Karyopharm Therapeutics Inc. (KPTI)

Read-throughs from ASCO Abstracts

MARKET OUTPERFORM | Price: $26.70 | Target Price: $50.00

MARKET DATA

Price	$26.70
52-Week Range:	$15.50 - $47.87
Shares Out. (M):	29.8
Market Cap ($M):	$795.7
Average Daily Vol. (000):	174.0
Cash (M):	$156
Cash/Share:	$5.24
Enterprise Value (M):	$785
Float (M):	14.6
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	$0.0	$0.0
	3Q	$0.0	$0.0	$0.0
	4Q	$0.0	$0.0	$0.0
	FY	**$0.0**	**$0.0**	**$0.0**
EPS	1Q	--	($0.46)A	--
	2Q	($5.39)	($0.44)	--
	3Q	($3.66)	($0.46)	--
	4Q	($0.47)	($0.53)	--
	FY	**($5.59)**	**($1.89)**	**($5.18)**

Source: Company reports and JMP Securities LLC

STOCK PRICE PERFORMANCE

INVESTMENT HIGHLIGHTS

Encouraging incremental activity from Selinexor dose escalation in NHL (DLBCL and CLL) and AML; we reiterate our Market Outperform rating and $50 price target on Karyopharm Therapeutics based on our DCF, CAGR, and SOTP methodologies.

Selinexor shows activity across all subtypes of NHL (Abstract #8518); we look forward to future data at doses above 45mg/m2. Data from this all-comers lymphoma study is impressive to us for two reasons: first, patients came into the study heavily pretreated (average three prior therapies, range 1-11) and progressing while on therapy, and; second, the data were generated in the dose escalation phase of study, with some patients receiving as little as 3mg/m2. Despite these limitations and an early 2014 data cut-off, the clinical benefit rate (CBR, PR+SD) was as high as 100% in certain subtypes (Figure 1). In the DLBCL subtype, three PRs and nine SDs were seen, vs. only five PD. Tolerability was as expected, with nausea and weight loss particularly prominent. However, Karyopharm has made recent adjustments to its protocols to include appetite stimulants and anti-nausea medications. We look forward to data at ASCO.

Abstract #8518. Oral presentation. Martin Gutierrez.

A phase 1 dose-escalation study of the oral selective inhibitor of nuclear export (SINE) KPT-330 (selinexor) in patients (pts) with heavily pretreated non-Hodgkin lymphoma (NHL).

Background: KPT-330 (Selinexor) is a SINE XPO1 antagonist that forces nuclear retention and activation of >10 tumor suppressor proteins (TSP) and associated with reduction in c-myc and Bcl-XL. Anti-NHL activity was observed in murine models and in spontaneous canine aggressive lymphomas.

Methods: Oral KPT-330 was given at 8-10 doses / 28-day cycle. XPO1 inhibition leads to rapid elevations in XPO1 mRNA, representing a pharmacodynamic (PDn) marker for KPT-330. Tumor biopsies were performed. Response evaluation was done in cycles 1, 2, and every 2 cycles. All patients had heavily pretreated NHL with progressive disease (PD) on study entry.

Results: Thirty-two pts (18 M, 14 F; median age 68 yrs; ECOG PS 0/1: 9/23; median prior regimens: 3 range 1-11) received KPT-330 across eight dose levels (3 to 60 mg/m2). Dosing at 60 mg/m2 twice weekly (BIW) is ongoing and MTD has not been reached. Cycle 1 (DLT period) Grade 3/4 events in >1 pt included thrombocytopenia (20%) and neutropenia (20%). The most common grade 1/2 AEs in cycle 1: anorexia (53%), nausea (50%), fatigue (50%), and vomiting (43%). Supportive care with appetite stimulants and anti-emetics diminished constitutional symptoms. Increases in XPO1 mRNA levels were observed at 4-48 hours, supporting BIW dosing.

Michael G. King, Jr.
mking@jmpsecurities.com
(212) 906-3520

Eric Joseph, PhD
ejoseph@jmpsecurities.com
(212) 906-3514

Tumor biopsies confirmed TSP nuclear localization, c-myc reduction, and apoptosis. Objective responses were observed in all histologies of NHL (Table). Five or sixteen pts have remained on therapy for an average of 9 months (>5-17) months without clinically significant toxicities.

Conclusions: KPT-330 is generally well tolerated and can be administered over prolonged periods. The recommended phase 2 dose is ≥45 mg/m^{2}BIW. Durable single agent activity was observed in heavily pretreated NHL pts, and phase 2 studies in DLBCL and Richter's Syndrome are planned.

FIGURE 1. Selinexor Phase I Activity in NHL

Response in 28 evaluable pts.

NHL	N	PR+SD (%)	PR (%)	SD (%) [%Change in LN Size]	PD
Follicular (FL)	6	6 (100%)	1 (17%)	5 (83%) [-17% to -44%]	–
Mantle Cell	2	2 (100%)	1 (50%)	1 (50%) [-36%]	–
DLBCL	14	9 (64%)	3 (21%)	6 (43%) [-12% to -19%]	5 (36%)
Transformed FL	3	1 (33%)	1 (33%)	–	2 (67%)
Richter's	3	3 (100%)	1 (33%)	2 (67%) [-22%]	–
Total	28	21 (75%)	7 (25%)	14 (50%)	7 (25%)

Source: Gutirrez M et al., ASCO '14

Impressive Phase I data of selinexor in heavily pretreated AML patients. We believe the results of this study are remarkable for the main reason that we cannot recall a study conducted with an experimental agent in AML in which the patient population had an average of three prior therapies. Despite this, selinexor managed to produce a CR/CRi rate of 12% (4/32 evaluable patients). An additional five patients had responses to varying degrees, amongst them two partial responses, while 12 patients (37%) had stable disease for more than 30 days. The highest dose received by patients in this study was 55mg/m2, suggesting that better results may be seen when a greater proportion of patients are treated at active doses above 45mg/m2.

Abstract #7032. Poster presentation. Karen Yee.

A phase 1 dose-escalation study of the oral selective inhibitor of nuclear export (SINE) KPT-330 (selinexor) in patients (pts) with relapsed/refractory acute myeloid leukemia (AML).

Background: KPT-330 (Selinexor) is a SINE XPO1 antagonist that forces nuclear retention and activation of >10 tumor suppressor proteins (TSP) and associated with reduction in c-myc and Bcl-X_L. Anti-NHL activity was observed in murine models and in spontaneous canine aggressive lymphomas.

Methods: Oral KPT-330 was given at 8-10 doses / 28-day cycle. XPO1 inhibition leads to rapid elevations in XPO1 mRNA, representing a pharmacodynamic (PDn) marker for KPT-330. Tumor biopsies were performed. Response evaluation was done in cycles 1, 2, and every 2 cycles. All pts had heavily pretreated NHL with progressive disease (PD) on study entry.

Results: Thirty-two pts (18 M, 14 F; median age 68 yrs; ECOG PS 0/1: 9/23; median prior regimens: 3 range 1-11) received KPT-330 across 8 dose levels (3 to 60 mg/m^2). Dosing at 60 mg/m^2 twice weekly (BIW) is ongoing and MTD has not been reached. Cycle 1 (DLT period) Grade 3/4 events in >1 pt included thrombocytopenia (20%) and neutropenia (20%). The most common grade 1/2 AEs in cycle 1: anorexia (53%), nausea (50%), fatigue (50%), and vomiting (43%). Supportive care with appetite stimulants and anti-emetics diminished constitutional symptoms. Increases in XPO1 mRNA levels were observed at 4-48 hours, supporting BIW dosing. Tumor biopsies confirmed TSP nuclear localization, c-myc reduction, and apoptosis. Objective responses were observed in all histologies of NHL (Table). 5/16 pts have remained on therapy for an average of 9 months (>5-17) months without clinically significant toxicities.

Conclusions: KPT-330 is generally well tolerated and can be administered over prolonged periods. The recommended phase 2 dose is ≥45 mg/m^{2}BIW. Durable single-agent activity was observed in heavily pretreated NHL pts, and phase 2 studies in DLBCL and Richter's Syndrome are planned.

Selinexor dose escalation in solid tumors confers increasing confidence in forthcoming Phase II signal finding studies. As with a number of other selinexor studies described in the ASCO abstracts, the greatest shortcoming of the incomplete datasets surrounds our lack of knowledge regarding the various numbers of patients treated at suboptimal (<50mg/m2) doses. Despite this, there are not only hopeful signs of activity in the form of partial responses, but also in a high degree of stable disease. Some, in particular, that caught our eye include five of five hormone and chemotherapy refractory prostate cancer patients who achieved prolonged stable disease, with patients on study 70-240+ days, nine of 13 patients with squamous cell cancer of the head and neck (SCCHN) who achieved stable disease with seven still on study 75-290 days, and three bona fide PRs in KRAS mutant colorectal cancer, BRAF wild-type melanoma, and ovarian adenocarcinoma. All adverse events were as previously described. The abstract indicates that Phase II studies are planned in SCCHN, ovarian, and prostate cancer.

Abstract #2537. Poster presentation. Morten Mau-Soerensen.
A first-in-class, first-in-human phase I trial of KPT-330 (selinexor), a selective inhibitor of nuclear export (SINE) in patients (pts) with advanced solid tumors.

Background: KPT-330 is an inhibitor of Exportin 1 (XPO1) that forces the nuclear retention and activation of over 10 Tumor Suppressor Proteins (TSPs) resulting in tumor cell death in preclinical models.

Methods: KPT-330 was administered orally for 8-10 doses in a 28-day cycles. Cycle 1 was the DLT period. Pharmacokinetic (PK) analyses were performed. XPO1 mRNA, a pharmacodynamic (PDn) marker of XP01 inhibition, was assessed in blood. Tumor biopsies were performed. Response was evaluated every 2 cycles (RECIST 1.1). All pts had to have documented progressive disease on study entry.

Results: 103 pts (59/44 M/F; median age 61 yrs; median treatment regimens: 3; ECOG PS 0/1: 24/79) received KPT-330 across 12 dose levels (3 to 65 mg/m^2) in dose escalation and expansion cohorts. 2 DLTs (fatigue, dehydration) at 40mg/m^2 on the 10-doses/cycle regimen; 1 DLT (nausea) at 35mg/m^2 on the 8-doses/cycle (twice weekly, BIW) regimen were noted. Dosing at 65mg/m^2 BIW is ongoing (MTD not reached). Grade 3/4 non-DLT, drug related, adverse events (AEs) in cycle 1 in >2 pts: hyponatremia (9%), fatigue (6%), thrombocytopenia (5%), vomiting (4%), anemia (3%), nausea (3%). The most common grade 1/2 AEs in cycle 1: nausea (63%), fatigue (52%), anorexia (42%) and vomiting (37%). The PK and PDn showed dose-dependent increases in C_{max} / $AUC_{0\text{-}inf}$ and XPO1 mRNA increases. Tumor biopsies showed nuclear localization of TSPs (p53, FOXO3A, IkB) and apoptosis induction. Of 87 response evaluable pts, three partial responses were observed in colorectal cancer (KRAS mutant), melanoma (BRAFwt) and ovarian adenocarcinoma (OvCa) pts. Stable disease (SD) was noted in 39 pts, with 12 pts for ≥6 months. Five of five evaluable pts with hormone and chemotherapy refractory prostate cancer (HRPC) achieved SD; all pts still on study 70-240+ days. Nine of 13 evaluable pts with squamous head and neck cancer (HNCa) achieved SD with seven on study 75-290+ days.

Conclusions: Oral KPT-330 has a manageable toxicity profile and prolonged dosing is feasible. Preliminary signals of durable antitumor activity were observed. The recommended dose for phase 2 is ≥50mg/m^2 BIW. Phase 2 studies in HNCa, OvCa, and HRPC are planned.

We are encouraged by the signs of activity across a wide range of tumor types, both solid and liquid, that are exemplified by the data in the ASCO abstracts. We believe Karyopharm is on the verge of bringing an entirely new class of chemotherapy agent to market with broad activity and acceptable tolerability. We remind the reader that Karyopharm holds the worldwide rights to selinexor. We encourage investors to build positions in the stock ahead of updated data presentations at both ASCO and EHA (European Hematology Association, June 12-15, Milan, Italy). We derive our price target through a synthesis of DCF, CAGR, and SOTP valuation methodologies.

FIGURE 2. Upcoming Catalysts

Timing	Drug	Catalyst
1H14	Selinexor	Initiation of first pivotal Phase II/III study in (elderly R/R AML)
1H14	Selinexor	Updated Phase I data in heme malignancy and solid tumors at ASCO (#2537, May 30, and #8518 and #7032, May 31)
1H14	Selinexor	Initiation of second Phase II trial in solid tumor indication (squamous cell cancer, head and neck, lung and esophageal cancer)
3Q14	Selinexor	Initiation of second pivotal Phase II/III study in (3L+ DLBCL)
2H14	KPT-350	IND completion for use in inflammation, auto-immune, and anti-viral indications
2H14	PAK Inhibitor	IND completion for use in oncology indications

Source: Company reports and JMP Securities LLC

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 their 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, we estimate that Karyopharm will end 4Q13 with approximately $153MM in cash and cash equivalents, which are adequate resources to fund operations into 2015, according to Karyopharm financial guidance. 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.

JMP FACTS AND DISCLOSURES

Analyst Certification:

The research analyst(s) who prepared this report does/do hereby certify that the views presented in this report are in accordance with my/our personal views on the securities and issuers discussed in this report. As mandated by SEC Regulation AC no part of my/our compensation was, is or will be directly or indirectly related to the specific views or recommendations expressed herein. This certification is made under the obligations set forth in SEC Regulation AC. Any other person or entity may not use it for any other purpose. This certification is made based on my/our analysis on the date of this report's publication. I/We assume no obligation to update this certification to reflect any facts,circumstances or events that may subsequently come to my/our attention. Signed Michael G. King and Eric Joseph

JMP Securities Disclosures:

JMP Securities currently makes a market in the security of Karyopharm Therapeutics Inc.

JMP Securities was manager or co-manager of a public offering of securities for Karyopharm Therapeutics Inc. (KPTI) in the past 12 months, and received compensation for doing so.

JMP Securities Investment Opinion Definitions:

Market Outperform (MO): JMP Securities expects the stock price to outperform relevant market indices over the next 12 months.

Market Perform (MP): JMP Securities expects the stock price to perform in line with relevant market indices over the next 12 months.

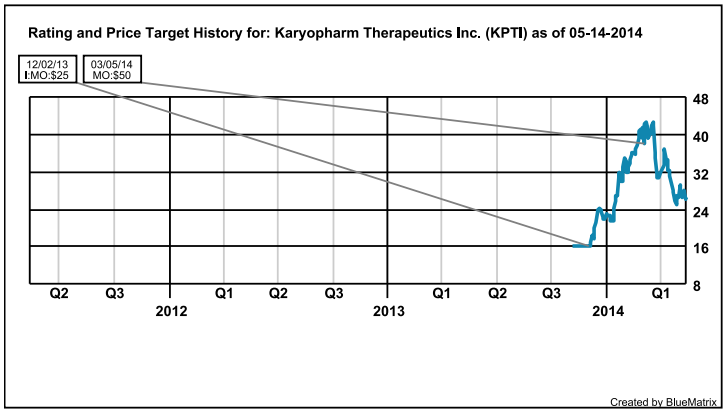
Market Underperform (MU): JMP Securities expects the stock price to underperform relevant market indices over the next 12 months.

JMP Securities Research Ratings and Investment Banking Services: (as of May 14, 2014)

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	255	*58.09%*	Buy	255	*58.09%*	98	*38.43%*
MARKET PERFORM	Hold	136	*30.98%*	Hold	136	*30.98%*	17	*12.50%*
MARKET UNDERPERFORM	Sell	5	*1.14%*	Sell	5	*1.14%*	0	*0%*
COVERAGE IN TRANSITION		43	*9.79%*		43	*9.79%*	0	*0%*
TOTAL:		439	*100%*		439	*100%*	115	*26.20%*

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.



JMP Disclaimer:

JMP Securities LLC (the “Firm”) compensates research analysts, like other Firm employees, based on the Firm’s profitability, which includes revenues from the Firm’s institutional sales, trading, and investment banking departments as well as on the quality of the services and activities performed that are intended to benefit the Firm’s institutional clients. These data have been prepared by JMP Securities LLC for informational purposes only and are based on information available to the public from sources that we believe to be reliable, but we do not guarantee their accuracy or completeness. Any opinions and projections expressed herein reflect our judgment at this date and are subject to change without notice. These data are neither intended nor should be considered as an offer to sell or a solicitation or a basis for any contract for the purchase of any security or other financial product. JMP Securities LLC, its affiliates, JMP Group LLC, Harvest Capital Strategies LLC, and their respective partners, directors, officers, and associates may have a long or short position in, may act as a market maker for, or may purchase or sell a position in the securities mentioned herein. JMP Securities LLC or its affiliates may be performing, have performed, or seek to perform investment banking, advisory, or other services and may have acted as manager or co-manager for a public offering of securities for any company mentioned herein. The reader should assume that JMP Securities LLC will solicit business from the company covered in this report. Members of our Sales and Trading Department provide oral and/or written market opinions and trading strategies to our clients that reflect their personal opinions about stocks that are the subject of the firm's research reports. Our research analysts discuss trading strategies with clients that sometimes reflect short-term expectations for the price of the securities that are the subject of research reports. These trading strategies are distinct from the analysts' fundamental rating for the stock, which is based upon the analysts' view compared to other stocks under coverage for the relevant time period. JMP Securities LLC is a member of FINRA, NASDAQ, and SIPC.

Jeffrey H. Spurr
Director of Research
(415) 835-3903

RESEARCH PROFESSIONALS

FINANCIAL SERVICES

Alternative Asset Managers
Devin Ryan (212) 906-3578
Brian McKenna (212) 906-3545

Commercial & Specialty Finance
Christopher York (415) 835-8965
Hannah Kim, CFA (415) 835-8962

Consumer Finance
David M. Scharf (415) 835-8942
Jeremy Frazer (312) 768-1796

Financial Processing & Outsourcing
David M. Scharf (415) 835-8942
Jeremy Frazer (312) 768-1796

Insurance
Matthew J. Carletti (312) 768-1784
Christine Worley (312) 768-1786

Investment Banks & Brokers
Devin Ryan (212) 906-3578
Brian McKenna (212) 906-3545

Mortgage Operating Companies
REITs: Agency, Hybrid, & Commercial Mortgage
Steven C. DeLaney (404) 848-7773
Trevor Cranston, CFA (415) 869-4431
Charter Robinson (757) 613-8955
Benjamin Zucker (212) 906-3529

HEALTHCARE

Biotechnology
Liisa A. Bayko (312) 768-1785
Heather Behanna, PhD (312) 768-1795
Andrew Prigodich (312) 768-1788
Jason N. Butler, PhD (212) 906-3505
Caroline Palomeque (212) 906-3509
Michael G. King, Jr. (212) 906-3520
Eric Joseph, PhD (212) 906-3514

Healthcare Services & Facilities
Peter L. Martin, CFA (415) 835-8904
Aaron Hecht (415) 835-3963
Arthur Kwok (415) 835-8908

Life Science Tools & Diagnostics
J. T. Haresco, III, PhD (415) 869-4477
Marie T. Casey, PhD (415) 835-3955

Medical Devices
J. T. Haresco, III, PhD (415) 869-4477
Marie T. Casey, PhD (415) 835-3955

Medical Devices & Supplies
David Turkaly (212) 906-3563
John Gillings (212) 906-3564

REAL ESTATE

Housing & Land Development
Peter L. Martin, CFA (415) 835-8904
Aaron Hecht (415) 835-3963
Bharathwajan Iyengar (415) 835-3902

Lodging & Leisure
Robert A. LaFleur (212) 906-3510
Whitney Stevenson (212) 906-3538

Property Services
Mitch Germain (212) 906-3546
Peter Lunenburg (212) 906-3537

REITs: Healthcare, Residential, & Specialty
Peter L. Martin, CFA (415) 835-8904
Aaron Hecht (415) 835-3963
Arthur Kwok (415) 835-8908

REITs: Office, Industrial, & Diversified
Mitch Germain (212) 906-3546
Peter Lunenburg (212) 906-3537

Residential Services
Peter L. Martin, CFA (415) 835-8904
Aaron Hecht (415) 835-3963
Bharathwajan Iyengar (415) 835-3902

TECHNOLOGY

Communications Equipment & Internet Security
Erik Suppiger (415) 835-3918
John Lucia (415) 835-3920

Internet & Digital Media
Ronald V. Josey III (212) 906-3528
Andrew Boone (415) 835-3957
Michael Wu (415) 835-8996

Software
Patrick Walravens (415) 835-8943
Peter Lowry (415) 869-4418
Caitlin Schields (415) 835-8960
Greg McDowell (415) 835-3934

Wireless & Cloud Computing Technologies
Alex Gauna (415) 835-8998

ADDITIONAL CONTACTS

Thomas R. Wright
Director of Equities
(212) 906-3599

Dan Wychulis
Director of Institutional Sales
(617) 235-8530

600 Montgomery Street, Suite 1100
San Francisco, CA 94111
www.jmpsecurities.com