Karyopharm Therapeutics Inc. (KPTI)

ENA2014 Wrap-Up: Selinexor Pre-Clinical Studies; Early Glimpse of PAK4 Inhibitor Activity

MARKET DATA

Price	$41.21
52-Week Range:	$15.82 - $47.98
Shares Out. (M):	32.6
Market Cap ($M):	$1,343.4
Average Daily Vol. (000):	101.0
Cash (M):	$156
Cash/Share:	$4.78
Enterprise Value (M):	$967
Float (M):	15.0
LT Debt (M):	$0

Source: Thomson Reuters and JMP Securities LLC

FY DEC		2013A	2014E	2015E
Revenue ($M)	1Q	--	$0.2A	$0.0
	2Q	$0.4	$0.0A	$0.0
	3Q	$0.0	$0.0A	$0.0
	4Q	$0.0	$0.0	$0.0
	FY	**$0.0**	**$0.0**	**$0.0**
EPS	1Q	--	($0.46)A	--
	2Q	($5.39)	($0.55)A	--
	3Q	($3.66)	($0.61)A	--
	4Q	($0.47)	($0.76)	--
	FY	**($5.59)**	**($2.50)**	**($6.55)**

Source: Company reports and JMP Securities LLC

STOCK PRICE PERFORMANCE

MARKET OUTPERFORM | Price: $41.21 | Target Price: $57.00

INVESTMENT HIGHLIGHTS

Presentations at last week's ENA2014 conference contained pre-clinical data that provided a fuller picture of Karyopharm Therapeutics' selinexor anti-cancer mechanisms; PAK4 inhibitor profile begins to take shape; reiterate Market Outperform rating and $57 price target, based on our DCF, CAGR, and SOTP methodologies. Multiple data presentations were provided at ENA2014, both by KPTI and outside investigators. Two pre-clinical presentations further elucidated selinexor's anti-tumor properties, while a discussion by outside investigators spoke to the drug's ability to synergistically or additively combine with other anti-neoplastic agents. Additionally, the next asset in the company's pipeline (PAK4 inhibitor) is demonstrating intriguing activity.

Selinexor blocks the expression of DNA damage repair genes, and sensitizes both solid and hematologic cell lines to DNA damage, inducing agents. In a poster presented by scientists from KPTI, selinexor, although not a DNA damaging agent, was shown to disrupt the expression of DNA repair proteins, including Rad51 and CHK1. Experiments showed that treatment of AML cells with selinexor after their exposure to doxorubicin and idarubicin inhibited the repair mechanism of DNA damage, and resulted in apoptosis as measured by PARP and caspase-3 cleavage. In a separate experiment, effects of single-agent selinexor, radiation, or the combination in lung tumor xenografts, showed a reduction in tumor size of 15%, 43%, and 96%, suggesting synergy between selinexor and radiation. Selinexor also provided additional cell killing when added to CHK1 inhibitors in a cervical adenocarcinoma cell line. Our interpretation of these data is that combination therapies, including selinexor, along with other chemotherapy agents and radiation, are likely to provide even more impressive clinical benefit than has been seen with single-agent selinexor. We have already seen a strong hint of combination therapy with selinexor in the myeloma results wherein the drug is combined with dexamethasone (albeit not a cytotoxic agent).

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Is selinexor on its way to becoming the partner of choice for a wide variety of anti-cancer agents? In a discussion by Dr. Daniel Sullivan of the Moffitt Cancer Center in Tampa, FL, selinexor was seen to be additive or synergistic with, and can restore sensitivity to, a wide variety of anti-cancer agents. While these experiments were all conducted in cell lines, much of the early pre-clinical work examining selinexor in cells has been recapitulated in humans. In combination with doxorubicin, selinexor was shown to sensitize drug-resistant cells to destruction, as well as to increase the number of double-strand breaks in DNA. Dr. Sullivan repeated his results with bortezomib (Velcade) and carfilzomib (Kyprolis), but also showed that these combinations did not increase toxicity to peripheral blood cells (PBMCs). Finally, in series of experiments wherein the sequence order of agents was varied (carfilzomib followed by selinexor, and then vice-versa), Dr. Sullivan once again confirmed the synergy with the aforementioned agents as well as with melphalan, a commonly used agent for the treatment of myeloma (particularly in Europe). Recall, this combination is the subject of an abstract to be presented at ASH. Oddly, Dr. Sullivan stated that his experiments showed no synergy with dexamethasone, a steroid commonly used in myeloma patients. We were surprised but not concerned about this finding; recall at EHA in June, the company showed robust synergy between selinexor and dexamethasone in a highly refractory myeloma patient population. Updated findings that confirm these results are also the subject of an oral presentation at ASH.

PAK4 inhibitor packs a wallop against cancer. At the Friday morning poster session, KPTI presented pre-clinical data on KPT-7523, an orally available, potent and specific small molecule inhibitor of PAK4, also known as p21 activated kinase. The PAK family of proteins regulates cell survival, cell division, and apoptosis (cell death). PAK4 is up-regulated or mutated in many tumor types. It is also downstream of the KRAS oncogene and mediates cell movement, division and survival by binding to certain essential cell proteins. KPTI investigators presented data to show that another PAK4 inhibitor, KPT-8752, inhibited 91 different tumor cell lines with an IC50< 1 uM while showing no inhibition against normal cells. The company also showed that a third compound, KPT-7682, has broad activity in a variety of tumor types, showing impressive activity in animal models of triple negative breast cancer (TNBC), colorectal cancer, and mantle cell lymphoma (MCL), wherein it completely obliterated the tumors (Figure 4). The IND-enabling studies for one of the compounds in the series should begin soon, and an IND should be filed by year-end 2015.

We remain encouraged by the signs of selinexor activity across a wide range of tumor types, solid and liquid, exemplified by the data presented at ASCO, EHA, ENA2014, as well as upcoming data at ASH. We believe Karyopharm is on the verge of bringing an entirely new class of chemotherapy agent to the market with broad activity and acceptable tolerability. We also note that Karyopharm holds the worldwide rights to selinexor.

FIGURE 1. Selinexor Clinical Trials

Trial No.	Sponsor	Phase	Indication	Combo Partner	Pt Size	FPI
NCT01607892	KPTI	I	Various Heme Malignancies (MAD)		250	May-12
NCT01607905	KPTI	I	Various advance solid tumors		90	May-12
NCT02146833	KPTI	II	Metastatic prostate cancer		50	May-14
TBD	KPTI	II	**SADAL** - ≥3L R/R DLBLC, low and hi dose Selinexor		200	4Q14
NCT02088541	KPTI	II	**SOPRA** - R/R Elderly AML vs physician's choice		150	Apr-14
NCT02138786	KPTI	II	**SIRRT** - R/R Richter's Transformation		50	4Q14
NCT02025985	KPTI	II	**SIGN** - Gynaecologic malignancies (ovarian, endometrial, cervical)		63	Apr-14
NCT01986348	KPTI	II	**KING** - Glioblastoma		30	Mar-14
NCT02178436	KPTI	I/II	Pancreatic cancer and PDAC	Gem/Abraxane	43	Not yet recruiting
NCT01896505	KPTI	I	Food effect study		20	Sep-13
NCT02186834	Moffit	I/II	Multiple myeloma	Dexamethasone, Doxil	47	Not yet recruiting
NCT02199665	U. Chicago, NCI	I	Refractory Multiple Myeloma	Kyprolis, Dexamethasone	48	Not yet recruiting
NCT02093403	Ohio State	I	R/R and Elderly Untreated AML	Dacogen	42	Mar-14
NCT02120222	Ohio State	I	Recurrent melanoma		20	Not yet recruiting
NCT02137356	Sheba Med Ctr	I	Neoadjuvant rectal neoplasms	Chemoradiation	28	Not yet recruiting
NCT02069730	U of T		Salivary gland cancers		30	Not yet recruiting
NCT02091245	Dana Farber	I	Childhood relapsed ALL/AML		28	Apr-14
NCT02078349	Ntl Univ. Hosp, Singapore	I	Asian solid tumor study		30	Mar-14

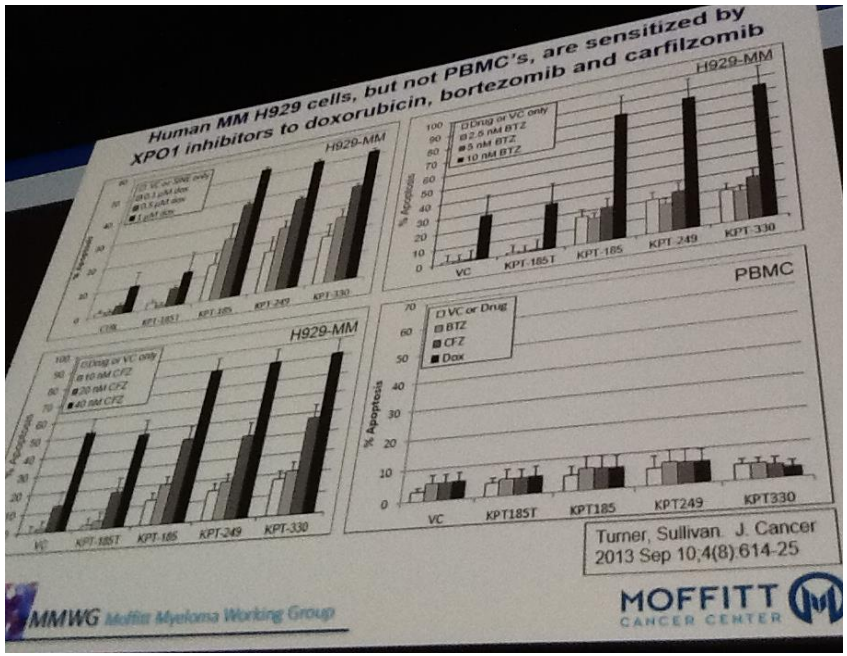
Source: JMP Securities LLC and company reports

FIGURE 2. Upcoming Potential Catalysts

Timing	Drug	Catalyst
ASH	Selinexor	Updated RRMM Phase I data in combination with dexamethasone
2H14E	KPT-350	IND completion for use in inflammation, auto-immune, and anti-viral indications
2H14E	PAK Inhibitor	IND completion for use in oncology indications

Source: JMP Securities LLC and company reports

FIGURE 3. Cell-Selective Selinexor Sensitization to Chemotherapy



Source: Poster Presentation

FIGURE 4. PAK4 Inhibitor Efficacy

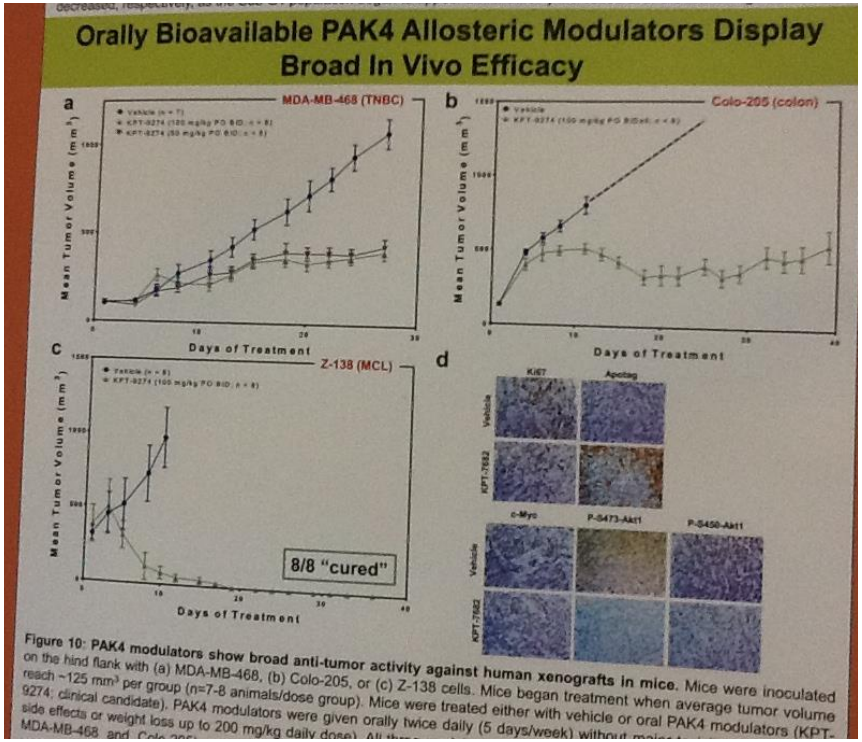


Figure 10: **PAK4 modulators show broad anti-tumor activity against human xenografts in mice.** Mice were inoculated on the hind flank with (a) MDA-MB-468, (b) Colo-205, or (c) Z-138 cells. Mice began treatment when average tumor volume reach ~125 mm³ per group (n=7-8 animals/dose group). Mice were treated either with vehicle or oral PAK4 modulators (KPT-9274; clinical candidate). PAK4 modulators were given orally twice daily (5 days/week) without

Source: Poster Presentation

Company Description

Karyopharm Therapeutics (KPTI) is a Natick, MA-based, clinical-stage biopharmaceutical company focused on the discovery and development of novel first-in-class drugs directed against nuclear transport targets for the treatment of cancer and other major diseases. Karyopharm's Selective Inhibitors of Nuclear Export (SINE) compounds function by preventing the export of tumor suppressor proteins from the nucleus, driving accumulation and restoration of function. The company's lead pipeline candidate, selinexor (KPT-330), is a Phase I orally available small molecule inhibitor of XPO1, set to initiate pivotal Phase II/III evaluation in various hematologic malignancies in 2014. Karyopharm is also developing selinexor and SINE as potential therapies for autoimmune and inflammatory disease, viral infections, and wound healing.

Investment Risks

Clinical. Drug development is an inherently risky business. Clinical trials always carry a risk of failure and Karyopharm's assets (Selinexor (KPT330), KPT-350, PAK4 inhibitor, verdinexor or future drug candidates) may fail to demonstrate meaningful enough levels of efficacy in current or future clinical trials.

Regulatory and commercial. The ability of Karyopharm to market its drugs depends upon the drugs obtaining approval from the FDA and foreign regulatory agencies. Failure to achieve approval or delays in the timelines to approval could negatively impact the company's share price.

Competitive. Hematologic malignancies, including multiple myeloma, indolent non-Hodgkin lymphoma, and acute myeloid leukemia represent increasingly competitive fields and Karyopharm faces competition from both commercial and development-stage companies with product(s) or product candidates addressing similar clinical indications. Some of these companies may possess substantially greater R&D and commercial resources than Karyopharm. As such, there is no assurance Karyopharm will be competitive or differentiated from other drug products.

Financial. Following its IPO, Karyopharm ended 1Q14 with approximately $156MM in cash and cash equivalents. We anticipate the company is likely to seek additional equity financing in the form of a secondary offering in order to complete the development of its drug candidates, creating dilution risk for existing shareholders.

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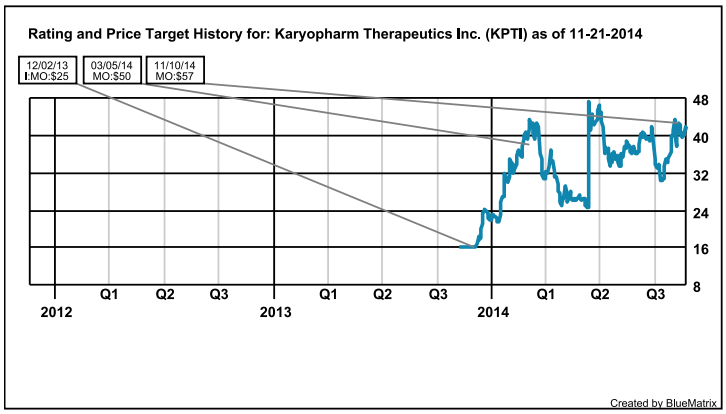
JMP Rating	Regulatory Equivalent	# Co's Under Coverage	*% of Total*	Regulatory Equivalent	# Co's Under Coverage	*% of Total*	# Co's Receiving IB Services in Past 12 Months	*% of Co's With This Rating*
MARKET OUTPERFORM	Buy	287	*61.06%*	Buy	287	*61.06%*	102	*35.54%*
MARKET PERFORM	Hold	142	*30.21%*	Hold	142	*30.21%*	16	*11.27%*
MARKET UNDERPERFORM	Sell	3	*0.64%*	Sell	3	*0.64%*	0	*0%*
COVERAGE IN TRANSITION		35	*7.45%*		35	*7.45%*	0	*0%*
TOTAL:		470	*100%*		470	*100%*	120	*25.53%*

Stock Price Chart of Rating and Target Price Changes:

Note: First annotation denotes initiation of coverage or 3 years, whichever is shorter. If no target price is listed, then the target price is N/A. In accordance with NASD Rule 2711, the chart(s) below reflect(s) price range and any changes to the rating or price target as of the end of the most recent calendar quarter. The action reflected in this note is not annotated in the stock price chart. Source: JMP Securities.



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