ESMO SUMMIT AFRICA 2020

15 years of progress in mCRPC; New Trial data in 2019

Ronald de Wit, Erasmus MC Cancer Institute
Rotterdam, The Netherlands
CONFLICT OF INTEREST
DISCLOSURE

• Consultancy:
  Sanofi, Merck, Bayer, Janssen, Roche, Clovis, Astellas

• Speaker fees:
  Sanofi, Merck

• Institutional financial interests:
  Sanofi, Bayer
Current options in metastatic PCa

mHSPC

mCRPC 1st line

mCRPC 2nd line

ADT

DOC (not licenced)

ABI

RT to prostate (low volume)

DOC (if no prior use)

CABA (if prior DOC)

ABI or ENZA (if no prior ABI)

Sipuleucel-T (not in Europe)

CABA (if prior DOC)

ABI or ENZA (if no prior use)

Radium-223 (after 2 lines of therapy)

Hormonal therapy

Vaccine

Chemotherapy

RT/Radioisotope

ABI: abiraterone acetate; CABA: cabazitaxel; DOC: docetaxel; ENZA: enzalutamide; mHSPC: metastatic hormone-sensitive prostate cancer; mCRPC: metastatic castration-resistant prostate cancer; RT: radiotherapy

Alison Birtle
Combination of ADT and taxanes in mHSPC setting

**CHAARTED (M1)**

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

**STAMPEDE (M0/M1)**

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

DOC: Docetaxel

2James N et al. Lancet. 2015
> Benefit of addition of docetaxel only in high volume disease
ADT +/- abiraterone (AA) + P in high risk mHSPC; LATITUDE

Bias by double blind design that was continued at mCRPC status; <20% of pts received ARTA at the time of CRPC (pts were denied life extending therapy)

LATITUDE tested early abiraterone vs no abiraterone

ASCO 2017, Fizazi et al, NEJM 2017
ADT +/- apalutamide in mHSPC, ASCO 2019

Similar concern with Double-blind design as with LATITUDE (minority received ARTA at time of CRPC)

Chi et al, NEJM 2019
ADT +/- enzalutamide in mHSPC (Enzamet ASCO 2019)

Enza did not appear to add in patients receiving ADT plus 6cy docetaxel

Davis et al NEJM 2019
STAMPEDE – ABI+ADT vs ADT alone 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

ASCO 2017 James ND et al. NEJM 2017; 377: 338-51
Which drug to choose?
2 cohorts in STAMPEDE

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

ESMO 2017, Matt Sydes
STAMPEDE: SOC+AAP vs SOC+DocP

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.

Recruitment: Nov-2011 to Mar-2013

Patients: 189 SOC+DocP, 377 SOC+AAP

Reported: ESMO 2017

Published: (paper in development)
STAMPEDE: SOC+AAP vs SOC+DocP

Summary of end-points

Summary

Head-to-head data in 566 pts (Nov-2011 to Mar-2013)

- Strong evidence favouring AAP
- Weak evidence favouring AAP
- No good evidence of a difference

Toxicity profiles quite different and well known
### STAMPEDE Adverse events – worst toxicity ever

<table>
<thead>
<tr>
<th>Safety population</th>
<th>SOC+DocP</th>
<th>SOC+AAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients included in adverse event analysis</td>
<td>172 (91%)</td>
<td>373 (&gt;99%)</td>
</tr>
<tr>
<td>Grade 1+ AE</td>
<td>172 (100%)</td>
<td>370 (99%)</td>
</tr>
<tr>
<td>Grade 3+ AE</td>
<td>86 (50%)</td>
<td>180 (48%)</td>
</tr>
</tbody>
</table>

#### 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 (<em>incl. hot flashes, impotence</em>)</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 (<em>incl. hypertension, MI, cardiac dysrhythmia</em>)</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 (<em>incl. increased AST, increased ALT</em>)</td>
<td>1 (1%)</td>
<td>32 (9%)</td>
</tr>
<tr>
<td>General disorder (<em>incl. fatigue, oedema</em>)</td>
<td>18 (10%)</td>
<td>21 (6%)</td>
</tr>
<tr>
<td>Respiratory disorder (<em>incl. breathlessness</em>)</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 (<em>incl. hypokalaemia</em>)</td>
<td>9 (5%)</td>
<td>11 (3%)</td>
</tr>
</tbody>
</table>
mHSPC phase 3 trials Conclusions 2018

- Docetaxel/pred 18 weeks; brief exposure
- CHAARTED and STAMPEDE open label, subsequent lines not biased
- Strongest evidence for High Volume

- Abiraterone/pred(5mg) 3 years;
- 3 y extra visits, cardiovasc morbidity, prednison adverse effects
- Evidence “HV” by LATITUDE criteria (bone m/visc m GI 9-10; 2 of 3)
- LATITUDE tested “early abi vs no abi” (rather than abi at time of CRPC); only 13% of pts exposed to abi/enza at time of report

- Expensive (+/- 10 fold as compared with docetaxel)
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
STAMPEDE (ADT+ABI/P in M1) in low and high risk PCa as per LATITUDE criteria

• STAMPEDE post-hoc analysis blinded to treatment arm
• M1 HSPC patients in ABI arm retrospectively classified as:
  • **High risk: at least 2 criteria**
    • Gleason ≥8
    • ≥3 bone mets
    • Visceral mets
  • **Low risk: 1 criterion only**

STAMPEDE\(^1\)

**High-risk**
(N=428)
Median FU: 41.5 mths

STAMPEDE\(^1\)

**Low-risk**
(N=473)
Median FU: 41.5 mths

FU: follow-up; mets: metastases

STAMPEDE (addition of RT, ESMO 2018)

Men with newly diagnosed metastatic prostate cancer

ADT +/- docetaxel (SOC) 1:1 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: metastatic burden subgroup analysis

Low burden

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

High burden

HR: 1.07 (95% CI 0.90-1.28); p=0.420
3 year OS (%): SOC = 54%
SOC+RT = 53%
Conclusions on STAMPEDE 2018 RESULTS

- ESMO 2018 STAMPEDE posthoc analysis;
  Supportive data for benefit also in LV setting,
  BUT benefit modest, may be nullified in case of cardiovascular co-morbidity

- ESMO 2018 STAMPEDE benefit Radiotherapy on prostate tumor
  OS benefit in LV metastatic disease;
  \[ HR: 0.68 \ (95\% \ CI \ 0.52-0.90); \ p=0.007 \]
  \[ 3 \text{ year OS (\%)}: \ SOC = 73\% \ SOC+RT = 81\% \]
ADDITION OF DOCETAXEL TO HORMONAL THERAPY IN LOW AND HIGH BURDEN METASTATIC HORMONE SENSITIVE PATIENTS: LONG TERM SURVIVAL RESULTS FROM THE STAMPEDE TRIAL

Presenter: Professor Nick James

Noel W. Clarke, Adnan Ali, Fiona Ingleby, Alex Hoyle, Claire Amos, Gerhardt Attard, Simon Chowdhury, David Dearnaley, Hassan Douis, Silke Gillessen, Rob Jones, Zafar Malik, Malcolm Mason, Robin Millman, Chris Parker, Hannah Rush, Aurelius Omlin, Matthew Sydes, Mahesh Parmar, Nick James on behalf of the STAMPEDE trial
Overall Survival: All Patients

Low Burden

HR 0.76
95% CI 0.54 – 1.07
P = 0.107
Non-PH 0.809

5-yr survival:
A 57%
C 72%

High Burden

HR 0.81
95% CI 0.64 – 1.02
P = 0.064
Non-PH 0.251

5-yr survival:
A 24%
C 34%
Conclusions (Nick James ESMO 2019)

• This analysis does not support the presence of a volume effect on docetaxel effect in men with newly-diagnosed metastatic prostate cancer
• Metastatic burden is however prognostic
• STAMPEDE has almost exclusively newly diagnosed patients
  • Better power to assess effects as homogenous group
  • Suggests differences with GETUG-15 + CHAARTED may relate to high proportions of relapsed patients in low metastatic burden groups in both trials
• Absolute gains in 5 year survivals:
  • 57➔72% for low metastatic burden
  • 24➔34% for high metastatic burden respectively
2020 Conclusions on LATITUDE / STAMPEDE

- LATITUDE and CHAARTED provide similar OS benefit
- Evidence strongest in “high-volume” (HV) patients
- ESMO2018 STAMPEDE posthoc analysis;
  Supportive data for use of abi in all pts with newly diagnosed mHSPC, but excess non-prostate cancer related death; concern with use in pts with cardiovascular co-morbidity
- ESMO 2019 STAMPEDE posthoc docetaxel analysis;
  also benefit in LV: HR 0.76 95% CI 0.54 – 1.07 (P = 0.107)
- ESMO 2018 provides level1 evidence for use of RT to the prostate in pts presenting with LV metastatic disease
- Limited data on ADT + RT +docetaxel ( > Peace1; results 2021?)
Cross-over between ARTAs vs Cabazitaxel

Very modest cross-over response in retrospective studies

<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>
</table>
| No prior ENZA
| De Bono et al.¹ (COU-AA-302) | 2011      | 79 7   | 8 mo                | 29%        | 5.6 mo     |
| ENZA → ABI
| Loriot et al.²      | 2013         | 38 3   | 3 mo                | 8%         | 2.7 mo     |
| Noonan et al.³      | 2013         | 30 3   | 3 mo                | 3%         | 3.6 mo     |

<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>
</table>
| No prior ENZ
| Scher et al.¹      | 2012         | 800   | 8.3 mo              | 54%        | 8.3 mo     |
| ABI → ENZ
| Schrader et al.²    | 2013         | 35    | 4.9 mo              | 29%        | -          |
| Thomsen et al.³     | 2014         | 24    | 4.0 mo              | 17%        | 2.8 mo     |
| Badrising et al.⁴   | 2014         | 61    | 3.0 mo              | 21%        | 2.8 mo     |
| Bianchini et al.⁵   | 2014         | 39    | 2.9 mo              | 23%        | 2.8 mo     |
| Schmid et al.⁶      | 2014         | 35    | 2.8 mo              | 10%        | 3.1 mo     |
| Azad et al.⁷        | 2015         | 68    | 4.1 mo              | 22%        | 4.6 mo     |
| Brasso et al.⁸      | 2014         | 137   | 3.2 mo              | 18%        | -          |
| Joshua et al.⁹      | 2015         | 507   | 2.6 mo              | -          | -          |
Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial

Primary end point:
- Time to second PSA progression
- PSA response (>30%)

Khalaf, Lancet Oncol 2019
Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial

Time to second PSA Progression

Best PSA decline (≥30%) during second line treatment

**Group A:** Abi-Enza

**Group B:** Enza-Abi

Khalaf, Lancet Oncol 2019
CARD: STUDY DESIGN

- Multicenter, randomized, open-label study
- Enrollment: Nov 2015 – Nov 2018
- Median follow-up: 9.2 months

Endpoints

Primary: rPFS
Key secondary: OS, PFS, PSA response, tumor response
Other secondary: Pain response, time to symptomatic skeletal event, safety, HRQoL, biomarkers

Patients with mCRPC who progressed ≤ 12 months on prior alternative ARTA (before or after docetaxel)  

N = 255

Stratification factors:
- ECOG PS (0/1 vs 2)
- Time to progression on prior alternative ARTA (0–6 vs > 6–12 months)
- Timing of ARTA (before vs after docetaxel)

Cabazitaxel (25 mg/m² Q3W) + prednisone + G-CSF  
n = 129

Abiraterone (1000 mg QD) + prednisone
OR
Enzalutamide (160 mg QD)  
n = 126

ECOG PS, Eastern Cooperative Oncology Group performance status; G-CSF, granulocyte-colony stimulating factor; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; QD, once daily; Q3W, every 3 weeks; rPFS, radiographic progression-free survival.
RADIOGRAPHIC PFS: IMPACT OF SEQUENCE*

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Median rPFS, months (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cabazitaxel</strong></td>
<td>56</td>
<td>7.4 (5.4–14.1)</td>
<td>0.57 (0.36–0.90)</td>
</tr>
<tr>
<td><strong>Enzalutamide</strong></td>
<td>66</td>
<td>4.8 (2.8–6.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Abiraterone</strong></td>
<td>72</td>
<td>8.2 (5.3–9.2)</td>
<td>0.44 (0.29–0.67)</td>
</tr>
<tr>
<td><strong>Abiraterone after docetaxel and enzalutamide</strong></td>
<td>60</td>
<td>3.4 (2.8–5.0)</td>
<td></td>
</tr>
</tbody>
</table>

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Enzalutamide after docetaxel and abiraterone

- **HR (95% CI): 0.57 (0.36–0.90)**

Abiraterone after docetaxel and enzalutamide

- **HR (95% CI): 0.44 (0.29–0.67)**

<table>
<thead>
<tr>
<th></th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cabazitaxel</strong></td>
<td>56 36 24 16 13 6 2 1</td>
</tr>
<tr>
<td><strong>Enzalutamide</strong></td>
<td>66 32 19 9 6 3 1 0</td>
</tr>
<tr>
<td><strong>Abiraterone</strong></td>
<td>72 54 40 25 10 3 0</td>
</tr>
<tr>
<td><strong>Abiraterone</strong></td>
<td>60 29 17 13 1 0 0</td>
</tr>
</tbody>
</table>

*Post-hoc analysis.
### Radiographic PFS: Preplanned Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of patients</th>
<th>HR for rPFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>255</td>
<td>0.54 (0.40–0.73)</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>242</td>
<td>0.56 (0.41–0.75)</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>0.33 (0.10–1.12)</td>
</tr>
<tr>
<td><strong>Time from prior alternative ARTA initiation to progression</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6 months</td>
<td>127</td>
<td>0.61 (0.40–0.92)</td>
</tr>
<tr>
<td>&gt; 6–12 months</td>
<td>128</td>
<td>0.51 (0.34–0.77)</td>
</tr>
<tr>
<td><strong>Timing of prior alternative ARTA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before docetaxel</td>
<td>99</td>
<td>0.61 (0.39–0.96)</td>
</tr>
<tr>
<td>After docetaxel</td>
<td>156</td>
<td>0.48 (0.32–0.70)</td>
</tr>
<tr>
<td><strong>Duration of first androgen deprivation therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>113</td>
<td>0.62 (0.39–0.96)</td>
</tr>
<tr>
<td>≥ 12 months</td>
<td>140</td>
<td>0.50 (0.34–0.75)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70 years</td>
<td>120</td>
<td>0.48 (0.31–0.73)</td>
</tr>
<tr>
<td>≥ 70 years</td>
<td>135</td>
<td>0.59 (0.39–0.89)</td>
</tr>
<tr>
<td><strong>Visceral metastases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>46</td>
<td>0.79 (0.41–1.52)</td>
</tr>
<tr>
<td>No</td>
<td>209</td>
<td>0.50 (0.36–0.69)</td>
</tr>
<tr>
<td><strong>Gleason 8–10 at diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>154</td>
<td>0.49 (0.34–0.71)</td>
</tr>
<tr>
<td>No</td>
<td>88</td>
<td>0.62 (0.36–1.05)</td>
</tr>
<tr>
<td><strong>M1 disease at diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>109</td>
<td>0.59 (0.38–0.92)</td>
</tr>
<tr>
<td>No</td>
<td>142</td>
<td>0.52 (0.34–0.77)</td>
</tr>
<tr>
<td><strong>Prior therapy with curative intent for localized disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>68</td>
<td>0.61 (0.35–1.09)</td>
</tr>
<tr>
<td>No</td>
<td>168</td>
<td>0.53 (0.37–0.77)</td>
</tr>
<tr>
<td><strong>Type of progression</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA only</td>
<td>21</td>
<td>0.56 (0.18–1.70)</td>
</tr>
<tr>
<td>Radiologic, no pain</td>
<td>39</td>
<td>0.54 (0.26–1.13)</td>
</tr>
<tr>
<td>Pain</td>
<td>176</td>
<td>0.52 (0.36–0.74)</td>
</tr>
</tbody>
</table>

The table above shows the number of patients and the hazard ratio (HR) for radiographic progression-free survival (rPFS) with 95% confidence intervals (CI) for various subgroups. The subgroups include ECOG PS, time from prior alternative ARTA initiation to progression, timing of prior alternative ARTA, duration of first androgen deprivation therapy, age, visceral metastases, Gleason 8–10 at diagnosis, M1 disease at diagnosis, prior therapy with curative intent for localized disease, and type of progression. The HR values indicate the relative risk of progression compared to the reference group. The subgroups are color-coded and summarized with a diagram at the bottom of the page.
Is CARD practice changing? ; yes

- Cross-over between ART inferior, including sequence abi-enza
- Similar results in sequence ARTA-doce-ARTA
- Affects majority of pts; median PSA-PFS on abi/enza in phase 3 registration studies has been ~10 months
  (PSA-PFS was used in CARD)
- Would results be different if 20 mg/m2 caba would be used?
  25 better OS in pts with pain at entry (66% of pts in CARD had pain at baseline*)

*Delanoye et al, EJC 2019
In 2020 Multiple Choices and Sequences

- mHSPC early taxane / late taxane / early abi / late abi
- mCRPC abi / enza (ART) pre-doce / post-doce / pre / post-caba
- 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
CPCT: Dutch Collab. study WGS 197pts

Van Dessel/ deWit et al, Nature Communications 2019
Future studies and hopefully treatment will be increasingly biology directed!

Remainder at this time: ART and taxanes
PROFOUND:
PHASE III STUDY OF OLAPARIB VERSUS ENZALUTAMIDE OR
ABIRATERONE FOR METASTATIC CASTRATION-RESISTANT PROSTATE CANCER WITH HOMOLOGOUS RECOMBINATION REPAIR GENE ALTERATIONS

Maha Hussain,1 Joaquin Mateo,2 Karim Fizazi,3 Fred Saad,4 Neal Shore,5 Shahneen Sandhu,6 Kim N Chi,7 Oliver Sartor,8 Neeraj Agarwal,9 David Olmos,10 Antoine Thiery-Vuillemin,11 Przemyslaw Twardowski,12 Niven Mehra,13 Carsten Goessl,14 Jinyu Kang,14 Joseph Burgents,15 Wenting Wu,14 Alexander Kohlmann,16 Carrie A Adelman,17 Johann de Bono18

1Robert H Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; 2Vall d’Hebron Institute of Oncology and Vall d’Hebron University Hospital, Barcelona, Spain; 3Institut Gustave Roussy; University of Paris Sud, Villejuif, France; 4Centre Hospitalier de l’Université de Montréal/CRCHUM, Montreal, Canada; 5Carolina Urologic Research Center, Myrtle Beach, SC, USA; 6Peter MacCallum Cancer Centre, Melbourne, Australia; 7BC Cancer Agency, Vancouver, Canada; 8Tulane University School of Medicine, New Orleans, LA, USA; 9Huntsman Cancer Institute, University of Utah (NCI-CCC), Salt Lake City, UT, USA; 10Spanish National Cancer Research Centre (CNIO), and Hospitales Universitarios Virgen de la Victoria y Regional de Málaga, Madrid, Spain; 11CU-PH Medical Oncology Unit, CHU Besançon, Besançon, France; 12John Wayne Cancer Institute, Santa Monica, CA, USA; 13Radboud University Medical Center, Nijmegen, The Netherlands; 14AstraZeneca, Global Medicines Development, Oncology, Gaithersburg, MD, USA; 15Merck & Co, Inc, Kenilworth, NJ, USA; 16AstraZeneca, Precision Medicine, R&D Oncology Unit, Gaithersburg, USA; 17AstraZeneca, Translational Medicine, Cambridge, UK; 18The Institute of Cancer Research and Royal Marsden, London, UK

ClinicalTrials.gov identifier: NCT02987543

This study was sponsored by AstraZeneca and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ, USA (MSD).
PROfound STUDY DESIGN

Key eligibility criteria
- mCRPC with disease progression on prior NHA, eg abiraterone or enzalutamide
- Alterations in ≥1 of any qualifying gene with a direct or indirect role in HRR*

Stratification factors
- Previous taxane
- Measurable disease

Cohort A:
BRCA1, BRCA2 or ATM
N=245

2:1 randomization
Open-label

Cohort B:
Other alterations
N=142

Olaparib 300 mg bid
n=162

Physician’s choice‡
n=83

Olaparib 300 mg bid
n=94

Physician’s choice‡
n=48

Primary Endpoint
Radiographic progression-free survival (rPFS) in Cohort A
(RECIST 1.1 & PCWG3 by BICR)

Upon BICR progression, physician’s choice patients were allowed to cross over to olaparib

Key Secondary Endpoints
- rPFS in Cohorts A+B
- Confirmed radiographic objective response rate (ORR) in Cohort A
- Time to pain progression (TTPP) in Cohort A
- Overall survival (OS) in Cohort A

*An investigational Clinical Trial Assay, based on the FoundationOne® CDx next-generation sequencing test
Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and/ or RAD54L in their tumor tissue

‡Physician’s choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd + prednisone [5 mg bid])
BICR, blinded independent central review
## PATIENT CHARACTERISTICS *

<table>
<thead>
<tr>
<th>Patients with alteration(s) in a single HRR gene, n (%)</th>
<th>Cohort A</th>
<th>Cohorts A+B †</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 or BRCA2</td>
<td>Olaparib (N=162)</td>
<td>Physician's choice (N=83)</td>
</tr>
<tr>
<td>ATM</td>
<td>68 (54.3)</td>
<td>52 (62.7)</td>
</tr>
<tr>
<td>Others</td>
<td>60 (37.0)</td>
<td>24 (28.9)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14 (8.6)</td>
<td>7 (8.4)</td>
<td>17 (6.6)</td>
</tr>
<tr>
<td><strong>68 (47–86)</strong></td>
<td><strong>67 (49–86)</strong></td>
<td><strong>69 (47–91)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with co-occurring alterations, n (%)</th>
<th>Cohort A</th>
<th>Cohorts A+B †</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median (range) age, years</th>
<th>Cohort A</th>
<th>Cohorts A+B †</th>
</tr>
</thead>
<tbody>
<tr>
<td>68 (47–86)</td>
<td>67 (49–86)</td>
<td>69 (47–91)</td>
</tr>
<tr>
<td>38 (23.5)</td>
<td>19 (22.9)</td>
<td>25 (19.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metastatic disease at initial diagnosis, n (%)</th>
<th>Cohort A</th>
<th>Cohorts A+B †</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 or BRCA2</td>
<td>Olaparib (N=162)</td>
<td>Physician's choice (N=83)</td>
</tr>
<tr>
<td>ATM</td>
<td>68 (54.3)</td>
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<td>60 (37.0)</td>
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</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
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<td>7 (8.4)</td>
<td>17 (6.6)</td>
</tr>
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<td><strong>68 (47–86)</strong></td>
<td><strong>67 (49–86)</strong></td>
<td><strong>69 (47–91)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measurable disease at baseline, n (%)</th>
<th>Cohort A</th>
<th>Cohorts A+B †</th>
</tr>
</thead>
<tbody>
<tr>
<td>95 (58.6)</td>
<td>46 (55.4)</td>
<td>149 (58.2)</td>
</tr>
<tr>
<td><strong>62.2 (21.9, 280.4)</strong></td>
<td><strong>112.9 (34.3, 317.1)</strong></td>
<td><strong>68.2 (24.1, 294.4)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median (Q1, Q3) baseline PSA, μg/L</th>
<th>Cohort A</th>
<th>Cohorts A+B †</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG performance status, n (%)</td>
<td>0–1</td>
<td>2</td>
</tr>
<tr>
<td>151 (93.2)</td>
<td>80 (96.4)</td>
<td>243 (94.9)</td>
</tr>
<tr>
<td>11 (6.8)</td>
<td>3 (3.6)</td>
<td>13 (5.1)</td>
</tr>
<tr>
<td><strong>182 (119, 227)</strong></td>
<td><strong>83 (67, 102)</strong></td>
<td><strong>256 (197, 309)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior new hormonal agent</th>
<th>Cohort A</th>
<th>Cohorts A+B †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzalutamide only</td>
<td>68 (42.0)</td>
<td>40 (48.2)</td>
</tr>
<tr>
<td>62 (38.3)</td>
<td>29 (34.9)</td>
<td>105 (41.0)</td>
</tr>
<tr>
<td>Abiraterone + enzalutamide</td>
<td>32 (19.8)</td>
<td>14 (16.9)</td>
</tr>
<tr>
<td>51 (19.9)</td>
<td>23 (17.6)</td>
<td>51 (19.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous taxane use, n (%)</th>
<th>Cohort A</th>
<th>Cohorts A+B †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>106 (65.4) ‡</td>
<td>52 (62.7)</td>
</tr>
<tr>
<td>Docetaxel only</td>
<td>74 (45.7)</td>
<td>32 (38.6)</td>
</tr>
<tr>
<td>2 (1.2)</td>
<td>0 (0.0)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>29 (17.9)</td>
<td>20 (24.1)</td>
<td>51 (19.9)</td>
</tr>
</tbody>
</table>

**Gene Prevalence Poster 847PD**

‡ Four patients were incorrectly assigned to Cohort B (one BRCA2, one BRCA2+CDK12 and two ATM), † One patient received paclitaxel
MOST COMMON AEs (≥10% OF PATIENTS IN EITHER ARM) IN COHORTS A+B

- 4.3% pulmonary embolism with olaparib vs 0.8% with physician’s choice; none were fatal
- No reports of myelodysplastic syndromes or acute myeloid leukemia

*Anemia (46.1%) and decreased Hb (0.4%)
Primary endpoint

rPFS BY BICR IN PATIENTS WITH ALTERATIONS IN BRCA1, BRCA2, OR ATM (COHORT A)

Time from randomization (months)

Probability of rPFS

6-mo rate 59.76%
22.63%

12-mo rate 28.11%
9.40%

Events (%) | Olaparib (N=162) | Physician's choice (N=83)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>106 (65.4)</td>
<td>68 (81.9)</td>
<td></td>
</tr>
</tbody>
</table>

Median rPFS (months) | Olaparib | Physician's choice
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>7.39</td>
<td>3.55</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI) | Olaparib | Physician's choice
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.34 (0.25, 0.47)</td>
<td>P&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>
Key secondary endpoint
rPFS BY BICR IN THE OVERALL POPULATION (COHORTS A+B)

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (N=256)</th>
<th>Physician's choice (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events (%)</td>
<td>180 (70.3)</td>
<td>99 (75.6)</td>
</tr>
<tr>
<td>Median rPFS (months)</td>
<td>5.82</td>
<td>3.52</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.49 (0.38, 0.63)</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

**Graph**
- **X-axis**: Time from randomization (months)
- **Y-axis**: Probability of rPFS
- **6-mo rate**: Olaparib 49.66%, Physician’s choice 23.67%
- **12-mo rate**: Olaparib 22.13%, Physician’s choice 13.47%

**Table**
- **No. at risk**: Olaparib 256, 131; Physician’s choice 188, 73; 145, 38; 106, 20; 67, 9; 48, 5; 31, 5; 21, 3; 11, 2; 2, 1; 0, 0
INTERIM* OVERALL SURVIVAL

**Cohort A**

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (N=162)</th>
<th>Physician's choice (N=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>18.50</td>
<td>15.11</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.64 (0.43, 0.97)</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.0173†</td>
<td></td>
</tr>
</tbody>
</table>

Of the physician's choice arm patients who progressed, 80.6% in Cohort A and 84.6% in Cohort B crossed over to olaparib

*38% maturity in Cohort A; 41% maturity in Cohort A+B; final analysis planned after ~146 deaths in Cohort A (60% maturity)

†Alpha spend at interim was 0.01; statistical significance not reached
### EFFICACY SUMMARY BY COHORT

<table>
<thead>
<tr>
<th></th>
<th>Cohort A</th>
<th>Cohort B</th>
<th>Cohorts A+B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N (Olaparib/ Physician’s choice)</strong></td>
<td>162/ 83</td>
<td>94/ 48</td>
<td>256/ 131</td>
</tr>
<tr>
<td><strong>rPFS (BICR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.34 (0.25, 0.47)</td>
<td>0.88 (0.58, 1.36)</td>
<td>0.49 (0.38, 0.63)</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>rPFS (investigator-assessed)</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.24 (0.17, 0.34)</td>
<td>0.60 (0.39, 0.93)</td>
<td>0.36 (0.27, 0.47)</td>
</tr>
<tr>
<td><strong>ORR (BICR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%, Olaparib vs Physician’s Choice</td>
<td>33.3 vs 2.3%</td>
<td>3.7 vs 8.3%</td>
<td>21.7 vs 4.5%</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>20.86 (4.18, 379.18)</td>
<td>Not calculated†</td>
<td>5.93 (2.01, 25.40)</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OS (interim)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.64 (0.43, 0.97)</td>
<td>0.73 (0.45, 1.23)</td>
<td>0.67 (0.49, 0.93)</td>
</tr>
<tr>
<td>P</td>
<td>0.0173</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Pre-specified sensitivity analysis
†N=2 responders each for olaparib vs physician’s choice.

---

Denotes multiplicity-controlled endpoint
# Ongoing Phase III studies in Prostate Cancer

<table>
<thead>
<tr>
<th>Study Drugs</th>
<th>Study Name (NCT #)</th>
<th>Phase</th>
<th>Patient Population</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzalutamide + Talazoparib vs Enzalutamide + Placebo</td>
<td>TALAPRO-2 (NCT03395197)</td>
<td>3</td>
<td>L1 mCRPC</td>
<td>PFS</td>
</tr>
<tr>
<td>Rucaparib vs Abiraterone, Enzalutamide, or Docetaxel</td>
<td>TRITON 3 (NCT02975934)</td>
<td>3</td>
<td>germline or somatic BRCA1, BRCA2, or ATM mutations and mCRPC who previously progressed on an androgen-receptor signaling inhibitor and who have not received chemotherapy</td>
<td>PFS</td>
</tr>
<tr>
<td>Niraparib + Abiraterone vs Placebo + Abiraterone</td>
<td>MAGNITUDE (NCT03748641)</td>
<td>3</td>
<td>L1 tmCRPC (DDRm cohort / no DDR cohort)</td>
<td>PFS</td>
</tr>
<tr>
<td>Abiraterone +/- Olaparib</td>
<td>PROpel (NCT03732820)</td>
<td>3</td>
<td>L1 mCRPC</td>
<td>PFS</td>
</tr>
<tr>
<td>Pembrolizumab + Olaparib vs Enzalutamide or Abiraterone</td>
<td>KEYLINK-010 (NCT03834519)</td>
<td>3</td>
<td>mCRPC progressed on Abiraterone or Enzalutamide</td>
<td>PFS, OS</td>
</tr>
</tbody>
</table>
Pembrolizumab for Treatment-Refractory Metastatic Castration-Resistant Prostate Cancer: Multicohort, Open-Label Phase II KEYNOTE-199 Study

Tumor size change from baseline

Response over time

ORR 3-5%

PSA change from baseline

Antonarakis, J Clin Onc 2019
Immunogenic mCRPC subtypes by WGS, 197 patients, ESMO 2018 poster Mehra et al

Tumor mutational load varies between CRPC subtypes
- 7.7% have highTMB (>10 mutations/Mb), of which 6.7% have a highTMB /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
Samples from 1551 mPC prospectively analyzed

3.1% MSI-H/dMMR

11 patients treated with ICI

PSA >50% Decline: 54.5%
Cyclin-Dependent Kinase 12, Immunity, and Prostate Cancer
<table>
<thead>
<tr>
<th>NCT</th>
<th>Trial phase</th>
<th>Therapy</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01804465</td>
<td>II</td>
<td>ipilimumab + sipuleucel-T</td>
<td>impact of timing of ipilimumab (Immediate vs delayed) on the induction of Ig responses</td>
</tr>
<tr>
<td>NCT03040791 (ImmunoProst)</td>
<td>II</td>
<td>nivolumab</td>
<td>PSA response rate</td>
</tr>
<tr>
<td>NCT03061539</td>
<td>II</td>
<td>nivolumab + ipilimumab</td>
<td>composite response rate</td>
</tr>
<tr>
<td>NCT02601014 (STARVE-PC)</td>
<td>II</td>
<td>nivolumab + ipilimumab</td>
<td>change in PSA response</td>
</tr>
<tr>
<td>NCT03570619 (IMPACT)</td>
<td>II</td>
<td>nivolumab + ipilimumab</td>
<td>proportion of patients with CDK12 loss of function that respond to treatment</td>
</tr>
<tr>
<td>NCT03333616</td>
<td>II</td>
<td>nivolumab + ipilimumab</td>
<td>ORR</td>
</tr>
<tr>
<td>NCT03572478</td>
<td>I/II</td>
<td>nivolumab + rucaparib</td>
<td>DLT rate</td>
</tr>
<tr>
<td>NCT03338790</td>
<td>II</td>
<td>nivolumab + rucaparib/docetaxel/ enzalutamide</td>
<td>ORR e RR-PSA</td>
</tr>
<tr>
<td>NCT02703623</td>
<td>II</td>
<td>abiraterone + apalutamide + ipilimumab/ cabazitaxel+CBDCA</td>
<td>OS</td>
</tr>
<tr>
<td>NCT02861573 (KEYNOTE -365)</td>
<td>I</td>
<td>pembrolizumab + olaparib/docetaxel/enzalutamide/ abiraterone</td>
<td>% of pts with a decrease ≥50% in PSA</td>
</tr>
<tr>
<td>NCT03093428</td>
<td>II</td>
<td>pembrolizumab + Radium-223</td>
<td>extent of Immune Cell Infiltration</td>
</tr>
<tr>
<td>NCT03810105</td>
<td>II</td>
<td>durvalumab + olaparib</td>
<td>number of participants with an undetectable PSA</td>
</tr>
<tr>
<td>NCT03204812</td>
<td>II</td>
<td>durvalumab + tremilimumab</td>
<td>safety and tolerability</td>
</tr>
<tr>
<td>NCT02788773</td>
<td>II</td>
<td>durvalumab +/- tremelimumab</td>
<td>ORR</td>
</tr>
<tr>
<td>NCT03821246</td>
<td>II</td>
<td>atezolizumab +/- enzalutamide</td>
<td>changes in tumor-infiltrating effector CD3+ T cells</td>
</tr>
</tbody>
</table>
Current options in metastatic PCa

**mHSPC**
- DOC (not licenced)
- ABI
- RT to prostate (low volume)

**mCRPC 1st line**
- ADT
- DOC (if no prior use)
- CABA (if prior DOC)
- ABI or ENZA (if no prior ABI)
- Sipuleucel-T (not in Europe)

**mCRPC 2nd line**
- CABA (if prior DOC)
- ABI or ENZA (if no prior use)
- Radium-223 (after 2 lines of therapy)

**ABI**: abiraterone acetate; **CABA**: cabazitaxel; **DOC**: docetaxel; **ENZA**: enzalutamide; **mHSPC**: metastatic hormone-sensitive prostate cancer; **mCRPC**: metastatic castration-resistant prostate cancer; **RT**: radiotherapy

Alison Birtle
Poor prognostic features should be considered regardless of age

- De novo metastatic disease\(^1\)
- Time to CRPC with first ADT \(\leq 12\) mths\(^2\)
- Liver metastases at treatment initiation\(^3\)
- Pain at treatment initiation\(^4\)\(^-\)\(^5\)
- High lactate dehydrogenase\(^6\)
- High alkaline phosphatase\(^7\)

Randomized phase II trial in poor prognosis mCRPC

- mCRPC
- Poor prognosis
  - Liver metastases
  - CRPC <12 mo of ADT for M1
  - Presence of ≥4 of:
    - LDH >ULN
    - ECOG PS 2
    - Visceral mets
    - Albumin <4 g/dl
    - ALP >ULN
    - <36 mo from time of ADT

- A planned accrual of 120 patients (60 per arm) to detect a an absolute difference of 20% in CBR (80% power, 2-sided significance level of 0.1 based on a two-group continuity-corrected chi-squared test)
- Due to slow accrual and changes in treatment standards, the trial was closed after 95 patients had been accrued

ClinicalTrials.gov: NCT02254785

Chi K et al Ann Oncol 2019;29(suppl 8):792O (podium presentation)
Randomized phase II trial in poor prognosis mCRPC

<table>
<thead>
<tr>
<th></th>
<th>CABA</th>
<th>ABI or ENZA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical benefit rate</td>
<td>38/43 (88.4%)</td>
<td>35/50 (70%)</td>
<td>0.043</td>
</tr>
<tr>
<td>TTPP</td>
<td>7.4 (4.9-9.1)</td>
<td>4.7 (3.4-13.2)</td>
<td>0.82</td>
</tr>
<tr>
<td>PFS*</td>
<td>6.2 (4.1-8.9)</td>
<td>3.1 (2.4-5.4)</td>
<td>0.18</td>
</tr>
<tr>
<td>OS</td>
<td>37.0 (18.9-NR)</td>
<td>15.5 (12.4-NR)</td>
<td>0.06 (unadjusted) 0.41 (adjusted)</td>
</tr>
</tbody>
</table>

*PFS: First of confirmed PSA progression (PCWG3), clinical or radiological progression, or death; Median values (95% CI), months

Main grade ≥3 toxicities with CABA
- Neutropenia: 31.8%
- Diarrhea: 9.1%
- No information on cardiac events

OS

P=0.06

CI: confidence interval; NR: not reached; OS: overall survival; PCWG3: Prostate Cancer Working Group 3; PFS: progression-free survival; TTPP: time to PSA progression; mo: months

Chi K et al Ann Oncol 2019;29(suppl 8):792O (podium presentation)
mCRPC n.743
- ECOG 0-2
- Adequate organ function
- previous ARTA

Carboplatin AUC 4 + Cabazitaxel 25 mg/mq + 10 mg of prednisone

Carbazitaxel 25 mg/mq + 10 mg of prednisone plus placebo

Primary end point: PFS

Secondary end point:
- PSA response
- overall survival (OS)
- effect of aggressive variant of PCA on response

Corn P. et al. Lancet Oncol 2019
Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: a randomised, open-label, phase 1–2 trial

PFS
HR: 0.69, 95% CI 0.50–0.95

OS
HR: 0.89, 95% CI 0.63–1.25

Corn P. et al. Lancet Oncol 2019
**mHSPC and mCRPC; Trial Conclusions 2020**

- Evidence of benefit by adding docetaxel to ADT and abiraterone to ADT in pts presenting with metastatic disease at diagnosis
- Benefit greatest in HV disease/ Some benefit in LV
- Benefit by ADT plus RT to the prostate in LV disease (level 1 evidence)
- Do not cross-over between ARTA
- Reduced efficacy of docetaxel in post ARTA setting,
  >do not lose opportunity to switch to cabazitaxel
- Rationale for use of PARP inhibitor (Olaparib, Niraparib etc) in pts with BRCA1, BRCA2 or ATM mutations
  No direct comparision PARP vs Canazitaxel
  (role of carboplatin if olaparib not available?)
- Some rationale for combo cabazitaxel+ carboplatin if “poor risk features”
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All recruiting physicians and research nurses
Patients and their families