S Y BANCORP INC
Form 4
April 30, 2014

FORM 4

UNITED STATES SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP OF SECURITIES

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

OMB APPROVAL

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(Print or Type Responses)

1. Name and Address of Reporting Person *
TASMAN NORMAN

(Last) (First) (Middle)

14417 RIVER GLADES

(Street)

PROSPECT, KY 40059

(City) (State) (Zip)

2. Issuer Name **and** Ticker or Trading Symbol
S Y BANCORP INC [SYBT]

3. Date of Earliest Transaction (Month/Day/Year)
04/28/2014

4. If Amendment, Date Original Filed(Month/Day/Year)

5. Relationship of Reporting Person(s) to Issuer

(Check all applicable)

__X__ Director _____ 10% Owner
_____ Officer (give title below) _____ Other (specify below)

6. Individual or Joint/Group Filing(Check Applicable Line)
_X_ Form filed by One Reporting Person
___ Form filed by More than One Reporting Person

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1.Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	04/28/2014		P		169.347	A	$ 29.23	31,697.034	I	Trust-Directors' Deferred Comp Plan
Common Stock								62,722.294 (1)	D	
Common Stock								4,685	I	By Spouse
Common Stock								1,000	I	Trust - Tasman Industries Retirement Plan fbo Principal Owners

Common Stock		69,824.5	I	Reflects beneficial interest in shares owned by Hayfield Investment Partners, LLC

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

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SEC 1474 (9-02)

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned
(*e.g.*, puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4, and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Underlying Securities (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Nu Deriv Secur Bene Owne Follo Repo Trans (Instr
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares		

Reporting Owners

Reporting Owner Name / Address	Relationships			
	Director	10% Owner	Officer	Other
TASMAN NORMAN 14417 RIVER GLADES PROSPECT, KY 40059	X			

Signatures

//Norman Tasman	04/30/2014
**Signature of Reporting Person	Date

Explanation of Responses:

***** If the form is filed by more than one reporting person, *see* Instruction 4(b)(v).

****** Intentional misstatements or omissions of facts constitute Federal Criminal Violations. *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

(1) Includes shares acquired through dividend reinvestment plan.

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Forward Looking Statements

This Annual Report on Form 10-K and the documents incorporated by reference may contain, in addition to historical information, forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, or the Exchange Act. These statements relate to our future plans, objectives, expectations, intentions and financial performance, and assumptions that underlie these statements. All statements other than statements of historical fact are forward-looking statements for the purposes of these provisions, including:

- any statements regarding future operations, plans, regulatory filings or approvals;
- any statement regarding the performance, or likely performance, or outcomes or economic benefit of any licensing or other agreement, including any agreement with Novartis International Pharmaceutical Ltd., or Novartis, or its affiliates, including whether or not such partner will elect to participate, terminate or otherwise make elections under any such agreement or whether any regulatory authorizations required to enable such agreement will be obtained;
- any projections of cash resources, revenues, operating expenses or other financial terms;
- any statements of the plans and objectives of management for future operations or programs;
- any statements concerning proposed new products or services;
- any statements on plans regarding proposed or potential clinical trials or new drug filing strategies or timelines;
- any statements regarding pending or future mergers or acquisitions; and
- any statement regarding future economic conditions or performance, and any statement of assumption underlying any of the foregoing.

When used in this Annual Report on Form 10-K, terms such as anticipates, believes, continue, could, estimates, expects, intends, may, potential, predicts, should, or will or the negative of those terms or other comparable terms are intended to identify such forward-looking statements. These statements involve known and unknown risks, uncertainties and other factors that may cause industry trends or actual results, level of activity, performance or achievements to be materially different from any future results, levels of activity, performance or achievements expressed or implied by these statements. Our actual results may differ significantly from the results discussed in such forward-looking statements. These factors include, but are not limited to, those listed under Part I, Item I Business, Item 1A Risk Factors, Item 7 Management s Discussion and Analysis of Financial Condition and Results of Operations, and elsewhere in this Annual Report on Form 10-K.

We do not intend to update any of the forward-looking statements after the date of this Annual Report on Form 10-K to conform these statements to actual results or changes in our expectations. Readers are cautioned not to place undue reliance on these forward-looking statements, which apply only as of the date of this Annual Report on Form 10-K.

You may review a copy of this Annual Report on Form 10-K, including exhibits and any schedule filed therewith, and obtain copies of such materials at prescribed rates, at the U.S. Securities and Exchange Commission s, or the SEC, Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC maintains a website (http://www.sec.gov) that contains reports, proxy and information statements and other information regarding registrants, such as Cell Therapeutics, Inc., that file electronically with the SEC.

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PART I

Item 1. Business

Overview

We develop, acquire and commercialize novel treatments for cancer. Our goal is to build a leading biopharmaceutical company with a diversified portfolio of proprietary oncology drugs. Our research, development, acquisition and in-licensing activities concentrate on identifying and developing new, less toxic and more effective ways to treat cancer. We are currently focusing our efforts on pixantrone, OPAXIO, brostallicin and bisplantinates.

We are developing pixantrone, a novel anthracycline derivative, for the treatment of non-Hodgkin s lymphoma, or NHL, and various other hematologic malignancies, solid tumors and immunological disorders. Pixantrone was studied in our EXTEND, or PIX301, clinical trial, which is the first randomized, controlled, phase III single-agent clinical trial of pixantrone for patients with relapsed, aggressive NHL who received two or more prior therapies and who were sensitive to treatment with anthracyclines. In November 2008, we announced that this trial achieved the primary efficacy endpoint. Based on the outcome of the EXTEND trial and on the basis of a pre-New Drug Application, or NDA, communication we received from the U.S. Food and Drug Administration, or FDA, relating to this phase III trial, we began a rolling NDA submission to the FDA in April 2009. We completed the submission in June 2009 and we have been notified by the FDA that a Prescription Drug User Fee Act, or PDUFA, action date of April 23, 2010 under standard review has been established. Based on this PDUFA date, if pixantrone is approved, it could be available to patients in the United States as early as the second quarter of 2010.

The FDA s Oncologic Drugs Advisory Committee, or ODAC, was scheduled to review the NDA for pixantrone on February 10, 2010, however that meeting was postponed due to severe winter weather conditions in the Washington D.C. area. The FDA indicated that it intends to reschedule the meeting as soon as the FDA can determine a schedule that will allow them to reconvene the advisory panel. ODAC is an independent panel of experts that evaluates data concerning the efficacy and safety of marketed and investigational products for use in the treatment of cancer and makes recommendations to the FDA. The FDA regulations indicate that although the FDA will consider the recommendation of the panel, the final decision regarding the approval of the product is made by the FDA.

The results of the EXTEND trial showed that patients randomized to treatment with pixantrone achieved a significantly higher rate of confirmed and unconfirmed complete remissions compared to patients treated with standard chemotherapy, had a significantly increased overall response rate and experienced a statistically significant improvement in median progression free survival. Pixantrone was safely administered at the proposed dose and schedule in the PIX301 clinical trial in heavily pre-treated patients. The most common (incidence greater than or equal to 10%) grade 3/4 adverse events reported for pixantrone-treated subjects across the studies were neutropenia and leucopenia. Use of growth factor support was minimal. Other common adverse events (any grade) included infection, anemia, leucopenia, thrombocytopenia, asthenia, pyrexia, and cough. Overall, the incidence of grade 3 or greater cardiac adverse events was 7% (5 patients) on the pixantrone arm and 2% (1 patient) on the comparator arm. There were an equal number of deaths due to an adverse event in both the pixantrone and comparator arm.

We also conducted the RAPID, or PIX203, phase II clinical trial study (CHOP-R vs. CPOP-R) in which pixantrone is substituted for doxorubicin in the CHOP-R regimen compared to the standard CHOP-R regimen in patients with aggressive NHL. An interim analysis of the RAPID trial, reported in July 2007, showed that to date, a majority of patients on both arms of the study achieved a major objective anti-tumor response (complete response or partial response). Patients on the pixantrone arm of the study had clinically significant less left ventricular ejection fraction (LVEF) drops, infections, and thrombocytopenia (a reduction in platelets in the blood), as well as significant reduction in febrile neutropenia. In early 2008, we closed enrollment on the RAPID

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trial because we had adequate sample size to demonstrate differences in cardiac events and other clinically relevant side effects between pixantrone and doxorubicin. We expect to report results from the RAPID trial in mid-2010.

In July 2009, we were notified by the European Medicines Agency, or EMEA, that pixantrone is eligible to be submitted for a Marketing Authorization Application, or MAA, through the EMEA s centralized procedure. The centralized review process provides for a single coordinated review for approval of pharmaceutical products that is conducted by the EMEA on behalf of all European Union, or EU, member states. The EMEA also designated pixantrone as a New Active Substance, or NAS; if approved, compounds designated as an NAS receive a 10-year market exclusivity period in EU member states. In September 2009, we submitted a Pediatric Investigation Plan, or PIP, to the EMEA as part of the required filing process for approval of pixantrone for treating relapsed, aggressive NHL in Europe. Based upon feedback from European authorities, we are requesting a waiver from executing a PIP. In September 2009, we also applied to the EMEA for orphan drug designation for pixantrone which was granted in December 2009. We anticipate the formal MAA filing for pixantrone for the treatment of relapsed or refractory aggressive NHL in mid-2010.

We are currently focusing our development of OPAXIO (paclitaxel poliglumex), which we have previously referred to as XYOTAX, as a potential maintenance therapy for women with advanced stage ovarian cancer who achieve a complete remission following first-line therapy with paclitaxel and carboplatin. This study, the GOG0212 trial, is under the control of the Gynecologic Oncology Group, or GOG, and is expected to enroll 1,100 patients with over 600 patients enrolled to date. Given the expected rate of progression in the control (no treatment) arm and the 5 year duration of study enrollment to date, we requested that the Data Monitoring Committee, or DMC, perform an interim futility analysis examining progression free survival as a surrogate for overall survival. We made this request based on input from our external statistical expert who proposed a boundary for futility that, if exceeded, would predict a likely positive effect on overall survival at study conclusion. Alternatively if the boundary was not met then the likelihood of positive benefit on overall survival would be low, thus making further enrollment futile. The GOG informed us that, in closed session deliberation, the DMC denied our request and plans to conduct an interim analysis for overall survival which is projected to occur in 2011.

In June 2009, we announced that, in a study released from Brown University at the 2009 American Society for Clinical Oncology Annual Meeting, patients with cancer of the lower esophagus had evidence of a high pathological complete response rate when given OPAXIO in addition to cisplatin and full-course radiotherapy. In this phase II clinical trial study, preliminary data suggests that OPAXIO may provide enhanced radiation sensitization as compared to standard therapy. We plan to meet with the FDA in 2010 to explore a potential phase III registration study utilizing OPAXIO as a radiation sensitizer in the treatment of esophageal cancer.

In March 2008, we submitted an MAA to the EMEA for first-line treatment of patients with advanced non-small cell lung cancer, or NSCLC, who are poor performance status, or PS2, based on a non-inferior survival and improved side effect profile which we believe was demonstrated in our previous clinical trials. The application was based on a positive opinion we received from the EMEA s Scientific Advice Working Party, or SAWP; the EMEA agreed that switching the primary endpoint from superiority to non-inferiority was feasible if the retrospective justification provided in the marketing application was adequate. In September 2009, we notified the EMEA of our decision to withdraw the MAA and we refocused our resources on the approval of OPAXIO for its potential superiority indication in maintenance therapy for ovarian cancer and as a radiation sensitizer in the treatment of esophageal cancer.

We are also continuing to develop OPAXIO for women with pre-menopausal levels of estrogen, regardless of age, who have advanced NSCLC with normal or poor performance status. We believe the lack of safe and effective treatment for women with advanced first-line NSCLC, who have pre-menopausal estrogen levels, represents an unmet medical need. Based on a pooled analysis of STELLAR 3 and 4 phase III trials for treatment of first-line NSCLC PS2 patients, we believe that there is a demonstrated statistically significant survival

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advantage among women receiving OPAXIO when compared to women or men receiving standard chemotherapy. A survival advantage for women over men was also demonstrated in a first-line phase II clinical trial of OPAXIO and carboplatin, known as the PGT202 trial, supporting the potential benefit observed in the STELLAR 3 and 4 trials. In September 2007, we initiated our PGT307 trial which focuses exclusively on NSCLC in women with pre-menopausal estrogen levels, the subset of patients where OPAXIO demonstrated the greatest potential survival advantage in the STELLAR trials. Although the FDA has established the requirement that two adequate and well-controlled pivotal studies demonstrating a statistically significant improvement in overall survival will be required for approval of OPAXIO in the NSCLC setting, we believe that compelling results from PGT307, along with supporting evidence from prior clinical trials, may enable us to submit an NDA in the United States. Currently, we have limited the enrollment on the PGT307 study to sites in the United States only and we will continue to consider the expansion of the trial.

We are developing brostallicin through our wholly owned subsidiary, Systems Medicine LLC, or SM, which holds worldwide rights to use, develop, import and export brostallicin, a synthetic DNA minor groove binding agent that has demonstrated anti-tumor activity and a favorable safety profile in clinical trials in which more than 230 patients have been treated to date. SM currently uses a genomic-based platform to guide the development of brostallicin. We expect to use that platform to guide the development of our licensed oncology products in the future. We also have a strategic affiliation with the Translational Genomics Research Institute, or TGen, and have the ability to use TGen s extensive genomic platform and high throughput capabilities to target a cancer drug s context-of-vulnerability, which is intended to guide clinical trials toward patient populations where the highest likelihood of success should be observed, thereby potentially lowering risk and shortening time to market.

A phase II clinical trial study of brostallicin in relapsed/refractory soft tissue sarcoma met its predefined activity and safety hurdles and resulted in a first-line phase II clinical trial study that is currently being conducted by the European Organization for Research and Treatment of Cancer, or EORTC. Planned enrollment for this study was completed in August 2008 and the EORTC conducted the final data analysis in 2009; and a study report is expected in 2010. Brostallicin has also demonstrated synergy with new targeted agents as well as established treatments in preclinical trials. A multi-arm combination study with brostallicin and other agents, including Avastin (bevacizumab) was completed in the first quarter of 2009. Results are pending.

In March 2009, we divested our interest in the radiopharmaceutical product Zevalin® (ibritumomab tiuxetan) by selling our 50% interest in the Zevalin joint venture, RIT Oncology, to Spectrum Pharmaceuticals, Inc., or Spectrum, for $16.5 million. Previously, in December 2008, we closed our transaction with Spectrum to form RIT Oncology, to commercialize and develop Zevalin in the United States. We originally acquired the U.S. rights to develop, market and sell Zevalin from Biogen Idec Inc., or Biogen, in December 2007. We received an initial payment of $6.5 million in gross proceeds from Spectrum in March 2009, $750,000 of which was used to pay a consent fee to Biogen, and an additional $6.5 million in gross proceeds in April 2009. The remaining $3.5 million we expected to receive from Spectrum, subject to certain adjustments, was disputed and was ultimately released to Spectrum based on the outcome of an arbitration hearing held in May 2009. In addition, as part of the divestiture transaction, we agreed to forego the right to receive up to $15 million in product sales milestone payments in connection with the original transaction establishing the joint venture.

Platinates constitute an important class of cornerstone chemotherapy agents used to treat a wide variety of cancers. There are three currently commercially available platinates (cisplatin, carboplatin, and oxaliplatin) which are first-line agents in ovarian cancer, lung cancer, testicular cancer, and colorectal cancer and are also used in a broad variety of other diseases. We are developing new analogues of the dinuclear-platinum complex CT-3610 that is more potent than any of the commercially available platinates. These bisplatinates have a different mechanism of action than the commercially available platinum compounds and are substantially more active on many preclinical models including those with resistance to monoplatinates. We have initiated an Investigational New Drug application, or IND, enabling activities for bisplatinates.

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We were incorporated in Washington in 1991. Our principal executive offices are located at 501 Elliott Avenue West, Suite 400, Seattle, Washington 98119. Our telephone number is (206) 282-7100. The address for our website is http://www.celltherapeutics.com. We make available free of charge on our website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and amendments to such filings, as soon as reasonably practicable after each is electronically filed with, or furnished to, the SEC.

CTI and OPAXIO are our proprietary marks. All other product names, trademarks and trade names referred to in this prospectus are the property of their respective owners.

The Oncology Market

Overview. According to the American Cancer Society, or ACS, cancer is the second leading cause of death in the United States, resulting in close to 560,000 deaths annually, or more than 1,500 people per day. The National Cancer Institute estimates that approximately 11.1 million people in the United States with a history of cancer were alive in January 2005, and it is estimated that slightly more than one in three American women, and slightly less than one in two American men will develop cancer in their lifetime. Approximately 1.5 million new cases of cancer were expected to be diagnosed in 2009 in the United States. The most commonly used methods for treating patients with cancer are surgery, radiation and chemotherapy. Patients usually receive a combination of these treatments depending upon the type and extent of their disease.

Despite recent advances in sequencing the human genome and the introduction of new biologic therapies for the treatment of cancer, almost all patients with advanced cancer will receive chemotherapy at some point during the treatment of their disease. The cornerstone classes of chemotherapy agents include anthracyclines, camptothecins, platinates and taxanes. Unfortunately, there are significant limitations and complications associated with these agents that result in a high rate of treatment failure. The principal limitations of chemotherapy include:

- treatment-related toxicities,
- inability to selectively target tumor tissue, and
- the development of resistance to the cancer-killing effects of chemotherapy.

Treatment-related toxicities. The majority of current chemotherapy agents kill cancer cells by disrupting the cell division and replication process. Although this mechanism often works in cancer cells, which grow rapidly through cell division, non-cancerous cells are also killed because they too undergo routine cell division. This is especially true for cells that line the mouth, stomach and intestines, hair follicles, blood cells and reproductive cells (sperm and ovum). Because the mechanism by which conventional cancer drugs work is not limited to cancer cells, their use is often accompanied by toxicities. These toxicities limit the effectiveness of cancer drugs and seriously impact the patient s quality of life.

Inability to selectively target tumor tissue. When administered, chemotherapy circulates through the bloodstream, reaching both tumor and normal tissues. Normally dividing tissues are generally as sensitive as tumor cells to the killing effects of chemotherapy and toxic side effects limit the treatment doses that can be given to patients with cancer.

Chemotherapy resistance. Resistance to the cancer killing effects of conventional chemotherapy is a major impediment to continued effective treatment of cancer. Many cancer patients undergoing chemotherapy ultimately develop resistance to one or more chemotherapy agents and eventually die from their disease. Because many chemotherapies share similar properties, when a tumor develops resistance to a single drug, it may become resistant to many other drugs as well. Drugs that work differently from existing chemotherapies and are less susceptible to the same mechanisms of resistance have consequently begun to play an important role in treating resistant tumors.

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We believe developing agents which improve on the cornerstone chemotherapy classes, in addition to novel drugs designed to treat specific types of cancer and cancer patients, fills a significant unmet need for cancer patients. Our cancer drug development pipeline includes a modified anthracycline, a taxane and a DNA minor groove binding agent, each of which has the potential to treat a variety of cancer types.

Pixantrone

Anthracyclines are one of the most potent classes of anti-cancer agents used in first-line treatment of aggressive NHL, leukemia and breast cancer. For these diseases, anthracycline-containing regimens can often produce long-term cancer remissions and cures. However, the currently marketed anthracyclines can cause severe, permanent and life-threatening cardiac toxicity when administered beyond widely recognized cumulative lifetime doses. This toxicity often prevents repeat use of anthracyclines in patients who relapse after first-line anthracycline treatment. In addition, the cardiac toxicity of anthracyclines prevents their use in combination with other drugs, such as trastuzumab, that also can cause cardiac toxicity. As a result, chemotherapy regimens that do not include anthracyclines often are used for the second-line treatment of relapsed NHL. There are no drugs approved in the United States for patients with aggressive NHL that relapse after, or are refractory to, second-line treatment.

We believe a next-generation anthracycline with better ease of administration, greater anti-tumor activity and less cardiac toxicity could gain a significant share of the anthracycline market. We also believe that such a drug could allow repeat therapy in relapsed patients and could allow combination therapy with a broader range of chemotherapies. Pixantrone (BBR 2778) is being developed to improve the activity and safety in treating cancers usually treated with the anthracycline family of anti-cancer agents. It is a novel DNA major groove binder with an aza-anthracenedione molecular structure, differentiating it from anthracycline chemotherapy agents. Pixantrone has been studied in both indolent and aggressive NHL. The drug has demonstrated encouraging activity as a single agent in aggressive NHL, and recent clinical results suggest the compound also may be synergistic with other agents commonly used in combination therapy.

Pixantrone is an azo-anthracenedione that has distinct structural and physiochemical properties that make its anti-tumor unique in this class of agents. Similar to anthracyclines, pixantrone inhibits topo-isomerase II but, unlike anthracyclines, rather than interacalation with DNA, pixantrone hydrogen bonds to and alkylates DNA, thus forming stable DNA adducts with particular specificity for CpG righ, hypermethylated sites. In addition, the structural motifs on anthracylcline-like agents are responsible for the generation of oxygen free radicals and the formation of toxic drug-metal complexes have also been modified in pixantrone to prevent iron binding and perpetuation of superoxide production, both of which are the putative mechanism of anthracycline induced acute cardiotoxicity. These novel pharmacologic differences may allow re-introduction of anthracycline-like potency in the treatment of relapsed/refractory aggressive lymphoma for patients who are otherwise at their lifetime recommended doxorubicin exposure.

Pixantrone for relapsed aggressive NHL

We have several clinical trials with pixantrone, including a pivotal phase III trial, known as the EXTEND, or PIX301, trial of pixantrone for the treatment of patients with relapsed aggressive NHL, a condition for which there are no chemotherapy drugs approved in the United States. This study was an international, randomized trial comparing pixantrone to a single agent of the treating physician s choice. The primary endpoint of the study was complete remission rate. The trial enrolled 140 patients from 24 countries and patients were randomized in a 1:1 fashion to receive either pixantrone or another single-agent drug currently used for the treatment of this patient population, as selected by the physician, for up to six cycles of treatment. Tumor assessments were performed at baseline and every eight weeks thereafter through an 18-month follow-up period. The primary efficacy analysis occurred when the last patient enrolled completed treatment in September 2008. All responses of efficacy were assessed by an independent assessment panel.

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We announced in November 2008 that we had achieved the primary efficacy endpoint of the PIX301 trial. Patients randomized to treatment with pixantrone achieved a high rate of confirmed and unconfirmed complete remissions compared to patients treated with standard chemotherapy (14/70 (20.0%) for pixantrone arm compared to 4/70 (5.7%) for the standard chemotherapy arm, p = 0.02). No patient (0%) in the standard chemotherapy arm achieved a confirmed complete remission compared to 8/70 (11%) of pixantrone recipients. Pixantrone treatment also significantly increased the overall response rate (CR/CRu+PR) with 26/70 (37.1%) for pixantrone arm compared to 10/70 (14.3%) for the control arm, p = 0.003. On an intent-to-treat analysis, pixantrone recipients who achieved a complete remission did so during the first 2 cycles of therapy, compared to 4 cycles among standard chemotherapy recipients, (1.9 months vs. 3.6 months, pixantrone vs. standard chemotherapy).

The duration of response in the patients was similar in the 37% of pixantrone patients who had either a partial or complete response compared to the 14% of comparator patients with a major response. However, the overall progression-free survival (PFS) results that show patients treated with pixantrone experienced a statistically significant improvement in median progression-free survival, compared with other single-agent chemotherapeutic (4.7 months vs. 2.6 months, hazard ratio = 0.6; p = 0.0074, pixantrone vs. standard chemotherapy) based on an intent-to-treat analysis. Progression-free survival, CR/CRu and ORR were determined by an independent assessment panel that was blinded to the treatment assignments.

Pixantrone was safely administered at the proposed dose and schedule in the PIX301 clinical trial in heavily pretreated patients. The most common (incidence greater than or equal to 10%) grade 3/4 adverse events reported for pixantrone-treated subjects across the studies were neutropenia and leucopenia. Febrile neutropenia occurred at a rate of 7% in pixantrone and 3% in comparator patients. Use of growth factor support was minimal. Other common adverse events (any grade) included infection, anemia, leucopenia, thrombocytopenia, asthenia, pyrexia, and cough.

During the conduct of the PIX301 trial, we conducted prospective monitoring for cardiac events. At baseline, more pixantrone patients had a pre-existing cardiac disease, including five patients with histories of CHF or cardiomyopathy with none reported in the comparator arm. Two pixantrone and one comparator patient had grade 3 troponin levels at study entry. Overall, the incidence of grade 3 or greater cardiac adverse events was 7% (5 patients) on the pixantrone arm and 2% (1 patient) on the comparator arm. One of these pixantrone patients had a reversible asymptomatic grade 3 decline in LVEF. Examination of LVEF values has shown no relationship between dose or cumulative exposure to pixantrone and the occurrence grade 3 or greater cardiac adverse events. There were an equal number of deaths due to an adverse event in both pixantrone and the comparator arm (15 each); in the pixantrone arm, three patients died due to progressive disease while nine comparator patients died due to progressive disease. An updated efficacy analysis was performed in conjunction with the Day 120 Safety Update in June 2009. The complete response rate, progression free survival and overall survival continued to improve on follow-up.

Based on the outcome of the EXTEND trial and on the basis of a pre-NDA communication we received from the FDA relating to this phase III trial, we began a rolling NDA submission to the FDA in April 2009. We completed the submission in June 2009 and we have been notified by the FDA that a PDUFA action date of April 23, 2010 has been established. Based on this PDUFA date, if pixantrone is approved, it could be available to patients in the United States as early as the second quarter of 2010.

In line with our company values, we have made pixantrone available on a compassionate use basis. Accordingly, in May 2009 we entered into an agreement with IDIS, Limited, or IDIS, to manage pixantrone as an investigational drug on a named-patient basis in Europe. Pixantrone will be supplied by IDIS to healthcare professionals for the treatment of individual patients with relapsing aggressive non-Hodgkin s lymphoma.

We also conducted the RAPID, or PIX203, phase II clinical trial study (CHOP-R vs. CPOP-R) in which pixantrone is substituted for doxorubicin in the CHOP-R regimen compared to the standard CHOP-R regimen in

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patients with aggressive NHL. Preliminary results of this trial were reported at the 49th Annual Meeting of the American Society of Hematology, or ASH, in December 2007. The interim analysis of the RAPID trial, in which 78 patients were evaluated for safety and 40 of the 78 patients were evaluated for efficacy, was reported in July 2007. In early 2008, we closed enrollment on the RAPID study, based on adequate sample size to demonstrate difference in cardiac events and other clinically relevant side effects between pixantrone and doxorubicin. We expect to report results from this trial in mid-2010.

In July 2009, we were notified by the EMEA that pixantrone is eligible to be submitted for a Marketing Authorization Application, or MAA, through the EMEA s centralized procedure. The centralized review process provides for a single coordinated review for approval of pharmaceutical products that is conducted by the EMEA on behalf of all EU member states. The EMEA also designated pixantrone as an NAS; if approved, compounds designated as an NAS receive a 10-year market exclusivity period in EU member states. In September 2009, we submitted a PIP to the EMEA as part of the required filing process for approval of pixantrone for treating relapsed, aggressive NHL in Europe. Based upon feedback from European authorities, we are requesting a waiver from executing a PIP. In September 2009, we also applied to the EMEA for orphan drug designation for pixantrone, which was granted in December 2009. We anticipate the formal MAA filing for pixantrone for the treatment of relapsed or refractory aggressive NHL in mid-2010.

Pixantrone for other indications

Other clinical data suggest pixantrone may be useful in treating indolent NHL, a less rapidly progressive but ultimately fatal form of NHL. In November 2005, we presented results from a multi-center randomized trial, known as AZA302. This trial, evaluating pixantrone plus rituximab versus rituximab alone among patients with relapsed or refractory indolent NHL, was modified and reduced as a result of our strategy to conduct a pivotal phase III trial in aggressive NHL, which we believe provides the fastest route to registration for pixantrone. Of the 38 patients evaluable for response, patients receiving the combination of rituximab and pixantrone had an 87% overall improvement in time to progression, or TTP, compared to rituximab alone. The median TTP estimate for the pixantrone/rituximab recipients was 13.2 months compared to 8.1 months for rituximab alone (hazard ratio 0.13, log rank p <0.001). The one- and two-year progression-free survival estimates were 66% and 44% for the pixantrone/rituximab recipients compared to 0% for the rituximab patients for both measurement intervals (p <0.001 and 0.003, respectively). The study also demonstrated a significant improvement in major objective responses (³ 50% shrinkage in tumor size). The pixantrone-rituximab combination produced a complete response (CR) in seven patients (35%), with eight patients (40%) experiencing a partial response (PR) and four patients (20%) with stable disease (SD). Rituximab monotherapy produced a CR in two patients (11%), PR in four patients (22%) with six patients having SD (33%). This corresponds to a major objective response rate of 75% in the combination therapy arm compared to 33% in the rituximab group (p=0.021). Side effects on pixantrone were generally mild to moderate (grade 1 or 2) with the exception of three cases of serious neutropenia associated with the pixantrone/rituximab arm. The median cumulative dose of pixantrone administered was 1014 mg/m²; no cases of treatment-related grade 3 or 4 cardiac toxicity were reported.

In May 2007, we received special protocol assessment, or a SPA, from the FDA for approval for a new protocol designed to evaluate the combination of fludarabine, pixantrone and rituximab versus fludarabine and rituximab in patients who have received at least one prior treatment for relapsed or refractory indolent NHL, and we received fast track designation from the FDA for pixantrone for the treatment of relapsed or refractory indolent NHL. The protocol, which became our phase III PIX303 trial, was launched in September 2007. However, we closed the trial in January 2008 based on, among other considerations, our plans to refocus the Company s resources on obtaining pixantrone approval based on the EXTEND phase III trial before making additional substantive investments in alternative indications for pixantrone as well as the changing landscape in second line follicular NHL.

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OPAXIO

OPAXIO (paclitaxel poliglumex, CT-2103) is our novel biologically enhanced chemotherapeutic agent that links paclitaxel to a biodegradable polyglutamate polymer, resulting in a new chemical entity. We are currently focusing our development of OPAXIO on ovarian and esophageal cancer.

OPAXIO was designed to improve the delivery of paclitaxel to tumor tissue while protecting normal tissue from toxic side effects. Unlike vessels in healthy tissue, those in tumor tissue have openings that make them porous. Due to the larger size of OPAXIO compared to standard paclitaxel, OPAXIO leaks through the pores in tumor blood vessels and is preferentially trapped and distributed to the tumor tissue. Once in the tumor tissue, OPAXIO is taken up by the tumor cells through a cellular process called endocytosis. Because the biopolymer OPAXIO is made up of biodigestible amino acids, it is slowly metabolized by lysosomal enzymes (principally cathepsin B) inside the lysosome of the tumor cell. This metabolism releases the active chemotherapy agent, paclitaxel. The activity of this enzyme, and thus the rate of release of OPAXIO, is increased in the presence of estrogen.

Because the polymer is water-soluble, OPAXIO can be administered without solvents and other routine pre-medications (such as steroids and antihistamines) generally used to prevent severe allergic reactions, and can be infused over an average of ten to twenty minutes. Patients can drive themselves to and from their treatment centers. OPAXIO remains stable in the bloodstream for several days after administration; this prolonged circulation allows the passive accumulation of OPAXIO in tumor tissue.

Taxanes, including paclitaxel (Taxol®) and docetaxel (Taxotere®), currently are widely used for the treatment of various solid tumors, including non-small cell lung, ovarian, breast and prostate cancers. Paclitaxel is considered a standard-of-care in lung and ovarian cancers, where it is most widely used. Because taxanes are small, hydrophobic agents, their therapeutic potential is limited by unfavorable pharmacokinetic properties. Solvents (such as Cremaphor) are needed for administration, and these solvents are often extremely irritating to blood vessels, requiring surgical placement of a large catheter for administration and a minimum of three hours for infusion. They also can cause severe life threatening allergic reactions that typically require pre-medications with steroids and antihistamines. Patients usually require transportation to and from their treatment location. Taxanes exhibit high peak levels of drug immediately following administration that expose normal tissues to toxic effects. Rapid elimination of the drug from blood limits tumor exposure.

The distribution and metabolism of OPAXIO to tumor tissue and subsequent release of active paclitaxel chemotherapy appears to be enhanced by estrogen, allowing for superior effectiveness in women with pre-menopausal estrogen levels. This gender-targeted benefit could also be exploited in post-menopausal women or men through estrogen supplementation. Preclinical data presented at the 2006 European Organization for Research and Treatment of Cancers, National Cancer Institute and American Association for Cancer Research, or EORTC-NCI-AACR, meeting demonstrated that the efficacy of OPAXIO is enhanced in certain human tumors when mice are given additional estrogen. In subsequent clinical studies, more than 1,900 patients were treated in our four pivotal phase III trials of OPAXIO for the treatment of NSCLC. While the STELLAR 2, 3 and 4 trials missed their primary endpoint of superior overall survival, women treated with OPAXIO for newly diagnosed advanced NSCLC in STELLAR 3 and 4 had a significant improvement in their overall survival compared to women or men treated with standard chemotherapy. In addition, with single-agent OPAXIO, we observed a significant reduction in most of the severe toxic side effects associated with the standard chemotherapy agents studied in the STELLAR trials.

OPAXIO for ovarian cancer

The ACS estimates that approximately 21,150 new cases of ovarian cancer will be diagnosed in the United States in 2009. The standard of care for first-line treatment of ovarian cancer is paclitaxel and carboplatin. In April 2004, we announced that we entered into a clinical trial agreement with the GOG to perform a phase III trial of OPAXIO as maintenance therapy in patients with ovarian cancer. In July 2004, the GOG submitted an

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IND along with the protocol for an SPA to the FDA. The GOG reached agreement with the FDA regarding the SPA in December 2004 and initiated the phase III study in March 2005. This study is expected to enroll 1,100 patients with over 600 patients enrolled to date. Given the expected rate of progression in the control (no treatment) arm and the 5 year duration of study enrollment to date, we requested that the Data Monitoring Committee, or DMC, perform an interim futility analysis examining progression free survival as a surrogate for overall survival. We made this request based on input from our external statistical expert who proposed a boundary for futility that, if exceeded, would predict a likely positive effect on overall survival at study conclusion. Alternatively if the boundary was not met then the likelihood of positive benefit on overall survival would be low, thus making further enrollment futile. The GOG informed us that, in closed session deliberation, the DMC denied our request and plans to conduct an interim analysis for overall survival which is projected to occur in 2011.

OPAXIO for esophageal cancer

In June 2009, we announced that, in a study released from Brown University at the 2009 American Society for Clinical Oncology Annual Meeting, patients with cancer of the lower esophagus had evidence of a high pathological complete response rate when given OPAXIO in addition to cisplatin and full-course radiotherapy. In this phase II clinical trial study, preliminary data suggests that OPAXIO may provide enhanced radiation sensitization as compared to standard therapy. We plan to meet with the FDA in 2010 to explore a potential U.S. phase III registration study utilizing OPAXIO as a radiation sensitizer in the treatment of esophageal cancer.

OPAXIO for non-small cell lung cancer

The ACS estimates that 187,000 new cases of NSCLC will be diagnosed in the United States in 2009. Nearly 60 percent of people with lung cancer die within one year of their diagnosis and the five-year survival rate is only 15 percent. Paclitaxel is among the most commonly used cancer drugs to treat NSCLC in the United States.

In March 2005, we announced that our OPAXIO phase III pivotal trial, known as STELLAR 3, for the potential use of OPAXIO in combination with platinum as first-line treatment of PS2 patients with NSCLC missed its primary endpoint of superior overall survival. However, in the STELLAR 3 trial, OPAXIO had a reduction in certain side effects, including hair loss, muscle and joint pain, and cardiac symptoms. In May 2005, we announced that both the STELLAR 2 and 4 clinical trials missed their primary endpoints of superior overall survival, but also had significant reductions in certain severe side effects compared to the comparator agents. The STELLAR 2 pivotal trial was evaluating OPAXIO for potential use as second-line single agent treatment for patients with NSCLC, and the STELLAR 4 pivotal trial was evaluating OPAXIO for potential use as first-line single agent treatment for PS2 patients with NSCLC.

In July 2005, at the 11th World Conference on Lung Cancer, we announced that in a pooled analysis of our STELLAR 3 and 4 pivotal trials the 97 women who received OPAXIO had a significant increase in median and overall survival (9.5 months vs. 7.7 months, hazard ratio 0.70, log rank p=0.03) and in 1-year survival (40% vs. 25%, p=0.013) compared to 101 women who received comparator control agents. These results pooled data from all women randomized on the STELLAR 3 and 4 trials (a so-called intent to treat analysis). Individually, neither study reached statistical significance for overall survival for women, although a positive trend was observed in both trials, with a strong trend in the STELLAR 4 trial (p=0.069). While analysis of survival by gender was pre-specified in the analysis plans for the trials, a gender specific survival advantage for women over men was not a pre-specified endpoint in either trial.

In September 2005, we presented results from a phase II clinical trial, known as PGT202, of OPAXIO in the first-line treatment of men and women with advanced NSCLC which demonstrated a survival advantage for women receiving OPAXIO as first-line therapy for NSCLC when compared to men. In this single-arm study, the 35 women who received OPAXIO plus carboplatin had a 36% probability of living at least one year compared to 16% in the 39 men receiving the same regimen. A pooled analysis of the 463 patients treated with OPAXIO in

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the STELLAR 3, STELLAR 4 and PGT202 trials demonstrated a statistically significant survival advantage for women treated when compared to men, with women having a 39% probability of surviving at least one year compared to 25% for men (hazard ratio 0.63, log rank p=0.014).

In December 2005, we initiated the PIONEER, or PGT305, study comparing OPAXIO to paclitaxel in the first-line treatment of PS2 women with advanced NSCLC. In addition, we initiated preclinical studies on the effect of gender/hormonal status on OPAXIO biodistribution, cellular uptake and metabolism to support the hypothesis for survival improvement in women.

In February 2006, we presented results that confirm the observation of enhanced efficacy in the presence of estrogen seen in the STELLAR first-line trials. In the three first-line trials of OPAXIO (PGT202, STELLAR 3, and STELLAR 4), women of pre-menopausal age or with normal estrogen levels had the strongest survival advantage over their counterparts. In an analysis of the 113 of 198 women in the pooled STELLAR 3 and 4 trial data who are of pre-menopausal age or have normal estrogen levels, women treated with OPAXIO had a highly significant prolongation in the 1-year and overall survival estimates compared to women treated with standard chemotherapy, with the OPAXIO patients having a 44% reduction in the overall risk of dying (log rank p=0.008) and a 43% 1-year survival estimate compared to 19% for women on standard chemotherapy (p=0.003). We believe these data indicate a potential favorable alternative for women with normal estrogen levels who have NSCLC.

In addition, our phase III trials demonstrated that, with the exception of neuropathy known to be associated with taxane therapy, single agent OPAXIO (175-210mg/m²) has a significantly reduced incidence of severe side effects, including a reduction in severe neutropenia, febrile neutropenia, infection and anemia when compared to patients receiving standard chemotherapy agents gemcitabine, vinorelbine or docetaxel. OPAXIO also resulted in less severe allergic reactions, less hair loss, and significant reduction in the requirement for transfusions and use of hematopoietic growth factor support, such as Neupogen®, Neulasta®, Aranesp® and/or Epogen® compared to patients receiving standard chemotherapy.

In December 2006, we agreed with the recommendation of the Data Safety Monitoring Board to close the PIONEER lung cancer clinical trial due, in part, to the diminishing utility of the PIONEER trial given our plans to submit a new protocol to the FDA. In early 2007, we submitted two new protocols under an SPA to the FDA. The new trials, known as PGT306 and PGT307, focus exclusively on NSCLC in women with pre-menopausal estrogen levels, the subset of patients where OPAXIO demonstrated the greatest potential survival advantage in the STELLAR trials. We believe the lack of safe and effective treatment for women with advanced first-line NSCLC who have pre-menopausal estrogen levels represents an unmet medical need. We initiated the PGT307 trial in September 2007. Although the FDA has established the requirement that two adequate and well-controlled pivotal studies demonstrating a statistically significant improvement in overall survival will be required for approval of OPAXIO in the NSCLC setting, we believe that compelling results from a single trial, PGT307, along with supporting evidence from prior clinical trials, may enable us to submit an NDA in the United States. Currently, we have limited enrollment on the PGT307 study to sites in the United States only and we will continue to consider the expansion of the trial.

In March 2008, we submitted an MAA to the EMEA for first-line treatment of patients with advanced NSCLC who are poor performance status, or PS2, based on a non-inferior survival and improved side effect profile which we believe was demonstrated in our previous clinical trials. The application was based on a positive opinion we received from the EMEA s Scientific Advice Working Party, or SAWP; the EMEA agreed that switching the primary endpoint from superiority to non-inferiority was feasible if the retrospective justification provided in the marketing application was adequate. In September 2009, we notified the EMEA of our decision to withdraw the MAA and we refocused our resources on the approval of OPAXIO for its potential superiority indication in maintenance therapy for ovarian cancer and as a radiation sensitizer in the treatment of esophageal cancer.

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Brostallicin

We are developing brostallicin, which is a small molecule, chemotherapeutic agent with a unique mechanism of action and composition of matter patent coverage. Data in more than 230 patients treated with brostallicin in phase I/II clinical trials reveal evidence of activity in patients with refractory cancer and patient/physician-friendly dosage and administration. A phase II clinical trial study of brostallicin in relapsed/refractory soft tissue sarcoma met its pre-defined activity and safety hurdles and resulted in a first-line phase II clinical trial study that is currently being conducted by the European Organization for Research and Treatment of Cancer, or EORTC. Planned enrollment for this study was completed in August 2008 and the EORTC plans to conduct the final data analysis in 2009 and a study report is expected in 2010. Brostallicin has also demonstrated synergy with new targeted agents as well as established treatments in preclinical trials. A multi-arm combination study with brostallicin and other agents, including Avastin (bevacizumab) was completed in the first quarter of 2009. The results of this study are pending.

Zevalin (Ibritumomab Tiuxetan)

In March 2009, we divested our interest in the radiopharmaceutical product Zevalin® (ibritumomab tiuxetan) by selling our 50% interest in the Zevalin joint venture, RIT Oncology, to Spectrum for $16.5 million. Previously, in December 2008, we closed our transaction with Spectrum to form RIT Oncology, to commercialize and develop Zevalin in the United States. We originally acquired the U.S. rights to develop, market and sell Zevalin from Biogen Idec Inc., or Biogen, in December 2007. We received an initial payment of $6.5 million in gross proceeds from Spectrum in March 2009, $750,000 of which was used to pay a consent fee to Biogen, and an additional $6.5 million in gross proceeds in April 2009. The remaining $3.5 million we expected to receive from Spectrum, subject to certain adjustments, was disputed and was ultimately released to Spectrum based on the outcome of an arbitration hearing held in May 2009. In addition, as part of the divestiture transaction, we agreed to forego the right to receive up to $15 million in product sales milestone payments in connection with the original transaction establishing the joint venture.

CTI s Ongoing Clinical Trials

The following table lists our active clinical trials (indicated by a status of open) and trials that have recently closed to enrollment.

Product Candidate	Indication/Intended Use	Phase/Enrollment Status
Pixantrone	Aggressive NHL, > 3 relapses, single-agent (PIX301)	III / closed
	Aggressive NHL, front-line, CPOP-R (PIX203)	II / closed
OPAXIO (CT-2103)	NSCLC, first-line, doublet therapy, PS0-2, females with pre-menopausal estrogen levels (PGT307)	III /open
	Ovarian first-line maintenance (GOG0212)	III / open
Brostallicin	Context of vulnerability (BRCA1 or BRCA2 Breast or Ovarian Cancer) (BRS201)	II / open
	Advanced or metastatic soft tissue sarcoma, first-line, single agent (EORTC 62061)	II / closed
	Myxoid liposarcoma with specific genomic translocations (BRS202)	II / closed
	Combination with other anti-cancer drugs (BRS101)	I / closed

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Research and Preclinical Development

Cisplatin is a platinum-based chemotherapy drug used to treat a wide variety of cancers. We are developing new analogues of the dinuclear-platinum complex, CT-3610, that is more potent than cisplatin. CT-3610 is endowed with a unique mechanism of action, active in preclinical studies on a large panel of tumor models, sensitive and refractory to cisplatin, and has a safety profile comparable to that of cisplatin. The novel bisplatinum analogues are rationally designed and synthesized to have improved biopharmaceutical properties that reduce the intrinsic reactivity of the molecule and that demonstrate preclinical anti-tumor efficacy in solid tumor models.

Research and development is essential to our business. We spent $30.2 million, $51.6 million and $72.0 million in 2009, 2008 and 2007, respectively, on company-sponsored research and development activities.

Collaboration, Licensing and Milestone Arrangements

Spectrum Pharmaceuticals, Inc. In December 2008, we formed our 50/50 owned joint venture, RIT Oncology, with Spectrum to commercialize and develop Zevalin in the United States. At the closing of the joint venture transaction, we contributed all assets exclusively related to Zevalin in exchange for a 50% membership interest in RIT Oncology, an initial payment from RIT Oncology of $7.5 million upon closing of the transaction and an additional payment of $7.5 million in early January 2009. In March 2009, we divested our interest in Zevalin by selling our 50% membership interest in RIT Oncology to Spectrum for $16.5 million. We received payments of $13.0 million in gross proceeds and the remaining $3.5 million, which was subject to certain adjustments, was disputed and ultimately released to Spectrum based on the outcome of an arbitration hearing held in May 2009. In addition, as part of the divestiture transaction, we agreed to forego the right to receive up to $15 million in product sales milestone payments in connection with the original transaction establishing the joint venture.

PG-TXL Company, L.P. We have an agreement with PG-TXL Company, L.P., or PG-TXL, which grants us an exclusive worldwide license for the rights to OPAXIO and to all potential uses of PG-TXL s polymer technology. Pursuant to this agreement, we acquired the rights to the research, development, manufacture, marketing and sale of anti-cancer drugs developed using this polymer technology. We are obligated to make payments to PG-TXL upon the achievement of certain development and regulatory milestones and we may be required make additional payments of up to $14.4 million in the future if additional milestones are met. The timing of the remaining milestone payments under the amended agreement is based on trial commencements and completions and regulatory and marketing approval with the FDA and EMEA.

Gynecologic Oncology Group. We have an agreement with the Gynecologic Oncology Group, or GOG, related to the GOG0212 trial which the GOG is conducting. Under this agreement we are required to pay up to $5.1 million in additional milestone payments related to the trial of which $1.6 million may become due in the first quarter of 2010 based on patient enrollment.

Acquisition of Systems Medicine, Inc. In connection with our acquisition of Systems Medicine, Inc., or SMI, we were required to pay its stockholders a maximum of $15.0 million in additional consideration (payable in cash or stock at our election, subject to certain limitations of The NASDAQ Stock Market, LLC, or NASDAQ, on the issuance of stock) upon the achievement of certain FDA regulatory milestones for brostallicin. In August 2009, we entered into an amended agreement under which these milestone payments were replaced by an immediate substitute payment of $6.0 million payable in shares of our common stock subject to certain conditions, including required shareholder approval. If the conditions were not satisfied, we would have been required to pay the SMI stockholders $5.0 million cash in lieu of the $6.0 million shares of our common stock. In October 2009, our shareholders approved the issuance of $6.0 million shares of our common stock and we issued approximately 5.6 million shares to SMI stockholders.

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Brostallicin. Under a license agreement entered into for brostallicin, we may be required to pay up to $80.0 million in milestone payments, based on the achievement of certain product development results. Because brostallicin is in an early stage of development, we are not able to determine whether the clinical trials will be successful and therefore cannot make a determination that the milestone payments are reasonably likely to occur at this time.

Cephalon. Pursuant to an acquisition agreement entered into with Cephalon, Inc. in connection with the sale of our former drug, TRISENOX, in June 2005, we may receive up to $100.0 million in payments upon achievement by Cephalon of specified sales and development milestones related to TRISENOX. However, the achievement of any such milestones is uncertain at this time.

Novartis International Pharmaceutical Ltd. In September 2006, we entered into an exclusive worldwide licensing agreement with Novartis for the development and commercialization of OPAXIO. Total product registration and sales milestones due from Novartis for OPAXIO under the agreement could reach up to $270 million. The agreement also provides Novartis with an option to develop and commercialize pixantrone based on agreed terms. If Novartis exercises its option on pixantrone under certain conditions and we are able to negotiate and sign a definitive license agreement with Novartis, Novartis would pay us a $7.5 million license fee, up to $104 million in registration and sales related milestones and a royalty on pixantrone worldwide net sales as well as reimbursement for certain expenses. As of December 31, 2009, we have not received any milestone payments and we will not receive any milestone payments unless Novartis elects to participate in the development and commercialization of pixantrone or OPAXIO.

Patents and Proprietary Rights

We dedicate significant resources to protecting our intellectual property, which is important to our business. We have exclusive rights to 12 issued U.S. patents and 129 pending or issued U.S. and foreign patent applications relating to our polymer drug delivery technology, of which seven issued U.S. patents and 83 pending or issued U.S. and foreign patent applications are directed to OPAXIO. We have three issued U.S. patents and another 19 pending or issued U.S. and foreign patent applications that are directed to CT-2106. Additionally, we have four issued U.S. patents and 76 pending or issued U.S. and foreign issued patents directed to pixantrone and have licensed five granted U.S. patents and 394 pending and issued U.S. and foreign patent applications directed to brostallicin.

Manufacturing

We currently use, and expect to continue to be dependent upon, contract manufacturers to manufacture each of our product candidates. We have established a quality control and quality assurance program, including a set of standard operating procedures and specifications, designed to ensure that our products and product candidates are manufactured in accordance with current Good Manufacturing Practices, or cGMPs, and other applicable domestic and European regulations. We will need to invest in additional manufacturing development, manufacturing and supply chain resources, and may seek to enter into additional collaborative arrangements with other parties that have established manufacturing capabilities. It is likely that we will continue to rely on third-party manufacturers for our development and commercial products on a contract basis. Currently, we have agreements with third-party vendors to produce, test, and distribute pixantrone, OPAXIO and brostallicin drug supply for clinical studies. We will be dependent upon these third-party vendors to supply CTI in a timely manner with products manufactured in compliance with cGMPs or similar standards imposed by U.S. and/or foreign regulatory authorities where our products are being developed, tested, and/or marketed.

We have a purchase agreement with Natural Pharmaceuticals, Inc., or NPI, which was assumed by Phyton Biotech, LLC, or Phyton, upon their purchase of NPI in 2009. Under this purchase agreement, Phyton currently must supply us with either 2.5 kilograms of paclitaxel or the cash equivalent of $0.5 million.

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In October 2009, the FDA inspected our contract manufacturing facility located in Milan, Italy and, based on its inspection, made observations regarding the manufacturing process and controls over our lead compound, pixantrone. Our contract manufacturer addressed and responded to the FDA s observations in November 2009. Neither our contract manufacturer nor the Company have received any further response from the FDA regarding our contract manufacturer s planned action as of February 22, 2010.

Competition

Competition in the pharmaceutical and biotechnology industries is intense. We face competition from a variety of companies focused on developing oncology drugs. We compete with large pharmaceutical companies and with other specialized biotechnology companies, including but not limited to: Bristol-Myers Squibb Company, Sanofi-Aventis, Wyeth, Roche Group, Genentech, Inc., OSI Pharmaceuticals, Inc., Eli Lilly and Company, Abraxis, Neopharm Inc., Telik, Inc., TEVA Pharmaceuticals Industries Ltd. and PharmaMar. Many of our existing or potential competitors have substantially greater financial, technical and human resources than us and may be better equipped to develop, manufacture and market products. Smaller companies may also prove to be significant competitors, particularly through collaborative arrangements with large pharmaceutical and established biotechnology companies. Many of these competitors have products that have been approved or are in development and operate large, well-funded research and development programs.

We expect to encounter significant competition for the principal pharmaceutical products we plan to develop. Companies that complete clinical trials, obtain required regulatory approvals and commence commercial sales of their products before us may achieve a significant competitive advantage if their products work through a similar mechanism as our products and if the approved indications are similar. We do not believe competition is as intense among products that treat cancer through novel delivery or therapeutic mechanisms where these mechanisms translate into a clinical advantage in safety and/or efficacy. A number of biotechnology and pharmaceutical companies are developing new products for the treatment of the same diseases being targeted by us. In some instances, such products have already entered late-stage clinical trials or received FDA approval. However, cancer drugs with distinctly different mechanisms of action are often used together in combination for treating cancer, allowing several different products to target the same cancer indication or disease type. Such combination therapy is typically supported by clinical trials that demonstrate the advantage of combination therapy over that of a single-agent treatment.

We believe that our ability to compete successfully will be based on our ability to create and maintain scientifically advanced technology, develop proprietary products, attract and retain scientific personnel, obtain patent or other protection for our products, obtain required regulatory approvals and manufacture and successfully market our products, either alone or through outside parties. We will continue to seek licenses with respect to technology related to our field of interest and may face competition with respect to such efforts.

Government Regulation

The research, development, testing, manufacture, labeling, promotion, advertising, distribution and marketing, among other things, of our products are extensively regulated by governmental authorities in the United States and other countries. In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, Public Health Service Act, or PHSA, and their implementing regulations. Failure to comply with applicable U.S. requirements may subject us to administrative or judicial sanctions, such as FDA refusal to approve pending new drug applications or supplemental applications, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions and/or criminal prosecution.

Drug Approval Process. None of our drugs may be marketed in the United States until such drug has received FDA approval. The steps required before a drug may be marketed in the United States include:

preclinical laboratory tests, animal studies and formulation studies;

submission to the FDA of an IND for human clinical testing, which must become effective before human clinical trials may begin;

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adequate and well-controlled human clinical trials to establish the safety and efficacy of the investigational product for each indication;

submission to the FDA of an NDA;

satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the drug is produced, tested, and distributed to assess compliance with cGMPs; and

FDA review and approval of the NDA.

Preclinical tests include laboratory evaluation of product chemistry, toxicity and formulation, as well as animal studies. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND, which must become effective before human clinical trials may begin. An IND will automatically become effective 30 days after receipt by the FDA unless, before that time, the FDA raises concerns or questions about issues such as the conduct of the trials as outlined in the IND. In such a case, the IND sponsor and the FDA must resolve any outstanding FDA concerns or questions before clinical trials can proceed. We cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin.

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators. Clinical trials are conducted under protocols detailing the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. Each protocol must be submitted to the FDA as part of the IND.

Clinical trials typically are conducted in three sequential phases, but the phases may overlap or be combined. The study protocol and informed consent information for study subjects in clinical trials must also be approved by an Institutional Review Board for each institution where the trials will be conducted. Study subjects must sign an informed consent form before participating in a clinical trial. Phase I usually involves the initial introduction of the investigational product into people to evaluate its short-term safety, dosage tolerance, metabolism, pharmacokinetics and pharmacologic actions, and, if possible, to gain an early indication of its effectiveness. Phase II usually involves trials in a limited patient population to (i) evaluate dosage tolerance and appropriate dosage, (ii) identify possible adverse effects and safety risks, and (iii) evaluate preliminarily the efficacy of the product candidate for specific indications. Phase III trials usually further evaluate clinical efficacy and test further for safety by using the product candidate in its final form in an expanded patient population. There can be no assurance that phase I, phase II or phase III testing will be completed successfully within any specified period of time, if at all. Furthermore, we or the FDA may suspend clinical trials at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk.

The FDA and IND sponsor may agree in writing on the design and size of clinical studies intended to form the primary basis of an effectiveness claim in an NDA application. This process is known as a special protocol assessment, or SPA. These agreements may not be changed after the clinical studies begin, except in limited circumstances. The existence of an SPA, however, does not assure approval of a product candidate.

Assuming successful completion of the required clinical testing, the results of the preclinical studies and of the clinical studies, together with other detailed information, including information on the manufacture and composition of the investigational product, are submitted to the FDA in the form of an NDA requesting approval to market the product for one or more indications. The testing and approval process requires substantial time, effort and financial resources. Submission of an NDA requires payment of a substantial review user fee to the FDA. The FDA will review the application and may deem it to be inadequate to support commercial marketing, and we cannot be sure that any approval will be granted on a timely basis, if at all. The FDA may also seek the advice of an advisory committee, typically a panel of clinicians practicing in the field for which the product is intended, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendations of the advisory committee.

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The FDA has various programs, including fast track, priority review and accelerated approval, that are intended to expedite or simplify the process for reviewing drugs and/or provide for approval on the basis of surrogate endpoints. Generally, drugs that may be eligible for one or more of these programs are those for serious or life threatening conditions, those with the potential to address unmet medical needs and those that provide meaningful benefit over existing treatments. We cannot be sure that any of our drugs will qualify for any of these programs, or that, if a drug does qualify, the review time will be reduced or the product will be approved.

Before approving an NDA, the FDA usually will inspect the facility or the facilities where the product is manufactured, tested and distributed and will not approve the product unless cGMP compliance is satisfactory. If the FDA evaluates the NDA and the manufacturing facilities as acceptable, the FDA may issue an approval letter, or in some cases, an approvable letter. An approvable letter contains a number of conditions that must be met in order to secure final approval of the NDA. When and if those conditions have been met to the FDA s satisfaction, the FDA will issue an approval letter. The approval letter authorizes commercial marketing of the drug for specific indications. As a condition of approval, the FDA may require post-marketing testing and surveillance to monitor the product s safety or efficacy, or impose other post-approval commitment conditions.

After approval, certain changes to the approved product, such as adding new indications, making certain manufacturing changes or making certain additional labeling claims, are subject to further FDA review and approval. Obtaining approval for a new indication generally requires that additional clinical studies be conducted.

Post-Approval Requirements. Holders of an approved NDA are required to: (i) report certain adverse reactions to the FDA, (ii) comply with certain requirements concerning advertising and promotional labeling for their products, and (iii) continue to have quality control and manufacturing procedures conform to cGMP after approval. The FDA periodically inspects the sponsor s records related to safety reporting and/or manufacturing and distribution facilities; this latter effort includes assessment of compliance with cGMP. Accordingly, manufacturers must continue to expend time, money and effort in the area of production, quality control and distribution to maintain cGMP compliance. We use and will continue to use third-party manufacturers to produce our products in clinical and commercial quantities, and future FDA inspections may identify compliance issues at our facilities or at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of problems with a product after approval may result in restrictions on a product, manufacturer or holder of an approved NDA, including withdrawal of the product from the market.

Marketing of prescription drugs is also subject to significant regulation through federal and state agencies tasked with consumer protection and prevention of medical fraud, waste and abuse. We must comply with restrictions on off-label use promotion, anti-kickback, ongoing clinical trial registration, and limitations on gifts and payments to physicians. In addition, we have entered into a corporate integrity agreement, or CIA, with the Office of the Inspector General, Health and Human Services, or OIG-HHS, as part of our settlement agreement with the United States Attorney s Office, or USAO, for the Western District of Washington arising out of their investigation into certain of our prior marketing practices relating to TRISENOX, which was divested to Cephalon Inc. in July 2005. The CIA, which became effective in December 2007 upon our acquisition of a commercially marketed drug, Zevalin, requires us to establish a compliance committee and compliance program and adopt a formal code of conduct.

Non-U.S. Regulation. Before our products can be marketed outside of the United States, they are subject to regulatory approval similar to that required in the United States, although the requirements governing the conduct of clinical trials, including additional clinical trials that may be required, product licensing, pricing and reimbursement vary widely from country to country. No action can be taken to market any product in a country until an appropriate application has been approved by the regulatory authorities in that country. The current approval process varies from country to country, and the time spent in gaining approval varies from that required for FDA approval. In certain countries, the sales price of a product must also be approved. The pricing review period often begins after market approval is granted. Even if a product is approved by a regulatory authority, satisfactory prices may not be approved for such product.

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In Europe, marketing authorizations may be submitted at a centralized, a decentralized or national level. The centralized procedure is mandatory for the approval of biotechnology products and provides for the grant of a single marketing authorization that is valid in all European Union members states. As of January 1995, a mutual recognition procedure is available at the request of the applicant for all medicinal products that are not subject to the centralized procedure. There can be no assurance that the chosen regulatory strategy will secure regulatory approvals on a timely basis or at all.

Environmental Regulation

In connection with our research and development activities, we are subject to federal, state and local laws, rules, regulations and policies governing the use, generation, manufacture, storage, air emission, effluent discharge, handling and disposal of certain materials, biological specimens and wastes. Although we believe that we have complied with these laws, regulations and policies in all material respects and have not been required to take any significant action to correct any noncompliance, we may be required to incur significant costs to comply with environmental and health and safety regulations in the future. Our research and development involves the controlled use of hazardous materials, including, but not limited to, certain hazardous chemicals and radioactive materials. Although we believe that our safety procedures for handling and disposing of such materials comply with the standards prescribed by federal, state and local regulations, the risk of accidental contamination or injury from these materials cannot be eliminated. In the event of such an accident, we could be held liable for any damages that result and any such liability could exceed our resources.

Employees

As of December 31, 2009, we employed 104 individuals in the United States and 3 in Europe. We have 11 employees who hold doctoral degrees. Our U.S. employees do not have a collective bargaining agreement. Our European employees were subject to a collective bargaining agreement. We believe our relations with our employees to be good.

Information regarding our executive officers is set forth in Item 10 of this Annual Report on Form 10-K, which information is incorporated herein by reference.

Item 1a. Risk Factors

This Annual Report on Form 10-K contains forward-looking statements that involve risks and uncertainties. The occurrence of any of the following risks described below and elsewhere in this document, including the risk that our actual results may differ materially from those anticipated in these forward-looking statements, could materially adversely affect our business, financial condition, operating results or prospects and the trading price of our securities. Additional risks and uncertainties that we do not presently know or that we currently deem immaterial may also impair our business, financial condition, operating results and prospects and the trading price of our securities.

Factors Affecting Our Operating Results and Financial Condition

We need to raise additional funds and expect that we will need to continue to raise funds in the future, and additional funds may not be available on acceptable terms, or at all; failure to raise significant additional funds may cause us to cease development of our products and operations.

We have substantial operating expenses associated with the development of our product candidates and as of December 31, 2009 we had cash and cash equivalents of $37.8 million.

As of December 31, 2009, our total current liabilities were $63.9 million, including $40.4 million related to our 4% convertible senior subordinated notes which are due in July 2010 and we also had additional debt outstanding. The aggregate long-term principal balance of our outstanding 7.5% and 5.75% convertible senior notes as of December 31, 2009 was $21.2 million.

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We do not expect that our existing cash and cash equivalents, securities available-for-sale, interest receivable as well as proceeds received from our offerings to date will provide sufficient working capital to fund our presently anticipated operations through the third quarter of 2010 and we would therefore need to raise additional capital. We may not be able to raise such capital or if we can, it may not be on favorable terms. There can be no assurance that we will have sufficient earnings, access to liquidity or cash flow in the future to meet our operating expenses and other obligations, including our debt service obligations.

Additional funds may not be available on acceptable terms, or at all; if we fail to raise significant additional funds, we may be forced to cease development of our products and operations.

We may seek to raise additional capital through public or private equity financings, partnerships, joint ventures, dispositions of assets, debt financings or restructurings, bank borrowings or other sources. However, additional funding may not be available on favorable terms or at all and we are subject to certain regulatory and contractual limitations on our financing activities, which may limit our ability to raise additional funding. If adequate funds are not otherwise available, we will further curtail operations significantly, including the delay, modification or cancellation of operations and plans related to pixantrone, OPAXIO and brostallicin, and may be forced to cease operations, liquidate our assets and possibly seek bankruptcy protection.

To obtain additional funding, we may need to enter into arrangements that require us to relinquish rights to certain technologies, drug candidates, products and/or potential markets, such as our transfer of Zevalin assets to RIT Oncology and our subsequent sale of our 50% interest in RIT Oncology.

In addition, some financing alternatives may require us to meet additional regulatory requirements in Italy and the United States, which may increase our costs and adversely affect our ability to obtain financing. To the extent that we raise additional capital through the sale of equity securities, or securities convertible into our equity securities, our shareholders may experience dilution of their proportionate ownership of us.

If our shareholders do not approve an increase in our authorized shares, we may not be able to raise additional funds through equity offerings.

Our shareholders have been asked to vote on a proposal to amend our articles of incorporation to increase the number of authorized shares of common stock at a special meeting of shareholders to be held on April 9, 2010. Even though a quorum requirement has been reduced to one-third of the shares entitled to vote being present or represented at a meeting of our shareholders, the proposed amendment to the articles of incorporation requires an approval of a majority of the shares entitled to vote on the proposal. There is a risk that we may not get shareholder approval to increase the number of authorized shares of common stock. Because of the number of shares reserved for issuance under various convertible securities, derivative securities and otherwise, we do not have enough shares authorized at present to effect an equity financing of any substantial amount. If we do not receive shareholder approval for the proposed increase in authorized shares, our ability to raise capital through equity financings may be adversely affected.

We may need to implement a reduction in expenses across our operations.

We may need substantial additional capital to fund our current operations. If we are unable to secure additional financing on acceptable terms in the near future, we may need to implement additional cost reduction initiatives, such as further reductions in the cost of our workforce and the discontinuation of a number of business initiatives to further reduce our rate of cash utilization and extend our existing cash balances. We believe that these additional cost reduction initiatives, if undertaken, would provide us with additional time to continue our pursuit of additional funding sources and also strategic alternatives. In the event that we are unable to obtain financing on acceptable terms and reduce our expenses, we may be required to limit or cease our operations, pursue a plan to sell our operating assets, or otherwise modify our business strategy, which could materially harm our future business prospects.

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During 2009, we finalized the closure our Italian operations that we used primarily for pre-clinical research. These operations were underutilized due to our current business model that is focused on the development of late-stage compounds and their commercialization. In connection with this closure, we entered into a severance agreement with the unions representing the employees of our Italian operations related to a reduction in force of 56 positions. In addition, we have entered into severance/termination agreements with four Bresso-based directors and are also in the final stages of negotiating severance agreements for the remaining two directors. We expect to save approximately $20.0 million in 2010 and beyond due to the closure of our Italian operations.

We may continue to incur net losses, and we may never achieve profitability.

We were incorporated in 1991 and have incurred a net operating loss every year since our formation. As of December 31, 2009, we had an accumulated deficit of $1.4 billion. We are pursuing regulatory approval for pixantrone, OPAXIO and brostallicin. We will need to conduct research, development, testing and regulatory compliance activities and undertake manufacturing and drug supply activities, expenses which, together with projected general and administrative expenses, may result in operating losses for the foreseeable future. We may never become profitable, even if we are able to commercialize products currently in development or otherwise.

Our debt and operating expenses exceed our net revenues.

We have a substantial amount of debt outstanding, and our annual interest expense with respect to our debt is significant. Unless we raise substantial additional capital and reduce our operating expenses, we may not be able to pay all of our operating expenses or repay our debt or the interest, liquidated damages or other payments that may become due with respect to our debt.

We may be unable to use our net operating losses.

We have substantial tax loss carryforwards for U.S. federal income tax purposes. As a result of prior changes in the stock ownership of the Company, our ability to use such carryforwards to offset future income or tax liability is limited under section 382 of the Internal Revenue Code of 1986, as amended. Moreover, future changes in the ownership of our stock, including those resulting from the issuance of shares of our common stock upon exercise of outstanding warrants, may further limit our ability to use our net operating losses.

We have received audit reports with a going concern disclosure on our consolidated financial statements.

As we may need to raise additional financing to fund our operations and satisfy obligations as they become due, our independent registered public accounting firm has included an explanatory paragraph in their reports on our December 31, 2009, 2008 and 2007 consolidated financial statements regarding their substantial doubt as to our ability to continue as a going concern. This may have a negative impact on the trading price of our common stock and we may have a more difficult time obtaining necessary financing.

Our common stock is listed on the NASDAQ Capital Market and the Mercato Telematico Azionario stock market in Italy, or the MTA, and we may not be able to maintain those listings or trading on these exchanges may be halted or suspended, which may make it more difficult for investors to sell shares of our common stock.

Effective with the opening of trading on January 8, 2009, the U.S. listing of our common stock was transferred to the NASDAQ Capital Market, subject to meeting a minimum market value of listed securities of $35 million. The NASDAQ Listing Qualifications Panel, or the Panel, approved this transfer after our market capitalization did not comply with the minimum market capitalization required for companies listed on the NASDAQ Global Market, and we presented a plan to the Panel for regaining compliance with the NASDAQ Marketplace Rules. On January 23, 2009, we received an Additional Staff Determination Letter, or the Determination Letter, from the NASDAQ that stated that the NASDAQ staff had concluded that we had violated

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Marketplace Rule 4350(i)(1)(C) (now Marketplace Rule 5635), which requires shareholder approval in connection with an acquisition if the issuance or potential issuance is greater than 20% of the pre-acquisition shares outstanding, and that we had at times not complied with Marketplace Rule 4310(c)(17) regarding submission of a Listing of Additional Shares form. On February 18, 2009, we updated the Panel on our plan for regaining compliance and requested an extension of the deadline to regain compliance with the minimum market capitalization requirement for the NASDAQ Capital Market. On March 6, 2009, we were notified by NASDAQ that the Panel had determined to continue the listing of our common stock on the NASDAQ Capital Market, subject to the condition that, on or before April 6, 2009, we demonstrate compliance with all applicable standards for continued listing on the NASDAQ Capital Market, including the $35 million minimum market capitalization requirement. In addition, the Panel issued a public reprimand for our prior failures to comply with the shareholder approval requirements and late filing of Listing of Additional Shares forms. On April 2, 2009, we were notified by the NASDAQ that we had complied with the Panel s decision dated March 6, 2009, and, accordingly, the Panel had determined to continue the listing of our common stock on the NASDAQ Capital Market.

NASDAQ reinstated the $1.00 minimum bid price requirement on August 3, 2009 and there can be no assurances that our stock price will be $1.00 or above. At our Special Meeting of Shareholders held on March 24, 2009, the proposal to allow the Board, in its discretion, to effect a reverse stock split of our common stock was not approved by the shareholders. At any time our stock price is below $1.00, we may not be able to effect a reverse stock split to increase our stock price if we are unable to obtain shareholder approval of a reverse stock split in the future.

In the event our common stock is delisted from NASDAQ, we currently expect that our common stock would be eligible to be listed on the OTC Bulletin Board or Pink Sheets. We do not know what impact delisting from NASDAQ may have on our listing with the Borsa Italiana.

Although we continue to be listed on the NASDAQ Capital Market, trading in our common stock may be halted or suspended due to market conditions or if NASDAQ, CONSOB or the Borsa Italiana determines that trading in our common stock is inadvisable. Trading in our common stock was halted by the Borsa Italiana on February 10, 2009, and, as a consequence, trading in our common stock was halted by NASDAQ. After we provided CONSOB with additional information and clarification on our business operations and financial condition, as requested, and published a press release containing such information in Italy, CONSOB and NASDAQ lifted the trading halt on our stock. In addition, on March 23, 2009, the Borsa Italiana halted trading of our common stock on the MTA stock market and resumed trading prior to opening of the MTA the next day after we filed a press release regarding the explanatory paragraph in our auditor s reports on our December 31, 2008 and 2007 consolidated financial statements regarding their substantial doubt as to our ability to continue as a going concern. As a consequence, NASDAQ also halted trading in our common stock on March 23, 2009, but re-initiated trading later that day. Although we file press releases with CONSOB at the end of each month regarding our business and financial condition, CONSOB may make additional inquiries about our business and financial conditions at any time, and there can be no guarantee that CONSOB or NASDAQ will not halt trading in our shares again in the future.

If our common stock ceases to be listed for trading on the NASDAQ Capital Market, the MTA, or both for any reason or if trading in our stock is halted or suspended on the NASDAQ Capital Market, the MTA or both, such events may harm the trading price of our securities, increase the volatility of the trading price of our securities and make it more difficult for investors to buy or sell shares of our common stock. Moreover, if our common stock ceases to be listed for trading on the NASDAQ Capital Market or if trading in our stock is halted or suspended on the NASDAQ Capital Market, we may become subject to certain obligations. In addition, if we are not listed on the NASDAQ Capital Market and/or if our public float falls below $75 million, we will be limited in our ability to file new shelf registration statements on SEC Form S-3 and/or to fully use one or more registration statements on SEC Form S-3. We have relied significantly on shelf registration statements on SEC Form S-3 for most of our financings in recent years, so any such limitations may have a material adverse effect on our ability to raise the capital we need.

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The global financial crisis may have an impact on our business and financial condition in ways that we currently cannot predict, and may further limit our ability to raise additional funds.

The ongoing credit crisis and related turmoil in the global financial system has had and may continue to have an impact on our business and our financial condition. We may face significant challenges if conditions in the financial markets do not improve or continue to worsen. In particular, our ability to access the capital markets and raise funds required for our operations may be severely restricted at a time when we would like, or need, to do so, which could have an adverse effect on our ability to meet our current and future funding requirements and on our flexibility to react to changing economic and business conditions.

We are required to comply with the regulatory structure of Italy because our stock is traded on the MTA, which could result in administrative challenges.

Our common stock is traded on the Italian MTA stock market in Italy and we are required to also comply with the rules and regulations of CONSOB, which is the public authority responsible for regulating the Italian securities market, and the Borsa Italiana, which ensures the development of the managed market in Italy. Collectively these entities regulate companies listed on Italy s public markets. Conducting our operations in a manner that complies with all of the applicable laws and rules requires us to devote additional time and resources to regulatory compliance matters. For example, the process of seeking to understand and comply with the laws of each country, including tax, labor and regulatory laws, might require us to incur the expense of engaging additional outside counsel, accountants and other professional advisors and might result in delayed business initiatives as we seek to ensure that each new initiative will comply with all of the applicable regulatory regimes. In addition, the Borsa Italiana and CONSOB have made several requests for information asking us to provide additional clarifications about our business operations and financial condition, and we have complied with such requests and have met with CONSOB on several occasions to answer questions. Compliance with Italian regulatory requirements may delay additional issuances of our common stock; we are currently taking steps to attempt to conform to the requirements of the Italian stock exchange and CONSOB to allow such additional issuances.

In addition, under Italian law, we must publish a listing prospectus that has been approved by CONSOB prior to issuing common stock that exceeds, in any twelve-month period, 10% of the number of shares of our common stock outstanding at the beginning of that period. We have attempted to publish a listing prospectus in Italy to cover our general offerings for the past two years, beginning in April 2007. After working with CONSOB to meet its requirements to publish that listing prospectus for the remainder of 2007, we were finally able to publish a listing prospectus in January 2008; however, that listing prospectus was limited to shares to be issued to Société Générale under the Step-Up Equity Financing Agreement we entered into with Société Générale in 2006, which has since terminated. After meeting with CONSOB in 2008 to further discuss its requirements for a more general listing prospectus, we filed a new listing prospectus on December 31, 2008, which was rejected by CONSOB on January 16, 2009. On January 28, 2009, we filed a registration document (i.e., one of the three documents that, according to European Regulation No. 809/2004 and together with the securities note and the summary, constitute a listing prospectus, which can be separately filed, examined and eventually approved by CONSOB).

On July 2, 2009, after several requests of supplements, clarifications and submissions of new drafts of our registration document, CONSOB informed us that the relevant administrative procedure for CONSOB s authorization to publish the registration document had expired since CONSOB alleged that we had not amended the text of the registration document to provide certain information CONSOB had requested. On July 23, 2009, we filed a new draft of the registration document and on September 24, 2009, CONSOB approved publication of such registration document. On September 29, 2009, we published the registration document in Italy and we may use it to register our securities on the Italian stock market.

The registration document will be effective for twelve months from the date of its publication (i.e., twelve months from September 29, 2009). Within such twelve-month period, we will also have to obtain CONSOB s

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clearance over the relevant securities note and summary, which together with the registration document, will constitute a listing prospectus. A listing prospectus will allow us to issue common stock and have it admitted to listing on the Italian MTA over the aforesaid threshold of 10% of the number of shares of our common stock outstanding at the beginning of any twelve-month period. Pending CONSOB s clearance of the securities note and the summary, we are required to raise money using alternative forms of securities. For example, we may need to use convertible preferred stock and convertible debt in lieu of our common stock because convertible preferred stock and convertible debt, subject to the provisions of European Directive No. 71/2003 and according to the interpretations of the Committee of European Securities Regulators (CESR), are not subject to the 10% limitation imposed by European Union and Italian law.

Moreover, on December 23, 2008, CONSOB sent a notice to us requesting that we issue (i) immediately, a press release providing, among other things, information about our debt restructuring plan, the current state of compliance with the relevant covenants regulating our debt and the equity line of credit agreement we entered into with Midsummer Investment Ltd., or Midsummer, on July 29, 2008, and (ii) by the end of each month and starting from the month of December 2008, a press release providing certain information relating to our management and financial situation, updated to the previous month, or the Monthly CONSOB Press Release. On July 31, 2009, CONSOB sent us a notice asserting three violations of the provisions of Section 114, paragraph 5 of the Italian Legislative Decree no. 58/98. The sanctions established by the Section 193, paragraph 1 of the Italian Legislative Decree no. 58/1998 for such violations are pecuniary administrative sanctions amounting to between 5,000 and 500,000, applicable to each one of the three asserted violations. According to the applicable Italian legal provisions, CONSOB may impose such administrative sanctions by means of a decree stating the grounds of its decision only after evaluating our possible defenses that were submitted to CONSOB on August 28, 2009 (within 30 days of July 31, 2009, the notification date of the relevant charges, according to the applicable Italian rules).

On December 10, 2009, CONSOB sent us a notice claiming two violations of the provisions of Section 114, paragraph 1 of the Italian Legislative Decree no. 58/98 due to the asserted late disclosure of certain information reported, at CONSOB s request, in the press release disseminated on December 19, 2008 and March 23, 2009. The sanctions established by the Section 193, paragraph 1 of the Italian Legislative Decree no. 58.1998 for such violations are pecuniary administrative sanctions amounting to between 5,000 and 500,000, applicable to each one of the two asserted violations. According to the applicable Italian legal provisions, CONSOB may impose such administrative sanctions by means of a decree stating the grounds of its decision only after evaluating our possible defenses that were submitted to CONSOB on January 8, 2010 (within 30 days of December 10, 2009, the notification date of the relevant charges, according to the applicable Italian rules).

Our assets and liabilities that remain in our Italian branch make us subject to increased risk regarding currency exchange rate fluctuations.

We are exposed to risks associated with the translation of euro-denominated financial results and accounts into U.S. dollars. As long as we continue to have assets and liabilities held in our Italian branch, the carrying value of these assets and liabilities will be affected by fluctuations in the value of the U.S. dollar as compared to the euro. Changes in the value of the U.S. dollar as compared to the euro might have an adverse effect on our reported results of operations and financial condition.

We may owe additional amounts for value added taxes related to our operations in Europe.

Our European operations are subject to Value Added Tax, or VAT, which is usually applied to all goods and services purchased and sold throughout Europe. The VAT receivable is $6.3 million as of December 31, 2009 and December 31, 2008. On April 14, 2009 and December 21, 2009, the Italian Tax Authority, or ITA, issued notices of assessment to CTI (Europe) based on the ITA s audit of CTI (Europe) s VAT returns for the years 2003 and 2005, respectively. The ITA audits concluded that CTI (Europe) did not collect and remit VAT on certain invoices issued to non-Italian clients for services performed by CTI (Europe). The assessment for the year

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2003 is 0.5 million, or approximately $0.8 million as of December 31, 2009, including interest and penalties. The assessment for the year 2005 is 5.5 million, or approximately $7.7 million as of December 31, 2009, including interest and penalties. We believe that the services were non-VAT taxable consultancy services and that the VAT returns are correct as originally filed and we intend to vigorously defend ourselves against the assessment and have requested a dismissal on procedural grounds and merits of the case. However, if we are unable to defend ourselves against the year 2003 and 2005 assessments and if we receive an assessment for subsequent years, it may harm our results of operations and financial condition.

Our financial condition may be adversely affected if third parties default in the performance of contractual obligations.

Because we do not currently have any marketed products producing revenue, our business is dependent on the performance by third parties of their responsibilities under contractual relationships and if third parties default on their performance of their contractual obligations, we could suffer significant financial losses and operational problems, which could in turn adversely affect our financial performance, cash flows or results of operations and may jeopardize our ability to maintain our operations.

We may not realize any royalties, milestone payments or other benefits under the License and Co-Development Agreement entered into with Novartis Pharmaceutical Company Ltd.

We have entered into a License and Co-Development agreement related to OPAXIO and pixantrone with Novartis pursuant to which Novartis received an exclusive worldwide license for the development and commercialization of OPAXIO and an option to enter into an exclusive worldwide license to develop and commercialize pixantrone. We will not receive any royalty or milestone payments under this agreement unless Novartis exercises its option related to pixantrone and we are able to reach a definitive agreement or Novartis elects to participate in the development and commercialization of OPAXIO. Novartis is under no obligation to make such election and enter into a definitive license agreement or exercise such right and may never do so. In addition, even if Novartis exercises such rights, any royalties and milestone payments we may be eligible to receive from Novartis are subject to the receipt of the necessary regulatory approvals and the attainment of certain sales levels. In the event Novartis does not elect to participate in the development of OPAXIO or pixantrone, we may not be able to find another suitable partner for the commercialization and development of those products, which may have an adverse effect on our ability to bring those drugs to market. In addition, we would need to obtain a release from Novartis prior to entering into any agreement to develop and commercialize pixantrone or OPAXIO with a third party. We may never receive the necessary regulatory approvals and our products may not reach the necessary sales levels to generate royalty or milestone payments even if Novartis elects to exercise its option with regard to pixantrone and enter into a definitive license agreement or to participate in the development and commercialization of OPAXIO. Novartis has the right under the agreement in its sole discretion to terminate such agreement at any time upon written notice to us.

We may be delayed, limited or precluded from obtaining regulatory approval of OPAXIO given that our three STELLAR phase III clinical trials for the treatment of non-small cell lung cancer did not meet their primary endpoints and we withdrew our Marketing Authorization Application, or MAA, from the EMEA for first-line treatment of patients with advanced non-small lung cancer, or NSCLC, to refocus our resources on approval of OPAXIO for other indications.

We cannot guarantee that we will obtain regulatory approval to manufacture or market any of our drug candidates. Obtaining regulatory approval to market drugs to treat cancer is expensive, difficult and risky. Preclinical and clinical data can be interpreted in different ways, which could delay, limit or preclude regulatory approval. Negative or inconclusive results or adverse medical events during a clinical trial could delay, limit or prevent regulatory approval.

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Our future financial success depends in part on obtaining regulatory approval of OPAXIO. In March 2005, we announced the results of STELLAR 3, and in May 2005, we announced the results of STELLAR 2 and 4, our phase III clinical trials of OPAXIO in non-small cell lung cancer. All three trials failed to achieve their primary endpoints of superior overall survival compared to current marketed agents for treating NSCLC.

In December 2006, we closed the PIONEER clinical trial, and in 2007 we initiated a new study in the United States, PGT307, which focuses on the primary efficacy endpoint of survival in women with NSCLC and pre-menopausal estrogen levels. To conserve limited financial resources, we decided not to initiate an additional study, the PGT306 trial, for which we had submitted an SPA. We also feel that compelling evidence from one trial, the PGT307 trial, along with supporting evidence from earlier clinical trials, may be adequate to submit an NDA for OPAXIO even though the FDA has established a requirement that two adequate and well-controlled pivotal studies demonstrating a statistically significant improvement in overall survival will be required for approval of OPAXIO in the NSCLC setting. We may not receive compelling evidence or any positive results from the PGT307 trial, which would preclude our planned submission of an NDA to the FDA, and would preclude us from marketing OPAXIO for this indication in the United States.

Based on discussions with the EMEA Scientific Advice Working Party, we submitted an MAA for OPAXIO in Europe on March 4, 2008 based on results of the STELLAR trials. In April 2009, the MAA was accepted for review by the EMEA; however, in September 2009, we notified the EMEA of our decision to withdraw the MAA and refocus our resources on the approval of OPAXIO for its potential superiority indication in maintenance therapy for ovarian cancer.

We are subject to extensive government regulation.

We are subject to rigorous and extensive regulation by the FDA in the United States and by comparable agencies in other states and countries. Failure to comply with regulatory requirements could result in various adverse consequences, including possible delay in approval or refusal to approve a product, withdrawal of approved products from the market, product seizures, injunctions, regulatory restrictions on our business and sales activities, monetary penalties, or criminal prosecution.

Our products may not be marketed in the United States until they have been approved by the FDA and may not be marketed in other countries until they have received approval from the appropriate agencies. None of our current product candidates have received approval for marketing in any country. On April 13, 2009, we began submission of a rolling NDA to the FDA for pixantrone to treat relapsed aggressive NHL. We completed the submission in June 2009 and we have been notified by the FDA that a PDUFA action date of April 23, 2010 under standard review has been established.

Obtaining regulatory approval requires substantial time, effort and financial resources, and we may not be able to obtain approval of any of our products on a timely basis, or at all. In addition, data obtained from preclinical and clinical trials are susceptible to varying interpretations, and government regulators and our collaborators may not agree with our interpretation of our clinical trial results. If our products are not approved quickly enough to provide net revenues to defray our debt and operating expenses, our business, financial condition and results of operations will be adversely affected.

In the event that we receive marketing approval for any of our product candidates, we will be subject to numerous regulations and statutes regulating the manner of selling and obtaining reimbursement for those products. For example, federal statutes generally prohibit providing certain discounts and payments to physicians to encourage them to prescribe our product. Violations of such regulations or statutes may result in treble damages, criminal or civil penalties, fines or exclusion of us or our employees from participation in federal and state health care programs. Although we have policies prohibiting violations of relevant regulations and statutes, unauthorized actions of our employees or consultants, or unfavorable interpretations of such regulations or statutes may result in third parties or regulatory agencies bringing legal proceedings or enforcement actions

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against us. Because we will likely need to develop a new sales force for any future marketed products, we may have a greater risk of such violations from lack of adequate training or experience. The expense to retain and pay legal counsel and consultants to defend against any such proceedings would be substantial, and together with the diversion of management s time and attention to assist in any such defense, may negatively affect our business, financial condition and results of operations.

In addition, both before and after approval, our contract manufacturers and our products are subject to numerous regulatory requirements covering, among other things, testing, manufacturing, quality control, labeling, advertising, promotion, distribution and export. Manufacturing processes must conform to current Good Manufacturing Practice, or cGMPs. The FDA and other regulatory authorities periodically inspect manufacturing facilities to assess compliance with cGMPs. Accordingly, manufacturers must continue to expend time, money and effort to maintain compliance.

In October 2009, the FDA inspected our contract manufacturing facility located in Milan, Italy and, based on its inspection, made observations regarding the manufacturing process and controls over our lead compound, pixantrone. Our contract manufacturer addressed and responded to the FDA s observations in November 2009. Neither our contract manufacturer nor the Company have received any further response from the FDA regarding our contract manufacturer s planned action as of February 22, 2010. Failure to comply with FDA, EMEA or other applicable regulations may cause us to curtail or stop the manufacture of such products until we obtain regulatory compliance.

The marketing and promotion of pharmaceuticals is also heavily regulated, particularly with regard to prohibitions on the promotion of products for off-label uses. In April 2007, we paid a civil penalty of $10.6 million and entered into a settlement agreement with the United States Attorney s Office for the Western District of Washington arising out of their investigation into certain of our prior marketing practices relating to TRISENOX, which was divested to Cephalon Inc. in July 2005. As part of that settlement agreement and in connection with the acquisition of Zevalin, we also entered into a corporate integrity agreement with the Office of Inspector General of the U.S. Department of Health and Human Services, which required us to establish a compliance committee and compliance program and adopt a formal code of conduct.

We face direct and intense competition from our competitors in the biotechnology and pharmaceutical industries, and we may not compete successfully against them.

Competition in the oncology market is intense and is accentuated by the rapid pace of technological development. We anticipate that we will face increased competition in the future as new companies enter the market. Our competitors in the United States and elsewhere are numerous and include, among others, major multinational pharmaceutical companies, specialized biotechnology companies and universities and other research institutions. Specifically:

Because pixantrone is intended to provide less toxic treatments to patients who have failed standard chemotherapy treatment, if we are successful in bringing pixantrone to market, it is not expected to compete directly with many existing chemotherapies. However, pixantrone will face competition from currently marketed anthracyclines, such as mitoxantrone (Novantrone®), and new anti-cancer drugs with reduced toxicity that may be developed and marketed.

If we are successful in bringing OPAXIO to market, we will face direct competition from oncology-focused multinational corporations. OPAXIO will compete with other taxanes. Many oncology-focused multinational corporations currently market or are developing taxanes, epothilones, and other cytotoxic agents, which inhibit cancer cells by a mechanism similar to taxanes, or similar products. Such corporations include, among others, Bristol-Myers Squibb Co. and others, which markets paclitaxel and generic forms of paclitaxel; Sanofi-Aventis, which markets docetaxel; Genentech, Roche and OSI Pharmaceuticals, which market Tarceva ; Genentech and Roche, which market Avastin ; Eli Lilly, which markets Alimta®; and Abraxis, which markets Abraxane . In addition, other companies such as NeoPharm Inc. and Telik, Inc. are also developing products, which could compete with OPAXIO.

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If we are successful in bringing brostallicin to market, we will face direct competition from other minor groove binding agents including Yondelis®, which is currently developed by PharmaMar and has received Authorization of Commercialization from the European Commission for soft tissue sarcoma.

Many of our competitors, particularly the multinational pharmaceutical companies, either alone or together with their collaborators, have substantially greater financial resources and substantially larger development and marketing teams than us. In addition, many of our competitors, either alone or together with their collaborators, have significantly greater experience than we do in developing, manufacturing and marketing products. As a result, these companies products might come to market sooner or might prove to be more effective, less expensive, have fewer side effects or be easier to administer than ours. In any such case, sales of our current or future products would likely suffer and we might never recoup the significant investments we are making to develop these product candidates.

Uncertainty regarding third-party reimbursement and healthcare cost containment initiatives may limit our returns.

The ongoing efforts of governmental and third-party payors to contain or reduce the cost of healthcare may affect our ability to commercialize our products successfully. Governmental and other third-party payors continue to attempt to contain healthcare costs by:

challenging the prices charged for health care products and services;

limiting both coverage and the amount of reimbursement for new therapeutic products;

denying or limiting coverage for products that are approved by the FDA but are considered experimental or investigational by third-party payors;

refusing in some cases to provide coverage when an approved product is used for disease indications in a way that has not received FDA marketing approval; and

denying coverage altogether.

The trend toward managed healthcare in the United States, the growth of organizations such as health maintenance organizations, and legislative proposals to reform healthcare and government insurance programs could significantly influence the purchase of healthcare services and products, resulting in lower prices and reducing demand for our products. In addition, in almost all European markets, pricing and choice of prescription pharmaceuticals are subject to governmental control. Therefore, the price of our products and their reimbursement in Europe will be determined by national regulatory authorities.

Even if we succeed in bringing any of our proposed products to the market, they may not be considered cost-effective and third-party reimbursement might not be available or sufficient. If adequate third-party coverage is not available, we may not be able to maintain price levels sufficient to realize an appropriate return on our investment in research and product development. In addition, legislation and regulations affecting the pricing of pharmaceuticals may change in ways adverse to us before or after any of our proposed products are approved for marketing.

Even if our drug candidates are successful in clinical trials, we may not be able to successfully commercialize them.

Since our inception in 1991, we have dedicated substantially all of our resources to the research and development of our technologies and related compounds. All of our compounds currently are in research or development, and have not received marketing approval.

Prior to commercialization, each product candidate requires significant research, development and preclinical testing and extensive clinical investigation before submission of any regulatory application for

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marketing approval. The development of anti-cancer drugs, including those we are currently developing, is unpredictable and subject to numerous risks. Potential products that appear to be promising at early stages of development may not reach the market for a number of reasons including that they may:

- be found ineffective or cause harmful side effects during preclinical testing or clinical trials;
- fail to receive necessary regulatory approvals;
- be difficult to manufacture on a scale necessary for commercialization;
- be uneconomical to produce;
- fail to achieve market acceptance; or
- be precluded from commercialization by proprietary rights of third parties.

The occurrence of any of these events could adversely affect the commercialization of our products. Products, if introduced, may not be successfully marketed and/or may not achieve customer acceptance. If we fail to commercialize products or if our future products do not achieve significant market acceptance, we will not likely generate significant revenues or become profitable.

If any of our license agreements for intellectual property underlying pixantrone, OPAXIO, brostallicin, or any other products are terminated, we may lose the right to develop or market that product.

We have licensed intellectual property, including patent applications relating to intellectual property for pixantrone and brostallicin. We have also in-licensed the intellectual property for our drug delivery technology relating to OPAXIO which uses polymers that are linked to drugs, known as polymer-drug conjugates. Some of our product development programs depend on our ability to maintain rights under these licenses. Each licensor has the power to terminate its agreement with us if we fail to meet our obligations under these licenses. We may not be able to meet our obligations under these licenses. If we default under any license agreement, we may lose our right to market and sell any products based on the licensed technology.

If we fail to adequately protect our intellectual property, our competitive position could be harmed.

Development and protection of our intellectual property are critical to our business. If we do not adequately protect our intellectual property, competitors may be able to practice our technologies. Our success depends in part on our ability to:

- obtain patent protection for our products or processes both in the United States and other countries;
- protect trade secrets; and
- prevent others from infringing on our proprietary rights.

When polymers are linked, or conjugated, to drugs, the results are referred to as polymer-drug conjugates. We are developing drug delivery technology that links chemotherapy to biodegradable polymers. For example, OPAXIO is paclitaxel, the active ingredient in Taxol®, one of the world s best selling cancer drugs, linked to polyglutamate. We may not receive a patent for all of our polymer-drug conjugates and we may be

challenged by the holder of a patent covering the underlying drug and/or methods for its use or manufacture.

The patent position of biopharmaceutical firms generally is highly uncertain and involves complex legal and factual questions. The U.S. Patent and Trademark Office has not established a consistent policy regarding the breadth of claims that it will allow in biotechnology patents. If it allows broad claims, the number and cost of patent interference proceedings in the United States and the risk of infringement litigation may increase. If it allows narrow claims, the risk of infringement may decrease, but the value of our rights under our patents, licenses and patent applications may also decrease. Patent applications in which we have rights may never issue as patents and the claims of any issued patents may not afford meaningful protection for our technologies or

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products. In addition, patents issued to us or our licensors may be challenged and subsequently narrowed, invalidated or circumvented. Litigation, interference proceedings or other governmental proceedings that we may become involved in with respect to our proprietary technologies or the proprietary technology of others could result in substantial cost to us. Patent litigation is widespread in the biotechnology industry, and any patent litigation could harm our business. Costly litigation might be necessary to protect a patent position or to determine the scope and validity of third-party proprietary rights, and we may not have the required resources to pursue any such litigation or to protect our patent rights. Any adverse outcome in litigation with respect to the infringement or validity of any patents owned by third parties could subject us to significant liabilities to third parties, require disputed rights to be licensed from third parties or require us to cease using a product or technology.

We also rely upon trade secrets, proprietary know-how and continuing technological innovation to remain competitive. Third parties may independently develop such know-how or otherwise obtain access to our technology. While we require our employees, consultants and corporate partners with access to proprietary information to enter into confidentiality agreements, these agreements may not be honored.

Our products could infringe upon the intellectual property rights of others, which may cause us to engage in costly litigation and, if unsuccessful, could cause us to pay substantial damages and prohibit us from selling our products.

We attempt to monitor patent filings for patents that may be relevant to our products and product candidates in an effort to guide the design and development of our products to avoid infringement but have not conducted an exhaustive search. We may not be able to successfully challenge the validity of these patents and could be required to pay substantial damages, possibly including treble damages, for past infringement and attorneys fees if it is ultimately determined that our products infringe a third-party s patents. Further, we may be prohibited from selling our products before we obtain a license, which, if available at all, may require us to pay substantial royalties. Moreover, third parties may challenge the patents that have been issued or licensed to us. Even if infringement claims against us are without merit, or if we challenge the validity of issued patents, lawsuits take significant time, may be expensive and may divert management attention from other business concerns.

We may be unable to obtain a quorum for meetings of our shareholders or obtain necessary shareholder approvals and therefore be unable to take certain corporate actions.

Our amended and restated articles of incorporation require that a quorum, consisting of one-third of the outstanding shares of voting stock, be represented in person or by proxy in order to transact business at a meeting of our shareholders. In addition, amendments to our amended and restated articles of incorporation, such as an amendment to increase our authorized capital stock, require the approval of a majority of our outstanding shares. A substantial majority of our common shares are held by Italian institutions and, under Italian laws and regulations, it is difficult to communicate with the beneficial holders of those shares to obtain votes. In 2006, when a quorum required a majority of the outstanding shares of our voting stock be represented in person or by proxy, we scheduled two annual meetings of shareholders, but were unable to obtain quorum at either meeting. Following that failure to obtain quorum, we contacted certain depository banks in Italy where significant numbers of shares of our common stock were held and asked them to cooperate by making a book-entry transfer of their share positions at Monte Titoli to their U.S. correspondent bank, who would then transfer the shares to an account of the Italian bank at a U.S. broker-dealer that is an affiliate of that bank. Certain of the banks contacted agreed to make the share transfer pursuant to these arrangements as of the record date of the meeting, subject to the relevant beneficial owner taking no action to direct the voting of such shares. Under Rule 452 of the New York Stock Exchange, the U.S. broker-dealer may vote shares absent direction from the beneficial owner on certain matters, such as the uncontested election of directors, an amendment to our amended and restated articles of incorporation to increase authorized shares that are to be used for general corporate purposes, and the ratification of our auditors. As a result of this custody transfer, we were able to hold special meetings of the shareholders in April 2007, January 2008 and March 2009 and annual meetings of the shareholders in September 2007, June 2008 and October 2009. At the meeting in June 2008, our shareholders approved a proposal to reduce

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our quorum requirement from a majority of outstanding voting shares to one-third of outstanding voting shares. However, obtaining a quorum at future meetings even at the lower threshold and obtaining necessary shareholder approvals will depend in part upon the willingness of the Italian depository banks to continue participating in the custody transfer arrangements, and we cannot be assured that those banks that have participated in the past will continue to participate in custody transfer arrangements in the future. We are continuing to explore other alternatives to achieve quorum for and shareholder representation at our meetings; however, we cannot be certain that we will find an alternate method if we are unable to continue to use the custody transfer arrangements. As a result, we may be unable to obtain a quorum at future annual or special meetings of shareholders or obtain shareholder approval of proposals when needed.

If we are unable to obtain a quorum at our shareholder meetings and thus fail to get shareholder approval of corporate actions, such failure could have a materially adverse effect on us. In addition, brokers may only vote on those matters for which broker discretionary voting is allowed under Rule 452 of the New York Stock Exchange, and we may not be able to obtain the required number of votes to approve certain proposals that require a majority of all outstanding shares to approve the proposal due to our reliance on broker discretionary voting. Therefore it is possible that even if we are able to obtain a quorum for our meetings of the shareholders we still may not receive enough votes to approve proxy proposals presented at such meeting and, depending on the proposal in question, including the proposal submitted to our shareholders to be determined at the special meeting of shareholders being held on April 9, 2010 to increase the number of authorized shares of our common stock, such failure could have a material adverse effect on us. For example, a proposal to approve a reverse stock split failed to receive sufficient votes to pass at the March 2009 shareholders meeting.

We could fail in financing efforts or be delisted from NASDAQ if we fail to receive shareholder approval when needed.

We are required under the NASDAQ Marketplace Rules to obtain shareholder approval for any issuance of additional equity securities that would comprise more than 20% of the total shares of our common stock outstanding before the issuance of such securities sold at a discount to the greater of book or market value in an offering that is not deemed to be a public offering by NASDAQ. Funding of our operations in the future may require issuance of additional equity securities that would comprise more than 20% of the total shares of our common stock outstanding, but we might not be successful in obtaining the required shareholder approval for such an issuance, particularly in light of the difficulties we have experienced in obtaining a quorum and holding shareholder meetings as outlined above. If we are unable to obtain financing due to shareholder approval difficulties, such failure may have a material adverse effect on our ability to continue operations.

We may be unable to obtain the raw materials necessary to produce our OPAXIO product candidate in sufficient quantity to meet demand when and if such product is approved.

We may not be able to continue to purchase the materials necessary to produce OPAXIO, including paclitaxel, in adequate volume and quality. Paclitaxel is derived from certain varieties of yew trees and the supply of paclitaxel is controlled by a limited number of companies. Paclitaxel is available and we have purchased it from several sources. We purchase the raw materials paclitaxel and polyglutamic acid from single sources. Should the paclitaxel or polyglutamic acid purchased from our sources prove to be insufficient in quantity or quality, should a supplier fail to deliver in a timely fashion or at all, or should these relationships terminate, we may not be able to qualify and obtain a sufficient supply from alternate sources on acceptable terms, or at all.

Our dependence on third-party manufacturers means that we do not always have direct control over the manufacture, testing or distribution of our products.

We do not currently have internal analytical laboratory or manufacturing facilities to allow the testing or production and distribution of drug products in compliance with cGMPs. Because we do not directly control our suppliers, these vendors may not be able to provide us with finished product when we need it.

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We will be dependent upon these third parties to supply us in a timely manner with products manufactured in compliance with cGMPs or similar manufacturing standards imposed by United States and/or foreign regulatory authorities where our products will be tested and/or marketed. While the FDA and other regulatory authorities maintain oversight for cGMP compliance of drug manufacturers, contract manufacturers and contract service providers may at times violate cGMPs. The FDA and other regulatory authorities may take action against a contract manufacturer who violates cGMPs. In October 2009, the FDA inspected our contract manufacturing facility located in Milan, Italy and, based on its inspection, made observations regarding the manufacturing process and controls over our lead compound, pixantrone. Our contract manufacturer addressed and responded to the FDA s observations in November 2009. Neither our contract manufacturer nor the Company have received any further response from the FDA regarding our contract manufacturer s planned action as of February 22, 2010. Failure to comply with FDA, EMEA or other applicable regulations may cause us to curtail or stop the manufacture of such products until we obtain regulatory compliance.

In addition, one of our other products under development, OPAXIO, has a complex manufacturing process and supply chain, which may prevent us from obtaining a sufficient supply of drug product for the clinical trials and commercial activities currently planned or underway on a timely basis, if at all. The active pharmaceutical ingredients and drug products for pixantrone and brostallicin are both manufactured by a single vendor. Finished product manufacture and distribution for both pixantrone and brostallicin are to be manufactured and distributed by different single vendors. We are currently disputing our right to cancel the exclusive manufacturing contract between us and the former manufacturer of pixantrone. We assert multiple grounds for terminating this exclusive manufacturing agreement, which the former manufacturer disputes. The former manufacturer has asserted that we do not have the right to terminate the manufacturing contracts and has filed a lawsuit in the Court of Milan to compel us to source pixantrone from that manufacturer. A hearing was held on January 21, 2010 to discuss preliminary matters and set a schedule for future filings and hearings. The next hearing date is scheduled for November 11, 2010.

If we do not successfully develop our product candidates into marketable products, we may be unable to generate significant revenue or become profitable.

We divested our commercial product, TRISENOX, in July 2005 and fully divested our commercial product, Zevalin, in March 2009. Currently, we do not have a marketed product, and unless we are able to develop one of our product candidates, such as pixantrone, into an approved commercial product, we will not generate any significant revenues from product sales, royalty payments, license fees or otherwise. Pixantrone, OPAXIO and brostallicin are currently in clinical trials; these clinical trials may not be successful and, even if they are, we may not be successful in developing any of them into a commercial product. For example, our STELLAR phase III clinical trials for OPAXIO for the treatment of non-small cell lung cancer failed to meet their primary endpoints. In addition, a number of companies in the pharmaceutical industry, including us, have suffered significant setbacks in advanced clinical trials, even after reporting promising results in earlier trials. We will need to commit significant time and resources to develop these and any additional product candidates. Our product candidates will be successful only if:

- our product candidates are developed to a stage that will enable us to commercialize them or sell related marketing rights to pharmaceutical companies;
- we are able to commercialize product candidates in clinical development or sell the marketing rights to third parties; and
- our product candidates, if developed, are approved by the regulatory authorities.

We are dependent on the successful completion of these goals in order to generate revenues. The failure to generate such revenues may preclude us from continuing our research and development of these and other product candidates.

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If we are unable to enter into new in-licensing arrangements, our future product portfolio and potential profitability could be harmed.

One component of our business strategy is in-licensing drug compounds developed by other pharmaceutical and biotechnology companies or academic research laboratories. All of our product candidates in clinical development are in-licensed from a third-party, including pixantrone, OPAXIO and brostallicin.

Competition for new promising compounds and commercial products can be intense. If we are not able to identify future in-licensing opportunities and enter into future licensing arrangements on acceptable terms, our future product portfolio and potential profitability could be harmed.

We may take longer to complete our clinical trials than we expect, or we may not be able to complete them at all.

Before regulatory approval for any potential product can be obtained, we must undertake extensive clinical testing on humans to demonstrate the safety and efficacy of the product. Although for planning purposes we forecast the commencement and completion of clinical trials, the actual timing of these events can vary dramatically due to a number of factors. For example:

- we may not obtain authorization to permit product candidates that are already in the preclinical development phase to enter the human clinical testing phase;
- authorized preclinical or clinical testing may require significantly more time, resources or expertise than originally expected to be necessary;
- clinical testing may not show potential products to be safe and efficacious and, as with many drugs, may fail to demonstrate the desired safety and efficacy characteristics in human clinical trials;
- clinical testing may show that potential products are not appropriate for the specific indication for which they are being tested;
- the results from preclinical studies and early clinical trials may not be indicative of the results that will be obtained in later-stage clinical trials;
- we or regulatory authorities may suspend clinical trials at any time on the basis that the participants are being exposed to unacceptable health risks or for other reasons; and
- completion of clinical trials depends on, among other things, the number of patients available for enrollment in a particular trial, which is a function of many factors, including the number of patients with the relevant conditions, the nature of the clinical testing, the proximity of patients to clinical testing centers, the eligibility criteria for tests as well as competition with other clinical testing programs involving the same patient profile but different treatments.

We have limited experience in conducting clinical trials. We expect to continue to rely on third parties, such as contract research organizations, academic institutions and/or cooperative groups, to conduct, oversee and monitor clinical trials as well as to process the clinical results and manage test requests, which may result in delays or failure to complete trials if the third parties fail to perform or to meet the applicable standards.

If we fail to commence, complete, experience delays in any of our present or planned clinical trials or need to perform more or larger clinical trials than planned, our development costs may increase and/or our ability to commercialize our product candidates may be adversely affected. If delays or costs are significant, our financial results and our ability to commercialize our product candidates may be adversely affected.

If we fail to establish and maintain collaborations or if our partners do not perform, we may be unable to develop and commercialize our product candidates.

We have entered into collaborative arrangements with third-parties to develop and/or commercialize product candidates and are currently seeking additional collaborations. For example, we entered into an agreement with

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the Gynecologic Oncology Group to perform a phase III trial of OPAXIO in patients with ovarian cancer. Additional collaborations might be necessary in order for us to fund our research and development activities and third-party manufacturing arrangements, seek and obtain regulatory approvals and successfully commercialize our existing and future product candidates. If we fail to enter into additional collaborative arrangements or fail to maintain our existing collaborative arrangements, the number of product candidates from which we could receive future revenues would decline. For example, in 2005 we sold our product TRISENOX to Cephalon and, pursuant to the terms of the purchase agreement under which TRISENOX was sold, we are entitled to receive milestone payments upon the approval by the FDA of new labeled uses for TRISENOX; however, Cephalon may decide not to submit any additional information to the FDA to apply for label expansion of TRISENOX, in which case we would not receive a milestone payment under the agreement.

Our dependence on collaborative arrangements with third parties will subject us to a number of risks that could harm our ability to develop and commercialize products, including that:

- collaborative arrangements may not be on terms favorable to us;
- disagreements with partners may result in delays in the development and marketing of products, termination of our collaboration agreements or time consuming and expensive legal action;
- we cannot control the amount and timing of resources partners devote to product candidates or their prioritization of product candidates and partners may not allocate sufficient funds or resources to the development, promotion or marketing of our products, or may not perform their obligations as expected;
- partners may choose to develop, independently or with other companies, alternative products or treatments, including products or treatments which compete with ours;
- agreements with partners may expire or be terminated without renewal, or partners may breach collaboration agreements with us;
- business combinations or significant changes in a partner s business strategy might adversely affect that partner s willingness or ability to complete its obligations to us; and
- the terms and conditions of the relevant agreements may no longer be suitable.

The occurrence of any of these events could adversely affect the development or commercialization of our products.

Because we base several of our drug candidates on unproven technologies, we may never develop them into commercial products.

We base several of our product candidates upon novel technologies that we are using to develop drugs for the treatment of cancer. These technologies have not been proven. Furthermore, preclinical results in animal studies may not predict outcomes in human clinical trials. Our product candidates may not be proven safe or effective. If these technologies do not work, our drug candidates will not develop into commercial products.

Because there is a risk of product liability associated with our products, we face potential difficulties in obtaining insurance.

Our business exposes us to potential product liability risks inherent in the testing, manufacturing and marketing of human pharmaceutical products, and we may not be able to avoid significant product liability exposure. While we have insurance covering the product use in our clinical trials for our product candidates, it is possible that we will not be able to maintain such insurance on acceptable terms or that any insurance obtained will not provide adequate coverage against potential liabilities. Our inability to obtain sufficient insurance coverage at an acceptable cost or otherwise to protect against potential product liability claims could prevent or limit the commercialization of any products we

develop. A successful product liability claim in excess of our insurance coverage could exceed our net worth.

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Since we use hazardous materials in our business, we may be subject to claims relating to improper handling, storage or disposal of these materials.

Our research and development activities involve the controlled use of hazardous materials, chemicals and various radioactive compounds. We are subject to international, federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of such materials and certain waste products. Although we believe that our safety procedures for handling and disposing of such materials comply with the standards prescribed by the regulations, the risk of accidental contamination or injury from these materials cannot be eliminated completely. In the event of such an accident, we could be held liable for any damages that result and any such liability not covered by insurance could exceed our resources. Compliance with environmental laws and regulations may be expensive, and current or future environmental regulations may impair our research, development or production efforts.

We may not be able to conduct animal testing in the future, which could harm our research and development activities.

Certain of our research and development activities involve animal testing. Such activities have been the subject of controversy and adverse publicity. Animal rights groups and other organizations and individuals have attempted to stop animal testing activities by pressing for legislation and regulation in these areas and by disrupting activities through protests and other means. To the extent the activities of these groups are successful, our business could be materially harmed by delaying or interrupting our research and development activities.

The unfavorable outcome of litigation and other claims against us could have a material adverse impact on our financial condition and results of operations.

We are subject to a variety of claims and lawsuits from time to time, some of which arise in the ordinary course of our business. Adverse outcomes in some or all of such pending cases may result in significant monetary damages or injunctive relief against us. While we currently believe that resolution of these matters, individually or in the aggregate, will not have a material adverse impact on our financial position, results of operations or trading price of our securities, the ultimate outcome of litigation and other claims is subject to inherent uncertainties, and our view of these matters may change in the future. It is possible that our financial condition and results of operations could be materially adversely affected in any period in which the effect of an unfavorable final outcome becomes probable and reasonably estimable.

Our financial condition and results of operations could be adversely affected by public health issues, wars and other military action, as well as terrorist attacks and threats and government responses thereto, especially if any such actions were directed at us or our facilities or customers.

Public health issues, terrorist attacks in the United States and elsewhere, government responses thereto, and military actions in Iraq, Afghanistan and elsewhere, may disrupt our operations or those of our customers and suppliers and may affect the availability of materials needed to manufacture our products or the means to transport those materials to manufacturing facilities and finished products to customers. In June 2009, the World Health Organization declared an H1N1 influenza, or swine flu, pandemic, and such pandemic could cause damage or disruption to international commerce by creating economic and political uncertainties that may have a strong negative impact on the global economy, us, and our customers or suppliers. Should the severity of the H1N1 influenza pandemic increase or other public health issues arise, we could be negatively impacted by the need for more stringent employee travel restrictions, additional limitations in the availability of freight services, governmental actions limiting the movement of products between various regions and disruptions in the operations of our customers or suppliers. The long-term effects of the H1N1 pandemic, the terrorist attacks, and the ongoing war on terrorism on our business and on the global economy remain unknown. In addition, any of these events could increase volatility in the United States and world financial markets which may depress the price of our common stock and may limit the capital resources available to us or our customers or suppliers,

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which could result in decreased orders from customers, less favorable financing terms from suppliers, and scarcity or increased costs of materials and components of our products. Additionally, terrorist attacks directly upon us may significantly disrupt our ability to conduct our business. Any of these occurrences could have a significant impact on our operating results, revenues and costs and may result in increased volatility of the trading price of our securities.

Risks Related To the Securities Markets

The market price for shares of our common stock is extremely volatile, which may affect our ability to raise capital in the future and may subject the value of your investment in our securities to sudden decreases.

The market price for securities of biopharmaceutical and biotechnology companies, including ours, historically has been highly volatile, and the market from time to time has experienced significant price and volume fluctuations that are unrelated to the operating performance of such companies. For example, during the twelve month period ended February 22, 2010, our stock price has ranged from a low of $0.05 to a high of $2.23. Fluctuations in the trading price or liquidity of our common stock may adversely affect the value of your investment in our common stock.

Factors that may have a significant impact on the market price and marketability of our securities include: