SOT102, a novel CLDN18.2-targeting antibody-drug conjugate for gastric and pancreatic cancer with wide range of the target expression

FPN: **2P**

Radek Spisek[1,2], Iva Valentova[1,2]

[1]SOTIO Biotech a.s., Jankovcova 1518/2, Prague 7, 170 00, Czech Republic; [2]Department of Immunology, 2nd Faculty of Medicine and University Hospital Motol, Charles University, V Uvalu 84, Prague 5, 150 06, Czech Republic

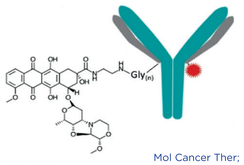
Abstract

Claudin (CLDN) 18.2, a member of a large family of transmembrane proteins with distinct functions, has been shown to have high prevalence, predominantly in gastric and pancreatic cancer. Ectopic expression of CLDN18.2 was also described in certain proportion of ovarian cancer, NSCLC, hepatocellular cancer and colorectal cancer. Healthy tissue expression is restricted to the stomach epithelium. SOT102 represents a novel CLDN18.2 targeting antibody-drug conjugate based on a proprietary monoclonal antibody conjugated to a derivative of PNU-159682 via site-specific sortase mediated conjugation. The CLDN18.2 protein sequence is highly conserved across species with a 100% identity in the targeted extracellular loop among rodents, cynomolgus monkeys and humans.

SOT102 showed an excellent specificity for CLDN18.2 and strong binding to the target followed by an efficient tumor cell killing. Preferential binding to selected patient-derived tumor tissues was observed *ex vivo* when compared to the healthy stomach tissues from mice and cynomolgus monkeys. Single-agent therapeutic activity of SOT102 was demonstrated in numerous patient-derived xenograft models (gastric, pancreatic, liver, colon and lung adenocarcinomas). Complete responses were observed in all CLDN18.2 positive models, irrespective of the intensity of staining. 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 the toxicity studies at 10 mg/kg (mouse), 6 mg/kg (rat) and 1 mg/kg (cynomolgus monkey), providing a therapeutic index of approximately 10. SOT102 demonstrated favorable pharmacokinetic properties with the half-live in the range of 8 days and 13 days in cynomolgus monkeys and rats, respectively. SOT102 remains stable without any significant loss of the payload both *in vitro* and in animal models.

After completion of formal IND enabling preclinical studies, the first in human dose escalation trial has been initiated in mid-2022 in patients with gastric and pancreatic cancer.

SOT102 (CLDN18.2 ADC)



PNU-EDA-Gly$_{(n)}$ linker-payload

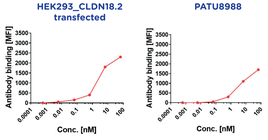
Mol Cancer Ther; 16(5) May 2017: 879-892

- 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.

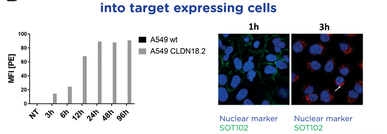
Figure 1

SOT102 internalizes efficiently and demonstrates target-specific cytotoxic activity

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



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



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

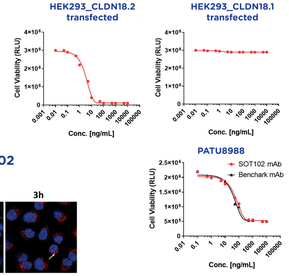
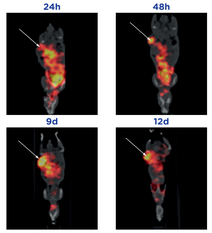


Figure 1. **(A)** SOT102 monoclonal antibody displays high target affinity (EC_{50}: 2-4nM), demonstrated with CLDN18.2 transfected (HEK293) and endogenously expressing (PATU8988) cell lines. **(B)** Internalization into target expressing cells (> 60% internalized within the first 12h) and efficient 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

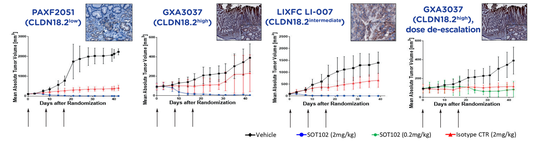
Organ	Radioactivity [MBq]		% Radioactivity	
	M02	M03	M02	M03
tumor	0.596	0.788	18.76%	9.75%
stomach	0.021	0.074	0.66%	0.92%
lungs	0.048	0.111	1.51%	1.37%
thyroid	0.346	0.584	10.89%	7.23%
renal	0.035	0.16	1.10%	1.98%
liver	0.082	0.315	2.58%	3.90%
blood	0.235	1.179	7.40%	14.59%
cadaver	2.04	4.851	64%	60.00%

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.

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.

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

Indication	PDX model	Target expression	Therapeutic response (TIC < 10%)
Pancreatic cancer	PAXF2051	low	+++
	PAXF1861	intermediate	+++
	PAXF2146*	intermediate	++
	PAXF2011	intermediate	+++
	PAXF2175	high	+++
Gastric cancer	GXA3037*	high	+
Lung Cancer	LXFA3109	intermediate	++
Colon cancer	CXF747**	intermediate	+
Liver cancer	LIXFC2050	low	+++
	LIXFC LI-007*	intermediate	+++



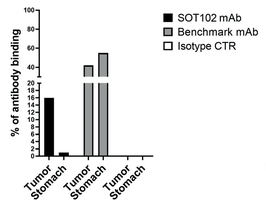
* BRCA2 mutation; ** BRCA1,2 mutation

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 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**

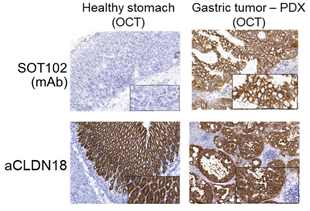
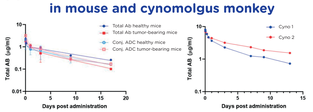


Figure 3. (A) SOT102 (mAb) exhibits stronger binding to tissue cell suspensions of CLDN18.2 positive gastric tumor tissue than to healthy stomach tissue ex vivo. SOT102 (mAb) binding is more tumor selective when compared to a benchmark CLDN18.2-specific monoclonal antibody. **(B)** SOT102 (mAb) presents 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
CO/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**

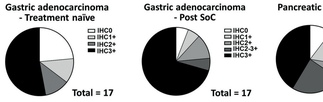
	Therapeutic dose	MTD	Therapeutic window
Mouse	0.2 to 0.6 mg/kg	10 mg/kg	~ 20-fold
Cynomolgus	0.05 to 0.15 mg/kg	1 mg/kg	~ 10-fold
	based on mouse doses and allometric inter-species factor of 4		

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 ade-nocarcinoma 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

- Beerli, R. R., Hell, T., Merkel, A., and Grawunder, U. (2015) Sortase Enzyme-Mediated Generation of Site-Specifically Conjugated Antibody Drug Conjugates with High In Vitro and In Vivo Potency. PLoS ONE 10, e0131177.
- Nikolas Stefan, Rémy Gébleux, Lorenz Waldmeier, Tamara Hell, Marie Escher, Fabian I. Wolter, Ulf Grawunder, and Roger R. Beerli. (2017) Highly Potent, Anthracycline-based Antibody–Drug Conjugates Generated by Enzymatic, Site-specific Conjugation. Mol Cancer Ther, DOI: 10.1158/1535-7163.MCT-16-0688.
- Christoph Rohde, Rin Yamaguchi, Svetlana Mukhina, Ugur Sahin, Kyogo Itoh and Özlem Türeci. (2019) Comparison of Claudin 18.2 expression in primary tumors and lymph node metastases in Japanese patients with gastric adenocarcinoma. Jpn J Clin Oncol. 49(9): 870–876.
- Matthias Dottermusch, Sandra Krüger, Hans-Michael Behrens, Christine Halske and Christoph Röcken. (2019) Expression of the potential therapeutic target claudin-18.2 is frequently decreased in gastric cancer: results from a large Caucasian cohort study. Virchows Archiv volume 475, p. 563–571.
- Mariko Tanaka, Junji Shibahara, Noriyoshi Fukushima, Aya Shinozaki, Makoto Umeda, Shumpei Ishikawa, Norihiro Kokudo and Masashi Fukayama. (2011) Claudin-18 Is an Early-Stage Marker of Pancreatic Carcinogenesis. J Histochem Cytochem. 59(10): 942–952.

Presenting authors have no conflicts of interest to declare.

For more information please contact corresponding author Radek Spisek, spisek@sotio.com.