detection of an increase in PFS of the experimental arm from 4 to 7.5 months (i.e. hazard ratio of 0.53), with 90% power and two-sided alpha of 0.2. Sample size of 100 was anticipated.
- Final analysis was performed after 74 patients were randomized with 67 events; the study had the same power to detect the same HR.
- Two-sided p-values less than 0.2 were considered as statistically significant.
- Primary analyses included stratification factor (prior paclitaxel Yes/No)
- Sensitivity analyses adjusted for potential prognostic factors prespecified in the analysis plan (baseline performance status [0 vs. 1-2], age [<65 vs. ≥ 65 years], baseline ER status [positive vs. negative], baseline PgR status [positive vs. negative], baseline HER2 status [positive vs. negative]).
- Exploratory analyses included other imbalanced baseline variables plus identified mutations present in at least 1 patient in each arm.
- All treated patients, including run-in patients, were included in the safety analysis; all randomized patients were included in demography and efficacy analyses.

RESULTS

- No DLTS occurred in the safety-run-in (n=7).

Demography

- One patient was ineligible in Arm A due to having no measurable disease. No one was lost to follow up.
- All patients received their assigned treatment.
- Baseline patient characteristics are listed in Table 1.
- Only age as a continuous variable (p=0.1) and time from relapse to randomization (p=0.04) were significantly different between the two arms.

RESULTS

Demography (continued)

- However, patients in Arm B tended to be a little younger and have slightly worse baseline characteristics: more performance status (PS) 1-2, more high grade/hormone receptor negative tumours, more liver metastases, and received more prior radiation, lines of chemotherapy and endocrine therapy.
- Baseline CTC counts were significantly higher in the control arm: median was 3.5 (range: 0-306) for Arm A and 11 (range: 0-6622) for Arm B, p=0.2. 7 patients were missing CTC at baseline (4 on Arm A and 3 on Arm B).

Table 1: Baseline Characteristics

	Arm A Paclitaxel/Pelareorep N=36 (%)	Arm B Paclitaxel N=38 (%)	Total N=74 (%)
Age in years median (range) <65	61 (44-78) 27 (75)	57 (36-73) 32 (84)	59 (36-78) 59 (80)
ECOG PS 0 1 2	17 (47) 17 (47) 2 (6)	13 (34) 20 (53) 5 (13)	30 (40.5) 37 (50) 7 (9.5)
Diagnosis to randomization (months) median (range)	46.4 (10-281.9)	57.5 (10-208.1)	53.2 (10-281.9)
First relapse to randomization (months) median (range)	4.4 (0.7-199)	11.9 (0.2-105.8)	8.1 (0.2-199)
Histology Inflammatory Ductal Lobular Medullary	1 (3) 30 (83) 5 (14) 0 (0)	0 (0) 33 (87) 4 (11) 0 (0)	1 (1) 63 (85) 9 (12) 0 (0)
Grade Low Moderate High	5 (14) 20 (56) 9 (25)	3 (8) 17 (45) 14 (37)	8 (11) 37 (50) 23 (31)
Liver metastases present	22 (61)	27(71)	49 (66)
Lung metastases present	16 (44)	15 (40)	31 (42)
Hormone receptor status positive negative	29 (81) 7 (19)	29 (76) 9 (24)	58 (78) 16 (22)
HER 2 positive	0 (0)	1 (3)	1 (1.4)
Prior surgery	36 (100)	38 (100)	74 (100)
Prior radiotherapy	29 (81)	34 (90)	63 (85)
Prior systemic therapy	36 (100)	38 (100)	74 (100)
# of prior chemotherapy 1 2 3+	25 (69) 8 (22) 3 (8)	20 (53) 9 (24) 9 (24)	45 (61) 17(23) 12 (16)
Prior palliative chemotherapy	23 (64)	25 (66)	48 (65)
Prior paclitaxel	9 (25)	8 (21)	17 (23)
Prior endocrine therapy	23 (64)	28 (74)	51 (69)
# of prior endocrine therapy 1 2 3+	11 (31) 4(11) 8 (23)	10(26) 11(29) 7(19)	21(28) 15(20) 15(20)
# of target lesions 1 2 3+	5 (14) 17 (47) 13 (36)	6 (16) 16 (42) 16 (42)	11(15) 33 (45) 29(40)
Number of disease sites 1 2 3 4+	6 (17) 10 (28) 8 (22) 11 (31)	6 (16) 12 (32) 6 (16) 14 (37)	12 (16) 22(30) 14 (19) 25 (34)
Elevated LDH	19 (53)	23 (63)	42 (57)

Objective Response

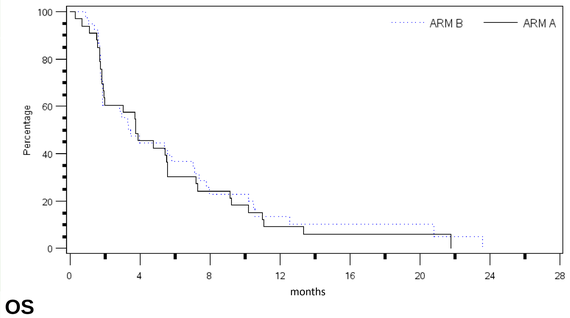
Table 2: Response Rate

	Arm A N=36 (%)	Arm B 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 for response	3 (8.3)	3 (7.9)	
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

RESULTS

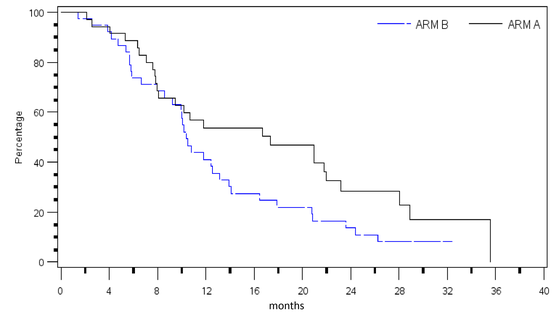
PFS

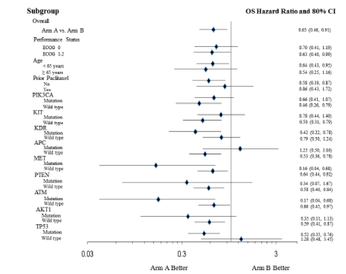
- Median PFS (Arm A:B) was 3.78 months and 3.38 months (HR 1.04, 80% CI 0.76-1.43, p=0.87).
- After adjusting for pre-specified potential prognostic factors the treatment difference was still non-significant (HR 1.11, 80% CI 0.77-1.60, p=0.71).
- There were no significant PFS differences by treatment arm at two-sided 0.2 level for pre-specified subsets.
- Only 9 biomarkers were found to have at least one mutation in both treatment groups. Significant PFS difference at two-sided 0.2 level was seen only in patients with PIK3CA mutation.



OS

- Median overall survival (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).
- After adjusting for pre-specified potential prognostic factors, the treatment difference was still statistically significant (HR 0.61, 80% CI 0.41 to 0.91, p=0.11).
- After adjusting the three baseline factors with significant imbalance between the arms (age, time from first relapse to randomization, and baseline CTC counts), HR was 0.80 (80% CI 0.42 to 1.55, p=0.51). However, 16 (22%) patients were excluded from this analysis due to missing data on one or more factors, lowering the statistical power.
- In exploratory analyses, Arm A patients with increased age, better PS, no prior paclitaxel therapy and mutations in TP53, PTEN, AKTI and KIT had longer OS, while those with PIK3CA, APC and ATM mutations had shorter OS.





RESULTS

Adverse Events

- Adverse events ≥ grade 3 and occurring in more than 5% of patients are shown in table 3.
- Fatigue was the only ≥ grade 3 adverse event with incidence of ≥10% in one or both treatment arms, not significant between arms, and attributed to paclitaxel in all patients in Arm B and to pelareorep in 5/7 patients in Arm A .
- Arm B patients had significantly more ≥ grade 3 diarrhea and nausea (p=0.1 for both), most not attributed to paclitaxel.
- Grade 3 or higher neutropenia was similar in both arms (23% Arm A vs. 26% Arm B).

Table 3: Percentages of ≥ Grade 3 Non-Hematologic Adverse Events occurring in ≥ 5% Patients

Adverse Event	ARM A N=43**	ARM B N=38
Any event	47	47
Fatigue	16.3	13.2
Anorexia	6.9	2.6
Diarrhea*	0.0	7.9
Vomiting*	0.0	7.9
Nausea	2.3	7.9
Pain	2.3	5.2
Fall	2.3	5.2
Other neoplasms benign, malignant and unspecified	2.3	7.9

***p=0.1**
****N=43 includes 36 randomized and 7 safety run-in patients**

CONCLUSIONS

- This first, phase II, randomized study of pelareorep + paclitaxel in advanced breast cancer previously exposed to chemotherapy did not meet its primary endpoint of PFS.
- Despite similar PFS and RR, an unexpected 7 month improvement in OS was seen.
- Our study was a small randomized controlled trial, not powered to detect OS differences.
- As well, the arms appeared imbalanced, due to small sample size, with prognostic factors favoring the pelareorep arm.
- In our study, KRAS mutations were not identified in both arms, so we could not confirm or refute an impact on outcomes for pelareorep in tumours with KRAS mutations.
- Although we cannot exclude bias in patient selection as a cause for our results, further exploration of this regimen in advanced breast cancer may be warranted.

ACKNOWLEDGEMENTS

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