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


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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 cancer. In addition, ectopic expression of CLDN18.2 was described for other cancer types including ovarian, lung 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 in 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 (HIC1+) to high (HIC3+), with minimal 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 accumulates rapidly in the tumor and exerts excellent anti-tumor potency in vivo in patient-derived xenografts across various indications

A) Spectral analysis of SOT102-15I biodistribution in BxPcs3_CLDN18.2 CDX model

B) Endpoint γ-counter analysis of SOT102-15I accumulation in selected organs ex vivo on day 12

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 immuno-compromised NMRI nude mice (4-6 weeks old). Tumor growth inhibition followed by tumor eradication was achieved in selected models independent of the CLDN18.2 expression level (low-high). Furthermore, durable complete responses were noted when the therapeutic dose was decreased 10-fold to 0.2 mg/kg.

Antimicrobial efficacy of SOT102 in subcutaneous patient-derived xenograft models

• SOT102 is a novel antibody-drug conjugate based on a proprietary mAb1G3 monoclonal antibody conjugated in a site-specific manner via a non-cleavable amido-peptide linker to a derivative of the potent anthracycline PNU-159682 payload in a DAR2 light chain format. Effector functions of the antibody have been modified to decrease FcγR interaction, while maintaining FcγRIIIa functions of the antibody. In the cell line with the published frequency (#) of CLDN18.2 expression in gastric and pancreatic carcinoma study, 100% binding and killing of tumor cells in a target-specific manner, enhanced by bystander killing effect (not shown), was observed for 6 out of 10 cancer models independent of the CLDN18.2 expression level (low-high). Furthermore, durable complete responses were noted when the therapeutic dose was decreased 10-fold to 0.2 mg/kg.

SOT102 was tolerated in mice up to a maximal dose of 10 mg/kg (single dose administration) and in cynomolgus monkey up to a maximal dose of 1 mg/kg.

Figure 5. (A) Immunohistochemical analysis of 34 gastric and 29 pancreatic adenocarcinoma cases expressing CLDN18.2. A low to intermediate level represents 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

• 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 pending.
• 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.

Conclusions & Outlook

• SOT102 shows strong anti-tumor 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. (A) SOT102 monoclonal antibody displays high target affinity (EC50: 2-4 nM), 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 EC50 ranging from 100 pM (CLDN18.2 transfected cell line) to 500 pM (PATU8988 cell line with endogenously target expression).

Figure 3. (A) Preferential in vivo binding of SOT102 to tumor tissue compared to healthy stomach tissue

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

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

Conclusions & Outlook

• SOT102 shows very promising results in vitro and in vivo, making it a strong candidate for further development in solid tumors expressing CLDN18.2.

References

• Matthias Dottermusch, Sandra Krüger, Hans-Michael Behrens, Christine Halske and Christoph Röcken. (2019) Preclinical combination studies with PD-1 inhibitor in gastric tumor models are ongoing. Preclinical combination studies with PD-1 inhibitor in gastric tumor models are ongoing. SOT102 was tolerated in mice up to a maximal dose of 10 mg/kg (single dose administration) and in cynomolgus monkey up to a maximal dose of 1 mg/kg.

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.

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• 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.
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