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 onto 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 non-clinical studies, ARX788 has demonstrated robust antitumor effects in multiple tumor cell lines, including breast, ovary, and gastric cancers, and has shown more potent antitumor activity when compared with T-DM1.2

As the cutoff date of 20 Nov 2019, 51 female Chinese participants received at least one dose of ARX788 (Table 1). With the one participant in 0.88 mg/kg Q3W cohort being undergone the treatment for almost two years (Figure 4). Six patients (11.8%) were reported AEs of grade ≥3. The most commonly reported AEs were liver enzymes (AST, ALT) elevation, fatigue, alopecia and dry eye (Table 3). Commonly reported AEs 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. 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 Two discontinued (one voluntarily withdrawn and one due to disease progression).

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 11 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).

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. 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

CONCLUSION
• ARX788 was well tolerated in heavily-pretreated metastatic breast cancer patients with HER2 expression.
• 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.
• 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.

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 in situ hybridization (ISH) or fluorescence in situ hybridization (FISH)
• ECOG performance status 0 or 1
• Adequate Organ function:
  - Absolute neutrophil count ≥1.5 x 10^9/L, Platelet count ≥100 x 10^9/L, Hemoglobin ≥9.0 g/dL
  - CHD ≤50 mL/min, total bilirubin ≤1.5 x ULN, AST/ALT ≤2.5 x ULN (≤5 x ULN in hepatic metastases present)
  - Left ventricular ejection fraction (LVEF) ≥50%
  - Chronic kidney disease epidemiology [CKD-EPI] collaboration equation ≥ 50 mL/min
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RESULTS
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 11 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).

Efficacy
As the cutoff date of 20 Nov 2019, there were 48 evaluable participants with 3 participants did not reach the time of first assessment. The efficacy in 1.5 mg/kg Q3W expansion cohort is still under observation (Figure 2-4).

• The ORR and PSF 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 62% at 1.5 mg/kg.

Safety
• A total of 488 treatment emergent adverse events (TEAE) were reported, most grade 1 or 2 severity. The most commonly reported TEAEs were liver enzyme elevation, fatigue, alopecia and dry eye (Table 2). Six (11.8%) were reported with Grade ≥3.

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• No Grade 4 toxicity was reported.

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• Encouraging overall responses rate were observed in 1.3 (56%) and 1.5 mg/kg (63%) cohorts.
• 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.

CONCLUSION
• ARX788 was well tolerated in heavily-pretreated metastatic breast cancer patients with HER2 expression.
• 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.
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APPLICATIONS
• ARX788 was well tolerated in heavily-pretreated metastatic breast cancer patients with HER2 expression.
• 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.
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REFERENCES