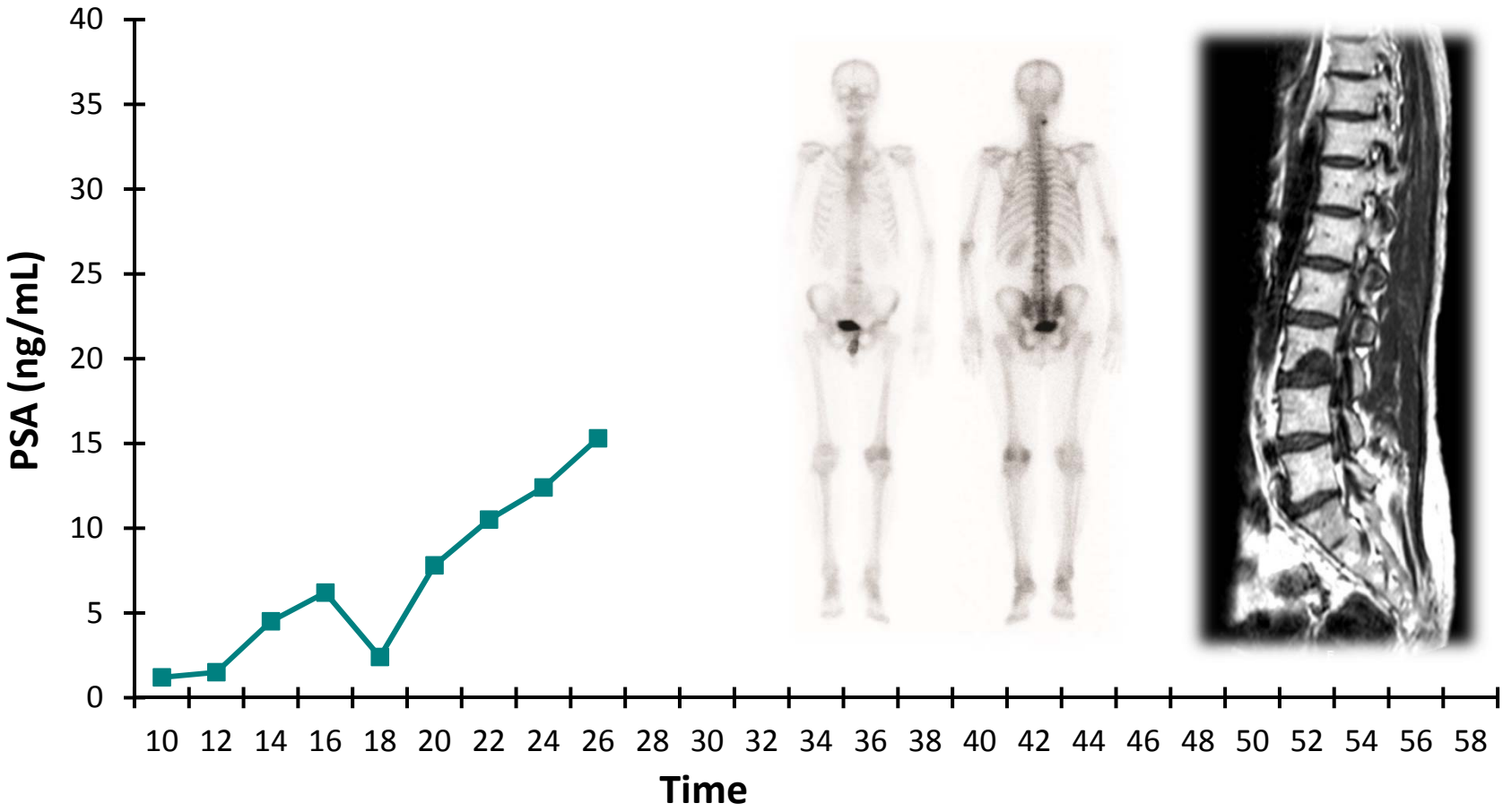
CME accredited educational module

# Metastatic castration-resistant prostate cancer (mCRPC)

Mirrors of medicine

PHNL/ZYT/0115/0002(1)

# What is castration resistance?




Data and images provided by B.Tombal & F.Lecouvet, Clinique Universitaires Saint-Luc, Belgium

# What is castration resistance?

**Castration resistance is defined as cancer progression***
**in a patient that is effectively castrated** (testosterone<1.7nmol/L)

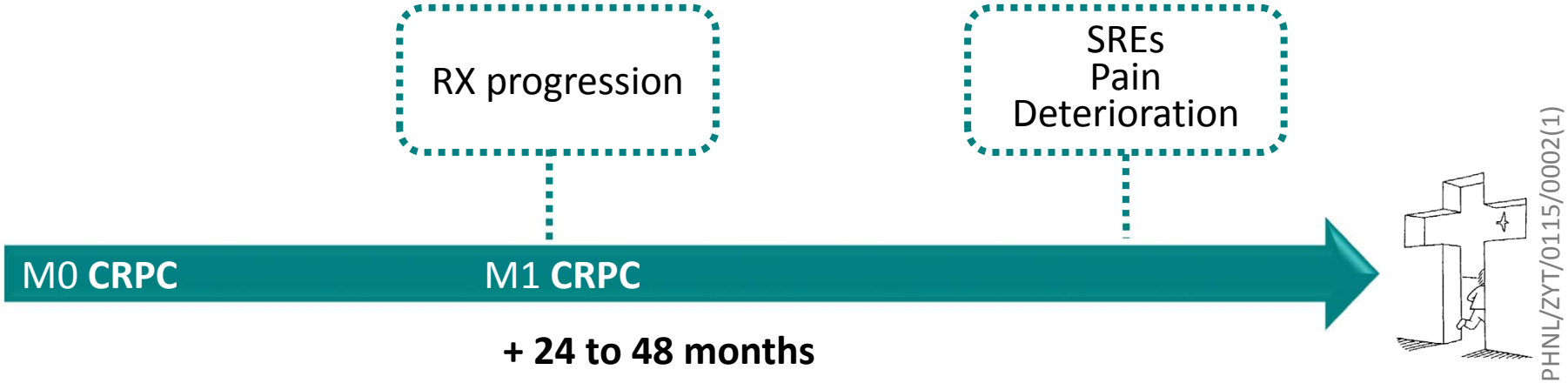
- First sign: often an isolated PSA rise
- First metastatic site: axial skeleton
- Most important morbidity: skeletal complications

*- Biochemical progression: 3 consecutive rises in PSA, 1 week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL or,
- Radiological progression: appearance of new lesions: either ≥2 new bone lesions on bone scan or a soft tissue lesion using RECIST
- Symptomatic progression alone must be questioned
  Should be further investigated
  Not sufficient to diagnose CRPC

Data and images provided by B.Tombal & F.Lecouvet, Clinique Universitaires Saint-Luc, Belgium
Mottet N, Bellmunt J, Briers E, et al. Guidelines on prostate cancer. European Association of Urology 2016

# The treatment of mCRPC

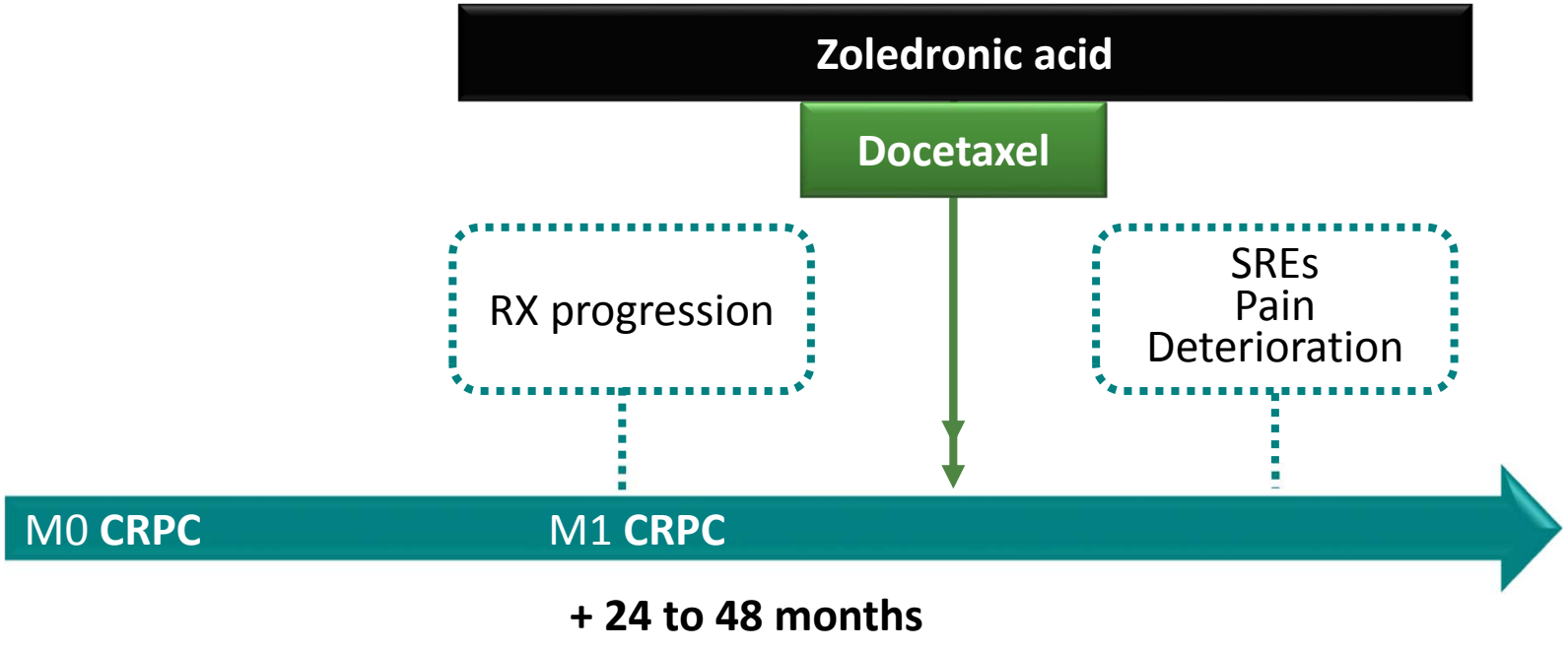
- The goals of the treatment are:
  - To improve disease-specific survival
  - To improve overall survival
  - To delay disease-related symptoms




M0: non-metastatic; M1: metastatic; RX: radiological; SREs: skeletal-related events

# The treatment of mCRPC – 2004

- The goals of the treatment are:
  - To improve disease-specific survival
  - To improve overall survival
  - To delay disease-related symptoms






Tannock IF et al. N Engl J Med 2004;351:1502-12

*M0: non-metastatic; M1: metastatic; RX: radiological; SREs: skeletal-related events*

# A portfolio of newly approved drugs…

| Agent | Comparator | Pre- or post-docetaxel | Change in OS (median, mo) | HR (95% CI; P value) |
|---|---|---|---|---|
| Abiraterone*[1] | Placebo* | Post- | 4.6 | 0.74 (0.64–0.86; *P*<0.001) |
| Abiraterone*[2] | Placebo* | Pre- | 4.4 | 0.81 (0.70-0.93; *P*=0.0033) |
| Cabazitaxel*[3] | Mitoxantrone* | Post- | 2.4 | 0.70 (0.59–0.83; *P*<0.0001) |
| Docetaxel*[4] | Mitoxantrone* | N/A | 2.9 | 0.76 (0.62–0.94; *P*=0.009) |
| Enzalutamide[5] | Placebo | Post- | 4.8 | 0.63 (0.53–0.75; *P*<0.001) |
| Enzalutamide[6] | Placebo | Pre- | 4.0 | 0.77 (0.67-0.88; *P*<0.0001) |
| Radium-223[7] | Placebo | Pre- and Post- | 3.6 | 0.70 (0.58–0.83; *P*<0.001) |
| Sipuleucel-T[8] | Placebo | Pre- | 4.1 | 0.78 (0.61–0.98; *P*=0.03) |


1. Fizazi K et al. Lancet Oncol 2012;13:983–92
2. Ryan CJ et al. Lancet Oncol 2015;16:152-60
3. de Bono JS et al. Lancet 2010;376:1147–54
4. Tannock IF et al. N Eng J Med 2004;351:1502–12
5. Scher HI et al. N Engl J Med 2012;367:1187–97
6. Beer TM et al. Eur Urol 2016 pii: S0302-2838(16)30437-7
7. Parker C et al. N Engl J Med 2013;369:213-23
8. Kantoff PW et al. N Engl J Med 2010;363:411–22


*CI: confidence interval; HR: hazard ratio; OS: overall survival; RR: relative reduction; *: administered with prednisone*



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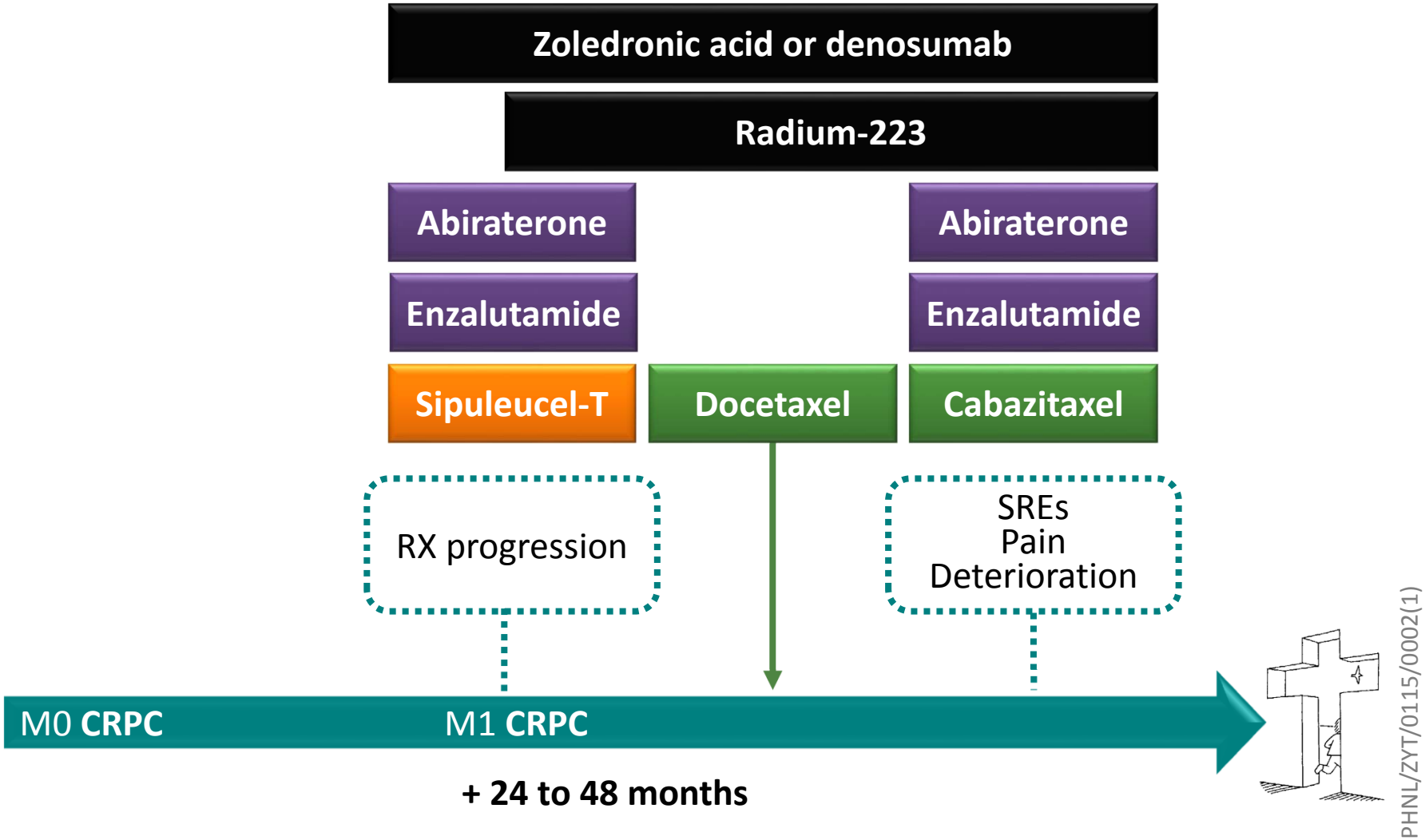
# The treatment of mCRPC – 2017

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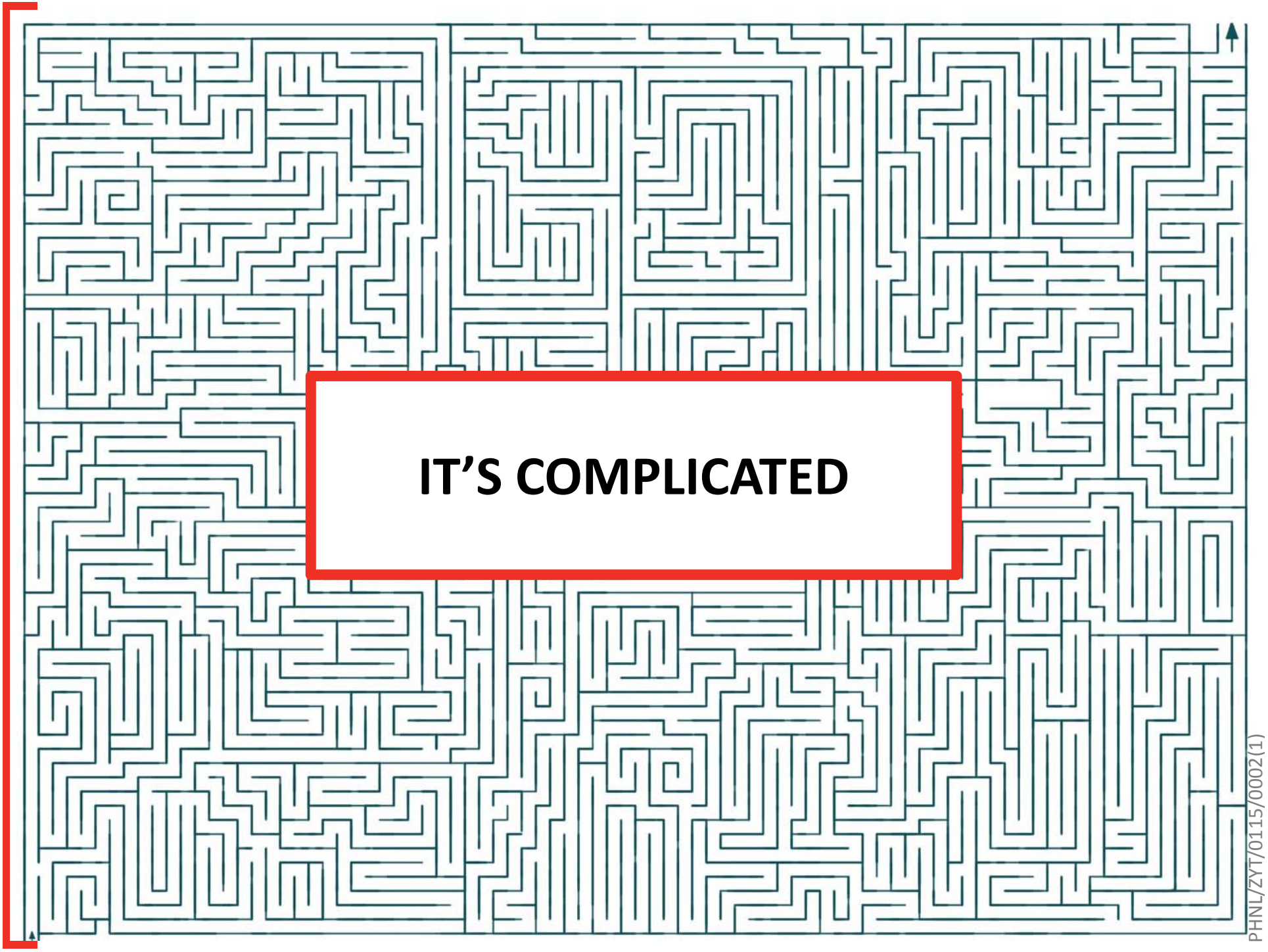
*M0: non-metastatic; M1: metastatic; RX: radiological; SREs: skeletal-related events*


IT'S COMPLICATED
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# We are different

- The patient population is highly heterogeneous
  - Even in the late stage of the disease

- We must learn to give the right drug to the right patient

# Clinical variables

**Previous treatment and response**

| | |
|---|---|
| No previous CRPC treatment | |
| AR, primary resistant | AR, secondary progressive |
| Docetaxel, primary resistant | Docetaxel, secondary progressive |

**Metastases**

| | | | |
|---|---|---|---|
| Bone only | LN+ only | Bone plus LN+ | Bone + visceral ± LN+ |

**Pain due to metastases**

| | |
|---|---|
| No (BPI ≤ 3) | Yes (BPI > 3) |

**Performance status**

| | |
|---|---|
| Good (WHO score 0-1) | Poor (WHO score = 2) |

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* a treatment coupled with a response represents a category (e.g. no response or rapid progression after docetaxel)
*WHO: World Health Organization*

# Performance status: definition in model

- WHO score:
  - **0 Asymptomatic**
    - Fully active, able to carry on all pre-disease activities without restriction
  - **1 Symptomatic but completely ambulatory**
    - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature

GOOD

  - **2 Symptomatic, <50% in bed during the day**
    - Ambulatory and capable of all self care but unable to carry out any work activities; up and about more than 50% of waking hours

POOR

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*WHO: World Health Organization*

# Patient case 1

# Patient profile:
## a rising PSA on ADT+RT

- Mark, 73 years old, retired hairdresser
  - Mild hypertension, well-controlled
- Diagnosed with PCa at the age of 71
  - cT3 N1 M0, Gleason sum 7
- Treated by ADT and radiotherapy
  - Ongoing for 26 months, planned for 3 years
- Consults regarding moderate back pain (no analgesics used)
  - PSA: 112 ng/mL
  - Bone scan: 2 bone metastases
  - CT scan: no visceral metastases

**What would be the most appropriate treatment for this patient?**

*PCa: prostate cancer, ADT: androgen-deprivation therapy; PSA: prostate-specific antigen; CT: computed tomography*

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# Clinical variables

**Previous treatment and response**

| No previous CRPC treatment | |
|---|---|
| AR, primary resistant | AR, secondary progressive |
| Docetaxel, primary resistant | Docetaxel, secondary progressive |

**Metastases**

| Bone only | LN+ only | Bone plus LN+ | Bone + visceral ± LN+ |
|---|---|---|---|

**Pain due to metastases**

| No (BPI ≤ 3) | Yes (BPI > 3) |
|---|---|

**Performance status**

| Good (WHO score 0-1) | Poor (WHO score = 2) |
|---|---|

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*WHO: World Health Organization*

# Multidisciplinary discussion

- Which data drives your treatment choice?
- Which data are you missing for your treatment choice?

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Stemronde geopend

# Treatment options?

1. Watchful waiting
2. Abiraterone
3. Enzalutamide
4. Docetaxel
5. Cabazitaxel
6. Radium-223
7. Zoledronic acid
8. Denosumab

# What do the Mirrors of Medicin (MoM) experts recommend?

Previous treatment and response

**No previous CRPC treatment**

Metastases

**Bone only**

Pain due to metastases

**Yes (BPI > 3)**

Performance status

**Good (WHO score 0-1)**

For this profile the available choices are:

- + AR-pathway inhibitor
- + Chemotherapy (docetaxel)
- + Chemotherapy (cabazitaxel)
- + Radium therapy
- + Bone-targeted treatment

# Would AR axis inhibition be a valid treatment option?

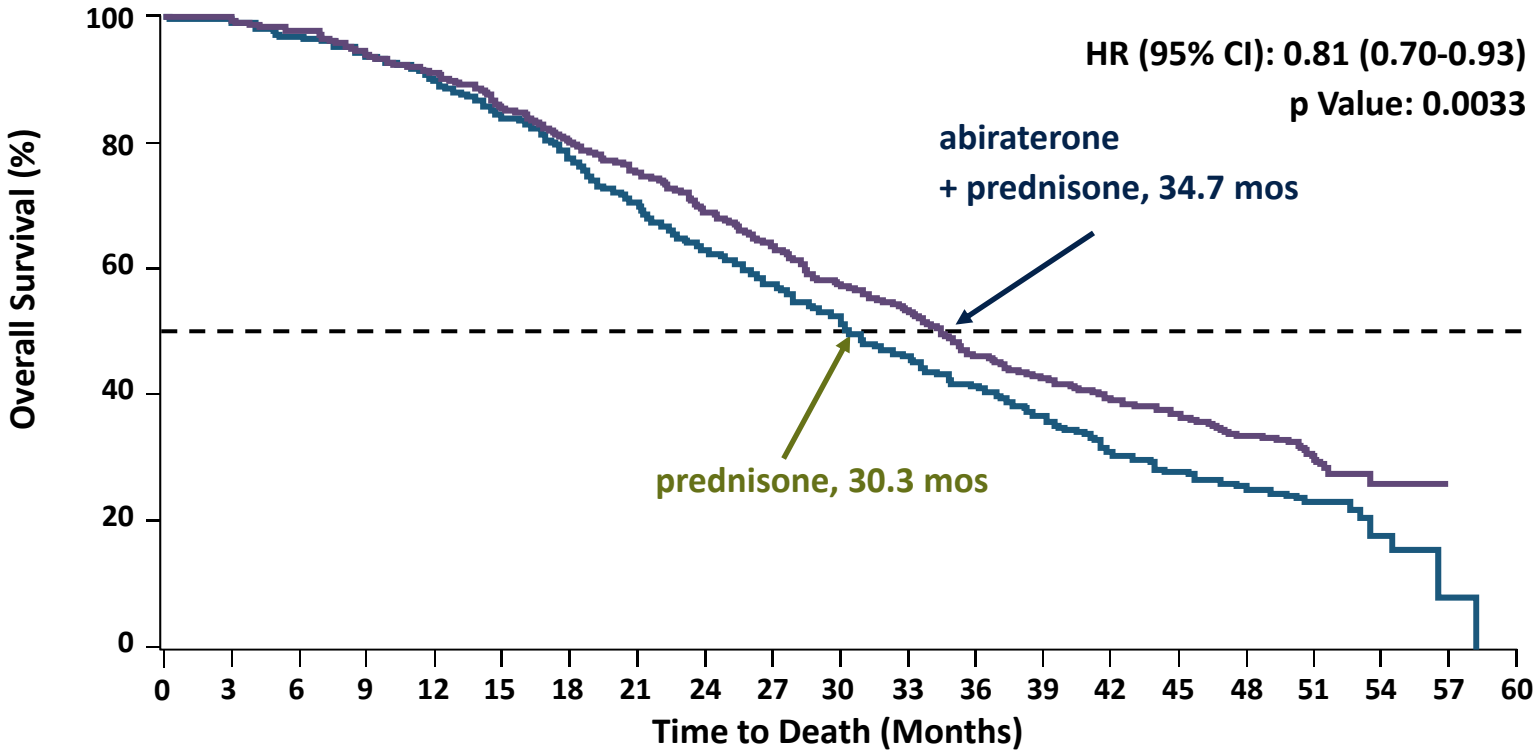
- AR-pathway inhibitor Hide evidence

Appropriate

**Panel considerations**

The panel considered an AR-pathway inhibitor (abiraterone or enzalutamide) to be an appropriate option for almost all patients without previous treatment for CRPC.

# Final OS Analysis COU-AA-302

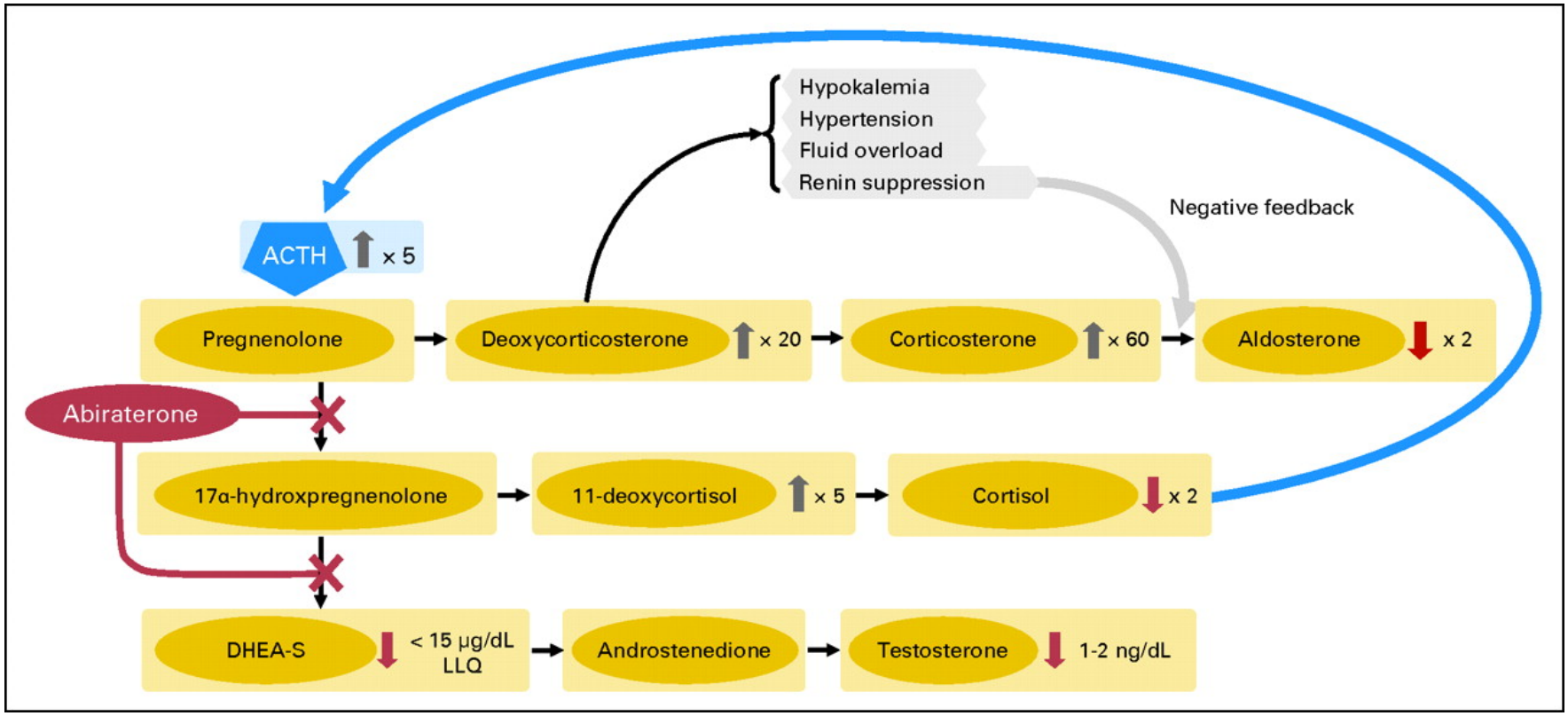



| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abiraterone | 546 | 538 | 525 | 504 | 483 | 453 | 422 | 394 | 359 | 330 | 296 | 273 | 235 | 218 | 202 | 189 | 118 | 59 | 15 | 0 | 0 |
| Prednisone | 542 | 534 | 509 | 493 | 466 | 438 | 401 | 363 | 322 | 292 | 261 | 227 | 201 | 176 | 148 | 132 | 84 | 42 | 10 | 1 | 0 |

- Median follow-up of 49.2 mos
- Abiraterone treatment effect more pronounced when adjusting for 44% of prednisone patients who received abiraterone after crossing over (HR = 0.74)

Ryan CJ et al. Lancet Oncology 2015; 16(2): 152-60
OS: overall survival

# Effects of abiraterone acetate on cortisol biosynthesis




Ryan et al. JCO 2010;28:1481-1488

# What is the underlying evidence related to abiraterone?

| Endpoint (median, months) | Abiraterone + P (N=546) | Prednison (N=542) | HR | *P* |
|---|---|---|---|---|
| rPFS | 16.5 | 8.2 | 0.52 | <0.001 |
| Time to chemotherapy | 25.2 | 16.8 | 0.58 | <0.001 |
| Time to decline in PS | 12.3 | 10.9 | 0.82 | 0.005 |
| Time to PSA progression | 11.1 | 5.6 | 0.49 | <0.001 |
| Time to opiate use | 33.4 | 23.4 | 0.72 | <0.0001 |

- COU-AA-302 trial
- N=1,088 mCRPC asymptomatic/mildly symptomatic patients
  - chemo-naïve, progressing on anti-androgen therapy
  - no known brain or visceral metastases

**Abiraterone significantly increased OS, rPFS, time to initiation of chemotherapy, time to deterioration of PS, time to PSA progression and time to opiate use in asymptomatic and minimally symptomatic patients with mCRPC**

Ryan CJ et al. N Engl J Med 2013;368:138-48, Ryan CJ et al. Lancet Oncology 2015; 16(2): 152-60

*rPFS: radiographic progression-free survival; PS: performance status, PSA: prostate-specific antigen; HR: hazard ratio*

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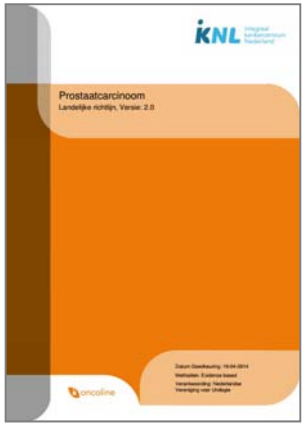
# What do guidelines say regarding abiraterone?

- **EAU 2016**
  - Treat patients with mCRPC with life-prolonging agents
  - Base the choice of first line treatment on the performance status, symptoms, comorbidities and extent of disease (alphabetical order: **abiraterone**, docetaxel, enzalutamide, radium-223, sipuleucel-T)
  - No definitive strategy regarding treatment choice (which drug/drug family first) can be devised
- **NCCN 2016**
  - **Abiraterone** is recommended with prednisone for men with mCRPC
    - Category 1 for men without visceral disease
    - Category 2A for men with visceral disease
- **ESMO 2015**
  - **Abiraterone** is recommended for asymptomatic/mildly symptomatic men with chemotherapy-naïve metastatic CRPC

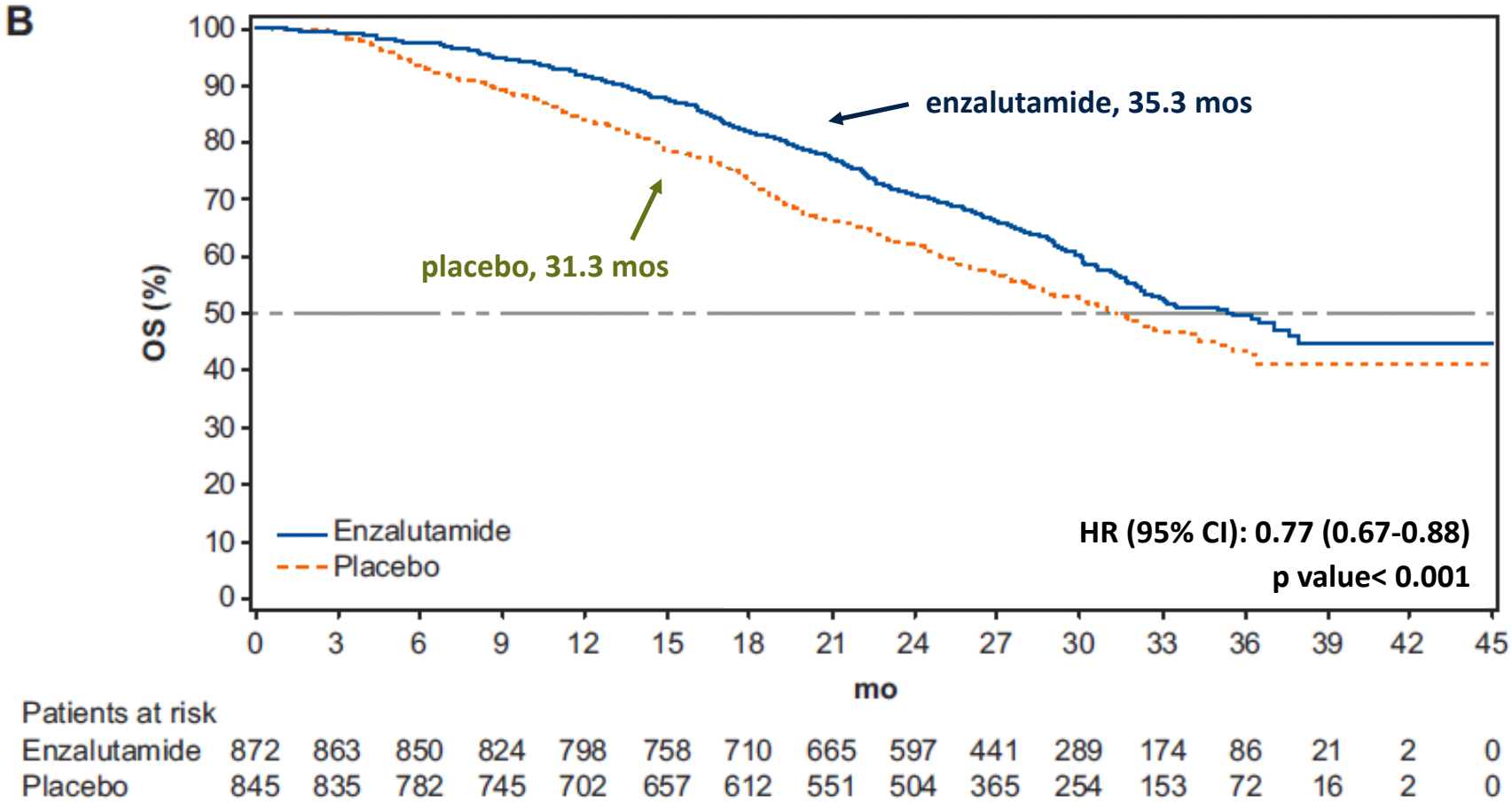
Category 1: based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A: based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate

# Wat zegt de NVU richtlijn (2016) over abiraterone en enzalutamide?

- Indien er sprake is van een progressief mCRPC bij een patiënt die ‘chemo-fit’ is, dan is docetaxel 75 mg/m2 plus prednison 5 mg bid iedere 3 weken maximaal 10 kuren een behandeloptie.
- Daarnaast dienen ook - voor behandeling van asymptomatisch of licht symptomatisch mCRPC - **abiraterone** 1000 mg plus prednison 5 mg bid en **enzalutamide** 160 mg of - bij symptomatische skeletmetastasering zonder bekende viscerale metastasen - radium-223 (6 injecties gegeven met intervallen van 4 weken) overwogen te worden.
- Bij patiënten met een progressief mCRPC die niet ‘chemo-fit’ zijn of om andere redenen niet aan chemotherapie toekomen, zijn alleen **abiraterone** 1000 mg plus prednison 5 mg bid en **enzalutamide** 160 mg of (indien geen viscerale metastasen) radium-223 (6 injecties gegeven met intervallen van 4 weken) een behandeloptie, afhankelijk van de symptomatologie en beeldvorming.
- De patiënt dient in een MDO te worden besproken, evenals beste timing en uiteindelijke keuze van de therapie.



# OS Analysis PREVAIL




- Median follow-up of 31 mos

Beer TM et al. Eur Urol 2016 pii: S0302-2838(16)30437-7
OS: overall survival

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# What is the underlying evidence related to enzalutamide?

| Endpoint (median, months) | Enzalutamide (N=872) | Placebo (N=845) | HR | *P* |
|---|---|---|---|---|
| rPFS | 20.0 | 5.4 | 0.32 | <0.0001 |
| Time to chemotherapy | 28.0 | 10.8 | 0.35 | <0.0001 |
| Time to decline in PS | 11.3 | 5.6 | 0.625 | 0.005 |
| Time to PSA progression | 11.2 | 2.8 | 0.169 | <0.0001 |

- PREVAIL trial
- N=1,717 mCRPC asymptomatic/mildly symptomatic patients
  - chemo-naïve, progressing on ADT

**Enzalutamide significantly increased OS, rPFS, time to initiation of chemotherapy, time to deterioration of PS and time to PSA progression in asymptomatic and minimally symptomatic patients with mCRPC**

*Beer et al. N Engl J Med. 2014 Jul 31;371(5):424-33, Beer et al. Eur Urology 2016 Jul S0302-2838 (16)30437-7*
*rPFS: radiographic progression-free survival; PS: performance status, PSA: prostate-specific antigen; HR: hazard ratio*

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# What do guidelines say regarding enzalutamide?

- **EAU 2016**
  - Treat patients with mCRPC with life prolonging agents
  - Base the choice of first line treatment on the performance status, symptoms, comorbidities and extent of disease (alphabetical order: abiraterone, docetaxel, **enzalutamide**, radium-223, sipuleucel-T)
  - No definitive strategy regarding treatment choice (which drug/drug family first) can be devised
- **NCCN 2016**
  - Use of **enzalutamide** in the setting of mCRPC prior to docetaxel chemotherapy is a category 1 recommendation
- **ESMO 2015**
  - **Enzalutamide** is recommended for asymptomatic/mildly symptomatic men with chemotherapy-naïve metastatic CRPC

Category 1: based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A: based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate

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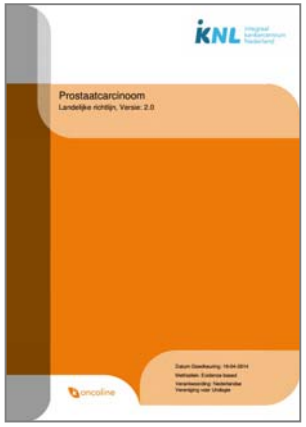
# Wat zegt de NVU richtlijn over abiraterone en enzalutamide?

- Indien er sprake is van een progressief mCRPC bij een patiënt die ‘chemo-fit’ is, dan is docetaxel 75 mg/m2 plus prednison 5 mg bid iedere 3 weken maximaal 10 kuren een behandeloptie.
- Daarnaast dienen ook - voor behandeling van asymptomatisch of licht symptomatisch mCRPC - **abiraterone** 1000 mg plus prednison 5 mg bid en **enzalutamide** 160 mg of - bij symptomatische skeletmetastasering zonder bekende viscerale metastasen - radium-223 (6 injecties gegeven met intervallen van 4 weken) overwogen te worden.
- Bij patiënten met een progressief mCRPC die niet ‘chemo-fit’ zijn of om andere redenen niet aan chemotherapie toekomen, zijn alleen **abiraterone** 1000 mg plus prednison 5 mg bid en **enzalutamide** 160 mg of (indien geen viscerale metastasen) radium-223 (6 injecties gegeven met intervallen van 4 weken) een behandeloptie, afhankelijk van de symptomatologie en beeldvorming.
- De patiënt dient in een MDO te worden besproken, evenals beste timing en uiteindelijke keuze van de therapie



# Would docetaxel be a valid treatment option?

## – Chemotherapy (docetaxel)

Hide evidence

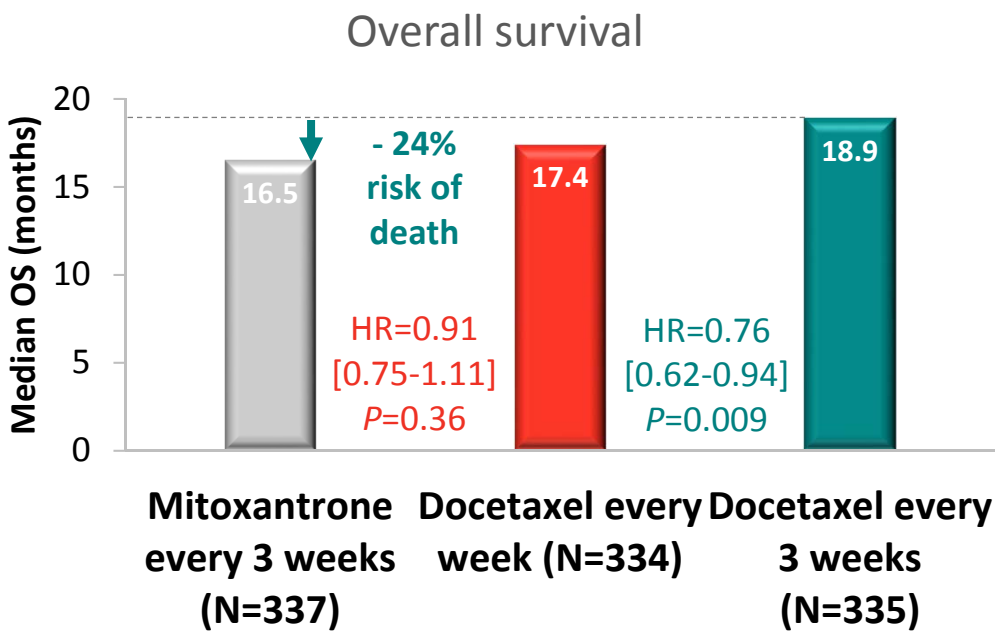
Appropriate

### Panel considerations

The panel considered chemotherapy with docetaxel to be an appropriate option for most patients without previous treatment for CRPC.

# What is the underlying evidence related to docetaxel?

- TAX 327 trial
- N=1,006 mCRPC patients
  - progressive PCa
  - chemo-naïve
  - no brain metastases




**Docetaxel (every 3 weeks) significantly prolonged OS vs. mitoxantrone in chemo-naïve patients with mCRPC, progressing on ADT**

Tannock IF et al. N Engl J Med 2004;351:1502-12

# What do guidelines say regarding docetaxel?

- **EAU 2016**
  - Treat patients with mCRPC with life prolonging agents
  - Base the choice of first line treatment on the performance status, symptoms, comorbidities and extent of disease (alphabetical order: abiraterone, **docetaxel**, enzalutamide, radium-223, sipuleucel-T)
  - No definitive strategy regarding treatment choice (which drug/drug family first) can be devised
  - In patients with metastatic CRPC and who are candidates for cytotoxic therapy, **docetaxel** 75 mg/m$^2$ every 3 weeks should be offered
- **NCCN 2016**
  - **Docetaxel** + prednisone is recommended for men with mCRPC
  - Most asymptomatic mCRPC patients are not treated with docetaxel, but it may be considered in asymptomatic patients with signs of rapid progression or visceral metastases
- **ESMO 2015**
  - **Docetaxel** chemotherapy is recommended for men with metastatic CRPC

*mCRPC: metastatic castration-resistant prostate cancer; PS: performance status*

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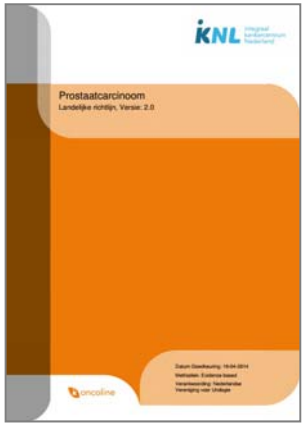
# Wat zegt de NVU richtlijn over docetaxel?

- Indien er sprake is van een progressief mCRPC bij een patiënt die ‘chemo-fit’ is, dan is **docetaxel** 75 mg/m$^2$ plus prednison 5 mg bid iedere 3 weken maximaal 10 kuren een behandeloptie.
- De patiënt dient in een MDO te worden besproken, evenals beste timing en uiteindelijke keuze van de therapie.



# What about the sequence of therapies?

- No strong clinical data to provide evidence-based guidance for the order in which taxanes and AR axis inhibitors are given[1,2].
- There is an urgent need for new clinical trials to provide critical insight into the optimal timing and sequence for the treatment of men with mCRPC[1,2]

- NCCN 2016
  - No data informs the proper sequence for delivery of these agents in men with CRPC.
  - No predictive models or biomarkers help to identify patients who are likely to benefit from any of these agents



[1] Loriot Y et al. Eur Urol 2014
[2] Fitzpatrick JM and De Wit R. Eur Urol 2014;65:1198-1204

# Would radium-223 be a valid treatment option?

– Radium therapy Hide evidence

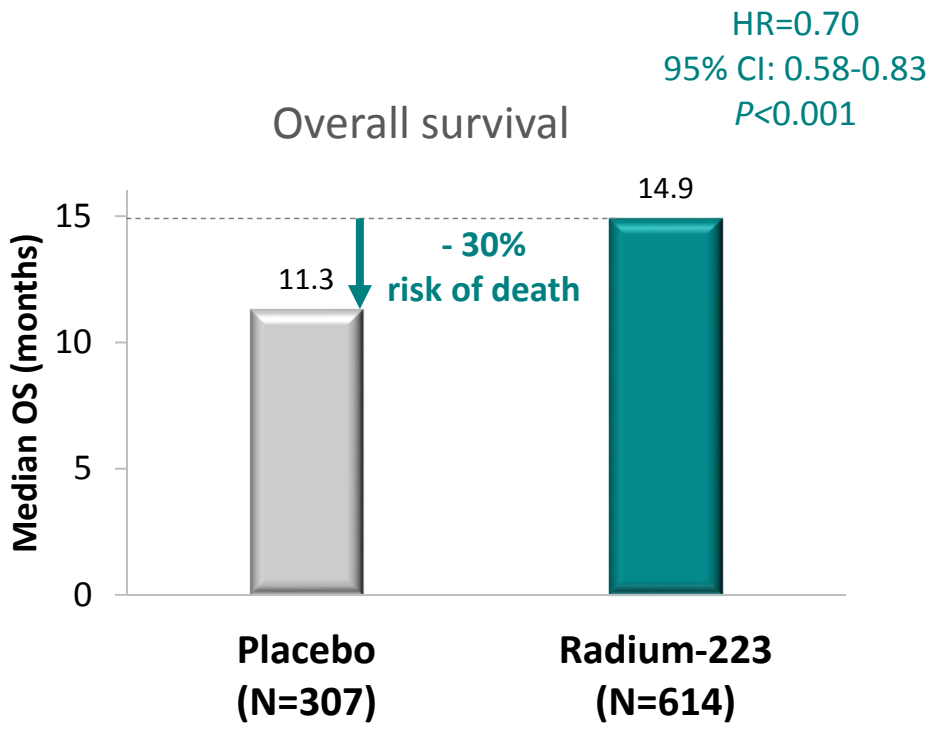
Appropriate

**Panel considerations**

Similar to the approved EMA indication, the panel considered radium therapy (radium-223) to be an appropriate option for patients with symptomatic bone metastases and no known visceral disease.

# What is the underlying evidence related to radium-223?

- ALSYMPCA trial
- N=921 mCRPC patients
  - symptomatic
  - ≥2 bone metastases
  - no visceral metastases
  - 43% of patients with no prior use of docetaxel




**Radium-223 significantly improved OS vs. placebo in patients with CRPC, symptomatic bone metastases and no known visceral metastases**

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Parker C et al. N Engl J Med 2013;369:213-23

# What do guidelines say regarding radium-223?

- **EAU 2016**
  - Treat patients with chemotherapy-naïve mCRPC with life prolonging agents
  - Base the choice of first line treatment on the performance status, symptoms, comorbidities and extent of disease (alphabetical order: abiraterone, docetaxel, enzalutamide, **radium-223**, sipuleucel-T)
  - No definitive strategy regarding treatment choice (which drug/drug family first) can be devised
  - In patients with mCRPC and progression following docetaxel offer further life prolonging treatment options, which include **radium-223**, abiraterone, enzalutamide and cabazitaxel
- **NCCN 2016**
  - **Radium-223** is a category 1 option for patients with symptomatic bone metastases and no known visceral disease
- **ESMO 2015**
  - **Radium-223** is recommended for men with bone-predominant, symptomatic metastatic CRPC without visceral metastasis

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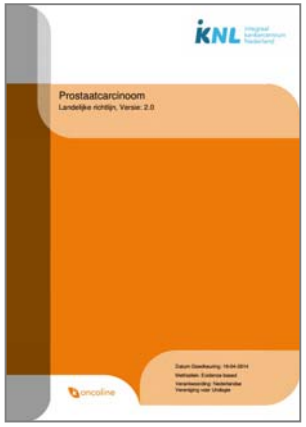
# Wat zegt de NVU richtlijn over radium-223?

- Behandeling met **Radium-223** (6 injecties gegeven met intervallen van 4 weken) overwogen te worden.
- De patiënt dient in een MDO te worden besproken, evenals beste timing en uiteindelijke keuze van de therapie



# Would denosumab or zoledronic acid be a valid treatment option?

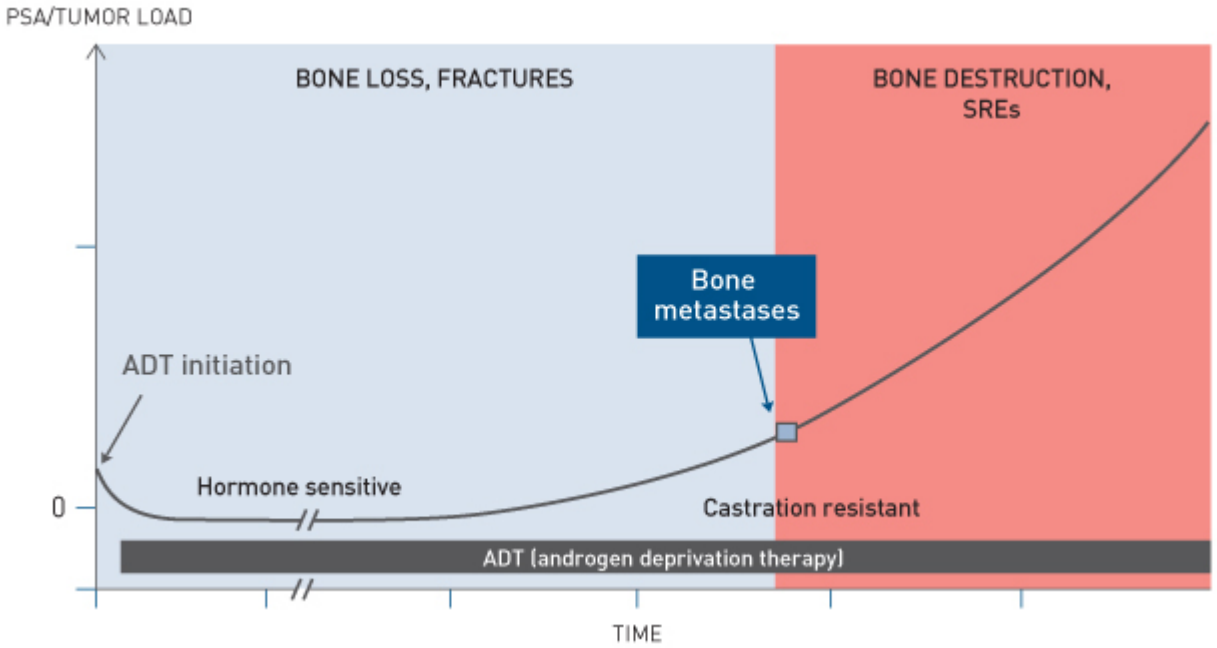
– Bone-targeted treatment Hide evidence

Appropriate

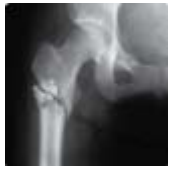
**Panel considerations**

Bone-targeted treatment (denosumab or zoledronic acid) was considered to be appropriate for all patients with bone metastases.

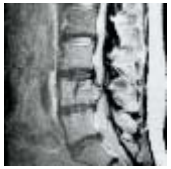
# A rising PSA despite ADT indicates risk for skeletal-related events and bone metastases




Radiation to bone



Pathological fracture



Spinal cord compression

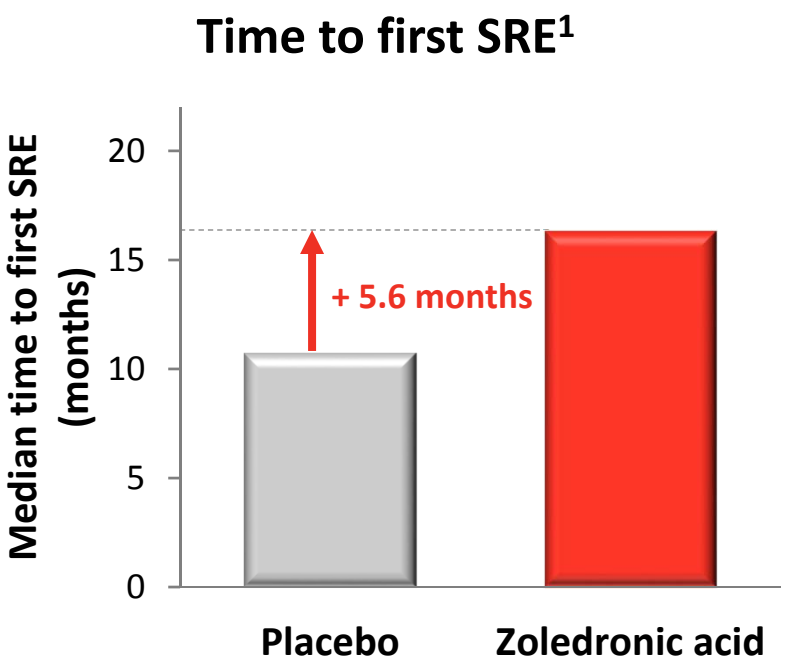
Surgery to bone

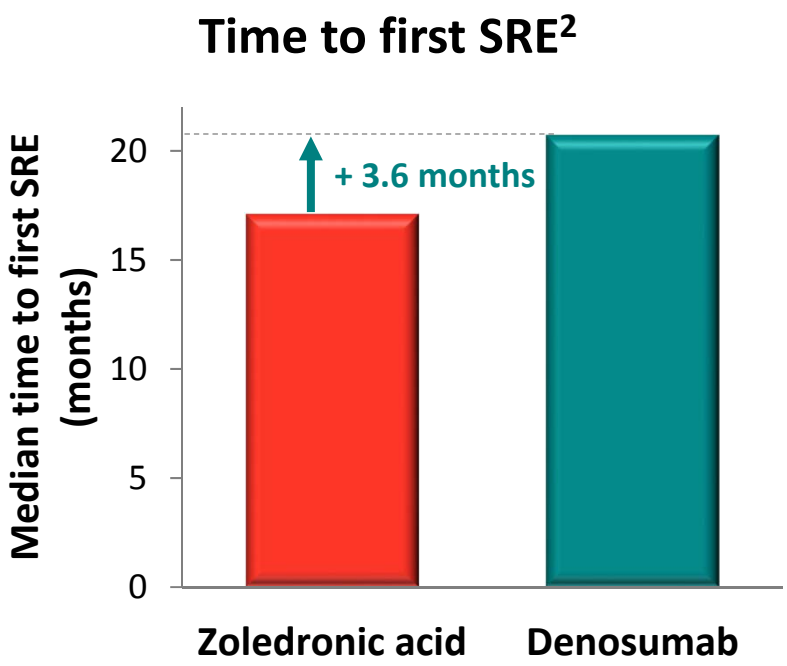
**Once a patient on ADT becomes castration resistant, he is at a greater risk for the development of SREs and bone metastases**

Tannock I, et al. N Eng J Med 2004;351:1502–12
Saad F et al. J Natl Cancer Inst 2004;96:879–82

*PSA: prostate-specific antigen; ADT: androgen-deprivation therapy; SRE: skeletal-related event*

# What is the underlying evidence related to zoledronic acid and denosumab?




**Zoledronic acid and denosumab have shown to significantly delay the time to SREs in CRPC patients with bone metastases and a PS≤2, despite the fact no significant differences in OS**


1. Saad F, et al. J Natl Cancer Inst 2004;96:879–82
2. Fizazi K, et al. Lancet 2011;377:813–22


*CRPC: castration-resistant prostate cancer; SRE: skeletal-related event; PS: performance status*

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# What do guidelines say regarding zoledronic acid and denosumab?

- **EAU 2016**
  - **Zoledronic acid** and **denosumab** should be offered to in men with CRPC and osseous metastases to prevent skeletal-related complications
  - The benefits must be balanced against the toxicity of these agents, and jaw necrosis in particular must be avoided
  - Calcium and vitamin D supplementation must be systematically considered when using either denosumab or bisphosphonates
- **NCCN 2016**
  - In men with CRPC and bone metastases, **denosumab** or **zoledronic acid** should be considered to prevent or delay disease-associated SREs
  - When compared to **zoledronic acid**, **denosumab** was shown to be superior in prevention of SREs
- **ESMO 2015**
  - In patients with bone metastases from CRPC at high risk for clinically significant SREs, **denosumab** or **zoledronic acid** can be recommended

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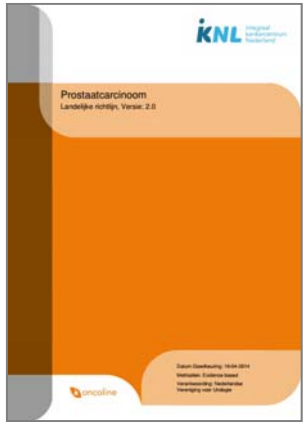
# Wat zegt de NVU richtlijn over zoledronaat en denosumab?




- **Zoledronaat** (4 mg i.v. elke 3-4 weken) of **denosumab** (120 mg s.c.) kan overwogen worden bij patiënten met CRPC en botmetastasen
  - Voornamelijk om SRE's te voorkomen
  - Ook ter vermindering van eventuele botpijn

- **Zoledronaat** vs. **denosumab**
  - Denosumab heeft statistisch een iets beter effect m.b.t. SRE's
  - Andere redenen kunnen ook een rol spelen in de keuze (kosten-effectiviteit)

# What else needs to be taken into consideration?

## Comorbidities and risk for AEs

- *Casus: mild, well-controlled hypertension*

| abiraterone (302) | hypertension (%)[1] | |
|---|---|---|
| | *treatment* | *predn.* |
| All grades | 23.8 | 13.7 |
| **- Grade ≥ 3** | **4.6** | **3.1** |

| enzalutamide (PREVAIL) | hypertension (%)[2] | |
|---|---|---|
| | *treatment* | *placebo* |
| All grades | 14.2 | 4.1 |
| **- Grade ≥ 3** | **7.2** | **2.3** |

| docetaxel (TAX-327) | hypertension (%)[3] | |
|---|---|---|
| | *treatment* | *mitox.* |
| not reported | n/a | n/a |

| Ra-223 (ALSYMPCA) | hypertension (%)[4] | |
|---|---|---|
| | *treatment* | *placebo* |
| not reported | n/a | n/a |

| Denosumab | hypertension (%)[5] | |
|---|---|---|
| | *treatment* | *zol. acid* |
| not reported | n/a | n/a |

| Zoledronic acid | Hypertension (%) [6] |
|---|---|
| | *treatment* |
| uncommon | 0,1-1% |




1. Ryan et al. Lancet Oncology 2015; 16(2):152-60
2. Graff et al. Expert Opin. Pharmacother. 2015; 16(5):749-754
3. SmpC Taxotere
4. SmPC Xofigo
5. SmPC Prolia, SmPC Xgeva
6. SmPC Zometa

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# Treatment options?

1. Watchful waiting
2. Abiraterone
3. Enzalutamide
4. Docetaxel
5. Cabazitaxel
6. Radium-223
7. Zoledronic acid
8. Denosumab

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# Treatment options?

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# Patient case 1

Case change

# Patient profile:
## a rising PSA on ADT+RT

- Mark, 73 years old, retired hairdresser
  - Mild hypertension, well-controlled
- Diagnosed with PCa at the age of 71
  - cT3 N1 M0, Gleason sum 7
- Treated by ADT and radiotherapy
  - Ongoing for 26 months, planned for 3 years
- Metastasized disease
  - PSA: 112 ng/mL
  - Bone scan: 2 bone metastases
  - But patient experiences no symptoms due to metastases

**What would be the most appropriate treatment for this patient?**

*PCa: prostate cancer, ADT: androgen-deprivation therapy; PSA: prostate-specific antigen; CT: computed tomography*

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# Clinical variables

**Previous treatment and response**

| No previous CRPC treatment | |
|---|---|
| AR, primary resistant | AR, secondary progressive |
| Docetaxel, primary resistant | Docetaxel, secondary progressive |

**Metastases**

| Bone only | LN+ only | Bone plus LN+ | Bone + visceral ± LN+ |
|---|---|---|---|

**Pain due to metastases**

| No (BPI ≤ 3) | Yes (BPI > 3) |
|---|---|

**Performance status**

| Good (WHO score 0-1) | Poor (WHO score = 2) |
|---|---|

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*WHO: World Health Organization*

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# Treatment options?

1. Watchful waiting
2. Abiraterone
3. Enzalutamide
4. Docetaxel
5. Cabazitaxel
6. Radium-223
7. Zoledronic acid
8. Denosumab

# What do the MoM experts recommend?

| | |
|---|---|
| AR-targeted therapy | Open |
| Chemotherapy (docetaxel) | Open |
| Chemotherapy (cabazitaxel) | Open |
| Radium therapy | Open |
| Bone-targeted treatment | Open |

The MiMe model was last updated in Dec 2016
*MiMe: Mirrors of Medicine*

# Would watchful waiting be a valid treatment option?

## Panel considerations

Watchful waiting (including the use of non-specific medications) is usually not considered as an appropriate option in metastatic CRPC. It may be considered in specific cases, particularly if the patient is asymptomatic.

Don't agree? **Tell us why.**

Share this recommendation

### Evidence

Studies on watchful waiting (observation, no active intervention) in prostate cancer only concern patients with localised or low-risk disease [1]. Evidence on the benefits and drawbacks of watchful waiting in metastatic patients is lacking. It may be reserved for asymptomatic patients with a strong wish to avoid treatment-related adverse events [2].

### Guidelines

The EAU states that in metastatic disease, watchful waiting (WW) may be offered to all patients not willing to accept the adverse events of active treatment, particularly in the case of a short life expectancy [2]. The NCCN [3] and ESMO [4] guidelines do not contain recommendations on WW in metastatic patients.

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# Would AR axis inhibition be a valid treatment option?

– AR-pathway inhibitor Hide evidence

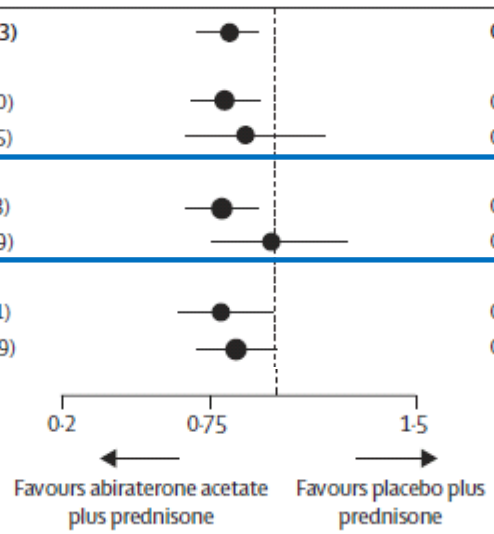
Appropriate

**Panel considerations**

The panel considered an AR-pathway inhibitor (abiraterone or enzalutamide) to be an appropriate option for almost all patients without previous treatment for CRPC.

**Subgroup analysis of overall survival: abiraterone in COU-AA-302 study**

| | Median (months) | | Hazard ratio (95% CI) | Events/N | |
|---|---|---|---|---|---|
| | Abiraterone acetate plus prednisone | Placebo plus prednisone | | Abiraterone acetate plus prednisone | Placebo plus prednisone |
| **All patients** | **34·7 (32·7–36·8)** | **30·3 (28·7–33·3)** | **0·81 (0·70–0·93)** | **354/546** | **387/542** |
| Baseline ECOG | | | | | |
| 0 | 35·4 (33·7–39·0) | 32·0 (29·9–35·0) | 0·79 (0·66–0·93) | 261/416 | 292/414 |
| 1 | 27·9 (24·6–34·4) | 26·4 (22·3–30·5) | 0·87 (0·65–1·16) | 93/130 | 95/128 |
| Baseline BPI-SF | | | | | |
| 0–1 | 38·1 (35·0–41·9) | 33·4 (30·1–37·3) | 0·77 (0·64–0·93) | 223/370 | 233/346 |
| 2–3 | 26·4 (24·4–28·8) | 27·4 (22·8–30·9) | 0·97 (0·75–1·27) | 100/129 | 120/147 |
| Bone metastasis only at entry | | | | | |
| Yes | 38·9 (34·9–45·2) | 34·1 (30·1–39·1) | 0·78 (0·62–0·97) | 147/238 | 162/241 |
| No | 31·6 (27·8–34·5) | 29·0 (26·0–30·9) | 0·83 (0·69–1·00) | 207/308 | 225/301 |




Ryan CJ et al. Lancet Oncology 2015; 16(2): 152-60

# Would docetaxel be a valid treatment option?

## Chemotherapy (docetaxel)

Hide evidence

Uncertain

### Panel considerations

The panel considered chemotherapy with docetaxel to be appropriate for most patients without previous treatment for CRPC.
In this patient, the metastatic profile (painless bone metastases only) may plea against this treatment option.

# Would radium-223 be a valid treatment option?

Radium therapy

Not applicable

**Panel considerations**

The EMA approved the use of radium therapy (radium-223) only for patients with symptomatic bone metastases and no known visceral disease.

# What else needs to be taken into consideration?

- Drug-drug interactions
  - What to avoid and where to be cautious

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# Abiraterone[1]

**Avoid**

- Strong inducers of CYP3A4
  - e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St John's wort [Hypericum perforatum]
- Intake with food

**Caution**

- Medicinal products activated by or metabolised by CYP2D6, particularly with medicinal products that have a narrow therapeutic index
  - e.g. metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol
- Medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA or class III
  - e.g. quinidine, disopyramide
  - e.g. amiodarone, sotalol, dofetilide, ibutilide, antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc.

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1. SmPC Zytiga

# Enzalutamide[1]

## Avoid

- Warfarin and coumarin-like anticoagulants
- Strong inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin) of CYP2C8

## Caution

- Enzymes that may be induced include CYP3A in the liver and gut, CYP2B6, CYP2C9, CYP2C19, and uridine 5'-diphospho-glucuronosyltransferase (UGTs - glucuronide conjugating enzymes), the transport protein P-gp:

  Groups of medicinal products that can be affected include, but are not limited to:

  Analgesics (e.g. fentanyl, tramadol), Antibiotics (e.g. clarithromycin, doxycycline)

  Anticancer agents (e.g. cabazitaxel), Anticoagulants (e.g. acenocoumarol, warfarin)

  Antiepileptics (e.g. carbamazepine, clonazepam, phenytoin, primidone, valproic acid)

  Antipsychotics (e.g. haloperidol) , Betablockers (e.g. bisoprolol, propranolol)

  Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)

  Cardiac glycosides (e.g. digoxin), Corticosteroids (e.g. dexamethasone, prednisolone)

  HIV antivirals (e.g. indinavir, ritonavir), Hypnotics (e.g. diazepam, midazolam, zolpidem)

  Statins metabolized by CYP3A4 (e.g. atorvastatin, simvastatin), Thyroid agents (e.g. levothyroxine)
- Medicinal products that lower the seizure threshold
- Medicinal products that might prolong the QT interval
- Medicinal products with a narrow therapeutic range that are substrates for P-gp e.g. colchicine, dabigatran etexilate, digoxin

1. SmPC Xtandi

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# Docetaxel[1]

**Avoid**

- Strong CYP3A4 inhibitors
  - e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole

**Caution**

- All compounds which induce, inhibit or are metabolised by cytochrome P450-3A

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1. SmPC Taxotere

# Radium 223[1]

**Avoid**

- -

**Caution**

- Calcium and phosphate and/or vitamin D
- Chemotherapy
- Bisphosphonates

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1. SmPC Xofigo

# Denosumab[1]

**Avoid**

- Other denosumab-containing medicinal products
- Bisphosphonates

**Caution**

- Corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck → ONJ

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ONJ: osteonecrosis of the jaw 1. SmPC Prolia, SmPC Xgeva

# Zoledronic acid[1]

**Avoid**

- Any other bisphosphonate → unknown effect

**Caution**

- Aminoglycosides, calcitonin or loop diuretics →lower serum calcium level
- Potentially nephrotoxic medicinal products
- Anti-angiogenic medicinal products, chemotherapy, radiotherapy to neck and head, corticosteroids → ONJ

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ONJ: osteonecrosis of the jaw

1. SmPC Zometa

# Multidisciplinary discussion

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# Treatment options?

1. Watchful waiting
2. Abiraterone
3. Enzalutamide
4. Docetaxel
5. Cabazitaxel
6. Radium-223
7. Zoledronic acid
8. Denosumab

# Treatment decision

1. Watchful waiting
2. Abiraterone
3. Enzalutamide
4. Docetaxel
5. Cabazitaxel
6. Radium-223
7. Zoledronic acid
8. Denosumab

1e Stemronde 2e Stemronde

# Key messages

## management options of mCRPC

# Key messages (1/3)

- Patient population is highly heterogeneous
- Give the right drug to the right patient

- Three bone-targeting agents have been shown to prevent and/or delay disease-related SREs
  - **zoledronic acid** (no survival benefit)
  - **denosumab** (no survival benefit)
  - **radium-223** (survival benefit)

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# Key messages (2/3)

- Since 2010, several agents have demonstrated a survival benefit in the pre-docetaxel setting
  - **abiraterone** (COU-AA-302)
  - **enzalutamide** (PREVAIL)
  - **radium-223** (ALSYMPCA)
  - **sipuleucel-T** (IMPACT)

- They have been approved for use in asymptomatic or mildly symptomatic patients with CRPC who have not received chemotherapy

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# Key messages (3/3)

- There is no data to support a specific sequence between the different drugs
  - awaiting outcomes of prospective clinical trials

# Thank you!

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