Practice changing studies in Prostate Cancer in 2017-2019

Name
Ronald de Wit, ErasmusMC Cancer Institute, Rotterdam, the Netherlands

Sao Paulo, 23 March 2019
CONFLICT OF INTEREST DISCLOSURE

- Consultancy:
  Sanofi, Merck, Lilly, Bayer, Janssen, Roche, Clovis

- Speaker fees:
  Sanofi, Merck

- Institutional financial interests:
  Sanofi, Bayer
Most recent developments in the management of Prostate Cancer

- Cross resistance in mCRPC (AR targeted agents)
- Progression of events during treatment
- mCNPC; Abiraterone (2017-8) in addition to ADT
  in men presenting with HV and LV M1 disease
- mCNPC; 2018 STAMPEDE addition of Radiotherapy to ADT
  in men presenting with LV M1 disease
  2018 STAMPEDE posthoc analysis abiraterone LV M1 disease
- WGS data on 197 patients; mutational landscape
### Poor response to ABI in patients progressing on ENZA

<table>
<thead>
<tr>
<th>Author</th>
<th>Year published</th>
<th>N pts</th>
<th>Median ABI duration</th>
<th>↓ PSA ≥50%</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No prior ENZA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Bono et al.¹ (COU-AA-302)</td>
<td>2011</td>
<td>797</td>
<td>8 mo</td>
<td>29%</td>
<td>5.6 mo</td>
</tr>
<tr>
<td><strong>ENZA → ABI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loriot et al.²</td>
<td>2013</td>
<td>38</td>
<td>3 mo</td>
<td>8%</td>
<td>2.7 mo</td>
</tr>
<tr>
<td>Noonan et al.³</td>
<td>2013</td>
<td>30</td>
<td>3 mo</td>
<td>3%</td>
<td>3.6 mo</td>
</tr>
</tbody>
</table>

## Poor response to ENZA in patients progressing on ABI

<table>
<thead>
<tr>
<th>Author</th>
<th>Year published</th>
<th>N pts</th>
<th>Median ENZ duration</th>
<th>↓ PSA ≥50%</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No prior ABI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scher et al.¹</td>
<td>2012</td>
<td>800</td>
<td>8.3 mo</td>
<td>54%</td>
<td>8.3 mo</td>
</tr>
<tr>
<td><strong>ABI → ENZ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schrader et al.²</td>
<td>2013</td>
<td>35</td>
<td>4.9 mo</td>
<td>29%</td>
<td>-</td>
</tr>
<tr>
<td>Thomsen et al.³</td>
<td>2014</td>
<td>24</td>
<td>4.0 mo</td>
<td>17%</td>
<td>2.8 mo</td>
</tr>
<tr>
<td>Badrising et al.⁴</td>
<td>2014</td>
<td>61</td>
<td>3.0 mo</td>
<td>21%</td>
<td>2.8 mo</td>
</tr>
<tr>
<td>Bianchini et al.⁵</td>
<td>2014</td>
<td>39</td>
<td>2.9 mo</td>
<td>23%</td>
<td>2.8 mo</td>
</tr>
<tr>
<td>Schmid et al.⁶</td>
<td>2014</td>
<td>35</td>
<td>2.8 mo</td>
<td>10%</td>
<td>3.1 mo</td>
</tr>
<tr>
<td>Azad et al.⁷</td>
<td>2015</td>
<td>68</td>
<td>4.1 mo</td>
<td>22%</td>
<td>4.6 mo</td>
</tr>
<tr>
<td>Brasso et al.⁸</td>
<td>2014</td>
<td>137</td>
<td>3.2 mo</td>
<td>18%</td>
<td>-</td>
</tr>
<tr>
<td>Joshua et al.⁹</td>
<td>2015</td>
<td>507</td>
<td>2.6 mo</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Cross-resistance between ART

- **PLATO** - Prospective, phase IV, double-blind, Pbo-controlled trial in 251 chemo-naïve mCRPC with PSA response to ENZA >3 months
- Randomized at PSA progression to ENZA+ABI/P vs Pbo+ABI/P
- PFS* (primary endpoint): 5.7 vs 5.6 months, \( P=0.22 \)

*PFS: progression free survival (radiological progression or unequivocal clinical progression)
Is a taxane in between the cross-over reversing cross-resistance to ART?

Best PSA response

302 patients with chemonaive mCRPC treated with new AR-targeted agents (ART), ABI or ENZA

mCRPC with primary resistance to an AR-targeted agent (progression ≤ 12 months on ABI or ENZA) before or after Docetaxel

n=234

Stratification factors: ECOG PS (0/1 vs 2), time to progression (≤6 vs 6–12 mo), timing of AR-targeted agent (before vs after DOC)

Sponsor: Sanofi

Swith to another AR-targeted agent (ABI or ENZA depending of first therapy)

n=117

Primary endpoint: radiographic PFS

Secondary endpoints: PSA response, objective tumor response, pain, QoL, OS, biomarkers

Enrollment completed nov 2018

NCT02485691. ClinicalTrials.gov.
Sequence of progression events

- Clinical Sequence of events is known in men treated with ART
- Influence of type of progression on overall survival is poorly documented

Of 265 chemonaive mCRPC patients with radiological progression and evaluable PSA levels on enzalutamide, 65 (24.4%) had a non rising PSA

Regular imaging is needed +++
Post-hoc analysis of VENICE and TAX327

Primary objective: Explore the prognostic impact of type of progression at initiation of first-line chemotherapy on overall survival

- **VENICE** - training dataset
  - $n = 1224$
  - 1st line DOC + aflibercept or placebo

- **TAX-327** - validation dataset
  - $n = 1006$
  - 1st line 3w DOC vs 1w DOC vs mitoxantrone

Robbrecht et al, ESMO 2018 poster
Post-hoc analysis of VENICE and TAX327

Type of progression at baseline:

**Group 1**  PSA progression only

**Group 2**  Radiological progression (+/- PSA progression)

**Group 3**  Clinical progression based on pain
             (+/- PSA progression, +/- radiological progression)
Results

Median OS in 3w DOC arm: 29.4, 24.4 and 15.5 months in G1, G2 and G3 resp. (p < 0.001)
Median OS in 3w DOC arm:
Not reached, 21.8 and 15.5 months in G1, G2 and G3, resp. (p<0.001)
Sequence of progression events during docetaxel treatment

PSA progression first event in the major part of study population (57%)

~50% clinical or radiological progression first event during treatment, irrespective of baseline type of progression

~ 30% clinical progression preceding radiological progression

No association between type of progression at baseline and a specific sequence of progression events during treatment

> Do not lose the window of opportunity for initiating effective treatment (s)
Adding docetaxel to ADT in mCNPC

CHAARTED (M1)
Median 57.6 mos
ADT+DOC

STAMPEDE (M0/M1)
Median 44.0 mos
ADT

HR=0.61
(95% CI: 0.47-0.80)

Phase III randomized trial in 790 men with metastatic hormone-naïve PCa

Phase III randomized trial in M0/M1 patients with hormone-naïve PCa

DOC: Docetaxel

2James N et al. Lancet. 2015
CHAARTED Update ESMO 2016

HV (4 bone/visc mets)    LV
ESMO 2016; CHAARTED QL ADT +/- DOC

FACT-P high volume

FACT-P low volume
CHAARTED / STAMPEDE

- CHAARTED mature results ESMO 2016
  Benefit only in high-volume patients (4 bone mets/visc m)
  HR in low-volume 1.04

- STAMPEDE benefit in M1 pts, but % of high vs low volume
  pts not reported; is benefit dictated by majority of high-volume
  patients? (85% had bonemets)

- By conventional imaging (bonescan/CT scan)!!
LATITUDE ASCO 2017

LATITUDE: A phase 3, double-blind, randomized trial of androgen deprivation therapy with abiraterone acetate plus prednisone or placebos in newly diagnosed high-risk metastatic hormone-naïve prostate cancer patients

Karim Fizazi,1 NamPhuong Tran,2 Luis Fein,3 Nobuaki Matsubara,4 Alfredo Rodriguez-Antolin,5 Boris Y. Alekseev,6 Mustafa Özgüroğlu,7 Dingwei Ye,8 Susan Feyerabend,9 Andrew Protheroe,10 Peter De Porre,11 Thian Kheoh,12 Youn C. Park,13 Mary B. Todd,14 Kim N. Chi,15 on behalf of the LATITUDE Investigators

1Gustave Roussy, University of Paris Sud, Villejuif, France; 2Janssen Research & Development, Los Angeles, CA; 3Instituto de Oncologia de Rosário, Rosário, Argentina; 4National Cancer Center Hospital East, Chiba, Japan; 512 de Octubre University Hospital, Madrid, Spain; 6P.A. Hertsen Moscow Cancer Research Institute, Moscow, Russian Federation; 7Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey; 8Fudan University Shanghai Cancer Center, China; 9Studienpraxis Urologie, Nürtingen, Germany; 10Oxford University Hospitals Foundation NHS Trust, Oxford, UK; 11Janssen Research & Development, Beerse, Belgium; 12Janssen Research & Development, San Diego, CA; 13Janssen Research & Development, Raritan, NJ; 14Janssen Global Services, Raritan, NJ; 15BC Cancer Agency, Vancouver, BC, Canada
Study design of LATITUDE

Patients
- Newly diagnosed adult men with high-risk mHNPC

Stratification factors
- 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

- High-risk defined as meeting at least 2 of 3 high-risk criteria:
- Gleason score of ≥ 8
- Presence of ≥ 3 lesions on bone scan
- Presence of measurable visceral lesion

Presented by: Karim Fizazi
LATITUDE: Co-primary End Points

38% Risk Reduction for Death

53% Risk Reduction for rPFS

Concern within design: double-blind study !! (abi vs no abi) >

<table>
<thead>
<tr>
<th>Patients eligible*</th>
<th>ADT + AA + P (n = 597)</th>
<th>ADT + placebos (n = 602)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
</tbody>
</table>

- Patients eligible: n = 314 (53%)
- Patients who received life-prolonging therapy:
  - Docetaxel: 106 (34)
  - Enzalutamide: 30 (10)
  - AA-P: 10 (3)
  - Cabazitaxel: 11 (4)
  - Radium-223: 11 (4)
  - 246 (52)
  - 187 (40)
  - 76 (16)
  - 53 (11)
  - 30 (6)
  - 27 (6)

*Patients who discontinued treatment and were eligible for subsequent therapy.
STAMPEDE – Abi+ADT vs ADT in newly diagnosed locally advanced or metastatic PC ASCO 2017

Phase 3 randomized trial in newly diagnosed M0/M1 prostate cancer. Primary end-point: OS

James ND et al. NEJM 2017; 377: 338-51
STAMPEDE ( +/- abi/pred) ASCO 2017
Treatment started since first progression

<table>
<thead>
<tr>
<th>Treatment started since first progression</th>
<th>A SOC</th>
<th>G SOC+AAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized</td>
<td>957</td>
<td>960</td>
</tr>
<tr>
<td>Patients with progression</td>
<td>535 (56%)</td>
<td>248 (26%)</td>
</tr>
<tr>
<td>Reported new treatment</td>
<td>477 (89%)</td>
<td>196 (79%)</td>
</tr>
<tr>
<td>Reported “life-prolonging” treatment</td>
<td>310 (58%)</td>
<td>131 (53%)</td>
</tr>
<tr>
<td></td>
<td>200 (37%)</td>
<td>115 (46%)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>138 (26%)</td>
<td>25 (10%)</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>120 (22%)</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Abiraterone acetate</td>
<td>28 (5%)</td>
<td>15 (6%)</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>24 (4%)</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>Radium-223</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SOC = standard-of-care (ADT)
AAP = abiraterone acetate + prednisolone

James et al NEJM 2017
Conclusions

- Docetaxel/pred 18 weeks; brief exposure
- QL in CHAARTED - LV at 9 months identical in both arms
- CHAARTED and STAMPEDE open label, choice subsequent lines not biased
- Strongest evidence for High Volume

- Abiraterone/pred (5mg) 3 years;
- 3 years extra visits, prednisone adverse effects
- Evidence “HV” by LATITUDE criteria (bone m/visc m Gl 9/10; 2 of 3)
- LATITUDE tested “early abi vs no abi” (rather than abi at time of CRPC);
  
  13% of pts exposed to abi/enza at time of interim analysis and report
- Expensive ( +/- 10 fold as compared with docetaxel)
## Cost of Treatment: Between ABIRATERONE or Docetaxel in mHSPC: Impact on Economic Health (Oudard ESMO Discussant 2017)

Computed for Georges Pompidou Med center, Paris, France

<table>
<thead>
<tr>
<th></th>
<th>Abiraterone(^{1,2})</th>
<th>Docetaxel(^{3,4})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Price of drugs</td>
<td>3071 € (one month)</td>
<td>13.80 € (for 160 mg)</td>
</tr>
<tr>
<td>Price G-CSF for 3-5 days</td>
<td>NA</td>
<td>97 € (per cycle)</td>
</tr>
<tr>
<td>Cost for daily hospital</td>
<td>NA</td>
<td>600 €</td>
</tr>
<tr>
<td>Cost for one cycle</td>
<td>NA</td>
<td>710.8 €</td>
</tr>
<tr>
<td>Average duration of TT</td>
<td>33 months</td>
<td>18 weeks (6 cycles)</td>
</tr>
<tr>
<td>Cost of hospitalization if case of toxicity (3 nights)</td>
<td>NA</td>
<td>2000 € per night</td>
</tr>
<tr>
<td>Total cost of care</td>
<td>101,355 €</td>
<td>10,265 €</td>
</tr>
</tbody>
</table>

2 cohorts in STAMPEDE, ESMO 2017

Adding abiraterone acetate plus prednisolone (AAP) or docetaxel for patients (pts) with high-risk prostate cancer (PCa) starting long-term androgen deprivation therapy (ADT): directly randomised data from STAMPEDE

Matthew Sydes
Statistician, Reader in Clinical Trials
MRC Clinical Trials Unit at UCL
Institute of Clinical Trials and Methodology
UCL, London, UK

Co-authors
Malcolm D Mason, Melissa R Spears, Noel W Clarke, David P Dearnaley, Alastair WS Ritchie, J Martin Russell, Clare Gilson, Rob Jones, Johann S de Bono, Silke Gillessen, Robin Millman, Shaun Tolan, John Wagstaff, Simon Chowdhury, Jason Lester, Denise Sheehan, Joanna Gale, Mahesh KB Parmar and Nicholas D James and the STAMPEDE Investigators

Trial registration: NCT00268476
STAMPEDE: SOC+DocP vs SOC

STAMPEDE: Docetaxel comparison

Recruitment: Oct 2005 to Mar 2013
Patients: 1184 SOC
592 SOC+DocP

Reported: ASCO 2015
Published: Lancet 2016
Allocation ratio: 2:1

HR (95% CI) 0.78 (0.66, 0.93)
P-value 0.006
**STAMPEDE: SOC+AAP vs SOC**

**Recruitment:** Nov-2011 to Jan-2014  
**Patients:** 957 SOC, 960 SOC+AAP

**Reported:** ASCO 2017  
**Published:** NEJM 2017  
**Allocation ratio:** 1:1

**HR (95%CI):** 0.63 (0.52, 0.76)  
**P-value:** 0.00000115
AAP and DocP may work in quite different ways

Evidence about whether to give both is pending

566 patients randomised contemporaneously to either research arm
Overall survival
(primary outcome measure)

HR (95%CI)  P-val  Interact\textsuperscript{n} test

All  1.16 (0.82 to 1.65)  0.40
M0   1.51 (0.58 to 3.93) 0.40
M1   1.13 (0.77 to 1.66) 0.53

Interact\textsuperscript{n} test: 0.69

Key:
HR<1 favours SOC+AAP
HR>1 favours SOC+DocP

Interact\textsuperscript{n} = test for interaction (heterogeneity of treatment effect)
## Cause-specific survival

<table>
<thead>
<tr>
<th>Status</th>
<th>SOC+DocP N</th>
<th>SOC+DocP %</th>
<th>SOC+AAP N</th>
<th>SOC+AAP %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>145</td>
<td>77%</td>
<td>272</td>
<td>72%</td>
</tr>
<tr>
<td>Dead</td>
<td>44</td>
<td>23%</td>
<td>105</td>
<td>28%</td>
</tr>
</tbody>
</table>

**PCa Death**

- SOC+DocP: 40 (21%)
- SOC+AAP: 86 (23%)

**Other cause**

- SOC+DocP: 4 (2%)
- SOC+AAP: 19 (5%)

Sub-HR (95%CI) | P-val  
--- | ---  
All | 1.02 (0.70 to 1.49) | 0.92 |

Competing risks approach

SOC+DocP death: 91% PCa and 9% other  
SOC+AAP deaths: 82% PCa and 18% other
# Adverse events – worst toxicity ever

## Safety population

- Patients included in adverse event analysis: 172 (91%) for SOC+DocP, 373 (>99%) for SOC+AAP
- Grade 1+ AE: 172 (100%) for SOC+DocP, 370 (99%) for SOC+AAP
- Grade 3+ AE: 86 (50%) for SOC+DocP, 180 (48%) for SOC+AAP

## Grade 3+ AEs by category (incl. expected AEs)

<table>
<thead>
<tr>
<th>Category</th>
<th>SOC+DocP</th>
<th>SOC+AAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine disorder (incl. hot flashes, impotence)</td>
<td>15 (9%)</td>
<td>49 (13%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>29 (17%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22 (13%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Musculoskeletal disorder:</td>
<td>9 (5%)</td>
<td>33 (9%)</td>
</tr>
<tr>
<td>Cardiovascular disorder (incl. hypertension, MI, cardiac dysrhythmia):</td>
<td>6 (3%)</td>
<td>32 (9%)</td>
</tr>
<tr>
<td>Gastrointestinal disorder:</td>
<td>9 (5%)</td>
<td>28 (8%)</td>
</tr>
<tr>
<td>Hepatic disorder (incl. increased AST, increased ALT):</td>
<td>1 (1%)</td>
<td>32 (9%)</td>
</tr>
<tr>
<td>General disorder (incl. fatigue, oedema):</td>
<td>18 (10%)</td>
<td>21 (6%)</td>
</tr>
<tr>
<td>Respiratory disorder (incl. breathlessness):</td>
<td>12 (7%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>5 (3%)</td>
<td>20 (5%)</td>
</tr>
<tr>
<td>Lab abnormalities (incl. hypokalaemia):</td>
<td>9 (5%)</td>
<td>11 (3%)</td>
</tr>
</tbody>
</table>
Role of Abiraterone Acetate + Prednisolone + ADT in High and Low Risk Metastatic Hormone Naïve Prostate Cancer

Mr Alex Hoyle MBChB MRCS
(Christie GenitoUrinary Research Group Fellow, UK)

Adnan Ali, Nick James, Chris Parker, Adrian Cook, Gert Attard, Simon Chowdhury, Bill Cross, David Dearnaley, Johann de Bono, Clare Gilson, Silke Gillessen, Rob Jones, David Matheson, Malcolm Mason, Alastair Ritchie, Martin Russell, Max Parmar, Matt Sydes, Noel Clarke;

for the STAMPEDE trial
HYPOTHESIS AND METHODS

Hypothesis

Do "low risk" mHNPC patients benefit from Abiraterone Acetate + Prednisolone + ADT?

Methods

1. Retrospectively stratified M1 STAMPEDE “Abiraterone comparison” patients into high/low risk, blinded to treatment arm
   - Primary stratification as per LATITUDE criteria
   - Exploratory stratification as per CHAARTED criteria

2. Analyse “risk” and “volume” based data against multiple measured endpoints
# SUBGROUP RISK/VOLUME DISTRIBUTION

<table>
<thead>
<tr>
<th>Population</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>LATITUDE Low</td>
<td>428</td>
<td>47.5</td>
</tr>
<tr>
<td>LATITUDE High</td>
<td>473</td>
<td>52.5</td>
</tr>
<tr>
<td>CHAARTED Low</td>
<td>402</td>
<td>44.6</td>
</tr>
<tr>
<td>CHAARTED High</td>
<td>499</td>
<td>55.4</td>
</tr>
</tbody>
</table>

## Individual

<table>
<thead>
<tr>
<th>CHAARTED</th>
<th>LATITUDE Low</th>
<th>LATITUDE High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>333 (37%)</td>
<td>69 (7.7%)</td>
</tr>
<tr>
<td>High</td>
<td>95 (10.5%)</td>
<td>404 (44.8%)</td>
</tr>
</tbody>
</table>

**18.2%**
RESULTS: LATITUDE RISK STRATIFICATION

<table>
<thead>
<tr>
<th></th>
<th>ADT alone</th>
<th>AAP</th>
<th>Adjusted HR* (95%CI)</th>
<th>p-value</th>
<th>Interaction by metastatic volume p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of events/No. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>195/452</td>
<td>135/449</td>
<td>0.609 (0.488-0.789)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>59/220</td>
<td>41/208</td>
<td>0.657 (0.438-0.983)</td>
<td>0.041</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>136/232</td>
<td>94/241</td>
<td>0.536 (0.411-0.699)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Failure free survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>354/452</td>
<td>191/449</td>
<td>0.316 (0.264-0.378)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>152/220</td>
<td>56/208</td>
<td>0.238 (0.174-0.325)</td>
<td>&lt;0.001</td>
<td>0.294</td>
</tr>
<tr>
<td>High risk</td>
<td>202/232</td>
<td>135/241</td>
<td>0.313 (0.250-0.392)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Skeletal related events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>164/452</td>
<td>93/449</td>
<td>0.467 (0.362-0.602)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>49/220</td>
<td>17/208</td>
<td>0.311 (0.179-0.543)</td>
<td>&lt;0.001</td>
<td>0.207</td>
</tr>
<tr>
<td>High risk</td>
<td>115/232</td>
<td>76/241</td>
<td>0.477 (0.356-0.639)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Progression free survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>267/452</td>
<td>158/449</td>
<td>0.446 (0.366-0.544)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>101/220</td>
<td>41/208</td>
<td>0.334 (0.232-0.482)</td>
<td>&lt;0.001</td>
<td>0.159</td>
</tr>
<tr>
<td>High risk</td>
<td>166/232</td>
<td>117/241</td>
<td>0.463 (0.364-0.588)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Prostate cancer specific death*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>172/452</td>
<td>114/449</td>
<td>0.587 (0.462-0.746)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>49/220</td>
<td>27/208</td>
<td>0.511 (0.312-0.836)</td>
<td>0.008</td>
<td>0.728</td>
</tr>
<tr>
<td>High risk</td>
<td>123/232</td>
<td>87/241</td>
<td>0.570 (0.432-0.754)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
CHAARTED VOLUME CRITERIA

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>ADT alone</th>
<th>AAP</th>
<th>Adjusted HR (95%CI)</th>
<th>p-value</th>
<th>Interaction by metastatic volume p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>195/452</td>
<td>135/449</td>
<td>0.609 (0.488-0.789)</td>
<td>&lt;0.001</td>
<td>0.771</td>
</tr>
<tr>
<td>Low volume</td>
<td>53/196</td>
<td>39/206</td>
<td>0.637 (0.420-0.966)</td>
<td>0.034</td>
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</tr>
<tr>
<td>High volume</td>
<td>142/256</td>
<td>96/243</td>
<td>0.601 (0.463-0.779)</td>
<td>&lt;0.001</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Failure free survival</th>
<th>ADT alone</th>
<th>AAP</th>
<th>Adjusted HR (95%CI)</th>
<th>p-value</th>
<th>Interaction by metastatic volume p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>354/452</td>
<td>191/449</td>
<td>0.316 (0.264-0.378)</td>
<td>&lt;0.001</td>
<td>0.472</td>
</tr>
<tr>
<td>Low volume</td>
<td>133/196</td>
<td>57/206</td>
<td>0.259 (0.189-0.356)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>High volume</td>
<td>221/256</td>
<td>134/243</td>
<td>0.327 (0.263-0.408)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skeletal related events</th>
<th>ADT alone</th>
<th>AAP</th>
<th>Adjusted HR (95%CI)</th>
<th>p-value</th>
<th>Interaction by metastatic volume p-value</th>
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</thead>
<tbody>
<tr>
<td>All patients</td>
<td>164/452</td>
<td>93/449</td>
<td>0.467 (0.362-0.602)</td>
<td>&lt;0.001</td>
<td>0.981</td>
</tr>
<tr>
<td>Low volume</td>
<td>46/196</td>
<td>25/206</td>
<td>0.459 (0.282-0.749)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>High volume</td>
<td>118/256</td>
<td>68/243</td>
<td>0.468 (0.347-0.632)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression free survival</th>
<th>ADT alone</th>
<th>AAP</th>
<th>Adjusted HR (95%CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>All patients</td>
<td>267/452</td>
<td>158/449</td>
<td>0.446 (0.366-0.544)</td>
<td>&lt;0.001</td>
<td>0.670</td>
</tr>
<tr>
<td>Low volume</td>
<td>86/196</td>
<td>45/206</td>
<td>0.401 (0.279-0.577)</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>High volume</td>
<td>181/256</td>
<td>113/243</td>
<td>0.457 (0.360-0.579)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prostate cancer specific death*</th>
<th>ADT alone</th>
<th>AAP</th>
<th>Adjusted HR (95%CI)</th>
<th>p-value</th>
<th>Interaction by metastatic volume p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>172/452</td>
<td>114/449</td>
<td>0.587 (0.462-0.746)</td>
<td>&lt;0.001</td>
<td>0.740</td>
</tr>
<tr>
<td>Low volume</td>
<td>43/196</td>
<td>31/206</td>
<td>0.627 (0.388-1.013)</td>
<td>0.057</td>
<td></td>
</tr>
<tr>
<td>High volume</td>
<td>129/256</td>
<td>83/243</td>
<td>0.579 (0.439-0.764)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions on STAMPEDE posthoc ESMO 2018

- Abi/pred provides OS benefit in LV/ LATITUDE 1 factor population
- **Magnitude of benefit is smaller**
- Risk/benefit concern with use in patients with *cardiovasc morbidity*
- Regrettably no post-hoc analysis on docetaxel in STAMPEDE HV/LV

- Cost will remain an issue at least until 2022
- 3 years abi/pred 10 fold more expensive (computed for France)
STAMPEDE (addition of RT, reported by Chris Parker ESMO 2018)

Men with newly diagnosed metastatic prostate cancer

1:1

ADT +/- docetaxel (SOC)

ADT +/- docetaxel (SOC) + prostate radiotherapy

36Gy/6 fractions/6 weeks or 55Gy/20 fractions/4 weeks

Schedule nominated before randomisation

Stratification variables

Age (<70 vs ≥70 years), nodal involvement (N0 vs N1 vs Nx), randomising site, WHO performance status (0 vs 1 or 2), type of ADT, aspirin or NSAID use, docetaxel use
Overall survival: subgroup analysis by radiotherapy schedule

No evidence that effect size differs by RT schedule (p=0.27)
### Overall survival: subgroup analysis by metastatic disease burden

<table>
<thead>
<tr>
<th>Subgroup (CHAAART volume classification)</th>
<th>High burden</th>
<th>Low burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (SOC+RT vs SOC-only)</td>
<td>0.92 (0.80, 1.06)</td>
<td>0.92 (0.80, 1.06)</td>
</tr>
</tbody>
</table>

Clear evidence that effect size does differ by disease burden ($p=0.0098$)
Overall survival: metastatic burden subgroup analysis

**Low burden**

- **SOC+RT** by Kaplan Meier
- **SOC** by Kaplan Meier
- **SOC+RT** by flexible parametric model
- **SOC** by flexible parametric model

**High burden**

- **SOC+RT** by Kaplan Meier
- **SOC** by Kaplan Meier
- **SOC+RT** by flexible parametric model
- **SOC** by flexible parametric model

**HR:** 0.68 (95% CI 0.52-0.90); p=0.007

**3 year OS (%):**
- **SOC** = 73%
- **SOC+RT** = 81%

**HR:** 1.07 (95% CI 0.90-1.28); p=0.420

**3 year OS (%):**
- **SOC** = 54%
- **SOC+RT** = 53%
Conclusions on LATITUDE / STAMPEDE

- LATITUDE provides similar OS benefit as CHAARTED
  inferior cross-over (early abi vs no abi)
- More/longer lasting side effects
- Evidence strongest in “high-volume” (HV) patients
- ESMO2018 STAMPEDE post hoc analysis;
  Supportive data for benefit abi also in LV setting, benefit modest, may be nullified in case of cardiovasc co-morbidity
- ESMO2018 STAMPEDE benefit Radiotherapy on prostate tumor OS benefit in LV metastatic disease;
  \[ \text{HR: 0.68 (95\% CI 0.52-0.90); p=0.007} \]
  \[ \text{3 year OS (\%): SOC = 73\% SOC+RT = 81\%} \]
In 2019 Multiple Choices and Sequences

- mHSPC early taxane /late taxane /early abi/late abi
- mCRPC abi/enza (ART) predoce/ postdoce/pre/postcaba
- mCRPC Radium 223 post ART pre/ post taxane

- >Even after 4 lines many mCRPC patients opt to receive systemic therapies
- >New avenue Precision Medicine;
  - Molecular targeted therapies
  - Immunotherapy
Genomic data on prostate cancer

Cell, Volume 161, Issue 5, 21 May 2015, Pages 1215–1228
CPCT: Dutch Collab. study WGS 197pts
Future studies and hopefully treatment will be increasingly biology directed!

Remainder at this time: ART and taxanes
Tumor mutational load varies between CRPC subtypes
• 7.7% have high TMB (>10 mutations/Mb), of which 6.7% have a high TMB/MSI signature and 1% with BRCA inactivation
• 11.7% of patients have BRCAness signature (BRCA2 biallelic inactivation)
• 6.7% of patients have CDK12 biallelic inactivation and focal tandem duplication signature

WGS identifies hTMB, BRCAness and focal tandem duplications in ~25% of patients with mCRPC. Patients with MSI and BRCAness have significant higher TMB compared to those with CDK12 biallelic inactivation and other molecular signatures.
Recent developments in Management of mCRPC

- 15 years of progress
- Many new agents, some remaining questions about sequence
- New data on progression events during treatment (imaging!)
- New data on management mCNPC
- New avenues that need to be tested in well designed Phase III trials
- Future studies will be increasingly biology directed