mHSPC Treatment Options: State of the Art in 2019

A/ Prof Ravindran KANESVARAN
Senior Consultant
National Cancer Centre Singapore
DISCLOSURES

• Speaker Bureau: Pfizer, J&J, Sanofi, Novartis, MSD, Eisai, Ipsen

• Advisory Board/ Consultant: GSK, Novartis, Bayer, J&J, Mundipharma, Astellas, MSD, BMS, Amgen. Ipsen

• Research support: Sanofi, J&J, Astellas, Eisai
Case Study

- 56 yr old Chinese man with hypertension
- Newly diagnosed mHSPC after presenting with LUTS and low back pain for 2 months prior
- DRE: hard craggy prostate
- Gleason 4+4, PSA- 63
- Imaging: > 5 bone mets, no visceral mets
- Was started on ADT by the urologist and referred for further management
What do you offer him?

a) Add docetaxel x 6 cycles
b) Add Abiraterone + pred
c) Add Enzalutamide
d) Add Apalutamide
d) Keep on ADT alone
Outline

- What is the current evidence?
- Guideline recommendations
- Loco-regional data
- Summary
What does the data show?

- **Efficacy**: Docetaxel in HSPC
  - Abiraterone in HSPC
  - Enzalutamide in HSPC
  - Apalutamide in HSPC

- **Safety**

- **Head to head and non head to head comparisons**
Study Design

Phase 3, multicenter, open label study

**Patient Characteristics**

- Diagnosis of prostate cancer with radiologic evidence of metastatic disease
- ECOG PS 0-2
- Prior adjuvant ADT was allowed if the duration of therapy was ≤24 months and progression had occurred >12 months after completion of therapy.
- Patients who were receiving ADT for metastatic disease were eligible if there was no evidence of progression and ADT had commenced ≤120 days before randomization

**Stratification**

- Extent of metastasis: high volume vs low volume*
- Age: ≥70 vs <70 years
- ECOG: 0-1 vs 2
- CAB > 30 days: yes vs no
- SRE prevention: yes vs no
- Prior adjuvant ADT: ≤12 vs >12 months

ARMS

**ARM A**

ADT + Docetaxel 75 mg/m² 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 up for time to progression and overall survival

Chemotherapy at investigator’s discretion at progression

**Randomized 1:1**

(N = 790)

*At study start only pts with high volume disease were to be enrolled. Study was amended to also include patients with low-volume disease.

Sweeney C J et al. Clin Oncol 32:5s, 2014 (suppl; abstr LBA2)
Estimates of OS: Long term data CHAARTED- ESMO 2016

CHAARTED Updated

Kyriakopoulus et al JCO 2018
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
Overall Survival for Metastatic Patients

Median OS:
- SOC + Doc: 60 months
- SOC: 45 months

HR (95% CI): 0.76 (0.62-0.92)
P-value: 0.005

James ND et al. The Lancet 2016 387, 1163-1177- Suppl Appendix
### Overall survival results

<table>
<thead>
<tr>
<th></th>
<th>GETUG-AFU 15</th>
<th>CHAARTED</th>
<th>STAMPEDE**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
<td>385</td>
<td>790</td>
<td>2962</td>
</tr>
<tr>
<td>De novo M1</td>
<td>71%</td>
<td>75%</td>
<td>61%</td>
</tr>
<tr>
<td><strong>Survival, all patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median survival, months</td>
<td>62.1</td>
<td>57.6</td>
<td>60</td>
</tr>
<tr>
<td>Survival benefit</td>
<td>13.5 months</td>
<td>13.6 months</td>
<td>15 months***</td>
</tr>
<tr>
<td></td>
<td>(48.6 to 62.1)</td>
<td>(44 to 57.6)</td>
<td>(45 to 60)</td>
</tr>
<tr>
<td>Survival</td>
<td>HR=0.88 P=0.3</td>
<td>HR=0.61 P&lt;0.001</td>
<td>HR 0.76 P=0.005</td>
</tr>
<tr>
<td><strong>Survival high-volume metastases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival benefit</td>
<td>4.7 months</td>
<td>17 months</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>(35.1 to 39.8)</td>
<td>(32.2 to 49.2)</td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>HR=0.78 P=0.14</td>
<td>HR=0.60 P&lt;0.001</td>
<td>NE</td>
</tr>
</tbody>
</table>

*Not head-to-head comparison studies

**Includes patients with M0 disease

***M1 61% patients only, no further subgroups

NE, not evaluated

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James et al. Lancet 2016; 387(10024):1163-77
Meta-analysis OS

- Results based on 2993 men/2198 events

OS – STAMPEDE “abiraterone plus prednisone comparison”

This represents a 37% improvement in survival

James N, et al. ASCO 2017. LBA5003 and Oral Abstract Session
LATITUDE

Patients
- Newly diagnosed adult men with high-risk mHNPC

Meets at least 2 of 3 high-risk criteria
- Gleason score of ≥ 8
- Presence of ≥ 3 lesions on bone scan
- Presence of measurable visceral lesion

Stratification factors
- Presence of visceral disease (yes/no)
- ECOG PS (0, 1 vs 2)

Screening Phase
28 days

Randomized (1:1)
n=1199

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

Placebo 1000 mg QD + Placebo 5 mg QD + ADT (n=602)

Efficacy end points
Co-primary:
- OS
- rPFS

Secondary: time to
- pain progression
- PSA progression
- next symptomatic skeletal event
- chemotherapy
- subsequent PC therapy

Treatment Phase
28 day cycles until end of treatment

Follow-up Phase
Every 4 months up to 60 months or until disease progression, withdrawal of consent, unacceptable toxicity or death
Overall Survival for LATITUDE

- At a median follow-up of 30.4 months (48% of total deaths), the addition of abiraterone acetate and prednisone to ADT significantly improved OS, with a **38% reduction in the risk of death**
- The 3-year OS rate was 66% in the ADT-abiraterone-prednisone group compared with 49% in the ADT-placebos group

Fizazi et al, NEJM 2017
Head to head comparison: STAMPEDE

STAMPEDE: Direct Comparison of ADT+ docetaxel and ADT + abiraterone

Sides et al. Annals Oncology Feb 26, 2018 (online)

Similar OS and better FFS implies better salvage Rx
TITAN OS: Apalutamide Significantly Reduced the Risk of Death by 33%

- **Patients Who Were Alive (%)**
  - No. at risk:
    - **Apalutamide** (n = 525):
      - 525
      - 513
      - 490
      - 410
      - 165
      - 14
      - 0
    - **Placebo** (n = 527):
      - 527
      - 509
      - 473
      - 387
      - 142
      - 16
      - 0

- **Median, mo (95% CI)**
  - **Apalutamide** (n = 525): NE (NE-NE)
  - **Placebo** (n = 527): NE (NE-NE)

- **Events**:
  - **Apalutamide**: 83
  - **Placebo**: 117

- **HR (95% CI)**
  - **Apalutamide**: 0.67 (0.51-0.89)
  - **Placebo**: NE (NE-NE)

- **P value**: 0.0053

- **82%** for Apalutamide + ADT
- **74%** for Placebo + ADT
ARCHES study design

Key eligibility criteria
- mHSPC (confirmed by bone scan, CT, or MRI), histologically confirmed adenocarcinoma
- ECOG Performance Status 0 to 1
- Current ADT duration ≤3 months unless prior docetaxel, then ≤6 months

Stratification factors
- Volume of disease (low vs. high*)
- Prior docetaxel therapy for mHSPC (none, 1–5, or 6 cycles)

Enzalutamide 160 mg/day + ADT

Placebo + ADT

N = 1150

R 1 : 1

March 21, 2016

First patient enrolled

October 14, 2018

rPFS final analysis

OS final analysis

Key discontinuation criteria
Radiographic progression, unacceptable toxicity, or initiation of an investigational agent or new therapy for prostate cancer

Primary endpoint
- rPFS: time from randomization to first objective evidence of radiographic progression assessed centrally, or death from any cause within 24 weeks of treatment discontinuation, whichever occurs first
  - Radiographic disease progression was defined by RECIST 1.1 criteria for soft tissue disease or by appearance of ≥2 new lesions on bone scan compared to baseline (at week 13) or vs. best response on treatment (week 25–26).
  - New bone scan lesions observed at week 13 required confirmation of ≥2 additional new bone lesions on subsequent scans

*Defined as metastases involving the viscera or, in the absence of visceral lesions, ≥4 bone lesions, ≥1 of which must be in a bony structure beyond the vertebral column and pelvic bone

Presented by: Andrew J. Armstrong, MD
Primary endpoint: rPFS

- At data cut-off, there were 262 events of radiographic progression (enzalutamide + ADT, 77; placebo + ADT, 185) and 25 deaths without radiographic progression (enzalutamide + ADT, 12; placebo + ADT, 13)
- Median follow-up time is 14.4 months; median duration of therapy was 12.8 (range 0.2–26.6) months for enzalutamide + ADT and 11.6 (range 0.2–24.6) months for placebo + ADT
- As of October 14, 2018 (cut-off date), 769 patients were still on treatment, 437 (76%) for enzalutamide + ADT and 332 (58%) for placebo + ADT
Subgroup analysis of rPFS

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N (E)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>574 (89) / 576 (198)</td>
<td>0.39 (0.30, 0.50)</td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td>149 (21) / 152 (57)</td>
<td>0.30 (0.18, 0.49)</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>426 (68) / 424 (141)</td>
<td>0.43 (0.32, 0.58)</td>
</tr>
<tr>
<td>Geographic region – Europe</td>
<td>341 (55) / 344 (121)</td>
<td>0.43 (0.31, 0.59)</td>
</tr>
<tr>
<td>Geographic region – North America</td>
<td>86 (12) / 77 (28)</td>
<td>0.27 (0.14, 0.54)</td>
</tr>
<tr>
<td>Geographic region – rest of the world</td>
<td>147 (22) / 155 (49)</td>
<td>0.41 (0.25, 0.68)</td>
</tr>
<tr>
<td>ECOG status 0 at baseline</td>
<td>448 (65) / 443 (143)</td>
<td>0.38 (0.28, 0.51)</td>
</tr>
<tr>
<td>ECOG status 1 at baseline</td>
<td>125 (24) / 133 (55)</td>
<td>0.43 (0.27, 0.70)</td>
</tr>
<tr>
<td>Gleason score at initial diagnosis &lt;8</td>
<td>171 (21) / 187 (47)</td>
<td>0.42 (0.25, 0.70)</td>
</tr>
<tr>
<td>Gleason score at initial diagnosis ≥8</td>
<td>386 (63) / 373 (148)</td>
<td>0.36 (0.27, 0.48)</td>
</tr>
<tr>
<td>Disease localization at baseline – bone only</td>
<td>268 (33) / 245 (81)</td>
<td>0.31 (0.21, 0.47)</td>
</tr>
<tr>
<td>Disease localization at baseline – soft tissue only</td>
<td>51 (5) / 45 (12)</td>
<td>0.42 (0.15, 1.20)</td>
</tr>
<tr>
<td>Disease localization at baseline – bone and soft tissue</td>
<td>217 (50) / 241 (102)</td>
<td>0.44 (0.31, 0.61)</td>
</tr>
<tr>
<td>Baseline PSA value at or below overall median</td>
<td>293 (40) / 305 (95)</td>
<td>0.37 (0.26, 0.54)</td>
</tr>
<tr>
<td>Baseline PSA value above overall median</td>
<td>279 (49) / 269 (102)</td>
<td>0.41 (0.29, 0.58)</td>
</tr>
<tr>
<td>Low volume of disease</td>
<td>220 (13) / 203 (46)</td>
<td>0.24 (0.13, 0.45)</td>
</tr>
<tr>
<td>High volume of disease</td>
<td>354 (76) / 373 (112)</td>
<td>0.44 (0.33, 0.67)</td>
</tr>
<tr>
<td>No prior docetaxel therapy</td>
<td>471 (68) / 474 (164)</td>
<td>0.36 (0.27, 0.48)</td>
</tr>
<tr>
<td>Prior docetaxel therapy</td>
<td>103 (21) / 102 (34)</td>
<td>0.53 (0.31, 0.92)</td>
</tr>
<tr>
<td>Previous use of ADT or orchiectomy</td>
<td>535 (86) / 515 (177)</td>
<td>0.41 (0.31, 0.52)</td>
</tr>
<tr>
<td>No previous use of ADT or orchiectomy</td>
<td>39 (3) / 61 (21)</td>
<td>0.20 (0.06, 0.66)</td>
</tr>
</tbody>
</table>
Overall survival: interim analysis (84 deaths)

- At the time of interim analysis, OS data are not mature, with 25% of 342 events required for final analysis (enzalutamide plus ADT, 39; placebo plus ADT, 45) and 19% reduction in risk of death that is not statistically significant.
- Final OS analysis will be conducted with ~342 deaths at 4% significance level.

**Graph Details:**
- **ENZA + ADT** (n = 574)
  - No. at risk: 574
  - OS (%)
    - 0: 18
    - 3: 24
    - 6: 30
    - 9: 33
    - 12: 33
    - 15: 33
    - 21: 30
    - 27: 27
    - 33: 19
- **PBO + ADT** (n = 576)
  - No. at risk: 576
  - OS (%)
    - 0: 10
    - 3: 8
    - 6: 8
    - 9: 7
    - 12: 7
    - 15: 7
    - 21: 7
    - 27: 7
    - 33: 0

**Median, month (95% CI):**
- **ENZA + ADT**: NR (NR, NR)
- **PBO + ADT**: NR (NR, NR)

**HR (95% CI):**
- **ENZA + ADT**: 0.81 (0.53, 1.25)
- **PBO + ADT**: 0.3361

**p value:**
- ENZA + ADT: 0.3361
- PBO + ADT: 0.3361

**No. at risk:**
- ENZA + ADT: 574
- PBO + ADT: 576
ENZAMET Treatment

**STRATIFICATION**
- Volume of metastases*
  - High vs Low
- Planned Early Docetaxel
  - Yes vs No
- ECOG PS
  - 0-1 vs 2
- Anti-resorptive therapy
  - Yes vs No
- Comorbidities
  - ACE-27**: 0-1 vs 2-3
- Study Site

**RANDOMIZE**

**ARM A:**
Testosterone Suppression + standard NSAA
Evaluate every 12 weeks

**ARM B:**
Testosterone Suppression + Enzalutamide (160 mg/d)
Evaluate every 12 weeks

**CRPC therapy at investigator’s discretion at progression**
Follow for time to progression and overall survival

- Prior to randomization testosterone suppression up to 12 weeks and 2 cycles of docetaxel was allowed.
- Intermittent ADT and cyproterone were not allowed
- NSAA: bicalutamide; nilutamide; flutamide
- *High volume: visceral metastases and/or 4 or more bone metastases (at least 1 beyond pelvis and vertebral column)
- **Adult Co-morbidity Evaluation-27
Primary endpoint: Overall survival

Proportion alive at 36 months (95% CI)

<table>
<thead>
<tr>
<th>NSAA</th>
<th>Enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.72 (0.68 to 0.76)</td>
<td>0.80 (0.75 to 0.83)</td>
</tr>
</tbody>
</table>

Hazard ratio = 0.67 (95% CI: 0.52 to 0.86)
Log-rank p = 0.002

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>NSAA</th>
<th>Enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>562</td>
<td>563</td>
</tr>
<tr>
<td>6</td>
<td>551</td>
<td>558</td>
</tr>
<tr>
<td>12</td>
<td>531</td>
<td>541</td>
</tr>
<tr>
<td>18</td>
<td>501</td>
<td>527</td>
</tr>
<tr>
<td>24</td>
<td>452</td>
<td>480</td>
</tr>
<tr>
<td>30</td>
<td>311</td>
<td>340</td>
</tr>
<tr>
<td>36</td>
<td>174</td>
<td>189</td>
</tr>
<tr>
<td>42</td>
<td>86</td>
<td>106</td>
</tr>
<tr>
<td>48</td>
<td>32</td>
<td>45</td>
</tr>
</tbody>
</table>
Concurrent Docetaxel: Prespecified Subgroup of Interest (Biology and Treatment Implications)

Clinical Progression-Free Survival

Testosterone Suppression + Docetaxel
N=503 (71% High Volume)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number at risk</th>
<th>Proportion Event-Free</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzalutamide</td>
<td>254</td>
<td>0.28</td>
<td>0.48 (0.37 to 0.62)</td>
</tr>
<tr>
<td>NSAA</td>
<td>249</td>
<td>0.38</td>
<td></td>
</tr>
</tbody>
</table>

Testosterone Suppression + No Docetaxel
N=622 (37% High Volume)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number at risk</th>
<th>Proportion Event-Free</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzalutamide</td>
<td>254</td>
<td>0.34</td>
<td>0.34 (0.26 to 0.44)</td>
</tr>
<tr>
<td>NSAA</td>
<td>249</td>
<td>0.44</td>
<td></td>
</tr>
</tbody>
</table>

Overall Survival

Testosterone Suppression + Docetaxel
N=503 (71% High Volume)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number at risk</th>
<th>Proportion Alive</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzalutamide</td>
<td>254</td>
<td>0.35</td>
<td>0.90 (0.62 to 1.31)</td>
</tr>
<tr>
<td>NSAA</td>
<td>249</td>
<td>0.45</td>
<td></td>
</tr>
</tbody>
</table>

Testosterone Suppression + No Docetaxel
N=622 (37% High Volume)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number at risk</th>
<th>Proportion Alive</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzalutamide</td>
<td>254</td>
<td>0.41</td>
<td>0.53 (0.37 to 0.75)</td>
</tr>
<tr>
<td>NSAA</td>
<td>249</td>
<td>0.52</td>
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</tbody>
</table>

Presented at: 2019 Genitourinary Cancers Symposium | #GU19

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## Primary endpoints (Not head-to-head trials)

<table>
<thead>
<tr>
<th>Study</th>
<th>Docetaxel</th>
<th>AAP+ADT</th>
<th>ENZA+ADT</th>
<th>APA+AFDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>GETUG-1S&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>CHAARTED&lt;sup&gt;3&lt;/sup&gt;</td>
<td>STAMPEDE (Arm C) M1 pts&lt;sup&gt;4&lt;/sup&gt;</td>
<td>LATITUDE&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>STAMPEDE (arm G) M1 pts&lt;sup&gt;7,12&lt;/sup&gt;</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>83.9 months</td>
<td>53.7 months</td>
<td>43 months</td>
<td>51.8 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OS</th>
<th>HR</th>
<th>(95% CI)</th>
<th>P-value</th>
<th>Benefit, mo</th>
<th>Active arm vs control arm, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS – HV</td>
<td>0.78</td>
<td>(0.56-1.09)</td>
<td>0.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>OS – LV</td>
<td>1.02</td>
<td>(0.67-1.55)</td>
<td>0.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>rPFS</td>
<td>HR</td>
<td>(95% CI)</td>
<td>P-value</td>
<td>Benefit, mo</td>
<td>Active arm vs control arm, mo</td>
</tr>
<tr>
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<tr>
<td>0.47</td>
<td>(0.39-0.55)</td>
<td>&lt; 0.001</td>
<td>18.2</td>
<td>(33.0 vs 14.8)</td>
<td>-</td>
</tr>
</tbody>
</table>

### Primary endpoints (Not head-to-head trials)

- OS data reported as immature and not statistically significant
- No head-to-head studies

## Safety (Not head-to-head trials)

<table>
<thead>
<tr>
<th></th>
<th>LATITUDE&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>STAMPEDE&lt;sup&gt;3,4&lt;/sup&gt;</th>
<th>ARCHES&lt;sup&gt;5&lt;/sup&gt;</th>
<th>ENZAMET&lt;sup&gt;6&lt;/sup&gt;</th>
<th>TITAN&lt;sup&gt;7,8&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADT + AAP</td>
<td>ADT + PBOs</td>
<td>SOC+AAP</td>
<td>SOC</td>
<td>ENZA+ADT</td>
<td>PBO+ADT</td>
</tr>
<tr>
<td>(n = 597)</td>
<td>(n = 602)</td>
<td>(n=960)</td>
<td>(n=957)</td>
<td>(n=572)</td>
<td>(n=574)</td>
</tr>
<tr>
<td>Any AE, n (%)</td>
<td>569 (95)</td>
<td>561 (93)</td>
<td>943 (99)</td>
<td>950 (99)</td>
<td>487 (85.1)</td>
</tr>
<tr>
<td>Grade 3 or 4 AEs, n (%)</td>
<td>403 (68)</td>
<td>299 (50)</td>
<td>443 (47)</td>
<td>315 (33)</td>
<td>139 (24.3)</td>
</tr>
<tr>
<td>Any SAE, n (%)</td>
<td>192 (32)</td>
<td>151 (25)</td>
<td>NA</td>
<td>NA</td>
<td>235 (42)</td>
</tr>
<tr>
<td>Any AE leading to treatment discontinuation, n (%)</td>
<td>93 (16)</td>
<td>63 (11)</td>
<td>NA</td>
<td>NA</td>
<td>42 (8.0)</td>
</tr>
<tr>
<td>AE leading to death, n (%)</td>
<td>38 (6)</td>
<td>27 (5)</td>
<td>9 (1)</td>
<td>3 (&lt;1)</td>
<td>10 (1.9)</td>
</tr>
</tbody>
</table>

Not head-to-head comparison studies ; NA: not available

Outline

- What is the current evidence
- Guideline recommendations
- Loco-regional data
- Summary (Come Monday)
What do the guidelines say?
ESMO Guidelines

Text update

Two phase III trials have compared ADT alone versus ADT plus abiraterone and prednisolone in men with metastatic, hormone-naive disease. The LATITUDE trial included men with high risk metastatic disease. Based on 406 events, abiraterone/prednisone improved overall survival (HR: 0.62, 95% CI: 0.51-0.76) [1]. The STAMPEDE trial included men with metastatic and non-metastatic disease. Based on 446 events, abiraterone/prednisone improved overall survival (HR: 0.63, 95% CI: 0.52-0.76) [2].

Recommendations

- ADT plus abiraterone/prednisone may be considered as first-line treatment for metastatic, hormone-naive disease [I, A].

References

NCCN Guidelines Version 4.2019
Prostate Cancer

SYSTEMIC THERAPY FOR CASTRATION-NAIVE DISEASE

M0
- Observation (preferred)\textsuperscript{8} or
  - ADT\textsuperscript{u,rr}

ADT\textsuperscript{u} with one of the following:
- Docetaxel 75 mg/m\textsuperscript{2} for 6 cycles\textsuperscript{ss} (category 1)
- Abiraterone with prednisone (category 1)
- Apalutamide (category 1)
- Enzalutamide (category 1)

M\textsubscript{1}dd,ee,qq
- EBRT\textsuperscript{q} to the primary tumor for low-volume M1
  - Abiraterone with methylprednisolone (category 2B)
  or
  - ADT\textsuperscript{u,rr}

<table>
<thead>
<tr>
<th>Studies negative for distant metastases</th>
<th>See Systemic Therapy for M0 CRPC (PROS-15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression\textsuperscript{hh,tt}</td>
<td></td>
</tr>
</tbody>
</table>

- Physical exam + PSA every 3–6 mo
- Bone imaging\textsuperscript{h} for symptoms and as often as every 6–12 mo

<table>
<thead>
<tr>
<th>Studies positive for distant metastases</th>
<th>See Systemic Therapy for M1 CRPC (PROS-16)</th>
</tr>
</thead>
</table>

NCCN Guidelines Index
Table of Contents
Discussion
Key Recommendations

- Docetaxel and abiraterone are two separate standards of care (SOCs) for metastatic non-castrate prostate cancer. The use of both standards in combination or in series has not been assessed and therefore cannot be recommended (Type: evidence based, benefits/harms ratio unknown; Evidence quality: no evidence available; Strength of recommendation: strong).

ADT Plus Docetaxel

- For men with metastatic non-castrate prostate cancer with high-volume disease (HVD) per CHAARTED who are candidates for treatment with chemotherapy, the addition of docetaxel to ADT should be offered (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong for patients with HVD as per CHAARTED).

- For patients with low-volume disease (LVD) per CHAARTED who are candidates for chemotherapy, docetaxel plus ADT may be offered (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate for patients with LVD as per CHAARTED).

  - The appropriate regimen of docetaxel is six doses of docetaxel administered every 3 weeks at 75 mg/m² either alone (per CHAARTED) or with prednisolone (per STAMPEDE) (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

ADT Plus Abiraterone

- For men with high-risk de novo metastatic non-castrate prostate cancer, the addition of abiraterone to ADT should be offered per LATITUDE (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong for patients with high-risk disease per LATITUDE).

- For men with lower-risk de novo metastatic non-castrate prostate cancer, abiraterone may be offered per STAMPEDE (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate for patients with lower-risk disease per STAMPEDE).

  - The appropriate regimen is abiraterone 1,000 mg with either prednisolone or prednisone 5 mg once daily until treatment(s) for mCRPC are initiated (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
Updated Guidelines for Metastatic Hormone-sensitive Prostate Cancer: Abiraterone Acetate Combined with Castration Is Another Standard☆

Nicolas Mottet\textsuperscript{a,∗}, Maria De Santis\textsuperscript{b,c}, Erik Briers\textsuperscript{k}, Silke Gillessen\textsuperscript{d,m}, Jeremy P. Grummet\textsuperscript{e}, Thomas B. Lam\textsuperscript{f,g}, Henk G. van der Poel\textsuperscript{h}, Olivier Rouvière\textsuperscript{i,j}, Roderick C. Van den Bergh\textsuperscript{h}, Philip Cornford\textsuperscript{j}

Table 6 – New guidelines to consider now for metastatic hormone-sensitive prostate cancer

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Offer surgical or medical castration (luteinizing-hormone-releasing hormone agonist or antagonist) as androgen deprivation therapy</strong></td>
</tr>
<tr>
<td><strong>Offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy</strong></td>
</tr>
<tr>
<td><strong>Offer castration combined with abiraterone acetate + prednisone to all patients whose first presentation is M1 disease and who are fit enough for the regimen</strong></td>
</tr>
<tr>
<td><strong>Offer castration, with or without an antiandrogen, to patients unfit for a combination with docetaxel or abiraterone acetate + prednisone, or who are unwilling to consider it</strong></td>
</tr>
</tbody>
</table>

Mottet et al, Eur Urol 2017
Outline

- What is the current evidence
- Guideline recommendations
- Loco-regional data
- Summary
What are the considerations (in the Asian context)?

- Efficacy
- Toxicity
- QOL
- Cost
- Patient Preference
What are the considerations (in the Asian context)?

- Efficacy
- Toxicity
- QOL
- Cost
- Patient Preference
Toxicity: Docetaxel in the local mCRPC population

Original Article

Outcomes of Dose-Attenuated Docetaxel in Asian Patients with Castrate-Resistant Prostate Cancer

Jia Wei Ang, 1 Min-Han Tan, 1,2 MBBS, MRCPath, PhD, Miah Hiang Tay, 3 MBBS, MRCPath, Chee Keong Toh, 1,2 MBBS, MRCPath, Quan Sing Ng, 1,2 MBBS, MRCPath, Ravindran Kanesvaran, 1,2 MD, MRCPath

Abstract

Introduction: High levels of toxicities have been observed when docetaxel is administered at the standard dose of 75 mg/m² every 3 weeks (Q3W) in the real-world treatment of Asian patients with metastatic castrate-resistant prostate cancer (mCRPC). This study aimed to evaluate the efficacy and tolerability of 2 attenuated regimens more widely used in an Asian setting to minimize toxicity — 60 mg/m² Q3W and weekly docetaxel (20 mg/m²) to 35 mg/m²). Materials and Methods: Medical records of 89 CRPC patients between December 2003 and April 2013 were reviewed. Pairwise statistical analysis was performed, comparing efficacy and safety outcomes of 75 mg/m² Q3W and weekly docetaxel with 60 mg/m² Q3W. Treatment endpoints used were prostate-specific antigen (PSA) response (decrease of ≥50% from baseline), pain improvement after cycle 2, overall survival, time to disease progression and radiological response. Results: Patients who received docetaxel at 75 mg/m² Q3W were younger than those who received 60 mg/m² Q3W (62 years and 66 years, respectively; P = 0.0489). Both groups had similar response rates. Compared with patients on 60 mg/m² Q3W, more patients on weekly regimen were symptomatic at baseline (63.3% and 87.5%, respectively; P = 0.0173). Longer overall survival was observed in the 60 mg/m² Q3W arm than the weekly docetaxel arm (16.9 months and 10.6 months, respectively; P = 0.0131), though other measures of response did not differ significantly. Conclusion: Our data supports the use of 60 mg/m² Q3W docetaxel which has similar efficacy and an acceptable toxicity profile compared to the standard 75 mg/m² Q3W regimen. Weekly docetaxel has significant palliative benefits among symptomatic patients despite lower overall survival.

Ann Acad Med Singapore 2017;46:xx-xx

Key words: Chemotherapy, Genitourinary, Toxicity
## Docetaxel Toxicities

Routine GCSF given

<table>
<thead>
<tr>
<th>Table 3. Toxicity Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>60 mg/m²</strong></td>
</tr>
<tr>
<td><strong>Q3W n (%)</strong></td>
</tr>
<tr>
<td>Hospitalised</td>
</tr>
<tr>
<td>Toxicity</td>
</tr>
<tr>
<td>PD</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>Stopping treatment due to toxicity</td>
</tr>
<tr>
<td>Grade 3 or 4 neutropenia</td>
</tr>
<tr>
<td>Death during chemotherapy</td>
</tr>
</tbody>
</table>
Preliminary efficacy and tolerability of chemohormonal therapy in metastatic hormone-naïve prostate cancer: The first real-life experience in Asia

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Comparison of grade 3 or above toxicities in related studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
<td>Current study (%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>12.5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>40.6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>3.1</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0</td>
</tr>
</tbody>
</table>

57 metastatic hormone-sensitive prostate cancer Chinese patients treated with docetaxel.
How about Docetaxel dose in local mHNPC patients?

- Younger, fitter patients in earlier part of disease course
- Data supported by 75mg/m2 dose, hence lower dose may impact efficacy (much longer mOS compared to mCRPC)
- My practice: start at 70mg/m2 and increase if tolerating
- Reduced febrile neutropenia rates with routine primary prophylaxis with GCSF
Is Abiraterone better tolerated in Asians?

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of patients with events (%)</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (4.2)</td>
<td>0</td>
</tr>
<tr>
<td>Fluid retention or edema</td>
<td>23 (13.9)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>16 (9.6)</td>
<td>0</td>
</tr>
<tr>
<td>General disorders</td>
<td>6 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>31 (18.7)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Hepatotoxicities</td>
<td>3 (1.8)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (17.5)</td>
<td>10 (6.0)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>20 (12.0)</td>
<td>0</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>18 (10.8)</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Incontinence</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Lethargy</td>
<td>2 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>4 (2.4)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>3 (1.8)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Skin toxicities</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Thoracic disorders</td>
<td>3 (1.8)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

*Thirty-four patients excluded because toxicity data not provided by TTSH.*
Patient Preference

- Chemotherapy Taboo (Toxicity related)
- Oral vs IV
- Post ADT symptoms relief
- PSA Addiction (comfort from PSA dropping)
Is First-Line ADT Monotherapy a Sufficient Standard of Care for Metastatic Prostate Cancer Today?

- NO: recent compelling data suggest we should use either ARI or Docetaxel with ADT

- In Singapore: Abiraterone available since 2012 for mCRPC and recently approved for mHSPC as well, Docetaxel has been used for mCRPC since 2005, Enzalutamide approved for mCRPC since 2013

- Physicians are familiar with efficacy and toxicity of the drugs especially from mCRPC experience

- Cost: Docetaxel is cheap (generic) vs ARI (still under patents)
## mHNPC/HSPC:
### Ongoing phase III studies with novel AR pathway inhibitors

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient group</th>
<th>Control arm</th>
<th>Experimental arm</th>
<th>Primary endpoint</th>
<th>Subject No.</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENZAMET (NCT02446405)</td>
<td>1st-Line ADT for M1 disease</td>
<td>ADT + NSAA</td>
<td>ADT + Enzalutamide</td>
<td>OS</td>
<td>1,100</td>
<td>Published</td>
</tr>
<tr>
<td>ARCHES (NCT02677896)</td>
<td>mHSPC identified by images, pelvic LN mets excluded</td>
<td>ADT + Placebo</td>
<td>ADT + Enzalutamide</td>
<td>rPFS</td>
<td>1.100</td>
<td>Published</td>
</tr>
<tr>
<td>LATTITUDE (NCT01715285)</td>
<td>Newly diagnosed M1, 2 of visceral disease, &gt;2 bone mets, Gleason &gt;7</td>
<td>ADT + placebo</td>
<td>ADT + Abiraterone</td>
<td>OS rPFS</td>
<td>1.270</td>
<td>Published</td>
</tr>
<tr>
<td>TITAN (NCT02489318)</td>
<td>Low-volume metastatic ≥1 bone lesions ± visceral mets</td>
<td>ADT + placebo</td>
<td>ADT + Apalutamide</td>
<td>OS rPFS</td>
<td>1,000</td>
<td>Published</td>
</tr>
<tr>
<td>PEACE1 (NCT01957436)</td>
<td>Newly diagnosed M1, asymptomatic</td>
<td>ADT (+/- docetaxel) + Abi; ADT (+/- docetaxel) + RT; ADT (+/- docetaxel) + Abi + RT</td>
<td>OS rPFS</td>
<td>916</td>
<td>Completed accrual 2018</td>
<td></td>
</tr>
<tr>
<td>STAMPEDE (NCT00268476)</td>
<td>Newly diagnosed locally advanced or metastatic</td>
<td>ADT</td>
<td>ADT + docetaxel; ADT + Abi; ADT + Zolendronic acid; ADT+ RT; ADT + Abi + Enza</td>
<td>OS Failure-free survival</td>
<td>&gt;5,000</td>
<td>Published</td>
</tr>
<tr>
<td>ARASENS (NCT02799602)</td>
<td>mHSPC, ≥1 bone lesions ± visceral mets</td>
<td>ADT + placebo + docetaxel</td>
<td>ADT + ODM-201 + docetaxel</td>
<td>OS</td>
<td>1,300</td>
<td>Actively enrolling</td>
</tr>
</tbody>
</table>

NSAA: non-steroidal anti-androgen; PFS: progression-free survival; rPFS: radiographic progression-free survival
Outline

- What is the current evidence
- Guideline recommendations
- Loco-regional data
- Summary
Summary

- Multiple efficacious therapies in the mHNPC setting
- Choice can be based on functional status and co-morbidities
- More local real world data is important in understanding treatment dosage and efficacy better
- Cost and patient preference will be key determinant in terms of access and usage
THANK YOU
Ravindran.kanesvaran@singhealth.com.sg