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A novel oral nucleoside prodrug in development as a treatment for both hematologic malignancies and solid tumors

A Novel Oral Nucleoside Analog

Sapacitabine¹ is a nucleoside analog with a dual mechanism of action against cancer cells unique among drugs of its class. It interferes with DNA synthesis and induces arrest of the cell division cycle.²

In preclinical studies sapacitabine was shown to be superior to gemcitabine and 5-FU, two widely used nucleoside analogs in delaying the onset and growth of liver metastasis.³

Preclinical studies with sapacitabine also suggest that sapacitabine works by a different mechanism than cisplatin, mitomycin C, 5-FU or vincristine and has the potential to be given in combination treatment with them.

Sapacitabine is an orally available drug. Virtually all available nucleoside drugs must be administered by injection or continuous infusion.

Sapacitabine is currently being investigated in the following clinical trials:

- elderly acute myeloid leukemia (AML) – *enrollment completed* **Phase 2**
- myelodysplastic syndromes (MDS) **Phase 2**
- cutaneous T-cell lymphoma (CTCL) **Phase 2**

In addition to ongoing clinical trials, Cyclacel's broad clinical development plan for sapacitabine calls for initiating additional clinical studies of sapacitabine as a single agent and/or in combination with other cytotoxic or targeted agents for both hematologic and solid tumor indications.

For more information on these trials, please visit the Cyclacel website at www.cyclacel.com or www.clinicaltrials.gov.

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¹ An experimental drug under clinical investigation. Not approved for human use.

² Hanaoka, K. et al, *Int J Cancer*, 1999;82:226-36.

³ Wu et al, *Cancer Research* 2003;63:2477-82.

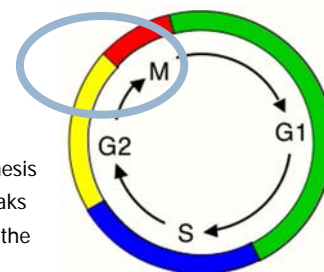
⁴ 1-(2-C-cyano-2-deoxy-b-D-arabino-pentofuranosyl)cytosine.

The Cell Cycle

The cell cycle is comprised of a series of events culminating in cell growth and division. Check points along the cell cycle are used to detect and repair flaws in cell DNA that could lead to cancer cell proliferation. Nucleoside drugs, like gemcitabine and sapacitabine, work by slowing down cell transit through different phases of the cell cycle, affecting the synthesis of DNA, arresting the cell cycle and forcing the cell into apoptosis or programmed cell death.

Mechanism of Action

Sapacitabine's dual mechanism of action against cancer cells (a) interferes with DNA synthesis causing single strand breaks and (b) induces arrest of the cell division cycle in predominantly G2 phase and delays progression in S phase resulting in apoptosis.²



After administration, sapacitabine converts into a metabolite called CNDAC.⁴ Both sapacitabine as an oral prodrug and CNDAC have demonstrated anticancer activity.

Clinical Results to Date



In December 2007, at the 49th Annual Meeting of the American Society of Hematology (ASH), Cyclacel reported interim results from a Phase 1 clinical trial of sapacitabine in patients with advanced leukemias and myelodysplastic syndromes (MDS). These patients were heavily pretreated and were administered sapacitabine after failure of azacitidine, clofarabine, cytarabine, decitabine, imatinib, transplantation, etc. Among 46 patients, the best responses were complete remissions or complete remissions without platelet recovery, in six patients. In addition, 15 patients had a significant decrease in bone marrow blasts, including seven with blast reduction to 5% or less. Sapacitabine appeared to be well tolerated in this patient population.

During 2008 Cyclacel completed enrollment of a randomized Phase 2 study of sapacitabine as a single agent in first relapse or untreated patients with AML aged 70 or higher.

At present Phase 2 enrollment is ongoing in patients with MDS aged 60 or higher who progressed after receiving treatment with hypomethylating agents.

Note: The results cited above, found in ASH Abstract No. 884, are available on the Cyclacel website at www.cyclacel.com.