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 tumours.

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Objectives: The primary objectives of this study are: • Part 1 (dose-escalation): To evaluate the safety of SYD985 in combination with niraparib to determine the maximum tolerated dose (MTD) and recommended combination dose regimen for expansion (...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON52764

Source
ToetsingOnline

Brief title
SYD985 - niraparib combination / solid tumours

Condition

- Other condition
- Miscellaneous and site unspecified neoplasms benign

Synonym
cancer, solid tumours

Health condition

Solid tumours (Study Part 1: solid tumours of any origin; Study Part 2: breast cancer, ovarian cancer or endometrial carcinoma/carcinosarcoma

Research involving

Human

Sponsors and support

Primary sponsor: Byondis BV
Source(s) of monetary or material Support: Byondis BV

Intervention

Keyword: Antibodydrug conjugate SYD982-niraparib, efficacy, HER-2 expressing solid tumours, locally advances or metastatic, PK, Safety

Outcome measures

Primary outcome

Primary endpoints:

The primary endpoint for Part 1 of the study is: • Incidence of Dose Limiting

Toxicity (DLT).

The primary endpoint for Part 2 of the study is: • Objective Response Rate

(ORR).

ORR is defined as the percentage of patients with a best overall tumour

response of complete response (CR) or partial response (PR) according to RECIST

1.1.

Secondary outcome

Safety endpoints. The endpoints related to safety include:

• Incidence and severity of (serious) AEs;

• Changes in vital signs and weight;

• Changes in ECOG performance status;

• Changes in laboratory parameters; • Percentage of patients with confirmed anti-SYD985 antibodies; • Number of patients with dose modifications due to AEs.

Efficacy endpoints. Preliminary efficacy will be assessed by:

• Objective tumour response rate (ORR);

• Clinical benefit rate (CBR);

• Number of patients with CR, PR, stable disease (SD) and progressive disease (PD);

• Best percent change in target lesion measurements;

• Time to response;

• Duration of response (DOR);

• Progression-free survival (PFS);

• Overall survival (OS).

CBR is defined as the percentage of patients with CR, PR, SD or non-CR/non-PD (SD or nonCR/non-PD for 6 or more months). Time to response is defined as the time from first day of IMP treatment to first observation of CR or PR. DOR is defined as the duration from first observation of response (CR or PR) to the time of disease progression. PFS is defined as the time from first day of IMP treatment to disease progression or death from any cause. OS is defined as the

time from first day of IMP treatment to death from any cause.

- Pharmacokinetic endpoints. PK endpoints will include standard parameters such as Cmax, tmax, area under the curve (AUC), Cmin (trough-levels), terminal half-life (t*), volume of distribution, and drug clearance.

- Other endpoints. Genetic tumour analysis will be summarized and correlated, if feasible, with response data.

Study description

Background summary

Therapeutic background and study rationale Antibody-drug conjugates (ADCs) have been recognized as a promising new class of therapeutic biological agents for the treatment of cancer.

1. Byondis developed a new HER2-targeting therapy, SYD985, which is comprised of Byondis' monoclonal IgG1 antibody trastuzumab (similar to Herceptin®) covalently bound to a linker-drug. The linker-drug contains a cleavable linker and the prodrug seco-DUocarmycin-hydroxyBenzamide-Azaindole (seco-DUBA). After binding to HER2 on the cell membrane, SYD985 undergoes receptor mediated internalization and the linker is cleaved in the lysosome at the dipeptide valine-citruline (vc) motif by proteases. Upon cleavage, two selfelimination reactions occur to generate the prodrug (seco-DUBA), which then spontaneously rearranges to form the active toxin (DUBA, SYD986). The active toxin alkylates DNA resulting in DNA damage in both dividing and non-dividing cells, and ultimately cell death. SYD985 most likely also induces a bystander effect through extra-cellular cleavage of the linker-drug within the tumour by extracellular proteases. This bystander effect may not only kill the HER2-positive cell but potentially also (HER2-negative) neighbouring cells. SYD985 has been successfully evaluated in a phase I trial comprising multiple HER2-expressing tumour types and is currently in phase III development as monotherapy for third line HER2 positive metastatic breast cancer in the SYD985.002/TULIP trial [ClinicalTrials.gov: NCT03262935].

2. Poly Adenosine diphosphate Ribose Polymerase (PARP) is a family of protein

enzymes involved in a number of cellular processes such as DNA repair, genomic stability, and programmed cell death. Multiple PARP inhibitors have now been successfully evaluated in several tumour types, including breast and ovarian cancer.

3 Research is ongoing to expand indications to include other tumour types and to further identify subgroups potentially sensitive to PARP inhibition due to inherent or acquired alterations of DNA repair pathways, particularly resulting from aberrations in DNA damage response (DDR) pathways such as BRCA gene mutations and/or homologous recombination deficiency (HRD). Combining the DNA-alkylating cytotoxic mechanism of SYD985 with drugs that impair DNA repair mechanisms theoretically increases the sensitivity of such tumours for the locally released cytotoxic payload of the ADC, resulting in synergistic effects on tumour cell killing.

4. This synergistic mechanism of action has been shown in preclinical experiments in which SYD985 has been combined with the PARP inhibitor niraparib (See Investigator*s Brochure). Subsequent in vivo experiments were performed in patient-derived xenograph models, with an example shown in Figure 1. Here, a triple negative breast cancer model was treated with niraparib, SYD985 or the combination. Resulting tumour volume changes indicate that the effect of the combined treatment (in green) was larger than observed in the animals exposed to either monotherapy (in red and blue) indicating an additive and/or synergistic in vivo effect of the combination (Figure 1).
Although combinations of systemic cytotoxic therapy and PARP inhibition have shown very good chemo-potentiation in preclinical models the combination of these mechanism has been associated with increased myelotoxicity in clinical trials.

5 Combining PARP inhibition with the SYD985 ADC may potentially reduce the risk of such toxicity as the bone marrow will be less affected as SYD985 delivers the cytotoxic load predominantly to the tumour. Moreover, a lower dose of both the SYD985 ADC and niraparib may suffice to induce or maintain sufficient tumour response with a similar or improved toxicity profile. This may be of particular relevance to patients with HER2-low expressing cancers where it would be possible to increase the response rate and/or to extend the duration of tumour control resulting in increased progression free survival and overall survival by introducing HER2-targeting treatment, which is currently not indicated for these patients, in combination with PARP inhibition.

This protocol describes the phase I study with SYD985 in combination with niraparib to determine the maximum tolerated dose (MTD) of the combination, select the recommended combination dose regimen for expansion (RDE), and to characterize the toxicity profile, pharmacokinetics, and preliminary anticancer activity.

Study objective

Objectives: The primary objectives of this study are:

• Part 1 (dose-escalation): To evaluate the safety of SYD985 in combination with niraparib to determine the maximum tolerated dose (MTD) and recommended combination dose regimen for expansion (RDE);

• Part 2 (expansion): To evaluate the objective tumour response rate (ORR) of the combined SYD985/niraparib dose regimen. The secondary objectives of this study are to evaluate the SYD985/niraparib combination at the RDE with respect to: • Safety (including immunogenicity); • Pharmacokinetic parameters; • Preliminary efficacy.

Study design

In Part 1, patients with locally advanced or metastatic HER2-expressing solid tumours of any origin can be enrolled, whereas in Part 2 only patients with advanced or metastatic breast, ovarian or endometrial cancer are eligible.

• Part 1: Dose-escalation Eligible patients will receive infusions of SYD985 every three weeks at a dose of 0.9 or 1.2 mg/kg in combination with niraparib and will be monitored for safety and the occurrence of dose-limiting toxicities (DLTs). Niraparib dosing will be explored per cohort by changing the daily dose or the number of dosing days (see planned dose escalation schedule). At least 3 patients will be enrolled at each combination dose level. There will be no further dose escalation once 2 or more patients out of 3 to 6 patients at a certain dose level experience a DLT during the first treatment cycle (one cycle is 21 days). The MTD is defined as the highest dose level at which doselimiting toxicities (DLTs) occurred in not more than 1 out of 6 patients. The RDE will be determined based on all available safety and pharmacokinetic data, and this dose regimen will be administered in Part 2 of the study. If considered needed, each dose level can be extended with additional patients. Based on Part 1 efficacy and safety data, it may be decided to further explore several suitable dose regimens in expanded patient cohorts (Part 2) to determine the optimal benefit/risk of these combinations.

• Part 2: Expanded cohorts. This part of the study will consist of 3 cohorts comprising patients with either breast, ovarian or endometrial cancer as per inclusion and exclusion criteria. Up to 16 patients will be enrolled in each cohort. If there are two or more responders in the 16 patients, a maximum of 14 additional patients may be enrolled for a total of 30 patients per cohort.

Intervention

Investigational medicinal product, mode of administration: SYD985 (Byondis BV,

The Netherlands): [vic-]trastuzumab duocarmazine Drug product vials contain 80 mg sterile lyophilized SYD985 which should be reconstituted prior to use with 8.0 mL sterile water for injection to yield a solution of 10 mg/mL. SYD985 drug product vials should be stored at 2 to 8 °C until use. All patients will be treated with SYD985 at a dose of 0.9 or 1.2 mg/kg every three weeks (Q3W). The calculated amount of reconstituted solution should be added to an infusion bag containing 100 mL 0.9% sodium chloride without other additives. SYD985 is to be administered intravenously over 60 minutes for the first infusion and, if well tolerated, subsequent infusions can be given over 30 minutes.

Niraparib (Zejula®, TESARO Bio Netherlands BV, The Netherlands): niraparib tosylate monohydrate Hard capsule (white/purple) containing 100 mg niraparib for oral administration as per protocol specific dosing instructions. Capsules should be swallowed whole with water and should not be chewed or crushed. Capsules can be taken without regard to meals.

Study burden and risks

Based on the Phase I experience with SYD985 it can be concluded that there is a positive benefit/risk for patients with late-line HER2-expressing cancers to consider treatment with SYD985 and that exploration of the SYD985/niraparib combination is scientifically, mechanistically and clinically plausible. Developing a tolerable combination regimen may provide a novel treatment option for heavily pre-treated cancer patients included in Part 1 of this study. Relevance is highest for the patients with breast, ovarian or endometrial cancer, included in Part 2 of this study, as the frequency of an aberrant DDR profile is relatively common in these patients for whom the combination of HER2-targeting treatment with PARP inhibition is expected to further increase benefit-risk compared to SYD985 or PARP inhibition alone.

Frequent safety assessments such as ophthalmological and physical examinations, hematology/biochemistry and ECG/LVEF measurements are included in the study to early detect and adequately monitor toxicities when they occur. Clear instructions for dose modifications, i.e. dose delay, reduction or discontinuation, are provided in Section 9.8 specifically for ocular, lung, cardiac and haematologic toxicity. In addition, investigators will be instructed to carefully evaluate the tumour evaluation scans for any lung changes. Patients with a history or presence of keratitis, impaired cardiac function and/or lung disease are excluded from the study as these patients may potentially be at higher risk to develop significant treatment-related toxicity.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

The study population will consist of patients with locally advanced or metastatic solid tumours, complying with the following in- and exclusion criteria: Inclusion criteria: 1. Male or female, age >= 18 years at the time of signing first informed consent; 2. Patient with a histologically-confirmed, locally advanced or metastatic tumour who has progressed on standard therapy or for whom no standard therapy exists, with the following restriction: Part 1: solid tumours of any origin; Part 2: breast cancer, ovarian cancer or endometrial carcinoma/carcinosarcoma; 3. HER2 tumour status at least 1+ as assessed by immunohistochemistry (IHC) as determined by the local laboratory; 4. Presence of a tumour lesion accessible for biopsy and patient should be willing to undergo a fresh biopsy for central HER2 testing and genetic testing, unless adequate (biopsy) tumour material is available obtained < 6 months prior to signing the main informed consent; 5. At least one measurable cancer lesion as defined by the Response Evaluation Criteria for Solid Tumours (RECIST version 1.1); 6. Eastern Cooperative Oncology Group (ECOG) performance status <=

1; 7. Adequate organ function, evidenced by the following laboratory results: - Absolute neutrophil count >= 1.5 x 109/L; - Platelet count >= 100 x 109/L; - Hemoglobin >= 10.0 g/dL or 6.2 mmol/L; - Total bilirubin <= 1.5 x the upper limit of normal (ULN); - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <= 3.0 x ULN (or <= 5.0 x ULN in the presence of liver metastases); - Serum creatinine <= 1.5 x ULN; 8. For women of childbearing potential and male patients with a female partner of childbearing potential, highly effective contraception must be used during the study and up to 6 months after last IMP treatment. This is not required in case the patient or sole partner is surgically sterilized or in case the patient truly abstains from sexual activity.

Exclusion criteria

Exclusion criteria: 1. Having been treated with: a. DUBA-containing ADCs at any time; b. Anthracycline treatment within 8 weeks prior to start of study treatment; c. Other anticancer therapy including chemotherapy, immunotherapy, or investigational agents within 4 weeks prior to start of study treatment or 5 times the half-life of the therapy, whichever is shorter; d. Radiotherapy within 4 weeks prior to start of study treatment or within 1 week for palliative care (as long as the lungs were not exposed); e. Hormone therapy within 1 week prior to start of study treatment. The patient must have sufficiently recovered from any treatment-related toxicities to NCI CTCAE Grade <= 1 (except for toxicities not considered a safety risk for the patient at the investigator*s discretion); 2. History of infusion-related reactions and/or hypersensitivity to trastuzumab containing treatment, niraparib or excipients of study drugs (e.g. lactose or tartrazine in niraparib) which led to permanent discontinuation of the treatment; 3. History or presence of keratitis; 4. Left ventricular ejection fraction (LVEF) < 50% as assessed by either echocardiography or multigated acquisition (MUGA) scan at screening, or a history of clinically significant decrease in LVEF during previous trastuzumab containing treatment leading to permanent discontinuation of treatment; 5. History (within 6 months prior to start of study treatment) or presence of clinically significant cardiovascular disease such as unstable angina, congestive heart failure, myocardial infarction, uncontrolled hypertension, or cardiac arrhythmia requiring medication; 6. History or presence of idiopathic pulmonary fibrosis, organizing pneumonia (e.g. bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan; 7. Severe, uncontrolled systemic disease (e.g. clinically significant cardiovascular, pulmonary, or metabolic disease) at screening; 8. Symptomatic brain metastases, brain metastasis requiring steroids to manage symptoms or treatment for brain metastases within 8 weeks prior to start of study treatment; 9. Known active Hepatitis B, C or E infection; 10. Major surgery within 4 weeks prior to start of study treatment; 11. Pregnancy or lactation; 12. Other condition, which in the opinion of the

investigator, would compromise the safety of the patient or the patient's ability to complete the study

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-05-2021
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	SYD985
Generic name:	SYD985 (trastuzamab vc seco-DUBA INN) - trastuzumab duocarmazine
Product type:	Medicine
Brand name:	zejula
Generic name:	niraparib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	23-03-2020
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-07-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-09-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-12-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-12-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-12-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-02-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-02-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-02-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-03-2023
Application type:	Amendment

Review commission: CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-002937-12-NL
CCMO	NL72514.091.20