PROSTATE CANCER
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A) PUBLIC HEALTH

EPIDEMIOLOGY
- Incidence: 99 per 100,000. Most common cancer among men (excluding non-melanoma skin cancers), accounts for 24% of all new male cancer cases in Canada.
- Mortality: 3rd leading cause of cancer death in men in Canada (17 deaths per 100,000).

RISK FACTORS
- Environmental/Chemical/Infections: consumption of a diet rich in red meat and saturated fat appears to increase risk, particularly of aggressive disease.
- Genetic: increasing age is the most important risk factor, higher incidence in North American blacks compared with other ethnic groups and often has a more aggressive course, risk increased twofold in men with one or more affected first-degree relatives, BRCA1 and BRCA2 carriers have an increased risk (1.8- and 4.7-fold).

PREVENTION & SCREENING
- Prevention: Finasteride and Dutasteride (5-AR inhibitors) have been shown to decrease the risk of prostate cancer, but with an elevated rate of high-grade prostate cancers and no change in overall survival.
- Screening: Serum PSA screening is of unknown value as a population screening test. RCTs have shown a small reduction in prostate-cancer mortality, but harms associated with screening, including over-diagnosis and treatment are common.
- Evidence for: The European Randomized Study of Screening for Prostate Cancer (ERSPC)
Study found a 20% reduction in prostate cancer death screening men aged 55-69, with an absolute risk reduction 0.71 deaths per 1000 men. To prevent 1 death: 1410 men need to be screened for 9 years and 48 additional cases diagnosed and treated.
- Evidence against: The Prostate, Lung, Colorectal, Ovarian (PLCO) trial followed 77,000 men between 55 and 74 for 13 years and found the death rate from prostate cancer was low and did not differ between the screened and control (unscreened) groups.
- Cancer Care Ontario does not support an organized, population-based screening program for prostate cancer.
- BCCA, Alberta Cancer Guidelines recommend that fit men between the ages of 50 and 75 years with at least 10 years life expectancy should be made aware of the availability of PSA as a detection test for prostate cancer, as well as the potential benefits and risks of early detection, so they can make an informed decision as to whether to have the test performed.
- Canadian Task Force recommends against PSA screening for prostate cancer (CMAJ 2014).

B) PRESENTATION & DIAGNOSIS

SYMPTOMS & SIGNS
- Localized disease - vast majority - present with an abnormal digital rectal examination (DRE) or PSA screening
- Locally advanced disease - lower urinary symptoms: hesitancy, weak stream, frequency, nocturia, incomplete bladder emptying
- Metastatic disease - constitutional symptoms, bony pain
INVESTIGATIONS
- History and Physical including DRE
- Laboratory: PSA, CBC, Calcium profile, Creatinine, ALP and LFTs
- Transrectal biopsy - typically 10-12 core
- Radiology: CT chest/abdo/pelvis and bone scan in intermediate/high risk
- If symptoms or signs of cord compression: MRI whole spine

PATHOLOGY & MOLECULAR BIOLOGY
- Most common histology is adenocarcinoma (>95%)
- **Gleason Score** = sum of two most common tumour patterns, most common stated first
- Other: sarcomatoid, endometrioid
- Transitional cell carcinoma should be treated as a urothelial cancer
- Sarcomas are rare and should be treated per sarcoma guidelines

STAGING
- **TNM**
  - **T1:** clinically inapparent tumour not palpable or visible by imaging
    - T1a: Tumor incidental histologic finding in 5% or less of tissue resected
    - T1b: Tumor incidental histologic finding in more than 5% of tissue resected
    - T1c: Tumor identified by needle biopsy (eg, because of elevated PSA)
  - **T2:** tumour confined within the prostate
    - T2a: tumour involves one lobe
    - T2b: tumour involves both lobes
  - **T3:** tumour extends through the prostatic capsule
    - T3a: extracapsular extension (unilateral or bilateral)
    - T3b: tumour invades seminal vesicle(s)
  - **T4:** tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall
  - **N1:** regional lymph node metastasis (pelvic nodes below the bifurcation of the common iliac arteries)
  - **M1a:** non-regional lymph node(s), M1b: bone(s), M1c: other site(s) with or without bone disease
  - **Stage 1:** T1aN0M0 + Gleason score 2-4
  - **Stage 2A:** T1aN0M0 + Gleason score 5-6, T1b-T1cN0M0 any Gleason
  - **Stage 2B:** T2N0M0 any Gleason
  - **Stage 3A:** T3N0M0 any Gleason
  - **Stage 4:** T4N0M0 any Gleason, anyTN1M0 any Gleason, anyT anyN M1 any Gleason
- **Low Risk:** PSA ≤10 ng/mL + Gleason ≤6 + Stage T1/T2a
- **Intermediate Risk:** neither low or high risk, any of: PSA 10-20, Gleason 7, Stage 2B
- **High Risk:** any of PSA > 20 ng/mL or Gleason ≥8 or Stage T3a or worse

C) TREATMENT
I) **LOCALIZED Prostate Cancer**
- **Bottom Line General Approach:**
  - Low Risk options: Active Surveillance (CCO & ASCO guideline preference; see below), Prostatectomy, EBRT, brachytherapy
  - Intermediate Risk options: Prostatectomy, EBRT + brachytherapy boost or brachytherapy alone. EBRT + short-term Androgen Deprivation Therapy (ADT; 4-6 months) option for non-brachy/non-surgical patients
  - High Risk options: EBRT + brachytherapy boost + 18-36 months ADT or Prostatectomy. EBRT + long-term ADT option for non-brachy/non-surgical patients
  - Prostatectomy and RT have not been compared head to head
  - 3 RCTs show brachy boost > EBRT for intermediate and high risk patients (+/- ADT)
o Adjuvant ADT following EBRT - multiple randomized trials have demonstrated improvement in cancer-specific and overall survival with adjuvant ADT following EBRT in high-risk disease (RTOG 86-10, EORTC 22863, RTOG 85-31). 3 years was found to be superior to 6 months of ADT but 18 months = 36 months (Quebec PCS3 study). Adjuvant ADT in intermediate risk is less clear for brachytherapy patients but data supports 4-6mo ADT with EBRT. The RTOG 0815 trial has recently closed in which adjuvant 6mo ADT is being investigated with modern high-dose radiation (data won’t be avail until at least 2021).

o Neoadjuvant ADT with Radical Prostatectomy has been explored in over 20 trials and although several studies demonstrated a reduction in the rate of positive surgical margins, this did not translate to improvements in biochemical progression free survival or overall survival and is not currently recommended.

o Adjuvant or Neoadjuvant Chemotherapy - Clinical trials currently ongoing:
  ▪ RTOG 0521 EBRT (72-75 Gy) + ADT x 2 years +/- adjuvant Docetaxel - presented at ASCO 2015. For high-risk, localized PCa, adjuvant Docetaxel improved OS from 89% to 93% at 4 years.
  ▪ CALGB 90203 - Phase III trial of neoadjuvant docetaxel plus ADT followed by radical prostatectomy versus immediate radical prostatectomy

o Adjuvant Radiation: patients with adverse histologic features (extracapsular extension, seminal vesicle involvement, positive margins, or lymph node involvement) should be referred to radiation oncology for consideration of adjuvant RT (CCO, ASCO & AUA guidelines)

o Salvage RT: persistent elevation or rising PSA after surgery should be referred to radiation oncology for consideration of salvage RT (> 0.2 ng/mL) (CCO, ASCO & AUA guidelines). 2 years of bicalutamide 150mg found to improve OS and MFS in salvage radiotherapy setting (RTOG 9601)

o If age or comorbidity preclude definitive therapy in men with intermediate or high-risk prostate cancer, systemic therapy with ADT may be useful as a palliative approach, although this has been associated with shorter overall survival than definitive therapy.

- Active Surveillance: observation rather than immediate therapy in low-risk patients as a means of avoiding over-treatment. Toronto prospective cohort protocol: serum PSA at three month intervals, with a PSA doubling time of three years or less as a criterion for active intervention; repeat prostate biopsy is performed at one year then repeated every four to five years to look for evidence of biologic progression to Gleason 4+3 or higher.

- Prognosis: low risk disease: 10-year prostate cancer survival rates >99%; intermediate risk 95-98%; high risk localized disease 80-90%.

- Surveillance after definitive treatment: serum PSA every 3-6 months for the first 2 years then q6mo thereafter. Biopsies done at 1y then q3y. Role of MR-guided biopsies has been investigated (ASIST - results expected late 2016)

II) Hormone-Sensitive Metastatic Prostate Cancer

I) Bottom Line General Approach: Initial options include Androgen Deprivation Therapy (ADT) or combined Chemohormonal Therapy (ADT + 6 cycles of Docetaxel)

I) ADT = lowering serum testosterone to castrate levels (<1.7 nmol/L or <50 ng/dL). Surgical orchietomy (castration) and Medical orchietomy with GnRH agonist or GnRH antagonist are equally effective. Anti-androgens (ie Bicalutamide) are often combined with GnRH agonists at the start of therapy for 2-4 weeks to prevent symptom flare due to transient increase in testosterone. Several meta-analyses have shown small improvements in OS with complete androgen blockade (GnRHa + anti-androgen) but with increased toxicity.

II) Early vs Delayed ADT - 2007 meta-analysis showing no significant OS benefit to early ADT, however, heterogeneous population and no prognostic factors incorporated into studies.

III) Intermittent vs Continuous ADT - controversial. INT-0162 Phase III trial showing intermittent ADT is NOT non-inferior to ADT with respect to OS.

IV) Side effects of ADT: vasomotor symptoms, decreased libido, decreased muscle mass, decreased energy, metabolic syndrome, osteopenic effects

V) Calcium and Vitamin D should be given to all men on ADT
VI) Biochemical progression on standard ADT is treated with secondary hormonal manipulations: addition of bicalutamide and bicalutamide withdrawal. Steroidal anti-androgens (i.e., ketoconazole) are not as commonly used since the development of abiraterone and enzalutamide.

VII) 3 Phase III RCT (CHAARTED, Stampede (ASCO 2015), GETUG-AFU 15) have evaluated early Docetaxel in combination with ADT in metastatic castrate sensitive prostate cancer. CHAARTED and Stampede showed improved PFS and OS with early Docetaxel + ADT compared to ADT alone (*GETUG-AFU 15 did not show a statistically significant increase in OS). Median OS in the low-volume disease subgroup has not been reached and additional follow-up is required. Stampede has not yet been published.

VIII) 2 Phase III RTCs (LATITUDE, STAMPEDE) have been published to show OS benefit of abiraterone/prednisone added to ADT within 3 months of initiation of ADT (see below for details). No data on docetaxel vs. abiraterone/prednisone in this setting.

II) Prognosis: 42-44 months with ADT alone vs 57 months with combined chemohormonal therapy – shorter with high volume disease, see CHAARTED

III) Important Phase III clinical trials:

| Regimen | Androgen Deprivation Therapy (ADT) with LHRHa alone vs ADT + Docetaxel 75 mg/m2 on day 1 every 3 weeks x 6 cycles |
| Primary Endpoint | OS |
| Inclusion/Exclusion Criteria | Pathological diagnosis of prostate cancer or clinical scenario consistent Radiographic evidence of metastatic disease ECOG 0-2 Prior adjuvant ADT allowed if ≤ 24 mos and completed ≥ 12 mos prior ADT commenced within 120 days of randomization |
| Size (N) | 790 |
| Results | Survival: mOS 57.6 mos vs 44.0 mos, HR 0.61 Subgroup with high volume disease: mOS 49.2 mos vs 32.2 mos HR 0.60 Subgroup with high volume disease: mOS not reached in low volume group Decrease in PSA to ≤ 0.2ng/ml at 12 mos: 27.7% vs 16.8% Time to development of castration-resistant PCa: 20.2 mos vs 11.7 mos |
| Toxicity | Grade 3 or 4 neutropenia 32%, febrile neutropenia 3% Common toxicities include fatigue, n/v/d, neuropathy (30%), edema |
| Conclusion | Six cycles of docetaxel at the beginning of ADT for metastatic prostate cancer resulted in significantly longer overall survival than that with ADT alone. |
| Other Comments | high volume disease defined as visceral mets or ≥ 4 bony mets with ≥ 1 outside axial skeleton |
**GETUG-AFU 15:** Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer: a randomized, open-label Phase 3 trial.

**Reference:** Gravis et al. Lancet Oncol 2013;14:149.

| Regimen | Androgen Deprivation Therapy (ADT) with LHRHa alone or orchiectomy vs ADT + Docetaxel 75 mg/m² on day 1 every 3 weeks x 9 cycles |
| Primary Endpoint | OS |
| Inclusion/Exclusion Criteria | Histologically confirmed adenocarcinoma of the prostate Radiographic evidence of metastatic disease Karnofsky PS ≥70% ADT commenced within 2 months of enrolment Prior neoadjuvant or adjuvant therapy completed ≥ 12 months prior |
| Size (N) | 385 |
| Results | **Survival:** mOS 62 mos vs 49 mos, HR 0.88 (0.68-1.14) NS **biochemical PFS:** 22.9 mos vs 12.9 mos, HR 0.67 **Median time to subsequent treatment:** 20 mos vs 15.4 mos **Fall in PSA ≥50% at 6 months:** 94% vs 85% |
| Toxicity | Neutropenia 21%, febrile neutropenia 3%, abnormal LFTs 2% |
| Conclusion | Docetaxel should not be used as part of first-line treatment for patients with non-castrate metastatic prostate cancer. |
| Other Comments | |

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


| Regimen | Standard of care was hormone therapy for at least 2 years; radiotherapy was encouraged for men with N0M0 disease to November, 2011, then mandated; radiotherapy was optional for men with node-positive non-metastatic (N+M0) disease. Stratified randomisation (via minimisation) allocated men 2:1:1:1 to standard of care only (SOC-only; control), standard of care plus zoledronic acid (SOC + ZA), standard of care plus docetaxel (SOC + Doc), or standard of care with both zoledronic acid and docetaxel (SOC + ZA + Doc). Zoledronic acid (4 mg) was given for six 3-weekly cycles, then 4-weekly until 2 years, and docetaxel (75 mg/m²) for six 3-weekly cycles with prednisolone 10 mg daily. |
| Primary Endpoint | OS |
| Inclusion/Exclusion Criteria | men with high-risk, locally advanced, metastatic or recurrent prostate cancer who are starting first-line long-term hormone therapy |
| Size (N) | N=2962 |
| Results | **Median age was 65 years (IQR 60–71).** **1817 (61%)** men had M+ disease, **448 (15%)** had N+/X M0, and **697 (24%)** had N0M0. |
• 165 (6%) men were previously treated with local therapy, and median prostate-specific antigen was 65 ng/mL (IQR 23–184). Median follow-up was 43 months (IQR 30–60).
• There were 415 deaths in the control group (347 [84%] prostate cancer). Median overall survival was 71 months (IQR 32 to not reached) for SOC-only, not reached (32 to not reached) for SOC + ZA (HR 0·94, 95% CI 0·79–1·11; p=0·450), 81 months (41 to not reached) for SOC + Doc (0·78, 0·66–0·93; p=0·006), and 76 months (39 to not reached) for SOC + ZA + Doc (0·78, 0·66–0·93; p=0·022). There was no evidence of heterogeneity in treatment effect (for any of the treatments) across prespecified subsets. Grade 3–5 adverse events were reported for 399 (32%) patients receiving SOC, 197 (32%) receiving SOC + ZA, 288 (52%) receiving SOC + Doc, and 269 (52%) receiving SOC + ZA + Doc.
• Subgroup analysis, OS
  - M0 HR 0.95 (crosses 1)
  - M1 HR 0.76 (significant)

Conclusion
• Zoledronic acid showed no evidence of survival improvement and should not be part of standard of care for this population. Docetaxel chemotherapy, given at the time of long-term hormone therapy initiation, showed evidence of improved survival accompanied by an increase in adverse events. Docetaxel treatment should become part of standard of care for adequately fit men commencing long-term hormone therapy.

Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer (LATITUDE)

Regimen
• Androgen-deprivation therapy plus abiraterone acetate (1000 mg daily, given once daily as four 250-mg tablets) plus prednisone (5 mg daily) (the abiraterone group) or androgen-deprivation therapy plus dual placebos (the placebo group).

Primary Endpoint
• OS
• Radiographic PFS

Inclusion/Exclusion Criteria
• Patients with newly diagnosed, metastatic, castration-sensitive prostate cancer starting ADT <3m
• All the patients had high-risk, metastatic, castration-sensitive prostate cancer, as documented by a positive bone scan or metastatic lesions at the time of diagnosis on computed tomography (CT) or magnetic resonance imaging (MRI), according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.
• In addition, the patients were required to have at least two of the three following high-risk factors associated with poor prognosis: a Gleason score of 8 or more (on a scale of 2 to 10, with higher scores indicating more aggressive disease), at least three bone lesions, and the presence of measurable visceral metastasis.

Size (N)
• N=1199

Results
• After a median follow-up of 30.4 months at a planned interim analysis (after 406 patients had died), the median overall survival was significantly longer in the abiraterone group than in the placebo group (not reached vs. 34.7 months) (hazard ratio for death, 0.62; 95% confidence interval [CI], 0.51 to 0.76; P<0.001).
• The median length of radiographic progression-free survival was 33.0 months in the abiraterone group and 14.8 months in the placebo group (hazard ratio for disease progression or death, 0.47; 95% CI, 0.39 to 0.55; P<0.001).
• Significantly better outcomes in all secondary end points were
observed in the abiraterone group, including the time until pain progression, next subsequent therapy for prostate cancer, initiation of chemotherapy, and prostate-specific antigen progression (P<0.001 for all comparisons), along with next symptomatic skeletal events (P=0.009).

- These findings led to the unanimous recommendation by the independent data and safety monitoring committee that the trial be unblinded and crossover be allowed for patients in the placebo group to receive abiraterone.

### Toxicity
- Similar to known S/E of abiraterone/prednisone
- Rates of grade 3 hypertension and hypokalemia were higher in the abiraterone group.

### Conclusion
- The addition of abiraterone acetate and prednisone to androgen-deprivation therapy significantly increased overall survival and radiographic progression-free survival in men with newly diagnosed, metastatic, castration-sensitive prostate cancer.

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### Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy (STAMPEDE)
*James N Engl J Med 2017; 377:338-351*

### Regimen
- ADT alone or ADT plus abiraterone acetate (1000 mg daily) and prednisolone (5 mg daily) (combination therapy)
- Local radiotherapy was mandated for patients with node-negative, nonmetastatic disease and encouraged for those with positive nodes. For patients with nonmetastatic disease with no radiotherapy planned and for patients with metastatic disease, treatment continued until radiologic, clinical, or prostate-specific antigen (PSA) progression; otherwise, treatment was to continue for 2 years or until any type of progression, whichever came first.

### Primary Endpoint
- OS

### Inclusion/Exclusion Criteria
- Eligible patients had prostate cancer that was newly diagnosed and metastatic, node-positive, or high-risk locally advanced (with at least two of following: a tumor stage of T3 or T4, a Gleason score of 8 to 10, and a PSA level ≥40 ng per milliliter) or disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features (in men no longer receiving therapy, a PSA level >4 ng per milliliter with a doubling time of <6 months, a PSA level >20 ng per milliliter, nodal or metastatic relapse, or <12 months of total ADT with an interval of >12 months without treatment).
- Patients were intended for treatment with long-term ADT that started no longer than 12 weeks before randomization. There were no age restrictions. Patients with clinically significant cardiovascular disease (e.g., severe angina, recent myocardial infarction, or a history of cardiac failure) were excluded.

### Size (N)
- N=1917

### Results
- There were 248 treatment-failure events in the combination group as compared with 535 in the ADT-alone group (hazard ratio, 0.29; 95% CI, 0.25 to 0.34; P<0.001); the hazard ratio was 0.21 in patients with nonmetastatic disease and 0.31 in those with metastatic disease.
- For OS, M0 – HR 0.75, crosses 1; M1 -HR 0.61, significant
- mFU 40m
- There were 184 deaths in the combination group as compared with 262 in the ADT-alone group (hazard ratio, 0.63; 95% confidence interval [CI], 0.52 to 0.76; P<0.001); the hazard ratio was 0.75 in patients with nonmetastatic disease and 0.61 in those with metastatic disease.
- Restricted mean failure-free survival time: 43.9 months in the combination group and 30.0 months in the ADT-alone group in the first 54 months after randomization, a difference of 13.9 months (95% CI, 12.3 to 15.4). The effect of abiraterone on failure-free survival was noted in all subgroups.
- The 3-year progression-free survival was 80% in the combination group and 62% in the ADT-alone group (hazard ratio for clinical or radiologic progression or death from prostate cancer, 0.40; 95% CI, 0.34 to 0.47; P<0.001).
- FFS M0 – HR 0.21; M1 – HR 0.31 Both significant.

### Toxicity
- Grade 3 to 5 adverse events occurred in 47% of the patients in the combination group (with nine grade 5 events) and in 33% of the patients in the ADT-alone group (with three grade 5 events).

### Conclusion
- Among men with locally advanced or metastatic prostate cancer, ADT plus abiraterone and prednisolone was associated with significantly higher rates of overall and failure-free survival than ADT alone.
III) Castrate-Refractory Metastatic Prostate Cancer (mCRPC)

I) Bottom Line General Approach:
   I) Treatment options for mCRPC include taxane chemotherapy (Docetaxel, Cabazitaxel), anti-androgens Abiraterone Acetate and Enzalutamide and Radium-223. 1st line options include Docetaxel, Abiraterone, Enzalutamide and Radium-223. Post-Docetaxel options include Abirterone, Enzalutamide, Radium-223 and Cabazitaxel.
   II) Palliative radiotherapy is also frequently used for cancer-related pain from bone metastases
   III) New treatment options were developed in parallel and the optimal sequencing of treatments is unknown but of increasing importance. Currently, decisions are based on patient factors (co-morbidities, performance status, cancer-related symptoms, contraindications) and disease factors (site of disease: lymph node or bone only sites vs visceral metastases, duration of response to ADT and aggressiveness: rate of progression/de novo metastatic disease/high Gleason score)
   IV) Abiraterone and Enzalutamide show decreased rates of PSA response when used subsequent to the other indicative of cross resistance.
   V) Use of bisphosphates (Zoledronic Acid) or Denosumab decreases skeletal related events but does not improve OS or QOL.
II) **Prognosis:** 35 months with most recent trials vs 16 months without treatment in TAX327 (Mitoxantrone does not improve OS)

III) **Important Phase III Clinical Trials**

<table>
<thead>
<tr>
<th><strong>TAX 327:</strong> Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer.</th>
<th><strong>Reference:</strong> Tannock IF et al. NEJM 2004;351:1502.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regimen</strong></td>
<td>Up to 10 cycles of Docetaxel (75 mg/m2 on day 1 every 3 weeks) OR up to 5 cycles of weekly Docetaxel (30 mg/m2 on day 1, 8, 15, 22, 29 of a 6 week cycle) plus plus prednisone 5mg BID vs. Mitoxantrone (12 mg/m2 on day 1 every 3 weeks) plus prednisone 5mg BID</td>
</tr>
<tr>
<td><strong>Mechanism of Action of Experimental Drug</strong></td>
<td>Docetaxel: inhibits polymerization of tubulin therefore inhibiting DNA, RNA and protein synthesis.</td>
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<tr>
<td><strong>Primary Endpoint</strong></td>
<td>OS</td>
</tr>
</tbody>
</table>
| **Inclusion/Exclusion Criteria** | No prior cytotoxic treatment
Karnofsky PS >/= 60%
Disease progression on hormonal treatment |
| **Size (N)** | 1006 |
| **Results** | **Survival:** mOS 18.9 mos in q3 weekly Docetaxel vs 16.5 mos in Mitoxantrone, no significant improvement with weekly Docetaxel
**PSA Response:** 45%, 48% Docetaxel vs 32% Mitoxantrone (p<0.01)
**QOL:** Improved QOL with both Docetaxel groups vs Mitoxantrone
**Pain:** decreased with q3 weekly Docetaxel |
| **Toxicity** | Grade 3 or 4 neutropenia 32%, febrile neutropenia 3%
Common toxicities include fatigue, n/v/d, neuropathy (30%), edema |
| **Conclusion** | Docetaxel q3 weeks (but not weekly Docetaxel) plus prednisone led to superior survival and improved rates of response in terms of pain, serum PSA level, and quality of life, as compared with mitoxantrone plus prednisone. This is the first study to show a survival benefit in mCRPC. |
| **Other Comments** | (e.g. any criticisms about the study) |

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Enzalutamide (MDV3100) 160mg PO daily vs. placebo</th>
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<tbody>
<tr>
<td>Mechanism of Action of Experimental Drug</td>
<td>Enzalutamide: androgen receptor antagonist, inhibits translocation of AR into cell nucleus and inhibits AR binding to DNA</td>
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<tr>
<td>Primary Endpoint</td>
<td>OS</td>
</tr>
</tbody>
</table>
| Inclusion/Exclusion Criteria | Castrate levels of testosterone (<50 ng/ deciliter [1.7 nmol/ liter])  
                         Previous treatment with Docetaxel  
                         ECOG 0-2  
                         Disease progression (radiographic or rising PSA on 3 occasions) |
| Size (N)              | 1199                                                |

#### Results

<table>
<thead>
<tr>
<th>Survival</th>
<th>mOS 18.4 mos vs 13.6 mos, HR 0.63</th>
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<tbody>
<tr>
<td>PSA Response</td>
<td>increased with Enzalutamide (54% vs 2%)</td>
</tr>
<tr>
<td>ORR</td>
<td>increased with Enzalutamide (29% vs 4%)</td>
</tr>
<tr>
<td>QOL</td>
<td>increased with Enzalutamide (43% vs 18%)</td>
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<tr>
<td>time to first skeletal event</td>
<td>increased with Enzalutamide (16.7 mos vs 13.3 mos)</td>
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<tr>
<td>time to PSA progression</td>
<td>increased with Enzalutamide 8.3 mos vs 3.0 mos</td>
</tr>
<tr>
<td>PFS</td>
<td>increased with Enzalutamide 8.3 mos vs 2.9 mos</td>
</tr>
</tbody>
</table>

#### Toxicity

- Seizure 0.6%
- Common: fatigue, diarrhea, hot flashes, headache, MSK pain

#### Conclusion

Enzalutamide significantly prolonged survival in men with metastatic castration resistant prostate cancer after chemotherapy.

#### Other Comments

- Drug interactions
COU-AA-301: Abiraterone and Increased Survival in Metastatic Prostate Cancer.


| Regimen | Abiraterone 1000mg PO daily + prednisone 5mg BID vs. placebo + prednisone 5mg BID |
| Mechanism of Action of Experimental Drug | Abiraterone: irreversible and specific inhibitor of CYP17 (inhibits androgen synthesis) |
| Primary Endpoint | OS |
| Inclusion/Exclusion Criteria | Castrate levels of testosterone (<50 ng/ deciliter [2 nmol/ liter]) Previous treatment with Docetaxel ECOG 0-2 Disease progression (radiographic or rising PSA on 2 occasions) |
| Size (N) | 1195 |
| Results | **Survival**: mOS 14.8 mos vs 10.9 mos, HR 0.65  **PSA Response**: increased with Abiraterone (29% vs 6%)  **ORR**: increased with Abiraterone (14% vs 3%)  **Rate of pain palliation**: increased with Abiraterone (44% vs 27%)  **Time to first skeletal event in 25%**: increased with Abiraterone (9.9 vs 4.9 mos)  **Time to PSA progression**: 10.2 mos vs 6.6 mos  **PFS**: 5.6 mos vs 3.6 mos |
| Toxicity | Common: fatigue, back pain, nausea, constipation, bone pain - similar frequency as placebo  Hypokalemia (17%), fluid retention (31%), hypertension (10%), cardiac events (13%), AST/ALT elevation (10%, same as placebo) |
| Conclusion | Abiraterone abiraterone acetate prolonged overall survival among patients with metastatic castration-resistant prostate cancer who previously received chemotherapy. |
| Other Comments | (e.g. any criticisms about the study) |
**TROPIC:** Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open label trial.

**Reference:** de Bono et al. Lancet 2010;376:1147.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Up to 10 cycles of Cabazitaxel (25 mg/m2 q21 days) + prednisone 10mg daily vs. Mitoxantrone (12mg/m2 q 21days) + prednisone 10mg daily. Prophylactic GCSF allowed after 1st occurrence of febrile neutropenia or neutropenia greater than 7 days</th>
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<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>Previous treatment with Docetaxel Disease progression (radiographic or rising PSA on 2 occasions) ECOG 0-2 Ongoing castration by orchiectomy or LHRHa &gt;/= Grade 2 peripheral neuropathy excluded</td>
</tr>
<tr>
<td>Size (N)</td>
<td>755</td>
</tr>
<tr>
<td>Results</td>
<td><strong>Survival:</strong> mOS 15.1 mos vs 12.7 mos, HR 0.7  <strong>PSA Response:</strong> increased with Cabazitaxel (39.2% vs 17.8%)  <strong>ORR:</strong> increased with Cabazitaxel (14% vs 4%)  <strong>Time to PSA progression:</strong> 8.8 mos vs 5.4 mos  <strong>mPFS:</strong> 2.8 mos vs 1.4 mos  <strong>Rate of pain palliation:</strong> no difference  <strong>Time to pain progression:</strong> no difference</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Grade 3 or 4 neutropenia 82%, febrile neutropenia 8%, diarrhea 6% Common toxicities include haematologic, diarrhea, fatigue, n/v</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Cabazitaxel plus prednisone improves overall survival in patients with metastatic castration-resistant prostate cancer whose disease has progressed during or after docetaxel-based therapy.</td>
</tr>
<tr>
<td>Other Comments</td>
<td>(e.g. any criticisms about the study)</td>
</tr>
</tbody>
</table>
**ALSYPMA:** Alpha emitter Radium-223 and Survival in Metastatic Prostate Cancer  

<table>
<thead>
<tr>
<th><strong>Regimen</strong></th>
<th>Up to 6 injections of Radium-223 50kBq/kg on Day 1 every 4 weeks vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action of Experimental Drug</strong></td>
<td>Radium-223: targeted alpha emitter that selectively binds to areas of increased bone turnover in bone metastases and induces double-stranded DNA breaks</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>OS</td>
</tr>
</tbody>
</table>
| **Inclusion/Exclusion Criteria** | Castrate levels of testosterone (<50 ng/ deciliter [1.7 nmol/ liter])  
2 or more bone metastases  
No visceral metastases, lymph node mets <3cm  
Symptomatic disease: regular use of analgesics or radiation for cancer-related bone pain in previous 12 weeks  
Previous treatment with Docetaxel, not a candidate for Docetaxel or declined Docetaxel**  
PSA of at least 5ng/ml and with 2 consecutive increases ECOG 0-2 |
| **Size (N)** | 921 |
| **Results** | **Survival:** mOS 14.9 mos vs 11.3 mos, HR 0.7  
**Time to first skeletal event:** 15.6 mos vs 9.8 mos, HR 0.66  
**Time to an increase in ALP:** 7.4 mos vs 3.8 mos  
**Time to an increase in PSA:** 3.6 vs 3.4 mos  
**PSA response:** 16% vs 6%  
**≥30% reduction in ALP:** 47% vs 3%  
**Normalization of ALP:** 34% vs 1%  
**Improved QOL:** 25% vs 16% |
| **Toxicity** | The number of patients experiencing an adverse event was consistently lower in the Radium-223 group than in the placebo group for all adverse events  
No clinically meaningful differences in the frequency of hematologic adverse events were observed between groups. |
| **Conclusion** | Radium-223 significantly prolonged overall survival in patients who had castration-resistant prostate cancer previously treated with (or ineligible for) Docetaxel and symptomatic bone metastases |
| **Other Comments** | **only ~60% were post-Docetaxel, others were “non”-Docetaxel** |
**Pre-Docetaxel**

**COU-AA-302:** Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy.  

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Abiraterone 1000mg PO daily + prednisone 5mg BID vs. placebo + prednisone 5mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action of Experimental Drug</strong></td>
<td>Abiraterone: irreversible and specific inhibitor of CYP17 (inhibits androgen synthesis)</td>
</tr>
</tbody>
</table>
| **Primary Endpoint** | OS*  
| | Radiographic PFS *co-primary endpoints |
| **Inclusion/Exclusion Criteria** | Castrate levels of testosterone (<50 ng/ deciliter [1.7 nmol/ liter])  
| | Disease progression (radiographic or rising PSA on 2 occasions)  
| | Chemotherapy-naive  
| | ECOG 0-1  
| | No symptoms or mild symptoms on BPI-SF  
| | Pts with visceral metastases excluded  
| | Pts treated with ketoconazole > 7 days were excluded |
| **Size (N)** | 1088 |
| **Results** | **mPFS:** 16.5 vs 8.3 mos, HR 0.53  
| | **Survival:** mOS 34.7 mos vs 30.3 mos, HR 0.81  
| | **PSA Response:** 62% vs 24%  
| | **ORR:** 36% vs 16%  
| | **Time to initiation of cytotoxic chemotherapy:** 25.2 mos vs 16.8 mos  
| | **Time to opiate use for cancer-related pain:** 33.4 mos vs 23.4 mos  
| | **Time to decline in ECOG PS:** 12.3 mos vs 10.9 mos  
| | **Time to PSA progression:** 11.1 mos vs 5.6 mos |
| **Toxicity** | Fatigue, arthralgia, peripheral edema - more common than placebo  
| | Hypokalemia (17%), fluid retention (28%), hypertension (22%), cardiac events (19%), AST/ALT elevation (8%) |
| **Conclusion** | Abiraterone improved radiographic PFS, overall survival, and delayed clinical decline, time to initiation of chemotherapy and time to opiate use in patients with metastatic castration-resistant prostate cancer. |
| **Other Comments** | (e.g. any criticisms about the study) |
# PREVAIL: Enzalutamide in Metastatic Prostate Cancer before Chemotherapy


<table>
<thead>
<tr>
<th>Regimen</th>
<th>Enzalutamide (MDV3100) 160mg PO daily vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action of Experimental Drug</td>
<td>Enzalutamide: androgen receptor antagonist, inhibits translocation of AR into cell nucleus and inhibits AR binding to DNA</td>
</tr>
</tbody>
</table>
| Primary Endpoint | OS*  
Radiographic PFS* co-primary endpoints |
| Inclusion/Exclusion Criteria | Castrate levels of testosterone (<50 ng/deciliter [1.7 nmol/liter])  
Disease progression (radiographic or rising PSA on 2 occasions)  
No prior cytotoxic chemotherapy, ketoconazole or abiraterone  
ECOG 0-1  
No symptoms or mild symptoms on BPI-SF  
Pts with visceral metastases eligible  
History of seizure or condition predisposing to seizure excluded |
| Size (N) | 1717 |
| Results | **Survival:** 12-month OS 72% vs 63%, HR 0.71  
**PFS:** 12-month Radiographic PFS 65% vs 14%, HR 0.19  
**PSA Response:** 78% vs 3%  
**ORR:** 59% vs 5%  
**Time to initiation of cytotoxic chemotherapy:** 28 mos vs 10.8 mos  
**Time to PSA progression:** 11.2 mos vs 2.8 mos  
**Time to first skeletal-related event:** 31.1 mos vs 31.3 mos  
**Time to decline in FACT-P global score:** 11.3 mos vs 5.6 mos |
| Toxicity | Common: fatigue, hypertension |
| Conclusion | Enzalutamide significantly decreased the risk of radiographic progression and death and delayed the initiation of chemotherapy in men with metastatic prostate cancer. |

Other Comments