Karyopharm Therapeutics Inc.
Form 10-K
February 28, 2019
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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.

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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.

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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

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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

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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.

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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)

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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%).

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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

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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®