William Blair

Tokai Pharmaceuticals, Inc.

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Highlights From Traveling With Management and ASCO-GU: Development Strategy Piques Investor and Academic Interest

We recently traveled with Tokai management to a number of investor meetings and attended the ASCO-GU conference (American Society of Clinical Oncology–Genitourinary Cancers Symposium, February 26-28, Orlando). **The tone of the investor meetings was positive, and addressing resistance to new blockbuster therapies such as Zytiga and Xtandi was the outstanding theme of the prostate cancer track at the GU conference. We came away with reaffirmed confidence in the company's ability to take its lead asset, galeterone, through the pivotal Phase III study and address an unmet need in the prostate cancer treatment paradigm.** Prominent topics discussed at the investor meetings and GU included: 1) the on-track development of the companion diagnostic for ARMOR3-SV, which should meet all the validation and consistency criteria; 2) the willingness of the Food and Drug Administration (FDA) to expedite the Phase III ARMOR3-SV study and of the European Medicines Agency (EMA) to concur with the FDA by accepting a single pivotal study for potential approval; 3) how galeterone is positioned with respect to the current market and other assets in development; and 4) the high interest at GU in researching resistance to Zytiga and Xtandi, and using AR-V7 as a potential predictive and prognostic marker in treating patients.

The galeterone development strategy has come together nicely in recent months, and management is confident in its potential to break into the prostate cancer treatment market by fulfilling an unmet need: M1 patients with the AR-V7 variant. Over the past year, an efficient path to potential approval was identified for galeterone; the niche population to conduct ARMOR3-SV in will be the chemo-naïve, metastatic castration-resistant prostate cancer (mCRPC) patients (or M1 patients) who express a splice variant of the androgen receptor (AR), AR-V7. M1 patients expressing AR-V7 are unresponsive to Xtandi (Astellas and Medivation [MDVN $121.05; Outperform]) or Zytiga (Johnson & Johnson [JNJ $103.22]). Although galeterone contains similar mechanisms to both drugs, it goes one step further with the additional ability to directly degrade the AR, including the AR-V7 variant. The Phase III ARMOR3-SV study is set to begin in first half 2015, with top-line data expected by the end of 2016.

Management commented on discussions with the FDA and EMA during the finalization of the ARMOR3-SV study design, which we believe confers a strong vote of confidence for galeterone.

- ***Single study to satisfy both FDA and EMA.*** In ARMOR3-SV, M1 patients harboring the AR-V7 variant will be randomized 1:1 to either galeterone or Xtandi with radiographic progression-free survival (rPFS), not overall survival (OS), as the primary endpoint, vastly reducing the study size and duration. We note that this is the first pivotal prostate cancer study to be granted rPFS over OS as the primary endpoint by the FDA. Recently, the EMA has also agreed that a single ARMOR3-SV study would be sufficient for EU approval. The support shown from regulatory authorities underscores the importance of the unmet need due to drug resistance, and galeterone could be an important player in fulfilling such need.

Tokai Pharmaceuticals, Inc. is a biopharmaceutical company based in Cambridge, Massachusetts, focused on the development of galeterone and an androgen receptor-degradation platform to address prostate cancer and potentially other hormone-driven cancers.

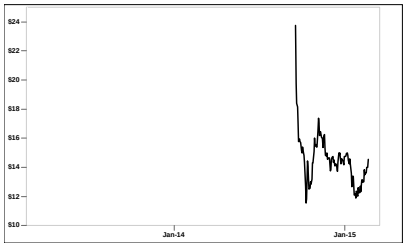
Stock Rating:	**Outperform**
Company Profile:	**Aggressive Growth**
Price Target:	$44.00
Symbol:	TKAI (NASDAQ)
Price:	$15.75 (52-Wk.: $10-$30)
Market Value (mil.):	$353
Fiscal Year End:	December
Long-Term EPS Growth Rate:	
Dividend/Yield:	None

	2013A	2014E	2015E
Estimates			
EPS FY	$-3.61	$-2.77	$-1.75
CY		$-2.77	$-1.75
Sales (mil.)	NA	0	0
Valuation			
FY P/E	NM	NM	NM
CY P/E		NM	NM

Trading Data (FactSet)	
Shares Outstanding (mil.)	2
Float (mil.)	10
Average Daily Volume	108,694

Financial Data (FactSet)	
Long-Term Debt/Total Capital (MRQ)	0.0
Book Value Per Share (MRQ)	4.7
Return on Equity (TTM)	-79.1

Two-Year Price Performance Chart



Sources: FactSet, William Blair & Company estimates

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- ***The CDRH (center for devices and radiological health) division of the FDA had agreed to exempt the investigational device exemption (IDE) application for the companion diagnostic assay that will accompany ARMOR3 to identify AR-V7 patients.*** We note that the IDE is equivalent to the IND (investigational new drug) application for a drug candidate. The exemption of IDE would save 30 days of review time and expedite the start of ARMOR3-SV.

- ***The size of the ARMOR3-SV study is now 148 patients, down from 170 previously.*** We note that ARMOR3-SV, with 148 patients, is 90% powered to detect 82% improvement in rPFS for galeterone over Xtandi in M1 patients with the AR-V7 variant. If a stratification factor is added to the design, the study size would be 170. As the company and the FDA jointly decided not to add stratification factors, the study size is now set at 148.

- ***Site set up.*** ARMOR3-SV will be conducted at 100 global centers, with no Asian sites.

- ***Number of M1 patients to screen.*** The prevalence of AR-V7 in the M1 setting has been reported in the range of 12% to over 20% from a number of small studies. Management is planning for a low 10% prevalence and prepared to screen 1,500 patients to enroll the target 148 patients. The scale of ARMOR3-SV will make it the best study to determine most accurately the prevalence of AR-V7 in the M1 population.

- ***High power to ensure high probability of success.*** In the Phase II single-arm ARMOR2 study, galeterone generated a time to PSA progression (TTTP) of 7.3 months in seven M1 AR-V7 patients, versus Xandi's 1.4 months in 12 patients as reported by Antonarakis et al. *(New England Journal of Medicine* 371:11; 1028-1038; 2014). For rPFS, it is not measured in galeterone-treated patients but was 2.1 months for the 12 Xtandi-treated patients. As TTTP is generally comparable to or shorter than rPFS, it is likely that the rPFS in the seven galeterone-treated patients was longer than 7.3 months. Although the aforementioned data was generated in very small number of patients, such sizable differential in rPFS (>7.3 months for galeterone versus 2.1 months for Xtandi) still bodes well for the ARMOR3-SV study, in our opinion. We assign 85% probability of success to the ARMOR3-SV study.

- ***Capital and time efficient path to first approval.*** The two recently conducted Phase III pivotal studies in the M1 setting, COU-AA-302 for Zytiga and PREVAIL for Xtandi, enrolled more than 1,000 and 1,700 patients, respectively, and had rPFS and OS as co-primary endpoints. Both studies took three to four years from start of enrollment to top-line data. In contrast, the FDA has approved Tokai to conduct a single pivotal study for galeterone in the same M1 setting, but specifically in the AR-V7 population and with rPFS as the primary endpoint; as a result, the target enrollment required is only 148. Such a design significantly reduces time and capital required for galeterone approval, as compared with the paths to approval taken by Zytiga and Xtandi.

  Assuming that the study is initiated in early 2015, Tokai guides top-line data release by the end of 2016, a relatively short period to conduct any Phase III oncology program, in our opinion. A new drug application (NDA) could be submitted in early 2017 and galeterone could hit the market in late 2017/early 2018, which represents a quick route to market. Furthermore, the 170-patient single pivotal study required for approval is also highly capital-efficient, as compared with most other Phase III oncology programs.

- ***High academic interest in resistance, personalized medicine, and companion diagnostics.*** Antonarakis et al. demonstrated that AR-V7 might be a predictive and prognostic marker for Zytiga and Xtandi resistance based on a 62-patient, single center study. Further, there are different types of assays being used currently to detect C-terminal loss and/or AR-V7 from patients' CTCs. To prospectively test the robustness of AR-V7 as a predictive and prognostic marker as well as to compare the different assay methods, a large prospective study (ClinicalTrials.gov NCT02269982) led by Duke University is now set up to validate Antonarakis's single-center experience; it will examine a broader array of AR mutations and splice variants in addition to AR-V7, and use at least two different AR-V7assays to correlate the molecular markers to clinical outcomes including rPFS and OS. This study will enroll 120 M1 patients.

Investors were focused on the progress of the companion diagnostic assay for ARMOR3-SV, as it is currently the bottleneck to initiating the study. The assay is going through final validation, and the FDA has signed off on the validation plan. Management commented that the consistency of the assay is excellent and is confident in being on track to start ARMOR3-SV in first half 2015.

- ***License from JHU and collaboration with Qiagen.*** Tokai recently announced that the company had licensed the AR-V7 assay from The Johns Hopkins University (JHU) and also had entered into an agreement with Qiagen (QGEN $25.01;

Market Perform) to create and execute a commercial companion diagnostic assay that would be used in ARMOR3-SV for the identification of patients carrying the AR-V7 variant. Qiagen or its affiliates will run the assays at four trial sites for ARMOR3-SV: two in the United States, one in the EU, and one in Australia. Qiagen is streamlining the assay, as the goal is to get the entire process down to a 48- to 72-hour turnaround time. The companion assay is on track to complete final validation in first half 2015, and ARMOR3-SV will immediately begin enrollment once the assay is in place.

- ***High consistency achieved and validation is to be completed soon.*** The companion diagnostic is a RT-PCR (reverse-transcriptase polymerase chain reaction) assay to quantify AR-V7 RNA in circulating tumor cells (CTCs) from the patient's blood. Management commented that to date the consistency of the assay was close to 100%; all patients whose CTCs had AR-V7 levels above a defined threshold via the assay were resistant to both Xtandi and Zytiga in the clinic.

- ***Cell-free method in development to test AR-V7 positivity in M0 patients***. The companion diagnostic to be used in ARMOR3-SV detects AR-V7 variants from the patients' circulating tumor cells (CTCs). For patients who are not yet metastatic such as M0 patients, there would be no CTCs to capture. Tokai commented that a cell-free assay is now in development with Qiagen to enable testing AR-V7 variants in M0 patients, so as to potentially push galeterone into this stage of patients in the future.

- ***AR-V7 screening could become standard of care.*** If ARMOR3-SV is successful, it is likely that AR-V7 screening becomes standard of care in M1 patients when selecting treatment options, in our opinion, and the next step would be to push galeterone earlier into the treatment paradigm.

Investors were acutely interested in the market potential and commercialization strategy of galeterone once approved. Estimates of M1 patients expressing the AR-V7 variant range from 12% to 26% of the 50,000-70,000 total M1 patients in the United States. Although this is a relatively small population, management noted that the AR-V7 indication is the beachhead strategy focus, used as a means to break into the prostate cancer treatment market. Once approved, the company will seek to begin label expansions into additional settings.

- ***A priority label expansion following first approval would be the urology setting.*** Management noted that even though Xtandi is making big pushes into the urology setting with multiple large studies ongoing, the seizure risk, although very low, might hold back its wider acceptance among urologists. Galeterone's lack of seizure risk and overall better safety profile could accelerate its penetrance into the large urology setting. Moreover, payers may push testing for AR-V7 into becoming a first step in the standard of care so as to streamline diagnosis and proper treatment and avoid paying for expensive drugs that may not work.

- ***A blue-sky scenario could be that galeterone, based on its superior resistance profile and comparable safety profile, will challenge Xtandi's foundational role in prostate cancer and becomes the frontline therapy.*** We believe that Xtandi is poised to start replacing Casodex, the most-prescribed prostate cancer drug with 600,000 annual scripts written in the United States. We believe that Xtandi could become a foundational therapy for prostate cancer based on its strong efficacy and benign safety profile. We project peak sales for Xtandi at $7.6 billion. Given its superior resistance profile, galeterone could have an advantage over Xtandi in the early settings, in our opinion, if galeterone demonstrates a comparable safety profile. Launching in early 2018, more than five years after Xtandi, galeterone could further move into earlier settings to challenge Xtandi's dominating position in the market, rivaling Xtandi as the next standard of care for prostate cancer.

- ***The only known competition in development that is similar to galeterone is a very early-stage compound from Essa Pharmaceuticals that we do not see as a threat.*** Essa, a private company, has drug candidates that target the N-terminus of the AR. This mechanism of action could overcome resistance issues as well. As the Essa candidates are not yet in the clinic, we do not see this as an immediate threat to galeterone.

The company reconfirmed that the current cash position would sustain operations through the top-line data release of the ARMOR3-SV study at the end of 2016. The company does not expect to partner out galeterone prior to Phase III data release. We believe that should ARMOR3-SV be successful, the most likely outcome is for Tokai to be acquired by a larger player in the field, who has the development and commercialization muscles to push galeterone and follow-on candidates from Tokai's AR degradation platform onto the market and expand their indications.

Key catalysts driving value in the next 12-24 months: 1) further data presentation of galeterone activity in AR mutations and variants at ASCO-GU later this month; 2) finalization of the companion diagnostic assay for ARMOR3-SV; 3) data presentation at ASCO in June; 4) initiation of the pivotal ARMOR3-SV study in chemo-naïve mCRPC patients with AR-V7 in first half 2015; 5) data presentation at ESMO in September; and 6) top-line data from ARMOR3-SV by the end of 2016.

We maintain our Outperform rating and price target at $44 (exhibit 1). Our Outperform rating is centered on our belief that Tokai's lead asset, galeterone, will become an essential component of the armamentarium against prostate cancer. We estimate worldwide sales for galeterone will reach $1.8 billion in the United States and Europe in 2027 in the AR-V7 variant population alone. Assuming an 85% probability of success, our probability-adjusted NPV model suggests a fair value for Tokai shares at $44.

Key risks to our Outperform rating and price target include: 1) clinical risk of the Phase III program; 2) regulatory risk related to receiving approval for galeterone in the United States and Europe; 3) development and approval of the companion diagnostic; 4) reimbursement risk; and 5) financing risk.

Exhibit 1
Tokai Pharmaceuticals, Inc.
Sum-of-the-Parts Fair Value
(dollars in thousands, except shares)

Drug	Peak Sales	Stage of Development	Estimated Launch Date	Probability of Commercialization	Percentage of Sales to Company	Probability-Adjusted NPV	Value per Share	Percentage of Fair Value
Galeterone	$ 1,814,414	Pre-Phase III	H1:2018	85%	100% US; 25% ex-US	$923,238	$41.78	94.5%
Subtotal						**$923,238**	**$41.78**	**94.5%**
Net Cash at year-end 2015						$61,539	$2.78	6.3%
Net Present Value of additional Gain (Loss)*						($8,000)	($0.36)	(0.8%)
Sum-of-Parts Fair Value						**$976,778**	**$44.20**	**100.0%**

Sources: William Blair & Company, L.L.C. estimates

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William Blair was a manager or co-manager of a public offering of equity securities for Tokai Pharmaceuticals, Inc. within the prior 12 months.

William Blair is a market maker in the security of Tokai Pharmaceuticals, Inc.

William Blair intends to seek investment banking compensation in the next three months from Tokai Pharmaceuticals, Inc.

Within the past 12 months William Blair has provided or is providing investment banking services to or has an investment services relationship with Tokai Pharmaceuticals, Inc.

Additional information is available upon request.

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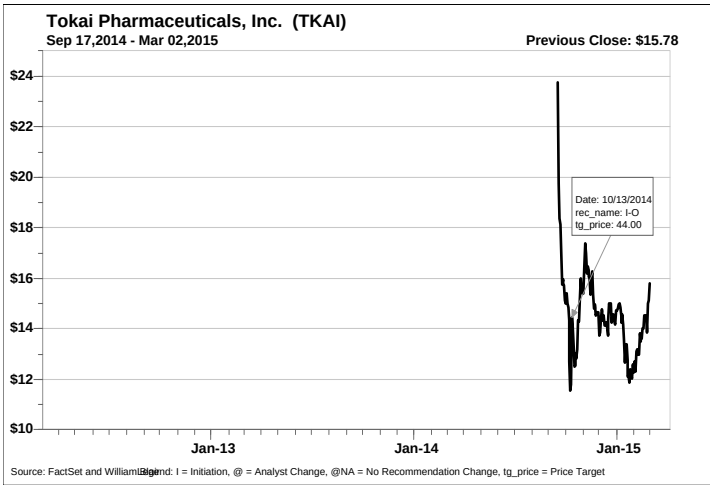
DOW JONES: 18,288.63
S&P 500: 2,117.39
NASDAQ: 5,008.10



Current Rating Distribution (as of 02/28/15)

Coverage Universe	Percent	Inv. Banking Relationships*	Percent
Outperform (Buy)	65	Outperform (Buy)	16
Market Perform (Hold)	32	Market Perform (Hold)	2
Underperform (Sell)	2	Underperform (Sell)	0

*Percentage of companies in each rating category that are investment banking clients, defined as companies for which William Blair has received compensation for investment banking services within the past 12 months.

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