Prostate Cancer

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Prostate Cancer

Diagram:
- Asymptomatic
  - Local Therapy
  - Androgen Deprivation
  - Therapies After LHRH Agonists and Antiandrogens
- Symptomatic
  - Castrate Sensitive
  - Castrate Resistant

2010
- Docetaxel every 2 or 3 weeks
Abirateron  
Enzalutamide  
Cabazitaxel  
Radium 223

Androgen Deprivation  
Local Therapy  
Therapies After LHRH Agonists and Antiandrogens

Asymptomatic  
Symptomatic

Castrate Sensitive  
Castrate Resistant

2013  
Docetaxel every 2 or 3 weeks
Abirateron Enzalutamide
Abirateron Enzalutamide
Cabazitaxel
Radium 223

Local Therapy
Androgen Deprivation
Therapies After LHRH Agonists and Antiandrogens
Post-chemotherapy
Death

Asymptomatic
Symptomatic

Castrate Sensitive
Castrate Resistant

2014
Docetaxel every 2 or 3 weeks
Docetaxel

Androgen Deprivation

Local Therapy

Therapies After LHRH Agonists and Antiandrogens

Abirateron Enzalutamide

Cabazitaxel
Radium 223

Death

Post-chemotherapy

Asymptomatic

Symptomatic

Castrate Sensitive

Castrate Resistant

2015

Docetaxel every 2 or 3 weeks
Abirateron
Docetaxel

Abirateron
Enzalutamide

Abirateron
Enzalutamide
Cabazitaxel
Radium 223

Androgen
Depression

Local
Therapy

Therapies After LHRH
Agonists
and Antiandrogens

Post-chemotherapy

Death

Asymptomatic

Symptomatic

Castrate Sensitive

Castrate Resistant

2018

Docetaxel every 2 or 3 weeks
Case No 1:

- 64 year old teacher. Follower of antroposophy.
- Presents on request of his daughter.
- Extensive bone metastases. PSA of 1600 ng/ml.
- Biopsy gives a Gleason score of 4+5=9.
- Patient started on ADT with Goserelin s.c. every three months plus two weeks of bicalutamide.
- Rapidly feeling much better.
Prostate Cancer

- Androgen Deprivation
- Local Therapy
- Therapies After LHRH Agonists and Antiandrogens
- Asymptomatic
- Symptomatic
- Castrate Sensitive
- Castrate Resistant
- 2010
- Docetaxel every 2 or 3 weeks
Blockade: LH-RH-Agonisten
Blockade: Flutamid, Bicalutamid
E3805
CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer

Christopher Sweeney, Yu-Hui Chen, Michael Carducci, Glenn Liu, Mario Eisenberger, Yu-Ning Wong, Noah Hahn, Manish Kohli, Robert Dreicer, Nicholas Vogelzang, Joel Picus, Daniel Shevrin, Maha Hussain, Jorge Garcia, Robert DiPaola
E3805 – CHAARTED Treatment

**STRATIFICATION**

- Extent of Mets
  - High vs Low
- Age
  - ≥70 vs < 70 yo
- 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

Follow for time to progression and overall survival

Chemotherapy at investigator’s discretion at progression

**ARM B:**
ADT (androgen deprivation therapy alone)

Evaluate every 12 weeks

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

Presented by: Christopher J. Sweeney, MBBS
Overall survival by volume of mets at start of ADT

In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival.

**High volume**
- 82 vs 110 deaths (192 events)
- p=0.0012
- HR=0.60 (0.45-0.81)
- Median OS:
  - ADT + D: 49.2 months
  - ADT alone: 32.2 months

**Low volume**
- 19 vs. 26 deaths (45 events)
- p=0.0836
- HR=0.63 (0.34-1.17)
- Median OS:
  - ADT + D: Not reached
  - ADT alone: Not reached

Sweeney, LBA2, ASCO 2014
What is extensive disease?

We need a more precise identification of disease distribution or volume to better identify those who most benefit from chemotherapy.
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 Özugüroğlu, 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

1 Gustave Roussy, University of Paris Sud, Villejuif, France; 2 Janssen Research & Development, Los Angeles, CA; 3 Instituto de Oncologia de Rosário, Rosário, Argentina; 4 National Cancer Center Hospital East, Chiba, Japan; 5 12 de Octubre University Hospital, Madrid, Spain; 6 P.A. Hertsens Moscow Cancer Research Institute, Moscow, Russian Federation; 7 Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey; 8 Fudan University Shanghai Cancer Center, China; 9 Studienpraxis Urologie, Nürtingen, Germany; 10 Oxford University Hospitals Foundation NHS Trust, Oxford, UK; 11 Janssen Research & Development, Beerse, Belgium; 12 Janssen Research & Development, San Diego, CA; 13 Janssen Research & Development, Raritan, NJ; 14 Janssen Global Services, Raritan, NJ; 15 BC Cancer Agency, Vancouver, BC, Canada
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

Overall Survival (%)

0 20 40 60 80 100

No. of events: 406 (48% of 852)
ADT + AA + P: 169
ADT + placebos: 237

ADT + placebos, 34.7 mo

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

No. at risk

ADT + AA + P
597 565 529 479 388 233 93 9

ADT + placebos
602 564 504 432 332 172 57 2

Median follow-up: 30.4 months
Case No 2: Referral from Neurosurgery

- 74 year old retired businessman
- Diagnosed with PCa 4 years ago.
- Treated with radical prostatectomy plus salvage radiation for PSA relapse. On ADT for further PSA progression.
- Resection of a single brain metastasis from PCa.
- Staging reveals enlarged lymphnodes and bone mets.
- Otherwise fit & active. Feels well after surgery.
Androgen Deprivation

Therapies After LHRH Agonists and Antiandrogens

Local Therapy

Asymptomatic

Symptomatic

Castrate Sensitive

Castrate Resistant

2010

Docetaxel every 2 or 3 weeks
Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer

Figure 1. Kaplan–Meier Estimates of the Probability of Overall Survival in the Three Groups.

Figure 2. Greatest Change and Median Change from Baseline in Normalized Scores on the Functional Assessment of Cancer Therapy–Prostate Questionnaire for Individual Domains of the Quality of Life during Treatment.
50 mg/m² every 2 weeks versus 75 mg/m² every 3 weeks
Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy

- Randomised Study
- Large Trial
- Chemotherapy-naive
- Oral treatment (4 Tbl)
- Well tolerated
- Trend for improved OS
- Progression and time to chemo delayed
- Alternative to Docetaxel in CRPC

1000 mg = 4 tablets
4305,00 CHF per month

Enzalutamide in Metastatic Prostate Cancer before Chemotherapy

✓ Randomised Study
✓ Large Trial
✓ Chemotherapy-naive
✓ Oral treatment (4 Tbl)
✓ Well tolerated
✓ Improved OS
✓ Improved QoL
✓ Progression and time to chemo delayed
✓ Alternative to Abiraterone and Docetaxel in CRPC

160 mg = 4 tablets
4409.40 CHF per month

Abirateron Enzalutamide

Androgen Deprivation

Therapies After LHRH Agonists and Antiandrogens

Death

Post-chemotherapy

Asymptomatic

Symptomatic

Castrate Sensitive

Castrate Resistant

2018

Docetaxel every 2 or 3 weeks
What would be YOUR choice in case No 2?

- Abiraterone
- Enzalutamide
- Docetaxel
- Cabazitaxel
- Other
Mechanism of action

**Abiraterone**

- Cholesterol
- Pregnenolone
- Progesterone
- Deoxycorticosterone
- Corticosterone
- Aldosterone

(17α-17α hydroxylase, 17, 20-α-lase-20 lyase)

**Enzalutamide**

1. Inhibits binding of androgens to AR
2. Inhibits AR nuclear translocation
3. Inhibits AR-mediated DNA binding
CONCLUSIONS

Detection of AR-V7 in circulating tumor cells from patients with castration-resistant prostate cancer may be associated with resistance to enzalutamide and abiraterone. These findings require large-scale prospective validation.
Case No 3: Call from an elderly colleague

• Metastatic prostate cancer for several years.

• Initial ADT mit GNRH agonist plus bicalutamide.

• Castration-refractory after 4 years, treated with six cycles of docetaxel and felt fine for a year or so.

• He feels off his feet, has bone pain and sweats a lot at night. Apart from this his is ok and sees his private patients regularly.

• His PSA is rapidly increasing from very low levels to 134 ng/ml.
The Site of Visceral Metastases Predicts Overall Survival in Castration-Resistant Prostate Cancer Patients: A Meta-Analysis of 5 Phase III trials

Susan Halabi¹, Wm. Kevin Kelly², Haojin Zhou¹, Andrew J. Armstrong¹, David I. Quinn³, Karim Fizazi⁴, Nicole C. Solomon¹, Ian F. Tannock⁵, Daniel P. Petrylak⁶, Michael J. Morris⁷, Eric J. Small⁸

¹Duke University, Durham, NC; ²Thomas Jefferson University, Philadelphia, PA; ³University of Southern California, Los Angeles, CA; ⁴Institut Gustave Roussy, Villejuif, France; ⁵Princess Margaret Cancer Centre, Toronto, ON, Canada; ⁶Yale University, New Haven, CT; ⁷Memorial Sloan Kettering Cancer Center, New York, NY; ⁸University of California, San Francisco, CA

PRESENTED AT THE 2014 ASCO ANNUAL MEETING. PRESENTED DATA IS THE PROPERTY OF THE AUTHOR.
## Patient Population (N=3,993)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sample size</th>
<th>Years of Recruitment</th>
<th>Treatment arms</th>
<th>Median Follow-up Length (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX 327</td>
<td>669</td>
<td>03/00 – 06/02</td>
<td>Docetaxel+prednisone</td>
<td>53</td>
</tr>
<tr>
<td>SWOG 9916</td>
<td>338</td>
<td>10/99 – 01/03</td>
<td>Docetaxel+estramustine</td>
<td>26</td>
</tr>
<tr>
<td>CALGB 90401</td>
<td>1,050</td>
<td>05/05 – 12/07</td>
<td>Docetaxel+prednisone, bevacizumab</td>
<td>67</td>
</tr>
<tr>
<td>ENTHUSE 33</td>
<td>942</td>
<td>01/08 - 05/11</td>
<td>Docetaxel+zibotentan, placebo</td>
<td>22</td>
</tr>
<tr>
<td>SWOG 0421</td>
<td>994</td>
<td>08/06 – 05/10</td>
<td>Docetaxel+Atrasentan, placebo</td>
<td>18</td>
</tr>
</tbody>
</table>

Presented by: Susan Halabi, Ph.D.
Overall Survival (OS) by Site of Metastases

- **LN only**: Median OS = 27 months (95% CI: 25, 32)
- **BONE**: Median OS = 20 months (95% CI: 19, 21)
- **VISC**: Median OS = 14 months (95% CI: 13, 15)

**No. at risk**
- LN only: 187, 157, 105, 56, 34
- BONE: 3147, 2296, 982, 381, 157
- VISC: 635, 370, 139, 56, 19

Presented by: Susan Halabi, Ph.D.
Hypothesis 2: Liver vs. Lung

Median OS in months (95% CI)
- LUNG: 17 (15-18)
- LIVER: 12 (10-14)

HR = 1.4 (95% CI = 1.2-1.7, p < 0.001)

Presented by: Susan Halabi, Ph.D.
## Survival in CRPC post chemo

<table>
<thead>
<tr>
<th>Metastatic Site</th>
<th>Median Overall Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphnode</td>
<td>27</td>
</tr>
<tr>
<td>Bone</td>
<td>20</td>
</tr>
<tr>
<td>Lung</td>
<td>17</td>
</tr>
<tr>
<td>Liver</td>
<td>12</td>
</tr>
</tbody>
</table>
Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial

- Randomized (open-label) study
- Large patient cohort
- Progression post docetaxel
- Compared to mitoxantrone
- Intravenous treatment
- Well tolerated, but: therapy-associated death!

- Better overall survival, but only in patients with < ECOG 2

Preis 5540.- CHF pro Applikation (60 mg Amp)
Abiraterone and Increased Survival in Metastatic Prostate Cancer

- Randomized study
- Large patient cohort
- Progression post docetaxel
- Oral treatment (4 Tbl)
- Well tolerated
- Improved overall survival
- Less pain

4305.00 CHF per month

Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy

- Randomised study
- Large patient cohort
- Progression post docetaxel
- Oral treatment (4 Tbl)
- Well tolerated
- Improved overall survival
- Better quality-of-life

4409,40 CHF per month

Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

Price 5985.- CHF per ampulle (6000 kBq)
## Treatment options in CRPC post docetaxel

<table>
<thead>
<tr>
<th>Drug</th>
<th>Primary Endpoint</th>
<th>Indication</th>
<th>Median OS HR; p-value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cabazitaxel</strong></td>
<td>Survival</td>
<td>mCRPC Post-Doc</td>
<td>+ 2.4 Monate 0.70; &lt;0.0001</td>
<td>Lancet 2010</td>
</tr>
<tr>
<td><em>(Jevtana®)</em></td>
<td></td>
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</tr>
<tr>
<td><strong>Abirateron</strong></td>
<td>Survival</td>
<td>mCRPC Post-Doc</td>
<td>+ 3.9 Monate 0.65; &lt;0.0001</td>
<td>NEJM 2011</td>
</tr>
<tr>
<td><em>(Zytiga®)</em></td>
<td></td>
<td></td>
<td></td>
<td>Lancet 2012</td>
</tr>
<tr>
<td><strong>Enzalutamid</strong></td>
<td>Survival</td>
<td>mCRPC Post-Doc</td>
<td>+ 4.8 Monate 0.63; &lt;0.0001</td>
<td>NEJM 2012</td>
</tr>
<tr>
<td><em>(Xtandi®)</em></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Radium 223</strong></td>
<td>Survival</td>
<td>mCRPC Post Doc</td>
<td>+ 3.6 Monate 0.70; 0.0018</td>
<td>NEJM 2013</td>
</tr>
<tr>
<td><em>(Alpharadin®)</em></td>
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</tbody>
</table>
What would be YOUR choice in case No 3?

- Abiraterone
- Enzalutamide
- Cabazitaxel
- Radium 223
- "Give 'em all"
Abirateron Docetaxel

Abirateron Enzalutamide

Abirateron Enzalutamide Cabazitaxel Radium 223

Androgen Deprivation

Therapies After LHRH Agonists and Antiandrogens

Local Therapy

Post-chemotherapy

Asymptomatic

Symptomatic

Castrate Sensitive

Castrate Resistant

2018

Docetaxel every 2 or 3 weeks
Risk depends on:

Stage

Intrinsic nature
Just a suggestion for mPCa

<table>
<thead>
<tr>
<th></th>
<th>Life expectancy ≥ 3 years</th>
<th>Life expectancy ≥ 3 years</th>
<th>Life expectancy &lt; 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fit for docetaxel (PS 0,1)</td>
<td>Unfit for docetaxel (PS &gt; 1)</td>
<td></td>
</tr>
<tr>
<td>High risk, 2 of 3:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Gleason 8-10,</td>
<td>ADT plus docetaxel</td>
<td>ADT plus Abi</td>
<td>ADT alone</td>
</tr>
<tr>
<td>• ≥ 3 bone mets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Visceral mets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk; all others</td>
<td>ADT alone</td>
<td>ADT alone</td>
<td>ADT alone</td>
</tr>
</tbody>
</table>
(My) take home messages

- Patients with high-risk metastatic PCa should receive ADT plus either docetaxel or abiraterone upfront
- Subsequent treatments should depend on response and response duration to upfront choices
- Patient and his expectations need to be factured into the equation