Optimal Management of Castration Resistant Prostate Cancer (CRPC) in 2014

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The presentation (does not include) discussion of the use of product(s) for which they are not labeled (e.g., off label use) is still investigational.

Acknowledgement
Daniel Petrylak MD (Yale University) for allowing me to “borrow” some of his slides!

CRPC therapy by state: 2010

- Metastatic, minimally symptomatic CRPC
- Symptomatic or poor-prognosis CRPC
- Progression after docetaxel chemotherapy

2010
Secondary hormonal Rx
Survival benefit
not known
Docetaxel
3 months
Mitoxantrone
Best supportive care
not known

Zoledronic acid with CRPC (metastatic disease)

CRPC therapy by state: 2014

- Metastatic, minimally symptomatic CRPC
- Symptomatic or poor-prognosis CRPC
- Progression after docetaxel chemotherapy

2014
Survival benefit
Enzalutamide – 2.2 months
Abiraterone – 5.2 months
Rad223 – 4.6 months
Sipuleucel-T
Docetaxel
4 months
3 months
Docetaxel
4 months
Astration or Cabazitaxel
4 months
2.5 months

Denosumab or Zoledronic acid (bone metastatic disease)

Development of CRPC

Hormone Therapy

- Androgen-receptor targeted
- Immunotherapeutic

- Selective pressure
- Adaptation
- Recurrent tumor development

CRPC

Classes of Agents in CRPC

- Immunotherapeutic
  - Sipuleucel T
- Androgen-receptor targeted
  - Enzalutamide, Abiraterone, Docetaxel
- Cytotoxic
  - Docetaxel, Cabazitaxel
- Radioisotope
  - Radium 223
**Abiraterone Acetate:**
**Androgen Biosynthesis Inhibitor**

- Cholesterol
- Pregnenolone
- 17αOH-Pregnenolone
- DHEA
- Androstenedione
- Testosterone
- DHT
- Androgens
- Aldosterone
- Cortisol
- 17αOH-Pregnenolone

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**COU 301: Abiraterone vs. Placebo in post-docetaxel setting**

- 2 prior chemo OS: 14.0 months abiraterone acetate vs 10.3 months placebo
- 1 prior chemo OS: 15.4 months abiraterone acetate vs 11.5 months placebo

Updated results: 4.6-month difference in median survival with abiraterone acetate

- Median OS: 14.0 months vs 10.3 months
- 37% reduction in risk of death

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**COU 302: Abiraterone vs. Placebo in pre-chemo setting**

- Oral drug rationally designed to target AR signaling, impacting multiple steps in AR signaling pathway
- No demonstrated agonist effects in pre-clinical models

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**Enzalutamide**

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- No demonstrated agonist effects in pre-clinical models

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**Enzalutamide vs. Placebo: Post-Docetaxel**

- Hazard Ratio: 0.706 (95% CI: 0.60, 0.84)
- P < 0.0001

- Median OS: Enzalutamide, 32.4 Months; Placebo, 30.2 months
- 37% reduction in risk of death

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**Enzalutamide**

- Inhibits Binding of Androgens to AR
- Inhibits Nuclear Translocation of AR
- Inhibits Association of AR with DNA
- Tumor Death

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**Enzalutamide**

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NCI Alliance Trial A031201: Enzalutamide +/- Abiraterone Acetate
Phase III Trial in Chemonaive mCRPC

Phase 3 multicenter, randomized study conducted through the NCI's National Clinical Trials Network (NCTN)

Androgen Receptor Splice Variants

Some variants still constitutively active as transcription factor despite lack of LBD

AR Splice Variant Mediated Resistance

Androgen Receptor Splice Variants

Some variants still constitutively active as transcription factor despite lack of LBD

UCDCC#243: Enzalutamide + Metformin Trial
(Pi: CP Evans)

SU2C West Coast Dream Team: Targeting Adaptive Pathways in Metastatic Castration Resistant Prostate Cancer
Radium 223 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 PHASE**
- **Radium-223 dichloride** (50 kBq/kg) + best standard of care†
- **Placebo (saline)** + best standard of care†

6 injections at 4-week intervals

>100 centers in 19 countries

Planned follow-up is 3 years

**Radium 223: Overall Survival**

3.6 month OS benefit

<table>
<thead>
<tr>
<th></th>
<th>Radium-223 dichloride (n = 614)</th>
<th>Placebo (n = 307)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>14.9</td>
<td>11.3</td>
</tr>
<tr>
<td>RR</td>
<td>0.695</td>
<td>0.00027</td>
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<tr>
<td>95% CI</td>
<td>0.581 - 0.832</td>
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</tbody>
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**Pivotal Docetaxel CRPC Trials**

**TAX 327**
- **Mitoxantrone** 12 mg/m²
- **Prednisone** 10 mg q day
- Q 21 days up to 10 cycles
- N=1006

**SWOG 9916**
- **Docetaxel** 75 mg/m²
- **Prednisone** 10 mg q day
- Q 21 days up to 10 cycles
- N=770

**S9916: Overall Survival**

# at Risk | # of Deaths | Median in Months
---|---|---
D+E | 336 | 235 | 16
M+P | 336 | 235 | 16

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

**Long-Term Overall Survival (October 2006)**

Docetaxel: q 3 wk
Weekly Docetaxel
Mitoxantrone
S9916: Overall Survival (October 2006)
Phase III Trials of Docetaxel Combinations in CRPC

<table>
<thead>
<tr>
<th>Docetaxel/Pred vs Docetaxel Combined</th>
<th>Status</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>DN-101</td>
<td>Terminated early</td>
<td>Negative</td>
</tr>
<tr>
<td>GVAX</td>
<td>Terminated early</td>
<td>Negative</td>
</tr>
<tr>
<td>Bevacizumab</td>
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<td>VEGF-Trap</td>
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<tr>
<td>Clustatins (OGX-011)</td>
<td>Completed</td>
<td>Negative</td>
</tr>
</tbody>
</table>

To date, no combination improves on docetaxel and pred

E3805 – CHAARTED
Chemotherapy in Hormone Sensitive Prostate Cancer

OS by extent of metastatic disease at start of ADT

Conclusions

- Taxanes are active against prostate cancer
  - Docetaxel SOC in “high-volume” metastatic HSPC and CRPC
  - Cabazitaxel improves OS in post-docetaxel CRPC setting
- AR-targeted therapies (Enzalutamide, Abiraterone) improve survival
  - Resistance mechanisms include selection of AR-splice variants
- Radium 223 and Sipuleucel-T improve survival in select CRPC subsets
- Optimal sequence of therapies is undefined