Advanced Therapeutic Strategies in the Successful Management of Patients with Castrate Resistant Prostate Cancer (CRCP)

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U Mass Medical School

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

• Disclosures not related to this presentation:
  • Pfizer – clinical trials, advisory board, speaker
  • Allergan – advisory board, speaker
  • Astellas – advisory board
Objectives

- Explore updated efficacy and safety data for therapeutic agents for CRPC that target androgen synthesis or androgen receptor signaling pathways
- Discuss current challenges and limitations of treatment strategies for CRPC
- Analyze different roles of optimal sequencing for approved chemotherapy, immunotherapy, and androgen deprivation therapy (ADT) in a clinical setting for patients with CRPC
- Assess appropriate management strategies to integrate current and novel therapies into practice for treatment of advanced prostate cancer
- Review the treatment strategies to the managed care side of CRPC, including individualized treatment plans, resource utilization and cost considerations

Prostate Cancer Statistics

<table>
<thead>
<tr>
<th>Male</th>
<th>As of January 1, 2012</th>
<th>Female</th>
<th>As of January 1, 2022</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>2,775,630 (43%)</td>
<td>Breast</td>
<td>2,971,610 (44%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>555,310 (9%)</td>
<td>Uterine corpus</td>
<td>606,510 (8%)</td>
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<tr>
<td>Melanoma</td>
<td>481,043 (7%)</td>
<td>Colon &amp; rectum</td>
<td>603,510 (8%)</td>
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<td>Urinary bladder</td>
<td>427,160 (7%)</td>
<td>Melanoma</td>
<td>496,210 (7%)</td>
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<td>Non-Hodgkin lymphoma</td>
<td>279,503 (4%)</td>
<td>Thyroid</td>
<td>430,590 (6%)</td>
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<tr>
<td>Testis</td>
<td>330,503 (5%)</td>
<td>Non-Hodgkin lymphoma</td>
<td>255,450 (6%)</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>213,000 (3%)</td>
<td>Uterine cervix</td>
<td>249,020 (3%)</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>155,080 (3%)</td>
<td>Lung &amp; bronchus</td>
<td>233,100 (3%)</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>185,260 (3%)</td>
<td>Ovary</td>
<td>192,750 (3%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>167,360 (3%)</td>
<td>Uterine cervix</td>
<td>217,200 (3%)</td>
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<tr>
<td>All sites</td>
<td>6,442,380</td>
<td>All sites</td>
<td>7,241,570</td>
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<table>
<thead>
<tr>
<th>Male</th>
<th>As of January 1, 2012</th>
<th>Female</th>
<th>As of January 1, 2022</th>
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</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>3,562,500 (45%)</td>
<td>Breast</td>
<td>3,795,010 (44%)</td>
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<tr>
<td>Colon &amp; rectum</td>
<td>751,590 (9%)</td>
<td>Uterine corpus</td>
<td>735,720 (8%)</td>
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<tr>
<td>Melanoma</td>
<td>601,090 (8%)</td>
<td>Colon &amp; rectum</td>
<td>753,520 (8%)</td>
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<td>Urinary bladder</td>
<td>546,500 (6%)</td>
<td>Melanoma</td>
<td>609,690 (7%)</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>371,980 (4%)</td>
<td>Thyroid</td>
<td>277,800 (3%)</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>305,800 (3%)</td>
<td>Non-Hodgkin lymphoma</td>
<td>341,800 (4%)</td>
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<tr>
<td>Testis</td>
<td>295,500 (3%)</td>
<td>Lung &amp; bronchus</td>
<td>244,210 (3%)</td>
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<tr>
<td>Oral cavity &amp; pharynx</td>
<td>232,330 (3%)</td>
<td>Uterine cervix</td>
<td>229,020 (2%)</td>
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<tr>
<td>Leukemia</td>
<td>220,910 (3%)</td>
<td>Lung &amp; bronchus</td>
<td>158,200 (3%)</td>
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<tr>
<td>All sites</td>
<td>6,794,630</td>
<td>All sites</td>
<td>9,184,530</td>
</tr>
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</table>
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


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)

Historical Management of CRPC – From ADT to Chemotherapy

• Continue ADT as only therapy until documented mCRPC
• Chemotherapy – poorly tolerated with low response rates and minimal clinical benefits prior to 1991
• 1990’s role of chemotherapy re-evaluated with development of better tolerated regimens that improved QoL and OS
• 2004 – docetaxel approved for first-line treatment of mCRPC
• 2010 – Cabazitaxel (Jevtana) + prednisone approved for use in mCRPC previously treated with docetaxel
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
    - a PSA RR (≥50% drop in PSA) of 43% vs 32% for mitoxantrone and
    - 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)\(^2\)

\(^{1}\)Tannock 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 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>
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<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>
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</table>

Taxanes and Mitoxantrone
Cost of Treatment

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

*a. Source Medispan through Cardinal Wholesaler
b. Representative generic source

From 2004 to 2010

Docetaxel chemotherapy was the only option for mCRPC

April 2010 – first immunotherapy approved but with strict indications and expensive

June 2010 – cabazitaxel approved for mCRPC previously treated with docetaxel
PROVENGE

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 (Provenge)

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

**DAYS 1**
LEUKAPHESIS
Apheresis Center

**DAYS 2 - 3**
SIPULEUCEL-T IS MANUFACTURED
Dendreon

**DAYS 3 - 4**
PATIENT IS INFUSED
Doctor's Office

COMPLETE COURSE OF THERAPY: 3 CYCLES

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Figure: The diagram illustrates the two steps involved in sipuleucel-T therapy: (1) harvesting the patient's dendritic cells and then culturing these ex vivo with a recombinant fusion protein made of prostatic 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

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

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.
Copyright © 2010 Massachusetts Medical Society. All rights reserved

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

- The problem – Blocks glucocorticoid synthesis also
  - May lead to increase in ACTH and increased mineralocorticoids
  - To prevent this, prednisone 5 mg twice daily\textsuperscript{1,3}

- Effective even in patients resistant to ketoconazole\textsuperscript{4}

Abiraterone v Placebo

Statistically Significant Improvement in Radiographic PFS Primary Endpoint

Abiraterone vs Placebo: 1546 vs 1542

Progression-free (%)

Time to Progression or Death (Months)

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

Data cutoff: 12/20/2010

Abbreviations: PFS, progression-free survival; AA, abiraterone acetate; P, placebo; 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

Abiraterone vs Placebo: 1546 vs 1542

Survived [%]

Time to Death (Months)

AA: P (median, mo): NR
PL: P (median, mo): 27.2
HR (95% CI): 0.75 (0.65-0.82)
P value: 0.0007

Data cutoff: 12/20/2010

Pre-specified significance level by O'Brien-Fleming Boundary = 0.0038
Abbreviations: OS, overall survival; AA, abiraterone acetate; P, placebo; 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

Understanding “Castrate Resistant” Prostate Cancer

Targeting the Androgen Receptor
Enzalutamide (Xtandi)

- FDA approved August 31, 2012
- Indication – rx of pts with mCRPC 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 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

(Chen CD et al. Nat Med 2004; 10: 33-9;
Enzalutamide (Xtandi)

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

(prescribing 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
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 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 cx
- 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

Comparison Denosumab vs Zoledronic Acid

<table>
<thead>
<tr>
<th>Major outcomes, denosumab vs. zoledronic acid</th>
<th>Denosumab N=1,026</th>
<th>Zoledronic acid N=1,020</th>
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</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>
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<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
- 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>
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</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
ALSEYMPCCA Trial: Alpharadin Significantly Improves OS compared to Placebo

HR = 0.698; 95% CI, 0.592-0.836
P = 0.00165

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

Figure. ALSYMPCA time to first skeletal-related event.

CL, confidence interval; HR, hazard ratio; SRE, skeletal-related events

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%
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?

Current Management of mCRPC

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

- Prospective data addressing optimal treatment sequencing are not available
- Head-to-head comparisons of new therapies, i.e., 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
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

- Only limited data available evaluating sequential administration of enzalutamide after abiraterone and docetaxel
- Enzalutamide appears to have higher activity in docetaxel-naïve patients
- Third line therapy after prior docetaxel and abiraterone –
  - One retrospective cohort analysis of 35 patients demonstrated that complete cross-resistance was not observed and 3/19 (16%) who had not responded to abiraterone achieved PSA declines of ≥ 50% on enzalutamide
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.
Future Therapies—Targeting AR

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

2. Second-generation pure AR antagonists
   a. Antiandrogens
      a. ARN-509 – clinical trials
      b. ODM-201 – clinical trials
      c. EXN-4176 – clinical trials

Other agents include OGX-427 which targets heat shock protein and EPR-001 an androgen receptor modulator.

Management of mCRPC – Future Therapies

• Prostavac – immunotherapy
• Ipilimumab – human monoclonal antibody – checkpoint inhibitor that binds to cytotoxic T lymphocyte antigen-4 receptors found on surface of T cells that down-regulate the T-cell response, mediating tumor-induced immune tolerance
• Programmed cell death protein (PD-1) – negative immune regulator expressed on surface of activated T cells, B cells and macrophages – in PCA, CD8+ T cell infiltrating the prostate gland commonly express PD-1, which may promote immune tolerance
• Others in development – cabozantinib, tasquinimod, Custirsen
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

Where Do We Go From Here?

AJ Armstrong – 5 principals that my help guide drug development for men with mCRPC
1. Optimize drug delivery and minimize unnecessary harms and costs to individuals and society by developing predictive biomarkers for the new systemic therapies
2. Prevent, not just delay, death from prostate cancer by studying the early use of effective systematic therapies prior to macrometastatic disease
3. Improve our preclinical models and human correlative studies to better understand the molecular underpinnings of how prostate cancer metastasizes, resists current therapies, and changes over time
4. Develop screening strategies and biomarkers that ID men with aggressive, potentially lethal organ-confined PCA but don’t detect the indolent nonlethal disease
5. Ensure the real clinical value of therapies by developing transparent guidelines that account for society-level values (Armstrong AJ. Eur Urol 2014; 65: 300-302)
Questions?