The HER2-targeting ADC SYD985 shows superior antitumor activity compared to T-DM1 in preclinical studies with an activity profile that includes low-HER2 expressing breast cancers.


**INTRODUCTION**

SYD985 is a HER2-targeting ADC based on Synthon’s newly developed, duocarmycin-based, linker-drug technology. SYD985 consists of a cleavable linker–drug (vc-seco-DUBA; Figure 1) coupled to the mAb trastuzumab. Head-to-head studies were performed comparing anti-tumor activity of SYD985 versus T-DM1 in cell lines in vitro and in (patient-derived) xenografts in vivo. SYD985 mainly consists of DAR2 and DAR4 species and is the fractionated form of SYD983 which we also refer to as poster 2651.

**OBJECTIVE**

To compare the anti-tumor activity of SYD985 to T-DM1.

**vc-seco-DUBA**

![Image of vc-seco-DUBA](image)

**RESULTS**

**Cytotoxicity in vitro**

![Figure 2. Cytotoxicity induced by SYD985 versus T-DM1 in a series of cell lines with different HER2 expression levels (indicated). Incubation times were 6 days (A-D, G-H) or 12 days (E-F) in the presence of ADC.](image)

**Anti-tumor activity and survival in vivo in (patient-derived) xenografts**

![Figure 3. SYD985 and T-DM1 were tested at different dosages for their anti-tumor activity in vivo in a series of cell-line-derived (BT-474) and breast-cancer PDX models. Xenograft models (names indicated) were performed by different CROs using different, well-established, methods (kits). FISH and IHC classification was independently confirmed using tumors prepared from vehicle-treated mice at the end of the study. IHC was performed on the Discovery automated platform (Ventana Roche) with the primary Ab anti-HER2/neu (485). (A) Anti-tumor activity of SYD985 versus a non-binding isotype control ADC (rituximab-based) in the respective xenograft models shows that activities induced by SYD985 are mediated through HER2. ADCs were administered intravenously by a single dose at the time indicated by the arrow. (B) Anti-tumor activity of SYD985 versus T-DM1. (C) Modified Kaplan-Meier curves indicating survival of mice in the xenograft studies.](image)

**PK of SYD985 and T-DM1 in tumor-bearing mice**

![Figure 4. Mean ADC plasma concentrations in BT-474 tumor bearing mice after a single intravenous bolus injection of SYD985 at 1 or 3 mg/kg and T-DM1 at 1 or 3 mg/kg (corrected from 5 mg/kg) (± SEM, n = 3).](image)

**SUMMARY**

- SYD985 is more potent than T-DM1 in vitro in low HER2 expressing cell lines.
- SYD985 is more active than T-DM1 in vivo in a HER2 3+ cell-line and breast cancer patient-derived xenograft.
- SYD985 shows remarkable anti-tumor activity in breast cancer PDX models with low (2+ & 1+) HER2 expression.
- T-DM1 is not active in these low HER2-expressing tumor xenograft models, not even at a 10-fold higher dose than the effective SYD985 dose.
- SYD985 PK in mice is poor (mouse specific issue; see poster 2651). Exposure and anti-tumor activity of SYD985 in mice is an underestimation of what is expected in humans.

**CONCLUSION**

The anti-tumor activity of SYD985 in preclinical models warrants clinical studies in breast-cancer patients with low (FISH-negative / IHC HER2 2+ & 1+) HER2 expression.

**OUTLOOK**

- SYD985 may double the target population of breast cancer patients that could benefit from HER2-mediated ADC therapy.
- A Phase I clinical trial will start 2nd half of 2014

Acknowledgement:

- BT-474 xenograft was performed at Oncodesign, Dijon, France
- MAXF 1162 and MX1 were performed at Oncotest, Freiburg, Germany
- HBCx-10 and 34 were performed at XenTech, Paris, France
- ST-313 was performed at Start, San Antonio, TX, USA