

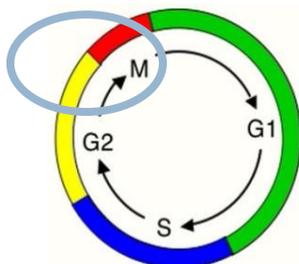
Winter 2018-19

DNA Damage Response (DDR) Program

Sapacitabine* 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 PARP inhibitors in breast cancer and BCL-2 inhibitors in leukemias. Preclinical data also 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 anticancer activity is mediated by interference with DNA synthesis by first causing single strand DNA breaks, which are subsequently converted to double strand breaks resulting in apoptosis.⁷ Sapacitabine treatment also 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.

Clinical Trial in Breast Cancer

Sapacitabine-PARP inhibitor. Investigators from the Department of Breast Cancer, Dana Farber Cancer Institute are enrolling a Phase 1b/2 **investigator-sponsored trial (IST)** with a combination of **sapacitabine and olaparib** (PARP inhibitor) in patients with BRCA mutant metastatic breast cancer.

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 novel oral 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 part 1 and 2 cohorts (n=67) a 35.6 % disease control rate (1 CR, 5 PRs 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 durations for breast/ovarian cancer responders (1 CR and 2 PRs) ranged between 54 and >240 weeks and for pancreatic cancer responders (2 PRs) between 16 and 21 weeks. Data were presented at the 2016 ASCO Annual Meeting.⁹

A part 1 expansion cohort to assess safety and efficacy in 20 patients with metastatic breast cancer and BRCA1/2 mutations has completed enrolment. Part 3 testing a different dosing schedule is enrolling.

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 mg 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 mg 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 patients with advanced solid tumors. A female patient with gastrointestinal stromal tumor (GIST) refractory to imatinib achieved SD for 50 months on sapacitabine treatment.¹⁰

Sapacitabine clinical trials in progress

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

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**

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) in elderly patients unfit for chemotherapy (n=482) has completed enrollment. An experimental arm of oral sapacitabine administered in alternating cycles with intravenous decitabine was compared with a control arm of intravenous decitabine only. In February 2017, it was reported that SEAMLESS did not reach statistically significant superiority in median overall survival (OS), although an improvement in CR rate was observed. 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. The data was presented at the 2017 ASH conference.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.

Other Clinical Studies in Hematological Malignancies

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), one year survival 35% and overall response rate (ORR) 41% (10 CRs, 4 PRs and 5 major hematological improvements). For patients 75 years or older, OS was 263 days and one year survival 36%. Fifty nine per cent of patients received 5 or more cycles.⁸

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 by 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).¹²

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). The mortality rate from all causes within thirty days of randomization was 5%.¹³

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 patients achieved bone marrow CRi.¹⁴

Future Plans

Sapacitabine-BCL-2 inhibitor. Following the recent FDA accelerated approval of venetoclax in elderly patients with newly-diagnosed AML unfit for intensive induction chemotherapy in combination with HMA or low-dose cytarabine, Cyclacel is interested in exploring the safety and efficacy of a sapacitabine-venetoclax combination as an oral regimen in a similar patient population.¹⁵

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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