

SAPACITABINE

WINTER 2019-20 DNA Damage Response (DDR) Program

Sapacitabine* (CYC682) is an orally-available, nucleoside analogue with a unique mechanism of action against cancer cells among drugs of its class. Cells with homologous recombination (HR) repair pathway defects are particularly susceptible to cell death induced by sapacitabine.¹ Based on preclinical data, unmet medical need and oral dosing convenience, Cyclacel is developing sapacitabine in combination with a BCL2 inhibitor in leukemias and through a collaboration with a PARP inhibitor in breast cancer. Preclinical data support combinations with other inhibitors of cell cycle checkpoints, survival and DNA repair, including DNA methylation, ATM, CDK, CHK1, DNA-PK, HDAC and PARP inhibitors.^{2,3,4,5,6}

Mechanism of Action

Sapacitabine affects DNA synthesis, arrests the cell cycle and triggers apoptosis (programmed cell death). Its anti-cancer activity is mediated by interference with DNA synthesis by first causing single strand DNA breaks, which are subsequently converted to double strand breaks that cannot be repaired resulting in apoptosis.⁷ Sapacitabine treatment delays S phase progression and causes cell cycle arrest in G2/M phase. In the background of defective DNA repair machinery, e.g. mutated BRCA1 and BRCA2, cancer cells show enhanced susceptibility to sapacitabine-induced cell death.

After oral administration sapacitabine is converted into its primary metabolite CNDAC. Both sapacitabine, as an oral prodrug, and CNDAC have demonstrated anticancer activity.

Selected Clinical Studies in Patients with Solid Tumors

Sapacitabine-CDK inhibitor. Phase 1 evaluation of sapacitabine administered sequentially with seliciclib (Cyclacel's 1st generation, oral CDK2/7/9 inhibitor), in

heavily treated, advanced cancer patients is ongoing. The objective of this regimen is to augment DNA damage and enhance sapacitabine induced apoptosis. Proof of mechanism was observed in skin biopsies with a marker of DNA damage. Anticancer activity was observed in the first two parts of the study.

In parts 1 and 2 (n=67) disease control rate of 35.6% (1 CR, 5 PR and 10 stable disease) was observed in 45 patients with breast, ovarian and pancreatic cancer who tested positive for BRCA mutation (44 germline and 1 sporadic). No CR or PR was observed in BRCA wild-type patients. Treatment duration for breast/ovarian cancer responders (1 CR and 2 PR) ranged between 54 and >240 weeks and pancreatic cancer responders (2 PR) between 16 and 21 weeks. Data were presented at the 2016 ASCO Annual Meeting.⁸

Data from a part 1 expansion cohort to assess safety and efficacy in 20 patients with metastatic breast cancer and BRCA1/2 mutations were reported at the 2018 AACR. A clinical benefit rate of 30% was observed. All eight PARP inhibitor naïve patients, half of the patients previously treated with platinum agents and one on previous PARP inhibitor benefited. Progression on previous platinum or PARP inhibitors was associated with lack of benefit.⁹ The data formed the basis of the Phase 1b/2 breast cancer IST of sapacitabine concomitantly with olaparib in PARP inhibitor-naïve patients with BRCA mutant breast cancer.

Phase 2 in NSCLC. Once and twice daily dosing schedules were evaluated in the dose escalation portion of a Phase 2 study in 25 patients with NSCLC treated below MTD who progressed after receiving at least one prior regimen. Among 25 patients treated with once daily dosing from 100 to 175 mg, 2 achieved PR and 10 stable disease receiving an average of 10 cycles. Among 15 patients treated with twice daily dosing from 50 to 75 mg, 4 achieved stable disease receiving an average of 7 cycles.

Phase 1 in solid tumors. In three Phase 1 dose escalation trials sapacitabine was administered to 124 all-comers with advanced solid tumors. A female patient with gastrointestinal stromal tumor (GIST) refractory to imatinib achieved SD for 50 months on sapacitabine treatment.¹⁰

Selected Clinical Studies in Hematological Malignancies

Phase 1 Sapacitabine Single Agent in R/R AML/MDS. In a Phase 1 dose escalation clinical trial, sapacitabine was administered to 47 patients with advanced leukemias or MDS. CR or CRp was achieved in 6 patients. In addition, 7

Sapacitabine clinical trials in progress

- in combination with *venetoclax* in advanced leukemias **Ph1/2**
- in combination with *olaparib* in BRCA+ breast cancer (IST) **Ph1b/2**
- in combination with *Cyclacel's oral seliciclib CDKi (Completed)* **Ph1b/2**

Sapacitabine clinical trials closed

- sapacitabine alternating with decitabine in elderly AML **Ph3**
- second line treatment in elderly AML or MDS **Ph2**
- non-small cell lung cancer (NSCLC) **Ph2**
- cutaneous T-cell lymphoma (CTCL) **Ph2**
- advanced hematological malignancies and solid tumors **Ph1**

patients achieved bone marrow CRi.¹⁵

Phase 2 Sapacitabine Single Agent in AML. 60 AML patients aged 70 or older who were untreated or in first relapse were randomly allocated to treatment with one of 3 schedules of sapacitabine in 28 day cycles: (A) 200 mg bid for 7 days, (B) 300 mg bid for 7 days and (C) 400 mg bid for 3 days for 2 weeks. Treatment with (C), the dosing schedule used in the SEAMLESS Phase 3, resulted in 1-year survival of 30%, OS of 213 days, durable CR of 25% and ORR of 45% (5 CR, 1 CRi and 3 hematological improvement).¹³

Phase 2 Sapacitabine Single Agent in MDS after HMA. In 63 patients aged 60 years and older with MDS who had progressed or relapsed after treatment with HMA, OS ranged from 227 to 291 days and one year survival from 24% to 38%. 48% of patients received 4 or more cycles. For 41/63 patients with 10% or more blasts in their bone marrow OS was 291 days (~ 9 months). Mortality rate from all causes within 30 days of randomization was 5%.¹⁴

Pilot/Lead-in Sapacitabine Alternating with Decitabine. Forty-six newly diagnosed AML patients aged 70 or older were administered the same regimen as the experimental arm in SEAMLESS. Thirty day mortality from all causes was 4% and 60-day 13%. OS was 238 days (~ 8 months), 1-year survival 35% and overall response rate (ORR) 41% (10 CR, 4 PR and 5 major hematological improvement). For patients 75 years or older, median overall survival (OS) was 263 days, one year survival 36%. Fifty nine per cent of patients received 5 or more cycles.¹²

Pivotal Trial in Hematological Malignancies

Sapacitabine alternating with HMA (decitabine). SEAMLESS, a pivotal Phase 3 trial of sapacitabine in front-line acute myeloid leukemia (AML) enrolled 482 elderly patients unfit for chemotherapy. An experimental arm of oral sapacitabine administered in alternating cycles with intravenous decitabine was compared with a control arm of intravenous decitabine. As reported at the 2017 ASH conference SEAMLESS did not reach statistically significant superiority in OS, although an improvement in CR rate was observed in the ITT population. In the stratified subgroup of patients with low baseline peripheral white blood cell count (2/3rds of the study), an improvement in OS was observed for the investigational arm. The opposite was true for patients with high white blood cell count.¹¹

Regulatory Discussions

Following submission of statistical and exploratory analyses of the SEAMLESS data, Cyclacel has received national scientific advice from three European regulatory authorities with regard to a potential approval pathway.

The Company believes that it has defined a patient population for whom the sapacitabine regimen may represent an improvement over low intensity treatment by decitabine alone.

Sapacitabine-venetoclax combination study in AML. FDA granted accelerated approval to venetoclax in elderly patients with newly-diagnosed AML unfit for intensive induction chemotherapy.¹⁶ Cyclacel is enrolling relapsed or refractory AML/MDS patients in a Phase 1 study at MD Anderson to explore the safety and efficacy of a sapacitabine-venetoclax combination as an oral regimen. Preclinical data support potential synergy of the combination in AML models.

Clinical Trial in Breast Cancer

Sapacitabine-PARP inhibitor. Investigators from the Department of Breast Cancer, Dana-Farber Cancer Institute are enrolling patients with BRCA mutant metastatic breast cancer in a Phase 1b/2 investigator-sponsored trial (IST) evaluating an oral combination of sapacitabine and olaparib (PARP inhibitor). Cyclacel and AstraZeneca are providing investigational drugs for this study.

Endnotes:

- * Sapacitabine (CYC682 or CS-682) is an experimental drug under clinical investigation. It is not approved for human use. HMA=hypomethylating agent (azacitidine or decitabine).
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