Bisphosphonates in Metastatic Prostate Cancer and RCC

Fred Saad MD FRCS

Professor and Chair of Urology
Director of Urologic Oncology
U of M Endowed Chair in Prostate Cancer
University of Montreal

Kuala Lumpur
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Greetings from Montreal

Hôpital Notre-Dame
Metastatic Prostate Cancer: A History Lesson

- Since the introduction of hormone therapy in the 1940’s, there has been little in the way of new therapy for metastatic prostate cancer...
  - ADT (Castration, DES, LHRH, MAB etc.)
  - mitoxantrone 1996
  - zoledronic acid 2002
  - docetaxel 2004
Case Study

- 58-year-old, professional male
- Initial PSA at diagnosis = 20 ng/mL
- Undergoes a radical prostatectomy and PLND
- pT3bN0, negative margins, Gleason 8
- PSA parameters after initial diagnosis
  - Undetectable for first 3 months after RRP
  - At 12 months, PSA level = 0.6 ng/mL
  - Patient declined radiation therapy
Case Study

- Patient did not return for further visits
  - 3 years later PSA level = 51 ng/mL
- No metastatic disease was detected
- ADT (LHRH therapy) was begun

PSA, prostate-specific antigen; LHRH, luteinizing hormone releasing hormone.
Early ADT Improves survival and delays time to bone mets
Would you prescribe a bisphosphonate with ADT?

1. Yes, because the risk of fracture is high
2. It would depend on BMD levels
3. Only in the presence of bone metastases
4. No
Advanced Prostate Cancer

Recurrent/advanced PCa

Androgen deprivation therapy

PSA rises

HRPC

Biochemical

Asymptomatic

Symptomatic

Clinical Metastases

Death
Advanced Prostate Cancer

Recurrent/advanced PCa

Androgen deprivation therapy

PSA rises

HRPC

Biochemical

Clinical Metastases

Asymptomatic

Symptomatic

Death
Bone Loss Is Accelerated With ADT

Overall prevalence of osteoporosis, osteopenia, and normal BMD according to ADT duration. *Patients had not received ADT at time of BMD measurement.

Relationship Between BMD and Fracture Risk

- Osteoporosis
- Osteopenia

BMD T-score, SD units

Fracture risk

-4 -3 -2 -1 0 1 2

-4 -3 -2 -1 0 1 2 3 4

18 16 14 12 10 8 6 4 2

Osteoporosis
Osteopenia
ADT and Risk of Fracture

- fractures in health claims database
- 19.4% vs. 12.6% (no ADT)

Fracture incidence over 4 years

Fractures Negatively Correlate With Survival

Pamidronate IV q 3months

P≤0.005 for each comparison

Final 12-month data

Zoledronic Acid IV q 3 months

BMD Percent Change

- Lumbar spine
- Total hip

$P < 0.001$ for each comparison

Final 12-month data

Zoledronic Acid IV q 12 Months

**BMD Percent Change**

- **Lumbar spine**
  - Placebo
  - Zoledronic acid

- **Total hip**
  - Placebo
  - Zoledronic acid

*Final 12-month data*

*P<0.005 for each comparison*

Proposed diagnostic and treatment algorithm

Risk factors for fracture
- ADT
- Prior fracture

Assess BMD

- T-score < −2.5 (osteoporosis)
- T-score 1.0 to −2.5 (osteopenia)
- T-score > −1.0

CALCIUM and Vitamin D

- Treatment of osteoporosis to prevent fracture
- Treat if risk factors Or Repeat BMD after 6 to 12 months
- Repeat BMD after 2 years

Case Study

- Patient was placed on continuous LHRH therapy
  - PSA nadir of 1.0 ng/mL
  - After 1 year, PSA = 15 ng/mL
  - Asymptomatic with normal labs
  - PSA continues to rise even with hormonal manipulation
Scenario 1:
No metastases are found

What is your preferred treatment for this patient?

1. Observation until metastases confirmed
2. Docetaxel
3. Zoledronic acid
4. Zoledronic acid and docetaxel
5. Other therapy
Advanced Prostate Cancer

Recurrent/advanced PCa → Androgen deprivation therapy

PSA rises → HRPC

Biochemical

Asymptomatic

Symptomatic

Clinical Metastases

MO M+ M+

Death
Time to bone mets or death in Non-Metastatic HRPC

- PSA >24.0 ng/mL
- PSA 7.7-24.0 ng/mL
- PSA <7.7 ng/mL

- PSADT <6.3 months
- PSADT 6.3-18.8 months
- PSADT >18.8 months
Prevention of Bone Metastasis: PC-3 cell line

Control

Zoledronic Acid

Padalecki et al. ASBMR, 2002.
Bone Metastases

Vehicle

Zoledronic Acid

Padalecki et al. ASBMR, 2002.
In event of bone metastasis, zoledronic acid monthly, as per standard care

**Patient population (n = 1,300):**
- High risk prostate cancer, M0, with one of the following criteria
  - Gleason score 8-10
  - pN+
  - PSA ≥ 20 at diagnosis

**Primary endpoint**
- Proportion of patients with bone metastases after 48 months of treatment

**Secondary endpoint**
- Time to BM, OS, PSA doubling time; bone marker substudy

**Zoledronic acid 4 mg every 3 months**

**Control group**

**48-month treatment period**
Prostate Cancer
CZOL446EAT03 CECOG Study

Endpoints
- Primary: Time to bone metastases
- Secondary: Pain (BPI), time to SRE, % of patients with SRE, PSA
- Safety

654 patients
- Locally advanced, M0
- Hormone-naive
- High risk
- No bone metastases diagnosed
- About to start ADT

ADT + Zoledronic acid 4 mg every 3 months

Control group
(ADT only)

Bone disease progression

Randomization

Zoledronic acid monthly

48 months

Endpoints

Endpoints

T3-4 and highest prestudy PSA > 20 ng/ml and Gleason score ≥ 8 (or Gleason grade ≥ 4).
Scenario 2: Metastases are detected in pelvic lymph nodes and bone (Lumbar Spine and right hip)

What is your preferred treatment for this patient?

1. Observation until metastases are symptomatic
2. Docetaxel
3. Zoledronic acid
4. Zoledronic acid and docetaxel
5. Other therapy
In the presence of bone metastases

How long would you bisphosphonate therapy in this patient?

1. 6 months
2. 12 months
3. 2 years
4. Until progression of bone metastases
5. Indefinitely, as long as therapy is well tolerated, even if bone metastases progress

LS, Lumbar spine.
Advanced Prostate Cancer

Recurrent/advanced PCa

Androgen deprivation therapy

PSA rises

HRPC

Biochemical

Mo

M+

M+

Clinical Metastases

Asymptomatic

Symptomatic

Death
Pathogenesis of Bone Metastases
Metastatic HRPC

ADT-Bone loss

Metastases

Decreased bone strength

SKELETAL COMPLICATIONS (SRE)

Almost all patients will experience bone complications!
Skeletal Complications Reduce Quality of Life

Change in FACT-G score for patients with an event compared with patients without an event

Health Economic Impact of Metastatic Bone Disease With or Without Complications

Preventing bone complications
## Results With Bisphosphonates:

<table>
<thead>
<tr>
<th>Test drug</th>
<th>N</th>
<th>Result</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate</td>
<td>57</td>
<td>No benefit</td>
<td>Smith 1989</td>
</tr>
<tr>
<td>Clodronate</td>
<td>99</td>
<td>No benefit</td>
<td>Elomaa 1992</td>
</tr>
<tr>
<td>Mitox/Pred</td>
<td>204</td>
<td>No benefit</td>
<td>Ernst 2003, JCO</td>
</tr>
<tr>
<td>IV clodron</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Clodron</td>
<td>311</td>
<td>No significant benefit</td>
<td>Dearnaley 2003, JNCI</td>
</tr>
<tr>
<td>vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV Pamidronate</td>
<td>378</td>
<td>No benefit</td>
<td>Small 2003, JCO</td>
</tr>
<tr>
<td>vs placebo</td>
<td></td>
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</tr>
</tbody>
</table>
HRPC Prostate Cancer: Trial Design

Zoledronic acid q3wk

Placebo q3wk

0 15 months 24 months
Core analysis Final analysis

Saad et al. JNCI 2002;94:1458
Saad et al. JNCI 2004; 96:879
## Demographics
(All HRPC with poor prognosis patients)

<table>
<thead>
<tr>
<th></th>
<th>Zol 4 mg N = 214</th>
<th>Placebo N = 208</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>71.8</td>
<td>72.2</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>463</td>
<td>517</td>
</tr>
<tr>
<td>ECOG 0 - 1</td>
<td>92%</td>
<td>91%</td>
</tr>
<tr>
<td>Baseline PSA (mean)</td>
<td>277</td>
<td>211</td>
</tr>
<tr>
<td>Pain at entry</td>
<td>73%</td>
<td>73%</td>
</tr>
</tbody>
</table>

Saad et al. *JNCI* 2002;94:1458
Saad et al. *JNCI* 2004; 96:879
Significantly Fewer Patients with Bone Complications on study with Zoledronic Acid

P = 0.028

22% Reduction

Placebo (n=208)
Zoledronic acid (n=214)

### Results of Breast vs Prostate Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>SRE’s</th>
<th>Relative Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aredia 18</td>
<td>67 vs 56%</td>
<td>16%</td>
</tr>
<tr>
<td>Aredia 19</td>
<td>56 vs 43%</td>
<td>23%</td>
</tr>
<tr>
<td>Zoled 039</td>
<td>49 vs 38%</td>
<td>22%</td>
</tr>
</tbody>
</table>

IV Bisphosphonates are standard of care for metastatic breast cancer.
Proportion (%) of Patients With Each SRE

- Radiation to bone: Zoled acid 4 mg (N = 214) - 26%, Placebo (N = 208) - 33%
- Fractures: Zoled acid 4 mg (N = 214) - 17%, Placebo (N = 208) - 25%
- Spinal cord compression: Placebo (N = 208) - 8%
- Antineoplastic therapy: Placebo (N = 208) - 6%
- Surgery to bone: Placebo (N = 208) - 2%
- Hypercalcemia: Placebo (N = 208) - 1%

Saad et al. JNCI 2004; 96:879
**Delayed Time to First SRE by > 5 months**

- **ZOL 4 mg**: Median = 488 days, *P* value = .009
- **Placebo**: Median = 321 days

Percent without event

<table>
<thead>
<tr>
<th>Time, days*</th>
<th>ZOL 4 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>214</td>
<td>208</td>
</tr>
<tr>
<td>120</td>
<td>149</td>
<td>128</td>
</tr>
<tr>
<td>240</td>
<td>97</td>
<td>78</td>
</tr>
<tr>
<td>360</td>
<td>70</td>
<td>44</td>
</tr>
<tr>
<td>480</td>
<td>47</td>
<td>32</td>
</tr>
<tr>
<td>600</td>
<td>35</td>
<td>20</td>
</tr>
<tr>
<td>720</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Median = 167 days

Overall Risk of Developing a Bone Complication

Reduced by 35%

Cumulative expected Bone Complications (n) per 100 patients

- Placebo
- Zoledronic acid 4 mg

$P = 0.002$

Mean change from baseline in BPI pain score

Zoledronic acid 4 mg

Placebo

*p<0.05

Incidence of Radiation to Bone for Pain

Reduced by 33%

Cumulative incidence of radiotherapy (n) per 100 patients

Time since randomization, months

Placebo
4 mg Zoledronic acid

$P = 0.034$
Multiple Event Analysis (Excluding First SRE)

Decreased risk of developing a future SRE’s by 41%

Risk ratio (zoledronic acid 4 mg versus placebo)

Risk reduction

P value

0.587

41%

.005

Short and long term benefit

- No increase in adverse events with ZOL (4 mg q 3 - 4 weeks) up to 24 months

Is pamidronate an alternative in prostate cancer?
Pamidronate Compared With Zoledronic Acid
6 month analysis

Pamidronate

N = 378

Proportion with SRE, %

PAM 90 mg
Placebo

Total

Zoledronic acid

N = 422

P = .025

ZOL 4 mg
Placebo

Total

Urinary N-telopeptide/creatinine (Lytic)

- Pamidronate 90 mg
- Placebo
- Zoledronic acid 4 mg
- Placebo
Serum bone alkaline phosphatase (Blastic)

- Pamidronate 90 mg
- Placebo

- Zoledronic acid 4 mg
- Placebo
Is earlier better?
Efficacy according to pain at Baseline
Proportion of patients with SRE vs No SRE

Efficacy according to Pain at baseline
Mean annual incidence of SREs

- Patients with no pain at baseline:
  - Zoledronic acid 4 mg: 0.55
  - Placebo: 1.07
  - 49% relative reduction

- Patients with pain at baseline:
  - Zoledronic acid 4 mg: 0.88
  - Placebo: 1.45
  - 39% relative reduction

Early Bisphosphonate Treatment May Provide Greater Clinical Benefit to Patients With HSPC

HSPC, hormone-sensitive prostate cancer; HRPC, hormone-refractory prostate cancer; IV, intravenous; SRE, skeletal-related event.

NCIC/CALGB 90202: Study Design

Randomize

Double-Blinded

ADT + placebo q4w

ADT + zoledronic acid q4w

PD or SRE

Open-label

zoledronic acid q3w

zoledronic acid q3w
Why every 3-4 weeks?
Efficacy of Zoledronic Acid Has an Established 3-to 4-Week Dosing Schedule

- In patients with bone metastases, no alternative schedules have been shown to be effective in protecting patients from potentially debilitating SREs

Phase I pharmacodynamic study in cancer patients.
Change from baseline in bone resorption marker after single dose of zoledronic acid (4 mg).
Novartis data on file.
ZA Dosing Schedule correlates with Monthly Rate of Skeletal Complications

Recommended dosing schedule of ZA (every 3 to 4 weeks)

Nonrecommended dosing schedule of ZA

Untreated

Monthly Rate of Skeletal Complications

Adverse events
Incidence of Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Zoledronic acid 4 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 214; n (%)</td>
<td>n = 208; n (%)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>114 (53.3)</td>
<td>134 (64.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>82 (38.3)</td>
<td>81 (38.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>79 (36.9)</td>
<td>80 (38.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>75 (35.0)</td>
<td>56 (26.9)</td>
</tr>
<tr>
<td>Anemia</td>
<td>66 (30.8)</td>
<td>42 (20.2)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>56 (26.2)</td>
<td>42 (20.2)</td>
</tr>
<tr>
<td>Weakness</td>
<td>51 (23.8)</td>
<td>44 (21.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>50 (23.4)</td>
<td>47 (22.6)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>49 (22.9)</td>
<td>39 (18.8)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>46 (21.5)</td>
<td>31 (14.9)</td>
</tr>
<tr>
<td>Dizziness (except vertigo)</td>
<td>44 (20.6)</td>
<td>27 (13.0)</td>
</tr>
<tr>
<td>Edema lower limb</td>
<td>44 (20.6)</td>
<td>32 (15.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42 (19.6)</td>
<td>36 (17.3)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>41 (19.2)</td>
<td>28 (13.5)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>34 (15.9)</td>
<td>33 (15.9)</td>
</tr>
<tr>
<td>Appetite decrease</td>
<td>33 (15.4)</td>
<td>25 (12.0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>31 (14.5)</td>
<td>31 (14.9)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>25 (11.7)</td>
<td>39 (18.8)</td>
</tr>
</tbody>
</table>

*Regardless of study drug relationship.

Renal function (serum creatinine increase)

Patients without increase, %

Time, days*

- **Zoledronic acid 4 mg**
- **Placebo**

<table>
<thead>
<tr>
<th>Patients without increase, %</th>
<th>100</th>
<th>90</th>
<th>80</th>
<th>70</th>
<th>60</th>
<th>50</th>
<th>40</th>
<th>30</th>
<th>20</th>
<th>10</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid 4 mg</td>
<td></td>
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<td></td>
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<tr>
<td>Placebo</td>
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</table>

Hazard ratio | 1.137 |
P value      | 0.752 |

*After start of study drug.
Saad et al. JNCI 2004.
Osteonecrosis of the Jaw: Background

- Spontaneous reports primarily in patients with advanced malignancies and skeletal metastases
  - Less than 1% in prostate cancer

- Etiology and pathogenesis poorly characterized

- Relative contribution of multiple factors?
  - Underlying cancer and cancer treatment
  - Dental pathology and procedures (eg, extractions)
  - Infections
  - Local ischemia
  - Bisphosphonates
Prevention and Management of ONJ

- Prior to treatment with bisphosphonates
  - Dental exam with appropriate preventive dentistry

- During treatment
  - Avoid invasive dental procedures if possible

- In case of ONJ
  - Conservative management
  - Stop bisphosphonate?
Can Bone targeted therapy improve survival?
ZOL Has Antitumor Activity in In Vitro and Animal Models of Human Prostate Cancer

- Proliferation and viability\(^1,2\)
- PC tumor growth and PSA levels in mice\(^3\)
- Efficacy of other anticancer therapies\(^4\) (cytostatics, steroids, radiation)
- Cell adhesion and matrix invasion\(^5,6\)
- Prostate vascularization in response to testosterone\(^7\)

Zoledronic Acid increased overall Survival by 2.6 months

Fractures and Survival

Pathologic fractures increase risk of death by 29%

Risk increase | P value
--- | ---
29% | .04

Hazard ratio (patients)

Saad et al. Cancer 2007
Evaualting Risk
Prognostic Implications of Bone Markers
Relative Risks in Prostate Cancer (Placebo)

- Ntx 50 - 100 nmol/mmol creatinine
- Ntx ≥ 100 nmol/mmol creatinine
- BAP ≥ 146 IU/L

Relative risk (versus lowest marker category)

- All SRE
  - Ntx 50 - 100 nmol/mmol creatinine: 3.82
  - Ntx ≥ 100 nmol/mmol creatinine: 3.25
  - BAP ≥ 146 IU/L: 3.03

- First SRE
  - Ntx 50 - 100 nmol/mmol creatinine: 4.31
  - Ntx ≥ 100 nmol/mmol creatinine: 3.05
  - BAP ≥ 146 IU/L: 3.10

- Death
  - Ntx 50 - 100 nmol/mmol creatinine: 2.65
  - Ntx ≥ 100 nmol/mmol creatinine: 4.59
  - BAP ≥ 146 IU/L: 3.19

P-values:
- <.001
- <.001
- .003

Percent Change From Baseline NTX

Exploratory Study Design

HRPC = Hormone-refractory prostate cancer; NTX = N-telopeptide of type I collagen; ZOL = Zoledronic acid; E = Elevated NTX; N = Normal NTX.

Normalization of NTX Levels vs Clinical Outcomes

Among Patients With High NTX at Baseline

- **First SRE**: Risk reduction 38%, P value .0411
- **Death**: Risk reduction 59%, P value < .0001

In favor of normalized NTX
In favor of persistently elevated NTX

Saad et al. ASCO G-U 2007
NTX Normalization Correlated With Improved Survival Versus Persistently Elevated NTX

59% ↓ risk of death vs persistent NTX elevation at 3 m

ZOL = Zoledronic acid; NTX = N-telopeptide of type I collagen; E = Elevated NTX; N = Normal NTX; RR = Relative risk.
Continuum of Survival Benefit by Percentage Reduction From Baseline NTX Within 3 Months of Zoledronic Acid

NTX correlated with risk of death

Patients with NTX decrease ≤ corresponding x-axis value

5 15 25 35 45 65 85 95

Relative risk of death

NTX decrease from baseline,* %

Median baseline NTX
(125 nmol/mmol creatinine)

NTX = N-telopeptide of type I collagen; BL = Baseline. High NTX = NTX > 64 nmol/mmol creatinine.
*Calculated as ([Baseline NTX minus 3-month NTX] / baseline NTX) × 100.
Continuum of Survival by Percentage Change From Baseline NTX in Placebo Group

- NTX ↑ correlated with ↑ risk of death

*Calculated as ((Baseline NTX minus 3-month NTX) / baseline NTX) × 100.
NTX = N-telopeptide of type I collagen; BL = Baseline. All patients in this analysis had baseline NTX > 64 nmol/mmol creatinine.
Guidelines
Guidelines

- All known guidelines (NCCN, EAU, BAUS, ICUD, CCO and others) recommend the use of bisphosphonates (zoledronic acid) in the presence of Bone Mets in prostate cancer
NCCN Guidelines for Patient Management
Advanced Prostate Cancer

**SYSTEMIC THERAPY**

Disseminated disease

- Orchietomy or LHRH agonist alone ± antiandrogen for ≥ 7 d for testosterone flare or LHRH agonist + antiandrogen → Relapse

Blastic bone and/or other metastases and rising PSA

- Discontinue antiandrogen

**SYSTEMIC SALVAGE THERAPY**

- Antianogren or Second-line hormonal therapy: ketoconazole ± glucocorticoids, or estrogens → Relapse

Clinical assessment

- Systemic chemotherapy (docetaxel-based preferred) or Supportive care or Systemic RT: samarium or strontium and Bisphosphonate treatment for prevention of skeletal-related events should be considered

**Visceral or lytic bone metastasis and low PSA or Rapidly progressing soft tissue masses**

- Biopsy

  - Not neuroendocrine (with or without small cell features)
  - Neuroendocrine (with or without small cell features)

  → Follow above pathway for blastic bone and/or other metastases

  - Cisplatin/etoposide or Carboplatin/etoposide

*Assure castrate level of testosterone.

*See Principles of Hormonal Therapy (PROS-G).

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**Note:** All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## Bone Targeted Therapies Under Investigation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti RANKL antibody</td>
<td>Denosumab</td>
</tr>
<tr>
<td>Endothelin receptor inhibitor</td>
<td>ZD4054</td>
</tr>
<tr>
<td>TGF beta kinase inhibitors (Ki26894)</td>
<td>Ki26894</td>
</tr>
<tr>
<td>Integrin inhibitors</td>
<td>L-000845704</td>
</tr>
<tr>
<td>Cathepsin K inhibitors</td>
<td>SB-462795 (relacatib) and AAE-581 (balicatib)</td>
</tr>
<tr>
<td>Src inhibitors</td>
<td>AZD0530</td>
</tr>
<tr>
<td>Stimulate Wnt pathway</td>
<td>Anti-DKK1/Sclerostin antagonist</td>
</tr>
</tbody>
</table>
My approach to Bone Health

- Early treatment in patients with metastatic HRPC

- Consider zoledronic acid in patients with metastatic HSPC
  - If significant bone mets
  - Pain or SRE at presentation
  - PSA reduction is not below 4 after 6 m of ADT

- Actively screen for bone mets in patients at risk

- BMD at start of ADT and repeat every 1 to 2 years
  - Calcium and Vitamin D
  - BP in patients with osteoporosis
  - BP in osteopenia with risk factors
Guidelines for Advanced Prostate Cancer

- No metastases
  - Progression on ADT
    - Consider 2nd Line Hormones
      - Bone Metastases
        - Asymptomatic Disease
          - Zoledronic Acid and consider Docetaxel
        - Symptomatic Disease
          - Zoledronic and Docetaxel (1st choice) Or Mitoxantrone
      - Evaluate for mets q 6-12 months
        - Slow PSADT
        - Rapid PSADT
      - Evaluate for mets q 3-6 months
      - Radiation, Radioisotopes Supportive care as needed
    - Progression (Rising PSA)
      - Supportive care as needed
  - Clinical trials should be considered whenever possible

*Saad et al. CJU 2006*
A few words about RCC
RCC Patient With Extensive Bone Metastases

- 58-year-old man with RCC 5-cm mass on left kidney
  - Retroperitoneal nodes affected
  - 2 nodules detected on left lower pulmonary lobe
- the patient had extensive bone disease

RCC, renal cell carcinoma.

Image courtesy of Ron Bukowski, Cleveland Clinic.
Placebo-Controlled Trial (011)

Trial Design

- **Zoledronic acid 4 mg q 3 weeks**
  - + Daily oral vitamin D 400 IU and calcium 500 mg
  - \( n = 257 \)

- **Placebo q 3 weeks**
  - + Daily oral vitamin D 400 IU and calcium 500 mg
  - \( n = 250 \)

Patients were randomized to 4 or 8 mg zoledronic acid. Results are not shown for patients randomized to 8 mg.

Zoledronic Acid Significantly Reduced the Proportion of RCC Patients With an SRE

RCC, renal cell carcinoma; SRE, skeletal-related event.

Zoledronic Acid Significantly Delays Time to First SRE in Patients With RCC

### Graph

- **Patients without event, %**
- **Days after start of study drug**
- **Median, days**
- **P value**

<table>
<thead>
<tr>
<th></th>
<th>ZOL (4 mg)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>424 days</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **ZOL (4 mg)**: 27 12 7 4 2 1
- **Placebo**: 19 4 1 1 0 0

### Median, days

- **ZOL (4 mg)**: 424
- **Placebo**: 72

### P value

- **ZOL (4 mg)**: 0.007
- **Placebo**: 1

### Table

<table>
<thead>
<tr>
<th></th>
<th>ZOL (4 mg)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>352 days</td>
<td>1</td>
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</table>

**RCC**, renal cell carcinoma; **ZOL**, zoledronic acid.

Zoledronic Acid Significantly Extends the Time to Bone Disease Progression in Patients With RCC

Zoledronic Acid Significantly Extends the Time to Bone Disease Progression in Patients With RCC

RCC, renal cell carcinoma; ZOL, zoledronic acid.

ZOL Demonstrated Improved Survival in RCC Patients

\[ P = .104 \]

\[ \sim 37\% \text{ increase} \]
RCC Patient with Extensive Bone Metastases

- Combination of chemotherapy and ZOL lowered disease burden in bone

Image courtesy of Ron Bukowski, Cleveland Clinic.
Case Study 1—Resolution of Spinal Deterioration

Pre-treatment After 5 cycles targeted therapy and ZOL 4 mg/mo

Patient did not require palliative radiotherapy to spine and did not develop spinal cord compression
Summary/Conclusions

- ADT Bone loss increases risk of fractures
- Bone mets associated with morbidity
- Fractures associated with worse survival
- Early therapy is more beneficial
- Bone markers appear useful in predicting outcome
Conclusions

- Zoledronic acid is presently the only effective bone targeted therapy in patients with metastatic Prostate Cancer and RCC

↓

- Intense Research ongoing
  - Prevention
  - Combination
  - Markers