Metastatic Hormone-Sensitive Prostate Cancer: State of the Art Management in 2018

A/Prof. Arun Azad MBBS PhD FRACP
Medical Oncologist – Monash Health, Melbourne, Australia
Translational Researcher - Monash University, Melbourne, Australia
Chair - Translational Research Committee, ANZUP Clinical Trials Group
# Disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support/P.I.</td>
<td>Astellas</td>
</tr>
<tr>
<td>Employee</td>
<td>N/A</td>
</tr>
<tr>
<td>Consultant</td>
<td>Astellas, Janssen, Novartis</td>
</tr>
<tr>
<td>Major Stockholder</td>
<td>N/A</td>
</tr>
<tr>
<td>Speakers Bureau</td>
<td>Astellas, Janssen, Novartis, Amgen, Bayer</td>
</tr>
<tr>
<td>Honoraria</td>
<td>Astellas, Janssen, Novartis, Tolmar, Amgen, Pfizer, Bayer</td>
</tr>
<tr>
<td>Scientific Advisory Board</td>
<td>Astellas, Novartis, Sanofi, Astra-Zeneca, Tolmar, Pfizer, Janssen</td>
</tr>
</tbody>
</table>
Overview

Metastatic hormone-sensitive prostate cancer (mHSPC)

• Docetaxel studies – CHAARTED, STAMPEDE
• Abiraterone studies – LATITUDE, STAMPEDE
• Influence on clinical practice
Disease continuum in prostate cancer

Clinically Localized Disease → Rising PSA Noncastrate → Clinical Metastases: Noncastrate → nmCRPC → mCRPC: 1st Line → mCRPC: 2nd Line → mCRPC: Line X

Noncastrate
Castration-resistant

mCRPC: 3rd Line, 4th Line, etc.
Background/Rationale

mHSPC

- Androgen Deprivation Therapy (ADT) has been mainstay of treatment for advanced prostate cancer for > 60 years

- We know that essentially all men will have rising PSA and/or develop new metastases despite castrate levels of testosterone i.e. castration-resistant prostate cancer (CRPC)

- Does more potent upfront treatment of mHSPC improve outcomes?
  - Non-AR mechanisms (docetaxel)
  - AR driven (abiraterone)
DOCETAXEL IN mHSPC
E3805 – CHAARTED Treatment

**STRATIFICATION**
- Extent of Mets: High vs Low
- Age: ≥70 vs < 70yo
- ECOG PS: 0-1 vs 2
- CAB > 30 days: Yes vs No
- SRE Prevention: Yes vs No
- Prior Adjuvant ADT: ≤12 vs > 12 months

**RANDOMIZE**

**ARM A:**
- ADT + Docetaxel 75mg/m2 every 21 days for maximum 6 cycles
- Evaluate every 3 weeks while receiving docetaxel and at week 24 then every 12 weeks

**ARM B:**
- ADT (androgen deprivation therapy alone)
- Evaluate every 12 weeks

**Follow for time to progression and overall survival**
- Chemotherapy at investigator’s discretion at progression

- ADT allowed up to 120 days prior to randomization.
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone

Presented By Christopher Sweeney at 2014 ASCO Annual Meeting
Primary endpoint: Overall survival

HR=0.61 (0.47-0.80) p=0.0003
Median OS:
ADT + D: 57.6 months
ADT alone: 44.0 months

Presented By Christopher Sweeney at 2014 ASCO Annual Meeting
In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival from 32.2 months to 49.2 months. We projected 33 months in ADT alone arm with collaboration of SWOG9346 team.
Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: First survival results from STAMPEDE

Nicholas James
University of Warwick and Queen Elizabeth Hospital Birmingham

on behalf of

Matthew Sydes, Malcolm Mason, Noel Clarke, David Dearnaley, Melissa Spears, Robin Millman, Chris Parker, Alastair Ritchie, J. Martin Russell, John Staffurth, Robert Jones, Shaun Tolan, John Wagstaff, Andrew Protheroe, Rajaguru Srinivasan, Alison Birtle, Joe O'Sullivan, Richard Cathomas, Mahesh Parmar and the STAMPEDE Investigators
STAMPEDE: All docetaxel and zoledronic acid comparisons

A = ~1200 pts --> ~404 primary outcome measure events
B = ~600 pts, C = ~600 pts, E = ~600 pts

Presented By Nicholas James at 2015 ASCO Annual Meeting
### Patient characteristics

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>WHO PS 2</td>
</tr>
<tr>
<td>21%</td>
<td>WHO PS 1</td>
</tr>
<tr>
<td>65yr</td>
<td>Median age (min 40, max 84)</td>
</tr>
<tr>
<td>61%</td>
<td>Metastatic (85% Bony mets)</td>
</tr>
<tr>
<td>15%</td>
<td>N+M0</td>
</tr>
<tr>
<td>24%</td>
<td>N0M0</td>
</tr>
<tr>
<td>98%</td>
<td>LHRH analogues</td>
</tr>
<tr>
<td>29%</td>
<td>Planned for RT (72% of N0M0 pts)</td>
</tr>
<tr>
<td>6%</td>
<td>Previous local therapy</td>
</tr>
</tbody>
</table>

Balanced by arm

[s] Stratification factors + hospital + NSAID/ aspirin

Presented By Nicholas James at 2015 ASCO Annual Meeting
Docetaxel: Survival

![Graph showing survival rates for SOC and SOC+Doc](image)

- **SOC**: 405 deaths
- **SOC+Doc**: 165 deaths
- **HR (95% CI)**: 0.76 (0.63, 0.91)
- **P-value**: 0.003
- **Non-PH p-value**: 0.51

**Median OS (95% CI)**
- SOC: 67m (60, 91m)
- SOC+Doc: 77m (70, NR)

**Restricted mean OS time**
- SOC: 58.8m
- SOC+Doc: 63.4m
- Diff (95% CI): -4.6m (-1.8, 7.3m)

Presented By Nicholas James at 2015 ASCO Annual Meeting
Docetaxel: Survival – M1 Patients

- SOC: 343 deaths
- SOC+Doc: 134 deaths
- HR (95% CI): 0.73 (0.59, 0.89)
- P-value: 0.002
- Non-PH p-value: 0.23

Median OS (95% CI):
- SOC: 43m (24, 88m)
- SOC+Doc: 65m (27, NR)

Restricted mean OS time:
- SOC: 49.3m
- SOC+Doc: 56.1m
- Diff (95% CI): 6.8m (2.8, 11.0m)

Presented By Nicholas James at 2015 ASCO Annual Meeting
ABIRATERONE IN mHSPC
≥2 of: GS ≥ 8; ≥ 3 bone mets; visceral mets

**Overall study design of LATITUDE**

**Patients**
- Newly diagnosed adult men with high-risk mHNPC
- Presence of visceral disease (yes/no)
- ECOG PS (0, 1 vs 2)

**Randomized 1:1**

**ADT**
- + Abiraterone acetate 1000 mg QD
- + Prednisone 5 mg QD (n = 597)

**ADT + placebos** (n = 602)

**Efficacy end points**
- Co-primary:
  - OS
  - rPFS
- Secondary: time to
  - pain progression
  - PSA progression
  - next symptomatic skeletal event
  - chemotherapy
  - subsequent PC therapy

- Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada
- Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results

Presented By Karim Fizazi at 2017 ASCO Annual Meeting
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

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

No. of events: 406 (48% of 852)
ADT + AA + P: 169
ADT + placebos: 237

Overall Survival [%]

0 20 40 60 80 100

Months

0 6 12 18 24 30 36 42

No. at risk

ADT + AA + P
597 565 529 479 388 233 93 9

ADT + placebos
602 564 504 432 332 172 57 2

Median follow-up: 30.4 months

Presented By Karim Fizazi at 2017 ASCO Annual Meeting
Safety

• Hypertension
  – Only rarely required treatment discontinuation

• Hypokalemia
  – Only 2 patients discontinued treatment due to hypokalemia
  – No hypokalemia-related deaths

• Cardiovascular events
  – 2 patients in each group died of cerebrovascular events;
  – 10 (ADT + AA + P) versus 6 (ADT + placebos) died of cardiac disorders
Adding abiraterone for men with high-risk prostate cancer starting long-term androgen deprivation therapy: Survival results from STAMPEDE

Nicholas James
University of Birmingham and Queen Elizabeth Hospital Birmingham

on behalf of

Johann De Bono, Melissa R Spears, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Alastair WS Ritchie, J Martin Russell, Clare Gilson, Rob Jones, Silke Gillessen, David Matheson, San Aung, Alison Birtle, Simon Chowdhury, Joanna Gale, Zafar Malik, Joe O’Sullivan, Anjali Zarkar, Mahesh KB Parmar, Matthew R Sydes and the STAMPEDE Investigators
**Patient characteristics**

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>WHO PS 2</td>
<td>[s]</td>
</tr>
<tr>
<td>21%</td>
<td>WHO PS 1</td>
<td>[s]</td>
</tr>
<tr>
<td>67yr</td>
<td>Median age</td>
<td>[s]</td>
</tr>
<tr>
<td></td>
<td>(min 39, max 85)</td>
<td></td>
</tr>
<tr>
<td>52%</td>
<td>Metastatic</td>
<td>[s]</td>
</tr>
<tr>
<td></td>
<td>(88% Bony mets)</td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td>N+M0</td>
<td></td>
</tr>
<tr>
<td>28%</td>
<td>N0M0</td>
<td></td>
</tr>
<tr>
<td>99%</td>
<td>LHRH analogues</td>
<td>[s]</td>
</tr>
<tr>
<td>41%</td>
<td>Planned for RT</td>
<td>[s]</td>
</tr>
<tr>
<td></td>
<td>(96% of N0M0 pts; 62% of N+M0 pts)</td>
<td></td>
</tr>
<tr>
<td>5%</td>
<td>Previous local therapy</td>
<td></td>
</tr>
</tbody>
</table>

[s] = Stratification factors

Also stratified on
:: hospital
:: NSAID/ aspirin

Balanced by arm
Overall Survival – STAMPEDE “abiraterone comparison”

Events
262 Control | 184 Abiraterone

This represents a 37% improvement in survival

<table>
<thead>
<tr>
<th></th>
<th>SOC</th>
<th>SOC+AAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (events)</td>
<td>937</td>
<td>960</td>
</tr>
<tr>
<td>Time from randomisation (Months)</td>
<td>37 (37)</td>
<td>26 (26)</td>
</tr>
<tr>
<td>Rate (95% CI)</td>
<td>999 (98)</td>
<td>917 (63)</td>
</tr>
<tr>
<td>HR</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.52 to 0.76</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.00000115</td>
<td></td>
</tr>
</tbody>
</table>
### Safety population

<table>
<thead>
<tr>
<th></th>
<th>SOC-only</th>
<th>SOC+AAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients included in adverse event analysis</td>
<td>960</td>
<td>948</td>
</tr>
<tr>
<td>Grade 1-5 AE</td>
<td>950 (99%)</td>
<td>943 (99%)</td>
</tr>
<tr>
<td>Grade 3-5 AE</td>
<td>315 (33%)</td>
<td>443 (47%)</td>
</tr>
<tr>
<td>Grade 5 AE</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

### Grade 3-5 AEs by category (*incl. expected AEs*)

<table>
<thead>
<tr>
<th>Category</th>
<th>SOC-only</th>
<th>SOC+AAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine disorder (<em>incl. hot flashes, impotence</em>)</td>
<td>133 (14%)</td>
<td>129 (14%)</td>
</tr>
<tr>
<td><strong>Cardiovascular disorder (<em>incl. hypertension, MI, cardiac dysrhythmia</em>)</strong></td>
<td>41 (4%)</td>
<td>92 (10%)</td>
</tr>
<tr>
<td>Musculoskeletal disorder:</td>
<td>46 (5%)</td>
<td>68 (7%)</td>
</tr>
<tr>
<td>Gastrointestinal disorder:</td>
<td>40 (4%)</td>
<td>49 (5%)</td>
</tr>
<tr>
<td><strong>Hepatic disorder (<em>incl. increased AST, increased ALT</em>)</strong></td>
<td>12 (1%)</td>
<td>70 (7%)</td>
</tr>
<tr>
<td>General disorder (<em>incl. fatigue, oedema</em>)</td>
<td>29 (3%)</td>
<td>45 (5%)</td>
</tr>
<tr>
<td>Respiratory disorder (<em>incl. breathlessness</em>)</td>
<td>23 (2%)</td>
<td>44 (5%)</td>
</tr>
<tr>
<td>Lab abnormalities (<em>incl. hypokalaemia</em>)</td>
<td>21 (2%)</td>
<td>34 (4%)</td>
</tr>
</tbody>
</table>
Summary

Docetaxel and Abiraterone in mHSPC

• Both highly active (and safe) agents
  • Significant increase in OS + secondary endpoints (data not shown)

• Transformed standard-of care management of mHSPC

• Treatment selection
  • Should all patients with mHSPC receive Docetaxel or Abiraterone? Or just high-volume/high-risk?
  • Is ADT alone sufficient for some patients?
  • How to choose between Docetaxel and Abiraterone?
High-Volume/High-Risk….or all?

mHSPC

- Docetaxel
  - Only benefit in high-volume patients on long-term follow up of CHAARTED….but overall positive trial
  - OS benefit seen in all-comers in STAMPEDE….no separation based on burden of metastatic disease

- Abiraterone
  - LATITUDE restricted to high-risk patients
  - OS benefit seen in all-comers in STAMPEDE….no separation based on burden of metastatic disease
High-Volume/High-Risk….or all?

My practice

• Depends on the patient…..

• High-volume patient fit enough for Docetaxel: YES
• Low-volume patient fit enough for Docetaxel: MAYBE/YES
• High-volume patient borderline fit for Docetaxel: MAYBE/YES
• Low-volume patient borderline fit for Docetaxel: NO
Is ADT alone sufficient for some?  
Answer is…..Possibly

### Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>ADT + Doc (N=397)</th>
<th>ADT alone (N=333)</th>
<th>P-value</th>
<th>Hazard Ratio (95%CI*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA &lt;0.2 ng/mL at 6 months</td>
<td>27.5%</td>
<td>14.0%</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>PSA &lt;0.2 ng/mL at 12 months</td>
<td>22.7%</td>
<td>11.7%</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Median time to CRPC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- biochemical, symptoms, or</td>
<td>20.7</td>
<td>14.7</td>
<td>&lt;0.0001</td>
<td>0.56 (0.44, 0.70)</td>
</tr>
<tr>
<td>radiographic (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>progression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- symptoms or radiographic</td>
<td>32.7</td>
<td>19.8</td>
<td>&lt;0.0001</td>
<td>0.49 (0.37, 0.65)</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CI: confidence intervals
Is ADT alone sufficient for some?

mHSPC

- Reasonable to start ADT and watch PSA closely in first 3 months in patients who are not optimal candidates based on age, co-morbidities and/or in patients with low-volume disease.
  - CHAARTED permitted commencement of Docetaxel up to 4 months after commencing ADT

- No biomarker or predictive factor for identifying the subset of patients who attain very low PSA nadir on ADT alone
Docetaxel vs. Abiraterone

mHSPC

- Toxicity
  - More short-term with Docetaxel….but more long-term with Abiraterone? (Due to Prednisolone)

- Patient choice
  - Tablets generally preferred over chemo

- Access
  - US vs. Australia (reimbursement)

- Efficacy
  - Very similar HR for OS (approx. 0.6)
Comparable efficacy of Abiraterone & Docetaxel in mHSPC

Overlay of LATITUDE KM Plot on CHAARTED (high volume) KM Plot
Comparable efficacy of Abiraterone & Docetaxel in mHSPC
THANK YOU