Karyopharm Therapeutics (KPTI)

Initiating Coverage with an OUTPERFORM Rating and $50 Price Target, Novel Broad-Spectrum Anti-Tumor Inhibition of Nuclear Export

- **KPTI's lead product, Selinexor (KPT-330), is a first-in-class oral nuclear export inhibitor that has demonstrated activity in a wide variety of cancers.** Selinexor targets XPO1, which is overexpressed in various cancer types and is associated with poor prognosis and resistance to chemotherapy. Given its novel mechanism, we see broad potential for Selinexor across multiple cancer indications.
- **The company is on track to have five registration studies running by early 2015 across various hematological and solid tumor settings.** In addition to an ongoing Phase II SOPRA study in relapsed/refractory AML patients, KPTI intends to start pivotal studies in relapsed/refractory DLBCL and Richter's transformation by the end of the year. KPTI also intends to start two additional registration studies in late 2014/early 2015 in undisclosed indications, including a solid tumor setting.
- **To date, Selinexor has been administered to over 450 heavily pre-treated patients, with greater than 50% disease control observed across multiple hematologic malignancies.** Based on early signs of activity, we believe Selinexor could show the greatest benefit in the difficult-to-treat indications Richter's transformation and the GCB subtype of DLBCL.
- **Selinexor has demonstrated safety with prolonged use, and has a toxicity profile that does not overlap with commonly used chemo-, radio- and targeted therapeutics.** We believe Selinexor's tolerability and complementary mechanism of action is likely to make it combinable with a variety of cancer therapies.
- **We estimate KPTI is well capitalized to take Selinexor through to approval in at least one indication with current funds.** We expect KPTI to end 2014 with at least $200M in cash, sufficient to fund operations into H2:17. We believe rapid approval for Selinexor may be possible in cancers with a high unmet need.
- **Initiating coverage of Karyopharm with an OUTPERFORM rating and $50 price target.** Our $50 price target is derived from a 6 multiple of 2020 sales of Selinexor in the US and EU across multiple cancer indications, discounted back by 30% for hematological malignancies and 35% for solid tumor indications.

FYE Dec	2013A	2014E			2015E		
REV	ACTUAL	CURR.	PREV.	CONS.	CURR.	PREV.	CONS.
Q1 Mar	--	0.2A		$0.2A	0.0E		$0.0E
Q2 Jun	--	0.0A		0.0A	0.0E		0.0E
Q3 Sep	0.0A	0.0E		0.1E	0.0E		0.0E
Q4 Dec	0.0A	0.0E		0.1E	0.0E		0.0E
Year*	**0.4A**	**0.2E**		**$0.4E**	**0.0E**		**$0.9E**
Change	--	-50%			-100%		
	2013A	2014E			2015E		
EPS	ACTUAL	CURR.	PREV.	CONS.	CURR.	PREV.	CONS.
Q1 Mar	--	($0.46)A		($0.46)A	($0.55)E		N/AE
Q2 Jun	--	($0.55)A		($0.55)A	($0.65)E		N/AE
Q3 Sep	$0.00A	($0.47)E		($0.55)E	($0.71)E		N/AE
Q4 Dec	($1.96)A	($0.48)E		($0.62)E	($0.75)E		N/AE
Year*	**($5.59)A**	**($1.97)E**		**($2.18)E**	**($2.65)E**		**($2.96)E**
P/E	--	--			--		
Change	--	65%			-35%		

Consensus estimates are from Thomson First Call. * *Numbers may not add up due to rounding.*

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Price
$32.59

Rating
OUTPERFORM

12-Month Price Target
$50

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Company Information

Shares Outst (M)	32.6
Market Cap (M)	$1062.1
52-Wk Range	$15.50 - $47.98
Book Value/sh	$4.43
Cash/sh	$7.19
Enterprise Value (M)	$827.7
LT Debt/Cap %	0.0
Cash Burn (M)	$57.8

Company Description

Karyopharm Therapeutics (KPTI) is focused on the development of novel small-molecule therapeutics targeting the nuclear export protein XPO1. KPTI's lead product, Selinexor, has demonstrated activity in Phase I trials across a wide variety of cancers.

Source: Thomson Reuters

Investment Thesis

Karyopharm Therapeutics Inc. (NASDAQ:KPTI) is focused on developing nuclear transport modulators for the treatment of cancer. The company's lead product candidate, Selinexor (KPT-330), is an oral inhibitor of Exportin-1 (XPO1) that is being developed for multiple tumor types. Selinexor is currently in a registration-directed trial in the relapsed/refractory elderly AML setting, and is set to enter two additional registration-directed studies in relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and Richter's transformation later this year. In addition, the company has announced plans to initiate two additional registration-directed trials, including one in a solid tumor, in late 2014 or early 2015.

We believe the early signs of efficacy seen with Selinexor in heavily pre-treated patients and across tumor types as validating its novel mechanism of action. Given its acceptable safety profile, we believe Selinexor will be used in various cancer settings with serious unmet needs, such as GCB DLBCL and Richter's transformation. We also expect approval in cancers that are driven by HPV, such as head-and-neck cancer and various gynecological cancers, since Selinexor's mechanism of action interferes with viral transformation of normal cells to cancer cells.

Valuation

We arrive at our $50 price target by taking the sum of the per-share values of Selinexor sales in the US and EU in 2020. We value the opportunity in hematological malignancies at ~$27 per share, which is derived by taking a 6 multiple to 2020 sales in DLBCL, multiple myeloma, AML and Richter's transformation and discounting back by 30% annually. We value the opportunity in HPV-associated solid tumors at ~$23 per share, which is derived by taking a 6 multiple to 2020 sales in HPV-linked head-and-neck and gynecological cancers and discounting back by 35%.

Risks

Risks to the achievement of our price target include the clinical, regulatory or commercial failure of Selinexor.

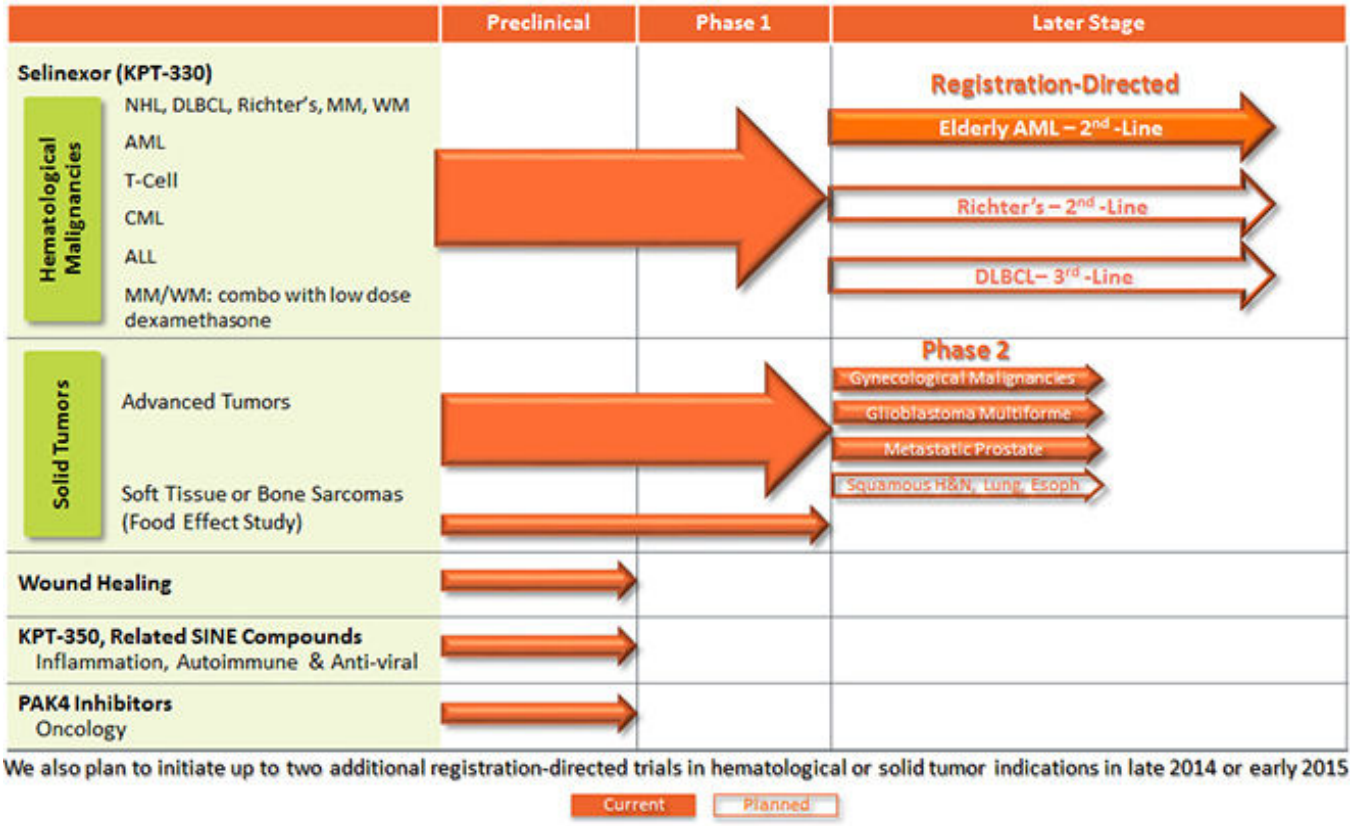
Key Points

- Selinexor (KPT-330) is an oral, first-in-class therapeutic that reversibly inhibits XPO1, a nuclear export protein. By targeting XPO1, which can be overexpressed in various cancer types and is associated with poor prognosis and resistance to chemotherapy, Selinexor has the potential to work across a wide range of hematological and solid cancers.
- Although early, Selinexor has demonstrated broad anti-tumor activity in patients who have exhausted all other options. Interim analysis of Phase I data has demonstrated efficacy in multiple tumor types, including DLBCL, AML and multiple myeloma.
- The company plans to have five registration-directed trials running by early 2015. This includes an ongoing trial in relapsed/refractory elderly AML, and planned studies in second-line Richter's syndrome (RT), third-line diffuse large B-cell lymphoma (DLBCL) and two undisclosed indications (we expect multiple myeloma and head and neck cancer).
- Selinexor could have an inhibitory effect on cancers induced by HPV, since inhibition of XPO1 interferes with viral replication. We forecast use primarily in head-and-neck and cervical cancers, where a majority of new cases are associated with HPV.
- Selinexor has a unique safety and tolerability profile without overlapping toxicity with commonly used chemo-, radio- and targeted therapeutics. We believe this safety profile and its novel mechanism of action will make Selinexor combinable with a variety of anti-cancer agents.
- Verdinexor success may predict success for Selinexor. KPTI has received conditional approval in the canine lymphoma setting for its SINE inhibitor, Verdinexor, a Selinexor-like compound. Given the documented similarities between canine lymphoma and human lymphoma, the Verdinexor studies may provide insight into the likely success of the Selinexor trials.

Karyopharm Therapeutics Inc. Overview

Karyopharm is headquartered in Natick, Massachusetts, and is focused on developing nuclear export inhibitors for the treatment of cancer and other diseases. Karyopharm's SINE molecules prevent the export of tumor suppressor proteins from the nucleus, thus promoting their nuclear retention and anti-tumor function. Karyopharm currently has one oncology product candidate in clinical development, Selinexor, which is in Phase I, II and registration-directed trials.

Figure 1: Karyopharm Pipeline



Source: Company data

Figure 2: Anticipated Milestones

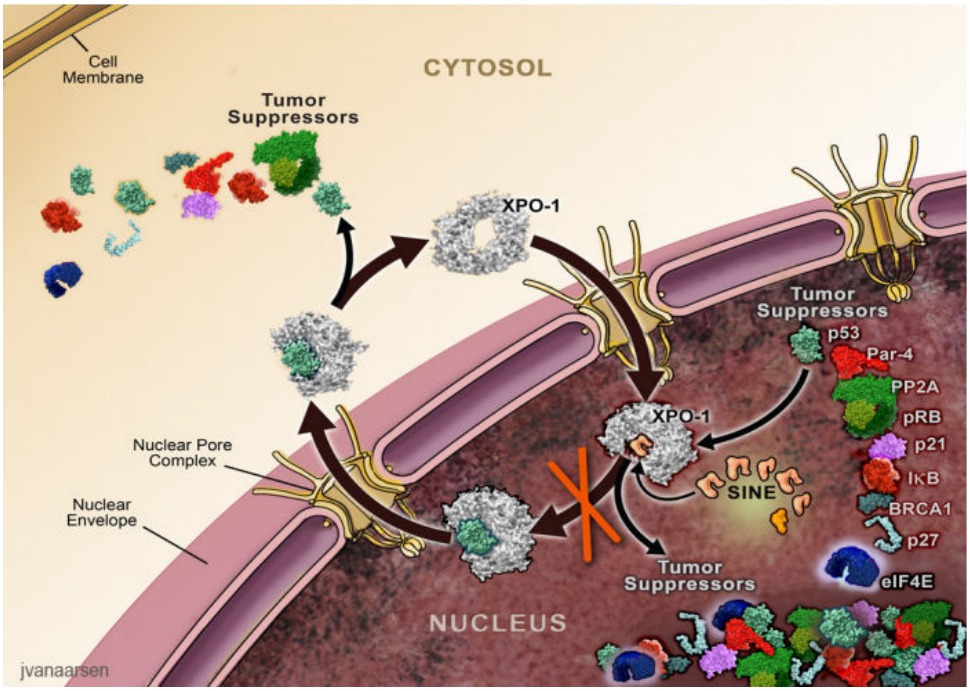
Date	Milestone
Q4:14	Initiate registration directed Phase II SIRRT trial of Selinexor in Richter's transformation
Q4:14	Possible data presentation at ASH
Q4:14	Initiate registration directed Phase II SADAL trial of Selinexor in DLBCL
2014/2015	Initiate two registration-directed Phase II/III trials for Selinexor in undisclosed indications (at least one solid tumor)
2015	Possible submission of IND for KPT-350
2015	Preliminary data from Phase II SOPRA trial of Selinexor in AML
2015	Possible submission of IND for Pak4 inhibitor
2015	Interim Phase II data for Selinexor in prostate cancer, gynecologic malignancies and glioblastoma multiforme
H1:15	Start of Phase II trial of Selinexor in r/r T-cell lymphoma
H1:16	Data from Phase II SIRRT trial of Selinexor in Richter's transformation
Mid:16	Data from Phase II SOPRA trial of Selinexor in elderly patients with relapsed/refractory AML
H2:16	Data from Phase II SADAL trial of Selinexor in relapsed/refractory DLBCL

Source: Company data, Wedbush Securities, Inc.

Selective Inhibitors of Nuclear Transport (SINEs)

There are several processes, such as degradation or post-translational modification, which regulate protein activity in cells. A less described method of regulation is the export of proteins from their functional location within the nucleus. In normal cells, the nuclear transport of proteins is a tightly regulated process that is mediated by specific transport proteins called karyopherins, which can be classified as importins or exportins, depending on whether it is transporting proteins into or out of the nucleus, respectively. Exportins bind to proteins with export signals in the nuclear membrane and transport them into the cytoplasm through a nuclear pore complex. Exportin-1 (XPO1), also known as CRM1, is the most characterized exportin to date. XPO1 mediates the nuclear-cytoplasm transport of proteins important in cell cycle regulation, inflammation and other cellular functions. Studies indicate that XPO1 transports over 220 different cellular proteins and appears to be the exclusive exporter of most tumor suppressor proteins, including FOXO, pRB, p53, p73, p21 and p27. Several studies have shown that during cancer progression, malignant cells gain the ability to over-express XPO1, thus facilitating the rapid export of proteins necessary for cell cycle regulation and tumor suppression. The lack of these proteins in the nucleus allows cells with damaged DNA to subvert apoptosis and continue malignant rapid growth. Thus XPO1 inhibition may restore tumor suppressor activity in a broad range of cancers.

Figure 3: Selinexor Mechanism of Action



Source: Company data

Scientists and clinicians have known for over a decade that the inhibition of XPO1 induces tumor apoptosis. Studies pioneered with the use of the antibiotic leptomycin b have demonstrated the anti-tumor activity of XPO1 inhibition *in vitro*. However, clinical trials with leptomycin b have also demonstrated the difficulty in finding a XPO1 inhibitor that has a therapeutic dose in a tolerable range. Additional XPO1 inhibitors that have been developed include KOS-2464 from Kosan Biosciences (acquired by Bristol-Myers) and CBS9106 from CanBas Co., but these agents have failed to advance into clinical trials. Until recently there have been no XPO1 inhibitors that have demonstrated efficacy and tolerability in clinical trials.

Karyopharm's SINE compound, Selinexor, is the first XPO1 inhibitor that has shown specific inhibition of the nuclear export protein, XPO1, while providing an acceptable tolerability profile. Selinexor's success can be attributed to its specific and reversible inhibition of XPO1 even at low nanomolar concentrations. Designed and optimized using molecular structure analysis, Selinexor inhibits XPO1 by binding specifically to the cys528 amino acid residue in the cargo-binding pocket of XPO1. By binding to this pocket, Selinexor prevents the nuclear export of proteins normally transported by XPO1. However, unlike previous XPO1 inhibitors, Selinexor has a transient effect (lasting about 12-24 hours), which allows normal cells that have survived despite the buildup of tumor suppressor proteins to proceed without apoptosis once Selinexor is removed. This reversibility of XPO1 inhibition is the basis of Selinexor's increased tolerability profile.

XPO1 Inhibition in Cancer

XPO1 facilitates the transport of over 220 different proteins across the nuclear–cytoplasm membrane, including tumor suppressors, cell cycle control and immunomodulator proteins. More importantly, XPO1 seems to be the sole nuclear-cytoplasm trafficker of several proteins linked to cancer, including p53, p21, p27, APC and others (Figure 4). The aberrant localization of these tumor suppressor proteins into the cytoplasm, where they are unable to function, promotes uncontrolled cell growth and immune evasion. There is a growing body of evidence supporting the notion that cancer cells often overexpress XPO1 to abrogate the normal cellular processes that prevent oncogenesis. Thus, restoring tumor suppressor localization in the nucleus through XPO1 inhibition may be a viable method to promote apoptosis in wide variety of cancers.

Figure 4: Drug Targets, Tumor Suppressors and Cell Cycle Inhibitors that Undergo XPO1-Mediated Export in Various Cancers

Protein	Functional significance	Export receptor	Modification required for nuclear export	Cancer type where protein is exported to the cytoplasm
Retinoblastoma	Tumor suppressor	CRM1	Phosphorylation by cyclin-dependent kinases	Retinoblastoma
APC	Tumor suppressor	CRM1	Single mutation causing frame-shift or premature termination	Colorectal cancer
p53	Tumor suppressor	CRM1	Ubiquitinylation by MDM2 E3 ubiquitin ligase	Colorectal cancer; breast cancer
BRCA1	Tumor suppressor	CRM1	BARD1 protein masks NES of BRCA1	Breast cancer
$p21^{CIP1}$	Cell cycle inhibitor	CRM1	HER2/neu mutation and phosphorylation by Akt; BCR-ABL translocation and phosphorylation by Akt; phosphorylation by PKC	Ovarian and breast cancer; chronic myeloid leukemia
Topoisomerase I	DNA topology, drug target	CRM1	Unknown	Anaplastic astrocytoma; neuroblastoma
Topoisomerase IIα	DNA topology, drug target	CRM1	Phosphorylation by casein kinase 2	Multiple myeloma
$p27^{KIP1}$	Cell cycle inhibitor	CRM1	Phosphorylation by human kinase-interacting stathmin (hKIS)	Breast cancer; acute myelogenous leukemia
FOXO	Tumor suppressor	CRM1	Phosphorylation by Akt kinase	Breast, prostate, and thyroid cancer; glioblastoma; melanoma
Inl1/hSNF5	Tumor suppressor	CRM1	Mutation of conserved hydrophobic residues within the NES	Malignant rhabdoid tumors
BCR-ABL	Oncogene, tyrosine kinase	CRM1	Unknown	CML
Galectin-3	Regulator of cell proliferation and apoptosis	CRM1	Phosphorylation, casein kinase I	Thyroid, prostate, breast cancer
Bok	Pro-apoptotic factor	CRM1	Unknown	Breast cancer, HeLa cells
N-WASP/FAK	Regulator of actin cytoskeleton	CRM1	Phosphorylation by FAK (focal adhesion kinase), promoted by 17β-estradiol stimulation	Neural Wiskott-Aldrich syndrome, breast cancer, ovarian cancer
Nucleophosmin	Tumor suppressor	CRM1	Mutation of 288 and 290 tryptophan residues (AML), NF-kB/RelA masking (breast cancer)	Acute myeloid leukemia, breast cancer
Hsp90	Molecular chaperone	CRM1	Unknown	Breast cancer
Estradiol receptor	Blocks S-phase entry, cell-cycle	CRM1	PI3-kinase	Breast cancer
Tob	Cell-cycle inhibitor	CRM1	Unknown	Breast cancer
RASSF2	Tumor suppressor	CRM1	MAPK/ERK-2 phosphorylation	Thyroid cancer, nasopharyngeal carcinoma
Merlin	Tumor suppressor	CRM1	Unknown	Neurofibromatosis

Source: Turner J., Dawson J. and Sullivan D. Nuclear export of proteins and drug resistance in cancer. *Biochemical Pharmacology (2012).*

Advanced Hematological Cancers

In non-Hodgkin lymphoma (NHL), p53 downregulation is a well-known prognostic factor for therapy resistance and poor overall survival. In studies using p53 mutant and wild type NHL cell lines, treatment with SINEs (KPT-185, -251 and -276) resulted in the nuclear retention of p53 and other tumor suppressor proteins, including p73, p27 and p21. Moreover, in a p53 mutant NHL xenograft mouse model, oral SINE administration (KPT–276) resulted in 70% tumor growth inhibition, which was comparable to CHOP therapy in that study. Histological examination of the tumor sections revealed p73 and pro-apoptotic BAX protein upregulation, and the suppression of genes that promote proliferation.

In acute myeloid leukemia (AML), the most common genetic mutation (50-60% of cases) is the modification of nucleophosmin (NPM1). NPM1 is normally located in the nucleus where it controls cell cycle processes and the tumor suppressor protein ARF. Mutations in NPM1 results in a *de novo* XPO1-mediated export signal that promotes the nuclear exclusion of the protein. In a study of samples taken from 511 AML patients, XPO1 expression was lower in samples with favorable genetic profiles compared to those with moderate to

unfavorable profiles. Moreover, overall survival decreased with increased XPO1 expression, with low XPO1-expressing AML patients surviving twice as long as high XPO1-expressing AML patients (66 vs. 37 weeks).

In multiple myeloma (MM) patients, XPO1 expression has been shown to be higher in cancerous cells when compared to normal cells. Moreover, the level of XPO1 expression has been shown to be a predictor of patient outcomes, with high XPO1 expression correlating with poor prognosis. SINE treatment of MM1S cell lines increased p53, p27, pp22a and FOXO3 expression and nuclear localization, which stalled uncontrolled cell growth. Moreover, treatment of MM patient samples with SINE compounds (KPT-185, -251 and -276) reduced expression of XPO1 and increased p53 and BAX (pro-apoptotic) expression.

Solid Tumors

Preclinical testing has established the relationship between XPO1 overexpression and various solid tumors. In samples of cervical cancer, XPO1 has been shown to be overexpressed when compared to normal cervical tissue samples. In samples of glioblastoma, higher XPO1 expression in cells was correlated with greater severity of disease and lower survival in patients.

In prostate samples, XPO1 expression has been shown to be higher in malignant cells when compared to benign tumors and normal surrounding tissue samples. Moreover, KPT-251 and -127 have been shown to inhibit growth and induce apoptosis in malignant prostate cells. Additionally, SINE compounds were able to inhibit growth in a hormone-resistant prostate cancer model (22RV1).

In several ovarian cancer cells, KPT-185 and Selinexor as single agents and in combination with various chemotherapeutic agents (cisplatin, gemcitabine, doxorubicin or topotecan) were able to inhibit growth and induce apoptosis. In an orthotopic model of ovarian cancer, SINE compounds demonstrated 90% growth inhibition as a single agent, and 98% growth inhibition when used in combination with topotecan.

Figure 5: Reference Tables

Cancer	Drugs used	Anti-tumor drug effects, in vitro and in vivo studies	Reference
AML	KPT-330 ± Cytarabine	KPT-330/Cytarabine showed additive anti-proliferative effects in acute promyelocytic leukemia cell lines. *In vivo* KPT-330/Cytarabine prolonged survival compared to monotherapy (P < 0.0001) in mice.	Rettig et al. Blood; 2013; 122
AML	KPT-330 ± Decitabine	KPT-330/Dct increased cytotoxicity compared to monotherapy in AML cells. In a mouse xenograft model, treatment with DCT followed by KPT-330 improved survival compared to KPT-330 alone (47 vs. 36.5 days) P = 0.008.	Ranganathan et al. Blood; 2013; 122
NHL	KPT-330 ± Carfilzomib	KPT-330/Cfz induced strong synergy (CI < 1.0) in aggressive NHL cell lines using MTS assay and Annexin-V apoptosis assays.	Lopez et al. Blood; 2013; 122
CML	KPT-330 ± Imatinib	KPT-330/Imatinib reduced colony formation significantly compared to Imatinib alone in primary CML cells.	Sorouri et al. Blood; 2013; 122
MM	KPT-330 ± Carfilzomib	KPT-330/Cfz synergistically increased cell death (CI 0.2–0.6) by both apoptosis and autophagy in MM cell lines. In a xenograft mouse KPT-330/Cfz was more effective than monotherapy and high dose completely impaired tumor growth with good tolerability.	Rosebeck et al. Blood; 2013 122
Neuro-blastoma	KPT-330 ± Irt, Tpt,Cisplat,Dox	Combination treatment with KPT-330 / Irinotecan, Topotecan, Cisplatin, and Doxorubicin showed additive effects in growth inhibition.	Attiyeh et al. Can Res; 2013; 73
Ovarian	KPT-185, KPT-330 ± Cisplatin	*In vitro* KPT/Cisplat showed additive effect on cell death<comma> overcoming cisplatinum resistance in the isogenic cell lines A2780 and CP70.	Chen et al.Can Res; 2013; 73
Renal	KPT-330 ± ABT-737	KPT-330/ABT-737 showed synergism in RCC cell lines and a normal human kidney cell line *in vitro*.	Inoue et al. J Clin Onco; 2013; 31

Source: Adapted from J.G. Turner et al., Company data, Wedbush Securities, Inc.

Selinexor in Hematological Cancer Malignancies

In July 2012, Karyopharm initiated an open-label randomized, multi-center, six-arm, Phase I study in patients with various types of advanced hematological malignancies to determine the safety profile, dosing regimen and preliminary efficacy of Selinexor (KPT-330). KPTI is evaluating oral Selinexor in an escalating dose regimen, 2-3 times/week for 4 weeks, at up to 80mg/m^2 in a study in patients with chronic B-cell malignancies (Arm 1) and AML (Arm 2). In August 2013, KPTI began evaluating KPT-330 in patients with pretreated relapse/refractory T cell lymphoma (Arm 3). Arm 4 and 5 are recruiting patients with acute lymphocytic leukemia (ALL) and chronic myeloid leukemia (CML), while Arm 6 includes patients with multiple myeloma (MM) taking up to 20 mg/m^2 of dexamethasone with each biweekly dose of Selinexor. Karyopharm has yet to report the treatment results of any patients in Arm 3, 4 or 5 of the Phase I trial.

Selinexor in NHL Malignancies

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin's lymphoma (NHL), accounting for about 1/3 cases. DLBCL is a fast growing and aggressive cancer that requires immediate treatment. First-line treatment is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), with 25%-50% of DLBCL patients failing to achieve remission. Only healthy patients younger than 65 years of age proceed to second-line treatment, which consists of high-dose chemotherapy with hematopoietic stem cell transplantation. This only cures 50% of patients. Patients who relapse after second-line treatment or patients who are not healthy or young enough for second line treatment have limited treatment options, and death usually occurs in less than one year. Although significant advances have been made in the treatment of patients with DLBCL, the majority are not cured with conventional therapy. Following relapse, at least 60 percent of patients remain sensitive to conventional treatment, but less than 10 percent of patients experience prolonged disease-free survival with second-line treatment regimens.

Another aggressive form of NHL is Richter's transformation, which is a rare condition that develops in 5-15% of patients with chronic lymphocytic leukemia (CLL). Additionally, reports have estimated that Epstein Barr Virus (EBV) can be found in as high as 20% of all cases of Richter's transformations. In all settings for Richter's transformation prognosis is poor. The median survival is five to eight months, which are marked with worsening lymphadenopathy, splenomegaly, anemia, thrombocytopenia and B-symptoms (fever, night sweats, and weight loss). Current treatment regimens for Richter's transformation are limited and marginal in improving overall survival. In all settings, remission is short-lived and it is recommended that patients enroll in an appropriate clinical trial.

Clinical Development Program

As of May 2014, KPTI has enrolled 51 heavily pre-treated patients (average 4 prior therapies) who have r/r NHL (including DLBCL and Richter's) into the first arm of its ongoing Phase I clinical trial. Arm 1 is a multicenter trial evaluating Selinexor doses ranging from 3 mg/m^2 to 80 mg/m^2 over a four-week cycle. Preliminary results from 43 evaluable patients in Arm 1 showed that 74% of patients experienced a response or disease stabilization and the ORR was 28%. Distribution of responses in various indications can be found in Figure 6. In patients with DLBCL (n=21) or Richter's Syndrome (n=5) the administration of Selinexor resulted in a reverse or stabilization of disease progression in 70% of DLBCL and 100% of Richter's Syndrome patients. In patients with Follicular (n=7), Mantle cell (n=3) Transformed (n=3) or T-cell (n=4) malignancies, stabilization or reversal of disease was seen in 86%, 67%, 33% and 75% of patients, respectively. Adverse events, which are listed in Figure 7, were manageable with supportive care.

The responses to Selinexor were similar across the two major DLBCL subtypes, segmented based on whether the tumor has a gene expression profile similar to germinal center B-cells (GCB) or activated blood memory B-cells (ABC, or non-GCB). This differentiates Selinexor from other targeted therapies which are primarily active against the ABC subtype. For example, Revlimid has demonstrated a 53% ORR in non-GBC DLBCL compared to 9% in GCB DLBCL, and Ibrutinib has demonstrated a 41% ORR in non-GCB DLBCL vs 5% for GCB DLBCL. Responses to Selinexor segregated based on GCB type can be found in Figure 8. Selinexor also demonstrated efficacy in "double-hit" (DH) DLBCL, a difficult-to-treat subset characterized by chromosomal translocations in the *MYC* and *BCL2* (and less commonly *BCL6*) genes. Of the four patients with DH DLBCL in the arm, treatment with Selinexor resulted in one CR, one PR and two cases of stable disease. The consistent efficacy Selinexor has demonstrated across DLBCL subtypes is indicative of the broad potential the drug has to treat disease regardless of cytogenic abnormalities or cell of origin.

Figure 6: Responses from Patients with NHL Malignancies as of May 2014

Cancer	N	DCR (%)	ORR (%)	CR (%)	PR (%)	SD (%)	PD (%)	WC (%)
DLBCL	21	15 (70%)	6 (29%)	1 (5%)	5 (25%)	9 (40%)	5 (25%)	1 (5%)
Follicular	7	6 (86%)	1 (14%)	—	1 (14%)	5 (71%)	—	1 (14%)
Mantle Cell	3	2 (67%)	1 (33%)	—	1 (33%)	1 (33%)	—	1 (33%)
Transformed	3	1 (33%)	1 (33%)	—	1 (33%)	—	2 (67%)	—
T-Cell	4	3 (75%)	1 (25%)	1 (25%)	—	2 (50%)	—	1 (25%)
Richter's Syndrome	5	5 (100%)	2 (40%)	—	2 (40%)	3 (60%)	—	—
Total	**43**	**32 (74%)**	**12 (28%)**	**2 (5%)**	**10 (23%)**	**20 (47%)**	**7 (16%)**	**4 (9%)**

Source: Company data, Wedbush Securities, Inc.

Figure 7: Adverse Events in Patients with DLBCL

Adverse Event	Grade 1/2	Grade 3/4
Nausea	51%	
Anorexia	41%	
Fatigue	36%	
Thrombocytopenia		20%
Neutropenia		16%
Hyponatremia		6%

Source: Company data, Wedbush Securities, Inc.

Figure 8: Responses from Patients with DLBCL Malignancies Categorized by GCB Type as of May 2014

	N	DCR (%)	ORR (%)	CR (%)	PR (%)	SD (%)	PD (%)	WC (%)
GCB	11	8 (72%)	3 (27%)	1 (9%)	2 (18%)	5 (45%)	2 (18%)	1 (9%)
non-GCB	4	3 (75%)	1 (25%)	—	1 (25%)	2 (50%)	1 (25%)	—
Unknown	6	4 (67%)	2 (33%)	—	2 (33%)	2 (33%)	2 (33%)	—

Source: Company data, Wedbush Securities, Inc.

In Q4:14, KPTI intends to begin the Phase II SADAL trial in ~200 heavily pretreated (2 to 4 prior therapies) DLBCL patients that are randomized to receive 35 mg/m^2 or 60 mg/m^2 twice-weekly doses of Selinexor. Patients will also be administered 8-12mg of dexamethasone, which is a dose level consistent with supportive care rather than anticancer activity. At least 50% of the patients in each arm will have the GCB subtype of DLBCL. The trial will be run in the US and Europe, and could potentially support accelerated approval in both regions. The registration-directed Phase II SIRRT trial in 50 patients with r/r Richter's transformation is also expected to start in Q4:14.

Market

Imbruvica and Revlimid are the recommended agents for r/r DLBCL patients, but these agents have shown little to no efficacy in DLBCL patients with GCB. In contrast, Selinexor has shown equal efficacy in non-GCB and GCB types of DLBCL, as well as in the DH subset of patients. Although the data is early, we view this as a point of differentiation for Selinexor.

Based on incidence data, we estimate that there are about 20,000 new cases of DLBCL in the US and Europe each year, with about a quarter of those patients having disease progression to the third-line treatment setting. Based on our review of published literature, we believe the GCB subtype accounts for about 40% of DLBCL cases, resulting in a potential DLBCL market opportunity for Selinexor of about 2,000 patients in the US and Europe each year. We also estimate the number of new cases of Richter's transformation in the US and EU at about 500 and 1,000 per year, respectively, with the latter figure higher due to the greater CLL incidence in Europe. We believe Selinexor can achieve significant market share in both indications, given the demonstrated efficacy and lack of alternative treatment options. We expect Selinexor to be priced at $12,000 per cycle and estimate it will achieve a peak market share of 40% in

the GCB DLBCL setting and 30% in the Richter's setting. We expect approval for both indications in the US in H2:17 and in Europe in H2:18, and forecast 2020 sales of $263M and $23M in the DLBCL and Richter's settings, respectively.

Selinexor in Acute Myeloid Leukemia (AML)

AML is a type of cancer that is characterized by the overproduction of cancerous myeloid progenitor cells, leading to the crowding out of normal cells in the bone marrow and blood. AML progression leads to anemia and increased susceptibility to infection, leukopenia and thrombocytopenia. The American Cancer Society expects there to be over 18,000 new cases of AML in the United States, with 75% of cases estimated to be in patients 65 years of age or older. With a growing elderly population, the cases of AML are expected to increase.

Treatment options for AML are extremely limited. The majority of patients will relapse, and the five year survival rate is less than 25%. Standard treatment for AML consists of aggressive induction chemotherapy (cytarabine and daunorubicin), followed by radiotherapy and hematopoietic stem cell transplantation.

Clinical Development Program

As of June 2014, Karyopharm has enrolled 65 patients (mean age of 67) in Arm 2 with actively progressing relapsed and/or refractory AML malignancies who have failed an average of 3 prior treatments. The multicenter trial is evaluating Selinexor doses ranging from 16 mg/m^2 to 70 mg/m^2 in a four week cycle. Patients, 36% of whom had adverse cytogenetics, were initially given lower doses ten times per cycle and higher doses twice per cycle. Results presented at the European Hematology Association in June 2014 showed that 32 (49%) patients had disease control irrespective of AML genetic subtype (Figure 9). Higher Selinexor doses corresponded to greater reduction in bone marrow blast count and this response was seen across several genetic subtypes of AML.

The most common side effects were mostly reversible Grade 1 and 2 adverse events, consisting of diarrhea (82%), anorexia (78%), nausea (74%) and fatigue (65%). Grade 3/4 AEs included fatigue (18%), thrombocytopenia (15%), neutropenia (11%) and nausea (8%). Selinexor was well tolerated at higher doses when administered with appetite stimulants and anti-nausea agents. As of June 2014, there have been no dose limited toxicities observed, and the maximum tolerated dose is 70mg/m^2 twice weekly.

Figure 9: Best Responses of Patients with AML

Best Responses in Patients with AML as 10-June-2014									
N	**DCR**	**ORR**	**CR**	**CR(i)**	**PR**	**MLFS**	**SD**	**PD**	**NE**
65	32	10	5	2	1	2	22	16	17
%	49%	15%	8%	3%	2%	3%	34%	25%	26%

DCR=Disease Control Rate (CR+CR(i)+PR+MLFS+SD), **ORR**=Overall Response Rate (CR+CR(i)+PR+MLFS), **CR**=Complete Response, **CR(i)**=Complete Response Incomplete, **MLFS**=Morphological Leukemia Free State, **SD**=Stable Disease, **PD**=Progressive Disease, **NE**=Non Evaluable

Source: Company data

On June 24, 2014, the company announced the initiation of the Phase II SOPRA trial, a registration directed study of Selinexor in patients with r/r AML. The company plans to enroll approximately 150 elderly AML patients who are unable to receive chemotherapy or transplantation. The primary endpoint for the study is overall survival and the secondary endpoint is interim (3 month) survival. The study will randomize patients 2:1 to receive either 55 mg/m^2 twice weekly Selinexor or best supportive care (which can include best supportive care plus low dose cytarabine, best supportive care plus a physician's choice of a hypomethylating agent, or best supportive care alone). Preliminary data is expected in 2015.

Investigator-sponsored studies are also evaluating the use of Selinexor in AML in combination with other agents. A Phase II study conducted by Cardiff University (UK) is evaluating Selinexor with low-dose cytarabine in newly diagnosed elderly AML or high-risk MDS patients who are not eligible for intensive chemotherapy. A Phase I study conducted by Ohio State University is assessing Selinexor in combination with decitabine in r/r AML and newly diagnosed elderly AML patients. Selinexor is also being evaluated in a Phase I pediatric study led by Dana-Farber/Boston Children's Cancer and Blood Disorders Center in children with r/r ALL or newly diagnosed elderly AML.

Market

The initial results generated by Selinexor monotherapy in AML thus far are numerically inferior to other therapies in development, such as Qinprezo (vosaroxin) from Sunesis (SNSS, NEUTRAL), which, when combined with cytarabine, has demonstrated a 25% ORR plus a survival benefit in relapsed/refractory AML patients during Phase II testing. We believe that Selinexor could be competitive if it were combined with an HMA and/or a chemotherapeutic agent, but approval as part of a combination regimen would require a separate study to be conducted, which we expect will delay a commercial launch until 2019. With an r/r AML incidence of 9k in the US and ~13k in the EU and an estimated peak penetration of 20% in both markets, we believe Selinexor could generate about $17M in sales in 2020, our last forecasted year.

Selinexor in Multiple Myeloma

Multiple myeloma (MM) is a cancer of the plasma cells in the bone marrow. MM causes tumors which weaken the bones and reduces the production of healthy blood cells and platelets, resulting in anemia, increased infection and abnormal bleeding. Front-line therapy for MM consists of dexamethasone, usually administered in combination with newer agents such as Thalomid (thalidomide), Revlimid (lenalidomide) and Velcade (bortezomib), followed by a hematopoietic stem cell (HSC) transplant. Patients over the age of 60 have limited options, however, as they are often ineligible for HSC transplant and/or do not tolerate the new MM agents well. Regardless, if remission is initially observed, all patients eventually relapse and require salvage therapy. First-line therapy for MM is usually Velcade in combination with dexamethasone. Patients who relapse after one to two years are often treated again with the same therapy, whereas patients who relapse after a shorter period of time receive Revlimid plus dexamethasone.

Selinexor plus dexamethasone demonstrate synergy in MM and an ideal tolerability profile

In a study of Selinexor as a single agent in 34 patients, one partial response (ORR=3%) and 5 mixed responses were observed (Figure 10). Efficacy improved when Selinexor (45 mg/m^2) was combined with low-dose (20 mg) dexamethasone, with a 75% clinical response rate (1 sCR, 3 PR and 2 MR) and a 50% ORR rate observed in eight evaluable patients. Patients in the combo study had a median of 5.5 prior lines of therapy, including proteasome inhibitors (such as Kyprolis or Velcade) and an immunomodulatory agent (such as Pomalyst). Additionally, seven of the eight patients also received stem cell transplantation. As of June 5, 2014, five of the eight patients were still on treatment, and two additional patients have been enrolled in the cohort. KPTI has also opened up an additional cohort evaluating a higher dose of Selinexor (60 mg/m^2) with low-dose dex in up to 12 patients.

Adverse events in patients receiving single-agent Selinexor were consistent with events seen in the other hematological malignancies studies. All patients responded to supportive care. The combination of Selinexor with dexamethasone resulted in fewer adverse events, as expected, given the appetite-stimulating and anti-nausea effects of steroids (Figure 12). Selinexor also has no contraindications with any other myeloma treatments, which supports the combinability of Selinexor. KPTI has indicated plans to begin combo studies of Selinexor with Velcade or other anti-myeloma therapies in late 2014/early 2015.

Figure 10: Best Responses in Patients with Multiple Myeloma as of June 5 2014

Treatment	N	CBR	ORR	sCR	PR	MR	SD	PD	NE
Selinexor Low Dose	17	4 (24%)	--	--	--	4 (24%)	8 (47%)	3 (18%)	2 (12%)
Selinexor High Dose	17	2 (12%)	1 (6%)	--	1 (6%)	1 (6%)	8 (47%)	3 (18%)	4 (24%)
Selinexor + Low Dex	**8**	**6 (75%)**	**4 (50%)**	**1 (12%)**	**3 (38%)**	**2 (25%)**	--	**1 (12%)**	**1 (12%)**

CBR=Clinical Benefit Response (MR+PR+sCR), ORR=Overall Response Rate (sCR+PR), sCR= Stringent Complete Response, PR=Partial Response, MR=Minor Response, SD=Stable Disease, PD=Progressive Disease, NE=Non Evaluable

Source: Company data

Figure 11: Individual Patient Responses from Selinexor + Dexamethasone Cohort

Patient	Age	MM Type	Maximal Δ	Response	# Prior Tx	Prior Therapies	Study Days
076	63	IgG-κ	–73%	PR	7	Dox+Vinc+Dex, TD, Carfil-Dex, VRD, Cyclo-Pred-BCNU, Doxil-Carfil-Dex	122+
077	62	FLC-λ	*	NE	5	Len-Dex, ASCT, VRD,Carfil-Cyclo-Dex, Carfil-Cyclo-Dex-Len	15
079	65	FLC-κ	–53%	PR	3	TD-ASCT, CyBor-D,Len-Dex	45
081	55	FLC-κ	–98%	sCR	5	VAD-ASCT, ASCT, Cyclo-Pred, Pom-Carfil-Dex	107+
084	59	IgG-κ	–81%	PR	7	Vel-Dex, VD-ASCT, Len-Dex, Vel-dex, Carfil, Pom-Dex, Carfil, DT-PACE	81+
090	65	IgG-κ	*	PD	4	Vel-Lenalid-Dex, Cyclo-Bortez-Dex, Carfil-Dex - ASCT, Pom-Carfil-Dex	38
092	69	IgA-κ	–48%	MR	6	VRD-ASCT, Reolysin, TGO2, Carfil-Dex, Carfil-Cyclo-Dex, Carfil-Pom-Dex	51+
093	43	IgG-κ	–32%	MR	7	VAD, VTD+ASCT, Vel-Rev-Dex, Investigational, Carfil-Panob, Len-Elotu-Dex, Pom-Dex	46+

Source: Company data

Figure 12: Adverse Events Observed in Multiple Myeloma Study

AE NAME	GRADE	Selinexor Low Doses ≤30mg/m² (N=17)	Selinexor High Doses ≥35mg/m² (N=17)	Selinexor 45mg/m² + Dex 20mg (N=6)
Gastrointestinal, Constitutional, and Others				
Nausea	GRADE 1	7 (41%)	3 (18%)	1 (17%)
	GRADE 2	6 (35%)	12 (71%)	--
Anorexia	GRADE 1	1 (6%)	3 (18%)	--
	GRADE 2	9 (53%)	5 (29%)	--
Fatigue	GRADE 1	4 (24%)	3 (18%)	--
	GRADE 2	6 (35%)	7 (41%)	--
	GRADE 3	--	1 (6%)	--
Diarrhea	GRADE 1	4 (24%)	1 (6%)	--
	GRADE 2	2 (12%)	1 (6%)	--
	GRADE 3		1 (6%)	--
Weight Loss	GRADE 1	2 (12%)	4 (24%)	--
	GRADE 2	1 (6%)	1 (6%)	--
Dehydration	GRADE 1	--	1 (6%)	--
	GRADE 2	1 (6%)	1 (6%)	1 (17%)
	GRADE 3	1 (6%)	2 (12%)	--
Dizziness	GRADE 1	2 (12%)	--	--
Dyspnea	GRADE 1	1 (6%)	1 (6%)	--
	GRADE 2	2 (12%)	--	--
Hair Loss	GRADE 1	1 (6%)	2 (12%)	--
Vomiting	GRADE 1	6 (35%)	2 (12%)	--
	GRADE 2	1 (6%)	6 (35%)	--
Cataract	GRADE 2		1 (6%)	--
	GRADE 3	1 (6%)	--	--
Flashing Lights	GRADE 1	2 (12%)	--	--
Dry Mouth	GRADE 1	2 (12%)	--	--
Fever	GRADE 1	--	1 (6%)	--
	GRADE 3	--	1 (6%)	--
Taste Alteration	GRADE 1	3 (18%)	1 (6%)	--
	GRADE 2	--	--	--
Blurred Vision	GRADE 1	1 (6%)	3 (18%)	--
	GRADE 2	1 (6%)	1 (6%)	--
Hematological				
Thrombocytopenia	GRADE 1	1 (6%)	--	--
	GRADE 2	--	--	--
	GRADE 3	1 (6%)	--	--
	GRADE 4	4 (24%)	6 (35%)	--
Anemia	GRADE 1	2 (12%)	--	--
	GRADE 2	1 (6%)	1 (6%)	--
	GRADE 3	--	--	--
Neutropenia	GRADE 2	2 (12%)	1 (6%)	--
	GRADE 3	1 (6%)	--	--
	GRADE 4	2 (12%)	--	--
Leukopenia	GRADE 1	1 (6%)	1 (6%)	--
	GRADE 4	1 (6%)	--	--
Biochemical				
Hyponatremia	GRADE 1	--	1 (6%)	--
	GRADE 3	3 (18%)	3 (18%)	--
Creatinine increased	GRADE 1	--	2 (12%)	--

Source: Company data

Although a dex monotherapy cohort was not included in the study, we note that single-agent high-dose (40 mg) dex has demonstrated a 27% ORR in refractory MM patients (Alexanian et al. *High-dose glucocorticoid treatment of resistant myeloma*, Annals of Internal Medicine 1986). Considering the higher responses Selinexor generated with lower-strength dex in a more heavily pre-treated MM

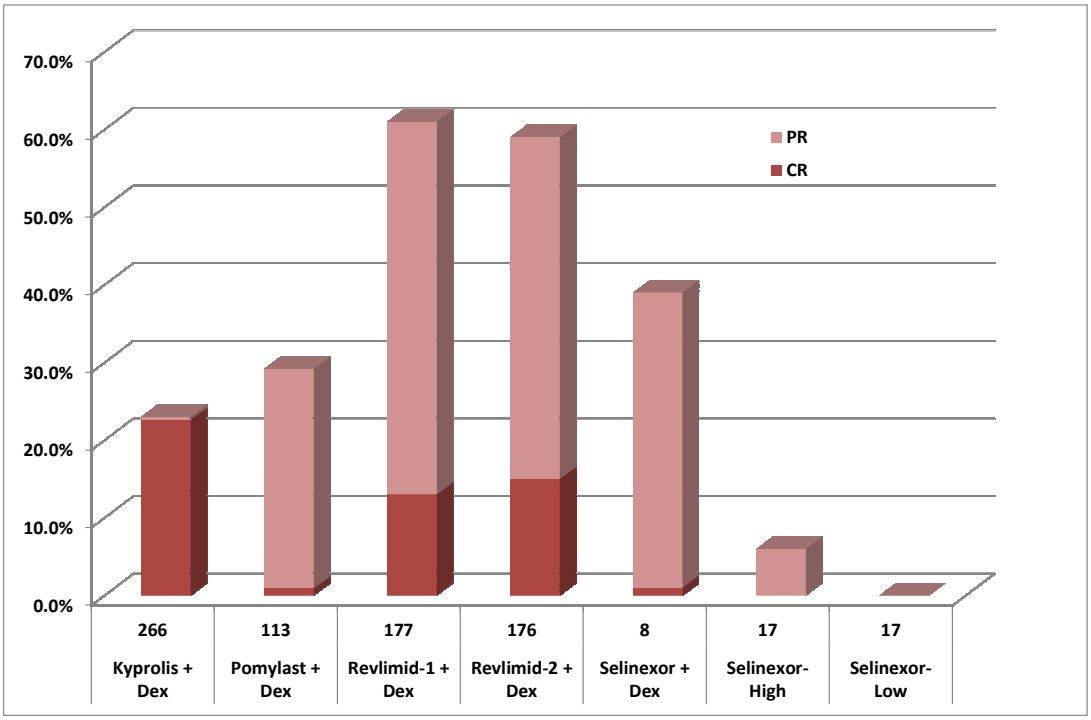
population, it is clear that the Selinexor + dex combo has synergistic activity. In treatment-naïve MM patients, low-dose (20mg) dex monotherapy has demonstrated a 47% ORR (Alexanian et al. *Primary dexamethasone treatment of multiple myeloma*, Blood 1992), which is similar to the response seen with the Selinexor + dex combo in pre-treated MM patients, suggesting that Selinexor could potentially be acting to resensitize myeloma cells to dex.

Market

Current treatments for r/r MM patients are typically administered in conjunction with dex. When comparing the responses Selinexor has generated thus far to currently available treatments, we believe Selinexor could be used in second-line therapy (see Figures 13 and 14).

There are about 24,000 and 40,000 new cases of MM in the US and EU, respectively, and we estimate about half will progress to the second-line relapsed setting. Based on this usage strategy, we believe Selinexor can achieve a peak market share of 25% at a price of $12K per cycle. We note that Selinexor + dex has demonstrated superior responses compared to Pomalyst + dex, which was approved in Feb. 2013 to treat MM patients who have failed two prior treatments. Pomalyst generated $305M in worldwide sales during its launch year, with peak sales estimates from the Street of $1B to $2B. We estimate Selinexor will launch in the MM setting in 2017 in the US and 2018 in the EU, and estimate global sales of $232M globally in 2019 and $396M in 2020, our last forecasted year.

Figure 13: Responses of Patients Receiving Low-Dose Dexamethasone vs. Selected Drugs



Source: Wedbush Securities, Inc.

Figure 14: Approved Therapies for Multiple Myeloma

Product	Kyprolis	Pomalyst		Revlimid	
Generic Name	Carfilzomib	Pomalidomide		Lenalidomide	
Company	Onyx/	Celgene		Celgene	
Description	IV proteasome inhibitor	Oral immunomodulatory		Oral immunomodulatory	
Approved Label	KYPROLIS is indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy	POMALYST is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate		REVLIMID in combination with dexamethasone is indicated for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy	
Registration-Trial	Phase II (accelerated approval)	Phase I/II (accelerated approval)		Phase III	
	Kyp + Dex (required with first dose)	Pom + Dex	Pom	Rev + Dex	Rev + Dex
Patients	N= 266	N=108	113	Study 1: 353	Study 2: 351
ORR	The ORR (stringent complete response [sCR] + complete response [CR] + very good partial response [VGPR] + partial response [PR]) was 61 (22.9) (95% CI: 18.0, 28.5) (N = 266)	Pom + low dose Dex 33 (29.2%)	Pom alone 8 (7.4%)	Study1:107 (61%) for Revlimid+dex Study 1 : 34 (19) for dex alone	Study 2: 104 (59%) for Revlimid+dex Study 2: 41 (23) for dex alone
Additional	Median DoR: 7.8 months	Median DoR: 7.4 months		Study 1: time-to-progression (TTP) is 13.9 mo vs 4.7mo for dex alone	Study 2: TTP is 12.1 mo vs 4.7 mo for dex alone
Complete Response	1 (0.4)	1 (0.9)	0 (0)	Study 1: 23 (13) for Rev+dex Study1: 1(1) for dex alone	Study 2: 27(15) for Rev+dex Study 2: 7(4) for dex alone
Partial Response	47 (17.7)	32 (28.3)	8 (7.4)	Study1: 84(48) for Rev+dex Study 1: 33(19) for dex alone	Study2: 74 (44) for Rev+dex Study 2: 34(19) for dex alone
Dex dose	4mg	20mg >75 years, 40mg <75 years or younger		40mg	40mg

Source: Wedbush Securities, Inc.

Selinexor in Solid Tumors

Karyopharm is conducting a Phase I trial of Selinexor in relapsed/refractory patients with advanced solid tumors and signs of disease progression. As in the hematological malignancies trials, patients included are heavily pretreated and have failed multiple lines of prior therapy (average of 3.7 prior therapies). Phase I was designed to evaluate safety and to determine the Phase II clinical trial dose and dosing schedule. Interim analyses of results have shown preliminary anti-cancer activity in various solid tumors.

Patients evaluated to date received Selinexor doses ranging from 3 mg/m^2 to 85 mg/m^2, two to three times per week, over a 28-day cycle. Responses were evaluated every two cycles in accordance with Response Evaluation Criteria in Solid Tumors (RECIST), the accepted criteria for solid tumor evaluation. As of May 13, 2014, 52 out of the 106 evaluable patients demonstrated disease control. Of those, 4% experienced PR and 45% experienced disease stabilization (Figure 15). Given the progressive and highly refractory nature of these diseases, we believe these initial results are promising. Common gastrointestinal-related AEs included nausea, anorexia and vomiting (Figure 16) and these events coincided with the first cycle of Selinexor dosing. Fatigue was also common in patients. The company notes that although AE rates are high, most were manageable with supportive care; also, moving patients to a 2x per week dosing regimen greatly improved the AEs in patients. There were two dose-limiting toxicities events reported in this arm of the trial, both in patients receiving twice weekly 85 mg/m^2. The dose-limiting toxicities (DLTs) were grade 3 asymptomatic hyponatremia in one patient and acute cerebellar syndrome that was treated over several weeks in a second patient. KPTI selected the 65 mg/m^2 twice weekly dose of Selinexor for further evaluation.

Figure 15: Responses in Patients with Solid Tumors

Cancer Type	N	PRs and SD (%)	PR (%)	SD (%)	PD (%)
Colorectal	39	14 (36%)	1 (3%)	13 (33%)	25 (64%)
Head & Neck	14	9 (64%)	--	9 (64%)	5 (36%)
Prostate	8	7 (88%)	--	7 (88%)	1 (12%)
Cervical	5	4 (80%)	1 (20%)	3 (60%)	1 (20%)
Ovarian	5	3 (60%)	1 (20%)	2 (40%)	2 (40%)
GBM	5	--	--	--	5 (100%)
Melanoma	3	2 (67%)	1 (33%)	1 (33%)	1 (33%)
Sarcoma	8	7 (88%)	--	7 (88%)	1 (12%)
Other	19	6 (32%)	--	6 (32%)	13 (68%)
Total	**106**	**52 (49%)**	**4 (4%)**	**48 (45%)**	**54 (51%)**

Source: Company data

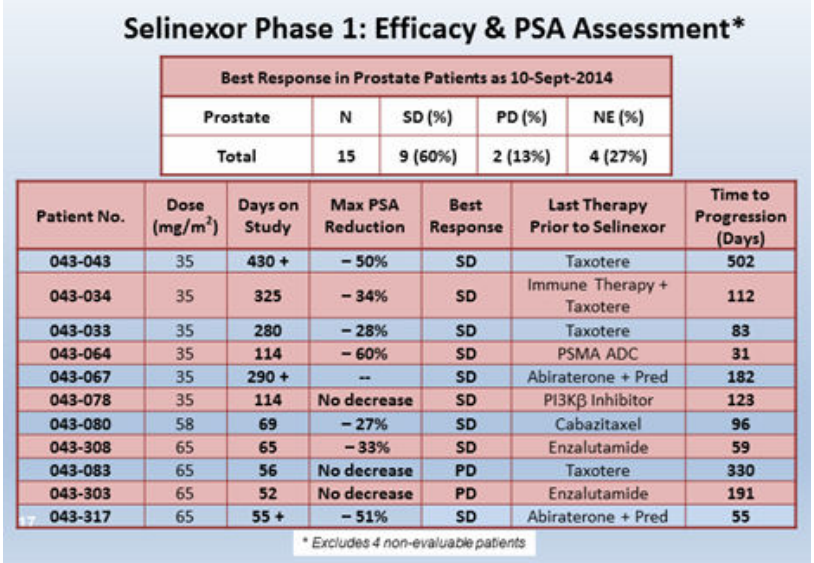
Figure 16: Adverse Events Observed in Patients with Solid Tumors

	Grade 1/2	Grade 3/4*
Nausea	**62%**	
Anorexia	**48%**	
Vomiting	**35%**	
Thrombocytopenia		**7%**
Fatigue	**52%**	**7%**
Fatigue hyponatremia		**8%**

Source: Company data, Wedbush Securities, Inc.

Updated data from the study that was presented at ESMO (Sept, 2014) highlighted the single-agent activity Selinexor had in platinum-resistant ovarian cancer, head-and-neck squamous cell carcinoma (HN-SCC) and prostate cancer. In the heavily pretreated (median 5 prior therapies) group of patients with platinum-resistant ovarian cancer, Selinexor demonstrated one partial response (5 months) and two cases of stable disease (4 and >10 months) in five evaluable patients. In the 17 patients enrolled with HN-SCC (median 2.6 prior therapies), 11 of 16 evaluable patients (69%) had stable disease. In the heavily pre-treated group (median 5.5 prior therapies) of castration-resistant prostate cancer (CRPC) patients, 9 of 11 evaluable patients had prolonged stable disease and 2 patients had progressive disease, with time-to-progression ranging from 31 days to 502 days on study (Figure 17). PSA levels fell between 27-60% during treatment in this highly refractory patient population, all of whom had failed on taxanes and the majority of whom had failed on Xtandi and/or Zytiga.

Figure 17: Outcomes of Prostate Cancer Patients in Phase I Solid Tumor Study as of Sept 10, 2014



Source: Company data

Phase II Studies in Solid Tumors

Karyopharm has decided to move forward with Phase II trials in metastatic prostate cancer, gynecological malignancies (ovarian, endometrial and cervical), head and neck sarcomas and glioblastoma. In June 2014, Karyopharm announced the initiation of its Phase II trial of 50 mg/m^2 twice weekly Selinexor in metastatic prostate cancer. This open-label trial will enroll 50 patients who have metastatic hormone-resistant prostate cancer and have failed at least one approved therapy (enzalutamide, abiraterone or radium 223). The primary outcome will assess DCR, according to RECIST, and the secondary endpoint will evaluate PSA, and we anticipate data read-out in 2015. We do not currently forecast sales for Selinexor in the indication, as the drug does not appear to be competitive at this stage, with approved therapies for refractory CRPC (like Xofigo). We await additional data from the study in 2015 before becoming more conclusive on Selinexor's potential in prostate cancer.

Selinexor may be particularly effective in treating virally induced cancers.

We find the planned Phase II studies in gynecological malignancies, specifically cervical cancer, and the proposed trial in head-and-neck sarcoma as particularly interesting given the important role of human papillomavirus (HPV) in these cancers. It is important to note that XPO1 shuttling of the HPV viral proteins E2 and E6 is required for HPV replication, and that the expression of HPV E6 and E7 alone are sufficient and necessary to transform primary cells into malignant/cancerous cells. It is well known that HPV can be found in over 90% of cervical cancers. HPV has also been associated with head-and-neck cancer. Meta-analysis of 55 different studies, which included a total of 2,559 laryngeal cancer patients, revealed that HPV could be found in 28% of patient samples. Genotype analysis of the samples revealed that HPV-16, the virus genotype that is most associated with cancer, had a prevalence of 19.8%. Moreover the study found that the risk of squamous cell carcinoma was significantly increased in those with HPV infection. Based on this data, we believe it is likely that Selinexor will be effective in treating head-and-neck cancer and gynecological malignancies, specifically in HPV positive patients, given its anti-cancer and possibly anti-viral activity. From discussions with management, we believe Karyopharm will likely conduct HPV viral assessment for patients in the gynecological malignancy and head-and-neck cancer trials.

According to reports, about 15% of all cancers worldwide have an underlying mechanism that can be associated with viruses. There are several viruses (Figure 18) known to cause cancer, including HPV in cervical cancer, and EBV in nasopharyngeal cancer. During the

process of viral infection and replication, the viruses transform the cell into a factory for continuous virus production, causing unregulated growth that can lead to cancer. Selinexor may prove to be exceptionally well suited to treat virally-caused cancers, due to its ability to increase the presence of tumor suppressor proteins in the nucleus which can trigger apoptosis in the context of viral replication (a way the body fights viral infections).

Figure 18: Viruses and Cancers that Selinexor may be Effective in Treating

Virus	Cancers Linked To	Essential Proteins in Viral Replication
Human papillomavirus (HPV) HPV -16 and -18 (high risk human papillomavirus genotypes, hrHPV)	Cervical Cancer Anal cancer Oral cancer Oropharyngeal cancer Penile cancer Vaginal cancer Vulvar cancer	E2 Immune evasion E6 regulator of gene expression
Epstein-Barr Virus (EBV) HHV-4	Nasopharyngeal Cancer Hodgkin Lymphoma Non Hodgkin Lymphoma (DLBCL) Stomach Cancer	SM Protein regulator of gene expression BMLF1
Human Immunodeficiency virus (HIV-1)	Kaposi Sarcoma* Cervical Cancer Non-Hodgkin Lymphoma CNS Lymphoma	REV regulator of gene expression
Kaposi sarcoma-associated herpes virus (KSHV) HHV-8	Kaposi Sarcoma Cervical Cancer Non-Hodgkin Lymphoma Central Nervous System Lymphoma Primary Effusion Lymphoma	ORF45 regulator of gene expression
Human T-Lymphotropic virus (HTLV-1)	Lymphocytic Leukemia T-Cell Leukemia/Lymphoma	Rex regulator of gene expression

*Note: *HIV-1 patients are more susceptible to KSHV infection due to compromised immune system*

Source: Cancer.gov, unipro.org, Wedbush Securities, Inc.

Food Effect Study in Patients with Metastatic Soft Tissue or Bone Sarcomas

In July 2013, Karyopharm initiated a Phase 1b open-label food effect study of Selinexor in heavily pretreated patients who have metastatic, locally advanced or locally recurrent soft tissue or bone sarcomas. This trial was primarily designed to evaluate the effects of using 30 mg/m^2 capsule or tablet formulations of Selinexor twice weekly on absorption when taken with food. Interim analysis of the 21 patients treated showed that Selinexor was effective in stabilizing disease in 52% of patients (Figure 19) and according to company reports, five patients continue to remain on the study. The study also confirmed that Selinexor is better absorbed when taken with food, and that the tablet formulation has similar pharmacokinetics and tolerability as the original capsule formulation. Karyopharm has initiated an expansion cohort study at 50 mg/m^2 twice weekly and we expect data from this study in 2015. The company will examine Selinexor alone and in combination with chemotherapy in patients with advanced and metastatic sarcomas. Although this initial data is promising, due to the small sample size, we are reserving the valuation of Selinexor in these indications until more data is presented.

Figure 19: Selinexor Efficacy in Food Effect Study

Sarcoma Type	N	SD (%)	PD (%)	NE (%)
Leiomyosarcoma	6	3 (50%)	2 (33%)	1 (17%)
Liposarcoma	4	4 (100%)	--	--
Synovial Cell Sarcoma	3	--	3 (100%)	--
Chondrosarcoma	2	1 (50%)	1 (50%)	--
Others	6	3 (50%)	2 (33%)	1 (17%)
Total	**21**	**11 (52%)**	**8 (38%)**	**2 (10%)**

Source: Company data, Wedbush Securities, Inc.

Market

We are forecasting approval for Selinexor in gynecological cancers that are associated with HPV. The most common HPV-associated cancer is cervical cancer, where almost all cases are caused by the virus. Other gynecological cancers that are linked to HPV include vulvar cancer and vaginal cancer, where about half of all cases are linked to HPV. We also forecast approval of Selinexor in oral cancers, where declining tobacco usage means that about 70%-80% of new cases are thought to be caused by HPV.

We expect the planned solid tumor registration study to be in the oral cancer indication, which should result in a 2018 approval for Selinexor in the US and EU. We believe approval in gynecological malignancies will follow a year later in both territories. We have assumed that there are about 41k patients in the US and 75k in the EU with HPV-linked oral cancer, and another 16k patients with HPV-linked gynecological cancers (including 12k with cervical, ~3k with vulvar and ~750 with vaginal cancer) in the US and ~38k in the EU (~35k cervical, ~2500 with vulvar and ~500 with vaginal cancer). We expect the incidence figures for HPV-linked cancers to gradually decline as HPV vaccination becomes more widespread. We forecast $601M in sales in 2020 in the oral cancer setting and $150M in sales in the gynecological malignancy setting in 2020, our valuation year.

Additional Small Molecules and Treatment Settings

Karyopharm is also developing other small molecules, including another SINE compound and a PAK-4 inhibitor, to treat other indications including autoimmune disorders, inflammatory diseases, wound healing complications and viral diseases. Karyopharm has released minimal data on these programs, thus we are reserving valuing these programs until more information is available.

KPT-350

KPT-350 is an oral SINE in preclinical development for autoimmune and inflammatory diseases. XPO1 is the exporter of multiple proteins (including I_KB, FOXO and COMMD1) that inhibit the nuclear factor $NF\text{-}_KB$, which drives multiple types of inflammation. Inhibition of XPO1 by SINEs leads to the accumulation of these proteins within the nucleus, resulting in the inhibition of $NF\text{-}_KB$ activity.

PAK-4 Inhibitors

PAK4 is a signaling protein important in regulating numerous cell activities, including cell survival, cell division and immune defense. Karyopharm's PAK4 inhibitors have demonstrated broad anti-cancer activity and minimal toxicity in mouse xenograft studies and in hematological and solid tumor cancer cells.

Verdinexor for the Treatment of Canine Lymphoma

KPTI is developing Verdinexor, a Selinexor-related molecule to treat canines with newly diagnosed or first-time relapse lymphoma. Dog lymphomas respond to chemotherapy in a similar manner to human NHLs, and as a result, success with Verdinexor would be a positive sign for Selinexor. In a Phase I study of 14 canines, tumor growth ceased or reversed in 64% of canines receiving treatment, with a median time to disease progression of 66 days. Dose expansion studies demonstrated cancer growth cessation or regression in 4/6 (67%) dogs treated, with a median time to progression of 83 days. Management stated that AEs were manageable with supportive care. In a subsequent Phase II study, designed to support FDA filing, Verdinexor demonstrated a clinical benefit in 55% of canines with naïve B, relapsed B, naïve T or relapsed T–cell malignancies. The median duration of benefit was 71 days.

Figure 20: Verdinexor Activity in Canine Non-Hodgkin's Lymphoma

	N	PR/CR	Clinical Benefit	Duration of Benefit
Phase 1				
Dose Escalation	14	2 (14%)	9 (64%)	66 days (35-256)
Dose Expansion	6	2 (33%)	4 (67%)	83 days (35-354)
Phase 2				
All	**58**	**20(34%)**	**32 (55%)**	**71 days (21-273)**
Naïve B	28	8 (29%)	16 (57%)	71 days (28-195)
Relapse B	14	4 (29%)	6 (43%)	70 days (23-214)
Naïve T	7	4 (57%)	5 (71%)	42 days (21-273)
Relapse T	7	4 (57%)	5 (71%)	72 days (30-194)

Source: Company data, Wedbush Securities, Inc.

In June 2014, the FDA granted conditional approval to the New Animal Drug Application (NADA) for Verdinexor, making it the first oral, targeted therapy for the treatment of dog lymphoma. KPTI is required, as part of the conditional approval, to complete a randomized study within the next five years that confirms the activity of Verdinexor. KPTI is currently seeking a marketing partner for Verdinexor. At this time, the value of Verdinexor is not incorporated into our price target.

IP

KPTI has global rights to all of its product candidates. The company has one issued patent in the US (No. 8,513,230) that expires in 2031 which covers compounds that modulate nuclear transport. The company also has 19 pending patent applications in the US and 15 pending internationally. The company's patent portfolio covers:

- Selinexor (KPT-330): one PCT application (covering the US) and four pending foreign applications that covers composition of matter, methods of use and manufacturing of Selinexor.
- Wound healing: one pending US provisional patent application that covers the use of Selinexor or Verdinexor for wound healing.
- KPT-350: one pending provisional and one pending non-provisional patent application in the US, and a PCT application.
- PAK4 inhibitors: eight pending US provisional patent applications that covers composition of matter and methods of use
- Verdinexor (KPT-335): the Selinexor patent family also covers the composition of matter, methods of use and manufacturing of Verdinexor

Valuation Table

Product	Tumor Type	Estimated Incidence	Peak Penetration	2020 Sales	Multiple	Discount	Value/share
Selinexor (KPT-350)	GCB DLBCL	9,405 (US) 8,775 (EU)	40%	$263M	6	30%	$10.06
	r/r Multiple myeloma	12,000 (US) 20,000 (EU)	25%	$396M	6	30%	$15.15
	Richter's Transformation	500 (US) 1,250 (EU)	30%	$23M	6	30%	$0.90
	r/r AML	9,050 (US) 12,950 (EU)	20%	$17M	6	30%	$0.64
	HPV-linked head and neck cancers	41,250 (US) 75,000 (EU)	20%	$601M	6	35%	$18.83
	HPV-linked gynecological cancers	15,750 (US) 37,500 (EU)	40% (cervical), 30% (vulvar & vaginal)	$150M	6	35%	$4.71
						Total	$50.29

Source: Wedbush Securities, Inc.

Management

Figure 21: Executive Officers

Name	Position	Experience
Michael G. Kauffman, M.D.	President, Chief Executive Officer, Chief Medical Officer and Director	Dr. Michael Kauffman co-founded Karyopharm in 2008 and has served as the CEO since January 2011 and Director since 2008. Prior to his most recent roles at Karyopharm, Dr. Kaufman served as the President from January 2011 to December 2013 and CMO from December 2012 to December 2013. From November 2008 to Decembers 2010, Dr. Kauffman served as the CMO of Proteolix and Onyx Pharmaceuticals, where he led the development of Kyprolis (carfilzomib). From 2006 to 2008, Dr. Kauffman was an operating partner at Bessemer Venture Partners. Prior to that, Dr. Kauffman was the President and CEO of Epix Pharmaceuticals and Predix Pharmaceuticals. From 2000 to 2002, Dr. Kauffman was the Vice President, Clinical at Millennium Pharmaceuticals. From September 1995 to 1997, Dr. Kauffman served in several senior positions at Biogen Idec. Dr. Kauffman received his B.A. in Biochemistry from Amherst College, his M.D. and Ph.D. from Johns Hopkins Medical School.
Sharon Shacham, Ph.D., M.B.A.	Chief Scientific Officer and President of Research and Development	Dr. Sharon Shacham co-founded Karyopharm in 2008, and has served as the President since December 2013 and CSO since October 2010. Prior to those roles, Dr. Shacham served as the President of R&D from December 2012 to December 2013 and Head of Research and Development form October 2010 to December 2012. Dr. Shacham was the Senior Vice President of Drug Development at Epix Pharmaceuticals, and Director of Algorithm and Software Development at Predix Pharmaceuticals from 2000 to 2009. Dr. Shacham received her B.Sc. in Chemistry, Ph.D. and M.B.A. from Tel Aviv University.
Mr. Justin Renz	Executive Vice President and Chief Financial Officer	Mr. Justin Renz joined Karyopharm as the Executive Vice President and Chief Financial Officer in August 2014. Prior to joining Karyopharm Mr. Renz served as the Executive Vice President and Chief Financial Officer at Zalicus Inc. Prior to Zalicus, Mr. Renz served in senior finance and accounting positions at Serono Inc and Coley Pharmaceuticals. Mr. Renz received a B.A. in Economics and Accounting from the College of the Holy Cross, a Master of Science in Taxation from Northwestern University and a Master of Business Administration from Suffolk University.

Source: Company data, Wedbush Securities, Inc.

Registered Clinical Trials

Figure 22: Selinexor Studies

NCT Number	Title	Phase	Sponsor	Status
NCT01986348	Phase 2 Study of Selinexor (KPT-330) in Patients With Recurrent Glioblastoma After Failure of Radiation and Temozolomide (**KING**)	2		Active
NCT02249091	Study of Selinexor (KPT-330) in Combination with Ara-C and Idarubicin in Patients With Relapsed Or Refractory AML	2		Active
NCT02227251	Study of Selinexor (KPT-330) in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma (**SADAL**)	2		Inactive
NCT02199665	Selinexor, Carfilzomib, and Dexamethasone in Treating Patients With Relapsed or Refractory Multiple Myeloma	1	University of Chicago, NCI	Inactive
NCT02088541	Selinexor (KPT-330) in Older Patients With Relapsed AML (**SOPRA**)	2		Active
NCT02212561	Selinexor With Fludarabine and Cytarabine for Treatment of Refractory/Relapsed Leukemia or Myelodysplastic Syndrome	1/2	St. Jude	Active
NCT02146833	Study of Selinexor (KPT-330) in Metastatic Castrate Resistant Prostate Adenocarcinoma	2		Active
NCT02228525	Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) in Patients With Myelodysplastic Syndromes	2	Memorial Sloan, MD Anderson, Columbia	Active
NCT02213133	Selinexor Treatment of Advanced Relapsed/Refractory Squamous Cell Carcinomas (**STARRS**)	2		Active
NCT02025985	Phase II Study of KPT-330 (Selinexor) in Female Patients With Advanced Gynecologic Malignancies (**SIGN**)	2		Active
NCT02093403	Decitabine and Selinexor in Treating Patients With Relapsed or Refractory Acute Myeloid Leukemia	1	Ohio State University	Active
NCT02215161	Selinexor (KPT-330) in Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC) and Prior Therapy With Abiraterone and/or Enzalutamide	2	University of California- San Francisco	Inactive
NCT02069730	A Study of Drug Therapies for Salivary Gland Cancers Based on Testing of Genes		University Health Network, Toronto	Active
NCT02250885	KPT-330 to Treat Poorly Differentiated Lung and Gastroenteropancreatic Tumors	2	Gabrail Cancer Center Research	Active
NCT02138786	Study of Selinexor (KPT-330) in Patients With Refractory and/or Relapsed Richter's Transformation (RT) (**SIRRT**)	2		Inactive
NCT02078349	Phase I Study of KPT330 in Asian Patients	1	National University Hospital, Singapore	Active
NCT02120222	Evaluating SINE KPT-330 in Treating Patients With Melanoma That Cannot Be Removed By Surgery	1	Ohio State University	Active
NCT02091245	Phase I Trial of the Selective Inhibitor of Nuclear Export, KPT-330, in Relapsed Childhood ALL and AML	1	Dana-Farber	Active

Active=recruiting, Inactive = not yet recruiting

Source: clinicaltrials.gov, Company data, Wedbush Securities, Inc.

Financial Model

KPTI received net proceeds of $112.9M in its recent follow-on that closed in July, and we estimate the company will end Q3:14 with ~$234M in cash and equivalents. Following the secondary offering we estimate KPTI currently has about 32.6M common shares outstanding.

Figure 23: KPTI Financial Model

10/1/2014
Ticker: (KPTI:Nasdaq)
Karyopharm Therapeutics, Inc

Wedbush PacGrow Life Sciences
David M. Nierengarten, Ph.D.
415-274-6862

	2013	Q1	Q2	Q3	Q4	2014E	2015E	2016E	2017E	2018E	2019E	2020E
Revenues:												
US Product Sales	$0	$0	$0	$0	$0	$0	$0	$0	$16,077	$232,860	$472,446	$762,073
ex-US sales	$0	$0	$0	$0	$0	$0	$0	$0	$0	$19,013	$335,523	$688,756
Licensing and other revenue	$387	$171	$21	$0	$0	$192	$0	$0	$0	$0	$0	$0
Total Revenues	**387**	**171**	**21**	**0**	**0**	**192**	**0**	**0**	**16,077**	**251,874**	**807,969**	**1,450,828**
Cost and Expenses:												
Cost of Sales	0	0	0	0	0	0	0	0	804	12,594	40,398	72,541
R&D	28,452	10,979	13,159	13,422	14,422	51,982	79,689	94,264	102,034	110,445	119,549	129,404
SG&A	5,885	2,904	3,310	2,962	3,021	12,197	12,702	13,412	17,522	136,007	315,239	443,811
Total Operating Expenses	**34,337**	**13,883**	**16,469**	**16,384**	**17,444**	**64,180**	**92,390**	**107,676**	**120,360**	**259,046**	**475,187**	**645,756**
Operating Income (Loss)	(33,950)	(13,712)	(16,448)	(16,384)	(17,444)	(63,988)	(92,390)	(107,676)	(104,283)	(7,172)	332,782	805,072
Net Interest Income (Expense)	3	18	17	992	1,758	2,786	5,692	4,305	4,422	5,200	6,375	16,231
Other non-operating Income (Expense)	0	0	0	0	0	0	0	0	0	0	0	0
Income Before Income Taxes	(33,947)	(13,694)	(16,431)	(15,392)	(15,685)	(61,202)	(86,698)	(103,370)	(99,861)	(1,972)	339,157	821,303
Provision for Income Taxes	0	0	0	0	0	0	0	0	0	1,977	132,271	158,386
Net Income (Loss)	(33,947)	(13,694)	(16,431)	(15,392)	(15,685)	(61,202)	(86,698)	(103,370)	(99,861)	(3,949)	206,886	662,917
Non-GAAP EPS	**(1.02)**	**(0.37)**	**(0.42)**	**(0.37)**	**(0.38)**	**(1.47)**	**(2.25)**	**(2.51)**	**(2.26)**	**(0.13)**	**5.46**	**17.56**
GAAP EPS	**(5.59)**	**(0.46)**	**(0.55)**	**(0.47)**	**(0.48)**	**(1.97)**	**(2.65)**	**(3.03)**	**(2.77)**	**(0.10)**	**5.49**	**17.59**
Total Shares Outstanding	29,587	29,619	29,720	32,590	32,615	32,615	32,715	35,715	37,715	37,690	37,690	37,690
Cash Burn	(34,007)	(12,680)	(16,119)	(12,775)	(16,258)	(57,832)	(93,672)	(106,419)	(105,902)	(31,656)	310,890	771,151
Cash Balance	155,974	144,893	132,307	234,437	218,656	218,656	131,959	174,643	170,125	141,062	325,199	952,198

Source: Wedbush Securities, Inc.

Covered Companies Mentioned Table

COMPANY	TICKER	RATING	PRICE TARGET	PRICE
Sunesis Pharmaceuticals, Inc.	SNSS	N	$10	$6.62

RATING SCALE / DEFINITION

O = Outperform
N = Neutral
U = Underperform

Analyst Biography

David is an Analyst covering stocks in the Biotechnology/Biopharmaceuticals/BioDefense sector. His prior sell-side research experience at Robert W. Baird & Co. covered biotechnology companies of all market capitalizations, with a focus on oncology and rare diseases.

David received his B.S. (Biochemistry) from the University of Wisconsin-Madison and Ph.D. (Molecular and Cell Biology) from the University of California-Berkeley.

David's Edge: David's early stage venture capital investing experience gives him a balanced perspective on developmental-stage biotechnology companies and their ultimate risk/reward potential. His experience on the other side of that equation in a clinical-stage, venture backed biotechnology company provides him with insights into corporate operations. The combination of experiences creates a focus on value creation in this event-driven space.

Analyst Certification
I, David M. Nierengarten, Ph.D., Heather Behanna, Ph.D., Dilip Joseph, certify that the views expressed in this report accurately reflect my personal opinion and that I have not and will not, directly or indirectly, receive compensation or other payments in connection with my specific recommendations or views contained in this report.

Disclosure information regarding historical ratings and price targets is available at http://www.wedbush.com/ResearchDisclosure/DisclosureQ214.pdf

Investment Rating System:
Outperform: Expect the total return of the stock to outperform relative to the median total return of the analyst's (or the analyst's team) coverage universe over the next 6-12 months.
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Underperform: Expect the total return of the stock to underperform relative to the median total return of the analyst's (or the analyst's team) coverage universe over the next 6-12 months.

The Investment Ratings are based on the expected performance of a stock (based on anticipated total return to price target) relative to the other stocks in the analyst's coverage universe (or the analyst's team coverage).*

Rating Distribution (as of June 30, 2014)	**Investment Banking Relationships (as of June 30, 2014)**
Outperform:54% Neutral: 42% Underperform: 4%	Outperform:25% Neutral: 1% Underperform: 0%

The Distribution of Ratings is required by FINRA rules; however, WS' stock ratings of Outperform, Neutral, and Underperform most closely conform to Buy, Hold, and Sell, respectively. Please note, however, the definitions are not the same as WS' stock ratings are on a relative basis.

The analysts responsible for preparing research reports do not receive compensation based on specific investment banking activity. The analysts receive compensation that is based upon various factors including WS' total revenues, a portion of which are generated by WS' investment banking activities.

Wedbush Equity Research Disclosures as of October 6, 2014

Company	Disclosure
Karyopharm Therapeutics Sunesis Pharmaceuticals	1,3,4,5 1

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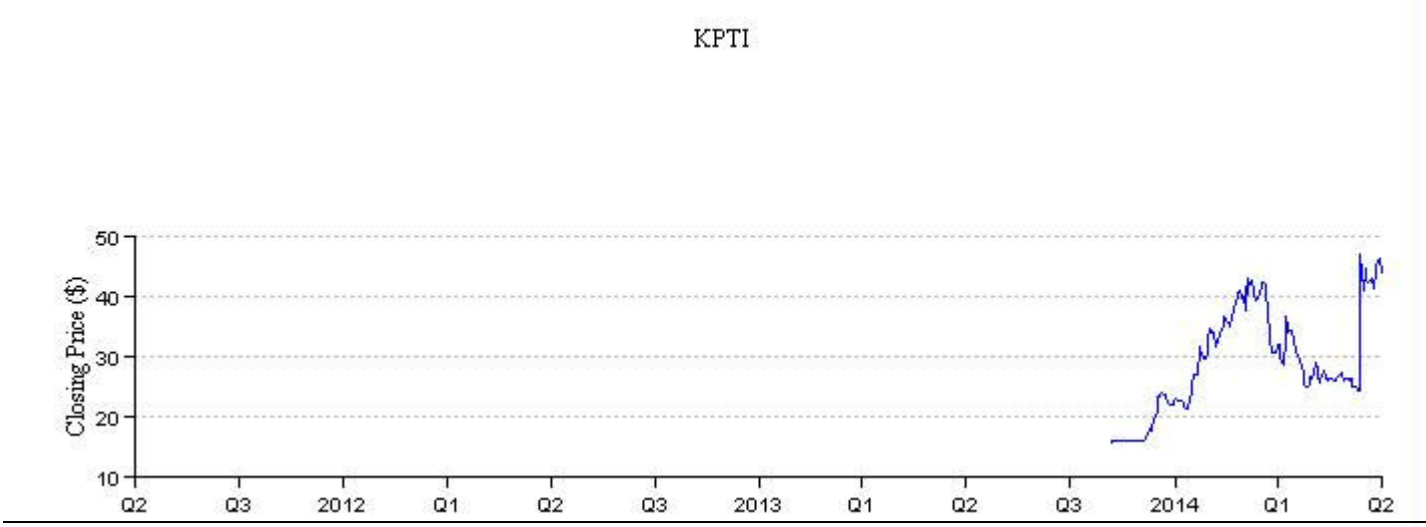

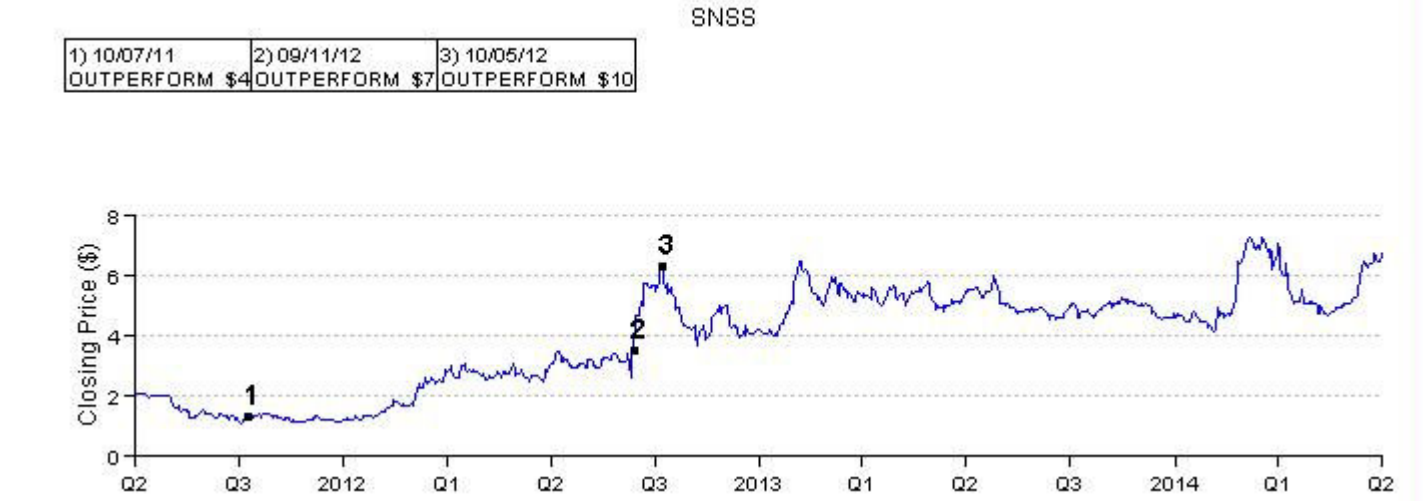

* WS changed its rating system from (Strong Buy/Buy/Hold/Sell) to (Outperform/ Neutral/Underperform) on July 14, 2009.
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