Preclinical development of SENTI-202, an off-the-shelf logic gated CAR-NK cell therapy, for the treatment of CD33/FLT3+ hematologic malignancies including AML

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**SENTI-202 Logic Gated CAR-NK cells**

*NOT Gated CAR-NK cells for the treatment of CD33/FLT3+ malignancies engineered to reduce on-target/off-tumor toxicities*

**Pharmacokinetics and Pharmacodynamics of SENTI-202**

In vitro persistence and pSTAT5 signaling

SENTI-202 CAR-NK CELLS HAVE INCREASED PERSISTENCE IN VITRO

SENTI-202 CAR-NK CELLS HAVE INCREASED PERSISTENCE IN VIVO

**Preclinical Pharmacology of SENTI-202**

In vitro cytotoxicity and cytokine production of SENTI-202

SENTI-202 CAR-NK CELLS HAVE INCREASED CYTOTOXICITY AGAINST CD33+/FLT3- TARGET CELLS COMPARED TO UNENGINEERED NK CELLS

**Summary and next steps**

SENTI-202 is a First In Class OR/NOT Logic Gated Off-The-Shelf CAR-NK Cell Therapy

**Preclinical development and in-house manufacturing capabilities**

Senti’s state of the art manufacturing facility and advanced GMP processes enable large scale production of SENTI-202 product from various healthy NK donors. Selected NK donors have been pre-clinically evaluated with demonstrated activity in-vivo in syngeneic mouse models, increasing the potential for donor-to-donor variability and scalability.

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Patients with CD33+ and/or FLT3 expressing malignancies, including myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), and chronic myelomonocytic leukemia (CMMoL) have very poor prognosis and high clinical unmet need. CD33 and FLT3 are well validated targets for myeloid malignancies, but current therapies targeted against these antigens present considerable limitations. On one hand, the presence of CD33 negative leukemia stem cells (LSCs) can contribute to minimal residual disease; on the other hand, expression of CD33 and/or FLT3 in the normal hematopoietic progenitor cells and progenitor cells (HSCs/PSCs) can lead to bone marrow toxicity, prolonged thrombocytopenia/neutropenia, and adverse post-transplant outcomes. SENTI-202 is a groundbreaking preclinical development to address these challenges and provide a broader therapeutic window, increasing the anti-tumor activity and safety for the treatment of CD33+ and/or FLT3+ malignancies. SENTI-202 is a first in class Logic gated CAR-NK product engineered with an OR and a NOT Logic Gate gene circuit approach to enhance therapeutic efficacy and safety, with additional aiming via expression of cytokine release (CR) (circ–10). A dual targeting approach (ANG CAR) that recognizes both CD33 and FLT3 tumor antigens improves the anti-tumor activity, ensuring the targeting of AML blasts and LSCs. Additionally, an inhibitory CAR (I-CAR) that recognizes endogenous (EMCN), a protective antigen expressed on the surface of healthy cells protects the CAR mediated cytotoxicity of healthy target cells including HSCs/HSPCs, improving the safety profile and reducing on-target/off-tumor toxicities. crk-15 promises NK cell activation and persistence.

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**SENTI-202**

*Engineered CARs for the treatment of CD33+/FLT3- and CD33+/FLT3+ hematologic malignancies*

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**Summary and next steps**

SENTI-202 is a First In Class OR/NOT Logic Gated Off-The-Shelf CAR-NK Cell Therapy

SENTI's novel logic-gated gene circuits have enhanced tumor targeting. The CD33/FLT3 OR Gate activating CAR successfully balances the targeting of primary AML blasts, LSCs, and MDS cells, while the NOT Gate decreases the killing of HSCs while preserving their function by an inhibitory CAR that detects a protective antigen, EMCN, found in healthy HSCs.

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