LEADING MEDICINE:
A TOWN HALL CONVERSATION
WITH DR. MARC BOOM

Town Hall Conversation 30
Due to the large file size, the slides of Dr. E. Brian Butler cannot be posted. Please email foundation@houstonmethodist.org to receive a copy of the slides.
The Houston Methodist Cancer Center Vision
A Therapy Development Strategy for Prostate Cancer

Eleni Efstathiou MD PhD
Genitourinary Oncology Section Chief
Dr. Mary and Ron Neal Cancer Center
Disclosures: Eleni Efstathiou MD PhD

Research Support / P.I.: Janssen, Sanofi-Genzyme, Astellas/ Pfizer/
Medivation, Oric-Pharma, Astra Zeneca, Eli Lilly,
Scientific Advisory Board, Steering Committee: Janssen, Sanofi-
Genzyme, Tolmar, Takeda, Bayer, Oric Pharma, Astra Zeneca, Merck,
Genentech,
“Drug vs Therapy Development”

Drug Development: Determine the efficacy of individual ‘agents’ (drug or intervention) and lead to their approval

Therapy Development: inform impactful sequences or combinations and strategy for their allocation over time to maximize benefit and minimize toxicity
Variables: Disease and Host / Patient Spectrum
Warranting a composite and multidisciplinary strategy

- Localised or locally advanced prostate cancer
- Biochemical recurrence
- Primary progressive mHSPC
- Newly diagnosed mHSPC
- mCRPC
- nmCRPC
- Terminal disease (death)

Unmet Needs

Heterogeneity Between Tumors of same stage
Temporal Heterogeneity

The Host: A unique being

Precision in Prostate Cancer Therapeutic Strategy Remains Elusive
And it always starts in the clinic!
Therapy Development Requirements

• Drug Development
• Biomarker Development
• Understanding man(host) – tumor ‘interaction’
• Real world practice research
• Education / Patient Access
Drug development in Prostate Cancer 1941-2010

*Docetaxel* (2004)

1941 - 2010

**ADT**

1st generation anti-androgens
Drug development in Prostate Cancer within last decade

1941 - 2010

Docetaxel (2004)

2010

Cabazitaxel

1st generation anti-androgens

2011

Enzalutamide

2nd generation anti-androgens

2012

Ra-223

1st and 2nd generation chemotherapy

2013

Darolutamide

2019

Abiraterone

2020

Aloparib

2021-'22

Rucaparib / Lu177-PSMA Talazoparib

Rise of precision medicine: PARPi and beyond
Therapy Development Requirements

✅ Drug Development
  • Biomarker Development
  • Understanding of host – tumor ‘interplay’
  • Real world practice research
  • Education / Patient Access
Precision Targeting in Prostate Cancer takes too long...

First evidence of genetic predisposition to prostate cancer

- Feasibility of multi-institutional molecular characterization in mCRPC

1997

Germline pathogenic DDR mutations in metastatic prostate cancer 11.8%

2015

NCCN 2017 first guidelines: DDR testing for m Pca and expanded to men with, high risk localized, metastatic or strong family history

2016

TOPAARP-A Study

2017

PROFOUND

10 20 30 40 50 60 70 80 90 100

Probability of rPFS

6-mo rate 59.76%

12-mo rate 28.11%

2019

6-mo rate 22.63%

12-mo rate 9.40%

2020

FDA Approvals

Olaparib for DDR mutated mCRPC post enhanced androgen signaling inhibition

FDA approval of companion diagnostics: FoundationOne CDx and BRACAnalysis


Robinson et al., 2015, Cell 161, 1215–1228


Androgen Signaling Inhibition Therapy Development

2006

- Endocrine mediated progression

2009

- Paracrine / Intracrine Progression

2012-2020

- Genomic / Non Genomic
  - Driven Resistance mCRPC

Progress Report:
Androgen Signaling Inhibition prevailing therapeutic strategy in advanced Prostate Cancer
✓ Reproducible outcomes
✓ Earlier is better
✓ ..more may be less..

Unmet Needs:
➢ Effective therapeutic strategies for Localized High Risk Disease
➢ Predictors of Outcome to guide therapy selection

2011-2012 mCRPC
- Abiraterone
- Enzalutamide
- Apalutamide

2017 -2019 mHNPC
- Abiraterone
- Enzalutamide

2018 -2019 nmCRPC
- Enzalutamide
- Apalutamide
- Darolutamide
### Preoperative High Risk Platform

**Goal: Create Knowledge from Tissue based Clinical Research**

<table>
<thead>
<tr>
<th>Protocol #</th>
<th>Protocol</th>
<th>Years</th>
<th>#RP</th>
<th>Frozen Tissue (FT) % of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>99-063</td>
<td>KAVE vs Horm. Abl. <em>(Prostate 12)</em></td>
<td>99-03</td>
<td>60</td>
<td>67</td>
</tr>
<tr>
<td>01-079</td>
<td>Thalidomide <em>(CCR 07)</em></td>
<td>2001-02</td>
<td>16</td>
<td>75</td>
</tr>
<tr>
<td>ID03-0112</td>
<td>Docetaxel &amp;LHRH</td>
<td>2003-05</td>
<td>36</td>
<td>92</td>
</tr>
<tr>
<td>2003-0492</td>
<td>CCI 779</td>
<td>2004-07</td>
<td>34</td>
<td>100</td>
</tr>
<tr>
<td>2004-0273</td>
<td>Horm. Abl. &amp; Docetaxel* <em>(JCO 2012)</em></td>
<td>2006-09</td>
<td>32</td>
<td>81</td>
</tr>
<tr>
<td>2005-0903</td>
<td>Sutent</td>
<td>2007-09</td>
<td>39</td>
<td>100</td>
</tr>
<tr>
<td>2008-0069</td>
<td>Sutent (Multi-Center)</td>
<td>2009-09</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>2009-0293</td>
<td>LHRH +Abiraterone (Multi-Center)</td>
<td>2010-11</td>
<td>13</td>
<td>92</td>
</tr>
<tr>
<td>2009-0473</td>
<td>LHRH +/- GDC-0449 (Single-Center) pending</td>
<td>2009-12</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>2013-0922</td>
<td>LHRH+Abi+/-Enza <em>(ASCO 2018)</em></td>
<td>2014-16</td>
<td>66</td>
<td>100</td>
</tr>
<tr>
<td>2017-0627</td>
<td>LHRH+ Apa +/- Abiraterone <em>(ASCO 2020)</em></td>
<td>2017-20</td>
<td>68</td>
<td>100</td>
</tr>
</tbody>
</table>
Association of Pre-Treatment Biopsy marker expression with Post treatment Prostatectomy Outcomes

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>AR-N</th>
<th>PTEN</th>
<th>nAR-V7</th>
<th>GR</th>
<th>Ki67</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 (4+4), G4</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
<td><img src="image5" alt="Image" /></td>
</tr>
<tr>
<td>9 (4+5), G5</td>
<td><img src="image6" alt="Image" /></td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
</tr>
<tr>
<td>7 (4+3), G3</td>
<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
<td><img src="image13" alt="Image" /></td>
<td><img src="image14" alt="Image" /></td>
<td><img src="image15" alt="Image" /></td>
</tr>
<tr>
<td>7 (4+3), G3</td>
<td><img src="image16" alt="Image" /></td>
<td><img src="image17" alt="Image" /></td>
<td><img src="image18" alt="Image" /></td>
<td><img src="image19" alt="Image" /></td>
<td><img src="image20" alt="Image" /></td>
</tr>
<tr>
<td>Intraductal Carcinoma</td>
<td><img src="image21" alt="Image" /></td>
<td><img src="image22" alt="Image" /></td>
<td><img src="image23" alt="Image" /></td>
<td><img src="image24" alt="Image" /></td>
<td><img src="image25" alt="Image" /></td>
</tr>
<tr>
<td>9 (4+5), G5</td>
<td><img src="image26" alt="Image" /></td>
<td><img src="image27" alt="Image" /></td>
<td><img src="image28" alt="Image" /></td>
<td><img src="image29" alt="Image" /></td>
<td><img src="image30" alt="Image" /></td>
</tr>
</tbody>
</table>

**Proposed Predictive Signature**

- Lack of nARV7, Ki67 <10%
- PTEN intact
- GR <10%

Efstathiou et al. ASCO 2021
1. Predictive Signature Testing: The “DarPa” Trial

Eligibility:
- Adenocarcinoma
- Gleason ≥ 8 OR Gleason 7 + ≥cT2b+PSA>10ng/ml
- Absent metastases by conventional imaging criteria
- Diagnostic biopsy availability for characterisation

Treatment: 6 months

End points:
- Cytoreduction/Therapy effect
- Test Diagnostic signature biopsy
- Residual cancer quantification, characterization
- PSA recurrence/MFS
- Safety

Group A
- Darolutamide + LHRHa

Group B
- LHRHa
THERANOSTICS ERA:
Prostate-specific membrane antigen (PSMA): molecular target for imaging and therapy in prostate cancer

- Transmembrane carboxypeptidase
- Highly expressed in prostate cancer including metastatic lesions
- Relatively restricted normal expression
  - e.g., salivary and lacrimal glands
- Excellent target for PET imaging
- Lu-PSMA FDA Approved targeted therapeutic

Houston Methodist is one of the first institutions in country with Lu-PSMA availability

Finite Advanced Androgen Signaling inhibition in oligorecurrent HNPC

- Link “driver biology” to outcomes by characterizing primary cancers
- Extend findings to propose a risk stratified, marker based, adjuvant therapy in men at risk for recurrence following surgery

Hazard Ratio 0.62 (95% CI 0.44-0.88)

No difference in time to eugonad state

Efstathiou et al Eur Urol 2020
2. Moving up Treatment Paradigm in Recurrent Disease: An effort at achieving cure

Eligibility:
- Adenocarcinoma of prostate
- PSA increase post treatment of primary
- Oligometastasis by enhanced imaging criteria
- Tissue availability for characterisation

End points:
- Time to progression (PSA, enhanced imaging)
- Evaluate Diagnostic signature biopsy for response
- Safety

Group A
- Apalutamide + Relugolix + LuPSMA
- Treatment: 6 months

Group B
- Apalutamide + Relugolix

Randomised

2:1

Men with oligorecurrent mHSPC by PET PSMA

Time to Progression
3. HSPC Adapting ‘precision’ to the data: targeting beyond DDR mutational status

Eligibility:
• Adenocarcinoma
• Gleason ≥ 8 OR Gleason 7 + ≥cT2b+PSA>10ng/ml
• Absent metastases by conventional imaging criteria
• Diagnostic biopsy availability for characterization
• Germline testing
• Baseline Thanatrace Pet Imaging

End points:
• Cytoreduction/Therapy effect
• Test Diagnostic signature biopsy
• Residual cancer quantification, characterization
• PSA recurrence/MFS
• Safety

PI: Dr Jian Guan
PSMA-CAR T cell therapy overcomes the immunological “cold” nature of Prostate Cancer.

Phase I feasibility end of 2023

He et al Unpublished
Therapy Development: Precision Medicine Development

Aim: A clinically meaningful Prostate Cancer Reclassification to Guide Therapeutic Strategies that maximize Therapeutic Index

Integrating Molecular Characterization & Clinical Data

Tissue/Liquid Biopsy and Molecular Imaging Driven Research

Discovery Testing Validation Clinic Deliverable

NIH manifesto 2011
How to Maximize “Therapeutic Index”
“Select and dose a therapeutic strategy” towards the most efficacious and least toxic for specific patient

Personalized Therapeutic Index:
Efficacy / Safety

Achieving the balance between Overtreatment and Undertreatment
A HealthCare “Corporation” to treat each man

1. Urology
2. Medical Oncology
3. Geneticists
4. Nursing
5. Social work
6. Radiation oncology
7. Lifestyle improvement strategists: (nutrition, exercise, mindset)
8. Radiology
9. Nuclear Medicine
10. Pathology/Molecular Pathology/Lab Medicine
11. Psycho-oncology
12. Internal medicine disciplines/Geriatrics
13. Pharmacy
14. Patient Advocacy
Adaptation to an evolving therapeutic paradigm
We are here to all work together to make progress and give back to our community

Urology: Drs. Miles, Satkunasivam
Rad Oncology: Drs. Butler, Farach
Oncology: Dr. Zhang
Nuclear Medicine: Drs. Fisher and Chang
Radiology: Dr. Gupta
Research Institute: Drs. Wong, He
Cyclotron Researchers,
Pathology, Internal Medicine, Cardiology Nutrition

‘Science is not cold and unfeeling. In scientific investigation one becomes emotionally contained in his problem. Head, heart and hand – the three H’s of experimentation – all are involved in creativity in the medical sciences. The combination enables us to recognize a solvable problem.’
Shortening Brachytherapy Treatment Time

Andrew Farach, MD
Associate Professor
Director of Brachytherapy
Department of Radiation Oncology

@andrewfarach
What is Brachytherapy?

**Brachytherapy** is the internal delivery of radiation as cancer therapy. Radioactive implants are placed very near or within a tumor and deliver high doses of radiation with less damage to other organs than external radiation.

- **Implant directly placed in tumor and surrounding tissue**
  - Prostate cancer
  - Implant seeds in the prostate

- **Implant placed in body cavity**
  - Cervical cancer
  - Implant device in the vagina

**Brachytherapy may be permanent or temporary**

- **Permanent brachytherapy**
  - Permanent implant
  - Single procedure

- **Temporary brachytherapy**
  - Temporary implant lasting minutes or days
  - Single or multiple procedures

HMH Brachytherapy
By the numbers

Total Brachytherapy Cases

Prostate Brachytherapy Cases


2019 2020 2021 2022

130 221 336 503 504 502 527

7 21 59 101

101
LDR vs HDR Brachytherapy

Prostate Cancer

Low Dose Rate (LDR)  High Dose Rate (HDR)
Brachytherapy for PCa
Role across the disease spectrum

Monotherapy

Combination Therapy

Low/Low Int Risk Localized

High Int/ High Risk Localized

Oligometastatic
Locally Recurrent
Intact Prostate
Locally Recurrent Prostate Bed

81 yo M s/p prostatectomy 25 years ago with salvage RT 10 years later (2007)

<table>
<thead>
<tr>
<th>PSA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2.79</td>
<td></td>
</tr>
<tr>
<td>4.19</td>
<td></td>
</tr>
<tr>
<td>1.11</td>
<td></td>
</tr>
<tr>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>0.28</td>
<td></td>
</tr>
</tbody>
</table>
ABS Designated Training Site
American Brachytherapy Society

2 Month Fellowship
1st in the Nation
National Presentations
Expedited HDR Brachytherapy

CT Based Work-flow

Patient In → OR Procedure → CT simulation → MD Contouring → Physicist Catheter ID → Physicist Planning → Plan approval → QA → Treatment → Patient Out → Removal
8:00 am → 8:30 – 9:30 → 11:00 → 11:00-2:00 → 2:30 → 2:45 → 3:00 pm

US Based Work-flow

Patient in → Ultrasound Imaging → Contouring → Dose planning → Needle insertion → Treatment delivery → Patient out
8:00 am → 8:30-10:30
HMH Brachytherapy of the Near Future

Image-guided Brachytherapy Suite
Thank you!
COVID-19 Viral Load Detected in City of Houston Wastewater

Viral Load: 75%
In comparison to July 6, 2020

Positivity Rate: 5%

https://covidwwtp.spatialstudieslab.org/
Confirmed COVID-19 Lab Tests

Houston Methodist Testing Trend
Influenza, Respiratory Syncytial Virus & Rhinovirus/Enterovirus Positivity
Molecular & Antigen, Basic View, 03/01/2015 - 11/13/2022

- Influenza A
- Influenza B
- Respiratory Syncytial Virus
- Rhinovirus/Enterovirus

Key dates:
- 3/8/16
- 2/7/17
- 12/26/17
- 2/12/19
- 12/24/19
- 10/18/22
- 11/6/22
- 11/13/22
- 3/8/22
GET A
FLU VACCINE NOW

#FIGHT FLU
Employee Recognition: $500 HEB Gift Card Distribution

THANK YOU
$500 GIFT CARD
THANK YOU FOR ATTENDING OUR TOWN HALL CONVERSATION

If you would like more information about the Dr. Mary and Ron Neal Cancer Center, please contact Josh Thiel at jjthiel@houstonmethodist.org

Take care and be well