Karyopharm Therapeutics Inc.
Form 10-K
February 28, 2019
**Table of Contents**

**UNITED STATES**

**SECURITIES AND EXCHANGE COMMISSION**

**Washington, D.C. 20549**

# FORM 10-K

**(Mark One)**

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

**For the fiscal year ended: December 31, 2018**

**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: 001-36167**

**KARYOPHARM THERAPEUTICS INC.**

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

| **Delaware** | **26-3931704** |
|---|---|
| **(State or other jurisdiction of incorporation or organization)** | **(I.R.S. Employer Identification No.)** |

**85 Wells Avenue, 2nd Floor, Newton, Massachusetts 02459**

**(Address of principal executive offices) (zip code)**

**Registrant s telephone number, including area code: (617) 658-0600**

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

| **(Title of each class)** | **(Name of each exchange on which listed)** |
|---|---|
| **Common Stock, $0.0001 par value** | **Nasdaq Global Select Market** |

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

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

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

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 No

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted 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 such files). Yes No

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

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

| Large accelerated filer | Accelerated filer |
|---|---|

Non-accelerated filer Smaller reporting company

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

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

The aggregate market value of the registrant s voting and non-voting common stock held by non-affiliates of the registrant (without admitting that any person whose shares are not included in such calculation is an affiliate) computed by reference to the price at which the common stock was last sold on June 30, 2018 was approximately $820,964,429. Shares of common stock held by each executive officer and director and by each holder of 10% or more of the outstanding common stock have been excluded in that such persons may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

Number of shares outstanding of the registrant s Common Stock as of February 15, 2019: 60,856,091.

**Documents incorporated by reference:**

Portions of our definitive proxy statement to be filed with the Securities and Exchange Commission no later than April 30, 2019 in connection with our 2019 annual meeting of stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

Table of Contents

## TABLE OF CONTENTS

Table of Contents

**Forward-Looking Information**

*This Annual Report on Form 10-K contains forward-looking statements regarding the expectations of Karyopharm Therapeutics Inc., herein referred to as Karyopharm, the Company, we, , or our, with respect to the possible achievement of discovery and development milestones, our future discovery and development efforts, our collaborations with third parties, our future operating results and financial position, our business strategy, and other objectives for future operations. We often use words such as anticipate, believe, estimate, expect, intend, may, plan, predict, project, target, potential, will, would, could, should, continue, and other words and terms of similar meaning to help identify forward-looking statements, although not all forward-looking statements contain these identifying words. You also can identify these forward-looking statements by the fact that they do not relate strictly to historical or current facts. There are a number of important risks and uncertainties that could cause actual results or events to differ materially from those indicated by forward-looking statements. These risks and uncertainties include those inherent in pharmaceutical research and development, such as adverse results in our drug discovery and clinical development activities, decisions made by the U.S. Food and Drug Administration and other regulatory authorities with respect to the development and commercialization of our drug candidates, our ability to obtain, maintain and enforce intellectual property rights for our drug candidates, dependence on any collaborators, competition, our ability to obtain any necessary financing to conduct our planned activities, and other risk factors. Please refer to the section entitled Risk Factors in Part I of this report for a description of these risks and uncertainties. Unless required by law, we do not undertake any obligation to update any forward-looking statements.*

# PART I

## Item 1. Business

## BUSINESS

### Overview

We are a clinical-stage pharmaceutical company focused on the discovery, development and subsequent commercialization of novel, first-in-class drugs directed against nuclear transport and related targets for the treatment of cancer and other major diseases. Our scientific expertise is focused on understanding the regulation of intracellular communication between the nucleus and the cytoplasm. We have discovered and are developing wholly-owned, novel, small molecule **S**elective **I**nhibitor of **N**uclear **E**xport (**SINE**) compounds that inhibit the nuclear export protein exportin 1 (XPO1). These SINE compounds represent a new class of drug candidates with a novel mechanism of action that have the potential to treat a variety of diseases in areas of unmet medical need. Our SINE compounds were the first oral XPO1 inhibitors in clinical development.

Our focus is on seeking the regulatory approval and commercialization of our lead drug candidate, selinexor (KPT-330), as an oral agent in cancer indications with significant unmet clinical need, initially for hematologic malignancies. We then plan to seek additional approvals for the use of selinexor in combination therapies to expand the patient populations that are eligible for selinexor, as well as to move selinexor towards front-line cancer therapy. We are also advancing the clinical development of selinexor in multiple solid tumor indications. Oral selinexor is being evaluated in company- and investigator-sponsored clinical trials in advanced hematologic malignancies and solid tumors. Clinical trials evaluating selinexor include the Phase 2b STORM (**S**elinexor **T**reatment **o**f **R**efractory **M**yeloma) study in multiple myeloma, the Phase 1b/2 STOMP (**S**elinexor and Backbone **T**reatments **o**f **M**ultiple Myeloma **P**atients) study in combination with standard therapies in multiple myeloma, the Phase 2b SADAL

(**S**elinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma) study in diffuse large B-cell lymphoma (DLBCL), the pivotal, randomized Phase 3 BOSTON (**Bo**rtezomib, **S**elinexor and Dexame**t**has**on**e) study in multiple myeloma, and the Phase 2/3 SEAL (**Se**linexor in **A**dvanced **L**iposarcoma) study in liposarcoma.

Table of Contents

During 2018, we reported positive top-line data from the STORM and SADAL studies as well as updated interim data for the STOMP and SEAL studies. As a result of the positive top-line results from the STORM and SADAL studies, we are pursuing or plan to pursue marketing approvals for selinexor in the United States and Europe.

Following the positive outcome from the expanded cohort for the STORM study, in August 2018, we announced the completion of the rolling submission of a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) with a request for accelerated approval for selinexor as a new treatment for patients based on the results of the STORM study in penta-refractory multiple myeloma. Patients with penta-refractory multiple myeloma have previously received the two proteasome inhibitors (PIs), Velcade® (bortezomib) and Kyprolis® (carfilzomib), the two immunomodulatory drugs (IMiDs), Revlimid® (lenalidomide) and Pomalyst® (pomalidomide), and the anti-CD38 monoclonal antibody Darzalex® (daratumumab), as well as alkylating agents; their disease is refractory to glucocorticoids, at least one PI and at least one IMiD, Darzalex®; and their disease has progressed following their most recent therapy. The FDA previously granted orphan drug designation and fast track designation to selinexor for the treatment of patients with penta-refractory multiple myeloma. In October 2018, the FDA accepted for filing our NDA and also granted our request for priority review of the NDA and assigned an action date of April 6, 2019 under the Prescription Drug User Fee Act (PDUFA).

We also announced the submission of a Marketing Authorization Application to the European Medicines Agency (EMA) in January 2019 with a request for conditional approval. The EMA s Committee for Medicinal Products for Human Use (CHMP) has granted accelerated assessment for the selinexor Marketing Authorization Application. An accelerated assessment is granted to products deemed by the CHMP to be of major interest for public health and represent therapeutic innovation. Accelerated assessments may reduce the active review time of an MAA from the standard 210 days down to 150 days once it has been validated by the EMA.

On February 26, 2019, the FDA convened its Oncologic Drugs Advisory Committee (ODAC) to review data supporting our NDA requesting accelerated approval of selinexor and hold an advisory vote. The proposed indication discussed at the ODAC meeting was for selinexor in combination with dexamethasone for the treatment of patients with refractory multiple myeloma who have received at least three prior therapies and whose disease is refractory to at least one PI, one IMiD, and one anti-CD38 monoclonal antibody. During the ODAC meeting, the FDA presented issues of concern, including the limitations of single arm studies, especially those involving the combination of two agents, the toxicities associated with selinexor therapy and whether the selinexor dose has been optimized. The ODAC recommended by a vote of eight to five that the FDA delay the approval of selinexor until the results of the randomized Phase 3 BOSTON study in multiple myeloma are available. In light of this recommendation, we plan to work with the FDA to evaluate the best path forward as it continues to review our NDA requesting accelerated approval of selinexor. In January 2019, we announced the completion of enrollment of our BOSTON study, and we anticipate top-line data from the BOSTON study at the earliest by the end of 2019 or into 2020 depending on the occurrence of progression events per protocol.

Provided that marketing approval is granted by the FDA, we plan to commercialize selinexor in the United States as a treatment of patients in the approved indication as early as the first half of 2019. We are completing the development of our U.S. commercial capabilities to support a potential launch of selinexor in the United States and recently hired our U.S. sales force and expanded our marketing and market access teams. We will either work with existing and potential partners to establish a commercial infrastructure outside the United States or may, in certain geographies, elect to establish the commercial infrastructure ourselves.

Based on the positive results of the SADAL study, we plan to submit an NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients with relapsed and/or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for stem cell transplantation (high dose chemotherapy with

stem cell rescue), including chimeric antigen receptor modified T (CAR-T) cell therapy and intend to work with the FDA to determine the appropriate timeline for the submission. In November 2018, the FDA granted fast track designation to selinexor for the treatment of patients that have relapsed and/or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for transplantation, including high dose

Table of Contents

chemotherapy with stem cell rescue. We also plan to submit a Marketing Authorization Application to the EMA with a request for conditional approval.

In addition to selinexor, we are also advancing a pipeline of novel drug candidates: our other oral SINE compounds eltanexor (KPT-8602) and verdinexor (KPT-335) as well as our oral dual PAK4/NAMPT inhibitor, KPT-9274. We began clinical testing of eltanexor, a second-generation SINE compound, in late 2015. Our clinical development program for eltanexor includes myelodysplastic syndrome, colorectal cancer, and metastatic castration-resistant prostate cancer. We began clinical testing of KPT-9274 in patients with lymphoma or solid tumors during 2016. Verdinexor is our lead compound that is being evaluated as a potential therapy for viral, rare disease and autoimmune indications as well as lymphoma in companion animals.

*Commercial Readiness*

During 2018 and early 2019, in preparation for a potential commercial launch of selinexor in the United States subject to marketing approval by the FDA, we had:

- expanded our organization with approximately 90 new employees deployed in customer facing activities, with broad experience and expertise in sales, marketing, patient access and product reimbursement and distribution with a focus on oncology; and

- developed our commercial capabilities with implementation of systems and infrastructure to support our commercial sales organization and patient-focused programs and appropriate quality systems and compliance policies, systems and procedures.

Following our discussions with the FDA to evaluate the best path forward as it continues to review our NDA requesting accelerated approval of selinexor, we may re-evaluate the investment in our U.S. commercial capabilities.

*Summary of Clinical Development*

Oral selinexor is being evaluated in multiple later-phase clinical trials in patients with hematological and solid tumor malignancies, often in the relapsed and/or refractory setting. In general, relapsed disease refers to disease that progresses following the expiration of a specified period of time after discontinuation of therapy and refractory disease refers to disease that progresses while the patient is on therapy or within a specified period of time after discontinuation of therapy. To date, oral selinexor has been administered to patients across company- and investigator-sponsored clinical trials; the vast majority of these patients have very heavily pretreated, relapsed or refractory disease. Evidence of single-agent anti-cancer activity has been observed in many patients and selinexor has been sufficiently well-tolerated to allow several of these patients to remain on therapy for prolonged periods.

During 2018, we reported several important clinical data sets for selinexor and executed on our plan to pursue a clinical development initiative focused on obtaining our first regulatory approval for selinexor in multiple myeloma. This strategy is based on the positive results from our Phase 2b STORM study. The STORM study is a single-arm clinical trial evaluating oral selinexor in combination with standard, low-dose dexamethasone in patients with penta-refractory multiple myeloma. Patients with penta-refractory multiple myeloma have previously received the two PIs, Velcade® (bortezomib) and Kyprolis® (carfilzomib), the two IMiDs, Revlimid® (lenalidomide) and Pomalyst® (pomalidomide), and the anti-CD38 monoclonal antibody Darzalex® (daratumumab), as well as alkylating agents; their disease is refractory to glucocorticoids, at least one PI and at least one IMiD, Darzalex®; and their disease has

progressed following their most recent therapy.

Based on the results of the clinical data set for Part 1 of the STORM study, which we reported in 2016, we expanded the STORM study, designated Part 2, which enrolled 122 heavily pretreated patients with penta-refractory multiple myeloma. During 2018, we reported the clinical data set from Part 2 of the STORM

Table of Contents

study in which selinexor demonstrated a compelling overall response rate, median duration of response and survival rates and a predictable and manageable tolerability profile. We believe the clinical data set from Part 2 of the STORM study supports our request for accelerated approval for selinexor as a new treatment for patients.

In April 2018, the FDA granted fast track designation to selinexor for the treatment of patients with penta-refractory multiple myeloma, which indicates that the cohort of patients evaluated in the STORM study represents an unmet medical need, meaning there is no standard of care therapy known to be effective in this population. In August 2018, we announced the completion of the rolling submission of our NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients based on the results from Part 2 of the STORM study in penta-refractory multiple myeloma. In October 2018, the FDA accepted for filing our NDA and also granted our request for priority review of the NDA and assigned an action date of April 6, 2019 under the PDUFA. We also announced the submission of a Marketing Authorization Application to the EMA in January 2019 with a request for conditional approval. The EMA s CHMP has granted accelerated assessment for the selinexor Marketing Authorization Application.

On February 26, 2019, the FDA convened its ODAC to review data supporting our NDA requesting accelerated approval of selinexor and hold an advisory vote. During the ODAC meeting, the FDA presented issues of concern, including the limitations of single arm studies, especially those involving the combination of two agents, the toxicities associated with selinexor therapy and whether the selinexor dose has been optimized. The ODAC recommended by a vote of eight to five that the FDA delay the approval of selinexor until the results of the randomized Phase 3 BOSTON study in multiple myeloma are available. In light of this recommendation, we plan to work with the FDA to evaluate the best path forward as it continues to review our NDA requesting accelerated approval of selinexor. In January 2019, we announced the completion of enrollment of our BOSTON study, and we anticipate top-line data from the BOSTON study at the earliest by the end of 2019 or into 2020 depending on the occurrence of progression events per protocol.

The STOMP study, a multi-arm clinical trial in patients with relapsed/refractory multiple myeloma, is evaluating selinexor and low-dose dexamethasone plus standard therapies, such as Revlimid®, Pomalyst®, Velcade®, Kyprolis® or Darzalex. In addition, in June 2018, we opened an additional arm of the STOMP study evaluating selinexor and low-dose dexamethasone plus Revlimid® in patients with newly diagnosed multiple myeloma in June 2018. We presented updated clinical data from the STOMP study at the American Society of Hematology (ASH) 2018 annual meeting demonstrating that selinexor and low-dose dexamethasone plus Darzalex® or Pomalyst® exhibits high response rates when combined. We also presented updated clinical data at the European Hematology Association (EHA) 2018 annual meeting demonstrating that selinexor and low-dose dexamethasone plus Velcade® exhibited high response rates and further supports the rationale for the ongoing Phase 3 BOSTON study. Data from the selinexor and low-dose dexamethasone plus Velcade® arm of the STOMP study was subsequently published in the journal, *Blood®,* in December 2018. At the ASH 2017 annual meeting, we presented data demonstrating that selinexor and low-dose dexamethasone plus Revlimid® exhibited high response rates. A year earlier at the ASH 2016 annual meeting, preliminary safety and efficacy of selinexor plus Kyprolis® (dosed twice weekly) and dexamethasone in patients with multiple myeloma was presented.

Data from the STOMP study have showed that selinexor plus low-dose dexamethasone and Velcade® demonstrated high disease response rates, including for patients whose disease was previously refractory to PIs including Velcade® and/or Kyprolis®. Based on the positive results from the Velcade® arm of the STOMP study, we are conducting the pivotal Phase 3 BOSTON study in patients with multiple myeloma who have had one to three prior lines of therapy. The BOSTON study is evaluating selinexor plus low-dose dexamethasone and Velcade® compared to low-dose dexamethasone plus Velcade®. For the BOSTON study, we have identified the combination dose of selinexor 100mg orally once weekly plus dexamethasone 20mg orally twice weekly and Velcade® 1.3mg/m$^2$ subcutaneously once

weekly for 4 of 5 weeks. In January 2019, we announced the completion of enrollment of 364 patients in the study. If successful, the BOSTON study may support regulatory approval for multiple myeloma previously treated with one to three prior lines of the therapy and could potentially serve as a confirmatory study if the STORM study serves as the basis for accelerated and/or conditional approval.

Table of Contents

The SADAL study is an open-label Phase 2b clinical trial evaluating single-agent oral selinexor in patients that have relapsed and/or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for stem cell transplantation (high dose chemotherapy with stem cell rescue), including CAR-T cell therapy. At the ASH 2018 annual meeting, we presented top-line clinical data from the SADAL study demonstrating that selinexor, when administered as a single agent, is clinically active and capable of producing durable responses associated with prolonged overall survival.

In November 2018, the FDA granted fast track designation to selinexor for the treatment of patients that have relapsed and/or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for transplantation, including high dose chemotherapy with stem cell rescue. Based on the positive results of the SADAL study, we plan to submit an NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients that have relapsed and/or refractory DLBCL and intend to work with the FDA to determine the appropriate timeline for the submission. We also plan to submit a Marketing Authorization Application to the EMA with a request for conditional approval.

Key clinical trials of selinexor are summarized in the chart below. In addition to these studies, there are several ongoing investigator-sponsored clinical trials in a variety of hematological and solid tumor malignancies.

We previously announced data from the STORM, STOMP, SADAL, SEAL and KING studies and these data are described further herein. We currently expect to provide additional data related to the ongoing studies of selinexor listed above as follows:

BOSTON: Randomized Phase 3 top-line data at the earliest by the end of 2019 or into 2020 depending on the occurrence of progression events per protocol;

SEAL: Randomized Phase 3 top-line data in 2020; and

STOMP: Updated data from study arms at future medical meetings.

In addition to selinexor, we are also advancing a pipeline of novel drug candidates in oncology. We began clinical testing of oral eltanexor (KPT-8602), a second-generation SINE compound, in late 2015. We reported results at the ASH 2017 annual meeting showing good tolerability in patients with relapsed/refractory multiple myeloma, and we expanded clinical development of eltanexor to include myelodysplastic syndrome (MDS), colorectal cancer (CRC), and metastatic castration-resistant prostate cancer (mCRPC). We presented encouraging results from the cohort of patients with mCRC at the 2018 European Society for Medical Oncology (ESMO)

Table of Contents

annual meeting. We began clinical testing of oral KPT-9274, a dual PAK4/NAMPT inhibitor, in patients with lymphoma or solid tumors during 2016, and we reported top-line data at the ESMO 2017 annual meeting showing a manageable safety profile and early signals of antitumor activity. During 2017, we licensed to Anivive Lifesciences (Anivive) exclusive worldwide rights for the development and commercialization of oral verdinexor (KPT-335) for the treatment of cancer in companion animals. Our pipeline of drug candidates in oncology other than selinexor is summarized in the chart below.

In addition to its role in cancer, XPO1 is known to play a role in neurological, inflammatory, viral, wound healing and other diseases. In the hands of academic collaborators, SINE compounds have shown activity in a variety of non-oncology models consistent with the biology of XPO1. In January 2018, we entered into an Asset Purchase Agreement with Biogen MA Inc., a subsidiary of Biogen Inc. (Biogen), pursuant to which Biogen acquired KPT-350, an investigational new drug application-ready, oral SINE compound with a preclinical data package supporting potential efficacy in a number of neuro-inflammatory conditions, as well as certain related assets with an initial focus in amyotrophic lateral sclerosis (ALS). SINE compounds have also demonstrated activity in animal models of viral diseases, certain rare diseases and other indications, and we are continuing to develop programs in these areas largely through academic collaborations and non-dilutive funding opportunities with the intent to out-license these programs for clinical development and future commercialization.

Since our founding by Dr. Sharon Shacham in 2008, our goal has been to establish a leading, independent oncology business. We are led by Dr. Shacham, our President and Chief Scientific Officer, and Dr. Michael Kauffman, our Chief Executive Officer. Dr. Kauffman played a leadership role in the development and approval of Velcade® at Millennium Pharmaceuticals and of Kyprolis® while serving as Chief Medical Officer at Proteolix and then Onyx Pharmaceuticals. Both prior to her founding of Karyopharm and while at Karyopharm, Dr. Shacham has played a leadership role in the discovery and development of many novel drug candidates, which have been or are being tested in human clinical trials.

Since our inception, we have devoted most of our efforts to research and development, and we have not generated any revenue to date from the commercial sale of any drugs. As of December 31, 2018, we had an accumulated deficit of $673.7 million. We had net losses of $178.4 million, $129.0 million and $109.6 million for the years ended December 31, 2018, 2017 and 2016, respectively.

*Summary of Mechanism of Action: Transient XPO1 Inhibition by SINE Compounds*

Certain functions may only occur within a particular location in the cell, so one of the ways a cell regulates the function of a particular protein is by controlling that protein s location within the cell. The nuclear pore is a complex gate between the nucleus and cytoplasm, regulating the import and export of most large molecules, called macromolecules, including many proteins, into and out of the nucleus. In healthy cells, nuclear transport, both into and out of the nucleus, is a normal and regular occurrence that is tightly regulated and requires the presence of specific carrier proteins. XPO1 mediates the export of over 220 mammalian cargo proteins and some

Table of Contents

growth-promoting mRNAs. Particularly, XPO1 mediates the transport of the majority of tumor suppressor proteins and appears to be the only mediator of nuclear export for these proteins. Cancer cells have increased levels of XPO1, causing the increased export of these tumor suppressor proteins from the nucleus. Since the tumor suppressor proteins must be located in the nucleus to survey for damage and initiate programmed cell death, or apoptosis, XPO1 overexpression in cancer cells counteracts the genome surveillance process that detects DNA damage which can promote cancer. By blocking XPO1, our SINE compounds inhibit the export of tumor suppressor proteins, leading to their accumulation in the nucleus. Subsequently, the accumulation of tumor suppressor proteins amplifies their natural apoptotic function in cancer cells, but with minimal effects on normal cells. Further, SINE compounds reduce the translation of certain growth-promoting and anti-apoptosis proteins often called oncoproteins by inhibiting the XPO1-mediated nuclear to cytoplasmic transport of the mRNAs that code for these proteins. The figure below depicts the process by which our SINE compounds inhibit the XPO1-mediated nuclear export of tumor suppressor proteins and oncoprotein mRNAs.

We believe that the XPO1-inhibiting SINE compounds that we have discovered and developed to date, including selinexor, have the potential to provide novel, oral, targeted therapies that enable tumor suppressor proteins to remain in the nucleus and promote the apoptosis of potentially any type of cancer cell. In multiple cancer types, patient tumor biopsies have confirmed that selinexor treatment induces nuclear localization of tumor suppressor proteins and, subsequently, cancer cell death, or apoptosis. We believe that no currently approved cancer treatments and only one current clinical-stage cancer drug candidate are selectively targeting the restoration and increase in the levels of multiple tumor suppressor proteins in the nucleus. Thus, we believe that selinexor s novel mechanism of action and oral administration and low levels of major organ toxicities observed to date in patients treated with selinexor in clinical trials, along with encouraging efficacy data, support the potential for selinexor s broad use across many cancer types, including both hematological and solid tumor malignancies. Our SINE compounds were the first oral XPO1 inhibitors in clinical development. We own all intellectual property rights related to the compounds that we are developing, including composition of matter and

Table of Contents

method of use patents covering selinexor issued by the U.S. Patent and Trademark Office in 2015 and which provide patent protection through at least 2032, prior to any adjustments or extensions.

**Our Strategy**

The critical components of our business strategy are to:

***Develop and Seek Regulatory Approval of Selinexor, Our Lead Novel Drug Candidate, in North America and Europe.*** We plan to seek regulatory approvals of selinexor in North America and Europe for each indication in which we receive favorable results in a trial with a survival endpoint that is registration-enabling. We may also seek regulatory approvals where a clinical trial demonstrates significant data in a surrogate endpoint, such as overall response rate, that could allow for accelerated or conditional approval. We or our current or future partners may seek marketing approvals in other geographies as well.

***Maximize the Commercial Value of Selinexor and Our Other Drug Candidates.*** To date, we have entered into several strategic arrangements. In October 2017, we entered into an exclusive license agreement with Ono Pharmaceutical Co., Ltd. for the development and commercialization of selinexor and eltanexor for all human oncology indications in Japan, South Korea, Taiwan, Hong Kong, and the ASEAN countries. In May 2018, we entered into an exclusive license agreement with Antengene Therapeutics Limited (Antengene) under which we granted Antengene exclusive rights to develop and commercialize selinexor, eltanexor and KPT-9274, each for the diagnosis, treatment and/or prevention of all human oncology indications, as well as verdinexor for the diagnosis, treatment and/or prevention of certain human non-oncology indications. We licensed the development and commercial rights to Antengene for selinexor and eltanexor in the oncology field in mainland China and Macau and licensed the development and commercial rights to Antengene for KPT-9274 in the oncology field and verdinexor in the non-oncology field in mainland China, Taiwan, Hong Kong, Macau, South Korea, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam. We currently hold development, marketing, and commercialization rights for selinexor in all other countries and are developing selinexor and seeking regulatory approval for its use in oncology indications without a collaborator in North America and Europe. During 2018 and early 2019, we worked to develop our U.S. commercial capabilities to support a potential launch of selinexor in the United States, including hiring a U.S. sales force in January 2019. Following our discussions with the FDA to evaluate the best path forward as it continues to review our NDA requesting accelerated approval of selinexor based on the STORM study, we may re-evaluate the investment in our U.S. commercial capabilities. We plan to either work with existing and potential partners to establish a commercial infrastructure outside the United States or may, in certain geographies, elect to establish the commercial infrastructure ourselves.

***Maintain Our Competitive Advantage and Scientific Expertise in the Field of Nuclear Transport.*** To further our understanding of the role nuclear transport plays in the underlying biology of cancer, as well other major diseases, we plan to continue research in the field of nuclear transport and related areas, primarily by fostering relationships with top scientific advisors and physicians. We have taken this approach in the past with KPT-350, an investigational new drug application-ready, oral SINE compound with a preclinical data package supporting potential efficacy in a number of neuro-inflammatory conditions, which Biogen acquired from us in early 2018. We believe that investing in the recruitment of exceptional advisors,

employees, and management is critical to our continued leadership in the nuclear transport field. We are collaborating with leading patient advocacy groups to provide education on the science behind our SINE compounds and to support the development and execution of clinical trials. We have advanced the understanding and potential application of SINE compounds in cancer treatment through a broad range of collaborations with leading institutions engaged in evaluating SINE compounds in clinical trials in the United States, Canada, many European countries, Australia, India, Israel, Singapore and elsewhere.

***Continue Developing our Pipeline of Novel Drug Candidates.*** To date, we have identified several drug candidates: our oral SINE compounds selinexor, eltanexor and verdinexor and our oral dual

Table of Contents

PAK4/NAMPT inhibitor, KPT-9274. A fifth program, KPT-350 for amyotrophic lateral sclerosis and other neuro-inflammatory conditions, was sold to Biogen in January 2018. We may also identify or in-license novel drug candidates for development in oncology in the future.

***Maximize the Value of Our Other SINE Compounds in Non-Oncology Indications through Collaborations.*** We may seek to enter into global or regional development, marketing, and commercialization collaboration arrangements for our other SINE compounds in non-oncology indications. For example, in May 2018, we licensed the development and commercial rights for verdinexor in the non-oncology field to Antengene in mainland China, Taiwan, Hong Kong, Macau, South Korea, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam. As described above, in January 2018, we entered into an asset purchase agreement with Biogen pursuant to which Biogen acquired KPT-350 as well as certain related assets with an initial focus in amyotrophic lateral sclerosis.

**Our Focus: Nuclear Transport**

Cancer is a disease characterized by unregulated cell growth. Cancer cells develop when DNA inside the nucleus of normal cells accumulates damage in genes that regulate cell growth and survival. In healthy cells, proteins called tumor suppressor proteins help prevent accumulation of DNA damage (mutations, chromosomal translocations and other abnormalities) by monitoring DNA for damage, and if damage is detected, the tumor suppressor proteins direct the cell to attempt to repair it. However, if the DNA damage is too severe, the tumor suppressor proteins direct the cell to die in a process called apoptosis.

Proteins, however, are not made inside the nucleus but rather made outside of the nucleus in an area called the cytoplasm. A membrane, called the nuclear membrane, separates the nucleus from the cytoplasm. All large nuclear proteins (larger than 40kDa), including tumor suppressor proteins, must be transported from the cytoplasm into the nucleus to perform their functions in keeping a cell healthy. Proteins are brought into the nucleus from the cytoplasm through a protein complex embedded in the nuclear membrane called the nuclear pore. The nuclear pore works like a gate through which large molecules, including many other proteins, enter and exit the nucleus. When molecules enter the nucleus from the cytoplasm, the process is called import, and when molecules exit from the nucleus to the cytoplasm, the process is called export. The import and export of most proteins and other large molecules between the nucleus and cytoplasm require specific carrier proteins to chaperone their cargo molecules through the nuclear pore complex. Carrier proteins which mediate the import of macromolecules into the nucleus are called importins, and those which mediate the export of macromolecules out of the nucleus are called exportins.

Eight exportins have been identified in human cells. One such export carrier protein was discovered in 1999 and is called exportin 1 (XPO1 or CRM1). XPO1 helps export over 220 cargo proteins. In particular, XPO1 appears to be the sole exporter for most of the tumor suppressor proteins including p53, p21, p27, APC, FOXO, pRB and survivin. In addition to exporting tumor suppressor proteins out of the nucleus, XPO1 mediates the nuclear export of a protein called eukaryotic initiation factor 4E (eIF4E), also called the mRNA cap binding protein. eIF4E binds to the mRNAs for many growth-regulating proteins, including c-myc, bcl-2, bcl-6, Atk1, hDM2 and cyclin D. eIF4E depends on XPO1 to help carry these growth-promoting mRNAs from the nucleus into the cytoplasm where the mRNAs are efficiently translated into proteins. XPO1 also exports the anti-inflammatory protein IkB, which inhibits a protein called NF-kB. NF-kB is found in the nucleus of most cancer cells and plays a role in cancer metastasis and chemotherapy resistance, as well as in many inflammatory and autoimmune diseases. By exporting IkB out of the nucleus, XPO1 augments NF-kB activity.

XPO1 levels are reported to be elevated in nearly all cancer cells when compared to their healthy cell counterparts. Therefore, these elevated levels of XPO1 in cancer cells mediate the rapid export of tumor suppressor proteins as well as IkB and eIF4E out of the nucleus. When compared to healthy cells, the increased export of tumor suppressor proteins in cancer cells may lead to reduced monitoring for DNA damage, the normal

Table of Contents

triggering of apoptosis and increased NF-kB activity. Higher levels of XPO1 expression in cancer cells is also generally correlated with resistance to chemotherapy and poor prognosis of patients.

Inhibiting XPO1 leads to accumulation of tumor suppressor proteins as well as eIF4E and IkB in the cell nucleus, which has been confirmed in a variety of preclinical models as well as in tumor biopsy tissues from patients treated with selinexor. Accumulation of tumor suppressor proteins increases monitoring for DNA damage and triggering of apoptosis in cancer cells. Also, blocking XPO1 can cause accumulation of bound growth-promoting mRNAs, which may cause a reduction in the levels of growth-promoting proteins in cancer cells; this has also been confirmed in preclinical models and tumor biopsy tissues. Accumulation of IkB in the nucleus inhibits NF-kB, which may be beneficial in overcoming chemotherapy resistance and in treating autoimmune, inflammatory, and neuro-inflammatory disease. For these reasons, we believe blocking XPO1 is a good strategy for treating cancer, autoimmune, inflammatory, and neuro-inflammatory diseases. The figure below depicts the process by which XPO1 mediates the nuclear transport process.

**XPO1 Mediation of Nuclear Transport**

**Our Approach: Targeting Nuclear Export with SINE Compounds**

Our lead drug candidates are first-in-class, oral, **Selective Inhibitor of Nuclear Export (SINE)** compounds. SINE compounds inhibit XPO1-mediated nuclear export by strongly, yet reversibly, binding to the XPO1 cargo binding site, effectively blocking the XPO1-cargo protein interaction. The transient XPO1 inhibition period that we have observed to date with our SINE compounds appears to be sufficient for elevation of tumor suppressor protein levels and IkB in the nucleus. Accumulation of tumor suppressor proteins in the nucleus of cancer cells allows them to perform their normal role of detecting DNA damage, thereby inhibiting a cancer cell s ability to divide and promoting apoptosis. Healthy cells also accumulate tumor suppressor proteins in the presence of a

Table of Contents

SINE compound, but they do not undergo apoptosis after transient XPO1 inhibition because they have minimal or no DNA damage. The figure below depicts the process by which SINE compounds inhibit the XPO1-mediated nuclear export of tumor suppressor proteins.

**Transient XPO1 Inhibition by SINE Compounds**

In addition to cancer, our SINE compounds have demonstrated the potential to provide therapeutic benefit in a number of other indications. Specifically, SINE compounds have shown evidence of activity in preclinical models of viral infections, neurological disorders, inflammation and autoimmune diseases.

**Our Initial Indication: Cancer**

Cancer is the second leading cause of death globally and was responsible for 8.8 million deaths in 2015. Globally, nearly one in six deaths is due to cancer. The American Cancer Society estimates that in the United States in 2019, approximately 1.8 million new cancer cases will be diagnosed and approximately 610,000 people will die of cancer. The International Agency for Research on Cancer projects that in 2030, 21.7 million people will be diagnosed with cancer, and 13 million people will die of cancer worldwide, as compared to 14.1 million new cancer diagnoses in 2012 and 8.8 million cancer deaths worldwide in 2015.

The most common methods for treating patients with cancer are a combination of surgery, radiation, and drug therapy. Locoregional therapies, such as surgery and radiation therapy, are particularly effective with localized disease. However, in situations where the cancer has spread beyond the primary site or cannot otherwise be treated through locoregional therapies, physicians generally use systemic drug therapies. In many cases, drug therapy includes combinations of several different drugs. An early approach to cancer treatment was through cytotoxic drugs that kill rapidly proliferating cancer cells by nonspecific mechanisms, such as disrupting

Table of Contents

cell metabolism or causing damage to cellular components required for survival and rapid growth. While these drugs have been effective in the treatment of some cancers, they act in an indiscriminate manner, killing healthy cells as well as cancer cells. Due to their mechanism of action, many cytotoxic drugs have a narrow dose range above which the toxicity causes unacceptable or even fatal levels of damage and below which the drugs are not effective in promoting cancer cell death. A different approach to pharmacological cancer treatment has been to develop drugs referred to as targeted therapeutics, which target specific biological molecules in the human body that play a role in the rapid cell growth and spread of cancer. Targeted therapeutics are designed specifically to exploit vulnerabilities in cancer cells to improve efficacy, and to minimize side effects. The drugs are designed to either attack a target that causes uncontrolled growth of cancer cells because of a genetic alteration more often found in cancer cells than in healthy cells or attack a target that cancer cells are more dependent on for their growth than are healthy cells.

Our SINE compounds are novel therapies specifically designed to force nuclear accumulation in the levels of multiple tumor suppressor and growth regulatory proteins. Tumor suppressor proteins assess a cell s DNA and in cells with heavily damaged DNA, such as cancer cells, these proteins induce cell death, or apoptosis. Unlike many other targeted therapeutic approaches that only work for a specific set of cancers or in a specific subgroup of patients, we believe that by restoring tumor suppressor proteins to the nucleus where they can assess a cell s DNA, our SINE compounds have the potential to provide therapeutic benefits across a broad range of both hematological and solid tumor malignancies and benefit a wider range of patients. Additionally, and as supported by its mechanism of action and preclinical and clinical data, we believe that selinexor has the potential for additive or synergistic benefit with approved and experimental therapies in treating cancer patients. As a result, we believe that selinexor has the potential to serve as a backbone therapy across multiple hematological and solid tumor malignancies as part of a variety of combination therapies.

**Our Oncology Drug Candidates**

***Selinexor (KPT-330)***

Selinexor is being evaluated in multiple later phase clinical trials in patients with hematological malignancies and solid tumors, often in the relapsed and/or refractory setting. Anti-cancer activity has been observed with tumor reductions and durable disease control across many hematologic malignancies and solid tumors.

In our lead hematologic indication of relapsed or refractory multiple myeloma, selinexor has demonstrated encouraging response rates, including a 26.2% response rate in patients with penta-refractory disease. In clinical trials when used in combination with other anti-myeloma agents, including Revlimid® (lenalidomide), Pomalyst® (pomalidomide), Velcade® (bortezomib) and Darzalex® (daratumumab), selinexor has generated response rates ranging from 50% to 92%. Based on the top-line data presented from our Phase 2b SADAL study, which evaluated patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), our next lead indication, selinexor has demonstrated a response rate of 29.6%, with a response rate of 34% in germinal center (GCB) subtype and a response rate of 21% in non-GCB subtypes of the disease. In addition, there were five patients in the SADAL study whose disease subtype was unable to be classified, and four of these patients experienced a partial response while on selinexor therapy. In liposarcoma, our lead solid tumor indication, patients treated with selinexor achieved progression-free survival of 5.5 months versus 2.7 months for placebo-treated patients, achieving a hazard ratio of 0.67, which represents a 33% reduction in the risk of disease progression or death.

To date, the most commonly reported adverse events (AEs) are predictable in the patient populations being studied and have been generally reversible and/or manageable with standard supportive care and/or dose modification. These AEs often decrease over time and are consistent with those previously reported by patients in our initial clinical trials. A preliminary analysis of safety and tolerability of selinexor was performed on unaudited AE data for 1,672 patients

enrolled in our company-sponsored hematological malignancy and solid tumor clinical trials as of the data cutoff point of March 31, 2018. Overall, the most commonly reported

Table of Contents

selinexor-related AEs in ongoing clinical studies were generally low-grade and included nausea (66.3%), fatigue (61.4%), anorexia (53.3%), thrombocytopenia (50.1%), anemia (41.8%), vomiting (40.1%), and diarrhea (36.1%). Thrombocytopenia, the most common hematologic treatment-related AE, was reported among 50.1% of patients, and approximately half of these were Grades 3 to 4. The dosing regimens used in our key clinical trials, including BOSTON, STORM, STOMP, SADAL and SEAL, have shown predictable and manageable tolerability, particularly when used once weekly in combination regimens. In certain studies, the AEs reported from treatment arms evaluating selinexor and dexamethasone in combination with other antimyeloma agents were similar to, or reduced, compared to selinexor and dexamethasone alone.

We describe below the key company-sponsored and an investigator-sponsored study evaluating selinexor in hematological malignancies and solid tumors, both as a single-agent and in combination. Additional data from company- and investigator-sponsored combination studies may be presented on an ongoing basis by us and/or our collaborators at scientific conferences or through other publications at various times. Unless otherwise indicated, response data presented herein are interim unaudited data based on reports by physicians at the clinical trial sites. Responses in hematological trials are measured using commonly accepted evaluation criteria for the specific indication. Responses in solid tumor trials are evaluated using RECIST unless otherwise noted.

*Advanced Hematological Malignancies*

**Multiple Myeloma**

Multiple myeloma (MM) is a hematological malignancy characterized by the accumulation of monoclonal plasma cells in the bone marrow, the presence of monoclonal immunoglobulin (M protein) in the serum or urine, bone disease, kidney disease and immunodeficiency. It is more common in elderly patients, with a median age at diagnosis of 65-70 years. In the United States, the American Cancer Society has estimated that there would be approximately 32,000 new cases of MM diagnosed and approximately 13,000 attributable deaths in 2019. The World Health Organization estimated that approximately 114,000 new cases of MM were diagnosed worldwide in 2012.

The treatment of MM has improved in the last 20 years due to the use of high-dose chemotherapy and autologous stem cell transplantation, which is restricted to healthier, often younger patients, and the subsequent introduction of IMiDs, such as Revlimid® and Pomalyst®, and the PIs Velcade®, Kyprolis® (carfilzomib), and Ninlaro® (ixazomib). Two monoclonal antibodies, Darzalex® and Empliciti (elotuzumab), have also been approved, as has the histone deacetylase inhibitor Farydak® (panobinostat). The introduction of non-chemotherapeutic agents has led to a significant increase in the survival of patients with MM. Although a wide variety of newly approved or experimental therapies are being used in relapsed and/or refractory patients, including new proteasome inhibitors (oprozomib and marizomib), monoclonal antibodies (with or without toxin conjugates) and cellular therapies like chimeric antigen receptor T-cell (CAR-T) therapy, nearly all patients will eventually relapse and succumb to their disease. With about 13,000 deaths from MM in the United States alone expected to occur, we believe that there remains a need for therapies for patients whose disease has relapsed after, or is refractory to, available therapy.

*STORM: Phase 2b Clinical Trial of Selinexor and Low-Dose Dexamethasone in Multiple Myeloma*

In May 2015, we initiated a Phase 2b clinical trial evaluating oral selinexor and low-dose dexamethasone in patients with heavily pretreated MM. The **S**elinexor **T**reatment **o**f **R**efractory **M**yeloma, or **STORM**, study is a single-arm study evaluating the treatment of relapsed/refractory MM with 80mg of selinexor and 20mg of dexamethasone, each dosed twice weekly. This 40mg per week dose of dexamethasone is considered low dose in the treatment of MM, compared with the high dose dexamethasone which uses three times more of the steroid.

At the ASH 2016 annual meeting, we presented positive results, adjudicated by an independent review committee, from the first cohort of patients enrolled in the STORM study, or Part 1 of the STORM study, which

Table of Contents

included patients with either quad-refractory or penta-refractory multiple myeloma. Patients with quad-refractory disease had previously received prior treatments that included alkylating agents, glucocorticoids, two IMiDs (Revlimid® and Pomalyst®), and two PIs (Velcade® and Kyprolis®), and their disease is refractory to at least one IMiD and at least one PI, and has progressed following their most recent therapy. Patients with penta-refractory multiple myeloma have previously received the two PIs, Velcade® and Kyprolis®, the two IMiDs, Revlimid® and Pomalyst®, and the anti-CD38 monoclonal antibody Darzalex®, as well as alkylating agents; their disease is refractory to glucocorticoids, at least one PI, at least one IMiD, Darzalex®; and their disease has progressed following their most recent therapy. Based on the results of the clinical data set for Part 1 of the STORM study, in 2016, we expanded the STORM study, designated Part 2, which enrolled 122 heavily pretreated patients with penta-refractory multiple myeloma.

We presented topline clinical data from Part 2 of the STORM study at the Society of Hematologic Oncology 2018 annual meeting and ASH 2018 annual meeting. Among the 122 patients, the median number of prior treatments regimens was seven and the overall response rate (ORR) as adjudicated by the IRC was 26.2%, which included two stringent complete responses (sCRs), six very good partial responses (VGPRs) and 24 partial responses (PRs). The two sCRs were negative for minimal residual disease, one at the level of $1x10^{-6}$ and one at $1x10^{-4}$. The ORR in patients who had previously received Darzalex® combination therapy (n=86) was 29.1%. The disease control rate for patients who had achieved stable disease or better was 78.7%. Median progression-free survival (PFS) was 3.7 months and the median duration of response (DOR) was 4.4 months. Median overall survival (OS) across the study was 8.6 months. Median OS in the approximately 40% of patients with at least a minimum response on selinexor and dexamethasone was 15.6 months compared to a median OS of 1.7 months in patients whose disease progressed or where response was not evaluable ($p<0.0001$).

In Part 2 of the STORM study, the most common treatment-related AEs were cytopenias, along with gastrointestinal and constitutional symptoms, and were consistent with those previously reported from Part 1 of the STORM study and from other selinexor studies. Most were manageable with dose modifications and/or standard supportive care. The most common non-hematologic treatment-related AEs were nausea (69%), fatigue (56%), anorexia (52%), and weight loss (47%) and mostly Grade 1 and 2 events. The most common Grade 3 and 4 treatment-related AEs were thrombocytopenia (54%), anemia (29%), neutropenia (19%) and fatigue (19%). No significant major organ toxicities were observed, and bleeding and infection rates were low. In Part 2 of the STORM study each patient experienced at least one AE, approximately 78.0% of patients received a dose modification of selinexor during the study as a result of AEs and approximately 26.8% of patients discontinued use of selinexor during the study as a result of AEs.

In August 2018, we announced the completion of the rolling submission of our NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients based on the positive outcome from Part 2 of the STORM study in penta-refractory multiple myeloma. In October 2018, the FDA accepted for filing our NDA and also granted our request for priority review of the NDA and assigned an action date of April 6, 2019 under the PDUFA. We also announced the submission of a Marketing Authorization Application to the EMA in January 2019 with a request for conditional approval. The EMA s CHMP has granted accelerated assessment for the selinexor Marketing Authorization Application. An accelerated assessment is granted to products deemed by the CHMP to be of major interest for public health and represent therapeutic innovation. Accelerated assessments may reduce the active review time of an MAA from the standard 210 days down to 150 days once it has been validated by the EMA.

On February 26, 2019, the FDA convened its ODAC to review data supporting our NDA requesting accelerated approval of selinexor and hold an advisory vote. The proposed indication discussed at the ODAC meeting was for selinexor in combination with dexamethasone for the treatment of patients with refractory multiple myeloma who have received at least three prior therapies and whose disease is refractory to at least one PI, one IMiD, and one anti-CD38 monoclonal antibody. During the ODAC meeting, the FDA presented issues of concern, including the

limitations of single arm studies, especially those involving the combination of two agents, the toxicities associated with selinexor therapy and whether the selinexor dose has been optimized. The

Table of Contents

ODAC recommended by a vote of eight to five that the FDA delay the approval of selinexor until the results of the randomized Phase 3 BOSTON study in multiple myeloma are available. In light of this recommendation, we plan to work with the FDA to evaluate the best path forward as it continues to review our NDA requesting accelerated approval of selinexor. In January 2019, we announced the completion of enrollment of our BOSTON study, and we anticipate top-line data from the BOSTON study at the earliest by the end of 2019 or into 2020 depending on the occurrence of progression events per protocol.

*STOMP: Phase 1b/2 Clinical Trial of Selinexor in Combination with Backbone Therapies in Multiple Myeloma*

Based on preclinical synergy in animal models of MM, in October 2015, we initiated a Phase 1b/2 clinical study of oral selinexor in combination with available treatments for relapsed/refractory MM. In this multi-arm study, **Selinexor and Backbone Treatments of Multiple Myeloma Patients** (**STOMP**), we are evaluating the combination of selinexor and low-dose dexamethasone with Revlimid®, Pomalyst®, Velcade®, Kyprolis® and Darzalex® in patients with previously treated MM. In addition, in June 2018, we opened an additional arm in the STOMP study evaluating selinexor and low-dose dexamethasone plus Revlimid® in patients with newly diagnosed multiple myeloma. Each combination is evaluated on a separate arm of the STOMP study and within each combination, two treatment cohorts evaluate once weekly versus twice weekly dosing of selinexor. The primary objectives of the Phase 1 portion are to determine the maximum tolerated dose and recommended Phase 2 and Phase 3 doses for selinexor in these combination therapies. The primary objectives of the Phase 2 portion are to assess preliminary efficacy through ORR, clinical benefit rate and DOR.

Selinexor in Combination with Velcade® and Low-dose Dexamethasone (SVd)

At the EHA 2018 annual meeting, we presented updated results from the selinexor, Velcade® and dexamethasone arm of the STOMP study, referred to as SVd. In this study arm, oral selinexor was dose-escalated in once-weekly (80 or 100mg) or twice-weekly (60 or 80mg) regimens. Velcade® (1.3mg/m$^2$ subcutaneously) was administered once-weekly or twice-weekly. Dexamethasone was administered orally either 40mg once-weekly or 20mg twice-weekly. The patients in this cohort were heavily pretreated and many (50%) had MM refractory to a proteasome inhibitor. Across the 42 patients enrolled in the SVd arm as of June 5, 2018, the median number of treatment regimens was three (range of one to 11 prior treatment regimens). Of the overall 40 patients evaluable for efficacy, as of June 5, 2018, 25 responded for an ORR of 63% (one patient having a sCR, four patients having a complete responses (CR), seven patients having a VGPR and 13 patients having a PR). Nearly all patients (38 of 40) had reductions in M-protein, including 33% with a 90% or greater reduction. Among the 19 patients with disease that has relapsed following, or is naïve to, PI therapy, the ORR was 84% and the median PFS was 17.8 months. The results were similar in the subgroup of 18 patients with disease that has relapsed following, or is naïve to, PI therapy and between one and three prior treatment regimens, which is also the patient population closest to those eligible for the BOSTON study. This indication of efficacy in the SVd combination, with weekly Velcade and selinexor, warranted the further evaluation of SVd versus Vd in the BOSTON study given the previously reported ORR of 60-65% and PFS of 7-9 months in the Vd regimen among similar patient populations. Amongst the 21 patients with PI-refractory disease where retreatment with Vd alone would not be expected to induce a significant response, the ORR following SVd treatment was 43%, suggesting that the addition of selinexor to Vd in patients with PI-refractory MM could re-sensitize their disease to a treatment regimen including a PI.

Based on these data, the recommended phase 2 dose regimen for the SVd arm was identified as selinexor (100mg once weekly), Velcade® (1.3mg/m$^2$ once weekly given sub-cutaneously for four of five weeks) and dexamethasone (40mg weekly), which represents 40% less Velcade® and 25% less dexamethasone compared to the approved standard Vd regimen. Among the 42 patients evaluable for safety as of the June 5, 2018 data cutoff date, the most common Grade 1/2 AEs were nausea (60%), anorexia (57%), fatigue (45%), diarrhea (40%), vomiting (29%) and weight loss

(24%). Importantly, the reported peripheral neuropathy across all patients was Grade 1/2 and limited to six patients (14%), of which five had prior Velcade® exposure. The most common Grade 3 or higher AEs were thrombocytopenia (45%), neutropenia (26%), fatigue (14%) and anemia (12%).

Table of Contents

Selinexor in Combination with Pomalyst® and Low-dose Dexamethasone (SPd)

At the ASH 2018 annual meeting, we also presented updated results from the selinexor, Pomalyst® and dexamethasone arm of the STOMP study, referred to as SPd. In this study arm, selinexor was dosed orally either once weekly (60 or 80mg) or twice weekly (60 or 80mg) with Pomalyst® (4mg orally, once daily) and dexamethasone (orally, 40mg once weekly or 20mg twice weekly). Across the 38 patients enrolled in the SPd arm as of November 15, 2018, the median number of prior treatment regimens was four (range of two to nine prior treatment regimens). Of the overall 34 patients evaluable for efficacy as of November 15, 2018, 17 responded for an ORR of 50% (five patients having a VGPR and 12 patients having a PR). Median PFS for all evaluable patients was 12.2 months, with a follow up of 9.4 months. Responses tended to occur rapidly with a median of one month to onset. In the Pomalyst®-naïve and Revlimid®-relapsed or -refractory population (26 patients), the ORR was 54% and media PFS was 12.2 months. ORR and median PFS in Pomalyst and Revlimid-refractory myeloma were 38% and 5.5 months, respectively.

Among the 38 patients evaluable for safety as of November 15, 2018, the most common treatment-related AEs were cytopenias, along with gastrointestinal and constitutional symptoms. Most were manageable with dose modifications and/or standard supportive care. The most common non-hematologic treatment-related AEs were nausea (53%), fatigue (50%) and weight decreased (34%). As expected, the most common treatment-related Grade 3 and 4 AEs were neutropenia (55%), thrombocytopenia (34%), anemia (29%) and leukopenia (18%). There were three Grade 5 treatment-related AEs (febrile neutropenia, intracranial hemorrhage and pneumonia). Based on the tolerability and efficacy data from this study arm, doses of oral selinexor of 60mg and 80mg once weekly are being evaluated in combination with Pomalyst® (3mg orally, once daily) and low dose dexamethasone to determine the recommended Phase 2 dose for this combination regimen.

Selinexor in Combination with Revlimid® and Low-dose Dexamethasone (SRd)

At the ASH 2017 annual meeting, we also presented new data from the selinexor, Revlimid® and dexamethasone arm of the STOMP study, referred to as SRd. In this study arm, oral selinexor was dose-escalated starting at either 60mg once weekly or 60mg twice weekly, with Revlimid® (25mg orally, once daily), and dexamethasone (orally, 40mg once weekly or 20mg twice weekly). Across the 19 patients enrolled in the SRd arm as of November 1, 2017, the median number of prior treatment regimens was one (range of one to seven prior treatment regimens). Of the 16 patients evaluable for efficacy, as of November 15, 2017, 13 responded for an ORR of 81% (three patients having a VGPR and 10 patients having a PR). Among the 12 patients in the Revlimid®-naïve population, the ORR was 92%. Median PFS was not reached for either the overall study population or for patients with Revlimid®-naïve disease. The median time on treatment for the overall study population was also not reached.

Among the 19 patients evaluable for safety as of November 15, 2017, the most common Grade 1/2 AEs were nausea (68%), anorexia (42%), fatigue (42%), weight loss (42%), constipation (32%) and vomiting (32%). The most common Grade 3 or higher AEs were thrombocytopenia (68%) and neutropenia (58%). Gastrointestinal AEs were generally manageable with antiemetics. Five DLTs (thrombocytopenia (four patients) and anorexia (one patient)) were observed in patients receiving selinexor 60mg twice weekly and 80mg once weekly. Thrombocytopenia and anorexia were reduced in the selinexor 60mg once weekly cohort versus the twice weekly groups. Based on the activity and tolerability observed in this study arm, the recommended dose of the all-oral SRd is selinexor (60mg orally, once weekly), Revlimid® (25mg orally, once daily) and dexamethasone (40mg orally, once weekly).

Selinexor in Combination with Darzalex® and Low-dose Dexamethasone (SDd)

At the ASH 2018 annual meeting, we presented new data from the selinexor, Darzalex® and dexamethasone arm of the STOMP study, referred to as SDd. In this study arm, oral selinexor was dose escalated using either 100mg once

weekly or 60mg twice weekly, with Darzalex® (16mg/kg intravenously once weekly) and

Table of Contents

dexamethasone (orally, 40mg once weekly or 20mg twice weekly). Across the 28 patients enrolled in the SDd arm as of November 15, 2018, the median number of prior treatment regimens was three (range of two to 10 prior treatment regimens). Of the 26 patients evaluable for efficacy, as of November 15, 2018, 19 responded for an ORR of 79% (seven patients having a VGPR and twelve patients having a PR). The 19 patients that responded were all among the 24 patients in the Darzalex®-naïve population. Responses tended to occur rapidly with a median of one month to onset. Median PFS and DOR had not been reached as of the cutoff date. Based on published data, the expected ORR for Darzalex therapy without selinexor in the Darzalex®-naïve population is approximately 30%. Thus, the ORR of 79% provides a basis for further evaluation of the SDd combination.

Among the 25 patients evaluable for safety as of November 15, 2018, the most common treatment-related AEs were cytopenias, along with gastrointestinal and constitutional symptoms. Most were manageable with dose modifications and/or standard supportive care. The most common non-hematologic treatment-related AEs were nausea (60%), fatigue (48%), diarrhea (32%), vomiting (24%) and anorexia (28%) and mostly Grade 1 and 2 events. The most common Grade 3 and 4 treatment-related AEs were thrombocytopenia (44%), anemia (28%), leukopenia (28%) and neutropenia (24%). No Grade 5 AEs were reported. The maximum tolerated dose was not reached. Two dose-limiting toxicities (DLTs) (Grade 3 thrombocytopenia and Grade 2 fatigue) were observed in patients receiving selinexor 60mg twice weekly. No DLTs were reported in the 100mg once weekly cohort. The longest duration of therapy is over 60 weeks. Based on the preliminary tolerability and efficacy data, the recommended phase 2 dose of SDd is selinexor (100mg orally, once weekly), Darzalex® (16mg/kg, once weekly) and dexamethasone (40mg orally, once weekly).

Selinexor in Combination with Kyprolis® and Low-dose Dexamethasone (SKd)

We are conducting an additional arm of the STOMP study evaluating selinexor, Kyprolis® and dexamethasone, referred to as SKd. Based on investigator-sponsored trial data reported in 2016 with this combination, the dosing regimen selected for STOMP is selinexor (100mg once weekly), Kyprolis® (56 or 70mg/m$^2$ intravenously once weekly) and dexamethasone (40mg orally, once weekly).

Selinexor in Combination with Revlimid® and Low-dose Dexamethasone in Newly Diagnosed Multiple Myeloma (SRd NDMM)

In June 2018, we initiated an additional arm of the STOMP study evaluating selinexor, Revlimid® and dexamethasone in patients with newly diagnosed multiple myeloma (NDMM), referred to as SRd NDMM. Patients eligible for this arm must have symptomatic NDMM requiring systemic therapy. Eligible patients must not have had any prior systemic therapy for NDMM other than corticosteroids. We expect that starting dose of oral selinexor will be 60mg (once weekly) with 40mg of dexamethasone (orally, weekly) and 25mg of Revlimid® (orally, once daily).

*BOSTON: Pivotal Phase 3 Clinical Trial of Selinexor, Velcade® and Low-Dose Dexamethasone vs. Velcade® and Low-Dose Dexamethasone in Multiple Myeloma*

Based on the data from the SVd arm of the STOMP study and following consultation with the FDA and the EMA, we are conducting a pivotal randomized Phase 3 study, known as the BOSTON (**Bortezomib, Selinexor and dexamethasone**) study, which is evaluating SVd compared to standard Velcade® and low-dose dexamethasone (Vd) in patients with MM who have had one to three prior lines of therapy. In January 2019, we completed enrollment of the BOSTON study; all enrolled patients have been randomized in a one-to-one fashion to receive either SVd or Vd. For the BOSTON study, we have identified the combination dose of selinexor 100mg orally once weekly plus dexamethasone 20mg orally twice weekly and Velcade® 1.3mg/m$^2$ subcutaneously once weekly for 4 of 5 weeks. The dosing schedule allows for only one scheduled clinic visit per week for patients on the SVd arm with selinexor and

Velcade® to be dosed not more frequently than once per week. Importantly, dosing on the SVd arm will use 40% less Velcade® and 25% less dexamethasone than the Vd arm, which follows the standard Vd dosing schedule. We expect that the reduced exposure provided by the SVd

Table of Contents

dosing schedule may significantly reduce common Velcade®- and dexamethasone-related toxicities, which is consistent with the safety data from the 42 patients described above who were treated with SVd on the STOMP study at the recommended dose. For the Vd arm, cross-over to the SVd arm based on objective progression will be permitted. The primary endpoints of the study are ORR and PFS and key secondary endpoints include DOR, OS, and certain other duration and quality of life endpoints. Top-line data from the Phase 3 BOSTON study is anticipated at the earliest by the end of 2019 or into 2020 depending on the occurrence of progression events per protocol.

**Non-Hodgkin s Lymphoma**

Non-Hodgkin s Lymphoma (NHL) is a cancer that starts in cells called lymphocytes, which are part of the body s immune system. Lymphocytes are found in the lymph nodes and other lymphoid tissues, such as the spleen and bone marrow, as well as in the blood. DLBCL is the most common and the most aggressive of the different forms of NHL. We estimate that approximately 25,000 patients are diagnosed with DLBCL in the United States each year, with approximately 10,000 deaths per year. Approximately 50% of newly diagnosed patients are currently cured with front-line (typically R-CHOP chemotherapy) and another approximately 10% of patients are cured with second line intensive chemotherapy followed by autologous stem cell transplantation. The remaining patients generally succumb to the disease, with the median overall survival of patients with relapsed or refractory DLBCL after two prior regimens less than one year, and often less than six months. Despite the recent approval of CAR-T therapy, many patients with relapsed/refractory DLBCL are not be medically stable enough to undergo CAR-T therapy and have no new or targeted agents approved for the treatment of their disease.

*SADAL: Phase 2b Clinical Trial of Selinexor in Diffuse Large B-Cell Lymphoma*

Our **S**elinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma, or **SADAL**, study is an open-label Phase 2b clinical trial evaluating single-agent oral selinexor in patients that have relapsed and/or refractory DLBCL, either de novo or transformed from a more indolent NHL such as follicular lymphoma, after two to five lines of therapy. At least 50% of patients on SADAL have the GCB subtype of DLBCL, which represents a particularly high unmet medical need given the lack of available therapies for patients with this relapsed/refractory subtype. The SADAL study had been conducted as a two-arm study with patients randomized on a one-to-one basis to receive either 100mg or 60mg of selinexor, each given twice weekly, with about 200 patients expected to be randomized evenly between the two arms with an inclusion requirement of least 14 weeks since a patient s last systemic anti-DLBCL therapy. The primary endpoint would be ORR on each arm, with the goal of determining the more optimal dose for patients with heavily pretreated DLBCL.

In December 2018, we reported updated results from the SADAL study at the ASH 2018 annual meeting. Across the 129 patients enrolled in SADAL as of November 15, 2018, the median number of prior treatment regimens was two (range of two to six prior treatment regimens). Based on the intention-to-treat analysis of the first 115 of 127 patients and as adjudicated by an independent central radiological review committee, as of November 15, 2018, 34 patients responded (11 patients having a CR and 23 patients with a PR) for an ORR of 29.6%. An additional eight patients experienced stable disease (SD), for a disease control rate (DCR) of 36.5%. The median DOR across all patients was 9.2 months and responses tended to occur rapidly. Patients with a CR had a median DOR of 23.0 months and patients with a PR had a median DOR of 7.8 months. As of the data cutoff date of November 15, 2018, seven patients who achieved a CR remained on treatment. In addition, as of the data cutoff date, 12 patients remained on treatment but had not reached their first response assessment and are not included in the top-line efficacy analyses. The median overall survival was 9.1 months for all patients on the study. As of the cutoff date, median survival for the patients with PR or CR was 29.7 months. The median survival for patients with best response of progressive disease or who were not evaluable for response was 3.2 months.

Among the 128 patients evaluated for safety as of the cutoff date, the most common treatment-related AEs were gastrointestinal and constitutional symptoms, along with cytopenias. Most were manageable with dose

Table of Contents

modifications and/or supportive care. The most common non-hematologic AEs were nausea (50.0%), fatigue (35.9%), and anorexia (32.0%) and mostly Grade 1 and 2 events. The most common Grade 3 and 4 AEs were thrombocytopenia (35.2%), neutropenia (20.3%), and anemia (10.9%) and were generally not associated with clinical sequelae. No significant major organ toxicities were observed, and bleeding and infection rates were low.

Selinexor showed robust, single-agent activity in patients with either GCB or non-GCB subtypes of DLBCL: of the 53 patients with the GCB-subtype, 18 responded (five patients with a CR and 13 patients with a PR) for an ORR of 34.0%. Of the 57 patients with the non-GCB subtype, 12 responded (six patients with a CR and six patients with a PR) for an ORR of 21.1%. In addition, there were five patients enrolled whose subtype was unclassified and 4 of these patients achieved a PR.

In November 2018, the FDA granted fast track designation to selinexor for the treatment of patients that have relapsed and/or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for transplantation, including high dose chemotherapy with stem cell rescue. Based on the positive results of the SADAL study, we plan to submit an NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients that have relapsed and/or refractory DLBCL and intend to work with the FDA to determine the appropriate timeline for the submission. We also plan to submit a Marketing Authorization Application to the EMA with a request for conditional approval.

**Advanced or Metastatic Solid Tumor Malignancies**

Solid tumors represent the vast majority of cancer incidences. Given the large patient population with solid tumors and the mechanistic activity of selinexor that makes it potentially suitable for treating any type of cancer, we are developing selinexor to potentially play a meaningful role across multiple solid tumor indications, either alone or in combination as a backbone therapy. We have seen encouraging single agent data for selinexor in a variety of solid tumors including PRs and durable SD with disease control greater than three months. Our Phase 1b study in patients with liposarcoma and other sarcomas demonstrated durable SD with single-agent selinexor, and our Phase 2 studies of selinexor in gynecological malignancies and glioblastoma multiforme (GBM) also demonstrated anti-cancer activity and disease control. Given the promising single-agent activity in difficult-to-treat indications and the potential to enhance activity in combination with existing therapies, we plan to further develop selinexor in unmet needs like certain gynecological malignancies or GBM, and to advance combination therapy development with both standard of care and emerging therapies like immune checkpoint inhibitors.

*SEAL: Phase 2/3 Clinical Trial of Selinexor vs. Placebo in Liposarcoma*

Liposarcoma represents an area of high unmet need with limited treatment options. Liposarcoma arises from fat cells or their precursors and represents up to 18% of all soft tissue sarcoma, or approximately 2,500 new cases per year in the United Sates. Liposarcoma most commonly occurs in the thigh, behind the knee, the groin, the gluteal area or behind the abdominal cavity. Dedifferentiated liposarcoma is an aggressive form of soft tissue sarcoma that is resistant to both standard chemotherapy and radiation. Liposarcoma has a particularly high rate of recurrence following surgery, especially in cases involving the abdomen. Except for cases that are cured with surgery, most patients with metastatic liposarcoma will succumb to this disease, and novel therapies are needed.

In our Phase 1b trial to evaluate the effects of food and formulation on selinexor pharmacokinetics in patients with soft-tissue or bone sarcoma, 31 of 54 sarcoma patients (57%) experienced SD with single-agent selinexor treatment. Of the 18 patients with liposarcoma, 14 (78%) experienced SD and eight (44%) experienced SD of four months or longer. Fifteen of these 18 patients with liposarcoma had dedifferentiated liposarcoma. Of these 15 patients with dedifferentiated liposarcoma, 13 (87%) experienced SD and seven (47%) experienced SD of four months or longer.

In light of the Phase 1b data, we are conducting the **Selinexor in Advanced Liposarcoma** (**SEAL**) study, a multi-center, randomized, double-blind, placebo-controlled Phase 2/3 clinical trial evaluating single-agent oral

Table of Contents

selinexor in patients with advanced unresectable dedifferentiated liposarcoma who received at least one line of prior systemic therapy. Patients are randomized to receive either 60mg of selinexor or placebo given twice weekly until progression or intolerability. Patients on placebo with confirmed progressive disease are permitted to cross over to the selinexor treatment arm. In June 2018, we reported a successful outcome from the Phase 2 portion of the SEAL study of 56 patients with previously treated, advanced unresectable dedifferentiated liposarcoma. The median number of prior treatment regimens was two (range of two to 10 prior treatment regimens). For the study s primary endpoint, patients treated with selinexor achieved PFS of 5.5 months, compared to 2.7 months for placebo-treated patients with a hazard ratio (HR) of 0.67, representing a 33% reduction in the risk of progression or death. PFS was assessed by an Independent Central Radiological Review (ICRR) based on RECIST v1.1. In this randomized, blinded Phase 2 portion of the study, selinexor demonstrated an expected and manageable safety profile, primarily with nausea, fatigue, anorexia and weight loss, and low levels of Grade 3/4 cytopenias, and no new or unexpected safety signals were identified. The majority of treatment-related AEs were low grade and reversible with dose modifications and/or standard supportive care. The data from the Phase 2 portion of the SEAL study, which is complete, demonstrate that treatment with selinexor improves PFS (RECIST v1.1) and supports the currently ongoing Phase 3 portion of the study using RECIST v1.1 response criteria, and for which top-line data are expected in the first half of 2020.

The Phase 3 portion of the SEAL study, which was originally initiated in North America, is ongoing and has been expanded to include Europe. In this blinded, placebo-controlled Phase 3 study, up to 222 patients are expected to be enrolled and randomized 2:1 to receive either oral selinexor (60mg twice weekly) until disease progression or intolerability, or placebo. Patients whose disease progresses on placebo will be permitted to cross over to the selinexor arm. The primary endpoint of the Phase 3 portion of the study is PFS as assessed by the ICRR based on RECIST v1.1. The Phase 3 study design and primary endpoint of PFS were agreed to by the FDA. Top-line data from the Phase 3 portion of the SEAL study are anticipated in 2020. Assuming a positive outcome, these data are intended to support a NDA for oral selinexor as a potential new treatment for patients with advanced unresectable dedifferentiated liposarcoma.

*SIENDO: Investigator-Sponsored Randomized Phase 3 Trial of Maintenance **S**elinexor/Placebo After Combination Chemotherapy **I**n Patients with Advanced or Recurrent **ENDO**metrial Cancer*

SIENDO is an investigator-sponsored Phase 3 trial of maintenance with selinexor or placebo after combination chemotherapy for patients with advanced or recurrent endometrial cancer. The overall objective is to obtain conclusive evidence of efficacy for maintenance selinexor in patients with advanced or recurrent endometrial cancer. This is a multi-center/multinational trial expected to enroll 192 patients. We expect that top-line data from this study will be presented in 2020.

This investigator-sponsored trial was designed based on the data from our SIGN study, a Phase 2, open-label study of efficacy and safety of oral selinexor in patients with heavily pre-treated, progressive gynecological cancers. In October 2016, we presented updated data at the ESMO 2016 annual meeting that showed selinexor s promising anti-tumor activity and disease control in gynecological malignancies. Of the 59 evaluable patients with ovarian cancer, 29 met the primary endpoint (8 patients (14%) achieved a confirmed PR and 21 patients achieved SD for at least 12 weeks), for a DCR of 49%. Median PFS for the ovarian cancer arm was three months and median OS was seven months. Of the 20 evaluable patients with endometrial cancer, nine met the primary endpoint (three confirmed PRs and six with SD for 12 or more weeks), for a DCR of 45%. Median PFS for the endometrial cancer arm was three months and median OS was eight months. Across all arms, the most common Grade 2 or 3 AEs were fatigue, nausea, anemia, anorexia, vomiting, weight loss and thrombocytopenia, which were manageable with supportive care and dose modifications. Notably, Grade 3 AEs were significantly reduced in patients with ovarian cancer receiving once weekly dosing compared to twice weekly dosing. One incidence of Grade 4 thrombocytopenia without bleeding was also reported. For the 44 patients who achieved at least SD for at least 12 weeks, the median time on study was 20

weeks. Fifteen patients remained on single-agent selinexor for greater than 6 months, including 4 patients continuing on treatment for greater than 12 months.

Table of Contents

*KING: Phase 2 Clinical Trial of Selinexor in Glioblastoma Multiforme*

The KING study is a Phase 2 study evaluating the efficacy and safety of oral selinexor in patients with recurrent GBM. In June 2016, we presented data at the American Society of Clinical Oncology Annual Meeting where we showed that single-agent oral selinexor demonstrated anti-tumor activity in patients with glioblastoma that recurred after temozolomide and radiation therapy, including selinexor brain penetration at clinically relevant levels, leading to durable anti-cancer activity and disease control of up to 6 months. Specifically, data as of May 23, 2016 from 33 surgically ineligible patients with GBM that progressed after treatment with temozolomide and radiation showed that selinexor dosed twice weekly at 50mg/$m^2$ demonstrated anti-tumor activity with a 12% ORR (PR or better) and a 33% DCR (SD or better) with durability of up to six months in two patients. The most common AEs were thrombocytopenia, fatigue, anorexia, and nausea.

We are evaluating the next steps for continued clinical development of selinexor in GBM.

**Our Other Pipeline Programs**

***Eltanexor (KPT-8602)***

Eltanexor is a second-generation SINE compound that, like selinexor, selectively blocks the nuclear export protein XPO1. The mechanism of action for the biological (anti-cancer) activity of eltanexor is believed to be the same as selinexor.

Eltanexor differs from selinexor primarily because it has much lower penetration into the brain in preclinical species, and, therefore, may cause fewer side effects such as nausea, fatigue and anorexia in patients. Following oral administration, animals treated with eltanexor show lower percentage of body weight loss and improved food consumption, as well as less fatigue behavior , in comparison to animals similarly treated with selinexor. This allows more frequent dosing of eltanexor, enabling a longer period of exposure at higher levels than is possible with selinexor, which allows for greater indication diversification among our SINE compounds. In many preclinical model systems, the more intensive dosing regimen leads to superior efficacy in comparison to selinexor treatment. As a result, we believe that eltanexor represents a second-generation SINE compound and are evaluating safety, tolerability and efficacy in humans.

We initiated our first-in-humans Phase 1/2 clinical trial for eltanexor in patients with relapsed/refractory multiple myeloma in January 2016. At the ASH 2017 annual meeting, we reported positive data from the ongoing Phase 1/2 study demonstrating good tolerability and promising activity in MM. Using a 3+3 dose escalation design, oral eltanexor (5, 10, 20, 30 and 40mg) was dosed once daily for five days per week or once every other day for three days each week (60mg) for a 28-day cycle. Patients with less than a minimal response after one cycle or partial response after two cycles were permitted to add dexamethasone. Of the 34 evaluable patients, 14 received dexamethasone with their eltanexor regimen from the first day of the first cycle. Deeper and faster responses were observed when dexamethasone was started on Day 1 of Cycle 1 versus a delayed start. As of January 2019, there were two active patients remaining on study. The median time on treatment for the overall study population was greater than 130 days, with a range of 10 to greater than 770 days.

Among the 39 patients evaluable for safety, the most common Grade 1/2 AEs in the MM patient population were nausea (54%), fatigue (46%), anemia (38%), diarrhea (38%), dysgeusia (33%), weight loss (33%) and neutropenia (31%). As expected in this patient population, the most common Grade 3/4 AEs were thrombocytopenia (56%), neutropenia (26%), anemia (15%), leukopenia (15%) and hyponatremia (10%). Importantly, nausea, fatigue, diarrhea and vomiting were nearly all Grade 1, manageable and transient, and bleeding was uncommon. The maximum

tolerated dose was not reached; however, dose escalation was halted as responses were achieved. Based on these data, the recommended phase 2 dose has been established as 20mg eltanexor dosed five times per week with 20mg dexamethasone dosed twice weekly.

This Phase 1/2 study has been expanded to include patients with high risk MDS, metastatic CRC or mCRPC to determine the safety, preliminary efficacy, and recommended phase 2 dose of eltanexor in patients with these

Table of Contents

advanced cancers. These are indications where selinexor and XPO1 inhibition has shown clear activity, but where side effects such as fatigue and anorexia were problematic for patients due to the underlying malignancies.

At the ESMO Congress in October 2018, positive data were reported from the ongoing Phase 1/2 investigator-sponsored study in the dose expansion cohort in patients with heavily pre-treated (median of four prior treatments) mCRC. The presented results showed that 37% of patients experienced disease control at ³8 weeks on eltanexor and the median preliminary PFS for all patients in the 30 mg cohort was 3.5 months. Adverse events were generally predictable and manageable. The highest observed treatment-related Grade 3 or higher AEs were hyponatremia (23%), fatigue (20%) and anemia (20%). These preliminary results demonstrated promising efficacy with a median PFS longer than currently available third line therapies and an acceptable safety and tolerability profile.

***KPT-9274***

KPT-9274 is a first-in-class orally bioavailable small molecule that is a non-competitive dual modulator of p21-activated kinase 4 (PAK4) and NAMPT (nicotinamide phosphoribosyltransferase; also known as PBEF or visfatin). Co-inhibition of these targets leads to synergistic anti-tumor effects through energy depletion, inhibition of DNA repair, cell cycle arrest, inhibition of proliferation, and ultimately apoptosis. Normal cells are more resistant to inhibition by KPT-9274 due in part to their relative genomic stability and lower metabolic rates. Hematologic and solid tumor cells become dependent on both PAK4 and NAMPT pathways and are therefore susceptible to single-agent cytotoxic effect of KPT-9274.

PAK4 is a signaling protein regulating numerous fundamental cellular processes, including several involved in the development of cancer. PAK4 interacts with key signaling molecules involved in cancer such as beta-catenin, CDC42, Raf-1, BAD and myosin light chain.

NAMPT is a pleiotropic protein with multiple intra- and extra-cellular functions that can be found in complex with PAK4 in the cell. NAMPT is of interest as an oncology target because it catalyzes the rate-limiting step in one of the two intracellular salvage pathways that generate nicotinamide adenine dinucleotide (NAD). NAD is a universal energy- and signal-carrying molecule involved in mitochondrial function and energy metabolism, as well as in DNA repair (through Poly-ADP-Ribose Polymerase, or PARP) and epigenetics (through sirtuims, or SIRTs). An alternate salvage pathway utilizes the rate-limiting enzyme NAPRT1 to convert nicotinic acid or niacin into NAD. NAPRT1 is often silenced through promoter hypermethylation in tumor samples while it remains expressed in normal tissues. Patients that have NAPRT1 negative tumors may be able to benefit from niacin co-dosing to alleviate KPT-9274 adverse effects while maintaining inhibitory activity in their tumors. Therefore, patients can be stratified according to their NAPRT1 tumor status.

KPT-9274 has shown broad evidence of anti-cancer activity against hematological and solid tumor malignant cells while showing minimal toxicity to normal cells in vitro. In mouse xenograft studies, KPT-9274 given orally has shown evidence of anti-cancer activity and tolerability. To our knowledge, we are the only company with an allosteric, PAK4 and/or NAMPT specific inhibitor currently in clinical development.

We initiated a first-in-humans Phase 1 open-label clinical trial evaluating the safety, tolerability, and efficacy of KPT-9274 in patients with advanced solid malignancies or non-Hodgkin s lymphoma. Top-line results from this Phase 1 study were presented in September 2017 at the ESMO annual meeting. Among the 18 patients evaluable for preliminary efficacy, there were six (33%) with SD, the longest for 7.3 months. Tumor reductions (shrinkage of 3.9%, 13.6% and 22.6%) were observed in three out of three patients (100%) with NAPRT1 deficient tumors. Among the 21 patients evaluated for safety, the most common Grade 2 AEs across dose levels were arthralgia (43%), anemia (24%) and fatigue (24%). The most common drug-related Grade 3 or higher AEs across dose levels include anemia (38%)

and fatigue (5%). Gastrointestinal-related AEs were infrequent and low grade. In addition, it was determined that niacin can be safely administered with KPT-9274 and may improve tolerability, particularly with respect to anemia. Dose escalation remains ongoing and further

Table of Contents

evaluation of effects in NAPRT1 deficient tumors is planned. Enrollment is planned to continue based on the patients NAPRT1 status in a 2:1 ratio (NAPRT1- : NAPRT1+). These study findings indicate that in patients whose disease has progressed despite most available therapies, KPT-9274 can induce tumor shrinkage and disease stabilization.

***Verdinexor (KPT-335):*** *Oral SINE Compound for Lymphoma in Companion Canines*

We have used spontaneously occurring canine cancers as a surrogate model for human malignancies. It is widely known that canine lymphomas display a comparable genetic profile and respond to chemotherapy in a fashion similar to their human counterparts (human NHL, most closely DLBCL). Lymphomas are one of the most common tumors in pet dogs. Lymphoma in dogs is very aggressive and, without treatment, the tumors are often fatal within weeks. The majority of dog lymphomas are DLBCL and most of the others are T-cell lymphomas. Given the similarities of dog and human lymphomas, prior to initiating clinical trials of selinexor in humans, we investigated verdinexor (KPT-335), a closely-related, orally available SINE compound in pet dogs with lymphomas. We have received a Minor Use / Minor Species (MUMS) designation from the FDA s Center for Veterinary Medicine (CVM) for the treatment of newly-diagnosed or first relapse after chemotherapy lymphomas in pet dogs with verdinexor.

Several different dog tumor cell lines, including those derived from lymphomas, exhibited growth inhibition and apoptosis in vitro upon exposure to nanomolar concentrations of verdinexor. Data from a Phase 1 clinical trial of verdinexor as well as dose expansion study involving pet dogs with cancer, primarily with lymphoma, show efficacy of verdinexor to treat dogs with lymphoma. Side effects included anorexia, weight loss, vomiting and diarrhea and were manageable with dose modulation and supportive care. We conducted an owner observation-based survey and the data indicated that the overall quality of life did not change significantly in dogs treated with verdinexor. Based on these findings, a Phase 2b clinical trial, intended to support regulatory approval under the MUMS designation in the United States, was performed in 58 pet dogs with either newly-diagnosed or first relapse after chemotherapy lymphomas. In this Phase 2b clinical trial, verdinexor was administered initially at doses ranging from 25mg/$m^2$ to 30mg/$m^2$ two or three days per week. Minimal or no supportive care was given. The total CRs and PRs of the 58 dogs was 34%, with one CR and 19 PRs. An additional 33 of 58 dogs (57%) experienced SD for at least four weeks. The median time to disease progression was approximately five weeks, with 20 dogs (34%) remaining on study for longer than eight weeks. A few dogs that received verdinexor in the Phase 1 or 2b studies remained on therapy for longer than eight months. We submitted the safety and effectiveness sections of a New Animal Drug Application for verdinexor to the CVM in December 2013.

In May 2017, we entered into an exclusive licensing agreement with Anivive, a privately-held biotech company focused on innovations in the veterinary drug and bioinformatics space, pursuant to which Anivive received worldwide rights to research, develop and commercialize verdinexor for the treatment of cancer in companion animals. In exchange, we received an upfront payment and are eligible to receive future milestone payments and royalties. If approved, we believe that verdinexor would represent the first oral, targeted therapy for the treatment of dog lymphoma.

**Our Non-Oncology Drug Candidates**

***Verdinexor (KPT-335):*** *Oral SINE Compound for Viral, Rare Disease and Autoimmune Indications*

Verdinexor (KPT-335) is an oral SINE compound and our lead compound that is being evaluated as a potential therapy for viral, rare disease and autoimmune indications, in addition to the canine lymphoma program described above. Several autoimmune indications are driven by aberrant pro-inflammatory responses, particularly uncontrolled NF-kB activation. These include systemic lupus erythematosus (SLE), a primary focus of our work with verdinexor. Funded by a grant under the Small Business Innovation Research program, we expect to complete pre-clinical

evaluation of verdinexor as a treatment for SLE by the end of year 2019, when we expect to be in position to file an IND application with the FDA.

Table of Contents

In addition to autoimmune disorders, several viruses exclusively utilize XPO1 to shuttle cargos necessary for viral replication, such as viral and host proteins from the nucleus to the cytoplasm. Due to the stability of host gene targets compared to viruses which rapidly adapt for best fitness in hosts, targeting host genes may offer an approach to limit drug resistance. We intend to extend preclinical research in viruses that may be relevant to patients with compromised immune systems, such as respiratory syncytial virus and cytomegalovirus, along with highly relevant pathogens currently causing outbreaks such as enterovirus 68 (acute flaccid myelitis). We also intend to investigate verdinexor to treat inflammation in virally-suppressed antiretroviral therapy-receiving individuals.

In 2015, we conducted a randomized, double-blind, placebo-controlled, dose-escalating Phase 1 clinical trial of verdinexor in healthy human volunteers in Australia. This study was designed to evaluate the safety and tolerability of verdinexor in healthy adult subjects. Verdinexor was found to be generally safe and well tolerated. Mild to moderate AEs of similar number and grade as placebo were reported, and no serious or severe AEs were observed. We plan to continue to explore strategies to pursue the clinical development of verdinexor as a treatment for viral, inflammatory, and autoimmune indications, including potentially partnering with a collaborator or through government-funded grant or contract opportunities.

As part of the exclusive license agreement we entered into with Antengene in May 2018, we granted Antengene exclusive rights to develop and commercialize verdinexor for the diagnosis, treatment and/or prevention of certain human non-oncology indications in mainland China, Taiwan, Hong Kong, Macau, South Korea, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam.

**Our Strategic Relationships**

On May 23, 2018, we entered into a license agreement (Antengene Agreement) with Antengene and a subsidiary of Antengene Corporation Co. Ltd., a corporation organized and existing under the laws of the People s Republic of China, pursuant to which we granted Antengene exclusive rights to develop and commercialize, at its own cost, selinexor, eltanexor and KPT-9274, each for the diagnosis, treatment and/or prevention of all human oncology indications, as well as verdinexor for the diagnosis, treatment and/or prevention of certain human non-oncology indications. We licensed the development and commercial rights to Antengene for selinexor and eltanexor in the oncology field in mainland China and Macau and licensed the development and commercial rights to Antengene for KPT-9274 in the oncology field, as well as verdinexor in the non-oncology field in mainland China, Taiwan, Hong Kong, Macau, South Korea, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam. Under the terms of the Antengene Agreement, we received an upfront cash payment of $11.7 million and are entitled to receive up to $105.0 million in milestone payments from Antengene if certain development goals are achieved and up to $45.0 million in milestone payments from Antengene if certain sales milestones are achieved. We are further eligible to receive tiered double-digit royalties based on future net sales of selinexor and eltanexor in China and Macau, and tiered single- to double-digit royalties based on future net sales of KPT-9274 and verdinexor in the licensed territories. Antengene s obligations under the Antengene Agreement have been guaranteed by Antengene Corporation Co. Ltd.

On January 24, 2018, we entered into an asset purchase agreement with Biogen pursuant to which Biogen acquired exclusive worldwide rights to develop and commercialize our oral SINE compound KPT-350 and certain related assets with an initial focus in amyotrophic lateral sclerosis. KPT-350 is an IND-ready oral SINE compound with a preclinical data package supporting potential efficacy across a number of neurological, autoimmune and inflammatory conditions. XPO1 mediates the nuclear export of multiple proteins that impact neurological, autoimmune and inflammatory processes. Consequently, inhibition of XPO1 by KPT-350 results in a reduction in autoimmunity and inflammation and an increase in anti-inflammatory and neuroprotective responses. KPT-350 penetrates the blood brain barrier to a greater degree than other SINE compounds. Preclinical data generated largely by external

collaborators show efficacy of KPT-350 and related SINE compounds in animal models of amyotrophic lateral sclerosis, multiple sclerosis, traumatic brain injury, epilepsy,

Table of Contents

systemic lupus erythematosus and rheumatoid arthritis. We received a one-time upfront payment of $10.0 million from Biogen and are eligible to receive additional payments of up to $207.0 million based on the achievement by Biogen of future specified development and commercial milestones. We are also eligible to receive tiered royalty payments that reach low double digits based on future net sales until the later of the tenth anniversary of the first commercial sale of the applicable product or the expiration of specified patent protection for the applicable product, determined on a county-by-country basis.

Effective October 11, 2017, we entered into an exclusive license agreement with Ono Pharmaceutical Co., Ltd. (Ono), whereby Ono received rights to develop and commercialize selinexor and eltanexor (KPT-8602), at its own cost and expense, for the diagnosis, treatment and/or prevention of all human oncology indications in Japan, South Korea, Taiwan, Hong Kong, and ASEAN countries, which we refer to as the Ono Territory. In exchange, we received a one-time upfront payment of ¥2.5 billion (approximately US$21.9 million) from Ono and retain all rights to selinexor and eltanexor outside the Ono Territory. We are eligible to receive up to an additional ¥19.2 billion (approximately US$170.7 million at the exchange rate on the effective date of the agreement) if specified future development and commercial milestones are achieved by Ono. We are also eligible to receive low double-digit royalties based on future net sales of selinexor and eltanexor in the Ono Territory. Ono will have the ability to participate in any global clinical study of selinexor and eltanexor and will bear the cost and expense for patients enrolled in clinical studies in the Ono Territory.

In May 2017, we entered into an exclusive licensing agreement with Anivive, pursuant to which Anivive received worldwide rights to research, develop and commercialize verdinexor for the treatment of cancer in companion animals. In exchange, we received an upfront payment of $1.0 million and a subsequent milestone of $250,000 and are eligible to receive up to $43.3 million in future regulatory, clinical and commercial milestone payments, assuming approval in both the United States and the European Union. In addition, Anivive agreed to pay us up to low double-digit royalty payments based on future net sales of verdinexor. If approved, we believe that verdinexor would represent the first oral, targeted therapy for the treatment of dog lymphoma.

**Intellectual Property**

Our commercial success depends in part on our ability to obtain and maintain proprietary or intellectual property protection for our drug candidates, our core technologies, and other know-how, to operate without infringing on the proprietary rights of others and to prevent others from infringing our proprietary or intellectual property rights. Our policy is to seek to protect our proprietary and intellectual property position by, among other methods, filing patent applications in the United States and in foreign jurisdictions related to our proprietary technology and drug candidates. We also rely on trade secrets, know-how and continuing technological innovation to develop and maintain our proprietary and intellectual property position.

We file patent applications directed to the composition of matter and methods of use and manufacture for our drug candidates. As of February 1, 2019, we were the sole owner of 13 patents in the United States and we had 16 pending patent applications in the United States, 47 granted patents and 117 pending patent applications in foreign jurisdictions. The technology underlying such pending patent applications has been developed by us and was not acquired from any in-licensing agreement.

The intellectual property portfolios for our key drug candidates as of February 1, 2019 are summarized below.

**Selinexor (KPT-330)**: Our selinexor patent portfolio covers the composition of matter and methods of use of selinexor, as well as methods of making selinexor, and consists of three issued U.S. patents (one patent is specific to selinexor, and the two other patents cover both selinexor and verdinexor), 19 issued foreign patents, 39 pending foreign patent applications, and two pending U.S. non-provisional application, one directed to polymorphs of selinexor. Any patents that may issue in the United States as part of our selinexor patent portfolio, with the exception of a patent directed to the polymorphs of

Table of Contents

selinexor, will expire in 2032, absent any terminal disclaimer, patent term adjustment due to administrative delays by the United States Patent and Trademark Office (USPTO) or patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act. Any patents that may issue in foreign jurisdictions will likewise expire in 2032. Any patents that may issue in the United States directed to the polymorphs of selinexor will expire in 2035, absent any terminal disclaimer, patent term adjustment due to administrative delays by the USPTO or patent term extension under the Hatch-Waxman Act. Any patent issued in foreign jurisdictions will likewise expire in 2035.

**Selinexor (Wound Healing)**: Our patent portfolio covering selinexor for wound healing, including acute and chronic wounds, burns and scars, covers methods of using selinexor or verdinexor for wound healing, including systemic and topical uses, and consists of one pending U.S. application and one pending European application. Any patents that may issue in the United States will expire in 2034, absent any terminal disclaimer, patent term adjustment due to administrative delay by the USPTO or patent term extension under the Hatch-Waxman Act. Any patents issued in Europe will likewise expire in 2034.

**Verdinexor (KPT-335)**: Our selinexor patent portfolio described above, with the exception of the applications directed to polymorphs of selinexor, also covers both the composition of matter and methods of use of verdinexor, as well as methods of making verdinexor. There are four issued U.S. Patents that cover verdinexor. One patent is specific to verdinexor, two patents cover both verdinexor and selinexor (also referenced above with respect to selinexor) and the other covers veterinary uses of verdinexor.

**Eltanexor** (**KPT-8602**): Our eltanexor patent portfolio covers both the composition of matter and methods of use of eltanexor, and consists of one issued U.S. patent, one pending provisional U.S. patent application, one pending non-provisional U.S. patent application, two issued foreign patents and 23 pending foreign patent applications. Any patents that may issue in the United States as part of our eltanexor patent portfolio, with the exception of a patent based on the pending provisional U.S. patent application, will expire in 2034, absent any terminal disclaimer, patent term adjustment due to administrative delays by the USPTO or patent term extension under the Hatch-Waxman Act. Any patents issued in foreign jurisdictions will likewise expire in 2034. Any patents that may issue in the United States based on the pending provisional U.S. patent application will expire in 2039, absent any terminal disclaimer, patent term adjustment due to administrative delays by the USPTO or patent term extension under the Hatch-Waxman Act. Any patents issued in foreign jurisdictions will likewise expire in 2039.

**PAK4/NAMPT Inhibitors**: Our PAK4/NAMPT inhibitors patent portfolio covers both the composition of matter and methods of use of the PAK4/NAMPT inhibitors described therein, such as KPT-9274, and consists of nine patent families with three issued U.S. patent, three issued foreign patents, seven pending U.S. non-provisional patent applications, and 34 pending foreign patent applications in total. Any patents that may issue in the United States based on the pending U.S. non-provisional applications will expire in 2033 for the earliest filed application and 2034, 2035 or 2036 for the remaining applications, absent any terminal disclaimer, patent term adjustment due to administrative delays by the USPTO or patent term extension under the Hatch-Waxman Act. Any patents that may issue based on the pending foreign patent applications will likewise expire in 2033, 2034 or 2036. Foreign patent applications covering the composition of matter and methods of use of KPT-9274 have been filed in 21 countries/regions.

In addition to the patent portfolios covering our key drug candidates, as of February 1, 2019, our patent portfolio also includes four patents (U.S. Patent Nos. 8,513,230, 9,303,000, 9,428,490 and 9,550,757) and 22 granted foreign patents and pending patent applications in the U.S. and foreign jurisdictions relating to other XPO1 inhibitors and their use in targeted therapeutics and biomarkers for XPO1 inhibitors. We also filed three Intent to Use Trademark Applications on August 29, 2013 covering our name, our logo and the two used

Table of Contents

together. Marks for the name and name and logo together were registered in the United States on January 20, 2015 as Registration Nos. 4,676,255 and 4,676,226. The mark for our logo was registered in the United States on February 24, 2015 as Registration No. 4,693,107. We also have registered PORE in the United States for our online portal. As of February 1, 2019, we have pending Intent to Use Trademark Applications in the United States for seven possible drug names for selinexor, and for KARYFORWARD for our financial assistance and charitable services. We have filed applications for all seven selinexor names in sixteen jurisdictions, and we have filed for two of those names in twelve additional jurisdictions. Some of the international filings for the drug names are registered, while some are pending.

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries, including the United States, the patent term is 20 years from the earliest filing date of a non-provisional patent application. In the United States, a patent s term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the USPTO in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a patent that covers a drug may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements are met. See Government Regulation Patent Term Restoration and Extension below for additional information on such extensions. In the future, if and when our drug candidates receive approval by the FDA or foreign regulatory authorities, we expect to apply for patent term extensions on issued patents covering those drugs, depending upon the length of the clinical trials for each drug candidate and other factors. There can be no assurance that any of our pending patent applications will issue or that we will benefit from any patent term extension or favorable adjustment to the term of any of our patents.

As with other biotechnology and pharmaceutical companies, our ability to maintain and solidify our proprietary and intellectual property position for our drug candidates and technologies will depend on our success in obtaining effective patent claims and enforcing those claims if granted. However, patent applications that we may file or license from third parties may not result in the issuance of patents. We also cannot predict the breadth of claims that may be allowed or enforced in our patents. Our issued patents and any issued patents that we may receive in the future may be challenged, invalidated or circumvented. For example, we cannot be certain of the priority of inventions covered by pending third-party patent applications. If third parties prepare and file patent applications that also claim technology or therapeutics to which we have rights, we may have to participate in interference proceedings to determine priority of invention, which could result in substantial costs to us, even if the eventual outcome is favorable to us. In addition, because of the extensive time required for clinical development and regulatory review of a drug candidate we may develop, it is possible that, before any of our drug candidates can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any advantage of any such patent.

In addition to patents, we rely upon unpatented trade secrets and know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, using confidentiality agreements with our collaborators, scientific advisors, employees and consultants, and invention assignment agreements with our employees. We also have agreements with selected consultants, scientific advisors and collaborators requiring assignment of inventions. The confidentiality agreements are designed to protect our proprietary information and, in the case of agreements or clauses requiring invention assignment, to grant us ownership of technologies that are developed through our relationship with a third party.

With respect to our proprietary drug discovery and optimization platform, we consider trade secrets and know-how to be our primary intellectual property. Trade secrets and know-how can be difficult to protect. We anticipate that with respect to this technology platform, these trade secrets and know-how may over time be disseminated within the industry through independent development, the publication of journal articles describing the methodology, and the movement of personnel skilled in the art from academic to industry scientific positions.

29

Table of Contents

**Competition**

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technology, knowledge, experience and scientific resources provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any drug candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

There are several companies developing or marketing treatments for cancer and the other indications on which we currently plan to focus, including major pharmaceutical and biotechnology companies. To our knowledge, only one other company with an XPO1 inhibitor has enrolled patients in clinical trials at the present time. Stemline Therapeutics, Inc. announced in January 2015 that it had exclusively licensed the rights to develop and commercialize SL-801, an oral XPO1 inhibitor, from CanBas Co., Ltd. In December 2015, Stemline announced the opening of its IND and planned initiation of a clinical development program in multiple cancer types. Stemline currently has a Phase 1 trial that is open and enrolling patients with advanced solid tumors.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

The key competitive factors affecting the success of any approved oncology drug product, including our drug candidates, if approved, are likely to be their efficacy, safety, convenience and price, the availability of alternative cancer therapies and the availability of reimbursement from government and other third-party payors.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize drugs, or commercialize existing drugs in new indications, and those drugs are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any drugs that we may develop. Our competitors also may obtain FDA or other regulatory approval for their drugs more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic drugs. Generic drugs for the treatment of cancer and the other indications on which we currently plan to initially focus are currently on the market, and additional drugs are expected to become available on a generic basis over the coming years. If we obtain marketing approval for our drug candidates, we expect that they will be priced at a significant premium over generic versions of older chemotherapy agents and other cancer therapies.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. While our drug candidates may compete with many existing drugs and other therapies, to the extent they are ultimately used in combination with or as an adjunct to these therapies, our drug candidates will be complimentary with them. Some of the currently-approved drug therapies are branded and subject to patent protection,

and others are available on a generic basis. Many of these approved drugs are well-established therapies and are widely-accepted by physicians, patients and third-party payors.

In addition to currently-marketed therapies, there are also a number of drugs in late stage clinical development to treat cancer and the other indications on which we plan to initially focus. These drugs in

Table of Contents

development may provide efficacy, safety, convenience and other benefits that are not provided by currently-marketed therapies. As a result, they may provide significant competition for any of our drug candidates for which we obtain marketing approval.

If our lead drug candidates are approved for the indications of our initial focus, they may compete with the investigational therapies and currently marketed drugs discussed below.

***Multiple Myeloma (MM)***

Over the past 15 years, ten agents have been approved in the United States for the treatment of patients with MM: Velcade® (bortezomib, Takeda), Revlimid® (lenalidomide, Celgene), Thalomid® (thalidomide, Celgene), Doxil® (liposomal doxorubicin, Janssen), Kyprolis® (carfilzomib, Amgen), Pomalyst® (pomalidomide, Celgene), Farydak® (panobinostat, Novartis), Darzalex® (daratumumab, Janssen), Empliciti® (elotuzumab, BMS), and Ninlaro® (ixazomib, Takeda). Approved indications range from the treatment of newly diagnosed patients to those with relapsed and/or refractory MM.

Several other anti-cancer agents are in late-stage development for the treatment of patients with MM, including anti-B cell maturation antigen (BCMA), based CAR-T therapies such as bb2121 (Bluebird Bio/Celgene), JCHARHI25 (Juno Therapeutics/Celgene), P-BCMA-101 (Johnson & Johnson/Poseida Therapeutics), LCAR-B38M (Johnson & Johnson/Legend BioTech) and CART-BCMA (Novartis); monocolonal antibodies such as isatuximab (Sanofi) and Opdivo® (nivolumab, BMS); antibody-drug conjugates such as GSK2857916 (GlaxoSmithKline); bi-specific antibodies such as AMG420 (Amgen), REGN5458 (Regeneron) and PF-06863135 (Pfizer); and other novel agents such as ibrutinib (Abbvie/Roche), venetoclax (Abbvie), plitidepsin (PharMar), masitinib (AB Sciences), filanesib (Array Biopharma), oprozomib (Amgen), ricolinostat (Celgene) and melflufen (Oncopeptides).

***Non-Hodgkin s Lymphoma (NHL)***

The initial therapy for DLBCL typically consists of multi-agent cytotoxic drugs in combination with the monoclonal antibody rituximab (Rituxan®, Roche). In patients with DLBCL who are not elderly and who have good organ function, high dose chemotherapy with stem cell transplantation is often used. Newer targeted agents such as the BTK inhibitor ibrutinib (Imbruvica®, Pharmacyclics) and the immunomodulatory drug lenalidomide (Revlimid®, Celgene) have shown activity in DLBCL. There are also a number of other widely used anti-cancer agents that have broad labels which include NHL, and some of these are being evaluated alone or in combination for the treatment of patients with DLBCL that have relapsed after treatment with chemotherapy. Other anti-cancer agents are also being evaluated in the treatment of DLBCL, including but not limited to, MOR-208 (MorphoSys), polatuzumab vedotin (Roche), umbralisib/ublituximab (TG Therapeutics), mosunetuzumab (Roche), ADCT-402 (ADC Therapeutics), zanubrutinib (Beigene), Afinitor® (everolimus, Novartis), venetoclax (Abbvie), acalabrutinib (Acerta Pharma), Blincyto (blinatumomab, Amgen), Imfinzi (durvalumab, AstraZeneca) , Opdivo® (nivolumab, BMS), Bavencio (avelumab, Pfizer/EMD Serono) and Adcetris® (brentuximab vendotin, Seattle Genetics). In addition, Kymriah (Novartis) and Yescarta (Kite/Gilead), both CAR-T therapies, have been approved as a treatment for patients with DLBCL and other CAR-T therapies are currently in clinical development.

***Competition with XPO1 Inhibitors***

Drug compounds currently in preclinical studies, if developed and approved, could also be competitive with our drug candidates, if approved. In January 2015, Stemline Therapeutics, Inc. announced that it had exclusively licensed the rights to develop and commercialize SL-801, an XPO1 inhibitor, from CanBas Co., Ltd. In December 2015, Stemline announced the opening of its IND application and planned initiation of a clinical development program in multiple

cancer types. Stemline currently has a Phase 1 trial that is open and enrolling patients with advanced solid tumors. Additionally, Kosan Biosciences Inc. (acquired by Bristol-Myers Squibb

Table of Contents

Company) has evaluated compounds derived from leptomycin B in preclinical studies. To our knowledge, the Kosan compounds are not currently being developed and have never entered human studies.

With respect to indications other than cancer, there are many currently-marketed therapies and drugs in late-stage clinical development to treat non-oncology indications on which we plan to initially focus development of our XPO1 inhibitors. However, to our knowledge, there are no other XPO1 inhibitors in clinical development for the treatment of any diseases other than cancer, including indications such as autoimmune and inflammatory diseases or wound healing. There is no published information on the use of the preclinical compounds that have been developed by Kosan Biosciences or CanBas Co. in models other than cancer.

***Competition with PAK4/NAMPT Dual Inhibitors***

Our first-in-class PAK4/NAMPT dual inhibitor KPT-9274, if developed and approved, would compete with currently-marketed therapies and drugs in clinical development to treat cancer. However, there are currently no marketed therapies that selectively target PAK4 and/or NAMPT. Pfizer Inc. developed PF-03758309, a non-selective PAK inhibitor, meaning that this compound inhibited several of the PAK family members, and not solely PAK4, through Phase 1 clinical development, but that compound had poor oral bioavailability in both animals and humans and, to our knowledge, development has been discontinued. We are aware that PAK4 biology is being evaluated preclinically by AstraZeneca plc and Genentech, Inc. (acquired by Roche Holding AG). We are not aware of any PAK4 inhibitors that are in clinical development at the present time.

In addition to KPT-9274, we are aware of three NAMPT inhibitors that have advanced into human clinical trials. These compounds include GMX1778 (also known as CHS-828), GMX1777 (water-soluble derivative of GMX1778), and APO866 (also known as FK866 and WK175). To our knowledge development of these inhibitors were discontinued. We are aware that NAMPT biology is being evaluated by Genentech, Inc., Eli Lilly & Company, Millennium/Takeda Pharmaceutical Company Ltd., OncoTartis, Inc., Aurigene Discovery Technologies Limited, and at some academic institutions. We are not aware of any other NAMPT inhibitors in clinical development.

**Manufacturing**

We do not have any manufacturing facilities or personnel. We currently rely, and expect to continue to rely, on third parties for the manufacture of our drug candidates for preclinical and clinical testing, as well as for commercial manufacture if our drug candidates receive marketing approval. In preparation for a potential commercial launch of selinexor in the United States subject to marketing approval by the FDA, we entered into a long-term supply arrangement with a third-party manufacture to provide commercial tablets of selinexor. We have engaged a third party manufacturer to obtain the active pharmaceutical ingredient for selinexor for preclinical and clinical testing and a separate third-party manufacturer for fill-and-finish services. We obtain our selinexor supplies for preclinical and clinical testing from these manufacturers on a purchase order basis and do not have a long-term supply arrangement in place for supplies for preclinical and clinical testing. We do not currently have arrangements in place for redundant supply.

All of our drug candidates are small molecules and are manufactured in reliable and reproducible synthetic processes from readily available starting materials. The chemistry is amenable to scale up and does not require unusual equipment in the manufacturing process. We expect to continue to develop drug candidates that can be produced cost-effectively at contract manufacturing facilities.

**Government Regulation**

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, or EU, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling,

Table of Contents

advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

**Review and Approval of Drugs in the United States**

In the United States, the FDA regulates drug products under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The failure to comply with applicable requirements under the FDCA and other applicable laws at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities.

An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA s good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must take effect before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each indication;
- preparation and submission to the FDA of an NDA;
- review of the product by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with current Good Manufacturing Practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product s identity, strength, quality and purity;

satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;

payment of user fees and securing FDA approval of the NDA; and

compliance with any post-approval requirements, including Risk Evaluation and Mitigation Strategies, or REMS, and post-approval studies required by the FDA.

***Preclinical Studies***

Preclinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated drug or drug product, as well as *in vitro* and animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive

Table of Contents

adverse events and carcinogenicity, may continue after the IND is submitted. In addition, companies usually must also develop additional information about the chemistry and physical characteristics of the investigational product and finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the candidate product and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the candidate product does not undergo unacceptable deterioration over its shelf life.

***The IND and IRB Processes***

An IND is an exemption from the FDCA that allows an unapproved drug to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer an investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug that is not the subject of an approved NDA. In support of a request for an IND, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. At any time during this 30-day period, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When the foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with FDA certain regulatory requirements in order to use the study as support for an IND or application for marketing approval. Specifically, on April 28, 2008, the FDA amended its regulations governing the acceptance of foreign clinical studies not conducted under an investigational new drug application as support for an IND or an NDA. The final rule provides that such studies must be conducted in accordance with good clinical practice, or GCP, including review and approval by an independent ethics committee and informed consent from subjects. The GCP requirements in the final rule encompass both ethical and data integrity standards for clinical studies. The FDA s regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must

conduct a continuing review and reapprove the study at least annually. The IRB must review and

Table of Contents

approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB s requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee or DSMB. This group provides authorization for whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or competitive climate.

Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on its ClinicalTrials.gov website.

***Human Clinical Trials in Support of an NDA***

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

Human clinical trials are typically conducted in four sequential phases, which may overlap or be combined:

Phase 1: The drug is initially introduced into a small number of healthy human subjects or patients with the target disease (e.g. cancer) or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.

Phase 2: The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

Phase 3: The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product. These clinical trials are commonly referred to as pivotal studies, which denotes a study that presents the data that the FDA or other relevant regulatory agency will use to determine whether or not to approve a drug.

Phase 4:

Post-approval studies may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the drug; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on

Table of Contents

various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB s requirements or if the drug has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Concurrent with clinical trials, companies often complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, must develop methods for testing the identity, strength, quality, purity, and potency of the final drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

***Submission of an NDA to the FDA***

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical studies and clinical trials, together with detailed information relating to the product s chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Under federal law, the submission of most NDAs is subject to an application user fee, which for federal fiscal year 2019 is $2,588,478 for an application requiring clinical data. The sponsor of an approved NDA is also subject to a program fee for fiscal year 2019 of $309,915. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for drugs with orphan designation and a waiver for certain small businesses.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and strives to inform the sponsor by the 74th day after the FDA s receipt of the submission to determine whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to certain performance goals in the review process of NDAs. Most such applications are meant to be reviewed within ten months from the date of filing, and most applications for priority review products are meant to be reviewed within six months of filing. The review process may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including drug component manufacturing (such as active pharmaceutical ingredients), finished drug product manufacturing, and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. The FDA must implement a protocol to expedite review of responses to inspection reports pertaining to certain drug applications, including applications for drugs in a shortage or drugs for which approval is dependent on remediation of conditions identified in the inspection report.

In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the

potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of

Table of Contents

treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU may include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The FDA may require a REMS before approval or post-approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product.

The FDA may refer an application for a novel drug to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

***Fast Track, Breakthrough Therapy, Priority Review and Regenerative Advanced Therapy Designations***

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are referred to as fast track designation, breakthrough therapy designation, priority review designation and regenerative advanced therapy designation.

Specifically, the FDA may designate a product for fast track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For fast track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a fast track product s application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA s time period goal for reviewing a fast track application does not begin until the last section of the application is submitted. In addition, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Second, a product may be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of

such applications, and to shorten the FDA s goal for taking action on a marketing application from ten months to six months.

Table of Contents

Finally, with passage of the 21st Century Cures Act, or Cures Act, in December 2016, Congress authorized the FDA to accelerate review and approval of products designated as regenerative advanced therapies. A product is eligible for this designation if it is a regenerative medicine therapy (as defined in the Cures Act) that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition. The benefits of a regenerative advanced therapy designation include early interactions with FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

***Accelerated Approval Pathway***

The FDA may grant accelerated approval to a drug for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a drug.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a drug, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of drugs for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit.

The accelerated approval pathway is usually contingent on a sponsor s agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the drug s clinical benefit. As a result, a drug candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the drug from the market on an expedited basis. All promotional materials for drug candidates approved under accelerated regulations are subject to prior review by the FDA.

***The FDA s Decision on an NDA***

On the basis of the FDA s evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may

Table of Contents

require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA s satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug s safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

***Post-Approval Requirements***

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and cor