

SAPACITABINE



A Novel Oral Nucleoside Analog

Sapacitabine¹ (CYC682) is a novel prodrug with a dual mechanism of action that appears to be active in preclinical tests against both solid tumors and hematologic malignancies. Sapacitabine is in Phase I clinical trials for multiple types of cancer.

Highlights

- More active than gemcitabine - (Gemzar[®], Eli Lilly) in preclinical studies
- Oral availability
- Dual novel antiproliferative mechanism
- Over 120 patients treated to date in Phase I trials

Sapacitabine is a nucleoside analog agent with a dual mechanism of action against cancer cells: it induces cell cycle arrest and, uniquely among nucleoside analogs, DNA strand breakage.² In preclinical studies sapacitabine was shown to be superior to gemcitabine or 5-FU, two widely used nucleoside analogs.

Sapacitabine can be taken by mouth, whereas most conventional nucleoside drugs must be administered by injection. Adverse events associated with sapacitabine administration are generally comparable to those associated with conventional nucleoside chemotherapies.

Sapacitabine has been administered to about 120 patients in the United States to date in two completed Phase I studies and a third Phase I study currently in progress for the treatment of patients with advanced solid tumors. Cyclacel initiated a fourth Phase I trial in patients with advanced blood cancers in 2006.

Preclinical Data and Mechanism

There are three classes of nucleoside analogs:

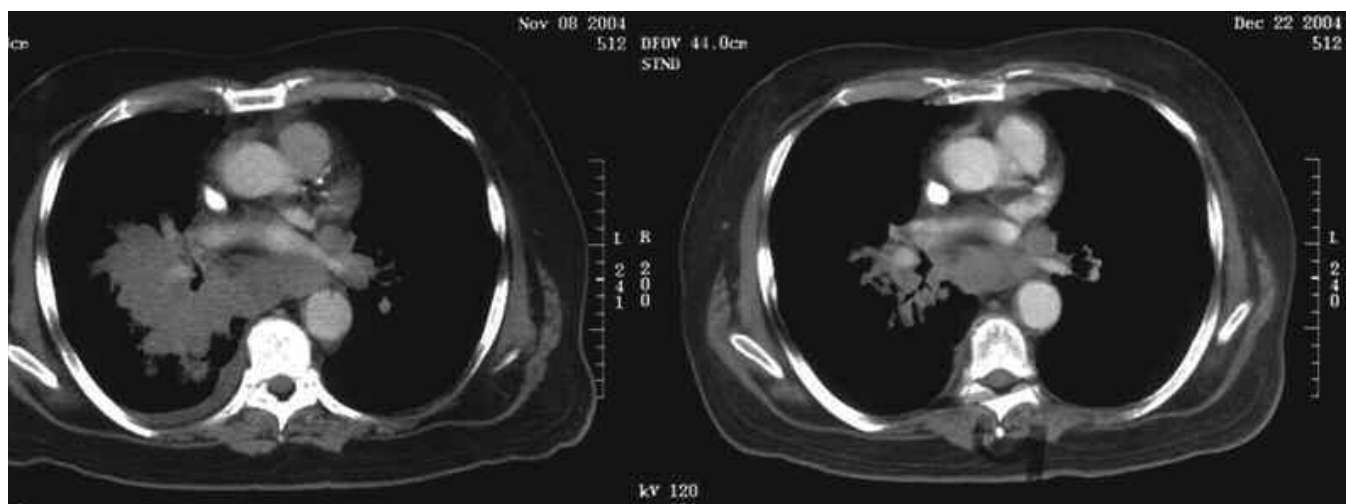
2-deoxycytidine analogs, such as cytarabine, gemcitabine and sapacitabine; fluorouracil analogs, such as capecitabine and 5-FU; and purine analogs, such as 6-mercaptopurine. In terms of tumor spectrum of activity sapacitabine more closely resembles that of gemcitabine rather than cytarabine.

Preclinical studies with sapacitabine found activity following oral administration across a broad range of solid and blood cancer models including breast, colon, gastric, lung, and ovarian xenografts. In addition, sapacitabine was also active against leukemia cell lines resistant to cisplatin, mitomycin C, 5-FU or vincristine. These studies suggest that sapacitabine works by a different mechanism than these drugs and has the potential to be given in combination treatment with them. In a mouse model of metastatic colorectal cancer, sapacitabine was found to be superior to either gemcitabine or 5-FU, in terms of increased survival and prevention of spread of metastases to the liver.³

Sapacitabine was designed as a prodrug to counter degradation of nucleosides *in vivo* by deaminase and phosphatase enzymes. The prodrug converts, after administration, into a metabolite called CNDAC⁴ but both the prodrug and metabolite appear to have anti-cancer activity. In addition to its mechanistic effects on the cell cycle, sapacitabine induces spontaneous DNA strand breaking activity leading to death of cancer cells by apoptosis.

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Stable disease with tumor shrinkage observed in a patient with advanced NSCLC after two cycles of sapacitabine administration.

Clinical Data

Sapacitabine has been the subject of three Phase I studies in the United States, exploring safety and pharmacokinetics and enrolling an aggregate of 120 patients with a variety of solid cancers treated at various doses and schedules. The dose limiting toxicities observed were febrile neutropenia, leucopenia and neutropenia.

Thirteen patients achieved stable disease (SD) of at least 4 months with many patients also experiencing tumor shrinkage. Among these were two patients with GIST, or gastrointestinal stromal tumors, one of whom failed three prior regimens including imatinib, was treated with sapacitabine as fourth line monotherapy and had a sustained SD lasting over 4 years. Two patients with kidney and bladder cancer achieved SD of 18 and 8 months respectively. Five patients with advanced non-small cell lung cancer treated with sapacitabine as third, fourth or fifth line monotherapy had prolonged SD lasting between 7 and 9 months. Three patients with advanced colon cancer had prolonged SD lasting between 6 and 7 months.

Cyclacel initiated a fourth Phase I pharmacologic trial in hematology patients with advanced leukemias or myelodysplastic syndromes (MDS) in 2Q06 with results expected to be reported in 2H06.

Target Indications

We intend to commence Phase II evaluation of sapacitabine as soon as feasible following release of the data from the Phase I hematology trial. We expect to target solid tumors where gemcitabine is in clinical use as well as tumors in which sapacitabine has shown potential superiority to gemcitabine. If the Phase I hematology data are supportive, we will also consider Phase II development in leukemias or MDS.

Other Indications Under Review

Future clinical development plans may include Phase II clinical studies in combination treatment regimens where gemcitabine is used in which we would expect to compare the use of sapacitabine versus the use of gemcitabine. We will also consider novel combination treatments of sapacitabine with other targeted agents.

Biomarker Investigations

Cyclacel is investigating multiple biomarker methodologies. For example, pharmacodynamic markers of apoptosis and cell death are being used to assist clinical dose determinations. We are analyzing biomarker samples from Phase I patients to assess the ability of sapacitabine to induce apoptosis and/or cell death in cancer cells. Our preliminary data suggest that we can quantify sapacitabine-induced cell death with the same biomarkers that we are using in Phase I and II trials with seliciclib, our lead drug candidate.

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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 Res 2003;63:2477-82.

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