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## A novel oral nucleoside prodrug in Phase 3 as a treatment for hematological malignancies & earlier stage for solid tumors including hereditary breast and ovarian cancers

### A Novel Oral Nucleoside Analogue

Sapacitabine\* is an orally-available, nucleoside analogue that, uniquely among drugs of its class, acts through a dual mechanism against cancer cells. "SEAMLESS", a pivotal Phase 3 trial of sapacitabine in front-line acute myeloid leukemia (AML) in elderly patients completed enrollment in December 2014. There is an urgent need for alternative treatments for this patient population as intensive chemotherapy does not benefit most AML patients aged 70 years or older. Median survival by intensive therapy is only 4.6 months and is associated with a death rate of 26% at 4 weeks and 36% at 8 weeks.<sup>1</sup> In a pilot/lead-in study of sapacitabine alternating with decitabine, the same treatment regimen used in SEAMLESS, 60-day death rate was 13%.<sup>2</sup>

In a Phase 2 randomized trial of sapacitabine in patients with AML aged 70 or older, one year survival of 30%, durable complete remission (CR) of 25% and median overall survival of 213 days were observed with the dosing schedule used in SEAMLESS.<sup>3</sup> In a Phase 2 study in patients with myelodysplastic syndromes (MDS) aged 60 or older randomized across 3 schedules, one year survival ranged from 24%-38% and median overall survival from 227-291 days.<sup>4</sup> Phase 1 evaluation of sapacitabine administered sequentially with seliciclib, Cyclacel's orally available cyclin dependent kinase inhibitor, in heavily treated advanced cancer patients is on-going. To date durable partial responses and prolonged stable disease have been observed, in particular in patients carrying BRCA mutations.

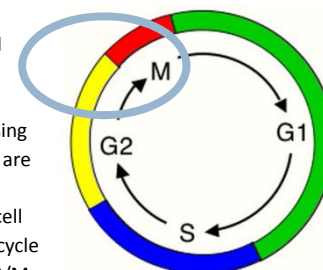
Cells with homologous recombination (HR) repair pathway defects are particularly sensitive to sapacitabine but not gemcitabine.<sup>5</sup> In preclinical models sapacitabine was superior to gemcitabine or ara-C, both widely used nucleoside analogues.<sup>6</sup> Gemcitabine is a palliative treatment of certain solid tumors, but is not active in leukemias or MDS. Ara-C, approved in 1969, is indicated for the treatment of AML in combination with an anthracycline but is often not tolerated by elderly patients. Unlike sapacitabine's oral route, nearly all available nucleoside analogue anticancer drugs must be administered by injection or continuous infusion.

### The Cell Cycle

The cell cycle is comprised of a series of events culminating in cell growth and division. Cell cycle checkpoint control detects and repairs flaws in DNA that could lead to cancer cell proliferation. Nucleoside analogues like sapacitabine work by slowing down cell transit through different phases of the cell cycle, affecting DNA synthesis, arresting the cell cycle and forcing cells into apoptosis or programmed cell death.

### Mechanism of Action

Sapacitabine acts by a dual mechanism against cancer cells: (a) interferes with DNA synthesis by first causing single strand breaks which are then converted to double strand breaks resulting in cell death and (b) induces cell cycle arrest in predominantly G2/M-Phase and delays progression in S-Phase resulting in apoptosis.<sup>7</sup> After administration, sapacitabine is converted into a metabolite called CNDAC. Both sapacitabine, as an oral prodrug, and CNDAC have demonstrated anticancer activity.



### Clinical Results

#### Pilot/Lead-in study of Sapacitabine Alternating with Decitabine

Forty-six newly diagnosed AML patients aged 70 or older were administered the same regimen as SEAMLESS. Thirty day mortality from all causes was 4% and 60-day 13%. Median overall survival was 238 days (~ 8 months), one year survival 35% and overall response rate 41%. For patients 75 years or older, median overall survival was 263 days and one year survival 36%. Approximately 60% of patients received 5 or more cycles.<sup>2</sup>

#### Phase 2 Sapacitabine as a Single Agent in AML

In a Phase 2 trial sapacitabine was administered to 60 AML patients aged 70 or older who were either untreated or in first relapse. Patients were randomized to 3 dosing schedules 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) resulted in 1-year survival of 30%, median overall survival of 213 days, overall response rate of 45% and produced the highest complete remission rate of 25%. Median overall survival in patients with CR was 525 days.<sup>3</sup>

#### Phase 2 Sapacitabine as a Single Agent in MDS

In a similar trial design being conducted in 63 patients aged 60 years and older with MDS who had progressed or relapsed after treatment with hypomethylating agents, median overall survival was 260 days (~ 8 months) and one year survival ranged from 24%-38%. Median overall survival for 41/63 patients with 10% or more blasts in their bone marrow is 291 days (~ 9 months). Approximately 48% of all patients received sapacitabine for 4 or more cycles. The mortality rate from all causes within thirty days of randomization was 5%.<sup>4</sup>

#### Phase 1 Sapacitabine as Single Agent in AML/MDS

In a Phase 1 dose escalation clinical trial, sapacitabine was administered to 46 patients with advanced leukemias and MDS. Complete remissions or complete remissions without platelet



#### Sapacitabine clinical trials in progress

- elderly AML SEAMLESS Phase 3 pivotal study **Phase 3**
- MDS high risk after front-line agent failure **Phase 2**
- in combination with Cyclacel's oral CDK inhibitor seliciclib **Phase 1**

#### Investigator-sponsored trial (IST)

- chronic lymphocytic leukemia (CLL) with del11q22-23 **Phase 2**

#### Sapacitabine completed clinical trials

- sapacitabine alternating with decitabine in elderly AML **Phase 2**
- elderly AML and MDS as second line treatment **Phase 2**
- non-small cell lung cancer (NSCLC) **Phase 2**
- cutaneous T-cell lymphoma (CTCL) **Phase 2**
- advanced hematological malignancies and solid tumors **Phase 1**

recovery were achieved in 6 patients. Fifteen patients had a significant decrease in bone marrow blasts, including seven with blast reduction to 5% or less.<sup>8,9</sup>

### Solid tumors

In three Phase 1 dose escalation trials sapacitabine was administered to 124 patients with advanced solid tumors. Stable disease of over 4 months and tumor shrinkage was observed in 20 patients including 5 out of 18 with non-small cell lung cancer (28%), 4/40 colorectal (10%), 1/12 breast (8%), 2/7 ovarian (28%), 2/4 bladder, 2/4 GIST, 1/3 renal, 3 unknown primary and 1 each small cell lung cancer and parotid tumors. A female patient with gastrointestinal stromal tumor or GIST refractory to imatinib achieved stable disease for 50 months on sapacitabine treatment.<sup>10</sup>

In a Phase 2 study in patients with NSCLC who progressed after receiving treatment with at least one platinum-containing regimen, of 25 patients treated below MTD, 2 achieved partial response and 10 stable disease. Responders received on average 10 cycles of sapacitabine.

### Combinations

Enrollment is ongoing in patients with advanced solid tumors who are receiving treatment with an all oral combination of sapacitabine and seliciclib, Cyclacel's CDK 2/9 inhibitor. The regimen was administered as sequential (Part 1) or concomitant (Part 2) treatment to 67 heavily-pretreated patients. Antitumor activity was demonstrated in a subgroup of 45 patients with breast, ovarian and pancreatic cancers who tested positive for BRCA mutations (44 germline and 1 sporadic) with a 35.6% disease control rate (1 CR, 5 PR and 10 SD). No CR or PR was observed in BRCA negative patients. Treatment durations for the 3 breast/ovarian cancer responders in Part 1 were 54, 93, over 240 weeks and the one breast cancer responder in Part 2 over 76 weeks respectively. Treatment durations for the two pancreatic cancer responders, one each in Parts 1 and 2, were 21 and 16 weeks respectively. Responders included patients who underwent prior treatment with PARP inhibitors and PARP naïve patients. SD was observed in 9 BRCA mutation carriers and 1 sporadic BRCA positive patient with treatment durations ranging from 16 to 88 weeks. Data were presented at an oral presentation at the 2016 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago.<sup>11</sup>

Pharmacodynamic effects of the seliciclib and sapacitabine combination were observed in skin biopsies. Part 1 biopsies following treatment showed a 2.3-fold increase in DNA damage induced by sapacitabine, as measured by gamma-H2AX immunohistochemistry. Additional DNA damage occurred after treatment with seliciclib with a 0.58-fold further increase in gamma-H2AX staining.

Cyclacel scientists and independent investigators have reported preclinical data supporting potential combinations of sapacitabine with novel targeted agents and other nucleoside analogues.<sup>12,13,14</sup> The combinations exploit sapacitabine's unique mechanism of action and were shown to be effective in models of leukemia and solid tumors. Robust synergy was shown when sapacitabine was combined with inhibitors of cell cycle checkpoints, cell survival, and DNA repair, including targeted inhibitors of PARP, DNA methylation, ATM, BCL-2, CDK, CHK1, DNA-PK and HDAC. Combinations were more effective in a homologous recombination (HR) repair defective than a wild-type background.

*This document contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995 about financial results and estimates, business strategy, clinical trial plans and research and development programs of Cyclacel Pharmaceuticals, Inc. By their nature, forward-looking statements and forecasts involve risks and uncertainties because they relate to events and depend on circumstances that will occur in the future. A number of factors could cause actual results and developments to differ materially and are discussed under "Risk Factors" in our quarterly and annual reports filed with the SEC. The information in this presentation is current as of this date. Cyclacel does not take any responsibility to update such information.*

### "SEAMLESS" Pivotal Phase 3 Trial in front-line AML

SEAMLESS is a multicenter, randomized, Phase 3 study of sapacitabine as a front-line treatment in approximately 485 elderly patients aged 70 years or older with newly diagnosed AML who are not candidates for or have refused intensive induction chemotherapy. In SEAMLESS an investigational arm of oral sapacitabine administered in alternating cycles with intravenous decitabine is compared with a control arm of intravenous decitabine administered alone. SEAMLESS completed enrollment in December 2014 with approximately 110 centers participating from the United States and Europe. The primary efficacy endpoint is overall survival. Secondary objectives are to compare complete remission (CR), complete remission with incomplete platelet recovery (CRp), partial response (PR), hematologic improvement (HI), stable disease (SD) and their corresponding durations, transfusion requirements, number of days in hospital, one-year survival and safety. SEAMLESS is being conducted under a Special Protocol Assessment agreement with the US FDA and is chaired by Hagop M. Kantarjian, M.D., Chairman and Professor, Department of Leukemia, The University of Texas MD Anderson Cancer Center.

In December 2014 the SEAMLESS independent Data Safety Monitoring Board determined in an interim analysis of approximately half of the required events that the futility boundary had been crossed, however they saw no reason for the trial to be discontinued and recommended recruited patients should stay on study. Cyclacel is following-up patients until the prespecified number of events has been observed, which is expected to occur during the second half of 2016. Subject to the outcome of SEAMLESS, Cyclacel is preparing for potential EU and US regulatory submissions and has submitted a Paediatric Investigation Plan (PIP) to the European Medicines Agency.

### Endnotes:

- \* Sapacitabine (formerly CYC682 or CS-682) is an experimental drug under clinical investigation and it is not approved for human use.
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