UPDATES ON NON SURGICAL MANAGEMENT OF PROSTATE CANCER

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To be discussed

Management of Non Metastatic PrCa
- Radiotherapy
- Hormone therapy (NA ADT/ADj ADT)

Metastatic Pr Ca
- Molecular Biology
- Chemotherapy
- Hormone therapy
- CRPC
- Newer Molecules
Hormonal pathways
Types of prostate cancer

- Prostate cancer growth may be fueled even after androgen deprivation therapies

  1. Androgen/Castration Naïve/sensitive/dependent
     Tumor cells grow in presence of DHT

  2. Androgen resistant/insensitive/independent/castration Resistant (CRPC)
     Tumor cells grow in androgen deprivation with a very low level of testosterone (<50ng/dl).
Progression of prostate cancer

Natural History and Treatment Progression of Prostate Cancer

**Time**
- Local therapy
- Androgen deprivation
- Therapies after LHRH* agonists and antiandrogens
- Chemotherapy
- Post-chemotherapy
- Pre-metastatic
- Radiographically metastatic
- Asymptomatic
- Symptomatic
- Death

* LHRH: Luteinizing hormone releasing hormone
Clinical states model of PrCa

Figure 68.1 Clinical states model of prostate cancer progression. Green boxes indicate castration-resistant prostate cancer (CRPC) and blue indicate noncastrate disease. PSA, prostate-specific antigen; mCA RPC, metastatic castration-resistant prostate cancer. (Modified from Scher HI, Heller G. Clinical states in prostate cancer: towards a dynamic model of disease progression. Urology 2000;55:323–327.)
Overview

Table 1. Risk groups for localised prostate cancer [7]

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>T1-T2a and GS ≤6 and PSA ≤10</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>T2b and/or GS7 and/or PSA10-20</td>
</tr>
<tr>
<td>High risk</td>
<td>≥T2c or GS8-10 or PSA &gt;20</td>
</tr>
</tbody>
</table>

GS, Gleason score; PSA, prostate-specific antigen.

Table 3. Stage-matched therapeutic strategies

<table>
<thead>
<tr>
<th>Localised disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
</tr>
<tr>
<td>Active surveillance</td>
</tr>
<tr>
<td>Brachytherapy</td>
</tr>
<tr>
<td>Radical prostatectomy</td>
</tr>
<tr>
<td>Radical radiotherapy</td>
</tr>
<tr>
<td>Intermediate risk</td>
</tr>
<tr>
<td>Neoadjuvant ADT + radical radiotherapy + adjuvant ADT</td>
</tr>
<tr>
<td>Neoadjuvant ADT + radical prostatectomy + pelvic lymphadenectomy</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>Neoadjuvant ADT + radical radiotherapy + adjuvant ADT</td>
</tr>
<tr>
<td>Neoadjuvant ADT + radical prostatectomy + pelvic lymphadenectomy</td>
</tr>
<tr>
<td>Metastatic disease</td>
</tr>
<tr>
<td>Hormone-naïve</td>
</tr>
<tr>
<td>ADT</td>
</tr>
<tr>
<td>Castration-resistant (first line)</td>
</tr>
<tr>
<td>Abiraterone</td>
</tr>
<tr>
<td>Docetaxel</td>
</tr>
<tr>
<td>Enzalutamide</td>
</tr>
<tr>
<td>Radium-223</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
</tr>
<tr>
<td>Second line (post-docetaxel)</td>
</tr>
<tr>
<td>Abiraterone</td>
</tr>
<tr>
<td>Cabazitaxel</td>
</tr>
<tr>
<td>Enzalutamide</td>
</tr>
<tr>
<td>Radium-223</td>
</tr>
</tbody>
</table>

ESMO guideline 2015
FAQs on metastatic PrCa/CRPC

- Role of ADTs?
- Intermittent vs Continuous ADT?
- Role of Chemotherapy in Hormone naïve Pr Ca?
- Issue of CRPC (Predictive model)?
- Role of Novel agents?
- Role of taxanes?
- Sequencing of therapies CT>HT/HT>CT/HT>HT?
- Novel chemotherapy options?
- Newer molecules?
ADT in mPrCa

- Gold standard initial treatment
- **Intermittent Vs Continuous ADT (SWOG 9346)**
- Hormone naïve mPrCa treated with 7 months of ADT with PSA <4ng/ml
- 1:1 RCT: Int. vs Cont. (n=3040)
- Median F/U 9.8 years
- MS Cont. Vs Int. (5.8yrs vs 5.2yrs) {inconclusive}
- No toxicity difference in long F/U

Hussain M NEJM 2013
Better **MS** of Int. ADT in extensive disease indicates replacing androgen before progression may prolong androgen dependency in extensive mPrCa.
Intermittent vs Continuous Androgen Deprivation Therapy for Prostate Cancer
A Systematic Review and Meta-analysis

Sindy Magnan, MD, MSc, FRCPC¹; Ryan Zarychanski, MD, MSc, FRCPC²,³; Laurie Pilote, MD¹; Laurence Bernier, MD¹; Michèle Shemilt, MSc⁴; Eric Vigneault, MD, MSc, FRCPC¹,⁴; Vincent Fradet, MD, PhD, FRCSC⁴,⁵; Alexis F. Turgeon, MD, MSc, FRCPC⁴,⁶

[+] Author Affiliations


Results From 10510 references, we included 22 articles from 15 trials (6856 patients) published between 2000 and 2013. All but 1 study had an unclear or high risk of bias. We observed no significant difference between intermittent and continuous therapy for overall survival (HR, 1.02; 95% CI, 0.93-1.11; 8 trials, 5352 patients), cancer-specific survival (HR, 1.02; 95% CI, 0.87-1.19; 5 trials, 3613 patients), and progression-free survival (HR, 0.94; 95% CI, 0.84-1.05; 4 trials, 1774 patients). There was minimal difference in patients’ self-reported quality of life between the 2 interventions. Most trials observed an improvement in physical and sexual functioning with intermittent therapy.

Conclusions and Relevance Intermittent androgen deprivation was not inferior to continuous therapy with respect to the overall survival. Some quality-of-life criteria seemed improved with intermittent therapy. Intermittent androgen deprivation can be considered as an alternative option in patients with recurrent or metastatic prostate cancer.
ADT: personalized approach

- Treat all mPrCa with 7 months ADT
- Risk categorization after 7 months: PSA

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA &lt;0.2ng/ml</td>
<td>PSA 0.2-4ng/ml</td>
<td>PSA &gt;4ng/ml</td>
</tr>
<tr>
<td>MS 75months</td>
<td>MS 44months</td>
<td>MS 13months</td>
</tr>
</tbody>
</table>

- Monitor ADT related adverse events
- Tailoring of Int vs Cont. on PSA and A/E

Hussain M J Clin Oncol 2006
ADT adverse events

- Osteoporosis (RR >21-50% than general pop)
- Calcium and Vit D3 supplementation
- Bisphosphonates/Denosumab
- DEXA scan

- Diabetes (HR 1.44) and CVS disorder (HR 1.31)
- Monitor regularly
Role of upfront chemotherapy in Hormone naïve metastatic Pr Ca

Role of Docetaxel
Docetaxel in Hormone Naïve mPrCa

- **CHAARTED trial (2006-2012)**
- Hormone Naïve mPrCa
- RCT (1:1) ADT alone vs ADT + Doce (6 cycles)
- High Volume [HV] (visc met + ≥ bone mets) vs Low Volume [LV]
- Median Follow up 29 months

### Table: Intent to treat analysis

<table>
<thead>
<tr>
<th>PSA &lt; 0.2 at 12 mos</th>
<th>ADT</th>
<th>ADT + D</th>
<th>P value</th>
<th>Hazard ratio (95%CI*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9.4%</td>
<td>19.7%</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Median OS (mos)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=790</td>
<td>42.3</td>
<td>52.7</td>
<td>0.0006</td>
<td>0.63 (0.48, 0.82)</td>
</tr>
<tr>
<td>N=520-HV</td>
<td>32.2</td>
<td>49.2</td>
<td>0.0012</td>
<td>0.62 (0.46, 0.83)</td>
</tr>
<tr>
<td>N=270-LV</td>
<td>NR**</td>
<td>NR</td>
<td>0.0836</td>
<td>0.58 (0.31, 1.08)</td>
</tr>
</tbody>
</table>

* CI: confidence intervals; **NR: not reached.

- ADT + D improves OS over ADT alone in men with High Volume mPrCa

Sweeney C et al. Clin Oncol 32:5s, 2014(abs)
Docetaxel in Hormone Naïve mPrCa

CHAARTED trial
Sweeney CJ et al.
NEJM 2015
(n= 790)
Hormone Sensitive mPrCa

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survival Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADT + Docetaxel Vs ADT alone</td>
<td>OS 57.6m vs 44m Survival benefit pronounced in High Vol disease PSA&lt;0.2ng/ml at 1yr 27.7 % vs 16.8% More neutropenia in doce arm</td>
</tr>
</tbody>
</table>

More neutropenia in doce arm
Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

Nicholas D James, Matthew R Sydes, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Melissa R Spears, Alastair W S Ritchie, Christopher C Parker, J Martin Russell, Gerhardt Attard, Johann de Bono, William Cross, Rob J Jones, George Thalmann, Claire Amos, David Matheson, Robin Millman, Mymoona Alzouebi, Sharon Beesley, Alison J Birtle, Susannah Brock, Richard Cathomas, Prabir Chakraborti, Simon Chowdhury, Audrey Cook, Tony Elliott, Joanna Gale, Stephanie Gibbs, John D Graham, John Hetherington, Robert Hughes, Robert Laing, Fiona McKinna, Duncan B McLaren, Joe M O’Sullivan, Omi Parikh, Clive Peedell, Andrew Protheroe, Angus J Robinson, Narayanan Srihari, Rajaguru Srinivasan, John Staffurth, Santhanam Sundar, Shaun Tolan, David Tsang, John Wagstaff, Mahesh K B Parmar, for the STAMPEDE investigators*

- Multi arm multi stage model (2006-2013)
- Hormone Naive M0/M1 Pr ca
- N= 2962

Multi arm multistage model

3981 patients enrolled and randomly assigned

- Arm A: 1184 to SOC-only
  - At most recent follow-up: 694 alive with data in past year, 175 alive but no data in past year, 415 died
  - 1184 included in efficacy analysis
  - 1282 received SOC-only
    - 1184 assigned to SOC-only, 8 assigned to SOC+ZA, 46 assigned to SOC+Doc, 44 assigned to SOC+ZA+Doc
    - 1228 included in safety analysis
      - 5 with no adverse event assessment excluded (1 SOC-only, 3 SOC-ZA, 12 SOC+Doc, 28 SOC+ZA+Doc)

- Arm B: 593 to SOC+ZA
  - At most recent follow-up: 351 alive with data in past year, 41 alive but no data in past year, 201 died
  - 593 included in efficacy analysis
  - 611 received SOC+ZA
    - 585 assigned to SOC+ZA, 26 assigned to SOC+ZA+Doc
    - 608 included in safety analysis
      - 3 with no adverse event assessment excluded (3 SOC+ZA)

- Arm C: 532 to SOC+Doc
  - At most recent follow-up: 377 alive with data in past year, 40 alive but no data in past year, 175 died
  - 532 included in efficacy analysis
  - 551 received SOC+Doc
    - 546 assigned to SOC+Doc, 5 assigned to SOC+ZA+Doc
    - 550 included in safety analysis
      - 1 with no adverse event assessment excluded (1 SOC+Doc)

- Arm E: 593 to SOC+ZA+Doc
  - At most recent follow-up: 354 alive with data in past year, 52 alive but no data in past year, 187 died
  - 593 included in efficacy analysis
  - 518 received SOC+ZA+Doc
    - 518 assigned to SOC+ZA+Doc
    - 516 included in safety analysis
      - 2 with no adverse event assessment excluded (2 SOC+ZA+Doc)

1021 to other study arms or accrued after March 31, 2013
STAMPEDE Trial:

FFS and OS (KMS plot)

James ND et al. Lancet March 2016
STAMPEDE trial

Time to first of any treatment after a FFS event and time to first life-extending therapy (defined as available agents with proven survival gain in castrate-refractory prostate cancer: docetaxel, abiraterone, cabazitaxel, enzalutamide, and radium-223).

James ND et al. Lancet March 2016
STAMPEDE trial
forest plots for treatment effects within subjects

Docetaxel (q21days) 6cycles after EBRT along with ADT in high risk & very high risk non metastatic Pr Ca

Docetaxel + ADT upfront in hormone naïve mPrCa (NCCN 2016)

James ND et al. Lancet  March 2016
Castration Resistant Prostate Cancer
Hormone resistance

Primary Resistance (innate resistance)
- No PSA decline, no radiological or soft tissue response, no clinical benefit to first-line therapies (HT).

Acquired Resistance
- Initial response (6 months - 1 yr) followed by progression after first-line therapies (HT)

Molecular mechanism of CRPC

- Prostate cancer adopt castration by
  - 1. Synthesis of intratumoral androgen/peripheral conversion of adrenal androgen to DHT for continued ligand mediated activation of AR
  - 2. Aberrant AR signaling
Peripheral conversion mechanism

- Enzyme up regulation of CYP 17 hydroxylase, CYP 17, 20 Lyase
  
  Increased conversion of:
  
  - Pregnenolone to DHAE
  - Progesterone to androstenedione

- Gain of stability mutation of 3β Hydroxysteroid dehydrogenase (3βHSD1)

  - Profound accumulation in cytoplasm
  - Increased conversion of DHEA to DHT
Molecular mechanism of CRPC

Karantanose T et al. European Urology March 2015
1. **AR gene rearrangements**

- Constitutively active AR gene truncated splice variants (AR-V)
- AR –Vs gene generate AR protein variants lacking ligand binding domain of AR
- Ligand independent AR signaling
- ARV 7 responsible for resistance to enzalutamide and abiraterone which acts through Ligand binding site of AR.
AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer

Emmanuel S. Antonarakis, M.D., Changxue Lu, Ph.D., Hao Wang, Ph.D., Brandon Luber, Sc.M., Mary Nakazawa, M.H.S., Jeffrey C. Roeser, B.S., Yan Chen, Ph.D., Tabrez A. Mohammad, Ph.D., Yidong Chen, Ph.D., Helen L. Fedor, B.S., Tamara L. Lotan, M.D., Qizhi Zheng, M.D., Angelo M. De Marzo, M.D., Ph.D., John T. Isaacs, Ph.D., William B. Isaacs, Ph.D., Rosa Nadal, M.D., Channing J. Paller, M.D., Samuel R. Denmeade, M.D., Michael A. Carducci, M.D., Mario A. Eisenberger, M.D., and Jun Luo, Ph.D.

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. (Funded by the Prostate Cancer Foundation and others.)
Androgen receptor splice variants (ARVs)

- Primary resistance to ENZ & AA in the AFFIRM III and COU-AA-301 trials, respectively\(^1\)
- Significantly inferior outcomes compared to men without ARV\(^7\) like
  - Lower PSA response
  - Shorter PFS
  - Shorter OS \(^2\)

Androgen receptor splice variants (ARVs)

- When comparing the AA & Enza treated patients, the ARV7-positive subset treated with docetaxel/cabazitaxel had better PSA response and longer median PFS.

- Taxanes may be less susceptible to primary resistance in ARV7-positive patients.¹,²

Aberrant AR signaling

2. Somatic Mutation of AR
   (N terminal domain of AR coding region)
   Infrequently these mutated AR are activated by endogenous steroids (progesterone, corticosteroids) and by anti-androgens

3. Novel AR mutation (ARF876L)
   agonist like structural conformation of Enza and ARN 509 binding leading to tumor growth in presence of Enza/ARN509 Bicalutamide escapes this pathway
Other mechanisms

- **The TMPRSS2–ERG fusion gene**
  
  Most frequent genetic rearrangement in PrCa
  
  ERG non rearranged PrCa have a better survival (90% CSS over 8 years)
  
  ERG rearranged (2+ Edel) PrCa have poor survival (28% CSS over 8 years)\(^1\)
  
  Validated also in COU – AA-301 trial\(^2\)

- **ROR – Ŷ gene overexpression\(^3\)**

1. Attard G Oncogene 2008
Therapy options in CRPC

- **Novel AR antagonists:**
  - Abiraterone acetate
  - Enzalutamide
- Sipulicel T
- Ra223
- ADT withdrawal
- Sequencing of HT
- Chemotherapy (Taxanes)
- Older Hormonal agents
  - Antiandrogens
  - Ketoconazole
  - Steroids

**Situations:**

M0 CRPC

1. Asymptomatic or Mild symptomatic

M1 CRPC

2. Bone metastasis

3. Visceral metastasis
Abiraterone acetate (2011/2012)

- **CYP17A1 inhibitor**
- 1000mg Once daily orally
- Interaction with food: Given in empty stomach
- A/E: (>10%)
  - Diarrhea
  - Fatigue
  - Hypertension
  - Hypokalemia
  - Peripheral Edema
- Monitor LFT
- Cardiac dysfunction
Abiraterone in CRPC (Post CT)

- COU- AA-301 trial (2012)
- Docetaxel failed CRPC (n = 512)
- AA + Pred vs placebo + Pred (1:1)
- Median F/U 20.2months
- Significant benefits in AA arm:
  - pain relief
  - delayed pain progression
  - prevention of SREs

Logothetis CJ et al. Lancet Oncol 2012
Abiraterone in CRPC (Pre CT)

- Chemo naïve CRPC patients (n= 1195)
- AA + Pred vs placebo + Pred (1:1)
- Median F/U 49months
- Median OS was significantly longer in AA group than in the placebo group (34.7 months vs 30.3 months; hazard ratio 0.81; p=0.0033)\(^1,2\).
- Men in AA group who had ERG rearranged gene prostate tumors, had a significantly improved radiographic PFS and time to PSA progression, compared with those with ERG non-rearranged tumors.\(^3\)

1. Fizazi K Lancet 2012
2. Ryne CJ Lancet 2015
3. Attar G J Clin Oncol 2013
Enzalutamide (MVD3100) (2012)

- AR signal inhibitor and antagonist
- Dose 160mg/day Oral

- Adverse events:
  - Fatigue/asthenia
  - Diarrhea
  - Hot flush/Gynaecomastia
  - QTc Prolongation
  - Hypertension
  - Risk of seizure
Enzalutamide in CRPC (Post CT)

- Post CT CRPC pts. Enzalutamide vs Placebo (2:1) (n= 1199)
- The median overall survival was 18.4 months in the enzalutamide group versus 13.6 months in the placebo group
- Increased Radiographic response, soft tissue response, PSA reduction rate, time to first SRE, QoL in Enza arm.
- Enza arm had more fatigue, diarrhoea & hot flushes

Sher HI et al. NEJM 2012
Enzalutamide in CRPC (Pre CT)

- PREVAIL study (n= 1717) (2014)
- Chemo naive mPrCa : Enza vs Placebo (1:1)
- Study stopped after planned interim analysis
- The rate of radiographic PFS(1yr) was 65% vs 14% among enza arm vs placebo arm.
- 72% in Enza arm vs 63% in the placebo arm, were alive at the data-cutoff date (HR, 0.71 P<0.001).
- Decreased time to SRE and PSA Progression

Beer TM NEJM 2014
Sipuleucel T (2010)

- Autologous vaccine:
  - Each pts. WBC (APC) exposed to PAP-GMCSF fusion protein
  - Minimally symptomatic / Asymptomatic CRPC

- Sipuleucel T vs Placebo (2:1 RCT) \( [n=512] \)
  - Median OS 25.8m vs 21.7m \( (p<0.001) \)
  - 22% Mortality reduction in Vaccine arm (HR 0.78)
  - No effect on time to progression
  - Minor A/E like fever, headache in Vaccine arm

Kantoff PW et al. NEJM 2010
## Chemotherapy in CRPC: Docetaxel

<table>
<thead>
<tr>
<th>Name</th>
<th>Arms</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tax 327 Tannock IF et al.</td>
<td>Doce + Pred q3wk vs Doce + Pred q1wk vs Mitoxatrone + Pred</td>
<td>OS (18.9m vs 17.4m vs 16.5m) PSA decline &gt;50% (45% vs 48% vs 32%) QoL improvement (23% vs 22% vs 12%) A/E more in Dpce arms</td>
</tr>
<tr>
<td>2004 NEJM (n= 1006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWOG 9916 Petrylak DP et al.</td>
<td>Doce + Estramustine Vs Mitoxantrone + Pred</td>
<td>OS (17.5m vs 15.6m) Median Time to progression (6.3m vs 3.2m) PSA decline rate &gt; 50% (50% vs 21%) Febrile Neutropenia more in Estramustine + Doce arm</td>
</tr>
<tr>
<td>2004 NEJM (n=770)</td>
<td></td>
<td></td>
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</tbody>
</table>
Cabazitaxel (2010)

- It binds to the β-subunit of the tubulin within the microtubule
- Stabilization of microtubules
- Dose: 25mg/m² IV q3wks with 10mg Prednisone
- A/E
- Febrile neutropenia
- Peripheral neuropathy
**Rationale**

- Some tumors do not respond to Docetaxel (acquired or constitutional resistance)
  
  This may be due to:
  - Affinity for multidrug resistant (MDR) membrane-associated P-glycoprotein (PgP) efflux pump,

- Cabazitaxel:
  - Poor affinity for the PgP efflux pump
  - Active in vitro and in vivo tumors resistant to Docetaxel

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

**Patients with mCRPC progressed during or after docetaxel treatment (n=755)**

- Cabazitaxel 25 mg/m² q 3 wk + prednisone* for 10 cycles (n=378)
  - Stratification factors: ECOG PS (0, 1 vs. 2)
  - Measurable vs non-measurable disease

- Mitoxantrone 12 mg/m² q 3 wk + prednisone* for 10 cycles (n=377)
  - *Oral prednisone/prednisolone: 10 mg daily.

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TROPIC trial: Results

Median OS (months)

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>CBZP</th>
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</thead>
<tbody>
<tr>
<td>Median</td>
<td>12.8</td>
<td>15.1</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.59–0.83</td>
<td></td>
</tr>
<tr>
<td>P Value</td>
<td>&lt;.0001</td>
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Median PFS (months)

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>CBZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.64–0.86</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td></td>
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</tbody>
</table>

TROPIC trial
Cabazitaxel vs mitoxantrone for mCRPC post-doctaxel

<table>
<thead>
<tr>
<th>Endpoints (months)</th>
<th>Cabazitaxel + prednisone</th>
<th>Mitoxantrone + prednisone</th>
<th>Hazard ratio (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Time to tumor progression</td>
<td>8.8</td>
<td>5.4</td>
<td>0.61 (p&lt;0.0001)</td>
</tr>
<tr>
<td>Median Time to PSA progression</td>
<td>6.4</td>
<td>3.1</td>
<td>0.75 (p=0.001)</td>
</tr>
<tr>
<td>PSA response rate</td>
<td>39.2%</td>
<td>17.8%</td>
<td>p=0.0002</td>
</tr>
<tr>
<td>Tumor response rate</td>
<td>14.4%</td>
<td>4.4%</td>
<td>P=0.0005</td>
</tr>
</tbody>
</table>

The most common ≥ grade 3 adverse events:
Febrile Neutropenia

TROPIC trial: Final analysis (2013)

Impact of tumour characteristics on survival in the TROPIC trial

A. Bahl, L. Shen, M. Bajamonde, C. L. Wels, K. J. Pritchard, F. E. Groome, S. C. Harris, and the TROPIC trial investigators.

Results:
- Mitoxantrone: HR 0.72; 95% CI 0.61-0.84, P < 0.0001
- Cabazitaxel: HR 1.00; 95% CI 0.84-1.19, P = 0.94
- Pain at baseline was lower in the mitoxantrone group (30% vs 42%), but similar at 12 months (37% vs 37%).

Conclusions: Cabazitaxel prolongs OS at 2 years versus mitoxantrone and has low rates of peripheral neuropathy. Palliation benefits of cabazitaxel were comparable to those of mitoxantrone. The study was registered with www.ClinicalTrials.gov (NCT00417079).
Sequencing strategy

Logic:

- Differential effectiveness of CT/HT due to different mechanism of Resistance.
- Impaired activity of AR pathway inhibitors when used sequentially helped to test sequencing of chemotherapy with hormonal agents.
Retrospective analysis to assess patients with mCRPC who received treatment with Doce and were subsequently treated with Cabazi or AA, or both

Patients (n=350) received 2 or 3 drugs: DA, DC, DAC, or DCA

Subsequent therapy distribution

- DA in 183 (52.3%)
- DC in 54 (15.4%)
- DCA in 77 (22.0%)
- DAC in 36 (10.3%)

3-drug sequences were associated with improved OS versus 2-drug sequences (hazard ratio [HR], 0.21; P =0.0002).

OS was significantly greater for DCA versus DAC (18.2 vs.11.8m;P=0.023)

In a multivariable analysis, adjusted comparisons suggested that significant lower risk of mortality in the DCA versus DAC cohorts (HR, 0.13;P=0.0210)
CAST: A retrospective analysis of cabazitaxel and abiraterone acetate sequential treatment in patients with metastatic castrate-resistant prostate cancer previously treated with docetaxel

- Retrospective, multicenter, observational study
- From collected data 63 patients had received cabazitaxel followed by abiraterone (DCA), and 69 patients had received abiraterone followed by cabazitaxel (DAC)
### Results

**CAST study**

- Compared outcomes of DCA vs. DAC in CRPC previously treated with docetaxel

<table>
<thead>
<tr>
<th>End point</th>
<th>DCA (n=63)</th>
<th>DAC (n=69)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>19.1</td>
<td>17.0</td>
<td>0.369</td>
</tr>
<tr>
<td>Median PFS</td>
<td>8.1</td>
<td>6.5</td>
<td>0.050</td>
</tr>
<tr>
<td>Biochemical PFS</td>
<td>9.5</td>
<td>7.7</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Other Chemotherapy

- Eribulin Mesylate Phase II study: (2006-2007)
- mPrCa (CRPC) [+/- Prior Taxane]
- Single arm (Eribulin iv) [end point : PSA response rate]
- Median cycle number of 4
- PSA decrease of >50% in 22.8% taxane naïve pts. and 8.5% taxane pretreated pts.
- Relatively favorable toxicity profile

de Bono JS et al. Ann Oncol 2012
New drugs for CRPC

Figure 1. Biology of castration-resistant prostate cancer and potential molecular targets for therapy.

Newer targeted therapy options

CYP 17 inhibitors
- Orteronel (TAK 700)

Androgen Receptor Inhibitor
- ARN 509
- ODM 201
- AZD 3514
- EPI- 001

Antibody Conjugate
- Anti PSMA antibody + Y99

Radioimmunotherapy
- Galoterone (TAK 700)

POX virus based vaccine
- PROSTVAC –VF

CTLA 4 Inhibitors
- Ipilimumb

Anti sense oligonucleotide
- Clustirsen (OGX 11)

HSP 27 Inhibitors (Antisense agents)
- OGX427

Dual androgen synthesis & signal inhibitors
- Galoterone (TAK 700)

Anti androgenic Immunomodulators
- Tasquimod
## Newer targeted therapy options

<table>
<thead>
<tr>
<th>Molecular target</th>
<th>Arrows</th>
<th>Population</th>
<th>Primary endpoint</th>
<th>Comments</th>
<th>Clinical trial ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP17</td>
<td>TAK-700 + Placebo + P</td>
<td>Docetaxel pretreated</td>
<td>OS</td>
<td>Preliminary results showed no improvement in the primary end point of OS, but significant improvement in rPFS (a secondary end point). Post-trial treatment with abiraterone may have confounded OS data.</td>
<td>NCT0 1193257</td>
</tr>
<tr>
<td>CYP17,17.20 lyase activity</td>
<td>TAK-700 + Placebo + P</td>
<td>Chemo naïve</td>
<td>OS, rPFS</td>
<td>Accrual: completed; results: pending.</td>
<td>NCT0 1193244</td>
</tr>
<tr>
<td>AR</td>
<td>MDV3100 Placebo</td>
<td>Chemo naïve</td>
<td>OS, PFS</td>
<td>Results showed significant improvement in the primary endpoints of OS, and rPFS.</td>
<td>PREVAIL NCT0 1212991</td>
</tr>
<tr>
<td>AR</td>
<td>ARN-509 Placebo</td>
<td>Nonmetastatic chemo naïve</td>
<td>Metastasis-free survival</td>
<td>Accrual: ongoing</td>
<td>SPARTAN NCT0 1946204</td>
</tr>
<tr>
<td>Clusterin mRNA</td>
<td>Custisren + CBZ-P Placebo + CBZ-P</td>
<td>Docetaxel pretreated</td>
<td>Pain palliation</td>
<td>Accrual: completed; results: pending.</td>
<td>SATURN NCT0 1083615</td>
</tr>
<tr>
<td>Clusterin mRNA</td>
<td>Custisren + DP Placebo + DP</td>
<td>Chemo naïve</td>
<td>OS</td>
<td>Accrual: completed; results: pending.</td>
<td>SYNERGY NCT0 1188187</td>
</tr>
<tr>
<td>Immune response</td>
<td>PROSTVAC ± GM-CSF versus placebo</td>
<td>Asymptomatic or minimally symptomatic chemo naïve disease</td>
<td>OS</td>
<td>Accrual: ongoing.</td>
<td>PROSPECT NCT0 1322490</td>
</tr>
<tr>
<td>c-MET and VEGFR2</td>
<td>Cabozantinib Prednisone</td>
<td>Docetaxel and abiraterone pretreated relatively asymptomatic disease</td>
<td>OS</td>
<td>Accrual: completed; results: pending.</td>
<td>NCT0 1605227</td>
</tr>
<tr>
<td>c-MET and VEGFR2</td>
<td>Cabozantinib</td>
<td>Docetaxel and abiraterone pretreated</td>
<td>Pain response</td>
<td>Accrual: completed; results: pending.</td>
<td>NCT0 1522443</td>
</tr>
</tbody>
</table>

Agarwal N et al., Ann Oncol 2014
Newer targeted therapy options

<table>
<thead>
<tr>
<th>Molecular target</th>
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<th>Population</th>
<th>Primary endpoint</th>
<th>Comments</th>
<th>Clinical trial ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Src-family kinases</td>
<td>Dasatinib + DP Placebo + DP</td>
<td>Chemonaïve disease</td>
<td>OS</td>
<td>Results showed no improvement in OS, the primary end point.</td>
<td>READY NCT00744497</td>
</tr>
<tr>
<td>Immune-modulatory protein S100A9</td>
<td>Tasquinimod Placebo</td>
<td>Asymptomatic or minimally symptomatic chemonaïve disease</td>
<td>PFS</td>
<td>Accrual: completed; results: pending.</td>
<td>NCT01234311</td>
</tr>
<tr>
<td>Immune-modulatory protein S100A9</td>
<td>Tasquinimod Placebo</td>
<td>Docetaxel pretreated stable disease</td>
<td>PFS</td>
<td>Currently accruing.</td>
<td>NCT01732549</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>Ipilimumab Placebo, (following a single dose of radiotherapy)</td>
<td>Docetaxel pretreated</td>
<td>OS</td>
<td>Preliminary results showed no improvement in OS, the primary end point. Prespecified subset analyses suggested improved efficacy of ipilimumab in men with lower disease burden.</td>
<td>NCT00861614</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>Ipilimumab Placebo, (following a single dose of radiotherapy)</td>
<td>Asymptomatic or minimally symptomatic chemonaïve disease</td>
<td>OS</td>
<td>Accrual: completed; results: pending.</td>
<td>CA-184-095</td>
</tr>
<tr>
<td>Microtubules</td>
<td>CBZ-P DP</td>
<td>Chemonaïve disease</td>
<td>OS</td>
<td>Accrual: completed; results: pending.</td>
<td>FIRSTANA NCT01308567</td>
</tr>
</tbody>
</table>
Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015


Situation M1

M1 first-line
- Management of men with castration-naïve metastatic prostate cancer
- Management of men with oligometastatic castration-naïve prostate cancer
- Value of endocrine manipulations without proven survival benefit in men with metastatic CRPC
- Treatment choice and sequencing for men with metastatic CRPC
- Staging and monitoring of treatment
- Use of osteoclast-targeted agents for reducing risk of SREs and SSEs in men with CRPC
- Value and use of predictive markers
- Multidisciplinary care of men with prostate cancer

M1 second-line

M1 third-line

ADT
iADT vs Cont. ADT

- In patients with metastatic prostate cancer achieving an adequate PSA decline (confirmed PSA fall below 4 ng/ml after 6 months of ADT), 71% of the panelists recommended intermittent ADT only for a minority of selected patients.
CAB vs ADT alone

- Half of the panel did not recommend CAB whereas 35% recommended it in a minority of selected patients and 15% recommended it in the majority of patients.
Docetaxel in castration Naïve PrCa

- Based on CHAARTED trial:
  - Definition of High volume disease:
    - visceral (lung or liver) and/or 4 bone metastases, beyond pelvis and vertebral column
  - High volume definition should be used in daily clinical practice.
- Half of the panel recommended docetaxel with ADT in castration-naïve M1 patients with high-volume disease.
ADT in M1 Castration Naïve PrCa

Based on CHAARTED and STAMPEDE data NCCN 2016 recommended docetaxel upfront with ADT in high risk M0/M1 PrCa
Definition of Oligometastases:

- According to 85% of the panel: ≤ 3 synchronous metastases (bone and/or lymph nodes)

- 62% of the panel recommended ADT.

- In minority of cases local treatment for primary and met focus will suffice.
As a consensus, 82% of the panel recommended a **testosterone level <50 ng/dl (<1.7 nmol/l)** as an appropriate cut-off value in daily clinical practice.

According to 94% of the panel a confirmed (by a 2nd value ≥ 3wks later) rising PSA on ADT in the presence of suppressed testosterone is sufficient.

If testosterone is not sufficiently suppressed in the presence of suppressed LH, the panel next management options:

- B/L orchiectomy (22%),
- Alternative GnRH agonist (22%),
- GnRH antagonist (44%),
- Addition of an AR antagonist (9%).
Non Metastatic CRPC (M0)

- A clear consensus (91% of the panel) that a PSA-based trigger (level and/or kinetics) should be used for restaging asymptomatic patients with rising PSA on ADT and no known metastases.
- To initiate imaging 2-10ng/ml (total PSA) should be the cutoff (56%).
- For PSA-DT as a trigger for imaging, 74% of the panel recommended a PSA-DT of 6 months.
- According to 77% of the panel daily clinical practice a negative CT (thorax and abdomen/pelvis) and a negative bone scan are sufficient for diagnosis of M0 disease.
M0 CRPC treatment

“withholding additional treatment in a patient who knows that his PSA is rising on ADT can be challenging”

Novel agents like abiraterone acetate or Enzalutamide are preferred

Endocrine manipulation without survival benefit:
- AR antagonist
  Bicalutamide/Flutamide/Nilutamide

Adv:
- Cheap
- Low A/E profile

Disadv:
- No OS benefit
**Metastatic CRPC: First Line**

- **Asymptomatic/mild symptomatic M1CRPC**
  - No pain medication/pain medication if needed.

  ![Graph showing treatment options and majority opinions](image)

  - Abiraterone (39%), Enzalutamide (27%) or either one of the two (33%)
  - Clinicians decision based on comorbidity
Metastatic CRPC: First Line

- Symptomatic M1 CRPC

**Prospective phase III trials**
- Docetaxel
- Radium-223

**Question G**: Do you recommend chemotherapy (usually taxane based) as first-line therapy for otherwise healthy symptomatic men with CRPC in addition to ADT?

**Question H**: Do you recommend radium-223 as a first-line treatment for symptomatic men with CRPC with bone but no visceral metastases?
M1 CRPC 2\textsuperscript{nd} line/3\textsuperscript{rd} line

**Metastatic CRPC Second-Line**

<table>
<thead>
<tr>
<th>Prospective phase III trials (post-docetaxel) 2nd line:</th>
<th>No prospective phase III trials for 2nd line after abiraterone, enzalutamide, radium-223 or sipuleucel-T. Options for patients with good PS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Abiraterone</td>
<td>• Abiraterone</td>
</tr>
<tr>
<td>• Cabazitaxel</td>
<td>• Cabazitaxel</td>
</tr>
<tr>
<td>• Enzalutamide</td>
<td>• Docetaxel</td>
</tr>
<tr>
<td>• Radium-223*</td>
<td>• Enzalutamide</td>
</tr>
</tbody>
</table>

I: Do you recommend second-line treatment with abiraterone or enzalutamide in otherwise healthy patients judged to have primary (innate) resistant disease (no PSA decline, no radiological improvement, no clinical benefit) to first-line abiraterone or enzalutamide?

K: Do you recommend second-line treatment with abiraterone or enzalutamide in otherwise healthy patients with secondary (acquired) resistance (initial response followed by progression) to first-line abiraterone or enzalutamide?

L: Do you recommend second-line treatment with cabazitaxel in otherwise healthy patients after second-line docetaxel (post first-line abiraterone or enzalutamide)?

**Consider clinical trial participation**

*Bone metastases and symptomatic, no visceral or bulky lymph node metastases, not fit, unwilling to have no access to chemotherapy or post-chemotherapy

** Low tumour volume, no visceral metastases

*** no visceral metastases
Staging & Monitoring treatment

Before newline of treatment:

- Blood ALP/LDH/PSA
- CECT Thx/Abdomen-pelvis
- Bone Scan +/- MRI spine (selective)
- ? PET (?? PSMA PET)

Monitoring:

- Blood ALP/LDH/PSA (2-4 monthly)
- +/- CECT scan
When to stop/change to next line

- Consensus of 82% of panel to fulfill ≥ criteria
  1. PSA progression
  2. Radiographic progression
  3. Clinical deterioration
- Unequivocal Visceral progression only:
  Stop treatment
  Re biopsy (search for 2nd cancer/NE histology)
Osteoclast targeted agents
Reducing risk of SRE/ for SRE in M0/M1 stage

- (Based on CALGB90202 trial)
- Castration Naïve M1 PrCa (bone mets)
Osteoclast targeted agents
Reducing risk of SRE/ for SRE in M0/M1 stage

- M0 CRPC

Ca and Vitamin D supplementation
For osteoporosis and increased risk of fractures:
- Bisphosphonate at osteoporosis dose
- Denosumab (60mg, 6-monthly)

C: Do you recommend an osteoclast-targeted therapy for CRPC patients without bone metastases for delaying onset of metastases?

- Majority: 88%
- Minority: 9%
- Other: 3%
Osteoclast targeted agents
Reducing risk of SRE/ for SRE in M0/M1 stage

☐ M1CRPC (Bone mets)

Calcium and Vitamin D supplementation
Dental check before initiation of osteoclast-targeted therapies

- Denosumab (120mg, 4 w)
- Zoledronic acid (4mg, 3-4 w)

D: Do you recommend an osteoclast-targeted therapy for reduction in risk of SRE in CRPC patients with bone metastases?
E: Do you recommend a dental check for CRPC patients with bone metastases prior to starting an osteoclast-targeted therapy?

47% of the panel recommended a total duration of 2 years for reducing risk of SREs/SSEs.

- zoledronic acid (30%),
- denosumab (42%)

and either of the two options (27%).
Predictive markers

- 92% consensus: No valid predictive tool

- Factors favoring CT > (ENZA/ AA):
  1. Expression of AR-V7 splice variants (47% vs 44%)
  2. Presence of visceral metastases (50% vs 50%)
  3. Short response (1 yr) to 1st line ADT (53% vs 47%)
  4. Low PSA (<20 ng/ml) in the setting of high tumor volume (65% vs 35%)
The unmet needs

- Role of ADT withdrawal in M0 CRPC (on ADT).
- Sequencing of AR antagonists in 1\textsuperscript{0} /acquired resistance in CRPC.
- Some CRPCs have differential response to HT/CT/Biologics.
- No predictive tool for selection of CT vs HT
- Optimal use (sequencing/choice/duration/frequency of Osteoclast targeted therapies.
- Overlapping SRE related effects of novel agents narrowing use of osteoclast targeted agents.