PROSTATE CANCER
HORMONE THERAPY AND BEYOND

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John Wayne Cancer Institute
Disclosures

I am a Consultant for Bayer and Sanofi-Aventis and On the Speakers Bureau for Janssen, Bayer, Sanofi-Aventis, Pfizer and Astellas.

I will be discussing the off-label and investigational use of Sipuleucel-T, Pembrolizumab, Olaparib, Rucaparib, Niraparib, Talazoparib, Daralutamide, CPI-1205.
# TREATMENTS FOR ADVANCED PROSTATE CANCER APPROVED IN THE LAST 14 YEARS

(all approved initially in castration resistance space)

<table>
<thead>
<tr>
<th>DRUG /MECHANISM</th>
<th>YEAR OF FDA APPROVAL</th>
<th>SURVIVAL IMPROVEMENT (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel (chemo)</td>
<td>2004</td>
<td>+ 2.4</td>
</tr>
<tr>
<td>Sipuleucel-T (immune)</td>
<td>2010</td>
<td>+ 4.1</td>
</tr>
<tr>
<td>Cabazitaxel (chemo)</td>
<td>2010</td>
<td>+ 2.4</td>
</tr>
<tr>
<td>Abiraterone (AR axis)</td>
<td>2011</td>
<td>+ 3.9</td>
</tr>
<tr>
<td>Enzalutamide (AR axis)</td>
<td>2012</td>
<td>+ 4.8</td>
</tr>
<tr>
<td>Alpharadin (isotope)</td>
<td>2013</td>
<td>+ 2.8</td>
</tr>
<tr>
<td>Apalutamide (AR axis)</td>
<td>2018</td>
<td>? (approved based on mPFS)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>20.4 ?</strong></td>
</tr>
</tbody>
</table>
# PROSTATE CANCER ADVANCES AND FAILURES IN 2018

<table>
<thead>
<tr>
<th>Advances</th>
<th>Failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit of treatment of CRPC M0 with apalutamide or enzalutamide</td>
<td>Only minimal benefits with PD-1 inhibitors</td>
</tr>
<tr>
<td>Benefit of treatment of primary tumor in metastatic setting (STAMPEDE Study)</td>
<td>Combining Radium-223 (Xofigo) with abiraterone is harmful (ERA 223 study)</td>
</tr>
<tr>
<td>AR-V7 test approved</td>
<td>PROSTVAC vaccine ineffective</td>
</tr>
<tr>
<td>Advances in Imaging</td>
<td>Modest application of biomarker-based treatment selection</td>
</tr>
</tbody>
</table>
Is there an alternative to castration for advanced prostate cancer in 2019?
Yes... more and better castration
ANDROGEN DEPRIVATION THERAPY

• Recent studies indicate that more profound testosterone suppression earlier in the course of metastatic / recurrent prostate cancer is beneficial
• Addition of abiraterone to standard LHRH agonist injection significantly improves survival in patients with metastatic prostate cancer
• Addition of enzalutamide or apalutamide in patients with rising PSA despite LHRH agonist delays development of metastases by 2 years
ADDITION OF ABIRATERONE AND PREDNISONE TO STANDARD ADT IN NEWLY DIAGNOSED METASTATIC HORMONE-NAÏVE PROSTATE CANCER IMPROVES OVERALL SURVIVAL

Statistically significant 38% risk reduction of death

Hazard ratio, 0.62 (95% CI, 0.51-0.76)
P<0.0001

ADT + AA + P, not reached

ADT + placebos, 34.7 mo

OS rate at 3 years:
ADT + AA + P: 66%
ADT + placebos: 49%

No. of events: 406 (48% of 852)
ADT + AA + P: 109
ADT + placebos: 237

No. at risk
ADT + AA + P
ADT + placebos
0 6 12 18 24 30 36 42
597 565 529 479 388 233 93 9
602 564 504 432 332 172 57 2

Median follow-up: 30.4 months
A Kaplan–Meier Estimates of Metastasis-free Survival


Hazard ratio for metastasis or death, 0.28 (95% CI, 0.23–0.35)
P<0.001

No. at Risk
Apalutamide 806 713 652 514 398 282 180 96 36 16 3 0
Placebo 401 291 220 153 91 58 34 13 5 1 0 0
Is There a Benefit of Treating Primary Tumor in the Metastatic Setting?
Radiotherapy to the Primary Tumor for Newly Diagnosed, Metastatic Prostate Cancer (STAMPEDE): Randomized Controlled Phase 3 trial
Radiotherapy to the Primary Tumor for Newly Diagnosed, Metastatic Prostate Cancer (STAMPEDE): Randomized Controlled Phase 3 trial
Radiotherapy to the Primary Tumor for Newly Diagnosed, Metastatic Prostate Cancer (STAMPEDE): Randomized Controlled Phase 3 trial
DEFINITION OF LOW-VOLUME METASTATIC DISEASE IN STAMPEDE STUDY

• Conventional imaging
• Opposite to “high-volume”
• High-volume: visceral mets, or > 4 bone mets with at least 1 long bone involvement
• Theoretically patient with 100 spinal mets and no long bone met is considered “low volume”
• Recent data indicates benefit of earlier application of new, powerful hormonal agents.
• I anticipate that trend will continue and patients with recurrent / advanced prostate cancer will be exposed to ADT including 2nd generation ADT for longer periods of time
• Management of chronic side effects of ADT is challenging and will require interdisciplinary approach
MECHANISMS OF RESISTANCE TO ANDROGEN RECEPTOR AXIS INHIBITION

Nelson, JCO 2012;30:644-646
FUTURE THERAPIES
Metastatic, castration-resistant prostate cancer can have genomic aberrations that interfere with DNA repair. They involve genes including: BRCA2, BRCA1, ATM, FANCA, CHEK2, PALB2, RAD50 and are present in 25-30% of cases of advanced PC.

These aberrations have been associated with sensitivity to platinum chemotherapy and poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors.

PARP inhibitors are already approved in BRCA-mutated breast cancer (olaparib) and ovarian cancer (olaparib and rucaparib).
PARP AND BRCA AND DNA REPAIR

A.

- Base-excision repair
- Homologous recombination

Pair of DNA strand break

B.

- PARP inhibitor
- BRCA mutation

- Base-excision repair
- Homologous recombination

No repair of DNA strand breaks → Cell death
Genomic Aberrations in DNA Repair in Patients with Metastatic Castration-Resistant Prostate Cancer Predict Response to Olaparib

# Selected Clinical Trials of PARP Inhibitors in Prostate Cancer

<table>
<thead>
<tr>
<th>Trial Phase</th>
<th>Disease state</th>
<th>Key eligibility criteria</th>
<th>Sample Size</th>
<th>Primary endpoint</th>
<th>Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib vs Enzalutamide or Abiraterone</td>
<td>3 mCRPC</td>
<td>DNA repair Defects, post 2\textsuperscript{nd} gen hormone therapy</td>
<td>340</td>
<td>PFS</td>
<td>NCT02987543</td>
</tr>
<tr>
<td>Rucaparib vs Abiraterone, Enzalutamide or Docetaxel</td>
<td>3 mCRPC</td>
<td>DNA repair defects, post 2\textsuperscript{nd} gen hormone therapy</td>
<td>400</td>
<td>PFS</td>
<td>NCT02975934</td>
</tr>
<tr>
<td>Niraparib</td>
<td>2 mCRPC</td>
<td>After chemo and 2\textsuperscript{nd} gen hormone therapy</td>
<td>160</td>
<td>RR</td>
<td>NCT0284436</td>
</tr>
<tr>
<td>Olaparib</td>
<td>2 Biochemical recurrence</td>
<td>Post- prostatectomy, nonmetastatic dx</td>
<td>50</td>
<td>PSA RR</td>
<td>NCT03047135</td>
</tr>
<tr>
<td>Talazoparib</td>
<td>2 mCRPC</td>
<td>DNA repair defects, post 2\textsuperscript{nd} gen hormone therapy and chemotherapy</td>
<td>150</td>
<td>RR</td>
<td>NCT03148795</td>
</tr>
</tbody>
</table>
NEW SIMPLIFIED CANCER CLASSIFICATION
(by Dr. Twardowski)

CANCER

PEMBROLIZUMAB SENSITIVE

PEMBROLIZUMAB RESISTANT
PROSTATE CANCER

• Mostly pembrolizumab (checkpoint inhibitor) resistant however............
On May 23, 2017, the US FDA approved the use of pembrolizumab, for the treatment of patients with “unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair (MMR)-deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options”.

2/59 patients in the study had metastatic castration-resistant prostate cancer (mCRPC): one achieved a partial objective response, and the other achieved stable disease for >9 months.

Pembrolizumab can be considered in MSI-H or MMR-deficient mCRPC particularly in patients who have previously received abiraterone or enzalutamide and/or docetaxel.

The prevalence of MMR deficiency in mCRPC is estimated at 2-5%
KEYNOTE-199: Pembrolizumab For Post-Docetaxel Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Johann S. de Bono, Jeffrey Goh, Kristiina Ojamaa, Marine Gross-Goupil, Josep Piulats, Charles G. Drake, Christopher J. Hoimes, Haiyan Wu, Ping Qiu, Christian Poehlein, Emmanuel S. Antonarakis

1Royal Marsden and The Institute of Cancer Research, London, UK; 2Royal Brisbane & Women’s Hospital, Herston, and University of Queensland, St. Lucia, QLD, Australia; 3East Tallinn Central Hospital, Tallinn, Estonia; 4Institut Bergonié, Bordeaux, France; 5Instituto Catalan de Oncologia, Hospital Duran i Reynals, Hospitalet de Llobregat, Barcelona, Spain; 6Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY, USA; 7Case Western Reserve University Hospitals Seidman Cancer Center, Cleveland, OH, USA; 8MSD China, Beijing, China; 9Merck & Co., Inc., Kenilworth, NJ, USA; 10Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA

Presented By Johann De Bono at 2018 ASCO Annual Meeting
**KEYNOTE-199 Study Design**

- **mCRPC**
- ≥1 prior targeted endocrine therapy
- 1-2 prior chemotherapy regimens, including docetaxel
- ECOG PS 0-2
- Measurable disease per RECIST v1.1

- **mCRPC**
- ≥1 prior targeted endocrine therapy
- 1-2 prior chemotherapy regimens, including docetaxel
- ECOG PS 0-2
- Bone mets with no measurable disease per RECIST v1.1
- Any PD-L1 status

- **mCRPC**
- ECOG PS 0-2
- Receiving enzalutamide
- No prior chemotherapy
- Any PD-L1 status

**Cohort 1**: PD-L1 positive

**Cohort 2**: PD-L1 negative

**Cohort 3**: RECIST-measurable disease

**Cohort 5**: Bone-only/predominant, RECIST-non-measurable disease

**Treatment in all cohorts**: pembrolizumab 200 mg Q3W for 35 cycles or until confirmed PD, intolerable toxicity, investigator decision, or patient withdrawal

ClinicalTrials.gov, NCT02787005.

Presented By Johann De Bono at 2018 ASCO Annual Meeting
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (PD-L1+)</th>
<th>Cohort 2 (PD-L1−)</th>
<th>Cohort 3 (Bone Predom)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (range), years</strong></td>
<td>68 (48-85)</td>
<td>68 (53-84)</td>
<td>70 (53-90)</td>
</tr>
<tr>
<td><strong>ECOG PS 0/1/2</strong></td>
<td>31% / 56% / 12%</td>
<td>39% / 54% / 6% a</td>
<td>43% / 47% / 10%</td>
</tr>
<tr>
<td><strong>Gleason score ≥8</strong></td>
<td>63%</td>
<td>64%</td>
<td>57%</td>
</tr>
<tr>
<td><strong>PSA, mean (SD), ng/mL</strong></td>
<td>308.4 (655.9)</td>
<td>346.4 (646.2)</td>
<td>175.5 (375.1)</td>
</tr>
<tr>
<td><strong>Visceral disease</strong></td>
<td>66%</td>
<td>45%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>≥2 prior chemotherapies</strong></td>
<td>32%</td>
<td>27%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>≥2 prior anti-endocrine therapies</strong></td>
<td>26%</td>
<td>22%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Prior targeted endocrine therapy</strong> b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzalutamide only</td>
<td>30%</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>Abiraterone only</td>
<td>44%</td>
<td>37%</td>
<td>45%</td>
</tr>
<tr>
<td>Enzalutamide plus abiraterone</td>
<td>26%</td>
<td>22%</td>
<td>25%</td>
</tr>
</tbody>
</table>

a 1 patient had missing ECOG PS. b One patient in cohort 1 received other targeted endocrine therapy. Data cutoff date: Oct 13, 2017.
Change From Baseline in Sum of Target Lesions, Cohorts 1+2

Change From Baseline | Patients\textsuperscript{a}
--- | ---
−1% to −100% | 36%
−30% to −100% | 10%
0% to +100% | 64%
0% to +19% | 33%

\textsuperscript{a}Percentages are calculated out of the 163 patients who had ≥1 post-baseline scan evaluable per RECIST v1.1 by independent, central review. Data cutoff date: Oct 13, 2017.

Presented By Johann De Bono at 2018 ASCO Annual Meeting
Change From Baseline in PSA, Cohorts 1+2+3

<table>
<thead>
<tr>
<th>Change From Baseline</th>
<th>Patients^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>−1% to −100%</td>
<td>19%</td>
</tr>
<tr>
<td>−50% to −100%</td>
<td>11%</td>
</tr>
<tr>
<td>−90% to −100%</td>
<td>5%</td>
</tr>
<tr>
<td>0% to +100%</td>
<td>81%</td>
</tr>
<tr>
<td>0% to +24%</td>
<td>11%</td>
</tr>
</tbody>
</table>

^aPercentages are calculated out of the 193 patients who had ≥1 post-baseline PSA assessment.

PD-1/PDL-1 inhibitors in combinations
selected clinical trials in mCRPC

- Ph Ib/II: pembrolizumab + olaparib or docetaxel or enzalutamide
- Ph II: durvalumab for MSI high mCRPC
- Ph III: enzalutamide +/- atezolizumab
- R Ph II: radium 223 +/- pembrolizumab
- Ph Ib: radium 223 + atezolizumab
- Ph Ib: sipuleucel-T + atezolizumab
- Pilot: pembrolizumab + TVG-HP plasmid DNA vaccine
- Ph I/II: prostvac + nivolumab or / and ipilimumab
- Pilot: durvalumab + tremelimumab
- Ph II: nivolumab + ipilimumab
Biomarkers for Prostate Cancer Treatment Selection

• DNA and mismatch repair mutations for PARP inhibitors and PD-1 inhibitors
• AR-V7 for androgen pathway inhibitors
Circulating tumor cell AR-V7 and Abiraterone/Enzalutamide Resistance

Presented By Andrew Armstrong at 2018 ASCO Annual Meeting

Epic AR-V7 Nuclear Protein CTC Assay

Example of a **nuclear** AR-V7 CTC: Positive Test

Example of a **non-nuclear** AR-V7 CTC: Negative Test

Example of an AR-V7 negative CTC: Negative Test

Presented By Andrew Armstrong at 2018 ASCO Annual Meeting
The PROPHECY Trial:
Multicenter Validation Study of AR-V7 as a Predictive Biomarker in the Context of the Molecular Landscape of CRPC CTCs

Men with progressive mCRPC, 2 or more high risk features, candidate for abiraterone acetate or enzalutamide, no prior taxane therapy for mCRPC, n=120

Enzalutamide or abiraterone acetate therapy until progression

Taxane therapy until second progression

CTC AR-V7 assays (Epic Nuclear AR-V7, Hopkins AR-V7 Adnatest, Cornell multiplex CTC assay)
Subset CTC and circulating biomarker profiling:
CTC WES, CTC CGH, CTC RNASeq, cell free ctDNA, PAXgene MSK multiplex PCR, ctRNA
Cellsearch CTC enumeration and validation metastatic biopies

Prospective CiRculating PrOstate Cancer Predictors in HighEr Risk mCRPC StudY

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AR-V7 Biomarker Comparison: Epic vs. Hopkins

- Prevalence of a positive baseline CTC AR-V7 test using pre-specified criteria was 24% (n=28, Hopkins) and 10% (n=11, Epic)
  - Hopkins: 41% AR-V7 (+) of CTC evaluable men, increasing to 44% at progression
  - Epic: 12% AR-V7 (+) of CTC evaluable men, increasing to 20% at progression

- Men with CTCs (+) for AR-V7 were more likely to have ≥5 Cellsearch CTCs than AR-V7 (-) men
  - 71% vs. 31% for Hopkins, 63% vs. 39% for Epic
- Concordance for AR-V7 testing was 82%
  - Discordances: non-nuclear V7 expression, AR N-terminal expression without AR-V7 detection, and low CTCs by Epic assay in some cases
Johns Hopkins Modified Adnatest AR-V7
Efficacy Prediction: rPFS and Overall Survival

Johns Hopkins CTC AR-V7: rPFS

HR 2.4 (95% CI 1.5-3.7)
Median rPFS 3.1 vs. 6.9 mo

Johns Hopkins CTC AR-V7: OS

HR 3.9 (95% CI 2.2-6.9)
Median OS 10.8 vs. 27.2 mo

AR-V7 (-)

AR-V7 (+)

JHU AR-V7 CTC assay met the primary endpoint of the study

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Epic Nuclear CTC AR-V7 Efficacy Prediction: rPFS and Overall Survival

**Epic Nuclear CTC AR-V7: rPFS**
- HR 2.5 (95% CI 1.3-4.7)
- Median rPFS 3.1 vs. 6.1 mo

**Epic Nuclear CTC AR-V7: OS**
- HR 4.5 (95% CI 2.1-9.8)
- Median OS 8.4 vs. 20.3 mo

Epic AR-V7 CTC assay also met the primary endpoint of the study

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Confirmed PSA Declines with Abiraterone or Enzalutamide by AR-V7 Status

Johns Hopkins CTC AR-V7

3 of 28 V7(+) men had a confirmed ≥50% PSA decline with PFS of 6-13 months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AR-V7+/ AR-V7-</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50% confirmed PSA decline</td>
<td>11% / 28%</td>
</tr>
<tr>
<td>Odds Ratio (95% CI)</td>
<td>0.31 (0.09 - 1.12)</td>
</tr>
</tbody>
</table>

Epic CTC AR-V7

0 of 11 V7(+) men had a confirmed 50% or greater PSA decline with abi/enza

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AR-V7+/ AR-V7-</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50% confirmed PSA decline</td>
<td>0% / 26%</td>
</tr>
<tr>
<td>Odds Ratio (95% CI)</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

17 JHU AR-V7(+) / Epic AR-V7 (-) patients: PFS 2.8 mo, OS 10.8 mo
SUMMARY

• Recent years significantly expanded therapeutic options for advanced prostate cancer

• Most efforts in the new drug development in prostate cancer continue to revolve around androgen receptor (AR) axis inhibition

• Ongoing studies focus on: combination therapies (ligand synthesis+ AR signaling inhibition), earlier application of potent AR axis inhibitors

• Other agents with therapeutic benefit include immunotherapy (sipuleucel-T), chemotherapy (docetaxel, cabazitaxel) and radioactive isotope (Radium-223)

• Mutations in DNA repair genes that occur in about 25 % of patients with advanced PC appear to be associated with responses to PARP inhibitors - multiple studies with these agents are ongoing

• PD-1 inhibitors that are so impressive in the treatment of melanoma, lung cancer and kidney cancer show very limited activity in the treatment of prostate cancer, but combination studies are ongoing
John Wayne Cancer Institute
Prostate Cancer Clinical Trials
Active Surveillance:
Sipuleucel-T (Provenge) vs Placebo

• Eligibility: meets criteria for active surveillance (low risk, favorable intermediate risk), not very low risk, diagnosis within 12 months of screening
• Design: Phase III, 2:1 randomization
• Treatment: Sipuleucel-T vaccine (Provenge) vs Active Surveillance
• Endpoints: upgrade to higher Gleason grade (biopsy months 18 and 36), disease progression requiring definitive therapy
• N=550
• Status: Activated 1/2019, 1st patient accrued
Neoadjuvant, High-risk Prostate Cancer: daralutamide, pembrolizumab (in development)

- Eligibility: Gleason $\geq 8$, or Gleason 4+3, or Gleason 3+4 with $>50\%$ positive cores or clinical stage $\geq T3$, or PSA $>20$, or clinical stage N1+, no evidence of metastatic disease (M0)
- Design: Pilot/Phase 1b.
- Treatment: Combination of daralutamide, pembrolizumab x 12 weeks
- Endpoints: Feasibility, changes in pre and post treatment immune infiltration (cytotoxic T-cells, T-regs), pathological CR and PR
- N=25-50
Metastatic Castration Resistant PC
CPI-1205 (EZH2 inhibitor) + enzalutamide or abiraterone
Metastatic Castration Resistant PC
CPI-1205 (EZH2 inhibitor) + enzalutamide or abiraterone

- N=72 for Phase 1 b, up to 70 for Phase II
- Patients who are failing either abiraterone or enzalutamide in the setting of mCRPC
- Phase 1b – at least 1 prior line of 2nd gen androgen pathway inhibitor (abiraterone, enzalutamide, apalutamide), prior chemo for mCRPC allowed
- Phase II – only 1 prior 2nd gen androgen pathway inhibitor (abiraterone, enzalutamide, apalutamide), no prior chemo for mCRPC allowed
- Phase II (HPEC – heavily pre-treated cohort) - 2 classes of prior 2nd gen androgen pathway inhibitor (ie. abiraterone and enzalutamide), 1-2 prior chemo for mCRPC, + lymph node(s)
Metastatic Castration Resistant PC
Talazoparib in Patients with DNA Repair Mutations

• Eligibility: metastatic castration resistant prostate cancer, progressing after abiraterone (Zytiga) and/or enzalutamide (Xtandi) and docetaxel. 1-2 prior chemo regimens. Must harbor mutation in DNA repair genes (BRCA2, ATM, FANCA or others) in archived or new tissue. Estimated prevalence of these mutations: 25%

• Design: Phase 2, single arm, open label

• Treatment: talazoparib 1 mg po daily

• Endpoints: ORR, PSA RR, CTC RR, rPFS, OS

• N=100
Sequencing of Therapies for Advanced Prostate Cancer-2019

Hormone-sensitive
Non-metastatic
Asymptomatic
CRPC
Metastatic
Symptomatic

Disease Burden

Surgical or Chemical Castration
Local therapy

Enzalutamide
or Abiraterone

Docetaxel
Abiraterone
Apalectamide

Sipuleucel-T
Bone directed therapy (zoledronic acid or denosumab)

Cabazitaxel
Radium 223

Time
Conclusions

- PROPHECY represents the first multicenter, multiassay, blinded prospective validation of CTC AR-V7 as a negative predictive biomarker of potent AR therapy inhibition.
- Both the Johns Hopkins AR-V7 CTC RNA test and the Epic nuclear AR-V7 CTC protein test were predictive of poor outcomes in men with mCRPC, independent of line of therapy and key prognostic factors including Cellsearch CTC enumeration.
- Men with CTC AR-V7(+) mCRPC have a very low probability of benefit from abiraterone or enzalutamide (0-12% chance).
- However, lack of AR-V7 detection does not guarantee response/benefit.
- The prevalence of CTC AR-V7 in men with mCRPC depends on prostate cancer prognostic factors and the assay used.
- CTC AR-V7 should be interpreted in the context of phenotypic and genomic heterogeneity associated with aggressive disease suggesting that developing therapies for men with AR-V7 + mCRPC will require a broad approach.
Multivariable Analysis:
CTC AR-V7 Independently Predicts Short Overall Survival

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Hazard Ratio (HR)</th>
<th>95% Confidence Limits (HR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR-V7 + (Adnatest)</td>
<td>4.74</td>
<td>2.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cellsearch CTCs, per 7.5 ml</td>
<td>0.98</td>
<td>0.51</td>
<td>1.86</td>
</tr>
<tr>
<td>PSA</td>
<td>1.00</td>
<td>0.99</td>
<td>1.00</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.77</td>
<td>0.64</td>
<td>0.93</td>
</tr>
<tr>
<td>Prior enza/abi tx (yes vs. no)</td>
<td>1.36</td>
<td>0.59</td>
<td>3.09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<th>95% Confidence Limits (HR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR-V7 + (Epic)</td>
<td>2.90</td>
<td>1.21</td>
<td>6.94</td>
</tr>
<tr>
<td>Cellsearch CTCs, per 7.5 mL</td>
<td>1.37</td>
<td>0.73</td>
<td>2.59</td>
</tr>
<tr>
<td>PSA</td>
<td>1.00</td>
<td>0.99</td>
<td>1.00</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.75</td>
<td>0.62</td>
<td>0.91</td>
</tr>
<tr>
<td>Prior enza/ AA (yes vs. no)</td>
<td>1.20</td>
<td>0.52</td>
<td>2.80</td>
</tr>
</tbody>
</table>

Prediction independent of CTC burden, prior therapy, and common validated prognostic factors