Impressive Efficacy and Safety Profile of a Novel Generation Duocarmycin-Based HER2-Targeting ADC.


INTRODUCTION

A new generation platform of linker-drugs (LDs) has been developed based on chemically synthesized duocarmycins which are DNA-alkylating cytotoxic drugs that induce cell death in both dividing and non-dividing cells. To assess the value of this new LD technology, ADCs were prepared based on the mAb trastuzumab to target HER2 positive tumors. A set of trastuzumab-based ADCs were produced by chemical linkage of different LDs to the thiol groups of cysteines generated by random reduction of interchain disulfides on the Ab, using thiomaleimide chemistry. The profile of lead candidate SYD983 is presented in this poster. Based on the preclinical profile as presented in this poster, SYD983 was fractionated, leading to SYD985 that mainly contains DAR2 and DAR4 species. SYD985 will be evaluated in clinical trials. SYD985 was profiled head-to-head to T-DM1 in efficacy studies as presented on poster 2652.

OBJECTIVE

To assess the value of our new generation linker-drug platform

Proposed MoA of SYD983/SYD985

RESULTS

Cytotoxicity in vitro is HER2-mediated

Figure 2. (A) % of internalization in time for SYD983 vs trastuzumab in SKBR3 cells. Cytotoxicity induced by seco-DUBA (B) or SYD983 (C) in a series of cell lines.

Anti-tumor activity in vivo is AUC-driven

Figure 3. Antitumor activity in BT-474 xenograft tumor model. Mice were treated i.v. as indicated by the arrow on the X-axis. (A) Effect of SYD983 in a dose range compared to trastuzumab. (B) Effect of adding free toxin to trastuzumab an anti-tumor activity. Seco-DUBA was added to 15 mg/kg trastuzumab at equimolar concentration compared to that present in SYD983. (C) Activity of SYD983 in the BT-474 xenograft model is AUC-driven.

Poor stability in mice due to species-specific esterase (CES1c). SYD983 stable in human and cyno plasma.

Figure 4. In vitro kinetics of SYD983 in different species. ADC concentration after 96 hrs incubation of 100 μg/mL SYD983 at 37°C in (A) human, monkey and mouse plasma or (B) plasma from mouse carboxylesterase 1c (CES1c) knockout mice versus wild type mice.

Poor PK in mice, stable PK in cynomolgus monkey

Figure 5. In vivo kinetics of SYD983 in mice and cynomolgus monkeys. (A) Time concentration curves of total antibody (TAb) or ADC concentration (n = 3, ± SEM) after single dose i.v. administration of 0.2, 1 or 5 mg/kg SYD983 to healthy Balb/c mice, or, (B) 1.3,10 or 30 mg/kg SYD983 in cynomolgus monkeys.

Potential differentiators SYD983 in Cynomolgus safety study

- SYD983 was well tolerated in cynomolgus monkeys up to 2 dosages of 30 mg/kg, 3.5 weeks apart. Exposure is shown in Fig 5.
- Effects were mild and/or transient; transient BW loss of 8.7% max in the 2nd cycle, mild transient decrease of WBCs at ≥ 10 mg/kg and hyperpigmentation in the skin at ≥ 10 mg/kg/cycle.
- The HNSTD was determined to be 30 mg/kg/cycle.
- Potential differentiators identified: no hepatotoxicity, no thrombocytopenia, and no signs for peripheral sensory neuropathy.

Fractionation of SYD983 to yield SYD985

Figure 6. Hydrophilic Interaction Chromatography (HIC) profiles of SYD983 (A) and SYD985 (B). SYD983 consists of mainly DAR0, DAR1, and DAR4 species. SYD985 is obtained after HIC fractionation of SYD983. SYD985 consists of mainly DAR2 and DAR4 species.

SUMMARY

- In vitro studies with SYD983 are in line with proposed MoA involving rapid HER2-mediated internalization and cell killing.
- Stability of SYD983 in mouse plasma is strongly reduced by mouse-specific CES1c. In vitro plasma stability for other relevant species is good. PK profile of SYD983 in cynomolgus monkey is in vivo in line with in vitro plasma stability data.
- Despite poor PK in mice, SYD983 shows potent anti-tumor activity.
- Anti-tumor activity observed in mice is most likely an underestimation of what will be obtained in humans.
- The safety profile of SYD983 indicates an acceptable TI and potential differentiators to T-DM1.
- HIC fractionation was used to fractionate SYD983, eliminating naked Ab, yielding SYD985 that consists mainly of DAR2 and DAR4 species.

CONCLUSIONS

1. HIC-fractionated SYD985 will be the (pre-)clinical candidate that will be evaluated in clinical trials.
2. The outcome of these experiments warranted head-to-head testing of the efficacy of SYD985 to T-DM1 in vitro and in vivo, in PDX models (see accompanying poster 2652).
3. More generally, this new generation duocarmycin-based linker drug technology could be combined to other mAbs to serve more indications in oncology.

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