Cyclacel Pharmaceuticals, Inc.
Form 10-K
March 31, 2011

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549
FORM 10-K

(Mark One)

þ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
FOR THE FISCAL YEAR ENDED DECEMBER 31, 2010
OR

o **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

Commission file number 00-50626

CYCLACEL PHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)

Delaware	91-1707622
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
200 Connell Drive Suite 1500 Berkeley Heights, New Jersey	07922
(Address of principal executive offices)	(Zip Code)

Registrant s telephone number, including area code: (908) 517-7330
Securities registered under Section 12(b) of the Exchange Act:

Title of Each Class	**Name of Each Exchange on Which Registered**
Common Stock, $0.001 par value	The NASDAQ Stock Market LLC
Preferred Stock, $0.001 par value	The NASDAQ Stock Market LLC

Securities registered pursuant to Section 12(g) of the Act: None.

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes o No þ

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Exchange Act. Yes o No þ

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes þ No o

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes o No o

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S- K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendments to this Form 10-K.

o

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act:

Large accelerated filer o	Accelerated filer o	Non-accelerated filer o	Smaller reporting company þ
		[Do not check if a smaller reporting company]	

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes o No þ

The aggregate market value of the registrant s voting and non-voting common stock held by non-affiliates of the registrant (without admitting that any person whose shares are not included in such calculation is an affiliate), as of June 30, 2010 (based upon the closing sale price of $1.72 of such shares on The NASDAQ Global Market on June 30, 2010) was $63,554,944.

As of March 30, 2011, there were 46,598,688 shares of the registrant s common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

None.

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Explanatory Note

Overview of Restatement

The Board of Directors of Cyclacel Pharmaceuticals, Inc. (the Company), based on the recommendation of its Audit Committee and in consultation with management, has concluded that the following previously issued consolidated financial statements must be restated and should no longer be relied upon because the Company erroneously accrued and included as a current liability its undeclared cumulative preferred stock dividends in such financial statements:

(a) consolidated balance sheets as of March 31, 2009, June 30, 2009, September 30, 2009, December 31, 2009, March 31, 2010, June 30, 2010, and September 30, 2010 and statement of stockholders equity for the year ended December 31, 2009; and

(b) Selected Financial Data as of and for the year ended December 31, 2009.

As a result, in this Annual Report on Form 10-K for the year ending December 31, 2010, the Company:

(a) restates its consolidated balance sheet as of December 31, 2009 and its statement of stockholders equity for the year ended December 31, 2009;

(b) amends its Management s Discussion and Analysis of Financial Condition and Results of Operations (MD&A) as it relates to the year ended December 31, 2009;

(c) restates its Selected Financial Data as of and for the year ended December 31, 2009; and

(d) restates its unaudited consolidated balance sheets as of March 31, 2009, June 30, 2009, September 30, 2009, March 31, 2010, June 30, 2010, and September 30, 2010.

Background on the Restatement

The restated financial statements correct the following error:

Accounting for Preferred Stock Dividends

During March 2011, the Company became aware of an error with respect to the historical accounting for undeclared dividends associated with the Company s outstanding preferred stock. The Company s management determined that undeclared cumulative preferred stock dividends need only be disclosed in the financial statements or in the notes thereto, and not accrued and included as a current liability in the Company s Consolidated Balance Sheets, as the Company had recorded in prior periods. The effect of correcting the error has been recorded in the applicable restated periods.

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Effects of the Restatement

The following table sets forth the effects of the restatement on affected items within our previously reported consolidated balance sheets:

	March 31, 2009 $000 (unaudited)	June 30, 2009 $000 (unaudited)	September 30, 2009 $000 (unaudited)	As of December 31, 2009 $000	March 31, 2010 $000 (unaudited)	June 30, 2010 $000 (unaudited)	September 30, 2010 $000 (unaudited)
Other current liabilities							
As originally reported	578	777	1,336	n/a	n/a	n/a	n/a
Adjustment	(307)	(614)	(921)	n/a	n/a	n/a	n/a
As restated	271	163	415	n/a	n/a	n/a	n/a
Accrued and other current liabilities							
As originally reported	n/a	n/a	n/a	6,709	5,818	5,255	5,641
Adjustment	n/a	n/a	n/a	(1,228)	(1,443)	(1,032)	(1,213)
As restated	n/a	n/a	n/a	5,481	4,375	4,223	4,428
Current liabilities							
As originally reported	8,549	10,686	9,328	9,822	9,511	8,155	7,965
Adjustment	(307)	(614)	(921)	(1,228)	(1,443)	(1,032)	(1,213)
As restated	8,242	10,072	8,407	8,594	8,068	7,123	6,752
Total liabilities							
As originally reported	9,966	11,212	9,595	9,822	9,511	8,155	7,965
Adjustment	(307)	(614)	(921)	(1,228)	(1,443)	(1,032)	(1,213)
As restated	9,659	10,598	8,674	8,594	8,068	7,123	6,752
Additional paid-in capital							
As originally reported	222,886	222,932	225,864	226,881	244,991	248,314	250,466
Adjustment	307	614	921	1,228	1,528	1,632	1,813
As restated	223,193	223,546	226,785	228,109	246,519	249,946	252,279

Deficit accumulated during the development stage							
As originally reported	(207,778)	(214,824)	(217,948)	(222,285)	(227,815)	(234,240)	(238,049)
Adjustment					(85)	(600)	(600)
As restated	(207,778)	(214,824)	(217,948)	(222,285)	(227,900)	(234,840)	(238,649)
Total stockholders equity							
As originally reported	15,201	8,248	7,947	4,644	17,265	14,154	12,426
Adjustment	307	614	921	1,228	1,443	1,032	1,213
As restated	15,508	8,862	8,868	5,872	18,708	15,186	13,639

n/a not applicable

The effects of the restatement did not in any way affect our results of operations, reported loss per share, or cash flows.

The adjustments made as a result of the restatement are also discussed in Note 3 Restatement of Previously Issued Financial Statements of the Notes to Consolidated Financial Statements included in this Annual Report on Form 10-K. To further review the effects of the accounting errors identified and the restatement adjustments see Part II Item 6. Selected Financial Data , Part II Item 7. Management s Discussion and Analysis of Financial Condition and Results of Operations and Note 17 Selected Quarterly Information of the Notes to Consolidated Financial Statements included in this Annual Report on Form 10-K. For a description of control deficiencies identified by management as a result of our internal reviews, and management s plan to remediate those deficiencies, see Part II Item 9A. Controls and Procedures .

The Company has not amended and does not intend to amend its previously filed Annual Report on Form 10-K/A and Quarterly Reports on Form 10-Q for the periods affected by the restatement. The information that has been previously filed or otherwise reported for these periods has been restated and is superseded by the information in this Annual Report on Form 10-K. As such, the consolidated financial statements and related financial information contained in such previously filed reports should no longer be relied upon, nor should any earnings releases or other communications relating to the Company s financial performance during these periods be relied upon.

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PART I

Item 1. Business

In this report, Cyclacel, the Company, we, us, and our refer to Cyclacel Pharmaceuticals, Inc.

General

Cyclacel Pharmaceuticals, Inc. was incorporated in the state of Delaware in 1996 and is headquartered in Berkeley Heights, New Jersey, with a research facility located in Dundee, Scotland. Cyclacel is a biopharmaceutical company developing oral therapies that target the various phases of cell cycle control for the treatment of cancer and other serious diseases. Cyclacel s strategy is to build a diversified biopharmaceutical business focused in hematology and oncology based on a portfolio of commercial products and a development pipeline of novel drug candidates. As a development stage enterprise, substantially all efforts of the Company to date have been devoted to performing research and development, conducting clinical trials, developing and acquiring intellectual property, raising capital and recruiting and training personnel.

Recent Developments

On February 1, 2011, we paid a quarterly cash dividend in the amount of $0.15 per share on the Company s 6% Convertible Exchangeable Preferred Stock (Preferred Stock). The dividend was paid to the holders of record of the Preferred Stock as of the close business on January 21, 2011.

On January 11, 2011, we opened enrollment of the SEAMLESS pivotal Phase 3 trial for our sapacitabine oral capsules as a front-line treatment of elderly patients aged 70 years or older with newly diagnosed acute myeloid leukemia (AML) who are not candidates for intensive induction chemotherapy under a Special Protocol Assessment, or SPA, reached with the U.S. Food & Drug Administration, or FDA.

Corporate information

Our corporate headquarters are located at 200 Connell Drive, Suite 1500, Berkeley Heights, New Jersey, 07922, and our telephone number is 908-517-7330. This is also where our medical and regulatory functions are located. Our research facility is located in Dundee, Scotland which is also the center of our translational work and development programs.

Overview

We are a biopharmaceutical company dedicated to the development and commercialization of novel, mechanism-targeted drugs to treat human cancers and other serious diseases. We are focused on delivering leading edge therapeutic management of cancer patients based on a clinical development pipeline of novel drug candidates.

Clinical programs

Our clinical development priorities are focused on orally-available sapacitabine in the following indications:

- AML in the elderly;
- Myelodysplastic syndromes, or MDS; and
- Non-small cell lung cancer, or NSCLC.

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Recent highlights of our sapacitabine clinical program are:

- In January 2011, we opened enrollment of the SEAMLESS pivotal Phase 3 trial as a front-line treatment of elderly patients aged 70 years or older with newly diagnosed AML who are not candidates for intensive induction chemotherapy under an SPA, reached with the FDA;
- In December 2010, we announced one-year survival data for sapacitabine Phase 2 trial for older patients with MDS refractory to the hypomethylating agents azacitidine and/or decitabine at the 2010 American Society of Hematology (ASH) annual meeting;
- In October 2010, we published preclinical model data demonstrating sapacitabine works synergistically with histone deacetylase (HDAC) inhibitors to induce tumor cell death in vitro and in vivo;
- In July 2010, we announced that the FDA granted orphan drug designation to our sapacitabine product candidate for the treatment of both AML and MDS; and
- In June 2010, we reported interim response data for the ongoing Phase 2 clinical trial of sapacitabine in older patients with MDS at the American Society of Clinical Oncology, or ASCO, meeting.

The planning, execution and results of our clinical programs are significant factors that can affect our operating and financial results.

Advancing our additional research and development programs

We have additional clinical programs in development awaiting further clinical data. Once data become available and are reviewed, we will determine the feasibility of pursuing further development and/or partnering these assets, including sapacitabine in combination with seliciclib, seliciclib in NSCLC and nasopharyngeal cancer or NPC and CYC116. Highlights of some recent developments related to our other research and development programs include:

- In December 2010, we announced topline data from the APPRAISE , Phase 2b, randomized discontinuation, double-blinded, placebo-controlled study of oral seliciclib capsules as a third line or later treatment in patients with NSCLC showing no difference in median progression free survival (PFS) between the seliciclib and placebo arms (48 versus 53 days respectively), but an increase in median overall survival (OS) favoring seliciclib over placebo (388 versus 218 days);

- In December 2010, preclinical data from a Cyclacel collaboration was presented at the 2010 ASH Annual Meeting demonstrating that CYC065 is cytotoxic at sub-micromolar concentrations against myeloma cell lines and CD138+ myeloma cells derived from patients. CYC065 demonstrated antiproliferative activity even in the presence of the growth stimulatory effects of both cytokines and bone marrow stromal cells. CYC065 induced apoptosis in myeloma cells as evidenced by the appearance of cleaved PARP;

- In April 2010, preclinical data from a Cyclacel collaboration was presented at the 2010 Annual Meeting of the American Association of Cancer Research (AACR) introducing CYC065, Cyclacel s oral CDK inhibitor, which has the same target profile as seliciclib, and showing that CYC065 induced apoptosis in HER2 positive breast cancer cell lines refractory to trastuzumab (Herceptin®). CYC065 was also shown in preclinical studies to have anticancer activity in AML cell lines, including those with human mixed-lineage leukemia (MLL) rearrangements, and chronic lymphocytic leukemia (CLL) cells;

- In February 2010, a peer-reviewed journal article demonstrated that seliciclib reversed resistance to the aromatase inhibitor letrozole (Femara®) and inhibited growth of hormone receptor positive breast cancer cells that had become insensitive to the effects of letrozole; and

- In January 2010, a peer-reviewed journal article demonstrated that seliciclib was effective against lung cancer cell lines and, in particular, those with activating mutations in K-RAS and N-RAS proteins.

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Our pipeline and expertise in cell cycle biology

Our core area of expertise is in cell cycle biology and we focus primarily on the development of orally-available anticancer agents that target the cell cycle with the aim of slowing the progression or shrinking the size of tumors, and enhancing the quality of life and improving survival rates of cancer patients. We are generating several families of anticancer drug candidates that act on the cell cycle including nucleoside analogues, cyclin dependent kinase, or CDK inhibitors and Aurora kinase/Vascular Endothelial Growth Factor Receptor 2, or AK/VEGFR2 inhibitors. Although a number of pharmaceutical and biotechnology companies are currently attempting to develop nucleoside analogues, CDK inhibitor and AK inhibitor drugs, we believe that our drug candidates are differentiated in that they are orally-available and interact with unique target profiles and mechanisms. For example we believe that our sapacitabine is the only orally-available nucleoside analogue to be tested in a Phase 3 trial for AML and in a Phase 2 trial in MDS and seliciclib is the most advanced orally-available CDK inhibitor in Phase 2 trials.

We have retained rights to commercialize our clinical development candidates and our business strategy is to enter into selective partnership arrangements with these programs.

Commercial products

We market directly in the United States Xclair® Cream for radiation dermatitis and Numoisyn® Liquid and Numoisyn® Lozenges for xerostomia. All three products are approved in the United States under FDA 510 (k) or medical device registrations. As described below under Results of Operations, for the three years ended December 31, 2008, 2009 and 2010, we recognized product revenue totaling $0.8 million, $0.9 million and $0.6 million, respectively.

General

From our inception in 1996 through December 31, 2010, we have devoted substantially all our efforts and resources to our research and development activities. We have incurred significant net losses since inception. As of December 31 2010, our accumulated deficit during the development stage was approximately $241.8 million. We expect to continue incurring substantial losses for the next several years as we continue to develop our clinical and preclinical drug candidates. Our operating expenses comprise research and development expenses and selling and general and administrative expenses.

To date, we have not generated significant product revenue but have financed our operations and internal growth through public offerings, private placements, licensing revenue, interest on investments, government grants and research and development tax credits. Prior to October 2007, our revenue consisted of collaboration and grant revenue. Beginning in 2008, we recognized revenue from sales of commercial products, for the first time, following the ALIGN acquisition in October 2007. We have recognized revenues from inception through December 31, 2010 totaling approximately $9.1 million of which approximately $2.3 million is derived from product sales, approximately $3.1 million from fees under collaborative agreements and approximately $3.7 million of grant revenue from various government grant awards.

Although our resources are primarily directed towards advancing our anticancer drug candidate sapacitabine through in-house development activities we are also progressing, but with significantly lower levels of investment, our other novel drug series which are at earlier stages. Taken together, our pipeline covers all four phases of the cell cycle, which we believe will improve the chances of successfully developing and commercializing novel drugs that work on their own or in combination with approved conventional chemotherapies or with other targeted drugs to treat human cancers. As a consequence of our continued focus on sapacitabine clinical development and related cost reduction program, research and development expenditures for the year ended December 31, 2010 decreased $3.4 million, or 34%, from $9.8 million for the year ended December 31, 2009 to $6.4 million for the year ended December 31, 2010. Research and development expenditures for the year ended December 31, 2009 were reduced by $9.1 million, or 48%, from $18.9 million for the year ended December 31, 2008 to $9.8 million for the year ended December 31, 2008.

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Research and Development Pipeline

The following table summarizes our clinical and preclinical programs.

Program	Indication	Development Status	Target	Cell Cycle Mechanism
Oncology				
Sapacitabine, CYC682	Elderly AML	Phase 3 trial on-going	DNA polymerase	G2 and S phase
Sapacitabine, CYC682	MDS	Phase 2 randomized trial on-going	DNA polymerase	G2 and S phase
Sapacitabine, CYC682	CTCL	Phase 2 randomized trial stopped. Not a company priority	DNA polymerase	G2 and S phase
Sapacitabine, CYC682	NSCLC	Phase 2 trial on-going	DNA polymerase	G2 and S phase
Sapacitabine + Seliciclib	Cancer	Phase 1 trial on-going		
Seliciclib, CYC202	NSCLC	Phase 2b randomized trial closed to accrual	CDK2, 7, 9	G1/S checkpoint and others
Seliciclib, CYC202	NPC	Phase 2 randomized trial. Lead-in phase only on-going	CDK2, 7, 9	G1/S checkpoint and others
CYC116	Cancer	Phase 1 trial completed	Aurora kinase & VEGFR2	Mitosis
CDK Inhibitors, Second Generation	Cancer	Preclinical	CDK	G1/S checkpoint and others
Plk1 Inhibitors	Cancer	Preclinical	Plk	G2/M checkpoint
Hdm2 Inhibitors	Cancer	On hold. Not a company priority	Hdm2	G1/2 phase
Cyclin Binding Groove Inhibitors	Cancer	On hold. Not a company priority	Cyclin binding groove	S phase
Other therapeutic areas				
Cell Cycle Inhibitors	Autoimmune & Inflammatory Diseases	Phase 1 trial completed On hold. Not a company priority	CDK	G1/S checkpoint and others
Cell Cycle Inhibitors	HIV/AIDS	On hold. Not a company priority	CDK	Other
GSK-3 Inhibitors	Type 2 Diabetes	On hold. Not a company priority	GSK-3	Other

Market opportunity in oncology

Cancer remains a major life-threatening disease in the United States with approximately 3.2 million people afflicted by cancer and approximately 1.4 million new cases of cancer diagnosed every year. Five common solid cancer types: non-small cell lung, breast, ovarian, prostate and colorectal cancers, represent over 50% of all new cases of cancer in the United States each year and account for more than 50% of all cancer deaths in the United States.

Acute myeloid leukemia is one of the most common types of leukemia or cancer in the blood and bone marrow. According to the American Cancer Society approximately 44,000 cases of leukemia are diagnosed annually in the United States of which about 13,000 are classified as AML. Leukemia is a deadly disease with an estimated 9,000 deaths annually in the United States, almost all in adults. The average age of a patient with AML is 67 and about two-thirds of AML patients are above 60 years old. The prognosis of AML in the elderly is poor.

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The American Cancer Society estimates that approximately 16,000 to 20,000 new cases of myelodysplastic syndromes are diagnosed annually in the United Sates. Patients currently receive hypomethylating agents as first-line treatment. There is no approved therapy for second-line treatment.

Lung cancer is a cancer starting in the lungs that often takes many years to develop. About 85% to 90% of all lung cancers are non-small cell or NSCLC type. According to the American Cancer Society, an estimated 215,000 patients are diagnosed annually with NSCLC in the United States. An estimated 380,000 new cases are diagnosed annually in the European Union. NSCLC is a deadly disease with an estimated 162,000 deaths annually in the United States.

NPC develops in the nasopharynx, an area in the back of the nose toward the base of the skull. Although it is sometimes considered a head and neck or an oral cancer, nasopharyngeal cancer is different from these cancers. It is frequently fatal, once the disease recurs after initial chemotherapy and radiotherapy, spreads widely and has different risk factors such as Epstein-Barr virus, or EBV infection. High EBV viral titers are considered an indicator of poor prognosis. According to the American Cancer Society, an estimated 2,100 patients are diagnosed annually with nasopharyngeal cancer in the United States. An estimated 2,500 are diagnosed annually in the European Union, but an estimated 70,000 new cases are diagnosed annually in the Asia Pacific region.

Lymphoma is a cancer of lymphoid tissue, a part of the lymphatic system. Lymphoid tissue is formed by several types of immune system cells that work together mainly to resist infections. About 5% of all lymphomas start in the skin often staying there without spreading to internal organs and are called cutaneous lymphomas. The main cell types found in lymphoid tissue are B lymphocytes and T lymphocytes resulting in B-cell or T-cell lymphoma, or CTCL. CTCL causes disfiguring skin lesions and severe itching. According to the American Cancer Society, an estimated 3,000 patients are diagnosed annually with lymphoma in the skin in the United States.

Oncology Development Programs

We are generating several families of anticancer drugs that act on the cell cycle, including nucleoside analogues, cyclin dependent kinase, or CDK, inhibitors and Aurora kinase/Vascular Endothelial Growth Factor Receptor 2, or AK/VEGFR2 inhibitors. Although a number of pharmaceutical and biotechnology companies are currently attempting to develop nucleoside analogues, CDK inhibitor, AK and/or VEGFR inhibitor drugs, we believe that our drug candidates, are differentiated in that they are orally-available and interact with unique target profiles and mechanisms. For example, we believe that our sapacitabine is the only orally-available nucleoside analogue presently being tested in Phase 3 trials in AML and in Phase 2 for MDS, and seliciclib is the most advanced orally-available CDK inhibitor currently in Phase 2 trials.

In our development programs, we have been an early adopter of biomarker analysis to help evaluate whether our drug candidates are having their intended effect through their assumed mechanisms at different doses and schedules. Biomarkers are proteins or other substances whose presence in the blood can serve as an indicator or marker of diseases. Biomarker data from early clinical trials may also enable us to design subsequent trials more efficiently and to monitor patient compliance with trial protocols. We believe that in the longer term biomarkers may allow the selection of patients more likely to respond to its drugs for clinical trial and marketing purposes and increase the benefit to patients.

Our approach to drug discovery and development has relied on proprietary genomic technology to identify gene targets, which are then progressed by means of structure-based drug design techniques through to the development stage. This approach is exemplified by our Aurora kinase, or AK, and Polo-like kinase, or Plk, inhibitor programs. Fundamentally, this approach to drug discovery and design aims to improve our ability to select promising drug targets in the early stages of the process so as to decrease compound attrition rates during the later, more expensive stages of drug development. By devoting resources initially to this process, we were able to focus our efforts on targets that have a higher probability of yielding successful drug candidates through the utilization of an integrated suite of sophisticated discovery and design technologies by highly skilled personnel. However, as a result of the reduction in our workforce in 2008 and 2009 our ability to identify, optimize and develop new targets has been significantly curtailed.

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Sapacitabine

Our lead candidate, sapacitabine, is an orally-available prodrug of CNDAC, which is a novel nucleoside analog, or a compound with a structure similar to a nucleoside. A prodrug is a compound that has a therapeutic effect after it is metabolized within the body. CNDAC has a significantly longer residence time in the blood when it is produced in the body through metabolism of sapacitabine than when it is given directly. Sapacitabine acts through a dual mechanism whereby the compound interferes with DNA synthesis and repair by causing single-strand DNA breaks and induces arrest of the cell division cycle at G2/M checkpoint. A number of nucleoside drugs, such as gemcitabine, or Gemzar®, from Eli Lilly, and cytarabine, also known as Ara-C, a generic drug, are in wide use as conventional chemotherapies. Both sapacitabine and its major metabolite, CNDAC, have demonstrated potent anti-tumor activity in both blood and solid tumors in preclinical studies. In a liver metastatic mouse model, 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. We have retained worldwide rights to commercialize sapacitabine, except for Japan, for which Daiichi-Sankyo Co., Ltd., or Daiichi-Sankyo, has a right of first negotiation.

We are currently exploring sapacitabine in both hematological cancers and solid tumors. To date, sapacitabine has been evaluated in approximately 400 patients in several Phase 1 and 2 studies and has shown signs of anti-cancer activity. In January 2011, we opened enrollment of the SEAMLESS pivotal Phase 3 trial, which will evaluate sapacitabine oral capsules as a front-line treatment in elderly patients aged 70 years or older with newly-diagnosed AML who are not candidates for intensive induction chemotherapy. The study will be conducted under an SPA.

Hematological Cancers

Phase 1 clinical trial in patients with advanced leukemias and myelodysplastic syndromes

In December 2007, at the ASH annual meeting, we reported interim results from a Phase 1 clinical trial of oral sapacitabine in patients with advanced leukemias and MDS. The data demonstrated that sapacitabine had a favorable safety profile and promising anti-leukemic activity in patients with relapsed and refractory AML and MDS when administered by two different dosing schedules. The primary objective of the study is to determine the maximum tolerated dose, or MTD, of sapacitabine administered twice daily for seven consecutive days every 21 days or three consecutive days per week for two weeks every 21 days. The MTD was reached at 375 mg on the seven-day schedule and 475 mg on the three-day schedule. Dose-limiting toxicity was gastrointestinal which included abdominal pain, diarrhea, small bowel obstruction and neutropenic colitis. One patient treated at the MTD of 375 mg on the seven-day schedule died of complications from neutropenic colitis. Among 46 patients, 42 with AML and 4 with MDS, in this dose escalating study, the best responses were complete remission, or CR, or complete remission without platelet recovery, or CRp, in six patients for an Overall Response Rate of 13%. In addition, 15 patients had a significant decrease in bone marrow blasts including seven with blast reduction to 5% or less. The study was conducted at The University of Texas M. D. Anderson Cancer Center and is led by Hagop Kantarjian, M.D., Professor of Medicine and Chairman of the Leukemia Department and Dr. William Plunkett, Professor and Chief, Section of Molecular and Cellular Oncology, Department of Experimental Therapeutics.

Phase 2 randomized clinical trial in elderly patients with AML previously untreated or in first relapse

In December 2007, we initiated an open-label, multicenter, randomized Phase 2 clinical trial of oral sapacitabine in 60 elderly patients with AML aged 70 or older who are previously untreated or in first relapse. The Phase 2 study, led by Dr. Kantarjian, has a primary endpoint of 1-year survival rate of three dosing schedules of sapacitabine in elderly patients with previously untreated or first relapsed AML. Secondary objectives are to assess CR or CRp, partial remission, or PR, duration of CR or CRp, or major hematological improvement and their corresponding durations, transfusion requirements, number of hospitalized days and safety. The study uses a selection design with the objective of identifying a dosing schedule among three different arms, A. 200 mg twice daily for seven days every 3-4 weeks, B. 300 mg twice daily for seven days every 3-4 weeks, and C. 400 mg twice daily for three days per week for two weeks every 3-4 weeks, which produces a better 1-year survival rate in the event that all three dosing schedules are active. Each arm enrolled and treated 20 patients. Approximately 55% of patients had AML de novo and the rest had AML preceded by antecedent hematological disorder, or AHD, such as MDS, or myeloproliferative disease. Eighty percent of the patients were untreated and 20% in first relapse. We completed enrollment of 60 AML patients in this study in October 2008. In December 2009, at the 51st Annual Meeting of ASH we reported 1-year survival data.

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The primary endpoint of 1-year survival was 35% on Arm A, 30% on Arm C and 10% on Arm B. The median overall survival was 212 days on Arm C (range of 13 to over 654 days), 197 days on Arm A (range of 26 to over 610 days) and 100 days on Arm B (range of 6 to over 646 days). Overall response rate, or ORR, a secondary endpoint, was 45% on Arm A, 35% on Arm C and 25% on Arm B with CR rate of 25% on Arm C and 10% on Arms A and B. Thirty-day mortality was 10% on Arm C and Arm A and 20% on Arm B. Approximately 30% of all patients received sapacitabine for at least 6 cycles. Fifteen patients who survived one year or more received an average of 12 treatment cycles.

Exploratory subgroup analysis suggests that (i) Arm C may be more effective for de novo AML and (ii) Arm A may be more effective for AML preceded by AHD, such as MDS.

The 3-day dosing schedule in Arm C was selected for further clinical development in elderly patients with de novo AML based on a 1-year survival rate of 30%, ORR of 35% with durable CRs. The 7-day dosing schedule in Arm A was selected for further clinical development in elderly patients with AML preceded by AHD based on a 1-year survival rate of 35%, ORR of 45% with durable hematological improvement.

Randomized Phase 2 clinical trial in older patients with MDS as a second-line treatment

In September 2008, we advanced sapacitabine into Phase 2 development as a second-line treatment in patients aged 60 or older with MDS who are previously treated with hypomethylating agents. The MDS stratum of the study is designed as a protocol amendment expanding the ongoing Phase 2 trial of sapacitabine in AML described above, to include a cohort of patients with MDS. Patients with MDS often progress to AML. The primary objective of the MDS stratum is to evaluate the 1-year survival rate of three dosing schedules of sapacitabine. Secondary objectives are to assess the number of patients who have achieved CR or CRp, PR, hematological improvement and their corresponding durations, transfusion requirements, number of hospitalization days and safety. The study uses a selection design with the objective of identifying a dosing schedule which produces a better 1-year survival rate for each stratum in the event that all three dosing schedules are active.

In December 2010, at the ASH annual meeting, we reported 1-year survival data from a Phase 2 randomized trial of oral sapacitabine capsules, a novel nucleoside analogue, in older patients with MDS refractory to hypomethylating agents, such as azacitidine and decitabine.

The study uses a selection design with the objective of identifying a dosing schedule that produces a better 1-year survival rate in the event that all three dosing schedules are active. The study enrolled 61 patients aged 60 or older with MDS refractory to hypomethylating agents randomized across three dosing schedules of sapacitabine: 21 patients in Arm A, a 7-day low dose regimen (200 mg b.i.d.); 20 patients in Arm B, a 7-day high dose regimen (300 mg b.i.d.) and 20 patients in Arm C, a 3-day high dose regimen (400 mg b.i.d.). Approximately 77% of patients were aged 70 years or older and 84% were scored as intermediate-2 or high risk by IPSS, the International Prognostic Scoring System. Baseline blast counts were between 11% and 29% in 51% of the patients. All patients were previously treated with hypomethylating agents: 43% with azacitidine, 34% with decitabine and 23% were double refractory patients as they were treated with both azacitidine and decitabine (7 on Arm A, 4 on Arm B and 3 on Arm C). Approximately 16% were previously treated with lenalidomide in addition to hypomethylating agents.

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The primary endpoint of 1-year survival was achieved in 29% of the patients on Arm A, 30% of the patients on Arm B and 35% of the patients on Arm C. The median overall survival was 217 days on Arm A (range of 15 to 663 days), 232 days on Arm B (range of 37 to over 811 days) and 236 days on Arm C (range of 16 to over 672 days). Overall response rate, a secondary endpoint consisting of the rate of CR, CRp, PR, CRi or hematological improvement, was 24% for patients on Arm A, 35% for patients on Arm B and 15% for patients on Arm C. Two patients achieved a CR both on Arm A. Approximately 20% of all patients received sapacitabine for 4 to 6 cycles and 15% for 7 or more cycles. The mortality rate from all causes within thirty days of randomization was 6.6%.

Randomized Phase 3 pivotal trial, SEAMLESS, as a front-line treatment in elderly patients aged 70 years or older with newly diagnosed AML who are not candidates for intensive induction chemotherapy

On January 11, 2011, we opened enrollment of the SEAMLESS pivotal Phase 3 trial for the Company s sapacitabine oral capsules as a front-line treatment of elderly patients aged 70 years or older with newly diagnosed AML who are not candidates for intensive induction chemotherapy. The study is being conducted under an SPA agreement that Cyclacel reached with the FDA. SEAMLESS builds on promising 1-year survival observed in elderly patients aged 70 years or older with newly diagnosed AML or AML in first relapse enrolled in a Phase 2 study of single agent sapacitabine.

The SEAMLESS study is chaired by Hagop M. Kantarjian, M.D., Chairman and Professor, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas. SEAMLESS is a multicenter, randomized, Phase 3 study comparing three treatment arms. In Arm A sapacitabine is administered in alternating cycles with decitabine, in Arm B sapacitabine is administered alone and in Arm C decitabine is administered alone. The primary efficacy endpoint is overall survival. The study is designed to demonstrate an improvement in overall survival of either of two pairwise comparisons: (1) Arm A versus Arm C or (2) Arm B versus Arm C. Approximately 150 patients per arm or a total of 450 patients from approximately 50 centers will be enrolled. SEAMLESS will be monitored by a Data Safety Monitoring Board (DSMB). A prespecified interim analysis for futility will be performed and reviewed by the DSMB.

On September 13, 2010, we reached agreement with the FDA regarding the SPA, on the design of a pivotal Phase 3 trial, the SEAMLESS trial. An SPA provides trial sponsors with an FDA agreement that the design and analysis of the trial adequately address objectives in support of a submission for a marketing application if the trial is performed according to the SPA. The SPA may only be changed through a written agreement between the sponsor and the FDA, or if the FDA becomes aware of a substantial scientific issue essential to product efficacy or safety. However, an SPA does not provide any assurance that a marketing application would be approved by the FDA. Furthermore, Phase 3 clinical trials are time-consuming and expensive, and because we have limited resources, we may be required to collaborate with a third party or raise additional funds. However, there is no assurance that we will be able to do so.

Solid Tumors

Phase 1 clinical trials in patients with refractory solid tumors or lymphomas

Two Phase 1 studies of sapacitabine were completed by Daiichi-Sankyo, from which we in-licensed sapacitabine, evaluating 87 patients in refractory solid tumors. In addition, we conducted a Phase 1b dose escalation clinical trial in patients with refractory solid tumors or lymphomas. Preliminary results of the Phase 1b study were reported at the EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics meeting in November 2006. The primary objective of the study was to evaluate the safety profile of sapacitabine administered twice daily for 14 consecutive days or 7 consecutive days every 21 days. Of the 37 treated patients, 28 received the drug twice daily for 14 days and 9 received the drug twice daily for 7 days. The dose-limiting toxicity was reversible myelosuppression. One patient treated at the maximum tolerated dose died of candida sepsis in the setting of grade 4 neutropenia and thrombocytopenia. Non-hematological toxicities were mostly mild to moderate. The best response by investigator assessment was stable disease in 13 patients, five with non-small cell lung cancer, two with breast cancer, two with ovarian cancer and one each with colorectal cancer, adenocarcinoma of unknown primary, gastrointestinal stromal tumor, and parotid acinar carcinoma.

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Phase 2 clinical trial in patients with non-small cell lung cancer

In January 2009, we began treating patients in a Phase 2, open label, single arm, multicenter, clinical trial in patients with NSCLC who have had one prior chemotherapy. This study builds on the observation of prolonged stable disease of four months or longer experienced by heavily pretreated NSCLC patients involved in two Phase 1 studies of sapacitabine. The multicenter Phase 2 trial is led by Philip D. Bonomi, M.D., at Rush University Medical Center, Chicago. The primary objective of the study is to evaluate the rate of response and stable disease in patients with previously treated NSCLC. Secondary objectives are to assess progression-free survival, duration of response, duration of stable disease, 1-year survival, overall survival and safety. The study will enroll approximately 40 patients and has a lead-in phase for dose escalation with the objective of defining a recommended dose followed by a second stage in which patients will be treated at the recommended dose.

Phase 2 clinical trial in patients with cutaneous T-cell lymphoma, or CTCL

In April 2007, we initiated a Phase 2 clinical trial in patients with advanced CTCL, a cancer of T-lymphocytes, or white blood cells, which causes disfiguring skin lesions and severe itching. The primary objective of the study is to evaluate tolerability and response rate of 50 mg and 100 mg regimens of sapacitabine both twice a day for three days per week for two weeks in a three week cycle in patients with progressive, recurrent, or persistent CTCL on or following two systemic therapies. The study uses a selection design to choose an optimal dose if both are active. Secondary objectives are to assess response duration, time to response, time to progression and relief of pruritus or itching. Non-hematological toxicities were mostly mild to moderate. The best response by investigator assessment was partial response in 3 patients out of 16 enrolled. We stopped the trial in order to re-direct our resources to sapacitabine clinica