Karyopharm Therapeutics Inc.
Form 10-K
March 16, 2017
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, 2016

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 and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes 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, or a smaller reporting company. See definitions of large accelerated filer, accelerated filer, and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

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

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the 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, 2016 was approximately $159,924,187. 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 March 10, 2017: 41,901,205.

Documents incorporated by reference:

Portions of our definitive proxy statement to be filed with the Securities and Exchange Commission no later than May 1, 2017 in connection with our 2017 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 in 2017, our future discovery and development efforts, our potential 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 we may have in the future, 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, or **SINE** , compounds that inhibit the nuclear export protein 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 initial 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. To date, over 1,900 patients have been treated with oral selinexor in company- and investigator-sponsored clinical trials in advanced hematologic malignancies and solid tumors. Selinexor is currently being evaluated in several mid- and later-stage clinical trials, including, among others, 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 backbone 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), and the Phase 2/3 SEAL (**Se**linexor in **A**dvanced **L**iposarcoma) study in liposarcoma.

Table of Contents

We plan to initiate the pivotal, randomized Phase 3 BOSTON (**Bo**rtezomib, **S**elinexor and Dexame**t**has**on**e) study in multiple myeloma in early 2017. We expect to provide data for the SADAL study in early 2017 with final topline data in mid-2018, topline data for the Phase 2 portion of the SEAL study in mid-2017 and topline data from the expanded cohort for the STORM study in early 2018. We are also preparing to establish the commercial infrastructure to support a potential launch of selinexor in North America and Western Europe.

Recent Regulatory Events

In February 2017, following the conclusion of a joint inspection conducted by the U.S. Food and Drug Administration, or FDA, and Danish Medicines Agency at our corporate headquarters, the FDA issued a Form 483 noting certain deficiencies in procedures and documentation that were identified in our selinexor development program. We have implemented corrective actions, preventative actions and other initiatives directed at resolving the deficiencies identified in the Form 483 observations. We provided the FDA with our responses to the Form 483 observations in February 2017.

In March 2017, the FDA notified us that it had placed the clinical trials under our investigational new drug application, or IND, for selinexor on partial clinical hold, which is an order by the FDA to delay or suspend part of a sponsor s clinical work requested under its IND as well as investigator-sponsored trials. The FDA has requested that we (i) revise relevant sections of our investigator brochure to, among other things, include a summary table of serious adverse events, or SAEs, associated with selinexor that was omitted from the existing version in order to accurately reflect the safety profile of selinexor, (ii) update the description of potential risks in our informed consent documents, and (iii) submit to the FDA recently completed narrative summaries of safety reporting events.

Under the partial clinical hold, new patients may not start treatment on any protocols. Patients who are responding to treatment with selinexor, which includes patients with progressive disease at study entry that currently have stable disease, may continue selinexor therapy after signing the updated informed consent.

We believe we have addressed the FDA s requests and, as of March 10, 2017, we had provided all requested materials to the FDA that we believe are required to lift the partial clinical hold. The FDA has 30 days from the date of its receipt of our submission to notify us if the partial hold is lifted. We can provide no assurances that the FDA will lift the partial clinical hold in a timely manner or at all.

Summary of Clinical Development

Oral selinexor is being evaluated in multiple later-phase clinical trials in patients with relapsed and/or refractory hematological and solid tumor malignancies. In general, relapsed disease refers to disease that progresses more than 60 days after discontinuation of therapy and refractory disease refers to disease that progresses while the patient is on therapy or within 60 days after discontinuation of therapy. To date, oral selinexor has been administered to more than 1,900 patients across company- and investigator-sponsored clinical trials. 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. Over 30 patients have remained on study for over 12 months, with the longest patients on study for over 24 months.

During 2016, we reported several important clinical data sets for selinexor and communicated 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 reported to date from the ongoing Phase 2b STORM study and the ongoing Phase 1b/2 STOMP study. The STORM study is a single-arm clinical trial evaluating oral selinexor in combination with low-dose dexamethasone in patients with quad-refractory or penta-refractory myeloma. Patients

with quad-refractory disease have previously received prior treatments with alkylating agents, glucocorticoids, two proteasome inhibitors, or PIs, bortezomib (Velcade®) and carfilzomib (Kyprolis®), and two immunomodulatory drugs, or IMiDs, lenalidomide (Revlimid®) and pomalidomide

Table of Contents

(Pomalyst®), and their disease is refractory to at least one PI, at least one IMiD, and has progressed following their most recent therapy. Patients with penta-refractory myeloma have quad-refractory disease that is also refractory to an anti-CD38 monoclonal antibody, such as daratumumab (Darzalex®) or isatuximab. The STOMP study is a multi-arm clinical trial evaluating selinexor and low-dose dexamethasone in combination with backbone therapies, including bortezomib, pomalidomide, lenalidomide or daratumumab, in patients with heavily pretreated relapsed/refractory multiple myeloma.

In the first part of the STORM study, selinexor demonstrated robust response rates and duration of response, compelling overall survival and a favorable safety profile in patients with heavily pretreated refractory multiple myeloma. In the STOMP study, selinexor demonstrated high response rates when combined with the proteasome inhibitor bortezomib, including in patients whose disease was previously refractory to proteasome inhibitors. Based on the positive results from these two studies, we have expanded the STORM study to include approximately 120 additional patients with penta-refractory multiple myeloma. We expect to report top-line data from the expanded STORM study in early 2018. Assuming a positive outcome, we intend to use the data from the expanded STORM study to support a request for accelerated approval for selinexor in multiple myeloma. In parallel, we plan to initiate the BOSTON study, which will evaluate selinexor in combination with bortezomib and low-dose dexamethasone compared to bortezomib and low-dose dexamethasone in patients with multiple myeloma who have had one to three prior lines of therapy. We have identified the combination dose of selinexor (100mg oral weekly), bortezomib (1.3 mg/m^2 weekly given sub-cutaneously for 4 of 5 weeks) and dexamethasone (40mg weekly) to be used in the BOSTON study and expect that the study will enroll approximately 360 patients. We expect to commence the BOSTON study in early 2017. If successful, the BOSTON study may qualify as a full approval study and we believe can serve as a confirmatory study if the STORM study is successful and results in accelerated approval.

Selinexor data were also previously presented showing preliminary safety and efficacy in combination with carfilzomib and dexamethasone to treat patients with multiple myeloma and in combination with standard of care chemotherapy to treat patients with acute myeloid leukemia, and as a single agent in patients with solid tumors including sarcoma, gynecological malignancies and glioblastoma.

Table of Contents

Our ongoing company-sponsored clinical trials of selinexor, along with anticipated timing of key data points, are summarized in the chart below. In addition, there are several ongoing investigator-sponsored clinical trials in a variety of hematological and solid tumor malignancies.

We have previously announced data from the STORM, STOMP, SIGN and KING studies and these data are further described herein. We currently expect to provide additional data related to STOMP later in 2017 and data related to the other studies of selinexor listed above as follows:

STORM: Phase 2b expansion topline data (overall response rate) in early 2018

BOSTON: Randomized Phase 3 topline data (Progression Free Survival) in 2019

SADAL: Phase 2b topline data (overall response rate) in early 2017 and mid-2018

SEAL: Randomized Phase 2 topline data (progression free survival) in mid-2017

In addition to selinexor, we are also advancing a pipeline of novel drug candidates in oncology as well as neurological, inflammatory, autoimmune and viral indications. We began clinical testing of oral KPT-8602, a second generation SINE compound, in late 2015 to treat patients with relapsed/refractory multiple myeloma, and we began clinical testing of oral KPT-9274, a dual PAK4/NAMPT inhibitor, during 2016 in patients with lymphoma or solid tumors. KPT-350 is an investigational new drug application-ready oral compound with a preclinical data package supporting potential efficacy in a number of neuro-inflammatory conditions. We plan to partner with a collaborator to undertake the clinical development and potential commercialization of KPT-350 in one or more mutually agreed indications. We began clinical testing of oral verdinexor (KPT-335) in 2015 in healthy human volunteers, and we are preparing to advance verdinexor for certain viral indications with an initial focus on influenza. Preclinical data provide strong support for other potential indications for verdinexor, including

Table of Contents

human immunodeficiency virus, or HIV, and respiratory syncytial virus, or RSV. Our pipeline of drug candidates is summarized in the chart below.

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. 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, prior to her founding of Karyopharm and while at Karyopharm.

Since our inception, we have devoted substantially all of our efforts to research and development, and we have not generated any revenue to date from sales of any drugs. As of December 31, 2016, we had an accumulated deficit of $366.1 million. We had net losses of $109.6 million, $118.2 million and $75.8 million for the years ended December 31, 2016, 2015 and 2014, respectively. See our Consolidated Statements of Operations and Note 2 to our consolidated financial statements for further information regarding our research and development expenses and financial information regarding the geographic areas in which we operate.

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

One of the ways in which a cell regulates the function of a particular protein is by controlling the protein s location within the cell, as certain functions may only occur within a particular location in the cell. In healthy cells, nuclear transport, both into and out of the nucleus, is a normal and regular occurrence that is tightly regulated and requires specific carrier proteins to be present. XPO1 mediates the export of over 220 different mammalian cargo proteins, including the vast majority of tumor suppressor proteins, as well as the transport of certain growth-promoting mRNAs which, when transported into the cytoplasm, are translated into functional proteins at high levels. Moreover, XPO1 appears to be the only nuclear exporter for the majority of these tumor suppressor proteins and for particular growth-promoting mRNAs. 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 promote programmed cell death, or apoptosis, XPO1 overexpression in cancer cells counteracts the natural apoptotic process that protects the body from cancer. Due to XPO1 inhibition by our SINE compounds, the export of tumor suppressor proteins is prevented, which leads to their accumulation in the nucleus. This accumulation subsequently reinitiates and amplifies their natural apoptotic function in cancer

Table of Contents

cells with minimal effects on normal cells. Further, SINE compounds reduce the translation of certain growth-promoting proteins (including some cancer-causing proteins) by inhibiting the XPO1-mediated transport of their mRNAs to the cytoplasm. The figure below depicts the process by which our SINE compounds inhibit the XPO1 nuclear export of tumor suppressor proteins.

We believe that the XPO1-inhibiting SINE compounds that we have discovered and developed to date, including selinexor, have the potential to provide a novel, oral, targeted therapy that enables tumor suppressor proteins to remain in the nucleus and promote the apoptosis of potentially any type of cancer cell. Moreover, our SINE compounds spare normal cells, which, unlike cancer cells, do not have significant damage to their genetic material, and we believe this selectivity for cancer cells minimizes side effects. We believe that the novel mechanism of action and oral administration of selinexor and the low levels of major organ toxicities observed to date in patients treated with selinexor in clinical trials create the potential for selinexor s broad use across many cancer types, including both hematological and solid tumor malignancies. Patient tumor biopsies have confirmed that selinexor treatment induces the nuclear localization of tumor suppressor proteins as well as cancer cell death, or apoptosis, in multiple different cancer types. 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. 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 method of use patents covering selinexor that were issued by the U.S. Patent and Trademark Office in 2015 and which provide patent protection through at least 2032, absent any adjustments or extensions.

Our Strategy

As a clinical-stage pharmaceutical company focused on the discovery and development of orally available, novel first-in-class drugs directed against nuclear transport targets for the treatment of cancer and other major diseases, 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 Western Europe. We plan to seek regulatory approvals of selinexor in North America and Western Europe in each indication with respect to which we receive positive clinical trial results in

Table of Contents

a trial with a survival endpoint that is designed to be registration-enabling. We may also seek regulatory approvals where a clinical trial demonstrates sufficiently significant data in a surrogate endpoint such as overall response rate that could allow for accelerated approval. We may seek full or conditional approvals in other geographies as well.

Maximize the Commercial Value of Selinexor. We currently have global development, marketing and commercialization rights for selinexor and are positioned to develop selinexor and to seek regulatory approval for its use in oncology indications without a collaborator in North America and Western Europe. We will evaluate potential collaborations within these geographies that enable us to further extend the selinexor development program into additional tumor types, earlier lines of therapy and additional combination regimens. We intend to enter into collaborations for further development, marketing and commercialization of selinexor in particular geographies outside of North America and Western Europe at an appropriate time.

Maintain Our Competitive Advantage and Scientific Expertise in the Field of Nuclear Transport. We plan to continue to conduct research in the field of nuclear transport and related areas to further our understanding of the role it plays in the underlying biology of cancer, as well other major diseases, primarily by fostering relationships with top scientific advisors and physicians. 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 selinexor to treat cancer through a broad range of collaborations with leading institutions engaged in clinical trials evaluating selinexor in the United States, Canada, Europe, Singapore and Israel.

Continue Developing our Pipeline of Novel Drug Candidates. To date, we have identified several drug candidates: our oral SINE compounds selinexor (KPT-330), verdinexor (KPT-335), KPT-350 and KPT-8602 and our oral dual PAK4/NAMPT inhibitor, KPT-9274. While we may identify or in-license novel drug candidates for development in oncology in the future, we are currently focused on the development of our existing pipeline of drug candidates.

Collaborate with Key Opinion Leaders to Conduct Investigator-Sponsored Trials of Selinexor. A significant part of our strategy for continuing to efficiently assess and confirm the breadth of activity of selinexor alone or in combination with other anti-cancer drugs includes the initiation of investigator-sponsored trials. We plan to continue to facilitate the investigation of the breadth of the clinical activity of selinexor through our established network of scientific advisors and physicians.

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. With respect to KPT-350, we plan to enter into one or more collaboration arrangements.

Our Focus: Nuclear Transport

A human cell is divided into various compartments, including the nucleus and the cytoplasm. The nucleus contains a cell s genetic material, or DNA, and is the compartment where gene expression and consequently cellular function is regulated. The cytoplasm is the compartment around the nucleus where translation of gene transcripts, or mRNA, to proteins, assembly of proteins into cellular structural elements, and cellular metabolism of fats, carbohydrates, and proteins, occur. One of the ways in which the cell regulates the function of a particular protein is by controlling the protein s location within the cell, as a specific function may only occur within a particular location. Certain proteins, including tumor suppressor proteins and other growth regulatory proteins, need to be transported from the cytoplasm, where they are made, into the nucleus where they need to be located for their primary functions to occur. The nuclear pore is a complex gate between the nucleus and cytoplasm,

Table of Contents

closely 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 processes of macromolecules in either direction through the nuclear pore is tightly regulated and requires specific carrier proteins, including nuclear export proteins, to occur. There are eight known nuclear export proteins. The most heavily studied export protein was discovered in 1999 and is called Exportin 1, or XPO1 (also called CRM1). XPO1 mediates the export of over 220 different mammalian cargo proteins, including some growth regulatory proteins and the vast majority of tumor suppressor proteins. Moreover, XPO1 appears to be the only nuclear exporter for the majority of these tumor suppressor proteins, including those generally referred to as p53, p73, FOXO, pRB, BRCA1, BRCA2, NPM1, IkB and PP2A.

Cancer is a disease characterized by unregulated cell growth. Cancer typically develops when DNA in normal cells begins to accumulate mutations or other abnormalities, causing genes that regulate cell growth to become disrupted. Tumor suppressor proteins are an integral part of the body s natural defense mechanism to identify and prevent cancer. When DNA damage is detected, tumor suppressor proteins promote apoptosis. Tumor suppressor proteins can also have an anti-cancer effect by dampening unregulated cell growth and division. Because tumor suppressor proteins need to be located in the nucleus in order to carry out their anti-cancer activities, their nuclear export, or exit from the nucleus, leads to their being unavailable in the nucleus to identify cancer cells and initiate their death. As XPO1 levels have been shown to be elevated by two- to four-fold in nearly all cancer cells compared to their normal cell counterparts, it appears that cancer cells have co-opted XPO1 to move tumor suppressor proteins out of the nucleus, thereby adversely affecting their ability to identify and initiate the death of cancer cells. Increased levels of XPO1 in cancer cells also lead to excessive nuclear export of growth regulatory proteins as well as oncoprotein mRNAs. All of these XPO1 effects allow cancer cells to divide continuously and inappropriately. Higher levels of XPO1 expression are also generally correlated with poor prognosis and/or resistance to chemotherapies.

In addition to transporting tumor suppressor proteins, XPO1 is the sole transporter of the eukaryotic initiation factor 4E (eIF4E) protein, also called the mRNA cap binding protein. eIF4E carries the mRNAs for many growth promoting proteins, including certain growth-promoting oncoproteins such as c-myc, Pim1, Atk1, hDM2 and cyclin D from the nucleus into the cytoplasm (dependent on XPO1) followed by association with ribosomes for translation into proteins. Blockade of XPO1 leads to accumulation of eIF4E in the cell nucleus and concomitant nuclear trapping of bound growth-promoting mRNAs, leading to reduced translation of these mRNAs, and reductions in their protein levels.

XPO1 is also the only exporter of the anti-inflammatory protein IkB, the inhibitor of NF-kB. NF-kB is known to play a role in cancer metastasis and resistance to chemotherapy as well as in many inflammatory and autoimmune diseases. Blockade of XPO1 leads to accumulation of IkB in the cell nucleus where it binds to and inhibits NF-kB function. SINE-mediated inhibition of NF-kB may be beneficial in overcoming chemotherapy resistance and in treating autoimmune, inflammatory and neuro-inflammatory disease.

Table of Contents

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

Since the discovery of XPO1, a growing body of research has documented that the high levels of XPO1 found in cancer cells are associated with the transport of tumor suppressor and other growth regulatory proteins from their site of action in the nucleus into the cytoplasm, where their anti-cancer activity is minimal. The inhibition of XPO1 cargo binding has been studied for over ten years. XPO1 inhibitors block the nuclear export of tumor suppressor and other cargo proteins, leading to accumulation of these proteins in the nucleus and enhancing their anti-cancer activity in the cell. The forced nuclear retention of these proteins can counteract a multitude of the oncogenic pathways that allow cancer cells with severe DNA damage to continue to grow and divide in an unrestrained fashion. XPO1 inhibitors also force the nuclear retention of eIF4E and its cargo growth-promoting protein mRNAs, preventing their transport to the cytoplasm for ribosomal translation, leading to reduced levels of oncoproteins. One naturally occurring XPO1 inhibitor called leptomycin B, which must be given intravenously, has been shown to have potent anti-cancer activity *in vitro*, but is toxic to normal cells. These toxicities to normal cells have been observed in both animals and humans, which we believe are most likely caused by the *irreversible* nature of leptomycin B binding to XPO1. Because of its observed toxicities in animals and humans, to our knowledge, leptomycin B is no longer being developed.

Our lead drug candidates are first-in-class, oral **Selective Inhibitor of Nuclear Export**, or **SINE**, compounds. We have discovered SINE compounds by applying our proprietary drug discovery and optimization expertise to the published X-ray structure of XPO1. SINE compounds inhibit XPO1-mediated nuclear-cytoplasmic transport by *transiently* binding to the XPO1 cargo binding site, meaning that they block XPO1 cargo binding over an extended period of time, but do not permanently do so. Transient XPO1 inhibition, or inhibition for approximately 12 to 24 hours, which corresponds to the inhibition period that we have observed to date with our SINE compounds, appears to be sufficient for nuclear retention and elevation of tumor suppressor protein levels in the nucleus. During this period, the inhibition of XPO1 cargo binding enables tumor suppressor proteins to accumulate in the nucleus of cancer cells and perform their normal role of detecting DNA damage,

Table of Contents

thereby inhibiting a cancer cell s ability to divide and promoting apoptosis. Healthy cells also build up tumor suppressor proteins in the presence of a SINE compound, but are able to resume normal activity after transient XPO1 inhibition because they have an intact genome with minimal or no DNA damage. The figure below depicts the process by which SINE compounds inhibit the XPO1 nuclear export of tumor suppressor proteins.

Transient XPO1 Inhibition by SINE Compounds

The XPO1-inhibiting SINE compounds that we have discovered and developed to date, including selinexor, have the potential to provide a novel targeted therapy that force tumor suppressor proteins to remain in the nucleus and promote apoptosis of cancer cells. Moreover, our SINE compounds spare normal cells, which, unlike cancer cells, do not have significant damage to their genetic material, and we believe this selectivity for cancer cells minimizes side effects. We believe that novel mechanism of action and oral administration of selinexor and the low levels of major organ toxicities observed to date in over 1,900 patients treated with oral selinexor in Phase 1 and Phase 2 clinical trials create the potential for its broad use across many cancer types, including both hematological and solid tumor malignancies. We believe that no currently approved cancer treatments are selectively targeting the restoration and increase in the levels of multiple tumor suppressor proteins in the nucleus.

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

Verdinexor (KPT-335) is our lead compound in development for the treatment of viral indications. Several viruses, such as influenza, HIV and RSV, exclusively utilize XPO1 to shuttle cargos necessary for virion replication and assembly from the nucleus to the cytoplasm. Verdinexor has the potential to treat viral diseases through both inhibition of viral replication and suppression of inflammatory cytokine-mediated symptoms and shows significant anti-influenza activity in murine and ferret models. In 2015, we conducted a randomized,

Table of Contents

double-blind, placebo-controlled, multiple dose-escalating Phase 1 clinical trial of oral 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 adverse events were observed. No serious laboratory abnormalities or cardiac changes were observed. We plan to continue to explore strategies to pursue the clinical development of verdinexor as a treatment for influenza, including potentially partnering with a collaborator or through government-funded grant or contract opportunities. Preclinical data also show efficacy of verdinexor and related SINE compounds in additional viral models, including HIV and RSV.

KPT-350 is our lead compound in development for the treatment of neurological disorders and inflammatory and autoimmune diseases. XPO1 mediates the nuclear export of multiple proteins that impact autoimmune, inflammatory and neurodegenerative 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 orally-administered KPT-350 and related SINE compounds in animal models of amyotrophic lateral sclerosis, or ALS, multiple sclerosis, or MS, traumatic brain injury, or TBI, epilepsy, systemic lupus erythematosus, or SLE, and rheumatoid arthritis, or RA.

Our Initial Indication: Cancer

Cancer is a leading cause of death worldwide, with approximately 8.2 million cancer deaths globally in 2012, according to the American Cancer Society. In the United States, the American Cancer Society estimates that in 2017, approximately 600,000 people will die of cancer and approximately 1.7 million new cancer cases will be diagnosed. 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 and 8.2 million cancer deaths worldwide in 2012.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy. A cancer patient often receives treatment with a combination of these methods. Surgery and radiation therapy are particularly effective in patients in whom the disease is localized. Physicians generally use systemic drug therapies in situations in which the cancer has spread beyond the primary site or cannot otherwise be treated through surgery. In many cases, drug therapy entails the administration of several different drugs in combination. An early approach to cancer treatment was to develop drugs, referred to as cytotoxic drugs, that kill rapidly proliferating cancer cells through non-specific mechanisms, such as disrupting 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, that target specific biological molecules in the human body that play a role in rapid cell growth and the spread of cancer. Targeted therapeutics are designed to specifically enable the death of cancer cells and spare normal 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 either a specific genetic alteration primarily found in cancer cells, but not in normal cells, or a target that cancer cells are more dependent on for their growth in comparison to normal cells.

Our SINE compounds are novel therapies specifically designed to force nuclear localization and elevation in the levels of multiple tumor suppressor and growth regulatory proteins. Tumor suppressor proteins assess a cell s DNA and in cells, like most cancer cells, with heavily damaged DNA, these proteins induce cell death, or apoptosis. Unlike many

other targeted therapeutic approaches which only work for a specific set of cancers or in

Table of Contents

a specific sub-group 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 wide range of patients. Additionally, and further supported by its mechanism of action and supported by preclinical and clinical data, we believe that selinexor has the potential to be additive or synergistic with approved and experimental therapies in treating many of these 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 relapsed and/or refractory hematological malignancies and solid tumors. Anti-cancer activity has been observed with tumor reductions and durable disease control across many hematologic malignancies and solid tumors. Over 30 patients have remained on oral selinexor, either as a single-agent or in combination with other agents, for over 12 months, with some patients on therapy for over 24 months. To date, selinexor has been generally well tolerated, with adverse events that are responsive to standard supportive care and/or dose modification, often decrease over time, and are consistent with those previously reported in patients in our initial clinical trials.

We have determined that the recommended Phase 2 dose of selinexor in most settings is 60mg dosed twice weekly. In December 2015, we and our collaborators presented an analysis of our Phase 1 clinical data in hematological malignancies at the American Society of Hematology, or ASH, annual meeting. The analysis demonstrated that doses of selinexor from 45-65mg (median 60mg) were better tolerated than doses greater than 65mg and showed less weight loss, lower incidence of high grade adverse events and greater numbers of days on study. 266 heavily pretreated patients with multiple myeloma, or MM, non-Hodgkin s lymphoma, or NHL, acute myeloid leukemia, or AML, and other hematological malignancies were included in the analysis and divided into three groups of evaluable patients: those that received 4-44mg (median 30mg), those that received 45-65mg (median 60mg) and those that received greater than 65mg (70-160mg; median 90mg) for comparison of safety and efficacy endpoints. Patients in the 4-44mg and 45-65mg groups remained on study longer than those receiving greater than 65mg, with average treatment duration of 120 days in the first two groups versus 90 days in the highest dose group, respectively. Overall efficacy was numerically superior in the 45-65mg dose group across multiple hematologic indications. The most common adverse events, or AEs, were nausea (63%), fatigue (62%), anorexia (57%), vomiting (38%), which were mostly grade 1/2, and thrombocytopenia (41%), which was mostly grade 3/4, but with very low incidents of bleeding. The incidence of certain selinexor-related high grade (3/4) AEs was lower in patients receiving 45-65mg selinexor as compared to those receiving greater than 65mg. These data from our extensive Phase 1 experience with selinexor are consistent with our belief that a flat dose of 60mg is the most appropriate selinexor dose for both efficacy and tolerability in most settings. However, as is the case for many other anti-cancer drugs, certain indications would likely be treated with different doses.

A preliminary analysis of safety and tolerability of selinexor was performed on unaudited AE data for 1,175 patients enrolled in our company-sponsored hematological malignancy and solid tumor clinical trials as of the data cutoff point of May 31, 2016. Overall, the most commonly reported selinexor-related AEs in ongoing clinical studies included generally low-grade nausea (62%), fatigue (55%), anorexia (50%), thrombocytopenia (43%), and vomiting (38%). Thrombocytopenia, the most common hematologic drug-related treatment emergent adverse event, was reported among 43% of patients, and approximately half of these were grades 3 or 4.

We describe below the key company- and investigator-sponsored studies 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. We expect such data will continue to inform our Phase 2 and Phase 3 dosing for selinexor in these combinations and allow us to

Table of Contents

evaluate the combinations with the greatest potential for durable responses and increased survival. 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

MM is a hematological malignancy characterized by the accumulation of monoclonal plasma cells in the bone marrow, the presence of monoclonal immunoglobulin, or 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 estimates that there will be approximately 30,000 new cases of MM, with about 12,600 attributable deaths, in 2017. 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 lenalidomide (Revlimid®) and pomalidomide (Pomalyst®), and the PIs bortezomib (Velcade®), carfilzomib (Kyprolis®), and ixazomib (Ninlaro®). Two monoclonal antibodies, daratumumab (Darzalex®) and elotuzumab (Empliciti), have also recently been approved, as has the histone deacetylase inhibitor panobinostat (Farydak®). 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 and cellular therapies like chimeric antigen receptor T-cell, or CAR-T, therapy, nearly all patients will eventually relapse and succumb to their disease. With around 37,000 deaths from MM in the United States and Europe expected, 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, or low-dose dex, in patients with heavily pretreated MM. The **Selinexor Treatment of Refractory Myeloma**, 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 annual meeting in December 2016, we presented results, adjudicated by an independent review committee, from the first cohort of patients enrolled in the STORM study, which included patients with either quad-refractory or penta-refractory MM. Patients with quad-refractory disease have previously received prior treatments with alkylating agents, glucocorticoids, two proteasome inhibitors bortezomib (Velcade®) and carfilzomib (Kyprolis®), and two IMiDs lenalidomide (Revlimid®) and pomalidomide (Pomalyst®), and their disease is refractory to at least one PI, at least one IMiD, and has progressed following their most recent therapy. Patients with penta-refractory myeloma have quad-refractory disease that is also refractory to an anti-CD38 monoclonal antibody, such as daratumumab (Darzalex®) or isatuximab.

Among the 78 evaluable patients, who had a median of seven prior treatment regimens, the overall response rate, or ORR, was 21% and included very good partial responses, or VGPRs, and partial responses, or PRs. Among the 48

patients in the quad-refractory group, the ORR was 21%. For comparison, in a similar patient population with quad-refractory disease, the anti-CD38 monoclonal antibodies Darzalex® and isatuximab had ORRs of 21% and 20%, respectively. Among the 30 patients in the penta-refractory group, the ORR was 20%.

Table of Contents

Clinical benefit rate, or CBR, which is percentage of patients with a minor response, or MR, or better, was 33% across all 78 patients, 29% among the patients with quad-refractory disease, and 40% among the patients with penta-refractory disease. To our knowledge, no other agents have reported response rates in patients with penta-refractory MM. Median overall survival, or OS, was 9.3 months for all patients, longer than 11 months without a median reached in patients with a minor response or better, and 5.7 months for patients who did not have any response. Median duration of response, or DOR, was 5 months. Cytopenias of grade 3 or grade 4 were the most common side effects and were generally not associated with clinical sequellae. Nausea, anorexia and fatigue were the most common non-hematological side effects, primarily grades 1 and 2, and were treatable with supportive care and/or dose modification. There were low rates of non-hematologic toxicities of grade 3 or 4, with no new safety signals identified. In particular, there was one reported case of grade 4 infection (1.3%), one reported case of grade 2 neuropathy (1.3%) and one reported case of sepsis (1.3%).

Based on these positive results, we have expanded the STORM study to include approximately 120 additional patients with penta-refractory multiple myeloma. To our knowledge, this will be the largest study ever undertaken in this patient population. We expect to report top-line data from the expanded STORM cohort in early 2018. Assuming a positive outcome, we intend to use the data from the expanded STORM study to support a request for accelerated approval for selinexor in multiple myeloma.

The primary endpoint of the STORM study is ORR. The trial has several secondary endpoints, including ORR in patients whose disease is relapsed/refractory to an anti-CD38 monoclonal antibody and DOR.

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 backbone treatments for relapsed/refractory MM. In this multi-arm study, **Selinexor and Backbone Treatments of Multiple Myeloma Patients**, or **STOMP**, we are evaluating the combination of selinexor and low-dose dex with backbone therapies bortezomib (Velcade®), lenalidomide (Revlimid®), pomalidomide (Pomalyst®) or daratumumab (Darzalex®) in patients with previously treated MM. Each combination is evaluated on a separate arm of the STOMP study and within each combination, two treatment cohorts will 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, CBR and DOR.

In December 2016, we presented updated results from the selinexor, bortezomib (Velcade®) and dexamethasone arm of the STOMP study, referred to as SVd, at the ASH 2016 annual meeting. The patients in this cohort were heavily pretreated and the majority (73%) had MM refractory to the proteasome inhibitors bortezomib (Velcade®) and/or carfilzomib (Kyprolis®). Across the 22 patients enrolled in the SVd arm, the median number of treatment regimens was four with a range of one to 11 prior treatment regimens. Seventeen of the 22 patients responded, with one patient having a stringent complete response, or sCR, two patients having a complete response, or CR, four patients having a VGPR and 10 patients having a PR. As a result, the ORR was 77%. An additional three patients experienced an MR, for a CBR of 91%. Only one patient had progressive disease. All seven patients whose disease was not refractory to a PI responded (one patient with a CR, two patients with a VGPR and four patients with a PR) for an ORR and CBR of 100%. Fifteen of the 22 patients in the SVd combination arm had MM previously refractory to a proteasome inhibitor and nine patients had high-risk cytogenetics including deletion of chromosome 17p. Ten of these 15 patients responded (one patient with a sCR, one with a CR, two with a VGPR and six with a PR) for an ORR of 67%. Three additional patients achieved an MR for a CBR of 87% in this subgroup with PI-refractory disease. Median DOR across the 22 patients was 7.8 months.

16

Table of Contents

The recommended Phase 2 dose regimen was identified as selinexor (100mg once weekly), bortezomib (1.3 mg/m^2 weekly given sub-cutaneously for four of five weeks) and dexamethasone (40mg weekly). Approximately 42 patients have been enrolled into an expansion cohort at the recommended Phase 2 dose. The most commonly reported AEs from the recommended Phase 2 dose were fatigue, nausea, anorexia and vomiting, which were primarily grade 1 and reversible. Grade 3 AEs included fatigue, diarrhea, thrombocytopenia and abdominal pain and each occurred at a rate of 6%, meaning only one occurrence of each event across all 22 patients. The only grade 4 AE was thrombocytopenia and occurred at a rate of 12%, meaning two occurrences across all 22 patients.

Also in December 2016, we presented preliminary data from 15 patients in the selinexor, pomalidomide and dexamethasone arm of the STOMP study, referred to as SPd, at the ASH 2016 annual meeting. The patients in this cohort had received a median of five prior therapies, with a range of two to nine prior therapies. All 15 patients had received prior treatment with lenalidomide and a PI. Nine of the 15 patients responded, with three patients having a VGPR and six patients having a PR. As a result, the ORR was 60%. An additional two patients experienced an MR, for a CBR of 73%. Only one patient had progressive disease. Five of the 15 patients had high-risk cytogenetics including deletion of chromosome 17p. Median progression-free survival, or PFS, was 10.3 months, with a follow up of 7.6 months. The most common AEs were anorexia, nausea, fatigue, and thrombocytopenia, mainly grades 1 and 2, and were similar to selinexor or pomalidomide used separately.

In addition, we plan to initiate a new arm of the STOMP study to evaluate oral selinexor in combination with the anti-CD38 monoclonal antibody daratumumab (Darzalex®) and low-dose dexamethasone, referred to as SDd, in patients with heavily pretreated MM. We expect the SDd arm of STOMP will enroll approximately 44 patients and top-line data will be reported in late 2017 or early 2018.

BOSTON: Pivotal Phase 3 Clinical Trial of Selinexor, Bortezomib and Low-Dose Dexamethasone vs. Bortezomib 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 European Medicines Agency, or EMA, we are planning a pivotal randomized Phase 3 study, known as the BOSTON (**Bortezomib, Selinexor and dexamethasone**) study, which is evaluating SVd compared to bortezomib and low-dose dexamethasone, or Vd, in patients with MM who have had one to three prior lines of therapy. We expect that the BOSTON study will enroll approximately 360 patients who will be randomized in a one-to-one fashion to receive either SVd or Vd. The dosing schedule allows for only one scheduled clinic visit per week for patients on the SVd with selinexor and bortezomib to be dosed not more frequently than once per week. In addition, dosing on the SVd arm will use 40% less bortezomib and 25% less dexamethasone than the Vd arm, which will follow the standard Vd dosing schedule. We expect that the reduced exposure provided by the SVd dosing schedule may significantly reduce common bortezomib- and dexamethasone-related toxicities, which is consistent with the safety data from the 22 patients described above who were treated with SVd on the STOMP study at the recommended Phase 2 and Phase 3 dose. For the Vd arm, cross-over to the SVd arm based on objective progression will be permitted. The primary endpoint of the study is PFS and key secondary endpoints include ORR, DOR, PFS, OS, and certain other duration and quality of life endpoints. Topline data from the Phase 3 BOSTON study is anticipated in 2019.

Investigator-Sponsored Clinical Trials

The safety and efficacy of selinexor is currently being evaluated in multiple investigator-sponsored trials, including in combination with existing therapies to treat MM: (i) carfilzomib, low-dose dex and selinexor and (ii) pegylated liposomal doxorubicin and selinexor.

In December 2016, final results from the Phase 1 investigator-sponsored study evaluating the tolerability and efficacy of the combination of oral selinexor with PI carfilzomib (Kyprolis®) and low-dose dex in patients with very heavily pretreated MM were presented at the ASH Annual Meeting. This study is being led by the University of Chicago and supported by a collaboration between Karyopharm, Onyx Pharmaceuticals (owned by

Table of Contents

Amgen Inc.) and the Multiple Myeloma Research Consortium. The primary objectives of this study were to determine the maximum tolerated dose, or MTD, and recommended Phase 2, or RP2D, doses for selinexor in combination with carfilzomib and dexamethasone, to assess preliminary efficacy through ORR, CBR, and DOR and to determine the efficacy of this combination in carfilzomib refractory patients.

The study enrolled 21 patients in 3 dose levels including an expansion cohort of 6 patients, and enrollment of an additional 12 carfilzomib refractory is planned. Patients had a median of four prior treatment regimens (with a range of 2 to 10), 17 patients had MM that was quad-refractory to carfilzomib, lenalidomide, bortezomib or pamolidomide, and all patients had received carfilzomib-based treatments to which their MM became refractory. Dexamethasone was dosed at either 20 mg or 10 mg twice weekly. Eight patients received 30 mg/m^2 (approximately 50 mg) of selinexor in combination with either 20/27 mg/m^2 or 20/36 mg/m^2 of carfilzomib, seven patients received a 60 mg flat dose of selinexor in combination with 20/27 mg m^2 of carfilzomib, which was identified to be the RP2D, and an additional six patients were dosed at the RP2D level as part of the dose expansion phase.

The combination achieved a 63% ORR and a 67% response rate in patients whose disease is refractory to carfilzomib in their last therapy. Median progression free survival on the study was 3.7 months in patients who responded with a PR or better, and median DOR was 3.3 months with a range of 0.6 to 13 months. The selinexor, carfilzomib and dexamethasone combination appears safe and has acceptable tolerability in these heavily pretreated MM patients. No unexpected toxicities were observed. Only one patient experienced a dose limiting toxicity at 60 mg flat dose selinexor in combination with 20/27 mg m^2 of carfilzomib. The most commonly reported AEs were thrombocytopenia and neutropenia, which were reversible and manageable with dose modifications and supportive care. Grade 3 and 4 AEs were predominantly hematological and included thrombocytopenia (64%), neutropenia (27%), lymphopenia (27%) and anemia (14%). The most common grade 3 and 4 non-hematologic AEs were GI-related (18%) and fatigue (14%). We believe these results provide early clinical evidence that the addition of selinexor has the ability to overcome carfilzomib resistance, warranting further investigation of the regimen.

Company-Sponsored Phase 1 Clinical Trial Data

As part of our Phase 1 clinical trial of oral selinexor in patients with advanced hematological malignancies, patients with MM were treated with either single-agent selinexor or selinexor in combination with low-dose (20mg) dexamethasone, all dosed twice weekly. As of December 6, 2015, 12 evaluable patients were treated with 45mg/m^2 of oral selinexor and 20mg of dexamethasone, each dosed twice weekly. This dose of selinexor, equivalent to approximately 80mg, was determined to be the recommended Phase 2 and Phase 3 dose for this combination therapy as higher doses like 60 mg/m^2 were not well tolerated. While the recommended phase 2 dose of selinexor in most settings is 60mg twice weekly, the addition of a steroid like dexamethasone in the multiple myeloma setting allows for higher dosing of selinexor. Additionally, this dose of dexamethasone is the standard low-dose dexamethasone (40mg weekly or 20mg twice weekly) used with nearly all other anti-myeloma drugs. The patients enrolled in this study had received a median of seven prior lines of therapy, each line typically consisting of two to four separate anti-myeloma agents. All had received prior therapy with at least one PI, such as carfilzomib or bortezomib, and at least one IMiD, such as lenalidomide or pomalidomide, and steroids (typically two or more times).

As of December 6, 2015, the best responses among the 12 evaluable patients were one sCR (8%), seven PRs (58%), two MRs (17%) and two PD (17%). Two patients left the trial before disease assessment and were therefore not evaluable for response. The CBR was 83% and the ORR was 67%. The median duration of response is approximately seven months and the longest response lasted over one year. AEs in patients receiving single-agent selinexor were generally low-grade, consistent with events observed in patients with other hematological malignancies and responsive to standard supportive care. Compared with selinexor given alone, fewer AEs in patients receiving selinexor in combination with low-dose dexamethasone were reported, particularly levels of nausea, vomiting and

weight loss. These observations are consistent with dexamethasone s expected reduction in nausea, anorexia and fatigue, which are selinexor s primary constitutional side effects.

Table of Contents

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. The World Health Organization estimated that approximately 386,000 new cases of NHL would be diagnosed worldwide in 2012, and the American Cancer Society projects that approximately 72,200 patients will be diagnosed with NHL in the United States in 2017.

SADAL: Phase 2b Clinical Trial of Low vs. High Dose Selinexor in Diffuse Large B-Cell Lymphoma

Diffuse Large B-Cell Lymphoma, or DLBCL, is the most common of the aggressive NHLs. We estimate that approximately 22,000 patients are diagnosed with DLBCL in the United States each year, with approximately 10,000 deaths per year. The fundamental treatment of DLBCL has changed little in the past two decades, with no new or targeted agents approved for this indication. Initial therapy with multi-agent cytotoxic drugs in combination with the monoclonal antibody rituximab (Rituxan®), most often in a combination therapy known as R-CHOP, leads to cures in approximately 50% of patients. Patients who are not cured with initial immune-chemotherapy have a poor prognosis. Of the approximately 30% of patients who are less than 65 years old and have good organ function, high dose chemotherapy with stem cell transplantation can lead to cures in up to half. Older patients relapsing after initial chemotherapy, and those relapsing after stem cell transplantation, have a very poor prognosis, and the expected survival of such patients is less than one year. Newer targeted agents such as the BTK inhibitor ibrutinib (Imbruvica®) and the immunomodulatory drug lenalidomide (Revlimid®) have shown some activity in the immunoblastic (activated B-cell or ABC) type of DLBCL in clinical trials, but responses are generally short. Responses to these newer agents are much lower in the germinal center, or GCB, type of DLBCL. Therefore, with approximately 10,000 deaths in United States each year due to DLBCL, we believe that novel, well-tolerated drugs are needed for the treatment of relapsed/refractory DLBCL.

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 will 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 has 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 2017, in consultation with the FDA, we decided to amend the SADAL study to become a single-arm study evaluating single-agent selinexor at 60mg given twice weekly and to make other protocol amendments, including to reduce the 14-week washout period to eight weeks in patients who achieved at least a PR on their most recent therapy. We reported to the FDA that we had observed an ORR of 28.4% across both the 100mg and 60mg arms in the first 63 patients with consistent response rates across both arms (adjudicated by independent Central Radiological Review per protocol), but greater durability and chronic tolerability were observed in the 60mg arm. The FDA agreed that the change to a single-arm study was reasonable and that the proposed trial design and indication appeared appropriate for accelerated approval, though the availability of accelerated approval will depend on the trial results and available therapies at the time of regulatory action. We expect to provide additional detailed information on the results in these first 63 patients in a late-breaking poster presentation at the American Associate for Cancer Research Annual Meeting in April 2017. We expect to enroll up to an additional 90 patients to the new cohort and expect to announce topline

data for the completed study in mid-2018.

Table of Contents

Investigator-Sponsored Trials

Ongoing investigator-sponsored clinical trials are evaluating the safety and efficacy of selinexor in combination with existing therapies to treat various lymphomas: (i) rituximab, ifosfamide, carboplatin and etoposide, or R-ICE, and selinexor to treat relapsed (at least one prior therapy) DLBCL and other aggressive lymphomas, (ii) ibrutinib and selinexor to treat chronic lymphocytic leukemia or NHL, and (iii) R-DHaOx and R-GDP in combination with selinexor in relapsed refractory B-cell lymphomas including DLBCL.

Company-Sponsored Phase 1 Clinical Trial Data

As of June 1, 2015, 77 heavily pretreated patients with relapsed and/or refractory NHL were enrolled in our Phase 1 clinical trial for oral selinexor. Of this group, 67 patients were evaluable for response. The DCR was 67% across all doses of selinexor and the ORR was 33%. Responses were observed across all subtypes of NHL, independent of genetic abnormalities, with durable cancer control observed across several patients who remained on study for longer than nine months, with the longest remaining on study for over 24 months.

Among the 41 patients with heavily pretreated DLBCL who were evaluable as of June 1, 2015, ORR and DCR were similar across the two major subtypes of DLBCL, namely GCB and ABC, also called non-GCB. Many targeted therapies such as ibrutinib or lenalidomide show activity primarily against the ABC subtype (although all patients relapse), but there are no viable treatment options for patients with relapsed/refractory GCB. However, consistent with the broadly applicable mechanism of action of selinexor, selinexor showed activity across both major subtypes of DLBCL with DCR equal to 60% and 40% between the GCB and non-GCB subtypes, respectively, and ORR equal to 35% and 20% between the GCB and non-GCB subtypes, respectively.

Acute Myeloid Leukemia

AML in elderly populations remains a vexing clinical problem with little progress in the last decade. There are no treatment agents specifically approved for this population in the United States. AML is a cancer that starts in the bone marrow and in most cases quickly moves into the blood. The incidence of AML dramatically increases after the age of 55. The American Cancer Society estimates that approximately 21,000 new cases of AML, most of which will be in adults, will be diagnosed in the United States in 2017, with approximately 10,600 deaths from AML in the United States in 2017. Approximately 40% of AML patients are young enough with sufficient major organ function to undergo stem cell transplantation for their AML, and approximately 50% of these patients can be cured of their disease. Therefore, approximately 20% of adults with AML are currently curable. Those who are not cured, and those patients who are elderly or unfit for transplant, have a very poor prognosis with a median survival of less than one year. Moreover, prognosis worsens continuously with advancing age to a median survival of as low as one month for those who are older than 85 years of age.

Over the past two decades, many compounds have been evaluated in elderly patients with AML, but due to significant toxicities and/or lack of efficacy, none has been approved to date in the United States. Adults who are not transplant candidates, and cannot safely receive intensive chemotherapy, such as anthracyclines and cytosine arabinoside, or Ara-C (often referred to as the 7+3 regimen), are usually treated with best supportive care, or BSC, including blood transfusions, antibiotics and hydroxyurea if indicated, along with hypomethylating agents decitabine (Dacogen®) or azacytidine (Vidaza®). These hypomethylating agents are approved in certain AML populations in the European Union. Some patients are treated with low dose Ara-C. All of these agents are given parenterally (subcutaneously or intravenously) in the clinic or hospital, and none of these agents are associated with cures, meaning that all older patients unfit for chemotherapy will relapse and eventually succumb to their disease. Median survival following initial treatment with front-line therapy in these patients is reported to be less than three months.

Three new therapies for specific subsets of AML patients may be approved in 2017. Novartis submitted a new drug application, or NDA, in late 2016 for midostaurin as a first line treatment in combination with 7+3 in

Table of Contents

patients with FLT3 mutations. The FDA has granted priority review and an approval is anticipated mid-year. Jazz Pharmaceuticals initiated a rolling NDA submission for Vyxeos/CPX-351 (cytarabine and daunorubicin liposome injection) in September 2016 with plans to complete the submission in early 2017 and request a priority review. Vyxeos was granted Breakthrough Therapy Designation for adults with therapy-related AML (tAML) or AML with myelodysplasia-related changes. In addition, Celgene submitted an NDA for the IDH2m inhibitor AG-221 (enasidenib) in patients with relapsed/refractory AML based on data from the ongoing Phase I/II study (NCT01915498) of enasidenib in patients with IDH2m+ hematologic malignancies.

SOPRA: Phase 2 Clinical Trial of Selinexor vs. Physician s Choice in Elderly AML

Our Phase 2 study of oral selinexor in patients 60 years of age or older with relapsed or refractory AML enrolled patients who were ineligible for standard intensive chemotherapy and/or transplantation. In our **Selinexor in Older Patient with Relapsed/Refractory AML**, or **SOPRA**, study we enrolled 176 patients who have AML that has relapsed after, or was refractory to, first line therapy. Patients were randomized in a 2:1 fashion to selinexor provided orally twice weekly in a dose of 60mg plus BSC versus one of three physician choices, or PC. Patients must have received at least one prior line of AML therapy given at standard doses and must have progressed after their most recent therapy. Prior therapy must have included at least two cycles of a hypomethylating agent. PCs include (i) BSC alone, (ii) BSC plus either azacytidine or decitabine or (iii) BSC plus low-dose Ara-C. OS is the primary endpoint. The SOPRA study was designed based on data from the Phase 1 study of selinexor in patients with advanced hematologic malignancies, including AML.

In March 2017, we reported that we had determined, in concert with SOPRA s Independent Data Safety Monitoring Board, or DSMB, that the study would not reach statistical significance for showing superiority of OS on selinexor versus OS on PC, the study s primary endpoint.

Based on unaudited site data, SOPRA enrolled 176 patients, with a median of two prior treatment regimens, in the U.S., Canada, Europe and Israel. Among patients on the selinexor arm, 13% demonstrated a CR with or without full hematologic recovery, or CRi, compared to 3% of patients on the PC control arm. Some patients remained on selinexor for over one year, but this did not result in a statistically superior OS compared to the PC arm. However, since the 13% of selinexor-treated patients who achieved a CR (with or without full hematologic recovery) showed a substantial OS benefit as compared with the PC arm, we and the DSMB agreed that patients would be permitted to continue on the selinexor arm or the PC arm, as applicable, following discussion between the patient and their treating physician.

The DSMB found no new clinically significant AEs in the patients receiving selinexor. Rates of sepsis and febrile neutropenia, or FN, were lower on the selinexor arm where the rate of sepsis was 4.9% and the rate of FN was 14.7%. In comparison, the rate of sepsis on the PC arm was 6.1% and the rate of FN was 36.4%. As expected, the most common selinexor-related AEs were nausea, anorexia, fatigue, vomiting, and thrombocytopenia.

We plan to continue clinical development of selinexor in AML through investigator-sponsored trials in multiple combination regimens, including with chemotherapy, given encouraging data to date across these settings.

Investigator-Sponsored Trials

SAIL: Phase 2 Clinical Trial of Selinexor, Ara-C and Idarubicin in AML

In December 2016, Walter Fiedler, MD of the University Medical Center Hamburg-Eppendorf in Germany and his colleagues presented updated data from the SAIL study, an investigator-sponsored trial evaluating the combination of

selinexor, Ara-C and idarubicin in patients with relapsed/refractory AML. Patients in this study had a range of one to five prior therapies and 39% had undergone a prior stem cell transplant or donor lymphocyte

Table of Contents

infusion. Data from 42 patients evaluable for safety (range of prior treatment regimens, all including intensive chemotherapy is 1-5), as of October 2016, demonstrated an ORR of 55% (with 4 patients excluded from evaluation due to early death) and included CR of 22% and 36% and CRi of 33% and 9% in Cohort 1 and 2, respectively. Median relapse free survival was 333 days and median OS was 435 days.

The most frequent Grade 3 or higher non-hematologic AEs of this intensive chemotherapy-containing regimen were diarrhea (50%) and nausea (12%). The most common Grade 3 or higher hematologic AEs were neutropenia (100%) and thrombocytopenia (100%) as expected with any intensive chemotherapy regimen. Two deaths occurred that were deemed possibly treatment-related, which were one reported case of systemic inflammatory response syndrome (SIRS; 2%) and one reported case of hemophagocytosis syndrome (2%). Other Ara-C-based combination therapies for AML have shown significantly lower response rates in patients with heavily pretreated AML: combination of Ara-C with gemtuzumab ozogamicin (Mylotarg®) 11.5% ORR; combination of Ara-C with doxorubic