Metastatic prostate cancer

Walid Obeid PGY IV
SGHUMC
Definition

• Stage IV prostate cancer: is defined by the American Joint Committee on Cancer's TNM classification system:
  • T4, N0, M0, any prostate-specific antigen (PSA), any Gleason.
  • Any T, N1, M0, any PSA, any Gleason.
  • Any T, any N, M1, any PSA, any Gleason
Incidence

• Approximately 10-20% of newly diagnosed prostate cancer cases involve locally advanced disease.

• Advanced disease is comparably less common, because more early stage cancer is being discovered with availability of PSA screening
### Prognosis

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic (limited) metastases</td>
<td>~18 to 24 months</td>
</tr>
<tr>
<td>Asymptomatic (extensive) metastases</td>
<td>~18 months</td>
</tr>
<tr>
<td>Symptomatic metastases</td>
<td>~9 to 16 months</td>
</tr>
</tbody>
</table>
Presentation

- Anemia
- Bone marrow suppression
- Weight loss
- Pathologic fractures
- Spinal cord compression
- Pain
- Hematuria

- Ureteral and/or bladder outlet obstruction
- Urinary retention
- Chronic renal failure
- Urinary incontinence
- Symptoms related to bony or soft-tissue metastases
Treatment

• Mainstay: “androgen suppression”.
• It is a palliative tool, no cure.
• Results of treatment:
  • median progression-free survival = 18-20 months
  • overall survival = 24-36 months
• All patients develop hormone-refractory disease.
• Take in consideration the toxic effects of treatment.

Any T, N1: Treatment includes ADT or radiation therapy (doses of 78-80+ Gy) with 3D-CRT/IMRT with IGRT plus long-term neoadjuvant/concomitant/adjuvant ADT for 2-3y
Any T, any N, M1: Treatment includes only ADT for patients with M1
Metas. prostate ca.

Initial therapy

CRPC
Castration-resistant

Standard

ADT
Androgen Deprivation

Supportive care.
Bisphosphonates

PSA doubling
Symptoms

Hormonal

Chemo.

2nd line
Androgen deprivation therapy

• Aim → Testosterone < 50 ng/dl

• Surgical castration by Bilateral orchiectomy

• Medical castration
  1. LHRH agonist: (e.g. goserelin, leuprolide) (+ oral antiandrogen ≥7 days to avoid testosterone flare)
  2. LHRH antagonist. (e.g. degarelix )
  3. CAB: combined androgen blockade: LHRH agonist + oral antiandrogen
Androgen deprivation therapy

- Patients who do not show an adequate suppression of serum testosterone (< 50 ng/dL) may be considered for CAB
- Monotherapy of nonsteroidal antiandrogens are less effective but are associated with fewer hot flashes and fatigue and do not impair libido
- If hormone therapy fails, that therapy should be continued into and through the next hormone manipulation.
- Recent data showed that CAB is not superior to LHRH agonists alone in treatment of metastatic PCa.
Luteneising-hormone-releasing hormone agonists:

- Therapy with LHRH analogs may induce medical castration by suppressing LH production.
- These agonists can potentially cause a transient surge of LH when therapy is initiated before the LH levels fall (flare phenomenon).
- LHRH agonists are offered in 1mo, 3mo, and once-yearly depots; it is necessary to pre-medicate with antiandrogen to prevent flare up phenomenon.

- Leuprolide: 7.5 mg IM monthly or 22.5 mg IM every 3ms or 30 mg IM every 4ms or 45 mg IV every 6ms.
- Histrelin: one 50mg implant SC every 12ms; continue therapy until disease progression.
- Goserelin: 3.6 mg implant SC monthly or a 10.8 mg implant SC every 3ms.
- Triptorelin: 3.75 mg IM monthly or 11.25 mg IM every 3mo or 22.5 mg IM every 6ms.
Luteneising-hormone-releasing hormone antagonists:

- Pure LHRH antagonists suppress testosterone and avoid the flare phenomenon associated with GnRH agonists.

Degarelix: 120 mg SC x 2 doses (i.e. 2 separate injections totaling 240 mg), and then, after 28 days, begin monthly maintenance dose of 80mg SC.
Nonsteroidal antiandrogens:

- Antiandrogens bind to androgen receptors and competitively inhibit their interaction with testosterone and dihydrotestosterone.
- These agents do not decrease LH levels and androgen production.
- Antiandrogens are usually used in combination with a GnRH agonist in order to prevent a disease flare caused by the transient increase in testosterone levels.

- Flutamide 250 mg PO TID.
- Bicalutamide 50 mg PO daily; patients refractory to other antiandrogen agents may start with 150 mg PO daily.
- Nilutamide 300 mg PO daily for 30 days, and then 150 mg PO daily.
Intermittent vs continuous ADT

SWOG TRIAL, negm 2013

SURVIVAL RESULTS ARE INCONCLUSIVE

According to NCCN guidelines: You can consider intermittent ADT when the adverse effects of ADT is a matter
Adverse effect of ADT

- Hot flushes
- Osteoporosis
- Fractures
- Obesity
- Insulin resistance
- DM
- Alteration in lipids
- Cardiovascular dis.
Castrate resistant prostate cancer
CRPC

<table>
<thead>
<tr>
<th>Castrate serum testosterone &lt; 50 ng/dL or 1.7 nmol/L plus either;</th>
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<tbody>
<tr>
<td>Biochemical progression: Three consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir, with PSA &gt; 2 ng/mL or</td>
</tr>
<tr>
<td>Radiological progression: The appearance of two or more new bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours) [822]. Symptomatic progression alone must be questioned and is not sufficient to diagnose CRPC.</td>
</tr>
</tbody>
</table>
Castrate resistant prostate cancer
CRPC

mCRP

Good performance status 0 or 1

PS 2+

Asymptomatic
Monitoring
Conventional anti-androgens

With evidence of progressive
disease
Radium 233

Mildly symptomatic or asymptomatic men
With no evidence or visceral metastasis
Abiraterone
Sipuleucel T
Enzalutamide
? Docetaxel

Men with symptomatic disease and/or visceral metastases

No visceral mets

Visceral mets

Docetaxel
Radium 233

Docetaxel

Second line therapies (dependent on previous treatments)
Docetaxel
Abiraterone
Enzalutamide
Cabazitaxel
Radium 233
Secondary hormonal therapy

- Abiraterone Acetate (® Zytiga 250 mg tab)
- Enzalutamide (® Xtandi 40 mg caps)
Abiraterone acetate

• 4 tabs once daily, on empty stomach.
• Androgen synthesis inhibitor
• To be taken with prednisone tab (5mg 1 x 2).
• FDA approval as first line therapy in asymptotic CRPC and as second line therapy after failure of Docetaxel.

• Precautions:
  Monitor liver functions, K+, Phosphorus / month
  Monitor Bld pressure / month.
• Most common S.E: Fatigue, back/joint pain, peripheral edema., HTN
• Serious S.E: hepatic, cardiac and electrolytes
Phase III trial by Ryan CJ et al, NEJM, 2013
Aberaterone acetate as first line in asymptomatic CRPC

~ 1080 pts.
Metas CRPC
Asympt or minimal sympt.

Zytiga + prednisone
Placebo + Prednisone

RAND

Improvement of radiograph PFS: 16.5 ms VS 8 ms (P<0.001)
Enzalutamide

• Anti-androgen: Inhibit signaling of androgen receptor at multiple levels.
• Dose: 4 caps once daily, +/- food.
• Not necessary to take prednisone with it.
• Could be used in pts with poor PS.
• Less S.E than Abiraterone.
• Given with GnRH agonists.
• Serious S.E: Seizures. (0.6 %)
Sipuleucel-T

Immunotherapy
• Provenge ®: IV over 60 min / 2 weeks x 3 cycles.

• Autologous cancer vaccine
  1) Collect blood from pt.
  2) Separate APC (Ag-presenting cells)
  3) Exposure to (PAP-GM-CSF recombinant fusion gene) ; “prostatic acid phosphatase”
  4) Re-infuse in the same patient.
Figure: The diagram illustrates the two steps involved in sipuleucel-T therapy: (1) harvesting the patient's dendritic cells and then pulsing 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.
Who are the candidates to Sipuleucel-T

- Metastatic CRPC.
- First line in asymptomatic or minimally symptomatic pts.
- Good PS.
- Life expectancy > 6 months.
- No visceral metastasis.

Resulted in 22% reduction in mortality when compared to placebo in a phase III trial, which was published by Kantoff PW et al, NEJM 2010.

Common S.E: chills, pyrexia and headache.
RADIUM-223

• Xofigo ® alpha particle-emitting radioactive therapeutic agent (half life~11 day)
• I.V injection over 1 min.
• Every 4 weeks X 6 cycles.
• Dose: 1.35 micro-curie/ Kg.
• Given for symptomatic CRPC + bone mets without visceral mets

• S.E: (≥ 10%) were nausea/vomiting and peripheral edema

Hematologic laboratory abnormalities (≥ 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia
ALSYMPCA, NEGM 2013

**Patients (N=921)\(^1,2\)**
- CRPC with symptomatic bone metastases
- No known visceral metastases\(^a\)

**Treatment\(^1,3\)**
- 6 injections at 4-week intervals
  - Xofigo\(^\circledR\) (50 kBq/kg) + Best standard of care (n=614)
  - Placebo (saline) + Best standard of care (n=307)

**Endpoints\(^1,2\)**
- Primary endpoint
  - Overall survival
- Secondary endpoints

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**Median Overall Survival Was Extended\(^1a\)**

- Xofigo + Best standard of care\(^b\) (n=614)
- Placebo + Best standard of care\(^b\) (n=307)

**Hazard Ratio (HR):** 0.695 (95% CI: 0.581-0.832)

**THE XOFIGO\(^\circledR\) BENEFIT**
- **3.6 month increase in median overall survival\(^1a\)**

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**Graph:**
- Xofigo: 14.9 months
- Placebo: 11.3 months

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>Xofigo</th>
<th>Placebo</th>
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<tr>
<td>3</td>
<td>614</td>
<td>307</td>
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<tr>
<td>6</td>
<td>578</td>
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<td>504</td>
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Bone health in metastatic PCa

• ADT associated with 20-50% relative increase of fracture risk.
• ADT decrease bone menial density.
• Longer treatment duration greater fracture risk.

• **NCCN recommendations: (with ADT)**

• Supplemental Calcium (1200 mg daily) + vit-D (1000 IU daily).
• Base line DEXA scan then annually.
• Denosumab: 60 mg / 6 months : phase III trial in non-metastatic PCa showed that Denosumab increase bone mineral density by 6.7% and reduces the risk of fracture (from 3.9% to 1.5%); Smith MR et al, NEJM 2009; 361(8):745-55.
• Or Zoledronic acid (5mg/12 ms).
A Randomized, Placebo-Controlled Trial of Zoledronic Acid in Patients With Hormone-Refractory Metastatic Prostate Carcinoma

Fred Saad, Donald M. Gleason, Robin Murray, Simon Tchekmedyan, Peter Venner, Lou the Zoledronic Acid Prostate Cancer Study Group

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Correspondence to: Fred Saad, M.D., Uro-Oncology Clinic, Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, 1560 Rue Sherbrooke East, Montréal, Quebec, Canada H2L 4M1 (e-mail: fred.saad(at)ssss.gouv.qc.ca).

Abstract

Background: Bone metastases are a common cause of morbidity in patients with prostate carcinoma. We studied the effect of a new bisphosphonate, zoledronic acid, which blocks bone destruction, on skeletal complications in prostate cancer patients with bone metastases. Methods: Patients with hormone-refractory prostate cancer and a history of bone metastases were randomly assigned to a double-blind, placebo-controlled trial of zoledronic acid, 4 mg intravenous infusion once weekly for 4 weeks, followed by placebo for 4 weeks, or placebo for 4 weeks followed by zoledronic acid. Results: Of 644 patients enrolled, 637 were evaluable for efficacy and 13 were evaluable for safety. At the planned interim analysis, 547 patients (85%) had efficacy data and 517 patients (79%) had safety data. CRPC: Asympt. Or minimal sympt. Zometa vs Placebo Increase median time To SRE No effect on OS.
Algorithm in mCRPC

- **mCRP**
  - Good performance status 0 or 1
  - PS 2+
  - Asymptomatic Monitoring
  - Conventional anti-androgens

- **Mildly symptomatic or asymptomatic men**
  - With no evidence of visceral metastasis
  - Abiraterone
  - Sipuleucel T
  - Enzalutamide
  - ? Docetaxel

- **Men with symptomatic disease and/or visceral metastases**
  - No visceral mets
    - Docetaxel
    - Radium 233
  - Visceral mets
    - Docetaxel

- **Second line therapies (dependent on previous treatments)**
  - Docetaxel
  - Abiraterone
  - Enzalutamide
  - Cabazitaxel
  - Radium 233
Cross resistance between new therapies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year published</th>
<th>N pts</th>
<th>Duration of 2\textsuperscript{nd} treatment</th>
<th>↓ PSA ≥ 50%</th>
<th>Median PFS</th>
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<td>ENZ → ABI</td>
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<tr>
<td>Loriot et al.\textsuperscript{1}</td>
<td>2013</td>
<td>38</td>
<td>3 mo</td>
<td>8%</td>
<td>2.7 mo</td>
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<td>Noonan et al.\textsuperscript{2}</td>
<td>2013</td>
<td>30</td>
<td>13 wks</td>
<td>3%</td>
<td>3.6 mo</td>
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<td>ABI → ENZ</td>
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<tr>
<td>Schrader et al.\textsuperscript{3}</td>
<td>2013</td>
<td>35</td>
<td>4.9 mo</td>
<td>29%</td>
<td>-</td>
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<tr>
<td>Badrising et al.\textsuperscript{4}</td>
<td>2014</td>
<td>61</td>
<td>3 mo</td>
<td>21%</td>
<td>-</td>
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<td>Bianchini et al.\textsuperscript{5}</td>
<td>2014</td>
<td>39</td>
<td>2.9 mo</td>
<td>13%</td>
<td>-</td>
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<tr>
<td>Schmid et al.\textsuperscript{6}</td>
<td>2014</td>
<td>35</td>
<td>2.8 mo</td>
<td>10%</td>
<td>-</td>
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<tr>
<td>Brasso et al.\textsuperscript{7}</td>
<td>2014</td>
<td>137</td>
<td>3.2 mo</td>
<td>18%</td>
<td>-</td>
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</table>

[1-7] trials are retrospective studies in mCRPC pts in post-DOC setting

Treatment Sequencing: Post STAMPEDE results

- **Metastatic Prostate Cancer**
  - **Low Volume/Poor PS**
    - Androgen Deprivation Therapy
      - Ra223/Abiraterone/Enzalutamide
      - Docetaxel/Cabazitaxel
      - Best supportive care
  - **High volume/High Risk/ Good PS**
    - Docetaxel chemotherapy + ADT
      - Docetaxel/Cabazitaxel/Ra223/Abiraterone/Enzalutamide
      - Best supportive care
Art of sequencing

• Based on the concept that more treatments => increased survival
• 2 ‘philosophical’ approaches:
  – Give the less toxic agent first
  – Give the more toxic agent first
Metastatic CRPC

Short response (<1 year) to 1st-line ADT
High Gleason score (>=8)
High Volume mets
• Or rapidly progressive/aggressive disease
• Or previous Abiraterone/Enzalutamide
• Or AR-V7 positive (if available)

Poor predicted response to further hormonal therapy (including abiraterone/enzalutamide)

Indication for chemotherapy (Docetaxel → Cabazitaxel)
Multi disciplinary approach

Urologists

Oncologists

Patient

Nurses/Pharmacists

Partnership

Support

Support
Second Line Therapy

Definitely depends on previous treatments
COU-AA-301 trial:
De Bono et al, NEJM, 2011

~ 1200 pts.
Progression on Docetaxel.
PS ≤ 2.
Testosterone ≤ 2nmol/liter

Excluded if:
• Liver enz ≥ 2.5 times norm.
• Chr liver dis.
• Active hepatitis.
• Uncontrolled HTN.
• Previous Ketoconazole.
• Signif cardiac dis.

Zytiga + prednisone
Prednisone

RAND

Increase OS:
15 ms VS 11 ms
(P < 0.001)

More SE:
HTN, edema, K+
AFIRM trial, NEG 2012

~ 1200 pts.
Progression on chemo.
Any PS
Visceral metas.

Ongoing PREVAIL trial to assess the role of Enzalutamide in pre-docetaxel settings

Enzalutamide

Increase MS:
13.5 ms VS 18.5 ms
(P < 0.001)
SE mild:
Fatigue, diarrhea, hot flushes

RAND

Placebo.
Cabazitaxel

- Marketed as JEVTANA
- Semi-synthetic taxane derivative
- Dose: 25 mg/m2 over 1 hour / 3 weeks.
- After failure of Docetaxel.

Updated Ann Oncol, 2013

755 pts. CRPC Progression on Docetaxel.

RAND

Cabazitaxel + prednisone  ➔  2.5ms Improv. in OS

Mitoxantrone + prednisone.
Meta-analysis of 10 retrospective studies

12-month OS rate by sequence in post-DOC

Possible better OS with the sequence DOC→CAB→ART?

ART: Androgen receptor targeted agents
Maines F et al. ASCO GU 2015 (abstract 258)
Maines F et al. ASCO GU 2015 (abstract 258)
Conclusions

• Management of metastatic prostate cancer is rapidly evolving.....potential change in paradigm

• New drugs in development: need to move to a tailored therapy

• The most appropriate sequencing of these new agents remains to be determined and chemotherapy remains a valid treatment option in mCRPC

‘The right drug, at the right time, for the right patient at the right place and by the right team’
** Systemic Therapy for M0 Castration-Recurrent Prostate Cancer

- Clinical trial (preferred)
- Observation especially if PSADT ≥10 mo
- Secondary hormone therapy especially if PSADT <10 mo
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole ± hydrocortisone
  - Corticosteroid
  - DES or other estrogen

- PSA rising
  - Yes → Imaging
  - No → Metastases (M1)

- No metastases (M0)

---

6 See Principles of Imaging (PROS-B).

DES has cardiovascular and thromboembolic side effects at any dose but frequency is dose and agent dependent. DES should be initiated at 1 mg/d and increased, if necessary, to achieve castrate levels of serum testosterone (<50 ng/dL). Other estrogens delivered topically or parenterally may have less frequent side effects but data are limited.
**NCCN Guidelines Version 2.2016**

**Prostate Cancer**

**SYSTEMIC THERAPY FOR M1 CASTRATION-RECURRENT PROSTATE CANCER**

- **CRPC, studies positive**
  - Maintain castrate levels of serum testosterone (<50 ng/dL)
  - Consider bone antiresorptive therapy with denosumab or zoledronic acid (both category 1) if bone metastases present
  - Immunotherapy with sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG performance status 0–1 (category 1)
  - Palliative RT for painful bony metastases
  - Best supportive care

- **Visceral metastases**
  - Docetaxel\(^{cc}\) with prednisone (category 1)
  - Enzalutamide (category 1)
  - Alternative chemotherapy (mitoxantrone with prednisone)\(^{x}\)
  - Clinical trial
  - Secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole ± hydrocortisone
  - Corticosteroid
  - DES or other estrogen\(^z\)

- **Progression after all other therapies**
  - Docetaxel\(^{cc}\) with prednisone (category 1)
  - Enzalutamide (category 1)
  - Abiraterone\(^{bb}\) with prednisone (category 1)
  - Clinical trial
  - Secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole ± hydrocortisone
  - Corticosteroid
  - DES or other estrogen\(^z\)

- **Progression after: Abiraterone, Enzalutamide, Docetaxel**
  - See Subsequent Therapy for M1 CRPC: No Visceral Metastases (PROS-12)
  - See Subsequent Therapy for M1 CRPC: Visceral Metastases (PROS-13)

---

\(^{cc}\)See Principles of Imaging (PROS-B).

\(^{bb}\)See Principles of Androgen Deprivation Therapy (PROS-F).

\(^{x}\)See Principles of Immunotherapy and Chemotherapy (PROS-G).

\(^{z}\)DES has cardiovascular and thromboembolic side effects at any dose but frequency is dose and agent dependent. DES should be initiated at 1 mg/day and increased, if necessary, to achieve castrate levels of serum testosterone (<50 ng/dL). Other estrogens delivered topically or parenterally may have less frequent side effects but data are limited.

\(^{x}\)Sipuleucel-T has not been studied in patients with visceral metastases.

\(^{bb}\)For patients who are not candidates for docetaxel-based regimens.

\(^{cc}\)Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or visceral metastases despite lack of symptoms.

\(^{dd}\)Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See Principles of Radiation Therapy (PROS-D, page 2 of 2).
SUBSEQUENT SYSTEMIC THERAPY FOR M1 CASTRATION-RECURRENT PROSTATE CANCER

Prior therapy enzalutamide/abiraterone

- Docetaxel with prednisone (category 1)
- Abiraterone with prednisone
- Enzalutamide
- Radium-223 for symptomatic bone metastases (category 1)
- Sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0–1
- Clinical trial
- Other secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole ± hydrocortisone
  - Corticosteroid
  - DES or other estrogen
  - Best supportive care

No visceral metastases

Prior therapy docetaxel

- Enzalutamide (category 1)
- Abiraterone with prednisone (category 1)
- Radium-223 for symptomatic bone metastases (category 1)
- Cabazitaxel with prednisone (category 1)
- Sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0–1
- Clinical trial
- Docetaxel rechallenge
- Alternative chemotherapy (mitoxantrone with prednisone)
- Other secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole ± hydrocortisone
  - Corticosteroid
  - DES or other estrogen
  - Best supportive care

\[\text{DES has cardiovascular and thromboembolic side effects at any dose but frequency is dose and agent dependent. DES should be initiated at 1 mg/day and increased, if necessary, to achieve castrate levels of serum testosterone (<50 ng/dL). Other estrogens delivered topically or parenterally may have less frequent side effects but data are limited.}\]

\[\text{Patients can continue through all treatment options listed. Best supportive care is always an appropriate option.}\]
Prostate Cancer

SUBSEQUENT SYSTEMIC THERAPY FOR M1 CASTRATION-RECURRENT PROSTATE CANCER ⁶⁶

Prior therapy enzalutamide/abiraterone

- Docetaxel with prednisone (category 1) ⁶
- Clinical trial
- Abiraterone ¹ with prednisone
- Enzalutamide
- Other secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole ± hydrocortisone
  - Corticosteroid
  - DES or other estrogen ²
- Best supportive care

Prior therapy docetaxel

- Enzalutamide (category 1)
- Abiraterone ¹ with prednisone (category 1)
- Cabazitaxel with prednisone (category 1) ⁶
- Clinical trial
- Docetaxel rechallenge ²
- Alternative chemotherapy (mitoxantrone with prednisone) ⁶
- Other secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole ± hydrocortisone
  - Corticosteroid
  - DES or other estrogen ²
- Best supportive care

²DES has cardiovascular and thromboembolic side effects at any but frequency is dose and agent dependent. DES should be init at 1 mg/day and increased, if necessary, to achieve castrate lev serum testosterone (<50 ng/dL). Other estrogens delivered topi parenterally may have less frequent side effects but data are lin

¹See Principles of Androgen Deprivation Therapy (PROS-F).

³Patients can continue through all treatment options listed. Rest
**TABLE.** Clinical Outcomes and Effect of Disease Volume From Phase III Trials of Early Docetaxel Therapy in mHSPC

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>GETUG-AFU 15</th>
<th>CHAARTED (E3805)</th>
<th>STAMPEDE (M1 subgroup)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADT + D (n=192)</td>
<td>ADT (n=193)</td>
<td>HR</td>
</tr>
<tr>
<td>All Patients</td>
<td>60.9</td>
<td>46.5</td>
<td>0.9</td>
</tr>
<tr>
<td>High-Volume</td>
<td>39</td>
<td>35.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Low-Volume</td>
<td>83.1</td>
<td>NR</td>
<td>1</td>
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</table>

<table>
<thead>
<tr>
<th>Secondary Endpoint</th>
<th>Biochemical PFS (months)</th>
<th>Time to Clinical Progression (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>22.9</td>
<td>12.9</td>
</tr>
<tr>
<td>High-Volume</td>
<td>15.2</td>
<td>9.2</td>
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<tr>
<td>Low-Volume</td>
<td>40.9</td>
<td>22.4</td>
</tr>
</tbody>
</table>

ADT indicates androgen-deprivation therapy; D, docetaxel; HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer; NR, not reached; PFS, progression free survival.
RESOURCES

• AUA GUIDELINES 2015
• EAU GUIDELINES 2016
• NCNN GUIDELINES 2016
• NEJM
Question 1

The *desired* Castrate testosterone levels is

1. Less than 10 ng/dL

2. *Less than 20 ng/dL*

3. Less than 50 ng/dL

4. More than 20 ng/dL

5. More than 50 ng/dL
Question 2

All these are side effects of ADT but one

1. Hot flashes
2. Osteoporosis
3. Obesity
4. **Headache**
5. Insulin resistance
Question 3

Enzalutamide is a:

1. 17-hydroxylase inhibitor
2. 17-20 lyase inhibitor
3. *Novel anti-androgen*
4. Type of chemotherapy
5. Given intravenously
Question 4

Sipuleucel-T is given to patients with all the above except:

1. Metastatic CRPC.
2. First line in asymptotic or minimally symptomatic pts.

3. *Poor PS.*
4. Life expectancy > 6 months.
5. No visceral metastasis.
Question 5

• According to EAU guidelines, in M1 patients anti-androgen short-term administration is recommended

1. Started prior to LHRH agonist treatment initiation

2. Started with LHRH agonist treatment initiation

3. Started 1 week post LHRH agonist initiation

4. Not necessary with LHRH agonists
Question 6

Which of these products was shown to improve OS in patients with CRPC:

1. Zoledronic acid
2. Denosumab
3. Radium 223
4. Steroids
Question 7

Radiographic progression in prostate cancer:
1. More than 1 new lesion on follow up bone scan
2. More than 2 new lesions on follow up bone scan
3. More than 3 new lesions on follow up bone scan
4. More than 4 new lesions on follow up bone scan
Question 8

Concerning continuous vs intermittent ADT- pick the correct answer

1. Survival results are inconclusive
2. Intermittent ADT showed improved survival
3. Continuous ADT showed improved survival
4. Side effects increase with intermittent therapy
Question 9

STAMPEDE trial:
Docetaxel plus standard therapy improved overall survival by an average of 10 months in men with newly diagnosed, hormone-naive, advanced prostate cancer.

1. TRUE
2. FALSE
Factors favoring early chemotherapy with docetaxel

1. *High volume disease*
2. Gleason <8
3. PSA-DT >10 months
4. Response to ADT for more than 12 months
THANK YOU