Byondis Initiates Phase I Study of ADC [Vic]-Trastuzumab Duocarmazine + Niraparib in HER2-Expressing Solid Tumors

Study Focused on Advanced HER2-Expressing Cancer Patients With No More Effective Therapy Options

Nijmegen, The Netherlands – 25 August 2020 – Byondis B.V. (formerly Synthon Biopharmaceuticals B.V.) today announced that the first patients have started treatment in a Phase I study of its investigational antibody-drug conjugate (ADC) [vic]-trastuzumab duocarmazine (SYD985) in combination with niraparib in patients with a HER2-expressing locally advanced or metastatic solid tumor.

A Two-part Phase I Study With the Antibody-drug Conjugate SYD985 in Combination With Niraparib to Evaluate Safety, Pharmacokinetics and Efficacy in Patients With HER2-expressing Locally Advanced or Metastatic Solid Tumors (SYD985.004) will enroll up to 120 patients who progressed on standard therapy or for whom no standard therapy of proven benefit exists. The first part of the study is taking place in leading European oncology centers in Belgium, United Kingdom and the Netherlands. Leading centers in France, Spain and Poland will join this trial at a later stage.

“We are excited to move to the clinical study phase of [vic]-trastuzumab duocarmazine in combination with PARP inhibitor niraparib,” said Byondis CEO Marco Timmers, Ph.D. “Preclinical investigation of SYD985 in combination with PARP inhibitors in HER2-expressing tumor cells suggested synergistic effects and we hope to confirm these effects in the clinic.”

SYD985 is Byondis’ most advanced ADC, in development for the treatment of a range of HER2-expressing tumor types including breast and endometrial cancer. Previously, the U.S. Food & Drug Administration granted SYD985 fast track designation based on promising data from heavily pre-treated last-line HER2-positive metastatic breast cancer patients participating in a two-part Phase
I clinical study (SYD985.001). The pivotal Phase III TULIP® study (SYD985.002) comparing the efficacy and safety of SYD985 to physician's choice treatment in patients with HER2-positive unresectable locally advanced or metastatic breast cancer is ongoing. In addition, Byondis recently announced the start of a Phase II study (SYD985.003) evaluating the safety and efficacy of SYD985 in patients with HER2-expressing recurrent, advanced or metastatic endometrial (uterine) cancer.

More About SYD985.004
SYD985.004 will explore the preclinically proven synergistic anti-tumor effects of the SYD985 and niraparib combination, which may result in increased efficacy. As both drugs will be given at lower doses than when applied as single agents, this could coincide with reduced toxicity. The study’s primary endpoint is dose-limiting toxicities in the first cycle (21 days). Secondary objectives include overall safety, pharmacokinetic and preliminary efficacy assessments for the combination treatment.

SYD985.004 will be conducted in two parts: Dose Escalation and Dose Expansion. Part 1, Dose Escalation, is expected to enroll about 30 patients with any HER2-expressing solid tumor to determine the maximum tolerated dose (MTD) and recommended dose for expansion (RDE). Part 2, Dose Expansion, is expected to enroll between 48 and 90 patients with one of three types of locally advanced or metastatic cancers: breast, ovarian or endometrial. All patients will be treated with SYD985 infusions once every three weeks in combination with oral niraparib. The latter will be administered once daily for one, two or three weeks, depending on the safety of the combination and the study cohort.

[Vic-]Trastuzumab Duocarmazine (SYD985), a Next Generation Antibody-Drug Conjugate
SYD985 uses Byondis’ proprietary linker-drug (LD) technology. Although in general, marketed ADCs have improved therapeutic indices compared to classical non-targeted chemotherapeutic agents, there is still room for improvement.

The ADC [vic-]trastuzumab duocarmazine is comprised of the monoclonal antibody trastuzumab and a cleavable linker-drug called valine-citrulline-seco-DUocarmycin-hydroxyBenzamide-Azaindole (vc-seco-DUBA). The antibody part of SYD985 binds to the HER2 antigen on the surface of the cancer cell and the ADC is internalized by the cell. After proteolytic cleavage of the linker, the inactive cytotoxin is activated and DNA damage is induced, resulting in tumor cell death. SYD985 can be considered a form of targeted chemotherapy.

Byondis’ Distinctive, Proprietary Linker-Drug Technology
In traditional chemotherapy, a cytotoxin enters the bloodstream and moves through the body to kill rapidly dividing cells that are common in tumors. The problem is that it also attacks rapidly dividing cells in normal tissue, potentially resulting in severe side effects.

Monoclonal antibodies are created to allow improved specificity by targeting receptors expressed on tumor cell membranes. In order to improve the cell-killing capability of antibodies, cytotoxic drugs can be attached to antibodies using a linker molecule, forming antibody-drug conjugates or ADCs.

While earlier generation ADCs improved targeting and cell killing, they were unstable in the bloodstream, which resulted in early release of the cytotoxic payload that impacted healthy tissue and narrowed the therapeutic window. Byondis’ next generation ADCs carry an intricate,
inactivated cytotoxic drug that rapidly self-destructs in case it is prematurely released, limiting damage to healthy tissue and improving the therapeutic window.

Byondis’ differentiated linker-drug, vc-seco-DUBA, owes its potent antitumor activity to a synthetic duocarmycin-based cytotoxin. Duocarmycins, first isolated from Streptomyces bacteria in the 1970s, bind to the minor groove of DNA and disrupt the nucleic acid architecture, which eventually leads to tumor cell death.

The distinctive design of the selectively cleavable linker connecting the antibody to the duocarmycin drug leads to high stability in circulation and induces efficient release of the cytotoxin in the tumor. Uptake of the activated payload by neighboring tumor cells with lower HER2 expression may improve the efficacy potential, the so-called bystander effect.

**Niraparib, a PARP Inhibitor**

Niraparib is a PARP inhibitor (PARPi) used in cancer therapy. PARP inhibitors are a type of targeted therapy used to treat cancers with existing defects in DNA repair. They block critical DNA repair pathways that these cancers rely on to repair their DNA as they grow and divide, thereby inducing tumor cell death. PARP inhibitors are used in ovarian, breast, prostate and pancreatic cancer.

Combining the DNA-alkylating cytotoxic mechanism of SYD985 with PARP inhibitors theoretically increases the sensitivity of tumors for the cytotoxic payload of the antibody-drug conjugate SYD985, resulting in synergistic effects on tumor cell killing. This was corroborated by Byondis’ preclinical data.

**About Byondis (formerly Synthon Biopharmaceuticals)**

Driven to improve patients’ lives, Byondis is an independent biopharmaceutical research and development company creating innovative precision medicines targeting intractable cancers and autoimmune diseases. The company is developing new biological entities (NBEs) and new chemical entities (NCEs) and differentiates itself from other biopharmaceutical companies by its proprietary molecular concepts, such as its linker-drug (LD) and site-specific conjugation technologies to generate antibody-drug conjugates (ADCs).

Byondis’ broad development portfolio comprises preclinical and early- and late-stage clinical programs, including the anti-HER2 ADC [vic-]trastuzumab duocarmazine (SYD985, Phase III). The company has a dedicated team of more than 350 staff including highly educated scientists and skilled technicians working in its state-of-the-art R&D and GMP manufacturing facilities in Nijmegen, the Netherlands. Byondis collaborates with global biotechnology and pharmaceutical companies and national and international academic research institutions. For more information visit www.byondis.com.

The SYD985.004 study is registered in ClinicalTrials.gov with identifier NCT04235101.

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