Discovery & Development of a Multi-mechanistic Agent VN/124-1 (TOK-001 or Galeterone) for Prostate Cancer Therapy

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Prostate Cancer

• Most common cancer in males worldwide

• Advanced prostate cancer remains incurable despite significant advances in treatment options

• Identification of new strategies (prevention and therapy) are needed
Prostate Cancer & Androgens

• ~ 90% Prostate cancers are androgen-dependent
• Blockage of androgen action = Effective treatment strategy

• Surgical castration/use of GnRH (LHRH) = current “gold standard” for therapy
  – Eliminates testosterone production from testes but not from adrenals

• Combination therapy: GnRH + antiandrogens – more effective
Androgens

- Steroids (testosterone and DHT) that stimulate male characteristics
- Implicated in prostate cancer progression
PCA Recurrence Following Anti-Hormonal Therapy

• Reasons advanced for PCA recurrence
  – Androgen receptor (AR) mutation
  – AR gene amplification and/or over expression
  – Androgen independent activation of AR

• However, anti-hormonal therapies produce most beneficial responses in multiple settings in PCA patients
Steroidal Biosynthetic Pathway

Cholesterol

- Pregnenolone
  - 17α-Hydroxy-Pregnenolone
    - DHEA
  - 17α-Hydroxy-Progesterone
    - Androstenedione
    - Testosterone
    - DHT

Progesterone

- 17α-Hydroxy-Progesterone
  - Cortisol

Corticosterone

Aldosterone

CYP17 (17α-Hydroxylase)

CYP17 (17,20-Lyase)
Relative Binding Affinity Casodex, VN/124-1 & Abiraterone to Androgen Receptor (Wild-type)

Graph showing competitive binding to the androgen receptor with log concentration [M] on the x-axis and % of control on the y-axis. The graph compares Casodex, Abiraterone, and VN/124-1. The structures of VN/124-1, Abiraterone, and Casodex are also included at the bottom of the image.
Antitumor Studies – Human LAPC4 Tumors in Male SCID Mice

• Wild type androgen receptors (AR)
• Mice inoculated with LAPC4 cells/2 sites (n = 5 per group)
• Tumors ~ 300 mm$^3$
• Treated with 50 mg/kg, sc (x1 or x2) for 28 days
Effects of Castration, VN/85-1 & VN/124-1 on Formation & Growth of LAPC4 Tumor Xenografts

% Change in mean tumor volume

Duration of Treatment (weeks)

Tumor (μg/ml) Liver (μg/ml) Testis (μg/ml)

Concentration of 5 in μg/mg

Castration

Control

VN/85-1 twice daily

VN/124-1 twice daily

* **
VN/124-1 Unlike Casodex Induces AR Degradation in LNCaP & LAPC-4 Cells

AR Expression in LNCaP cells after 24 h treatments

AR Protein Expression in LNCaP Cells Treated with VN/124-1 and Casodex

Androgen Receptor (AR) Protein Expression from LAPC4 Tumors Following Various Treatments

![AR Protein Expression - LAPC4 Xenograft](image)

Multiple Mechanisms of VN/124-1 Inhibition Along Androgen Axis

Progestins \rightarrow CYP17 \rightarrow Androgens

1. VN/124-1

2. Androgens \rightarrow AR

3. Growth Arrest/ Apoptosis
Effects of VN/124-1 & Abiraterone on Growth of LAPC-4 Tumors *In Vivo*

Bruno RD et al., Steroids, 2011, 76: 1268-1279
Androgen-dependent & -independent Mechanisms of Action of VN/124-1

Androgen Dependent

Inhibition of CYP17

Ca2+ Release From the ER

Androgen Independent

Rise [Ca2+]i

ER Stress Response

p-eIF2α

CHOP
Bip/Grp78
ATF4
ASNS
S100P
4e-bp1

G1

S

AR

Growth Arrest/ Apoptosis
Localized prostate cancer → Recurrent cancer (rising serum PSA) → Metastatic prostate cancer → Castration refractory cancer (rising serum PSA) → Metastatic androgen-independent cancer

Radiation Therapy
Radical Prostatectomy

New Therapeutics
Proteasome inhibitors (ARDA's)

Chemotherapy
Docetaxel-based

VN/124-1 May be Effective Treatment at All Stages of PCA Development
Development of VN/124-1 for the Treatment of Prostate Cancer: VN/124-1 Technology

- Licensed to Tokai Pharmaceuticals Inc., Cambridge, Mass., USA - 2006

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<th>Pre-clinical</th>
<th>Phase I/II</th>
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Potent CYP17 inhibitor endowed with multiple desirable anti-prostate cancer activities

- Tokai License of Technology
- VN/124-1 Technology
- November 5, 2009 (Completed)
- 4th quarter of 2012

VN/124-1
Galeterone (TOK-001 or VN/124-1)

- Oral small molecule for treatment of Castration Resistant Prostate Cancer (CRPC)
- Tokai licensed technology from University of Maryland, Baltimore in 2006
  - Inventors: Vincent C. O. Njar, Ph.D. & Angela M. H. Brodie, Ph.D.
- Three Mechanisms of Action (MOA):
  - Androgen Receptor (AR) antagonist
  - CYP17 Lyase inhibitor
  - Decrease AR levels
Galeterone: ARMOR1 (Androgen Receptor Modulation Optimized for Response) - Design

• **Dose escalation trial in eight clinical centers**
  - Standard dose escalation safety trial; 6 patients per group
  - Doses: 650 mg/day, 975 mg/day, 1300 mg/day, 1950 mg/day, 2600 mg/day
  - Single agent
  - Patient instructed to take galeterone with food

• **Dosing daily for 12 weeks (followed by optional continued dosing for eligible patients)**
  - Single and Split oral dosing
  - With and without supplement

• **Entry Criteria**
  - CRPC patients ≥ 18 y.o.
  - Metastatic and non-metastatic disease
  - Chemotherapy and ketoconozole naive
An increase in response rate was seen with higher doses.
Reduction in tumor size reported in 3 patients treated with high doses of Galeterone

- Decrease in left pelvic lymphadenopathy
- Corresponding 80% PSA reduction

Baseline (2/9/2011): 3.9 x 2.9 cm

3 month (5/6/2011): 2.8 x 1.3 cm
Summary of Clinical Trials & Further Development of Galeterone

- Galeterone, well tolerated
- Significant & long-term PSA responses observed
- Excellent safety profile
- Tumor reduction observed radiologically
- Human proof-of-concept achieved: PSA reductions with soft tissue disease shrinkage
- Undergone successful formulation optimization
- Phase 2b trials planned for 4th quarter of 2012

On June 12, 2012 Galeterone (TOK-001 or VN/124-1) received Fast Track designation from the U.S. Food and Drug Administration (FDA) for the potential treatment of metastatic castration-resistant prostate cancer (CRPC)
Thank You

Vincent Njar, Ph.D
Njar Laboratory Members

Angela Brodie, Ph.D.
Brodie Laboratory Members