Systemic Treatment of metastatic prostate cancer

Phichai Chansriwong, MD
Ramathibodi Hospital, Mahidol University
Past-Present-Future

- HSPC vs CRPC
- Treatment for CRPC
- Treatment for HSPC
- What we learned in 2016
- What is new knowledge in 2017
Treatment for Prostate cancer

- Radical Prostatectomy
  - 24 months (12-144)
- PSA Failure
  - 32 months (2-129)
- Metastasis
  - 82 months (7-181)
- Prostate Cancer-Specific Mortality
  - 168 months (24-216)

132 months (12-204)

N=91

N=41

2-4 years

Following orchiectomy, the prostate shrinks, the oxidative phase of carbohydrate metabolism declines, and secretion stops. (...) The prostatic cell does not die in the absence of testosterone, it merely shrivels.
HSPC vs CRPC

- Castration (hormonal) -sensitive: disease controlled by androgen suppression
  - Median OS may reach 69 months
    - Hussain NEJM 2013

Castration-resistant:

- Median OS may reach 34 months (asymptomatic or low-symptomatic patients)
  - Ryan Lancet Oncol 2015, Beer NEJM 2014
Castration-Resistant Prostate Cancer (CRPC): Definition

Castrate serum testosterone
<50 ng/mL or 1.7 nmol/L

+ either

Biochemical progression
3 consecutive increases in PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA >2 ng/mL

OR

Radiological progression
The appearance of ≥2 bone lesions on a bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumors)

PSA: prostate-specific antigen
Identify right diagnosis with criteria “CRPC”

**Serum testosterone**

< 50 ng/dL (1.7 nmol/L)

By using Androgen Deprivation Therapy

---

**Biochemical progression**

Three consecutive rises in PSA

1. PSA increases ≥ 50% and ≥ 2 ng/mL above nadir
2. PSA increases ≥ 50% and ≥ 2 ng/mL above nadir
3. Confirm the trend of PSA increase

---

**Radiological progression**

1. Presence ≥ 2 bone lesions
2. Presence soft tissue lesions with nodes >2 cm in diameter

---

**EAU guideline 2015; PCWG2; RECIST 1.1**
TAX 327: 3 arms

- 5 mg prednisolone BID
- Mitoxantrone 12 mg / m² q 3 wk
- Docetaxel 75 mg / m² q 3 wk 10 cycle
- Docetaxel 30 mg / m² wkly for 6 wk 5 cycle
Two randomised phase 3 trials have demonstrated a significant improvement in overall survival (OS) for docetaxel-based chemotherapy, compared with the mitoxantrone-prednisone combination.

---

**Overall Survival — TAX 327**

- **Docetaxel 3 wkly**
- **Docetaxel wkly**
- **Mitoxantrone**

**30 months**

<table>
<thead>
<tr>
<th>Survival</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined:</td>
<td>18.2</td>
<td>0.83</td>
</tr>
<tr>
<td>D 3 wkly:</td>
<td>18.9</td>
<td>0.76</td>
</tr>
<tr>
<td>D wkly:</td>
<td>17.3</td>
<td>0.91</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>16.4</td>
<td>-</td>
</tr>
</tbody>
</table>

HRPC: chemotherapy

---

**Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>D+E</th>
<th>M+P</th>
</tr>
</thead>
<tbody>
<tr>
<td># at Risk</td>
<td>338</td>
<td>336</td>
</tr>
<tr>
<td># of Deaths</td>
<td>217</td>
<td>235</td>
</tr>
<tr>
<td>Median in Months</td>
<td>18</td>
<td>16</td>
</tr>
</tbody>
</table>

HR: 0.80 (95% CI 0.67, 0.97), p = 0.01

---

Tannock IF et al NEJM 2004; 351: 1502–12


Docetaxel given at the dose of 75 mg/m² every 21 d is the sole regimen approved by the FDA and EMA for the treatment of mCRPC.
CRPC is not truly CRPC

- Transit-amplifying cells and intermediate cells (both AR−)
- Luminal secretory cells (AR+)

- Deprived of circulating androgen, the AR+ luminal cells will induce apoptosis

http://www.peervoice.com/o1/pvr121
PCa progression in low testosterone environment: 2 leading theories

Luminal secretory cells (AR+)

Intermediate cells (AR-)

Transit amplifying cells (AR-)

Prostate adult stem cells (AR-)

ADT

ADAPTATION

Allows growth in low testosterone environment

Massive apoptosis of luminal AR+ cells

CLONAL PROLIFERATION

(AR negative cells)

In most patients, both theories coexist: ADT response in some mets may be associated with radiological/clinical progression of other mets


AR: androgen receptor; ADT: androgen deprivation therapy; mets: metastases
Chemotherapy

AR pathways inhibitor

Presenter: G. Daugaard, DK
ESMO 2015
Treatment landscape of prostate cancer: post-chemotherapy era
Zytiga (Abiraterone acetate) overview

- Prostate cancer still sensitive to blockade of androgen signaling after castration-resistance
- Abiraterone unique mechanism of action
  - Oral irreversible inhibitor of CYP-17
  - Mineralocorticoid excess manageable with prednisone/prednisolone
- FDA approved Zytiga (abiraterone acetate) for the treatment of men with metastatic castration-resistant prostate cancer after docetaxel failure
Steroid Synthesis Pathway
MOA of Abiraterone Acetate & Related Side Effects

Cholesterol

Desmolase

Pregnenolone → Progesterone → CYP21 → Deoxy-corticosterone → Corticosterone

CYP17: 17α-hydroxylase

17α-OH-pregnenolone → 17α-OH-progesterone → CYP21 → 11-Deoxy-cortisol → Cortisol

11β-Hydroxylase

CYP19: aromatase

Estradiol

Testosterone

5α-reductase → DHT

Enzalutamide (MDV3100)

- Oral investigational drug rationally designed to target AR signaling, impacting multiple steps in AR signaling pathway.

- No demonstrated agonist effects in pre-clinical models.

Charles Sawyers & Michael Jung
COU-AA-301 Study Design

- 1195 patients with progressive, mCRPC
- Failed 1 or 2 chemotherapy regimens, one of which contained docetaxel

Randomized 2:1

Abiraterone 1000 mg daily Prednisone 5 mg BID N=797

Placebo daily Prednisone 5 mg BID n=398

Primary end point:
- OS (25% improvement; HR 0.8)

Secondary end points (ITT):
- TTPP
- rPFS
- PSA response

- Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled study (147 sites in 13 countries; USA, Europe, Australia, Canada)
- Stratification according to:
  - ECOG performance status (0-1 vs. 2)
  - Worst pain over previous 24 hours (BPI short form; 0-3 [absent] vs. 4-10 [present])
  - Prior chemotherapy (1 vs. 2)
  - Type of progression (PSA only vs. radiographic progression with or without PSA progression)
COU-AA-301: Abiraterone Acetate Improves OS in mCRPC

OS 14.8 mo VS 10.9 mo

HR = 0.646 (0.54-0.77)
P < 0.0001

Abiraterone acetate:
14.8 months
(95% CI: 14.1, 15.4)

Placebo:
10.9 months
(95% CI: 10.2, 12.0)
GLUCOCORTICOIDS WERE NOT REQUIRED BUT ALLOWED.
PCWG2 criteria used (continue therapy through minor PSA changes; confirm bone scan ‘progression’; focus on benefit not response).*

Recruitment in 156 centers from 15 countries and 5 continents. Enrollment between September 2009 and November 2010.

* Scher et al, 2008
Enzalutamide Prolonged Survival, Reducing Risk of Death

HR = 0.631 (0.529, 0.752) P <0.0001
37% reduction in risk of death

Enzalutamide: 18.4 months
(95% CI: 17.3, NYR)

Placebo: 13.6 months
(95% CI: 11.3, 15.8)

<table>
<thead>
<tr>
<th>Duration of Overall Survival, Months</th>
<th>Enzalutamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>800</td>
<td>399</td>
</tr>
<tr>
<td>3</td>
<td>775</td>
<td>376</td>
</tr>
<tr>
<td>6</td>
<td>701</td>
<td>317</td>
</tr>
<tr>
<td>9</td>
<td>627</td>
<td>263</td>
</tr>
<tr>
<td>12</td>
<td>400</td>
<td>167</td>
</tr>
<tr>
<td>15</td>
<td>211</td>
<td>81</td>
</tr>
<tr>
<td>18</td>
<td>72</td>
<td>33</td>
</tr>
<tr>
<td>21</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Radium-223 acts as a calcium mimic. It targets new bone growth and bone metastases. Radium-223 is excreted by the small intestine.

Presented at the 2015 ASCO Annual Meeting by Tanya Dorff.
ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design

**Patients**
- Confirmed symptomatic CRPC
- ≥ 2 bone metastases
- No known visceral metastases
- Post-docetaxel or unfit for docetaxel

**Stratification**
- Total ALP: < 220 U/L vs ≥ 220 U/L
- Bisphosphonate use: Yes vs No
- Prior docetaxel: Yes vs No

**Treatment**
- 6 injections at 4-week intervals
- Radium-223 (50 kBq/kg) + Best standard of care
- Placebo (saline) + Best standard of care

**Randomised**
2:1
N = 922

Planned follow-up is 3 years

Primary endpoint: OS
Cabazitaxel: selected to overcome taxane resistance

- **Cabazitaxel:**
  - Poor affinity for the PgP efflux pump
  - Greater penetration of the blood brain barrier compared with docetaxel and paclitaxel
  - Active in vitro and in vivo on tumors resistant to Docetaxel

- Docetaxel and paclitaxel have a strong affinity for the PgP pump
- If the PgP pump is surexpressed, it drives drug out of tumour cell

Mita AC et al, Clin Cancer Res. 2009, 15, 723-730
TROPIC: Phase III registration study
146 Sites in 26 Countries

Primary endpoint: OS
Secondary endpoints: Progression-free survival (PFS), response rate, and safety

Inclusion: Patients with measurable disease must have progressed by RECIST; otherwise must have had new lesions or PSA progression

ECOG PS (0, 1 vs. 2) • Measurable vs. non-measurable disease

mCRPC patients who progressed during and after treatment with a docetaxel-based regimen (N=755)

Stratification factors

- cabazitaxel 25 mg/m² q 3 wk + prednisone* for 10 cycles (n=378)
- mitoxantrone 12 mg/m² q 3 wk + prednisone* for 10 cycles (n=377)

*Oral prednisone/prednisolone: 10 mg daily

2010 ASCO Genitourinary Cancers Symposium & ASCO 2010
De Bono JS et al Lancet 2010; 376: 1147–54
Primary endpoint: TROPIC
Overall survival (updated ITT analysis*)

28% reduction in risk of death

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>CBZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>12.7</td>
<td>15.1</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.61–0.84</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

Number at Risk

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Number at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>MP 377, CBZP 378</td>
</tr>
<tr>
<td>6</td>
<td>299, 321</td>
</tr>
<tr>
<td>12</td>
<td>195, 241</td>
</tr>
<tr>
<td>18</td>
<td>94, 137</td>
</tr>
<tr>
<td>24</td>
<td>31, 60</td>
</tr>
<tr>
<td>30</td>
<td>9, 19</td>
</tr>
</tbody>
</table>

Combined median follow-up: 13.7 months

* Data cut-off 3/10/2010

2010 ASCO Genitourinary Cancers Symposium & ASCO 2010
De Bono JS et al Lancet 2010; 376: 1147–54
TROPIC Progression-free survival

25% reduction in risk of progression

- Median PFS (months): MP 1.4, CBZP 2.8
- Hazard ratio: 0.75
- 95% CI: 0.65–0.87
- P-value: 0.0002

Number at Risk

MP | 377 | 117 | 55 | 30 | 12 | 9 | 6 | 4
CBZP | 378 | 168 | 92 | 55 | 18 | 6 | 1 | 1

Combined median follow-up: 13.7 months

* Data cut-off 3/10/2010

2010 ASCO Genitourinary Cancers Symposium & ASCO 2010
De Bono JS et al Lancet 2010; 376: 1147–54
### TROPIC : Hematological Results

<table>
<thead>
<tr>
<th>Hematology</th>
<th>MP (n=371)</th>
<th>CBZP (n=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades (%)</td>
<td>Grade ≥3 (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>81.4</td>
<td>4.9</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>92.5</td>
<td>42.3</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>87.6</td>
<td>58.0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>43.1</td>
<td>1.6</td>
</tr>
</tbody>
</table>

*Prophylactic use of G-CSF was permitted except for cycle 1 of treatment at the discretion of the investigator.

- Higher rate of grade ≥ 3 neutropenia than in TAX 327 but patients enrolled in TROPIC had more advanced disease, were heavily pretreated and had weekly hematological testing.
### New therapeutic agents in last decade

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Pts</th>
<th>HR</th>
<th>N</th>
<th>Survival (months)</th>
<th>Delta (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPACT</td>
<td>Sipuleucel-T</td>
<td>CRPC</td>
<td>0.78</td>
<td>512</td>
<td>25.8 vs 21.7</td>
<td>4.1</td>
</tr>
<tr>
<td>TAX 327</td>
<td>Docetaxel+Prednisone vs Mitoxantrone+Prednisone</td>
<td>CRPC</td>
<td>0.76</td>
<td>1006</td>
<td>18.9 vs 16.5</td>
<td>2.4</td>
</tr>
<tr>
<td>TROPIC</td>
<td>Cabazitaxel+Prednisone</td>
<td>CRPC</td>
<td>0.70</td>
<td>755</td>
<td>15.1 vs 12.7</td>
<td>2.4</td>
</tr>
<tr>
<td>COU-AA-301</td>
<td>Abiraterone +Prednisone vs Prednisone</td>
<td>CRPC</td>
<td>0.74</td>
<td>1195</td>
<td>15.8 vs 11.2</td>
<td>4.6</td>
</tr>
<tr>
<td>ALSYMCA</td>
<td>Alpharadin vs Placebo</td>
<td>CRPC</td>
<td>0.695</td>
<td>809</td>
<td>14.0 vs 11.2</td>
<td>3.6</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>MDV3100 vs Placebo</td>
<td>CRPC</td>
<td>0.63</td>
<td>1199</td>
<td>18.4 vs 13.6</td>
<td>4.8</td>
</tr>
</tbody>
</table>

**However, survival prolongation on average 3.5 months!**

---

5. Parker C et al. ASCO 2012 (LBA 4512).
More treatment options are available for mCRPC patients!

- Abiraterone acetate
- Enzalutamide
- Cabazitaxel
- Radium-223

Short response to AA ARV-7

No Biomarker to choose agents

Year 2012

Post-chemotherapy era
Treatment landscape of prostate cancer: pre-chemotherapy era
Abiraterone and Enzalutamide in mCRPC Phase III Studies Pre-docetaxel (Primary Endpoint: rPFS and OS)

**COU-AA-302**
- n=1088 progressive chemonaive patients with mCRPC
- Asymptomatic or mildly symptomatic
- Abiraterone 1000 mg QD + prednisone 5 mg BID
- Placebo BID + prednisone 5 mg BID

**PREVAIL**
- n=1715 progressive chemonaive patients with mCRPC
- Asymptomatic or mildly symptomatic
- Visceral mets permitted
- Enzalutamide 160 mg QD
- Placebo QD
- No prednisone

No prednisone
## Summary of pre-chemo studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Time of f/u (months)</th>
<th>OS (months)</th>
<th>rPFS (months)</th>
<th>Time to opiate use (months)</th>
<th>Time to initiate use of chemo (months)</th>
<th>Time to PSA progression (months)</th>
<th>Time to ECOG deterioration (months)</th>
<th>PSA response</th>
</tr>
</thead>
<tbody>
<tr>
<td>COU-AA-302&lt;sup&gt;1-2&lt;/sup&gt;</td>
<td>Abiraterone acetate 1000 mg + Prednisone</td>
<td>49.2</td>
<td>34.7</td>
<td>16.5</td>
<td>33.4</td>
<td>26.5</td>
<td>11.1</td>
<td>12.3</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
<td></td>
<td>30.3</td>
<td>8.2</td>
<td>23.4</td>
<td>16.8</td>
<td>5.6</td>
<td>10.9</td>
<td>29%</td>
</tr>
<tr>
<td>PREVAIL&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Enzalutamide 160 mg</td>
<td>22</td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td>28.0</td>
<td>11.2</td>
<td>-</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>30.2</td>
<td>-</td>
<td>-</td>
<td>10.8</td>
<td>2.8</td>
<td>-</td>
<td>3%</td>
</tr>
</tbody>
</table>

Year 2013

Pre-chemotherapy era

More treatment options are available for mCRPC patients!
Presenter: G. Daugaard, DK
ESMO 2015
The Art of Sequencing

- Based on the concept that more treatments = increased survival
- No head to head study to compare efficacy.
Early Chemo+ADT: A debate in one slide – a need for a randomized phase 3 trial

• **Pro**
  - Attack de-novo testosterone independent clones early - allow ADT to keep PrCa in remission longer
  - Some patients at the time of progression are too frail for chemo

• **Con**
  - ADT will take cells out of cycle and be less responsive to cytotoxics
  - Some patients respond for a long time and never need chemo

---

**Chemotherapy in HSPC**
Chemohormonal upfront therapy has a role in high volume hormone-sensitive prostate cancer

**1 Study**

"GETUG-AFU15"

- **Negative result**
- **29 centers in France and 1 center in Belgium**

**2 Studies**

"STAMPEDE" and "CHAARTED"

- **Positive result**
- **STAMPEDE**
  - 119 centers in UK and 6 centers in Switzerland
- **CHAARTED**
  - US
E3805 / CHAARTED Treatment

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

RANDOMIZE

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

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

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

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

26-30 September 2014, Madrid, Spain
Different Definitions of High Volume Disease

- SWOG: S8894: *NEJM* 1998: Orchietomy +/- Flutamide\(^1\)
  Extensive disease: included appendicular skeletal involvement (with or without axial skeletal involvement), visceral (lung or liver) metastasis or both
  Median OS = 27 months

- MDACC: *J Clin Oncol* 2008; ADT +/- KAVE\(^2\)
  High volume: 3 or more bone mets and / or visceral mets
  Median OS = 37 months

---

**E3805 Definition of High Volume**

- **High volume:**
  - visceral metastases and/or
  - 4 or more bone metastases with at least 1 beyond pelvis and vertebral column

- At inception, only patients with high volume disease were to be accrued

---

\(^1\)Eisenberger et al *NEJM*, 1998;
OS for Patients with High Volume Metastatic Disease at Start of ADT

In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival from 32.2 months to 49.2 months. We projected 33 months in ADT alone arm with collaboration of SWOG 9346 team.
Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: First survival results from STAMPEDE

Nicholas James
University of Warwick and Queen Elizabeth Hospital Birmingham
on behalf of
Matthew Sydes, Malcolm Mason, Noel Clarke, David Dearnaley, Melissa Spears, Robin Millman, Chris Parker, Alastair Ritchie, J. Martin Russell, John Staffurth, Robert Jones, Shaun Tolan, John Wagstaff, Andrew Protheroe, Rajaguru Srinivasan, Alison Birtle, Joe O'Sullivan, Richard Cathomas, Mahesh Parmar and the STAMPEDE Investigators
Inclusion criteria

**Newly-diagnosed**
- Any of:
  - Metastatic
  - Node-Positive
  - ≥2 of: Stage T3/4
    PSA ≥ 40 ng/ml
    Gleason 8-10

**Relapsing after previous RP or RT with ≥1 of:**
- PSA ≥ 4 ng/ml and rising with doubling time < 6 m
- PSA ≥ 20 ng/ml
- Node-positive
- Metastatic

**All patients**
- Fit for all protocol treatment
- Fit for follow-up
- WHO performance status 0-2
- Written informed consent

**Full criteria**
www.stampedetrial.org
STAMPEDE: All docetaxel and zoledronic acid comparisons

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

Presented By Nicholas James at 2015 ASCO Annual Meeting
Treatment effect by metastatic status: FFS

Pre-planned analysis

+ZA

<table>
<thead>
<tr>
<th>Mets status</th>
<th>FFS events</th>
<th>No. pts</th>
<th>Haz. Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>255</td>
<td>686</td>
<td>0.98 (0.75, 1.28)</td>
</tr>
<tr>
<td>M1</td>
<td>866</td>
<td>1091</td>
<td>0.90 (0.78, 1.04)</td>
</tr>
<tr>
<td>Overall</td>
<td>1121</td>
<td>1777</td>
<td>0.93 (0.82, 1.05)</td>
</tr>
</tbody>
</table>

+Doc

<table>
<thead>
<tr>
<th>Mets status</th>
<th>FFS events</th>
<th>No. pts</th>
<th>Haz. Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>229</td>
<td>689</td>
<td>0.57 (0.42, 0.76)</td>
</tr>
<tr>
<td>M1</td>
<td>832</td>
<td>1087</td>
<td>0.62 (0.54, 0.73)</td>
</tr>
<tr>
<td>Overall</td>
<td>1061</td>
<td>1776</td>
<td>0.62 (0.54, 0.70)</td>
</tr>
</tbody>
</table>

+ZA+Doc

<table>
<thead>
<tr>
<th>Mets status</th>
<th>FFS events</th>
<th>No. pts</th>
<th>Haz. Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>232</td>
<td>687</td>
<td>0.70 (0.52, 0.94)</td>
</tr>
<tr>
<td>M1</td>
<td>832</td>
<td>1090</td>
<td>0.60 (0.52, 0.70)</td>
</tr>
<tr>
<td>Overall</td>
<td>1064</td>
<td>1777</td>
<td>0.62 (0.54, 0.71)</td>
</tr>
</tbody>
</table>

Presented By Nicholas James at 2015 ASCO Annual Meeting
Treatment effect by metastatic status: Overall survival

Pre-planned analysis

**+ZA**

<table>
<thead>
<tr>
<th>Mets status</th>
<th>OS events</th>
<th>No. pts</th>
<th>Haz. Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>93</td>
<td>686</td>
<td>0.96 (0.62, 1.48)</td>
</tr>
<tr>
<td>M1</td>
<td>509</td>
<td>1091</td>
<td>0.92 (0.76, 1.11)</td>
</tr>
<tr>
<td>Overall</td>
<td>602</td>
<td>1777</td>
<td>0.93 (0.79, 1.11)</td>
</tr>
</tbody>
</table>

**+Doc**

<table>
<thead>
<tr>
<th>Mets status</th>
<th>OS events</th>
<th>No. pts</th>
<th>Haz. Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>93</td>
<td>689</td>
<td>1.01 (0.65, 1.56)</td>
</tr>
<tr>
<td>M1</td>
<td>477</td>
<td>1087</td>
<td>0.73 (0.59, 0.89)</td>
</tr>
<tr>
<td>Overall</td>
<td>570</td>
<td>1776</td>
<td>0.76 (0.63, 0.91)</td>
</tr>
</tbody>
</table>

**+ZA+Doc**

<table>
<thead>
<tr>
<th>Mets status</th>
<th>OS events</th>
<th>No. pts</th>
<th>Haz. Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>91</td>
<td>687</td>
<td>1.03 (0.66, 1.61)</td>
</tr>
<tr>
<td>M1</td>
<td>495</td>
<td>1090</td>
<td>0.78 (0.65, 0.95)</td>
</tr>
<tr>
<td>Overall</td>
<td>586</td>
<td>1777</td>
<td>0.81 (0.68, 0.97)</td>
</tr>
</tbody>
</table>
Docetaxel: Survival – M1 Patients

**SOC**
- 343 deaths

**SOC+Doc**
- 134 deaths

HR (95%CI) 0.73 (0.59, 0.89)

P-value 0.002

Non-PH p-value 0.23

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

**Group**
<table>
<thead>
<tr>
<th>At risk (events)</th>
<th>SOC</th>
<th>SOC+Doc</th>
</tr>
</thead>
<tbody>
<tr>
<td>725 (27)</td>
<td>362 (9)</td>
<td></td>
</tr>
<tr>
<td>645 (49)</td>
<td>242 (27)</td>
<td></td>
</tr>
<tr>
<td>469 (27)</td>
<td>251 (13)</td>
<td></td>
</tr>
<tr>
<td>254 (8)</td>
<td>134 (10)</td>
<td></td>
</tr>
<tr>
<td>58 (5)</td>
<td>24 (5)</td>
<td></td>
</tr>
<tr>
<td>10 (9)</td>
<td>24 (0)</td>
<td></td>
</tr>
</tbody>
</table>

**Restricted mean OS time**
- SOC 49.3m
- SOC+Doc 56.1m

Diff (95%CI) 6.8m (2.8, 11.0m)

Presented By Nicholas James at 2015 ASCO Annual Meeting
Conclusions

- Docetaxel improves survival for hormone-naive prostate cancer
- Zoledronic acid does not improve survival
- Adding both improves survival but offers no obvious benefit over adding just docetaxel
- Multi-arm, multi-stage trials are practicable and efficient

- Docetaxel should be:
  - Considered for routine practice in suitable men with newly-diagnosed metastatic disease
  - Considered for selected men with high-risk non-metastatic disease in view of substantial prolongation of failure-free survival
Forest plot of overall survival for the 3 studies
(thanks to Dr Eitan Amir)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight *</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAARTED</td>
<td>30.3%</td>
<td>0.61 [0.47, 0.80]</td>
</tr>
<tr>
<td>GETUG-15</td>
<td>30.8%</td>
<td>0.90 [0.70, 1.18]</td>
</tr>
<tr>
<td>STAMPEDE</td>
<td>38.9%</td>
<td>0.73 [0.59, 0.89]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>0.74 [0.60, 0.90]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.02; Chi² = 4.26, df = 2 \( P = 0.12 \)
Test for overall effect: Z = 2.92 \( P = 0.003 \)

* weight by inverse variance

31/05/2015

Presented By Ian Tannock at 2015 ASCO Annual Meeting
RECOMMENDATION #1
Men with high-risk metastatic prostate cancer, especially those presenting with metastases at or soon after diagnosis, who are judged fit to receive chemotherapy, should be offered 6 cycles of docetaxel in addition to ADT

• Summary

• 6 cycles of docetaxel in addition to ADT represents the standard of care for men with metastatic prostate cancer commencing ADT who are suitable for docetaxel therapy

• The benefit in patients with a high volume of metastases is clear and justifies the treatment burden

• In non-metastatic or low volume metastatic disease a case by case discussion is required

31/05/2015

Presented By Ian Tannock at 2015 ASCO Annual Meeting
Androgen Deprivation Therapy

- Denosumab, Zoledronic Acid

Surgery
Radiation
Surveillance

Abiraterone
Enzalutamide

Radium-223

Chemotherapy

Docetaxel
Sipuleucel-T

Cabazitaxel

Local Therapy

Androgen Deprivation

Death

Resistance

Presented By Himisha Beltran at 2016 ASCO Annual Meeting
What did We Learned in 2016?
Randomized Phase III Trial of Ipilimumab vs Placebo in Chemonaive mCRPC

No positive phase 3 RCT of immunotherapy

602 chemonaive mCRPC patients with no or mild symptoms randomized to ipilimumab (n=400) or placebo (n=202); Primary end-point: OS; Secondary end-point: PFS and safety

mCRPC: metastatic castrate-resistant prostate cancer; OS: overall survival; PFS: progression-free survival

2 Randomise Phase III Trials of Cabazitaxel

• FIRSTANA

• PROSELICA
FIRSTANA: Randomized, Open-Label Phase III Trial of CABA (25 or 20 mg/m²) vs DOC in Chemo-naive mCRPC

159 centers worldwide

mCRPC pts who have not previously received chemotherapy
N=1,168

- Primary endpoint: OS
- Secondary: safety, PFS, tumor response, PSA response, pain response, QoL, time to SREs

- Prophylactic G-CSF **NOT** allowed at cycle 1
- Statistics: superiority trial (HR 0.75)

What is the best first regimen?

G-CSF: granulocyte colony stimulating factor; q3w: every 3 weeks; PFS: progression-free survival; SREs: skeletal related events; P: prednisone or prednisolone
**FIRSTANA – Key Results**

### OS (primary endpoint)

**Median OS, mo (95% CI)**
- **DOC + P**: 24.3 (22.18-27.60)
- **CABA 20 + P**: 24.5 (21.75-27.20)
- **CABA 25 + P**: 25.2 (22.90-26.97)

**CABA 20 vs DOC**
- HR=1.009 (0.85-1.197)
- *P*=0.9967

**CABA 25 vs DOC**
- HR=0.97 (0.819-1.16)
- *P*=0.7574

### PFS (composite)*

**Median PFS, mo (95% CI)**
- **DOC + P**: 5.3 (4.86-5.78)
- **CABA 20 + P**: 4.4 (3.91-5.09)
- **CABA 25 + P**: 5.1 (4.60-5.72)

**CABA 20 vs DOC**
- HR=1.063 (0.913-1.236)
- *P*=0.4218

**CABA 25 vs DOC**
- HR=0.989 (0.849-1.152)
- *P*=0.8035

---

*PFS: progression-free survival defined as tumor progression or PSA progression or pain progression or death

### FIRSTANNA - Selected Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>DOC + P N=387</th>
<th>CABA 20 + P N=369</th>
<th>CABA 25 + P N=391</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Grades %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>8.3</td>
<td>2.4</td>
<td>12.0</td>
</tr>
<tr>
<td>Neutropenic infection</td>
<td>4.9</td>
<td>1.6</td>
<td>6.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37.0</td>
<td>32.5</td>
<td>49.9</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>25.1</td>
<td>11.7</td>
<td>12.3</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>20.4</td>
<td>9.8</td>
<td>7.7</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>13.7</td>
<td>4.9</td>
<td>6.6</td>
</tr>
<tr>
<td>Nail disorder</td>
<td>9.0</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Hematuria</td>
<td>3.6</td>
<td>20.3</td>
<td>25.1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2.3</td>
<td>10.8</td>
<td>9.5</td>
</tr>
<tr>
<td>Alopecia</td>
<td>39.0</td>
<td>8.9</td>
<td>13.0</td>
</tr>
</tbody>
</table>

PROSELICA: Randomized, Open-label, Non-inferiority Phase III Trial Comparing 2 Doses of CABA Post-DOC

172 centers worldwide

mCRPC pts progressing during or after treatment with a DOC-based regimen N=1,200

- Primary endpoint: OS
- Secondary: safety, PFS, tumor response, PSA response, pain, QoL

What is the proper dose in 2nd line?

CABA 25 mg/m² q3w + P (10 mg/d) for 10 cycles N=598

CABA 20 mg/m² q3w + P (10 mg/d) for 10 cycles N=602

- Prophylactic G-CSF **NOT** allowed at cycle 1
- Statistics: **non-inferiority trial design** (CABA 20 maintains **at least 50%** of the OS benefit of CABA 25 vs mito in TROPIC)

PROSELICA – Key Results

OS (primary endpoint)

Median OS, months (95% CI)

PFS (composite)*

Median PFS, months (95% CI)
- CABA 20 + P: 2.9 (2.79-3.45)
- CABA 25 + P: 3.5 (3.12-3.94)

HR (20 vs 25): 1.099 (0.974-1.24)
One-sided 98.9% upper-bound CI: 1.184 within the non-inferiority margin (1.214)

*PFS: progression-free survival defined as tumor progression or PSA progression or pain progression or death

PROSELICA – PSA and Tumor Responses

**PSA response**

<table>
<thead>
<tr>
<th>Group</th>
<th>Response Rate</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABA 20</td>
<td>29.5%</td>
<td>160/543</td>
</tr>
<tr>
<td>CABA 25</td>
<td>42.9%</td>
<td>231/538</td>
</tr>
</tbody>
</table>

Assessed in evaluable patients: with baseline ≥10 ng/ml and at least on post-baseline measurement

**RECI ST response**

<table>
<thead>
<tr>
<th>Group</th>
<th>Response Rate</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABA 20</td>
<td>18.5%</td>
<td>50/271</td>
</tr>
<tr>
<td>CABA 25</td>
<td>23.4%</td>
<td>60/256</td>
</tr>
</tbody>
</table>

$P=0.1924$

Assessed in patients with measurable disease at baseline and evaluable data to meet the criteria for RECI ST derivation
DNA Damage Repair Defects (DRD)
“Homozygous deletions/deleterious mutations”

N=22/87 (25%)

“Personalize treatment for case of DRD”

For Metastatic Castration-Resistant Prostate Cancer Patients (NCI9012). A University of Chicago Phase II Consortium Trial

Presented by Maha Hussain at 2016 ASCO Annual Meeting
Reported studies

Abi + veliparib

Veliparib + TMZ

TOPARP


Presented By Michael Morris at 2016 ASCO Annual Meeting
Systematic Review of 13 Published Retrospective Studies in mCRPC (N=1,016)

12-month cumulative OS rate by sequence (post-DOC)

Poor outcome when novel AR-targeted agents are prescribed in sequence

ART: novel AR-targeted agent (abiraterone acetate or enzalutamide)

Retrospective analysis of 574 consecutive patients with mCRPC treated with **CABA (after DOC)** in 44 centers from 6 countries (France, Greece, Poland, Spain, Turkey, UK)

- **DOC → CABA → ART (N=124)**
- **DOC → ART → CABA (N=183)**
- **DOC → CABA (N=267)**

**FLAC International Database (HEGP)**

**ART:** novel AR-targeted agent (enzalutamide or abiraterone); **HEGP:** Hôpital Européen Georges-Pompidou

*Historical reference – First recruited patients (ART were not yet available)*

FLAC - OS from First DOC Cycle

DOC → CABA → ART
Median 40.1 mo
[95% CI, 34.6-51.8]

DOC → CABA
Median 30.1 mo
[95% CI, 26.8-32.7]

DOC → ART → CABA
Median 37.1 mo
[95% CI, 32.5-40.5]

CATS International Database (HEGP)

- Retrospective analysis of 560 consecutive patients treated with DOC, CABA and one ART in 31 centers in 7 countries (France, Austria, Greece, Italy, Israel, Spain, UK)

560 mCRPC pts treated with DOC, CABA and ART

DOC → CABA → ART (N=129)

DOC → ART → CABA (N=390)

ART → DOC → CABA (N=41)

CATS – OS from First Life-Extending Therapy Initiation by Sequence

DOC → CABA → ART

Median 37.3 mo
[95% CI, 32.4–45.2]

ART → DOC → CABA

Median 36.0 mo
[95% CI, 33.4–39.7]

DOC → ART → CABA

Median 30.1 mo
[95% CI, 24.3–52.7]

And, what is new knowledge in 2017
A randomized phase II cross-over study of abiraterone + prednisone vs enzalutamide for patients with metastatic, castration-resistant prostate cancer

Kim N. Chi, Matti Annala, Katherine Sunderland, Daniel Khalaf, Daygen Finch, Conrad D. Oja, Joanna Vergidis, Muhammad Zulfiqar, Kevin Beja, Gillian Vandekerkhove, Martin Gleave, Alexander W. Wyatt

British Columbia Cancer Agency, Vancouver, BC; Institute of Biosciences and Medical Technology, Tampere, Finland; BC Cancer Agency - Vancouver Centre, Vancouver, BC; BC Cancer Agency - Centre for the Southern Interior, Kelowna, BC; British Columbia Cancer Agency, Fraser Valley Centre, Vancouver, BC; British Columbia Cancer Agency, Vancouver Island Centre, Victoria, BC; BC Cancer Agency, Abbotsford, BC; Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Vancouver, BC; Vancouver Prostate Centre, University of British Columbia, Vancouver, BC

Presented By Charles Ryan at 2017 ASCO Annual Meeting
**Study Schema**

**Randomize 1:1**

- **Plasma and Whole Blood**
  - Treatment naïve metastatic CRPC
  - Eligible for treatment with ABI or ENZA
  - N = 200

**Progression 1**

- Abiraterone 1000 mg
  - Prednisone 5 mg
- Enzalutamide 160 mg

**Progression 2**

- Abiraterone 1000 mg
  - Prednisone 5 mg
- Enzalutamide 160 mg

---

**Primary Objective**
- Response and Time to PSA progression (TTPP) after 2nd line therapy

**Secondary Objectives**
- TTP/TTPP with 1st line therapy
- PSA decline from baseline
- Correlation with deep targeted sequencing of cfDNA

ClinicalTrials.gov: NCT02125357

---

Presented By Charles Ryan at 2017 ASCO Annual Meeting
Best PSA decline: 12 weeks

<table>
<thead>
<tr>
<th></th>
<th>Abiraterone (N=99)</th>
<th>Enzalutamide (N=98)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA Decline ≥ 30%</td>
<td>64 (65%)</td>
<td>83 (85%)</td>
<td>0.0012</td>
</tr>
<tr>
<td>PSA Decline ≥ 50%</td>
<td>54 (55%)</td>
<td>75 (77%)</td>
<td>0.0012</td>
</tr>
<tr>
<td>No PSA Decline</td>
<td>20 (20%)</td>
<td>10 (10%)</td>
<td>0.0501</td>
</tr>
</tbody>
</table>

Presented By Charles Ryan at 2017 ASCO Annual Meeting
Time to Progression

ABI Median TTP: 7.4 m (95% CI: 5.1, 9.7)
ENZ Median TTP: 7.4 m (95% CI: 4.8, 10.0)

*First of confirmed PSA progression (PCWG3), clinical or radiological progression, or death from disease

Phase 2: high response in Enz, but not different in time to PD
A Phase 4, Randomized, Double-Blind, Placebo-Controlled Study of Continued Enzalutamide Post Prostate-Specific Antigen Progression in Men With Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer

Gerhardt Attard,¹ Michael Borre,² Howard Gurney,³ Yohann Loriot,⁴ Corina Andresen-Daniil,⁵ Ranjith Kalleda,⁵ Trinh Pham,⁵ Mary-Ellen Taplin⁶

¹The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK; ²Aarhus University Hospital, Aarhus, Denmark; ³Macquarie University, Sydney, Australia; ⁴Institut Gustave Roussy, University of Paris Sud, Villejuif, France; ⁵Medivation, Inc. (Medivation was acquired by Pfizer Inc in September 2016), San Francisco, CA; ⁶Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Presented By Charles Ryan at 2017 ASCO Annual Meeting

Adding AA beyond progression of enza
PLATO: Novel Trial Design

Open-Label Enzalutamide - Period 1

Enzalutamide

PSA evaluation (week 13 and week 21) → Follow for PSA progression → PSA rise → Safety follow-up

Enrolled n = 509 (Target n = 500)
PSA Responders n = 412 (Target n = 415)
Randomized n = 251 (Target n = 250)

1:1 randomization* at confirmed PSA progression

Enzalutamide + abiraterone/prednisone → Radiographic or unequivocal clinical progression
Placebo + abiraterone/prednisone

Safety follow-up and survival → Subsequent therapy

Total 16 weeks of follow-up

*Randomization stratified by confirmed PSA response at week 13 in period 1 (≥ 0% to < 30% vs ≥ 30%):
9 patients (≥ 0% to < 30%) and 242 patients (≥ 30%)

Patients enrolled in 51 study centers in North America, Europe, and Australia.
Abbreviation: PFS, progression-free survival.

Presented By Charles Ryan at 2017 ASCO Annual Meeting
Primary Endpoint: PFS

Progression-Free Survival, %

Time, mo

ENZA + Abi/Pred (n = 126)
Median (95% CI) 5.7 (4.6-8.1) mo
Stratified hazard ratio (95% CI) 0.828 (0.612-1.119)

Placebo + Abi/Pred (n = 125)
Median (95% CI) 5.6 (4.5-7.3) mo
Stratified log-rank test 0.2176

Event/Cumulative Events

ENZA + Abi/Pred 27/27 30/57 10/67 9/76 5/81 1/82 1/83
Placebo + Abi/Pred 33/33 26/59 13/72 8/80 6/86 4/90 2/92

Abbreviations: CI, confidence interval; mo, months.
Practice Changing?

- Suggests adding second AR targeted drug is not effective.

- Supports my ‘One shot on goal’ theory

- Await phase III study of Abi+Enz vs Enz alone
Abiraterone + Prednisone (Abi) +/- Veliparib (Vel) For Metastatic Castration-Resistant Prostate Cancer Patients (CRPC pts): NCI 9012 Updated Clinical and Genomics Data


Northwestern University Robert H. Lurie Comprehensive Cancer Center; Department of Biostatistics, University of Michigan; City of Hope Comprehensive Cancer Center; Indiana University Melvin and Bren Simon Cancer Center; Rutgers Cancer Institute of New Jersey; University of Michigan; University of Michigan Health System; University of Utah; University of Washington; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University; NorthShore University Health System; The University of Texas MD Anderson Cancer Center; The University of North Carolina at Chapel Hill; University of Michigan Comprehensive Cancer Center; The Sidney Kimmel Cancer Center at Thomas Jefferson University; The University of Chicago; University of California, San Francisco, University of Michigan

DRD : what is the proper treatment?
Key inclusion criteria
- Progressive mCRPC by at least 1 criteria:
  a. PSA progression;
  b. Measurable disease;
  c. Bone disease
- No prior abiraterone.
- Prior ketoconazol & chemo is allowed
- Agree to undergo a biopsy of metastatic site with adequate fresh tissue unless adequate metastatic archival tissue is available

Study Design

**Registration**

Metastatic tissue biopsy adequate for ETS fusion status evaluation

ETS status stratification (+/-)

Arm A
Abiraterone + prednisone

Arm B
Abiraterone/prednisone + veliparib *

Metastatic tissue biopsy inadequate for ETS fusion status evaluation

Off Protocol

*Veliparib dose: 200 (300) mg PO bid daily
Progression Free Survival & Overall Survival

Arm A: 10.1 (8.2-13.8)
Arm B: 11.0 (8.1-13.6)

P=0.89

- No difference in PFS by ETS status

Arm A: Abi/Pred, Arm B: Abi+Veliparib

Median OS (95% CI): Arm A: 30.6 m (28.4 – NR), Arm B 32.3 m (28.4 – NR)
PFS by DRD status: Overall & By Arm

PFS by DRD status (N= 75)

Arm A: Abiraterone (N=31)
- DRD: 16.6 (13.5-19.5)
- WT: 8.2 (3.9-10.3)
- P=0.27

Arm B: Abiraterone + Veliparib (N=44)
- DRD: 13.8 (8.2-32.9)
- WT: 8.0 (5.3-13.8)
- P=0.03
Practice Changing?

• Not entirely, but suggests that treating a patient with BRCA2 /ATM with Abi is reasonable.

• You may not need to go right to the parp inhibitor or to carboplatin.

• Goes against other data consistently showing a worse prognosis in patients with BRCA2
Adding abiraterone for men with high-risk prostate cancer starting long-term androgen deprivation therapy: Survival results from STAMPEDE

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

Abiraterone in HSPC

Presented By Charles Ryan at 2017 ASCO Annual Meeting
Abiraterone comparison: patients

STAMPEDE: Abiraterone comparisons

SOC = ADT(+/- RT)
SOC + zoledronic acid
SOC + docetaxel
SOC + celecoxib
SOC + zoledronic acid + docetaxel
SOC + zoledronic acid + celecoxib
SOC + abirone
SOC + M1 | RT (M1)
SOC + metformin
SOC + E2

A = ~900 pts --> ~257 primary outcome measure events
G = ~900 pts

Presented By Charles Ryan at 2017 ASCO Annual Meeting
Conclusions

• In hormone naïve prostate cancer abiraterone acetate + prednisolone improves
  – Overall survival by 37%
  – Failure free survival by 71%
  – Symptomatic skeletal events by 55%
• Treatment was well tolerated
• Abiraterone acetate + prednisolone should be part of the standard of care for men starting long term androgen deprivation therapy
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 Özlüroğlu,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 Oncología 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
De novo metastatic prostate cancer

- Metastatic castration-naïve prostate cancer (mCNPC) incidence is\(^1\)\(^-{5}\):
  - \(~3\%\) in US and rising;
  - \(~6\%\) across Europe
  - \(\sim 10\%\) in Latin America
  - \(~60\%\) in Asia-Pacific

- Historically, androgen deprivation therapy (ADT) has been the standard of care\(^6\)

- Most men with metastases progress to mCRPC largely driven by reactivation of AR signaling\(^6\)
Overall 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

- Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada
- Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results
Statistically significant **38%** risk reduction of death

Hazard ratio, 0.62 (95% CI, 0.51-0.76)
P<0.0001

ADT + AA + P, not reached

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

Median follow-up: 30.4 months
Statistically significant 70% risk reduction of time to PSA progression

Hazard ratio, 0.30 (95% CI, 0.26-0.35)
P < 0.0001

ADT + AA + P, 33.2 mo
ADT + placebos, 7.4 mo

<table>
<thead>
<tr>
<th>Months</th>
<th>ADT + AA + P</th>
<th>ADT + placebos</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>597</td>
<td>602</td>
</tr>
<tr>
<td>4</td>
<td>520</td>
<td>393</td>
</tr>
<tr>
<td>8</td>
<td>447</td>
<td>250</td>
</tr>
<tr>
<td>12</td>
<td>379</td>
<td>172</td>
</tr>
<tr>
<td>16</td>
<td>340</td>
<td>129</td>
</tr>
<tr>
<td>20</td>
<td>285</td>
<td>102</td>
</tr>
<tr>
<td>24</td>
<td>227</td>
<td>65</td>
</tr>
<tr>
<td>28</td>
<td>162</td>
<td>33</td>
</tr>
<tr>
<td>32</td>
<td>95</td>
<td>19</td>
</tr>
<tr>
<td>36</td>
<td>48</td>
<td>8</td>
</tr>
<tr>
<td>40</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>44</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Conclusions

- In the phase 3 LATITUDE, addition of AA + P to ADT led to:
  - Significantly improved OS with a 38% reduction in the risk of death
  - Significantly prolonged rPFS (53% reduction) and all secondary end points

- The overall safety profile of ADT + AA + P was consistent with prior studies in patients with mCRPC
# Comparing CHAARTED High Volume Patients and LATITUDE Patients

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Eligibility Criteria</th>
</tr>
</thead>
</table>
| LATITUDE All Patients | 1199 | Meets at least 2 of 3 high-risk criteria:  
  - Presence of ≥ 3 lesions on bone scan  
  - Presence of measurable visceral lesion  
  - Gleason score of ≥ 8 |
| CHAARTED High Volume   | 513  | Meets one or both criteria:  
  - Presence of ≥ 4 lesions on bone scan  
    (with at least one lesion outside pelvis and spine)  
  - Presence of measurable visceral lesion |
Comparing LATITUDE Patients and CHAARTED High Volume Patients

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Overall Survival (Control Arm: ADT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LATITUDE</td>
<td>1199</td>
<td>34.7 mos</td>
</tr>
<tr>
<td>(406 deaths)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHAARTED (High Volume)</td>
<td>513</td>
<td>34.4 mos</td>
</tr>
<tr>
<td>(299 deaths)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Similar Overall Survival in ADT-only (control) groups suggests similar populations.
### Comparing Overall Survival Across Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Median OS</th>
<th>3 yr OS rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>Control (months)</td>
</tr>
<tr>
<td>LATITUDE</td>
<td>0.62 (0.51-0.76)</td>
<td>34.7 mo</td>
</tr>
<tr>
<td>CHAARTED High Volume</td>
<td>0.63 (0.50-0.79)</td>
<td>34.4 mo</td>
</tr>
</tbody>
</table>

* Estimated from KM plots
Take Homes from Latitude

- The benefit obtained from adding abiraterone to ADT appears to be the same as that seen with docetaxel.

- The use of abiraterone
  - Avoids Chemotherapy
  - Avoids (rare) neutropenic complication/ treatment-associated deaths
  - Replaces short term IV treatment with long term oral treatment
  - May be more appropriate in elderly or debilitated

- Future evaluation
  - QOL and financial toxicity
  - Testing earlier (eg climbing PSA patients)
  - Combination with docetaxel
Progress in Metastatic CRPC

Presented By Fred Saad at Genitourinary Cancers Symposium 2016
Overall conclusions

- Management of CRPC is rapidly evolving
- New drugs in development: need to move to a tailored therapy
- The most appropriate sequencing of these new agents remains to be determined and chemotherapy remains a valid treatment option in mCRPC

‘The right drug, at the right time, for the right patient, at the right place and by the right team’