Novel Agents in the Treatment of Metastatic Castration-Resistant Prostate Cancer (CRCP)

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Disclosures

• Jones and Bartlett Publishers – Royalties from several books including “100 Questions and Answers on Prostate Cancer”, “20 Questions on metastatic Castrate Resistant Prostate Cancer”

• No other financial disclosures pertinent to the subject of this presentation
Objectives

• Evaluate the mechanism of action, safety and efficacy of the available and emerging clinical trial data on the use of current and novel agents or combination with other agents
• Assess the current diagnosis of CRPC and have a working knowledge of treatments and the proper order for administration
• Describe differences among agents for CRPC in order to make evidence-based, individualized treatments for patients with CRPC
• Analyze the need for a multidisciplinary approach to the care of CRPC patients in regards to the management of pain
• Assess the mechanism of action and risks/benefits of using systemic agents in the treatment of CRPC

Prostate Cancer Statistics

Siegel R et al. CA Cancer J Clin 2012;61:10
Hormone Therapy – Initial Therapy for Recurrent/Advanced Prostate Cancer -Limitations

- 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

- mCRPC KILLS – prostate cancer is the second leading cause of cancer deaths among american men
  

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 (mCRPC) 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 T and DHT 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 and mCRPC**
Chemotherapy for mCRPC

- Docetaxel – taxane-based chemotherapy – binds and stabilizes tubulin, induces cell cycle arrest and inhibits cell proliferation
  - Two pivotal studies: TAX 327 and SWOG 9916 (docetaxel + prednisone 5mg BID)
  - TAX 327 – docetaxel Q 3 wks showed
    - PSA RR (≥50% drop in PSA) of 43% vs 32% for mitoxantrone
    - Median OS of 18.9 mos versus 16.5 mos
  - SWOG 9916 – docetaxel + prednisone + estramustine vs mitoxantrone
    - PSA RR higher in docetaxel arm (50% vs 27%)
    - Median OS higher in docetaxel arm (17.5 mos vs 15.6 mos)

1Tannock IF et al. NEJM 2004; 2 Petrylak DP et al NEJM 2004

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
Cabazitaxel Approved for Pts Previously Treated with Docetaxel

- FDA approved June 2010
- TROPIC Trial – treatment of mCRPC – 775 pts
- Cabazitaxel + prednisone or mitoxantrone + prednisone

- Median OS 15.1 mos in cabazitaxel group vs 12.7 mos in mitoxantrone group (HR 0.70; 95% CI 0.59-0.83; P<0.0001)

- Pain response rate and median time to pain not different between 2 groups (DeBono JS. Lancet 2010; 376: 1147-1154)

Taxanes and Mitoxantrone
Cost of Treatment

<table>
<thead>
<tr>
<th>Average Wholesale Price (AWP) for Comparative chemotherapy Agents*</th>
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<tbody>
<tr>
<td><strong>AWP ($)</strong></td>
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<tr>
<td>Per patient/cycle</td>
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<tr>
<td>Per patient/regimen (average six cycles)</td>
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</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
Immunotherapy for mCRPC- Sipuleucel-T

FDA approved April 2010 for treatment of asymptomatic or minimally symptomatic metastatic CRPC

Figure: The diagram illustrates the two steps involved in sipuleucel-T therapy: (1) harvesting the patient’s dendritic cells and then pulsing them ex vivo with a recombinant fusion protein made of prostastic acid phosphatase (PAP) and granulocyte–macrophage colony-stimulating factor (GM-CSF), and (2) infusing the cultured cells into the patient, where the PAP–GM-CSF-loaded antigen-presenting cells induce the proliferation of T-cells that recognize and target prostate tumor cells. APC = antigen-presenting cell.
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 antihistamine 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

N=512 men with asymptomatic or minimally symptomatic mCRPC

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

IMPACT=Immunotherapy Prostate Adenocarcinoma Treatment.
**IMPACT: Overall Survival in ITT Population**

- **P = 0.032 (Cox model)**
- **HR = 0.775 (95% CI, 0.614-0.979)**
- **Median survival benefit = 4.1 months**

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

**Placebo (n=171)**
- Median survival: 21.7 mo

**ITT=intent to treat.**
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**THEREAFTER, ATTENTION DIRECTED TO**

- **TARGETING**
- **ANDROGEN PRODUCTION**
- **ANDROGEN RECEPTOR**
Abiraterone Acetate (Zytiga)

- FDA approved 4/28/2011- mCRPC pts with progression after rx with docetaxel
- 12/20/2012– FDA expanded approval to treat men with mCRPC prior to receiving chemotherapy
- Dose – 1000mg (4, 250mg tabs) orally QD+ prednisone 5 mg BID orally. No food 2hrs before dose and for at least 1 hr after
- Cost – 12 weeks of abiraterone is $18,000 (Cancer Control 2013; 20(3): 161-8)

Rational for Abiraterone Acetate in CRPC

- CYP 17 essential for biosynthesis of androgens and adrenal hormones
- CYP 17 implicated in aberrant intra-tumoral 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 = more potent and durable androgen suppression than ketoconazole

Abiraterone Acetate

- Blocks 2 critical steps in testosterone biosynthesis
  - Conversion of pregnenolone to 17 OH-pregnenolone
  - Conversion of 17 OH-pregnenolone to dehydroepiandrosterone
- Blocks glucocorticoid synth
  May increase ACTH & increase mineralocorticoids
  - To prevent, prednisone 5 mg twice daily
  - Effective in pts resistant to ketoconazole


Abiraterone vs Placebo

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

Understanding “Castrate Resistant” Prostate Cancer

Targeting the Androgen Receptor
Enzalutamide (Xtandi)

- FDA approved August 31, 2012
- Indication – rx of pts with mCRPC
- 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 common difference btn CRPC cells and hormone sensitive PC cells is AR over-expression
- Bicalutamide has partial agonist activity in the presence of AR over-expression
- Enzalutamide has high affinity binding to the AR-ligand binding domain with inhibitory activity
- Enzalutamide has no observable agonist activity in setting of AR over expression

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/out 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 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

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, seizure

(Warning Information)

PREVAIL TRIAL

- Randomized, dble-blind, PBO-controlled, multi-national trial with more than 1,700 chemotherapy NAIVE mCRPC pts
- Interim analysis after a median f/up of 20 months enzalutamide associated with
  - Significant reduction in risk of death by 29% (p<0.001)
  - Significant reduction in risk of radiographic progression by 81% (p<0.001)
  - CR or PR soft tissue disease on imaging in 59% compared to 5% with PBO
  - Delayed median time to chemotherapy initiation by 17 months compared to PBO

Phase III Studies in Patients with CRPC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study Name (number of included patients)</th>
<th>Median Time to Radiographic Progression</th>
<th>Objective Response</th>
<th>Median Time to PSA Progression, Months</th>
<th>Median Overall Survival, Months</th>
</tr>
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<tbody>
<tr>
<td>Before Castration</td>
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<tr>
<td>Sporadic vs placebo</td>
<td>MNTC (n = 152)</td>
<td>3.7 vs 4.0 months</td>
<td>0.003 vs 0.003</td>
<td>25.6 vs 21.7</td>
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<tr>
<td>Hormone-potency vs placebo alone</td>
<td>CRPC (n = 150)</td>
<td>3.6 vs 4.0 months</td>
<td>0.003 vs 0.003</td>
<td>24.7 vs 20.3</td>
<td></td>
</tr>
<tr>
<td>Sporadic vs placebo</td>
<td>PRAML (n = 175)</td>
<td>4.1 vs 4.5 months</td>
<td>1.9 vs 1.9</td>
<td>22.4 vs 20.2</td>
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<tr>
<td>Castration</td>
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<tr>
<td>Castration vs placebo</td>
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<td>Castration vs placebo</td>
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Bone-Targeted Therapy in Patients With mCRPC

- Bone loss associated with ADT increases risk of fracture
- > 90% pts with mCRPC develop bone mets and decreased bone integrity
- Pts at significant risk of developing skeletal cx 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

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

(BJU Int 2007; 101: 1071-5; NEJM 2009; 361: 745-55; J Clin Oncol 2010; 28; 18s)
Comparison Denosumab vs Zoledronic Acid

### Major outcomes, denosumab vs. zoledronic acid

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Denosumab N=1,026</th>
<th>Zoledronic acid N=1,020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to first on-study skeletal-related event</td>
<td>Not yet reached (P&lt;.001 for non-inferiority; P=.10 for superiority)</td>
<td>26.4 months</td>
</tr>
<tr>
<td>Skeletal-related events/patient time at risk</td>
<td>0.45 events/patient-year (P=.004)</td>
<td>0.58 events/patient-year</td>
</tr>
<tr>
<td>Acute-phase (&quot;flu-like&quot;) reactions</td>
<td>10.4%</td>
<td>27.3%</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>4.9% (P=.001)</td>
<td>8.5%</td>
</tr>
<tr>
<td>Osteonecrosis of jaw</td>
<td>2% (P=.39)</td>
<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
- 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>11 m v 7.2 m</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

New Therapy - Radium-223 (Alpharadin)

- Granted Fast Track designation by FDA May 2013 for rx patients with CRPC, symptomatic bone metastases, and no known visceral metastatic disease

- 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

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

Clinical Oncology News November 2011 volume: 06:11. accessed 4/7/2013
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 non-hematologic 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)
The Dilemma – A wealth of Agents with Incremental Improvements in Survival BUT

We do not know how to best use these agents
  ? Best sequencing of the approved agents
  ? Duration of use of each agent
  ? How to combine agents to maximize survival and minimize toxicity

We do not know which patients will benefit the most (or the least)

Can society (or should society) afford the agents in the absence of curing the disease?

Treatment Sequencing and Combination Therapy – Choosing Therapies Wisely – The Dilemma

• Prospective data addressing optimal treatment sequencing are not available
• Head-head comparisons of new therapies, ie abiraterone vs enzalutamide, are not available
• Pre-clinical data suggest that use of additional treatments may allow expansion of prostate cancer clones with mutations conferring resistance to subsequent therapies
• Issues that remain– what is the optimal treatment sequence? Lack of predictors of poor response to one or more therapies and how long to treat with each therapy for best outcome?

What Do We Know about Treatment Sequencing for mCRPC?

• Studies combining docetaxel with other agents generally associated with increased toxicity and equal or inferior survival when compared to std regimen

• Sequential use of docetaxel
  • Prior abiraterone rx may adversely impact docetaxel activity – small studies, further data needed
  • Recent retrospective review of 58 pts - did not observe any differences in clinical outcomes based on alternative sequencing of abiraterone and docetaxel in men with mCRPC (Maughan et al. Prostate 2015; 75(15): 1814-20)

Treatment Sequencing - Abiraterone

• First vs second-line abiraterone
  • No direct comparisons
  • Extrapolated from pre and post-docetaxel studies
  • Abiraterone appears to have higher rates of PSA decline and soft tissue responses when admin to chemotherapy naïve pts

• Third line abiraterone
  • Activity of abiraterone appears to be reduced after exposure to both enzalutamide and docetaxel

• Combination therapy
  • A variety of studies are ongoing evaluating combination therapy with abiraterone
Treatment Sequencing - Enzalutamide

- Limited data available evaluating sequential administration of enzalutamide after abiraterone and docetaxel
- Enzalutamide appears to have higher activity in docetaxel-naïve Third line therapy after prior docetaxel and abiraterone –
  - Retrospective cohort analysis of 35 pts demonstrated that complete cross-resistance not observed - 3/19 (16%) nonresponder to abiraterone had PSA declines of ≥ 50% on enzalutamide (Schrader et al. Eur Urol 2014; 65(1):30-36
  - Multicenter study in pts who didn’t tolerate or progressed on docetaxel + abiraterone – 46% with ≥ 30% PSA decline, 21% with ≥ 50% PSA decline and 3% with ≥ 90% PSA decline with enzalutamide – median treatment duration 14.9 wks (Badrising S et al. Cancer 2014; 120(7): 968-75)

Treatment Sequencing - Cabazitaxel

- Study comparing first line cabazitaxel with docetaxel
- Concerns regarding third line cabazitaxel - clinical data suggests that both docetaxel and abiraterone may target the AR signaling pathway
  - No prospective data available
  - Retrospective cohort data suggests that cabazitaxel retains significant activity when used in third line setting.

<table>
<thead>
<tr>
<th>Treatment Sequence</th>
<th>No. of Patients</th>
<th>PSA Decline ≥ 50%</th>
<th>Partial Response ≥ 30%</th>
<th>Partial Response</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>38</td>
<td>3 (8%)</td>
<td>7 (18%)</td>
<td>8%</td>
<td>Same rate of response to abiraterone regardless of response to enzalutamide</td>
<td>Lomot et al.[70]</td>
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<tr>
<td>Enzalutamide</td>
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<td>Abiraterone</td>
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<tr>
<td>Docetaxel</td>
<td>30</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
<td>0%</td>
<td>Same rate of response to abiraterone regardless of response to enzalutamide</td>
<td>Noonan et al.[71]</td>
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<td>Enzalutamide</td>
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<tr>
<td>Docetaxel</td>
<td>35</td>
<td>14 (44%)</td>
<td>1 (3%)</td>
<td>9%</td>
<td>Higher rate of response to enzalutamide if patient had responded to abiraterone</td>
<td>Schueller et al.[72]</td>
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<tr>
<td>Enzalutamide</td>
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<tr>
<td>Abiraterone</td>
<td>54</td>
<td>9 (20%)</td>
<td>13 (37%)</td>
<td>11%</td>
<td>No patient who did not respond to abiraterone responded to docetaxel</td>
<td>Mozynski et al.[80]</td>
</tr>
</tbody>
</table>

Hurwitz M et al. Oncology November 2013
http://www.cancernetwork.com/oncology-journal/sequencing-agents-castration-resistant-prostate-cancer
Current AUA Guidelines

- Asymptomatic or minimally symptomatic, mCRPC with good performance status without prior docetaxel chemotherapy
  - Abiraterone + prednisone
  - Enzalutamide
  - Docetaxel
  - Sipuleucel T

No direct studies comparing the agents that can be used to inform optimal sequencing
Preferable to give the least toxic agent first, but must also look at ease of administration and other factors also
(www.auanet.org/education/guidelines)

Symptomatic Patient , Good Performance Status , No Prior Docetaxel

Symptomatic – sx clearly attributable to mets and pt should require regular opiate pain meds

- Abiraterone + prednisone
- Enzalutamide
- Docetaxel

- Should offer radium-223 to pts with sx from bone mets with good performance status and no prior docetaxel and without evidence of visceral disease.
  (www.auanet.org/education/guidelines)
Symptomatic, mCRPC with poor performance status, no prior docetaxel

- Challenge – these patients have traditionally been excluded from clinical trials – thus most data is extrapolated from clinical trials involving pts with better performance status
- Consider therapies with more acceptable safety profiled
  - Abiraterone + prednisone
  - Enzalutamide

Consider Radium-223 in pts with sxic bone pain and no visceral mets particularly if the poor performance status is thought to be related to the sxic bone pain
(www.auanet.org/education/guidelines)

Symptomatic, mCRPC with good performance status, prior docetaxel

- Offer treatment with
  - Abiraterone + prednisone
  - Enzalutamide or
  - Cabazitaxel

- Preference is for abiraterone + prednisone or enzalutamide over cabazitaxel as they have significantly less acute toxicity and no apparent cumulative toxicity
- Cabazitaxel may show cumulative bone marrow toxicity (pancytopenia) and cumulative neurotoxicity
- (www.auanet.org/education/guidelines)
Impact of Sequencing on Cost
(Dragomir Q, et al. BMC Health Services Research 2014; 14:252)

• Canadian study evaluating the drug costs in the rx mCRPC
  • Mean cost of mCRPC drug treatments over an average period of 28.1 months estimated at $48,428 per patient (95% CI: 47,624-49,232)
  • Mean cost increased to $104,071 (95% CI: $102,373-105,770) per patient when include abiraterone used prior to docetaxel
  • Over the mCRPC period
    • LHRH 20.4% of cost
    • Denosumab 30.5% of cost
  • Cost increased by 60.2% when cabazitaxel used in sequence after abiraterone and docetaxel

Treatment Sequences and Pharmacy Costs of 2 New Therapies for mCRPC
(Ellis et al. American Health & Drug Benefits June 2015, vol 8, No. 4)

• 3 healthcare claims data sets - pts with mCRPC no prior use of and newly initiated abiraterone or enzalutamide - 9/1/2012 until data cut off or lost to f/up
• 3 data sets: 9/1/2012-10/31/2013 - data set 1 (n=3525) and 2 (n=499), to July 31, 2014 data set 3 (1949)
  • 1 – Symphony Health Solutions’ Patient Transactional datasets
  • 2 – IMS PharMetrics Plus database
  • 3 – Truven Health MarketScan Research Databases
• First line abiraterone acetate in 74%, 82% & 80% data sets 1,2, and 3 respectively- most received only 1 therapy during study
• Corticosteroids in 81.2-86.4% rx first line abiraterone and 32.1%-38.0% receiving enzalumatide
Treatment Sequences and Pharmacy Costs of 2 New Therapies for Metastatic Castration-Resistant Prostate Cancer

- Monthly pharmacy payer cost for abiraterone significantly lower than monthly payer cost for enzalutamide in all 3 data sets.

<table>
<thead>
<tr>
<th>Data Set</th>
<th>Abiraterone</th>
<th>Enzalutamide</th>
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<tbody>
<tr>
<td>Data set 1</td>
<td>$5756</td>
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<td>Data set 2</td>
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<td>Data set 3</td>
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</table>


What are Physicians/Patients Choosing – First Line Therapy CRPC

- Docetaxel use declined from 100% in 2011 to slightly more than 20% in 2014
- Zytiga increased to 40% in 2014
- Enzalutamide increased to a little more than 20% in 2014
- Sipuleucel T and Cabazitaxel stayed essentially the same from 2011-2014 with < 10%
  (Kantar Health Cancer MPact)
What are Physicians/Patients Choosing


Future Therapies

Thoreson GR et al. Can J Urol 2014; 21(suppl 1): 98-105
Conclusions

- Several new agents have been recently approved for the management of CRPC with unique MOA and indications
- Patients with CRPC will ultimately require multiple agents over time
- Currently, new therapies are used in patients with metastatic disease, ? Role earlier ? Better dx of met dz
- The timing of use of each of these therapies is not well defined
- The efficacy of therapy may be affected by prior therapy
- The cost of management of CRPC is not without significant economic consequences

Questions?