Hormone Sensitive Metastatic Prostate Cancer: intensification is a winning strategy, how can we do even better?

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City of Hope Comprehensive Cancer Center
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HORMONE SENSITIVE METASTATIC PROSTATE CANCER

RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

SPEAKERS BUREAU: EXELIXIS, PROMETHEUS
CONSULTING: JANSSEN, ASTRA ZENECA

THE SPEAKER WILL DIRECTLY DISCLOSE THE USE OF PRODUCTS FOR WHICH ARE NOT LABELED (E.G., OFF LABEL USE) OR IF THE PRODUCT IS STILL INVESTIGATIONAL.
Overview

• Intensified up-front therapy
  • Abiraterone: LATITUDE, STAMPEDE
  • Docetaxel: CHAARTED, STAMPEDE
• “Personalized” intensification in mHSPC; integrating genomics
• Treating the primary and/or oligo-mets with local therapy
Early chemotherapy improved survival in metastatic hormone sensitive prostate cancer (HSPC): CHAARTED

<table>
<thead>
<tr>
<th></th>
<th>HR (ADT+D/ADT)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.73</td>
<td>0.59 - 0.89</td>
<td>0.0018</td>
</tr>
<tr>
<td>High volume</td>
<td>0.63</td>
<td>0.50 - 0.79</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Low volume</td>
<td>1.04</td>
<td>0.70 - 1.55</td>
<td>0.86</td>
</tr>
</tbody>
</table>

ESMO update: med f/u 57 mo, no OS benefit for low volume (aka oligomets)
Sweeney CJ et al. NEJM 2015; 373:737-46
Sweeney CJ et al, ESMO 2016; abstr 720pd
GETUG AFU-15 Study: no benefit for up-front docetaxel

<table>
<thead>
<tr>
<th></th>
<th>ADT</th>
<th>ADT + D</th>
<th>p-value</th>
<th>Hazard ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>N = 193</td>
<td>N = 192</td>
<td>0.44</td>
<td>0.9 [0.7-1.2]</td>
</tr>
<tr>
<td>Median OS</td>
<td>46.5 [39.1-60.6]</td>
<td>60.9 [46.1-71.4]</td>
<td>0.44</td>
<td>0.9 [0.7-1.2]</td>
</tr>
<tr>
<td>Biological PFS</td>
<td>12.9 [11.9-17.7]</td>
<td>22.9 [19.5-28.4]</td>
<td>0.0021</td>
<td>0.7 [0.6-0.9]</td>
</tr>
<tr>
<td>HVD * Pts</td>
<td>N = 91</td>
<td>N = 92</td>
<td>0.35</td>
<td>0.8 [0.6-1.2]</td>
</tr>
<tr>
<td>Median OS</td>
<td>35.1 [29.9-44.2]</td>
<td>39 [28-52.6]</td>
<td>0.35</td>
<td>0.8 [0.6-1.2]</td>
</tr>
<tr>
<td>Biological PFS</td>
<td>9.2 [8.3-12.2]</td>
<td>15.2 [12-21.2]</td>
<td>0.0039</td>
<td>0.6 [0.5-0.9]</td>
</tr>
<tr>
<td>LVD Pts</td>
<td>N = 102</td>
<td>N = 100</td>
<td>0.87</td>
<td>1 [0.6-1.5]</td>
</tr>
<tr>
<td>Median OS</td>
<td>NR [61.8-NR]</td>
<td>83.1 [69.5-NR]</td>
<td>0.87</td>
<td>1 [0.6-1.5]</td>
</tr>
<tr>
<td>Biological PFS</td>
<td>22.4 [16.8-37]</td>
<td>40.9 [28.4-62.5]</td>
<td>0.0533</td>
<td>0.7 [0.5-1]</td>
</tr>
</tbody>
</table>

* HVD: visceral (lung or liver) metastases and/or 4 or more bone metastases with at least 1 beyond the pelvis and the vertebral column.

Gravis G et al. 2015
ASCO GU abstr 140
STAMPEDE (Doce): James N et al., Lancet 2016; 387:1163

For Overall Survival:
HR 0.79, 95% CI 0.65-0.96, p=0.019 – all patients
HR 0.82, 95% CI 0.48-1.4, p=0.475 – pts with mets

BUT...
Toxicity must be considered
Early abiraterone improves survival in metastatic HSPC: LATITUDE

Fizazi K et al. NEJM 2017; DOI:10.1056/NEJMoa1704174

2 of 3 high risk features:
- Gleason 8-10
- 2+ bone metastases
- Visceral metastases
Hi risk local or Node+
≥2 of: Stage T3/4
PSA≥40ng/ml
Gleason 8-10

Relapsing p definitive tx
≥1 of: PSA≥4 & PSADT <6 mo
PSA≥20
Mets or Node +
Should every newly diagnosed metastatic prostate cancer patient receive abiraterone or docetaxel?

Is one better than the other?

Should we give both?
No difference between abiraterone and docetaxel for mHSPC.

https://doi.org/10.1093/annonc/mdy072
Patient characteristics may impact benefit of mHSPC treatments


<table>
<thead>
<tr>
<th>TABLE 4. Proportional Hazard Models for Prostate Cancer-Specific Mortality</th>
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</thead>
<tbody>
<tr>
<td>Multivariable Analysis</td>
</tr>
<tr>
<td>Covariate</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>White Non-Hispanic</td>
</tr>
<tr>
<td>White Hispanic</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
</tr>
<tr>
<td>Marital status</td>
</tr>
<tr>
<td>Unmarried</td>
</tr>
<tr>
<td>Married or domestic partner</td>
</tr>
<tr>
<td>County-wide median annual family income</td>
</tr>
<tr>
<td>&lt;$66,610</td>
</tr>
<tr>
<td>$66,610</td>
</tr>
<tr>
<td>Percentage of adults not completing high school</td>
</tr>
<tr>
<td>≥14.1%</td>
</tr>
<tr>
<td>&lt;14.1%</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
</tr>
<tr>
<td>≤73</td>
</tr>
<tr>
<td>&gt;73</td>
</tr>
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</table>
Trials will answer the combination and other agents’ utility for intensification questions

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent(s)</th>
<th>Accrual Goal</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARASENS (Bayer) NCT02799602</td>
<td>Docetaxel ADT +/- ODM-201</td>
<td>1300</td>
<td>Completed Accrual</td>
</tr>
<tr>
<td>SWOG S1216</td>
<td>ADT +/- orteronel (TAK700)</td>
<td>1313</td>
<td>Completed Accrual</td>
</tr>
<tr>
<td>TITAN NCT02489318</td>
<td>ADT +/- apalutamide</td>
<td>1052</td>
<td>Completed Accrual</td>
</tr>
</tbody>
</table>
Are there genomic predictors of ADT response that could be leveraged for personalized treatment plans?
Could a genomic classifier be developed to determine who does well with ADT alone, vs who benefits from adding chemo?

J Urol 2013, 190: 2047-53
DNA repair deficiencies may be associated with responsiveness to AR targeted therapy

PFS by DRD status (N= 75)

Arm A: Abiraterone (N=31)

DRD: 14.5 (11.0-19.5)
WT: 8.0 (5.4-13.0)
P=0.02

Arm B: Abiraterone + Veliparib (N=44)

DRD: 16.6 (13.5-19.5)
WT: 8.2 (3.9-10.3)
P=0.27

DRD: 13.8 (8.2-32.9)
WT: 8.0 (5.3-13.8)
P=0.03

Presented by: M. Hussain, MD, FACP, FASCO
Luminal and Basal Subtyping of Prostate Cancer correlates with Prognosis and response to ADT

PAM50 Clustering and Clinical Outcomes in Prostate Cancer: The PAM50 genes cluster prostate cancer samples into 3 subtypes, luminal A (LumA), luminal B (LumB), and basal, in the pooled prostate cancer cohorts (Mayo Clinic I and II, Cleveland Clinic, Thomas Jefferson University, Johns Hopkins University, and Durham Veterans Affairs) using hierarchical clustering of the genes. Each column represents a patient sample, and each row represents a gene. B, Kaplan-Meier curves showing that the PAM50 clusters risk stratify biochemical recurrence-free survival, distant metastasis–free survival, prostate cancer–specific survival, and overall survival.
Genomically targeted trials are a reality! Starting to target the HSPC space

<table>
<thead>
<tr>
<th>Agent</th>
<th>Genomic Alteration</th>
<th>Treatment setting</th>
<th>N</th>
<th>Status</th>
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<tbody>
<tr>
<td>GSK 2636771</td>
<td>PTEN deficient</td>
<td>mCRPC, prog dz on enzalutamide</td>
<td>64</td>
<td>ongoing</td>
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<tr>
<td>Ipatasertib</td>
<td>PTEN loss</td>
<td>mCRPC 1\textsuperscript{st} line; abiraterone +/- ipat</td>
<td>850</td>
<td>ongoing</td>
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<tr>
<td>Palbociclib</td>
<td>RB+</td>
<td>mHSPC</td>
<td>60</td>
<td>Completed accrual</td>
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<tr>
<td>Rucaparib (TRIUMPH)</td>
<td>Germline DNA repair def</td>
<td>mHSPC</td>
<td>30</td>
<td>ongoing</td>
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</tbody>
</table>
Migration of Metastases

A – L humerus BM
D – Seminal vesicle
C – Prostate
E – L adrenal
F – R adrenal
G – Bladder
H – Pelvic LN
I – L pelvic LN
J – R pelvic LN
K – L pelvic LN
L – L media LN
Prospective RANDOMIZED ADT +/- Local Therapy in M1 Disease

HORRAD

Study Design

Randomization

Arm 1 - N=213
Neoadjuvant treatment with LHRH agonist
Enzalutamide

Arm 2 - N=213
Standard Hormonal Treatment with LHRH agonist
Radiotherapy (55 Gy)

N=436
Primary prostate metastatic cancer

STAMPEDE

Patients eligible for STAMPEDE

NEWLY DIAGNOSED M1 PATIENTS
ALL OTHER PATIENTS

RANDOMISATION

A: ADT
B: Arm A + zolendronic acid
C: Arm A + docetaxel
D: Arm A + ZA + docetaxel
E: Arm A + abiraterone
F: Arm A + RT to prostate

RANDOMISATION

A: ADT
B: Arm A + zolendronic acid
C: Arm A + docetaxel
D: Arm A + ZA + docetaxel
E: Arm A + abiraterone

PEACE-1

Androgen deprivation therapy (ADT)

Arm A + Abiraterone 1000mg Prednisone 5mg BID

Arm A + Local radiotherapy

Arm A + Local radiotherapy + Abiraterone-Pred

Co-primary endpoints: OS and PFS (HR: 0.75)

PEACE-1

M1b PCa Limited skeletal lesions

ADT

ADT plus Radical Prostatectomy

Survival

HORRAD

STAMPEDE

PEACE-1

NCT01957136

BST + DT
(Radiation or surgery)

CRPC

BST

CRPC

BST Only

BST
The HORRAD Study
high volume metastatic disease

Presented by: Boeve at AUA 2018

Slide courtesy of Brian Chapin, MDACC
Randomized, Phase III Trial of Standard Systemic Therapy (SST) or SST Plus Definitive Treatment of the Primary Tumor in Metastatic Prostate Cancer (S1802)

Castration Sensitive ≥M1a PCa

SST

SST + Definitive treatment (Surgery or Radiation)

SST only

Progression (PCWG2)

Overall Survival

0wks 22-28 wks 36wks X mos

PI: Brian F Chapin, MD
SWOG: Dan Lin, David Quinn, Ana Aparicio, Cathy Tangen, Nicholas Vogelzang, Ian Thompson

Supported by: NCTN
Surveillance or Metastasis Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Phase II Trial

**Graph C**

- Surveillance
- MDT

Biochemical Recurrence-Free Survival (%)

HR, 0.53 (95% CI, 0.30 to 0.94); P = .03

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>No. at risk: MTD</th>
<th></th>
<th>No. at risk: Surv.</th>
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<tbody>
<tr>
<td>0</td>
<td>31</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>14</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>10</td>
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<td>24</td>
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<td>48</td>
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<tr>
<td>54</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**Graph B**

- Surveillance
- MDT

Best PSA Response (% change)

Ost P et al. JCO. Dec 2017
AR-targeted therapies and XRT to primary or (oligo)met sites: which agent?

AACR 2018 abstr 858: radiosensitization of cell lines with abi or enza

Maryam Ghashghaei, Thierry Muanza,  
**DOI:** 10.1158/1538-7445.AM2018-858

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ENZA</td>
<td>ABI</td>
<td>ENZA</td>
<td>ABI</td>
<td>ENZA</td>
<td>ABI</td>
</tr>
<tr>
<td>AD</td>
<td>1.35±0.02</td>
<td>1.05±0.01</td>
<td>1.75±0.08</td>
<td>1.00</td>
<td>1.30±0.05</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>ENZA</td>
<td>ABI</td>
<td>ENZA</td>
<td>ABI</td>
<td>ENZA</td>
<td>ABI</td>
</tr>
<tr>
<td>PC3-AR T877A</td>
<td>1.30±0.03</td>
<td>1.00</td>
<td>1.65±0.01</td>
<td>1.00</td>
<td>1.35±0.06</td>
<td>1.05±0.02</td>
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<tr>
<td>AI</td>
<td>PC3</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>PC3-AR V7</td>
<td>1.00</td>
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</tbody>
</table>
Conclusions

Almost all metastatic prostate cancer patients should receive up-front intensification (Abi/Doce)

Future: use genomic classification to select for even more tx or de-intensification?

Novel therapies adding to ADT in mHSPC are targeting molecular sub-populations

Treatment of the primary and/or oligomets is best done as part of a clinical trial