# SOT102, a novel CLDN18.2-targeting antibody-drug conjugate with strong therapeutic potential in solid tumors expressing low target levels

Poster nr. 1204

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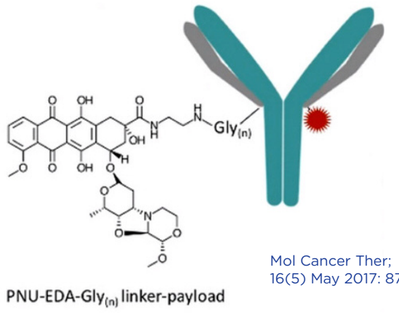
## Abstract

Claudin (CLDN) 18.2, a member of a large family of transmembrane proteins with distinct functions, has been shown to have a high prevalence, predominantly in gastric and pancreatic cancer. In addition, ectopic expression of CLDN18.2 was described for other cancer types including ovarian, lung, liver and colon, whereas healthy tissue expression is restricted to the stomach. SOT102 represents a CLDN18.2 targeting antibody-drug conjugate based on a novel proprietary highly specific monoclonal antibody conjugated to a derivative of PNU-159682 using site-specific conjugation technology for the therapy of patients with various CLDN18.2-positive solid tumors, mainly of gastric and pancreatic origin. The CLDN18.2 protein sequence is highly conserved in mammalians with 100% identity in the targeted extracellular loop among rodents, cynomolgus monkey and human.

SOT102 showed excellent specificity for CLDN18.2 and strong binding to the target followed by efficient tumor cell killing. Preferential binding to selected patient-derived tumor tissues was observed *ex vivo* when compared to healthy stomach tissues from mice and cynomolgus monkey. Single-agent therapeutic activity of SOT102 was demonstrated in 10 patient-derived mouse xenograft models (gastric, pancreatic, liver, colon and lung adenocarcinomas). Complete responses were observed in all models, independent of CLDN18.2 expression levels, ranging from low (IHC1+) to high (IHC3+), with minimum effective doses between 0.2 mg/kg and 0.6 mg/kg. An acceptable tolerability profile was observed in preliminary toxicity studies at 10 mg/kg (mouse), 6 mg/kg (rat) and 1 mg/kg (cynomolgus monkey). SOT102 demonstrated favorable pharmacokinetic properties with half-lives in the range of 8 days and 13 days in cynomolgus monkey and rat, respectively. Stability of SOT102 without any significant loss of the payload was demonstrated *in vitro* and in animals.

Further toxicology studies in rats and cynomolgus monkeys were initiated, paralleled by process development and manufacturing activities with the plan to initiate the first clinical study with SOT102 in the first half of 2022.

## SOT102 (CLDN18.2 ADC)



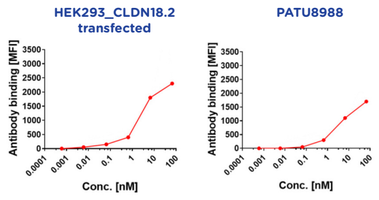

Mol Cancer Ther; 16(5) May 2017: 879-892

- SOT102 is a novel antibody-drug conjugate based on a proprietary IgG1 monoclonal antibody conjugated in a site-specific manner via a non-cleavable amide/peptide linker to a derivative of the highly potent anthracycline PNU-159682 payload in a DAR2 light chain format. Effector functions of the antibody have been modified to decrease FcRγ interaction, while maintaining FcRn binding.
- SOT102 shows strong antitumor efficacy *in vitro* and *in vivo* in mice in different cancer models, including those with very low target expression. SOT102 demonstrated a manageable safety profile. The developability parameters are favorable, and the humanness score is in the range of fully human FDA approved antibodies.

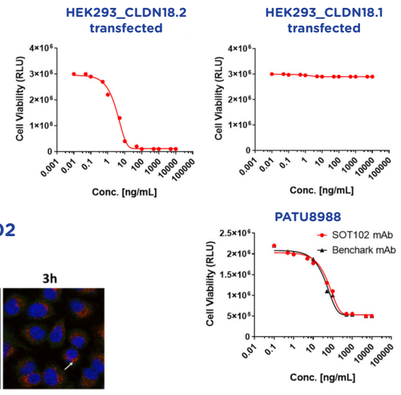
## Figure 1

### SOT102 internalizes efficiently and demonstrates target-specific cytotoxic activity

**A** Efficient binding of SOT102 to target expressing cells




**C** Target-specific killing of SOT102 in target expressing cells




**B** Efficient internalization of SOT102 into target expressing cells

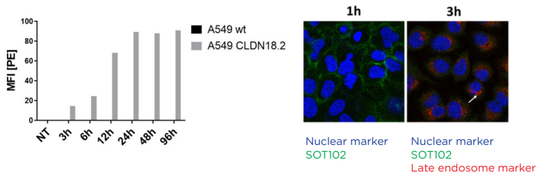




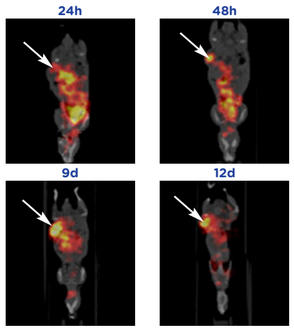


**Figure 1**. **(A)** SOT102 monoclonal antibody displays high target affinity ($EC_{50}$: 2-4nM), demonstrated with CLDN18.2 transfected (HEK293) and endogenously expressing (PATU8988) cell lines. **(B)** Internalization into target expressing cells (> 60% internalized within the first 12h) and efficient delivery to late endosomes is followed by **(C)** target-specific and efficient killing at an $EC_{50}$ ranging from 10 pM (HEK293_CLDN18.2 transfected cell line) to 500 pM (PATU8988 cell line with endogenous target expression).

## Figure 2

### SOT102 accumulates rapidly in the tumor and exerts excellent anti-tumor potency in vivo in patient-derived xenografts across various indications

**A** SPECT analysis of SOT102-$^{125}$I biodistribution in BxPC3_CLDN18.2 CDX model




Note: Tumor implantation site is marked with white arrow.

Endpoint γ-counter analysis of SOT102-$^{125}$I accumulation in selected organs ex vivo on day 12

| Organ | Radioactivity [MBq] | | % Radioactivity | |
|---|---|---|---|---|
| | M02 | M03 | M02 | M03 |
| tumor | 0.596 | 0.788 | 18.76% | 9.75% |
| stomach | 0.021 | 0.074 | 0.66% | 0.92% |
| lungs | 0.048 | 0.111 | 1.51% | 1.37% |
| thyroid | 0.346 | 0.584 | 10.89% | 7.23% |
| renal | 0.035 | 0.16 | 1.10% | 1.98% |
| liver | 0.082 | 0.315 | 2.58% | 3.90% |
| blood | 0.235 | 1.179 | 7.40% | 14.59% |
| cadaver | 2.04 | 4.851 | 64% | 60.00% |

Notes: Tissues with target unrelated accumulation of the signal are marked in red.
M02 and M03 represent individual animals as a representative example of inter-animal variability.
% is calculated in relation to the administered dose.

**B** Antitumor efficacy of SOT102 in subcutaneous patient-derived xenograft models

| Indication | PDX model | Target expression | Therapeutic response (T/C < 10%) |
|---|---|---|---|
| Pancreatic cancer | PAXF2051 | low | +++ |
| | PAXF1861 | intermediate | +++ |
| | PAXF2146* | intermediate | ++ |
| | PAXF2011 | intermediate | +++ |
| | PAXF2175 | high | +++ |
| Gastric cancer | GXA3037* | high | + |
| Lung Cancer | LXFA3109 | intermediate | ++ |
| Colon cancer | CXF742** | intermediate | + |
| Liver cancer | LIXFC2050 | low | +++ |
| | LIXFC LI-007* | intermediate | +++ |

* BRCA2 mutation; ** BRCA1,2 mutation

Scoring of the therapeutic response:
+.....response observed in 1/3 of treated animals
++.....response observed in 2/3 of treated animals
+++....response observed in all animals

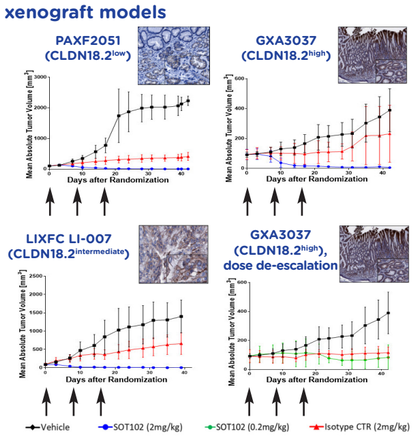
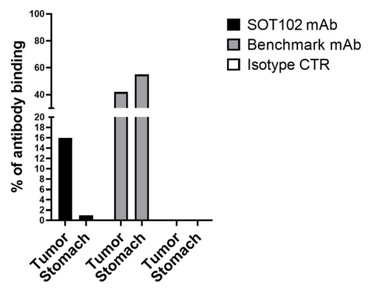



**Figure 2. (A)** Biodistribution of radioactively labelled SOT102 in mice showed effective accumulation in the tumor (subcutaneously implanted target expressing xenograft) with limited binding to healthy stomach tissue. **(B)** In vivo efficacy experiments conducted in patient-derived xenografts upon subcutaneous implantation into partially immunocompromised NMRI nude mice (q3w; 2 mg/kg). Tumor growth inhibition followed by tumor burden reduction to less than 10% of the respective vehicle-treated control group was observed for 6 out of 10 cancer models independent of the CLDN18.2 expression level (low-high). Furthermore, durable complete responses were noted also when the therapeutic dose was decreased 10-fold to 0.2 mg/kg.

## Figure 3

### SOT102 shows preferential binding to CLDN18.2 expressed in tumor compared to healthy stomach tissue

**A** Preferential ex vivo binding of SOT102 to tumor tissue compared to healthy stomach in mice




**B** Preferential binding of SOT102 to gastric tumor over healthy frozen human stomach

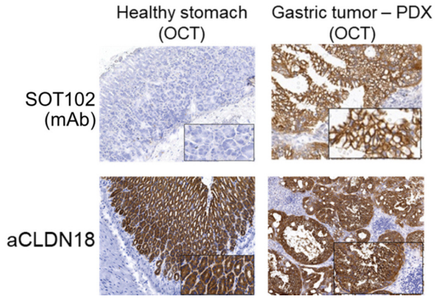
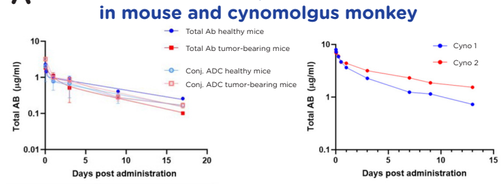



**Figure 3. (A)** SOT102 (mAb) exhibits stronger binding to tissue cell suspensions of CLDN18.2 positive gastric tumor tissue than to healthy stomach tissue ex vivo. SOT102 (mAb) binding is more tumor selective when compared to a benchmark CLDN18.2-specific monoclonal antibody. **(B)** SOT102 (mAb) presents with strong staining in frozen sections of CLDN18.2 positive gastric tumor tissue compared to healthy stomach tissue. A commercially available aCDLN18 monoclonal antibody was used for comparison.

## Figure 4

### SOT102 has a favorable pharmacokinetic profile and is well-tolerated in both, mice and cynomolgus monkeys

**A** Pharmacokinetic profile of SOT102 in mouse and cynomolgus monkey




**B** Selected pharmacokinetic parameters of SOT102 in mouse and cynomolgus monkey

| SOT102 | Mouse | Cyno |
|---|---|---|
| Nominal Dose (mg/kg) | 0.2 | 0.3 |
| C0/dose (µg/ml per mg/kg) | 14.4 | 25 |
| AUC0-inf/Dose ratio (h*µg/ml per mg/ml) | 1568 | 3581 |
| T1/2 Terminal (days) | 7.9 | 7.8 |

#) AUC/Real Dose ratio calculated based on the measurement of the dose formulation concentration.
±) C0: calculated concentration at T0.

**C** Currently estimated therapeutic index based on available animal data

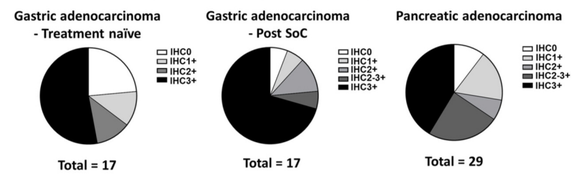
| | Therapeutic dose | MTD | Therapeutic window |
|---|---|---|---|
| Mouse | 0.2 to 0.6 mg/kg | 10 mg/kg | ~ 20-fold |
| Cynomolgus | 0.05 to 0.15 mg/kg<br>*based on mouse doses and allometric inter-species factor of 4* | 1 mg/kg | ~ 10-fold |

**Figure 4. (A)** Concentration profiles of SOT102 after single dose administration to healthy and tumor-bearing mice and cynomolgus monkeys. **(B)** Selected pharmacokinetic parameters showing favorable properties. **(C)** SOT102 was tolerated in mice up to a maximal dose (MTD) of 10 mg/kg (single dose administration) and in cynomolgus monkey up to a maximal dose of 1 mg/kg.

## Figure 5

### A large proportion of patients suffering from gastric and pancreatic adenocarcinoma expressing CLDN18.2 at low to intermediate levels represent the targeted population for SOT102 therapy

**A** Assessment of the frequency and prevalence of CLDN18.2 expression in gastric and pancreatic carcinoma




**B** Published frequency and prevalence of CLDN18.2 expression in gastric and pancreatic carcinoma

| Study reference | Indication | Nr. of samples | % of CLDN18.2 positive | % of ≥IHC2+ |
|---|---|---|---|---|
| Rohde et al., 2019 | Gastric | 262 | 87 | 51.5 |
| Dottermusch et al., 2019 | Gastric | 274 | 84.5 | N/A |
| Tanaka et al., 2011 | Pancreatic | 156 | 69.9 | 64 |

**Figure 5. (A)** Immunohistochemical analysis of 34 gastric and 29 pancreatic adenocarcinoma patients. High prevalence of CLDN18.2 expression was observed, however, a significant proportion of patients showed low or intermediate CLDN18.2 expression levels. Pie charts show the frequency (%) of samples with a respective level of target positivity. **(B)** Presented data are in line with the published prevalence of CDLN18.2 expression in gastric adenocarcinoma and pancreatic (here PDAC) patients.

## Conclusions & Outlook

- **SOT102 represents a novel antibody-drug conjugate with a strong potential to eliminate tumor cells in a target-specific manner, enhanced by bystander killing effect (not shown), mediated by the PNU-159682 derived payload.**
- **SOT102 GLP studies in rats and cynomolgus monkeys and CMC manufacturing are currently ongoing with IND filing planned for Q4/2021.**
- **SOT102 first-in-human study in gastric and pancreatic cancer patients will follow in early 2022.**
- **A target-specific companion diagnostic is planned to correlate target expression with clinical outcome.**
- **Preclinical combination studies with PD-1 inhibitor in gastric tumor models are ongoing.**
- **Patent applications covering SOT102 monoclonal antibody and antibody-drug conjugate are pending.**

## References

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