A multicenter, single-arm, open-label Phase I study of AN1004 (Pelareorep) oncolytic virus plus paclitaxel in Chinese patients with Hormone receptor-positive and HER2-negative advanced/metastatic breast cancer (REO 026-1)

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BACKGROUND

AN1004, also known as Pelareorep, is an intravenously delivered immuno-oncolytic unmodified reovirus being evaluated to treat multiple malignancies. AN1004 has been shown to be safe and well-tolerated in both monotherapy and combination therapy in multiple clinical trials in North American and European populations, including two completed and two ongoing breast cancer studies. The completed phase 2 study (NCT01656538) in advanced/metastatic breast cancer demonstrated improved median overall survival (OS) in Canadian patients treated with AN1004 plus paclitaxel (PTX) versus PTX alone, and the greatest benefit in OS was observed in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) subtype. Since there was no clinical trial assessing AN1004 in Chinese population, a bridging study (REO 026-1) was initiated to evaluate its safety and tolerability in combination with paclitaxel in Chinese patients with HR+/HER2- advanced/metastatic breast cancer.

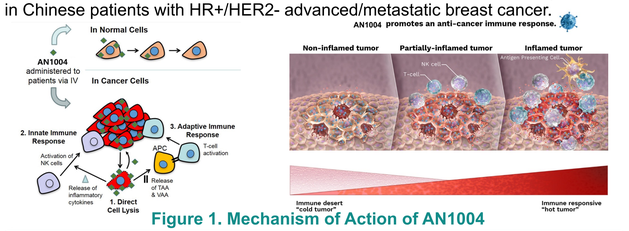
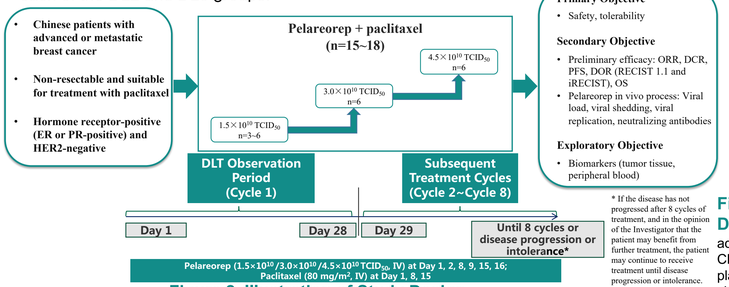


Figure 1. Mechanism of Action of AN1004

STUDY DESIGN AND METHODS

Eligible Chinese patients must be female with good performance status (ECOG: 0 or 1), have had histopathological diagnosis with HR+/HER2- advanced/metastatic breast cancer, and were previously treated with at least one endocrine therapy with no more than one line of chemotherapy regimen for recurrent/metastatic disease. Patients are intravenously infused with AN1004 at escalating dose levels of 1.5X10^{10} TCID$_{50}$ (Dose Level 1, **DL1** group), 3X10^{10}TCID$_{50}$ (**DL2** group) and 4.5X10^{10} TCID$_{50}$ (**DL3** group) on days 1, 2, 8, 9, 15, and 16 every 28 days plus paclitaxel 80 mg/m^2 intravenously on days 1, 8, and 15 every 28 days. Three to six patients will be enrolled in the DL1 group, and 6 patients will be enrolled in each of the DL2 and DL3 groups.



* If the disease has not progressed after 8 cycles of treatment, and in the opinion of the Investigator that the patient may benefit from further treatment, the patient may continue to receive treatment until disease progression or intolerance.

Figure 2. Illustration of Study Design

RESULTS

Trial Enrollment Diagram

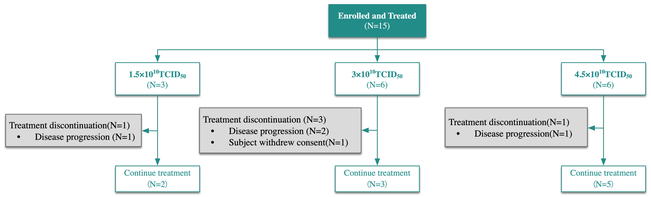


Figure 3. Trial Enrollment Outcomes. By the data cutoff date of September 26th, 2022, a total of 15 patients were enrolled. One patient in DL2 group withdrew consent in the first cycle and did not complete the dose-limiting toxicity (DLT) evaluation.

Patient Demographics, Baseline Characteristics and Exposure

	1.5×10^{10} TCID$_{50}$ group (N=3)	3×10^{10} TCID$_{50}$ group (N=6)	4.5×10^{10} TCID$_{50}$ group (N=6)	Study Total (N=15)
Age (years)				
Median (range)	51 (49 - 59)	58 (36 - 67)	47 (38 - 65)	51 (36 - 67)
≤40	0	1 (16.7%)	1 (16.7%)	2 (13.3%)
Ethnicity				
Han	3 (100%)	6 (100%)	4 (67%)	13 (87%)
Other	0	0	2 (33%)	2 (13%)
ECOG at baseline				
Score 0	0	1 (17%)	3 (50%)	4 (27%)
Score 1	3 (100%)	5 (83%)	3 (50%)	11 (73%)
Metastasis at baseline				
Visceral (liver/lung)	3 (100%)	4 (67%)	4 (67%)	11 (73%)
Exposure to study drugs				
Median (range) no. of AN1004 doses	50 (36, 61)	36 (4, 38)	17 (14, 22)	26 (4, 61)
Median (range) no. of paclitaxel doses	25 (18, 33)	19 (2, 22)	9 (7, 12)	13 (2, 33)

Table 1. Demographics, Baseline Characteristics, and Exposure to Study Drugs. A total of 15 female patients were enrolled, with a median age of 51 years (range 36 - 67) and age of ≤40 years accounted for 13.3% (2 patients). ECOG score 1 at baseline was 73% (11 patients). Visceral (liver/lung) metastasis accounted for 73%.

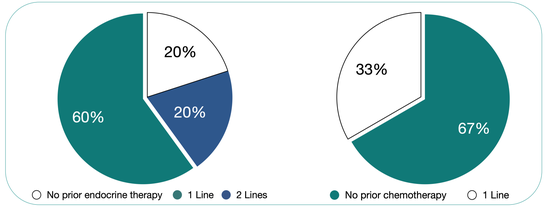


Figure 4. Prior Systemic Therapy Lines for Advanced/Metastatic Disease. Three (20%) patients had failed more than one prior line of endocrine therapy for advanced/metastatic (A/M) disease, and 5* (33%) patients were previously treated with a CDK4/6 inhibitor (*among the five patients, three of them received prior CDK4/6 inhibitor or placebo in other blinded studies). Five (33%) patients received one prior line of chemotherapy for A/M disease.

RESULTS

Treatment-Emergent Adverse Events

Number (%) of patients with at least one event of	1.5×10^{10} TCID$_{50}$ (N=3)	3×10^{10} TCID$_{50}$ (N=6)	4.5×10^{10} TCID$_{50}$ (N=6)	Study Total (N=15)
Any TEAE	3 (100%)	6 (100%)	6 (100%)	15 (100%)
Related to study drugs	3 (100%)	6 (100%)	6 (100%)	15 (100%)
Grade >= 3 AE	0	4 (67%)	6 (100%)	10 (67%)
Related to study drugs	0	4 (67%)	6 (100%)	10 (67%)
AE Leading to AN1004 Interruption	0	2 (33%)	0	2 (13%)
AE Leading to paclitaxel Interruption	0	1 (17%)	0	1 (7%)
AE Leading to Drug Discontinuation	0	0	0	0
Serious AE	0	0	0	0
Fatal AE	0	0	0	0
Dose-Limiting Toxicity (DLT)	0	0	0	0

Table 2. Summary of Treatment-Emergent Adverse Events (TEAE). A total of 15 female patients were enrolled and treated. No serious adverse event (SAE) or AE leading to treatment discontinuation was reported to date. One patient was not evaluable for dose-limiting toxicity (DLT) due to early withdrawal, and there were no DLTs observed in the 14 evaluable patients.

Preferred term (≥30% occurrence)	1.5*10^{10}TCID$_{50}$ (N=3)		3*10^{10}TCID$_{50}$ (N=6)		4.5*10^{10}TCID$_{50}$ (N=6)		Study Total (N=15)	
	Number (%) of patients							
	All grade n (%)	Grade≥3 n (%)	All grade n (%)	Grade≥3 n (%)	All grade n (%)	Grade≥3 n (%)	All grade n (%)	Grade≥3 n (%)
Total	3 (100)	0	6 (100)	4 (67)	6 (100)	6 (100)	15 (100)	10 (67)
Neutrophil count decreased	3 (100)	0	5 (83)	3 (50)	6 (100)	5 (83)	14 (93)	8 (53)
White blood cell count decreased	3 (100)	0	5 (83)	1 (17)	6 (100)	4 (67)	14 (93)	5 (33)
Pyrexia	1 (33)	0	6 (100)	0	6 (100)	0	13 (87)	0
Hypertriglyceridaemia	3 (100)	0	4 (67)	1 (17)	4 (67)	1 (17)	11 (73)	2 (13)
Anaemia	3 (100)	0	5 (83)	0	3 (50)	0	11 (73)	0
Asthenia	2 (67)	0	4 (67)	2 (33)	3 (50)	1 (17)	9 (60)	3 (20)
Alanine aminotransferase increased	2 (67)	0	3 (50)	1 (17)	4 (67)	0	9 (60)	1 (7)
Hypoalbuminaemia	2 (67)	0	4 (67)	0	3 (50)	0	9 (60)	0
Urinary tract infection	3 (100)	0	3 (50)	1 (17)	2 (33)	0	8 (53)	1 (7)
Sinus tachycardia	2 (67)	0	2 (33)	0	4 (67)	0	8 (53)	0
Peripheral sensory neuropathy	2 (67)	0	2 (33)	1 (17)	2 (33)	1 (17)	6 (40)	2 (13)
Gamma-glutamyltransferase increased	1 (33)	0	3 (50)	1 (17)	2 (33)	0	6 (40)	1 (7)
Platelet count decreased	1 (33)	0	2 (33)	0	3 (50)	0	6 (40)	0
Aspartate aminotransferase increased	1 (33)	0	2 (33)	0	2 (33)	0	5 (33)	0
Blood alkaline phosphatase increased	1 (33)	0	2 (33)	0	2 (33)	0	5 (33)	0
Hypercholesterolaemia	2 (67)	0	3 (50)	0	0	0	5 (33)	0
Hyperglycaemia	1 (33)	0	2 (33)	0	2 (33)	0	5 (33)	0

Table 3. Treatment-Emergent Adverse Events by Preferred Term. The most common (≥60%, and/or liver function related) treatment emergent adverse events (TEAEs) included neutrophil count decreased, white blood cell count decreased, pyrexia, hypertriglyceridemia, anaemia, asthenia, ALT increased, hypoalbuminaemia, GGT increased and AST increased. Ten patients had Grade 3 or above TEAEs, including neutrophil count decreased as the most common, white blood cell count decreased, asthenia, hypertriglyceridemia, peripheral sensory neuropathy, ALT increased, GGT increased and urinary tract infection.

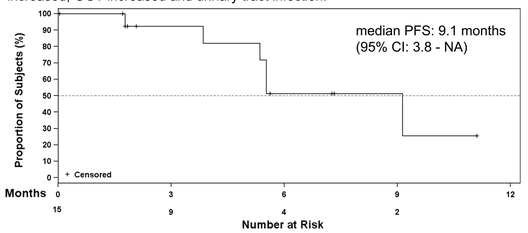


Figure 5. Progression-Free Survival (PFS) Kaplan-Meier Curve

RESULTS

Objective Response

Efficacy Evaluation of Tumor Therapy	1.5×10^{10} TCID$_{50}$ (N=3)	3×10^{10} TCID$_{50}$ (N=6)	4.5×10^{10} TCID$_{50}$ (N=6)	Study Total (N=15)
Best Overall Response (BOR) Evaluation [1]				
Complete response (CR)	0	0	0	0
Partial response (PR)	2 (67%)	1 (17%)	0	3 (20%)
Stable disease (SD)	1 (33%)	4 (67%)	5 (83%)	10 (67%)
Progressive disease (PD)	0	0	1 (17%)	1 (7%)
Not evaluable/ Not available (NE/NA)	0	1 (17%)	0	1 (7%)
Objective response rate (95%CI)	67% (9%, 99%)	17% (0%, 64%)	0% (0%, 46%)	20% (4%, 48%)
Disease control rate (95% CI)	100% (29%, 100%)	83% (36%, 100%)	83% (36%, 100%)	87% (60%, 98%)

[1] Categorization of BOR is based on the RECIST 1.1 criteria. CR or PR is confirmed only if the criteria for each are met at a subsequent timepoint.

Table 4. Efficacy Analysis and Objective Response. Among the 15 treated patients, 3 (20%) patients achieved confirmed PR, and 10 (67%) patients achieved SD, giving an ORR of 20% and a DCR of 87%.

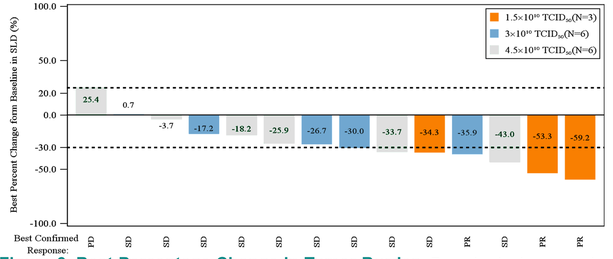


Figure 6. Best Percentage Change in Tumor Burden. Tumor burden is measured as sum of longest diameters of the target lesions. Best change from baseline is available for 14 patients with at least one post-baseline tumor assessment.

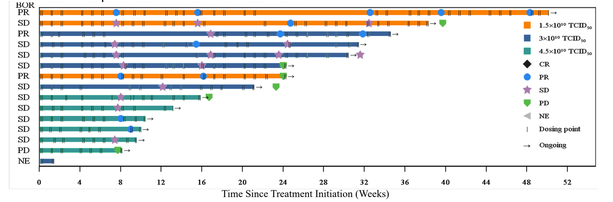


Figure 7. Time on Treatment and Tumor Assessment

CONCLUSIONS

- This phase I bridging study shows that intravenous administration of AN1004 plus paclitaxel is safe and well-tolerated in Chinese patients with advanced/metastatic (A/M) breast cancer. No dose-limiting toxicities (DLTs) or serious AEs (SAEs) were observed in the study to date.
- Combination of AN1004 and paclitaxel therapy in Chinese breast cancer patients with A/M disease demonstrates anti-tumor activity.
- Follow-up of the study will continue to evaluate safety, tolerability and efficacy.