CELL THERAPEUTICS INC
Form 10-K
February 28, 2013
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**UNITED STATES**

# SECURITIES AND EXCHANGE COMMISSION

**WASHINGTON, D.C. 20549**

## FORM 10-K

**(Mark One)**

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

**For the fiscal year ended December 31, 2012**

**OR**

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

**For the transition period from _____ to _____**

**Commission file number: 001-12465**

# CELL THERAPEUTICS, INC.

**(Exact name of registrant as specified in its charter)**

| **Washington** | **91-1533912** |
|---|---|
| **(State or other jurisdiction of incorporation or organization)** | **(I.R.S. Employer Identification Number)** |
| **3101 Western Avenue, Suite 600** | |
| **Seattle, WA** | **98121** |
| **(Address of principal executive offices)** | **(Zip Code)** |

**Registrant s telephone number, including area code: (206) 282-7100**

**Securities registered pursuant to Section 12(b) of the Act:**

| Title of each class | Name of each exchange on which registered |
|---|---|
| **Common Stock, no par value** | **The NASDAQ Stock Market LLC** |

**Securities registered pursuant to Section 12(g) of the Act:**

**Preferred Stock Purchase Rights**

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

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

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

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

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

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

| | |
|---|---|
| Large accelerated filer ¨ | Accelerated filer x |
| Non-accelerated filer ¨ (Do not check if a smaller reporting company) | Smaller reporting company ¨ |

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

As of June 29, 2012, the aggregate market value of the registrant s common equity held by non-affiliates was $121,317,591. Shares of common stock held by each executive officer and director and by each person known to the registrant who beneficially owns more than 5% of the outstanding shares of the registrant s common stock have been excluded in that such persons may under certain circumstances be deemed to be affiliates. This determination of executive officer or affiliate status is not necessarily a conclusive determination for other purposes. The registrant has no non-voting common stock outstanding.

The number of outstanding shares of the registrant s common stock as of February 22, 2013 was 109,810,743.

**DOCUMENTS INCORPORATED BY REFERENCE**

None.

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**CELL THERAPEUTICS, INC.**

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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 compliance with the listing standards of The NASDAQ Stock Market, or NASDAQ;
- 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, Part I, Item 1A Risk Factors, Part II, 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 are a biopharmaceutical company focused on the acquisition, development, and commercialization of less toxic and more effective ways to treat cancer. Our goal is to build a profitable company by generating income from products we develop and commercialize, either alone or with one or more potential strategic partners. We are currently concentrating our efforts on treatments that target blood-related cancers where there is an unmet medical need. We are primarily focused on commercializing PIXUVRI® (pixantrone) in the European Union, or the E.U., for multiply relapsed or refractory aggressive non-Hodgkin lymphoma, or NHL, and conducting a Phase 3 clinical trial of pacritinib for the treatment of myelofibrosis.

Our most clinically advanced compound is PIXUVRI. PIXUVRI is a novel aza-anthracenedione derivative that is structurally related to anthracyclines and anthracenediones, but does not appear to be associated with the same level of cardiotoxic effects. PIXUVRI was structurally designed so that it cannot bind iron and perpetuate oxygen radical production or form a long-lived hydroxyl metabolite both of which are the putative mechanisms for anthracycline-induced acute and chronic cardiotoxicity.

In May 2012, the European Commission, or the EC, granted conditional marketing authorization in the E.U., of PIXUVRI as a monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive NHL, a cancer caused by the abnormal proliferation of lymphocytes, which are cells key to the functioning of the immune system. NHL usually originates in lymph nodes and spreads through the lymphatic system. PIXUVRI is the first approved treatment for patients with multiply relapsed or refractory aggressive B-cell NHL. This approval was based on the results from our pivotal Phase 3 clinical trial known as EXTEND or PIX301. In connection with the conditional marketing authorization, we are required to conduct a post-approval study that is intended to confirm PIXUVRI s clinical benefit. We are currently accruing patients into a Phase 3 clinical trial comparing pixantrone and rituximab with gemcitabine and rituximab in the setting of aggressive B-cell NHL.

In September 2012, we began making PIXUVRI available for commercial sale in parts of the E.U. PIXUVRI is currently available in eight countries: Austria, Denmark, Finland, Germany, Netherlands, Norway, Sweden and the United Kingdom. We plan to extend the availability of PIXUVRI to France, Italy and Spain, as well as other European countries, in 2013. We have established commercial operations organization, including sales, marketing, supply chain management, and reimbursement capabilities, to commercialize PIXUVRI in the E.U. We are pursuing potential partners for commercializing PIXUVRI in other markets outside the E.U. and the United States (U.S.). PIXUVRI is not approved in the U.S.

In May 2012, we expanded our late-stage pipeline of product candidates with the acquisition of pacritinib, an oral, once-daily JAK2 inhibitor that demonstrated meaningful clinical benefits and good tolerability in myelofibrosis patients in Phase 2 clinical trials. Myelofibrosis is a blood-related cancer caused by the accumulation of malignant bone marrow cells that triggers an inflammatory response, scarring the bone marrow and limiting its ability to produce red blood cells prompting the spleen and liver to take over this function. Symptoms that arise from this disease include enlargement of the spleen, anemia, extreme fatigue and pain. We believe pacritinib may offer an advantage over other JAK inhibitors through effective relief of symptoms with less treatment-emergent thrombocytopenia and anemia. We initiated the first Phase 3 clinical trial in myelofibrosis in January 2013, and plan to initiate a second Phase 3 trial in the second half of 2013.

Tosedostat is an oral aminopeptidase inhibitor that has demonstrated significant responses in patients with acute myeloid leukemia, or AML, and is currently in two Phase 2 investigator-sponsored trials examining the activity of combining tosedostat with hypomethylating agents (HMAs) in AML and myelodysplastic syndrome, cancers of the blood and bone marrow. We expect data from these trials may be used to determine the appropriate design for a Phase 3 trial.

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We continue to work with our other pipeline candidates targeting solid tumors including Opaxio (paclitaxel poliglumex), or Opaxio, and brostallicin through a cooperative group and investigator-sponsored studies.

**Our Strategy**

Our strategy is to become a leader in the acquisition, development and commercialization of novel therapeutics for the treatment of blood-related cancers. The key elements of our strategy are to:

**Successfully Commercialize PIXUVRI.** Our most important commercial objective is to continue our efforts to build a successful PIXUVRI franchise in Europe. PIXUVRI is currently available in eight countries in the E.U., and we plan to extend the availability to other European countries in 2013. We are currently focused on educating physicians on the unmet medical need and building brand awareness for PIXUVRI among physicians in the countries where PIXUVRI is currently available. We are also focused on achieving favorable reimbursement in the five major market European countries (France, Germany, Italy, Spain and the United Kingdom), as well as smaller territories in Western and Northern Europe, in 2013. We also seek to expand the availability of PIXUVRI into additional geographic markets in the rest of the world through one or more strategic partnerships in 2013.

**Develop Pacritinib in Myelofibrosis.** Pacritinib has the potential to build value for us through the successful enrollment of the first of two Phase 3 registration trials in patients with myelofibrosis within 12-14 months from the initiation of the trial in January 2013. We plan to initiate a second Phase 3 trial in the second half of 2013 and anticipate patient accrual to take approximately one year. Data for each trial is expected to be available approximately six months after completion of enrollment.

**Continue to Develop our Other Pipeline Programs.** We believe that it is important to maintain a diverse pipeline to sustain our future growth. To accomplish this, we continue to advance the development of our other novel, clinical-stage product candidates, particularly tosedostat, Opaxio and brostallicin through investigator-sponsored trials, or ISTs. Sponsoring ISTs provides us with a more economical approach for further developing our promising investigational products.

**Enter into Strategic Product Collaborations to Generate Capital and Supplement our Internal Resources.** We enter into collaborations to broaden and accelerate clinical trial development and potential commercialization of our product candidates. Collaborations can generate significant non-equity based operating capital, supplement our own internal expertise and provide us with access to the marketing, sales and distribution capabilities of our collaborators in specific territories.

**Identify and Acquire Additional Pipeline Opportunities.** Our current pipeline is the result of licensing and acquiring assets that we believe to be undervalued opportunities. We plan to continue to seek out additional product candidates in an opportunistic manner.

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**PIXUVRI and Product Development Candidates**

The following table summarizes our development pipeline for PIXUVRI and our late-stage product candidates:

| Name of Product or Product Candidate | Indications/Intended Use | Status |
|---|---|---|
| **PIXUVRI** | Multiply relapsed or refractory aggressive NHL, EXTEND pivotal | Conditional Approval-Marketed in E.U. |
| **(pixantrone dimaleate)** | Aggressive NHL,2nd line > 1 relapse, combination with rituximab (PIX-R/PIX306) post-approval study | Phase 3 ongoing |
| **Pacritinib** | Myelofibrosis, PERSIST-1 All platelet levels | Phase 3 ongoing |
| | Myelofibrosis, PERSIST-2 Platelet counts <100,000/μL | Phase 3 planning to initiate in the second half of 2013 |
| **Opaxio*** | Ovarian Cancer, first-line maintenance | Phase 3 ongoing |
| **(paclitaxel poliglumex)** | Newly diagnosed glioblastoma without MGMT methylation | Phase 2 ongoing |
| | Head and Neck Cancer | Phase 2 ongoing |
| **Tosedostat*** | First-line Acute Myeloid Leukemia<br>Relapsed/Refractory Acute Myeloid Leukemia/Myelodysplastic Syndrome | Phase 2 ongoing<br>Phase 2 ongoing |
| **Brostallicin*** | Metastatic Triple-Negative Breast Cancer | Phase 2 ongoing |

* We support the development of these investigational agents through investigator-sponsored studies.

**Oncology Market Overview and Opportunity**

*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 580,350 deaths annually, or more than 1,600 people per day and approximately 1.7 million new cases of cancer were expected to be diagnosed in 2013 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.

We believe developing agents which improve on the cornerstone chemotherapy classes, in addition to novel drugs designed to target biological pathways to treat specific types of cancer and cancer patients, fills a significant unmet medical need for cancer patients.

**Approved Product**

**Pixuvri**

*Overview*. 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 that can also cause cardiac toxicity. As a result, chemotherapy regimens that do not include anthracyclines often are used for the second-line treatment of aggressive

NHL, leukemia and breast cancer.

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PIXUVRI is being developed in an effort to improve the activity and safety in treating cancers usually initially treated with the anthracycline family of anti-cancer agents. We believe a next-generation anthracycline with 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. PIXUVRI is a novel DNA major groove binder with an aza-anthracenedione molecular structure, differentiating it from anthracycline chemotherapy agents. Similar to anthracyclines, PIXUVRI inhibits topo-isomerase II, but, unlike anthracyclines, rather than interacalation with DNA, PIXUVRI hydrogen bonds to and alkylates DNA, thus forming stable DNA adducts with particular specificity for CpG rich, hypermethylated sites. In addition, the structural motifs on anthracycline-like agents are responsible for the generation of oxygen free radicals and the formation of toxic drug-metal complexes have also been modified in PIXUVRI 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 patients who are otherwise at their lifetime recommended doxorubicin exposure.

*PIXUVRI for the Treatment of NHL*

We are specifically developing PIXUVRI, a novel aza-anthracenedione derivative, for the treatment of NHL. NHL is caused by the abnormal proliferation of lymphocytes, which are cells key to the functioning of the immune system. NHL usually originates in lymph nodes and spreads through the lymphatic system. The ACS estimated that there would be 70,130 people diagnosed with NHL in the U.S. and approximately 18,940 people would die from this disease in 2012. In Europe, the World Health Organization s International Agency for Research on Cancer s 2008 GLOBOCAN database estimates that in the European Union approximately 74,162 people will be diagnosed with NHL and 31,371 are estimated to die from NHL annually. NHL is the seventh most common type of cancer. NHL can be broadly classified into two main forms, each with many subtypes aggressive NHL is a rapidly growing form of the disease that moves into advanced stages much faster than indolent NHL, which progresses more slowly.

Aggressive NHL is one of the more common types of NHL and accounts for about 60% of all NHL cases. After initial therapy for aggressive NHL with anthracycline-based combination therapy, one-third of patients typically develop progressive disease. Approximately half of these patients are likely to be eligible for intensive second-line treatment and stem cell transplantation, although 50% are expected not to respond. For those patients who fail to respond or relapse following second-line treatment, treatment options are limited and usually palliative only. PIXUVRI is the first treatment approved in the E.U. for treatment of patients with multiply relapsed or refractory aggressive B-cell NHL. There are no drugs approved for this indication in the United States.

*Clinical Trials and Conditional Marketing Approval of PIXUVRI in the E.U.*

The pivotal Phase 3 EXTEND, or PIX301, trial evaluated PIXUVRI for patients with relapsed or refractory aggressive NHL. The trial enrolled 140 patients randomized to receive either PIXUVRI or another single-agent drug currently used for the treatment of this patient population and selected by the physician. Twenty percent (20%) of patients in the trial who received pixantrone achieved a complete or unconfirmed complete response at end of treatment compared with 5.7% in the comparator group (p=0.021). Median progression-free survival in the intent-to-treat population was also greater with pixantrone than with comparators: 5.3 versus 2.6 months (p=0.005). PIXUVRI had predictable and manageable toxicities when administered at the proposed dose and schedule in heavily pre-treated patients. The most common (incidence greater than or equal to 10%) grade 3/4 adverse events reported for PIXUVRI-treated subjects across trials were neutropenia and leukopenia. Other common adverse events (any grade) included infection, anemia, thrombocytopenia, asthenia, pyrexia and cough. Overall, the incidence of grade 3 or greater cardiac adverse events was 7% (five patients) on the PIXUVRI arm and 2% (one patient) on the comparator arm. There were an equal number of deaths due to an adverse event in both the PIXUVRI and comparator arm. The EXTEND study was published in *Lancet Oncology* in May 2012.

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In May 2012, PIXUVRI was granted conditional marketing authorization by the European Commission, or the E.C., as a monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive NHL. The E.C. granted conditional approval based on the results from the EXTEND pivotal trial. The decision authorized us to market PIXUVRI in the 27 Member States of the E.U. as well as in Iceland, Liechtenstein and Norway.

Similar to accelerated approval regulations in the U.S., conditional marketing authorizations are granted in the E.U. to medicinal products with a positive benefit/risk assessment that address unmet medical needs and whose availability would result in a significant public health benefit. A conditional marketing authorization is renewable annually. Under the provisions of the conditional marketing authorization for PIXUVRI, we are required to complete a post-marketing study aimed at confirming the clinical benefit previously observed.

An ongoing randomized, controlled Phase 3 clinical trial, known as PIX-R® or PIX306, compares PIXUVRI-rituximab to gemcitabine-rituximab in patients who have relapsed after one to three prior regimens for aggressive B-cell NHL and who are not eligible for autologous stem cell transplant. The PIX-R trial utilizes overall survival, or OS, as the primary endpoint of the study, with a secondary endpoint of progression free survival, or PFS. The PIX306 trial was initiated in March 2011. Planned enrollment in this study is approximately 350 patients. As a condition of approval, we have agreed to submit the results of the Phase 3 PIX-R study to the E.C. by June 2015. We plan to meet with the European regulatory authorities in 2013 in regards to the endpoint of the ongoing trial.

*Commercialization of PIXUVRI in the E.U.*

In September 2012, we initiated E.U. commercialization of PIXUVRI and by the end of 2012 made PIXUVRI available to healthcare providers in eight E.U. countries, including Austria, Denmark, Finland, Germany Netherlands, Norway, Sweden and the United Kingdom. We plan to extend the availability of PIXUVRI to France, Italy and Spain as well as other European countries in 2013. PIXUVRI is currently available elsewhere in the E.U. and Turkey through a named patient program where it is not otherwise commercially available. A named patient program is a mechanism through which physicians can prescribe investigational drugs under individual country-specific guidelines for patients prior to marketing approval.

We entered into an agreement with Quintiles Commercial Europe Limited, or Quintiles, in July 2012 under which we will interview, approve for hire, train and manage a sales force for PIXUVRI in the E.U. While the sales force would be dedicated to PIXUVRI, they are not our employees, but Quintiles employees. We believe this is a cost effective way to commercialize PIXUVRI in the E.U. We have also entered into a third-party logistics agreement with Movianto Nederland BV in September 2012 to provide us with warehousing, transportation, distribution, order processing and cash collection services for PIXUVRI as well as an agreement with LogixX Pharma Solutions, Ltd to act as our interim wholesaler dealers license holder while we apply for our own license.

We signed a manufacturing supply agreement with NerPharMa, S.r.l. in July 2010 for PIXUVRI drug product manufacture for both the commercial and clinical supply of PIXUVRI drug product. In July 2010, the Italian Medicines Agency, or AIFA, the national authority responsible for drug regulation in Italy, approved the facility at NerPharMa DS, S.r.l. for the production of PIXUVRI drug substance.

*Clinical Development of PIXUVRI in the United States*

We are not currently pursuing regulatory approval of PIXUVRI in the U.S., but may evaluate a possible resubmission strategy in the U.S. based on the data generated from the ongoing PIX306 clinical trial. In the U.S. we began a rolling NDA submission to the FDA in April 2009 and completed the submission in June 2009. In March 2010, the FDA s ODAC panel voted unanimously that the clinical trial data was not adequate to support approval of PIXUVRI for this patient population. In early April 2010, we received a complete response letter

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from the FDA regarding our NDA for PIXUVRI recommending that we design and conduct an additional trial to demonstrate the safety and efficacy of PIXUVRI and other items. We filed an appeal in December 2010 with the FDA s Center for Drug Evaluation and Research regarding the FDA s decision in April 2010 to not approve PIXUVRI for relapsed/refractory aggressive NHL and to ask the Office of New Drugs, or the OND, to conclude that PIX301 demonstrated efficacy.

In April 2011, the OND responded to our December 2010 appeal of the FDA s April 2010 decision to not approve PIXUVRI for relapsed or refractory aggressive NHL. In its response, the OND indicated that after considering the data available in the appeal, it did not believe that accelerated approval of our NDA is necessarily out of reach based on a single controlled clinical trial, provided that two key matters can be resolved satisfactorily. First, the circumstances of stopping the PIX301 trial early must be resolved to assure that ongoing results assessment were not dictating the decision to stop. Second, ascertainment of the primary endpoint in the PIX301 study must be determined to have been sound and not subject to bias.

The OND also indicated that our request that the OND find that the data in our NDA demonstrate efficacy and return the NDA to the Office of Oncology Drug Products for consideration of safety and other issues was denied because the OND was not able to conclude that efficacy had been demonstrated. However, the OND also did not find that it could be concluded that PIX301 was a failed study, which warranted application of interim analysis statistical thresholds.

In June 2011, we met with the FDA s Division of Oncology Drug Products, or DODP, in a meeting that focused on the documents we proposed to provide regarding the circumstances of stopping the enrollment of PIX301 prior to achieving the original planned patient accrual and the make-up of the new radiology expert panel, as well as our plan to address the items noted in the FDA s complete response letter. Subsequently, a second independent radiology assessment of response and progression endpoint data from our PIX301 clinical trial of PIXUVRI was achieved with statistical significance. We believe this assessment confirmed the statistical robustness of the PIX301 efficacy data that was previously submitted by us to the FDA in our NDA for PIXUVRI.

In October 2011, we resubmitted the NDA to the FDA s Division of Oncology Products 1, or DOP1, for accelerated approval to treat relapsed or refractory aggressive NHL in patients who failed two or more lines of prior therapy. In December 2011, the DOP1 notified us that our resubmitted NDA is considered a complete, Class 2 response to the FDA s April 2010 complete response letter. The FDA set a PDUFA goal date of April 24, 2012 for a decision on our resubmitted NDA. ODAC was scheduled to review our resubmitted NDA for PIXUVRI in February 2012, but we voluntarily withdrew our resubmitted NDA for PIXUVRI because, after communications with the FDA, we needed additional time to prepare for the review of the NDA by ODAC at its February 2012 meeting. Prior to withdrawing the NDA, we requested that the FDA consider rescheduling the review of the NDA to the ODAC meeting to be held in late March. The FDA was unable to accommodate our request to reschedule, and given the PDUFA goal date, the only way to have PIXUVRI possibly considered at a later ODAC meeting was to withdraw and later resubmit the NDA. We are not currently pursuing regulatory approval of PIXUVRI in the U.S., but may evaluate a possible resubmission strategy in the U.S. based on the data generated from the ongoing PIX306 clinical trial. We had discussions with the DHP relating to a Special Protocol Assessment, or SPA, and following these discussions we determined that we would not pursue a SPA. The DHP noted that we could conduct a study utilizing PFS along with OS as co-primary endpoints which would be an acceptable design outside of the formal SPA process. At the initiation of the study, co-primary endpoints of OS and PFS were used. Subsequently, an amendment was made to the study protocol in January 2012, to make OS the sole primary endpoint, and PFS a secondary endpoint. As this study is being conducted without a SPA, regulatory acceptability will depend on the magnitude of the difference between the trial study arms as well as a risk and benefit analysis.

Novartis International Pharmaceutical Ltd., or Novartis, has an option to negotiate a license to develop and commercialize PIXUVRI as discussed under Part I, Item 1, Business License Agreements and Additional Milestones Novartis.

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**Development Candidates**

**Pacritinib**

Pacritinib is an oral, once-daily, tyrosine kinase inhibitor, or TKI, with dual activity against JAK2 and FMS-like tyrosine kinase 3, or FLT3. Mutations in these kinases have been shown to be directly related to the development of a variety of blood related cancers including myeloproliferative neoplasms, leukemia, and lymphoma. Pacritinib has been studied in two Phase 2 trials in a total of 65 myelofibrosis patients. In these trials, 30-74% improvement in seven of the myelofibrosis symptom assessment form (MF-SAF) scores was observed relative to baseline at cycle 4, 7 or 10 (28 day cycles). Among evaluable patients, 31% achieved 35% or greater reduction in spleen volume measured by MRI. We believe these effects appear to be independent of patient platelet count. Pacritinib appears to be associated with less myelosuppression than other JAK2 inhibitors. In January 2013, we initiated the first of two planned Phase 3 clinical trials in patients with myelofibrosis. PERSIST-1 is a multicenter, randomized, controlled Phase 3 trial comparing the efficacy and safety of pacritinib with that of best available therapy in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. A total of 270 eligible patients are planned to be randomized 2:1 to receive either pacritinib 400 mg taken orally, once daily or the best available therapy. The best available therapy includes any physician-selected treatment other than JAK inhibitors. There will be no exclusion by patient platelet count. The primary endpoint will be the percentage of patients achieving a 35% or greater reduction in spleen volume measured by MRI or CT at 24 weeks of treatment. The trial is expected to enroll patients at clinical sites in Europe, Australia and the United States.

The second Phase 3 clinical trial, PERSIST-2, is currently being planned to evaluate pacritinib compared to best available therapy, including JAK inhibitors, in patients with myelofibrosis whose platelet counts are <100,000 / μL. This trial is expected to initiate in the second half of 2013, and we expect it will have the same primary endpoint as PERSIST-1.

We acquired all right, title and interest of S*BIO and assumed certain liabilities relating to, certain intellectual property and other assets related to compounds SB1518 (also referred to as pacritinib ) and SB1578, which inhibit Janus kinase 2, commonly referred to as JAK2. Under the S*BIO Agreement, we are solely responsible for development and commercialization activities of pacritinib worldwide and agreed to make regulatory success and sales-based milestone payments, as well as single-digit royalties on net sales.

**Opaxio** (paclitaxel poliglumex)

Opaxio is our novel biologically-enhanced chemotherapeutic agent that links paclitaxel to a biodegradable polyglutamate polymer, resulting in a new chemical entity. Taxanes, including paclitaxel (Taxol®) and docetaxel (Taxotere®), are widely used for the treatment of various solid tumors, including non-small cell lung, ovarian, breast and prostate cancers. We are currently focusing our development of Opaxio through investigator-sponsored studies in the following indications: ovarian, glioblastoma multiforme, and head and neck cancers.

Opaxio was designed to deliver paclitaxel preferentially to tumor tissue. By linking paclitaxel to a biodegradable amino acid carrier, the conjugated chemotherapeutic agent is inactive in the bloodstream, sparing normal tissues the toxic side effects of chemotherapy. Once inside tumor tissue the conjugated chemotherapeutic agent is activated and released by the action of an enzyme called cathepsin B. Opaxio remains stable in the bloodstream for several days after administration; this prolonged circulation allows the passive accumulation of Opaxio in tumor tissue.

*Opaxio for ovarian cancer*

We are currently focusing our development of Opaxio 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. In March 2004, we entered into a clinical trial agreement with the Gynecologic Oncology Group, or

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GOG, to perform a Phase 3 trial, known as the GOG-0212 trial. As such, the GOG-0212 trial is conducted and managed by the GOG. We expect the trial to enroll 1,100 patients. In February 2012, we were informed that the Data Monitoring Committee for GOG-0212 adopted an amendment to the study s statistical analysis plan, or SAP, to perform four interim analyses instead of the previously-planned single interim analysis allowing for an earlier analysis of survival results than previously noted. There are early stopping criteria for either success or futility. In January 2013, we reported that the GOG informed us that the Data Safety Monitoring Board (DSMB) recommended continuation of the GOG-0212 Phase 3 clinical trial of Opaxio for maintenance therapy in ovarian cancer with no changes following a planned interim survival analysis. Enrollment in the trial is expected to be completed in 2013.

*Opaxio for glioblastoma multiforme (malignant brain cancer)*

In November 2010, results were presented by the Brown University Oncology Group from a Phase 2 trial of Opaxio combined with temozolomide, or TMZ, and radiotherapy in patients with newly-diagnosed, high-grade gliomas, a type of brain cancer. The trial demonstrated a high rate of complete and partial responses and an encouragingly high rate of six month PFS. Based on these results, the Brown University Oncology Group has initiated a randomized, multicenter, Phase 2 study of Opaxio and standard radiotherapy versus TMZ and radiotherapy for newly diagnosed patients with glioblastoma with an active gene termed MGMT that reduces responsiveness to TMZ. The trial goals are to estimate disease free and overall survival for the two study arms. Preliminary results are expected to be available in the second half of 2013. In September 2012, Opaxio was granted orphan-drug designation by the FDA for the treatment of a type of brain cancer called glioblastoma multiforme.

*Opaxio for head and neck cancer*

A Phase 1-2 study of Opaxio combined with radiotherapy and cisplatin was initiated by SUNY Upstate Medical University, in patients with locally advanced head and neck cancer. Preliminary results are expected to be presented mid-2013. We acquired an exclusive worldwide license for rights to Opaxio and certain polymer technology from PG-TXL in November 1998 as discussed below in License Agreements and Additional Milestone Activities PG-TXL.

We have entered into an exclusive worldwide licensing agreement for Opaxio with Novartis as discussed below in License Agreements and Additional Milestone Activities Novartis.

**Tosedostat**

Tosedostat is an oral, aminopeptidase inhibitor that has demonstrated significant anti-tumor responses in blood related cancers and solid tumors in Phase 1-2 clinical trials. In December 2011, final results from the Phase 2 OPAL study of tosedostat in elderly patients with relapsed or refractory AML were presented at the American Society of Hematology Annual Meeting. These results showed that once-daily, oral doses of tosedostat had predictable and manageable toxicities and results demonstrated encouraging response rates including a high-response rate among patients who received prior hypomethylating agents, which are used to treat myelodysplastic syndrome, or MDS, a precursor of AML. There are three ongoing Phase 2 investigator-sponsored trials examining the activity of tosedostat in combination with standard agents in patients with AML or MDS. We expect data from these trials may be used to determine the appropriate design for a Phase 3 trial. We have entered into an exclusive license agreement with Chroma Therapeutics, Ltd., or Chroma. Our agreement with Chroma is discussed in more detail in Part I, Item 1, Business, License Agreements and Additional Milestone Activities.

**Brostallicin**

We are developing brostallicin through our worldwide rights to use, develop, import and export brostallicin. Brostallicin is a synthetic DNA minor groove binding agent that has demonstrated anti-tumor activity and a favorable safety profile in clinical trials.

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An investigator-sponsored study of brostallicin with the North Central Cancer Treatment Group, or the NCCTG, opened for enrollment a Phase 2 study of brostallicin in combination with cisplatin in patients with metastatic triple-negative breast cancer, or mTNBC. mTNBC is defined by tumors lacking expression of estrogen, progesterone receptors and without over-expression of HER2. Women with mTNBC have very limited effective treatments and, based on the novel mechanism of action of brostallicin and the recognized activity of cisplatin in this disease, the combination of the two agents will be explored by the NCCTG. In addition to standard clinical efficacy measures, biological endpoints will also be evaluated to assist in understanding the specific activity of brostallicin in this disease. In December 2012, preliminary results of this study were presented at the San Antonio Breast Cancer Symposium. As of the preliminary analysis, 10 of 47 evaluable patients (21%) achieved a confirmed tumor response with nine patients having a partial response (PR) and one complete response (CR). The 3-month PFS was at 51%. Adverse events were manageable. Final results are expected to be presented in 2013. We have entered into a license agreement with Nerviano Medical Sciences, S.r.l., or Nerviano. Our agreement with Nerviano is discussed in more detail in Part I, Item 1, Business, License Agreements and Additional Milestone Activities.

**Research and Development Costs**

Research and development is essential to our business. We spent $33.2 million, $34.9 million and $27.0 million in 2012, 2011 and 2010, respectively, on company-sponsored research and development activities. Because of the risks and uncertainties associated with the development of a product candidate, we cannot accurately predict when or whether we will successfully complete the development of our product candidates or the ultimate product development cost.

We are unable to provide the nature, timing, and estimated costs of the efforts necessary to complete the development of PIXUVRI, Opaxio, pacritinib, tosedostat and brostallicin because, among other reasons, we cannot predict with any certainty the pace of enrollment of our clinical trials. Further, third parties are conducting key clinical trials for Opaxio and brostallicin. Even after a clinical trial is enrolled, preclinical and clinical data can be interpreted in different ways, which could delay, limit or preclude regulatory approval and advancement of this compound through the development process. For these reasons, among others, we cannot estimate the date on which clinical development of these product candidates will be completed or when we will generate material net cash inflows from PIXUVRI or be able to begin commercializing Opaxio, pacritinib, tosedostat and brostallicin to generate material net cash inflows.

The risks and uncertainties associated with completing development of our product candidates on schedule and the consequences to operations, financial position and liquidity if our research and development projects are not completed timely are discussed in more detail in the following risk factors, which begin on page 20 of this Form 10-K: *Our financial condition may be harmed if third parties default in the performance of contractual obligations.* ; *We may be delayed, limited or precluded from obtaining regulatory approval of Opaxio as a maintenance therapy for advanced-stage ovarian cancer and as a radiation sensitizer.* ; *We may not obtain or maintain the regulatory approvals required to commercialize some or all of our products.* ; *Even if our drug candidates are successful in clinical trials and receive regulatory approvals, we may not be able to successfully commercialize them.* ; *If we do not successfully develop our product candidates into marketable products, we may be unable to generate significant revenue or become profitable.* ; and *We may take longer to complete our clinical trials than we expect, or we may not be able to complete them at all.*

**License Agreements and Additional Milestone Activities**

*Novartis*

In September 2006, we entered into an exclusive worldwide licensing agreement, or the Novartis Agreement, with Novartis International Pharmaceutical Ltd., or Novartis, for the development and commercialization of Opaxio. Under the Novartis Agreement, total product and registration milestones to us for

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Opaxio could amount to approximately $270 million. Royalty payments to us for Opaxio are based on worldwide Opaxio net sales volumes and range from the low- to mid-twenties as a percentage of net sales.

Pursuant to the Novartis Agreement, we are responsible for the development costs of Opaxio and have control over development of Opaxio unless and until Novartis exercises its development rights, or the Development Rights. In the event that Novartis exercises the Development Rights, then from and after the date of such exercise, or the Novartis Development Commencement Date, Novartis will be solely responsible for the development of Opaxio. Prior to the Novartis Development Commencement Date, we are solely responsible for all costs associated with the development of Opaxio, but will be reimbursed by Novartis for certain costs after the Novartis Development Commencement Date. After the Novartis Development Commencement Date, Novartis will be responsible for costs associated with the development of Opaxio, subject to certain limitations; however, we are also responsible for reimbursing Novartis for certain costs pursuant to the Novartis Agreement.

The Novartis Agreement also provides Novartis with an option to develop and commercialize PIXUVRI based on agreed terms. If Novartis exercises its option on PIXUVRI under certain conditions and we are able to negotiate and sign a definitive license agreement with Novartis, Novartis would be required to pay us a $7.5 million license fee, up to $104 million in registration and sales related milestones and a royalty on PIXUVRI worldwide net sales. Royalty payments to us for PIXUVRI are based on worldwide PIXUVRI net sales volumes and range from the low-double digits to the low-thirties as a percentage of net sales.

Royalties for Opaxio and PIXUVRI are payable from the first commercial sale of a product until the later of the expiration of the last to expire valid claim of the licensor or the occurrence of other certain events, or the Royalty Term. Unless otherwise terminated, the term of the Novartis Agreement continues on a product-by-product and country-by-country basis until the expiration of the last-to-expire Royalty Term with respect to a product in such certain country. In the event Novartis does not exercise its Development Rights until the earlier to occur of (i) the expiration of 30 days following receipt by Novartis of the product approval information package pursuant to the Novartis Agreement or (ii) Novartis determination, in its sole discretion, to terminate the Development Rights exercise period by written notice to us (events (i) and (ii) collectively being referred to as the Development Rights Exercise Period ), the Novartis Agreement will automatically terminate upon expiration of the Development Rights Exercise Period. In the event of an uncured material breach of the Novartis Agreement, the non-breaching party may terminate the Novartis Agreement. Either party may terminate the Novartis Agreement without notice upon the bankruptcy of the other party. In addition, Novartis may terminate the Novartis Agreement without cause at any time (a) in its entirety within 30 days written notice prior to the exercise by Novartis of its Development Rights or (b) on a product-by-product or country-by-country basis on 180 days written notice after the exercise by Novartis of its Development Rights. If we experience a change of control that involves certain major pharmaceutical companies, Novartis may terminate the Novartis Agreement by written notice within a certain period of time to us or our successor entity.

As of December 31, 2012, we have not received any milestone payments and we will not receive any milestone payments unless Novartis elects to exercise its option to participate in the development and commercialization of PIXUVRI or exercise its Development Rights for Opaxio.

*University of Vermont*

We entered into an agreement with the University of Vermont, or UVM Agreement, in March 1995, as amended in March 2000, which grants us an exclusive license, with the right to sublicense, for the rights to PIXUVRI. Pursuant to the UVM Agreement, we acquired the rights to make, have made, sell and use PIXUVRI, and we are obligated to make royalty payments to UVM ranging from low-single digits to mid-single digits as a percentage of net sales. The higher royalty rate is payable for net sales in countries where specified UVM licensed patents exist, or where we have obtained orphan drug protection, until such UVM patents or such protection no longer exists. For a period of ten years after first commercialization of PIXUVRI, the lower royalty rate is payable for net sales in such countries after expiration of the designated UVM patents or loss of orphan

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drug protection, and in all other countries without such specified UVM patents or orphan drug protection. Unless otherwise terminated, the term of the UVM Agreement continues for the life of the licensed patents in those countries in which a licensed patent exists, and continues for ten years after the first sale of PIXUVRI in those countries where no such patents exist. We may terminate the UVM Agreement, on a country-by-country basis or on a patent-by-patent basis, at any time upon advance written notice. UVM may terminate the UVM Agreement upon advance written notice in the event royalty payments are not made. In addition, either party may terminate the UVM Agreement (a) in the event of an uncured material breach of the UVM Agreement by the other party; or (b) in the event of bankruptcy of the other party.

*S*BIO Pte Ltd*

Pursuant to the S*BIO Agreement, we acquired the compounds SB1518 (which is referred to as pacritinib ) and SB1578, which inhibit Janus Kinase 2, commonly referred to as JAK2, and we made an initial payment of $2 million in cash at signing. In consideration of the assets and rights acquired under the S*BIO Agreement, we made an additional payment of $13 million in cash and issued 15,000 shares of our Series 16 Preferred Stock to S*BIO, which were automatically converted into 2.5 million shares of our common stock. The S*BIO Agreement also provides S*BIO with a contingent right to certain milestone payments from us up to an aggregate amount of $132.5 million if certain U.S., E.U. and Japanese regulatory approvals are obtained or if certain worldwide net sales thresholds are met in connection with any pharmaceutical product containing or comprising any Seller Compound for use for specific diseases, infections or other conditions. At our election, we may pay up to 50% of any milestone payments to S*BIO through the issuance of shares of our common stock or shares of our preferred stock convertible into our common stock. In addition, S*BIO will also be entitled to receive royalty payments from us at incremental rates in the low-single digits based on certain worldwide net sales thresholds on a product-by-product and country-by-country basis.

*Chroma Therapeutics, Ltd.*

We entered into an agreement with Chroma, or the Chroma License Agreement, in March 2011 under which we have an exclusive license to certain technology and intellectual property controlled by Chroma to develop and commercialize the drug candidate, tosedostat, in North, Central and South America, or the Licensed Territory. Pursuant to the terms of the Chroma License Agreement, we paid Chroma an upfront fee of $5.0 million upon execution of the agreement and will make a milestone payment of $5.0 million upon the initiation of the first pivotal trial. The Chroma License Agreement also includes additional development- and sales-based milestone payments related to AML and certain other indications, up to a maximum amount of $209.0 million payable by us to Chroma if all development and sales milestones are achieved.

Under the Chroma License Agreement, we are required to pay Chroma royalties on net sales of tosedostat in any country within the Licensed Territory, commencing on the first commercial sale of tosedostat in any country in the Licensed Territory and continuing with respect to that country until the later of (a) the expiration date of the last patent claim covering tosedostat in that country, (b) the expiration of all regulatory exclusivity periods for tosedostat in that country or (c) ten years after the first commercial sale in that country. Royalty payments to Chroma are based on net sales volumes in any country within the Licensed Territory and range from the low- to mid-teens as a percentage of net sales.

Under the Chroma License Agreement, we are required to oversee and be responsible for performing the development operations and commercialization activities in the Licensed Territory and Chroma will oversee and be responsible for performing the development operations and commercialization activities worldwide except for the Licensed Territory, or the ROW Territory. Development costs may not exceed $50.0 million for the first three years of the Chroma License Agreement unless agreed by the parties and we will be responsible for 75% of all development costs, while Chroma will be responsible for 25% of all development costs, subject to certain exceptions. Chroma is responsible for the manufacturing of tosedostat for development purposes in the Licensed Territory and the ROW Territory in accordance with the terms of the Chroma Supply Agreement. We have the

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option of obtaining a commercial supply of tosedostat from Chroma or from another manufacturer at our sole discretion in the Licensed Territory. The Chroma License Agreement may be terminated by us at our convenience upon 120 days written notice to Chroma. The Chroma License Agreement may also be terminated by either party following a material breach by the other party subject to notice and cure periods.

By a letter dated July 18, 2012, Chroma notified us that Chroma alleges breaches under the Chroma License Agreement. Chroma asserts that we have not complied with the Chroma License Agreement because we made decisions with respect to the development of tosedostat without the approval of the joint committees to be established pursuant to the terms of the Chroma License Agreement, did not hold meetings of those committees and have not used diligent efforts in the development of tosedostat. We dispute Chroma s allegations and intend to vigorously defend our development activities and judgments. In particular, we dispute Chroma s lack of diligence claim based in part on the appropriateness of completing the ongoing Phase 2 combination trials prior to developing a Phase 3 trial design. In addition, we believe that Chroma has failed to comply with its antecedent obligations with respect to the joint committees and failed to demonstrate an ability to manufacture tosedostat to the required standards under the terms of the Chroma License Agreement. Under the Chroma License Agreement there is a 90 day cure period for any nonpayment default, which period shall be extended to 180 days if the party is using efforts to cure. A party may terminate the Chroma License Agreement for a material breach only after arbitration in accordance with the terms of the Chroma License Agreement.

Effective September 25, 2012, we and Chroma entered into a three month standstill with respect to the parties respective claims under the Chroma License Agreement, but otherwise reserving the parties respective rights as of the commencement of the standstill period. Effective December 25, 2012, the standstill was subsequently extended until March 25, 2013 and is terminable by either party on one month s notice.

*Gynecologic Oncology Group*

We entered into an agreement with the GOG, or the GOG Agreement, in March 2004, as amended on August 2008, related to the GOG-0212 trial of Opaxio in patients with ovarian cancer, which the GOG is conducting. We recorded a $1.7 million payment due to the GOG based on the 800 patient enrollment milestone achieved in the second quarter of 2011, of which $0.4 million was outstanding and included in *accounts payable* as of December 31, 2012. Under this agreement, we are required to pay up to $1.8 million in additional milestone payments related to the trial, of which $0.5 million will become due upon receipt of the interim analysis and data transfer and $0.9 million will become due upon completion of the 1,100 patient enrollment milestone, both of which may occur in 2013.

*PG-TXL*

In November 1998, we entered into an agreement with PG-TXL Company, L.P., or the PG-TXL Agreement (as amended in February 2006), 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 the PG-TXL Agreement, we acquired the rights to research, develop, manufacture, market and sell anti-cancer drugs developed using this polymer technology. Pursuant to the PG-TXL Agreement, we are obligated to make payments to PG-TXL upon the achievement of certain development and regulatory milestones of up to $14.4 million. The timing of the remaining milestone payments under the PG-TXL Agreement is based on trial commencements and completions for compounds protected by PG-TXL license rights, and regulatory and marketing approval of those compounds by the FDA and the EMA. Additionally, we are required to make royalty payments to PG-TXL based on net sales. Our royalty payments range from low-single digits to mid-single digits as a percentage of net sales. Unless otherwise terminated, the term of the PG-TXL Agreement continues until no royalties are payable to PG-TXL. We may terminate the PG-TXL Agreement (i) upon advance written notice to PG-TXL in the event issues regarding the safety of the products licensed pursuant to the PG-TXL Agreement arise during development or clinical data obtained reveal a materially adverse tolerability profile for the licensed product in humans or (ii) for any reason upon advance written notice. In addition, either party may terminate the PG-TXL Agreement (a) upon advance

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written notice in the event certain license fee payments are not made; (b) in the event of an uncured material breach of the respective material obligations and conditions of the PG-TXL Agreement; or (c) in the event of liquidation or bankruptcy of a party.

*Nerviano Medical Sciences*

Under a license agreement entered into with Nerviano Medical Sciences for brostallicin, or the Nerviano Agreement, we may be required to pay up to $80.0 million in milestone payments based on the achievement of certain product development results. Due to the early stage of development that brostallicin is in, 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., or Cephalon, in June 2005, we have the right to 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.

**Patents and Proprietary Rights**

We dedicate significant resources to protecting our intellectual property, which is important to our business. We have filed numerous patent applications in the U.S. and various other countries seeking protection of inventions originating from our research and development and we have also obtained rights to various patents and patent applications under licenses with third parties. Patents have been issued on many of these applications. We have pending patent applications or issued patents in the U.S. and foreign countries directed to PIXUVRI, Opaxio, pacritinib, tosedostat, brostallicin and other product candidates. Patents for the individual products extend for varying periods according to the date of the patent filing or grant and the legal term of patents in the various countries where patent protection is obtained. The PIXUVRI-directed patents in the U.S. will expire in 2014. The Opaxio-directed U.S. patents will expire on various dates ranging from 2017 through 2018. The pacritinib-directed U.S. patents will expire from 2026 through 2029. The tosedostat-directed U.S. patents will expire in 2017. The brostallicin-directed U.S. patents will expire on various dates ranging between 2017 through 2021. The PIXUVRI-directed patents in Europe will expire from 2013 through 2023. Such patent expirations do not account for potential extensions that may be available in certain countries. For example, certain PIXUVRI-directed patents may be subject to possible patent-term extensions that could provide extensions through 2019 in the U.S. and through 2027 in some countries in Europe. Supplementary Protection Certificates extending certain PIXUVRI-directed patents have been granted in Italy and Luxembourg, but there can be no guarantee of extensions in other countries. The risks and uncertainties associated with our intellectual property, including our patents, are discussed in more detail in the following risk factors, which begin on page 20 of this Annual Report on Form 10-K: *We hold rights under numerous patents that we have acquired or licensed or that protect inventions originating from our research and development, and the expiration of any one or more of these patents may allow our competitors to copy the inventions that are currently protected. ; If we fail to adequately protect our intellectual property, our competitive position could be harmed. ; Patent litigation is widespread in the biotechnology industry, and any patent litigation could harm our business. ; and We may be unable to obtain or protect our intellectual property rights and we may be liable for infringing 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.*

**Manufacturing**

We currently use, and expect to continue to be dependent upon, contract manufacturers and contract service providers to manufacture, test and distribute each of our product candidates and commercial product. We have established a quality control and quality assurance program, including a set of standard operating procedures and

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specifications with the goal that our products and product candidates are manufactured in accordance with current Good Manufacturing Practices, or cGMPs, and other global regulations. We expect that 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 PIXUVRI, Opaxio, pacritinib, tosedostat and brostallicin drug supply for clinical trials and commercial product for PIXUVRI. We will be dependent upon these third-party vendors to supply us in a timely manner with products manufactured in compliance with cGMPs or similar s