The Evolving Role of Current and Emerging Therapies in the Management of Castrate Resistant Prostate Cancer

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Disclosures

- Jones and Bartlett Publishers – Royalties from several books including “100 Questions and Answers on Prostate Cancer”
- No other financial disclosures pertinent to the subject of this presentation
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  - Pfizer – clinical trials, advisory board, speaker
  - Allergan – advisory board, speaker
  - Astellas – advisory board
Objectives

- Analyze available efficacy and safety data for current and emerging targeted therapies in the treatment of castrate resistant prostate cancer (CRPC)

- Assess the role of new diagnostic techniques and therapeutic approaches as applied to the care and management of patients with CRPC

- Discuss the appropriate treatment choices for patients with non-metastatic, metastatic, asymptomatic and symptomatic disease based upon treatment guidelines

Objectives

- Explore recent advances in the role of the androgen receptor (AR) axis in prostate tumor biology and pathogenesis

- Properly manage treatment-related adverse events associated with current and emerging therapies used in prostate cancer
Prostate Cancer Statistics

Hormone Therapy – Initial Therapy for Recurrent/Advanced Prostate Cancer

- GnRH agonists/antagonists
  - GnRH agonists – all formulations of leuprolide, goserelin
  - GnRH antagonists – only one FDA approved, Degarelix

- Role of addition of androgen receptor blocker
  - Flutamide (Eulexin)
  - Bicalutamide (Casodex)
  - Nilutamide (Nilandron)

- Rational
  - 3 large studies suggested that MAB conferred a survival advantage

Increasing PSA on GnRH agonist/antagonist: The role of maximum androgen blockade (MAB)

- **Approach**
  - Check testosterone level → if non-castrate testosterone level, consider changing GnRH analog or surgical castration
  - If castrate, consider adding an antiandrogen

  Castrate level of testosterone considered to be < 20-50ng/dL

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Rational for Maximum Androgen Blockade

- Up to 40% of DHT is derived from adrenal precursors

- Three large trials suggest MAB confers a survival advantage

- Prostate Cancer Trialists’ Collaborative group
  - Meta-analysis of 27 randomized trials, 8275 men with metastatic or locally advanced prostate cancer
  - 5-year survival rate: 25.4% with MAB vs. 23.6% with androgen suppression alone

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The management of Increasing PSA on MAB

- Stop anti-androgen continue LHRH Agonist/Antagonist
- PSA decreases in about 30% of patients for about 3 months duration
- Consider alternative therapies

Limitations of Hormonal Therapy

- For patients with metastatic prostate cancer on hormonal therapy the median progression-free survival ranges from 12-30 mos once treatment is initiated.
- Once the state of androgen independency occurred, historically the median overall survival was only 8-16 mos from the time of its appearance

Castrate Resistant Prostate Cancer

- Defined by disease progression despite androgen deprivation therapy (ADT) and castrate levels of testosterone (< 20ng/dL)

- Presents a spectrum of disease ranging from increasing PSA levels without metastases or symptoms and despite ADT, to metastases and significant debilitation from cancer symptoms


Castrate Resistant Prostate Cancer (CRPC)

- CRPC does not necessarily imply hormonal resistance altogether

- Molecular basis underlying retained hormone sensitivity in CRPC
  - Amplification of the androgen receptor locus (AR) occurs in approximately 30% of CRPC tumors, but not in tumors prior to therapy
  - Enhanced intracellular conversion of adrenal androgens to testosterone and dihydrotestosterone in PC cells
  - Intratumoral androgen synthesis
  - Increased expression of AR messenger RNA
  - Ligand-independent AR activation

(Leibowitz-Amit, Joshua AM. Current Oncology 2012, vol 19)
Role of ADT in CRPC

• AR remains active in most patients with CRPC

• Such groups as ASCO (American Society of Clinical Oncology), NCCN (National Comprehensive Cancer Network), CCO (Cancer Care Ontario) and others recommend that

     **ADT be continued in pts with CRPC**

(Saad F et al. Can Urol Assoc J 2010; 4(6): 360-64)
Prevention of Skeletal Complications in CRPC

• Vitamin D and Calcium supplementation

• Several guidelines (including NCCN, EAU and International Consultation on Urological Diseases) recommend bisphosphonates (or Denusomab) to preserve bone health and prevent skeletal cxs in CRPC patients with bone mets, asymptomatic or symptomatic.
NCCN recommends PROVENGE as first line treatment for asymptomatic or minimally symptomatic metastatic CRPC. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer V.2.2013
Immunotherapy For CRPC
Sipuleucel-T

FDA approved for treatment of asymptomatic or minimally symptomatic metastatic CRPC
Sipuleucel-T

- Cost – about $31,000 per infusion, $93,000 total

- Dosing:
  - 3 doses given approximately 2 weeks apart
  - Pre-medicate with oral acetaminophen and an anti-histamine such as diphenhydramine

- Acute infusion reaction (reported w/in 1 day of infusion) reported in 71.2% clinical trial pts
  - Fever, chills, respiratory events, N/V, fatigue, HTN, tachycardia
IMPACT: Randomized, Phase 3 Trial of Sipuleucel-T vs Placebo

- Primary end point: overall survival
- Secondary end point: time to objective disease progression

N=512 men with asymptomatic or minimally symptomatic mCRPC

Sipuleucel-T q2wk × 3 → Treated at MD discretion

Placebo q2wk × 3 → Treated at MD discretion and/or salvage protocol

Sipuleucel-T (n=341) Median survival: 25.8 mo

Placebo (n=171) Median survival: 21.7 mo

P=.032 (Cox model)
HR = 0.775 (95% CI, 0.614-0.979)
Median survival benefit = 4.1 months

ITT=intent to treat.
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Docetaxel in the Treatment of CRPC

- Two clinical trials confirmed the efficacy of docetaxel chemotherapy in patients with CRPC\(^1,2\)
- TAX-327
- SWOG Intergroup Protocol 9916

TAX-327 Study Design

Patient Stratification (N=1006):
- Pain Level
  - PPI ≥ 2 or AS ≥10 vs.
  - PPI <2 or AS <10
- Karnofsky Performance Status
  - ≤70% vs. ≥80%

Randomize

Treatment duration in all 3 arms: 30 weeks
Primary end point: 25% improvement in survival

Premedication: Docetaxel q3wk arm: dexamethasone 8 mg, 12 h, 3 h, and 1 h prior to infusion; weekly docetaxel arm: dexamethasone 8 mg, 1 h prior to infusion.
AS=analgesic score (mean); PPI=Patient Pain Intensity score (median).
TAX-327 Results:
Overall Survival

![Graph showing overall survival of Docetaxel 3 weekly, Docetaxel weekly, and Mitoxantrone.]  

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TAX-327 Results:
Quality-of-Life Response

<table>
<thead>
<tr>
<th>Quality of Life</th>
<th>Docetaxel q3wk</th>
<th>Docetaxel weekly</th>
<th>Mitoxantrone q3wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable, n</td>
<td>278</td>
<td>270</td>
<td>267</td>
</tr>
<tr>
<td>Response, %*</td>
<td>22 (17-27)</td>
<td>23 (18-28)</td>
<td>13 (9-18)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value†</td>
<td>.009</td>
<td>.005</td>
<td></td>
</tr>
</tbody>
</table>

* Defined as 16-point improvement from baseline in FACT-P score on 2 measurements obtained at least 3 weeks apart.  
† Versus mitoxantrone.  
FACT-P=Functional Assessment of Cancer Therapy-Prostate.  
**SWOG Intergroup Protocol 9916**

**Randomize**
- **D/E**: Docetaxel 60 mg/m² IV D2 q21d + Estramustine 280 mg PO TID, D1-5
  - Premedication: Dexamethasone 20 mg PO TID starting evening of D1
- **M/P**: Mitoxantrone 12 mg/m² q21d + Prednisone 5 mg PO BID continuously

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*Per protocol amendment January 15, 2001: Coumadin 2 mg PO daily + ASA 325 mg PO daily was added.*

Docetaxel and mitoxantrone doses could be increased to 70 mg/m² and 14 mg/m², respectively, if no grade 3 or 4 toxicities were seen in cycle 1.

NCI-CTC=National Cancer Institute Common Toxicity Criteria; SWOG=Southwest Oncology Group.


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**SWOG 9916 Results**

<table>
<thead>
<tr>
<th>PFS, Stratified by Treatment Arm</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td># at Risk</td>
<td># of Events</td>
<td>Median in Months</td>
<td>P Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Docetaxel + estramustine</td>
<td>324</td>
<td>297</td>
<td>6</td>
<td>&lt;.0001</td>
<td>0.73 (0.63-0.86)</td>
</tr>
<tr>
<td>Mitoxantrone + prednisone</td>
<td>324</td>
<td>300</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Overall Survival**

<table>
<thead>
<tr>
<th>Treatment</th>
<th># at Risk</th>
<th># of Deaths</th>
<th>Median in Months</th>
<th>P Value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel + estramustine</td>
<td>338</td>
<td>217</td>
<td>18</td>
<td>.01</td>
<td>0.80 (0.67-0.97)</td>
</tr>
<tr>
<td>Mitoxantrone + prednisone</td>
<td>336</td>
<td>235</td>
<td>16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PFS=progression-free survival.

Docetaxel Side Effects

- Hematologic
  - Bone marrow suppression
- Hypersensitivity reaction
- CV
- Renal
  - Fluid retention
- Hepatic abnls
- GI
- Dermatologic
  - Reversible cutaneous reactions
- Respiratory
  - Dyspnea, acute pulmonary edema, RDS and interstitial pneumonia

Docetaxel Combinations – Possible Future Therapies

- D + tyrosine kinase inhibitors (mediators of intracellular signaling pathways controlling cell growth, migration and invasion)
  - Dasatinib
  - Cabozantinib
- D + endothelin receptor antagonists (endothelins implicated in tumor growth and mets)
  - Atrasentan
  - Zibotentan
- D + anti-angiogenics
  - Afibrecpt – VEGF Trap - (prevents binding of VEGF to its receptor, inhibiting angiogenesis)
  - Bevacizumab – monoclonal AB against VEGF
  - Lenalidomide – thalidomide analogue which is anti-angiogenic
Taxanes and Mitoxantrone
Cost of Treatment

<table>
<thead>
<tr>
<th>AWP ($)</th>
<th>Cabazitaxel 25mg/m²</th>
<th>Doxetaxelb 75mg/m²</th>
<th>Mitoxantrone 12mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient/cycle</td>
<td>45 mg = $7,200</td>
<td>135 mg = $3,341</td>
<td>22 mg = $462</td>
</tr>
<tr>
<td>Per patient/regimen (average six cycles)</td>
<td>$43,200</td>
<td>$20,046</td>
<td>$2,772</td>
</tr>
</tbody>
</table>

*Based on a male patient: 5ft 9in (175 cm) 147lbs (67kg), BSA=1.8m²
a. Source Medispan through Cardinal Wholesaler
b. Representative generic source

Cabazitaxel Approved for Pts Previously Treated with Docetaxel

- FDA approved 2010
- TROPIC Trial – treatment of hormone refractory metastatic prostate cancer
- 775 pts; cabazitaxel + prednisone or mitoxantrone + prednisone
- Median OS 15.1 months in cabazitaxel group compared with 12.7 months in mitoxantrone group (HR 0.70; 95% CI 0.59-0.83; P<0.0001)
- Pain response rate and median time to pain was not different btn 2 groups (DeBono JS. Lancet 2010; 376: 1147-1154)
Summary of Results of TROPIC Trial

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cabazitaxel</th>
<th>Mitoxantrone</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival mos</td>
<td>15.1</td>
<td>12.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median progression-free survival mos</td>
<td>2.8</td>
<td>1.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median time to tumor progression mos</td>
<td>5.4</td>
<td>8.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median time to PSA progression mos</td>
<td>3.1</td>
<td>6.4</td>
<td>0.001</td>
</tr>
<tr>
<td>PSA response %</td>
<td>39.2</td>
<td>17.8</td>
<td>0.0002</td>
</tr>
<tr>
<td>Tumor response %</td>
<td>14.4</td>
<td>4.4</td>
<td>0.0005</td>
</tr>
</tbody>
</table>


Management of CRPC – Targeting AR

1. Agents that target steroidogenesis
   a. CYP17 modulator
      1. Abiraterone acetate – approved
      2. TAK-700 (orteronel) – clinical trials
      3. TOK-001 (galertone)-completed phase III

2. Second-generation pure AR antagonists
   a. Antiandrogens
      a. Enzalutamide (Xtandi) – approved
      b. ARN-509 – clinical trials
      c. ODM-201 – clinical trials
      d. EXN-4176 – clinical trials

Other agents include OGX-427 which targets heat shock protein and EPR-001 an androgen receptor modulator
**Abiraterone Acetate (Zytiga)**

- FDA approved 4/28/2011 - PC pts with progression after rx with docetaxel

- 12/20/2012 – FDA expanded approval to treat men with late-stage (metastatic) CRPC prior to receiving chemotherapy

- Dose – 1000mg (4, 250mg tabs) orally QD+ prednisone 5 mg orally. No food 2hrs before dose and for at least 1 hr after

- Cost – approximately $5000.00/mos
Rational for Abiraterone Acetate in CRPC

- CYP 17 essential for biosynthesis of androgens and adrenal hormones and implicated in aberrant intratumoral androgen production
- Abiraterone (active metabolite) inhibits both 17 alpha-hydroxylase and c 17,20 lyase function of CYP 17
- Binds more specifically and irreversibly to CYP 17 resulting in more potent and durable androgen suppression than ketoconazole

Abiraterone v Placebo

Statistically Significant Improvement in Radiographic PFS Primary Endpoint

- **AA + P** (median, mos): NR
- **PL + P** (median, mos): 8.3
- **HR (95% CI):** 0.43 (0.35-0.52)
- **P value:** < 0.0001

Data cutoff: 12/30/2011

Abiraterone: PFS, progression-free survival; AA, abiraterone acetate; P, prednisone; mos, months; NR, not reached; PL, placebo; HR, hazard ratio; CI, confidence interval

Ryan et al. ASCO June 2012, Chicago. Abstract LBA4518

Abiraterone v Placebo

Strong Trend in OS Primary Endpoint

- **AA + P** (median, mos): NR
- **PL + P** (median, mos): 27.2
- **HR (95% CI):** 0.75 (0.65-0.82)
- **P value:** 0.0001

Data cutoff: 12/20/2011

Prespecified significance level by O'Brien-Fleming Boundary = 0.0003

Abiraterone: OS, overall survival; AA, abiraterone acetate; P, prednisone; mos, months; NR, not reached; PL, placebo; HR, hazard ratio; CI, confidence interval

Ryan et al. ASCO June 2012, Chicago. Abstract LBA4518
Abiraterone Acetate (Zytiga)

- Warning – mineralocorticoid excess, adrenal insufficiency if interrupt daily steroid, infection or stress, hepatotoxicity

- AEs–fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, HTN, dyspnea, UTI and contusion

- Lab abnls – anemia, hypercholesterolemia, hyperglycemia, increased ALT/AST, hyperphosphatemia, hypokalemia

Orteronel (Tak-700) and Galeterone (TOK-001)

- Both investigational at present

- Orteronel is a CYP17 inhibitor with relative selectivity for 17,20-lyase over 17alpha-hydroxylase

- May have less mineralocorticoid effects than abiraterone acetate

- Galaterone is an inhibitor of CYP17 enzyme but also a potent pure AR antagonist

Leibowitz-Amit R, Joshua R. Current Oncology 2012; 19
Agents that Block The Androgen Receptor

- Enzalutamide (Xtandi)
- ARN-509
- ODM-201
- EZN-4176

Enzalutamide (Xtandi)

- FDA approved August 31, 2012
- Indication – rx of pts with metastatic CRPC with prior docetaxel rx
- Whole sale price - $7,450/mos
- Dose – 160mg (4, 40 mg capsules) orally QD, w or w/out food
- Warning – seizure occurred in 0.9%
  (prescribing information, Xtandi)
Rational for Enzalutamide in CRPC

- Most commonly observed difference between CRPC cells and hormone-sensitive PC cells is AR overexpression
- Bicalutamide has partial agonist activity in the presence of AR overexpression
- Enzalutamide has high affinity binding to the AR-ligand binding domain with inhibitory activity
- Enzalutamide has no observable agonist activity in the setting of AR overexpression


Enzalutamide (Xtandi)

- Enzalutamide inhibits AR-testosterone binding with higher affinity than bicalutamide
- Enzalutamide receptor inhibition blocks the activational change induced by AR-testosterone binding
- Enzalutamide inhibits AR-testosterone nuclear translocation and DNA transcription
- Enzalutamide lacks partial AR agonist activity that occurs with bicalutamide resistance
A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV 3100 (AFFIRM)

- International, phase 3, randomized double-blind, PBO-controlled study of enzalutamide in pts with PC previously treated with one or two chemotherapy regimens, at least one of which contained docetaxel

- Inclusion criteria – PC, castrate levels of testosterone (< 50ng/dL), previous rx with docetaxel and progressive disease incl 3 increasing values for PSA or radiographically confirmed progression w or w/o increase in PSA

- Design – 2:1 randomization to receive enzalutamide (160mg orally once daily as four 40mg capsules) or matched PBO

Scher HI et al. NEJM 2012; 367(13): 1187-1197

AFFIRM: Study Endpoints

Primary endpoint

Overall survival defined as time from randomization to death from any cause

Secondary endpoints

Measures of response (in PSA level, in soft tissue and in QoL score)

Measures of progression (time to PSA progression, radiographic progression-free survival and time to the first skeletal-related event)
**AFFIRM RESULTS**

- Median OS 18.4 months (95% CI, 17.3 to not yet reached) in enzalutamide and 13.6 months (95% CI, 11.3 to 15.8) in PBO group

- At time of prespecified interim analysis, enzalutamide 37% reduction in risk of death as compared with PBO (HR for death, 0.63; 95% CI, 0.53 to 0.75; P<0.001)

- OS benefit consistent across all subgroups, incl age, baseline pain intensity, geographic region and type of disease progression at entry

Scher HI et al. NEJM 2012; 367(13): 1187-1197

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**AFFIRM Results: Enzalutamide Superior to PBO for All Secondary Endpoints**

- PSA-level response rate (54% vs 2%, P<0.001)

- Soft-tissue response rate (29% vs 4%, P<0.001)

- FACT-P QoL response (43% vs 18%, P<0.001)

- Time to PSA progression (8.3 vs 3.0 mos; HR, 0.25; P<0.001)

- Radiographic progression-free survival (8.3 vs 2.9 mos; HR, 0.40, P<0.001)

- Time to first skeletal-related event (16.7 vs 13.3 mos; HR, 0.69; P<0.001)

Scher HI et al. NEJM 2012; 367(13): 1187-1197
Enzalutamide (Xtandi)

- DDIs – avoid strong CYP2C8 inhibitors, may increase xtandi exposure; avoid CYP3A4, CYP2C9 and CYP2C19 substrates with narrow therapeutic index; if coadmin warfarin (CYP2C9 substrate) monitor INRs

- AEs – asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, HA, URI, muscular weakness, dizziness, insomnia, LRI, spinal cord compression, cauda equina syn, hematuria, paresthesia, anxiety, HTN

(prescribing information)

Investigational Agents that Block the AR

- ARN-509 – competitive AR inhibitor, fully antagonistic to AR overexpression
  - Binds to AR and inhibits growth and androgen-mediated gene transcription in vitro, impairs nuclear localization and DNA binding of AR, and inhibits tumor growth in a xenograft model

- ODM-201 –AR antagonist that blocks AR nuclear translocation, with no agonist activity in the context of AR overexpression

- EZN-4176 – nucleic acid-based antisense oligonucleotide targeted against the mRNA of AR

Leibowitz-Amit R, Joshua AM. Current Oncology 2012, vol 19
Targeting Heat Shock Proteins

- Heat shock protein 27 (Hsp27) is a cytoprotective chaperone of AR – its levels increase after androgen ablation and facilitate cancer growth

- OGX-427 is a second-generation antisense oligonucleotide that inhibits Hsp27 expression

Bone-Targeted Therapy

- Bone loss associated with ADT increases risk of fracture

- > 90% pts with metastatic CRPC develop bone mets and decreased bone integrity

- Pts at significant risk of developing skeletal cxs including fx, bone pain, spinal cord compression

- QoL affected by these bone-related cx

- NCCN recommends rx to preserve bone health and to prevent skeletal cx in pts with bone mets from CRPC

**Bone-Targeted Therapy**

- Zoledronic acid (4mg IV) every 3 to 4 wks recommended in men with CRPC and bone mets to prevent disease-related skeletal ex

- Rx not recommended if baseline serum creatinine < 30ml/min

- Good oral hygiene, baseline dental evaluation for high risk pts, avoidance of invasive dental surgery during rx recommended to reduce risk of ONJ

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**Prevention of Skeletal-related events (SREs)**

- Denosumab (Xgeva, Amgen) - RANK ligand inhibitor

- Dose - 120 mg subQ every 4 wks in upper arm, upper thigh, or abdomen.

- NCCN - denosumab as an alternative to zoledronic acid for prevention of SREs

- RCT - denosumab effective in delaying and reducing SREs compared to zoledronic acid

- All patients rxd with denosumab should receive vitamin D and calcium and have periodic serum calcium levels

Comparison Denosumab vs Zoledronic Acid

<table>
<thead>
<tr>
<th>Major outcomes, denosumab vs. zoledronic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosumab N=1,026</td>
</tr>
<tr>
<td>Zoledronic acid N=1,020</td>
</tr>
<tr>
<td>Median time to first on-study skeletal-related event</td>
</tr>
<tr>
<td>Not yet reached (P&lt;.001 for non-inferiority; P=.10 for superiority)</td>
</tr>
<tr>
<td>26.4 months</td>
</tr>
<tr>
<td>Skeletal-related events/patient time at risk</td>
</tr>
<tr>
<td>0.45 events/patient-year (P=.004)</td>
</tr>
<tr>
<td>0.58 events/patient-year</td>
</tr>
<tr>
<td>Acute-phase (“flu-like”) reactions</td>
</tr>
<tr>
<td>10.4%</td>
</tr>
<tr>
<td>27.3%</td>
</tr>
<tr>
<td>Renal toxicity</td>
</tr>
<tr>
<td>4.9% (P=.001)</td>
</tr>
<tr>
<td>8.5%</td>
</tr>
<tr>
<td>Osteonecrosis of jaw</td>
</tr>
<tr>
<td>2% (P=.39)</td>
</tr>
<tr>
<td>1.4%</td>
</tr>
</tbody>
</table>

Denosumab versus Zoledronic Acid for Treatment of Bone Metastases in Men with Castrate-Resistant Prostate Cancer: A Cost-Effectiveness Analysis

• From a US payer perspective

• Literature-based Markov model developed to estimate survival, quality-adjusted life-years (QALYs), number and costs of SREs and drug and admin costs for pts receiving denosumab or zoledronic acid over 27 mos

• QALYs estimated by assigning health-state utilities

• SRE-related costs and utilities were literature-based

• Outcomes discounted 3% per annum


Results

• Denosumab resulted in

  • Fewer estimated SREs (-0.241; 1036 vs 1.277)
  • More QALYs (0.0074; 0.9306 vs 0.9232)
  • Lower SRE-related costs (-$2340; $4424 vs $11,164)
  • Higher drug-related costs ($10,181; $23,144 vs $12,963)
  • Higher total costs ($7841; $31,968 vs $24,127)

Targeted Therapy For Pain Related to Bone Metastases

- Strontium 89 is close to calcium in the periodic table

- Sr-89 is a beta-emitter that has a higher affinity for tumor containing bone than normal bone and half-life in normal bone (14 days) is considerably shorter than in tumor containing bone (50 days)

- Double-blind trial showed higher efficacy for Sr89 compared to Sr86 and Sr88 radionuclides


Comparison Sr-89 and Radiotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Study Design</th>
<th>Radiotherapy</th>
<th>Pain Reduction</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dearnaley et al (1992)</td>
<td>78</td>
<td>Matched control</td>
<td>Hemibody</td>
<td>63% v 52%</td>
<td>20w v 21w</td>
</tr>
<tr>
<td>Quilty et al (1994)</td>
<td>284</td>
<td>Randomized</td>
<td>Hemibody/local</td>
<td>64% v 66%</td>
<td>28w v 33w</td>
</tr>
<tr>
<td>Oosterhof et al (2003)</td>
<td>203</td>
<td>Randomized</td>
<td>Local</td>
<td>33% v 35%</td>
<td>11m v 7.2m</td>
</tr>
</tbody>
</table>

Side Effects of Sr-89

• Most frequently observed toxicities are associated with bone marrow suppression between 11-65% in more than 50% patients

• Blood counts return to normal within 8 weeks and rarely cause Grade 3 or 4 toxicity when admin to patients with normal hematological parameters

• In a randomized trial no difference btn External beam and Sr-89 in hematological toxicity


Future Therapies -Radium-223 (Alpharadin)

• Granted Fast Track designation by FDA

• First bone-targeted therapy to show increase in OS compared to PBO

• Alpha-particle-emitting radionuclide

• Mimics calcium - incorporated in osteoblastic bone lesions

• Delivers short range, high energy –spares bone marrow, decreasing myelotoxicity

• Administered IV as a bolus once a month for 4-6 mos in clinical trials

Zhao S, Yu EY. Cur Opin Urol 2013; 23: 201-207
Overall Survival Benefit of Radium-223 Chloride (Alpharadin) in the Treatment of Patients With Symptomatic Bone Metastases in Castration-Resistant Prostate Cancer (CRPC): A Phase III Randomised Trial (ALSYMPCA)

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Presented September 24, 2011 at European Multidisciplinary Cancer Congress in Stockholm

ALSYMPCA Trial: Alpharadin Significantly Improves OS compared to Placebo

ALSYMPCA Trial: Alpharadin Exended Time to First SRE Compared To Placebo

Updated Analysis Presented at ASCO 2012

- Further extended median survival benefit to 3.6 months (14.9 vs 11.3 months; HR 0.695; 95% CI 0.581-0.832, P=0.00007)

- Further extended median time to first SREs (15.6 vs 9.8 mos; HR 0.658; 95% CI 0.522-0.830; P=0.00037)

- Significant OS benefit demonstrated in both chemotherapy naive and postdocetaxel group
Side Effects of Alpharadin

- Most common nonhematologic side effects – diarrhea, nausea, vomiting and constipation – incidence nausea and constipation = PBO

- Neutropenia in 4% and thrombocytopenia in 8% in ALSYMPCA trial

- Grade 3 or 4 neutropenia in 2% and thrombocytopenia in 4%

(Parker C. J Clin Oncol 2021; 30 (suppl): LBA4512; Parker C. J Clin Oncol 2012; 30 (suppl 5): abstr. 8)

PROSTVAC VF mechanism of Action
PROSTVAC-VF

- Phase 2 controlled, double-blind randomised trial
- 125 pts with chemotherapy naïve, minimally symptomatic mCRPC
- Demonstrated safety but no significant effect on time to disease progression
- PROSTVAC-VF treated pts (82) experienced longer median survival of 8.5 months compared to controls (40) (25.1 vs 16.6 mos, p=0.0061) and extended 3-yr survival (30% vs 17%)


Clinical Trials - CRPC

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CRPC, castration-resistant prostate cancer; P, prednisone; OS, overall survival; RANK-L, receptor activator of nuclear factor kappa B ligand; SRE, skeletal-related event; BMFS, bone metastasis-free survival.

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### Conclusion

- Prostate cancer remains the most common cancer in men
- Treatment of prostate cancer has resulted in improved survival rates
- Hormonal therapy remains first line therapy in advanced prostate cancer, however, with time most patients will progress despite castrate levels of testosterone
Conclusions

• Several new agents have been recently approved for the management of CRPC with unique mechanisms of action and indications

• Patients with CRPC will ultimately require multiple agents over time

• The cost of management of CRPC is not without significant economic consequences

Questions?