New horizons in Prostate Cancer Treatment

Expanding options, extending survival, and improving quality of life

Chip Reninger
Hematology and Oncology Consultants of Pa
1. Expanding Treatment Options for metastatic Prostate Cancer for hormone sensitive disease and castrate resistant disease
2. Evolving Biology of CRPC
3. Taxotere emerging role in first line treatment of HSMPC/high risk local disease
4. Novel Agents for the treatment of CRPC
   - Immunotherapies
     - Sipuleucel-T
   - Androgen Biosynthesis Inhibitors (ABI’s)/novel anti-androgens
     - Abiraterone, Enzalutamide (MDV-3100)
   - Cytotoxics
     - Cabazitaxel
   - Bone/micro-environment directed therapies
     - Radium 223/Xofigo
5. "Picking the right treatment for the right patients at the right time"
Diagnoses

**Non-Castrate**
Androgen depletion / blockade (bicalutamide)

1. Clinically Localized Disease
2. Rising PSA: Castrate
3. Rising PSA: Non-Castrate
4. Clinical Metastases: Castrate 2nd Line

Castration resistant: deaths from disease

- 28,660
- 186,320

With detectable metastases: deaths from cancer exceed that from other causes
Typical Timing of Available Treatments
Systemic Medical Treatments of Prostate Cancer

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- LHR agonists
- Mitoxantrone
- Zoledronic Acid
- Docetaxel
- Cabazitaxel
- Enzalutamide
- Abiraterone
- Denosumab
- Sipuleucel-T
- Radium - 223

Timeline:
- 1984 - 1989
- 1996
- 2002
- 2004 ...
- 2010
- 2011
- 2012
- 2013

Reversible AR blockers
Disease States and Possible Treatment in Prostate Cancer

- Localized Disease Confined to the Prostate newly diagnosed- surgery/RT +/- hormones +/- chemotx
- Localized Disease with spread to adjacent organs or pelvic lymph nodes – RT+ hormones +/- Chemotx
- Biochemical (psa) recurrence after surgery - +/- salvage radiation +/- hormones
- Biochemical (psa) recurrence after Radiation - +/- salvage surgery +/- hormones
Typical Timing of Available Treatments
First Line Hormone Sensitive disease -

The Basics of Hormone Therapy

- GNRH analogs (lupron)
- GNRH antagonists (firmaion)
- Casodex – binds to AR to block testosterone affects

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## Understanding the Biology of CRPC

### Driver Pathways of Dependency of PC

<table>
<thead>
<tr>
<th></th>
<th>Primary</th>
<th>Mets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgen Receptor (AR)</td>
<td>100%</td>
<td>55%</td>
</tr>
<tr>
<td>PTEN loss</td>
<td>80%</td>
<td>25%</td>
</tr>
<tr>
<td>PI3K/Akt, Ras/Raf, RB</td>
<td>100%</td>
<td>42%</td>
</tr>
<tr>
<td>TMPRSS2-ETS fusion</td>
<td>33%</td>
<td>50%</td>
</tr>
</tbody>
</table>

**Genetic variants of androgen transporter genes**

Tomlins, S. A. Eur Urol 2009  
Taylor, B et al, Cancer Cell 2010  
Kong D. Cancer Sci 2008  
Jenkins, R. B. Cancer Res 1997  
Prostate Cancer: “Adapting” to castrate environment

Hormone Therapy

- MUTATION (gain of function)
- ABERRANT MODIFICATION (GF, cytokines, Src)
- ALTERN. SPlicing
- COFACTOR PERTURBATION (CoAct gain, CoR loss/dismissal)
- INTRACRINE ANDROGEN SYNTHESIS (amplification, overexpression)
- AR DEREGULATION
- RESTORED AR ACTIVITY (rising PSA)
- RECURRENT TUMOR DEVELOPMENT

>30% CRPC

Penning & Knudsen 2010
Chemotherapy in Prostate Cancer – Taxotere

An old dog with new tricks

2004

- Taxotere approved in CRPC
  - only tx shown to improve survival after failure on gnrh analog and casodex
  - Modest benefit of 2.5 months over standard treatment with median survival of 19 mos vs 16.5 months

2014 / 2015

- Taxotere improved survival in:
  - 2014: Newly diagnosed “high volume” metastatic disease in combination with hormones vs hormones alone(SOC) at the time of diagnoses. 13 months improvement in overall survival from 3.5 yrs to 4.75 yrs
  - 2015: improved survival in all men with newly diagnosed metastatic prostate cancer
  - 2015: possible survival benefit in men with localized high risk cancer in 2 trials
Chemotherapy in Prostate Cancer
Castrate Resistant Disease
Taxotere 2004

“Traditional” use of chemotherapy for CRPC

Survival in TAX-327 Study

- Docetaxel 3wkly
- Mitoxantrone 3 wkly

HR=0.76 (0.62-0.94)

Median = 16.5 months
Median = 18.9 months (p=0.009)
Chemotherapy in Prostate Cancer
Hormone Sensitive Metastatic
– Taxotere - 2014
Role of chemotherapy for hormone-naïve PC

E3805 CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer

Interim analysis: Median follow-up = 29 months

OS by extent of metastatic disease at start of ADT

High volume

Median OS:
- ADT + D: 57.6 months
- ADT alone: 44.0 months

Low volume

Median OS:
- ADT + D: Not reached
- ADT alone: Not reached

In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival from 32.2 months to 49.2 months. We projected 33 months in ADT alone arm with collaboration of SWOG9346 team.

Adding docetaxel to ADT improves survival in men with metastatic castration-sensitive prostate cancer.
High risk local and metastatic disease
Taxotere 2015
### Inclusion criteria

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

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

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### Patient characteristics

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>WHO PS 2</td>
</tr>
<tr>
<td>21%</td>
<td>WHO PS 1</td>
</tr>
<tr>
<td>65%</td>
<td>Median age (min 40, max 84)</td>
</tr>
<tr>
<td>61%</td>
<td>Metastatic (85% Bony mets)</td>
</tr>
<tr>
<td>15%</td>
<td>N+M0</td>
</tr>
<tr>
<td>24%</td>
<td>N0M0</td>
</tr>
<tr>
<td>98%</td>
<td>LHRH analogues</td>
</tr>
<tr>
<td>29%</td>
<td>Planned for RT (72% of N0M0 pts)</td>
</tr>
<tr>
<td>6%</td>
<td>Previous local therapy</td>
</tr>
</tbody>
</table>

All patients: WHO performance status 0-2

Balanced by arm

[s] Stratification factors + hospital + NSAID/aspirin
**Consistency of treatment effect**

- **Subgroups included:**
  - Metastatic status (M0, M1)
  - Nodal status (N0, N+, NX)
  - Gleason sum score (≤7, 8+, unknown)
  - PSA pre-hormone therapy (0-20ng/ml, 20-40, 40-100, 100+)
  - Age at randomisation (under 70, 70 or over)
  - WHO PS (0, 1-2)
  - NSAID/Aspirin use (no use, uses either)

- No good evidence of heterogeneity

**Conclusions**

- Docetaxel improves survival for hormone-naive prostate cancer
- Zoledronic acid does not improve survival
- Adding both improves survival but offers no obvious benefit over adding just docetaxel
- Multi-arm, multi-stage trials are practicable and efficient
- Docetaxel should be:
  - Considered for routine practice in suitable men with newly-diagnosed metastatic disease
  - Considered for selected men with high-risk non-metastatic disease in view of substantial prolongation of failure-free survival
Taxotere 2015 – high risk locally advanced RTOG 0521
Taxotere 2015 – high risk locally advanced RTOG 0521
## Taxotere 2015 – High Risk Locally Advanced RTOG 0521

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Arm 1 and Arm 2 (N=563)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Category (stratification)</td>
<td>(%)</td>
</tr>
<tr>
<td>Gleason ≥9, PSA ≤150, Any T-stage</td>
<td>53</td>
</tr>
<tr>
<td>Gleason 8, PSA &lt;20, ≥T2</td>
<td>21</td>
</tr>
<tr>
<td>Gleason 8, PSA ≥20-150, Any T-stage</td>
<td>10</td>
</tr>
<tr>
<td>Gleason 7, PSA ≥20-150, Any T-stage</td>
<td>16</td>
</tr>
<tr>
<td>Gleason score, no.</td>
<td>(%)</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td>9-10</td>
<td>53</td>
</tr>
<tr>
<td>Serum PSA, ng/mL, Median (Q1-Q3)</td>
<td>15 (7-34)</td>
</tr>
<tr>
<td>Age, Median</td>
<td>66</td>
</tr>
<tr>
<td>cT3-T4</td>
<td>27%</td>
</tr>
<tr>
<td>pN0</td>
<td>33%</td>
</tr>
</tbody>
</table>
Role of chemotherapy for localized high-risk PC (M0) after radiation therapy

Overall Survival

4 yr OS: 93% vs. 89%
HR 0.70 (90% CI: 0.51-0.98)

Presented By Ian Tannock at 2015 ASCO Annual Meeting
Taxotere 2015 – high risk locally advanced RTOG 0521

Distant Metastasis at Any Time

<table>
<thead>
<tr>
<th>Time Since Randomization (Years)</th>
<th>AS+RT</th>
<th>AS+RT+CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>281</td>
<td>282</td>
</tr>
<tr>
<td>1</td>
<td>273</td>
<td>271</td>
</tr>
<tr>
<td>2</td>
<td>262</td>
<td>264</td>
</tr>
<tr>
<td>3</td>
<td>244</td>
<td>246</td>
</tr>
<tr>
<td>4</td>
<td>224</td>
<td>230</td>
</tr>
<tr>
<td>5</td>
<td>188</td>
<td>207</td>
</tr>
<tr>
<td>6</td>
<td>113</td>
<td>114</td>
</tr>
</tbody>
</table>

Biochemical Failure

6 yr BF 74% vs. 66%
HR 0.81 (95%CI: 0.58-1.11)

Disease-Free Survival

6 yr DFS 65% vs. 55%
HR 0.76 (95%CI: 0.58-0.99)
Chemotherapy in Prostate Cancer

**Taxotere: Possible option in localized disease**

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**Forest plot for Failure-Free Survival in men with M0 disease (thanks to Dr. Eitan Amir)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GETUG-12</td>
<td>33.4%</td>
<td>0.71</td>
<td>[0.54, 0.94]</td>
</tr>
<tr>
<td>RTOG 0521</td>
<td>36.6%</td>
<td>0.76</td>
<td>[0.58, 0.99]</td>
</tr>
<tr>
<td>STAMPEDE</td>
<td>30.0%</td>
<td>0.57</td>
<td>[0.42, 0.76]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>0.68</td>
<td>[0.57, 0.81]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00; \chi^2 = 2.27, df = 2 (P = 0.32)$
Test for overall effect: $Z = 4.40 (P < 0.0001)$

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*Given that only RTOG-0521 reports a difference in overall survival (93% vs 89%, p=0.04 one-sided)*....

*....is this sufficient evidence to recommend docetaxel +ADT after radiotherapy for men with M0 disease?*

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31/05/2015

Presented By Ian Tannock at 2015 ASCO Annual Meeting

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ASCO
Conclusions

- For the first time an improvement in overall survival observed with adjuvant chemotherapy for localized high risk hormone sensitive prostate cancer
- The effect and role of Docetaxel in hormone sensitive prostate cancer is consistent with and supported by other studies such as chaarted and stampede
- This analysis is early and additional follow up is needed in both stampede and RTOG0521
Metastatic Castrate Resistant Disease- asymptomatic or minimally symptomatic chemotherapy naive

- Observation
- Antiandrogen withdrawal
- Ketoconazole
- Taxotere and prednisone*

*Overall survival in RCT

- Immunotherapy
  - Provenge (Sipuleucel-T)*

- Hormone
  - Abiraterone (Zytiga) and Prednisone*
  - Enzalutamid (Xtandi)*

- Chemotx

Prior to 2010
- After 2010

*Overall survival in RCT

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25
Immunotherapy Approaches in PC

- **Active immunotherapy**
  - Tumor associated antigen is directly targeted by loading in that antigen in APC or into vaccine vector at protein or DNA level
  - Antigen specific immunotherapy
    - Sipuleucel-T
    - Poxvirus-based vectors
    - DNA based vaccines
- **Passive immunotherapy**
  - Antibodies to specific receptors/antigens
    - Prostate Specific Membrane Antigen (PSMA)
- **Immune Checkpoint Inhibitors**
  - Strategies to maintain activated tumor specific T-cells by neutralizing co-inhibitory receptors
Active Cellular Immunotherapy (Sipuleucel-T)

- Patient’s white blood cells harvested
- Short-term culture with protein “cassette”
  - GM-CSF
  - Prostatic acid phosphatase
- Shipping
- Cells infused back into patient (IV)
Phase 3 Study Design: the IMPACT Trial (D9902B)  
(Immunotherapy Prostate Adenocarcinoma Treatment)

Endpoints for IMPACT
Primary endpoint: Overall Survival  
Secondary endpoint: Time to Objective Disease Progression

* Control was nonactivated, autologous peripheral blood mononuclear cells

Provenge (sipuleucel–t)

- Median survival benefit
- Survival above the control group

Can be given with other hormonal therapies and well tolerated

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Targeting the Androgen Pathway

- **Androgen Biosynthesis Inhibitors**
  - *Abiraterone Acetate*
  - *TAK 700*
  - *VN/124-1 (TOK-001)*

- **Novel Anti-Androgens**
  - *Enzalutamide*
  - *RD 162*
  - *EPI-001 (AR N-Terminal)*
  - *SNARE-1 (selective nuclear receptor exporter-1)*

* FDA approved
Hormonal Therapy

ZYTIGA (abiraterone acetate)

- Abiraterone acetate (ZYTIGA®)
  - converted in the body to abiraterone, an androgen biosynthesis inhibitor, that inhibits an enzyme vital to producing testosterone (androgens).
  - enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.
Zytiga in chemotx non naïve pts-

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

- **Randomized 2:1**
  - Abiraterone 1000 mg daily
    - Prednisone 5 mg BID
    - n=797
  - Placebo daily
    - Prednisone 5 mg BID
    - n=398

- **Efficacy endpoints (ITT)**
  - **Primary end point**
    - OS (25% improvement; HR 0.8)
  - **Secondary endpoints (ITT)**
    - TTPP
    - PFS
    - PSA response

- **Stratification according to**
  - ECOG performance status (0-1 vs 2)
  - Worst pain over previous 24 hours (BPI short form; 0-3 [absent] vs 4-10 [present])
  - Prior chemotherapy (1 vs 2)

**Abbreviations**: BPI= Brief Pain Inventory; TTPP= time to PSA progression; ITT= intent to treat; mCRPC= metastatic castrate-resistant prostate cancer.

**Source**: Clinicaltrials.gov identifier: NCT00638690.

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COU-AA-301: Abiraterone Acetate Improves OS in mCRPC

HR = 0.646 (0.54-0.77)  \( P < 0.0001 \)

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

Placebo: 10.9 months (95% CI: 10.2, 12.0)

1 Prior Chemo OS:
15.4 months abiraterone vs 11.5 months placebo

Abiraterone

<table>
<thead>
<tr>
<th>Days from Randomization</th>
<th>0</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
<th>600</th>
<th>700</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone</td>
<td>797</td>
<td>728</td>
<td>631</td>
<td>475</td>
<td>204</td>
<td>25</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>398</td>
<td>352</td>
<td>296</td>
<td>180</td>
<td>69</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Overall Study Design of COU-AA-302

- Patients
  - Progressive chemonaïve mCRPC patients (Planned N = 1088)
  - Asymptomatic or mildly symptomatic

- Patients are randomized in a 1:1 ratio to:
  - AA 1000 mg daily
  - Prednisone 5 mg BID (Actual n = 546)

- Efficacy end points
  - Co-Primary:
    - rPFS by central review
    - OS
  - Secondary:
    - Time to opiate use (cancer-related pain)
    - Time to initiation of chemotherapy
    - Time to ECOG-PS deterioration
    - TTPP

- Phase 3 multicenter, randomized, double-blind, placebo-controlled study conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada

- Stratification by ECOG performance status 0 vs 1
Statistically Significant Improvement in rPFS
Primary End Point

Data cutoff 12/20/2010.
NR, not reached; PL, placebo.

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Ryan et al. ASCO 2012
Strong Trend in OS Primary End Point

Survival (%)

Time to Death (Months)

AA + P (median, mos): NR
PL + P (median, mos): 27.2
HR (95% CI): 0.75 (0.61-0.93)
P value: 0.0097

Updated GU ASCO 2013: Rathkopf et al. Abstract # 5
- r PFS 16.5 vs. 8.3 mo. HR 0.53 (0.45-0.62) p = <0.0001
- OS 35.3 vs. 30.1 mo. HR 0.79 (0.66-0.96) p = 0.0151
Enzalutamide, an AR Signaling Inhibitor: Targets Multiple Steps in the (AR) Signaling Pathway

1. Competitively inhibits androgen binding to AR
2. Impairs AR nuclear translocation
3. Inhibits AR interaction with DNA

AFFIRM: Phase 3 Trial of Enzalutamide vs Placebo in Post-Chemotherapy Castration-Resistant Prostate Cancer (CRPC)

Patient Population:
1199 patients with progressive CRPC
* Failed docetaxel chemotherapy

Randomized 2:1

*Glucocorticoids were not required but allowed
## AFFIRM: Clinical Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Enzalutamide (800 pts.)</th>
<th>Placebo (399 pts.)</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (months)</td>
<td>18.4</td>
<td>13.6</td>
<td>0.631</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSA progression (months)</td>
<td>8.3</td>
<td>3.0</td>
<td>0.218</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>rPFS (months)</td>
<td>8.3</td>
<td>2.9</td>
<td>0.404</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1st SRE (months)</td>
<td>16.7</td>
<td>13.3</td>
<td>0.621</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CR + PR</td>
<td>28.9%</td>
<td>3.8%</td>
<td>-</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FACT-P</td>
<td>43.3%</td>
<td>17.8%</td>
<td>-</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Enzalutamide in chemotx naïve patients

PREVAIL Phase III Trial: Enzalutamide Pre-Docetaxel CRPC:

- Enzalutamide 160 mg/d
- Placebo
- 1717 Patients with CRPC
- Radiographic PFS
- OAS

NEJM, 01 June 2014
Xtandi-Prior to chemotx in castrate resistant Prostate

**Median Time to Chemotherapy**

- Placebo + GnRH therapy* (n = 845) 10.8 months
- XTANDI + GnRH therapy* (n = 872) 28.0 months

**Median Duration of Therapy**

- Placebo + GnRH therapy* 4.6 months
- XTANDI + GnRH therapy* 17.5 months
Radium-223 (XOFIGO)

- Based on alpha emitter Radium-223
- Ideal half-life of 11.4 days
- Excreted via small bowel
- Safe and easy to produce, deliver and handle

<table>
<thead>
<tr>
<th></th>
<th>Alpha</th>
<th>Beta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative particle mass</td>
<td>7000</td>
<td>1</td>
</tr>
<tr>
<td>Initial energy (MeV)</td>
<td>3-8</td>
<td>0.01-2.5</td>
</tr>
<tr>
<td>Range in tissue (µm)</td>
<td>40-90</td>
<td>50-5000</td>
</tr>
<tr>
<td>LET (KeV/µm)</td>
<td>60-230</td>
<td>0.015-0.4</td>
</tr>
<tr>
<td>Charge</td>
<td>+2</td>
<td>-1</td>
</tr>
<tr>
<td>Ion pairs/µm</td>
<td>2000-7000</td>
<td>5-20</td>
</tr>
<tr>
<td>DNA hits to kill cell</td>
<td>1-5</td>
<td>100-1000</td>
</tr>
</tbody>
</table>
SYMPPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design

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

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

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

N = 922

Planned follow-up is 3 years
**AlsymPCA Overall Survival**

- **Radium-223, n = 541**
  - Median OS: 14.0 months
  - HR 0.695; 95% CI, 0.552-0.875
  - \( P = 0.00185 \)

- **Placebo, n = 268**
  - Median OS: 11.2 months

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**EORTC 2011** 44
Xofigo - Prior to chemotx in castrate resistant Prostate cancer

Before Xofigo

After Xofigo
Metastatic castrate resistant prostate cancer after progression on Taxotere – Jevtana (Cabazitaxel)

- Microtubule stabilizer
- Developed in docetaxel-resistant prostate cancer cell lines
- a favorable pharmacokinetic and safety profile
- decreased propensity for P-glycoprotein (P-gp)-mediated drug resistance.

Phase III TROPIC trial: OS of Jevtana + prednisone versus mitoxantrone + prednisone

<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS (months) (95% CI)</th>
<th>Hazard Ratio (HR) (95% CI)</th>
<th>P value</th>
<th>Number of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jevtana + prednisone</td>
<td>15.1 (14.1–16.3)</td>
<td>0.70 (0.59–0.83)</td>
<td>&lt;.0001</td>
<td>234 (62%)</td>
</tr>
<tr>
<td>Mitoxantrone + prednisone</td>
<td>12.7 (11.6–13.7)</td>
<td></td>
<td></td>
<td>279 (74%)</td>
</tr>
</tbody>
</table>
Support Medications not shown to improve survival but reduce complications of disease

- Bone Building Drugs
  - Zometa
  - Xgeva (denosumab)

- Drugs for Man flashes
  - SSRI
  - gabapentin
New treatments on the Horizon

- **Hormonal therapy**
- **Targeted therapy**
  - Dasatinib, Cabozantinib, Custirsen, Tasquinimod
- **Immunotherapy**
  - **CHECKPOINT INHIBITORS**
    - **ANTI-CTLA4 IMMUNOTHERAPY: IPILIMUMAB**
    - anti pd1, anti pdl1
    - Immunostimulatory monoclonal antibodies
  - **VACCINE, ,**
    - PROSTVAC-VF
Conclusion

- 5 new agents since 2015 approved for metastatic castrate resistant prostate cancer all of which have been shown to improve survival
  - 2004 median survival from 17 to 20 months with taxotere
  - 2015 median survival has increased to between 3-4 years
  - More therapies are on the way, cost will be an issue, finding targets that are indicators for response are desperately needed
  - Getting closer to disease state that we can control, immunotherapy may allow us to get long term remission in some pts

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