

A Phase 1 Study of ARX788, a HER2-Targeting Antibody-Drug Conjugate, in Patients with Metastatic HER2-Positive Breast Cancer

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BACKGROUND

Amplification or overexpression of human epidermal growth factor receptor 2 (HER2) occurs in approximately 20-30% of primary breast cancers and is associated with a negative prognosis, shortened overall survival.¹

ARX788 is a novel site-specific antibody drug conjugate (ADC) that consists of a HER2-targeting monoclonal antibody (mAb) linked to the cytotoxic payload AS269, a highly potent tubulin inhibitor. Through a proprietary technology, a non-natural amino acid is precisely incorporated into the pre-determined site on the heavy chain of the mAb, and AS269 is covalently conjugated to the non-natural amino acid through a single-step conjugation reaction in an aqueous solution. In nonclinical studies, ARX788 has demonstrated robust anticancer effects in multiple tumor cell lines, including breast, ovarian, and gastric cancers, and has shown more potent anticancer activity when compared with T-DM1.²

ARX88 phase 1 studies are on-going in USA and Australia (NCT03255070) and in China (CTR20171162). Here we present results of a phase I study (CTR20171162) to evaluate safety, pharmacokinetics and preliminary antitumor effect of ARX788 in Chinese patients with metastatic HER2-positive breast cancer. (pharmacokinetics results not included with this poster)

METHODS

Key inclusion criteria:

- Female between 18 and 70 years old
- Life expectancy of more than 3 months
- Pathologically documented breast cancer
 - Unresectable or metastatic
 - HER2-positive expression or gene-amplified confirmed via immunohistochemistry [IHC3+] or fluorescence in situ hybridization [FISH+]
- ECOG performance status is 0 or 1
- Adequate Organ function
 - Absolute neutrophil count $\geq 1.5 \times 10^9/L$, Platelet count $\geq 100 \times 10^9/L$, Hemoglobin $\geq 9.0 g/dL$
 - CrCl $\geq 50 mL/min$, total bilirubin $\leq 1.5 \times ULN$, AST/ALT $\leq 2.5 \times ULN$ ($\leq 5.0 \times ULN$, if hepatic metastases present)
 - Left ventricular ejection fraction (LVEF) $\geq 50\%$
 - Chronic kidney disease epidemiology [CKD-EPI] collaboration equation $\geq 50 mL/min$

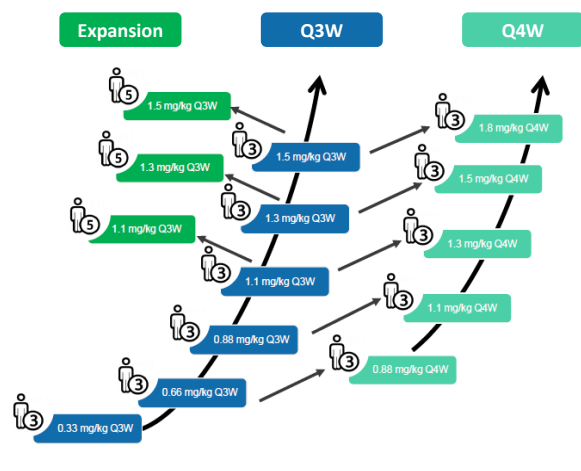


Figure 1. Dose escalation and dose expansion scheme.

Characteristic	No. (%); n=51
Age, years	
Median	52
Range	30-66
Gender	
Female	51 (100%)
Race	
Asian	51 (100%)
HER2	
IHC3+	32 (62.7%)
IHC2+ FISH+	16 (31.4%)
ICH unknown/FISH+	3 (5.9%)
Prior treatment	
Herceptin	51 (100%)
Lapatinib	24 (47.1%)
Pyrotinib/Lapatinib	3 (5.9%)

Table 1. The characteristic of enrolled study participants

RESULTS

ENROLLMENT

As the cutoff date of 20 Nov 2019, 51 female Chinese participants received at least one dose of ARX788 (Table 1). All enrolled participants were HER2 positive and IHC3+ accounted for 63.7%. There were 17 participants still active on study, with the one participant in 0.88 mg/kg Q3W cohort being undergone the treatment for almost two years (Figure 4).

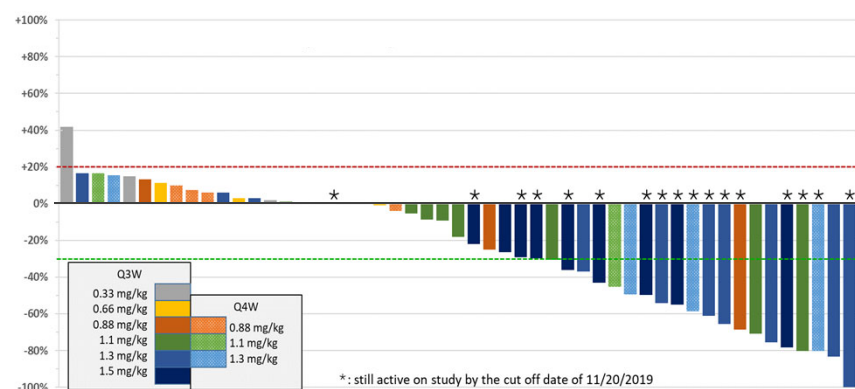


Figure 2. Waterfall plot of best response of target lesion from baseline. Different color represents different dose level or dose schedule.

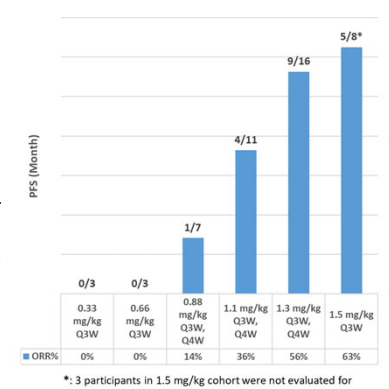


Figure 3. Best response of target lesion from baseline. The ORR increased with escalated dose level.

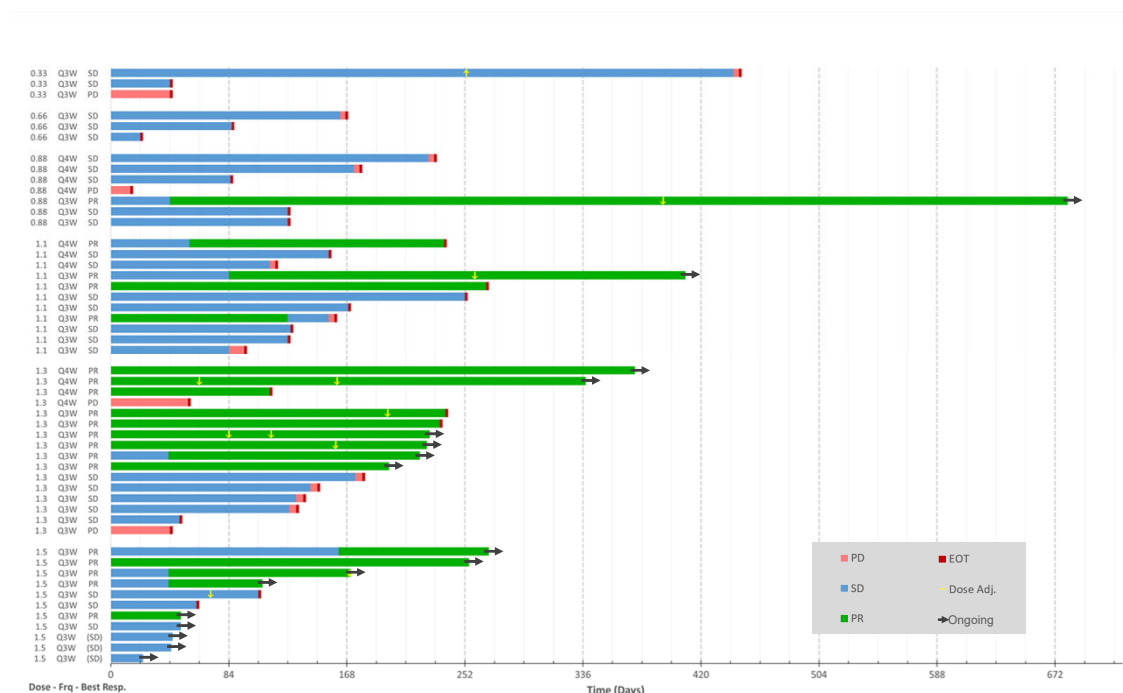


Figure 4. Swimming plot of individual overall response during the study.

EFFICACY

As the cutoff date, there were 48 evaluable participants with 3 participants did not reach the time of first assessment. The efficacy in 1.5mg/kg Q3W expansion cohort is still under observation. (Figure 2-4)

- The best responses were PR in 19 patients and SD in 25 patients with disease control rate of 91.7% (44/48).
- The ORR and PFS improved with increasing dose levels. The ORR increased from 0% at 0.33 mg/kg dose level to 56% at 1.3 mg/kg, and further increased to 63% at 1.5 mg/kg. (Figure 3)

SAFETY

- A total of 488 treatment emergent adverse events (TEAE) (Table 2), most were Grade 1 or 2 in severity. The most commonly reported TEAEs were liver enzymes (AST, ALT) elevation, fatigue, alopecia and dry eye (Table 3).
- Six SAEs were reported, with 1 (Grade 3 pneumonitis, 2.0%) considered to be ARX788 related and reversible. The event was improved after treatment with steroid/antibiotics, and the study drug was resumed at a reduced dose.
- Eight cases (15.7%) of drug-related pulmonary toxicities were reported in 51 subjects. Among the eight cases of lung toxicities, seven (13.7%) were Grade 1 mild to Grade 2 moderate in severity and one (2.0%) was in Grade 3.
 - Six participants improved after treated with antibiotics alone or in combination with steroids, and ARX788 treatments were resumed at a decreased dose afterwards.
 - Two discontinued (one voluntarily withdrawn and one due to disease progression).

	0.33mpk Q3W N=3, n(%)E	0.66mpk Q3W N=3, n(%)E	0.88mpk Q3W/Q4W N=7, n(%)E	1.1mpk Q3W/Q4W N=11, n(%)E	1.3mpk Q3W/Q4W N=16, n(%)E	1.5mpk Q3W N=11, n(%)E	Total N=51, n(%)E
ANY TEAE	3(100)14	3(100)21	7(100)73	11(100)133	16(100)192	7(63.6)55	47(92.2)488
Drug Related	3(100)11	3(100)15	7(100)65	10(90.9)96	15(93.4)175	7(63.6)46	45(88.2)408
CTCAE Grade 1-2	3(100)14	3(100)19	7(100)71	10(90.9)130	15(93.4)190	7(63.6)54	47(92.2)478
Drug Related	3(100)11	3(100)15	7(100)64	10(90.9)96	15(93.4)172	7(63.6)45	45(88.2)405
CTCAE Grade ≥ 3	0	2(66.7)2	2(28.6)2	3(27.3)3	2(12.5)2	1(9.1)1	10(19.6)10
Drug Related	0	0	1(14.3)1	0	0	1(9.1)1	2(3.9)2
Death	0	0	0	0	0	0	0
All SAE	0	1(33.3)1	1(14.3)1	1(12.5)1	2(12.5)2	1(9.1)1	6(11.8)6
Drug Related	0	0	0	0	0	1(9.1)1	1(2.0)1
AESI	0	1(33.3)1	3(42.8)6	7(63.6)14	12(75.0)34	4(36.4)8	27(52.9)63
Any Ocular Tox.	0	0	2(28.6)2	5(45.5)10	11(68.8)24	3(27.3)5	21(41.2)41
Any Pulmonary Tox.	0	0	1(14.3)1	2(18.2)3	6(37.5)16	1(9.1)1	10(19.6)12

Table 2. The summary of adverse events encountered during the study.

The most commonly reported AEs	n(%)
Elevated AST level	30(58.8)
Elevated ALT level	21(43.8)
Fatigue	15(29.4)
Alopecia	15(29.4)
Dry eye	15(29.4)
Hypokalaemia	14(27.5)
Abnormal ACTH level	12(23.5)
Dry mouth	11(21.6)
Cough	11(21.6)

Table 3. The most commonly reported AEs (>20%).

CONCLUSION

- ARX788 was well tolerated in heavily-pretreated metastatic breast cancer patients with HER2 expression.
- Pulmonary toxicities and ocular toxicities appear to be manageable at dose up to 1.5 mg/kg Q3W. Only one drug-related Grade 3 pneumonitis was reported among 51 enrolled subjects.
- Response rate increased with increased dose levels, but the accompanying toxicities did not increase significantly. Encouraging overall responses rate were observed in 1.3 (56%) and 1.5 mg/kg (63%) cohorts.
- No DLT was observed and MTD has not been reached.
- Given the benefit/risk profile, 1.5 mg/kg may be considered as the recommended dose for further development of ARX788 in HER2-positive breast cancer.

REFERENCES

- F. Meric-Bernstam and M. C. Hung, "Advances in targeting human epidermal growth factor receptor-2 signaling for cancer therapy" Clinical Cancer Research, vol. 12, no. 21, pp.6326-6330, 2006.
- Shastri P, Zhu JJ, et al. Nonclinical development of next generation site-specific HER2 targeting antibody drug conjugate (ARX788) for breast cancer treatment. Molecular Cancer Therapeutics. (minor revision submitted)