New Horizons in Prostate Cancer: Exploiting Disease Heterogeneity to Develop Marker Driven Curative Intent Treatment Strategies

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Precision Medicine Development
A matter of integration

Common Goal: Integration of Knowledge as a means to improve disease outcome and hence human lives
SU2C Prostate Dream Team Leaders and Principals
West Coast Dream Team Locations

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Martin Gleave
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Charles Ryan
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Kit Lam
Josh Stuart
Ted Goldstein
Owen Witte
Robert Reiter

Oregon Health & Science University
UCSF
UC Davis
UC Santa Cruz
UCLA

Research Treatment
Vancouver Prostate Centre
A UBC & VGH Centre of Excellence
mCRPC Tissue Collection and Analysis

Blood ———— Biopsy ———— Clinical Samples

Spin/FACS  Frozen  Fixed  Fresh  Preparation

Spin/FACS  LCM  IHC  FISH  Dissection  Processing

CTC  Serum  RNA  DNA  DNA  Analytes

aCGH  miRNA  RNAseq  Exome Sequencing  aCGH  Biomarker Expression  Copy Number  Mutation Panel  Primary Data

Exome Sequencing  aCGH  Tumor Characterization  Tumor Propagation

In Vivo Testing  Future Projects
**Efforts within phase III setting**

Teaming up with Investigators creates a unique potential

**Discovery** : Study COU-AA-302: An Association of Improved rPFS in Pts with Tumors harboring Erg Rearrangements

![Graph showing progression-free survival](attachment:image.png)

**2+ Edel vs NR; HR (95% CI) = 0.54 (0.28, 1.06), p = 0.0744**

1 Edel vs NR; HR (95% CI) = 1.04 (0.62, 1.73), p = 0.8924

NR, ERG non-rearranged.

**Attard et al ASCO 2013**
Discovery: Candidate (RNA) Androgen Signaling signature predictive of benefit with Abiraterone Acetate

Ricci et al ASCO 2014
Single Institution Efforts
ARV7 detected in CTC associated with resistance to novel androgen signaling inhibition

Antonarakis et al NEJM 2014
Hypothesis: Optimum use of available prostate cancer ‘agents’ can lead to the Cure of “select” men with prostate cancer and secondary prevention in more advanced disease.
MDACC Efforts towards Precision Medicine

Prometheus
Integrating Molecular Characterisation & Clinical Data

Tissue and Liquid Biopsy Based Clinical Research Co-Clinical Research

Discovery Testing Validation
Create Knowledge from Data

Clinical Data

Specimen Acquisition
Eckstein Lab
(Efstathioiu)

Distribution

Tissue Bank

Clinical Pathology
(Troncoso)

Xenograft
(Navone/Maity)

Independent Lab

Alexander Lab
(Efstathioiu)

Genetics
(Futreal)

(Allison)
Immunopathology
(Blandon)

Platform

Estimate: 3.5 million analyses annually!
Prometheus Platform
Clinical Research Integration with molecular characterisation

- Infrastructure “customized informatics”
- Acquire, chain of custody, inventory, distribute.
- Analytics platform

From tissue to knowledge bank
A working Model for Reclassification of Prostate Cancer to incorporate intra patient and temporal disease heterogeneity

A Roadmap to New Taxonomy
Tools
Prometheus: A Knowledge bank
Tissue and Liquid Biopsy Based Clinical Research
Co-Clinical Research

Logothetis et al Cancer Discovery 2013
Informative Transilial Bone Marrow Biopsy

The MDACC Bone Biopsy Androgen Signaling mCRPC Program.

Goal: Create Knowledge from Tissue based Clinical Research

<table>
<thead>
<tr>
<th>Study</th>
<th>Agents</th>
<th>mCRPC pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>09-0590 (JCO 2012)</td>
<td>Abiraterone Acetate</td>
<td>60</td>
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<tr>
<td>09-0886 (Eur Urol 2014)</td>
<td>Enzalutamide</td>
<td>60</td>
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<tr>
<td>12-0086 (ASCO 2014)</td>
<td>ABI +ENZA</td>
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<tr>
<td>10-0070 (ESMO 2014)</td>
<td>ABI +randomization to Dasatinib or</td>
<td>170</td>
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</table>

Endpoints:
Inform regarding Tumor microenvironment Impact of agents tested
Explore Identify Test and Validate predictive markers
Develop Assay Driven Therapy Strategies to guide treatment sequencing and combination
AR & Androgen Modulation Following Abiraterone Acetate (MDACC 09-0590)

Testosterone Depletion

- Blood Testosterone
- Bone Marrow Testosterone

AR Copy Number Modulation

qPCR on ≥500 cells.

AR & Androgen Modulation Following Enzalutamide (MDACC 09-0886)

AR Shift in Subcellular Localization

Marrow Testosterone Increase

Pretreatment  Week 8
Adaptive Androgen Signaling in mCRPC Effectively Targeted by Novel Androgen Signaling Inhibitors

Androgen Signaling Inhibition: Feedback mechanisms following
A. Androgen biosynthesis inhibition
B. Androgen receptor blockade

Efstathiou et al JCO 2012;
Efstathiou et al Eur Urology (in press).
mCRPC, metastatic castration-resistant prostate cancer

Efstathiou et al ASCO 2014
Study 12-0083

Enzalutamide + Abiraterone acetate (+ prednisone)

- Enzalutamide 160 mg once daily
- Abiraterone acetate 1 g once daily
  - (5 mg twice daily)

Hypothesis Confirmed:
Combination of ABI + ENZA will dissipate physiologic feedbacks incurred by each agent alone

Baseline

Week 9

Bone marrow biopsy
Bone marrow aspirate
Blood collection

Median time on treatment 337 days (95% CI: 224, 600+)
With 30 pts still on treatment

Primary Resistance:
Not related to feedback mechanisms

Ensuing Resistance:
maybe Affected as evidenced by time on combination

Efstathiou et al ASCO 2014
“Primary Resistance” as a Prognosticator in mCRPC

Time on treatment

Overall survival

Efstathiou et al ASCO 2014
Androgen Signaling in mCRPC and association benefit

Nuclear over-expression of N terminal AR + CYP17 correlates with benefit (p<0.01)

AR V7 expression linked primary resistance to enzalutamide (p=0.02)

Efstathiou et al JCO 2012; Efstathiou et al Eur Urology 2014; Antonarakis et al AACR 2014

AR, androgen receptor
Androgen Receptor Expression & Alterations

Transcriptional-activation  DNA-binding  Ligand-binding

N terminus  C terminus

AR-N  AR-V7+  AR-C

AR-N  AR-V7-  Efstathiou et al ASCO 2014
C Terminal / N Terminal Ratio
AR Expression May Enhance Predictive Performance

<table>
<thead>
<tr>
<th>Marker</th>
<th>ARN (n3+) + CYP 17</th>
<th>ARC/ARN (n) ~1 + ARN(n3) + CYP17</th>
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<tbody>
<tr>
<td>Benefit (n=9)</td>
<td>9</td>
<td>9</td>
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<tr>
<td>Primary resistance (n=6)</td>
<td>2</td>
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<td>P value</td>
<td>0.03</td>
<td>0.0002</td>
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</table>

Efstathiou et al ASCO 2014
MDACC 10-0070 Testing Primary Resistance associations with androgen signaling molecular signature

Efstathiou et al ESMO 2014
Prostate Cancer in the Bone Marrow

AR amplification (17/37 CK+ cells)
3 months on abiraterone and enzalutamide

AR gain (5/5 cells)
Progressing to abiraterone
Negative BM (path)

Zurita et al
Acquiring Knowledge with a Curative Intent

The preoperative high risk model

Cancer early in spiral does not possess “plasticity” to resist therapy!
<table>
<thead>
<tr>
<th>Protocol #</th>
<th>Protocol</th>
<th>Years</th>
<th>#RP</th>
<th>Frozen Tissue (FT) % of cases</th>
<th>% FT with Ca</th>
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<td>TNP</td>
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<td>99-063</td>
<td>KAVE vs Horm. Abl. <em>(Prostate 12)</em></td>
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<td>01-079</td>
<td>Thalidomide <em>(CCR 07)</em></td>
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<td>ID03-0112</td>
<td>Docetaxel &amp;LHRH. <em>(JCO 12)</em></td>
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<td>36</td>
<td>92</td>
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<td>2003-0492</td>
<td>CCI 779 <em>(ASCO 09)</em></td>
<td>2004-07</td>
<td>34</td>
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<td>97*</td>
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<td>2004-0273</td>
<td>Horm. Abl. &amp; Docetaxel*</td>
<td>2006-09</td>
<td>32</td>
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<td>2005-0903</td>
<td>Sutent</td>
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<td>Sutent (Multi-Center)</td>
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<td>1</td>
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<td>2009-0293</td>
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<td>2009-0473</td>
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<td>2009-0322</td>
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<td>2012-0922</td>
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<td>2013</td>
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High Risk Pre–op Model (Curative Intent)

RANDOMIZE

1. LHRH

2. LHRH + Abiraterone

PROSTATECTOMY
Primary Resistance in high risk locally advanced disease

Tumor Volume (cc)
Dominant Focus

% “Occupancy”
by PCa

- LHRHa + Abiraterone
- LHRHa

Near PCr

Efstathiou et al ASCO 2013
Androgen Receptor Expression and lack of Splice Variant detection

LHRH+ Abiraterone Acetate

H&E  AR-N  AR-C19  ARV7

LHRH

AR-C/AR-N≈ 1  NO ARV7 DETECTED

In line with data on untreated primary PCA Plymante et al

Efstathiou et al ASCO 2013
High Risk Pre–op Model (Curative Intent)

1. LHRH + Abiraterone

2. LHRH + Enzalutamide Abiraterone

RANDOMIZE

PROSTATECTOMY
Model for Reclassification of Prostate Cancer

Microenvironment Dependence
Osteoblasts secrete factors (osteocrines) in the tumor microenvironment thus mediating therapy resistance of PCa bone metastasis.

Lin et al 2012
Rad-223 efficacy attributed to microenvironment targeting;

Determining bone marrow secretome of patients treated will identify candidate predictive markers

MDA-PCa-118b

X-ray

Histology

Prostate cancer xenograft MDA-PCa-118b secretes bone forming soluble factors

Resistant Tumor Cells Are Found Close to Newly Formed Bone Matrix

J Araujo, S Lin
Model for Reclassification of Prostate Cancer

DHT Dependent

Cyp17  AR  Src

(FGFR, c-Met, Akt, etc)
AR amplification, mutation paracrine factors

Oncogene Activation
AR/oncogene cross talk microenvironment dependence

Entry into spiral

Exit from spiral

Altered Cell Cycle
Chemotherapy Responsive

**Hypothesis**

*Clinically defined* “anaplastic” prostate cancers share the **chemotherapy responsiveness** of the small cell prostate carcinomas *(despite morphologic heterogeneity)*
Morphologically heterogeneous CRPC with variant clinical features have a chemotherapy response profile similar to that observed in SCPC.
Activation of the Mitotic and Neural Precursor Programs in Small Cell Prostate Carcinomas

**Hypothesis**

Functional characterization of patient derived xenografts (PDX) from men with ‘anaplastic’ prostate cancers will enable the identification of predictive markers and therapy targets.
Molecular Profiling of Anaplastic disease

EARLY

Pre-chemo

Post-chemo

The Clinical “anaplastic” tumors show alterations in 3 domains:

1. Loss of tumor suppressors (RB, p53 and/or REST)
2. Gain of neural development program
3. Alteration of the mitotic apparatus

The transitions and mixed profiles observed are consistent with the presence of a biologic continuum.
Translational Chemotherapy Trials

CT Guided Biopsy/BMB – Cabazitaxel Trial

1. Cabazitaxel
2. Cabazitaxel + Carboplatin

Local Consolidation
Systemic

Week 8*
Maximum Response*/**
Discontinuation*

Efstathiou HeCoG- MDACC
Corn MDACC
Building on Findings

- DHT Dependence
- Endocrine (androgen ablation)
- Paracrine ("Combination Targeting")
- Paracrine/Autocrine (Chemotherapy Sensitive)

"Anaplastic"

Discovery ➔ Testing ➔ Validation
Drug Sequencing and Combination era
WARRANTS Integration of Knowledge towards a
BIOMARKER STRATEGY

- Immunotherapy
- Taxanes
- Micro-environment targeted
- AR targeted
Precision Medicine Requirements

Knowledge Network for Biomedical Research

integrating:
Molecular Characterisation
& Clinical Data

New Taxonomy of Disease

Biomedical Research Clinical Medicine
Precision Medicine delivered

**Right** treatment strategy at the **right**
dose at the **right** time, **with minimum ill**
consequences and **maximum efficacy**
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