Androgen Deprivation Therapy (ADT) and other hormonal treatments

Silke Gillessen, MD
Medical Oncology
Oncology Institute of Southern Switzerland (IOSI), Bellinzona, Switzerland
Universita della Svizzera Italiana, Lugano, Switzerland
Division of Cancer Sciences, University of Manchester, UK
silke.gillessen@eoc.ch
Disclosures

- **Personal financial interests:** Bayer; Dendreon; Janssen; MaxiVAX SA; Millennium; Orion; Roche; Sanofi

- **Institutional financial interests:** AAA International; Active Biotech; Astellas; Bayer; Bristol-Myers Squibb; Clovis; CureVac; Ferring; Innocrin; Janssen; Menarini Silicon Biosystems; Orion; Roche; Sanofi; Tolero Pharmaceuticals

- **Non-financial interests:** Amgen; Aranda; Astellas; Bayer; ESSA; Janssen; Menarini Silicon Biosystems; Nectar; ProteoMediX; Sanofi

- Co-inventor on patent application (WO 2009138392 A1) for a method for biomarker discover (granted in China, Europe, Japan and the US)

- Deputy of the ESMO guidelines committee for GU cancers, member of the EAU guideline panel for prostate cancer, past chair of the EORTC GU group; Member of the STAMPEDE trial management group
Prostate Cancer: Castration resistant (CRPC)

**Localised Prostate Cancer**

**Advanced Prostate Cancer:**
- Castration-sensitive/naive
- Castration-resistant

**Advanced Prostate Cancer:**
- **M0:** By imaging no evidence of metastases
- **M1:** Metastases detected by imaging

**Local Therapy**
- (RT/OP) or Active Surveillance)

**Salvage Therapy**

**PSA Rise**

**De Novo M1**

**ADT**

- **M0**
  - **1st-line**
    - **ADT + Docetaxel**
  - **2nd-line**
    - **ADT + Abiraterone**
  - **3rd-line**
    - **mCRPC treatments with OS benefit:**
      - Abiraterone
      - Cabazitaxel
      - Docetaxel
      - Enzalutamide
      - Radium-223
      - Sipuleucel-T

**mCRPC treatments with OS benefit:**
- ADT: Androgen Deprivation Therapy
- M0: By imaging no evidence of metastases
- M1: Metastases detected by imaging

**AR-antagonists**

**Local Therapy**
- (RT/OP) or Active Surveillance)

**Salvage Therapy**

**PSA Rise**

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**ADT: Androgen Deprivation Therapy**

M0: By imaging no evidence of metastases

M1: Metastases detected by imaging
Androgen Deprivation Therapy

LHRH Analogues
- GnRH agonist
- GnRH antagonist

Orchiectomy

To prevent flare:
- Earlier generation androgen receptor inhibitor
  - Bicalutamide
  - …
Androgen Deprivation Therapy for metastatic disease: Other Forms

**Intermittent ADT:**
Not generally recommended  
*Hussain M et al, N Engl J Med 2013*

**Combined (maximal) Androgen Blockade (CAB):**
Permanent combination of ADT and an earlier generation of AR antagonist (e.g. bicalutamide or flutamide)  
Not generally recommended  
*Caubet JF et al, Urology 1997*  
*Prostate Cancer Trialists Collaborative Group Lancet 2000*  
*Samson DJ et al, Cancer 2002*
What can we expect from ADT alone?

917 patients with *de novo* M1 PCa (2005-2014) treated by ADT alone (STAMPEDE randomized trial control arm)

Median OS from diagnosis: 42 mo

**Patient Characteristics:**
- Age: 66y
- PSA: 112
- Bone only: 62%
- Liver: 2%
- Lung: 4%

*James ND et al, Eur Urol 2015*
ADT plus Chemotherapy vs ADT alone

Castration-sensitive/naïve men (mostly M1)

Randomised

ADT

ADT + Docetaxel 75mg/m²
Every 21d x 6/9 Zyklenn

CHAARTED  n=790  Accrual: 2006-2012
STAMPEDE  n= 2962  Accrual: 2005-2013

Addition of Docetaxel on OS in CHAARTED

Update with 54 mo FU: HR 0.72 (95% CI, 0.59 to 0.89)

Kyriakopoulos C et al. J Clin Oncol 2018

ADT + Docetaxel Overall Survival – Metaanalysis

M1 Patients

A

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Treatment</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAARTED³</td>
<td>136/393</td>
<td>101/397</td>
<td>0.61 (0.47–0.80)</td>
</tr>
<tr>
<td>GETUG-15⁹¹⁰</td>
<td>NA/193</td>
<td>NA/192</td>
<td>0.90 (0.69–1.81)</td>
</tr>
<tr>
<td>STAMPEDE⁸ (SOC+/-Doc)</td>
<td>350/724</td>
<td>144/362</td>
<td>0.76 (0.62–0.93)</td>
</tr>
<tr>
<td>STAMPEDE⁸ (SOC+ZA+/-Doc)</td>
<td>170/366</td>
<td>158/365</td>
<td>0.85 (0.65–1.10)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.77 (0.68–0.87)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=4.80$; df=3; $p=0.187$; $I^2=37.5\%$

Subgroup-Analysis

A: high-volume
B: low-volume
HR: 1.04 (0.7-0.1.55)

C: de-novo high-volume
D: de-novo low-volume

E: After local tx high-volume
F: after local tx low-volume

Gravis Eur Urol 2018
Kyriakopoulos JCO 2018
Warning

- "Marked heterogeneity of the treatment comparison in different strata can arise by chance more easily than would intuitively be expected...."

- Subgroup analysis is a machine for producing false negative and false positive results.

Peto et al., Br. J. Cancer 1977
Overall Survival: Subgroup Analysis by Metastatic Burden in STAMPEDE

No evidence that the beneficial effect varies by metastatic burden interaction p-value = 0.827
Prostate Cancer: Castration resistant (CRPC)

Localised Prostate Cancer

Advanced Prostate Cancer:
Castration-sensitive/naive

M0: By imaging no evidence of metastases
M1: Metastases detected by imaging

Advanced Prostate Cancer:
Castration-resistant

Local Therapy (RT/OP) or Active Surveillance

Salvage Therapy

Local Therapy

PSA Rise

De Novo M1

M0

ADT

M0

AR-antagonists

1st-line

2nd-line

3rd-line

De Novo M1

ADT

ADT + Docetaxel

mCRPC treatments with OS benefit:
- Abiraterone
- Cabazitaxel
- Docetaxel
- Enzalutamide
- Radium-223
- Sipuleucel-T

ADT: Androgen Deprivation Therapy
M0: By imaging no evidence of metastases
M1: Metastases detected by imaging
ADT plus Abiraterone/Pred vs ADT alone

Castration-sensitive/naïve men

LATITUDE
- only «high-risk» M1 at least 2/3 Criteria
  - Gleason score ≥8
  - ≥3 Bone metastases
  - Visceral metastases

STAMPEDE

Newly-diagnosed
- Any of:
  - Metastatic
  - Node-Positive
- ≥2 of:
  - Stage T3 or T4
  - PSA≥40ng/ml
  - Gleason 8, 9 or 10

Relapsing after previous RP or RT
- Any of:
  - Metastatic
  - Node-Positive
  - PSA≥4ng/ml, rising & doubling time <6m
  - PSA≥20ng/ml

LATITUDE
- n= 1199
- Accrual: 2013 - 2014

STAMPEDE
- n= 1917
- Accrual: 2011 - 2014

ADT

ADT +
- Abiraterone acetate 1000mg OD until PD
- Prednisone 5mg OD
LATITUDE: ADT vs ADT + Abiraterone/Pred

LATITUDE only «high-risk» M1 at least 2/3 Criteria
- Gleason score ≥8
- ≥3 Bone metastases
- Visceral metastases

«High-risk» Criteria:
- Gleason score ≥8 + ≥3 bone lesions  ca. 95%
- Gleason score ≥8 + visceral disease  ca. 14%
- ≥3 bone lesions + visceral disease  ca. 14%
- Gleason score ≥8 + ≥3 bone lesions + visceral disease  ca. 12%

Median age: ca. 68 years
Practise changing!
**STAMPEDE: ADT vs ADT + Abiraterone/Pred**

**Newly-diagnosed**
- Any of:
  - Metastatic
  - Node-Positive
- ≥ 2 of:
  - Stage T3 or T4
  - PSA ≥ 40ng/ml
  - PSA ≥ 2.0ng/ml
  - Gleason 8, 9 or 10

**Relapsing after previous RP or RT**
- Any of:
  - Metastatic
  - Node-positive
  - PSA ≥ 4ng/ml, rising & doubling time < 6m

**Metastatic:**
- Newly diagnosed M1: ca. 50%
- M1 after local therapy: ca. 4%

**Non-metastatic**
- De novo N+: ca. 20%
- Newly diagnosed node negative: ca. 27%
- Biochemical recurrence: ca. 2%

**Median age:** 67 years

*James N et al, New Engl J Med 2017*
Effect of adding AAP to ADT on (A) overall survival and (clinical/radiological) progression-free survival (B) in M1 CNPC

Rydzewska et al Eur J Cancer 2017
Comparison Abi/P and Docetaxel

STAMPEDE patients
Included in arm SOC + Docetaxel (n=189) or arm SOC + Abiraterone/P (n=377) between Nov 2011 and Mar 2013

Comparison not planned and powered in the usual way!

No evidence of a difference on overall or prostate cancer-specific survival

Sydes M et al ESMO 2017, Ann Oncol 2018
AAP has highest probability of being the most effective, but uncertainty remains...
Prostate Cancer: Castration resistant (CRPC)

Advanced Prostate Cancer: Castration-sensitive/naive

Localised Prostate Cancer

Advanced Prostate Cancer: Castration-resistant

M0: By imaging no evidence of metastases
M1: Metastases detected by imaging

Local Therapy (RT/OP) or Active Surveillance → Salvage Therapy → PSA Rise → M1

M0 → ADT → M0

M1 → ADT + Docetaxel → AR-antagonists

De Novo M1

mCRPC treatments with OS benefit:
- Abiraterone
- Cabazitaxel
- Docetaxel
- Enzalutamide
- Radium-223
- Sipuleucel-T

ADT: Androgen Deprivation Therapy
M0: By imaging no evidence of metastases
M1: Metastases detected by imaging
Radiotherapy to the primary in mCSPC patients

Parker C et al. Lancet 2018

* Radiotherapy:
  36Gy/6 fractions over 6 wks or
  55Gy/20 fractions over 4 wks
  Schedule nominated before randomisation

Stratification:
Age, nodal involvement, site,
WHO PS, type of ADT, docetaxel use, co-medication

2013-2016
120 centres in UK and Switzerland

n=2061

1° Endpoint: Overall Survival

2° Endpoints: Failure Free Survival, Symptomatic local events, Toxicity...

Pre-specified subgroup analysis (powered!)
- Radiotherapy schedule (weekly vs daily)
- Metastatic burden (lower vs higher) - directionally hypothesized

Parker C et al. Lancet 2018
Radiotherapy to the primary in mCSPC patients

Primary endpoint: Overall Survival

Low burden

In all patients

High burden

HR: 0.68 (95% CI 0.52-0.90)
p=0.007
3 year OS: SOC = 73%
SOC+RT = 81%

HR: 0.92 (95% CI 0.80-1.06)
p=0.266
3 years OS: SOC = 62%
SOC+RT = 65%

HR: 1.07 (95% CI 0.90-1.28)
p=0.420
3 year OS: SOC = 54%
SOC+RT = 53%

Parker C et al. Lancet 2018
Prostate Cancer: Castration resistant (CRPC)

**Localised Prostate Cancer**

**Advanced Prostate Cancer: Castration-sensitive/naive**

**Advanced Prostate Cancer: Castration-resistant**

**M0:** By imaging no evidence of metastases

**M1:** Metastases detected by imaging

**ADT:** Androgen Deprivation Therapy

**Local Therapy (RT/OP) or Active Surveillance**

Salvage Therapy → PSA Rise → M1 → M0

De Novo M1

ADT

**1st-line** → 2nd-line → 3rd-line

**mCRPC treatments with OS benefit:**
- Abiraterone
- Cabazitaxel
- Docetaxel
- Enzalutamide
- Radium-223
- Sipuleucel-T

ADT: Androgen Deprivation Therapy

M0: By imaging no evidence of metastases

M1: Metastases detected by imaging
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

Christopher Sweeney, MBBS

Courtesy Chris Sweeney; Davis I et al NEJM 2019
Primary endpoint: Overall survival

Proportion alive at 36 months (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>NSAA</th>
<th>Enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion</td>
<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 months</td>
<td>562</td>
<td>563</td>
</tr>
<tr>
<td>6 months</td>
<td>551</td>
<td>558</td>
</tr>
<tr>
<td>12 months</td>
<td>531</td>
<td>541</td>
</tr>
<tr>
<td>18 months</td>
<td>501</td>
<td>527</td>
</tr>
<tr>
<td>24 months</td>
<td>452</td>
<td>480</td>
</tr>
<tr>
<td>30 months</td>
<td>311</td>
<td>340</td>
</tr>
<tr>
<td>36 months</td>
<td>174</td>
<td>189</td>
</tr>
<tr>
<td>42 months</td>
<td>86</td>
<td>106</td>
</tr>
<tr>
<td>48 months</td>
<td>32</td>
<td>45</td>
</tr>
</tbody>
</table>

Courtesy Chris Sweeney; Davis I et al NEJM 2019
**TITAN: Apalutamide**

The NEW ENGLAND JOURNAL of MEDICINE

Apalutamide

Kim N. Ch
Andrea J. P
Axel S. Merseb
Kris Deprince, M.I
Ke Zhang, Ph.D.,

A Overall Survival

<table>
<thead>
<tr>
<th>Months</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>36</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Median Overall Survival (95% CI)</th>
<th>Patients with Overall Survival at 24 Mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apalutamide</td>
<td>525</td>
<td>NE</td>
</tr>
<tr>
<td>Placebo</td>
<td>527</td>
<td>NE</td>
</tr>
</tbody>
</table>

Hazard ratio for death, 0.67 (95% CI, 0.51–0.89)
P=0.005
Prostate Cancer: Castration resistant (CRPC)

Localised Prostate Cancer

Advanced Prostate Cancer: Castration-sensitive/naive

Advanced Prostate Cancer: Castration-resistant

Local Therapy (RT/OP) or Active Surveillance) → Salvage Therapy → PSA Rise → De Novo M1

M0

ADT → M0

M1

ADT → 1st-line

ADT + Docetaxel

ADT + Abiraterone

ADT + RT primary in low volume

ADT +/- AR-antagonists

2nd-line

3rd-line

mCRPC treatments with OS benefit:
- Abiraterone
- Cabazitaxel
- Docetaxel
- Enzalutamide
- Radium-223
- Sipuleucel-T

ADT: Androgen Deprivation Therapy
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Metastatic castration-sensitive disease

State-of-the art 2019 after ASCO and ESMO: ADT mainstay, addition of:

<table>
<thead>
<tr>
<th><strong>OS benefit</strong></th>
<th><strong>High volume/burden/risk</strong></th>
<th><strong>Low volume/burden/risk</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>+</td>
<td>+ (less certain for relapsed, not “de novo” metastatic disease)</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Enzalutamide/Apalutamide</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prostate Radiotherapy</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
34. What is your preferred treatment in addition to ADT in patients with de-novo high-volume metastatic (M1) castration-sensitive/naïve prostate cancer (CNPC) without symptoms from the primary tumour?

1. AR pathway inhibitor (abiraterone or apalutamid or enzalutamide) as sole additional therapy
2. Docetaxel as sole additional therapy
3. Any one of docetaxel or abiraterone or apalutamid or enzalutamide as sole additional therapy
4. Docetaxel plus an AR pathway inhibitor (abiraterone or apalutamide or enzalutamide)
5. ADT alone, no additional treatment
6. Abstain

Uncorrected version – not published data
36. What is your preferred treatment in addition to ADT in patients with de-novo low-volume metastatic (M1) castration-sensitive/naïve prostate cancer (CNPC) without symptoms from the primary tumour?

1. AR pathway inhibitor (abiraterone or apalutamide or enzalutamide) as sole additional therapy
2. Docetaxel as sole additional therapy
3. Any one of docetaxel or abiraterone or apalutamide or enzalutamide as sole additional therapy
4. AR pathway inhibitor (abiraterone or apalutamide or enzalutamide) plus treatment of the primary
5. Docetaxel plus treatment of the primary tumour
6. Treatment of the primary alone
7. ADT alone, no additional treatment
8. Abstain

<table>
<thead>
<tr>
<th>Option</th>
<th>Votes</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Option 1</td>
<td>6</td>
<td>11%</td>
</tr>
<tr>
<td>Option 2</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Option 3</td>
<td>3</td>
<td>5%</td>
</tr>
<tr>
<td>Option 4</td>
<td>30</td>
<td>54%</td>
</tr>
<tr>
<td>Option 5</td>
<td>7</td>
<td>13%</td>
</tr>
<tr>
<td>Option 6</td>
<td>7</td>
<td>13%</td>
</tr>
<tr>
<td>Option 7</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Abstain</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Total votes</td>
<td>55</td>
<td></td>
</tr>
</tbody>
</table>

Uncorrected version – not published data
Take home messages mCSPC

- ADT mainstay in metastatic castration sensitive prostate cancer (Side effects!)
- Addition of Docetaxel to ADT has OS benefit
- Addition of Abiraterone/Pred to ADT has OS benefit
- Addition of AR-Antagonists (Enzalutamide, Apalutamide) to ADT has OS benefit
- Addition of radiotherapy to the primary has OS benefit in patients with low volume disease
Take home messages mCSPC II

• Bisphosphonates (in dose/schedule to reduce incidence of SRE/SSEs) have no survival improvement and no reduction of SRE/SSEs in metastatic castration sensitive disease

• Triplets/Quadruplets no standard yet, likely to arrive soon... (Toxicity!)

• Other (personalized) substances will likely follow (PARP-inhibitors, immune checkpoint inhibitors...) in this space

• Our task is the find predictive markers!
Thank you very much for your attention!
### AEs of Abi/Pred given at start of ADT (mCSPC)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Abiraterone Group (N = 597)</th>
<th>Placebo Group (N = 602)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>219 (37)</td>
<td>121 (20)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>122 (20)</td>
<td>57 (10)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>98 (16)</td>
<td>31 (5)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>75 (13)</td>
<td>26 (4)</td>
</tr>
<tr>
<td>AST increased</td>
<td>87 (15)</td>
<td>25 (4)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>74 (12)</td>
<td>20 (3)</td>
</tr>
<tr>
<td><strong>Cardiac disorder</strong></td>
<td><strong>74 (12)</strong></td>
<td><strong>15 (3)</strong></td>
</tr>
<tr>
<td>Any</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8 (1)</td>
<td>2 (&lt;1)</td>
</tr>
</tbody>
</table>

*Fizazi K et al, New Engl J Med 2017*
# Metastatic disease: castration-sensitive

<table>
<thead>
<tr>
<th>AR-Antagonist</th>
<th>rPFS Benefit: <strong>ARCHES</strong>, OS data immature</th>
<th>OS-Benefit: <strong>ENZAMET</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzalutamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apalutamide</td>
<td></td>
<td><strong>OS-Benefit: TITAN</strong></td>
</tr>
<tr>
<td>Darolutamide</td>
<td></td>
<td><strong>OS-Benefit?: ARASENS</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Docetaxel-Combinations</th>
<th>Arm or Stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEACE 1</td>
<td>Abiraterone/P +/- Radiotherapy to the primary</td>
</tr>
<tr>
<td>ENZAMET</td>
<td>Enzalutamide</td>
</tr>
<tr>
<td>ARASENS</td>
<td>Darolutamide</td>
</tr>
</tbody>
</table>

S1216 testing TAK-700, SWOG 1802 testing cytoreductive therapy.
Also trials with combinations of Abiraterone/P plus AR-Antagonists ongoing...
Castration-sensitive/naïve prostate cancer: Very rapidly changing space

<table>
<thead>
<tr>
<th>Study</th>
<th>Identifier</th>
<th>Study Drugs</th>
<th>Pts (N)</th>
<th>Primary End Point</th>
<th>Status/Read Out</th>
</tr>
</thead>
<tbody>
<tr>
<td>LATITUDE</td>
<td>NCT01715285</td>
<td>ADT ± AA</td>
<td>1209</td>
<td>rPFS, OS</td>
<td>ASCO 2017</td>
</tr>
<tr>
<td>STAMPEDE (Arm G)</td>
<td>NCT00268476</td>
<td>ADT ± AA</td>
<td>1800</td>
<td>OS</td>
<td>LBA ASCO 2017</td>
</tr>
<tr>
<td>PEACE-1</td>
<td>NCT01957436</td>
<td>ADT ± DOC vs ADT + AA ± DOC (± local RT)</td>
<td>916</td>
<td>PFS, OS</td>
<td>Recruiting/2020</td>
</tr>
<tr>
<td>STAMPEDE (Arm J)</td>
<td>NCT00268476</td>
<td>ADT ± AA + ENZ*</td>
<td>1800</td>
<td>OS</td>
<td>Closed-will report in 2-3 yrs</td>
</tr>
<tr>
<td>SWOG-1216</td>
<td>NCT01809691</td>
<td>ADT + TAK-700 vs ADT + BIC</td>
<td>1304</td>
<td>OS</td>
<td>Recruiting/2027</td>
</tr>
<tr>
<td>ENZAMET</td>
<td>NCT02446405</td>
<td>ADT + ENZ vs ADT + antiandrogen</td>
<td>1100</td>
<td>OS</td>
<td>Recruiting/2020</td>
</tr>
<tr>
<td>TITAN</td>
<td>NCT02489318</td>
<td>ADT ± APA (ARN 509)</td>
<td>1000</td>
<td>rPFS, OS</td>
<td>Recruiting/2021</td>
</tr>
<tr>
<td>ARCHES</td>
<td>NCT02677896</td>
<td>ADT ± ENZ</td>
<td>1100</td>
<td>rPFS</td>
<td>Recruiting/2023</td>
</tr>
<tr>
<td>ARASENS</td>
<td>NCT02799602</td>
<td>ADT + DOC ± ODM-201</td>
<td>1300</td>
<td>OS</td>
<td>Recruiting/2022</td>
</tr>
</tbody>
</table>

Sternberg ESMO 2017
## Ongoing randomized de novo mCSPC trials: role of local therapy

<table>
<thead>
<tr>
<th>Control Arm</th>
<th>Experimental Arm</th>
<th>Acronyms</th>
<th>Sponsor</th>
</tr>
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<tbody>
<tr>
<td>SOC</td>
<td>SOC + Prostate RT</td>
<td>STAMPEDE Arm H</td>
<td>MRC: <strong>ESMO 2018</strong> Unicancer</td>
</tr>
<tr>
<td>ADT +/- Abi</td>
<td>ADT +/- Prostate RT +/- Abi +/- Docetaxel</td>
<td>PEACE 1</td>
<td></td>
</tr>
<tr>
<td>Best systemic therapy</td>
<td>BST + RP or RT</td>
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<td>MDACC (Fox Chase/UCSF)</td>
</tr>
<tr>
<td>ADT</td>
<td>ADT + Prostate RT</td>
<td>HORRAD</td>
<td>Netherlands*</td>
</tr>
<tr>
<td>Best systemic Rx</td>
<td>BST + local therapy</td>
<td>TROMBONE g-RAMPP</td>
<td>UK Martini-Klinik</td>
</tr>
<tr>
<td></td>
<td>(some limited to oligometastasis only)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- **BST** + RP or RT
- **BST** + local therapy (some limited to oligometastasis only)
- **MRC:** MRC: ESMO 2018 Unicancer
- **MDACC:** MDACC (Fox Chase/UCSF)
- **Netherlands:** Netherlands*
- **UK:** UK Martini-Klinik

*Boeve et al Eur Urol 2018*
Take home messages mCSPC

- ADT mainstay in metastatic castration sensitive prostate cancer (Side effects!)
- Addition of Docetaxel to ADT has overall survival benefit
- Addition of Abiraterone/Pred to ADT has overall survival benefit
- Bisphosphonates (in dose/schedule to reduce incidence of SRE/SSEs) have no survival improvement and no reduction of SRE/SSEs in metastatic castration sensitive disease
- Castration-sensitive metastatic prostate cancer is a rapidly evolving field: Stay tuned: ESMO 2018!
**Table 5 - Chemo-hormonal therapy with docetaxel**

<table>
<thead>
<tr>
<th>Do you recommend docetaxel in addition to ADT:</th>
<th>Yes, in the majority of patients (%)</th>
<th>In a minority of selected patients (%)</th>
<th>No (%)</th>
<th>Abstain (%)</th>
<th>Unqualified to answer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In men with de novo metastatic castration-naive prostate cancer and high-volume disease as defined by CHAARTED (visceral metastases and/or ≥ 4 bone lesions with ≥ 1 beyond vertebral bodies and pelvis)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In men with de novo metastatic castration-naive and low-volume disease as per CHAARTED?</td>
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<td></td>
<td></td>
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<td>In men with metastatic castration-sensitive/naive disease relapsing after prior treatment for localised prostate cancer and with high-volume disease as per CHAARTED?</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In men with castration-sensitive/naive N1 M0 prostate cancer?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In men with castration-sensitive/naive N0 M0 (nonmetastatic) prostate cancer with biochemical relapse?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADT = androgen deprivation therapy.

Gillessen et al. Eur Urol 2017

* Results of STAMPEDE/LATITUDE not published at time of consensus conference
### Table 5 - Chemo-hormonal therapy with docetaxel

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<th>Do you recommend docetaxel in addition to ADT:</th>
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<th>In a minority of selected patients (%)</th>
<th>No (%)</th>
<th>Abstain (%)</th>
<th>Unqualified to answer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In men with de novo metastatic castration-naive prostate cancer and high-volume disease as defined by CHAARTED (visceral metastases and/or ≥ 4 bone lesions with ≥ 1 beyond vertebral bodies and pelvis)?</td>
<td>96</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>In men with de novo metastatic castration-naive and low-volume disease as per CHAARTED?</td>
<td>29</td>
<td>65</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>In men with metastatic castration-sensitive/naive disease relapsing after prior treatment for localised prostate cancer and with high-volume disease as per CHAARTED?</td>
<td>74</td>
<td>24</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>In men with metastatic castration-sensitive/naive disease relapsing after prior treatment for localised prostate cancer with low-volume bone metastases as per CHAARTED criteria?</td>
<td>19</td>
<td>54</td>
<td>25</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>In men with castration-sensitive/naive N1 M0 prostate cancer?</td>
<td>4</td>
<td>25</td>
<td>71</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>In men with castration-sensitive/naive N0 M0 (nonmetastatic) prostate cancer with biochemical relapse?</td>
<td>0</td>
<td>10</td>
<td>90</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ADT = androgen deprivation therapy.

Gillessen et al. Eur Urol 2017

*Results of STAMPEDE/LATITUDE not published at time of consensus conference.
### Guidelines

<table>
<thead>
<tr>
<th></th>
<th>ESMO</th>
<th>NCCN</th>
<th>EAU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Docetaxel</strong></td>
<td>ADT plus docetaxel is recommended as first-line treatment of metastatic, hormone-naïve disease in men fit enough for chemotherapy</td>
<td>For M1: ADT + Docetaxel (patients with low-volume disease have less certain benefit from early docetaxel).</td>
<td>In newly diagnosed M1 patients, offer castration combined with docetaxel, provided patients are fit enough to receive chemotherapy.</td>
</tr>
<tr>
<td><strong>Abiraterone</strong></td>
<td>ADT plus abiraterone/prednisone may be considered as first-line treatment for metastatic, hormone-naive disease</td>
<td>For M1: ADT +Abiraterone</td>
<td>Offer castration combined with abiraterone acetate plus prednisone to all patients whose first presentation is M1 disease and who are fit enough for the regimen</td>
</tr>
</tbody>
</table>
## Chemo-hormonal Therapy

<table>
<thead>
<tr>
<th></th>
<th>GETUG-15 N=385</th>
<th>ECOG-ACRIN Group CHAARTED N=790</th>
<th>STAMPEDE N=1776</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADT</td>
<td>ADT+Doc</td>
<td>ADT</td>
</tr>
<tr>
<td>(mOS) in M1</td>
<td>48.6m</td>
<td>62.1m*</td>
<td>44m</td>
</tr>
<tr>
<td>mOS in High-Volume***</td>
<td>35.1m</td>
<td>39.8m**</td>
<td>32.2m****</td>
</tr>
<tr>
<td>mOS in M0 + M1 pts</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Prior Tx</td>
<td>0.9 (0.61; 1.33)</td>
<td>0.55 (0.23-1.31)</td>
<td>0.8 (0.26-2.48)</td>
</tr>
<tr>
<td>de novo M1</td>
<td>0.76 (0.63; 0.92)</td>
<td>0.66 (0.55-0.89)</td>
<td>0.78 (0.66-0.94)</td>
</tr>
</tbody>
</table>

* Statistically not significant: HR 0.88 (95% CI, 0.68-1.14)
** GETUG-15: 47% high-volume, statistically not significant: HR 0.78 (95% CI, 0.56-1.09)
*** High-volume: Visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis
**** In CHAARTED: 64% high-volume

---

Gravis Lancet Oncol 2013
Gravis Eur Urol 2016
Sweeney NEJM 2015
James Lancet 2015
Prostate Cancer: Castration sensitive/naïve

Localised Prostate Cancer

Advanced Prostate Cancer: Castration-sensitive/naïve

M0: By imaging no evidence of metastases

M1: Metastases detected by imaging

ADT: Androgen Deprivation Therapy

Advanced Prostate Cancer: Castration-resistant

M0

Salvage RT

PSA Rise

M1

1st-line

De Novo M1

2nd-line

Docetaxel

3rd-line

2nd-line

ADT +/− Abiraterone

3rd-line

ADT +/− Docetaxel

ADT: Androgen Deprivation Therapy

M0: By imaging no evidence of metastases

M1: Metastases detected by imaging
STAMPEDE Trial – MAMS design

Practise changing!

Expected soon!

Q2-2015: launch of metformin comparison
--- Trial recruits from population; powered in M1
STAMPEDE Addition of Zoledronic acid: Skeletal events
( Newly-diagnosed w/bone metastases)

HR=0.94
(95% CI: 0.76-1.16)
P=0.564

Excluding ONJ
SOC  0 reports
SOC + ZA  2 reports

No effect on survival

James ND et al, Lancet 2016
Randomized Controlled Trial of Early Zoledronic Acid in Men With Castration-Sensitive Prostate Cancer and Bone Metastases: Results of CALGB 90202 (Alliance)

Matthew R. Smith, Susan Halabi, Charles J. Ryan, Arif Hussain, Nicholas Vogelzang, Walter Stadler, Ralph J. Hauke, J. Paul Monk, Philip Saylor, Nirmala Bhoopalam, Fred Saad, Ben Sanford, W. Kevin Kelly, Michael Morris, and Eric J. Small

A

SRE-Free Survival (probability)

Placebo

ZA, one-sided stratified log-rank \( P = .385 \)

C

Overall Survival (probability)

Placebo

ZA, stratified log-rank \( P = .29 \)

No. at risk

Time From Randomization (months)

Placebo

ZA

## Future: Ongoing randomized de novo mCSPC trials: role of local therapy

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<td>STAMPEDE Arm H</td>
<td>MRC</td>
</tr>
<tr>
<td>ADT +/- abi (strat docet)</td>
<td>ADT + Prostate rad +/- abi (strat docet)</td>
<td>PEACE 1</td>
<td>Unicancer</td>
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<td>Best systemic therapy</td>
<td>BST + RP or RT</td>
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<td>Best systemic Rx</td>
<td>BST+ local Rx (some limited to oligometastases only)</td>
<td>TROMBONE RAMPP</td>
<td>UK, German, GETUG (planned), SWOG (planned), EORTC (planned)</td>
</tr>
</tbody>
</table>
Phase III randomized trials in metastatic castration-sensitive PCa (mCSPC)

<table>
<thead>
<tr>
<th></th>
<th>CHAARTED(^{1-2}) (N=790)</th>
<th>GETUG 15(^{2-4}) (N=385)</th>
<th>STAMPEDE(^{2, 5}) (N=2,962)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1 at diagnosis</td>
<td>72.8%</td>
<td>72%</td>
<td>61%</td>
</tr>
<tr>
<td>Stage at inclusion</td>
<td>M1</td>
<td>M1</td>
<td>M0 or M1</td>
</tr>
<tr>
<td>High tumor burden at inclusion</td>
<td>65%*</td>
<td>48%**</td>
<td>Not collected</td>
</tr>
<tr>
<td># DOC cycles</td>
<td>6</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Daily prednisone</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>DOC at progression in ADT arm</td>
<td>48%</td>
<td>85%</td>
<td>40%</td>
</tr>
<tr>
<td>mOS in M1 patients</td>
<td>44 vs 57.6 mo</td>
<td>48.6 vs 62.1 mo</td>
<td>45 vs 60 mo</td>
</tr>
</tbody>
</table>

* Tumor volume was a stratification factor in CHAARTED; **Tumor volume retrospectively analysed in GETUG 15


Adapted from Maria de Santis
GnRH antagonist (Degarelix) vs. agonist (Leuprolide)

Effect on hormonal flare

Klotz L et al, AUA Meeting, Orlando, May 2008

Courtesy Bertrand Tombal