Predictive Medicine for Men with Metastatic Prostate Cancer

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Duke Urologic Assembly March 2018
Disclosures

• Dr. Armstrong receives research funding (to Duke) from Janssen, Pfizer/Medivation, Astellas, Bayer, Dendreon/SanPower, Genentech/Roche, Novartis, Sanofi Aventis, Gilead, Active Biotech

• Consultant for Janssen, Bayer, Pfizer, Astellas, Dendreon

• Speaker for Bayer, Dendreon, Sanofi aventis
Three Key Points

• Germline and Somatic DNA testing in aggressive prostate cancer: Who to test, when, and why?
• Precision medicine approaches: AR-variant testing, ctDNA, and DNA repair defects
  • PARP inhibition sensitivity, abiraterone/enzalutamide resistance
• Novel immunotherapies for metastatic prostate cancer: pembrolizumab in MSI high PC, sipuleucel-T in AA men
Natural History of Lethal Prostate Cancer and Treatment Options

Nonmetastatic
- Local Therapy
- Castration Hormone Therapy

Metastatic
- Sipuleucel-T
- Docetaxel
- Abiraterone or Enzalutamide
- Radium-223

Asymptomatic
Symptomatic

Time
Castration Resistance

- LHRH is standard management for castration
- All prostate cancers will eventually progress
- Defined as progressive disease despite castration

Levels of testosterone (<50 ng/dl)
  - Progression defined by PSA, radiologic criteria, or clinical (pain) criteria

- Does not mean that the cancer is not utilizing androgen for growth as evident from scientific findings below
  - Many tumors remain sensitive to novel AR antagonists or androgen synthesis inhibitors
  - Amplification of AR can overpower low testosterone states/levels
  - Prostate cancers can manufacture their own androgenic ligands

Montgomer RB. *Cancer Res*. 2008;68:4447-4454
Prognosis in Men with mCRPC

Based on existing nomograms, multivariate models

Pre-treatment prognostic factors

- Performance Status
- Pain
- Lactate Dehydrogenase
- Visceral spread
- Type of Progression (PSA vs. radiographic)
- Anemia
- Circulating Tumor Cell Count
- PSA and PSA kinetics
- AR-V7 in CTCs
- C-reactive protein
- Albumin
- Bone markers: Alkaline Phosphatase, Urine NTx…
- Gleason sum
- Number of sites of disease
- Duration of hormone responsiveness
- VEGF, IL-6, Chromogranin levels

Post-treatment prognostic factors:

- PSA declines
- Pain improvements or worsening
- Quality of life improvements
- Change in CTC count (≥5→<5)
- PSA PFS and radiographic PFS
- Bone turnover marker changes
- Immunologic response to tumor antigens
- Skeletal-related event development

Frequent misuse of the word “predictive” in the literature

Smaletz et al, JCO 2002;20:3972
Halabi et al, JCO 2003;21:1232
Armstrong et al Eur Urol 2012
Precision Medicine: Defining Clinical Utility

• Federal guidance: clinical utility refers to the usefulness of the test and value of information to medical practice and clinical benefit
  • Analytic validity ≠ clinical validity!
  • Sensitivity, specificity, accuracy, precision, external reproducibility at the analyte and disease level should be established first to determine thresholds, defining what a positive or negative test means

• Net benefits vs. net harms compared with best available alternative test or using no test depending on standard of care
  • Patient level, family level
  • Health care and societal levels
  • Context and condition dependent

DHHS/AHRQ Technology Assessment 2010

"Off hand, I'd say you're suffering from an arrow through your head, but just to play it safe, I'm ordering a bunch of tests."
Precision Medicine: Molecular Profiling of mCRPC

- Commonly identified aberrations in AR, p53, PI3K, WNT, epigenetic, and DNA repair pathways (germline and somatic)
- Most would consider truly actionable genomic alterations to be HRD (10-20%) and MMRD (3-6%) in this setting; others are speculative
  - PARPi, platinums and PD-1 inhibition would not normally be given without this clinical clue

**Driver Aberrations in mCRPC**

**Potentially Actionable Mutations in mCRPC**

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Precision medicine: role of biology in mCRPC

Genomic Aberrations in DNA Repair in Patients with Metastatic, Castration-Resistant Prostate Cancer


Pritchard NEJM 2016

~10-12% germline, 10% somatic

RESPONDERS

NON-RESPONDERS

Precision medicine: role of biology in mCRPC

Men with HRD Respond to PARP Inhibition

## Ongoing Clinical Trials of PARP Inhibitors in mCRPC

<table>
<thead>
<tr>
<th>PARP Inhibitor</th>
<th>Clinical Trial Number</th>
<th>Study Overview</th>
<th>Disease setting</th>
<th>Trial status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>NCT02987543</td>
<td>Phase 3 trial of olaparib vs enzalutamide or abiraterone acetate (PROfound Study)</td>
<td>mCRPC after failure of front-line, novel hormonal therapy, presence of DNA-repair defect</td>
<td>Open, recruiting</td>
</tr>
<tr>
<td>Olaparib</td>
<td>NCT01972217</td>
<td>Randomized, phase 2, double-blind, placebo-controlled study of olaparib with abiraterone vs placebo with abiraterone</td>
<td>mCRPC, candidate for abiraterone, no more than 2 prior courses of chemotherapy</td>
<td>Open, not recruiting</td>
</tr>
<tr>
<td>Olaparib</td>
<td>NCT03012321</td>
<td>Three-arm, randomized, phase 2 study of abiraterone vs olaparib, vs olaparib with abiraterone</td>
<td>mCRPC with DNA-repair defects, before chemotherapy</td>
<td>Open, recruiting</td>
</tr>
<tr>
<td>Veliparib</td>
<td>NCT01576172</td>
<td>Randomized, phase 2 study of veliparib with abiraterone vs placebo with abiraterone</td>
<td>mCRPC, candidate for abiraterone</td>
<td>Open, not recruiting</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>NCT02975934</td>
<td>Randomized phase 3 study of rucaparib vs physician’s choice (enzalutamide, abiraterone, or docetaxel)</td>
<td>mCRPC with homologous recombination gene deficiencies, prechemotherapy</td>
<td>Open, recruiting</td>
</tr>
<tr>
<td>Niraparib</td>
<td>NCT02854436</td>
<td>An efficacy and safety study of niraparib (GALAHAD)</td>
<td>mCRPC with DNA-repair anomalies, postchemotherapy</td>
<td>Open, recruiting</td>
</tr>
</tbody>
</table>

Abbreviations: mCRPC, metastatic, castrate-resistant prostate cancer; PARP, poly(adenosine diphosphate-ribose) polymerase.
STAMPEDE: SOC+AAP vs SOC+DocP

Recruitment: Nov-2011 to Mar-2013
Reported: ESMO 2017
Published: (paper in development)

Patients: 189 SOC+DocP
377 SOC+AAP

566 patients randomised contemporaneously to either research arm

Underpowered but the only head-to-head data

Last year of recruitment to “abiraterone comparison” overlap with a question of radiotherapy to the prostate in men with M1 disease

Sydes et al ESMO 2017
When to consider germline genetic testing?

• NCCN recommends germline testing in all men with metastatic prostate cancer regardless of family history and age
  • Prevalence of DNA repair defects is 11-12%, particularly BRCA2
  • Prevalence is lower in localized high risk disease (3-6%) but reasonable to test these men if + FH suggestive of hereditary cancer syndrome
  • Prevalence of mismatch repair defects is 3-6%, MSI high in 3-6% or higher
• Initial testing on blood or saliva in clinic with pre-testing counseling and taking a family history is reasonable, followed by reflex referral to a hereditary cancer clinic for genetic counseling if (+) result
  • Family and personal implications for breast, ovarian, pancreatic, melanoma, GI cancer screening, early detection and family testing/counseling
• Example tests include Invitae and Color assay
  • Insurance coverage typically follows guidelines for these tests, and costs continue to come down for testing, typically $150 and less for family members if positive
When to consider somatic tumor genetic testing?

• Not yet incorporated into NCCN guidelines to guide therapy
• Foundation Medicine tumor tissue testing now FDA approved as of 2017 for solid tumor molecular profiling
  • Reasonable in men with metastatic PC (HSPC or CRPC) to identify the 10-20% of men with homologous repair deficiencies and 3-6% of men with MMRD
  • Turnaround time is 4-6 weeks
• ctDNA testing may be useful in men where tissue testing is not evaluable or available
  • Guardant360 is available but not FDA approved, reimbursement is not well defined yet
  • Discordant results between ctDNA assays in PC has been reported, thus consistency and reliability remains a major issue
• Reflex germline testing is reasonable if a somatic HR or MMR enzyme mutation is found
  • With referral for genetic counseling if positive
ctDNA vs. Metastatic Biopsies

Wyatt et al JNCI 2017
ctDNA vs. Metastatic Biopsies

• Wyatt et al identified 42 patients who provided ctDNA targeted sequencing and a metastatic site biopsy for exome sequencing in the mCRPC setting
• Depth of sequencing 839x for ctDNA (targeted) and 78x for WES (metastases)
• 94% overlap/consistency in mutational calls
• Discordant results largely due to depth of coverage issues rather than true divergence but 5-10% may be due to a unique ctDNA clone not detected with a biopsy (TP53, APC, RB1, PTEN)
• High concordance (89%) for copy number alterations if ctDNA fraction was >35%
• Not yet validated for DNA repair defect testing due to challenges in detection of copy loss in ctDNA
Mismatch Repair Deficiencies: RESPONSES to Pembrolizumab in MSI high CRPC

2-3% prevalence of MMRD/MSI high

Typically involve mutations or rearrangements in MSH2 or MSH6 in PC, challenging to detect with current molecular profiling tests

Dung T. Le et al. Science 2017;science.aan6733
Responders to Pembrolizumab

Response rate appears to be 15-20% in unselected men with enza resistant mCRPC treated with enzalutamide.

Phase 3 trial of enza +/- atezolizumab is ongoing.

Duke has launched an avelumab trial in these men.

M1 CRPC Overview

**SYSTEMIC THERAPY FOR M1 CRPC**

- **CRPC**, studies positive for metastases
  - Consider tumor testing for MSI-H or dMMR
  - Consider genetic counseling and germline testing for homologous recombination gene mutations

- **CRPC**, studies positive for metastases
  - Continue ADT to maintain castrate levels of serum testosterone (<50 ng/dL)
  - Additional treatment options:
    - Bone antiresorptive therapy with denosumab or zoledronic acid (both in category 1 if bone metastases present)
    - Immunotherapy with sipuleucel-T (category 1) (See PROS-G
    - Palliative RT for painful bone metastases
  - Best supportive care

  **Visceral metastases**

  - **Yes**
  - **No**
    - Abiraterone with prednisone (category 1)
    - Docetaxel (category 1)
    - Enzalutamide (category 1)
    - Radium-223 for symptomatic bone metastases (category 1)
    - Clinical trial
    - Other secondary hormone therapy

  **At progression**
  - Re-stage and 
    - See Subsequent Therapy for M1 CRPC: No Visceral Metastases (PROS-16)
    - or
    - See Systemic Therapy for M1 CRPC: Visceral Metastases (PROS-17)

- **HR repair deficiencies**: BRCA2/1, ATM, PALB2, FANCA
- **MMR deficiencies**: MSH2, MLH1/2, PMS2, MSI testing

“Prostate Cancer” NCCN guidelines. 2018
**IMPACT: Sipuleucel-T Trend Toward Greater Survival Benefit With Lower Baseline PSA**

<table>
<thead>
<tr>
<th>Baseline PSA, ng/mL</th>
<th>≤22.1 (n=128)</th>
<th>&gt;22.1-50.1 (n=128)</th>
<th>&gt;50.1-134.1 (n=128)</th>
<th>&gt;134.1 (n=128)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Median OS, months</th>
<th>Sipuleucel-T</th>
<th>Control</th>
<th>Difference</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>41.3</td>
<td>27.1</td>
<td>20.4</td>
<td>18.4</td>
</tr>
<tr>
<td></td>
<td>28.3</td>
<td>20.1</td>
<td>15.0</td>
<td>15.6</td>
</tr>
<tr>
<td>Difference</td>
<td>13.0</td>
<td>7.0</td>
<td>5.4</td>
<td>2.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.51</td>
<td>0.74</td>
<td>0.81</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>(0.31-0.85)</td>
<td>(0.47-1.17)</td>
<td>(0.52-1.24)</td>
<td>(0.55-1.29)</td>
</tr>
</tbody>
</table>

Overall Survival with Sipuleucel-T in a PSA-matched Subset of PROCEED Patients

- Estimated median follow-up: 57.2 months in CAUs and 45.0 months in AAs

AA = African American; CAU = Caucasian; CI = confidence interval; HR = hazard ratio; OS = overall survival; PSA = prostate-specific antigen.

Sartor, Armstrong
AUA 2017
Overall Survival in CAUs and AAs by Median PSA

Below Median PSA

- Median PSA: 26.8 ng/mL
- Median OS: 33.4 mo
- Difference in median OS: 20.9 mo
- CAU (N=205)
- AA (N=105)
- HR (95% CI): 0.531 (0.378, 0.746)
- p<0.001

Above Median PSA

- Median PSA: 26.8 ng/mL
- Median OS: 25.5 mo
- Difference in median OS: 3.9 mo
- CAU (N=204)
- AA (N=100)
- HR (95% CI): 0.854 (0.644, 1.131)
- p=0.270

Sartor, Armstrong
AUA 2017

AA = African American; CAU = Caucasian; CI = confidence interval; HR = hazard ratio; OS = overall survival; PSA = prostate-specific antigen.
## Overall Survival in CAUs and AAs by PSA Quartiles

<table>
<thead>
<tr>
<th>Overall Survival by PSA Quartiles</th>
<th>Baseline PSA, ng/mL</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1 &lt; 7.5</td>
<td>Q2 7.5-26.8</td>
<td>Q3 26.81-68.49</td>
<td>Q4 ≥68.5</td>
</tr>
<tr>
<td><strong>Median OS, months</strong></td>
<td>AA</td>
<td>CAU</td>
<td>AA</td>
<td>CAU</td>
</tr>
<tr>
<td>AA</td>
<td>54.3</td>
<td>37.4</td>
<td>46.7</td>
<td>31.9</td>
</tr>
<tr>
<td>CAU</td>
<td>28.7</td>
<td>22.0</td>
<td>20.5</td>
<td>18.3</td>
</tr>
<tr>
<td><strong>Difference, mo</strong></td>
<td><strong>16.9</strong></td>
<td><strong>14.8</strong></td>
<td><strong>6.7</strong></td>
<td><strong>2.2</strong></td>
</tr>
<tr>
<td>HR</td>
<td>0.442</td>
<td>0.602</td>
<td>0.800</td>
<td>0.913</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.260, 0.753)</td>
<td>(0.386, 0.939)</td>
<td>(0.537, 1.194)</td>
<td>(0.614, 1.360)</td>
</tr>
<tr>
<td>p-value</td>
<td><strong>0.003</strong></td>
<td><strong>0.025</strong></td>
<td><strong>0.275</strong></td>
<td><strong>0.655</strong></td>
</tr>
</tbody>
</table>

AA = African American; CAU = Caucasian; CI = confidence interval; HR = hazard ratio; OS = overall survival; PSA = prostate-specific antigen.
Immunotherapy in CRPC

• Biomarkers can help identify responding patients, particularly MSI/MMR deficiency and response to PD-1 blockade
  • Ongoing studies examining novel settings for PD-1/PD-L1 benefit such as neuroendocrine phenotype PC (PICK study to open fall 2017)

• African American men have a particularly robust survival benefit with sipuleucel-T
  • Focus within DCI on PC disparity biology

• Many immunotherapy approaches under study in 2017-18
  • Prostvac, PD-1+/ CTLA4 combinations with hormonal therapy, RT, abi/enza
  • Oncolytic viruses, dendritic cell vaccines
Abiraterone and Enzalutamide for Men with mCRPC: Timing and Selection of Therapy

• Choice of abiraterone vs. enzalutamide cannot be dictated based on differences in efficacy
  – Similar OS, PFS from cross-trial comparisons
  – Enzalutamide has been evaluated in men with visceral metastases in the chemo-naïve setting
  – Both considered level 1 evidence in NCCN guidelines

• Therefore choice is based on differential toxicity
  – Abiraterone acetate for seizure-prone men and those more frail elderly (>75) men at high risk for falls
  – Enzalutamide for men with significant CV risk factors, contraindications to prednisone, brittle diabetes and metabolic syndrome, contraindications to prednisone
M1 CRPC Overview

**SYSTEMIC THERAPY FOR M1 CRPC**

- **CRPC**, studies positive for metastases → Consider tumor testing for MSI-H or dMMR
- Consider genetic counseling and germline testing for homologous recombination gene mutations

- **Continue ADT to maintain castrate levels of serum testosterone (<50 ng/dL)**
- **Additional treatment options:**
  - Bone antiresorptive therapy with denosumab or zoledronic acid (both category 1) if bone metastases present
  - Immunotherapy with sipuleucel-T (category 1) (See PROS-G)
  - Palliative RT for painful bone metastases
  - Best supportive care

- **Visceral metastases**

  - **Yes**: Abiraterone with prednisone (category 1)
  - Docetaxel (category 1)
  - Enzalutamide (category 1)
  - Radium-223 for symptomatic bone metastases (category 1)
  - Clinical trial
  - Other secondary hormone therapy

  **At progression**: Re-stage and See Subsequent Therapy for M1 CRPC: No Visceral Metastases (PROS-16) or See Systemic Therapy for M1 CRPC: Visceral Metastases (PROS-17)

  **No**: See Systemic Therapy for M1 CRPC: Visceral Metastases (PROS-17)
TERRAIN and STRIVE: Enzalutamide vs. Bicalutamide

• First randomized trials to compared enzalutamide to bicalutamide
• STRIVE only trial include M0 CRPC patients
• Randomized men to enzalutamide vs bicalutamide
• Improved response and delayed PFS (PSA, radiographic) with enzalutamide in all settings
• Delays metastasis (see PROSPER and SPARTAN, GU ASCO 2018)
  – Significant delays in MFS by 2 years with apalutamide or enzalutamide
• Unclear if early M0 vs standard M1 CRPC use of enzalutamide is more advantageous…no OS data yet
STRIVE: Enzalutamide vs. Bicalutamide

Similar results observed with TERRAIN in M1 CSPC (n=375):
median PFS $5.8 \rightarrow 15.7$ months with enzalutamide vs. bicalutamide
($HR = 0.44; 95\% CI, 0.34-0.57; P < .0001$), time to FACT-P deterioration $8.5 \rightarrow 13.8$ mo

M0 CRPC: Apalutamide and Enzalutamide

- Randomized placebo controlled trials of 1207 and 1401 men to novel AR inhibitor or placebo, all had M0 CRPC, rapid PSADT <10 mo. N1 disease allowed.
- MFS improved in SPARTAN (16.2 vs 40.5 mo) and PROSPER (14.7 vs. 36.6 mo), similar HR’s (0.28-0.29), positive for primary endpoint. Significant delays in PSA PFS, time to next therapy, symptomatic progression (SPARTAN)
- OS data immature but favorable trends at first interim analysis (HR 0.7 p=0.07 and 0.8 p=0.15) with insufficient efents
Apalutamide vs Enzalutamide: Adverse events

### Table of Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Enzalutamide + ADT (n = 930)</th>
<th>Placebo + ADT (n = 465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>808 (87)</td>
<td>360 (77)</td>
</tr>
<tr>
<td>Any grade ≥ 3 adverse event</td>
<td>292 (31)</td>
<td>109 (23)</td>
</tr>
<tr>
<td><strong>Most common adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>Grade ≥ 3</td>
<td>All grades</td>
</tr>
<tr>
<td>Fatigue</td>
<td>303 (33)</td>
<td>64 (14)</td>
</tr>
<tr>
<td>Hot flush</td>
<td>121 (13)</td>
<td>36 (8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>106 (11)</td>
<td>40 (9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>91 (10)</td>
<td>45 (10)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>111 (12)</td>
<td>24 (5)</td>
</tr>
<tr>
<td>Fall</td>
<td>106 (11)</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>65 (9)</td>
<td>32 (7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>91 (10)</td>
<td>20 (4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>78 (8)</td>
<td>32 (7)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>82 (9)</td>
<td>28 (6)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>89 (10)</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Back pain</td>
<td>73 (8)</td>
<td>33 (7)</td>
</tr>
<tr>
<td>Headache</td>
<td>65 (9)</td>
<td>21 (5)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>62 (7)</td>
<td>36 (8)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>38 (4)</td>
<td>30 (6)</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>55 (6)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>20 (2)</td>
<td>28 (6)</td>
</tr>
</tbody>
</table>

### Other adverse events of interest

<table>
<thead>
<tr>
<th>Event</th>
<th>Enzalutamide + ADT (n = 930)</th>
<th>Placebo + ADT (n = 465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension†</td>
<td>114 (12)</td>
<td>25 (5)</td>
</tr>
<tr>
<td>Major cardiovascular event‡</td>
<td>43 (5)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Mental impairment disorder§</td>
<td>42 (5)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>11 (1)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>9 (1)</td>
<td>1 (&lt; 1)</td>
</tr>
<tr>
<td>Convulsion</td>
<td>3 (&lt; 1)</td>
<td>0</td>
</tr>
<tr>
<td>Posterior reversible encephalopathy syndrome</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Discussion Points

• Should we be using enzalutamide in men with M0 CRPC to prevent/delay metastases based on STRIVE outside of a clinical trial?
  – If resistance develops early to enza/apa, how do we treat these men?
• Apalutamide now approved for men with M0 CRPC based on improved MFS, enzalutamide likely to come
• Ongoing trials (SPARTAN, PROSPER, ARAMIS) will determine the net clinical benefit but prevention of symptomatic metastases, delays in MFS indicate benefit even without mature OS data
  – What data would you need to see (OS, MFS, SSE’s, etc) to convince you of the net benefit of using these agents prior to M1 CRPC development?
  – NCCN Guidelines released 3/2018
M0 CRPC

- No level 1 evidence with survival data
- Secondary hormonal manipulations (excluding abiraterone, enzalutamide)
  - Median duration of PSA response 3-6 months, but some respond for >1 year
  - Guidelines updated March 2018 (enzalutamide once published)
The Need for Predictive Biomarkers in Men with mCRPC

**Enzalutamide**
- Primary resistance to enza in 10-20% of chemo-naïve men with mCRPC
- Acquired resistance is universal after median 15-18 months
- Diversity of mechanisms

Ryan et al NEJM 2012
Enzalutamide Outcomes

Figure 3. Best Radiographic Response by Level of Greatest Confirmed PSA Decline From Baseline Within First 3 Months of Treatment in Enzalutamide Arm of PREVAIL (ITT Patients With Measurable Disease)

- Complete Response
- Partial Response
- Progressive Disease
- Stable Disease
- Not Evaluable

Time to Death

*P < .001 vs no PSA decline/PSA decline < 30% based on Fisher’s exact test.

Abbreviations: ITT, intent to treat; ORR, objective response rate; PSA, prostate-specific antigen.
Abiraterone Acetate

- Superior to prednisone both before and after docetaxel in mCRPC
- Improved OS (30.2 → 34.7 mo), QOL, pain, PFS (8.3 → 16.5 mo), PSA and radiographic, pain response rates
- Delay in pain progression, PS deterioration, and need for chemotherapy

Final OS chemo-naïve mCRPC: p=0.0033
**Enzalutamide after abiraterone** can result in PSA responses (>50% decline) but this was observed in <1/3 of men in the post-docetaxel CRPC setting with a TTP of 4-6 months and rare radiographic responses.

- Response to enzalutamide was **not** possible to predict based on prior response to abiraterone/enzalutamide.
- Increasingly important after LATTITUDE and STAMPEDE data and new SPARTAN/PROSPER with potential early use of potent AR inhibitors.


**Abi-Enza Clinical Cross-Resistance**
Cross-Resistance

All men had >6 months of prior Abi and were treated with enzalutamide

PSA response rate of ~30%

Choudhury et al Eur Urol 2017
Subsequent Therapy for mCRPC

“Prostate Cancer” NCCN guidelines. 2018
Visceral Metastases

SYSTEMIC THERAPY FOR M1 CRPC

Visceral metastases → Consider biopsy

Adenocarcinoma

Small cell

Consider brain MRI with and without contrast

Prior therapy:
- Enzalutamide
- Abiraterone

Progression

Prior therapy:
- Docetaxel
- Mitoxantrone
- Other secondary hormone therapy

SUBSEQUENT THERAPY

- Chemotherapy
  - Cisplatin/etoposide
  - Carboplatin/etoposide
  - Docetaxel/carboplatin
- Clinical trial
- Docetaxel (category 1)
- If not previously received:
  - Abiraterone with prednisone
  - Enzalutamide
  - Pembrolizumab for MSI-H or dMMR (category 2B)
- Clinical trial
- Other secondary hormone therapy
- Best supportive care

See Principles of Androgen Deprivation Therapy (PROS-F).

"Prostate Cancer" NCCN guidelines. 2018
Androgen Receptor (AR) Variants and Abiraterone/Enzalutamide Resistance

Primary Resistance:
prevalence of V7 likely depends on setting, prior therapy

Acquired resistance: unknown at this time

AR-V7: Clinical Utility? (N=202)
P < 0.001

40/53 = 76%
59/113 = 52%
5/36 = 14%

Nuclear AR-V7 (EPIC) Distinguishes Response to Abiraterone/Enzalutamide

Scher et al. Eur Urol 2016 {Epub: December 12}
The Duke PROPHECY Trial:
Validation of AR-V7 as a Predictive Biomarker in the Context of the Molecular Landscape of CRPC CTCs

Men with progressive mCRPC, at least one high risk feature, candidate for abiraterone acetate or enzalutamide, no prior taxane therapy for mCRPC, n=120

Enzalutamide or abiraterone acetate therapy, Progression #1, n=80

Taxane therapy Progression #2 n=30

AR-v7 assays (all men), n=230 total samples (120, 80, 30 at each time point, respectively)

 Subset CTC and circulating biomarker profiling: CTC WES, CGH, RNASeq, cell free ctDNA sequencing (n=40, 30, 20, respectively)

Metastatic site biopsy for CTC biomarker validation (n=20 each)

Results anticipated at ASCO 2018

US.National Institutes of Health. 2016 Clinicaltrials.gov/NCT02269982
Duke Prostate Cancer Trials 2018

**Localized**
- Prostate Cancer Trials 2018
- Investigator Initiated
- ALLIANCE or PCCTC
- Industry

**SPARC**: pre-op cabozantinib vs placebo in intermediate/high risk PC
- ASCENT (Movember), startups
- Pre-op RT plus Pembrolizumab and ADT (LOI)
- Provenge Active Surveillance Low risk (urology) and DUCIMAS

**Rising PSA**
- Pfizer VBIR*
- EMBARK (urology) enza/ADT
- STARTAR* apalutamide/ADT plus RT → docetaxel* pending contract

**mHSPC**
- Pfizer VBIR*
- Entra/ADT
- STREAM (PSA Prog FU)- IIT
- AbiCure- (PSA Prog FU)- PCTCC

**Chemo-Noa CRPC**
- Denileukin Lymphoid Node Biopsy Trial
- PANTHER: Apa/Abi Race
- Enza plus CC-115 (coming 2017)*
- JHU Provenge plus Radium-223 PD study, OPEN*
- Enza Exercise Study pre-abi/enza or sip-T, OPEN

**Chemotherapy Combinations**
- Pembrolizumab or enza or docetaxel (Merck)
- BMS SDK: Nivo + Rucaparib or Enza or Docetaxel (Startups)*
- Roche Radium + Atezolizumab OPEN*, prior chemo OK

**Post-Chemotherapy CRPC**
- PICK NEPC phase 2 (Pfizer Avelumab) OPEN
- GALAHAD Niraparib trial (phase 1 in men with DNA repair defects)*
- Copper Disulfiram phase 1 OPEN

**Chemotherapy Combinations**
- Pfizer VBIR phase 1 post-abi/enza adenovirus + treme +/- sunitinib OPEN*
- CPI-1205 + abi or enza in mCRPC (Constellation), start ups

**Studies with Close out pending:**
- Radium 223 (final publication, IIT), Cornell (PCTCC, paper submitted), Prevail (summer 2018), Enza IV, STRIVE, Sutent Pre-prostatectomy (final publication IIT), Provenge Registry (final publication)

**Phase 1:** AZ Refmal durvalumab plus Adenosine R inhibitor AZ4635
- COMRADE: Radium-223 +/- olaparib
- MERRIMACK nano-docetaxel Stemcentryl NEPC Ab

** Injectable:**
- Gadolinium feasibility study

**HERO: Relugolix vs Lupron for >/= 1y planned ADT**

**Studies with Active Patients:**
- AbiRace (proj completion Nov 2018), Viamet (1 pt active), ARN (1 pt active), PROSPER (2 pt active), Abi/Enza Alliance (3 pt active)

**Industries**
- Gilead GS-5829 +/- enza in post-abi mCRPC, Phase 1 complete, Phase 2? (1 active patient)*

**Multi-Site Studies**
* = DOD consortium
Presently, approved agents do not require a predictive biomarker other than clinical phenotype (pattern of spread, symptoms)
  - Sipuleucel-T, abi/enza, docetaxel, cabazitaxel, radium-223 for men with mCRPC
  - Abi or docetaxel for mHSPC patients

Precision medicine approaches are evolving for men with mCRPC
  - AR-V7 testing undergoing external validation now for abi/enza resistance
  - MSI high patients: pembrolizumab
  - HRD patients: platinum chemotherapy, PARPi trials
  - Novel approaches, combinations

Consideration of molecular profiling studies may help identify actionable mutations in 10-20% of men
  - Goals is prediction>prognosis, non-invasive > invasive testing (ctDNA, CTCs)
  - Maximizing benefits and minimizing harms and costs