

CYTRX CORP
Form S-3
November 27, 2013
Table of Contents

As filed with the Securities and Exchange Commission on November 27, 2013

Reg. No. 333-

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM S-3

REGISTRATION STATEMENT

UNDER

THE SECURITIES ACT OF 1933

CYTRX CORPORATION

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

CytRx Corporation

58-1642750
(I.R.S. Employer
Identification No.)

Edgar Filing: CYTRX CORP - Form S-3

11726 San Vicente Boulevard, Suite 650

Los Angeles, California 90049

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

Steven A. Kriegsman

President and Chief Executive Officer

CytRx Corporation

11726 San Vicente Boulevard, Suite 650

Los Angeles, California 90049

(310) 826-5648

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

With copies to:

Benjamin S. Levin

General Counsel

CytRx Corporation

11726 San Vicente Boulevard, Suite 650

Los Angeles, California 90049

Telephone: (310) 826-5648

Facsimile: (310) 826-6139

Dale E. Short

TroyGould PC

1801 Century Park East, Suite 1600

Los Angeles, California 90067

Telephone: (310) 789-1259

Facsimile: (310) 789-1459

Approximate date of commencement of proposed sale to public: From time to time after the effective date of this registration statement.

Table of Contents

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, 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. (Check one):

Large accelerated filer <input type="checkbox"/>	Accelerated filer <input checked="" type="checkbox"/>
Non-accelerated filer <input type="checkbox"/> (Do not check if a smaller reporting company)	Smaller reporting company <input type="checkbox"/>

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Amount to be registered	Proposed maximum offering price per share	Proposed maximum aggregate offering price	Amount of registration fee
---	--------------------------------	--	--	-----------------------------------

Edgar Filing: CYTRX CORP - Form S-3

Common stock, par value \$.001 per share	6,440,045 shares(1)(2)	\$4.48(3)	\$28,851,402(3)	\$ 3,717
Common stock, par value \$.001 per share(2)	(2)(4)			
Preferred stock, \$.01 par value per share(4)	(4)			
Warrants(4)(5)	(4)			
Units(4)(5)	(4)			
Subtotal			\$100,000,000(5)	\$12,880(6)
Total			\$128,851,402	\$16,597(6)

- (1) Represents shares issuable upon exercise of outstanding warrants. In accordance with Rule 416, there is also being registered hereunder such indeterminate number of additional shares of common stock as may become issuable upon exercise of the warrants to prevent dilution resulting from stock splits, stock dividends or similar transactions.
- (2) Each share of common stock will be accompanied by one Series A Junior Participating Preferred Stock Purchase Right that trades with the common stock. The value, if any, attributable to this right is reflected in the market price of common stock. Prior to the occurrence of certain events, none of which has occurred as of the date of this registration statement, the rights will not be exercisable or evidenced separately from the common stock.
- (3) The price is estimated in accordance with Rule 457(g) under the Securities Act of 1933 solely for the purpose of calculating the registration fee and represents the exercise price of the warrants.

Table of Contents

- (4) Pursuant to Rule 457(o) under the Securities Act of 1933 and General Instruction II.D to Form S-3 under the Securities Act of 1933, the number of shares, warrants or units is not specified. There is being registered hereunder an indeterminate amount of common stock, preferred stock, warrants and units of the registrant as may from time to time be issued at indeterminate prices. The maximum offering price per class of securities will be determined from time to time by the registrant in connection with the issuance of the securities. However, in no event will the maximum aggregate offering price of the securities issued exceed \$100,000,000 or such lesser aggregate amount permitted under General Instruction I.B.6 to Form S-3 under the Securities Act of 1933. Pursuant to Rule 416 under the Securities Act of 1933, this registration statement also registers such indeterminate amounts of securities as may be issued upon conversion of, or in exchange for, the securities registered hereunder and such indeterminate number of shares of common stock and preferred stock as may be issued from time to time upon conversion or exchange as a result of stock splits, stock dividends or similar transactions.
- (5) Estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(o) under the Securities Act of 1933.
- (6) Pursuant to Rule 415(a)(6) under the Securities Act of 1933, \$27,764,800 of the securities registered by this registration statement consists of unsold securities previously registered under the registration statement on Form S-3 (Reg. No. 333-170437) declared effective on December 14, 2010. Pursuant to Rule 457(p) under the Securities Act of 1933, the registration fee of \$1,979 paid with respect to such unsold securities in connection with such previous registration statement is offset against the filing fee due hereunder.

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 OR UNTIL THIS REGISTRATION STATEMENT SHALL BECOME EFFECTIVE ON SUCH DATE AS THE COMMISSION, ACTING PURSUANT TO SAID SECTION 8(A), MAY DETERMINE.

Table of Contents

EXPLANATORY NOTES

This Registration Statement contains two prospectuses, as described below:

a prospectus relating to up to 6,440,045 shares of common stock of the registrant issuable upon the exercise of outstanding August 2011 warrants of the registrant; and

a prospectus relating to up to \$100,000,000 of securities of the registrant that the registrant may offer and sell in one or more transactions utilizing the shelf registration process described in the prospectus.

The two prospectuses are substantively identical, except for the following principal differences:

they contain different outside front covers and back covers;

the August 2011 warrants prospectus refers throughout to the registrant's offer and sale of shares of common stock issuable upon the August 2011 warrants, and the shelf registration prospectus refers throughout to the registrant's offer and sale of its common stock, preferred stock and warrants, either separately, together or as units, described in the prospectus;

the August 2011 warrants prospectus has additional risk factors in the Risk Factors Associated with Our Common Stock section relating to dilution and to management's discretion as to the use of proceeds of the offering under the August 2011 warrants prospectus;

the August 2011 warrants prospectus contains a Dilution section;

the two prospectuses contain different Use of Proceeds sections;

the shelf registration prospectus also contains a Financial Ratio section, while the August 2011 warrants prospectus does not;

the two prospectuses contain different Plan of Distribution sections; and

the August 2011 warrants prospectus contains a description of the August 2011 warrants in the Description of Capital Stock section and the shelf registration prospectus contains The Securities That We May Offer, Description of Capital Stock, Description of Warrants and Description of Units sections.

The registrant has included in this registration statement, after the prospectus relating to the August 2011 warrants, the shelf registration prospectus, which prospectus reflects the foregoing principal differences from the August 2011 warrants prospectus.

Table of Contents

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 it is not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED NOVEMBER 27, 2013

PROSPECTUS

6,440,045 Shares of Common Stock

Issuable Upon Exercise of August 2011 Warrants

This prospectus relates to shares of our common stock issuable upon the exercise of our outstanding August 2011 warrants. The August 2011 warrants were offered and sold by us pursuant to a prospectus supplement dated July 27, 2011 and a related base prospectus dated December 13, 2010. The prospectus supplement and base prospectus also covered the offer and sale by us of the shares of our common stock underlying the August 2011 warrants. The ongoing offer for sale by us of the shares of our common stock issuable upon exercise of the August 2011 warrants is being made pursuant to this prospectus. The August 2011 warrants are exercisable until August 1, 2016 at a current exercise price of \$4.48 per share of our common stock, subject to adjustment in events specified in the August 2011 warrants.

Our common stock is traded on The NASDAQ Capital Market under the symbol CYTR. On November 26, 2013, the closing sale price of our common stock on The NASDAQ Capital Market was \$2.3799.

An investment in our common stock involves a high degree of risk. See Risk Factors beginning on page A-7 of this prospectus.

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.

Edgar Filing: CYTRX CORP - Form S-3

The date of this prospectus is _____, 2013.

Table of Contents

TABLE OF CONTENTS

	Page
<u>ABOUT THIS PROSPECTUS</u>	A-1
<u>NOTE ON FORWARD-LOOKING STATEMENTS</u>	A-1
<u>INDUSTRY DATA</u>	A-1
<u>TRADEMARKS</u>	A-1
<u>PROSPECTUS SUMMARY</u>	A-2
<u>RISK FACTORS</u>	A-6
<u>USE OF PROCEEDS</u>	A-15
<u>DILUTION</u>	A-16
<u>DIVIDEND POLICY</u>	A-16
<u>PLAN OF DISTRIBUTION</u>	A-16
<u>DESCRIPTION OF SECURITIES</u>	A-17
<u>WHERE YOU CAN FIND MORE INFORMATION</u>	A-19
<u>INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE</u>	A-20
<u>LEGAL MATTERS</u>	A-20
<u>EXPERTS</u>	A-20

Table of Contents

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or the SEC. As permitted by the rules and regulations of the SEC, the registration statement filed by us includes additional information not contained in this prospectus. You may read the registration statement and the other reports we file with the SEC at the SEC's web site or its offices described under the heading "Where You Can Find More Information" in this prospectus.

You should rely only on the information provided in this prospectus, including any information incorporated by reference. For more details on information incorporated herein by reference, you should review the discussion contained under the heading "Incorporation of Certain Documents by Reference." We have not authorized anyone to provide you with information different from that contained or incorporated by reference in this prospectus. We are offering the securities only in jurisdictions where offers are permitted. You should not assume that the information in this prospectus is accurate at any date other than the date indicated on the cover page of this prospectus.

NOTE ON FORWARD-LOOKING STATEMENTS

Some of the statements contained or incorporated by reference in this prospectus may include forward-looking statements that reflect our current views with respect to our ongoing and planned clinical trials, business strategy, business plan, financial performance and other future events. These statements include forward-looking statements both with respect to us, specifically, and the biotechnology sector, in general. We make these statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Statements that include the words "expect," "intend," "plan," "believe," "project," "estimate," "may," "should," "anticipate," "will" and similar statements of forward-looking nature identify forward-looking statements for purposes of the federal securities laws or otherwise.

All forward-looking statements involve inherent risks and uncertainties, and there are or will be important factors that could cause actual results to differ materially from those indicated in these statements. We believe that these factors include, but are not limited to, those factors set forth under the caption "Risk Factors" in this prospectus and under the captions "Risk Factors," "Business," "Legal Proceedings," "Management's Discussion and Analysis of Financial Condition and Results of Operations," "Quantitative and Qualitative Disclosures About Market Risk" and "Controls and Procedures" in our most recent Annual Report on Form 10-K and most recent Quarterly Report on Form 10-Q, all of which you should review carefully. Please consider our forward-looking statements in light of those risks as you read this prospectus. We undertake no obligation to publicly update or review any forward-looking statement, whether as a result of new information, future developments or otherwise.

If one or more of these or other risks or uncertainties materializes, or if our underlying assumptions prove to be incorrect, actual results may vary materially from what we anticipate. All subsequent written and oral forward-looking statements attributable to us or individuals acting on our behalf are expressly qualified in their entirety by this Note. Before purchasing any shares of our common stock, you should consider carefully all of the factors set forth or referred to in this prospectus supplement and in the accompanying prospectus that could cause actual results to differ.

INDUSTRY DATA

Unless otherwise indicated, information contained or incorporated by reference in this prospectus concerning our industry, including our general expectations and market opportunity, is based on information from our own management estimates and research, as well as from industry and general publications and research, surveys and studies conducted by third parties. Management estimates are derived from publicly available information, our knowledge of our industry and assumptions based on such information and knowledge, which we believe to be

reasonable. In addition, assumptions and estimates of our and our industry's future performance are necessarily subject to a high degree of uncertainty and risk due to a variety of factors, including those described in "Risk Factors" beginning on page A-7 of this prospectus. These and other factors could cause our future performance to differ materially from our assumptions and estimates.

TRADEMARKS

CytRx is one of our trademarks used in this prospectus. This prospectus also includes trademarks, trade names and service marks that are the property of other organizations. Solely for convenience, trademarks and trade names referred to in this prospectus sometimes appear without the ® and ™ symbols, but those references are not intended to indicate that we will not assert, to the fullest extent under applicable law, our rights, or that the applicable owner will not assert its rights, to these trademarks and trade names.

A-1

Table of Contents**PROSPECTUS SUMMARY**

This summary highlights selected information appearing elsewhere in this prospectus or incorporated by reference in this prospectus and does not contain all of the information that may be important to you or that you should consider before investing in our common stock. This prospectus includes or incorporates by reference information about the securities we are offering, as well as information regarding our business and detailed financial data. Before making an investment decision, you should read this prospectus and the information incorporated by reference herein in their entirety, including Risk Factors beginning on page A-6 of this prospectus.

The Company**Overview**

We are a biopharmaceutical research and development company specializing in oncology. We currently are focused on the clinical development of aldoxorubicin (formerly known as INNO-206), our modified version of the widely-used chemotherapeutic agent, doxorubicin. We are conducting a global Phase 2b clinical trial with aldoxorubicin as a treatment for soft tissue sarcoma, have completed a Phase 1b/2 clinical trial primarily in the same indication, a Phase 1b study of aldoxorubicin in combination with doxorubicin in patients with advanced solid tumors, and a Phase 1b pharmacokinetics clinical trial in patients with metastatic solid tumors. We plan to initiate under a Special Protocol Assessment, or SPA, granted by the U.S. Food and Drug Administration, or FDA, a potential pivotal Phase 3 global trial of aldoxorubicin as a therapy for patients with soft tissue sarcoma whose tumors have progressed following treatment with chemotherapy. We also have initiated a Phase 2 clinical trial with aldoxorubicin in patients with late-stage glioblastoma (brain cancer), and will be initiating a Phase 2 clinical trial with aldoxorubicin in patients with AIDS-related Kaposi's sarcoma. We plan to expand our pipeline of oncology candidates based on a linker platform technology that can be utilized with multiple chemotherapeutic agents and may allow for greater concentration of drug at tumor sites. We also have rights to two additional drug candidates, tamibarotene and bafetinib. We completed our evaluation of bafetinib in the ENABLE Phase 2 clinical trial in high-risk B-cell chronic lymphocytic leukemia (B-CLL), plan to seek a partner for further development of bafetinib.

Our Product Candidate Pipeline

The following table summarizes our product candidates and their current or impending stages of development:

	Product		Stage of
Technology	candidate	Indication(s)	development
Doxorubicin conjugate	Aldoxorubicin	Soft tissue sarcoma	Phase 3 1Q14
		Glioblastoma multiforme	Phase 2b ongoing
		Kaposi's sarcoma	Phase 2 ongoing
		In combination with doxorubicin in patients with advanced solid tumors	Phase 2 4Q13
			Phase 1b complete

Our Clinical Development Programs

Our current clinical development programs are summarized below.

Aldoxorubicin

Aldoxorubicin is a conjugate of the commonly prescribed chemotherapeutic agent doxorubicin that binds to circulating albumin in the bloodstream and is concentrated at the site of tumors. Specifically, it is the (6-Maleimidocaproyl) hydrazone of doxorubicin attached to an acid-sensitive linker known as EMCH. We are initiating a potential pivotal Phase 3 global trial of aldoxorubicin as a therapy for patients with soft tissue sarcoma whose tumors have progressed following treatment with chemotherapy under an SPA granted by the FDA. The SPA means that the FDA agrees with the design, execution and analyses proposed in the Phase 3 trial protocol and will not subsequently change its perspective on these matters, unless previously unrecognized public or animal health concerns were to arise. It also means that if the study demonstrates the acceptable benefit-risk profile as described in the protocol, it would suffice as the single pivotal trial that would likely support registration of aldoxorubicin for this indication.

A-2

Table of Contents

Aldoxorubicin for the Treatment of Cancer. Anthracyclines are a class of drugs that are among the most commonly used agents in the treatment of cancer. Doxorubicin, the first anthracycline to gain FDA approval, has demonstrated efficacy in a wide variety of cancers, including breast cancer, lung cancer, sarcomas, and lymphomas. However, due to the uptake of doxorubicin by various parts of the body, it is associated with side effects such as cumulative cardiotoxicity, myelosuppression (decreased production of blood cells by bone marrow), gastrointestinal disorders, mucositis (inflammation of the mucous membranes lining the mouth and digestive tract), stomatitis (inflammation of soft tissue of the mouth), and extravasation (the leakage of intravenous drugs from the vein into the surrounding tissue).

We believe aldoxorubicin has attributes that may improve on doxorubicin, alone, which we sometimes refer to as native doxorubicin, including the potential to reduce adverse events, improve efficacy and achieve increased concentration at tumor sites.

Our postulated mechanism of action for aldoxorubicin is as follows:

after administration, aldoxorubicin rapidly binds circulating albumin through the EMCH linker;

circulating albumin preferentially accumulates in tumors, bypassing concentration in other non-tumor sites, including the heart, liver and gastrointestinal tract due to a mechanism called Enhanced Permeability and Retention by Solid Tumors ;

once albumin-bound aldoxorubicin reaches the tumor, the acidic environment of the tumor causes cleavage of the acid-sensitive linker; and

free doxorubicin is released at the site of the tumor and is taken up by the cancer cells.

Pre-clinical data. In a variety of preclinical models, aldoxorubicin was superior to doxorubicin at equitoxic doses in its ability to allow an increase in the total doxorubicin dose, its antitumor efficacy and its safety. Toxicology studies in rodents also demonstrated a reduction in cardiotoxicity. Animal studies conducted by aldoxorubicin inventor Dr. Felix Kratz of the Department of Medical Oncology, Clinical Research, at the Tumor Biology Center in Freiburg, Germany, demonstrated statistically significant efficacy compared to either placebo or native doxorubicin against breast, ovarian, pancreatic and small cell lung cancers growing in immunodeficient mice.

We also recently announced additional data from a study of aldoxorubicin in immunodeficient mice transplanted with human glioblastoma cells in their brain that showed those animals treated with aldoxorubicin had a median survival rate of more than 63 days, compared with approximately 25 days for animals treated with doxorubicin or saline. The data also indicated evidence of drug concentration inside tumors growing in the brain and significant tumor regression in aldoxorubicin-treated animals, while doxorubicin did not appear to enter the tumor to any significant degree and showed little or no efficacy in the treatment of these brain tumors. Aldoxorubicin significantly reduced the number of dividing cells within the brain tumors in this trial and showed a statistically relevant increased expression of apoptosis or cell death markers.

Clinical data. A Phase 1 study of aldoxorubicin that demonstrated safety and objective clinical responses in several tumor types was completed in 2005 and presented at the March 2006 Krebskongress meeting in Berlin. In this study,

doses were administered every three weeks at up to six times the standard dose of doxorubicin without an increase in the types of side effects compared with those historically observed with native doxorubicin. Twenty-three of thirty-five evaluable patients had either an objective clinical (partial) response or stable disease. Objective clinical responses were observed in patients with sarcoma, breast and small cell lung cancers.

We completed a Phase 1b/2 clinical trial with aldoxorubicin in patients with advanced solid tumors and presented favorable data at the American Society for Clinical Oncology Meeting in June 2012. In that Phase 1b/2 clinical trial, clinical benefit (defined as partial response or stable disease of more than four months following up to eight cycles of treatment) with aldoxorubicin at the maximum tolerated dose was shown in ten of 13 (76.9%) evaluable patients with relapsed or refractory soft tissue sarcoma.

In addition, best responses for the 13 evaluable soft tissue sarcoma trial subjects included the following: five (38.5%) achieved partial response, as defined as shrinkage of target tumors of more than 30%; seven (53.8%) showed prolonged stable disease (defined as tumor shrinkage <30% from baseline or tumor growth <20% from the nadir); eight (61.5%) had tumor shrinkage; and five of eight patients (62.5%) who demonstrated either partial responses or prolonged stable disease after treatment with aldoxorubicin had been previously treated with doxorubicin and had failed to respond. There were no observed cardiac toxicities and no drug-related patient deaths. The most common adverse event, neutropenia, also observed with doxorubicin treatment, resolved prior to the start of the next treatment. Median estimated progression-free survival for advanced soft tissue sarcoma patients in the trial was 6.4 months with a range of 1.0 to more than 10.7 months.

Table of Contents

In our Phase 1b pharmacokinetics clinical trial evaluating the pharmacokinetics and safety of aldoxorubicin in patients with metastatic solid tumors who have either relapsed or not responded to treatment with standard therapies, we recently announced data demonstrating that aldoxorubicin has a circulating half-life of approximately 20 to 24 hours, with narrow volume of distribution to healthy tissue and slow clearance from the circulation. These characteristics distinguish aldoxorubicin from published pharmacokinetics data for doxorubicin.

Development Plan. We plan to initiate under a SPA granted by the FDA a potential pivotal Phase 3 global trial with aldoxorubicin as a therapy for patients with soft tissue sarcomas whose tumors have progressed following treatment with chemotherapy. The Phase 3 clinical trial's primary endpoint will be progression-free survival. The trial also will assess overall survival, objective tumor response and safety. We expect to enroll approximately 400 patients, commencing in the first quarter of 2014.

In December 2011, we initiated our international Phase 2b clinical trial to evaluate the preliminary efficacy and safety of aldoxorubicin as a first-line therapy in patients with advanced soft tissue sarcoma who are ineligible for surgery. The Phase 2b clinical trial will provide the first direct clinical trial comparison of aldoxorubicin and native doxorubicin, which is dose-limited due to toxicity, as a first-line therapy.

The Phase 2b clinical trial with aldoxorubicin in patients with soft tissue sarcoma is an international trial under the direction of Sant P. Chawla, M.D., F.R.A.C.P., Director of the Sarcoma Oncology Center in Santa Monica, California. The Phase 2b clinical trial's primary objectives are to measure the progression-free survival, tumor response and overall survival of patients with advanced soft tissue sarcomas treated with aldoxorubicin. This clinical trial also will assess the safety of aldoxorubicin compared to doxorubicin in this patient population through a number of indicators, including the frequency and severity of adverse events.

Preliminary data based on the first 82 evaluated patients in the Phase 2b clinical trial showed that aldoxorubicin-treated patients demonstrated a significantly greater percentage of overall responses compared with those treated with doxorubicin, the current standard-of-care for advanced, metastatic soft-tissue sarcoma. This was based on a blinded reading of tumor scans by an independent radiology review. We expect to report in December 2013 final, top-line data for the global Phase 2b clinical trial, including data related to the trial's primary endpoint of progression-free survival.

We have initiated a Phase 2 clinical trial to evaluate the preliminary efficacy and safety of aldoxorubicin in patients with unresectable glioblastoma whose tumors have progressed following prior treatment with surgery, radiation and with the drug temozolomide. The clinical trial is expected to enroll approximately 28 patients at sites including the John Wayne Cancer Center in Santa Monica, California, City of Hope in Duarte, California, and the LSU Medical Center in New Orleans, Louisiana.

We also plan to initiate in 2013 a Phase 2 clinical trial evaluating the preliminary efficacy of aldoxorubicin in patients with AIDS-related Kaposi's sarcoma, a common HIV-associated tumor. The current standard-of-care for severe dermatological and systemic Kaposi's sarcoma is liposomal doxorubicin (Doxil); however, a significant proportion of patients exhibit minimal or no clinical response to this agent, and the drug's toxicity often prevents continued therapy. The Phase 2 trial will enroll up to 30 patients and will be conducted at the LSU Medical Center in New Orleans, Louisiana.

In 2012, we completed a Phase 2 trial for patients with advanced pancreatic ductal adenocarcinomas who had relapsed or failed to respond to two prior regimens, one regimen containing gemcitabine (Gemzar) and the other a fluoropyrimidine such as 5-fluorouracil. No objective clinical responses were observed in 14 patients treated with native aldoxorubicin, and we are considering testing the aldoxorubicin in combination with the commonly-prescribed

drug Abraxane as a second-line treatment in that indication.

Bafetinib

Bafetinib (formerly INNO-406) is an orally bioavailable, rationally-designed inhibitor of several Src kinases developed by the Japanese pharmaceutical company Nippon Shinyaku, to overcome some of the limitations of Gleevec and other tyrosine kinase inhibitors in resistant chronic myelogenous leukemia, or CML. In addition to its Bcr-Abl inhibitory properties, bafetinib is a potent and specific inhibitor of Lyn and Fyn kinases. These kinases are reported to be involved in both solid and hematological cancers. Lyn kinase's involvement in the B-cell signaling pathway led us to evaluate bafetinib in B-cell malignancies such as chronic lymphocytic leukemia, or CLL. We hold rights to bafetinib in all territories, except in Japan.

We plan to seek a partner for any further development of bafetinib in order to focus our resources on the development of adoxorubicin.

A-4

Table of Contents

Tamibarotene

Tamibarotene is an orally available, synthetic retinoid rationally designed to overcome resistance and reduce the toxic side effects of differentiation therapy with all-trans retinoic acid, or ATRA, a component of the current first-line treatment for acute promyelocytic leukemia, or APL. We ceased our Phase 2b clinical trial of tamibarotene in patients with non-small-cell lung cancer after it failed to show efficacy.

Reverse Stock Split

On May 16, 2012, we effected a 1-for-7 reverse stock split of our outstanding shares of common stock and our common stock began trading on The NASDAQ Capital Market on a split-adjusted basis. All share and per share amounts in this prospectus have been adjusted to reflect the reverse stock split as if it had occurred at the beginning of the earliest period presented.

Corporate Information

We are a Delaware corporation, incorporated in 1985. Our corporate offices are located at 11726 San Vicente Boulevard, Suite 650, Los Angeles, California 90049, and our telephone number is (310) 826-5648. Our web site is located on the worldwide web at <http://www.cytrx.com>. We do not incorporate by reference into this prospectus the information on, or accessible through, our website, and you should not consider it as part of this prospectus.

The Offering

The August 2011 warrants were sold and issued in our public offering completed on August 1, 2011. See the Plan of Distribution section in this prospectus for more information regarding this offering.

Issuer	CytRx Corporation
Shares offered by us	6,440,045 shares of our common stock issuable upon exercise of our outstanding August 2011 warrants
Shares outstanding	41,975,412 shares (excluding treasury shares) as of November 26, 2013, excluding 5,050,017 shares subject to outstanding stock options and warrants (other than the August 2011 warrants)
Shares outstanding following this offering	48,415,457 shares (excluding treasury shares) assuming all August 2011 warrants are exercised in full and without giving effect to any other issuances of common stock subsequent to November 26, 2013
Use of proceeds	We intend to use the net proceeds of any exercises of the August 2011 warrants pursuant to this offering to augment our working capital and for general corporate purposes
Trading	Our common stock is traded on The NASDAQ Capital Market under the symbol CYTR

A-5

Table of Contents

RISK FACTORS

You should carefully consider the risks described below before deciding whether to exercise the August 2011 warrants. The risks described below are not the only ones we face. Additional risks we are not presently aware of or that we currently believe are immaterial may also impair our business. Our business could be harmed by any of these risks. The trading price of our common stock could decline due to any of these risks, and you may lose all or part of your investment. In assessing these risks, you should also refer to the other information contained or incorporated by reference into this prospectus, including our financial statements and related notes. We have attempted to identify below the major factors that could cause differences between actual and planned or expected results, but we cannot assure you that we have identified all such factors.

Risks Associated With Our Business

We have operated at a loss and will continue to operate at a loss for the foreseeable future.

We have operated at a loss due to our ongoing expenditures for research and development of our product candidates and for general and administrative purposes and lack of significant recurring revenue. We incurred a net loss of approximately \$18.0 million for the year ended December 31, 2012 and of approximately \$20.3 million for the nine months ended September 30, 2013, and had an accumulated deficit as of September 30, 2013 of approximately \$249.2 million. We will continue to incur losses unless and until we are able to commercialize aldoxorubicin or one or more of our other current or future product candidates. These losses, among other things, have had and will continue to have an adverse effect on our stockholders' equity and working capital. Because of the numerous risks and uncertainties associated with our product development efforts, we are unable to predict when we may become profitable, if at all. If we do not become profitable or are unable to maintain future profitability, the market value of our common stock will be adversely affected.

Because we have no source of significant recurring revenue, we must depend on financing to sustain our operations.

Developing products and conducting clinical trials require substantial amounts of capital. To date, we have relied primarily upon proceeds from sales of our equity securities, sales of our shares of common stock of our former RXi subsidiary and the exercise of options and warrants to generate funds needed to finance our business and operations. We will need to raise additional capital to, among other things:

fund our clinical trials and pursue regulatory approval of aldoxorubicin and our other existing and possible future product candidates;

expand our research and development activities;

finance our general and administrative expenses;

acquire or license new technologies;

prepare, file, prosecute, maintain, enforce and defend our patent and other proprietary rights; and

develop and implement sales, marketing and distribution capabilities to successfully commercialize any product for which we obtain marketing approval and choose to market ourselves.

Our revenue was \$100,000 for the year ended December 31, 2012 and \$200,000 for the nine months ended September 30, 2013. We will have no significant recurring revenue unless we are able to commercialize aldoxorubicin, our lead product candidate, or one of our preclinical candidates, either of which may require us to first enter into strategic arrangements with third parties.

At September 30, 2013, we had cash and cash equivalents of approximately \$6.0 million and short-term investments of \$17.0 million. Management believes that our current cash and cash equivalents and short-term investments, including the net proceeds of approximately \$24.1 million from our public offering completed on October 15, 2013, will be sufficient to fund our operations for the foreseeable future. These expectations are based upon numerous assumptions and subject to many uncertainties, and our actual experience may be significantly different from these expectations.

If we obtain marketing approval and successfully commercialize aldoxorubicin or other product candidate, we anticipate it will take a minimum of several years, and likely longer, for us to generate significant recurring revenue, and we will be dependent on future financing until such time, if ever, as we can generate significant recurring revenue. Our ability to raise capital may be adversely affected by the weak economic recovery in the United States. We have no commitments from third parties to provide us with any additional financing, and we may not be able to obtain future financing on favorable terms, or at all. Failure to obtain adequate financing would adversely affect our ability to operate as a going concern. If we raise additional funds by issuing equity securities, dilution to stockholders may result and new investors could have rights superior to holders of the shares issued in this offering. In addition, debt financing, if available, may include restrictive covenants. If adequate funds are not available to us, we may have to liquidate some or all of our assets or to delay or reduce the scope of or eliminate some portion or all of our development programs or clinical trials. We also may have to license to other companies our product candidates or technologies that we would prefer to develop and commercialize ourselves.

Table of Contents

If we do not achieve our projected development goals in the time frames we estimate, the commercialization of our products may be delayed and our business prospects may suffer. Our financial projections also may prove to be materially inaccurate.

From time to time, we estimate the timing of the accomplishment of various scientific, clinical, regulatory and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of scientific studies and clinical trials and the submission of regulatory filings such as the discussion in this prospectus supplement of the expected timing of certain milestones relating to our aldoxorubicin clinical development programs.

We also may disclose projected expenditures or other forecasts for future periods. These and other financial projections are based on management's current expectations and do not contain any margin of error or cushion for any specific uncertainties, or for the uncertainties inherent in all financial forecasting.

The actual timing of milestones and actual expenditures or other financial results can vary dramatically compared to our estimates, in some cases for reasons beyond our control. If we do not meet milestones or financial projections as announced from time to time, the development and commercialization of our products may be delayed and our business prospects may suffer. The assumptions management has used to produce these projections may significantly change or prove to be inaccurate. Accordingly, you should not unduly rely on any of these financial projections.

If our products are not successfully developed and approved by the FDA or foreign regulatory authorities, we may be forced to reduce or curtail our operations.

All of our product candidates in development must be approved by the FDA or corresponding foreign governmental agencies before they can be marketed. The process for obtaining FDA and foreign government approvals is both time-consuming and costly, with no certainty of a successful outcome. This process typically includes the conduct of extensive pre-clinical and clinical testing, including post-approval testing, which may take longer or cost more than we or our licensees, if any, anticipate, and may prove unsuccessful due to numerous factors. Product candidates that may appear to be promising at early stages of development may not successfully reach the market for a number of reasons. The results of preclinical and initial clinical testing of these product candidates may not necessarily be predictive of the results that will be obtained from later or more extensive testing. Companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in advanced clinical trials, even after obtaining promising results in earlier trials.

Numerous factors could affect the timing, cost or outcome of our product development efforts, including the following:

difficulty in enrolling patients in conformity with required protocols or projected timelines;

requirements for clinical trial design imposed by the FDA; unexpected adverse reactions by patients in trials;

difficulty in obtaining clinical supplies of the product;

changes in or our inability to comply with FDA or foreign governmental product testing, manufacturing or marketing requirements;

regulatory inspections of clinical trials or manufacturing facilities, which may, among other things, require us or our manufacturers or licensees to undertake corrective action or suspend or terminate the affected clinical trials if investigators find them not to be in compliance with applicable regulatory requirements;

inability to generate statistically significant data confirming the safety and efficacy of the product being tested;

modification of the product during testing; and

reallocation of our limited financial and other resources to other clinical programs.

On October 1, 2013, the U.S. federal government suspended services deemed non-essential as a result of the failure by Congress to enact regular appropriations for the 2014 fiscal year. Although the impasse has been resolved until at least January 2014, if another similar or more prolonged shutdown were to occur, it could result in significant delays in the FDA's ability to timely review and process any submissions we have filed or may file, or cause other regulatory delays affecting our development or commercial operations, which delays could have a material adverse effect on our business.

It is possible that none of the product candidates we develop will obtain the regulatory approvals necessary for us to begin selling them. The time required to obtain FDA and foreign governmental approvals is unpredictable, but often can take years following the commencement of clinical trials, depending upon the complexity of the product candidate. Any analysis we perform on data from clinical activities is subject to confirmation and interpretation by regulatory authorities, which could delay, limit or prevent regulatory approval.

Table of Contents

Furthermore, even if we obtain regulatory approvals, our products and the manufacturing facilities used to produce them will be subject to continual review, including periodic inspections and mandatory post-approval clinical trials by the FDA and other U.S. and foreign regulatory authorities. Any delay or failure in obtaining required approvals or to comply with post-approval regulatory requirements could have a material adverse effect on our ability to generate revenue from the particular product candidate. The failure to comply with any post-approval regulatory requirements also could result in the rescission of the related regulatory approvals or the suspension of sales of the offending product.

Our current and planned clinical trials of our lead product candidate may fail to show that it is clinically safe and effective, or that it is better than alternative treatments.

Aldoxorubicin has shown encouraging preliminary clinical results in our Phase 1b/2 clinical trial and in preliminary data from our Phase 2b clinical trial of aldoxorubicin as a treatment for soft tissue sarcomas; however, these conclusions may not be reproduced in future clinical trial results, including the final, top-line data from the Phase 2b clinical trial or the planned global Phase 3 clinical trial testing aldoxorubicin as a treatment for soft tissue sarcomas.

Top-line data from our Phase 2b clinical trial of aldoxorubicin as a treatment for soft tissue sarcomas may differ from our recently announced preliminary data. Even if our current trials are successful, subsequent trials may not yield statistically significant data indicating that aldoxorubicin is clinically effective. Accordingly, we, or any development partners, may ultimately be unable to provide the FDA with satisfactory data on clinical safety and efficacy sufficient to obtain FDA approval of aldoxorubicin for any indication.

Our SPA with the FDA for our pivotal study of aldoxorubicin does not guarantee marketing approval in the United States.

We have an SPA with the FDA for the pivotal trial of aldoxorubicin for the treatment of soft-tissue sarcomas. The SPA means that the FDA agrees with the design, execution, and analyses proposed in a protocol, and constitutes a commitment that the FDA will not subsequently change its perspectives on these matters, unless a previously unrecognized public or animal health concern were to arise or changes were to be made to the protocol, itself. Even under a SPA, marketing approval by the FDA is not guaranteed, because a final determination that the agreed-upon protocol satisfies a specific objective, such as the demonstration of efficacy and safety (positive benefit-risk ratio), or supports an approval decision, will be based on a complete review of all the data submitted to the FDA.

We rely upon third parties for the manufacture of our clinical product supplies.

We do not have the facilities or expertise to manufacture supplies of aldoxorubicin or any of our other product candidates. Accordingly, we are dependent upon third-party manufacturers, or potential future strategic alliance partners, to manufacture these supplies. We have manufacturing supply arrangements in place with respect to a portion of the clinical supplies needed for the clinical development programs for aldoxorubicin. However, we have no supply arrangements for the commercial manufacture of this product candidate or any manufacturing supply arrangements for any other potential product candidates, and we may not be able to secure needed supply arrangements on attractive terms, or at all. Our failure to secure these arrangements as needed could have a materially adverse effect on our ability to complete the development of our products or to commercialize them.

If aldoxorubicin, our lead product candidate, or our other product candidates cannot be manufactured in suitable quantities and in accordance with regulatory standards, our clinical trials, regulatory approvals and marketing efforts for such products may be delayed. Such delays could adversely affect our competitive position and our chances of generating significant recurring revenues. If any of our products that are approved for marketing cannot be

manufactured at an acceptable cost, the commercial success of such product candidates may be adversely affected.

We may rely upon third parties in connection with the commercialization of our products.

The completion of the development of aldoxorubicin or our other product candidates, as well as marketing and commercialization, may require us to enter into strategic alliances or other collaborative arrangements with other pharmaceutical companies under which those companies will be responsible for one or more aspects of the eventual marketing and commercialization of our products.

Our products, if approved for marketing, may not have sufficient potential commercial value to enable us to secure strategic arrangements with suitable companies on attractive terms, or at all. If we are unable to enter into such arrangements, we may not have the financial or other resources to complete the development of any of our products and may have to sell our rights in them to a third party or abandon their development altogether.

Table of Contents

To the extent we enter into collaborative arrangements, we will be dependent upon the timeliness and effectiveness of the development and marketing efforts of our contractual partners. If these companies do not allocate sufficient personnel and resources to these efforts or encounter difficulties in complying with applicable FDA and other regulatory requirements, we may not obtain regulatory approvals as planned, if at all, and the timing of receipt or the amount of revenue from these arrangements may be materially and adversely affected. By entering into these arrangements rather than completing the development and then marketing these products on our own, the profitability to us of these products may decline.

We may be unable to protect our intellectual property rights, which could adversely affect our ability to compete effectively.

We will be able to protect our technologies from unauthorized use by third parties only to the extent that we have rights to valid and enforceable patents or other proprietary rights that cover them. Although we have rights to patents and patent applications directed to aldoxorubicin and other product candidates, these patents and applications may not prevent third parties from developing or commercializing similar or identical technologies. In addition, our patents may be held to be invalid if challenged by third parties, and our patent applications may not result in the issuance of patents.

The patent positions of pharmaceutical and biotechnology companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in biotechnology patents has emerged to date in the United States and in many foreign countries. The application and enforcement of patent laws and regulations in foreign countries is even more uncertain. Accordingly, we may not be able to effectively file, protect or defend our proprietary rights on a consistent basis. Many of the patents and patent applications on which we rely were issued or filed by third parties prior to the time we acquired rights to them. The validity, enforceability and ownership of those patents and patent applications may be challenged, and if a court decides that our patents are not valid, we will not have the right to stop others from using our inventions. There is also the risk that, even if the validity of our patents is upheld, a court may refuse to stop others on the ground that their activities do not infringe our patents.

Any litigation brought by us to protect our intellectual property rights could be costly and have a material adverse effect on our operating results or financial condition, make it more difficult for us to enter into strategic alliances with third parties to develop our products, or discourage our existing licensees from continuing their development work on our potential products. If our patent coverage is insufficient to prevent third parties from developing or commercializing similar or identical technologies, the value of our assets is likely to be materially and adversely affected.

We also rely on certain proprietary trade secrets and know-how, especially where we believe patent protection is not appropriate or obtainable. However, trade secrets and know-how are difficult to protect. Although we have taken measures to protect our unpatented trade secrets and know-how, including the use of confidentiality and invention assignment agreements with our employees, consultants and some of our contractors, it is possible that these persons may disclose our trade secrets or know-how or that our competitors may independently develop or otherwise discover our trade secrets and know-how.

If our product candidates infringe the rights of others, we could be subject to expensive litigation or be required to obtain licenses from others to develop or market them.

Our competitors or others may have patent rights that they choose to assert against us or our licensees, suppliers, customers or potential collaborators. Moreover, we may not know about patents or patent applications that our

products would infringe. For example, because patent applications do not publish for at least 18 months, if at all, and can take many years to issue, there may be currently pending applications unknown to us that may later result in issued patents that our product candidates would infringe. In addition, if third parties file patent applications or obtain patents claiming technology also claimed by us or our licensors in issued patents or pending applications, we may have to participate in interference proceedings in the U.S. Patent and Trademark Office to determine priority of invention. If third parties file oppositions in foreign countries, we may also have to participate in opposition proceedings in foreign tribunals to defend the patentability of our foreign patent applications.

If a third party claims that we infringe its proprietary rights, any of the following may occur:

we may become involved in time-consuming and expensive litigation, even if the claim is without merit;

we may become liable for substantial damages for past infringement if a court decides that our technology infringes a competitor's patent;

a court may prohibit us from selling or licensing our product without a license from the patent holder, which may not be available on commercially acceptable terms, if at all, or which may require us to pay substantial royalties or grant cross licenses to our patents; and

we may have to redesign our product candidates or technology so that it does not infringe patent rights of others, which may not be possible or commercially feasible.

If any of these events occurs, our business and prospects will suffer and the market price of our common stock will likely decline substantially.

Table of Contents

Any products we develop may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which could have a material adverse effect on our business.

We intend to sell our products that may be approved for marketing primarily to hospitals, which receive reimbursement for the health care services they provide to their patients from third-party payors, such as Medicare, Medicaid and other domestic and international government programs, private insurance plans and managed care programs. Most third-party payors may deny reimbursement if they determine that a medical product was not used in accordance with cost-effective treatment methods, as determined by the third-party payor, or was used for an unapproved indication. Third-party payors also may refuse to reimburse for experimental procedures and devices. Furthermore, because our programs are in the early stages of development, we are unable at this time to determine their cost-effectiveness and the level or method of reimbursement. Increasingly, the third-party payors who reimburse patients are requiring that drug companies provide them with predetermined discounts from list prices, and are challenging the prices charged for medical products. If the price we are able to charge for any products we develop is inadequate in light of our development and other costs, our profitability could be adversely affected.

We currently expect that any drugs we develop may need to be administered under the supervision of a physician. Under currently applicable law, drugs that are not usually self-administered may be eligible for coverage by the Medicare program if:

they are incidental to a physician's services;

they are reasonable and necessary for the diagnosis or treatment of the illness or injury for which they are administered according to accepted standard of medical practice;

they are not excluded as immunizations; and

they have been approved by the FDA.

We are subject to intense competition, and we may not compete successfully.

We and our strategic partners or licensees may be unable to compete successfully against our current or future competitors. Soft tissue sarcoma patients are typically treated with surgery followed by radiation therapy. For patients ineligible for surgery, radiation and/or chemotherapy is the only option. Doxorubicin is the only approved drug for treating soft tissue sarcoma patients who are ineligible for surgery and is often used in combination with radiation. The National Comprehensive Cancer Network also includes the use of ifosfamide, epirubicin, gemcitabine, dacarbazine and liposomal doxorubicin marketed in the United States as Doxil by Johnson & Johnson. GlaxoSmithKline's Votrient was approved in the United States and Europe in 2012 for the treatment of advanced soft tissue sarcomas following prior chemotherapy. There are other approaches to treating soft tissue sarcoma in late-stage clinical development, including Threshold Pharmaceuticals' TH-302 and trabectedin being co-developed by Johnson and Johnson and PharmaMar.

Patients with glioblastoma multiforme (GBM) generally undergo invasive brain surgery, although disease progression following surgery is nearly 100%. The front-line therapy for GBM following surgery is Temozolomide (Temodar®) in combination with radiation. Bevacizumab (Avastin®) has been approved for the treatment of GBM in patients

failing Temodar®. Drugs in development to treat GBM include rindopepimut by Celldex Therapeutics, DCVax by Northwest Biotherapeutics, TRC105 from Tracoon Pharmaceuticals, and buparlisib by Novartis. Kaposi's sarcoma is generally treated with radiation, surgery and/or liposomal doxorubicin. Other drugs in development for Kaposi's sarcoma include selumetinib by AstraZeneca and pomalidamide by Celgene.

Many companies, including large pharmaceutical and biotechnology firms with financial resources, research and development staffs, and facilities that may be substantially greater than those of ours or our strategic partners or licensees, are engaged in the research and development of pharmaceutical products that could compete with our potential products. To the extent that we seek to acquire, through license or otherwise, existing or potential new products, we will be competing with numerous other companies, many of which will have substantially greater financial resources, large acquisition and research and development staffs that may give those companies a competitive advantage over us in identifying and evaluating these drug acquisition opportunities. Any products that we acquire will be competing with products marketed by companies that in many cases will have substantially greater marketing resources than we have. The industry is characterized by rapid technological advances and competitors may develop their products more rapidly and such products may be more effective than those currently under development or that may be developed in the future by our strategic partners or licensees. Competitive products for a number of the disease indications that we have targeted are currently being marketed by other parties, and additional competitive products are under development and may also include products currently under development that we are not aware of or products that may be developed in the future.

A-10

Table of Contents

As a result, these competitors may:

succeed in developing competitive products sooner than us or our strategic partners or licensees;

obtain FDA or foreign governmental approvals for their products before we can obtain approval of any of our products;

obtain patents that block or otherwise inhibit the development and commercialization of our product candidate candidates;

develop products that are safer or more effective than our products;

devote greater resources than us to marketing or selling products;

introduce or adapt more quickly than us to new technologies and other scientific advances;

introduce products that render our products obsolete;

withstand price competition more successfully than us or our strategic partners or licensees;

negotiate third-party strategic alliances or licensing arrangements more effectively than us; and

take better advantage than us of other opportunities.

We will be required to pay substantial milestone and other payments relating to the commercialization of our products.

The agreement relating to our worldwide rights to aldoxorubicin provides for our payment of an aggregate of \$7.5 million upon meeting specified clinical and regulatory milestones up to and including the product's second, final marketing approval. We also will be obliged to pay:

commercially reasonable royalties based on a percentage of net sales (as defined in the agreement);

a percentage of non-royalty sub-licensing income (as defined in the agreement); and

milestones of \$1,000,000 for each additional final marketing approval that we might obtain.

The agreements under which we have North American and European rights to tamibarotene provide for our payment of royalties based on net sales of any products, as well as aggregate payments of ¥ 490 million for North America and ¥ 480 million for Europe upon meeting specified clinical, regulatory and sales milestones up to and including the first commercial sale of tamibarotene for the treatment of APL.

Our agreement relating to our worldwide (except Japan) rights to bafetinib provides for our payment of an aggregate of \$13.35 million (including \$5 million upon the product's initial final marketing approval) upon the achievement of specified clinical and regulatory milestones up to and including approvals in the United States and Europe. We also will be obliged to pay:

commercially reasonable royalties based on a percentage of net sales (as defined in the agreement), dependent on reaching certain revenue thresholds;

annual minimum payments if sales of bafetinib do not meet specified levels; and

a percentage of non-royalty sub-licensing income (as defined in the agreement).

If we are required to pay any third party in order to exercise our rights under the agreement, we will deduct a percentage of those payments from the royalties due under the agreement, up to an agreed-upon cap.

Under the merger agreement by which we acquired Innovive, we agreed to pay the former Innovive stockholders a total of up to approximately \$18.3 million of future earnout merger consideration, subject to our achievement of specified net sales under the Innovive license agreements. The earnout merger consideration, if any, will be payable in shares of our common stock, subject to specified conditions, or, at our election, in cash or by a combination of shares of our common stock and cash. Our common stock will be valued for purposes of any future earnout merger consideration based upon the trading price of our common stock at the time the earnout merger consideration is paid.

Table of Contents

We are subject to potential liabilities from clinical testing and future product liability claims.

If any of our products are alleged to be defective, they may expose us to claims for personal injury by patients in clinical trials of our products or, if we obtain marketing approval and commercialize our products, by patients using our commercially marketed products. Even if one or more of our products is approved by the FDA, users may claim that such products caused unintended adverse effects. We maintain clinical trial insurance for our ongoing clinical trials, and we plan to seek to obtain similar insurance for any other clinical trials that we conduct. We also would seek to obtain product liability insurance covering the commercial marketing of our product candidates. We may not be able to obtain additional insurance, however, and any insurance obtained by us may prove inadequate in the event of a claim against us. Any claims asserted against us also may divert management's attention from our operations, and we may have to incur substantial costs to defend such claims even if they are unsuccessful.

We may be unable to successfully acquire additional technologies or products. If we require additional technologies or products, our product development plans may change and the ownership interests of our shareholders could be diluted.

We may seek to acquire additional technologies by licensing or purchasing such technologies, or through a merger or acquisition of one or more companies that own such technologies. We have no current understanding or agreement to acquire any technologies, however, and we may not be able to identify or successfully acquire any additional technologies. We also may seek to acquire products from third parties that already are being marketed or have been approved for marketing, although we have not currently identified any of these products. We do not have any prior experience in acquiring or marketing products approved for marketing and may need to find third parties to market any products that we might acquire.

We have focused our product development efforts on our oncology drug candidates, which we believe have the greatest revenue potential. If we acquire additional technologies or product candidates, we may determine to make further changes to our product development plans and business strategy to capitalize on opportunities presented by the new technologies and product candidates.

We may determine to issue shares of our common stock to acquire additional technologies or products or in connection with a merger or acquisition of another company. To the extent we do so, the ownership interest of our stockholders will be diluted accordingly.

We are conducting certain of our clinical trials in foreign countries, which exposes us to additional risks.

We are conducting international clinical development of aldoxorubicin. The conduct of clinical trials outside the United States could have a significant impact on us. Risks inherent in conducting international clinical trials include:

foreign regulatory requirements that could restrict or limit our ability to conduct our clinical trials;

administrative burdens of conducting clinical trials under multiple foreign regulatory schema;

foreign exchange fluctuations;

diminished protection of intellectual property in some countries; and

possible nationalization and expropriation.

In addition, there may be changes to our business and political position if there is instability, disruption or destruction in a significant geographic region, regardless of cause, including war, terrorism, riot, civil insurrection or social unrest, and natural or man-made disasters, including famine, flood, fire, earthquake, storm or disease, which could seriously harm the development of our current operating strategy.

A-12

Table of Contents

In the event of a dispute regarding our international clinical trials, it may be necessary for us to resolve the dispute in the foreign country of dispute, where we would be faced with unfamiliar laws and procedures.

The resolution of disputes in foreign countries can be costly and time consuming, similar to the situation in the United States. However, in a foreign country, we face the additional burden of understanding unfamiliar laws and procedures. We may not be entitled to a jury trial, as we might be in the United States. Further, to litigate in any foreign country, we would be faced with the necessity of hiring lawyers and other professionals who are familiar with the foreign laws. For these reasons, we may incur unforeseen expenses if we are forced to resolve a dispute in a foreign country.

Risks Associated With This Offering And Our Common Stock

You will experience immediate and substantial dilution in the net tangible book value per share of the stock you purchase.

If the exercise price per share of the August 2011 warrants is higher than the net tangible book value per share of our common stock when you exercise the August 2011 warrants, you will suffer immediate dilution in the net tangible book value of the common stock you acquire on exercise. See **Dilution** in this prospectus for a more detailed discussion of the dilution you may incur if you purchase common stock in this offering.

You may experience future dilution as a result of future equity offerings or other equity issuances.

To raise additional capital, we may in the future offer additional shares of our common stock, preferred stock or other securities convertible into or exchangeable for our common stock. We cannot assure you that we will be able to sell shares or other securities in any other offering at a price per share that is equal to or greater than the price per share paid by investors in this offering. The price per share at which we sell additional shares of our common stock or other securities convertible into or exchangeable for our common stock in future transactions may be higher or lower than the price per share in this offering.

We may experience volatility in our stock price, which may adversely affect the trading price of our common stock.

The market price of our common stock has ranged from a low of \$1.83 to a high of \$3.65 per share from January 1, 2013 through November 26, 2013, and it may continue to experience significant volatility from time to time. Factors that may affect the market price of our common stock include the following:

announcements of regulatory developments or technological innovations by us or our competitors;

changes in our relationship with our licensors and other strategic partners;

Table of Contents

our quarterly operating results;

litigation involving or affecting us;

shortfalls in our actual financial results compared to our guidance or the forecasts of stock market analysts;

developments in patent or other technology ownership rights;

acquisitions or strategic alliances by us or our competitors;

public concern regarding the safety of our products; and

government regulation of drug pricing.

Our outstanding options and warrants and the availability for resale of the underlying shares may adversely affect the trading price of our common stock.

As of September 30, 2013, there were outstanding stock options to purchase approximately 3.4 million shares of our common stock at a weighted-average exercise price of \$4.15 per share and outstanding warrants (other than the August 2011 warrants) to purchase approximately 1.6 million shares of common stock at a weighted-average exercise price of \$6.58 per share. Our outstanding options and warrants could adversely affect our ability to obtain future financing or engage in certain mergers or other transactions, since the holders of options and warrants can be expected to exercise them at a time when we may be able to obtain additional capital through a new offering of securities on terms more favorable to us than the terms of outstanding options and warrants. For the life of the options and warrants, the holders have the opportunity to profit from a rise in the market price of our common stock without assuming the risk of ownership. The issuance of shares upon the exercise of outstanding options and warrants will also dilute the ownership interests of our existing stockholders.

We have registered with the SEC the resale by the holders of all or substantially all shares of our common stock issuable upon exercise of our outstanding options and warrants. The availability of these shares for public resale, as well as any actual resales of these shares, could adversely affect the trading price of our common stock.

Our management will have broad discretion as to the use of the proceeds of this offering.

We have not designated the amount of net proceeds we will receive from this offering for any particular purpose. Accordingly, our management will have broad discretion as to the application of these net proceeds and could use them for purposes other than those contemplated at the time of this offering. Our stockholders may not agree with the manner in which our management chooses to allocate and spend the net proceeds.

Our anti-takeover measures may make it more difficult to change our management, or may discourage others from acquiring us, and thereby adversely affect stockholder value.

We have a stockholder rights plan and provisions in our bylaws that are intended to protect our stockholders' interests by encouraging anyone seeking control of our company to negotiate with our board of directors. These provisions may discourage or prevent a person or group from acquiring us without the approval of our board of directors, even if the acquisition would be beneficial to our stockholders.

We have a classified board of directors, which means that at least two stockholder meetings, instead of one, will be required to effect a change in the majority control of our board of directors. This applies to every election of directors, not just an election occurring after a change in control. The classification of our board increases the amount of time it takes to change majority control of our board of directors and may cause potential acquirers to lose interest in a potential purchase of us, regardless of whether our purchase would be beneficial to us or our stockholders. The additional time and cost to change a majority of the members of our board of directors makes it more difficult and may discourage our existing stockholders from seeking to change our existing management in order to change the strategic direction or operational performance of our company.

Our bylaws provide that directors may only be removed for cause by the affirmative vote of the holders of at least a majority of the outstanding shares of our capital stock then entitled to vote at an election of directors. This provision prevents stockholders from removing any incumbent director without cause. Our bylaws also provide that a stockholder must give us at least 120 days notice of a proposal or director nomination that such stockholder desires to present at any annual meeting or special meeting of stockholders. Such provision prevents a stockholder from making a proposal or director nomination at a stockholder meeting without us having advance notice of that proposal or director nomination. This could make a change in control more difficult by providing our directors with more time to prepare an opposition to a proposed change in control. By making it more difficult to remove or install new directors, these bylaw provisions may also make our existing management less responsive to the views of our stockholders with respect to our operations and other issues such as management selection and management compensation.

Table of Contents

We are subject to the anti-takeover provisions of Section 203 of the Delaware General Corporation Law, which may also prevent or delay a takeover of us that may be beneficial to our stockholders.

Our amended and restated by-laws designate the Court of Chancery of the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or other employees.

Our amended and restated by-laws provide that, unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for (i) any derivative action or proceeding brought on our behalf, (ii) any action asserting a claim of breach of a fiduciary duty owed by any director, officer or other employee to us or our stockholders, (iii) any action asserting a claim arising pursuant to any provision of the Delaware General Corporation Law, or (iv) any action asserting a claim that is governed by the internal affairs doctrine. Any person purchasing or otherwise acquiring any interest in any shares of our capital stock shall be deemed to have notice of and to have consented to this provision of our amended and restated by-laws. This choice-of-forum provision may limit our stockholders' ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits. Alternatively, if a court were to find this provision of our amended and restated by-laws inapplicable or unenforceable with respect to one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business and financial condition.

We may issue preferred stock in the future, and the terms of the preferred stock may reduce the value of our common stock.

We are authorized to issue shares of preferred stock in one or more series. Our board of directors may determine the terms of future preferred stock offerings without further action by our stockholders. If we issue preferred stock, it could affect your rights or reduce the value of our outstanding common stock. In particular, specific rights granted to future holders of preferred stock may include voting rights, preferences as to dividends and liquidation, conversion and redemption rights, sinking fund provisions, and restrictions on our ability to merge with or sell our assets to a third party.

We do not expect to pay any cash dividends on our common stock.

We have not declared or paid any cash dividends on our common stock or other securities, and we currently do not anticipate paying any cash dividends in the foreseeable future. Because we do not anticipate paying cash dividends for the foreseeable future, our stockholders will not realize a return on their investment in our common stock except to the extent of any appreciation in the value of our common stock. Our common stock may not appreciate in value, or may decline in value.

USE OF PROCEEDS

We do not know whether any of the August 2011 warrants will be exercised or, if any of the August 2011 warrants are exercised, when they will be exercised or at what price they will be exercised. It is possible that the August 2011 warrants may expire and never be exercised, or that the current exercise price of the August 2011 warrants may be reduced as a result of subsequent events that would trigger applicable anti-dilution adjustments under the August 2011 warrants. Also, as discussed in the Description of Securities August 2011 Warrants section of this prospectus, there are certain circumstances under which the August 2011 warrants may be exercised on a cashless basis. In these circumstances, even if the August 2011 warrants are exercised, we may not receive any proceeds, or the proceeds that

we do receive may be significantly less than what we might expect. We estimate that the maximum net proceeds that we may receive from the exercise of the August 2011 warrants, assuming all of the August 2011 warrants are exercised at the current exercise price of \$4.48 per share of common stock, will be approximately \$28.8 million, after deducting estimated offering expenses payable by us.

We currently intend to use the net proceeds from the exercise of the August 2011 warrants, if any, to augment our working capital and for general corporate purposes.

The amounts and timing of our use of proceeds will vary depending on a number of factors, including the amount of cash used by our operations, and we will retain broad discretion in the allocation of the net proceeds from the exercise of the August 2011 warrants. In addition, while we have not entered into any agreements, commitments or understandings relating to any significant transaction as of the date of this prospectus, we may use a portion of the net proceeds to pursue acquisitions, joint ventures and other strategic transactions.

Pending the final application of the net proceeds from the exercise of the August 2011 warrants, we intend to invest such net proceeds in short-term, interest bearing, investment-grade securities.

A-15

Table of Contents**DILUTION**

Our net tangible book value as of September 30, 2013, was \$11.0 million, or \$0.36 per share of common stock. Net tangible book value per share is calculated by subtracting our total liabilities from our total tangible assets, which is total assets less intangible assets, and dividing this amount by the number of shares of common stock outstanding. After giving effect to the issuance of shares of our common stock upon the exercise, in full, of the August 2011 warrants at the exercise price of \$4.48 per share, and after deducting estimated offering expenses payable by us, we would have had a net tangible book value as of September 30, 2013 of \$39.8 million, or \$1.07 per share of common stock. This represents an immediate increase in the net tangible book value of \$0.71 per share to our existing stockholders and an immediate dilution in net tangible book value of \$3.41 per share to purchasers of shares of our common stock in this offering. The following table illustrates this per share dilution:

Exercise price per share	\$ 4.48
Net tangible book value per share as of September 30, 2013	\$ 0.36
Increase per share attributable to this offering	\$ 0.71
As adjusted net tangible book per share after this offering	\$ 1.07
Net dilution per share to new investors	\$ 3.41

The number of shares of common stock to be outstanding after this offering is 37,048,437 shares based on 30,608,392 shares outstanding as of September 30, 2013 and excludes:

3,406,881 shares of our common stock subject to options outstanding as of September 30, 2103 having a weighted-average exercise price of \$4.15 per share;

7,595,701 shares of our common stock reserved for issuance in connection with future awards under our 2008 Stock Incentive Plan; and

1,643,136 shares of our common stock subject to outstanding warrants (other than the August 2011 warrants) as of September 30, 2013 having a weighted-average exercise price of \$6.58 per share.

To the extent our outstanding options and warrants are exercised, you may experience further dilution. The above illustration of dilution per share to investors participating in this offering assumes no exercise of outstanding options or outstanding warrants to purchase shares of our common stock other than the August 2011 warrants. The exercise of outstanding options and warrants having an exercise price less than the exercise price of the August 2011 warrants will further increase dilution to investors in this offering.

DIVIDEND POLICY

Our board of directors sets our dividend policy. We have never paid any cash dividends on our common stock and do not intend to declare cash dividends on our common stock in the foreseeable future. We currently intend to retain all available funds and any future earnings for use in the operation and expansion of our business, but we may determine

in the future to declare or pay cash dividends on our common stock. Any future determination as to the declaration and payment of dividends will be at the discretion of our board of directors and will be dependent upon our results of operations and cash flows, our financial position and capital requirements, general business conditions, legal, tax, regulatory and any contractual restrictions on the payment of dividends, and any other factors our board of directors deems relevant.

PLAN OF DISTRIBUTION

This prospectus relates to shares of our common stock issuable upon the exercise of our outstanding August 2011 warrants. The August 2011 warrants were offered and sold by us pursuant to a prospectus supplement dated July 27, 2011 and a related base prospectus dated December 13, 2010. The prospectus supplement and base prospectus also covered the offer and sale by us of the shares of our common stock underlying the August 2011 warrants, but those prospectuses can no longer be used for this purpose. The ongoing offer for sale by us of the shares of our common stock issuable upon exercise of the August 2011 warrants is being made pursuant to this prospectus. The August 2011 warrants are exercisable until August 1, 2016 at a current exercise price of \$4.48 per share of our common stock, subject to adjustment in events specified in the August 2011 warrants.

All of the August 2011 warrants are outstanding, and no additional August 2011 warrants will be issued. We will deliver shares of our common stock upon exercise of an August 2011 warrant, in whole or in part. We will not issue fractional shares. Each August 2011 warrant contains instructions for exercise. In order to exercise an August 2011 warrant, the holder must deliver to us, or our transfer agent, the information required by the August 2011 warrants, along with payment of the exercise price for the shares to be purchased. We will then deliver shares of our common stock in the manner described below in the section titled **Description of Securities August 2011 Warrants**.

Table of Contents

DESCRIPTION OF SECURITIES

The following summary of the terms of our capital stock is subject to and qualified by reference to our amended and restated certificate of incorporation and our restated bylaws, copies of which are on file with the SEC as exhibits to previous SEC filings. Please refer to **Where You Can Find More Information** below for directions on obtaining these documents.

Common Stock

As of November 26, 2013, we were authorized to issue 250,000,000 shares of common stock and had 41,975,412 shares (excluding treasury shares) of common stock outstanding.

Holders of our common stock are entitled to one vote per share on matters on which our stockholders vote, including with respect to the election of directors. Holders of common stock are entitled to receive dividends, if declared by our board of directors, out of funds that we may legally use to pay dividends. See the section of this prospectus entitled **Market Price of Our Common Stock and Related Stockholder Matters** **Dividend Policy** for further information. If we liquidate or dissolve, holders of common stock are entitled to share ratably in our assets once our debts and any liquidation preference owed to holders of any then-outstanding preferred stock are paid. No shares of our preferred stock are outstanding as of the date of this prospectus. All shares of common stock that are outstanding as of the date of this prospectus are, and all shares we are selling in this offering, upon their issuance and sale upon exercise of the August 2011 warrants as provided in the August 2011 warrants, will be, fully-paid and nonassessable.

Preferred Stock

We are currently authorized to issue 5,000,000 shares of preferred stock, of which 25,000 shares have been designated as Series A Junior Participating Preferred Stock. We have reserved all of the shares of our Series A Junior Participating Preferred Stock for issuance upon the exercise of the rights under our Shareholder Protection Rights Agreement described below.

Our board of directors has the authority to issue shares of preferred stock in one or more series and to fix the rights of each series. These rights may include dividend rights, dividend rates, conversion rights, voting rights, terms of redemption, redemption prices, liquidation preferences, sinking fund terms, and the number of shares that constitute any series. The board of directors may exercise this authority without any further action by our stockholders.

We believe the power to issue preferred stock will provide our board of directors with flexibility in connection with certain possible corporate transactions. The issuance of preferred stock, however, could adversely affect the voting power of holders of our common stock, restrict their rights to receive payment upon liquidation, and have the effect of delaying, deferring, or preventing a change in control which may be beneficial to our stockholders.

Anti-Takeover Measures

Delaware Law

Section 203 of the Delaware General Corporation Law is applicable to takeovers of certain Delaware corporations, including us. Subject to exceptions enumerated in Section 203, Section 203 provides that a corporation shall not engage in any business combination with any interested stockholder for a three-year period following the date that the stockholder becomes an interested stockholder unless:

prior to that date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;

upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, though some shares may be excluded from the calculation; or

on or subsequent to that date, the business combination is approved by the board of directors of the corporation and by the affirmative votes of holders of at least two-thirds of the outstanding voting stock that is not owned by the interested stockholder.

Except as specified in Section 203, an interested stockholder is generally defined to include any person who, together with any affiliates or associates of that person, beneficially owns, directly or indirectly, 15% or more of the outstanding voting stock of the corporation, or is an affiliate or associate of the corporation and was the owner of 15% or more of the outstanding voting stock of the corporation, any time within three years immediately prior to the relevant date. Under certain circumstances, Section 203 makes it more difficult for an interested stockholder to effect various business combinations with a corporation for a three-year period, although the stockholders may elect not to be governed by this section, by adopting an amendment to the certificate of incorporation or by-laws, effective 12 months after adoption. Our amended and restated certificate of incorporation and by-laws do not opt out from the restrictions imposed under Section 203. We anticipate that the provisions of Section 203 may encourage companies interested in acquiring us to negotiate in advance with the board because the stockholder approval requirement would be avoided if a majority of

Table of Contents

the directors then in office excluding an interested stockholder approve either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder. These provisions may have the effect of deterring hostile takeovers or delaying changes in control, which could depress the market price of our common stock and deprive stockholders of opportunities to realize a premium on shares of common stock held by them.

Charter and By-Law Provisions

In addition to the board of directors' ability to issue shares of preferred stock, our amended and restated certificate of incorporation and by-laws contain the following provisions that may have the effect of discouraging unsolicited acquisition proposals:

our by-laws classify the board of directors into three classes with staggered three-year terms;

under our by-laws, our board of directors may enlarge the size of the board and fill the vacancies;

our by-laws provide that a stockholder may not nominate candidates for the board of directors at any annual or special meeting unless that stockholder notifies us of its intention a specified period in advance and provides us with certain required information;

stockholders who wish to bring business before the stockholders at our annual meeting must provide advance notice; and

our by-laws provide that special meetings of stockholders may only be called by our board of directors or by an officer so instructed by our board.

Shareholder Protection Rights Agreement

Our board of directors adopted a Shareholder Protection Rights Agreement, or Rights Agreement, dated April 16, 1997, as amended, between us and American Stock Transfer & Trust Co., as Rights Agent. The Rights Agreement will expire on April 16, 2017, unless renewed or extended by our board of directors. A series of our preferred stock, designated as Series A Junior Participating Preferred Stock, par value \$.01 per share, was created in accordance with the Rights Agreement. The Rights Agreement is designed to deter coercive takeover tactics, including the accumulation of shares in the open market or through private transactions, and to prevent an acquirer from gaining control of us without offering a fair and adequate price and terms to all of our stockholders. As such, the Rights Agreement is intended to enhance our board of directors' ability to protect stockholder interests and help to assure that stockholders receive fair and equal treatment in the event any proposed takeover of CytRx is made in the future. Pursuant to the Rights Agreement, our board of directors declared a dividend distribution of one preferred stock purchase right for each outstanding share of our common stock. The preferred stock purchase rights are attached to, and trade with, our common stock. The purchase rights are exercisable only upon the occurrence of certain triggering events described in the Rights Agreement.

Transfer Agent

The transfer agent for our common stock is American Stock Transfer & Trust Company, 40 Wall Street, New York, New York 10005.

August 2011 Warrants

The following summary of the material terms and provisions of the August 2011 warrants is not complete and is subject to, and qualified in its entirety by the provisions of the August 2011 warrants, the form of which has been filed as an exhibit to the registration statement of which this prospectus is part:

Term. The August 2011 warrants are exercisable at any time on or before August 1, 2016.

Exercise Price. The current exercise price of the August 2011 warrants is \$4.48 per share of common stock. The exercise price is subject to appropriate adjustment in the event of certain stock dividends and distributions, stock splits, stock combinations, distributions of assets, reclassifications or similar events affecting our common stock.

Table of Contents

Exercisability. The August 2011 warrants are exercisable at the option of each holder, in whole or in part, by delivering to us a duly executed exercise notice accompanied by payment in full for the number of shares of our common stock purchased upon such exercise (except in the case of a cashless exercise as discussed below). A holder (together with its affiliates) may not exercise any portion of the August 2011 warrants to the extent that the holder would own more than 4.99% of the outstanding common stock after exercise, except that upon at least 61 days prior notice from the holder to us, the holder may increase the amount of ownership of outstanding stock after exercising the holder's August 2011 warrants to up to 9.99% of the number of shares of our common stock outstanding immediately after giving effect to the exercise, as such percentage ownership is determined in accordance with the terms of the August 2011 warrants.

Cashless Exercise. If, at the time a holder exercises an August 2011 warrant, there is no effective registration statement registering, or the prospectus contained therein is not available for an issuance of the shares underlying the August 2011 warrant to the holder, then in lieu of making the cash payment otherwise contemplated to be made to us upon such exercise in payment of the aggregate exercise price, the holder may elect instead to receive upon such exercise, either in whole or in part, the net number of shares of common stock determined according to a formula set forth in the August 2011 warrants.

Transferability. Subject to applicable laws, the August 2011 warrants may be transferred at the option of the holder upon surrender of the August 2011 warrants to us together with the appropriate instruments of transfer.

Authorized Shares. During the period the August 2011 warrants are outstanding, we will reserve from our authorized and unissued common stock a sufficient number of shares to provide for the issuance of shares of common stock upon the exercise of the August 2011 warrants.

Exchange Listing. The August 2011 warrants are not listed for trading on The NASDAQ Capital Market, any national securities exchange or other nationally recognized trading system.

Fundamental Transactions. In the event of any fundamental transaction, as described in the August 2011 warrants and generally including any merger with or into another entity, sale of all or substantially all of our assets, tender offer or exchange offer, or reclassification of our common stock, then upon any subsequent exercise of an August 2011 warrant, the holder shall have the right to receive as alternative consideration, for each share of our common stock that would have been issuable upon such exercise immediately prior to the occurrence of such fundamental transaction, the number of shares of common stock of the successor or acquiring corporation or of CytRx, if we are the surviving corporation, and any additional consideration receivable upon or as a result of such transaction by a holder of the number of shares of our common stock for which the August 2011 warrant is exercisable immediately prior to such event. In addition, in the event of a fundamental transaction that is an all-cash transaction, a going private transaction or a transaction with a person or entity not traded on an eligible securities market, then we or any successor entity shall pay at the holder's option, exercisable at any time commencing on the earlier of the public disclosure of the fundamental transaction or the consummation of the fundamental transaction and continuing for 90 days after the public disclosure of the consummation of the fundamental transaction, an amount of cash equal to the value of the warrant as determined in accordance with the Black Scholes option pricing model.

Right as a Stockholder. Except as otherwise provided in the August 2011 warrants or by virtue of such holder's ownership of shares of our common stock, the holders of the August 2011 warrants do not have the rights or privileges of holders of our common stock, including any voting rights, until they exercise their August 2011 warrants.

Waivers and Amendments. Any term of the warrants issued in the offering may be amended or waived with our written consent and the written consent of the holders of warrants representing a majority of the shares of our common

stock underlying the August 2011 warrants then outstanding, except that no such action may increase the exercise price of any August 2011 warrant or decrease the number of shares or class of stock obtainable upon exercise of any August 2011 warrant without the written consent of the holder of the August 2011 warrant.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at <http://www.sec.gov>. The SEC's website contains reports, proxy and information statements and other information regarding issuers, such as us, that file electronically with the SEC. You may also read and copy any document we file with the SEC at the SEC's Public Reference Room at 100 F Street, N.E., Room 1580, Washington D.C. 20549. You may also obtain copies of these documents at prescribed rates by writing to the SEC. Please call the SEC at 1-800-SEC-0330 for further information on the operation of its Public Reference Room.

Table of Contents

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to incorporate by reference the information we have filed with it, which means that we can disclose important information to you by referring you to another document that we have filed separately with the SEC. You should read the information incorporated by reference because it is an important part of this prospectus. Any statement in a document we incorporate by reference into this prospectus will be considered to be modified or superseded to the extent a statement contained in this prospectus or any other subsequently filed document that is incorporated by reference into this prospectus modifies or supersedes that statement. The modified or superseded statement will not be considered to be a part of this prospectus, except as modified or superseded.

We incorporate by reference the following information or documents that we have filed with the SEC (excluding those portions of any Form 8-K that are not deemed filed pursuant to the General Instructions of Form 8-K):

our Annual Report on Form 10-K for the year ended December 31, 2012;

our Quarterly Reports on Form 10-Q for the quarterly periods ended March 31, 2013, June 30, 2013 and September 30, 2013, respectively;

our Current Reports on Form 8-K filed with the SEC on January 3, 2013, March 11, 2013, May 9, 2013, July 16, 2013, August 6, 2013, October 9, 2013 and October 29, 2013, respectively;

the description of our securities as described in our Registration Statement on Form 8-A filed under the Exchange Act on March 17, 1987 (File No. 0 15327), and any amendment or report filed for the purpose of updating any such description; and

the description of our Series A Junior Participating Preferred Stock Purchase Rights as described in our Registration Statement on Form 8-A filed under the Exchange Act on April 17, 1997 (File No. 000 15327), and any amendment or report filed for the purpose of updating any such descriptions.

We also incorporate by reference all documents filed pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus and prior to the termination of this offering (excluding those portions of any Form 8-K that are not deemed filed pursuant to the General Instructions of Form 8-K).

Statements made in this prospectus or in any document incorporated by reference in this prospectus as to the contents of any contract or other document referred to herein or therein are not necessarily complete, and in each instance reference is made to the copy of such contract or other document filed as an exhibit to the documents incorporated by reference, each such statement being qualified in all material respects by such reference.

You may obtain a copy of the foregoing documents from us without charge by writing or calling us at the following address and telephone number: 11726 San Vicente Blvd., Suite 650 Los Angeles, California 90049, Attention: Corporate Secretary; (310) 826-5648.

Copies of these documents are also available, without charge, through the Investors section of our website (www.cytrx.com) as soon as reasonably practicable after they are filed with the SEC. The information contained on our website is not a part of this prospectus.

LEGAL MATTERS

TroyGould PC, Los Angeles, California, has rendered an opinion with respect to the validity of the shares of common stock offered by this prospectus.

EXPERTS

The consolidated financial statements and schedules as of December 31, 2012 and 2011 and for each of the three years in the period ended December 31, 2012 and management's assessment of the effectiveness of internal control over financial reporting as of December 31, 2012 incorporated by reference in this prospectus have been so incorporated in reliance on the reports of BDO USA, LLP, an independent registered public accounting firm, incorporated herein by reference, given on the authority of said firm as experts in auditing and accounting.

A-20

Table of Contents

PROSPECTUS

6,440,045 Shares of Common Stock

Issuable Upon Exercise of August 2011 Warrants

The date of this prospectus is , 2013

Table of Contents

The information in this prospectus is not complete and may be changed. These securities may not be sold until the registration statement filed with the Securities and Exchange Commission becomes effective. This prospectus is not an offer to sell these securities, and it is not a solicitation of an offer to buy these securities, in any state where the offer or sale is not permitted.

SUBJECT TO COMPLETION, November 27, 2013

PROSPECTUS

\$100,000,000

We may offer and sell from time to time up to \$100,000,000 in the aggregate of shares of our common stock, shares of our preferred stock and warrants in amounts, at prices and on terms that we will decide at the time of the offering. These securities may be offered and sold separately, together or as units with other securities. Each share of our common stock to be offered and sold is accompanied by one Series A Junior Participating Preferred Stock Purchase Right that trades with our common stock.

We will provide the specific terms of these offers and sales in supplements to this prospectus. This prospectus may not be used to sell securities unless accompanied by a prospectus supplement. You should read this prospectus and the prospectus supplement carefully before you invest. We may offer securities directly to investors or through agents, underwriters or dealers. If any agents, underwriters or dealers are involved in the sale of any of our securities, their names and any applicable purchase prices, fees, commissions or discount arrangements will be set forth in the prospectus supplement.

Our common stock is traded on The Nasdaq Capital Market under the symbol CYTR. On November 26, 2013, the last sale price of our common stock as reported on The NASDAQ Capital Market was \$2.3799.

An investment in our securities involves significant risks. Before purchasing any securities, you should consider carefully the risks referred to under Risk Factors on page B-5 in this prospectus and in the prospectus supplement.

NEITHER THE SECURITIES AND EXCHANGE COMMISSION NOR ANY STATE SECURITIES COMMISSION HAS APPROVED OR DISAPPROVED THESE SECURITIES OR DETERMINED THAT THIS PROSPECTUS IS COMPLETE OR ACCURATE. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

The date of this prospectus is , 2013

Table of Contents

TABLE OF CONTENTS

	Page
<u>ABOUT THIS PROSPECTUS</u>	B-1
<u>NOTE ON FORWARD-LOOKING STATEMENTS</u>	B-1
<u>INDUSTRY DATA</u>	B-1
<u>ABOUT CYTRX</u>	B-2
<u>RISK FACTORS</u>	B-5
<u>USE OF PROCEEDS</u>	B-13
<u>FINANCIAL RATIOS</u>	B-13
<u>DIVIDEND POLICY</u>	B-14
<u>THE SECURITIES THAT WE MAY OFFER</u>	B-14
<u>DESCRIPTION OF CAPITAL STOCK</u>	B-14
<u>DESCRIPTION OF WARRANTS</u>	B-17
<u>DESCRIPTION OF UNITS</u>	B-18
<u>PLAN OF DISTRIBUTION</u>	B-19
<u>WHERE YOU CAN FIND MORE INFORMATION</u>	B-20
<u>INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE</u>	B-20
<u>LEGAL MATTERS</u>	B-21
<u>EXPERTS</u>	B-21

Table of Contents

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement utilizing the shelf registration process that we filed with the Securities and Exchange Commission, or the SEC, to permit us to offer and sell the securities described in this prospectus in one or more transactions. The plan of distribution of the securities is described in this prospectus under the heading Plan of Distribution.

As permitted by the rules and regulations of the SEC, the registration statement filed by us includes additional information not contained in this prospectus. You may read the registration statement and the other reports we file with the SEC at the SEC's web site or at the SEC's offices described below under the heading Where You Can Find Additional Information.

This prospectus provides you with a general description of the securities we may offer. Each time securities are sold, we will provide a prospectus supplement that will contain specific information about the terms of that offering. The prospectus supplement may also add, update or change information contained in this prospectus. You should read both this prospectus and the prospectus supplement, together with additional information described in this prospectus under the heading Where You Can Find More Information.

You should rely only on the information provided in this prospectus and in the prospectus supplement, including any information incorporated by reference. For more details on information incorporated herein by reference, you should review the discussion contained under the heading Incorporation of Certain Documents by Reference. We have not authorized anyone to provide you with information different from that contained or incorporated by reference in this prospectus and in the prospectus supplement. We are offering the securities only in jurisdictions where offers are permitted. You should not assume that the information in this prospectus or the prospectus supplement is accurate at any date other than the date indicated on the cover page of these documents.

NOTE ON FORWARD-LOOKING STATEMENTS

Some of the statements contained or incorporated by reference in this prospectus or in the prospectus supplement may include forward-looking statements that reflect our current views with respect to our research and development activities, business strategy, business plan, financial performance and other future events. These statements include forward-looking statements both with respect to us, specifically, and the biotechnology sector, in general. We make these statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Statements that include the words expect, intend, plan, believe, project, estimate, may, should, anticipate, similar statements of a future or forward-looking nature identify forward-looking statements for purposes of the federal securities laws or otherwise.

All forward-looking statements involve inherent risks and uncertainties, and there are or will be important factors that could cause actual results to differ materially from those indicated in these statements. We believe that these factors include, but are not limited to, those factors set forth under the caption Risk Factors in this prospectus and in any prospectus supplement and under the captions Business, Legal Proceedings, Management's Discussion and Analysis of Financial Condition and Results of Operations, Quantitative and Qualitative Disclosures About Market Risk and Controls and Procedures in our most recent Annual Report on Form 10-K and our most recent Quarterly Report on Form 10-Q, all of which you should review carefully. Please consider our forward-looking statements in light of those risks as you read this prospectus and the prospectus supplement. We undertake no obligation to publicly update or review any forward-looking statement, whether as a result of new information, future developments or otherwise.

If one or more of these or other risks or uncertainties materializes, or if our underlying assumptions prove to be incorrect, actual results may vary materially from what we anticipate. All subsequent written and oral forward-looking statements attributable to us or individuals acting on our behalf are expressly qualified in their entirety by this Note. Before purchasing any securities, you should consider carefully all of the factors set forth or referred to in this prospectus and in the prospectus supplement that could cause actual results to differ.

INDUSTRY DATA

Unless otherwise indicated, information contained or incorporated by reference in this prospectus concerning our industry, including our general expectations and market opportunity, is based on information from our own management estimates and research, as well as from industry and general publications and research, surveys and studies conducted by third parties. Management estimates are derived from publicly available information, our knowledge of our industry and assumptions based on such information and knowledge, which we believe to be reasonable. In addition, assumptions and estimates of our and our industry's future performance are necessarily subject to a high degree of uncertainty and risk due to a variety of factors, including those described in "Risk Factors" beginning on page B-6 of this prospectus. These and other factors could cause our future performance to differ materially from our assumptions and estimates.

B-1

Table of Contents**ABOUT CYTRX****Overview**

We are a biopharmaceutical research and development company specializing in oncology. We currently are focused on the clinical development of aldoxorubicin (formerly known as INNO-206), our modified version of the widely-used chemotherapeutic agent, doxorubicin. We are conducting a global Phase 2b clinical trial with aldoxorubicin as a treatment for soft tissue sarcoma, have completed a Phase 1b/2 clinical trial primarily in the same indication, a Phase 1b study of aldoxorubicin in combination with doxorubicin in patients with advanced solid tumors, and a Phase 1b pharmacokinetics clinical trial in patients with metastatic solid tumors. We plan to initiate under a Special Protocol Assessment, or SPA, granted by the U.S. Food and Drug Administration, or FDA, a potential pivotal Phase 3 global trial of aldoxorubicin as a therapy for patients with soft tissue sarcoma whose tumors have progressed following treatment with chemotherapy. We also are initiating Phase 2 clinical trials with aldoxorubicin in patients with late-stage glioblastoma (brain cancer) and AIDS-related Kaposi's sarcoma. We plan to expand our pipeline of oncology candidates based on a linker platform technology that can be utilized with multiple chemotherapeutic agents and may allow for greater concentration of drug at tumor sites. We also have rights to two additional drug candidates, tamibarotene and bafetinib. We completed our evaluation of bafetinib in the ENABLE Phase 2 clinical trial in high-risk B-cell chronic lymphocytic leukemia (B-CLL), plan to seek a partner for further development of bafetinib.

Our Product Candidate Pipeline

The following table summarizes our product candidates and their current or impending stages of development:

	Product		Stage of
Technology	candidate	Indication(s)	development
Doxorubicin conjugate	Aldoxorubicin	Soft tissue sarcoma	Phase 3 1Q14 Phase 2b ongoing
		Glioblastoma multiforme	Phase 2 4Q13
		Kaposi's sarcoma	Phase 2 4Q13
		In combination with doxorubicin in patients with advanced solid tumors	Phase 1b complete

Our Clinical Development Programs

Our current clinical development programs are summarized below.

Aldoxorubicin

Aldoxorubicin is a conjugate of the commonly prescribed chemotherapeutic agent doxorubicin that binds to circulating albumin in the bloodstream and is concentrated at the site of tumors. Specifically, it is the (6-Maleimidocaproyl) hydrazone of doxorubicin attached to an acid-sensitive linker known as EMCH. We are initiating a potential pivotal Phase 3 global trial of aldoxorubicin as a therapy for patients with soft tissue sarcoma whose tumors have progressed following treatment with chemotherapy under an SPA granted by the FDA. The SPA means that the FDA agrees with the design, execution and analyses proposed in the Phase 3 trial protocol and will not subsequently change its perspective on these matters, unless previously unrecognized public or animal health concerns were to arise. It also

means that if the study demonstrates the acceptable benefit-risk profile as described in the protocol, it would suffice as the single pivotal trial that would likely support registration of aldorubicin for this indication.

Aldorubicin for the Treatment of Cancer. Anthracyclines are a class of drugs that are among the most commonly used agents in the treatment of cancer. Doxorubicin, the first anthracycline to gain FDA approval, has demonstrated efficacy in a wide variety of cancers, including breast cancer, lung cancer, sarcomas, and lymphomas. However, due to the uptake of doxorubicin by various parts of the body, it is associated with side effects such as cumulative cardiotoxicity, myelosuppression (decreased production of blood cells by bone marrow), gastrointestinal disorders, mucositis (inflammation of the mucous membranes lining the mouth and digestive tract), stomatitis (inflammation of soft tissue of the mouth), and extravasation (the leakage of intravenous drugs from the vein into the surrounding tissue).

We believe aldorubicin has attributes that may improve on doxorubicin, alone, which we sometimes refer to as native doxorubicin, including the potential to reduce adverse events, improve efficacy and achieve increased concentration at tumor sites.

Our postulated mechanism of action for aldorubicin is as follows:

after administration, aldorubicin rapidly binds circulating albumin through the EMCH linker;

circulating albumin preferentially accumulates in tumors, bypassing concentration in other non-tumor sites, including the heart, liver and gastrointestinal tract due to a mechanism called Enhanced Permeability and Retention by Solid Tumors ;

B-2

Table of Contents

once albumin-bound doxorubicin reaches the tumor, the acidic environment of the tumor causes cleavage of the acid-sensitive linker; and

free doxorubicin is released at the site of the tumor and is taken up by the cancer cells.

Pre-clinical data. In a variety of preclinical models, aldorubicin was superior to doxorubicin at equitoxic doses in its ability to allow an increase in the total doxorubicin dose, its antitumor efficacy and its safety. Toxicology studies in rodents also demonstrated a reduction in cardiotoxicity. Animal studies conducted by aldorubicin inventor Dr. Felix Kratz of the Department of Medical Oncology, Clinical Research, at the Tumor Biology Center in Freiburg, Germany, demonstrated statistically significant efficacy compared to either placebo or native doxorubicin against breast, ovarian, pancreatic and small cell lung cancers growing in immunodeficient mice.

We also recently announced additional data from a study of aldorubicin in immunodeficient mice transplanted with human glioblastoma cells in their brain that showed those animals treated with aldorubicin had a median survival rate of more than 63 days, compared with approximately 25 days for animals treated with doxorubicin or saline. The data also indicated evidence of drug concentration inside tumors growing in the brain and significant tumor regression in aldorubicin-treated animals, while doxorubicin did not appear to enter the tumor to any significant degree and showed little or no efficacy in the treatment of these brain tumors. Aldorubicin significantly reduced the number of dividing cells within the brain tumors in this trial and showed a statistically relevant increased expression of apoptosis or cell death markers.

Clinical data. A Phase 1 study of aldorubicin that demonstrated safety and objective clinical responses in several tumor types was completed in 2005 and presented at the March 2006 Krebskongress meeting in Berlin. In this study, doses were administered every three weeks at up to six times the standard dose of doxorubicin without an increase in the types of side effects compared with those historically observed with native doxorubicin. Twenty-three of thirty-five evaluable patients had either an objective clinical (partial) response or stable disease. Objective clinical responses were observed in patients with sarcoma, breast and small cell lung cancers.

We completed a Phase 1b/2 clinical trial with aldorubicin in patients with advanced solid tumors and presented favorable data at the American Society for Clinical Oncology Meeting in June 2012. In that Phase 1b/2 clinical trial, clinical benefit (defined as partial response or stable disease of more than four months following up to eight cycles of treatment) with aldorubicin at the maximum tolerated dose was shown in ten of 13 (76.9%) evaluable patients with relapsed or refractory soft tissue sarcoma.

In addition, best responses for the 13 evaluable soft tissue sarcoma trial subjects included the following: five (38.5%) achieved partial response, as defined as shrinkage of target tumors of more than 30%; seven (53.8%) showed prolonged stable disease (defined as tumor shrinkage <30% from baseline or tumor growth <20% from the nadir); eight (61.5%) had tumor shrinkage; and five of eight patients (62.5%) who demonstrated either partial responses or prolonged stable disease after treatment with aldorubicin had been previously treated with doxorubicin and had failed to respond. There were no observed cardiac toxicities and no drug-related patient deaths. The most common adverse event, neutropenia, also observed with doxorubicin treatment, resolved prior to the start of the next treatment. Median estimated progression-free survival for advanced soft tissue sarcoma patients in the trial was 6.4 months with a range of 1.0 to more than 10.7 months.

In our Phase 1b pharmacokinetics clinical trial evaluating the pharmacokinetics and safety of aldorubicin in patients with metastatic solid tumors who have either relapsed or not responded to treatment with standard therapies, we recently announced data demonstrating that aldorubicin has a circulating half-life of approximately 20 to 24 hours, with narrow volume of distribution to healthy tissue and slow clearance from the circulation. These characteristics

distinguish aldoxorubicin from published pharmacokinetics data for doxorubicin.

Development Plan. We plan to initiate under a SPA granted by the FDA a potential pivotal Phase 3 global trial with aldoxorubicin as a therapy for patients with soft tissue sarcomas whose tumors have progressed following treatment with chemotherapy. The Phase 3 clinical trial's primary endpoint will be progression-free survival. The trial also will assess overall survival, objective tumor response and safety. We expect to enroll approximately 400 patients, commencing in the first quarter of 2014.

In December 2011, we initiated our international Phase 2b clinical trial to evaluate the preliminary efficacy and safety of aldoxorubicin as a first-line therapy in patients with advanced soft tissue sarcoma who are ineligible for surgery. The Phase 2b clinical trial will provide the first direct clinical trial comparison of aldoxorubicin and native doxorubicin, which is dose-limited due to toxicity, as a first-line therapy.

The Phase 2b clinical trial with aldoxorubicin in patients with soft tissue sarcoma is an international trial under the direction of Sant P. Chawla, M.D., F.R.A.C.P., Director of the Sarcoma Oncology Center in Santa Monica, California. The Phase 2b clinical trial's primary objectives are to measure the progression-free survival, tumor response and overall survival of patients with advanced soft tissue sarcomas treated with aldoxorubicin. This clinical trial also will assess the safety of aldoxorubicin compared to doxorubicin in this patient population through a number of indicators, including the frequency and severity of adverse events.

B-3

Table of Contents

Preliminary data based on the first 82 evaluated patients in the Phase 2b clinical trial showed that aldoxorubicin-treated patients demonstrated a significantly greater percentage of overall responses compared with those treated with doxorubicin, the current standard-of-care for advanced, metastatic soft-tissue sarcoma. This was based on a blinded reading of tumor scans by an independent radiology review. We expect to report in December 2013 final, top-line data for the global Phase 2b clinical trial, including data related to the trial's primary endpoint of progression-free survival.

We plan to initiate in 2013 a Phase 2 clinical trial to evaluate the preliminary efficacy and safety of aldoxorubicin in patients with unresectable glioblastoma whose tumors have progressed following prior treatment with surgery, radiation and with the drug temozolomide. The clinical trial is expected to enroll approximately 28 patients at sites including the John Wayne Cancer Center in Santa Monica, California, City of Hope in Duarte, California, and the LSU Medical Center in New Orleans, Louisiana.

We also plan to initiate in 2013 a Phase 2 clinical trial evaluating the preliminary efficacy of aldoxorubicin in patients with AIDS-related Kaposi's sarcoma, a common HIV-associated tumor. The current standard-of-care for severe dermatological and systemic Kaposi's sarcoma is liposomal doxorubicin (Doxil); however, a significant proportion of patients exhibit minimal or no clinical response to this agent, and the drug's toxicity often prevents continued therapy. The Phase 2 trial will enroll up to 30 patients and will be conducted at the LSU Medical Center in New Orleans, Louisiana.

In 2012, we completed a Phase 2 trial for patients with advanced pancreatic ductal adenocarcinomas who had relapsed or failed to respond to two prior regimens, one regimen containing gemcitabine (Gemzar) and the other a fluoropyrimidine such as 5-fluorouracil. No objective clinical responses were observed in 14 patients treated with native aldoxorubicin, and we are considering testing the aldoxorubicin in combination with the commonly-prescribed drug Abraxane as a second-line treatment in that indication.

Bafetinib

Bafetinib (formerly INNO-406) is an orally bioavailable, rationally-designed inhibitor of several Src kinases developed by the Japanese pharmaceutical company Nippon Shinyaku, to overcome some of the limitations of Gleevec and other tyrosine kinase inhibitors in resistant chronic myelogenous leukemia, or CML. In addition to its Bcr-Abl inhibitory properties, bafetinib is a potent and specific inhibitor of Lyn and Fyn kinases. These kinases are reported to be involved in both solid and hematological cancers. Lyn kinase's involvement in the B-cell signaling pathway led us to evaluate bafetinib in B-cell malignancies such as chronic lymphocytic leukemia, or CLL. We hold rights to bafetinib in all territories, except in Japan.

We plan to seek a partner for any further development of bafetinib in order to focus our resources on the development of aldoxorubicin.

Tamibarotene

Tamibarotene is an orally available, synthetic retinoid rationally designed to overcome resistance and reduce the toxic side effects of differentiation therapy with all-trans retinoic acid, or ATRA, a component of the current first-line treatment for acute promyelocytic leukemia, or APL. We ceased our Phase 2b clinical trial of tamibarotene in patients with non-small-cell lung cancer after it failed to show efficacy.

Reverse Stock Split

On May 16, 2012, we effected a 1-for-7 reverse stock split of our outstanding shares of common stock and our common stock began trading on The NASDAQ Capital Market on a split-adjusted basis. All share and per share amounts in this prospectus have been adjusted to reflect the reverse stock split as if it had occurred at the beginning of the earliest period presented.

Corporate Information

We are a Delaware corporation, incorporated in 1985. Our corporate offices are located at 11726 San Vicente Boulevard, Suite 650, Los Angeles, California 90049, and our telephone number is (310) 826-5648. Our web site is located on the worldwide web at <http://www.cytrx.com>. We do not incorporate by reference into this prospectus the information on, or accessible through, our website, and you should not consider it as part of this prospectus.

B-4

Table of Contents

RISK FACTORS

You should carefully consider the risks described below before making an investment decision. The risks described below are not the only ones we face. Additional risks we are not presently aware of or that we currently believe are immaterial may also impair our business operations. Our business could be harmed by any of these risks. The trading price of our common stock could decline due to any of these risks, and you may lose all or part of your investment. In assessing these risks, you should also refer to the other information contained or incorporated by reference in this prospectus, including our financial statements and related notes. We have attempted to identify below the major factors that could cause differences between actual and planned or expected results, but we cannot assure you that we have identified all such factors.

Risks Associated With Our Business

We have operated at a loss and will continue to operate at a loss for the foreseeable future.

We have operated at a loss due to our ongoing expenditures for research and development of our product candidates and for general and administrative purposes and lack of significant recurring revenue. We incurred a net loss of approximately \$18.0 million for the year ended December 31, 2012 and of approximately \$20.3 million for the nine months ended September 30, 2013, and had an accumulated deficit as of September 30, 2013 of approximately \$249.2 million. We will continue to incur losses unless and until we are able to commercialize aldoxorubicin or one or more of our other current or future product candidates. These losses, among other things, have had and will continue to have an adverse effect on our stockholders' equity and working capital. Because of the numerous risks and uncertainties associated with our product development efforts, we are unable to predict when we may become profitable, if at all. If we do not become profitable or are unable to maintain future profitability, the market value of our common stock will be adversely affected.

Because we have no source of significant recurring revenue, we must depend on financing to sustain our operations.

Developing products and conducting clinical trials require substantial amounts of capital. To date, we have relied primarily upon proceeds from sales of our equity securities, sales of our shares of common stock of our former RXi subsidiary and the exercise of options and warrants to generate funds needed to finance our business and operations. We will need to raise additional capital to, among other things:

fund our clinical trials and pursue regulatory approval of aldoxorubicin and our other existing and possible future product candidates;

expand our research and development activities;

finance our general and administrative expenses;

acquire or license new technologies;

prepare, file, prosecute, maintain, enforce and defend our patent and other proprietary rights; and

develop and implement sales, marketing and distribution capabilities to successfully commercialize any product for which we obtain marketing approval and choose to market ourselves.

Our revenue was \$100,000 for the year ended December 31, 2012 and \$200,000 for the nine months ended September 30, 2013. We will have no significant recurring revenue unless we are able to commercialize aldoxorubicin, our lead product candidate, or one of our preclinical candidates, either of which may require us to first enter into strategic arrangements with third parties.

At September 30, 2013, we had cash and cash equivalents of approximately \$6.0 million and short-term investments of \$17.0 million. Management believes that our current cash and cash equivalents and short-term investments, including the net proceeds of approximately \$24.1 million from our public offering completed on October 15, 2013, will be sufficient to fund our operations for the foreseeable future. These expectations are based upon numerous assumptions and subject to many uncertainties, and our actual experience may be significantly different from these expectations.

If we obtain marketing approval and successfully commercialize aldoxorubicin or other product candidate, we anticipate it will take a minimum of several years, and likely longer, for us to generate significant recurring revenue, and we will be dependent on future financing until such time, if ever, as we can generate significant recurring revenue. Our ability to raise capital may be adversely affected by the weak economic recovery in the United States. We have no commitments from third parties to provide us with any additional financing, and we may not be able to obtain future financing on favorable terms, or at all. Failure to obtain adequate financing would adversely affect our ability to operate as a going concern. If we raise additional funds by issuing equity securities, dilution to stockholders may result and new investors could have rights superior to holders of the shares issued in this offering. In addition, debt financing, if available, may include restrictive covenants. If adequate funds are not available to us, we may have to liquidate some or all of our assets or to delay or reduce the scope of or eliminate some portion or all of our development programs or clinical trials. We also may have to license to other companies our product candidates or technologies that we would prefer to develop and commercialize ourselves.

Table of Contents

If we do not achieve our projected development goals in the time frames we estimate, the commercialization of our products may be delayed and our business prospects may suffer. Our financial projections also may prove to be materially inaccurate.

From time to time, we estimate the timing of the accomplishment of various scientific, clinical, regulatory and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of scientific studies and clinical trials and the submission of regulatory filings such as the discussion in this prospectus supplement of the expected timing of certain milestones relating to our aldoxorubicin clinical development programs.

We also may disclose projected expenditures or other forecasts for future periods. These and other financial projections are based on management's current expectations and do not contain any margin of error or cushion for any specific uncertainties, or for the uncertainties inherent in all financial forecasting.

The actual timing of milestones and actual expenditures or other financial results can vary dramatically compared to our estimates, in some cases for reasons beyond our control. If we do not meet milestones or financial projections as announced from time to time, the development and commercialization of our products may be delayed and our business prospects may suffer. The assumptions management has used to produce these projections may significantly change or prove to be inaccurate. Accordingly, you should not unduly rely on any of these financial projections.

If our products are not successfully developed and approved by the FDA or foreign regulatory authorities, we may be forced to reduce or curtail our operations.

All of our product candidates in development must be approved by the FDA or corresponding foreign governmental agencies before they can be marketed. The process for obtaining FDA and foreign government approvals is both time-consuming and costly, with no certainty of a successful outcome. This process typically includes the conduct of extensive pre-clinical and clinical testing, including post-approval testing, which may take longer or cost more than we or our licensees, if any, anticipate, and may prove unsuccessful due to numerous factors. Product candidates that may appear to be promising at early stages of development may not successfully reach the market for a number of reasons. The results of preclinical and initial clinical testing of these product candidates may not necessarily be predictive of the results that will be obtained from later or more extensive testing. Companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in advanced clinical trials, even after obtaining promising results in earlier trials.

Numerous factors could affect the timing, cost or outcome of our product development efforts, including the following:

difficulty in enrolling patients in conformity with required protocols or projected timelines;

requirements for clinical trial design imposed by the FDA; unexpected adverse reactions by patients in trials;

difficulty in obtaining clinical supplies of the product;

changes in or our inability to comply with FDA or foreign governmental product testing, manufacturing or marketing requirements;

regulatory inspections of clinical trials or manufacturing facilities, which may, among other things, require us or our manufacturers or licensees to undertake corrective action or suspend or terminate the affected clinical trials if investigators find them not to be in compliance with applicable regulatory requirements;

inability to generate statistically significant data confirming the safety and efficacy of the product being tested;

modification of the product during testing; and

reallocation of our limited financial and other resources to other clinical programs.

On October 1, 2013, the U.S. federal government suspended services deemed non-essential as a result of the failure by Congress to enact regular appropriations for the 2014 fiscal year. Although the impasse has been resolved until at least January 2014, if a similar or more prolonged shutdown were to occur, it could result in significant delays in the FDA's ability to timely review and process any submissions we have filed or may file, or cause other regulatory delays affecting our development or commercial operations, which delays could have a material adverse effect on our business.

It is possible that none of the product candidates we develop will obtain the regulatory approvals necessary for us to begin selling them. The time required to obtain FDA and foreign governmental approvals is unpredictable, but often can take years following the commencement of clinical trials, depending upon the complexity of the product candidate. Any analysis we perform on data from clinical activities is subject to confirmation and interpretation by regulatory authorities, which could delay, limit or prevent regulatory approval.

Furthermore, even if we obtain regulatory approvals, our products and the manufacturing facilities used to produce them will be subject to continual review, including periodic inspections and mandatory post-approval clinical trials by the FDA and other U.S. and foreign regulatory authorities. Any delay or failure in obtaining required approvals or to comply with post-approval regulatory

Table of Contents

requirements could have a material adverse effect on our ability to generate revenue from the particular product candidate. The failure to comply with any post-approval regulatory requirements also could result in the rescission of the related regulatory approvals or the suspension of sales of the offending product.

Our current and planned clinical trials of our lead product candidate may fail to show that it is clinically safe and effective, or that it is better than alternative treatments.

Aldoxorubicin has shown encouraging preliminary clinical results in our Phase 1b/2 clinical trial and in preliminary data from our Phase 2b clinical trial of aldoxorubicin as a treatment for soft tissue sarcomas; however, these conclusions may not be reproduced in future clinical trial results, including the final, top-line data from the Phase 2b clinical trial or the planned global Phase 3 clinical trial testing aldoxorubicin as a treatment for soft tissue sarcomas.

Top-line data from our Phase 2b clinical trial of aldoxorubicin as a treatment for soft tissue sarcomas may differ from our recently announced preliminary data. Even if our current trials are successful, subsequent trials may not yield statistically significant data indicating that aldoxorubicin is clinically effective. Accordingly, we, or any development partners, may ultimately be unable to provide the FDA with satisfactory data on clinical safety and efficacy sufficient to obtain FDA approval of aldoxorubicin for any indication.

Our SPA with the FDA for our pivotal study of aldoxorubicin does not guarantee marketing approval in the United States.

We have an SPA with the FDA for the pivotal trial of aldoxorubicin for the treatment of soft-tissue sarcomas. The SPA means that the FDA agrees with the design, execution, and analyses proposed in a protocol, and constitutes a commitment that the FDA will not subsequently change its perspectives on these matters, unless a previously unrecognized public or animal health concern were to arise or changes were to be made to the protocol, itself. Even under a SPA, marketing approval by the FDA is not guaranteed, because a final determination that the agreed-upon protocol satisfies a specific objective, such as the demonstration of efficacy and safety (positive benefit-risk ratio), or supports an approval decision, will be based on a complete review of all the data submitted to the FDA.

We rely upon third parties for the manufacture of our clinical product supplies.

We do not have the facilities or expertise to manufacture supplies of aldoxorubicin or any of our other product candidates. Accordingly, we are dependent upon third-party manufacturers, or potential future strategic alliance partners, to manufacture these supplies. We have manufacturing supply arrangements in place with respect to a portion of the clinical supplies needed for the clinical development programs for aldoxorubicin. However, we have no supply arrangements for the commercial manufacture of this product candidate or any manufacturing supply arrangements for any other potential product candidates, and we may not be able to secure needed supply arrangements on attractive terms, or at all. Our failure to secure these arrangements as needed could have a materially adverse effect on our ability to complete the development of our products or to commercialize them.

If aldoxorubicin, our lead product candidate, or our other product candidates cannot be manufactured in suitable quantities and in accordance with regulatory standards, our clinical trials, regulatory approvals and marketing efforts for such products may be delayed. Such delays could adversely affect our competitive position and our chances of generating significant recurring revenues. If any of our products that are approved for marketing cannot be manufactured at an acceptable cost, the commercial success of such product candidates may be adversely affected.

We may rely upon third parties in connection with the commercialization of our products.

The completion of the development of aldoxorubicin or our other product candidates, as well as marketing and commercialization, may require us to enter into strategic alliances or other collaborative arrangements with other pharmaceutical companies under which those companies will be responsible for one or more aspects of the eventual marketing and commercialization of our products.

Our products, if approved for marketing, may not have sufficient potential commercial value to enable us to secure strategic arrangements with suitable companies on attractive terms, or at all. If we are unable to enter into such arrangements, we may not have the financial or other resources to complete the development of any of our products and may have to sell our rights in them to a third party or abandon their development altogether.

To the extent we enter into collaborative arrangements, we will be dependent upon the timeliness and effectiveness of the development and marketing efforts of our contractual partners. If these companies do not allocate sufficient personnel and resources to these efforts or encounter difficulties in complying with applicable FDA and other regulatory requirements, we may not obtain regulatory approvals as planned, if at all, and the timing of receipt or the amount of revenue from these arrangements may be materially and adversely affected. By entering into these arrangements rather than completing the development and then marketing these products on our own, the profitability to us of these products may decline.

B-7

Table of Contents

We may be unable to protect our intellectual property rights, which could adversely affect our ability to compete effectively.

We will be able to protect our technologies from unauthorized use by third parties only to the extent that we have rights to valid and enforceable patents or other proprietary rights that cover them. Although we have rights to patents and patent applications directed to aldoxorubicin and other product candidates, these patents and applications may not prevent third parties from developing or commercializing similar or identical technologies. In addition, our patents may be held to be invalid if challenged by third parties, and our patent applications may not result in the issuance of patents.

The patent positions of pharmaceutical and biotechnology companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in biotechnology patents has emerged to date in the United States and in many foreign countries. The application and enforcement of patent laws and regulations in foreign countries is even more uncertain. Accordingly, we may not be able to effectively file, protect or defend our proprietary rights on a consistent basis. Many of the patents and patent applications on which we rely were issued or filed by third parties prior to the time we acquired rights to them. The validity, enforceability and ownership of those patents and patent applications may be challenged, and if a court decides that our patents are not valid, we will not have the right to stop others from using our inventions. There is also the risk that, even if the validity of our patents is upheld, a court may refuse to stop others on the ground that their activities do not infringe our patents.

Any litigation brought by us to protect our intellectual property rights could be costly and have a material adverse effect on our operating results or financial condition, make it more difficult for us to enter into strategic alliances with third parties to develop our products, or discourage our existing licensees from continuing their development work on our potential products. If our patent coverage is insufficient to prevent third parties from developing or commercializing similar or identical technologies, the value of our assets is likely to be materially and adversely affected.

We also rely on certain proprietary trade secrets and know-how, especially where we believe patent protection is not appropriate or obtainable. However, trade secrets and know-how are difficult to protect. Although we have taken measures to protect our unpatented trade secrets and know-how, including the use of confidentiality and invention assignment agreements with our employees, consultants and some of our contractors, it is possible that these persons may disclose our trade secrets or know-how or that our competitors may independently develop or otherwise discover our trade secrets and know-how.

If our product candidates infringe the rights of others, we could be subject to expensive litigation or be required to obtain licenses from others to develop or market them.

Our competitors or others may have patent rights that they choose to assert against us or our licensees, suppliers, customers or potential collaborators. Moreover, we may not know about patents or patent applications that our products would infringe. For example, because patent applications do not publish for at least 18 months, if at all, and can take many years to issue, there may be currently pending applications unknown to us that may later result in issued patents that our product candidates would infringe. In addition, if third parties file patent applications or obtain patents claiming technology also claimed by us or our licensors in issued patents or pending applications, we may have to participate in interference proceedings in the U.S. Patent and Trademark Office to determine priority of invention. If third parties file oppositions in foreign countries, we may also have to participate in opposition proceedings in foreign tribunals to defend the patentability of our foreign patent applications.

If a third party claims that we infringe its proprietary rights, any of the following may occur:

we may become involved in time-consuming and expensive litigation, even if the claim is without merit;

we may become liable for substantial damages for past infringement if a court decides that our technology infringes a competitor's patent;

a court may prohibit us from selling or licensing our product without a license from the patent holder, which may not be available on commercially acceptable terms, if at all, or which may require us to pay substantial royalties or grant cross licenses to our patents; and

we may have to redesign our product candidates or technology so that it does not infringe patent rights of others, which may not be possible or commercially feasible.

If any of these events occurs, our business and prospects will suffer and the market price of our common stock will likely decline substantially.

Any products we develop may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which could have a material adverse effect on our business.

We intend to sell our products that may be approved for marketing primarily to hospitals, which receive reimbursement for the health care services they provide to their patients from third-party payors, such as Medicare, Medicaid and other domestic and international government programs, private insurance plans and managed care programs. Most third-party payors may deny

Table of Contents

reimbursement if they determine that a medical product was not used in accordance with cost-effective treatment methods, as determined by the third-party payor, or was used for an unapproved indication. Third-party payors also may refuse to reimburse for experimental procedures and devices. Furthermore, because our programs are in the early stages of development, we are unable at this time to determine their cost-effectiveness and the level or method of reimbursement. Increasingly, the third-party payors who reimburse patients are requiring that drug companies provide them with predetermined discounts from list prices, and are challenging the prices charged for medical products. If the price we are able to charge for any products we develop is inadequate in light of our development and other costs, our profitability could be adversely affected.

We currently expect that any drugs we develop may need to be administered under the supervision of a physician. Under currently applicable law, drugs that are not usually self-administered may be eligible for coverage by the Medicare program if:

they are incidental to a physician's services;

they are reasonable and necessary for the diagnosis or treatment of the illness or injury for which they are administered according to accepted standard of medical practice;

they are not excluded as immunizations; and

they have been approved by the FDA.

We are subject to intense competition, and we may not compete successfully.

We and our strategic partners or licensees may be unable to compete successfully against our current or future competitors. Soft tissue sarcoma patients are typically treated with surgery followed by radiation therapy. For patients ineligible for surgery, radiation and/or chemotherapy is the only option. Doxorubicin is the only approved drug for treating soft tissue sarcoma patients who are ineligible for surgery and is often used in combination with radiation. The National Comprehensive Cancer Network also includes the use of ifosfamide, epirubicin, gemcitabine, dacarbazine and liposomal doxorubicin marketed in the United States as Doxil by Johnson & Johnson. GlaxoSmithKline's Votrient was approved in the United States and Europe in 2012 for the treatment of advanced soft tissue sarcomas following prior chemotherapy. There are other approaches to treating soft tissue sarcoma in late-stage clinical development, including Threshold Pharmaceuticals' TH-302 and trabectedin being co-developed by Johnson and Johnson and PharmaMar.

Patients with glioblastoma multiforme (GBM) generally undergo invasive brain surgery, although disease progression following surgery is nearly 100%. The front-line therapy for GBM following surgery is Temozolomide (Temodar®) in combination with radiation. Bevacizumab (Avastin®) has been approved for the treatment of GBM in patients failing Temodar®. Drugs in development to treat GBM include rindopepimut by Celldex Therapeutics, DCVax by Northwest Biotherapeutics, TRC105 from Tracoon Pharmaceuticals, and buparlisib by Novartis. Kaposi's sarcoma is generally treated with radiation, surgery and/or liposomal doxorubicin. Other drugs in development for Kaposi's sarcoma include selumetinib by AstraZeneca and pomalidamide by Celgene.

Many companies, including large pharmaceutical and biotechnology firms with financial resources, research and development staffs, and facilities that may be substantially greater than those of ours or our strategic partners or licensees, are engaged in the research and development of pharmaceutical products that could compete with our potential products. To the extent that we seek to acquire, through license or otherwise, existing or potential new products, we will be competing with numerous other companies, many of which will have substantially greater financial resources, large acquisition and research and development staffs that may give those companies a competitive advantage over us in identifying and evaluating these drug acquisition opportunities. Any products that we acquire will be competing with products marketed by companies that in many cases will have substantially greater marketing resources than we have. The industry is characterized by rapid technological advances and competitors may develop their products more rapidly and such products may be more effective than those currently under development or that may be developed in the future by our strategic partners or licensees. Competitive products for a number of the disease indications that we have targeted are currently being marketed by other parties, and additional competitive products are under development and may also include products currently under development that we are not aware of or products that may be developed in the future.

As a result, these competitors may:

succeed in developing competitive products sooner than us or our strategic partners or licensees;

obtain FDA or foreign governmental approvals for their products before we can obtain approval of any of our products;

obtain patents that block or otherwise inhibit the development and commercialization of our product candidate candidates;

develop products that are safer or more effective than our products;

devote greater resources than us to marketing or selling products;

introduce or adapt more quickly than us to new technologies and other scientific advances;

introduce products that render our products obsolete;

B-9

Table of Contents

withstand price competition more successfully than us or our strategic partners or licensees;

negotiate third-party strategic alliances or licensing arrangements more effectively than us; and

take better advantage than us of other opportunities.

We will be required to pay substantial milestone and other payments relating to the commercialization of our products.

The agreement relating to our worldwide rights to aldorubicin provides for our payment of an aggregate of \$7.5 million upon meeting specified clinical and regulatory milestones up to and including the product's second, final marketing approval. We also will be obliged to pay:

commercially reasonable royalties based on a percentage of net sales (as defined in the agreement);

a percentage of non-royalty sub-licensing income (as defined in the agreement); and

milestones of \$1,000,000 for each additional final marketing approval that we might obtain.

The agreements under which we have North American and European rights to tamibarotene provide for our payment of royalties based on net sales of any products, as well as aggregate payments of ¥ 490 million for North America and ¥ 480 million for Europe upon meeting specified clinical, regulatory and sales milestones up to and including the first commercial sale of tamibarotene for the treatment of APL.

Our agreement relating to our worldwide (except Japan) rights to bafetinib provides for our payment of an aggregate of \$13.35 million (including \$5 million upon the product's initial final marketing approval) upon the achievement of specified clinical and regulatory milestones up to and including approvals in the United States and Europe. We also will be obliged to pay:

commercially reasonable royalties based on a percentage of net sales (as defined in the agreement), dependent on reaching certain revenue thresholds;

annual minimum payments if sales of bafetinib do not meet specified levels; and

a percentage of non-royalty sub-licensing income (as defined in the agreement).

If we are required to pay any third party in order to exercise our rights under the agreement, we will deduct a percentage of those payments from the royalties due under the agreement, up to an agreed-upon cap.

Under the merger agreement by which we acquired Innovive, we agreed to pay the former Innovive stockholders a total of up to approximately \$18.3 million of future earnout merger consideration, subject to our achievement of

specified net sales under the Innovive license agreements. The earnout merger consideration, if any, will be payable in shares of our common stock, subject to specified conditions, or, at our election, in cash or by a combination of shares of our common stock and cash. Our common stock will be valued for purposes of any future earnout merger consideration based upon the trading price of our common stock at the time the earnout merger consideration is paid.

We are subject to potential liabilities from clinical testing and future product liability claims.

If any of our products are alleged to be defective, they may expose us to claims for personal injury by patients in clinical trials of our products or, if we obtain marketing approval and commercialize our products, by patients using our commercially marketed products. Even if one or more of our products is approved by the FDA, users may claim that such products caused unintended adverse effects. We maintain clinical trial insurance for our ongoing clinical trials, and we plan to seek to obtain similar insurance for any other clinical trials that we conduct. We also would seek to obtain product liability insurance covering the commercial marketing of our product candidates. We may not be able to obtain additional insurance, however, and any insurance obtained by us may prove inadequate in the event of a claim against us. Any claims asserted against us also may divert management's attention from our operations, and we may have to incur substantial costs to defend such claims even if they are unsuccessful.

We may be unable to successfully acquire additional technologies or products. If we require additional technologies or products, our product development plans may change and the ownership interests of our shareholders could be diluted.

We may seek to acquire additional technologies by licensing or purchasing such technologies, or through a merger or acquisition of one or more companies that own such technologies. We have no current understanding or agreement to acquire any technologies, however, and we may not be able to identify or successfully acquire any additional technologies. We also may seek to acquire products from third parties that already are being marketed or have been approved for marketing, although we have not currently identified any of these products. We do not have any prior experience in acquiring or marketing products approved for marketing and may need to find third parties to market any products that we might acquire.

Table of Contents

We have focused our product development efforts on our oncology drug candidates, which we believe have the greatest revenue potential. If we acquire additional technologies or product candidates, we may determine to make further changes to our product development plans and business strategy to capitalize on opportunities presented by the new technologies and product candidates.

We may determine to issue shares of our common stock to acquire additional technologies or products or in connection with a merger or acquisition of another company. To the extent we do so, the ownership interest of our stockholders will be diluted accordingly.

We are conducting certain of our clinical trials in foreign countries, which exposes us to additional risks.

We are conducting international clinical development of aldoxorubicin. The conduct of clinical trials outside the United States could have a significant impact on us. Risks inherent in conducting international clinical trials include:

foreign regulatory requirements that could restrict or limit our ability to conduct our clinical trials;

administrative burdens of conducting clinical trials under multiple foreign regulatory schema;

foreign exchange fluctuations;

diminished protection of intellectual property in some countries; and

possible nationalization and expropriation.

In addition, there may be changes to our business and political position if there is instability, disruption or destruction in a significant geographic region, regardless of cause, including war, terrorism, riot, civil insurrection or social unrest, and natural or man-made disasters, including famine, flood, fire, earthquake, storm or disease, which could seriously harm the development of our current operating strategy.

In the event of a dispute regarding our international clinical trials, it may be necessary for us to resolve the dispute in the foreign country of dispute, where we would be faced with unfamiliar laws and procedures.

The resolution of disputes in foreign countries can be costly and time consuming, similar to the situation in the United States. However, in a foreign country, we face the additional burden of understanding unfamiliar laws and procedures. We may not be entitled to a jury trial, as we might be in the United States. Further, to litigate in any foreign country, we would be faced with the necessity of hiring lawyers and other professionals who are familiar with the foreign laws. For these reasons, we may incur unforeseen expenses if we are forced to resolve a dispute in a foreign country.

Risks Associated With Ownership of Our Common Stock

You may experience future dilution as a result of future equity offerings or other equity issuances.

To raise additional capital, we may in the future offer additional shares of our common stock, preferred stock or other securities convertible into or exchangeable for our common stock. We cannot assure you that we will be able to sell shares or other securities in any other offering at a price per share that is equal to or greater than the price per share paid by investors in this offering. The price per share at which we sell additional shares of our common stock or other securities convertible into or exchangeable for our common stock in future transactions may be higher or lower than the price per share in this offering.

We may experience volatility in our stock price, which may adversely affect the trading price of our common stock.

The market price of our common stock has ranged from a low of \$1.83 to a high of \$3.65 per share from January 1, 2013 through November 26, 2013, and it may continue to experience significant volatility from time to time. Factors that may affect the market price of our common stock include the following:

announcements of regulatory developments or technological innovations by us or our competitors;

changes in our relationship with our licensors and other strategic partners;

our quarterly operating results;

litigation involving or affecting us;

shortfalls in our actual financial results compared to our guidance or the forecasts of stock market analysts;

developments in patent or other technology ownership rights;

Table of Contents

acquisitions or strategic alliances by us or our competitors;

public concern regarding the safety of our products; and

government regulation of drug pricing.

Our outstanding options and warrants and the availability for resale of the underlying shares may adversely affect the trading price of our common stock.

As of September 30, 2013, there were outstanding stock options to purchase approximately 3.4 million shares of our common stock at a weighted-average exercise price of \$4.15 per share and outstanding warrants to purchase approximately 1.6 million shares of common stock at a weighted-average exercise price of \$6.58 per share. Our outstanding options and warrants could adversely affect our ability to obtain future financing or engage in certain mergers or other transactions, since the holders of options and warrants can be expected to exercise them at a time when we may be able to obtain additional capital through a new offering of securities on terms more favorable to us than the terms of outstanding options and warrants. For the life of the options and warrants, the holders have the opportunity to profit from a rise in the market price of our common stock without assuming the risk of ownership. The issuance of shares upon the exercise of outstanding options and warrants will also dilute the ownership interests of our existing stockholders.

We have registered with the SEC the resale by the holders of all or substantially all shares of our common stock issuable upon exercise of our outstanding options and warrants. The availability of these shares for public resale, as well as any actual resales of these shares, could adversely affect the trading price of our common stock.

Our anti-takeover measures may make it more difficult to change our management, or may discourage others from acquiring us, and thereby adversely affect stockholder value.

We have a stockholder rights plan and provisions in our bylaws that are intended to protect our stockholders' interests by encouraging anyone seeking control of our company to negotiate with our board of directors. These provisions may discourage or prevent a person or group from acquiring us without the approval of our board of directors, even if the acquisition would be beneficial to our stockholders.

We have a classified board of directors, which means that at least two stockholder meetings, instead of one, will be required to effect a change in the majority control of our board of directors. This applies to every election of directors, not just an election occurring after a change in control. The classification of our board increases the amount of time it takes to change majority control of our board of directors and may cause potential acquirers to lose interest in a potential purchase of us, regardless of whether our purchase would be beneficial to us or our stockholders. The additional time and cost to change a majority of the members of our board of directors makes it more difficult and may discourage our existing stockholders from seeking to change our existing management in order to change the strategic direction or operational performance of our company.

Our bylaws provide that directors may only be removed for cause by the affirmative vote of the holders of at least a majority of the outstanding shares of our capital stock then entitled to vote at an election of directors. This provision prevents stockholders from removing any incumbent director without cause. Our bylaws also provide that a stockholder must give us at least 120 days notice of a proposal or director nomination that such stockholder desires to present at any annual meeting or special meeting of stockholders. Such provision prevents a stockholder from making a proposal or director nomination at a stockholder meeting without us having advance notice of that proposal or

director nomination. This could make a change in control more difficult by providing our directors with more time to prepare an opposition to a proposed change in control. By making it more difficult to remove or install new directors, these bylaw provisions may also make our existing management less responsive to the views of our stockholders with respect to our operations and other issues such as management selection and management compensation.

We are subject to the anti-takeover provisions of Section 203 of the Delaware General Corporation Law, which may also prevent or delay a takeover of us that may be beneficial to our stockholders.

Our amended and restated by-laws designate the Court of Chancery of the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders ability to obtain a favorable judicial forum for disputes with us or our directors, officers or other employees.

Our amended and restated by-laws provide that, unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for (i) any derivative action or proceeding brought on our behalf, (ii) any action asserting a claim of breach of a fiduciary duty owed by any director, officer or other employee to us or our stockholders, (iii) any action asserting a claim arising pursuant to any provision of the Delaware General Corporation Law, or (iv) any action asserting a claim that is governed by the internal affairs doctrine. Any person purchasing or otherwise acquiring any interest in any

Table of Contents

shares of our capital stock shall be deemed to have notice of and to have consented to this provision of our amended and restated by-laws. This choice-of-forum provision may limit our stockholders' ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits. Alternatively, if a court were to find this provision of our amended and restated by-laws inapplicable or unenforceable with respect to one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business and financial condition.

We may issue preferred stock in the future, and the terms of the preferred stock may reduce the value of our common stock.

We are authorized to issue shares of preferred stock in one or more series. Our board of directors may determine the terms of future preferred stock offerings without further action by our stockholders. If we issue preferred stock, it could affect your rights or reduce the value of our outstanding common stock. In particular, specific rights granted to future holders of preferred stock may include voting rights, preferences as to dividends and liquidation, conversion and redemption rights, sinking fund provisions, and restrictions on our ability to merge with or sell our assets to a third party.

We do not expect to pay any cash dividends on our common stock.

We have not declared or paid any cash dividends on our common stock or other securities, and we currently do not anticipate paying any cash dividends in the foreseeable future. Because we do not anticipate paying cash dividends for the foreseeable future, our stockholders will not realize a return on their investment in our common stock except to the extent of any appreciation in the value of our common stock. Our common stock may not appreciate in value, or may decline in value.

USE OF PROCEEDS

Unless we state otherwise in the accompanying prospectus supplement, we intend to use the net proceeds from the sale of securities offered by this prospectus for working capital and general corporate purposes, including the clinical trials of our product candidates. General corporate purposes also may include repayment of our existing indebtedness, financing of capital expenditures and future acquisitions and strategic investments.

We have not determined the amounts we plan to spend on any of the areas listed above or the timing of these expenditures. As a result, our management will have broad discretion to allocate the net proceeds from this offering. Pending application of the net proceeds as described above, we expect to invest the net proceeds in short-term, interest-bearing, investment-grade securities pursuant to our investment policy.

FINANCIAL RATIOS

The following table sets forth our ratio of earnings, if any, to fixed charges for each of the periods presented:

Year Ended December 31	Three Months Ended September 30,
-------------------------------	---

	2008	2009	2010	2011	2012	2013
Ratio of earnings to fixed charges (1)(2)						
Deficiency of earnings available to cover fixed charges	N/A	N/A	N/A	N/A	N/A	N/A

(1) *Fixed charges*. The term *fixed charges* means the sum of the following, if any: (a) interest expensed and capitalized, (b) amortized premiums, discounts and capitalized expenses related to indebtedness, (c) an estimate of the interest within rental expense, and (d) preference security dividend requirements of consolidated subsidiaries.

Earnings. The term *earnings* is the amount resulting from adding and subtracting the following items, if any: Add the following: (a) pre-tax income from continuing operations before adjustment for income or loss from equity investees; (b) fixed charges; (c) amortization of capitalized interest; (d) distributed income of equity investees; and (e) our share of pre-tax losses of equity investees for which charges arising from guarantees are included in fixed charges. From the total of the added items, subtract

Table of Contents

the following: (a) interest capitalized; (b) preference security dividend requirements of consolidated subsidiaries; and (c) the noncontrolling interest in pre-tax income of subsidiaries that have not incurred fixed charges. Equity investees are investments that we account for using the equity method of accounting. The ratio of earnings to fixed charges is computed by dividing earnings by fixed charges as defined below, respectively.

- (2) Our net losses were insufficient to cover fixed charges in the periods indicated. For this reason, the ratio information is not applicable.

DIVIDEND POLICY

Our board of directors sets our dividend policy. We have never paid any cash dividends on our common stock and do not intend to declare cash dividends on our common stock in the foreseeable future. We currently intend to retain all available funds and any future earnings for use in the operation and expansion of our business, but we may determine in the future to declare or pay cash dividends on our common stock. Any future determination as to the declaration and payment of dividends will be at the discretion of our board of directors and will be dependent upon our results of operations and cash flows, our financial position and capital requirements, general business conditions, legal, tax, regulatory and any contractual restrictions on the payment of dividends, and any other factors our board of directors deems relevant.

THE SECURITIES THAT WE MAY OFFER

We, directly or through agents, dealers or underwriters designated from time to time, may offer, issue and sell, together or separately, up to \$100,000,000 in the aggregate of:

shares of our common stock, par value \$.001 per share;

shares of our preferred stock, par value \$.01 per share;

warrants to purchase our common stock or preferred stock; and

any combination of the securities listed above, separately or as units, each on terms to be determined at the time of sale.

The common stock, preferred stock, warrants and units collectively are referred to in this prospectus as the securities.

We have summarized below the material terms of the various types of securities that we may offer. We will describe in the applicable prospectus supplement the detailed terms of the securities offered by that supplement. If indicated in the prospectus supplement, the terms of the offered securities may differ from the terms summarized below.

DESCRIPTION OF CAPITAL STOCK

As of November 26, 2013, our authorized capital stock consisted of 250,000,000 shares of common stock, \$.001 par value per share, of which 41,975,412 shares were outstanding (exclusive of treasury shares), and 5,000,000 shares of

preferred stock, \$.01 par value per share, none of which was outstanding.

The following summary of certain provisions of our common and preferred stock does not purport to be complete. You should refer to our amended and restated certificate of incorporation and our restated bylaws, which are filed with or incorporated by reference in the registration statement relating to this offering filed by us with the SEC. The summary below is also qualified by reference to the provisions of applicable Delaware corporation law.

Common Stock

Holders of our common stock are entitled to one vote per share on matters on which our stockholders vote, including with respect to the election of directors. Holders of common stock are entitled to receive dividends, if declared by our board of directors, out of funds that we may legally use to pay dividends. See the section of this prospectus entitled **Dividend Policy** for further information. If we liquidate or dissolve, holders of common stock are entitled to share ratably in our assets once our debts and any liquidation preference owed to holders of any then-outstanding preferred stock are paid. No shares of preferred stock will be outstanding immediately after the closing of this offering. All shares of common stock that are outstanding as of the date of this prospectus supplement are, and all shares we are selling in this offering, upon their issuance and sale, will be, fully-paid and nonassessable.

B-14

Table of Contents

Preferred Stock

We are currently authorized to issue 5,000,000 shares of preferred stock, of which 25,000 shares have been designated as Series A Junior Participating Preferred Stock. We have reserved all of the shares of our Series A Junior Participating Preferred Stock for issuance upon the exercise of the rights under our Shareholder Protection Rights Agreement described below.

Our board of directors has the authority to issue shares of preferred stock in one or more series and to fix the rights of each series. These rights may include dividend rights, dividend rates, conversion rights, voting rights, terms of redemption, redemption prices, liquidation preferences, sinking fund terms, and the number of shares that constitute any series. The board of directors may exercise this authority without any further action by our stockholders.

Our board of directors will fix the rights, preferences, privileges, qualifications and restrictions of the preferred stock of each series that we sell under this prospectus in the certificate of designation relating to each such series. We will incorporate by reference as an exhibit to the registration statement of which this prospectus is a part or as an exhibit to one or more current reports on Form 8-K, the form of any certificate of designation that describes the terms of the series of preferred stock we are offering before the issuance of the related series of preferred stock. This description will include:

the title and stated value;

the number of shares we are offering;

the liquidation preference per share;

the purchase price per share;

the dividend rate per share, dividend period, payment date or dates and method of calculation of dividends;

whether dividends will be cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;

our right, if any, to defer payment of dividends and the maximum length of any such deferral period;

the procedures for any auction and remarketing, if any;

the provisions for a sinking fund, if any;

the provisions for redemption or repurchase, if applicable, and any restrictions on our ability to exercise those redemption and repurchase rights;

any listing of the preferred stock on any securities exchange or market;

whether the preferred stock will be convertible into our common stock or other securities of ours, including warrants, and, if applicable, the conversion price, or how it will be calculated, and under what circumstances and the mechanism by which it may be adjusted, and the conversion period;

whether the preferred stock will be exchangeable into debt securities or other securities of ours, and, if applicable, the exchange price, or how it will be calculated, and under what circumstances it may be adjusted, and the exchange period;

voting rights, if any;

preemptive rights, if any;

restrictions on transfer, sale or other assignment, if any;

a discussion of any material United States federal income tax considerations applicable to the preferred stock;

the relative ranking and preferences of the preferred stock as to dividend rights and rights if we liquidate, dissolve or wind up our affairs;

any limitations on issuances of any class or series of preferred stock ranking senior or on a parity with the series of preferred stock being issued as to dividend rights and rights if we liquidate, dissolve or wind up our affairs; and

any other specific terms, rights, preferences, privileges, qualifications or limitations of, or restrictions on, the preferred stock.

If we issue and sell shares of preferred stock pursuant to this prospectus, the shares will be fully paid and nonassessable and will not have, or be subject to, any preemptive or similar rights.

The laws of the State of Delaware, the state of our incorporation, provide that the holders of preferred stock will have the right to vote separately as a class on any proposal involving fundamental changes in the rights of holders of such preferred stock. This right is in addition to any voting rights that may be provided for in the applicable certificate of designation.

B-15

Table of Contents

We believe the power to issue preferred stock will provide our board of directors with flexibility in connection with certain possible corporate transactions. The issuance of preferred stock, however, could adversely affect the voting power of holders of our common stock, restrict their rights to receive payment upon liquidation, and have the effect of delaying, deferring, or preventing a change in control which may be beneficial to our stockholders.

Anti-Takeover Measures

Delaware Law

Section 203 of the Delaware General Corporation Law is applicable to takeovers of certain Delaware corporations, including us. Subject to exceptions enumerated in Section 203, Section 203 provides that a corporation shall not engage in any business combination with any interested stockholder for a three-year period following the date that the stockholder becomes an interested stockholder unless:

prior to that date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;

upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, though some shares may be excluded from the calculation; or

on or subsequent to that date, the business combination is approved by the board of directors of the corporation and by the affirmative votes of holders of at least two-thirds of the outstanding voting stock that is not owned by the interested stockholder.

Except as specified in Section 203, an interested stockholder is generally defined to include any person who, together with any affiliates or associates of that person, beneficially owns, directly or indirectly, 15% or more of the outstanding voting stock of the corporation, or is an affiliate or associate of the corporation and was the owner of 15% or more of the outstanding voting stock of the corporation, any time within three years immediately prior to the relevant date. Under certain circumstances, Section 203 makes it more difficult for an interested stockholder to effect various business combinations with a corporation for a three-year period, although the stockholders may elect not to be governed by this section, by adopting an amendment to the certificate of incorporation or by-laws, effective 12 months after adoption. Our amended and restated certificate of incorporation and by-laws do not opt out from the restrictions imposed under Section 203. We anticipate that the provisions of Section 203 may encourage companies interested in acquiring us to negotiate in advance with the board because the stockholder approval requirement would be avoided if a majority of the directors then in office excluding an interested stockholder approve either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder. These provisions may have the effect of deterring hostile takeovers or delaying changes in control, which could depress the market price of our common stock and deprive stockholders of opportunities to realize a premium on shares of common stock held by them.

Table of Contents

Charter and By-Law Provisions

In addition to the board of directors' ability to issue shares of preferred stock, our amended and restated certificate of incorporation and restated by-laws contain the following provisions that may have the effect of discouraging unsolicited acquisition proposals:

our restated by-laws classify the board of directors into three classes with staggered three-year terms;

under our restated by-laws, our board of directors may enlarge the size of the board and fill the vacancies;

our restated by-laws provide that a stockholder may not nominate candidates for the board of directors at any annual or special meeting unless that stockholder notifies us of its intention a specified period in advance and provides us with certain required information;

stockholders who wish to bring business before the stockholders at our annual meeting must provide advance notice; and

our restated by-laws provide that special meetings of stockholders may only be called by our board of directors or by an officer so instructed by our board.

Our restated by-laws also provide that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for:

any derivative action or proceeding brought on our behalf;

any action asserting a claim of breach of a fiduciary duty owed by any director, officer or other employee of the company to us or our stockholders;

any action asserting a claim arising pursuant to any provision of the Delaware General Corporation Law; or

any action asserting a claim governed by the internal affairs doctrine.

Our restated by-laws further provide that any person or entity purchasing or otherwise acquiring any interest in shares of capital stock of the company is deemed to have notice of and consented to the foregoing provision.

Shareholder Protection Rights Agreement

Our board of directors adopted a Shareholder Protection Rights Agreement, or Rights Agreement, dated April 16, 1997, as amended, between us and American Stock Transfer & Trust Co., as Rights Agent. The Rights Agreement will expire on April 16, 2017, unless renewed or extended by our board of directors. A series of our preferred stock, designated as Series A Junior Participating Preferred Stock, par value \$.01 per share, was created in accordance with the Rights Agreement. The Rights Agreement is designed to deter coercive takeover tactics, including the accumulation of shares in the open market or through private transactions, and to prevent an acquirer from gaining control of us without offering a fair and adequate price and terms to all of our stockholders. As such, the Rights Agreement is intended to enhance our board of directors' ability to protect stockholder interests and help to assure that stockholders receive fair and equal treatment in the event any proposed takeover of CytRx is made in the future. Pursuant to the Rights Agreement, our board of directors declared a dividend distribution of one preferred stock purchase right for each outstanding share of our common stock. The preferred stock purchase rights are attached to, and trade with, our common stock. The purchase rights are exercisable only upon the occurrence of certain triggering events described in the Rights Agreement.

Transfer Agent

The transfer agent for our common stock is American Stock Transfer & Trust Company, 40 Wall Street, New York, New York 10005.

DESCRIPTION OF WARRANTS

We may offer and issue warrants to purchase shares of our common stock or preferred stock. The warrants may be issued independently or as a part of units consisting of shares of our common stock or preferred stock and warrants to purchase additional shares of our common stock or preferred stock. If the warrants are issued pursuant to warrant agreements, we will so specify in the prospectus supplement relating to the warrants being offered pursuant to the prospectus supplement.

The following description will apply to the warrants offered by this prospectus unless we provide otherwise in the applicable prospectus supplement. The applicable prospectus supplement for a particular series of warrants may specify different or additional terms. The forms of any warrant certificates or warrant agreements evidencing the warrants that we issue will be filed with the SEC and incorporated by reference into this prospectus, and you should carefully review such documents.

Table of Contents

The prospectus supplement will describe the following terms of warrants to purchase our common stock, preferred stock or debt securities to the extent applicable:

the title of the warrants;

the common stock or preferred stock for which the warrants are exercisable;

the price at which the warrants will be issued and the exercise price of the warrants;

the aggregate number of warrants offered;

the number of shares of common stock or preferred stock that may be purchased upon the exercise of each warrant;

whether the warrants are being offered separately or as a part of units consisting of shares of our common stock or preferred stock and warrants to purchase additional shares of our common stock or preferred stock;

the terms of any right by us to redeem the warrants;

the date on which the right to exercise the warrants will commence and the date on which this right will expire;

the procedures for exercising the warrants;

the terms on which the warrants may be amended;

the terms of any adjustments in the warrant exercise price and the number of shares of common stock or preferred stock purchasable upon the exercise of each warrant to be made in certain events, including the issuance of a stock dividend to holders of common stock or preferred stock or a stock split, reverse stock split, combination, subdivision or reclassification of common stock;

the effect on the warrants of our merger or consolidation with another entity or our sale of all or substantially all of our assets;

the maximum or minimum number of warrants which may be exercised at any time; and

the material United States federal income tax consequences applicable to the warrants and their exercise.

Holders of warrants to purchase common stock or preferred stock will not be entitled, by virtue of being such holders, to vote, consent, receive dividends, receive notice as stockholders with respect to any meeting of stockholders for the election of our directors or any other matter, or to exercise any rights whatsoever as our stockholders.

Warrants may be exercised at any time up to the close of business on the expiration date set forth in the prospectus supplement relating to the warrants offered thereby. After the close of business on the expiration date, unexercised warrants will become void. Upon our receipt of the exercise price of the warrants upon the due exercise of the warrants, we will, as soon as practicable, forward the securities purchasable upon exercise. If less than all of the warrants represented by such warrant certificate are exercised, a new warrant certificate will be issued for the remaining warrants.

DESCRIPTION OF UNITS

We may offer and issue units that consist of shares of our common stock or preferred stock and warrants to purchase additional shares of our common stock or preferred stock. For example, we may elect to issue units for a specified price per unit, with each unit consisting of one share of our common stock or preferred stock and one warrant to purchase an additional share of our common stock or preferred stock at a specified price. The holder of a unit will also hold each of the securities that is included in the unit.

We have provided in the preceding sections of this prospectus a general description of our common stock, preferred stock, and warrants that we may offer. If we elect to offer units, we will describe the specific terms of the units in a supplement to this prospectus. Among other things, the prospectus supplement will describe, to the extent applicable:

the price of each unit;

the securities comprising each unit;

the exercise price of the warrants comprising part of the units;

the aggregate number of units offered;

the number of shares of common stock or preferred stock that may be purchased upon the exercise of each warrant comprising part of a unit;

the terms of any right by us to redeem any of the securities comprising the units;

Table of Contents

the date on which the right to exercise the warrants forming part of the units will commence and the date on which this right will expire;

any transfer restrictions on the units, including whether the securities comprising the units may be transferred separately;

the terms on which the units or warrants forming part of the units may be amended;

with respect to preferred stock forming part of the units, the other matters listed above under Description of Capital Stock Preferred Stock ;

with respect to warrants forming part of the units, the other matters listed above under Description of Warrants ; and

the material United States federal income tax consequences applicable to the units.

PLAN OF DISTRIBUTION

We may sell the securities being offered hereby in one or more of the following ways from time to time:

through agents to the public or to investors;

to one or more underwriters for resale to the public or to investors;

in at the market offerings, within the meaning of Rule 415(a)(4) of the Securities Act of 1933, as amended, or the Securities Act, to or through a market maker or into an existing trading market, on an exchange or otherwise;

directly to investors; or

through a combination of these methods of sale.

We will set forth in a prospectus supplement the terms of an offering of shares of our securities, including.

the name or names of any agents or underwriters;

the purchase price of the securities being offered and the proceeds we will receive from the sale;

any over-allotment options under which underwriters may purchase additional securities from us;

any agency fees or underwriting discounts and other items constituting agents' or underwriters' compensation;

the public offering price; and

any discounts or concessions allowed or reallocated or paid to dealers.

We may distribute the securities from time to time in one or more transactions;

at a fixed price or prices, which may be changed;

at market prices prevailing at the time of sale;

at prices related to such prevailing market prices; or

at negotiated prices.

We may also, from time to time, authorize dealers, acting as our agents, to offer and sell securities upon the terms and conditions set forth in the applicable prospectus supplement. We, or the purchasers of securities for whom the underwriters may act as agents, may compensate underwriters in the form of underwriting discounts or commissions, in connection with the sale of securities. Underwriters may sell the securities to or through dealers, and those dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters or commissions from the purchasers for whom they may act as agent. Unless otherwise indicated in a prospectus supplement, an agent will be acting on a "best efforts" basis and a dealer will purchase securities as a principal, and may then resell the common stock at varying prices to be determined by the dealer.

We will describe in the applicable prospectus supplement any compensation we will pay to underwriters or agents in connection with the offering of securities, and any discounts, concessions or commissions allowed by underwriters to participating dealers. The dealers and agents participating in the distribution of securities may be deemed to be underwriters, and any discounts and commissions received by them and any profit realized by them on resale of the securities may be deemed to be underwriting discounts and commissions. We may enter into agreements to indemnify underwriters, dealers and agents against certain civil liabilities, including liabilities under the Securities Act and to reimburse these persons for certain expenses. We may grant underwriters who participate in the distribution of securities we are offering under this prospectus an option to purchase additional shares to cover over-allotments, if any, in connection with the distribution.

Table of Contents

To facilitate the offering of securities, certain persons participating in the offering may engage in transactions that stabilize, maintain, or otherwise affect the price of the securities. This may include over-allotments or short sales of the securities, which involve the sale by persons participating in the offering of more securities than we sold to them. In these circumstances, these persons would cover such over-allotments or short positions by making purchases in the open market or by exercising their over-allotment option, if any. In addition, these persons may stabilize or maintain the price of the securities by bidding for or purchasing securities in the open market or by imposing penalty bids, whereby selling concessions allowed to dealers participating in the offering may be reclaimed if securities sold by them is repurchased in connection with stabilization transactions. The effect of these transactions may be to stabilize or maintain the market price of the securities at a level above that which might otherwise prevail in the open market. These transactions may be discontinued at any time.

Any underwriters who are qualified market makers on the Nasdaq Capital Market may engage in passive market making transactions in the securities on the Nasdaq Capital Market in accordance with Rule 103 of Regulation M, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the securities. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker's bid, however, the passive market maker's bid must then be lowered when certain purchase limits are exceeded.

Certain underwriters, dealers or agents and their associates may engage in transactions with and perform services for us in the ordinary course of our business.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at <http://www.sec.gov>. The SEC's website contains reports, proxy and information statements and other information regarding issuers such as us that file electronically with the SEC. You may also read and copy any document we file with the SEC at the SEC's Public Reference Room at 100 F Street, N.E., Room 1580, Washington, D.C. 20549, and may obtain copies of these documents at prescribed rates by writing to the SEC. Please call the SEC at 1-800-SEC-0330 for further information on the operation of its Public Reference Room.

Information about us is also available at our website at www.cytrx.com; however, information on our website is not incorporated into this prospectus and is not a part of this prospectus.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to incorporate by reference the information we have filed with it, which means that we can disclose important information to you by referring you to another document that we have filed separately with the SEC. You should read the information incorporated by reference because it is an important part of this prospectus. Any statement in a document we incorporate by reference into this prospectus will be considered to be modified or superseded to the extent a statement contained in this prospectus or any other subsequently filed document that is incorporated by reference into this prospectus modifies or supersedes that statement. The modified or superseded statement will not be considered to be a part of this prospectus, except as modified or superseded.

We incorporate by reference the following information or documents that we have filed with the SEC (excluding those portions of any Form 8-K that are not deemed filed pursuant to the General Instructions of Form 8-K):

our Annual Report on Form 10-K for the year ended December 31, 2012;

our Quarterly Reports on Form 10-Q for the quarterly periods ended March 31, 2013, June 30, 2013 and September 30, 2013, respectively;

our Current Reports on Form 8-K filed with the SEC on January 3, 2013, March 11, 2013, May 9, 2013, July 16, 2013, August 6, 2013, October 9, 2013 and October 29, 2013, respectively;

the description of our securities as described in our Registration Statement on Form 8-A filed under the Exchange Act on March 17, 1987 (File No. 0 15327), and any amendment or report filed for the purpose of updating any such description; and

the description of our Series A Junior Participating Preferred Stock Purchase Rights as described in our Registration Statement on Form 8-A filed under the Exchange Act on April 17, 1997 (File No. 000 15327), and any amendment or report filed for the purpose of updating any such descriptions.

B-20

Table of Contents

We also incorporate by reference all documents filed pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus and prior to the termination of this offering (excluding those portions of any Form 8-K that are not deemed filed pursuant to the General Instructions of Form 8-K).

Statements made in this prospectus or in any document incorporated by reference in this prospectus as to the contents of any contract or other document referred to herein or therein are not necessarily complete, and in each instance reference is made to the copy of such contract or other document filed as an exhibit to the documents incorporated by reference, each such statement being qualified in all material respects by such reference.

You may obtain a copy of the foregoing documents from us without charge by writing or calling us at the following address and telephone number: 11726 San Vicente Blvd., Suite 650 Los Angeles, California 90049, Attention: Corporate Secretary; (310) 826-5648.

LEGAL MATTERS

The validity of the securities being offered hereby has been passed upon for us by TroyGould PC, Los Angeles, California.

EXPERTS

The consolidated financial statements and schedules as of December 31, 2012 and 2011 and for each of the three years in the period ended December 31, 2012 and management's assessment of the effectiveness of internal control over financial reporting as of December 31, 2012 incorporated by reference in this prospectus have been so incorporated in reliance on the reports of BDO USA, LLP, an independent registered public accounting firm, incorporated herein by reference, given on the authority of said firm as experts in auditing and accounting.

B-21

Table of Contents

PROSPECTUS

\$100,000,000

The date of this prospectus is , 2013

Table of Contents**PART II****INFORMATION NOT REQUIRED IN PROSPECTUS****ITEM 14. OTHER EXPENSES OF ISSUANCE AND DISTRIBUTION**

We estimate that the expenses incurred in connection with the distribution described in this registration statement will be as set forth below. We will bear all of such expenses.

SEC registration fee	\$ 16,597
Transfer agent fees and expenses	\$ 10,000*
Nasdaq Capital Market listing fees	\$ 50,000*
FINRA corporate filing fees	\$ 0*
Accounting fees and expenses	\$ 50,000*
Legal fees and expenses	\$ 75,000*
Printing expenses	\$ 30,000*
Miscellaneous	\$ 8,403*
Total	\$ 240,000*

* Estimated expenses, if any, not presently known.

ITEM 15. INDEMNIFICATION OF DIRECTORS AND OFFICERS

Section 102(b)(7) of the Delaware General Corporation Law authorizes a corporation in its certificate of incorporation to eliminate or limit personal liability of directors of the corporation for violations of the directors' fiduciary duty of care. However, directors remain liable for breaches of duties of loyalty, failing to act in good faith, engaging in intentional misconduct, knowingly violating a law, paying a dividend or approving a stock repurchase which was illegal under Delaware General Corporation Law Section 174 or obtaining an improper personal benefit. In addition, equitable remedies for breach of fiduciary duty of care, such as injunction or recession, are available.

Our amended and restated certificate of incorporation eliminates the personal liability of the members of our board of directors to the fullest extent permitted by law. Specifically, Article Eleven of our amended and restated certificate of incorporation provides as follows:

A director of the corporation shall not be personally liable to the corporation or its stockholders for monetary damages for breach of fiduciary duty as a director, except for liability (i) for any breach of the director's duty of loyalty to the corporation or its stockholders, (ii) for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) under Section 174 of the Delaware General Corporation Law, or (iv) for any transaction from which the director derived any improper personal benefit. If the Delaware General Corporation Law is amended after approval by the stockholders of this Article to authorize corporate action further eliminating or limiting the personal liability of directors, then the liability of a director of the corporation shall be eliminated or limited to the fullest extent permitted by the Delaware General Corporation Law as so amended.

Any repeal or modification of the foregoing paragraph by the stockholders of the corporation shall not adversely affect any right or protection of a director of the corporation existing at the time of such repeal or modification.

In addition, our amended and restated certificate of incorporation and restated by-laws provide for indemnification of our officers and directors to the fullest extent permitted by law. In particular, Article Nine of our amended and restated certificate of incorporation provides as follows:

The corporation shall, to the fullest extent permitted by Section 145 of the General Corporation Law of the State of Delaware, as the same may be amended and supplemented, indemnify any and all persons whom it shall have power to indemnify under said section from and against any and all of the expenses, liabilities or other matters referred to in or covered by said section, and the indemnification provided for herein shall not be deemed exclusive of any other rights to which those indemnified may be entitled under any bylaw, agreement, vote of stockholders or disinterested directors or otherwise, both as to action in his official capacity and as to action in another capacity while holding such office, and shall continue as to a person who has ceased to be a director, officer, employee or agent and shall inure to the benefit of the heirs, executors and administrators of such a person.

Section 145 of the Delaware General Corporation Law empowers a corporation to indemnify any person who was or is party or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative, by reason of the fact that he is or was a director, officer or agent of the corporation or another enterprise if serving at the request of the corporation. Depending on the character of the proceeding, a corporation may indemnify

Table of Contents

against expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred in connection with such action, suit or proceeding if the person indemnified acted in good faith in respect to any criminal action or proceeding, had no reasonable cause to believe his conduct was unlawful. In the case of an action by or in the right of the corporation, no indemnification may be made with respect to any claim, issue or matter as to which such person shall have been adjudged to be liable to the corporation unless and only to the extent that the Court of Chancery or the court in which such action or suit was brought shall determine that despite the adjudication of liability such person is fairly and reasonably entitled to indemnity for such expenses which the court shall deem proper. Section 145 further provides that to the extent a director, officer, employee or agent of a corporation has been successful in the defense of any action, suit or proceeding referred to above or in the defense of any claim, issue or matter therein, he shall be indemnified against expenses (including attorneys' fees) actually and reasonably incurred by him in connection therewith. Our restated by-laws permit us to purchase insurance on behalf of such person against any liability asserted against him and incurred by him in any such capacity, or arising out of his status as such, whether or not we would have the power to indemnify him against such liability under the foregoing provision of the restated by-laws.

We hold an insurance policy covering directors and officers under which the insurer agrees to pay, with some exclusions, for any claim made against our directors and officers for a wrongful act that they may become legally obligated to pay or for which we are required to indemnify our directors or officers.

Insofar as indemnification for liabilities arising under the Securities Act of 1933, as amended, or the Securities Act, may be permitted for directors, officers and controlling persons of the Company under the above provisions, or otherwise, the Commission has advised us that, in its opinion, such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Company of expenses incurred or paid by a director, officer or controlling person of the Company in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the Company will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

ITEM 16. EXHIBITS

The exhibits listed in the accompanying Exhibit Index are filed or incorporated by reference as part of this registration statement.

ITEM 17. UNDERTAKINGS

(a) The undersigned registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:

(i) To include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;

(ii) To reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental

change in the information set forth in the registration statement; notwithstanding the foregoing, any increase or decrease in the volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Securities and Exchange Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20 percent change in the maximum aggregate offering price set forth in the Calculation of Registration Fee table in the effective registration statement; and

(iii) To include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement; provided, however, that paragraphs (a)(1)(i), (a)(1)(ii) and (a)(1)(iii) of this section do not apply if the registration statement is on Form S-3 and the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Securities and Exchange Commission by the registrant pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in the registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is part of the registration statement.

(2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

Table of Contents

(4) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:

(i) Each prospectus filed by the registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and

(ii) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii), or (x) for the purpose of providing the information required by Section 10(a) of the Securities Act of 1933 shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof; provided, however, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is a part of the registration statement will, as to a purchaser with a time of contract sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was a part of the registration statement or made in any such document immediately prior to such effective date.

(5) That, for the purpose of determining liability of the registrant under the Securities Act of 1933 to any purchaser in the initial distribution of securities, the undersigned registrant undertakes that in a primary offering of securities of the undersigned registrant pursuant to this registration statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, the undersigned registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:

(i) Any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;

(ii) Any free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or used or referred to by the undersigned registrant;

(iii) The portion of any other free writing prospectus relating to the offering containing material information about the undersigned registrant or its securities provided by or on behalf of the undersigned registrant; and

(iv) Any other communication that is an offer in the offering made by the undersigned registrant to the purchaser.

(b) The undersigned registrant hereby undertakes that, for purposes of determining any liability under the Securities Act of 1933, each filing of the registrant's annual report pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934 and (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Securities Exchange Act of 1934) that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(c) Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public

policy as expressed in the Securities Act of 1933 and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act of 1933 and will be governed by the final adjudication of such issue.

Table of Contents**SIGNATURES**

Pursuant to the requirements of the Securities Act of 1933, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this Registration Statement on Form S-3 to be signed on its behalf by the undersigned, thereunto duly authorized in the City of Los Angeles, State of California, on November 27, 2013.

CYTRX CORPORATION

By: /s/ STEVEN A. KRIEGSMAN
 Steven A. Kriegsman
 President and Chief Executive Officer

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Steven A. Kriegsman as his true and lawful attorney-in-fact and agent, with full power of substitution, for him and in his name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this registration statement on Form S-3, and to sign any registration statement for the same offering covered by this registration statement that is to be effective upon filing pursuant to Rule 462(b) promulgated under the Securities Act of 1933, and all post-effective amendments thereto, and to file the same and all prospectus supplements, with all exhibits thereto and all documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorney-in-fact and agent full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully to all intents and purposes as he might or could do in person, hereby ratifying and confirming all that said attorney-in-fact and agent, or his substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, this registration statement has been signed by the following persons in the capacities and on the dates indicated:

Signature	Title	Date
/s/ STEVEN A. KRIEGSMAN Steven A Kriegsman	President and Chief Executive Officer and Director (principal executive officer)	November 27, 2013
/s/ JOHN Y. CALOZ John Y. Caloz	Chief Financial Officer and Treasurer (principal financial and accounting officer)	November 27, 2013
/s/ LOUIS J. IGNARRO Louis J. Ignarro, Ph.D.	Director	November 27, 2013

Edgar Filing: CYTRX CORP - Form S-3

/s/ MAX LINK	Director	November 27, 2013
Max Link		
/S/ JOSEPH RUBINFELD	Director	November 27, 2013
Joseph Rubinfeld		
/s/ MARVIN R. SELTER	Director	November 27, 2013
Marvin R. Selter		
/s/ RICHARD L. WINNEKAMP	Director	November 27, 2013
Richard L. Winnekamp		

II-4

Table of Contents**EXHIBIT INDEX**

The following exhibits are filed herewith or incorporated herein by reference.

Exhibit Number	Description
1.1	Form of Underwriting Agreement.*
3.1	Restated Certificate of Incorporation (incorporated by reference to Exhibit 3.1 to the Registrant's Annual Report on Form 10-K filed on April 1, 2008).
3.2	Restated By-Laws (incorporated by reference to Exhibit 4.2 to the Registrant's Registration Statement on Form S-8 (File No. 333-37171) filed on July 21, 1997).
4.1	Form of August 2011 Warrants (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K filed on July 27, 2011)
4.2	Shareholder Protection Rights Agreement dated April 16, 1997 between CytRx Corporation and American Stock Transfer & Trust Company as Rights Agent (incorporated by reference to Exhibit 99.1 to the Registrant's Current Report on Form 8-K filed April 17, 1997).
4.3	Amendment No. 1 to Shareholder Protection Rights Agreement (incorporated by reference to Exhibit 4.2 to the Registrant's Annual Report on Form 10-K filed on April 1, 2002).
4.4	Amendment No. 2 to Shareholder Protection Rights Agreement (incorporated by reference to Exhibit 4.3 to the Registrant's Annual Report on Form 10-K filed on April 2, 2007).
4.5	Form of Preferred Stock Certificate.*
4.6	Certificate of Designation regarding the rights, preferences, privileges and restrictions with respect to any preferred stock issued under this registration statement.*
4.7	Form of Warrant Agreement for Common Stock, including form of Warrant.*
4.8	Form of Warrant Agreement for preferred stock, including form of Warrant.*
4.9	Form of Unit Certificate.*
5.1	Opinion of TroyGould PC.
23.1	Consent of TroyGould PC (included in Exhibit 5.1).
23.2	Consent of BDO USA, LLP.
24.1	Power of Attorney (included on Page II-5).

* To be filed, if applicable, subsequent to the effectiveness of this registration statement (1) by an amendment to this registration statement or (2) as an exhibit to a Current Report on Form 8-K and incorporated herein by reference.