

Cyclacel Pharmaceuticals, Inc.
Form S-3/A
April 18, 2013
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As filed with the Securities and Exchange Commission on April 18, 2013

Registration No. 333-187801

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Pre-Effective Amendment No.1

Form S-3

REGISTRATION STATEMENT UNDER THE SECURITIES ACT OF 1933

CYCLACEL PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

91-1707622
(IRS employer
Identification number)

200 Connell Drive, Suite 1500
Berkeley Heights, NJ 07922
(908) 517-7330

(Address, including zip code, and telephone number, including area code, of
registrant's principal executive offices)

Spiro Rombotis
President and Chief Executive Officer

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Cyclacel Pharmaceuticals, Inc.
200 Connell Drive, Suite 1500
Berkeley Heights, NJ 07922
(908) 517-7330

(Name, address, including zip code, and telephone number, including area code,
of agent for service)

With a copy to:

Joel I. Papernik, Esq.
Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C.
666 Third Avenue
New York, New York 10017
(212) 935-3000

Approximate date of commencement of proposed sale to the public: From time to time after this Registration Statement becomes effective.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box.

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.

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.

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Large accelerated filer

Accelerated filer

Non-accelerated filer

Smaller reporting
company

(Do not check if a smaller reporting company)

CALCULATION OF REGISTRATION FEE

Title of each Class of Securities to be Registered (1)	Proposed Maximum Aggregate Offering Price (2)(3)	Amount of Registration Fee(4)
Common Stock, \$0.001 par value per share	(5)	
Preferred Stock, \$0.001 par value per share	(5)	
Warrants to purchase Common Stock	(5)	
Debt Securities	(5)	
Units	(5)	
Total	\$ 75,000,000	\$ 10,230.00

(1) There are being registered under this registration statement such indeterminate number of shares of common stock, shares of preferred stock, warrants to purchase common stock, debt securities, rights and purchase contracts to purchase common stock and a combination of such securities, separately or as units, as may be sold by the registrant from time to time, which collectively shall have an aggregate initial offering price not to exceed \$75,000,000. If any debt securities are issued at an original issue discount, then the offering price of such debt securities shall be in such greater principal amount as shall result in an aggregate initial offering price not to exceed \$75,000,000, less the aggregate dollar amount of all securities previously issued hereunder. Any securities registered hereunder may be sold separately or as units with other securities registered hereunder. The securities registered also include such indeterminate amounts and numbers of common stock as may be issued upon conversion of preferred stock or pursuant to the anti-dilution provisions of any such securities. The securities registered also include such indeterminate amounts and numbers of common stock as may be issued upon exercise of warrants or pursuant to the anti-dilution provisions of any such securities. The securities registered also include such indeterminate amounts and numbers of common stock and debt securities as may be issued upon conversion of or exchange for debt securities that provide for conversion or exchange, upon exercise of warrants or pursuant to the anti-dilution provisions of any such securities. In addition, pursuant to Rule 416 under the Securities Act of 1933, as amended (the **Securities Act**), the shares of common stock being registered hereunder include such indeterminate number of shares of common stock as may be issuable with respect to the shares being registered hereunder as a result of stock splits, stock dividends, or similar transactions.

(2) The proposed maximum per unit and aggregate offering prices per class of security will be determined from time to time by the registrant in connection with the issuance by the registrant of the securities registered hereunder.

(3) Estimated solely for purposes of determining the registration fee pursuant to Rule 457(o) under the Securities Act. The aggregate maximum offering price of all securities issued pursuant to this registration statement will not exceed \$75,000,000.

(4) Calculated pursuant to Rule 457(o) based on an estimate of the proposed maximum aggregate offering price. Amount previously paid.

(5) Not required to be included in accordance with General Instruction II.D of Form S-3 and Rule 457(o) under the Securities Act.

The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment which specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until the registration statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to said Section 8(a), may determine.

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The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and is not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED APRIL 18, 2013

PROSPECTUS

\$75,000,000

CYCLACEL PHARMACEUTICALS, INC.

**Common Stock
Preferred Stock
Warrants
Debt Securities
Rights
Purchase Contracts
Units**

We may, from time to time at prices and on terms to be determined at or prior to the time of one or more offerings, issue up to \$75,000,000 of any combination of the securities described in this prospectus, either individually or in units. We may also offer common stock or preferred stock upon conversion of the debt securities, common stock upon conversion of the preferred stock, or common stock, preferred stock or debt securities upon the exercise of warrants, rights or performance of purchase contracts; or any combination of these securities upon the performance of purchase contracts.

This prospectus described the general terms of these securities and the general manner in which these securities will be offered. We will provide you with the specific terms of any offering in one or more supplements to this prospectus. The prospectus supplements will also describe the specific manner in which these securities will be offered and may also supplement, update or amend information contained in this document. You should read this prospectus and any prospectus supplement, as well as any documents incorporated by reference into this prospectus or any prospectus supplement, carefully before you invest.

Our common stock is listed on The NASDAQ Global Market under the symbol CYCC, and our preferred stock is listed on the NASDAQ Global Market under the symbol CYCCP. On April 17, 2013, the last reported sale price of our common stock was \$5.00 per share, and the last reported sale price of our preferred stock was \$8.50. The applicable prospectus supplement will contain information, where applicable, as to any other listing, if any, on The NASDAQ Global Market or any securities market or other securities exchange of the securities covered by the prospectus supplement. Prospective purchasers of our securities are urged to obtain current information as to the market prices of our securities, where

applicable.

Investing in our securities involves a high degree of risk. Before deciding whether to invest in our securities, you should consider carefully the risks that we have described on page 13 of this prospectus under the caption Risk Factors. We may include specific risk factors in supplements to this prospectus under the caption Risk Factors. This prospectus may not be used by us to offer or sell our securities unless accompanied by a prospectus supplement.

Our securities may be sold directly by us to investors, through agents designated from time to time or to or through agents, underwriters or dealers. For additional information on the methods of sale, you should refer to the section entitled "Plan of Distribution" in this prospectus and in the applicable prospectus supplement. If any agents, underwriters or agents are involved in the sale of our securities with respect to which this prospectus is being delivered, the names of such underwriters or agents and any applicable fees, commissions or discounts and over-allotment options will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds that we expect to receive from such sale will also be set forth in a prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The date of this prospectus is April [], 2013.

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You should read this prospectus and the documents incorporated by reference carefully before you invest. Such documents contain important information you should consider when making your investment decision. See Incorporation of Documents by Reference on page 51. You should rely only on the information provided in this prospectus or documents incorporated by reference in this prospectus. We have not authorized anyone to provide you with different information. The information contained in this prospectus is accurate only as of the date of this prospectus and any information we have incorporated by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus or of any sale of our common stock. Our business, financial condition, results of operations and prospects may have changed since that date.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, utilizing a shelf registration process. Under this shelf registration process, we may offer shares of our common stock, preferred stock, warrants to purchase common stock, and/or debt securities, either individually or in units, in one or more offerings, with a total value of up to \$75,000,000. This prospectus provides you with a general description of the securities we may offer. Each time we offer a type or series of securities under this prospectus, we will provide a prospectus supplement that will contain specific information about the terms of that offering.

This prospectus does not contain all of the information included in the registration statement. For a more complete understanding of the offering of the securities, you should refer to the registration statement, including its exhibits. The prospectus supplement may also add, update or change information contained or incorporated by reference in this prospectus. However, no prospectus supplement will fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness. This prospectus, together with the applicable prospectus supplements and the documents incorporated by reference into this prospectus, includes all material information relating to the offering of securities under this prospectus. You should carefully read this prospectus, the applicable prospectus supplement, the information and documents incorporated herein by reference and the additional information under the heading **Where You Can Find More Information** before making an investment decision.

You should rely only on the information we have provided or incorporated by reference in this prospectus or any prospectus supplement. We have not authorized anyone to provide you with information different from that contained or incorporated by reference in this prospectus. No dealer, salesperson or other person is authorized to give any information or to represent anything not contained or incorporated by reference in this prospectus. You must not rely on any unauthorized information or representation. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so.

You should assume that the information in this prospectus or any prospectus supplement is accurate only as of the date on the front of the document and that any information we have incorporated herein by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus or any sale of a security. To the extent there is a conflict between the information contained in this prospectus and the prospectus supplement, you should rely on the information in the prospectus supplement, provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference in this prospectus or any prospectus supplement—the statement in the document having the later date modifies or supersedes the earlier statement.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference in the accompanying prospectus were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

This prospectus may not be used to consummate sales of our securities, unless it is accompanied by a prospectus supplement. To the extent there are inconsistencies between any prospectus supplement,

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this prospectus and any documents incorporated by reference, the document with the most recent date will control.

Unless the context otherwise requires, Cyclacel, the Company, we, us, our and similar terms refer to Cyclacel Pharmaceuticals Inc.

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PROSPECTUS SUMMARY

The following is a summary of what we believe to be the most important aspects of our business and the offering of our securities under this prospectus. We urge you to read this entire prospectus, including the more detailed consolidated financial statements, notes to the consolidated financial statements and other information incorporated by reference from our other filings with the SEC or included in any applicable prospectus supplement. Investing in our securities involves risks. Therefore, carefully consider the risk factors on page 13 of this prospectus and in any prospectus supplements and in our most recent annual and quarterly filings with the SEC, as well as other information in this prospectus and any prospectus supplements and the documents incorporated by reference herein or therein, before purchasing our securities. Each of the risk factors could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our securities.

Our Business

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

Oncology Development Programs

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

- Acute Myeloid Leukemia, or AML, in the elderly;

- Myelodysplastic syndromes, or MDS; and

- Non-small cell lung cancer, or NSCLC.

The U.S. Food and Drug Administration, or FDA, and the European Medicines Agency, or EMA, have designated sapacitabine as an orphan drug for the treatment of both AML and MDS.

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We are currently evaluating sapacitabine in a Phase 3 study being conducted under a Special Protocol Assessment, or SPA, with the FDA for the front-line treatment of AML in the elderly. We are also exploring sapacitabine in Phase 2 studies for MDS, NSCLC and chronic lymphocytic leukemia, or CLL, and in a Phase 1 study in solid tumors in combination with our own drug candidate, seliciclib.

In our second development program, we are evaluating cyclin dependent kinase, or CDK, inhibitors. CDKs are involved in cancer cell growth, metastatic spread and DNA damage repair. Seliciclib, our lead CDK inhibitor, selectively inhibits a spectrum of enzyme targets - CDK2/E, CDK2/A, CDK7 and CDK9 - that are central to the process of cell division and cell cycle control. In breast and lung tumors, overexpression of cyclin E is associated with poor prognosis and drug resistance. Resistant breast and lung tumor cell lines overexpressing cyclin E are resensitized to apoptotic cell killing by seliciclib. NSCLC cell lines with Ras-activating mutations, such as KRAS and NRAS, have been found to be

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sensitive to seliciclib-induced apoptosis. To date, seliciclib has been evaluated in approximately 450 patients in several Phase 1 and 2 studies and has shown signs of anti-cancer activity. We have retained worldwide rights to commercialize seliciclib. Seliciclib has completed a Phase 2B randomized study in third-line NSCLC and is currently undergoing a study in solid tumors in combination with our own drug candidate, sapacitabine.

Our second generation CDK inhibitor, CYC065, is a highly selective inhibitor of CDKs targeting CDK -2, -5 and -9 enzymes. CYC065 has shown to have increased anti-proliferative potency and improved pharmaceutical properties compared to seliciclib. Investigational new drug (IND)-enabling studies with CYC065 are in progress supported by a \$1.9 million grant from the UK Government's Biomedical Catalyst.

In addition to these development programs, we have allocated limited resources, if the funds are available, to other programs allowing us to maintain and build on our core competency in cell cycle biology and related drug discovery. In our polo-like kinase, or Plk, inhibitor program, we have discovered potent and selective small molecule inhibitors of Plk1, a kinase active during cell division, targeting the mitotic phase of the cell cycle. Plk was discovered by Professor David Glover, our Chief Scientist, and CYC116, an orally-available inhibitor of Aurora kinase, or AK, A and B and Vascular Endothelial Growth Factor Receptor 2, or VEGFR2, has completed a multicenter Phase 1 trial.

We also have a number of earlier stage programs for which limited or no resources will be allocated in the foreseeable future. For example, extensive preclinical data published by independent investigators evidence activity by our CDK inhibitors, including seliciclib, in various autoimmune and inflammatory diseases and conditions associated with aberrant cell proliferation including graft-versus-host disease, idiopathic pulmonary fibrosis, lupus nephritis, polycystic kidney disease and rheumatoid arthritis. In our GSK-3 inhibitor program, we have demonstrated evidence of activity in preclinical models of Type 2 Diabetes.

Sapacitabine

Sapacitabine (previously known as CYC682) is an orally-available nucleoside analogue. Both sapacitabine and CNDAC, its major metabolite, have demonstrated potent anti-tumor activity in preclinical studies. 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 novel mechanism whereby the compound interferes with DNA synthesis through the incorporation of CNDAC into DNA during replication or repair, triggering a β -elimination reaction and leading to the formation of SSBs, which can activate the G2 checkpoint transcription coupled nucleotide excision repair, or TC-NER. During subsequent rounds of replication, SSBs are converted to double-strand breaks (DSBs); these can be repaired by the homologous recombination repair (HRR) pathway, or, if unrepaired, result in cell death.

We are currently exploring sapacitabine in both hematological cancers and solid tumors and over 500 patients have received sapacitabine in Phase 1, 2 and 3 studies.

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Hematological Cancers

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

The SEAMLESS study is being conducted under an SPA agreement that Cyclacel reached with the FDA. SEAMLESS builds on promising one 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 two treatment arms. In Arm A, sapacitabine is administered in alternating cycles with decitabine and in Arm C decitabine is administered alone. The primary efficacy endpoint is overall survival and the study is designed to demonstrate an improvement in overall survival. Approximately 242 patients per arm, or a total of 485 patients from approximately 50 centers, will be enrolled. The SEAMLESS study is designed to have a 90% probability of detecting a 27.5% difference in overall survival and a prespecified interim analysis for futility will be performed and reviewed by the Data Safety Monitoring Board, or DSMB. In addition, the DSMB will periodically convene to review data for safety or efficacy from each approximately 100 patients enrolled.

In December 2012, the DSMB met and recommended that the study should continue as planned after reviewing available data from 119 randomized patients. The DSMB noted that no safety or efficacy concerns were identified. Results from an on-going, multicenter, Phase 1/2 clinical trial examining the safety and efficacy of oral sapacitabine administered sequentially with decitabine, the same treatment regimen as Arm A in SEAMLESS, was reported during a poster session at the 2012 American Society of Hematology, or ASH, Annual Meeting in Atlanta, Georgia. Forty-six patients were treated with alternating cycles of sapacitabine and decitabine. Median age was 77 years (range 70-90). Thirty-three patients (72%) were 75 years or older. Median overall survival was 238 days, or approximately 8 months. The number of patients still alive at 3 months was 38 (83%), at 6 months 30 (65%), at 12 months 16 (35%) and at 18 months 12 (26%). Sixteen patients (35%) survived 1 year or longer. Among 33 patients who were 75 years or older, median overall survival was 263 days, or approximately 9 months, and 1-year survival was 36%. Nineteen patients (41%) responded with 10 complete responses (CRs), 4 partial responses (PRs) and 5 major hematological improvements (HIs). Median time to response was 2 cycles, i.e., one cycle of decitabine and one cycle of sapacitabine (range 1-10). Twenty-seven patients (59%) received 5 or more cycles of treatment. Two dose-limiting toxicities (DLT) were observed (lung infection/sepsis, typhlitis). Thirty-day mortality from all causes was 4%. Sixty-day mortality from all causes was 13% with one death from typhlitis considered to be possibly related to decitabine by investigator assessment.

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, had 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 were to assess complete remission, or CR, partial remission, or PR, duration of CR

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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 one year survival rate in the event that all three dosing schedules are active.

In November 2012, the results from the Phase 2 study were published in *The Lancet Oncology*, demonstrating the safety and efficacy of sapacitabine in this patient population. The Phase 2 study enrolled and treated between December 27, 2007 and April 21, 2009, a total of 105 patients aged 70 years or above with untreated or first relapse AML. The median age of patients was 77 years (range 70 - 91). The group was comprised of a randomized cohort of 60 patients and an expanded, non-randomly assigned cohort enrolling a further 45 patients. Of the 105 patients, 86 were previously untreated and 19 in first relapse. Approximately 50% of patients had AML de novo and 50% had AML preceded by antecedent hematological disorder (AHD), such as MDS or myeloproliferative disease, or treatment-related AML. All but one enrolled patients had intermediate or unfavorable cytogenetics. The randomized cohort of patients were randomly assigned to one of three dosing schedules: 200 mg twice a day for 7 days (group A); 300 mg twice a day for 7 days (group B); and 400 mg twice a day for 3 days each week for 2 weeks (group C). All schedules were given in 28 day cycles. The 3-day dosing schedule in group C was selected for further clinical development in elderly patients with untreated AML. This decision was based on the schedule's overall efficacy profile, which included a 1-year survival rate of 30%, median overall survival of 213 days and durable complete remissions (CRs) in 25% of patients. The median overall survival of patients from all groups who achieved CR was 525 days (95% C.I. 192 - 798). The most common grade 3 - 4 adverse events regardless of causality were anemia, neutropenia, thrombocytopenia, febrile neutropenia and pneumonia. Seven deaths were thought to be probably or possibly related to sapacitabine treatment. Approximately 31% of all patients received sapacitabine for at least 4 cycles.

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

In September 2008, we advanced sapacitabine into an open-label, multi-center, randomized Phase 2 trial as a second-line treatment in patients aged 60 or older with intermediate-2 or high-risk MDS after treatment failure of front-line hypomethylating agents, such as azacitidine and/or decitabine. The Phase 2 study randomized 63 patients aged 60 years or older with MDS of intermediate-2 (n=52) or high-risk (n=11) classification by the International Prognostic Scoring System (IPSS) at study entry to receive sapacitabine every 4 weeks on one of 3 dosing schedules: 200 mg twice daily for 7 days (Arm G), 300 mg once daily for 7 days (Arm H), or 100 mg once daily for 5 days per week for 2 weeks (Arm I). The primary efficacy endpoint of the study is 1-year survival 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. All patients in the study progressed after receiving azacitidine, decitabine, or both agents. 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.

In October 2012, at The Eighth Annual Hematologic Malignancies 2012 Conference, we reported updated data from the ongoing Phase 2 trial. Median overall survival to date for all 63 patients in the study was 252 days or approximately 8 months. Median overall survival for 41 out of 63 patients with 10% or more blasts in their bone marrow was 274 days or approximately 9 months. Updated median survival for all three arms was 252 days (approximately 8 months). The median survival for each arm is 291 days (approximately 10 months) for Arm G, 274 days (approximately 9 months) for Arm H, and 227

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days (approximately 8 months) for Arm I. Twenty-seven percent of all patients received 6 or more cycles. Twenty-two percent of patients were still alive and longer follow-up is needed to assess 1-year survival and overall survival of each arm.

Median survival for patients with intermediate-2 or high-risk disease, as defined by the International Prognostic Scoring System (IPSS), is 4.3 to 5.6 months as reported in literature. Patients with high IPSS scores also have a high probability of experiencing transformation of their MDS into AML, an aggressive form of blood cancer with typically poor survival.

Solid Tumors

Phase 2 clinical trial in patients with NSCLC

We are evaluating sapacitabine in 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, one year survival, overall survival and safety.

Forty-eight patients have been treated with two dosing schedules, either twice daily or once a day. In the twice daily schedule 15 patients were treated with escalating doses. The recommended Phase 2 dose was reached at 75 mg twice daily for 5 days per week for 2 weeks every 3 weeks. Among 12 patients treated at this recommended Phase 2 dose, 4 achieved stable disease. All 4 responders had at least 2 prior therapies and have been discontinued from the study. Responders received an average of 7 treatment cycles.

In the once daily schedule 33 patients were treated with escalating doses. Maximum tolerated dose has not been reached at the upper limit of the dosing range as per protocol. Patients are currently being entered into the 200 mg once daily dosing level for 5 days per week for 2 weeks every 3 weeks. Among 25 patients treated with daily doses ranging from 100 mg to 175 mg, two patients achieved PR and 10 stable disease. The two PR responders had 3 or 4 prior therapies, respectively, and one remains on study. Among the 10 stable disease responders, 9 had at least 2 prior therapies and 2 remain on study. Responders received an average of 10 treatment cycles.

Phase 1 clinical trial of sapacitabine and seliciclib in patients with advanced cancers

In an open label Phase 1, single-arm dose escalation study, sapacitabine and seliciclib were administered sequentially in patients with incurable advanced solid tumors unresponsive to conventional treatment or for which no effective therapy exists. Sapacitabine was dosed twice daily for 7 days (Day 1-7) and seliciclib twice daily for 3 days (Day 8-11). One treatment cycle is three weeks. At least 3 patients were enrolled at each escalating dose level. The first tumor imaging study is conducted after 2 cycles of treatment and every 3 cycles thereafter. The primary objective of the study is to determine the maximum tolerated dose, or MTD, and recommended Phase 2 dosing schedule of sapacitabine and seliciclib administered sequentially. The secondary objective was to evaluate the antitumor activity of sequential treatment and to explore the

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pharmacodynamic effect of this treatment in skin and peripheral blood mononuclear cells. We reported at the 2012 American Society of Clinical Oncology Annual Meeting that

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34 heavily-pretreated patients with advanced solid tumors had been treated with escalating doses. The MTD for sequential administration of sapacitabine and seliciclib was reported as sapacitabine 50 mg twice daily followed by seliciclib 1200 mg twice daily. Pharmacodynamic effects of sapacitabine and seliciclib were observed in skin biopsies showing a 2.3-fold increase in H2AX staining post-sapacitabine and a further 0.58-fold increase post-seliciclib.

Among 19 patients treated at the MTD, 3 partial responses (PR) occurred in patients with breast, ovarian and pancreatic cancer and 1 stable disease in a patient with ovarian cancer. Thirteen out of the 19 patients are BRCA-mutation carriers, in their germ line. Stable disease was achieved in 6 additional patients treated with the other dosing schedules. The number of treatment cycles administered ranges from 2 to over 15 cycles. The breast cancer patient who achieved PR remains on study with over 15 cycles and both ovarian cancer patients remain on study with over 2 and 12 cycles, respectively.

BRCA1 and BRCA2, or breast cancer susceptibility genes, are tumor suppressor genes that help ensure the stability of DNA, the cell's genetic material, and help prevent uncontrolled cell growth. Genetic testing for BRCA-status is routinely available. BRCA mutation has been linked to predisposition to breast and ovarian cancer. According to the US National Cancer Institute, during her life time a woman has a 60% chance of developing breast cancer and 15-40% chance of developing ovarian cancer if she inherits a harmful BRCA mutation. These risks are 5 times and over 10 times more likely than for women without the mutation, respectively.

Orphan Designation

European Union

During May 2008, we received designation from the EMA for sapacitabine as an orphan medicine in two separate indications: AML and MDS. The EMA's Committee for Orphan Medicinal Products, or COMP, adopted a positive opinion on our application to designate sapacitabine as an orphan medicinal product for the indications of AML and MDS. The objective of European orphan medicines legislation is to stimulate research and development of medicinal products for rare diseases by providing incentives to industry. An orphan designation in the European Union confers a range of benefits to sponsor companies including market exclusivity for a period of 10 years, EMA scientific advice on protocol development, direct access to the centralized procedure for review of marketing authorizations, EMA fee reductions and eligibility for grant support from European agencies.

United States

In June 2010, we announced that the FDA granted orphan drug designation to our sapacitabine product candidate for the treatment of both AML and MDS. An orphan designation in the United States confers a range of benefits to sponsor companies, including market exclusivity for a period of seven years from the date of drug approval, the opportunity to apply for grant funding from the United States government to defray costs of clinical trial expenses, tax credits for clinical research expenses and a potential waiver of the FDA's application user fee. Orphan status is granted by the FDA to promote the development of new drug therapies for the treatment of diseases that affect fewer than 200,000 individuals in the United States.

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Seliciclib

Although our current clinical development priorities are focused on sapacitabine only, our second drug candidate, seliciclib, is a novel, first-in-class, orally-available, CDK inhibitor. The compound selectively inhibits a spectrum of enzyme targets - CDK2, CDK5, CDK7 and CDK9 - that are central to the process of cell division and cell cycle control. The target profile of seliciclib is differentiated from the published target profile of other CDK inhibitors. Its selectivity is differentiated by recent publications by independent investigators which showed that seliciclib (i) is more active against NSCLC cells with K-Ras or N-Ras mutations than those with wild type Ras and (ii) overcomes resistance to letrozole (Femara®) in breast cancer cells caused by a particular form of cyclin E in complex with CDK2. Preclinical studies have shown that the drug works by inducing cell apoptosis, or cell suicide, in multiple phases of the cell cycle. To date, seliciclib has been evaluated in approximately 450 patients in several Phase 1 and 2 studies and has shown signs of anti-cancer activity. We have retained worldwide rights to commercialize seliciclib.

Phase 2 clinical trial in patients with NSCLC

Four Phase 2 trials have been conducted in cancer patients to evaluate the tolerability and antitumor activities of seliciclib alone or in combination with standard chemotherapies used in the treatment of advanced NSCLC or breast cancer. Interim data from two Phase 2 open-label studies of a total of 52 patients with NSCLC, suggests that seliciclib treatment neither aggravated the known toxicities of standard first and second-line chemotherapies nor appeared to cause unexpected toxicities, although these trials were not designed to provide statistically significant comparison.

On December 21, 2010, we announced topline results from APPRAISE, our Phase 2b, randomized discontinuation, double-blinded, placebo-controlled, study of oral seliciclib capsules as a third line or later treatment in patients with NSCLC. APPRAISE was led by Chandra P. Belani, M.D. at Milton S. Hershey Medical Center, Penn State University. Topline results, after unblinding the treatment assignment among randomized patients, showed that there was no difference between the seliciclib and placebo arms in terms of progression free survival, or PFS, (48 versus 53 days respectively) but an increase in median overall survival, or OS, was observed favoring the seliciclib arm over the placebo arm (388 versus 218 days respectively). A total of 187 patients from 21 centers in the United States were entered in the study after having progressed on at least two prior therapeutic regimens for their NSCLC. Of these, 53 (28%) were randomized, 27 on seliciclib and 26 on placebo. Forty-five out of 53 randomized patients (85%) received 3 or more prior therapies and 45 out of 53 randomized patients (85%) previously received at least one EGFR inhibitor drug (22 on seliciclib and 23 on placebo). Fourteen patients were crossed-over to the seliciclib arm after their cancer progressed while they were receiving placebo. Study data demonstrated seliciclib to be safe at the administered dose. There was no difference between the seliciclib and placebo arms in terms of PFS of 48 days on the seliciclib arm versus 53 days on the placebo arm. However an increase in median overall survival was observed of 388 days on the seliciclib arm versus 218 days on the placebo arm.

Published pre-clinical work indicated that K-Ras mutational status, cyclin D1 and cyclin E1 protein levels correlated strongly with tumor sensitivity towards seliciclib. In order to explore this possible molecular rationale for the difference in OS, we retrospectively collected and analyzed available biopsy samples from APPRAISE patients who granted informed consent. As only 30 patient samples were available from the 152 APPRAISE patients who gave consent, results of the retrospective analysis were insufficient to allow meaningful correlation. A new prospectively designed study is required to test

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the hypothesis that these biomarkers can predict therapeutic effect of seliciclib in patients with advanced stage NSCLC.

Phase 2 clinical trials in patients with NPC

In November 2007, we commenced a Phase 2 multicenter, international, blinded randomized study of oral seliciclib as a single agent in patients with nasopharyngeal cancer, or NPC. The primary objective is to evaluate 6-month progression free survival, or PFS, of two dosing schedules of seliciclib in approximately 75 patients with previously treated NPC. Secondary objectives are OS, response rate, response duration, safety and tolerability. The first part of the study is designed to confirm safety and tolerability of 400 mg twice a day for four days per week or 800 mg once a day for four days per week of seliciclib. It is open to approximately 12 to 24 patients with advanced solid tumors as well as patients with NPC. The second part of the study, which is dependent on clinical data from the lead-in phase and available resources to fund the study, is designed to detect major differences between the two dosing schedules of seliciclib and a placebo group in terms of 6-month PFS in approximately 51 patients.

In May 2009, at the ASCO annual meeting, we reported interim data from the lead-in portion of the Phase 2 study which demonstrated that oral seliciclib could be safely administered in two dosing schedules which were well tolerated and met the criteria for proceeding to the randomized stage of the study. Seliciclib treatment resulted in prolonged stable disease in 70% of previously-treated NPC patients, including 3 with stable disease lasting longer than 8 months, suggesting seliciclib inhibits tumor growth in NPC. The data support further clinical development of oral seliciclib in NPC.

CYC065

CYC065 is a highly-selective, orally-available, 2nd generation inhibitor of CDK -2, -5 and -9; enzyme complexes that play pivotal roles in cancer cell growth, metastatic spread and DNA damage repair. CYC065 causes apoptotic cell death of cancer cells at sub-micromolar and antitumor efficacy has been achieved in vivo with once a day oral dosing at well tolerated doses. CYC065 has been shown to target key components of leukemogenic and survival pathways in acute leukemias, including the MCL1 anti-apoptotic protein, and also transcription, driven by the rearranged mixed lineage leukemia gene. Strong preclinical data supports expansion into solid tumor indications which overexpress cyclin E or CDK5 such as trastuzumab resistant breast cancer and metastatic pancreatic cancer. CYC065 is currently in IND-directed preclinical development.

In addition CYC065 was shown to have preclinical efficacy in proliferative kidney disease models (Cyclacel data on file). Cyclacel discovered CYC065 and other novel CDK inhibitors in collaboration with the Cancer Research UK Centre for Cancer Therapeutics at The Institute of Cancer Research.

Plk inhibitors

In our Plk inhibitor program, CYC140, we have discovered potent and selective small molecule inhibitors of Plk1, a kinase active during cell division, targeting the mitotic phase of the cell cycle. At the 2012 Annual Meeting of the AACR we reported on one of these compounds

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selected for further preclinical development. In a panel of esophageal cancer cell lines, sensitivity to CYC140 correlated with p53 status. Esophageal cell lines lacking functional p53 showed the greatest sensitivity to Compound 4. Short drug exposure times demonstrated differential sensitivity between cancerous esophageal cells versus control, outlining the potential broad therapeutic index for Compound 4 in treating esophageal