# Tokai Pharmaceuticals

(TKAI-NASDAQ)

**Stock Rating:** **Outperform**
**Industry Rating:** **Outperform**

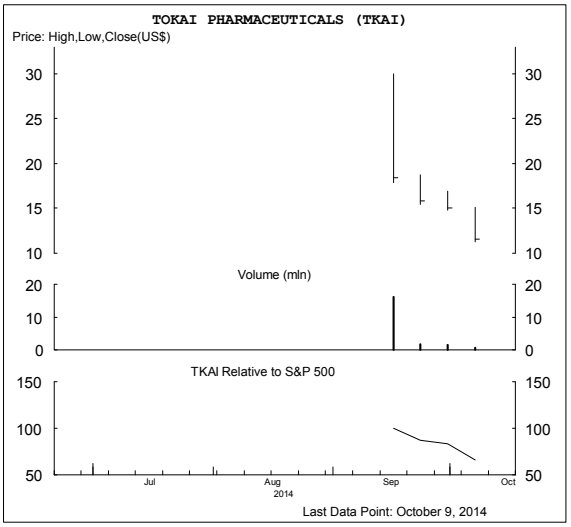
October 13, 2014

**Jim Birchenough, M.D.** **415-591-2129**
BMO Capital Markets Corp
jim.birchenough@bmo.com

Chuck Whitesell / Nick Abbott, PhD / Yanan Zhu, PhD
BMO Capital Markets Corp.
212-885-4120 / 206-542-2492 / 415-591-2141
charles.whitesell@bmo.com / nicholas.abbott@bmo.com / yanan.zhu@bmo.com

## Initiating With Outperform Rating on Galeterone Opportunity in CRPC

| | | | |
|---|---|---|---|
| **Price (10-Oct)** | $11.55 | **52-Week High** | $30.00 |
| **Target Price** | $28.00 | **52-Week Low** | $11.24 |




| (FY-Dec.) | 2012A | 2013A | 2014E | 2015E |
|---|---|---|---|---|
| **EPS** | - $2.97 | - $3.63 | - $2.55 | - $0.84 |
| **P/E** | | | na | na |
| **CFPS** | na | na | na | na |
| **P/CFPS** | | | na | na |
| **Rev. ($mm)** | $0 | $0 | $0 | $0 |
| **EV ($mm)** | na | na | $256 | $256 |
| **EBITDA ($mm)** | -$10 | -$16 | -$22 | -$23 |
| **EV/EBITDA** | na | na | na | na |

| **Quarterly EPS** | **Q1** | **Q2** | **Q3** | **Q4** |
|---|---|---|---|---|
| **2012A** | na | na | na | na |
| **2013A** | na | na | na | na |
| **2014E** | -$1.03a | -$1.03a | -$0.25 | -$0.25 |

| | | | |
|---|---|---|---|
| **Dividend** | $0.00 | **Yield** | 0.0% |
| **Book Value** | $0.90 | **Price/Book** | 12.8x |
| **Shares O/S (mm)** | 21.8 | **Mkt. Cap (mm)** | $252 |
| **Float O/S (mm)** | 6.5 | **Float Cap (mm)** | $75 |
| **Wkly Vol (000s)** | 6,539 | **Wkly $ Vol (mm)** | $138.7 |
| **Net Debt ($mm)** | -$21 | **Next Rep. Date** | na |

**Notes:** All values in US$
**First Call Mean Estimates:** Not Available

## Investment Thesis

We are initiating coverage on Tokai (TKAI) with an Outperform rating and $28 price target. Our favorable rating is supported by what we believe is a best-in-class profile for galeterone in castrate resistant prostate cancer (CRPC) and a favorable risk-reward proposition for phase 3 development, head-to-head against XTANDI in CRPC patients with ARV7 mutation. With 12% of the primary treatment-naive CRPC population expressing ARV7 mutation and not responsive to marketed drugs ZYTIGA and XTANDI, and with 67% of patients failing both ZYTIGA and XTANDI expressing ARV7 mutation, we believe that significant unmet need exists for a drug like galeterone with a unique triple mechanism of action, effects on androgen receptor degradation, and high response rate in patients harboring ARV7 mutation. Indeed, with a PSA50 response rate of 77% in treatment-naive metastatic CRPC patients, comparable to ZYTIGA and XTANDI rates of 79% and 62%, and with 6/7 patients with ARV7 mutation demonstrating PSA response to galeterone, we believe that a sufficiently differentiated profile has emerged already to support superiority to XTNADI and establish dominant positioning beyond patients harboring ARV7 mutation. We expect additional phase 2 data follow-up in 2015, phase 3 progress, and expansion into other indications like early-stage prostate cancer to support upside in TKAI shares and believe that valuation is attractive relative to a conservative peak sales opportunity of $554 million.

## Forecast & Valuation

We forecast losses annually for 2014-2018. We anticipate initial profitability in 2019 with EPS of $0.28. We arrive at our $28 price target by applying a 20x multiple to our 2020 EPS estimate of $4.25 and discounting at 30%.

## Valuation & Recommendation

We rate TKAI shares Outperform.

## Table of Contents

## Review of Financials

We estimate initial launch of galeterone in the U.S. in 2019 with $63 million in estimated sales, increasing to over $400 million in 2025. We anticipate an initial EU launch of Galeterone in 2019 with sales of $9 million, increasing to $60 million in 2025. We forecast initial profitability for TKAI in 2019 with EPS of $0.28. These 2019 earnings come on a revenue base of roughly $72 million. We expect this revenue stream to increase steadily to more than $460 million in 2025.

## Valuation

We arrive at our $28 price target by applying a 20x multiple to our 2020 EPS estimate of $4.25 and discounting at 30%.

Our sum-of-the-parts NPV analysis suggests a present value of roughly $16.50 per share for the product pipeline, including cash. Our product NPV is driven by estimates for Galeterone in the U.S. and EU. For Galeterone in the U.S., we assume launch in 2019 with 25% likelihood of success and a 10% discount rate. For Galeterone in the EU, we also assume launch in 2019 with 10% likelihood of success and a 10% discount rate.

We base our valuation of TKAI on a relative value P/E multiple on future earnings. We arrive at our $28 price target by applying 20x to our 2020 EPS estimate of $4.25 and discounting at 30% per year. Our $28 price target can also be supported by the probability-adjusted NPV of Galeterone in the U.S. and EU.

In evaluating development stage oncology comparables, we believe that Exelixis (EXEL), Infinity Pharmaceuticals (INFI), and Array BioPharma (ARRY) are the most suitable comparables with enterprise values (EV) of roughly $400 million, $500 million, and $400 million, respectively. At an EV of over $200 million, TKAI trades at a discount to the average EV of these oncology comparables.

## Risks

Risks to investment in development-stage biotechnology stocks include, but are not limited to, general development risk, clinical trial risk, regulatory risk, commercial risk, manufacturing risk, reimbursement risk, and patent risk. Risks to investment in TKAI include, but are not limited to, phase 2 PSA responses will not translate into PFS benefit in phase 3, benefit in ARV7 mutation may be overstated by small patient numbers, a commercially viable diagnostic based on circulating tumor cells (CTCs) may be more difficult to develop, phase 3 initiation could be delayed, additional capital may need to be raised to fund full galeterone approval and launch, and patent challenge beyond 2017 expiry of composition of matter claims.

## Exhibit 1: Tokai Pharmaceuticals Comps

| CANCER COMPANIES | | | | | | |
|---|---|---|---|---|---|---|
| **Company** | **Ticker** | **Market Cap (M)** | **Cash (M)** | **EV (M)** | **Stage of Development** | **Therapeutic Focus** |
| Array BioPharma | ARRY | $406.0 | $111.0 | $399.0 | Phase 2 | Cancer |
| Clovis Oncology | CLVS | $1,568.1 | $273.2 | $1,294.9 | Phase 3 | Cancer |
| Endocyte | ECYT | $223.5 | $121.1 | $102.5 | Phase 2 | Cancer |
| Exelixis | EXEL | $302.4 | $245.7 | $405.7 | Marketed | Cancer |
| Infinity Pharmaceuticals | INFI | $620.9 | $141.2 | $479.8 | Phase 3 | Cancer |
| Medivation | MDVN | $7,316.4 | $290.0 | $7,241.4 | Marketed | Cancer |
| Sunesis Pharmaceuticals | SNSS | $64.7 | $58.5 | $19.9 | Phase 3 | Cancer |
| Tesaro | TSRO | $949.4 | $151.1 | $798.3 | Phase 3 | Cancer |
| Mean | | $1,431.4 | | $1,342.7 | | |
| Median | | 513.5 | | 442.7 | | |
| Tokai Pharmaceuticals | TKAI | $240.5 | $21.2 | $219.3 | Phase 2 | Cancer |

| TOKAI PHARMACEUTICALS SUM-OF-THE-PARTS | | | | | |
|---|---|---|---|---|---|
| **Product & Indication** | **Market** | **Launch Year** | **Peak Sales ($M)** | **Probability** | **NPV ($M)** |
| Galeterone - Prostate Cancer | U.S. | 2019 | $481.6 | 25% | $285.7 |
| Galeterone - Prostate Cancer | EU | 2019 | 72.2 | 10% | 17.1 |
| **Total** | | | | | $302.8 |

Source: Company reports, Thomson Reuters, and BMO Capital Markets.

## Company Overview

Tokai is a development-stage biopharmaceutical company focused on developing novel therapies for the treatment of prostate cancer and other hormonally driven diseases. Its lead drug candidate for prostate cancer, galeterone, is a selective, multi-targeted, oral small-molecule drug candidate with a highly differentiated activity profile.

Galeterone acts by disrupting the androgen receptor (AR) signaling pathway, a key driver for prostate cancer cell growth. Male hormones (androgens), including testosterone and dihydrotestosterone (DHT), bind to the ligand-binding domain of AR in the prostate cancer cells and activate downstream signaling. Galeterone disrupts this process through multiple mechanisms of action, including (1) blocking CYP17, an enzyme necessary for the biosynthesis of testosterone; (2) blocking the binding of testosterone/DHT to the AR (i.e. AR antagonism); and (3) the degradation of the AR.

The mechanism of AR degradation distinguishes galeterone from all other therapies currently available for prostate cancer. As a result, galeterone could potentially address the unmet medical need in a population of castration-resistant prostate cancer (CRPC) patients who express a C-terminus truncated form of AR.

The C-terminus truncation deletes the ligand-binding domain, and as a result, the truncated AR protein is constitutively active, capable of driving prostate tumor cell proliferation and survival in the absence of androgens. C-terminal truncation of AR can result from alternative RNA splicing, with the most prevalent species responsible for C-terminal loss being the AR-V7 splice variant. AR-V7 and other C-terminal loss variants may present a challenge for existing therapies for CRPC, including recently approved drugs, ZYTIGA and XTANDI. These drugs target AR in a ligand-dependent manner, and therefore are not expected to be active against C-terminal loss AR variants. In a clinical study conducted at the Johns Hopkins University, CRPC patients with AR-V7 experienced worse outcomes in overall survival following treatment with ZYTIGA and XTANDI, compared with patients who did not have AR-V7.

Galeterone's ability to degrade ARs, including those with C-terminal loss, could represent a unique opportunity to improve the outcomes of patients whose tumors express C-terminal truncated ARs. Consistent with this hypothesis, a retrospective subgroup analysis of an ongoing phase 2 trial, ARMOR2, demonstrated meaningful PSA reductions in galeterone-treated patients that were retrospectively identified as having AR C-terminal loss.

Based on its discussion with FDA in August 2014, Tokai is currently finalizing its plan for ARMOR3-Splice Variant (SV), a pivotal phase 3 study of galeterone to support initial new drug approval. The ARMOR3-SV study will be a randomized, open label study comparing galeterone with XTANDI in up to 170 treatment-naïve metastatic CRPC patients whose prostate tumors express the AR-V7 splice variant. The primary endpoint of the study will be radiographic progress-free survival, and secondary endpoints will include reduction of PSA levels, overall survival and safety. Tokai expects to commence the ARMOR3-SV study in 1H15 and, subject to the rate of patient enrollment and disease progression, to have top-line data from the trial by year-end 2016.

Beyond the population of patients with AR C-terminal loss, galeterone's multi-targeted mechanisms of action may also provide advantage over existing therapies in other CRPC patient populations, for example by reducing the risk of developing resistance to therapy or providing efficacy in patients with tumors resistant to other treatments. The ongoing phase 2 ARMOR2 trial evaluates galeterone in multiple CRPC patient populations. Subject to the results of the ARMOR2 trial and the availability of resources, Tokai expects to continue the clinical development of galeterone in multiple CRPC populations, as well as in hormone-sensitive prostate cancer.

Initiated in December 2012, the ARMOR2 trial is a two-part phase 2 open label study of galeterone in CRPC. Part 1 of the trial was a dose escalation study designed to confirm the dose of galeterone to be evaluated in Part 2 of the trial. Tokai is currently conducting Part 2 of the trial, evaluating the 2,550 mg/day dose of galeterone in four distinct CRPC patient populations: treatment-naïve patients (no prior treatment with chemotherapy, ZYTIGA, or XTANDI) who are either non-metastatic or metastatic, and patients whose disease progressed during treatment with ZYTIGA (ZYTIGA-refractory) or XTANDI (XTANDI-refractory). Patients were treated with 2,550 mg/day galeterone for 12 weeks, and those who tolerated treatment and did not show signs of disease progression had the option of treatment continuation in an extension phase of the study.

Tokai announced interim data from the ARMOR2 trial at the American Society of Clinical Oncology (ASCO) 2014 Annual Meeting in May 2014, and provided additional updates at the European Society of Medical Oncology (ESMO) 2014 Congress in September 2014. The interim data included treatment-naïve CRPC patients and ZYTIGA-refractory patients. Tokai reported that, as of the August 15, 2014 cut-off date, galeterone demonstrated clinically meaningful reductions in PSA. Specifically, in all evaluable treatment-naïve CRPC patients (n=60), 83% and 70% of patients achieved maximal reduction in PSA levels of at least 30% and 50%, respectively, during the first 12 weeks of dosing. In metastatic treatment-naïve CRPC patients (n=39), 85% and 77% of patients achieved maximal reduction in PSA levels of at least 30% and 50%, respectively, during the first 12 weeks of dosing. Tokai also reported that 37% of ZYTIGA-refractory patients (n=30) and 44% of XTANDI-refractory patients (n=9) had a PSA decline during the treatment period.

Most importantly, a retrospective subgroup analysis of seven treatment-naïve CRPC patients with AR C-terminal loss demonstrated that six of these seven patients had a maximal PSA reduction of at least 50%. The seventh patient discontinued therapy after approximately six weeks due to an adverse event unrelated to galeterone; this patient did not receive the full treatment regimen and did not show any PSA reduction. Four of the six responders elected to continue into the optional extension phase of the study, and as of the data cut-off, the time on treatment for these patients in the extension phase ranged from 155 to 274 days.

Galeterone has been described as well tolerated in over 250 prostate cancer patients and healthy volunteers across Tokai's phase 1 and phase 2 clinical trials. Approximately 90% of adverse events reported in the ARMOR2 trial were classified as Grade 1 or 2 in severity and were generally manageable and reversible. Compared with ZYTIGA, which is associated with mineralocorticoid excess syndrome and requires co-administration of steroids, galeterone has not been shown in clinical trials to cause mineralocorticoid excess and does not require co-administration of steroids. Compared with XTANDI, which has antagonist activity on $GABA_A$ (an ion channel) and is associated with a risk for seizure, galeterone is not a $GABA_A$ antagonist, and there was no report of seizures in clinical trials of galeterone.

In June 2012, FDA granted galeterone Fast Track designation for the treatment of CRPC. The Fast Track designation is for products that are being investigated for the treatment of a serious or life-threatening disease with the potential to address unmet medical needs. The Fast Track designation allows for more frequent interactions between the sponsor and FDA, submission of some sections of the new drug application (NDA) for review before the whole application is complete (rolling review), and eligibility for priority review of the application (6-month review time vs. regular 10-month review time).

Prostate cancer represents a large and growing market. In the U.S. alone, an estimated 233,000 new cases of prostate cancer will be diagnosed in 2014, with an estimated 29,000 deaths from the disease. Sales of prostate cancer drugs are expected to increase from approximately $6.0 billion in 2013 to more than $9.0 billion in 2021, due to a growing aged population, rising incidence, and the introduction of new treatments. Two of the newly approved therapies for metastatic CRPC, ZYTIGA (approved in 2011) and XTANDI (approved in 2012), have both experienced rapid growth, with global sales of $1.7 billion and $445 million, respectively, in 2013. Despite the success of these new drugs, the need for new treatment options remains, as each of these drugs has treatment limitations and may not be effective in CRPC patients whose prostate tumors express AR with C-terminal loss.

Tokai has worldwide development and commercialization rights to galeterone. If galeterone is approved in the U.S., Tokai intends to build a urology/oncology-focused specialty sales organization to support the commercialization of galeterone in the U.S., and to seek collaboration with third parties to commercialize galeterone outside the U.S.

Tokai licensed galeterone from University of Maryland, Baltimore (UMB). The patent covering compositions and methods of use of a class of compounds encompassing galeterone is expected to expire in 2017. Tokai does not expect this patent to provide significant protection for galeterone, given its expiration date and the anticipated timing of development and commercialization of galeterone. Therefore, Tokai has no patent protection specifically covering the chemical structure of galeterone. Tokai has, however, filed for or licensed patents and patent applications covering methods of use, pharmaceutical compositions, combination treatments, prodrugs, metabolites, and analogs of galeterone and their use.

Beyond galeterone, Tokai plans to continue to identify and develop additional AR degradation agents under the exclusive license agreement with UMB.

# Prostate Cancer Primer

## Biology of Prostate Gland, Androgens, and Androgen Receptors

### Prostate Gland

The prostate gland is part of the male reproductive system. It resides at the base of the bladder and wraps around the urethra. The main function of the prostate is to produce fluid that protects and nourishes sperm. The fluid produced in the prostate, together with sperm cells from the testicles and fluids produced in other glands (e.g. seminal vesicles), makes up semen. The adult prostate gland is approximately the size of a walnut, and the size increases with age.

There are three layers (referred to as "zones") of the prostate tissue, which are the transitional zone (innermost), central zone, and peripheral zone (outermost). Prostate cancer most often develops in the outermost peripheral zone (70%), and less commonly in the transitional zone (20%) or the central zone (10%). In a common condition in older men known as benign prostatic hyperplasia (BPH), the innermost transitional zone, which surrounds the urethra, keeps growing and presses on the urethra, causing difficulties urinating. BPH is not cancer and does not turn into prostate cancer.

There are several cell types in the prostate, but nearly all (95%) prostate cancers start in the gland cells. The glandular tissue of the prostate is dependent on androgens (hormones that promote male characteristics) for normal growth and development.

### Androgens

Androgens are male sex hormones, with testosterone being the prototype. These hormones are produced mostly in the testes (90%) and to a lesser extent in the adrenal glands (10%). Androgens secreted by the testes include testosterone, dihydrotestosterone (DHT), and androstenedione. Androgens secreted by the adrenal gland include dehydroepiandrosterone (DHEA), DHEA sulfate, and androstenedione. Testosterone is the most abundant androgen in circulation, and often considered the primary androgen; however, most of the testosterone is ultimately converted into the more potent DHT in peripheral tissues, particularly in the prostate.

The testicular production of androgens is controlled by the hypothalamus and anterior pituitary gland in the brain. The hypothalamus secretes gonadotropin-releasing hormone, or GnRH, every 90 to 120 minutes. The pulsatile stimulation with GnRH leads to the production of two hormones in the anterior pituitary gland: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH mainly stimulates testosterone production, whereas FSH mainly stimulates spermatogenesis. LH is released into the blood stream and circulates to testes, where it activates Leydig cells, which produce testosterone. (Leydig cells accounts for 20% of the mass of the adult testes.) Once produced, testosterone exerts a negative feedback on GnRH production through androgen receptors expressed on the hypothalamus and pituitary glands.

Androgen production in the adrenal glands is controlled by the hypothalamus, which secretes corticotrophin-releasing hormone (CRH) to stimulate the pituitary to release adrenocorticotrophic hormone (ACTH). ACTH in turn stimulates the adrenal cortex to produce the adrenal androgen, DHEA. DHEA is converted to testosterone in target tissues.

Prostate is one of the organs most affected by androgens. In prostatic tissues, androgens signal through the androgen receptor (AR) to promote normal growth and homeostasis of the prostate gland. However, it has also been discovered that the AR signaling pathway is also a fundamental pathway driving tumor cell proliferation and survival in prostate cancer.

## Androgen Receptor

In the prostate, testosterone and DHEA are converted by 5α-reductase into DHT. Both DHT and testosterone can bind to and activate AR under physiological conditions, but DHT has a significantly higher affinity for AR than testosterone.

AR is a member of the steroid hormone nuclear receptor superfamily. The gene encoding AR is located on the X chromosome; therefore males only have one copy of the AR gene. The AR gene consists of 8 exons, encoding functionally distinct regions of the protein. The 919-amino acid AR protein consists of four structurally and functionally distinct domains, including an N-terminal domain (NTD) encoded by exon 1, a DNA-binding domain (DBD) encoded by exons 2 and 3, and a short hinge region and a C-terminal ligand-binding domain (LBD) encoded by exons 4-8.

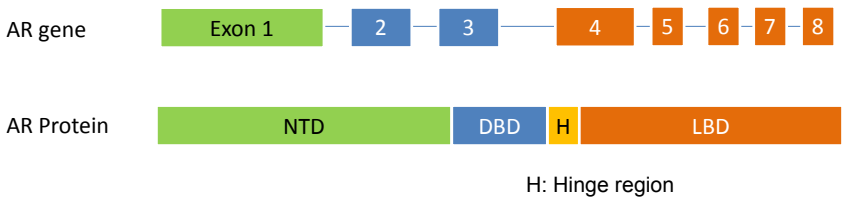
The NTD is the primary effector region. It contains an activation function 1 (AF1) domain, which is responsible for the majority of AR transcriptional activity through the recruitment of diverse co-regulatory proteins. In fact, the NTD is fully capable of initiating the assembly of the transcriptional complex, including binding to AR coactivators, even when the LBD is absent.

The DBD contains two zinc finger motifs. The first zinc finger mediates the recognition of the androgen response element (ARE) in the promoter and enhancer regions of target genes. The second zinc finger mediates AR dimerization.

The hinge domain provides flexibility to the protein and regulates the nuclear translocation of AR through a nuclear localization signal.

The LBD mediates binding of DHT and testosterone. It also contains a secondary transcriptional activation domain termed AF-2. Importantly, unlike other steroid hormone receptors in which AF-2 is the dominant transactivation domain, AF-2 plays mainly a regulatory role in AR, with AF-1 in NTD being responsible for the majority of AR transactivation in AR.

### Exhibit 2: Functional Domains of the Androgen Receptor




Source: BMO Capital Markets

In the absence of ligand, AR is maintained in an inactive state in the cytoplasm through the interaction with heat shock proteins and other chaperones. Binding of ligand induces a conformational change in AR, resulting in the dissociation of the chaperone proteins and the exposure of the nuclear localization signal in the hinge region. This in turn results in nuclear translocation.

Once in the nucleus, the AR DBD engages with genomic AREs and mediates chromosomal looping and structural reorganization of the genome. AR interacts with a large number of transcriptional co-regulators (~200 identified to date) and forms large complexes, which in turn recruit the basal transcriptional machinery and fulfill finely controlled androgen-responsive gene transcription. These androgen-responsive genes are important for normal homeostasis and function in healthy prostate tissue, but they can also drive prostate cancer growth by supporting the proliferation and survival of tumor cells.

Most prostate cancer cells are dependent on AR signaling for growth. For prostate cancer cases that are not amenable to surgery or radiation therapies, including locally advanced, relapsed, or metastatic prostate cancer, the standard of care is androgen deprivation therapy (ADT). In ADT, AR signaling is suppressed through one of several distinct mechanisms, including AR antagonism with antiandrogens (e.g. CASODEX), and reducing testosterone to castrate levels by surgery (bilateral orchiectomy) or with gonadotropin releasing hormone (GnRH) analogs.

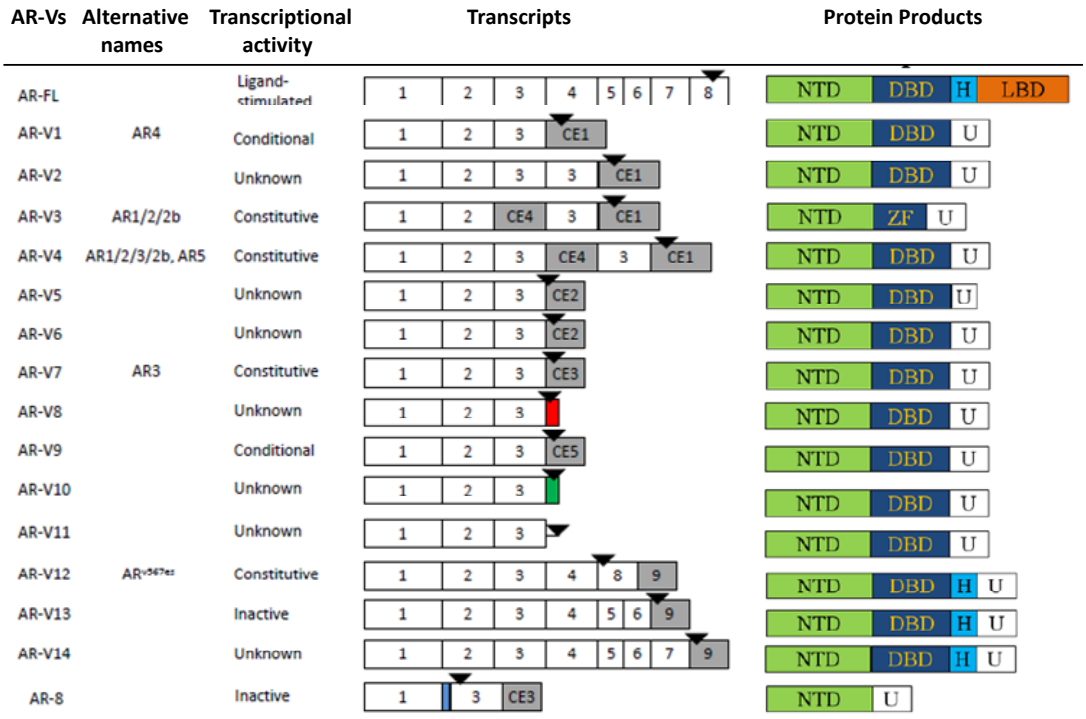
ADT initially provides a robust benefit in most prostate cancer patients, leading to clinical regression. However, AR signaling is inevitably reactivated over time, resulting in disease progression despite castrate levels of testosterone and marking the transition of the disease to castration-resistant prostate cancer (CRPC). Several mechanisms underlying resistance to ADT have been elucidated, including (1) increased production of testosterone and DHT, including by prostate cancer cells; (2) increased wild type or mutant AR levels; (3) alterations in AR such as splice variants and point mutations; (4) mutations in the AR that allow activation by other steroid hormones such as prednisone and progesterone; and (5) AR mutations that convert antiandrogens into AR agonists, leading to activation of the AR.

To address these mechanisms of disease progression, secondary hormonal treatments, such as XTANDI and ZYTIGA, have been developed. These therapies provided overall survival benefit of approximately four to five months in metastatic CRPC patients. However, a significant proportion of patients continue to experience disease progression, including 20-40% of patients who have primary resistance (rising PSA despite ZYTIGA or XTANDI therapy).

## AR C-Terminal Loss Splice Variants

One possible driver for resistance to XTANDI and ZYTIGA is the expression of AR splice variants, which result in truncated AR protein products that lack the LBD. More than a dozen such splice variants have been recently identified. The LBD is lost in these variants either because of insertions of cryptic exons immediately downstream of the exons 3 or because of deletions. As discussed earlier, the NTD and DBD domains of AR can function independently of the LBD and retain almost all of the full-length AR's transcriptional activity. Therefore, AR proteins with C-terminal loss are constitutively active, even in the absence of androgens. Tumor cells that express AR with C-terminal loss are not responsive to agents whose activity requires a functional ligand binding domain, such as XTANDI and ZYTIGA.

### Exhibit 3: Structures of AR Splice Variants




AR-FL: Full-length AR
CE: Cryptic exon
H: Hinge region
U: Unique sequence

Source: BMO Capital Markets, adapted from Zhang et al, *Am J Clin Exp Urol* 1:18, 2013 and from Lu et al, *Trans Androl Urol* 2:178, 2013

One of the C-terminal loss splice variants, AR-V7, is of particular interest, because it is the most abundant and the only known AR splice variant with a protein product that is detectable in clinical specimens. AR-V7 has been shown to be capable of regulating target gene expression in the absence of full-length AR. Another AR splice variant, $Ar^{v567es}$, also known as AR-V12, has also demonstrated similar unequivocal constitutively active activity. Other AR splice variants may be active only in certain specific cell lines. For example, AR-V1 and AR-V9 are not active in cells that do not express full-length AR (e.g., the PC-3 cell line).

In clinical specimens, AR splice variants coexist with full length AR. The expression levels of individual AR variants normally accounts for a small fraction of that of full-length AR. Expression of AR splice variants have also been found in benign prostate epithelium.

## AR-V7 and Resistance to ZYTIGA and XTANDI

Emerging evidence from clinical studies suggests that CRPC patients with tumors expressing AR-V7 respond poorly to secondary hormonal treatments, including ZYTIGA and XTANDI.

Researchers at the Johns Hopkins University have conducted a prospective study to evaluate the ability of baseline AR-V7 status, as measured in circulating tumor cells (CTCs), to predict response or resistance to ZYTIGA or XTANDI. The study enrolled mCRPC patients who were

beginning standard-of-care treatment with XTANDI or ZYTIGA. Prior chemotherapy was permitted. Prior XTANDI therapy was permitted if the patient was to be assigned to receive ZYTIGA, and vice versa. The study screened 71 men to identify 62 patients with detectable CTCs. The 62 patients were assigned to receive either ZYTIGA (n=31) or XTANDI (n=31). At baseline, a total of 18 patients had detectable AR-V7 in CTCs, including 12 patients assigned to receive XTANDI and 6 patients assigned to receive ZYTIGA. The ratio of AR-V7 to full-length AR mRNA ranged from 1.8% to 208%, with a mean of 21%.

The primary endpoint of the study was the proportion of patients with a PSA response, defined as ≥50% decline in PSA from baseline, maintained for ≥4 weeks. **In the XTANDI cohort, 0% of AR-V7-positive patients had a PSA response, vs. 53% of AR-V7-negative patients (p=0.004).** In addition, AR-V7-positive patients also had shorter PSA progression-free survival (1.4 months vs. 6.0 months, p<0.001), clinical or radiographic PFS (2.1 months vs. 6.1 months, p<0.001), and overall survival (5.5 months vs. not reached, p=0.002) compared with AR-V7-negative patients. **In the ZYTIGA cohort, 0% of AR-V7-positive patients had a PSA response, vs. 68% of AR-V7-negative patients (p=0.004).** In addition, AR-V7-positive patients also had shorter PSA progression-free survival (1.3 months vs. not reached, p<0.001), clinical or radiographic PFS (2.3 months vs. not reached months, p<0.001), and overall survival (10.6 months vs. not reached, p=0.006) compared with AR-V7-negative patients.

Conversion of AR-V7 status was also studied. All patients who were AR-V7-postive at baseline remained positive. Of 42 patients who were AR-V7-negative at baseline who had follow-up samples available, 6 patients (4 receiving XTANDI and 2 receiving ZYTIGA) subsequently converted to AR-V7-positive status during the course of treatment (mean follow-up ~5 months).

Researchers at MD Anderson Cancer Center have conducted a phase 2 study that assessed expression of molecular components of AR signaling in bone marrow-infiltrating CRPC cells and associated this with clinical findings following treatment with XTANDI. Most of the patients enrolled had prior chemotherapy and several lines of hormonal treatments. AR-V7 protein was detected by immunohistochemistry on bone marrow biopsy using a monoclonal antibody specific for AR-V7. Of 7 patients who tested as AR-V7 positive at baseline, 86% had primary resistance (symptomatic/imaging progression within 4 months of study entry), and 14% had moderate benefit (on treatment 4-6 months). In contrast, of 16 patients who were tested as AR-V7 negative, 38% had primary resistance, 31% had moderate benefit, and 31% had prolonged benefit. In another study conducted by the same group that evaluated a sequential combination regimen of ZYTIGA and XTANDI, 2 patients were tested as having AR-V7 and another 2 patients were tested as having C-terminal loss; all 4 patients (100%) had primary resistance to the combination regimen. In contrast, of 11 patients who were tested negative for AR-V7 and C-terminal loss, 18% had primary resistance and 82% had treatment benefit.

### Exhibit 4: AR-V7 Expression Predicts Resistance to ZYTIGA and XTANDI

**Johns Hopkins Study**

| Treatment[1] | Baseline AR-V7+ | Response | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | AR-V7 status | PSA50 | P- value | rPFS | P- value | OS (95% CI) | P value |
| Abiraterone (N=31) | 19% (6/31) | + | 0% (0/6) | .004 | 2.3 mos | <.001 | 10.6 mos (8.5–NR) | .002 |
| | | – | 68% (17/25) | | >6.3 mos | | >11.9 mos (11.9–NR) | |
| Enzalutamide (N=31) | 39% (12/31) | + | 0% (0/12) | .004 | 2.1 mos | <.001 | 5.5 mos (3.9–NR) | .006 |
| | | – | 53% (10/19) | | 6.1 mos | | NR (NR–NR) | |

| Patient Treatment Status[2] | Before enzalutamide or abiraterone | Post enzalutamide | Post abiraterone | Post abiraterone & enzalutamide |
|---|---|---|---|---|
| AR-V7 Prevalence | 12% | 25% | 51% | 67% |

**MD Anderson Study**

| Enzalutamide[1] | | | | |
|---|---|---|---|---|
| | N | Primary Resistance[a] | Benefit | |
| | | | Moderate[b] | Prolonged[c] |
| AR-V7 Positive | 7 | 86% | 14% | 0% |
| AR-V7 Negative | 16 | 38% | 31% | 31% |

| Sequential Combination Abiraterone and Enzalutamide[2] | | | |
|---|---|---|---|
| | N | Primary Resistance | Benefit |
| AR-V7 Positive | 2 | 100% | 0% |
| C-terminal loss | 2 | 100% | 0% |
| No AR-V7 or C-terminal loss | 11 | 18% | 82% |

Source: Tokai Pharmaceuticals

## Epidemiology of Prostate Cancer

Prostate cancer is the second most commonly diagnosed malignancy in American men and the second leading cause of cancer death in this population. The American Cancer Society estimates that approximately 233,000 new cases of prostate cancer will be diagnosed in the U.S. in 2014, and approximately 29,000 men will die from the disease. Overall, about 1 in 7 men will be diagnosed with prostate cancer in his lifetime, and about 1 in 36 men will die from the disease. In the U.S., African-American men are at higher risk of developing prostate cancer and dying of the disease compared with men of other races. Prostate cancer occurs mainly in older men, with a median age of 66-70 years at diagnosis.

Advances in screening and diagnosis, especially the widespread PSA screening, have allowed detection of the disease in its early stages, when the tumor cells are confined to the prostate gland and its immediate surroundings. Currently, approximately 85% of all prostate cancer cases diagnosed in the U.S. are early stage diseases.

The majority of patients with early-stage prostate cancer are cured with surgery and/or radiation therapy. For the rest of the patients, prostate cancer ultimately recurs. In addition, approximately 15% of patients diagnosed with prostate cancer have metastatic disease at the time of diagnosis. Patients whose cancer recurs and those who have metastatic disease are considered to have advanced prostate cancer, and these patients have to be treated with drug therapy. **It is estimated that 310,000 men in the U.S. have advanced prostate cancer and are eligible for treatment with drug therapy.**

## Diagnosis of Prostate Cancer

Symptoms of prostate cancer can include erectile dysfunction, blood in the semen, pain in the lower back, hips and/or upper thighs, urinary problems, or enlargement of the prostate. Patients whose cancer has metastasized to the bones may also have bone pain or fracture.

Early prostate cancer usually causes no symptoms, and most prostate cancers are discovered incidentally during routine screenings, including PSA testing and digital rectal exams (DRE).

### PSA Testing

PSA is an enzyme (more specifically a serine protease) produced by the prostate. PSA is mostly found in semen, but a small amount of PSA is also found in the blood. Normal serum PSA values range from 0 to 4 ng/mL depending on age and ethnicity. Because cancerous cells in the prostate gland also produce PSA, the serum PSA levels usually rise above 4 ng/mL when prostate cancer develops. With a PSA value between 4 and 10, there is a 25% chance of having prostate cancer; if the PSA value is greater than 10, the chance of having prostate cancer is greater than 50%.

However, rising PSA levels are not specific to prostate cancer, and other conditions that may result in increases in PSA levels include benign prostatic hyperplasia (BPH), inflammation of the prostate, prostatic infection, urinary retention, and prostatic manipulation.

The widespread use of PSA screening has led to an increase in the diagnosis of early stage prostate cancer, and the mortality rate of prostate cancer has declined 40% since the advent of PSA screening two decades ago. However, PSA testing has also led to the diagnosis and treatment of many men with very low grade cancers that would not have required treatment if left undetected.

### Digital Rectal Examination

Digital rectal examination (DREs) is a physical examination of the prostate via the rectum for any bumps, enlargements, or suspicious hard areas. DREs lack sensitivity and may miss early prostate cancer tumors, and should be used in conjunction with other diagnostic tests when screening for prostate cancer.

Although screening is helpful in identifying suspected prostate cancers, the actual diagnosis can only be made with a histologic evaluation of prostate tissue sampled from a prostate needle biopsy. The procedure is most often performed under transrectal ultrasonographic guidance.

## Staging of Prostate Cancer

The most widely used staging system for prostate cancer is the American Joint Committee on Cancer (AJCC) TNM staging system. The TNM staging system is based on five factors: (1) the evaluation of the primary tumor (T category); (2) whether the cancer has spread to regional (nearby) lymph nodes (N category); (3) whether there is evidence of distant metastasis (M category); (4) the PSA level at the time of diagnosis; (5) the Gleason score based on the prostate biopsy or surgery.

## The TNM Staging System

### T Category

- T1: Tumor present, but the physician cannot feel the tumor or see it with imaging such as transrectal ultrasound.
    - T1a: tumor was found incidentally during a transurethral resection of the prostate (TURP), a surgery procedure for the treatment of BPH. Tumor is ≤5% of the tissue removed.
    - T1b: tumor was found incidentally during a TURP, and is >5% of the tissue removed.
    - T1c: Tumor was found by needle biopsy that was done because of an elevated serum PSA.
- T2: Tumor can be felt on examination or seen with imaging such as transrectal ultrasound, but has not spread outside the prostate.
    - T2a: Tumor is in ≤ half of one of two lobes of the prostate gland.
    - T2b: Tumor is in > half of one lobe, but not both.
    - T2c: Tumor is in both lobes of the prostate gland.
- T3: Tumor has spread through the prostate capsule
    - T3a: Tumor has spread outside the prostate but not to the seminal vesicles.
    - T3b: Tumor has spread to the seminal vesicles.
- T4: Tumor has invaded other nearby tissues, such as the urethral sphincter, the rectum, the bladder and/or the wall of the pelvis.

### N Category

- NX: Nearby lymph nodes were not assessed.
- N0: Tumor has not spread to any nearby lymph nodes.
- N1: Tumor has spread to ≥1 nearby lymph nodes in the pelvis.

### M Category

- M0: There is no distant metastasis (beyond nearby lymph nodes)
- M1: There is distant metastasis
    - M1a: Cancer has spread to distant lymph nodes (outside of the pelvis).
    - M1b: Cancer has spread to the bones.
    - M1c: Cancer has spread to other organs such as lungs, liver, or brain (with or without spread to the bones).

## The Gleason Scoring System

The Gleason scoring system, developed in the early 1970s, has become the preferred histological grading system of prostate cancer. The Gleason system is based upon the degree of loss of normal glandular tissue structure. This system assigns a grade to each of the two largest areas in a biopsy. Grades range from 1 to 5, based on how much the cells in the cancerous tissue look like normal tissue. The two numbers are added together to yield the Gleason Score.

The higher the Gleason score, the more likely the cancer will grow and spread quickly. Cancers with a Gleason score ≤6 are called well differentiated or low grade; cancers with a score of 7 are considered moderately differentiated or intermediate grade; cancers with a score of 8-10 are called poorly differentiated or high grade.

## Stage Grouping

To assess the overall stage of the disease, the T, N, and M category scores are combined with the Gleason score and PSA results, a process called stage grouping. If the Gleason score or PSA results are not available, the staging can be based on the T, N, and M categories.

### Stage I

- T1-T2a, N0, M0, Gleason score ≤6, PSA <10.
    - The tumor was found incidentally or by needle biopsy done for a high PSA, and the doctor cannot feel the tumor or see it with transrectal ultrasound. The tumor is still within the prostate and has not spread to nearby lymph nodes or elsewhere in the body. The Gleason score is 6 or less and the PSA level is less than 10.

### Stage IIA

- T1, N0, M0, Gleason score of 7, PSA <20, or
- T1, N0, M0, Gleason score ≤6, 10≤ PSA <20, or
- T2a/T2b, N0, M0, Gleason score ≤7, PSA <20.

### Stage IIB

- T2c, N0, M0, any Gleason score, any PSA, or
- T1 or T2, N0, M0, any Gleason score, PSA ≥20, or
- T1 or T2, N0, M0, Gleason score ≥8, any PSA.

### Stage III

- T3, N0, M0, any Gleason score, any PSA.

### Stage IV

- T4, N0, M0, any Gleason score, any PSA, or
- Any T, N1, M0, any Gleason score, any PSA, or
- Any T, any N, M1, any Gleason score, any PSA.

Stage I and stage II are also referred to as "local stage," because the cancer has not spread outside the prostate. Approximately 80% of prostate cancers are found in local stage. State III cancers, as well as the stage IV cancers that have not spread to distant parts of the body, are referred to as "regional stage" diseases. The remaining stage IV cancers, including those that have spread to distant lymph nodes or other organs, are referred to as "distant stage" disease.

## Prognosis

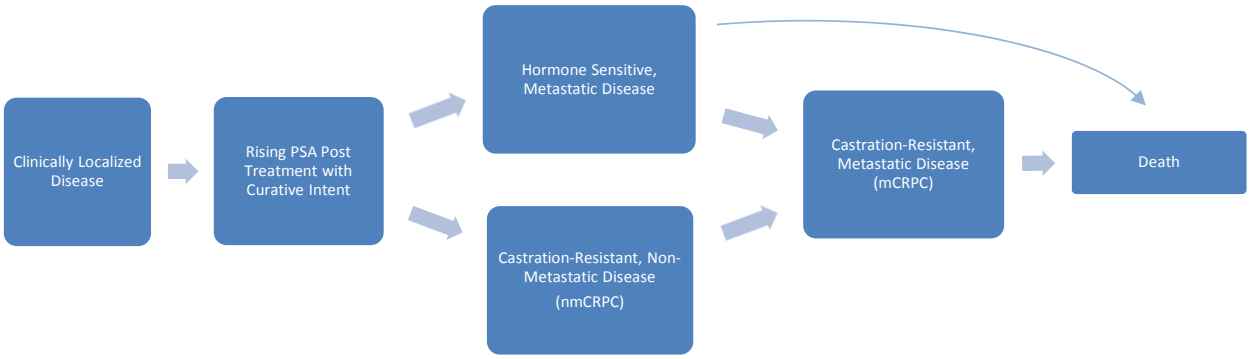
Prostate cancer has one of the highest survival rates of any cancer, with an overall relative five-year survival rate of 99%. The high survival rate can be attributed to several factors: (1) prostate cancer is frequently slow-growing and slow to spread; (2) prostate cancers are also often diagnosed at early stages, thanks to PSA screening; (3) prostate cancers occur in older men, with a median age at diagnosis of 70 years, therefore many patients die from other causes long before prostate cancer becomes life-threatening.

Overall, the relative five-year survival rate for all prostate cancer patients is 99%, and the relative 10-year survival rate is 91%. Local and regional stage prostate cancers have a five-year survival rate of essentially 100%. Distant stage prostate cancer, however, has a much poorer prognosis, with a five-year survival rate of approximately 30%.

## Prostate Cancer Clinical States

Patients with prostate cancer pass through a long disease process that can be summarized as several clinical states. Following a diagnosis of localized or locally advanced disease, patients are placed on active surveillance/observation or are treated with local therapies with curative intent. After treatment, some patients experience PSA relapse, and are subsequently treated with androgen-deprivation therapy (ADT), also known as hormone therapy. Most patients initially respond to primary ADT; however, despite this treatment, most patient eventually experience disease progression within 18-24 months, as manifested by rising PSA, increasing tumor size, or new metastases. This represents the lethal form of the disease and is referred to as castration-resistant prostate cancer (CRPC). Exhibit 5 depicts the various clinical states of prostate cancer.

**Exhibit 5: Clinical States of Prostate Cancer**




Source: BMO Capital Markets, adapted from Silberstein et al., *Transl Androl Urol* 2:122, 2013 and Drake, *Nat Rev Immunol* 10:580, 2010

## NCCN Treatment Guidelines for Prostate Cancer

This section focuses on the overall treatment guideline for prostate cancer recommended by the National Comprehensive Cancer Network (NCCN). Major treatment modalities mentioned in this section are further elucidated in two later sections entitled *Treatment Options for Hormone-Sensitive Prostate Cancer* and *Treatment Options for Castration-Resistant Prostate Cancer*.

### NCCN Risk Groups

NCCN has designated six risk groups in prostate cancer: Very low risk, Low risk, Intermediate risk, High risk, Very high risk, and Metastatic diseases. These risk groups predict treatment outcomes well and provide a better basis for treatment recommendation than just the stage of the cancer.

Diseases that fall into the first four risk groups are clinically localized disease. Very low risk disease is characterized by T1c tumor, Gleason score ≤6, PSA <10 ng/mL, fewer than 3 prostate biopsy cores positive, ≤50% cancer in each core, and PSA density <0.15 ng/mL/g. Low risk disease is characterized by T1-T2a tumor, Gleason score ≤6, PSA <10 ng/mL. Intermediate disease is characterized by T2b-T2c, or Gleason score =7, or PSA 10-20 ng/mL. High risk diseases is characterized by T3a or Gleason score 8-10, or PSA >20ng/mL.

Very high risk disease is locally advanced disease, and is characterized by T3b-T4 tumor. Metastatic disease is characterized by N1 or M1 tumor.

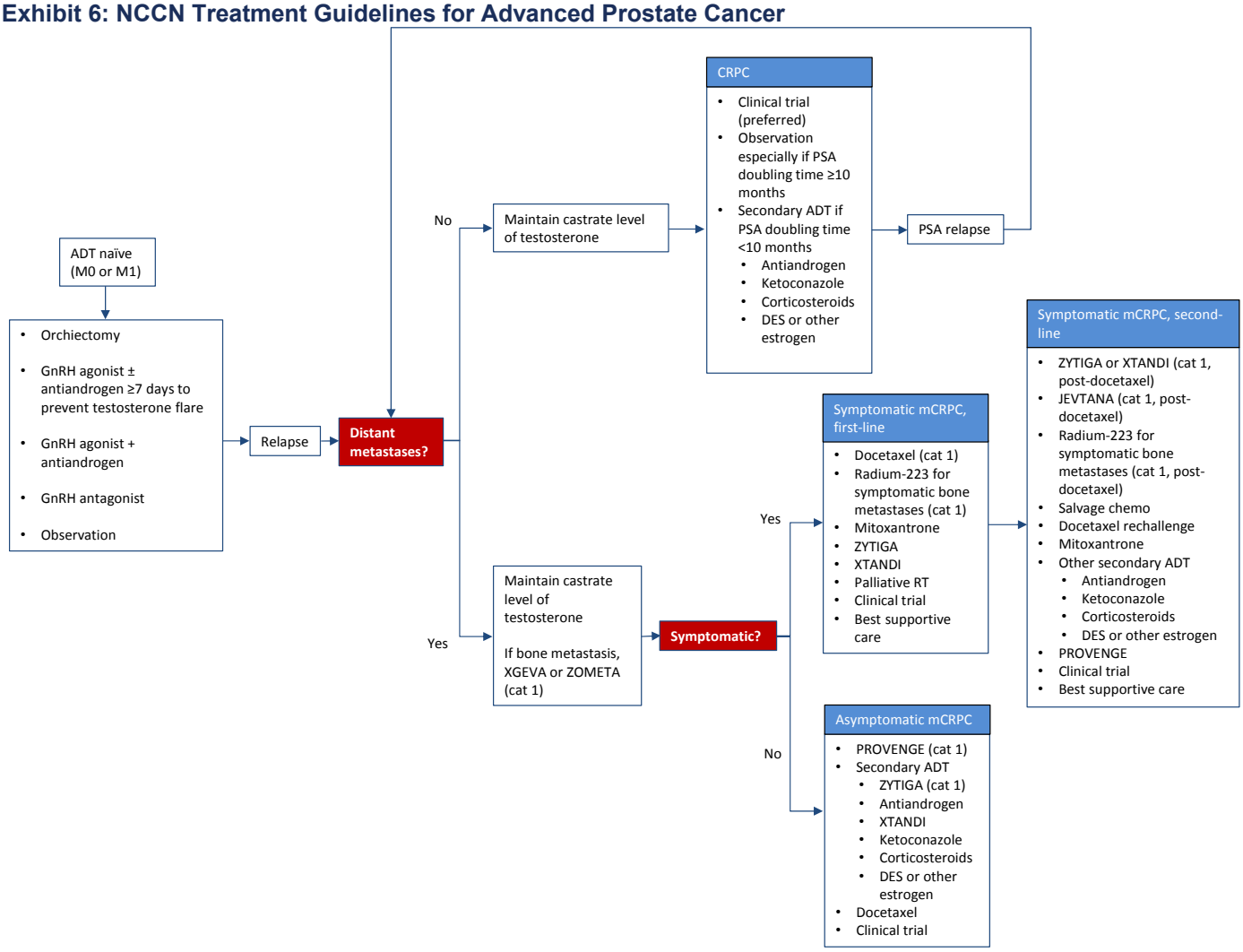
### NCCN Treatment Guidelines

#### Localized Disease

For very low risk disease, NCCN recommends active surveillance (for patients with life expectancy ≥10 years) or observation (for patients with life expectancy <10 years). Patients with life expectancy ≥20 years have the additional options of undergoing radiation therapy (RT), brachytherapy, or radical prostatectomy (RP).

For low risk disease, NCCN recommends activate surveillance (for patients with life expectancy ≥10 years) or observation (for patients with life expectancy <10 years). Patients with life expectancy ≥10 years have the additional options of undergoing RT, brachytherapy, or RP.

## Exhibit 6: NCCN Treatment Guidelines for Advanced Prostate Cancer




Cat 1 = Recommendation based on Category 1 evidence; All other recommendations are based on Category 2A evidence

Source: BMO Capital Markets and NCCN

For Intermediate risk disease, patients with life expectancy ≥10 years have the options of undergoing RP, or RT ± ADT (4-6 months) ± brachytherapy, or brachytherapy alone. Patients with life expectancy <10 years have the options of observation, or RT ± ADT (4-6 months) ± brachytherapy, or brachytherapy alone.

For high risk and very high risk disease, initial treatment options include RT + ADT (category 1), RT + brachytherapy ± ADT (2-3 years), or RP + pelvic lymph node dissection (PLND).

For metastatic disease, initial treatment options include RT + ADT (category 1) or ADT for patients with N1 tumor, and ADT for patients with M1 tumor.

Note that "Category 1" designates treatment options that have high-level evidence and uniform NCCN consensus that the treatment is appropriate. Category 1 recommendations are the highest awarded. Unless otherwise specified, all treatment options described are Category 2A recommendations, which are based on lower-level evidence, but also have uniform NCCN consensus that the treatment is appropriate.

### Advanced Disease

Advanced disease refers to patients who present with locally advanced or metastatic disease at diagnosis or those with recurrent cancer (either locally or systematically) following definitive therapy.

Patients with advanced disease who have not been treated with ADT have the following treatment options: (1) orchiectomy; (2) GnRH agonist with or without antiandrogen for at least 7 days to prevent flare; (3) GnRH antagonist; (4) combined androgen blockade (CAB); (5) observation for asymptomatic patients without metastasis.

Prostate cancer that recurred during ADT is referred to as castration-resistant prostate cancer (CRPC). For CRPC patients without metastasis (M0), clinical trial is the preferred choice. Other treatment options include observation for patients with PSA doubling time ≥10 months, and secondary hormonal treatments for patients with PSA doubling time <10 months (because the androgen receptor may still be active).

ZOMETA (zoledronic acid) every 3 to 4 weeks or XGEVA (denosumab) 120 mg every 4 weeks is recommended for CRPC patients with bone metastases to prevent or delay disease-associated skeletal-related events (SREs), such as pathologic fractures, spinal cord compression, and operation or radiation therapy to bone.

For metastatic CRPC (mCRPC) patients with no symptoms who have good performance level (ECOG 0-1) and an estimated life expectancy ≥6 months, PROVENGE is a category 1 recommendation. ZYTIGA with prednisone is another category 1 option for mCRPC patients with no symptoms. Other secondary ADT (including XTANDI, antiandrogens, ketoconazole, corticosteroids, and estrogen) and docetaxel are also options. (We expect XTANDI to become a category 1 recommendation, following the recent update to its label.)

For symptomatic mCRPC, every three-week docetaxel and prednisone is the preferred first-line chemotherapy treatment (category 1). ZYTIGA + prednisone and XTANDI are also reasonable options for patients who are not candidates for docetaxel or who decline chemotherapy. Alternatively, mitoxantrone may provide palliative benefit for patients who cannot tolerate docetaxel.

For symptomatic bone metastases with no known visceral disease, radium-223 is a category 1 first-line option. Hematologic evaluation should be performed before treatment initiation and before each subsequent dose according to the prescription label of radium-223.

For mCRPC patients after docetaxel failure, there is no consensus for the best additional therapy. Category 1 options include ZYTIGA, XTANDI, JEVTANA, radium-223, and other options include salvage chemotherapy, docetaxel rechallenge, mitoxantrone, secondary ADT, PROVENGE, and participation in clinical trials.

## Treatment Options for Hormone-Sensitive Prostate Cancer

Treatment approaches for prostate cancer vary depending on the stage of the disease and patient-specific factors including overall health status, risk benefit evaluation, age, and tolerance to therapy.

### Active Surveillance

Active surveillance, formerly called watchful waiting, may be appropriate for men with a life expectancy of 10 years or less, low-volume cancer, low PSA, and early-stage disease. The active surveillance protocol includes, among other assessments, periodic PSA testing, DRE, and prostate biopsies. Active surveillance offers the advantages of avoiding side effects of therapy that may not be necessary and retaining quality of life and normal activities. When the cancer is found to progress or become aggressive, patients should be offered definitive therapy.

It is worth noting that despite several clinical guidelines recommending active surveillance for patients with low-risk prostate cancer, more than 90% of low-risk patients nevertheless undergo aggressive treatment. Rationales for choosing definitive therapy over active surveillance may include (1) chance of missing the opportunity for cure; (2) the cancer may progress or metastasize before treatment; (3) treatment of a larger and more aggressive tumor may be more difficult and have more side effects, and nerve sparing at subsequent radical prostatectomy may be more difficult; (4) the anxiety of living with an untreated cancer; (5) the requirement for periodic prostate biopsies.

### Observation

For elderly men or frail patients with comorbidity that is likely to out-compete prostate cancer, observation is appropriate, which involves monitoring with PSA and DRE. When symptoms develop or are imminent, palliative therapy (more specifically palliative ADT) should be offered. Observation is different from active surveillance in that the goal of observation is to maintain quality of life by avoiding non-curative treatment in patients whose prostate cancer is unlikely to cause mortality or significant morbidity.

### Surgery

Radical prostatectomy (RP) is a surgical operation that removes the entire prostate gland, seminal vesicles, and sometimes other tissues. RP is appropriate for any patient whose tumor is clinically confined to the prostate (T1 and T2 tumors). Because of the potential perioperative morbidity, the procedure is typically reserved for patients with ≥10 years of life expectancy. There are several kinds of RP, including open radical prostatectomy (retropubic or perineal), and minimally invasive radical prostatectomy (laparoscopic radical prostatectomy, and robot-assisted laparoscopic radical prostatectomy). A nerve-sparing approach may be used if the cavernous nerves (necessary for natural erections) are cancer-free.

After a radical prostatectomy, almost every patient experiences the side effects of urinary incontinence and impotence (inability to have an erection). These side effects may be short-lived, but may also be permanent in some patients. Urinary continence typically returns within a few months, whereas erection recovery takes substantially longer and is typically achieved within two years. The rates of these side effects are similar between the open prostatectomy procedure and the laparoscopic prostatectomy procedure.

Pelvic lymphadenectomy is often performed at the same time as the radical prostatectomy. Pelvic lymphadenectomy is recommended for patients with a T1 or T2 tumor who are predicted to have

a ≥2% risk for cancer in the lymph nodes. Extended pelvic lymphadenectomy (involving more lymph nodes) is often preferred over standard pelvic lymphadenectomy, because extended pelvic lymphadenectomy finds metastases twice as often and also stages cancer more completely.

## Radiation Therapy

Radiation therapy is one of the mainstays of prostate cancer treatment. There are two forms of radiation treatment: external beam radiation therapy (EBRT) and brachytherapy. Expert consensus (from the NCCN Guidelines Panel) is that modern radiation therapy show a similar progress-free survival (PFS) in low-risk patients compared with RP. For example, a PFS of 73% with 15-25 years of follow-up has been demonstrated in a study of 3,546 patients treated with brachytherapy plus EBRT.

EBRT is one of the principle treatment options for clinically localized prostate cancer. In addition, in patients with high risk or very high risk diseases (e.g., T3 tumor), EBRT + ADT has been shown to be more efficacious than ADT alone. In EBRT, radiation is given using a machine outside the body. Radiation regimens, including dose, number and shape of radiation beams and the number of treatment sessions, are formulated based on the risk level of the prostate cancer. Typically, EBRT is given five days a week for eight to nine weeks.

Brachytherapy is traditionally used for low-risk diseases, but experts expect technical advancement may allow brachytherapy to play a role in treating high-risk localized and locally advanced prostate cancer. Brachytherapy involves placing small radioactive seeds into the prostate under transrectal ultrasound image guidance. Brachytherapy can be given either as permanent low dose rate (LDR) or temporary high dose rate (HDR). LDR brachytherapy uses needles to place into the prostate 40 to 100 seeds (typically radioactive iodine or palladium), which emit low-dose radiation for weeks or months and eventually stop radiating. For HDR brachytherapy, seeds made of iridium-194 are loaded into the prostate through soft catheters. After radiation is given, the catheters and seeds are removed.

As with surgical treatment, a common side effect of EBRT and brachytherapy is erectile dysfunction. Unlike the case of surgery, erectile dysfunction may develop many years after radiation therapy. Other side effects include urinary urgency and frequency, dysuria, diarrhea, and proctitis (inflammation in the rectum). The bowel-related side effects are due to radiation exposure to the rectum.

## Cryosurgery

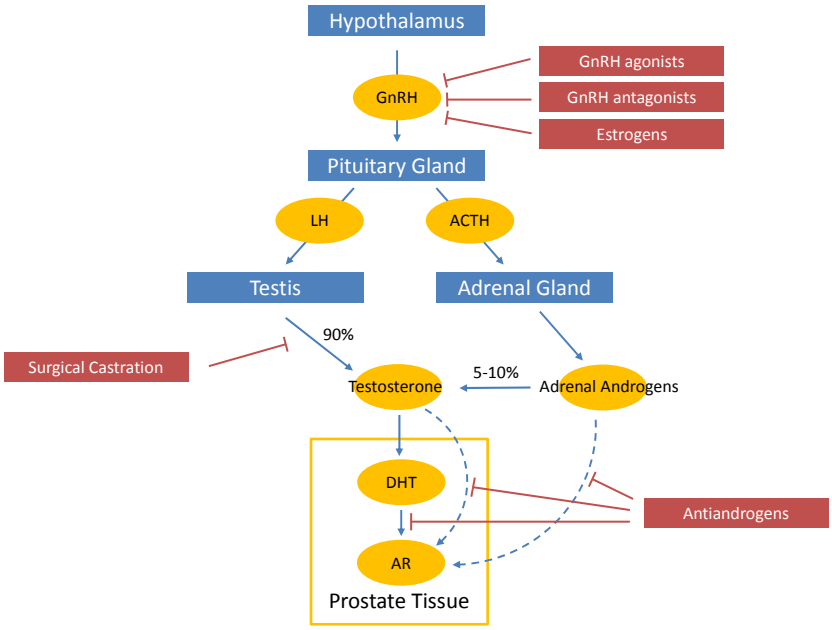
Cryosurgery is generally used as a salvage treatment after radiation therapy; however, in patients with localized high-risk disease for whom radiation therapy or radical prostatectomy are contraindicated, cryosurgery can be the treatment of choice.

Cryotherapy involves freezing the prostate to kill cancer cells. Under ultrasound guidance, thin needles (cryoprobes) are inserted into the prostate, and the cryoprobes are then cooled to a temperature of -100° F to -200° F (e.g. with liquid nitrogen). The urethra is protected from thermal injury by using a urinary catheter filled with warmed liquid. Complications of cryotherapy can include erectile dysfunction, urinary incontinence, and retention.

## Androgen Deprivation Therapy (ADT)

Most prostate cancer cells rely on the androgen testosterone for their growth. A major treatment approach for advanced prostate cancer is to target testosterone, either by reducing its levels or by blocking its signaling in cancer cells. These therapies are referred to as androgen deprivation therapy (ADT). ADT is frequently used as the primary treatment for locally advanced and metastatic prostate cancer. Exhibit 7 summarizes various approaches of ADT and their biological targets.

### Exhibit 7: Molecular Targets for ADT and Antiandrogen




Source: BMO Capital Markets

### Bilateral Orchiectomy

Bilateral orchiectomy, or surgical removal of both testicles, is a simple and cost-effective way to achieve androgen ablation. On average, testosterone falls to 15 ng/dL (or 0.5 nmol/L) after the procedure. In patients with symptomatic metastasis, improvement in symptoms (e.g., bone pain) may be seen within one to two days.

Historically the gold standard, orchiectomy is performed much less frequently today, as patients generally prefer medical castration over surgical castration, mainly for psychological reasons.

### GnRH Agonists

Due to patient preference, medical castration with GnRH agonists is the standard of care for newly diagnosed metastatic prostate cancer.

The natural GnRH hormone is a 10-amino acid peptide with a highly conserved sequence. Synthetic analogs of GnRH are generated by a single amino acid substitution, and are approximately 100-fold more potent than the natural GnRH molecule. These GnRH agonists bind to GnRH receptors on pituitary gonadotropin-producing cells. Initially, this binding causes an initial release of LH and FSH, with a concomitant increase in testosterone production. However, the GnRH agonists bind to the

receptor for a much longer time compared with natural GnRH (e.g., 3.5-5.5 hours vs. 6 minutes), and such constant stimulation of the GnRH receptor disrupts the normal pulsatile stimulation pattern and eventually leads to the down-regulation of the GnRH receptor. As a result, the pituitary production of LH and FSH declines after one week of therapy. Within three to four weeks after the initiation of therapy, the decline in serum LH causes a 95% reduction in serum testosterone to approximately 50 ng/dL, a level in line with the level achieved with surgical castration (orchiectomy). Continued treatment with GnRH agonists maintains serum testosterone at the castrate level.

Although historically the castration level of testosterone was believed to be 50 ng/dL, modern assays with higher sensitivity have revealed that the level of serum testosterone after orchiectomy is approximately 15-17 ng/dL. Experts agree that a level of ≤20 ng/dL should be used to define medical castration therapies as well; in addition, experts agree that a serum testosterone level ≥50 ng/dL (referred to as "testosterone surge") during GnRH analog therapy is clinically relevant and could have implications on treatment outcome.

This transient surge in testosterone at the beginning of the GnRH agonist therapy (caused by the initial rise in LH) may stimulate prostate cancer growth, resulting in an increase in bone pain, bladder obstruction, or other symptoms. This so-called testosterone flare can be effectively prevented with antiandrogen therapy given concomitantly with GnRH agonist for a minimum of seven days in at-risk patients.

The decrease in testosterone is generally reversible upon cessation of GnRH agonist therapy; however, depending on duration of therapy, patient age, and other factors, testosterone production does not always return to baseline levels.

Commonly used GnRH agonists include LUPRON (leuprolin), SUPREFACT (buserelin), ZOLADEX (goserelin), TRELSTAR (triptorelin), and VANTAS (histrelin). They are either injected into a muscle or implanted under the skin. GnRH agonists may be used as monotherapy or in combination with a nonsteroidal antiandrogen for combined androgen blockage.

### GnRH Antagonists

GnRH antagonists act by competing with natural GnRH for receptor binding, thus preventing the release of LH by the pituitary gonadotropin-producing cells. GnRH antagonists decrease serum testosterone more quickly than GnRH agonists; GnRH antagonists also do not cause testosterone flare. However, the development of GnRH antagonists has been limited by severe allergic reactions. PLENAXIS was the first GnRH antagonist approved; it carried a black-box warning for anaphylactic reactions (observed in 1.7% of patients after one year of therapy in clinical studies). The risk mitigation program for PLENAXIS required a special consent form prior to drug administration and resuscitative equipment in the office setting. Not surprisingly, PLENAXIS was rarely used and the manufacturer withdrew it from the U.S. market. The third-generation GnRH antagonist FIRMAGON (degarelix), designed with a view toward avoiding histamine release, is the only GnRH antagonist with a low risk of hypersensitivity available in the U.S. No hypersensitivity reactions were observed in FIRMAGON's clinical studies (although there were hypersensitivity reactions reported in post-marketing experience).

Although the overwhelming majority of prostate cancer patients treated with GnRH analogs (including both agonists and antagonists) achieve serum testosterone values within the castrate level, some patients may experience testosterone surge (testosterone values ≥50 ng/dL) while on treatment. The prescribing labels for all FDA-approved GnRH analogs recommend monitoring testosterone levels to ensure that castrate level is maintained.

## Antiandrogens

Antiandrogens are agents that competitively inhibit ligand binding to the androgen receptor (AR). Depending on their structure, antiandrogens can be classified as steroidal or non-steroidal.

Steroidal antiandrogens include cyproterone acetate and megestrol acetate. Cyproterone acetate was the first antiandrogen used to treat prostate cancer in Europe. Cyproterone acetate has a dual mechanism of action. It competitively binds to AR, exerting its antiandrogen effect. In addition, it also competitively binds to the progesterone receptors (which are structurally similar to AR) in the pituitary gland and therefore has mild antigonadotropic effects, leading to a decrease in the plasma levels of LH and testosterone (by 70-80%). Unfortunately, cyproterone acetate induces severe cardiovascular complications in approximately 10% of patients. Steroidal antiandrogens are not available in the U.S.

Nonsteroidal antiandrogens are "pure" antiandrogens that bind only to AR (and not to progesterone receptors, thus no antigonadotropic and progestational effects). Because of the higher specificity and better pharmacokinetics, nonsteroidal antiandrogens are more commonly used in current practice than steroidal antiandrogens. However, nonsteroidal antiandrogens inhibit the negative feedback of androgens in the central nervous system, leading to an increase in GnRH production, which in turn increases testicular androgen production by up to 50%. This has led to concerns over the use of nonsteroidal antiandrogens as a monotherapy. Therefore nonsteroidal antiandrogens are used predominantly in combination with medical or surgical castration to achieve complete androgen blockade (see below). In addition, nonsteroidal antiandrogens are also used for the prevention of testosterone flare in GnRH agonist therapy.

Commonly used nonsteroidal antiandrogens include CASODEX (bicalutamide), EULEXIN (flutamide), and ANANDRON (nilutamide).

## Combined/Complete Androgen Blockade (CAB)

Loss of circulating testosterone as a result of medical or surgical castration only leads to a reduction of intraprostatic DHT by 70-80%, with the remaining 20-30% derived from adrenal androgens. It was therefore hypothesized that adding an antiandrogen to castration could further block AR signaling by adrenal androgens. This approach is referred to as Complete (or Combined) Androgen Blockade. A meta-analysis of 21 randomized clinical trials of GnRH agonists alone or in combination with antiandrogen concluded that there was a modest and statistically significant survival advantage to combined antigen blockade at five years (but not at two years). Because of this survival advantage and the minimal added toxicity, combined androgen blockade has become one of the standard treatment options for metastatic prostate cancer.

## Estrogen Therapy

Estrogens such as diethylstilbestrol (DES) have been used to treat advanced prostate cancer. Exogenous administration of estrogens is thought to disrupt the hypothalamic-pituitary-adrenal axis by decrease GnRH synthesis with a subsequent suppression of LH and testicular production of testosterone. Although DES is effective at reducing testicular production of testosterone, its excessive cardiovascular and thromboembolic toxicity have made it unsuitable as a mainline therapy.

## Treatment Options for Castration-Resistant Prostate Cancer

### Secondary Hormonal Treatments – ZYTIGA and XTANDI

Objective response can be achieved in >80% of prostate cancer patients upon initiation of ADT. However, remissions are temporary because surviving tumor cells usually recur with castration-resistant phenotype. Castration resistance typically occurs within 2-3 years in high grade disease and within 1.5-2 years in metastatic disease.

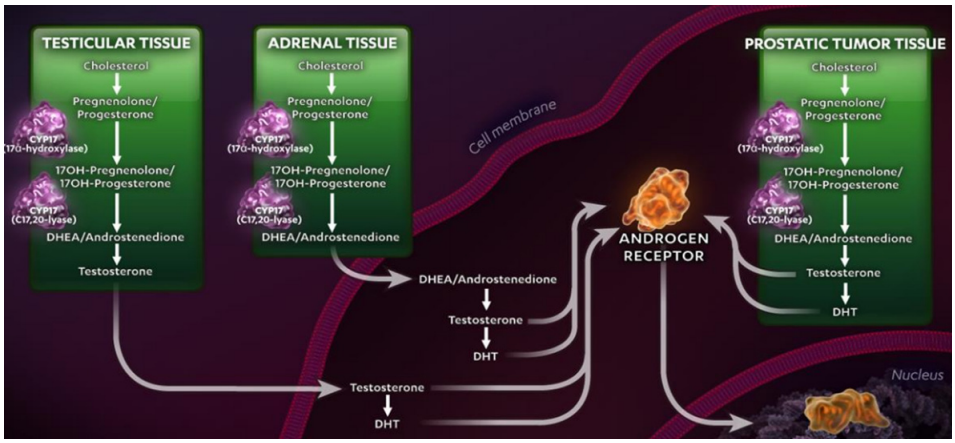
Studies on the mechanisms of resistance to hormone therapy have uncovered two main themes. First, androgen production is not limited to the testes and adrenal glands. Prostate cancer cells and their surrounding microenvironment can contribute to androgen synthesis, through overexpression of key androgen synthetic enzymes (such as CYP17A), increased expression of enzymes converting DHEA to testosterone, and DHT in tumor tissue, and reductions in androgen-metabolizing enzymes that degrade androgens. Second, prostate cancer cells also acquire androgen receptor abnormalities, including increased AR expression, mutation in the ligand binding domain, and constitutively active AR mutants.

The realization that CRPC remains dependent on AR signaling via AR amplification, mutation, and extragonadal production of androgens rekindled interest in exploring more potent suppression of AR signaling as a therapeutic approach for the treatment of CRPC. These efforts have led to the development of two new hormonal drugs for mCRPC (referred to as secondary hormonal treatments): ZYTIGA and XTANDI.

#### ZYTIGA

CYP17 (17α-hydroxylase/C17,20-lyase) is a key enzyme for androgen biosynthesis. CYP17 is present in testicular tissues, adrenal cortex, as well as prostate tumor tissues. CYP17 catalyzes two sequential reactions. The first reaction converts progesterone and pregnenolone into their 17α-hydroxy derivatives through the 17α-hydroxylase activity of CYP17. Subsequently, through the C17,20-lyase activity of CYP17, the 17α-hydroxy derivatives are converted into androstenedione and dehydroepiandrosterone (DHEA), respectively. DHEA and androstenedione are precursors of testosterone. Therefore inhibition of CYP17 could lead to a decrease in circulating androgen levels.

**Exhibit 8: The Role of CYP17 in Androgen Biosynthesis**




Source: www.zytiga.com

Historically, ketoconazole, an antifungal agent, has been used off-label to treat prostate cancer because it inhibits CYP17. However, ketoconazole has only modest therapeutic effects because it is a weak, reversible CYPT17 inhibitor. In addition, ketoconazole is not selective for CYP17; it also inhibits a number of other CYP enzymes including CYP3A4 in the liver, and these non-specific effects limit its clinical use due to toxicity.

Johnson & Johnson's ZYTIGA (abiraterone acetate) is an irreversible CYP17 inhibitor that is 20x more potent than ketoconazole. ZYTIGA has demonstrated efficacy in mCRPC, but the use of ZYTIGA is associated with mineralocorticoid excess (ME) syndrome. This is because CYP17 inhibition also blocks the synthesis of cortisol (see page 32 for detailed mechanism), which in turn leads to a feedback upregulation of mineralocorticoid precursors. The overproduction of mineralocorticoid precursors could result in side effects including hypertension, hypokalemia, fluid retention, and edema, collectively referred to as mineralocorticoid excess (ME) syndrome. To reduce the risk of ME, the use of ZYTIGA requires concomitant use of oral glucocorticoids (e.g., low-dose prednisone).

ZYTIGA has demonstrated OS benefit in mCRPC in both post-chemotherapy and chemotherapy-naïve mCRPC settings. **In a phase 3 study in 1,195 patients with mCRPC showing disease progression during or after docetaxel therapy, ZYTIGA + prednisone demonstrated a median OS of 15.8 months vs. 11.2 months in the placebo + prednisone group (HR 0.740, 95% CI: 0.638-0.859).** Baseline disease characteristics were balanced across the arms and included 89% ECOG performance status score of 0-1, 45% Brief Pain Inventory-Short Form score ≥4, 90% bone metastases, 30% visceral involvement, 70% radiographic evidence of disease progression, 30% PSA-only progression, 30% with two chemotherapy regimens. **In another phase 3 study in 1,088 chemotherapy-naïve patients with mCRPC who had failed ADT, ZYTIGA + prednisone demonstrated a median OS of 35.3 months vs. 30.1 months in the placebo group (HR 0.79, 95% CI: 0.66-0.96, p=0.0151) at an interim analysis that was conducted when approximately 55% of deaths had occurred, although the pre-specified p-value for statistical significance for the OS co-primary endpoint was not met.** However, the study did demonstrate a statistically significant benefit in the other co-primary endpoint, radiographic progression-free survival (rPFS), with a 47% reduction for the ZYTIGA + prednisone arm (rPFS of 16.5 months) compared with the prednisone alone arm (rPFS of 8.3 months) [HR 0.53, 95% CI: 0.45-0.62, p<0.0001]. **In a final analysis of the study recently presented at the 2014 ESMO Congress, ZYTIGA + prednisone demonstrated a statistically significant OS benefit compared with placebo, with a median OS of 34.7 months vs. 30.3 months (HR 0.81, 95% CI: 0.70-0.93, p=0.0033).** Baseline disease characteristics were balanced across the arms and included 76% ECOG score of 0, 24% ECOG score of 1, 66% pain assessment of 0-1 (asymptomatic), and 26% pain assessment of 2-3 (mildly symptomatic) as defined by the Brief Pain Inventory-Short Form.

In the two phase 3 studies, the most common adverse events (AEs) that occurred more frequently in the ZYTIGA + prednisone arm included fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection, and contusion. Laboratory abnormalities that occurred more frequently in the ZYTIGA + prednisone arm included hypertriglyceridemia, lymphopenia, hyperglycemia, elevated AST/ALT, hypophosphatemia and hypokalemia. Cardiac failure occurred more frequently in patients treated with ZYTIGA compared to patients in the control arm (2.1% vs. 0.7%). Grade 3-4 cardiac failure

occurred in 1.6% of patients taking ZYTIGA (vs. 0.2% placebo) and led to five treatment discontinuations and two deaths.

FDA approved ZYTIGA in combination with prednisone for patients with mCRPC, first in post-chemotherapy setting (approval in April 2011) and then in chemotherapy-naïve setting (approval in December 2012). The recommended dose of ZYTIGA is 1,000 mg (four 250 mg tablets) administered orally once daily in combination with prednisone 5 mg orally twice daily. ZYTIGA has to be taken on an empty stomach. The Warnings and Precautions section of the prescription label for ZYTIGA cites risks of mineralocorticoid excess, andrenocortical insufficiency, hepatotoxicity (increases in liver enzymes), and food effect (10-fold increase in exposure when taken with food).

Another second-generation CYP17A inhibitor, orteronel (TAK-700) was developed by Takeda. Following disappointing phase 3 results, Takeda terminated the development of this compound in June 2014. Orteronel (TAK-700) is a CYP17A inhibitor designed with a higher selectivity for the lyase function of CYP17A, based on the assumption that selectivity for lyase function could reduce the drug's impact on the mineralocorticoid pathway, thus reducing the risk of ME. Two large phase 3 studies have been conducted in patients with mCRPC, one in post-chemotherapy setting and one in chemotherapy-naïve setting. In both studies, orteronel demonstrated a benefit PFS, but did not show a statistically significant improvement in OS.

**XTANDI**

Medivation's XTANDI (enzalutamide) is a second-generation AR antagonist that binds to AR with five-fold greater affinity than first-generation antiandrogen CASODEX (bicalutamide). XTANDI is also distinct from the first-generation antiandrogens in that it inhibits nuclear translocation of the AR, as well as the subsequent DNA binding and coactivator recruitment.

In phase 3 studies, XTANDI demonstrated efficacy in both pre- and post-chemotherapy mCRPC settings. **In a 1,199-patient phase 3 study in patients with mCRPC who had progressed following chemotherapy, XTANDI demonstrated a median OS of 18.4 months vs. 13.6 months placebo (HR 0.63, 95% CI: 0.53-0.75, p<0.0001).** Patient demographics and baseline disease characteristics were balanced and included 92% ECOG score of 0-1, 28% mean Brief Pain Inventory score ≥4, 91% bone metastasis, 23% visceral involvement in lung/liver, 59% radiographic evidence of disease progression, 41% PSA-only progression, 24% with two chemotherapy regimens. Patients with previous history of seizure or with other risk factors for seizure were excluded. **In a 1,717-patient phase 3 study in chemotherapy-naïve patients with mCRPC who had failed ADT, XTANDI demonstrated a median OS of 32.4 months vs. 30.2 months placebo (HR 0.71, 95% CI: 0.60-0.84, p<0.0001) at the pre-specified interim analysis.** In addition, XTANDI demonstrated an impressive 83% reduction in rPFS, with median rPFS >21 months (not yet reached at the time of analysis) vs. 3.7 months placebo (HR 0.17, 95% CI: 0.14-0.21, p<0.0001). Baseline disease characteristics were balanced between the arms and included 68% ECOG score of 0, 32% ECOG score of 1, 67% baseline pain assessment of 0-1 (asymptomatic), 32% baseline pain assessment of 2-3 (mildly symptomatic), 54% radiographic evidence of disease progression, 43% PSA-only progression, 12% visceral (lung and/or liver) disease involvement. Patients with previous history of seizure or with other risk factors for seizure and patients with moderate or severe pain from prostate cancer were excluded.

In the two phase 3 studies of XTANDI, the most common AEs that occurred more frequently in the XTANDI arm included asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight loss, headache, hypertension (11% vs. 4% placebo), and dizziness/vertigo.

In the study in post-chemotherapy patients, 0.9% of XTANDI-treated patients experienced seizure (vs. 0% placebo) and discontinued treatment. Seizure occurred from 31 to 603 days after initiation of XTANDI. In the study in chemotherapy-naïve patients, the seizure rates were similar between the XTANDI and placebo arms (both 0.1%). Note that patients with previous history and predisposing factors for seizure were excluded from the trials. The post-chemo study excluded the use of concomitant medications that may lower the seizure threshold, whereas the chemo-naïve study permitted the use of such medications. The risk for seizures with XTANDI use has been linked to the inhibition of $GABA_A$, a receptor associated with the nervous system.

FDA approved XTANDI for the treatment of mCRPC, first in the post-docetaxel setting (approval in August 2012) and subsequently in the chemotherapy-naïve setting (approval in September 2014). The recommended dose of XTANDI is 160 mg (four 40 mg capsules) administered orally once daily. XTANDI can be taken with or without food. The Warnings and Precautions section of the prescription label for XTANDI specifies the risk of seizure.

## Chemotherapy – Docetaxel and JEVTANA

Overall, approximately 30-50% of CRPC patients are eligible for chemotherapy. The first chemotherapy used for the treatment of advanced prostate cancer was mitoxantrone used in combination with prednisone. The combination demonstrated a benefit in palliative response compared with prednisone alone (28.8% vs. 12.3%) in a landmark study led by Tannock et al. No OS benefit was observed for the mitoxantrone/prednisone combination therapy, but this could be partially caused by significant crossover from the prednisone arm to the combination arm.

**Two landmark studies published in 2004 demonstrated that docetaxel was superior to mitoxantrone and established docetaxel as the standard of care in mCRPC.** One study compared weekly or every three-week docetaxel vs. the Tannock mitoxantrone regimen, and the other study compared a combination of docetaxel with estramustine vs. the same Tannock regimen. Overall survival benefit was observed for the every three-week docetaxel and the docetaxel/estramustine combination regimens compared with mitoxantrone, with hazard ratios of 0.76 and 0.8, respectively, despite significant crossover to docetaxel from the mitoxantrone arms in both studies.

A number of chemotherapy agents have been studied in the second-line setting (post-docetaxel) in mCRPC. Sanofi's novel taxane, JEVTANA (cabazitaxel), has demonstrated a survival benefit and obtained FDA approval. In a phase 3 study (TROPIC) in 755 mCRPC patients previously treated with a docetaxel-containing regimen, JEVTANA + prednisone demonstrated a median OS of 15.1 months vs. 12.7 months for the mitoxantrone + prednisone arm (hazard ratio 0.70, 95% CI 0.59-0.83, $p<0.0001$). Rates of side effects are high, and NCCN Treatment Guidelines recommend use of prophylactic white blood cell growth factors as well as supportive care regimens including antiemetics, and symptom-directed antidiarrheal agents.

## Immunotherapy - PROVENGE

Dendreon's PROVENGE (sipuleucel-T) is an autologous cellular therapy for the treatment of mCRPC. PROVENGE was approved by FDA in 2010 for the treatment of asymptomatic or minimally symptomatic mCRPC. Patients with bone pain requiring narcotics, with visceral metastases, and with a life expectancy <6 months are not candidates for this therapy.

PROVENGE is designed to train the patient's immune system to better target prostate cancer cells. PROVENGE therapy involves an initial leukapheresis to collect a small fraction of white blood cells, which are then transported to a Dendreon production facility. The cells are incubated with an Antigen Delivery Cassette, which is a recombinant protein consisting of prostatic acid phosphatase (PAP) fused to granulocyte-macrophage colony-stimulating factor (GM-CSF). PAP is present in 95% of prostate cancer cells and GM-CSF is a cytokine that helps a group of white blood cells known as antigen presenting cells (APCs) to mature. One advantage of this *ex vivo* stimulation process is that it bypasses the immunosuppressive environment present in tumor tissues. After 36 to 44 hours in culture, the APCs are ready for the stimulation of T cells, with PAP peptide fragments presented on their cell surface, along with upregulated expression of costimulatory molecules such as CD54 and CD80. The cell product, PROVENGE, is then transported back to the infusion center and infused back into the patient three days after the initial cell collection. This process is repeated two more times over a course of a month.

In a phase 3 study (IMPACT), PROVENGE demonstrated a 4.1-month median OS benefit over placebo (25.8 months vs. 21.7 months, HR 0.775, 95% CI: 0.61-0.98, p=0.032). PROVENGE was very well tolerated in clinical trial experience. Side effects included infusion-related reactions (fever, headache, perioral numbness, chills, muscle aches, and back pain), which were typically mild and transient (1-3 days).

Notably, treatment with PROVENGE did not lead to improvement in the usual markers of benefit, including PSA decline, tumor response, palliation, and delayed tumor progression, and therefore benefit cannot be ascertained using currently available testing.

Given the availability of newer agents such as ZYTIGA and XTANDI, a major question regarding PROVENGE is the timing of treatment initiation. A retrospective subgroup analysis of the IMPACT trial demonstrated a greater survival improvement in patients who had lower PSA, suggesting that immunotherapy may result in greater benefits when used early in the disease process. **The HR and OS benefit for PROVENGE-treated patients vs. placebo were 0.51 and 13 months among patients with a PSA <22 ng/mL, and 0.84 and 2.8 months among patients with a PSA >134 ng/mL.**

# Galeterone for mCRPC

## Mechanisms of Action and Preclinical Studies

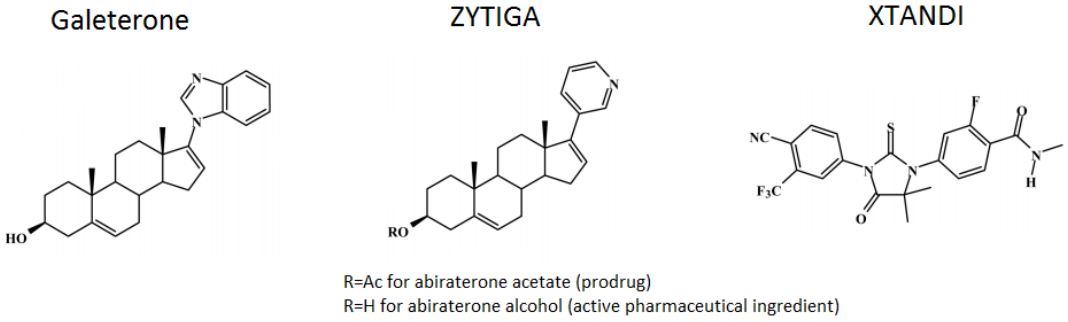
The growth and survival of prostate cancer tumor cells are critically dependent on the androgen receptor (AR) signaling pathway. This pathway is activated when testosterone and DHT bind to the ligand binding domain (LBD) of androgen receptors. Therapies that block the AR signaling pathway, such as ZYTIGA and XTANDI, have demonstrated proven activity in controlling prostate tumor cell growth. However, the effectiveness of these therapies is dependent on the presence of a functional LBD in the AR. Thus, tumors that express constitutively active ARs with truncated C-termini, such as the AR-V7 splice variant, may not be effectively treated by currently available therapies (see section titled *AR-V7 and Resistance to ZYTIGA and XTANDI* on page 11 for a detailed discussion).

Tokai's galeterone disrupts the AR signaling pathway through multiple mechanisms of action, including the inhibition of CYP17, AR antagonism, and AR degradation. Most notably, the mechanism of AR degradation does not require a functional LBD, and can be effective in controlling the growth of tumor cells that express ARs with truncated C-termini.

### CYP17 Lyase Inhibition

Galeterone was originally designed as a CYP17 inhibitor. Galeterone shares structural similarity with ZYTIGA, and both are steroidal CYP17 inhibitors (Exhibit 9). (In contrast, XTANDI is a non-steroidal, AR inhibitor).

**Exhibit 9: The Structures of Galeterone, ZYTIGA, and XTANDI**



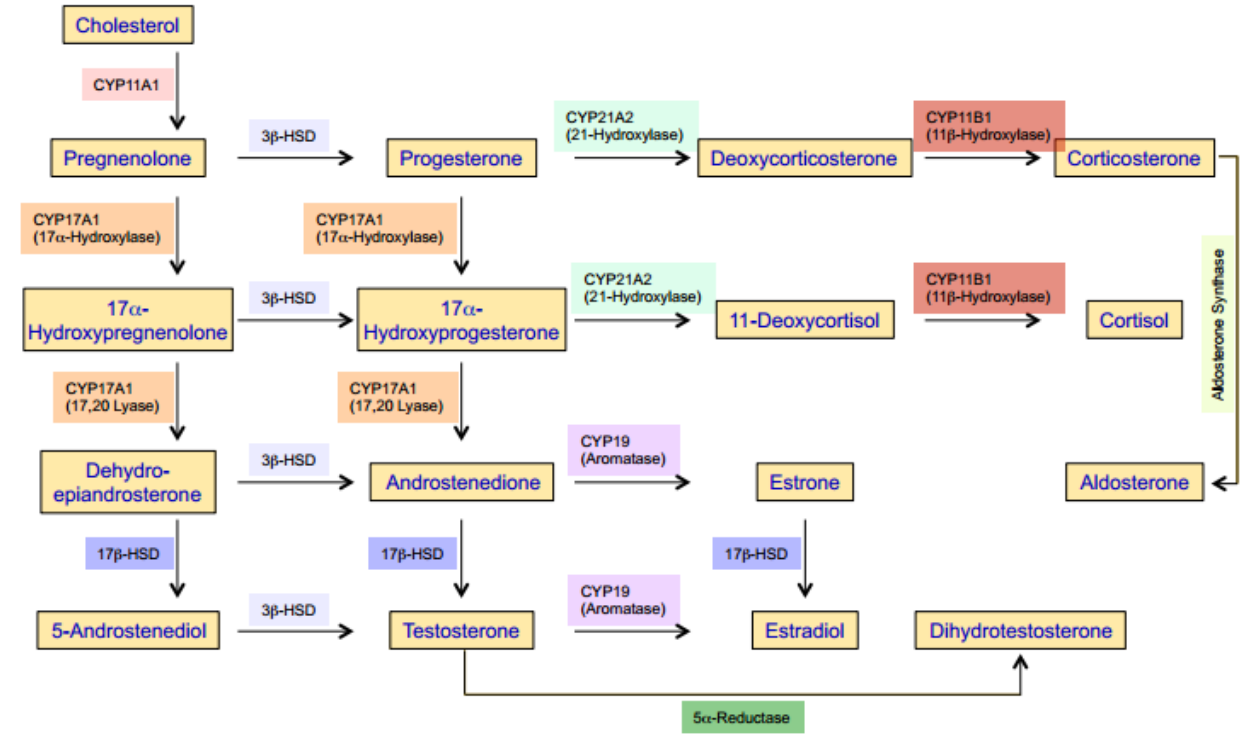

Source: BMO Capital Markets, adapted from Purushottamachar et al, *J Med Chem* 56:4880, 2013

As discussed earlier, CYP17 is a key enzyme for androgen biosynthesis. CYP17 has both 17α-hydroxylase and 17,20-lyase activities and catalyzes two sequential reactions, converting progesterone and pregnenolone first to their 17α-hydroxy derivatives (hydroxylase activity) and then to androgens (lyase activity). These androgens, androstenedione and DHEA, can be subsequently converted to testosterone by other enzymes. Therefore, inhibition of either the hydroxylase or the lyase activity of CYP17, or both, reduces circulating testosterone levels.

Notably, the biosynthesis of cortisol, the major glucocorticoid hormone that regulates glucose, fat and protein metabolism, also requires CYP17. Therefore, CYP17 inhibition could lead to a reduction in cortisol, which in turn leads to a compensatory response in the pituitary, which releases ACTH in an effort to stimulate the steroidogenic pathway (Exhibit 10). This leads to the elevation of certain mineralocorticoids, and result in side effects such as fluid retention, hypokalemia and hypertension, collectively referred to as mineralocorticoid excess (ME). To reduce the risk of ME, concomitant administration of a glucocorticoid, such as prednisone, may be necessary. In the case of ZYTIGA, approximately 90% of patients demonstrated symptoms of ME when prednisone was not used concomitantly, and approximately 55% of patients demonstrated symptoms of ME with the use of prednisone.

Importantly, cortisol synthesis requires only the hydroxylase activity, but not the lyase activity, of CYP17 (Exhibit 10). Therefore, an ideal CYP17 inhibitor could be designed to avoid impacting the cortisol biosynthesis pathway by selectively targeting the lyase activity of CYP17 relative to its hydroxylase activity.

**Exhibit 10: The Steroidogenic Pathway**




Source: Tokai Pharmaceuticals

Tokai studied galeterone and three other CYP17 inhibitors in cell-based assays to evaluate their activity against hydroxylase and lyase functions of CYP17, as well as their effects on the steroidogenic pathway. All four inhibitors, including galeterone, ZYTIGA, orteronel, and ketoconazole, inhibited testosterone synthesis ≥94% at 1 μM, but their selectivity for lyase varied significantly. (See pages 27 and 28 for background on orteronel and ketoconazole.) Compared with other inhibitors, ZYTIGA was a more potent lyase inhibitor and a far more potent hydroxylase inhibitor, and therefore demonstrated an overall selectivity for hydroxylase. The remaining three inhibitors all demonstrated selectivity for lyase, with galeterone having the

highest potency for lyase. **Therefore, galeterone appeared to be the most potent lyase-selective CYP17 inhibitor.**

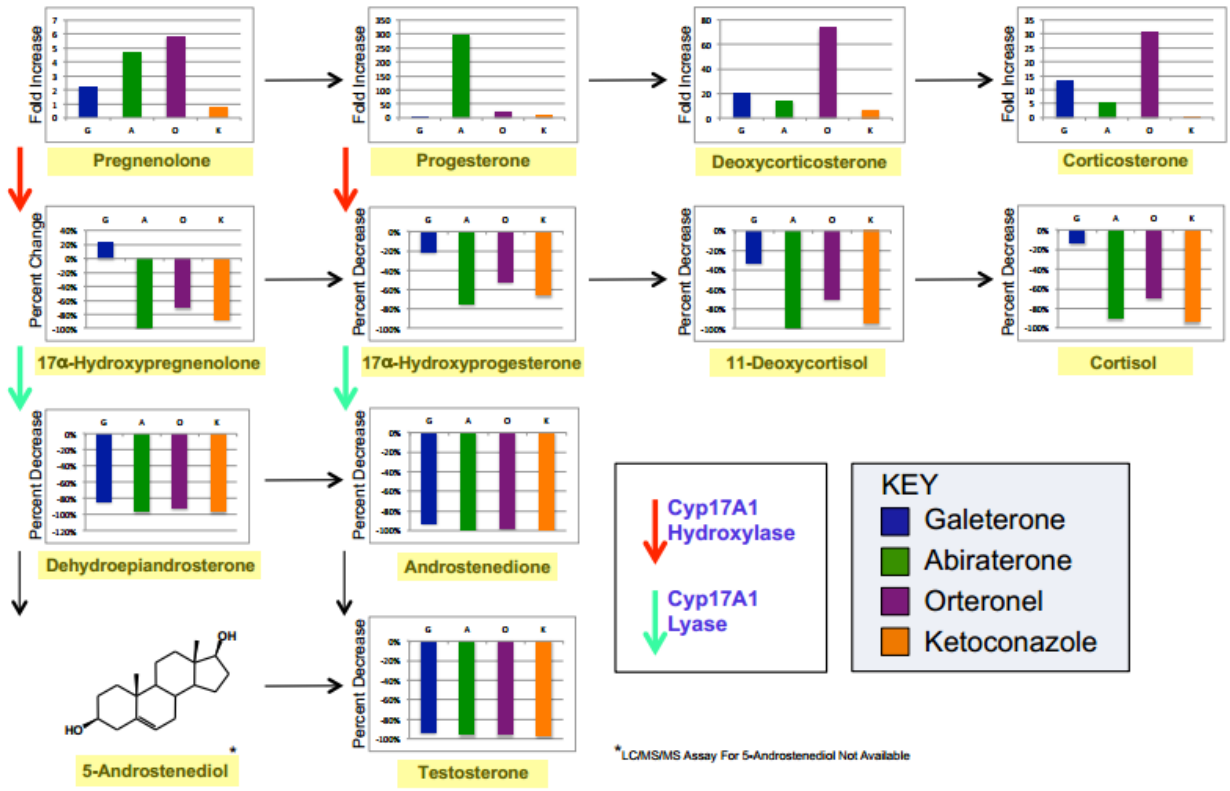
### Exhibit 11: Potencies of CYP17 Inhibitors

| Compound | Hydroxylase $IC_{50}$ (nM) | Lyase $IC_{50}$ (nM) | Lyase:Hydroxylase Selectivity |
|---|---|---|---|
| Galeterone | 73 | 23 | 3.2 |
| Abiraterone | 7 | 12 | 0.6 |
| Orteronel | 348 | 64 | 5.4 |
| Ketoconazole | 190 | 31 | 6.1 |

Source: Tokai Pharmaceuticals

In addition, these studies also demonstrated that galeterone caused the smallest effect on cortisol, with a 14% reduction compared with 91%, 70%, and 94% reduction for ZYTIGA, orteronel, and ketoconazole, respectively (Exhibit 12). **The absence of significant impact on cortisol was consistent with galeterone's phase 1 clinical experience, which demonstrated no signs of ME and required no concomitant use of prednisone.**

### Exhibit 12: Drug Effects on Steroidogenesis



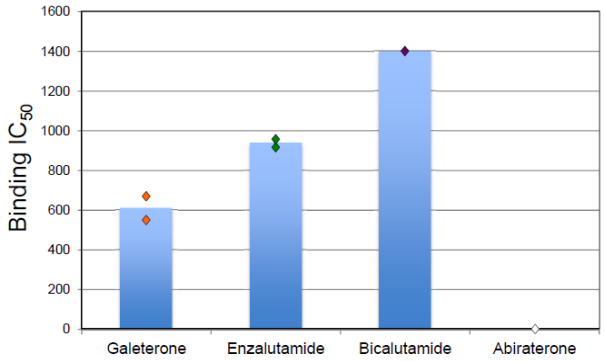

Note: all drugs at 1μM.

Source: Tokai Pharmaceuticals

## AR Antagonism

In addition to being a CYP17 inhibitor, galeterone is also an antagonist of AR. Galeterone was the first reported example bearing such an unusual dual activity. The AR antagonism activity of galeterone was demonstrated in a competitive binding assay. In this assay, LNCaP cells, a human prostate cancer cell line that expresses the wild-type AR, were incubated with radiolabeled methyltrienolone (R1881), a synthetic androgen. Galeterone was added into the culture at various concentrations to determine the concentration necessary to achieve 50% displacement of R1881 ($IC_{50}$). **Galeterone demonstrated an IC50 of 670 nM in the competitive AR binding assay.** In the same experiment, XTANDI demonstrated an $IC_{50}$ of 915 nM, and CASODEX, an antiandrogen agent known to have a lower binding affinity to AR, demonstrated an $IC_{50}$ of 1,400 nM. **Therefore, galeterone binds to AR in cells with twice the potency of CASODEX and with a potency comparable to, if not greater than, XTANDI.** ZYTIGA was also examined in this experiment; it demonstrated an unusual AR binding curve with a shallow steepness, which was indicative of interaction with more than one receptor population, and as a result its $IC_{50}$ value was not determined. (In an earlier experiment carried out in LAPC4 cells, another human prostate cancer cell line, galeterone demonstrated an $IC_{50}$ of 405 nM vs. 4,300 nM for CASODEX.)

### Exhibit 13: Galeterone Demonstrates Potent AR Binding




Enzalutamide = XTANDI; Bicalutamide= CASODEX

Source: Tokai Pharmaceuticals

To evaluate the functional impact of AR binding by galeterone, a luciferase reporter assay was performed. In this assay, androgen-sensitive human prostate cancer cell lines, LNCaP and LAPC4, were transfected with a construct carrying the luciferase reporter gene under the control of a promoter that could be activated by AR in response to dihydrotestosterone (DHT). Transfected cells were incubated with DHT and various concentrations of galeterone or CASODEX, and luciferase expression was measured to assess the extent of AR activation. In this assay, galeterone demonstrated a similar potency as CASODEX in blocking DHT-induced luciferase reporter expression.

In another set of experiments, galeterone also inhibited DHT-stimulated growth of LNCaP and LAPC4 cells (both were androgen-sensitive human prostate cancer cell lines), with $IC_{50}$ values in the low micromolar range. Lastly, in an LAPC4 xenograft model in severe combined immunodeficient (SCID) mice, galeterone demonstrated greater antitumor activity than castration.

These studies suggest that, like XTANDI, galeterone could act as an AR antagonist, blocking the binding of androgen to AR, reducing AR translocation to the nucleus, and reducing the expression of AR-responsive genes, including those that could drive tumor growth. Nevertheless, given galeterone's another mechanism of action, AR degradation (see below), the relative contribution of AR antagonism vs. AR degradation in the functional assays described above remains to be clarified.

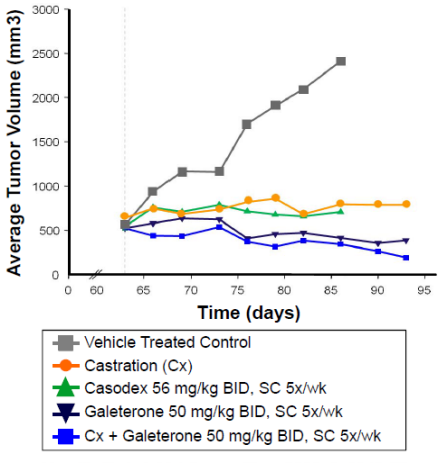
## AR Degradation

Preclinical studies also revealed that galeterone could also act through a third mechanism, the degradation of AR. After 24 hours of incubation with 15 μM galeterone, the levels of AR were reduced by 89% and nearly 100% in LNCaP and LAPC4 cells, respectively. CASODEX, on the other hand, did not cause reduction of AR protein levels.

To determine whether the down-regulation of AR was due to reduced synthesis or increased degradation, cells were treated with galeterone in combination with cycloheximide, a compound that inhibits protein synthesis. Treatment with galeterone and cycloheximide resulted in stronger down-regulation of AR compared with either agent alone, suggesting that galeterone acted independently from inhibiting protein synthesis. In another line of experiments, galeterone-mediated down-regulation of AR was blocked by MG132, a proteasomal inhibitor, suggesting that galeterone-mediated AR degradation is linked to the proteasome, the main cellular machinery for protein degradation.

Galeterone-mediated AR down-regulation has also been observed in the tumor xenograft model. SCID mice were injected with LAPC4 cells, and received one of five treatments after tumors had formed at approximately 9 weeks: vehicle control, castration, CASODEX, galeterone, and castration plus galeterone. Mice were treated for 23 - 30 days. Compared with control groups, all treatments, except CASODEX, demonstrated statistically significant benefit in reducing the total tumor volume from two weeks after treatment initiation to the end of the treatment. (CASODEX treatment was terminated earlier due to drug shortage.)

**Exhibit 14: Antitumor Activity of Galeterone in Hormone Sensitive Prostate Cancer Xenograft Model**




*Vasaitis T et al. Mol Cancer Ther. 2008, 8: 2348-57.*

Source: Tokai Pharmaceuticals

**Analysis of AR expression in tumor xenografts revealed that treatments with galeterone or galeterone + castration caused 10- and 5-fold reduction in AR protein levels, respectively.** In contrast, treatment with CASODEX or castration caused AR protein up-regulation of 2.3- and 2.8-fold, respectively.

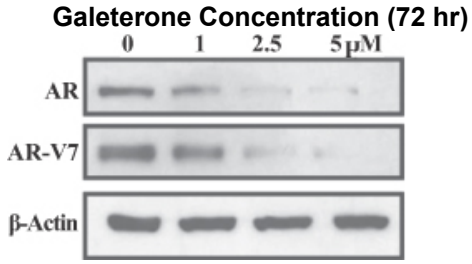
These studies suggest that galeterone decreases the amount of androgen receptor protein in prostate tumor cells by enhancing degradation of the androgen receptor. In contrast, AR reduction in prostate cancer cells has not been consistently observed in studies involving ZYTIGA, XTANDI or CASODEX.

## Degradation of Altered Forms of AR

Importantly, the AR degradation activity of galeterone is not limited to wild-type AR. Preclinical studies conducted by Tokai's collaborators in independent laboratories have demonstrated that galeterone also causes AR degradation in AR splice variant proteins, including AR-V7.

Researchers at the University of Maryland measured AR degradation using cell lines that expressed both full-length and splice variant ARs. The co-expression of both full-length and splice variants is consistent with the expression patterns in human tumor samples. As shown in Exhibit 15, levels of both full-length AR and AR-V7 were both reduced in a dose-dependent manner following galeterone treatment.

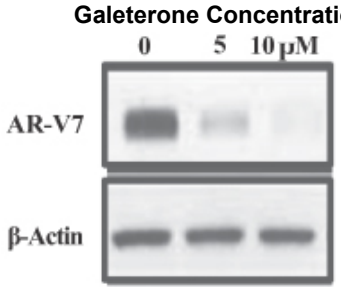
### Exhibit 15: Galeterone Causes Decreased Levels of AR and AR-V7 in Cell Line




Source: Tokai Pharmaceuticals

Furthermore, the researchers demonstrated that galeterone was able to degrade AR-V7 in a prostate cancer cell line that expresses only AR-V7 and not the full-length AR (Exhibit 16). This result suggests that galeterone can act directly on AR-V7 (as opposed to acting through an indirect mechanism that requires full-length AR, for example by targeting a heterodimer of full-length AR and AR-V7).

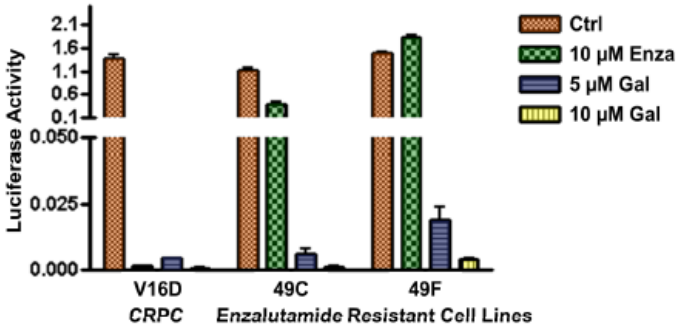
### Exhibit 16: Galeterone Causes Decreased Levels of AR-V7 in Cell Line Expressing Only AR-V7




Source: Tokai Pharmaceuticals

Tokai also collaborated with the Vancouver Prostate Centre to examine whether degradation of AR translated into reduced AR signaling and reduced tumor growth in prostate cancer tumor cells which express AR-V7. Galeterone reduced tumor cell proliferation, reduced AR levels, and decreased nuclear translocation of the AR, and XTANDI was weakly effective in these experiments. In a luciferase reporter assay, galeterone and XTANDI both reduced luciferase activity in a tumor cell line that expressed full-length AR but not AR-V7. When similar experiments were performed using XTANDI-resistant cell lines that express AR-V7 (49C and 49F), treatment with galeterone, but not XTANDI, resulted in significantly decreased luciferase activity (Exhibit 17).

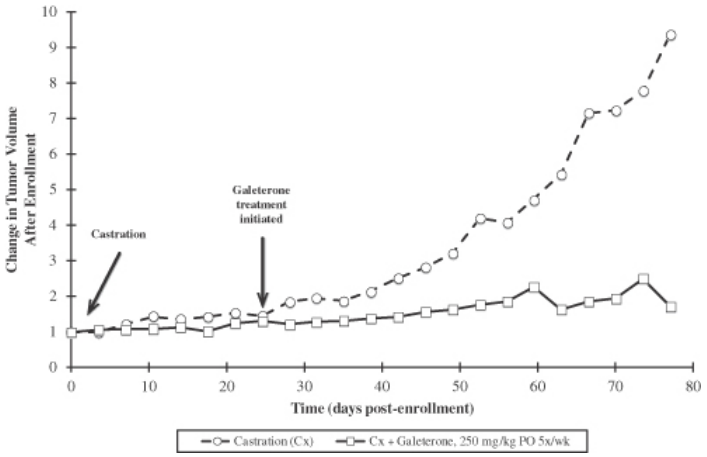
### Exhibit 17: Galeterone (but not XTANDI) Decreases AR Signaling in AR-V7 Positive Cells




Source: Tokai Pharmaceuticals

Tokai and collaborators at the University of Washington evaluated the *in vivo* activity of galeterone in an AR-V7-positive prostate cancer xenograft model. In this model, LuCaP136, a prostate cancer cell line that expresses AR-V7, is injected into castrated mice. The tumors grew in the castrated animals, and treatment with galeterone resulted in inhibition of tumor growth (Exhibit 18).

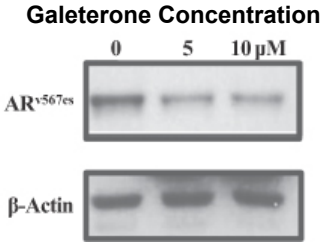
### Exhibit 18: Galeterone Inhibits Tumor Growth in LuCaP136 (AR-V7 Positive) Castration-Resistant Xenograft Model




Source: Tokai Pharmaceuticals

Tokai also evaluated galeterone against a second splice variant, $AR^{v567es}$. Like AR-V7, $AR^{v567es}$ is a truncated AR with C-terminal loss. As shown in Exhibit 19, treatment with galeterone led to reduction of $AR^{v567es}$ in a dose-dependent manner in a prostate cancer cell line that only expresses $AR^{v567es}$ and not the full-length AR, confirming that galeterone can act directly on $Ar^{v567es}$.

### Exhibit 19: Galeterone Causes Decreased Levels of AR-V7 in Cell Line Expressing Only ARv567es




Source: Tokai Pharmaceuticals

Tokai has also studied galeterone's activity against prostate cancer cells that express AR point mutations, such as AR-F876L and AR-T878A. These mutations have been shown to underlie resistance to ZYTIGA or XTANDI. Tokai noted that in preclinical studies, galeterone was active against these point mutations.

## Galeterone in Combination with Other Therapeutics

Growing evidence suggests that the PI3K/Akt/mTOR pathway, one of the most frequently altered pathways in human cancer, plays a role in prostate cancer tumor progression. Recent research has demonstrated that there may be cross-talk between the AR signaling pathway and the PI3K/Akt/mTOR pathway, such that blockade of AR signaling may lead to a compensatory upregulation of the PI3K/Akt/mTOR pathway, enhancing tumor cell growth. As a result, combination therapies that target both pathways may have enhanced activity compared with monotherapy approaches.

In preclinical studies, Tokai observed that galeterone is synergistic with certain Akt, mTOR, and PI3K inhibitors in suppressing prostate cancer cell proliferation. Tokai plans to conduct *in vivo* studies to test combination therapies of galeterone with Akt, mTOR and PI3K inhibitors in xenograft models.

## Clinical Development

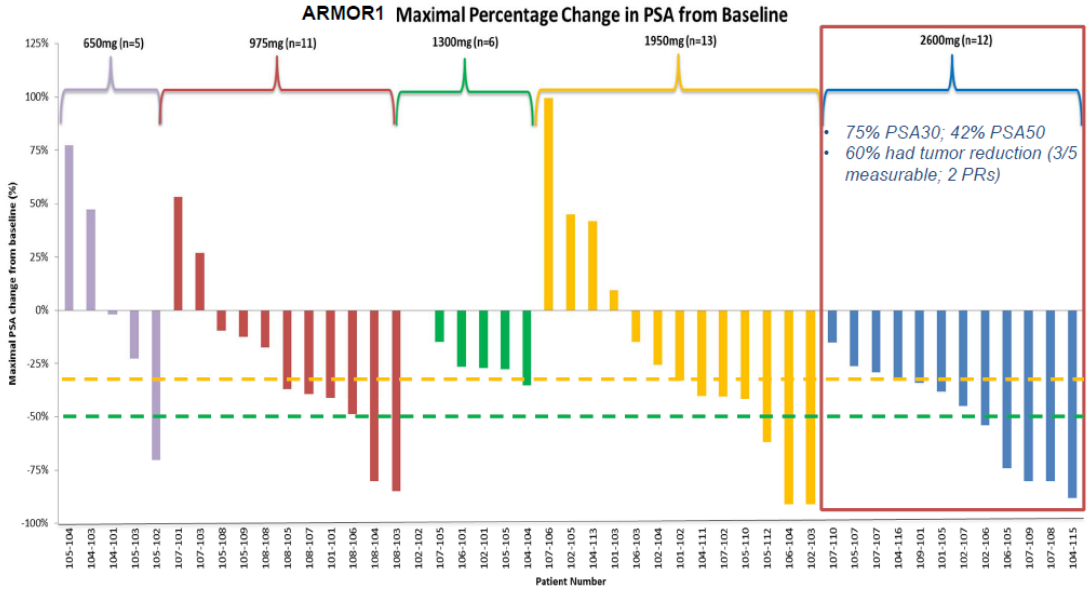
### Phase 1 ARMOR1 Study

Tokai initiated ARMOR1, an open-label, dose escalation phase 1 study of galeterone, in November 2009. The study enrolled 49 metastatic and non-metastatic treatment-naïve CRPC patients at eight sites in the U.S. Patients were enrolled into eight dose cohorts, with escalating doses of galeterone from 650 to 2600 mg/day, either as a single daily dose or as a twice-daily split dose. The study used a prior formulation (micronized active pharmaceutical ingredient in capsule, referred to as PIC formulation) of galeterone. Galeterone was taken with a patient choice of meal or with a food supplement. Patients were treated for an initial period of 12 weeks, followed by optional continuation for those who tolerated the treatment and did not show signs of disease progression. Treatment was continued until disease progression or intolerance. The primary endpoints for the trial were incidence of AEs and change from baseline in safety parameters. Secondary endpoints included the percentage of patients with ≥50% decrease in PSA during the period from baseline to the earlier of the end of the 12-week treatment period or PSA nadir, and changes in disease status from baseline in CT/MRI scans and bone scans over the 12-week treatment period.

Thirty-seven of the 49 patients enrolled completed the 12-week treatment period, and 22 patients entered the extension phase of the trial. Of the 12 patients who did not complete the 12-week treatment period, 5 patients discontinued due to disease progression, 5 patients discontinued due to AEs, and 2 patients voluntarily withdrew from the trial.

Reductions in PSA were observed in all dose cohorts. Of the 12 patients who received the highest dose of 2600 mg/day, 75% achieved maximal PSA decreases of ≥30%, and 42% achieved maximal PSA decreases of ≥50%. Of all 49 patients in the trial, 22% achieved maximal PSA decreases of ≥50%, and 49% achieved maximal PSA decreases of ≥30%. Tokai believed that these results, while favorable, were adversely affected by the exposure variability associated with the food effect of the PIC formulation.

### Exhibit 20: PSA Response in ARMOR1

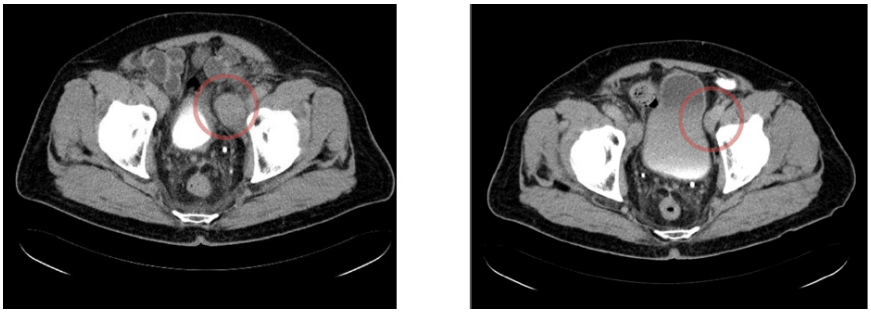



Source: Tokai Pharmaceuticals

Radiographic evidence of tumor shrinkage and overall tumor stabilization, as assessed by CT/MRI scans and bone scans, was seen in several patients. Of 39 patients who had measurable disease at baseline, 22 patients had stable disease (SD) and 2 patients (both from the 2600 mg/day dose cohort) had partial response (PR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Of 5 patients who had measurable disease at baseline in the 2600mg/day cohort, 2 had partial responses (PR), and a third patient had a near PR with a 28% reduction in maximal PSA levels. (The RECIST criteria define PR as a decrease of tumor size by ≥30%, and stable disease is achieved when the tumor has not increased in size by 20% and has not decreased by 30%, a partial response occurs when the tumor has decreased in size by at least 30%, and progressive disease occurs when the tumor has increased in size by at least 20% or new tumor lesions are identified.

### Exhibit 21: Representative CT Scan From a Patient in the 2600 mg/day Dose Cohort (#107-109)

**Baseline: 3.9 x 2.9 cm** **12 weeks: 2.8 x 1.3 cm**



**PR by RECIST, with 80% maximal PSA decrease**

Source: Tokai Pharmaceuticals

Galeterone was described as well tolerated in the ARMOR1 trial, with an aggregated 8,000 patient-days of dosing and individual exposure for up to 20 months. A maximum tolerated dose was not reached. Approximately 90% of treatment-emergent AEs reported for the first 12 weeks of treatment were grade 1 or 2 in severity and were generally manageable and reversible, with the majority considered not related or unlikely related to galeterone. The most common treatment-emergent AEs reported for the first 12 weeks of treatment were fatigue, increased aminotransferase, nausea, diarrhea and pruritus. The incidence of treatment-emergent AEs was comparable between cohorts and was not dose related. Eight patients (16%) experienced a grade 3 increase in aminotransferase indicating elevated liver enzyme levels; these events were asymptomatic and transient. Of the eight patients, two patients withdrew from the trial, and six patients restarted at the same dose level or one dose level below with no recurrence of a grade 3 or higher AE. There was one serious adverse event (SAE) assessed by the investigator as possibly related to galeterone: a 77-year old patient developed rhabdomyolysis (acute disintegration of muscle tissue) and acute renal failure. The patient was taking ZOCOR, a statin known to be associated with rhabdomyolysis; the patient also had underlying chronic renal insufficiency, renal artery stenosis, and hydronephrosis requiring stents and presented after a fall, all of which are risk factors for either acute renal failure or rhabdomyolysis.

### Phase 1 Healthy Volunteer Study (Reformulation)

During the ARMOR1 trial, Tokai conducted retrospective analysis that suggested the PIC formulation of galeterone had a food effect, which could have introduced variability into drug exposure levels. On the basis of this data, Tokai conducted two phase 1 trials (TOK-200-06 and TOK-200-07) in a total of 36 healthy volunteers to further evaluate the food effect of the PIC formulation. In these trials, volunteers received a 975 mg/day dose of galeterone in a fed state (FDA standardized high calorie/high fat meal or food supplement) or in a fasted state. The studies had a cross-over design with a 7-day washout between treatments. Galeterone was well tolerated by all volunteers in these trials.

The pharmacokinetic (PK) results from the trials demonstrated a substantial food effect with increased absorption of 10- to 12-fold in the fed state vs. the fasted state. As a result, Tokai pursued development of a new formulation to eliminate the food effect.

In another phase 1 trial of galeterone (TOK-200-08), Tokai explored a coated tablet using the active ingredient of the PIC formulation but decided not to take this formulation forward.

In the fourth phase 1 trial (TOK-200-09) in healthy volunteers (n=24), Tokai evaluated a proprietary spray dried dispersion formulation, a manufacturing technology that enhances bioavailability of poorly soluble compounds (such as galeterone), therefore minimizing food effect and decreasing exposure variability. To manufacture the spray dried dispersion formulation, galeterone and an inert polymer are dissolved in organic solvents and spray dried to produce solid dispersion powder, which is then tableted.

The fourth phase 1 trial was designed to assess single dose PK and relative bioavailability of the spray dried dispersion formulation under fed and fasted states as compared with the PIC formulation under fed state. Treatment with galeterone was well tolerated by all volunteers in this trial. This study demonstrated that the new formulation eliminated the food effect observed with the PIC formulation, reduced drug exposure variability and increased drug exposure levels. Tokai is using the proprietary spray dried dispersion formulation in tablet form in the ongoing ARMOR2 trial and plans to use it in all future trials.

### Phase 2 ARMOR2 Study

In December 2012, Tokai initiated ARMOR2, an open-label, two-part phase 2 study of galeterone. Part 1 is the dose-escalation portion of the study, whereas Part 2 evaluates the efficacy and safety of galeterone at the dose selected in Part 1.

Part 1 of the ARMOR2 trial has been completed. Part 1 enrolled 25 treatment-naïve CRPC patients with progressive disease and 3 ZYTIGA-refractory patients (defined as disease progression during treatment with ZYTIGA). The treatment-naïve CRPC patients received one of three escalating doses of galeterone: 1700, 2550, or 3400 mg/day. The ZYTIGA-refractory patients received doses of 2550 mg/day.

Patients were treated for an initial period of up to 12 weeks, followed by optional continuation for those who tolerated treatment and did not show signs of disease progression. Treatment was continued until disease progression or intolerance.

**At all dose levels in Part 1, at least 50% of patients achieved a ≥30% decrease in PSA.** Based on the recommendation from the trial's monitoring committee following review of safety, efficacy and PK data, Tokai selected the 2550 mg/day dose for further evaluation in Part 2.

Part 2 is designed to evaluate galeterone at the selected dose in four distinct advanced prostate cancer populations: Non-metastatic (M0) and metastatic (M1) treatment-naïve (TN) CRPC patients, ZYTIGA-refractory patients, and XTANDI-refractory patients (Exhibit 22).

**Exhibit 22: Patient Populations and Corresponding Primary Endpoints for Part 2 of ARMOR2**

| Patient Population | Patient Number | Primary Endpoint |
|---|---|---|
| Non-metastatic CRPC treatment-naïve patients | Up to 48 | Percentage of patients with a maximal reduction in PSA levels of ≥30% from baseline to week 12 |
| Metastatic CRPC treatment-naïve patients | | |
| ZYTIGA-refractory patients | Up to 30 | Percentage of change in PSA levels from baseline to week 12 |
| XTANDI-refractory patients | Up to 30 | |

Source: Tokai Pharmaceuticals

All patients in Part 2 receive treatment for an initial period of 12 weeks, followed by optional continuation for those who tolerated treatment and did not show signs of disease progression. Treatment will be continued until disease progression or intolerance. As of August 15, 2014, 93 patients had been enrolled in Part 2 of the trial.

The primary endpoint for the treatment-naïve CRPC cohort is percentage of patients with a maximal reduction in PSA levels of ≥30% from baseline to week 12. The primary endpoint for the ZYTIGA- and XTANDI-refractory CRPC cohorts is percentage of change in PSA levels from baseline to week 12. Additional endpoints include safety, response rate, circulating tumor cell (CTC) counts, and characterization, including the evaluation of C-terminal AR expression vs. N-terminal AR expression to identify C-terminal loss.

Enrollment inclusion criteria included pathologically-confirmed adenocarcinoma of the prostate with ongoing androgen blockade and serum testosterone <50 ng/dL, disease progression by PCWG2 guidelines, and ECOG performance status ≤2.

Recently, Tokai presented interim efficacy and safety data from the ARMOR2 trial at the European Society of Medical Oncology (ESMO) 2014 Congress in September 2014. As of August 15, 2014, the ARMOR2 study enrolled 107 patients with CRPC, including 22 TN M0 patients, 39 TN M1 patients, 37 ZYTIGA-refractory patients, and 9 XTANDI-refractory patients. Baseline patient and disease characteristics included a median age of 71 years, median PSA of 24 ng/dL, 8% Gleason score of 6, 36% Gleason score of 7, 49% Gleason score of 8-10, 77% metastatic disease (M1) at screening, 9% prior immunotherapy, 67% prior radiation therapy, 50% prior surgery, and 8% prior chemotherapy (Exhibit 23).

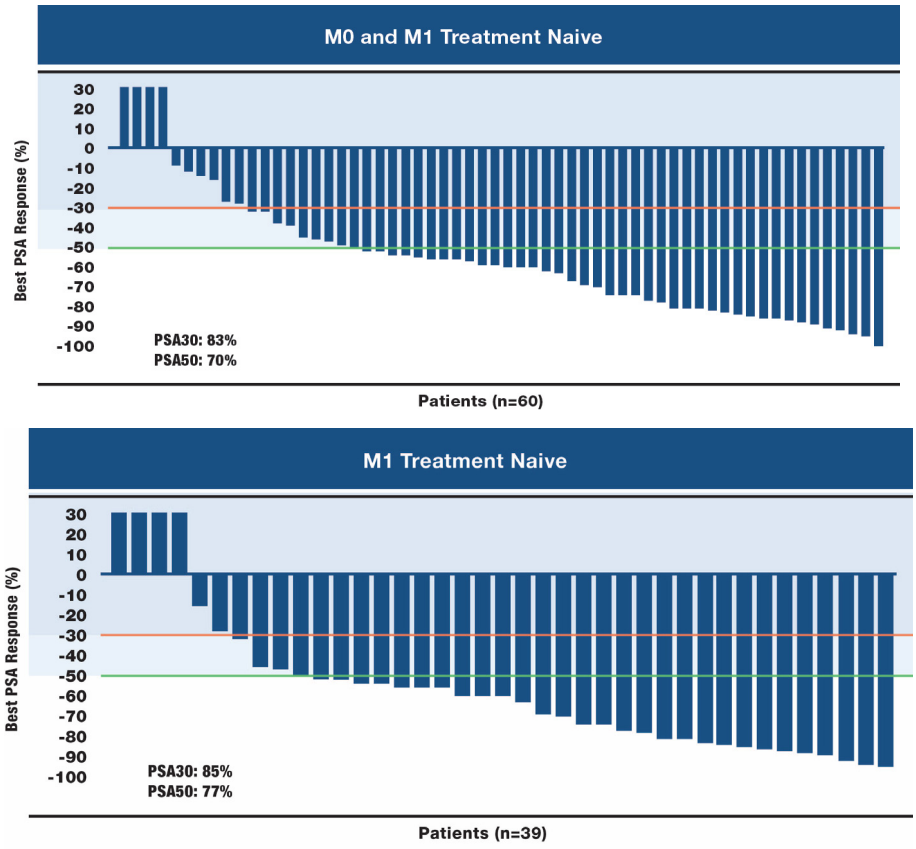
**Exhibit 23: Baseline Patient and Disease Characteristics in ARMOR2 (n=107)**

| Patient and Tumor Characteristics (N=107) | |
|---|---|
| Age, median (range), y | 71 (48–94) |
| Metastatic disease (M1) at screening, n (%) | 82 (76.6) |
| ECOG Status, n (%) | |
| 0 | 68 (63.6) |
| 1 | 36 (33.6) |
| 2 | 3 (2.8) |
| Prior therapies, n (%) | |
| Immunotherapy | 10 (9.3) |
| Radiation therapy | 72 (67.3) |
| Surgery | 53 (49.5) |
| Chemotherapy | 8 (7.5) |
| PSA, median (range), ng/dL | 24.1(2.0–1114) |
| Gleason score at diagnosis, n (%) | |
| 6 | 8 (7.5) |
| 7 | 38 (35.5) |
| 8–10 | 52 (48.6) |
| Missing data | 9 (8.4) |

Source: Tokai Pharmaceuticals

**ARMOR2's interim efficacy readout demonstrated that galeterone treatment resulted in clinically meaningful PSA reductions. Of 60 evaluable CRPC treatment-naïve patients (including both metastatic and non-metastatic), 83% achieved a maximal reduction in PSA levels of ≥30%, and 70% achieved a maximal reduction in PSA levels of ≥50% during the first 12 weeks of dosing (Exhibit 24, upper panel). Of 39 metastatic CRPC (mCRPC) treatment-naïve patients who received the 2550 mg/day dose, 85% had a maximal reduction in PSA levels ≥30%, and 77% had a maximal reduction in PSA levels ≥50% during the first 12 weeks of dosing (Exhibit 24, lower panel).** For context, in a phase 2 study of ZYTIGA in patients with treatment-naïve mCRPC (n=33), 79% of patients achieved a maximal reduction in PSA levels of ≥50% during the first 12 weeks of therapy. Baseline characteristics for the ZYTIGA phase 2 call included a median PSA of 23.0 ng/mL, median Gleason score of 8 (range 5-9), and a median of 2 prior hormonal therapies. Also for context, in a phase 1/2 study of XTANDI in patients with mCRPC, among 65 patients who were chemotherapy-naïve, 62% of patients achieved a maximal reduction in PSA levels of ≥50%, and 71% of patients achieved a maximal reduction in PSA levels of ≥30% during the first 12 weeks of therapy.

**Exhibit 24: Maximal PSA Reduction in Treatment-Naïve CRPC Patients Within 12 Weeks in ARMOR2**




Source: Tokai Pharmaceuticals

Of the 21 TN M0 patients in ARMOR2, 21% of patients achieved PSA decline, and there was no evidence of metastasis in any patient at 12 weeks.

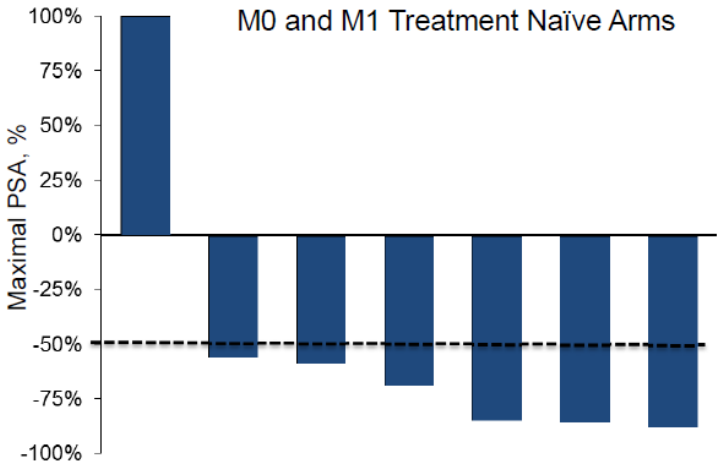
Of the 39 TN M1 patients, 90% of patients achieved PSA decline; among 18 patients evaluable according to the RECIST criteria (soft tissue/visceral), 17% had PR and 72% had SD; among 36 patients evaluable according to the Prostate Cancer Working Group 2 (PCWG2) bone scan criteria, 75% had SD. (According to the RECIST criteria, SD is defined as tumor size not increasing by 20% and not decreasing by 30%, and PR is defined as tumor decreasing by at least 30%. PCWG2 defines disease progression as ≥2 new lesions on bone scan compared with prior scan). For context, among chemotherapy-naïve mCRPC patients in XTANDI's phase 1/2 study (n=25), 36% of patients achieved PR and 44% had SD; according to bone scan at week 12, 63% had SD.

Of the 30 ZYTIGA-refractory patients, 37% achieved PSA decline; among 11 patients evaluable according to the RECIST criteria, 36% had SD; among 28 patients evaluable according to the PCWG2 criteria, 47% had SD.

Of the 9 XTANDI-refractory patients, 44% achieved PSA decline; among 7 patients evaluable according to the PCWG2 criteria, 57% had SD.

Tokai has conducted a retrospective subset analysis in 7 TN CRPC patients who were identified as having C-terminal loss. **In this subset analysis, galeterone demonstrated impressive activity in patients with AR C-terminal loss. Specifically, six of these seven patients had maximal PSA reduction ≥50%. All six responders completed the primary 12-week study phase and four are continuing in the extension phase, with time on treatment for extension patients ranging from 155 to >274 days (ongoing).** One patient with AR C-terminal loss did not respond; this patient discontinued therapy due to an unrelated AE after ~6 weeks in the study and did not complete the primary study phase.

**Exhibit 25: Galeterone Activity in Patients with AR C-terminal Loss**




Source: Tokai Pharmaceuticals

The AR C-terminal loss status was determined by analyzing circulating tumor cells (CTCs) on Epic Science's digital pathology-based CTC identification and characterization platform. The process involves staining of blood cells on slides using an antibody specific for the N-terminus of AR and another antibody specific for the C-terminus of AR. CTCs from a prostate tumor that harbors AR C-terminal loss will be stained positive for the N-terminus antibody but negative for the C-terminus antibody staining, whereas CTCs from a prostate tumor that has full-length AR will be stained with both antibodies. Blood samples were collected at baseline and on day 7 and day 84 (week 12). Tokai reported that 94% of samples (44 of 47 evaluable) had ≥1 CTCs/mL and that mean CTC count was higher in later-stage patients.

Galeterone was described as well tolerated. Approximately 90% of all treatment-emergent adverse events (AEs) were grade 1 or 2 in severity and were generally manageable and reversible. The majority of these events were considered not related or unlikely related to galeterone. In addition, **there were no reported cases of mineralocorticoid excess or seizure.** The most common AEs were nausea, fatigue, diarrhea, pruritus, vomiting, decreased appetite, hypokalemia, and elevated liver enzyme levels. Hypokalemia was more common in ZYTIGA-refractory (16.2%) and XTANDI-refractory (33%) patients compared with TN patients (10%). Grade 3/4 alanine/aspartate aminotransferase increases were observed in 7% of patients; these events were asymptomatic, transient and all patients recovered following temporary drug withdrawal. Serious adverse events (SAEs) that were assessed by the investigators as possibly related to treatment with galeterone included a case of angioedema in a patient who was taking a medication

associated with angioedema, an episode of dizziness and fainting in a patient with a history of nausea, diabetes, and hypertension who had discontinued treatment with galeterone four days prior to the episode, and a case of hypocalcemia and hyperparathyroidism in a patient with a history of hypocalcemia and hyperparathyroidism.

### Exhibit 26: Treatment-Emergent AEs in ARMOR2

| Treatment-Emergent Related AEs in ≥10% of Patients or Any CTCAE Grade 3/4 (N=107) | | |
|---|---|---|
| | CTCAE All Grades, n (%) | CTCAE Grade 3/4, n (%) |
| Nausea | 36 (33.6) | 1 (<1) |
| Fatigue | 35 (32.7) | 3 (2.8) |
| Pruritus | 28 (26.2) | 4 (3.7) |
| Decreased appetite | 22 (20.6) | 0 |
| Diarrhea | 17 (15.9) | 1 (<1) |
| Hypokalemia | 15 (14.0) | 3 (2.8) |
| Vomiting | 13 (12.1) | 0 |
| ALT increased | 9 (8.4) | 5 (4.7) |
| AST increased | 9 (8.4) | 2 (1.9) |
| Rash | 8 (7.5) | 1 (<1) |
| Bilirubin elevated | 7 (6.5) | 1 (<1) |
| Alkaline phosphatase increased | 5 (4.7) | 1 (<1) |
| Hypertension | 4 (3.7) | 2 (1.9) |
| Creatinine phosphokinase increased | 2 (1.9) | 1 (<1) |
| Dyspnea | 2 (1.9) | 1 (<1) |
| Transaminases increased | 2 (1.9) | 1 (<1) |
| Anemia | 1 (<1) | 1 (<1) |
| Angioedema | 1 (<1) | 1 (<1) |
| Fluid retention | 1 (<1) | 1 (<1) |
| Hyperparathyroidism | 1 (<1) | 1 (<1) |
| Hypocalcemia | 1 (<1) | 1 (<1) |
| Hyponatremia | 1 (<1) | 1 (<1) |
| Malaise | 1 (<1) | 1 (<1) |
| Syncope | 1 (<1) | 1 (<1) |

Source: Tokai Pharmaceuticals

## Phase 3 ARMOR3-SV Study Design

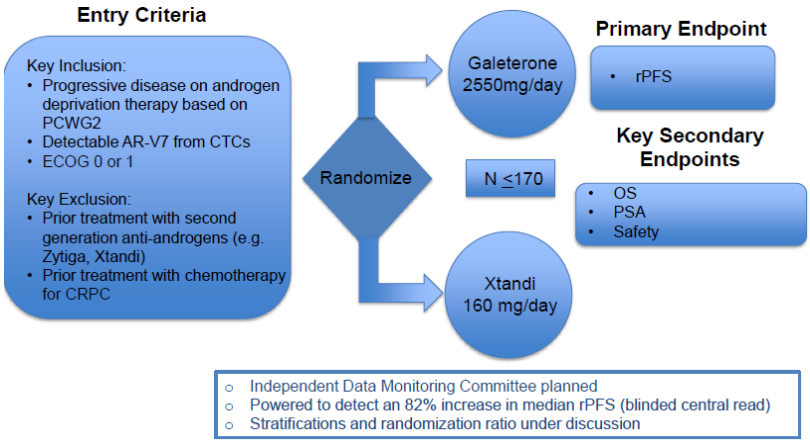
Tokai is currently finalizing its plans for the pivotal phase 3 clinical trial of galeterone, referred to as ARMOR3-Splice Variant (ARMOR3-SV). Tokai met with FDA in August 2014 and discussed its plans for a pivotal phase 3 clinical trial to support the approval for galeterone. Based on these discussions, **Tokai expects its ARMOR3-SV to be a randomized, open-label study comparing galeterone vs. XTANDI in up to 170 treatment-naïve mCRPC patients whose prostate tumors express the AR-V7 splice variant.** Tokai expects the trial to be conducted at approximately 60-80 sites worldwide. Patients will be randomized to receive either galeterone 2550 mg/day or XTANDI 160 mg/day. All patients will continue to receive treatment until radiographic evidence of disease progression or patient withdrawal due to AEs or other reasons. **The primary endpoint of the study, as agreed upon by FDA, is radiographic progression-free survival (rPFS) measured from the time of patient randomization to the time of radiographic evidence of disease progression or time of death from any cause.** Secondary endpoints will include PSA reduction, overall survival

and safety. To achieve the primary endpoint, results from the trial must demonstrate an 82% increase in median rPFS in the galeterone arm compared with the XTANDI arm, an outcome likely to be deemed as clinically relevant.

Tokai believes that it may need to screen more than 1,000 patients to identify and enroll the target AR-V7-positive patients. The proportion of CRPC patients with AR-V7 is subject to varying projections in the literature. **A recent study based on a small number of patients (n=62) suggested that the prevalence of AR-V7 was 12% in the pre-XTANDI, pre-ZYTIGA CRPC patient population (and 25% in post-XTANDI, 51% in post-ZYTIGA, and 67% in post-XTANDI & ZYTIGA).**

Other details of the trial design, such as randomization ratio, stratification factors and plans for a futility analysis, are still being considered by Tokai and will be contained in the final protocol submitted to FDA. Tokai plans to establish an independent data monitoring committee and to have the data collected and analyzed in such a way that Tokai is blind to the data (even though the study is open-label).

### Exhibit 27: Study Design of Phase 3 ARMOR3-SV




Source: Tokai Pharmaceuticals

Tokai expects patients with the AR-V7 splice variant to be identified by a central laboratory using a validated, sensitive, CTC-based AR-V7 specific assay. Tokai plans to contract with third parties to develop an *in vitro* diagnostic test for AR-V7 using widely available technologies. According to discussions with FDA, Tokai will need to submit an investigational device exemption application (IDE) to FDA before screening patients in the trial. Tokai also understands from its discussion with FDA that the companion diagnostic test will need to be approved by FDA through the Premarket Approval (PMA) process. Tokai is currently finalizing its strategy for developing the AR-V7 assay.

**Tokai expects to initiate the pivotal ARMOR3-SV study in 1H15 (after submitting the IDE for the AR-V7 assay), with top-line results targeted in 2016.**

Tokai also plans to explore galeterone's utility in other patient populations in prostate cancer, including early-stage prostate cancer and the treatment of prostate cancer in combination with currently marketed prostate cancer therapies, including with XOFIGO (radium-223), and novel targeted agents. Lastly, Tokai also plans to explore galeterone's utility in other diseases in which the androgen receptor signaling pathway plays a role.

# Other Secondary Hormonal Therapies in Development

## XTANDI

Medivation and partner Astellas are developing XTANDI in various additional CRPC indications.

The 1,500-patient phase 3 PROSPER trial evaluates XTANDI in a high-risk subgroup of non-metastatic CRPC patients who are progressing despite ADT, but who are asymptomatic and have no prior or present evidence of metastatic disease. Patients are randomized to XTANDI or placebo. The primary endpoint of the trial is metastasis-free survival at ≥16 weeks. The estimated primary completion of the PROSPER study is in August 2015.

XTANDI is also in two phase 2 trials in CRPC. The TERRAIN trial evaluates XTANDI in ~370 men with mCRPC, whereas the STRIVE trial evaluates XTANDI in ~400 patients with either metastatic or non-metastatic CRPC. Both studies compare XTANDI vs. CASODEX, with a primary endpoint of PFS. Both studies have completed enrollment. The estimated primary completion date is October 2014 for TERRAIN and June 2015 for STRIVE.

The phase 4 PLATO trial evaluates the potential clinical benefit of continuing XTANDI treatment in patients with chemotherapy-naive mCRPC who progressed on XTANDI. The study compares continued treatment with XTANDI + ZYTIGA + prednisone vs. ZYTIGA + prednisone alone in patients with pre-chemotherapy mCRPC whose disease has progressed following XTANDI therapy. The primary endpoint of the study is PFS. The study is designed to enroll 500 patients, with an estimated primary completion date of June 2016.

The Alliance for Clinical Trials in Oncology is conducting a 1,200-patient phase 3 study evaluating XTANDI vs. XTANDI + ZYTIGA + prednisone in patients with mCRPC. The primary endpoint is OS, and the estimated primary completion date is in December 2019.

## ZYTIGA

Johnson & Johnson is evaluating ZYTIGA in additional CRPC indications.

An ongoing phase 3 study compares ZYTIGA + prednisone + ADT vs. ADT alone in newly diagnosed, high-risk metastatic, hormone-naïve prostate cancer. This study plans to enroll 1,200 patients with newly diagnosed (within 3 months prior to randomization) metastatic prostate cancer with at least two of the following high-risk prognostic factors: Gleason score ≥8, presence of ≥3 lesions on bone scan, presence of measurable visceral (exclude lymph node disease) metastasis on CT or MRI scan. Patients will be randomized 1:1 to ZYTIGA + prednisone + ADT (GnHR agonists or surgical castration according to local guidelines) or placebo + ADT. Patients are treated until disease progression, unexpected toxicity, or withdrawal of consent. The primary endpoints are OS and radiographic PFS. The primary completion date is in July 2018.

A single-arm phase 2 study (IMAAGEN) evaluates ZYTIGA + prednisone added to standard of care GnRH analogs in high-risk non-metastatic CRPC patients. The study enrolled 131 patients with non-metastatic CRPC but with clinical features placing them at high risk of developing metastatic disease, including PSA ≥10 ng/mL or PSA doubling time ≤10 months. The primary endpoint was PSA response at 6 months. Baseline median PSA was 13.7 ng/mL. In an interim analysis reported at the 2014 ASCO annual meeting, 87% of patients had ≥50% reduction in PSA, and 60% had ≥90% reduction in PSA at the end of the 6-month treatment. The primary completion of the IMAAGEN study is in October 2014.

## ARN-509

Johnson & Johnson's ARN-509 is a second-generation antiandrogen that selectively binds to the ligand-binding domain of the AR, blocks its nuclear translocation and suppresses DNA binding to androgen responsive elements.

ARN-509 is currently in a phase 3 study (SPARTAN) in non-metastatic CRPC. The study plans to randomize 1,200 patients at a ratio of 2:1 to ARN-509 (240 mg capsules administered orally once daily) or placebo. All study participants continue to receive their previous treatments before trial entry. Patients previously treated with CYP17 inhibitors or second-generation anti-androgens are excluded. The primary endpoint of the phase 3 study is metastasis-free survival. Secondary endpoint included overall survival, time to symptomatic progression, time to initiation of cytotoxic chemotherapy, PFS, and time to metastasis. The estimated primary completion of the study is in December 2016.

ARN-509 is in a phase 2 study in several distinct populations of CRPC, including high-risk non-metastatic CRPC, chemotherapy-naïve mCRPC, and chemotherapy-naïve mCRPC post-ZYTIGA.

Results in high-risk non-metastatic CRPC were recently presented at the 2014 ESMO Congress (February 2014 data cut-off). These patients had no radiographic evidence of metastases, and had high risk for disease progression based on PSA ≥8 ng/mL within 3 months of enrollment and/or PSA doubling time ≤10 months. All patients received ARN-509 240 mg/d. The primary endpoint of the study is the percentage of patients reaching at least a 50% reduction in PSA as compared with baseline at 12 weeks according to the PCWG2 criteria. The study enrolled 47 high-risk non-metastatic CRPC patients, with baseline characteristics including median PSA of 10.7 ng/mL, 45% PSA doubling time ≤10 months, 57% Gleason score ≤7, and 76% ECOG performance status score of 0. All patients received prior treatment with a GnRH analog with or without a first-generation antiandrogen.

At 12 weeks, 91% of patients achieved PSA decline ≥50% from baseline. At 24 and 36 weeks, 87% and 48% of patients, respectively, achieved PSA decline ≥50%. At a median follow-up of 20.2 months, 57% of patients remained on study. Reasons for discontinuation included disease progression (14%), AEs (14%), or other reasons (16%). ARN-509 was described as well tolerated in the phase 2 study. Most common treatment-emergent AEs included fatigue (57%), diarrhea (41%), nausea (29%), dysgeusia (20%), arthralgia (18%), and weight loss (16%). No seizures were reported.

Results in patients with chemotherapy-naïve mCRPC with or without prior ZYTIGA treatment were presented at the 2014 ASCO annual meeting (July 2013 data cut-off). All patients had progressive disease based on rising PSA and/or imaging. Patients with prior chemotherapy were excluded. The post-ZYTIGA cohort required treatment with ZYTIGA for ≥ 6 months. All patients received 240 mg/d ARN-509. The primary endpoint was PSA response at 12 weeks per PCWG2 criteria. The study enrolled 25 mCRPC and 21 post-ZYTIGA mCRPC patients, with baseline characteristics including 57% ECOG score of 0, 52% Gleason score ≥ 8, median PSA 14.7 ng/mL (mCRPC) and 58.4 ng/mL (post-ZYTIGA).

In the mCRPC cohort (n=25), PSA response (≥50% decline from baseline) was achieved in 88% of patients at week 12, 76% of patients at week 24, and 68% of patients at week 36, with median time to PSA progression of 16.3 months. Among eight patients with measurable disease, 50% of patients achieved PR and 25% of patients achieved SD. Median PFS was 19.2 months.

In the post-ZYTIGA mCRPC cohort (n=21), PSA response (≥50% decline from baseline) was achieved in 24% of patients at week 12, 10% of patients at week 24, and 0% of patients at week 36, with median time to PSA progression of 3.7 months. Among 11 patients with measurable disease, there was no PR and 36% of patients achieved SD. Median PFS was 8.3 months.

Median duration on ARN-509 treatment was 9.2 months, and 67% of patients discontinued study due to disease progression (39%), AEs (11%), consent withdrawal (9%), or other reasons (9). ARN-509 was described as well tolerated. The most common treatment-related AEs were fatigue (46%), nausea (28%), diarrhea (22%) and abdominal pain (17%).

Lastly, ARN-509 is also in a phase 2 study in patients with biochemically relapsed hormone sensitive prostate cancer. This phase 2 study plans to evaluate 12 months of therapy with ARN-509 alone, physician's choice of GnRH agonist alone (e.g. ELIGARD, LUPRON DEPOT, ZOLADEX, TRELSTAR), or ANR-509 + GnRH agonist in 90 patients. Enrollment criteria include rising PSA levels after local therapy (radical prostatectomy, external beam radiation, or brachytherapy), PSA doubling time ≤12 months, no metastasis, no previous ADT (including CASODEX) within 12 months of study entry, and no bilateral orchiectomy. The primary endpoint of the study is mean change in quality of life measured by total FACT-P score after 12 months of treatment. The estimated primary completion of the study is in February 2015.

## ODM-201

Orion Corporation and partner Bayer Healthcare are developing ODM-201, an AR antagonist that is more potent than XTANDI and ARN-509 (Exhibit 28). ODM-201 also has negligible brain penetration at pharmacological doses, as demonstrated in nonclinical studies. This could result in a reduced risk for seizure, a class AE for second-generation AR antagonists due to their cross-reactivity with the $GABA_A$ channel.

### Exhibit 28: Potency of ODM-201 vs. Other Second-Generation AR Antagonists

| Compound | AR affinity Ki (nM) | Antagonism WT AR IC50 (nM) |
|---|---|---|
| Enzalutamide | 78 | 155 |
| ARN-509 | 53 | 168 |
| ODM-201 | 9 | 65 |
| ORM-15341 (main metabolite) | 8 | 25 |

Source: www.orion.fi

The ARADES trial was an open-label phase 1/2 study with a phase 1 dose-escalation part and a phase 2 dose expansion part. The phase 1 part evaluated doses of ODM-201 ranging from 200-1800 mg, with no dose-limiting toxic effects observed and maximum tolerated dose not reached. . The phase 2 part evaluated three dose levels of ODM-201 (100, 200, and 700 mg twice daily) in 124 patients with progressive mCRPC, including patients who were chemotherapy- and ZYTIGA-naïve (n=37), post-chemotherapy but ZYTIGA-naïve (n=32), and post-ZYTIGA (including both pre- and post-chemotherapy) (n=55). The primary endpoint of the phase 2 part was PSA response (≥50% reduction) at week 12.

In the chemotherapy-naïve/ZYTIGA-naïve cohort, 69% and 86% of patients from the 200 mg BID (n=13 evaluable) and 700 mg BID group (n=7 evaluable) achieved ≥50% PSA reduction from base line at 12 weeks, with ~45% from either group achieving ≥90% PSA reduction. In terms of soft tissue and bone responses, 30% of 20 soft-tissue evaluable patients achieved CR or PR, and 55% achieved SD; 82% of 28 bone scan evaluable patients achieved SD.

In the post-chemotherapy/ZYTIGA-naïve cohort, 11% and 36% of patients from the 200 mg BID (n=9 evaluable) and 700 mg BID group (n=11 evaluable) achieved ≥50% PSA reduction from base line at 12 weeks. In terms of soft tissue and bone responses, 10% of 20 soft-tissue evaluable patients achieved CR or PR, and 50% achieved SD; 62% of 26 bone scan evaluable patients achieved SD.

In the post-ZYTIGA cohort, 18% and 7% of patients from the 200 mg BID (n=17 evaluable) and 700 mg BID group (n=15 evaluable) achieved ≥50% PSA reduction from base line at 12 weeks. In terms of soft tissue and bone responses, 6% of 34 soft-tissue evaluable patients achieved CR or PR, and 53% achieved SD; 54% of 37 bone scan evaluable patients achieved SD.

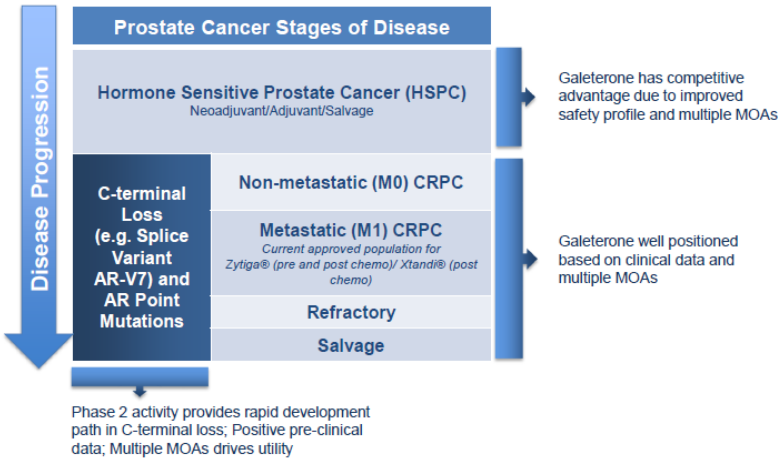
ODM-201 was described as having a favorable safety profile in phase 1/2 experience. The most common AEs were fatigue or asthenia (12%), hot flush (5%), and decreased appetite (4%). One patient (1%) had a Grade 3 AE (fatigue), and no patients had a Grade 4 AE.

In September 2014, Bayer and Orion initiated a phase 3 study, ARAMIS, to evaluate ODM-201 in patients with non-metastatic CRPC who are at high risk for developing metastatic disease. The study plans to randomize 1,500 patients 2:1 to ODM-201 600 mg twice daily or matching placebo. Randomization will be stratified by PSA doubling time (≤6 months vs >6 months) and use of osteoclast-targeted therapy. The primary endpoint of the study is metastasis-free survival (MFS). The primary completion date of the ARAMIS study is in March 2018.

## Commercial Strategy and Opportunity

The initial target indication for galeterone, and the focus of the current phase 3 study, is treatment-naïve mCRPC with AR C-terminal loss. This patient population accounts for approximately 12% of all CRPC patients. Tokai may also explore galeterone in additional prostate cancer indications, such as a broader prostate cancer patient population with the goal of preventing resistance to therapy, or in the population of ZYTIGA- and XTANDI-refractory patients given their increased tendency to harbor AR-V7 splice variants.

### Exhibit 29: Potential Patient Segments for Galeterone




Source: Tokai Pharmaceuticals

Tokai has worldwide development and commercialization rights to galeterone. If galeterone is approved in the U.S., Tokai intends to build a urology/oncology-focused specialty sales organization to support the commercialization of galeterone in the U.S., and to seek collaboration with third parties to commercialize galeterone outside the U.S.

Prostate cancer represents a large and growing market. In the U.S. alone, an estimated 233,000 new cases of prostate cancer will be diagnosed in 2014, with an estimated 29,000 deaths from the disease. It is estimated that 310,000 men in the U.S. have advanced prostate cancer and are eligible for treatment with drug therapy.

Sales of prostate cancer drugs are expected to increase from approximately $6.0 billion in 2013 to more than $9.0 billion in 2021, due to a growing aged population, rising incidence, and the introduction of new treatments. Two of the newly approved therapies for metastatic CRPC, ZYTIGA (approved in 2011) and XTANDI (approved in 2012), have both experienced rapid growth, with global sales of $1.7 billion and $445 million, respectively, in 2013. Despite the success of these new drugs, the need for new treatment options remains, as each of these drugs has treatment limitations and may not be effective in CRPC patients whose prostate tumors express AR with C-terminal loss.

## Intellectual Property

As of July 31, 2014, Tokai's galeterone patent portfolio included 2 issued U.S. patents, 10 U.S. provisional and non-provisional patent applications, 1 issued foreign patent, and 34 foreign applications. Tokai also had rights under its license agreement with the University of Maryland, Baltimore (UMB) to 5 issued U.S. patents and 42 issued foreign patents as well as 3 U.S. patent applications and 11 foreign applications. Tokai's owned and licensed patent and patent applications, if issued, are expected to expire on various dates from 2017 through 2034, without taking into account any possible patent term extensions.

Tokai has an exclusive license from UMB for a U.S. patent covering compositions and methods of use of a class of compounds encompassing galeterone, which expires in 2017. Tokai does not expect this patent to provide significant protection for galeterone, given its expiration date and the anticipated timing of development and commercialization of galeterone. Tokai has no patent protection specifically covering the chemical structure of galeterone. As a result, Tokai has filed for or licensed galeterone-related patents and patent applications covering methods of use, pharmaceutical compositions, combination treatments, prodrugs, metabolites, and analogs of galeterone and their use.

### Method of Use

Tokai has licensed from UMB a U.S. patent covering a method of treating prostate cancer in a human subject by administering galeterone (US 5994335), which is expected to expire in 2027. The license also includes granted patents in the European Patent Convention and Japan covering the use of galeterone to treat prostate disease, including prostate cancer and prostatic hyperplasia. Similar patents have been granted or allowed in Australia, Canada, Hong Kong, South Korea, Mexico, New Zealand, Singapore, South Africa, and the Eurasian Patent Organization. These patents are expected to expire in 2026. In addition, Tokai has pending applications in Brazil, China, the European Patent Convention, India, Israel, Indonesia, and Japan.

Tokai has also filed a Patent Cooperation Treaty (PCT) application covering the use of galeterone in treating prostate cancer mediated by AR variants, including splice variants such as AR-V7, as well as the use of biomarkers in identifying patients who are expected to respond to treatment with galeterone. This application is jointly owned with UMB and the University of Washington. The term of a patent derived from this PCT application, if issued, would be expected to expire in 2034.

### Pharmaceutical Compositions

Tokai has filed U.S. and international patent applications relating to a galeterone formulation and its use where the galeterone is present in a spray dried dispersion. Tokai has pending applications in the U.S., EU, Australia, Brazil, Canada, China, India, and Japan, with patent terms, if issued, expected to expire in 2032. In addition, Tokai has licensed from UMB a U.S. patent application covering a pharmaceutical composition of galeterone, and if issued, the term of any patent claiming priority to this application would be expected to expire in 2026.

### Combination Treatments

Tokai has filed patent applications or licensed from UMB patent applications covering the use of galeterone in combination with other therapeutic drugs (inhibitors of the PI3K/Akt pathway). Tokai has pending applications in the U.S., EU, Australia, Canada, and Japan. The term of any patent in this family, if issued, would be expected to expire in 2032.

### Prodrugs, Metabolites, and Analogs

Tokai has filed patent applications or licensed from UMB patent applications directed to prodrugs, metabolites, or analogs of galeterone. If issued, the term of the resulting patent would be expected to expire in 2029. Tokai has also filed patent applications in the U.S. and certain other countries including Australia, Brazil, Canada, China, the EU, India, and Japan directed to other prodrugs of galeterone. If issued, the term of the resulting patents would be expected to expire in 2030. In addition, Tokai has filed patent applications in the U.S. and certain other countries including Australia, Brazil, Canada, China, the EU, India, and Japan directed to compounds that have been identified as metabolites of galeterone and which may be biologically active. If issued, the term of the resulting patents would be expected to expire in 2030. Tokai has also obtained a license to a UMB PCT patent application directed to analogs of galeterone that disrupt AR signaling by degrading the androgen receptor. The term of any patent, if issued, claiming priority to this PCT patent application would be expected to extend to 2034.

### License Agreement With University of Maryland, Baltimore

In May 2006, Tokai entered into a master license agreement with UMB. Pursuant to the license agreement, UMB granted Tokai an exclusive worldwide license, with the right to sublicense, under certain patents and patent applications to make, have made, use, sell, offer to sell, and import certain anti-androgen steroids including galeterone (referred to as licensed products), and to otherwise practice the patent rights in any manner, for the prevention, diagnosis, treatment or control of any human or animal disease. Tokai subsequently acquired exclusive rights to certain improvements to the licensed products (licensed improvements) under three amendments to the license agreement. In March 2009, the license agreement was amended to grant Tokai an exclusive license to oral prodrugs of the licensed products. In April 2012, the license agreement was amended to grant Tokai an exclusive license to compositions and methods of inducing endoplasmic reticulum stress. In October 2013, the license agreement was amended to grant Tokai an exclusive license to a patent application directed to analogs of galeterone that disrupt AR signaling by degrading the androgen receptor.

In consideration for the rights granted, Tokai made an upfront payment to UMB of $20,000 following the execution of the license agreement and a payment of $10,000 following the execution of each of the March 2009, April 2012, and October 2013 amendments. Tokai is obligated to pay UMB an annual maintenance fee of $10,000 each year until the first commercial sale. In addition, Tokai paid UMB a $50,000 milestone payment upon the submission of its IND for galeterone and a $40,000 milestone payment upon the issuance of the first patent related to UMB's prodrug patent application. Tokai is obligated to make an additional $50,000 milestone payment to UMB for each additional IND and a $100,000 milestone payment upon the approval of each NDA by FDA. Tokai must also pay UMB low-single-digit percentage royalties on aggregate worldwide net sales of licensed products, on a product-by-product and country-by-country basis until the later of the expiration of the last-to-expire applicable licensed patent or ten years after first commercial sale of the applicable licensed product. The minimum annual royalty payment to UMB is $50,000 beginning in the first year after commercial sales.

## Management

**Jodie P. Morrison** has served as president and chief executive officer and as a member of the board of directors since March 2013. From December 2006 to March 2013, Ms. Morrison held senior positions at the company, including chief operating officer, head of clinical affairs and program operations, and vice president of clinical affairs and program operations. Prior to joining Tokai, Ms. Morrison served as director of clinical operations and medical affairs at Dyax Corporation. Prior to joining Dyax, Ms. Morrison held clinical management positions at both Curis and at Diacrin. Ms. Morrison received a B.A. in neuroscience from Mount Holyoke College, her clinical research certification from the Boston University School of Medicine, and her business training through the Greater Boston Executive Program at the MIT Sloan School of Management.

**John S. McBride** has served as chief operating officer since February 2014 and chief financial officer from April to September 2014. From March 2012 to February 2014, Mr. McBride founded and served as president of Alliance Life Science Advisors, a consulting firm focused on assisting life science companies with strategic planning, business development, and financing projects. Prior to founding Alliance Life Science Advisors, Mr. McBride was an independent consultant from January 2009 until March 2012. In addition, Mr. McBride previously served as executive vice president and chief operating officer of Gloucester Pharmaceuticals, global head of oncology licensing at Pharmacia Corporation, executive vice president, business operations and chief financial officer at CytoTherapeutics, vice president, business development and treasurer at Phytera, vice president, commercial development at Sparta Pharmaceuticals, and vice president, business development at U.S. Bioscience. Currently, Mr. McBride serves as a member of the board of directors of Intezyne. From August 2008 to June 2013, Mr. McBride served as a member of the board of directors of Niiki Pharma. Mr. McBride holds a B.S. in biochemistry and an M.S. in chemical engineering from the University of Wisconsin and an M.B.A. from the Wharton School, University of Pennsylvania.

**Karen J. Ferrante, M.D.** has served as head of research and development and chief medical officer since April 2014. Prior to joining the company, Dr. Ferrante served as oncology therapeutic area head and Takeda Cambridge, USA site head for Takeda Pharmaceuticals from May to July 2013, and held senior positions at Millennium Pharmaceuticals, which was acquired by Takeda in May 2008, including chief medical officer, and head of research and development and senior vice president, clinical development from September 2007 to May 2013. Dr. Ferrante previously held positions of increasing responsibility at Pfizer Global Research & Development, including vice president and therapeutic area clinical leader in oncology development, and served as associate director of clinical oncology at Bristol-Myers Squibb Company (BMS). Prior to joining BMS, Dr. Ferrante was a staff physician at the Beth Israel Deaconess Hospital. She also served as instructor, clinical instructor, and clinical fellow in medicine at the Harvard Medical School while completing her internship and residency in internal medicine followed by her fellowship in hematology and oncology at Beth Israel Deaconess Hospital. Currently, Dr. Ferrante serves as a member of the board of directors of Progenics Pharmaceuticals. Dr. Ferrante holds a B.S. in chemistry and biology from Providence College and an M.D. from Georgetown University.

**Lee H. Kalowski** has served as chief financial officer since September 2014. Prior to joining the company, Mr. Kalowski served in global biotechnology equity research at Credit Suisse where he covered companies in the biopharmaceutical industry, including companies developing prostate cancer therapies, as a vice president from January 2012 to September 2014, as a senior analyst

from May 2011 to September 2014, and as an associate from June 2010 until May 2011. Prior to joining Credit Suisse, Mr. Kalowski worked in mergers and acquisitions for the pharmaceutical division of Johnson & Johnson from May to August 2009 while attending the Wharton School from July 2008 to May 2010. Prior to that, Mr. Kalowski held global pharmaceutical equity research positions at Sanford C. Bernstein & Co. and Prudential Equity Group. Mr. Kalowski received a B.A. in biology and economics from Union College and an M.B.A. in finance and health care management from the Wharton School, University of Pennsylvania.

**Other companies mentioned (priced as of the close on October 10, 2014):**

Array BioPharma (ARRY, $3.13, Market Perform)
Clovis Oncology (CLVS, $44.67, Not Rated)
Dendreon (DNDN, $0.90, Not Rated)
Endocyte (ECYT, $5.48, Not Rated)
Exelixis (EXEL, $1.45, Not Rated)
Infinity Pharmaceuticals (INFI, $12.51, Not Rated)
Johnson & Johnson (JNJ, $101.23, Outperform, covered by Joanne Wuensch)
Medivation (MDVN, $93.00, Not Rated)
Sanofi (SNY, $52.43, Not Rated)
Sunesis Pharmaceuticals (SNSS, $1.05, Not Rated)
Tesaro (TSRO, $26.09, Outperform)

## Exhibit 30: TKAI Income Statement 2014E-2020E

| INCOME STATEMENT ($M) | 2014E | 2015E | 2016E | 2017E | 2018E | 2019E | 2020E |
|---|---|---|---|---|---|---|---|
| **REVENUES** | | | | | | | |
| Product Revenue | $ - | $ - | $ - | $ - | $ - | $ 72.4 | $ 344.1 |
| Collaboration Revenue | - | - | - | - | - | - | - |
| Sponsored Research and Other Revenue | - | - | - | - | - | - | - |
| **TOTAL REVENUES** | **$ -** | **$ -** | **$ -** | **$ -** | **$ -** | **$ 72.4** | **$ 344.1** |
| **EXPENSES (GAAP)** | | | | | | | |
| Cost of Goods Sold (COGS) | $ - | $ - | $ - | $ - | $ - | $ 7.2 | $ 32.7 |
| R&D Expense | 15.9 | 16.8 | 17.6 | 18.4 | 24.5 | 28.0 | 32.0 |
| SG&A Expense | 5.6 | 6.0 | 6.8 | 7.6 | 8.0 | 20.0 | 33.0 |
| Other | - | - | - | - | - | - | - |
| **TOTAL EXPENSES** | 21.6 | 22.8 | 24.4 | 26.0 | 32.5 | 55.2 | 97.7 |
| **Operating Income** | **(21.6)** | **(22.8)** | **(24.4)** | **(26.0)** | **(32.5)** | **17.1** | **246.4** |
| Depreciation and amortization | - | - | - | - | - | - | - |
| EBIT | (21.6) | (22.8) | (24.4) | (26.0) | (32.5) | 17.1 | 246.4 |
| Interest and other income | - | - | - | - | - | - | - |
| Interest and other expense | - | - | - | - | - | - | - |
| Other Income (Expense) | 0.1 | - | - | - | - | - | - |
| Interest and Other Income (Expense) | 0.1 | - | - | - | - | - | - |
| Pre-Tax Income | (21.5) | (22.8) | (24.4) | (26.0) | (32.5) | 17.1 | 246.4 |
| Income Taxes | - | - | - | - | - | - | - |
| **Net Income (GAAP)** | **$ (21.5)** | **$ (22.8)** | **$ (24.4)** | **$ (26.0)** | **$ (32.5)** | **$ 17.1** | **$ 246.4** |
| EPS (GAAP) (basic) | $ (2.55) | $ (0.84) | $ (0.74) | $ (0.63) | $ (0.73) | $ 0.28 | $ 4.25 |
| **EPS (GAAP) (diluted)** | **$ (2.55)** | **$ (0.84)** | **$ (0.74)** | **$ (0.63)** | **$ (0.73)** | **$ 0.28** | **$ 4.25** |
| Total of Reconciliation Items | - | - | - | - | - | - | - |
| Net Income (Non-GAAP) | $ (21.5) | $ (22.8) | $ (24.4) | $ (26.0) | $ (32.5) | $ 17.1 | $ 246.4 |
| Impact of Adjustments to EPS | - | - | - | - | - | - | - |
| EPS (Non-GAAP) (basic) | $ (2.55) | $ (0.84) | $ (0.74) | $ (0.63) | $ (0.73) | $ 0.28 | $ 4.25 |
| EPS (Non-GAAP) (diluted) | $ (2.55) | $ (0.84) | $ (0.74) | $ (0.63) | $ (0.73) | $ 0.28 | $ 4.25 |
| Weighted average shares outstanding (basic) | 13.5 | 27.0 | 32.9 | 41.6 | 44.6 | 53.4 | 57.8 |
| Weighted average shares outstanding (diluted) | 13.5 | 27.0 | 32.9 | 41.6 | 44.6 | 53.3 | 57.7 |

Source: Company reports and BMO Capital Markets.

## Exhibit 31: TKAI Balance Sheet 2014E-2020E

| BALANCE SHEET (M) | 2014E | 2015E | 2016E | 2017E | 2018E | 2019E | 2020E |
|---|---|---|---|---|---|---|---|
| **Current Assets** | | | | | | | |
| Cash and cash equivalents | $ 9.9 | $ 37.1 | $ 87.7 | $ 61.7 | $ 29.2 | $ 46.4 | $ 292.7 |
| Short-term investments | - | - | - | - | - | - | - |
| **Total cash, cash equivalents, and short-term investments** | $ 9.9 | $ 37.1 | $ 87.7 | $ 61.7 | $ 29.2 | $ 46.4 | $ 292.7 |
| Accounts Receivables | - | - | - | - | - | - | - |
| Restricted Cash | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Inventories | - | - | - | - | - | - | - |
| Prepaid and other current assets | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| **Total Current Assets** | $ 10.2 | $ 37.4 | $ 88.0 | $ 62.0 | $ 29.5 | $ 46.7 | $ 293.0 |
| Leasehold improvements | - | - | - | - | - | - | - |
| Property and equipment, net | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Patents and licensed technology | - | - | - | - | - | - | - |
| Intangibles, net | - | - | - | - | - | - | - |
| Other assets | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 |
| **TOTAL ASSETS** | **$ 12.3** | **$ 39.5** | **$ 90.1** | **$ 64.1** | **$ 31.6** | **$ 48.7** | **$ 295.1** |
| | | | | | | | |
| **Current Liabilities** | | | | | | | |
| Accounts payable | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 |
| Accrued payroll | - | - | - | - | - | - | - |
| Accrued expenses | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Accrued interest | - | - | - | - | - | - | - |
| Payables to related parties | - | - | - | - | - | - | - |
| Income taxes payable | - | - | - | - | - | - | - |
| Current portion of other long-term obligations | - | - | - | - | - | - | - |
| Current portion of deferred rent | - | - | - | - | - | - | - |
| Current portion of deferred revenue | - | - | - | - | - | - | - |
| Other current liabilities | - | - | - | - | - | - | - |
| **Total Current Liabilities** | $ 3.7 | $ 3.7 | $ 3.7 | $ 3.7 | $ 3.7 | $ 3.7 | $ 3.7 |
| Convertible notes payable | - | - | - | - | - | - | - |
| Accrued interest on convertible notes payable | - | - | - | - | - | - | - |
| Other long-term obligations, less current portion | - | - | - | - | - | - | - |
| Deferred revenue, less current portion | - | - | - | - | - | - | - |
| Deferred rent | - | - | - | - | - | - | - |
| Other liabilities | - | - | - | - | - | - | - |
| **TOTAL LIABILITIES** | $ 3.7 | $ 3.7 | $ 3.7 | $ 3.7 | $ 3.7 | $ 3.7 | $ 3.7 |
| | | | | | | | |
| **Shareholder's Equity** | | | | | | | |
| Series A-E convertible preferred stock | - | - | - | - | - | - | - |
| Other | - | - | - | - | - | - | - |
| Common stock, at par | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Additional paid-in capital | 93.3 | 143.3 | 218.3 | 218.3 | 218.3 | 218.3 | 218.3 |
| Accumulated other comprehensive income | - | - | - | - | - | - | - |
| Accumulated deficit | (84.9) | (107.7) | (132.1) | (158.1) | (190.6) | (173.5) | 72.9 |
| **TOTAL SHAREHOLDER'S EQUITY (DEFICIT)** | $ 8.6 | $ 35.8 | $ 86.4 | $ 60.4 | $ 27.9 | $ 45.0 | $ 291.4 |
| **TOTAL LIABILITIES AND SHAREHOLDER'S EQUITY** | **$ 12.3** | **$ 39.5** | **$ 90.1** | **$ 64.1** | **$ 31.6** | **$ 48.7** | **$ 295.1** |

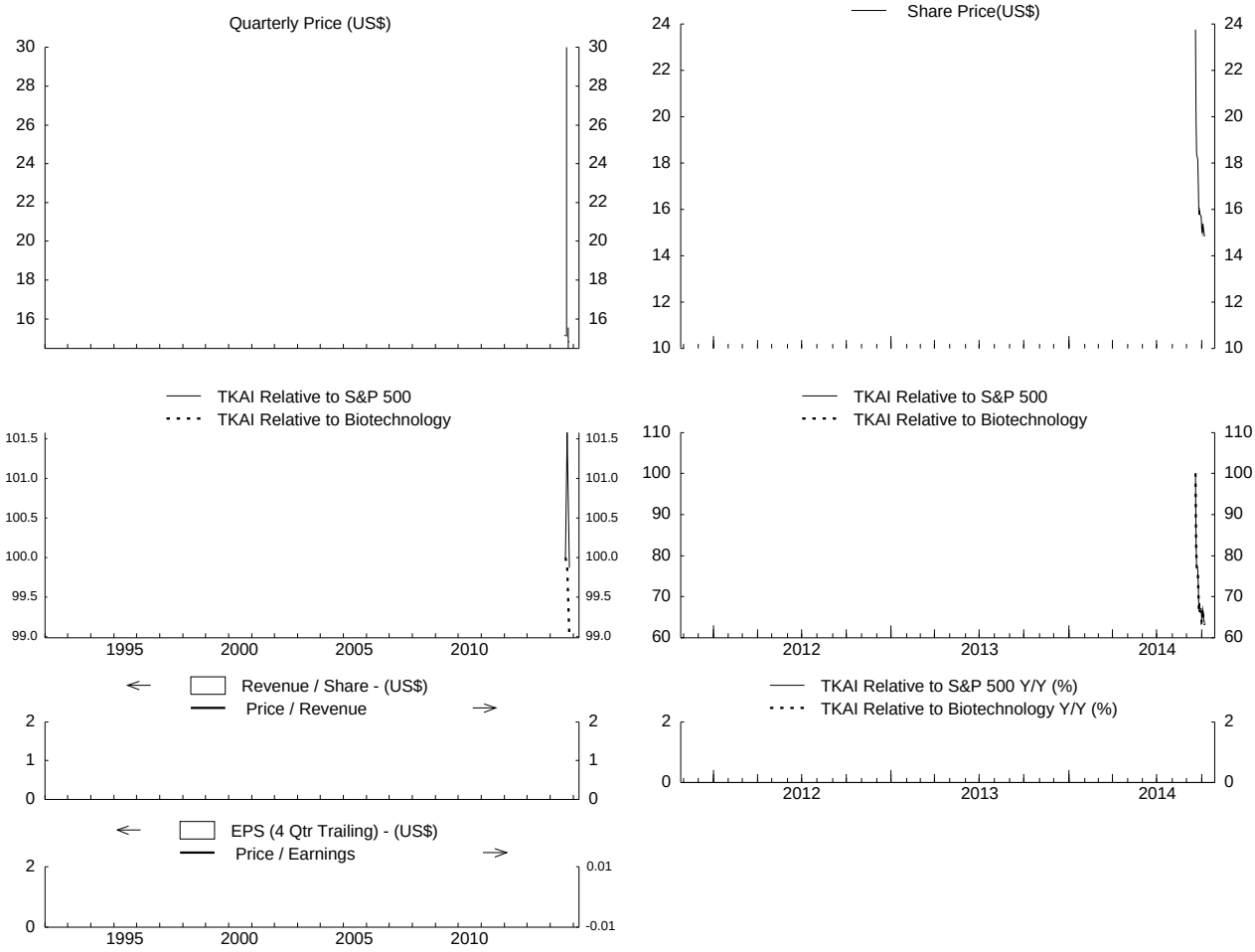
Source: Company reports and BMO Capital Markets.

## Exhibit 32: TKAI Cash Flow Statement 2014E-2020E

| CASH FLOW STATEMENT (M) | 2014E | 2015E | 2016E | 2017E | 2018E | 2019E | 2020E |
|---|---|---|---|---|---|---|---|
| **Cash Flow From Operating Activities** | | | | | | | |
| Net Income | $ (5.4) | $ (5.7) | $ (6.1) | $ (6.5) | $ (8.1) | $ 19.5 | $ 92.8 |
| Adjustments to reconcile net income to cash from operations | | | | | | | |
| Depreciation & amortization | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) | (0.0) |
| Amortization of premium on investments, net | - | - | - | - | - | - | - |
| Gain on disposal of property and equipment | - | - | - | - | - | - | - |
| Stock-based compensation | (0.3) | (0.3) | (0.3) | (0.3) | (0.3) | (0.3) | (0.3) |
| Deferred income taxes | - | - | - | - | - | - | - |
| Other | - | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| Working Capital Adjustments | | | | | | | |
| Prepaids and other assets | - | - | - | - | - | - | - |
| Accounts payable | - | - | - | - | - | - | - |
| Accrued payroll | - | - | - | - | - | - | - |
| Accrued expenses | - | - | - | - | - | - | - |
| Accrued interest | - | - | - | - | - | - | - |
| Receivable from collaborative partners | | | | | | | |
| Payable to related parties | - | - | - | - | - | - | - |
| Income taxes payable | - | - | - | - | - | - | - |
| Deferred revenue | - | - | - | - | - | - | - |
| Deferred rent | - | - | - | - | - | - | - |
| Other assets and liabilities, net | - | - | - | - | - | - | - |
| Total Working Capital Increase (Decrease) | $ - | $ - | $ - | $ - | $ - | $ - | $ - |
| **TOTAL CASH FROM OPERATIONS** | **$ (5.8)** | **$ (5.7)** | **$ (6.1)** | **$ (6.5)** | **$ (8.1)** | **$ 19.5** | **$ 92.8** |
| **Cash From Investing Activities** | | | | | | | |
| Purchases of short-term investments | - | - | - | - | - | - | - |
| Maturities and sales of short-term investments | - | - | - | - | - | - | - |
| Purchases of property and equipment | - | - | - | - | - | - | - |
| Acquisitions of patents | - | - | - | - | - | - | - |
| Acquisitions of licenses | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Increase in patents, deposits and other assets | - | - | - | - | - | - | - |
| **TOTAL CASH FROM INVESTING** | $ 0.0 | $ 0.0 | $ 0.0 | $ 0.0 | $ 0.0 | $ 0.0 | $ 0.0 |
| **Cash From Financing Activities** | | | | | | | |
| Proceeds from long-term debt borrowings | - | - | - | - | - | - | - |
| Repayment of borrowings | - | - | - | - | - | - | - |
| Payments of financing costs for an initial public offering | - | - | - | - | - | - | - |
| Proceeds from exercise of preferred and common stock options | - | - | - | - | - | - | - |
| Payments under capital lease obligation | - | - | - | - | - | - | - |
| Common stock issuance | - | - | - | - | - | - | - |
| **TOTAL CASH FROM FINANCING** | $ - | $ - | $ - | $ - | $ - | $ - | $ - |
| **Increase (decrease) in cash and cash equivalents** | (5.7) | (5.7) | (6.1) | (6.5) | (8.1) | 19.5 | 92.8 |
| Cash and cash equivalents at beginning of year | 15.7 | 42.8 | 93.8 | 68.2 | 37.3 | 26.8 | 199.9 |
| Cash and cash equivalents at end of year | $ 9.9 | $ 37.1 | $ 87.7 | $ 61.7 | $ 29.2 | $ 46.4 | $ 292.7 |

Source: Company reports and BMO Capital Markets.

# TOKAI PHARMACEUTICALS (TKAI)



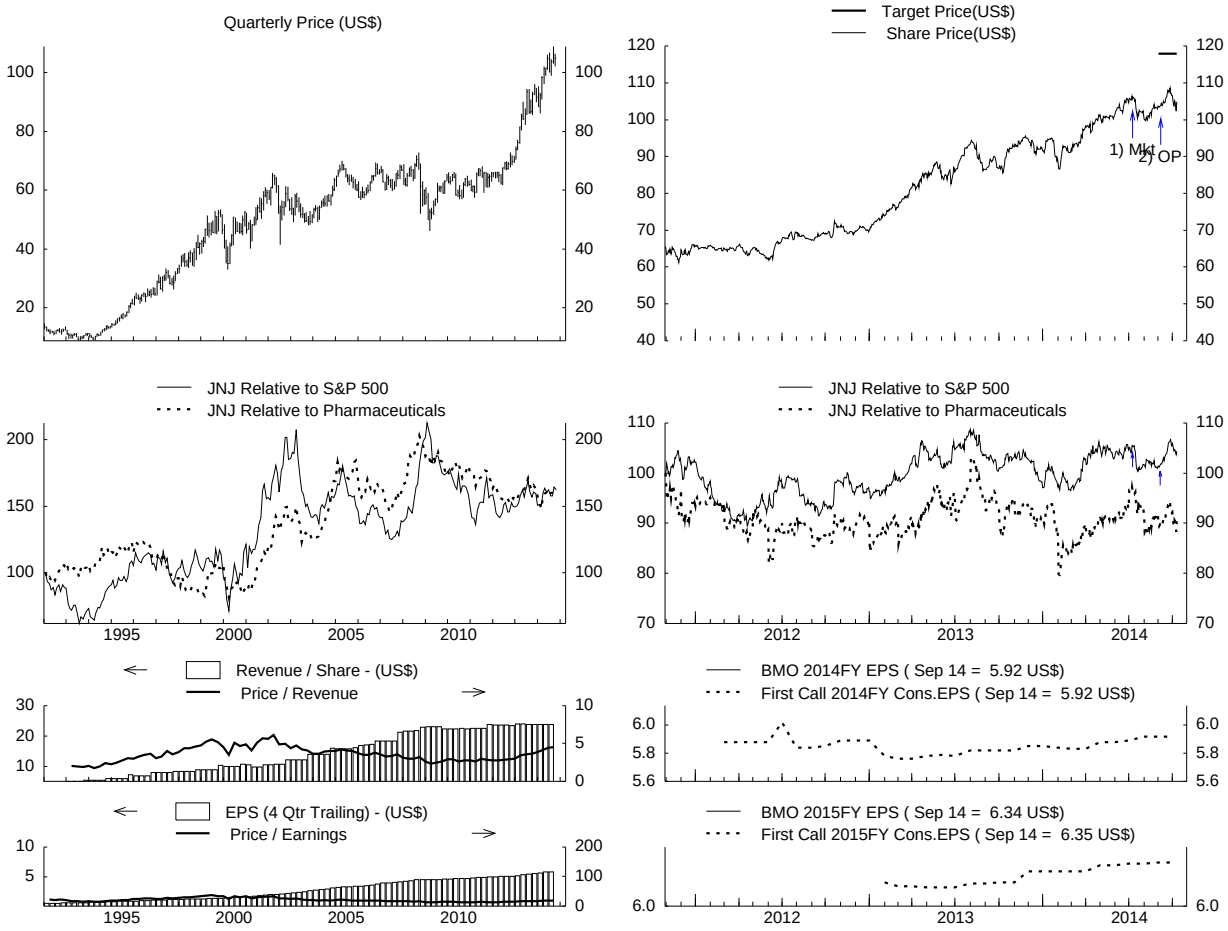

| FYE (Dec.) | EPS US$ | P/E Hi - Lo | DPS US$ | Yield% Hi - Lo | Payout % | BV US$ | P/B Hi - Lo | ROE % |
|---|---|---|---|---|---|---|---|---|
| Range*: | | na na | | NC | | | >15 >15 | |
| Current* | ND | na | 0.00 | 0.0 | na | NA | NA | na |

TKAI - Rating as of 1-Oct-14 = NR

* Current EPS is the 4 Quarter Trailing to Q2/2014.
* Valuation metrics are based on high and low for the fiscal year.
* Range indicates the valuation range for the period presented above.

Last Price ( October 6, 2014): $14.83
Sources: IHS Global Insight, Thomson Reuters, BMO Capital Markets.

# Johnson & Johnson (JNJ)




| FYE (Dec.) | EPS US$ | P/E Hi | P/E Lo | DPS US$ | Yield% Hi | Yield% Lo | Payout % | BV US$ | P/B Hi | P/B Lo | ROE % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1992 | 0.62 | 23.7 | 17.3 | 0.22 | 2.1 | 1.5 | 36 | 2.0 | 7.4 | 5.5 | |
| 1993 | 0.69 | 19.8 | 12.9 | 0.26 | 2.9 | 1.9 | 38 | 2.2 | 6.3 | 4.1 | 33 |
| 1994 | 0.78 | 18.1 | 11.5 | 0.29 | 3.2 | 2.1 | 37 | 2.8 | 5.1 | 3.2 | 32 |
| 1995 | 0.93 | 24.8 | 14.0 | 0.33 | 2.5 | 1.4 | 35 | 3.5 | 6.6 | 3.7 | 30 |
| 1996 | 1.06 | 25.5 | 19.6 | 0.38 | 1.8 | 1.4 | 36 | 4.1 | 6.6 | 5.1 | 28 |
| 1997 | 1.17 | 28.8 | 20.5 | 0.44 | 1.8 | 1.3 | 38 | 4.6 | 7.3 | 5.2 | 27 |
| 1998 | 1.31 | 34.3 | 24.1 | 0.50 | 1.6 | 1.1 | 38 | 5.1 | 8.9 | 6.2 | 27 |
| 1999 | 1.42 | 37.6 | 26.8 | 0.56 | 1.5 | 1.0 | 39 | 5.8 | 9.2 | 6.5 | 26 |
| 2000 | 1.63 | 32.5 | 20.3 | 0.64 | 1.9 | 1.2 | 39 | 6.8 | 7.8 | 4.9 | 26 |
| 2001 | 1.91 | 31.9 | 21.1 | 0.72 | 1.8 | 1.2 | 38 | 8.0 | 7.7 | 5.1 | 26 |
| 2002 | 2.23 | 29.5 | 18.6 | 0.82 | 2.0 | 1.2 | 37 | 7.7 | 8.6 | 5.4 | 29 |
| 2003 | 2.65 | 22.3 | 18.1 | 0.96 | 2.0 | 1.6 | 36 | 9.1 | 6.5 | 5.3 | 32 |
| 2004 | 3.10 | 20.7 | 15.7 | 1.14 | 2.3 | 1.8 | 37 | 10.7 | 6.0 | 4.6 | 31 |
| 2005 | 3.39 | 20.6 | 17.6 | 1.32 | 2.2 | 1.9 | 39 | 12.7 | 5.5 | 4.7 | 29 |
| 2006 | 3.76 | 18.5 | 15.1 | 1.50 | 2.6 | 2.2 | 40 | 13.6 | 5.1 | 4.2 | 29 |
| 2007 | 4.15 | 16.6 | 14.4 | 1.66 | 2.8 | 2.4 | 40 | 15.3 | 4.5 | 3.9 | 29 |
| 2008 | 4.55 | 16.0 | 11.4 | 1.84 | 3.5 | 2.5 | 40 | 15.4 | 4.7 | 3.4 | 30 |
| 2009 | 4.63 | 14.1 | 10.0 | 1.96 | 4.2 | 3.0 | 42 | 18.4 | 3.6 | 2.5 | 27 |
| 2010 | NA | 13.9 | 11.9 | 2.16 | 3.8 | 3.3 | 45 | 20.7 | 3.2 | 2.8 | na |
| 2011 | NA | 13.6 | 11.5 | 2.28 | 4.0 | 3.4 | 46 | 21.0 | 3.2 | 2.7 | na |
| 2012 | NA | 14.2 | 12.1 | 2.44 | 4.0 | 3.4 | 48 | 23.3 | 3.1 | 2.6 | na |
| 2013 | 5.52 | 17.4 | 12.5 | 2.64 | 3.8 | 2.8 | 48 | 26.3 | 3.7 | 2.6 | 22 |
| Range*: | | 37.6 | 10.0 | | 4.2 | 1.0 | | | 9.2 | 2.5 | |
| Current* | 5.80 | 18.4 | | 2.80 | 2.6 | | 48 | 27.2 | 3.9 | | 21 |
| Growth(%): | | | | | | | | | | | |
| 5 Year: | 5.0 | | | 7.4 | | | | 12.1 | | | |
| 10 Year: | 6.8 | | | 9.4 | | | | 11.6 | | | |
| 20 Year: | 10.6 | | | 12.0 | | | | 13.5 | | | |

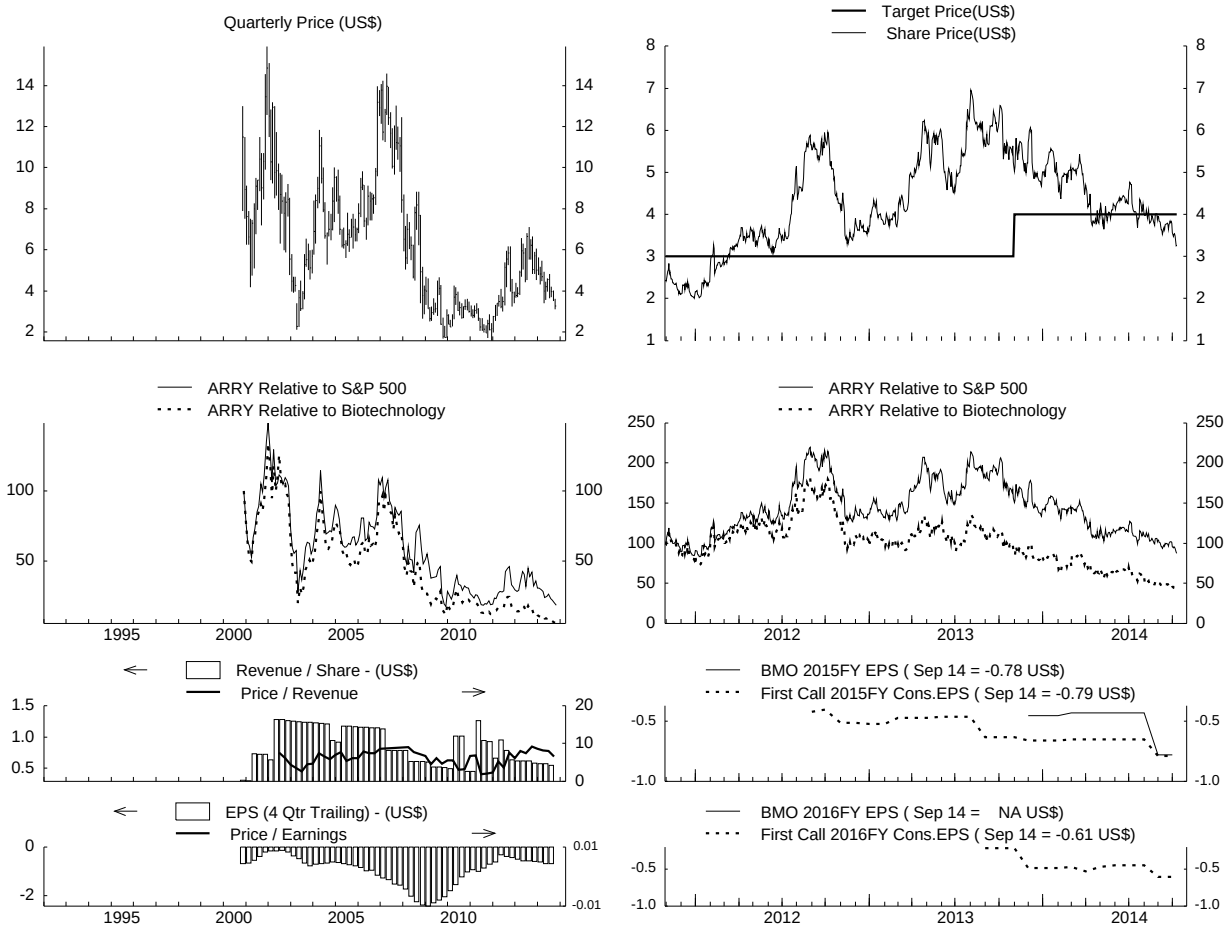
* Current EPS is the 4 Quarter Trailing to Q2/2014.
* Valuation metrics are based on high and low for the fiscal year.
* Range indicates the valuation range for the period presented above.

JNJ - Rating as of 27-Oct-11 = NR

| | Date | Rating Change | Share Price |
|---|---|---|---|
| 1 | 8-Jul-14 | NR to Mkt | $105.72 |
| 2 | 4-Sep-14 | Mkt to OP | $103.84 |

Last Price ( October 8, 2014): $104.91
Sources: IHS Global Insight, Thomson Reuters, BMO Capital Markets.

# ARRAY BIOPHARMA INC (ARRY)




| FYE (Jun.) | EPS US$ | P/E Hi | P/E Lo | DPS US$ | Yield% Hi | Yield% Lo | Payout % | BV US$ | P/B Hi | P/B Lo | ROE % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2000 | | na | na | 0.00 | ND | ND | na | 2.0 | >15 | >15 | |
| 2001 | -0.54 | na | na | 0.00 | 0.0 | 0.0 | 0 | 2.7 | 4.8 | 1.6 | na |
| 2002 | -0.18 | na | na | 0.00 | 0.0 | 0.0 | 0 | 3.4 | 4.7 | 2.0 | na |
| 2003 | -0.49 | na | na | 0.00 | 0.0 | 0.0 | 0 | 2.8 | 3.7 | 0.8 | na |
| 2004 | -0.69 | na | na | 0.00 | 0.0 | 0.0 | 0 | 1.9 | 6.1 | 1.6 | na |
| 2005 | -0.69 | na | na | 0.00 | 0.0 | 0.0 | 0 | 2.2 | 4.6 | 2.4 | na |
| 2006 | -0.99 | na | na | 0.00 | 0.0 | 0.0 | 0 | 1.3 | 7.8 | 4.5 | na |
| 2007 | -1.35 | na | na | 0.00 | 0.0 | 0.0 | 0 | 1.5 | 9.6 | 4.7 | na |
| 2008 | -2.02 | na | na | 0.00 | 0.0 | 0.0 | 0 | 0.8 | >15 | 5.8 | na |
| 2009 | -2.30 | na | na | 0.00 | 0.0 | 0.0 | 0 | -1.9 | -4.6 | -1.3 | >50 |
| 2010 | -1.55 | na | na | 0.00 | 0.0 | 0.0 | 0 | -2.2 | -2.1 | -0.8 | >50 |
| 2011 | -1.02 | na | na | 0.00 | 0.0 | 0.0 | 0 | -1.0 | -3.9 | -2.0 | >50 |
| 2012 | -0.33 | na | na | 0.00 | 0.0 | 0.0 | 0 | -0.2 | -21.6 | -8.3 | >50 |
| 2013 | -0.57 | na | na | 0.00 | 0.0 | 0.0 | 0 | -0.2 | -32.8 | -15.0 | >50 |
| 2014 | -0.69 | na | na | 0.00 | 0.0 | 0.0 | 0 | -2.6 | -2.8 | -1.3 | >50 |
| Range*: | | na | na | | 0.0 | 0.0 | | | >15 | -15.0 | |
| Current* | -0.68 | na | | 0.00 | 0.0 | | 0 | -0.1 | -32.5 | | >50 |

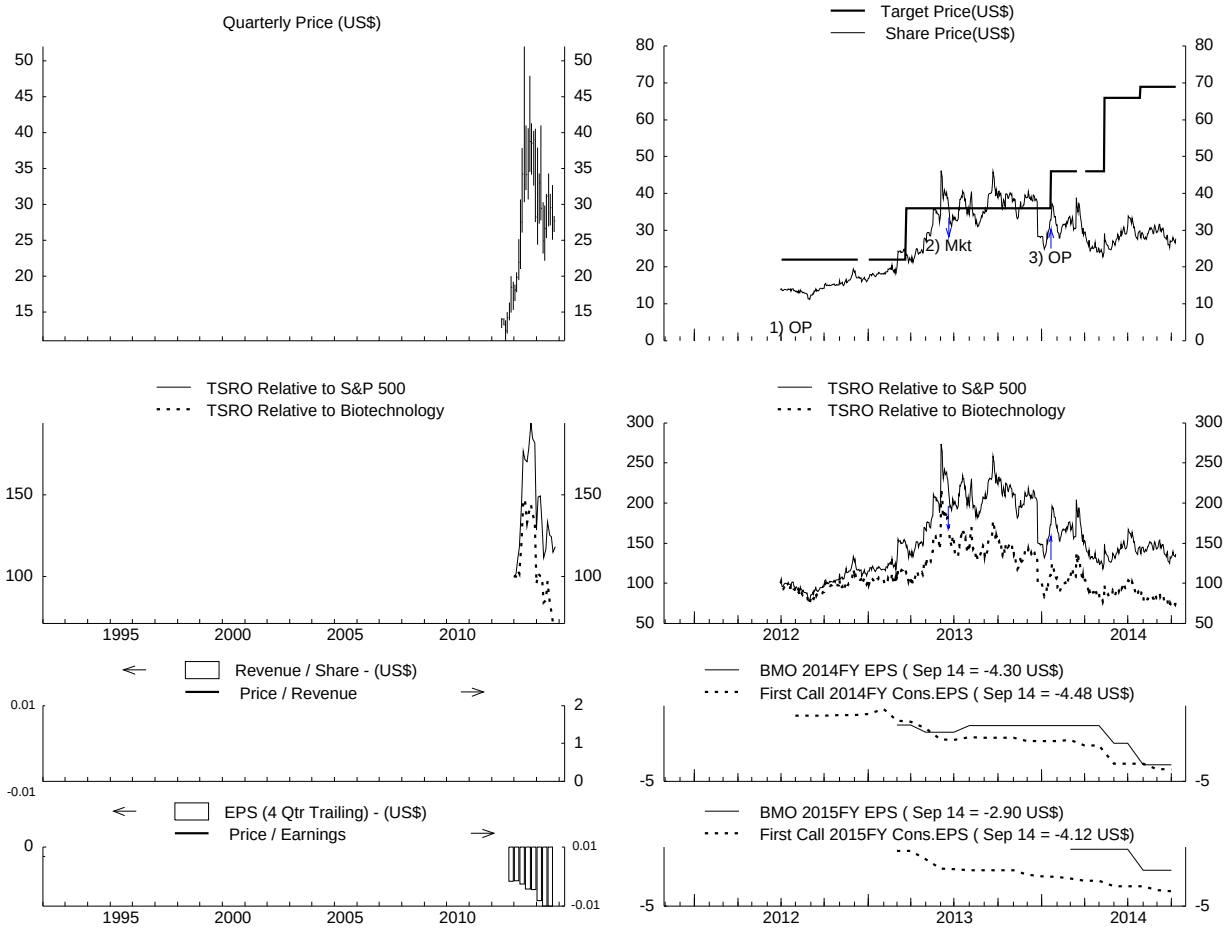
Growth(%):
5 Year: nm nm nm
10 Year: nm nm nm

* Current EPS is the 4 Quarter Trailing to Q4/2014.
* Valuation metrics are based on high and low for the fiscal year.
* Range indicates the valuation range for the period presented above.

ARRY - Rating as of 7-Sep-11 = Mkt

Last Price ( October 8, 2014): $3.26
Sources: IHS Global Insight, Thomson Reuters, BMO Capital Markets.

# Tesaro Inc. (TSRO)




| FYE (Dec.) | EPS US$ | P/E Hi | P/E Lo | DPS US$ | Yield% Hi | Yield% Lo | Payout % | BV US$ | P/B Hi | P/B Lo | ROE % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2012 | -4.51 | na | na | 0.00 | 0.0 | 0.0 | 0 | 4.3 | 4.7 | 2.6 | |
| 2013 | -2.93 | na | na | 0.00 | 0.0 | 0.0 | 0 | 3.8 | 13.8 | 4.1 | na |
| Range*: | | na | na | | 0.0 | 0.0 | | | 13.8 | 2.6 | |
| Current* | -4.06 | na | | 0.00 | 0.0 | | 0 | 3.5 | 7.6 | | na |

TSRO - Rating as of 23-Jul-12 = OP

| | Date | Rating Change | Share Price |
|---|---|---|---|
| 1 | 23-Jul-12 | NR to OP | $13.90 |
| 2 | 18-Jun-13 | OP to Mkt | $35.99 |
| 3 | 20-Jan-14 | Mkt to OP | $32.82 |

* Current EPS is the 4 Quarter Trailing to Q2/2014.
* Valuation metrics are based on high and low for the fiscal year.
* Range indicates the valuation range for the period presented above.

Last Price ( October 8, 2014): $27.66
Sources: IHS Global Insight, Thomson Reuters, BMO Capital Markets.

**IMPORTANT DISCLOSURES**

**Analyst's Certification**
I, Jim Birchenough, M.D., hereby certify that the views expressed in this report accurately reflect my personal views about the subject securities or issuers. I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the specific recommendations or views expressed in this report.

Analysts who prepared this report are compensated based upon (among other factors) the overall profitability of BMO Capital Markets and their affiliates, which includes the overall profitability of investment banking services. Compensation for research is based on effectiveness in generating new ideas and in communication of ideas to clients, performance of recommendations, accuracy of earnings estimates, and service to clients.

Analysts employed by BMO Nesbitt Burns Inc. and/or BMO Capital Markets Limited are not registered as research analysts with FINRA (exception: Alex Arfaei). These analysts may not be associated persons of BMO Capital Markets Corp. and therefore may not be subject to the NASD Rule 2711 and NYSE Rule 472 restrictions on communications with a subject company, public appearances and trading securities held by a research analyst account.

**Company Specific Disclosure for Tokai Pharmaceuticals**
Disclosure 1: BMO Capital Markets has undertaken an underwriting liability with respect to this issuer within the past 12 months.
Disclosure 2: BMO Capital Markets has provided investment banking services with respect to this issuer within the past 12 months.
Disclosure 3: BMO Capital Markets has managed or co-managed a public offering of securities with respect to this issuer within the past 12 months.
Disclosure 4: BMO Capital Markets or an affiliate has received compensation for investment banking services from this issuer within the past 12 months.
Disclosure 6: This issuer is a client (or was a client) of BMO NB, BMO Capital Markets Corp., BMO CM Ltd. or an affiliate within the past 12 months: Investment Banking Services.
Disclosure 9: BMO Capital Markets makes a market in this security.

**Methodology and Risks to Price Target/Valuation**
**Methodology**: We arrive at our $28 price target by applying a 20x multiple to our 2020 EPS estimate of $4.25 and discounting at 30%.
**Risks**: There are a number of risks associated with investment in biotechnology companies. These risks include, but are not limited to, risk of clinical trial delay or failure, adverse regulatory decisions including product non-approval, unanticipated adverse effects of drugs which may result in removal from market, risk of manufacturing difficulties, capital market risk which may impair the ability to fund product discovery, research, regulatory filing, manufacture and/or commercialization, risk in attaining and retaining appropriate development or commercial partners, lower-than-expected product adoption, difficulties in gaining appropriate reimbursement for products from payors, unforeseen generic and branded competition, risk to patents being invalidated, and failure to meet earnings and revenue expectations.

**Company specific disclosures for Johnson & Johnson**
Disclosure 9: BMO Capital Markets makes a market in this security.

**Methodology and Risks to Our Price Target**
**Methodology**: Our price target is based on three methodologies: 1) 17x our 2015 Cash EPS; 2) SOTP; and 3) 18.5x our 2015E EPS.
**Risks**: Risks to price target include the utilization of health care products by consumers, hospitals and physicians; new product regulatory approval; competition (particularly in Pharma); the implementation of the Affordable Care Act; and the ability of the company to execute and manage in a changing health care environment.

**Company specific disclosures for Array BioPharma**
Disclosure 9: BMO Capital Markets makes a market in this security.

**Methodology and Risks to Our Price Target**
**Methodology**: We arrive at our price target by applying a 15x multiple to our 2017 GAAP EPS estimate of $0.46 and discounting at 25%. We believe the multiple appropriately reflects long-term EPS growth estimated at 16% and that the 25% discount rate adequately reflects risk to achieving that growth.
**Risks**: There are a number of risks associated with investment in biotechnology companies. These risks include, but are not limited to, risk of clinical trial delay or failure, adverse regulatory decisions including product non-approval, unanticipated adverse effects of drugs which may result in removal from market, risk of manufacturing difficulties, capital market risk which may impair the ability to fund product discovery, research, regulatory filing, manufacture and/or commercialization, risk in attaining and retaining appropriate development or commercial partners, lower-than-expected product adoption, difficulties in gaining appropriate reimbursement for products from payors, unforeseen generic and branded competition, risk to patents being invalidated, and failure to meet earnings and revenue expectations.

Specific risks to ARRY include, but are not limited to, failure to demonstrate a benefit to selumetinib in melanoma or NSCLC, failure to maintain collaboration agreements with Astra Zeneca and Novartis, failure to move early stage pipeline programs forward and inability to finance further development activities of its proprietary pipeline.

**Company specific disclosures for Tesaro**
Disclosure 1: BMO Capital Markets has undertaken an underwriting liability with respect to this issuer within the past 12 months.
Disclosure 2: BMO Capital Markets has provided investment banking services with respect to this issuer within the past 12 months.
Disclosure 3: BMO Capital Markets has managed or co-managed a public offering of securities with respect to this issuer within the past 12 months.
Disclosure 4: BMO Capital Markets or an affiliate has received compensation for investment banking services from this issuer within the past 12 months.
Disclosure 6: This issuer is a client (or was a client) of BMO NB, BMO Capital Markets Corp., BMO CM Ltd. or an affiliate within the past 12 months: Investment Banking Services.
Disclosure 9: BMO Capital Markets makes a market in this security.

**Methodology and Risks to Our Price Target**
**Methodology**: We arrive at our price target by applying a 25x multiple to our 2017E EPS of $3.58 discounted 20%.
**Risks**: There are a number of risks associated with investment in biotechnology companies. These risks include, but are not limited to, risk of clinical trial delay or failure, adverse regulatory decisions including product non-approval, unanticipated adverse effects of drugs which may result in removal from market, risk of manufacturing difficulties, capital market risk which may impair the ability to fund product discovery, research, regulatory filing, manufacture and/or commercialization, risk in attaining and retaining appropriate development or commercial partners, lower-than-expected product adoption, difficulties in gaining appropriate reimbursement for products from payors, unforeseen generic and branded competition, risk to patents being invalidated, and failure to meet earnings and revenue expectations.

**Distribution of Ratings (June 30, 2014)**

| Rating Category | BMO Rating | BMOCM US Universe* | BMOCM US IB Clients** | BMOCM US IB Clients*** | BMOCM Universe**** | BMOCM IB Clients***** | Starmine Universe |
|---|---|---|---|---|---|---|---|
| Buy | Outperform | 44.1% | 21.1% | 67.5% | 43.3% | 58.6% | 55.4% |
| Hold | Market Perform | 50.9% | 8.4% | 31.3% | 51.2% | 39.9% | 39.5% |
| Sell | Underperform | 5.0% | 3.4% | 1.3% | 5.5% | 1.5% | 5.1% |

* Reflects rating distribution of all companies covered by BMO Capital Markets Corp. equity research analysts.
** Reflects rating distribution of all companies from which BMO Capital Markets Corp. has received compensation for Investment Banking services as percentage within ratings category.
*** Reflects rating distribution of all companies from which BMO Capital Markets Corp. has received compensation for Investment Banking services as percentage of Investment Banking clients.
**** Reflects rating distribution of all companies covered by BMO Capital Markets equity research analysts.
***** Reflects rating distribution of all companies from which BMO Capital Markets has received compensation for Investment Banking services as percentage of Investment Banking clients.

**Rating and Sector Key (as of April 5, 2013):**
We use the following ratings system definitions:
OP = Outperform - Forecast to outperform the analyst's coverage universe on a total return basis
Mkt = Market Perform - Forecast to perform roughly in line with the analyst's coverage universe on a total return basis
Und = Underperform - Forecast to underperform the analyst's coverage universe on a total return basis
(S) = speculative investment;
NR = No rating at this time;
R = Restricted – Dissemination of research is currently restricted.

BMO Capital Markets' seven Top 15 lists guide investors to our best ideas according to different objectives (CDN Large Cap, CDN Small Cap, US Large Cap, US Small cap, Income, CDN Quant, and US Quant have replaced the Top Pick rating).

**Prior BMO Capital Markets Ratings System (January 4, 2010–April 4, 2013):**
http://researchglobal.bmocapitalmarkets.com/documents/2013/prior_rating_system.pdf

**Other Important Disclosures**
For Other Important Disclosures on the stocks discussed in this report, please go to

http://researchglobal.bmocapitalmarkets.com/Public/Company_Disclosure_Public.aspx or write to Editorial Department, BMO Capital Markets, 3 Times Square, New York, NY 10036 or Editorial Department, BMO Capital Markets, 1 First Canadian Place, Toronto, Ontario, M5X 1H3.

**Dissemination of Research**
BMO Capital Markets Equity Research is available via our website https://research-ca.bmocapitalmarkets.com/Public/Secure/Login.aspx?ReturnUrl=/Member/Home/ResearchHome.aspx. Institutional clients may also receive our research via Thomson Reuters, Bloomberg, FactSet, and Capital IQ. Research reports and other commentary are required to be simultaneously disseminated internally and externally to our clients.

**General Disclaimer**
BMO Capital Markets" is a trade name used by the BMO Investment Banking Group, which includes the wholesale arm of Bank of Montreal and its subsidiaries BMO Nesbitt Burns Inc., BMO Capital Markets Limited in the U.K. and BMO Capital Markets Corp. in the U.S. BMO Nesbitt Burns Inc., BMO Capital Markets Limited and BMO Capital Markets Corp are affiliates. Bank of Montreal or its subsidiaries ("BMO Financial Group") has lending arrangements with, or provide other remunerated services to, many issuers covered by BMO Capital Markets. The opinions, estimates and projections contained in this report are those of BMO Capital Markets as of the date of this report and are subject to change without notice. BMO Capital Markets endeavours to ensure that the contents have been compiled or derived from sources that we believe are reliable and contain information and opinions that are accurate and complete. However, BMO Capital Markets makes no representation or warranty, express or implied, in respect thereof, takes no responsibility for any errors and omissions contained herein and accepts no liability whatsoever for any loss arising from any use of, or reliance on, this report or its contents. Information may be available to BMO Capital Markets or its affiliates that is not reflected in this report. The information in this report is not intended to be used as the primary basis of investment decisions, and because of individual client objectives, should not be construed as advice designed to meet the particular investment needs of any investor. This material is for information purposes only and is not an offer to sell or the solicitation of an offer to buy any security. BMO Capital Markets or its affiliates will buy from or sell to customers the securities of issuers mentioned in this report on a principal basis. BMO Capital Markets or its affiliates, officers, directors or employees have a long or short position in many of the securities discussed herein, related securities or in options, futures or other derivative instruments based thereon. The reader should assume that BMO Capital Markets or its affiliates may have a conflict of interest and should not rely solely on this report in evaluating whether or not to buy or sell securities of issuers discussed herein.

**Additional Matters**
To Canadian Residents: BMO Nesbitt Burns Inc. furnishes this report to Canadian residents and accepts responsibility for the contents herein subject to the terms set out above. Any Canadian person wishing to effect transactions in any of the securities included in this report should do so through BMO Nesbitt Burns Inc.
The following applies if this research was prepared in whole or in part by Andrew Breichmanas, Iain Reid, Tony Robson, David Round, Edward Sterck or Brendan Warn: This research is not prepared subject to Canadian disclosure requirements. This research is prepared by BMO Capital Markets Limited and subject to the regulations of the Financial Conduct Authority (FCA) in the United Kingdom. FCA regulations require that a firm providing research disclose its ownership interest in the issuer that is the subject of the research if it and its affiliates own 5% or more of the equity of the issuer. Canadian regulations require that a firm providing research disclose its ownership interest in the issuer that is the subject of the research if it and its affiliates own 1% or more of the equity of the issuer that is the subject of the research. Therefore BMO Capital Markets Limited will only disclose its and its affiliates ownership interest in the subject issuer if such ownership exceeds 5% of the equity of the issuer.
To U.S. Residents: BMO Capital Markets Corp. furnishes this report to U.S. residents and accepts responsibility for the contents herein, except to the extent that it refers to securities of Bank of Montreal. Any U.S. person wishing to effect transactions in any security discussed herein should do so through BMO Capital Markets Corp.
To U.K. Residents: In the UK this document is published by BMO Capital Markets Limited which is authorised and regulated by the Financial Conduct Authority. The contents hereof are intended solely for the use of, and may only be issued or passed on to, (I) persons who have professional experience in matters relating to investments falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the "Order") or (II) high net worth entities falling within Article 49(2)(a) to (d) of the Order (all such persons together referred to as "relevant persons"). The contents hereof are not intended for the use of and may not be issued or passed on to, retail clients.



Click here for data vendor disclosures when referenced within a BMO Capital Markets research document.