Genitourinary Masterclass

Putting patients at the center: Case studies

Dr Po-Hung Lin and Prof. Chang Gon Kim

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Genitourinary Masterclass

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The drained flame:
Life, fatigue, and the hormonal fight against prostate cancer

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Disclosures

- **Principal investigator of clinical trials:** Johnson & Johnson, Merck & Co., Inc.
- **International conference:** AstraZeneca, Intuitive, Johnson & Johnson
- **Advanced surgical training:** Intuitive
- **Local consultant:** Bayer, Johnson & Johnson

National Cancer Institute: Fatigue

- An extreme sense of tiredness
- Lack of energy that can interfere with daily activities
- Feeling weak, worn out, heavy, slow, or run-down
- May also have trouble speaking or concentrating, short-term memory loss, and mood or emotional changes
- May not be completely relieved by sleep
- May last for a long time after treatment ends

National Cancer Institute. Cancer Fatigue. Available at: https://www.cancer.gov/about-cancer/treatment/side-effects/fatigue. Last accessed: July 2025.

National Cancer Institute: Cancer fatigue symptoms

- Having no energy; feeling extremely tired, drained, or lethargic
- Having difficulty moving; feeling heavy or slow
- Having difficulty thinking, remembering, or paying attention
- Having a sense of **physical, emotional, and/or mental exhaustion**
- Not feeling rested, even after sleeping

National Cancer Institute. Cancer Fatigue. Available at: https://www.cancer.gov/about-cancer/treatment/side-effects/fatigue. Last accessed: July 2025.

National Cancer Institute: Causes of cancer fatigue

- Fatigue from cancer: **cancer-related symptoms**
- **Fatigue** directly from cancer treatments
- Fatigue from **other side effects** of cancer treatment
  - Anemia
  - Appetite loss
  - Diarrhea
  - Hot flashes
  - Infection
  - Pain
  - Sleep problems
  - Vomiting
- Fatigue from the **emotional impact** of cancer

National Cancer Institute. Cancer Fatigue. Available at: https://www.cancer.gov/about-cancer/treatment/side-effects/fatigue. Last accessed: July 2025.

Fatigue in prostate cancer

- Cancer-related fatigue affects up to **90% of patients** with advanced prostate cancer
- Distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is unrelated to recent activity, and which interferes with usual functioning
- **ADT often causes fatigue that is persistent and often intertwined with depression and insomnia**
- Adversely impacts the patient's ability to work and carry out daily activities, thereby negatively affecting their personal relationships and overall quality of life
- When patients **undergo more than one type of treatment concurrently**, such as ADT and radiotherapy, **this effect is magnified**

ADT, androgen deprivation therapy.
Cornford P, et al. *Eur Urol Open Sci* 2024;63:119–125.

Association between fatigue and treatment selection [1/2]

- The lowest rates of cancer-related fatigue (14–22%) are seen in men who have **undergone a radical prostatectomy**[1,2]
- The prevalence of cancer-related fatigue after radiotherapy is estimated to be in the region of 33–56%[1,2]

1. Cornford P, et al. *Eur Urol Open Sci* 2024;63:119–125; 2. Storey DJ, et al. *Ann Oncol* 2012;23:65–72.

Association between fatigue and treatment selection [2/2]

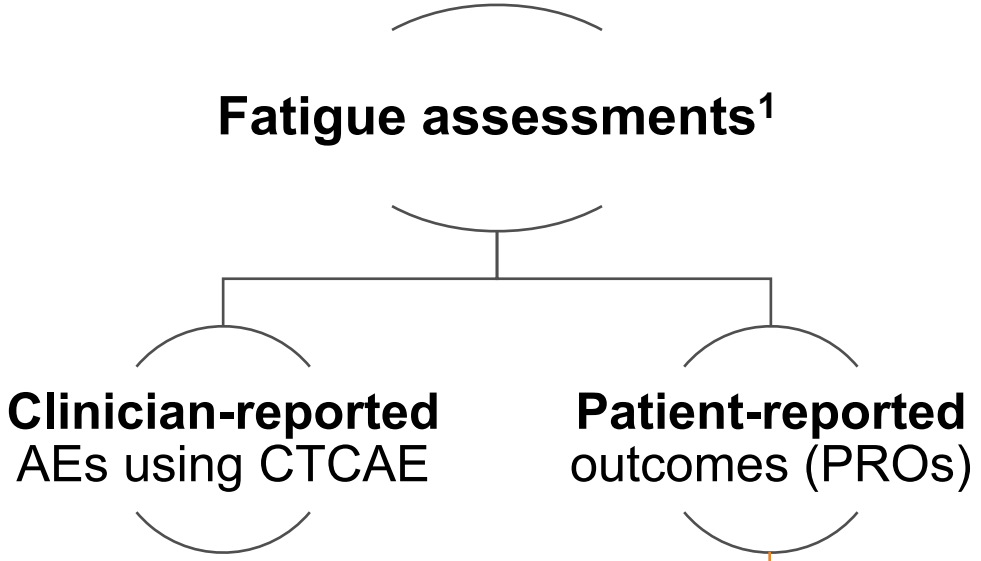
Overview of fatigue rates: Recent and large prostate cancer clinical trials

Trial and treatment	Incidence of fatigue (%)	
	Any grade	Grade ≥3
STAMPEDE (high risk, non-metastatic)[1]		
ADT alone	56	1.6
ADT + ABI	66	2
STAMPEDE (metastatic)[1]		
ADT alone	58	2
ADT + ABI	68	2
ARCHES (metastatic)[1]		
ADT alone	19.5	1.6
ADT + ENZ	24.1	1.7
ARASENS (mHSPC)[1]		
ADT + docetaxel	32.9	NA
ADT + docetaxel + DAR	33.1	NA
TITAN (mHSPC)[2]		
ADT + placebo	16.9	NA
ADT + APA	20.4	NA

ABI, abiraterone; ADT, androgen deprivation therapy; APA, apalutamide; DAR, darolutamide; ENZ, enzalutamide; mHSPC, metastatic hormone-sensitive prostate cancer; NA, not available.

1. Cornford P, et al. *Eur Urol Open Sci* 2024;63:119–125; 2. Chi KN, et al. *J Clin Oncol* 2021;39:2294–2303 (supplementary appendix).

Types of fatigue assessments



AE frequency and grade

- Typically, no AE duration, time of occurrence, or recurrence reported

Fatigue questionnaires

- BFI

Fatigue-specific items on other questionnaires

- FACT-P GP1 item

Functional assessments

- Physical, social, emotional, and functional well-being

PRO data can assess treatment and disease-related symptoms

Brief Fatigue Inventory (BFI)

Validated fatigue measure with high internal consistency and reliability[2,3]

Functional Assessment of Cancer Therapy-Prostate Cancer (FACT-P)

Captures several aspects of the patient experience relating to fatigue

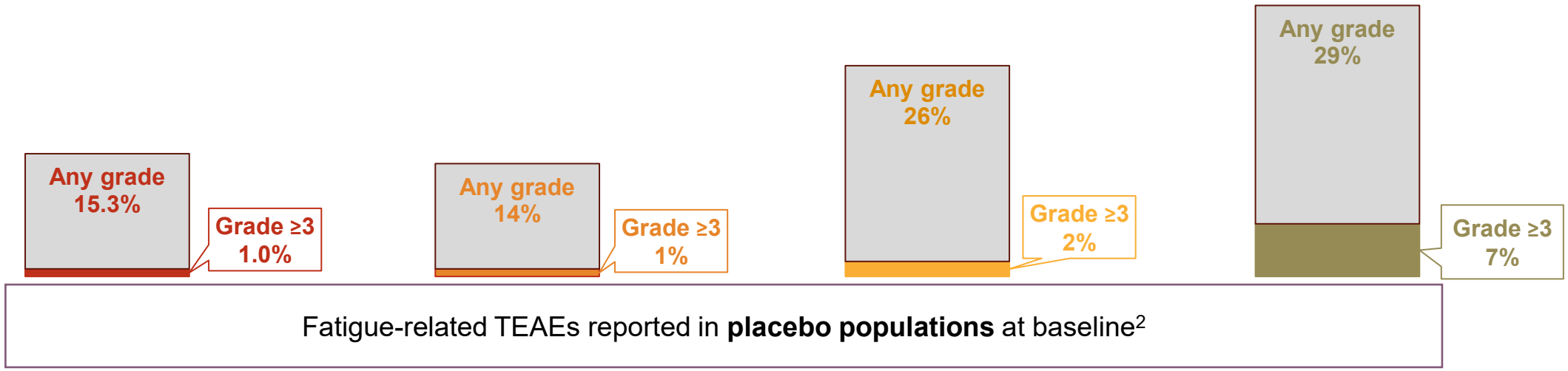
- GP1 item, "I have a lack of energy", was demonstrated to be a proxy for fatigue via correlation analyses[3]

AE, adverse event; BFI, Brief Fatigue Inventory; CTCAE, Common Terminology Criteria For Adverse Events; FACT-P, Functional Assessment of Cancer Therapy-Prostate Cancer; PRO, patient reported outcome.

1. National Cancer Institute. Fatigue (PDQ®)–Health Professional Version. Available at: https://www.cancer.gov/about-cancer/treatment/side-effects/fatigue/fatigue-hp-pdq#_35. Last accessed: July 2025;
2. Shuman-Paretsky MK, et al. *Arch Phys Med Rehabil* 2014;95:1533–1539; 3. Ganguli A, et al. *Value Heal* 2020;23:S72 (abstract PCN278).

Clinician-reported fatigue in prostate cancer

Clinician-reported fatigue is greater in patients in **later stages** of disease, especially **after chemotherapy**[1]



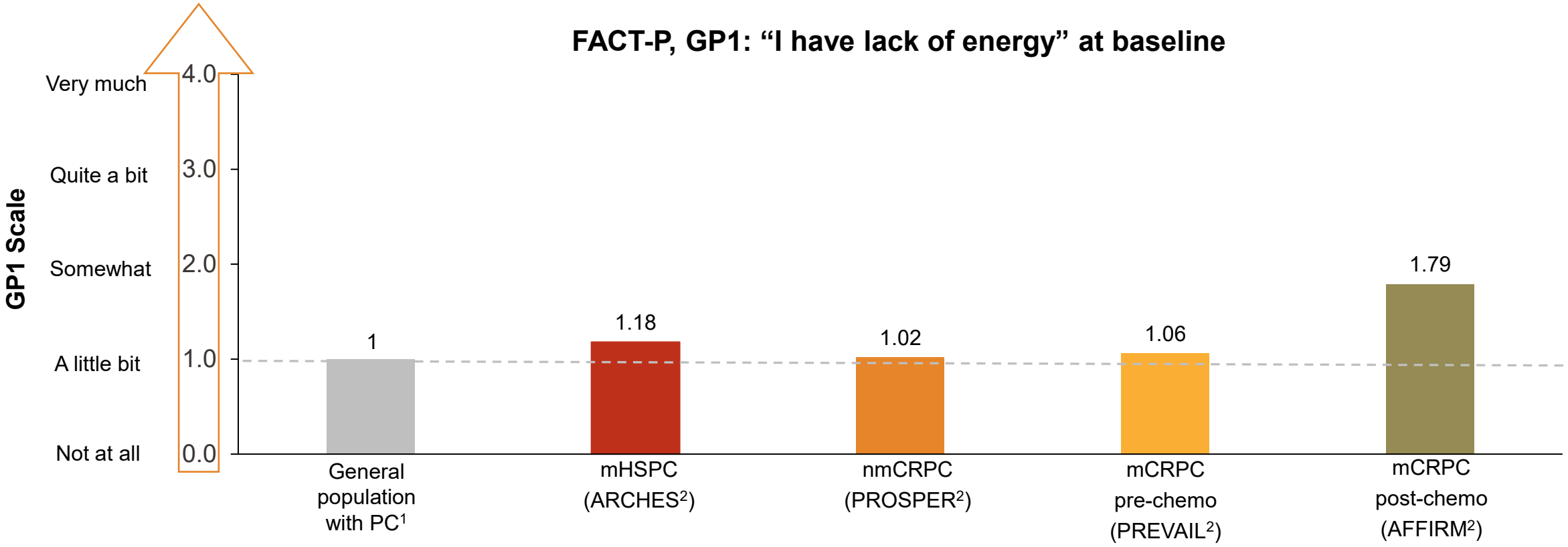
Clinician-reported fatigue using CTCAE v4.0 across control arms of **Phase III enzalutamide clinical trials**[3]

CTCAE, Common Terminology Criteria for Adverse Events; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; TEAE, treatment-emergent adverse event.

1. National Cancer Institute. Fatigue (PDQ®)–Health Professional Version. Available at: https://www.cancer.gov/about-cancer/treatment/side-effects/fatigue/fatigue-hp-pdq#_35. Last accessed: July 2025; 2. DOF, data available by request; 3. Armstrong AJ, et al. *J Clin Oncol* 2019;37:2974–2986; 4. Hussain M, et al. *N Engl J Med* 2018;378:2465–2474; 5. Beer TM, et al. *N Engl J Med* 2014;371:424–433; 6. Scher HI, et al. *N Engl J Med* 2012;13:1187–1197.

Patient-reported fatigue in prostate cancer

In clinical trials, patients report a **"lack of energy" at baseline**, which is **at least comparable to a national representative sample** of a general male population in the US, matched by age.*[1,2]
Fatigue is greater in patients in **later stages** of disease, especially **after chemotherapy**



*Based on measurement using FACT-P GP1 item at baseline among enzalutamide arm subjects across Phase III studies.
FACT-P, Functional Assessment of Cancer Therapy-Prostate Cancer; mHSPC, metastatic hormone-sensitive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; PC, prostate cancer.
1. Cella D, et al. *Adv Ther* 2022;39:3696-3710; 2. Tombal BF, et al. *Prostate Cancer Prostatic Dis* 2022;25:288-295.

Treatment-related fatigue in prostate cancer

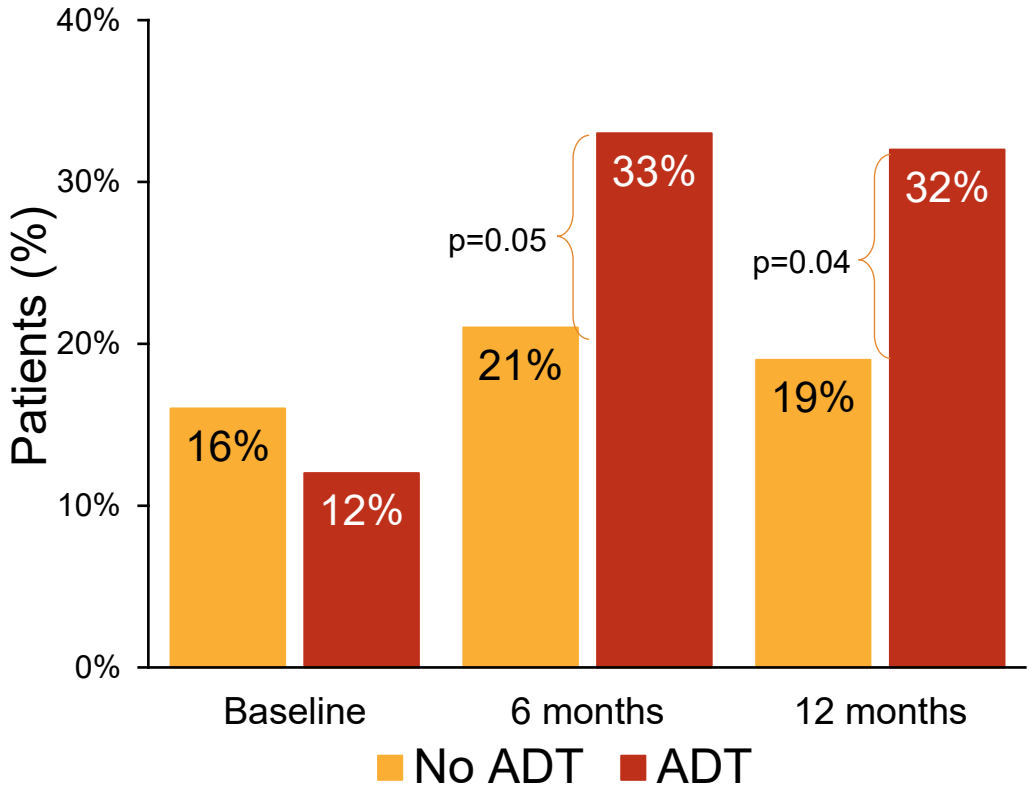
In a **controlled, longitudinal comparison** of:

- Prostate cancer patients **receiving ADT** (N=60), and
- Prostate cancer patients receiving **prostatectomy only** (N=85)

Fatigue Symptom Inventory was administered at **baseline** (treatment initiation)**, 6 months, and 12 months**

- Among ADT-treated patients, rate of fatigue worsened over time
- **ADT** treatment was demonstrated to have a **significant impact** on **fatigue severity, disruptiveness,** and **duration**

Clinically meaningful fatigue in patients with prostate cancer*



*Meaningful fatigue defined as scores >4 for the average of fatigue severity items.
ADT, androgen deprivation therapy.
Nelson AM, et al. *Support Care Canc* 2016;24:4159–4166.

Treatment-associated fatigue in prostate cancer

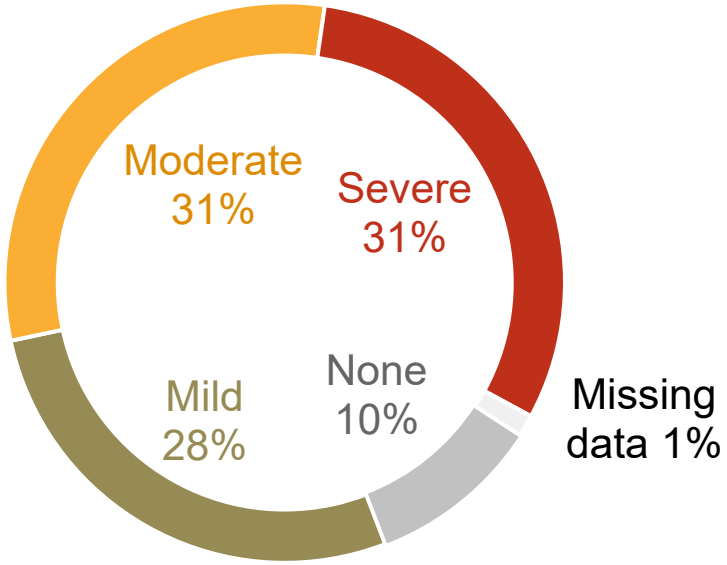
Fatigue is **common** in men with prostate cancer **receiving ADT**

In a **cross-sectional survey** of 160 patients with biochemically controlled prostate cancer* receiving ADT therapy, the **BFI** was used to determine the prevalence of clinically-relevant fatigue

After a median duration of 26 months on ADT:

- **43% reported clinically-relevant fatigue (BFI >3)**

Answer distribution for BFI "worst fatigue" item

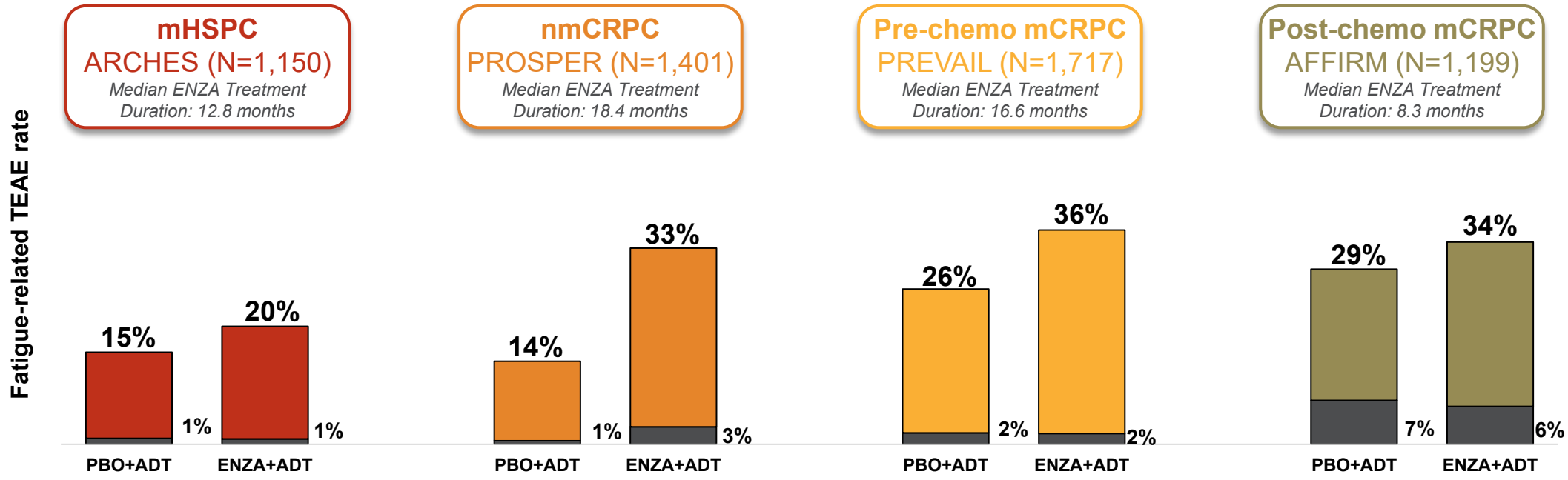


The **majority** of patients surveyed reported fatigue to be **moderate or severe** at its worst after a median duration of 26 months

*Biochemically controlled was defined as having received GnRH analogs for >6 months; PSA <0.2 µg/L within the last 3 months or if >0.2 µg/L then stable at nadir for two consecutive readings >3 months apart.
ADT, androgen deprivation therapy; BFI, Brief Fatigue Inventory; GnRH, gonadotropin-releasing hormone; PSA, prostate-specific antigen.
Storey DJ, *Annals of Oncol* 2012;23:1542–1549.

Enzalutamide and clinician-reported fatigue across trials

Fatigue-related TEAE Rates Across Trials

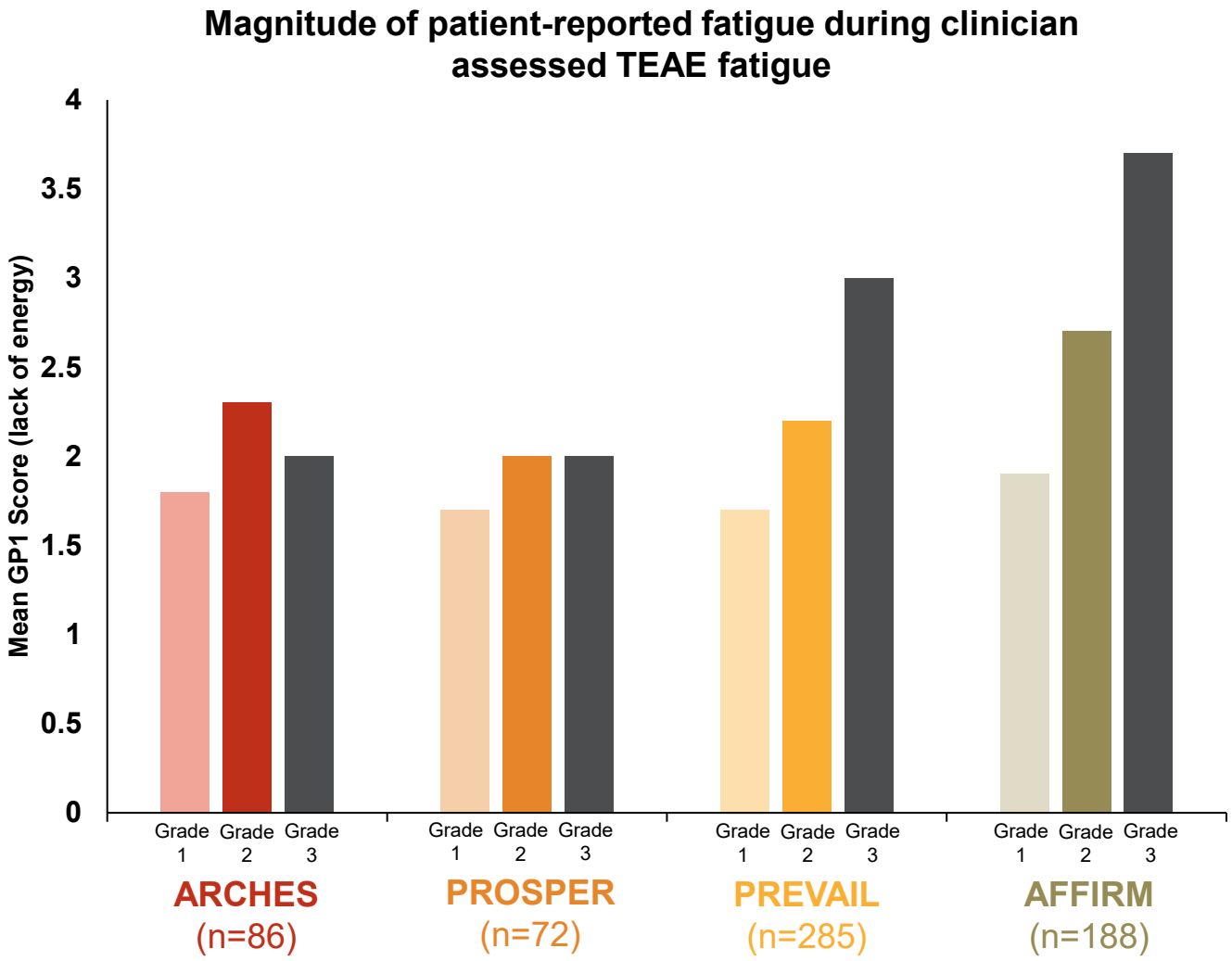


Order All grades Grade 3+	mHSPC		nmCRPC		Pre-chemo mCRPC		Post-chemo mCRPC	
	PBO+ADT	ENZA+ADT	PBO+ADT	ENZA+ADT	PBO+ADT	ENZA+ADT	PBO+ADT	ENZA+ADT
Dose interruption due to any grade fatigue	0.2%	0.5%	0.2%	2.8%	0.9%	1.0%	0.5%	1.5%
Dose reduction due to any grade fatigue	0.5%	1.4%	0.6%	3.9%	0.1%	0.6%	0.3%	0.5%
Treatment discontinuation due to any grade fatigue	0.3%	0.3%	0.0%	1.6%	1.3%	0.2%	0.5%	0.6%

ADT, androgen deprivation therapy; chemo, chemotherapy; ENZ, enzalutamide; mCRPC, metastatic castration-resistance prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistance prostate cancer; PBO, placebo; TEAE, treatment emergent adverse event.

Tombal BF, et al. *Prostate Cancer Prostatic Dis* 2022;25:288-295 (supplementary appendix).

Clinician- and patient-reported fatigue



Patient-reported **fatigue severity** generally corresponds to clinician-reported fatigue, which further supports GP1 as a proxy measure of fatigue

Patient-reported "lack of energy" item (**GP1**) **scores** were consistently **higher** for clinician-reported **Grade 2 and 3 fatigue**

*Where 0 refers to 'not at all', 1 refers to 'a little bit', 2 refers to 'somewhat', 3 refers to 'quite a bit', 4 refers to 'very much'.
TEAE, treatment emergent adverse event.
Tombal BF, et al. *Prostate Cancer Prostatic Dis* 2022;25:288-295.

Treatments for fatigue in prostate cancer patients

- Psychosocial methods, such as education and cognitive behavioral therapy, can be beneficial in reducing cancer-related fatigue[1]
- Guided imagery and progressive muscle relaxation[2]
- Exercise:[3]
  - Moderate exercise, such as resistance training
  - Resistance training or high-intensity interval training
  - Low-volume resistance-based exercise of medium to high intensity reduced fatigue significantly

1. Larkin DRN, et al. *JBI Libr Syst Rev* 2012;10:3764–3811; 2. Zuniga KB, et al. *Urol Oncol* 2020;38:105–117; 3. Cornford P, et al. *Eur Urol Open Sci* 2024;63:119–125.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Nonpharmacologic interventions for cancer-related fatigue for patients on active treatments

- Physical activity (NCCN Category 1)
  - **Maintain optimal level of activity for daily living**
  - **Cautions in determining level of activity:**
    - Bone metastases
    - Thrombocytopenia
    - Anemia
    - Fever, active infection, or post-surgery
    - Limitations secondary to metastases or other comorbid conditions
    - Safety issues (i.e., assessment of risk of falls)
  - **Consider initiation and/or encourage maintenance of a physical activity/exercise program, as appropriate per healthcare provider, consisting of cardiovascular endurance (walking, jogging, or swimming) and resistance (weights) training**
  - **Consider referral to specialty providers such as exercise oncology, physical therapy, occupational therapy, and physical medicine and rehabilitation**
  - **Yoga (Category 1)**
- Massage therapy (Category 1)
- Acupuncture
- Psychosocial interventions
  - **Cognitive behavioral therapy (CBT)/behavioral therapy (BT) (Category 1)**
  - **CBT for insomnia (CBT-I)**
  - **Psycho-educational therapies/educational therapies (Category 1)**
  - **Supportive expressive therapies**
- Nutrition consultation
- Bright white light therapy

All recommendations are Category 2A unless otherwise indicated

Category Definitions

Category 1: Based upon high-level evidence (≥1 randomized Phase III trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.

For further information, refer to NCCN Guidelines® for Cancer-Related Fatigue

BT, behavioral therapy; CBT, cognitive behavioral therapy; I, insomnia; NCCN, National Comprehensive Cancer Network.

Case 1

Age: 71 years

Occupation: Retired worker (plumber)

Patient characteristics/ medical history:

Diabetes/hypertension

Caregiver: Son

ECOG: 0

Family support: Good

Diagnosis: 2024/12

iPSA 277 Gleason 4+4
cT3N1M1b

Assessment

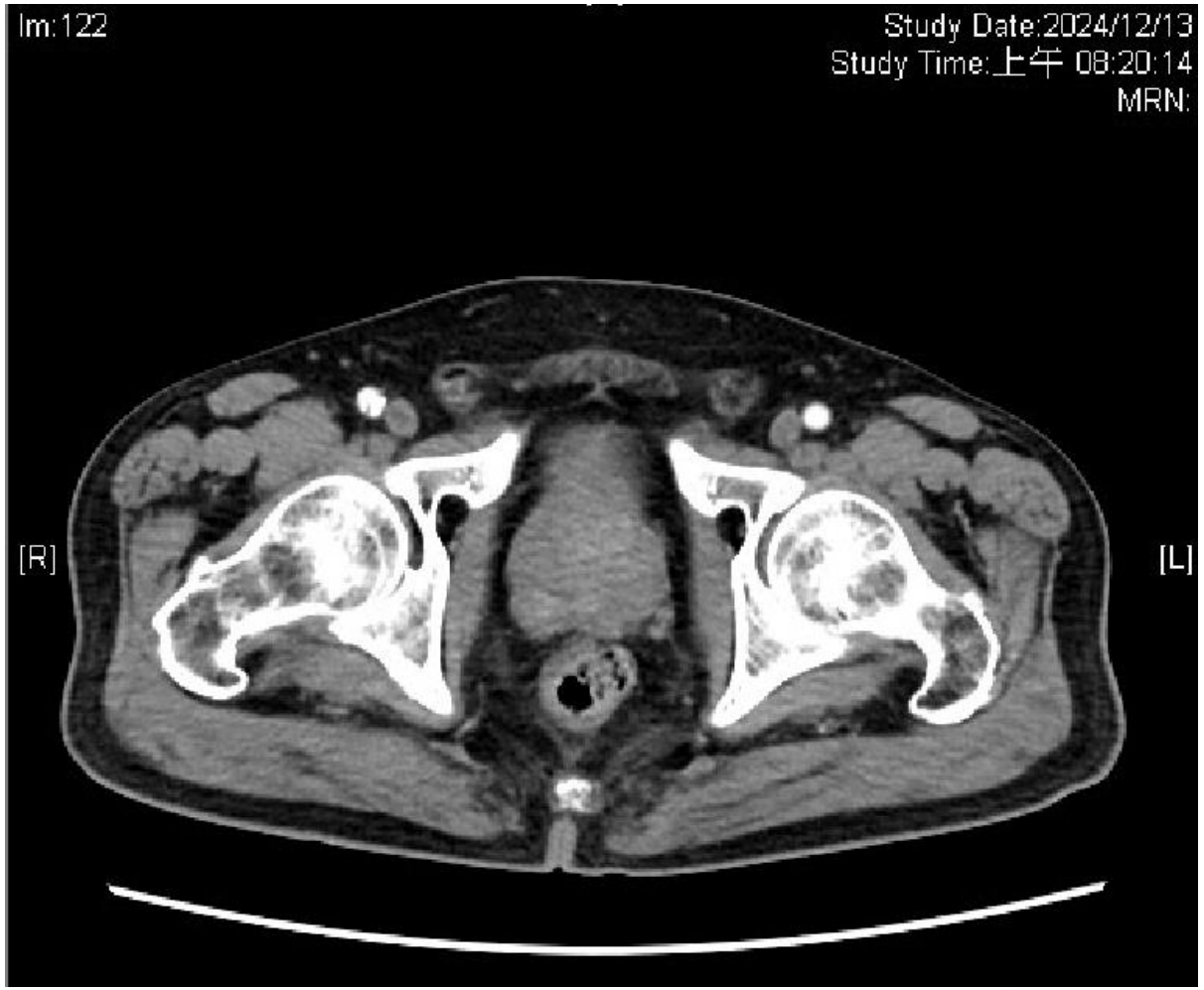
PSA 0.77 ng/mL (2025/02/18) →
0.37 ng/mL (2025/04/11)

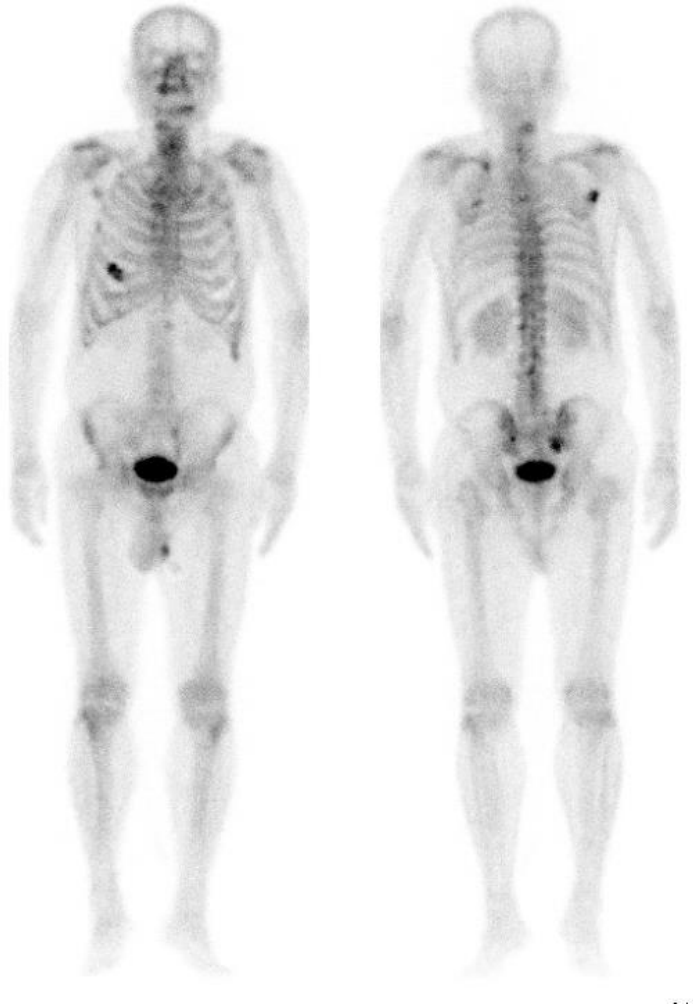
Treatment

Diphereline QM
Enzalutamide for mHSPC

ECOG, Eastern Cooperative Oncology Group; iPSA, initial prostate-specific antigen; mHSPC, metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen, QM, once monthly.
Speaker's own case.

Imaging results





Slide content provided by the speaker. Patient permission has been obtained for all images.
Speaker's own case.

Fatigue status

- **Before treatment**: No pain, daily function well and no fatigue
- **After 1 month treatment:** Grade 1 fatigue
- **Treatment for fatigue:** Exercise (light walking), regular naps, and sleep
- **Fatigue improved 2 months after treatment**

Speaker's own case.

Case 2

Age: 64 years

Occupation: Owner of plumbing and heating shop

Patient characteristics/ medical history:

No systemic disease

Caregiver: Wife

ECOG: 0

Family support: Good

Diagnosis 2020/07

iPSA 123 Gleason 4+5
cT3bN1M1b

Assessment

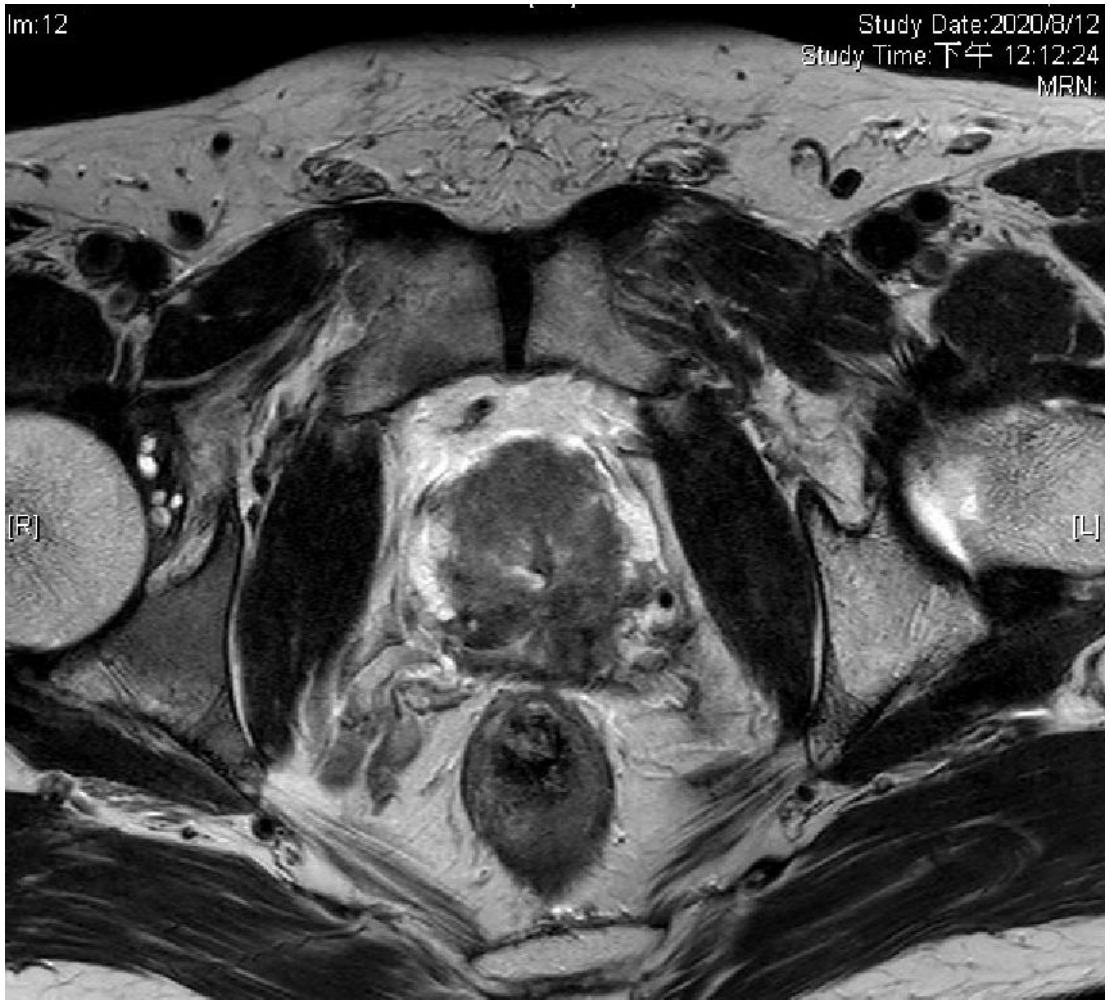
PSA 0.78 ng/mL (2020/10) →
0.03 ng/mL (2021/04) →
undetectable (2021/07 – present)

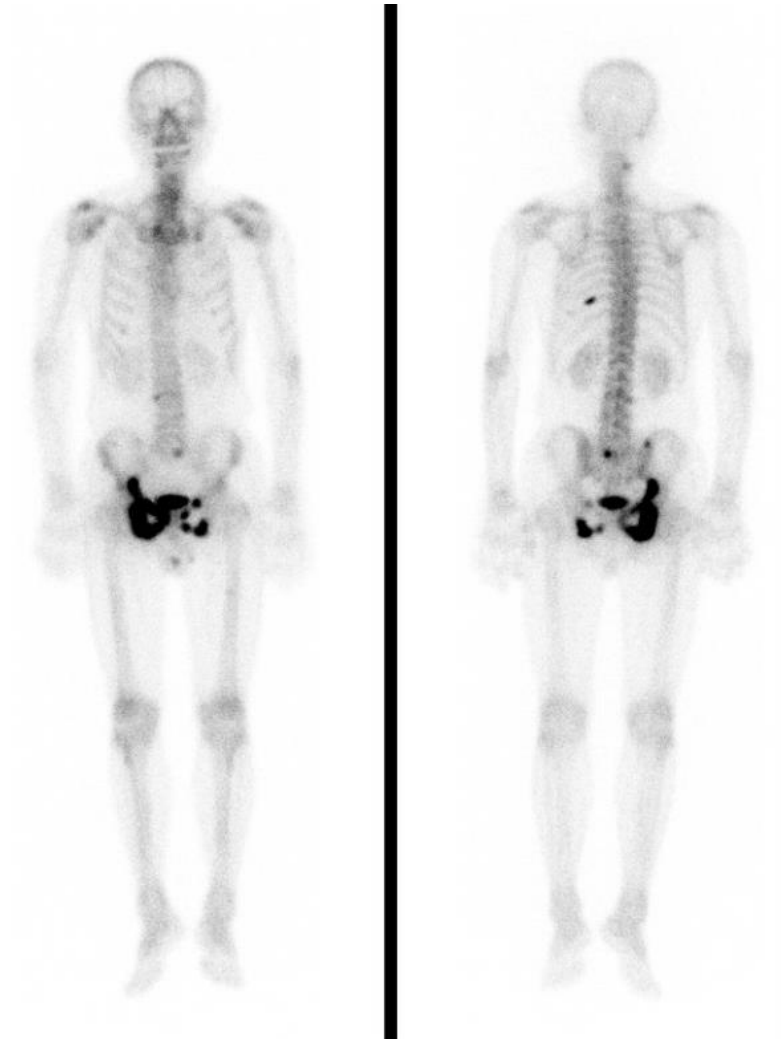
Treatment

Diphereline QM
Enzalutamide for mHSPC

ECOG, Eastern Cooperative Oncology Group; iPSA, initial prostate-specific antigen; mHSPC, metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen; QM, once monthly.
Speaker's own case.

Imaging results





Slide content provided by the speaker. Patient permission has been obtained for all images.
Speaker's own case.

Clinical course

- Initially mild symptoms: Discomfort over bilateral subcostal region
- 2020/12: Common cold, took NSAIDs → drug eruption and admission, complicated with anemia and thrombocytopenia, steroid therapy was given
- Reported Grade 2 fatigue → enzalutamide was discontinued for 2 weeks
- Restarted enzalutamide after 2 weeks
- Intermittent Grade 1 fatigue with interval of months, improved after light exercise without dose reduction or interruption

NSAID, non-steroidal anti-inflammatory drug.
Speaker's own case.

Question for the audience

- Is this episode of fatigue related to enzalutamide?

A Yes

B No

C Unsure

Question for the audience

- Should enzalutamide be discontinued?

A Yes

B No

C Unsure

Clinical course

- **2023/05:** Near fainting episode without seizure → brain CT revealed no brain metastasis or organic lesions → kept taking enzalutamide

- **2023/07:** Progressive fatigue with depression mood and physical impairment

CT, computed tomography.
Speaker's own case.

Question for the audience

- Are these symptoms related to AEs of enzalutamide?

A Yes

B No

C Unsure

AE, adverse event.

Question for the audience

- Should enzalutamide be discontinued?

A Yes

B No

C Unsure

Clinical course

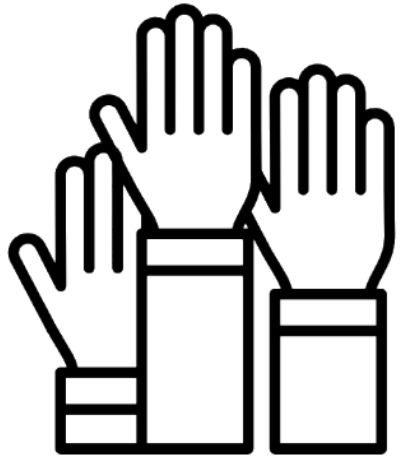
- **2023/08:** Early stage of Parkinsonism was diagnosed by neurologist
- **2024/01:** Seizure episode
- **2024/08:** Severe fatigue (Grade 3)
- **2024/08:** Dose reduction to enzalutamide 2/QD
- **2024/12:** ECOG 1–2, discontinued enzalutamide

- PSA remained undetectable until **2025/03**

ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; QD, once daily.
Speaker's own case.

Question for the audience

In your daily practice, do you usually use questionnaires, such as FACT-P/BFI, to assess your patients' daily function, quality of life, and fatigue status?



BFI, Brief Fatigue Inventory; FACT-P, Functional Assessment of Cancer Therapy-Prostate.

Question for the audience

- Regarding the possible enzalutamide-related fatigue, would you…

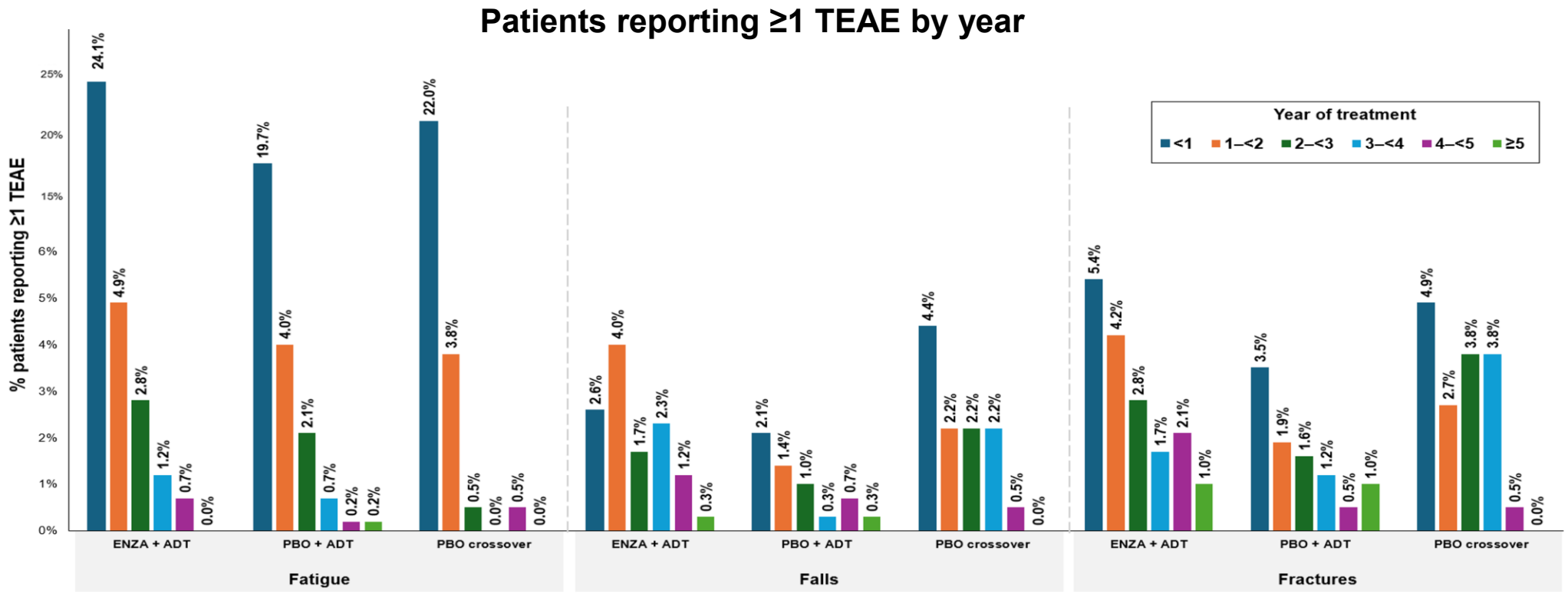
A **Inform the patient about the possible AE in advance before treatment initiation**

B **Only assess fatigue status after treatment initiation**

AE, adverse event.

ARCHES: First onset of fatigue was slightly more common in enzalutamide + ADT and placebo crossover groups vs. the placebo + ADT group during the first year and decreased thereafter

- Lower incidences of fatigue, falls, and fractures were generally observed in the placebo + ADT group vs. the enzalutamide + ADT and placebo crossover groups
- AEs were mostly reported in the first couple of years



Data cutoff: July 31, 2024.
ADT, androgen deprivation therapy; AE, adverse event; TEAE, treatment-emergent adverse event.
Armstrong AJ, et al. Presented at ASCO 2025, May 30–June 3, 2025, Chicago, IL, USA.

Question for the audience

- If your patient developed moderate to severe fatigue (Grade >2), what is your next step?

A Treatments for fatigue (exercise/nutrition/massage/etc.)

B Dose reduction

C Hold enzalutamide treatment

Take-home message

- The prevalence of fatigue is high in patients with prostate cancer[1]
- Fatigue may be related to cancer, treatments of cancer, and AEs of cancer treatments[1]
- Be aware of fatigue; early intervention can improve patient's quality of life and increase compliance[1]
  - An improvement in long-term survival was accompanied by an increase in enzalutamide-associated TEAEs, which tended to diminish substantially over time[2]
- Always look for underlying causes of fatigue[1]

AE, adverse event; TEAE, treatment-emergent adverse event.

1. Speaker's own opinion; 2. Armstrong AJ, et al. Presented at ASCO 2025, May 30–June 3, 2025, Chicago, IL, USA.

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Thank you for your attention!

Image provided by speaker.

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Putting patients at the center: Focusing on bone health

Prof Chang Gon Kim, MD, PhD
Department of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

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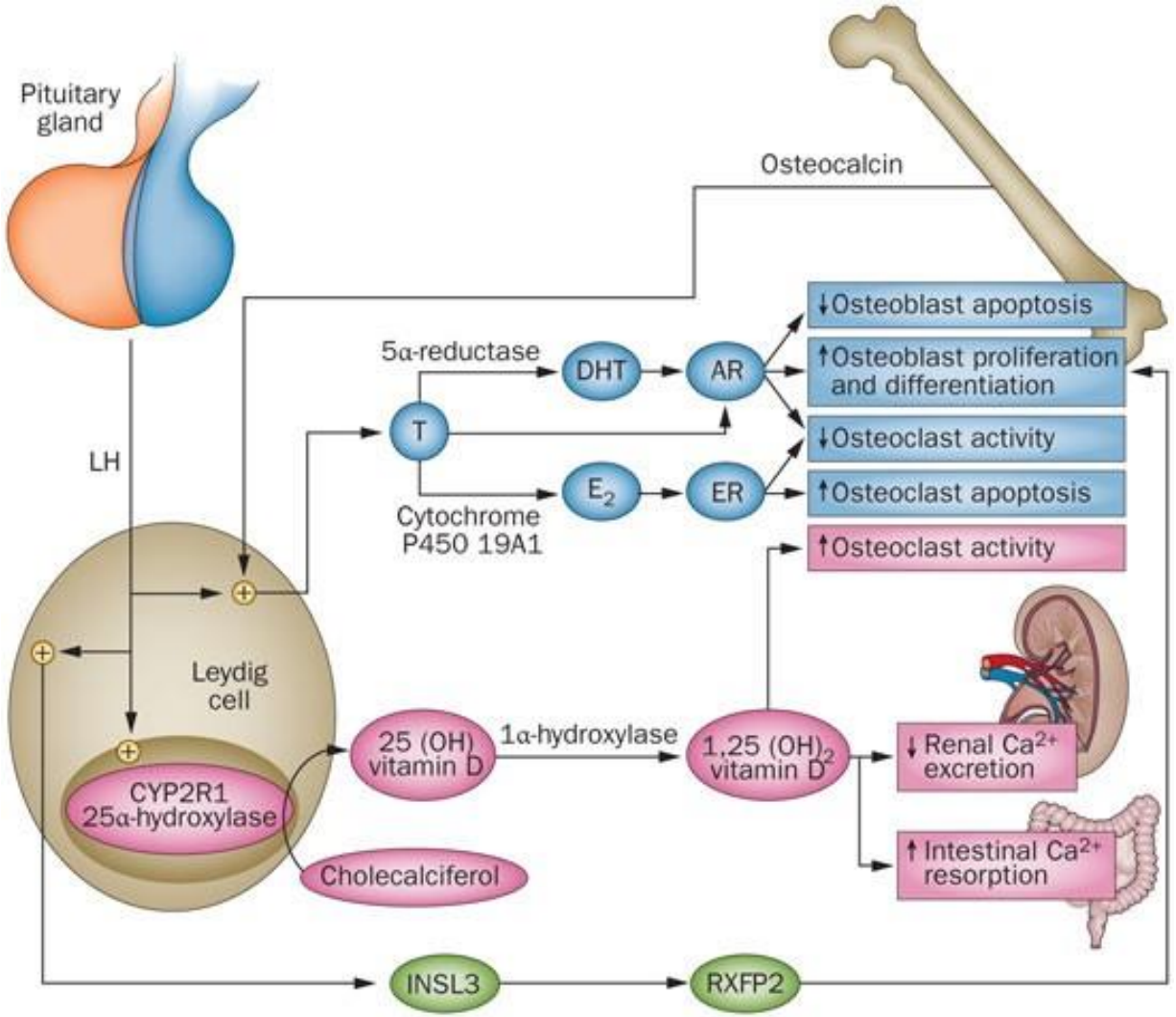
- **Research funding:** Handok, Ipsen

Crosstalk between testis and bone



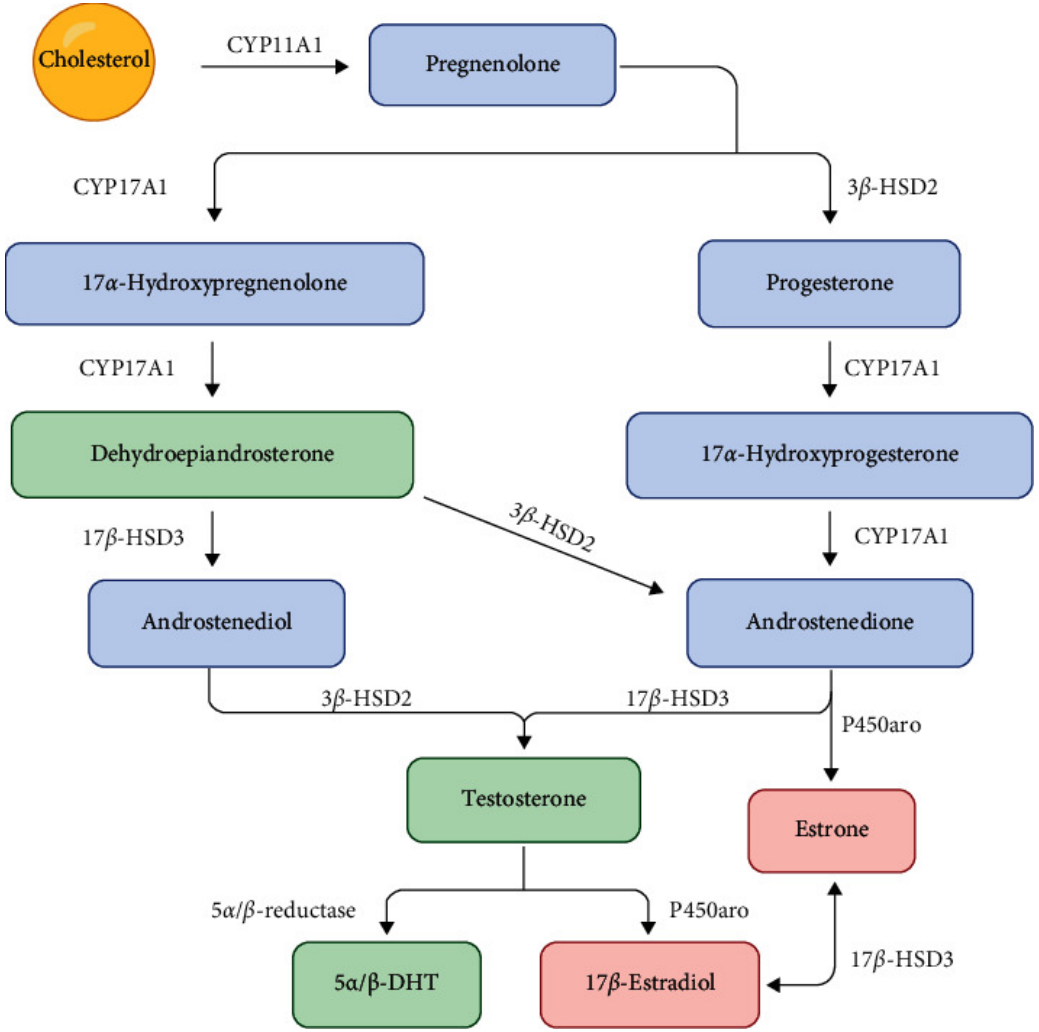
- Testosterone and bone health
  - Testosterone, primarily produced in the testes, plays a crucial role in maintaining bone health and density in males
- Bone-derived factors and testicular function
  - Osteocalcin, produced by bone cells, has been shown to promote testosterone production in Leydig cells of the testes. This highlights a feed-forward loop in which bone health influences testicular function, which in turn, affects bone health
- Beyond testosterone
  - The interplay between testis and bone is not solely dependent on testosterone. Leydig cells also produce other substances like INSL3, which plays a role in osteoblast function. Additionally, Leydig cells contribute to the 25-hydroxylation of vitamin D, a process crucial for bone health

1,25 (OH)2 vitamin D, 1,25-dihydroxyvitamin D; 25 (OH) vitamin D, 25-hydroxyvitamin D; AR, androgen receptor; DHT, dihydrotestosterone; E2, 17β-Estradiol; ER, estrogen receptor; INSL3, insulin-like 3; LH, luteinizing hormone; RXFP2, relaxin family peptide receptor 2; T, testosterone.

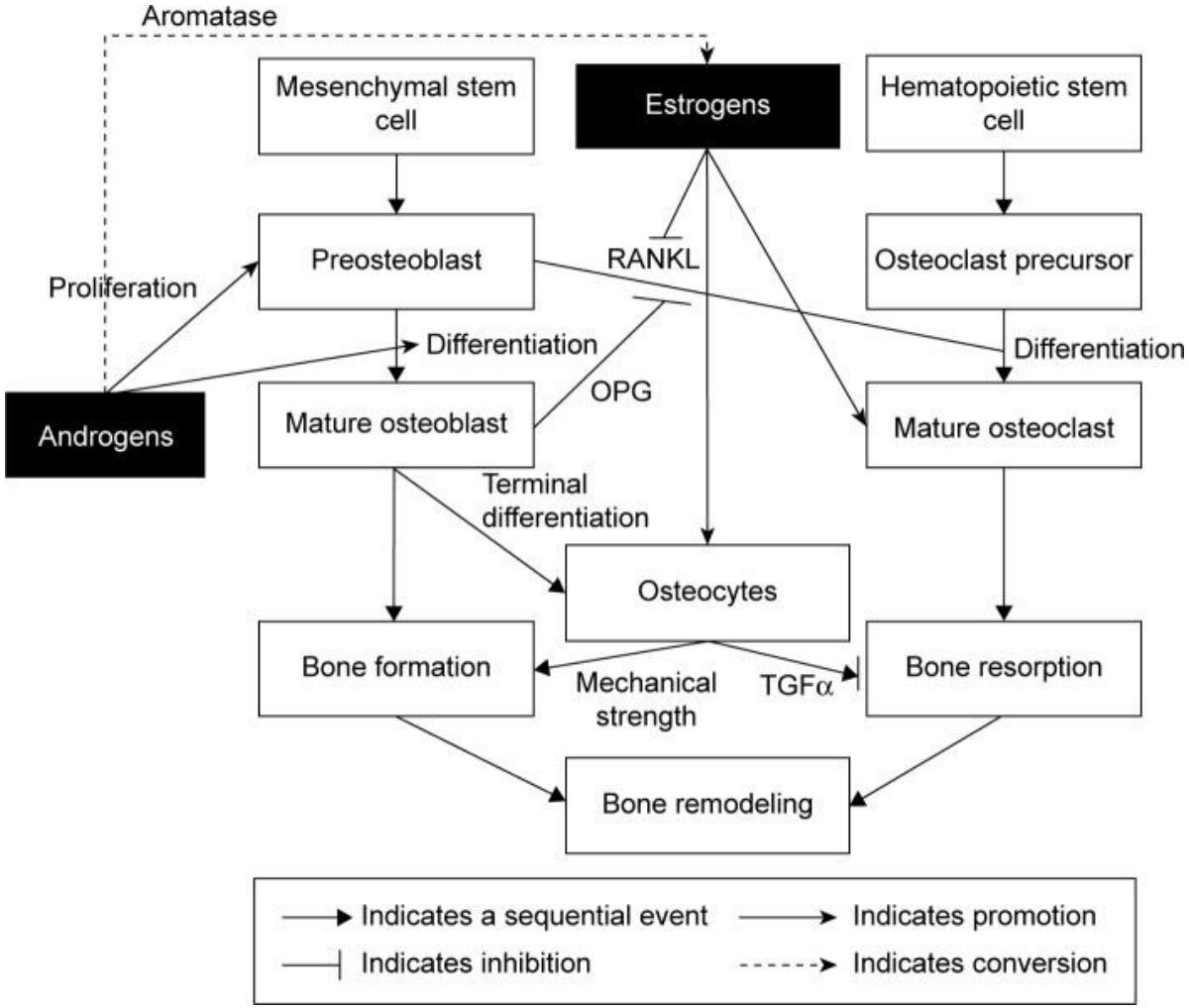
Ferlin A, et al. *Nat Rev Endocrinol* 2013;9:548–554.

Effects of testosterone/estrogen on bone cells

Androgen synthesis from cholesterol[1]



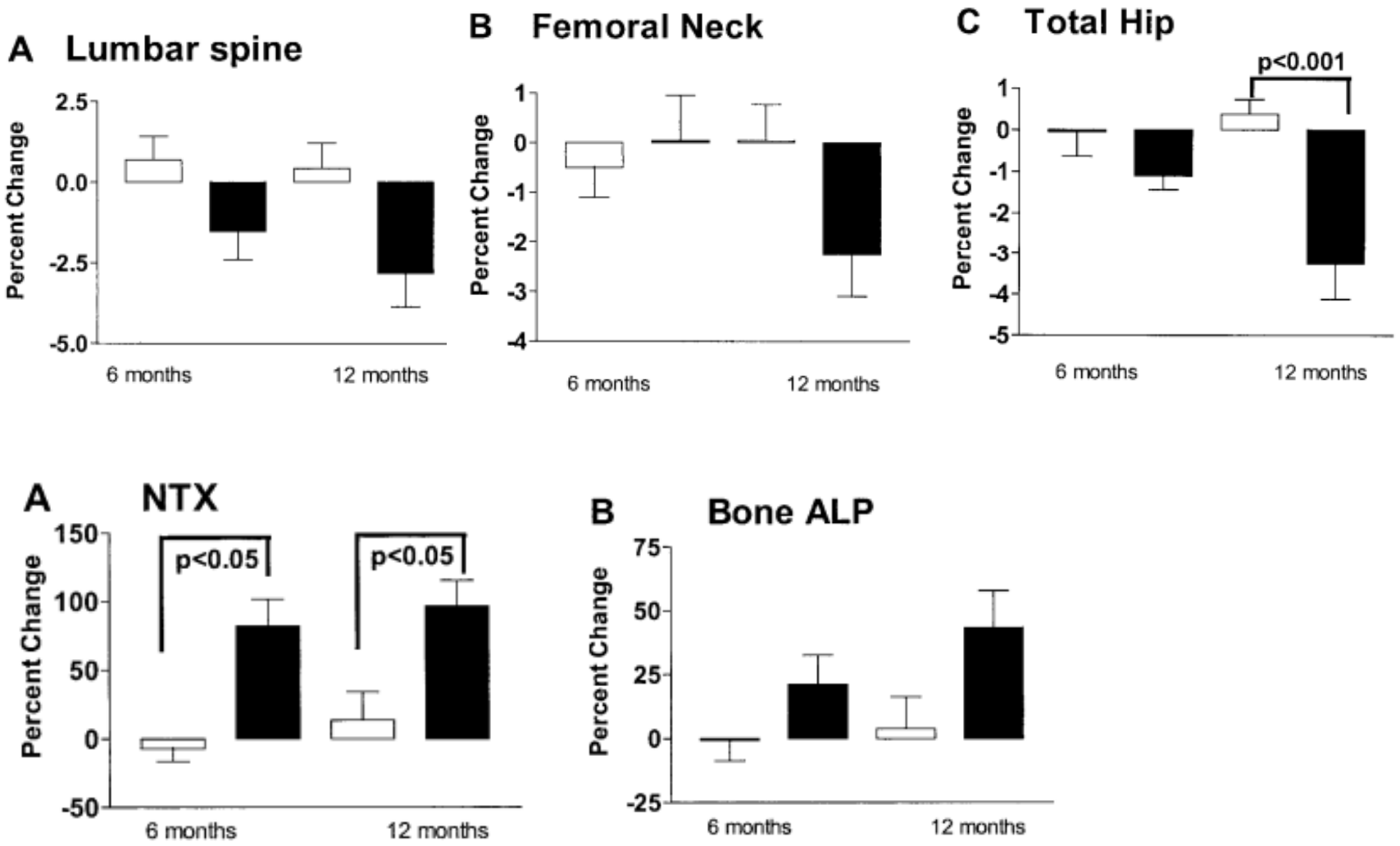
The effects of testosterone on bone cells[2]



OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor kappa-B ligand; TGFα, transforming growth factor-alpha.

1. Carbajal-García A, et al. *Int J Endocrinol* 2020;2020:8849641; 2. Mohamad NV, et al. *Clin Interv Aging* 2016;11:1317–1324.

Rapid bone loss after ADT in patients with prostate cancer



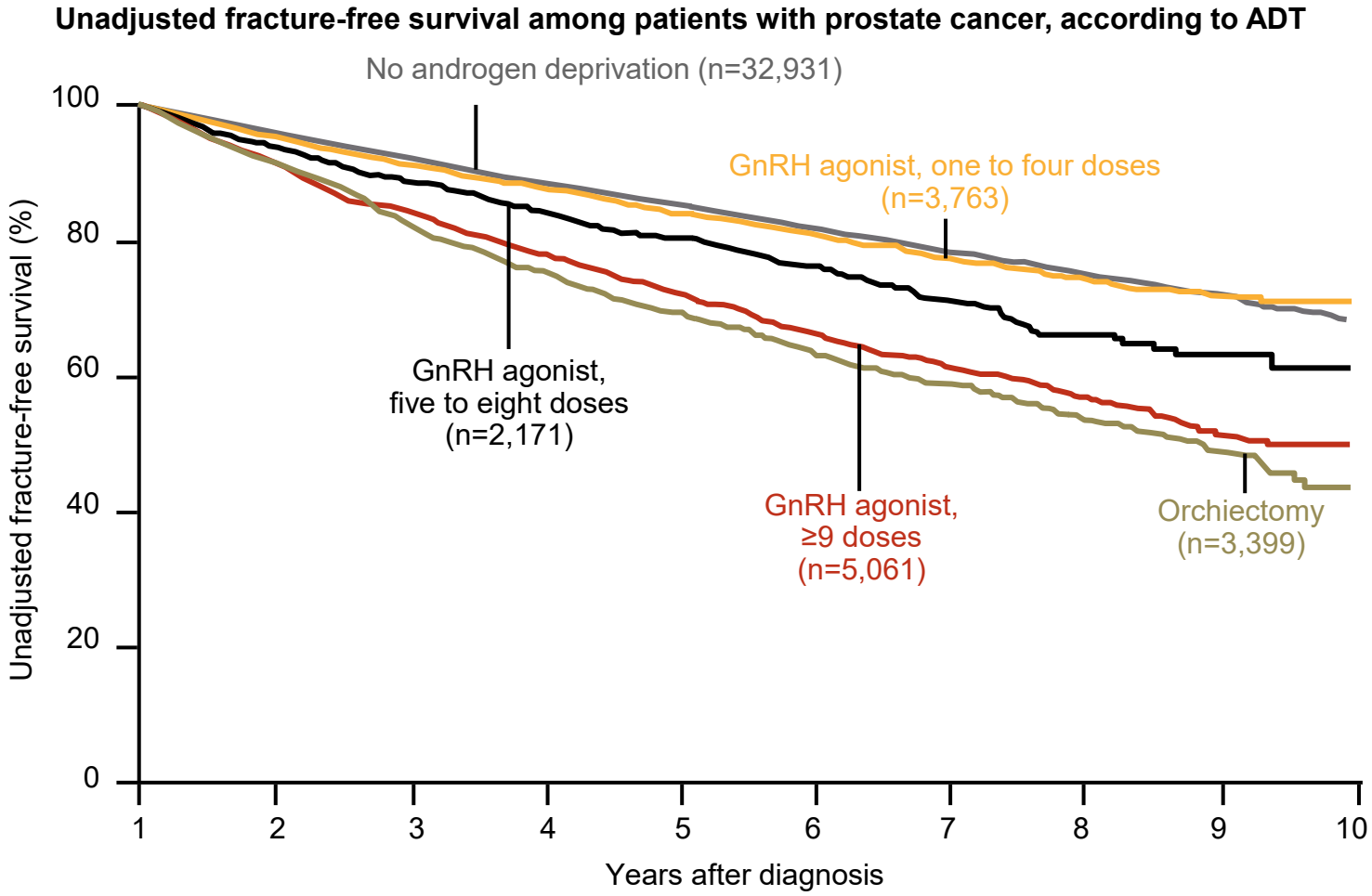
ADT, androgen deprivation therapy; ALP, alkaline phosphatase; NTX, n-telopeptide.
Mittan D, et al. *J Clin Endocrinol Metab* 2002;87:3656–3661.

Prevalence of osteoporosis in patients on ADT: Sensitivity analysis

Studies selected if:	Osteoporosis prevalence, % (95 %CI)	Osteopenia prevalence, % (95 %CI)	Normal bone mass prevalence, % (95% CI)
Age			
≥70 years	0.270 (0.176–0.361)	0.485 (0.420–0.526)	0.245 (0.158–0.331)
<70 years	0.436 (0.233–0.612)	0.361 (0.261–0.434)	0.204 (0.074–0.351)
Publication year			
<2007	0.270 (0.156–0.391)	0.487 (0.387–0.573)	0.244 (0.172–0.316)
≥2007	0.329 (0.193–0.450)	0.416 (0.317–0.482)	0.255 (0.141–0.362)
Ethnicity			
Asian population	0.158 (0.043–0.309)	0.444 (0.338–0.530)	0.398 (0.241–0.546)
Non-Asian population	0.347 (0.233–0.449)	0.432 (0.345–0.495)	0.221 (0.137–0.302)
Median ADT duration			
<24 months/intermittent	0.198 (0.067–0.346)	0.506 (0.367–0.594)	0.297 (0.114–0.485)
24–30 months	0.202 (0.067–0.363)	0.416 (0.307–0.500)	0.381 (0.236–0.510)
>30 months	0.427 (0.279–0.568)	0.395 (0.301–0.480)	0.179 (0.110–0.253)
ROI			
Hip/lumber spine	0.314 (0.187–0.426)	0.400 (0.320–0.445)	0.287 (0.179–0.381)
Third distal radius (alone or with hip/lumber spine)	0.343 (0.270–0.420)	0.496 (0.420–0.588)	0.161 (0.108–0.222)
ADT			
Primary gonadal ablation therapy	0.355 (0.287–0.426)	0.482 (0.397–0.567)	0.164 (0.119–0.214)
Combination androgen blockage	0.302 (0.170–0.422)	0.402 (0.317–0.452)	0.295 (0.179–0.396)

ADT, androgen deprivation therapy; CI confidence interval; ROI, region of interest.
Lassemillante AC, et al. *Endocrine* 2014;45:370–381.

ADT and fracture risk in patients with prostate cancer



Relative risk of fracture increased steadily with the increasing number of doses of GnRH agonist (p<0.001 for linear trend)

ADT , androgen deprivation therapy; GnRH, gonadotropin-releasing hormone.
Shahinian VB, et al. *N Engl J Med* 2005;352:154–164.

Risk of fracture after ADT for prostate cancer

Toxic effect	12 months before diagnosis, %	P value	12–16 months after diagnosis, %	P value
Osteoporosis		0.19		<0.001
ADT	0.59		6.92	
No ADT	0.46		3.69	
Any fracture		0.01		<0.001
ADT	3.41		19.37	
No ADT	2.80		12.63	
Fracture resulting in hospitalization		0.49		<0.001
ADT	0.26		5.19	
No ADT	0.21		2.37	

Toxic effect	12 months before diagnosis, %	P value	12–16 months after diagnosis, %	P value
Spine		0.44		<0.001
ADT	0.36		3.20	
No ADT	0.30		1.64	
Upper arm		0.62		<0.001
ADT	0.30		2.21	
No ADT	0.26		1.19	
Femoral neck (hip)		0.02		<0.001
ADT	0.44		4.06	
No ADT	0.26		2.06	
Other parts of the femur		0.47		<0.001
ADT	0.06		1.17	
No ADT	0.09		0.64	
Lower leg		0.36		<0.001
ADT	0.36		2.24	
No ADT	0.29		1.56	

ADT , androgen deprivation therapy.
Shahinian VB, et al. *N Engl J Med* 2005;352:154–164.

Bone health issues in patients with prostate cancer

	Fragility fractures/ osteoporosis	Skeletal-related events
Population at risk[1]	All men	Men with bone metastases
Anatomic site[1]	Normal bone	Bone metastases
Effects of cancer treatment:		
ADT[1,2]	↑	↓
Abiraterone acetate[1,2]	↑	↓
Enzalutamide, darolutamide, apalutamide[3]	↑	↓
Osteoclast activation[3]	+	+++

ADT, androgen deprivation therapy; mCRPC, metastatic castrate-resistant prostate cancer.

1. Speaker's clinical experience; 2. Coleman R, et al. *Ann Oncol* 2020;31:1650–1663; 3. Hussain A, et al. *Prostate Cancer Prostatic Dis* 2021;24:290–300.

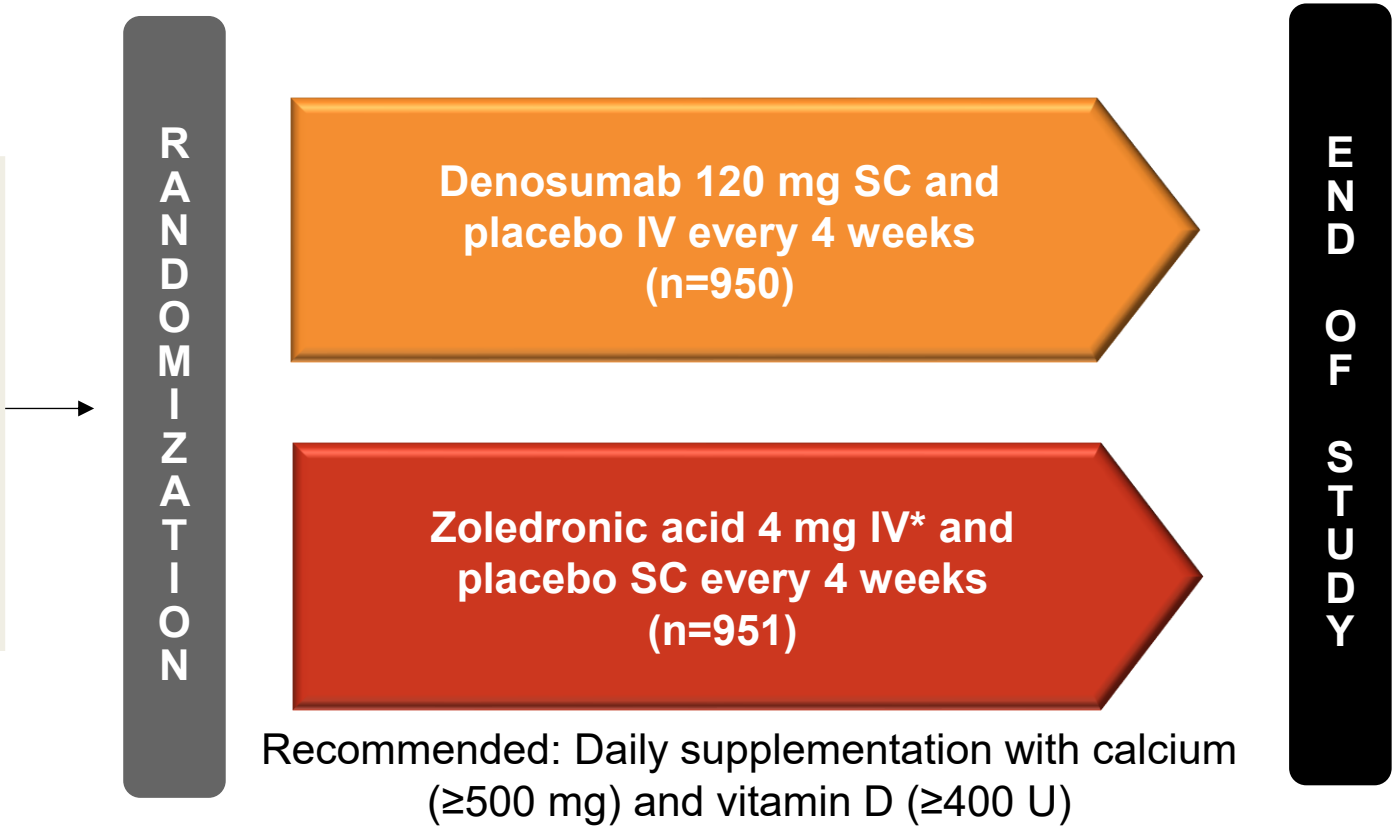
Denosumab Phase III study in mCRPC

Key inclusion criteria

Castration-resistant prostate cancer and at least one bone metastasis, and documented failure of at least one hormonal therapy

Key exclusion criteria

Current or prior IV bisphosphonate treatment



Recommended: Daily supplementation with calcium (≥500 mg) and vitamin D (≥400 U)

Primary endpoint: Time to first on-study SRE (non-inferiority)

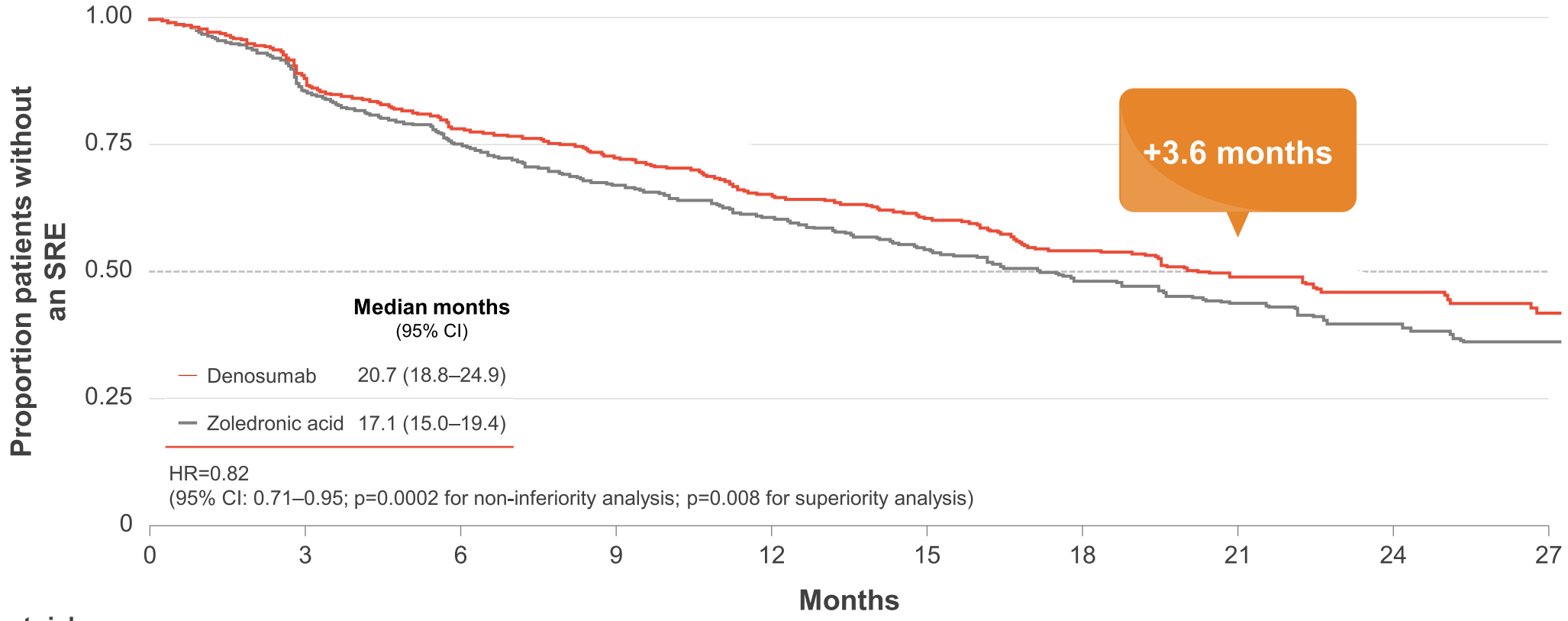
Secondary: Time to first on-study SRE (superiority), time to first and subsequent on-study SRE (superiority)

One of the approved indications of denosumab in Korea is prevention of SRE in patients with multiple myeloma and in patients with bone metastases from solid tumors.

IV, intravenous; mCRPC, metastatic castrate-resistant prostate cancer; SC, subcutaneous; SRE, skeletal-related event.

Fizazi K, et al. *Lancet* 2011;377:813–822.

Primary endpoint: Time to first on-study SRE



Patients at risk

Denosumab	950	758	582	472	361	259	168	115	70	39
Zoledronic acid	951	733	544	407	299	207	140	93	64	47

One of the approved indications of denosumab in Korea is prevention of SRE in patients with multiple myeloma and in patients with bone metastases from solid tumors.

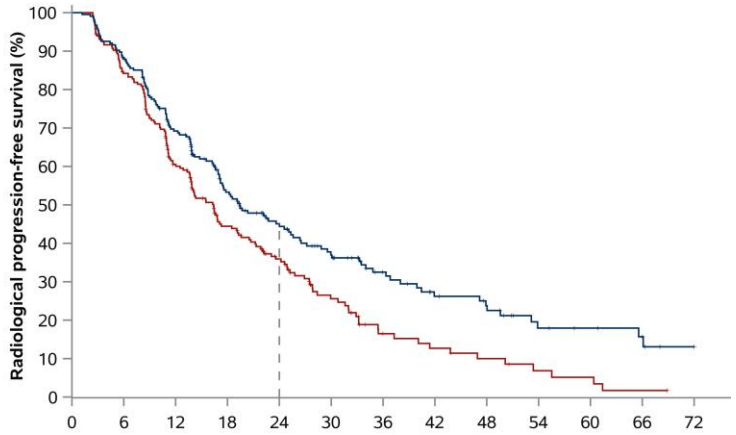
CI, confidence interval; HR, hazard ratio; SRE, skeletal-related event.

Fizazi K, et al. *Lancet* 2011;377:813–822.

Lessons from ERA-223 and PEACE-3: Cumulative incidence of fractures by treatment arm and use of BPAs

- The ERA-223 trial, which combined Ra-223 with abiraterone (another ARPI), showed a higher fracture rate than abiraterone alone[1]
- This led to the mandatory use of BPAs in the PEACE-3 trial and other studies[1,2]

Radiological progression-free survival was assessed by the local investigator in the ITT population[2]



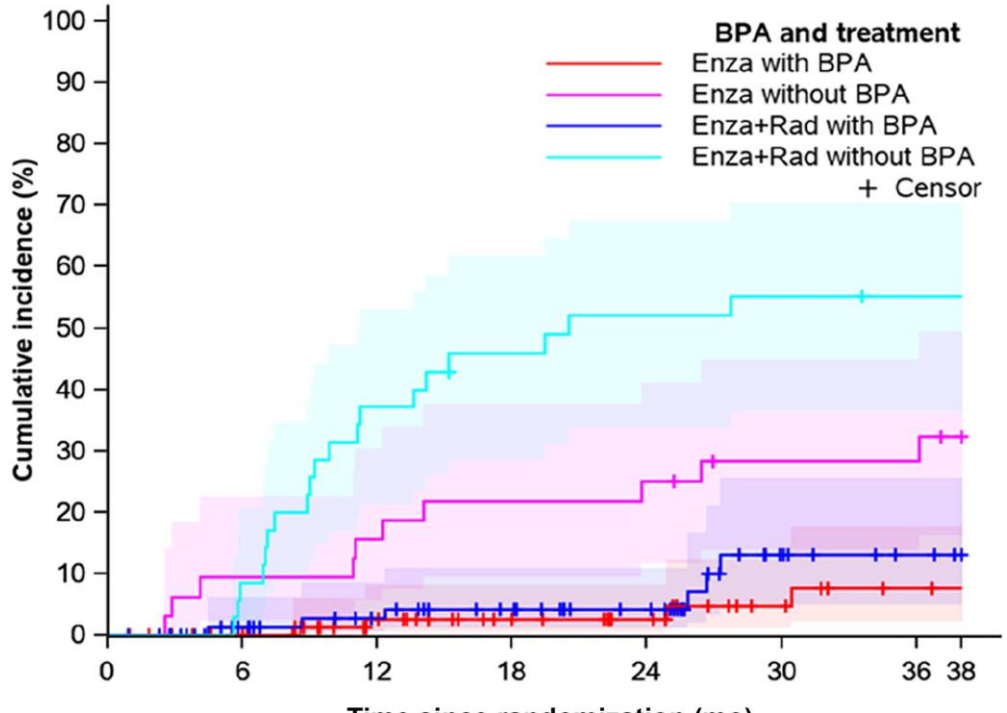
Patients at risk

Enza-	224	180	122	77	52	28	13	10	7	4	3	1	0
Enza + Ra223-	222	188	138	91	64	48	32	23	19	11	9	7	3

No. cumulative events

Enza-	0	34	84	114	128	141	150	153	155	157	158	160	160
Enza + Ra223-	0	26	65	94	107	118	123	129	131	135	135	136	137

Fine–Gray cumulative incidence of fractures by treatment arm and BPA use[1]



Patients at risk

Enza with BPA	97	82	68	48	36	21	14
Enza without BPA	32	29	26	21	13	5	5
Enza+Rad with BPA	87	74	59	46	36	18	12
Enza+Rad without BPA	35	31	18	12	6	4	3

ARPI, androgen receptor pathway inhibitor; BPA, bone-protecting agent; Enza, enzalutamide; ITT, intent-to-treat; Ra223, radium-223.

1. Gillessen S, et al. *Eur Urol* 2025;87:285–288; 2. Tombal B, et al. *Ann Oncol* 2025:S0923–7534.

Current evidence for BPAs in mCRPC

- Reduced fracture rates[1]
  - BPAs, including denosumab and zoledronic acid, significantly reduce the risk of fractures and other SREs in patients with mCRPC and bone metastases
- Efficacy in combination therapy[2]
  - Studies show that BPAs are particularly important when combined with treatments like radium-223 or androgen receptor pathway inhibitors (e.g. enzalutamide, abiraterone) to mitigate the risk of SREs
- Mandatory use[3]
  - The importance of BPAs in this context is well established, with some trials even mandating their use to ensure patient safety
- Improved quality of life[4]
  - By preventing or delaying SREs, BPAs help maintain patient independence, reduce pain, and improve overall quality of life

BPA, bone-protecting agent; mCRPC, metastatic castration-resistant prostate cancer; SRE, skeletal-related event.

1. Suzman DL, et al. *Cancer Metastasis Rev* 2014;33:619–628. 2. Trieu J, et al. *Clin Genitourin Cancer* 2022;20:399–403. 3. von Moos R, et al. *Bone* 2022;154:116243. 4. Thomas C, et al. *Dent J (Basel)* 2016;4:28.

Current evidence for zoledronic acid in mHSPC

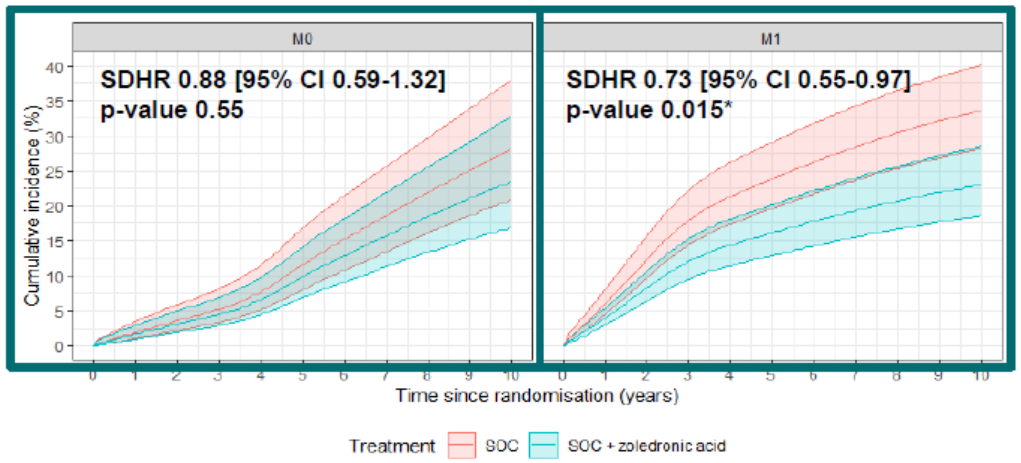
	CALGB 90202[1]	STAMPEDE[2]	ZAPCA[3]
Patient cohort	M1b	M0/M1	M1b
N, randomization	645 (target: 680), 1:1	1,777, 2:1	227, 1:1
SRE, %	299 (target: 470), 46.4%	-	92, 40.5%
Control	ADT + placebo	ADT only	ADT + bicalutamide
Treatment	ADT + 4 mg zoledronic acid once monthly until first SRE	ADT + 4 mg zoledronic acid for six 3-weekly cycles, then 4-weekly until 2 years	ADT + bicalutamide + 4 mg zoledronic acid once monthly for 2 years
HR (SRE)	HR=0.89 (95% CI 0.74–1.07), p=0.22	HR=0.94 (95% CI 0.79–1.11), p=0.450	HR=0.58 (95% CI 0.38–0.88), p=0.009

ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; M, metastasis; mHSPC, metastatic hormone-sensitive prostate cancer; SRE, skeletal-related event.

1. Smith MR, et al. *J Clin Oncol* 2014;32:1143–1150. 2. James ND, et al. *Lancet* 2016;387:1163–1177. 3. Kamba T, et al. *Int J Clin Oncol* 2017;22:166–173.

Updated results of the STAMPEDE study (ESMO 2023)

	Model-based cumulative incidence (95% CI)			
	Non metastatic		Metastatic	
Treatment	5 years (%)	10 years (%)	**5 years (%)**	10 years (%)
ADT only	11 (8–15)	26 (20–33)	**23 (19–28)**	32 (27–37)
ADT + zoledronic acid	10 (7–13)	23 (18–30)	**17 (14–21)**	24 (20–28)
ADT + docetaxel	10 (7–13)	24 (19–30)	**23 (19–27)**	34 (29–39)
ADT + docetaxel + zoledronic acid	9 (6–13)	21 (15–30)	**17 (13–23)**	26 (20–33)



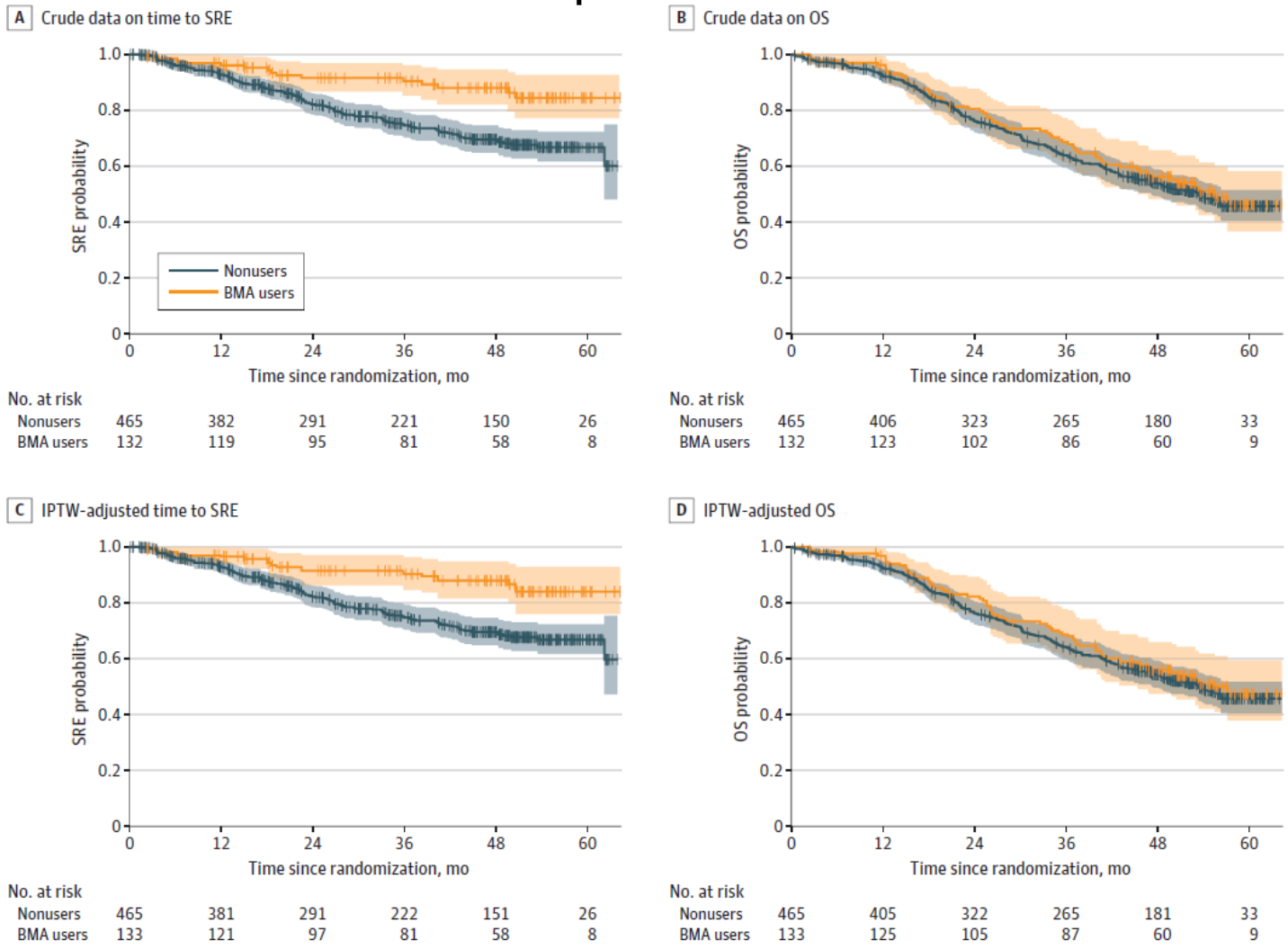
Average treatment effect (difference in 5-year incidence [95% CI])			
Control	Treatment	Non metastatic	Metastatic
ADT	ADT + **zoledronic acid**	-1.2 (-5.1; 2.7)	-5.6 (-10.9; -0.4)
ADT	ADT + docetaxel	-1.2 (-5.0; 2.5)	-0.1 (-5.3; 5.0)
ADT	ADT + docetaxel + **zoledronic acid**	-2.3 (-8.1; 3.4)	-5.6 (-13.4; 2.2)
ADT + docetaxel	ADT + docetaxel + **zoledronic acid**	-1.1 (-4.5; 2.3)	-5.4 (-10.3; -0.5)

ADT, androgen deprivation therapy; CI confidence interval; ESMO, European Society for Medical Oncology; SDHR, subdistribution hazard ratio.

Jones C, et al. Presented at ESMO 2023. 20–24 October 2023. Madrid, Spain. (1768MO)

Post hoc analysis of the LATITUDE study in mHSPC

Crude and IPTW–adjusted Kaplan–Meier curves based on BMA use in the abiraterone acetate + prednisone cohort

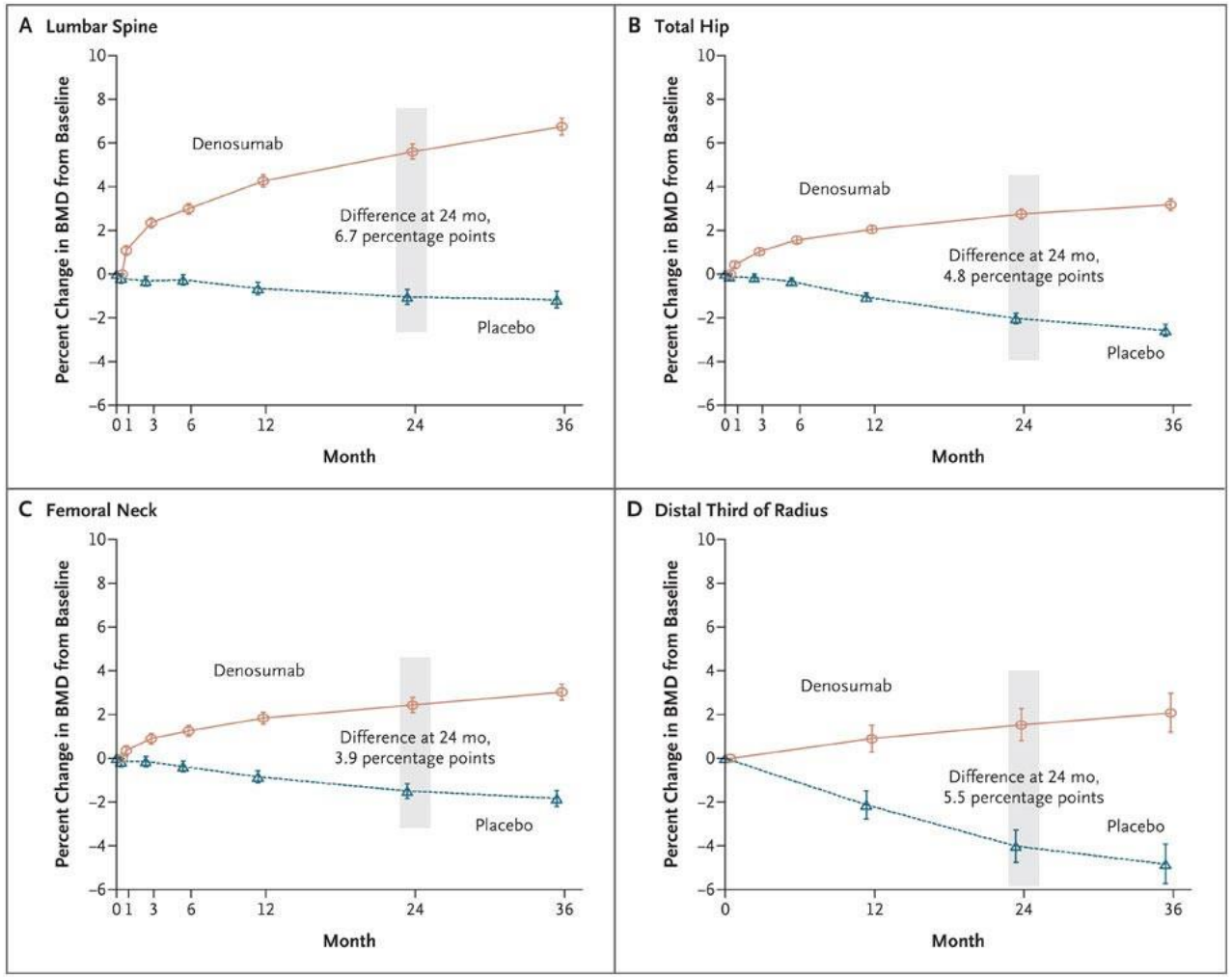


BMA, bone-modifying agent; IPTW, inverse probability of treatment weighting; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; SRE, skeletal-related event.

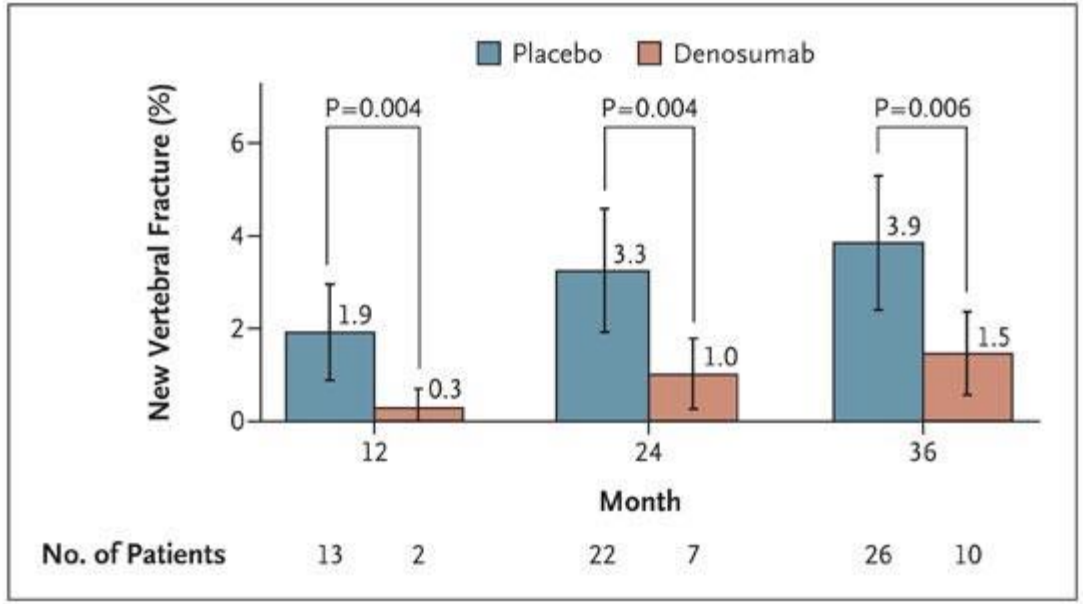
Fukuokaya W, et al. *JAMA Netw Open* 2024;7:e242467.

Denosumab in M0 HSPC

Mean percent changes from baseline BMD values during the study period, according to skeletal site and study group



Denosumab at a dose of 60 mg subcutaneously every 6 months or placebo



One of the approved indications of denosumab in Korea is prevention of SRE in patients with multiple myeloma and in patients with bone metastases from solid tumors.

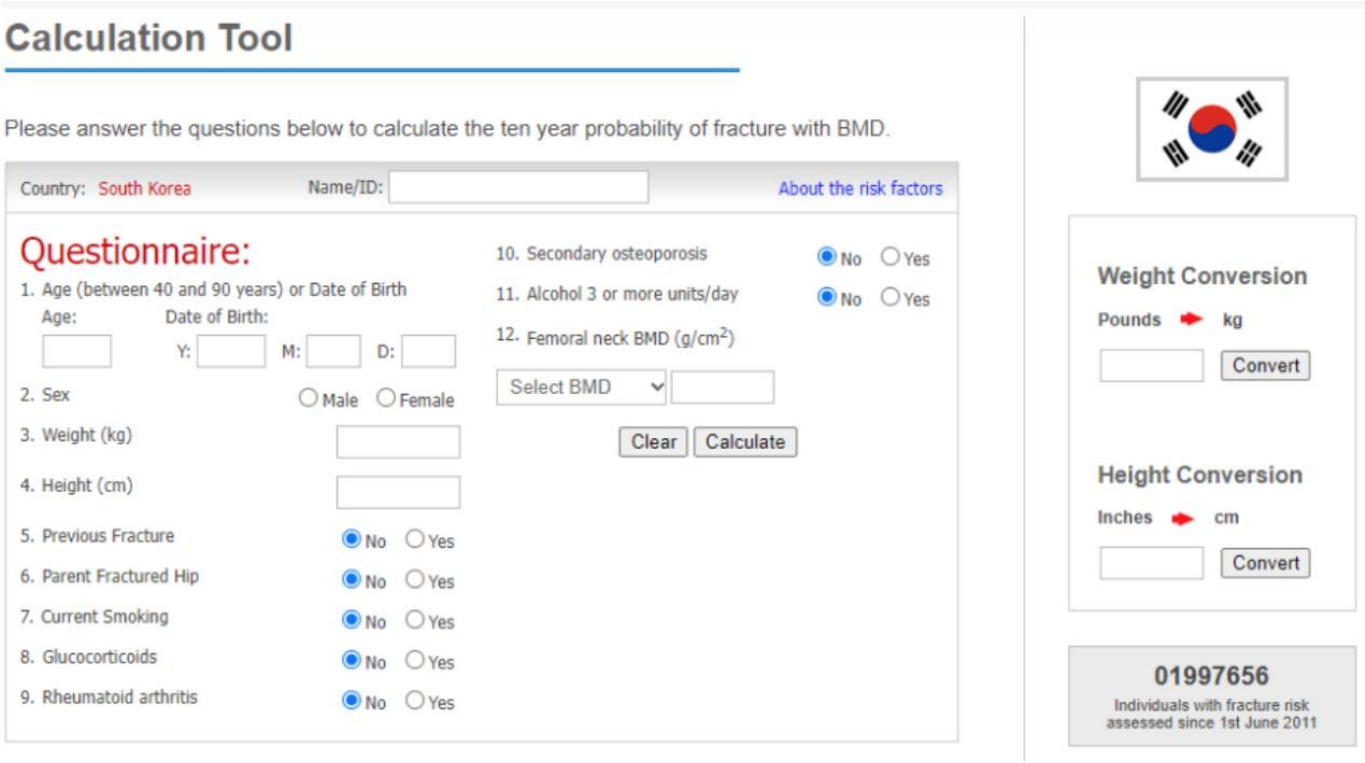
BMD, bone mineral density; HSPC, hormone-sensitive prostate cancer; M, metastasis.

Smith MR, et al. *N Engl J Med* 2009;361:745–755.

Current evidence for BPAs in mHSPC

- Target population[1]
  - May be beneficial in some patients
  - Risk stratification tool may be considered
- Appropriate drugs*[2]
  - RANKL inhibitors may be superior to bisphosphonate
- Risk[1]
  - Hypocalcemia can be prevented with vitamin D and calcium supplementation
  - ONJ should be prevented by regular dental checkups

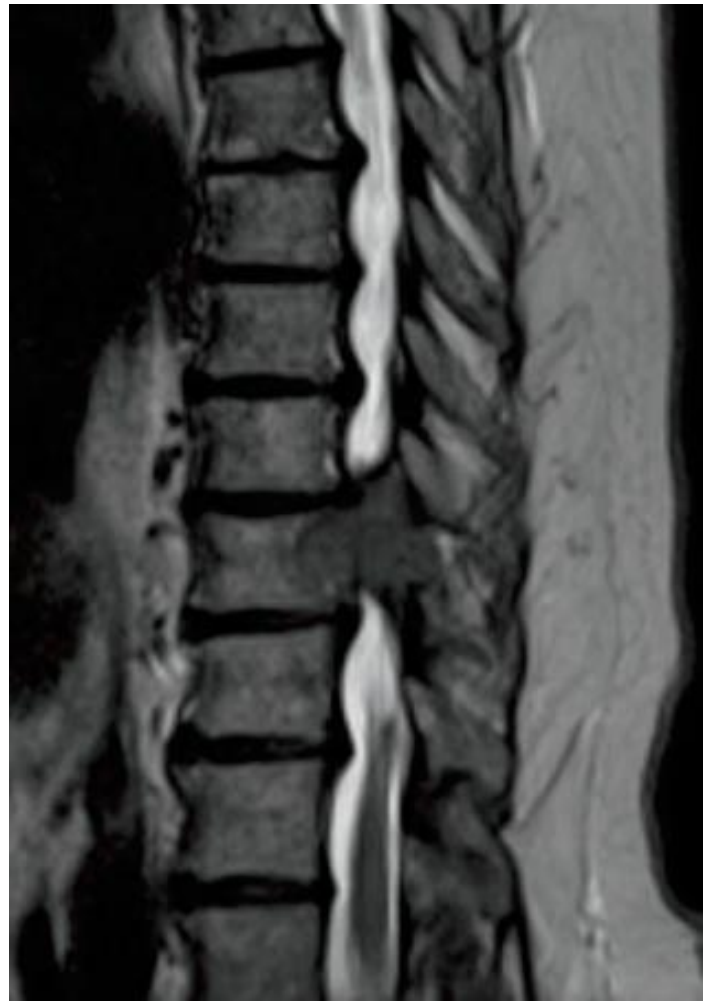
FRAX[3]



From a randomized, double blind study in patients with CRPC.
BMD, bone mineral density; BPA, bone-protecting agent; CRPC, castration-resistant prostate cancer; FRAX, Fracture Risk Assessment Tool; mHSPC, metastatic hormone-sensitive prostate cancer; ONJ, osteonecrosis of the jaw; RANKL, receptor activator of nuclear factor kappa-B ligand.
1. Speaker's own experience; 2. Fizazi K, et al. *Lancet* 2011;813–822; 3. FRAX. Calculation tool. Available at: https://frax.shef.ac.uk/FRAX/tool.aspx?lang=en Lat accessed: July 2025.

Case 1: mHSPC with bone metastasis

- Male, aged 77 years
- Height and weight: 170 cm and 70 kg
- Never smoker
- Alcohol consumption (+)
- Sudden back pain with walking/voiding difficulty
- Lumbar fusion surgery for spinal cord compression
- Diagnosed as mHSPC
- Start ADT + enzalutamide



Slide content provided by the speaker. Patient permission has been obtained for all images.
ADT, androgen deprivation therapy: mHSPC, metastatic hormone-sensitive prostate cancer.
Speaker's own case.

Question for the audience

- What are the appropriate next steps for this patient?

A **Palliative radiotherapy for bone metastasis**

B **Check bone mineral density**

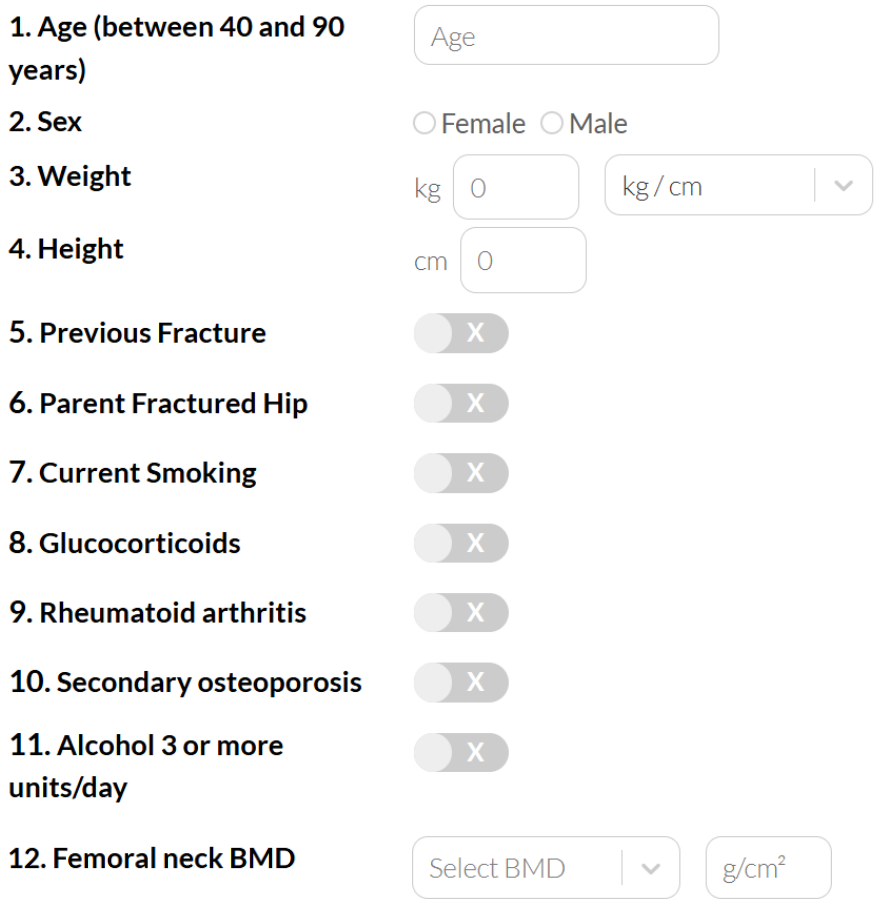
C **Check FRAX probability**

D **Regular dental examination**

FRAX, Fracture Risk Assessment Tool.

Case 1: mHSPC with bone metastasis

- Several factors of increasing fracture risk
  - Steroid use: modifiable
  - Smoking: modifiable
  - Alcohol consumption: modifiable
  - Low BMI: modifiable
  - Age, sex, family history, previous fracture, osteoporosis, BMD, RA: unmodifiable



BMD, bone mineral density; BMI, body mass index; mHSPC, metastatic hormone-sensitive prostate cancer; RA, rheumatoid arthritis.
Speaker's own case.

Case 1: mHSPC with bone metastasis

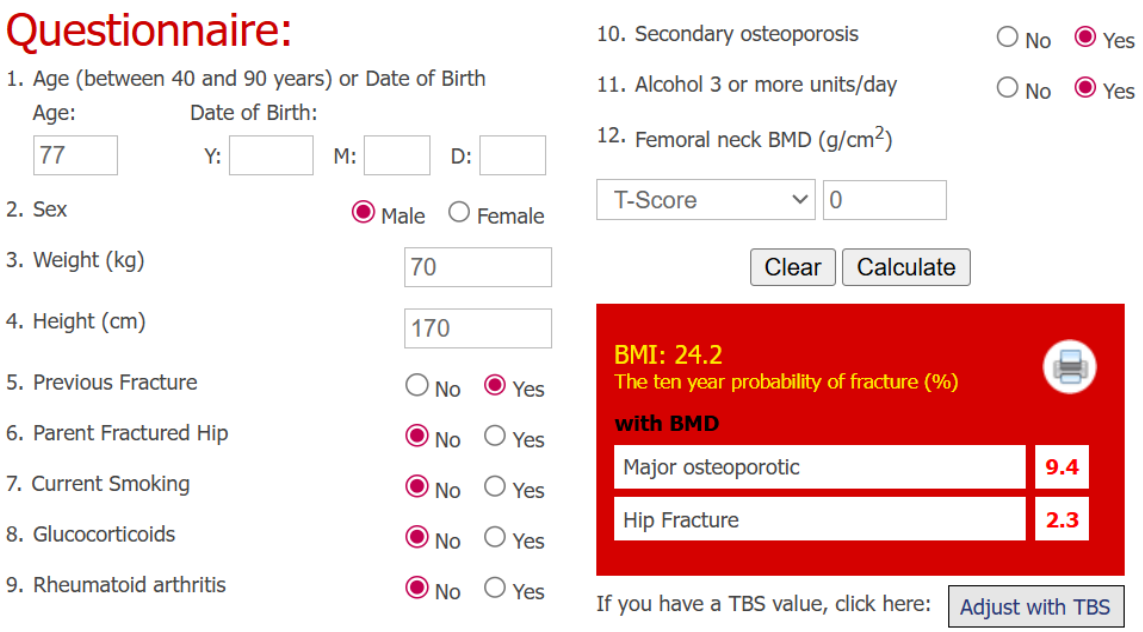
- Use of BPA based on FRAX score[1]
- National Osteoporosis Foundation recommended thresholds for bone resorptive agents[2]
  - ≥20% 10-year risk of major osteoporotic fracture
  - ≥3% 10-year risk of hip fracture

BPA, bone-protecting agent; FRAX, Fracture Risk Assessment Tool; mHSPC, metastatic hormone-sensitive prostate cancer.

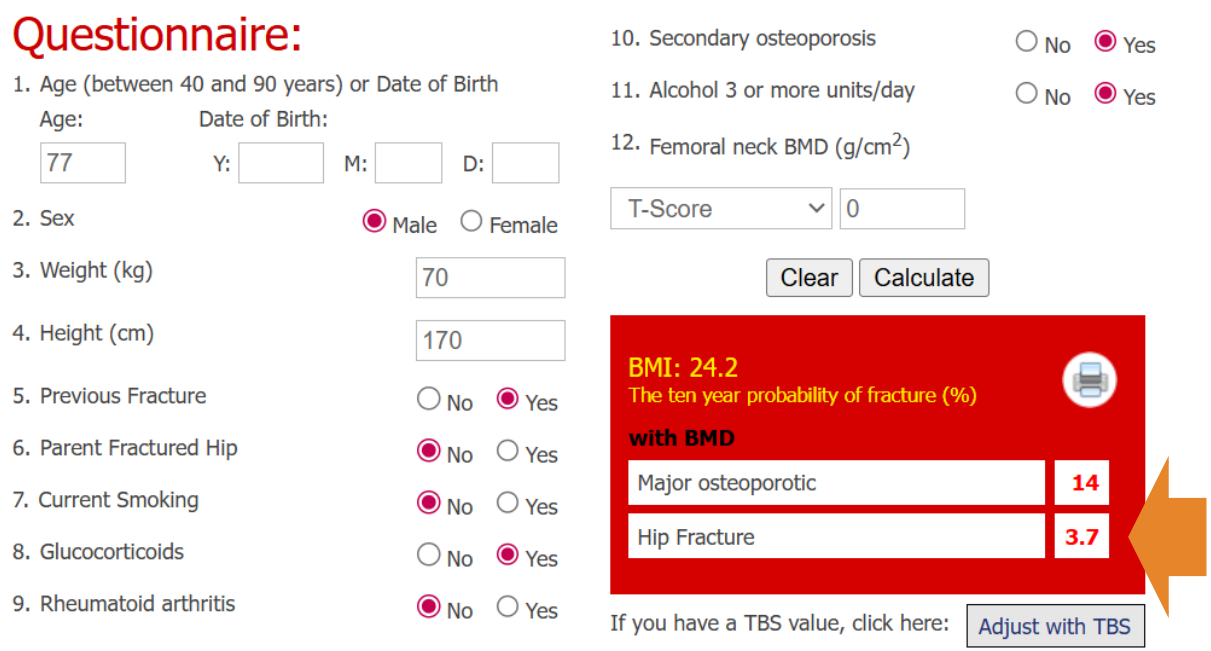
1. Speaker's own case; 2. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis; Available at: https://www.natap.org/2008/HIV/NOF_Clinicians_Guide-1.pdf. Last accessed: July 2025.

What if the patient received abiraterone + prednisolone instead of enzalutamide?

Use of enzalutamide[1]



Use of abiraterone + prednisolone[1]



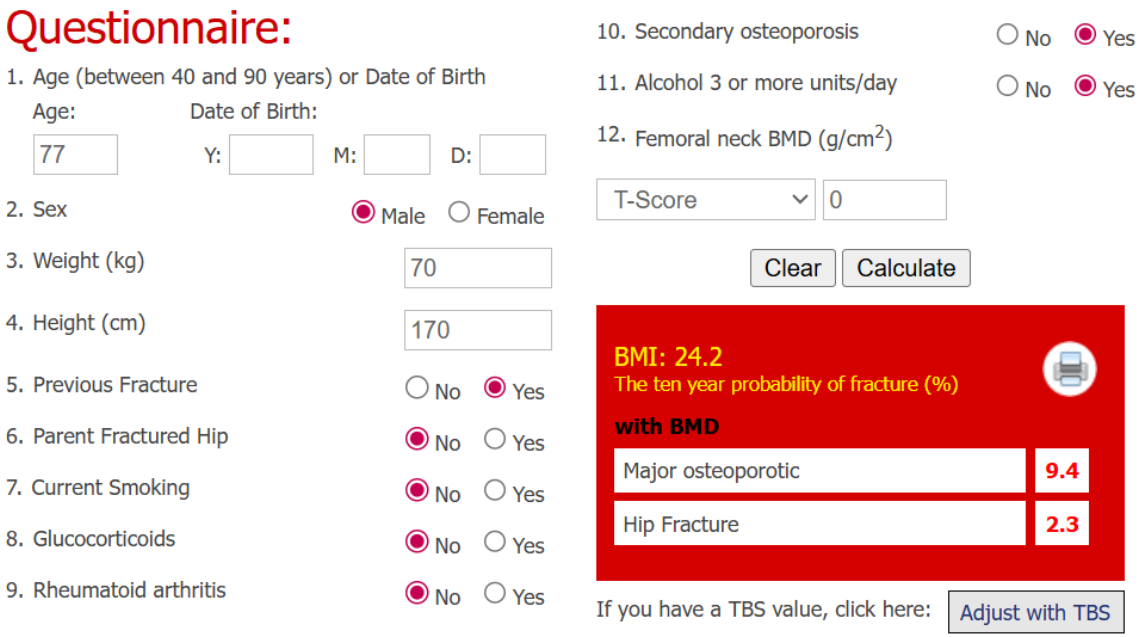
- National Osteoporosis Foundation recommended thresholds for bone resorptive agents[2]
  - ≥20% 10-year risk of major osteoporotic fracture
  - ≥3% 10-year risk of hip fracture

BMD, bone mineral density; BMI, body mass index; TBS, trabecular bone score.

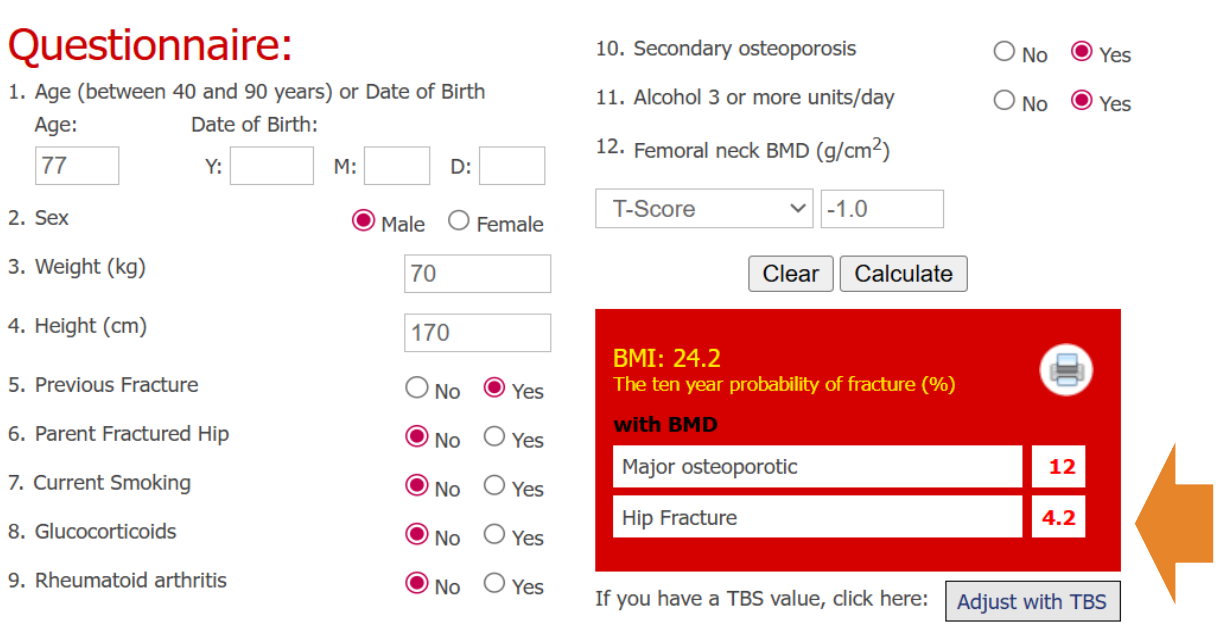
1. Speaker's own case; 2. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis; Available at: https://www.natap.org/2008/HIV/NOF_Clinicians_Guide-1.pdf. Last accessed: July 2025.

What if this was a patient with osteopenia?

BMD T-Score= 0[1]



BMD T-score= -1.0[1]



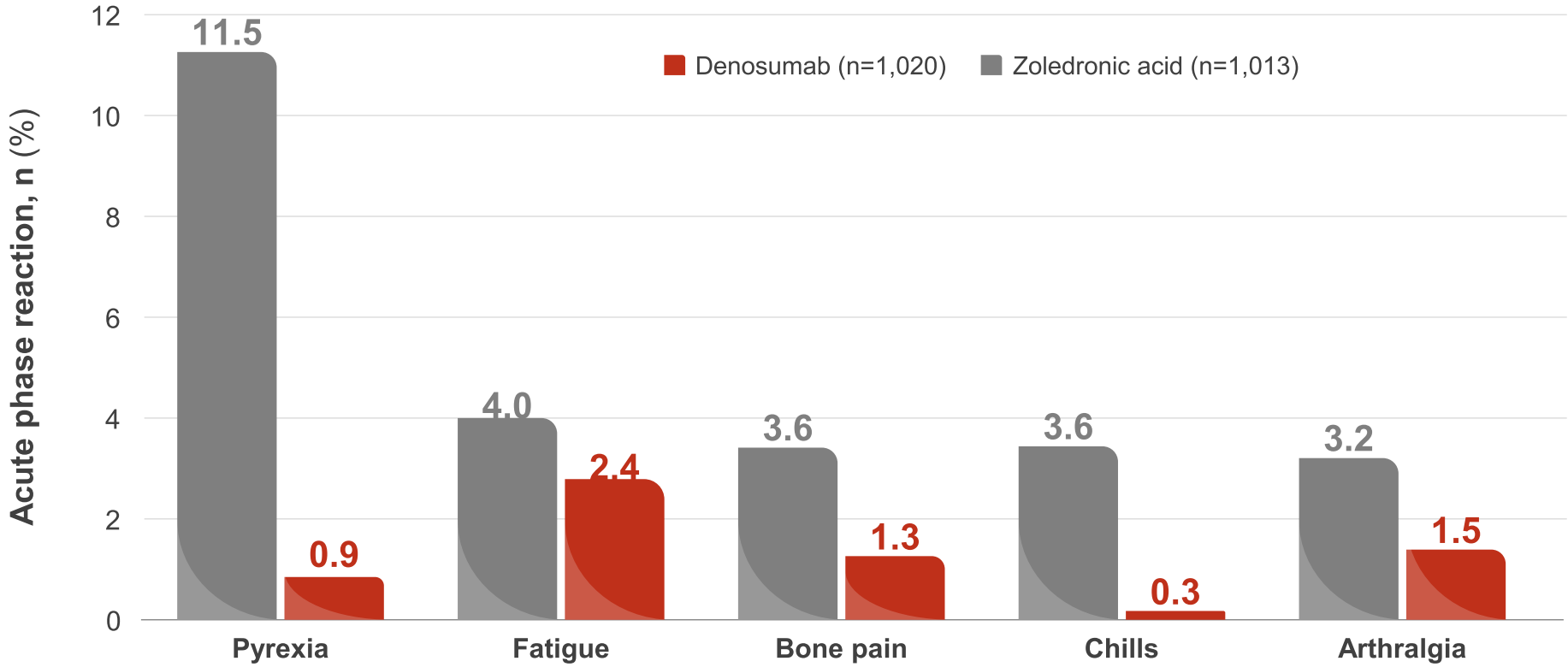
- National Osteoporosis Foundation recommended thresholds for bone resorptive agents[2]
  - ≥20% 10-year risk of major osteoporotic fracture
  - ≥3% 10-year risk of hip fracture

BMD, bone mineral density; BMI, body mass index; TBS, trabecular bone score.

1. Speaker's own case; 2. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis; Available at: https://www.natap.org/2008/HIV/NOF_Clinicians_Guide-1.pdf. Last accessed: July 2025.

What is your choice between bisphosphonate vs. RANKL inhibitors?

- IV bisphosphonates are currently used to treat bone metastases and prevent SREs in patients with advanced breast cancer. In a phase 3 study, denosumab, a fully human monoclonal antibody against RANKL, was shown to be superior to zoledronic acid in delaying or preventing SREs in patients with breast cancer and bone metastases



IV, intravenous; RANKL, receptor activator of nuclear factor kappa-B ligand; SRE, skeletal-related event.
Stopeck AT, at al. *Cancer Res* 2010;24:Abstract P6-14–09.

Question for the audience

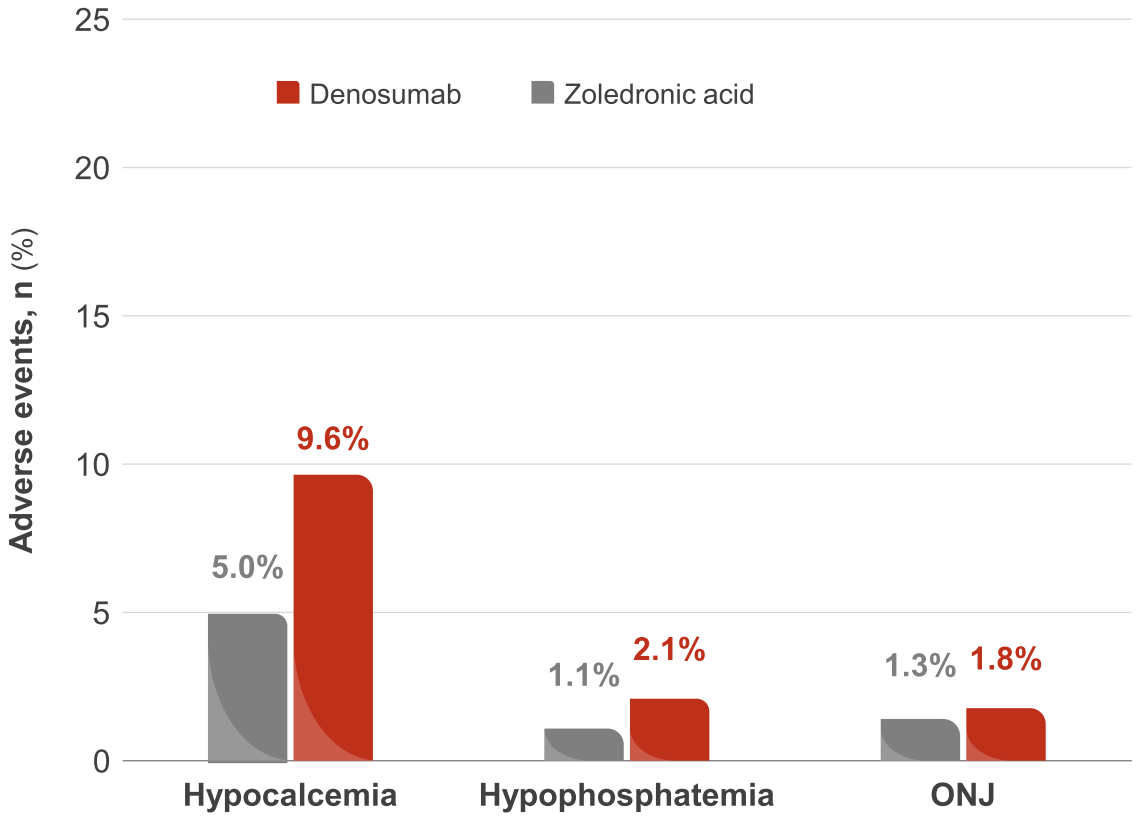
- What is your choice between bisphosphonate vs. RANKL inhibitors?

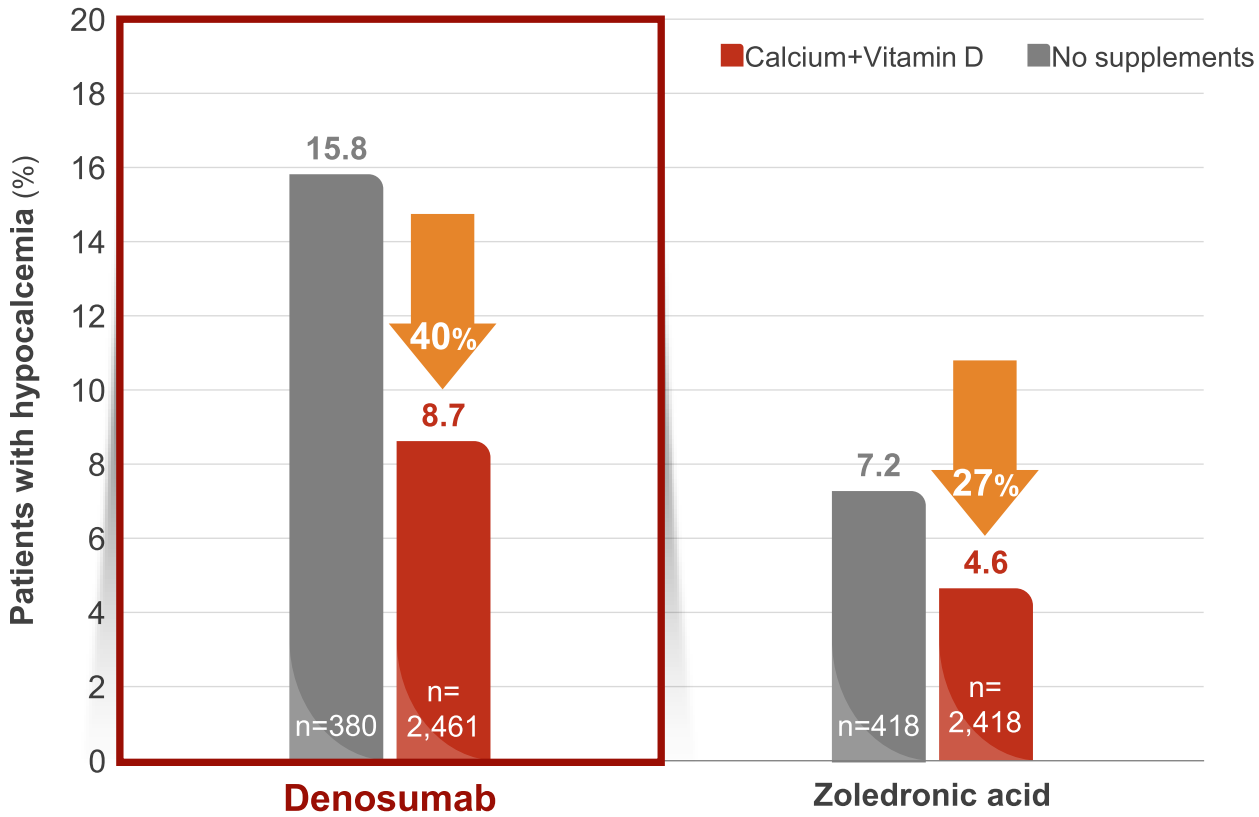
A **Bisphosphonate**

B **RANKL inhibitor**

RANKL, receptor activator of nuclear factor kappa-B ligand.

Are there any tips for managing adverse events regarding denosumab?





ONJ, osteonecrosis of the jaw.

1. Lipton A, et al. *Eur J Cancer* 2012;48:3082–3092; 2. Body JJ, et al. *Eur J Cancer* 2015;51:1812–1821.

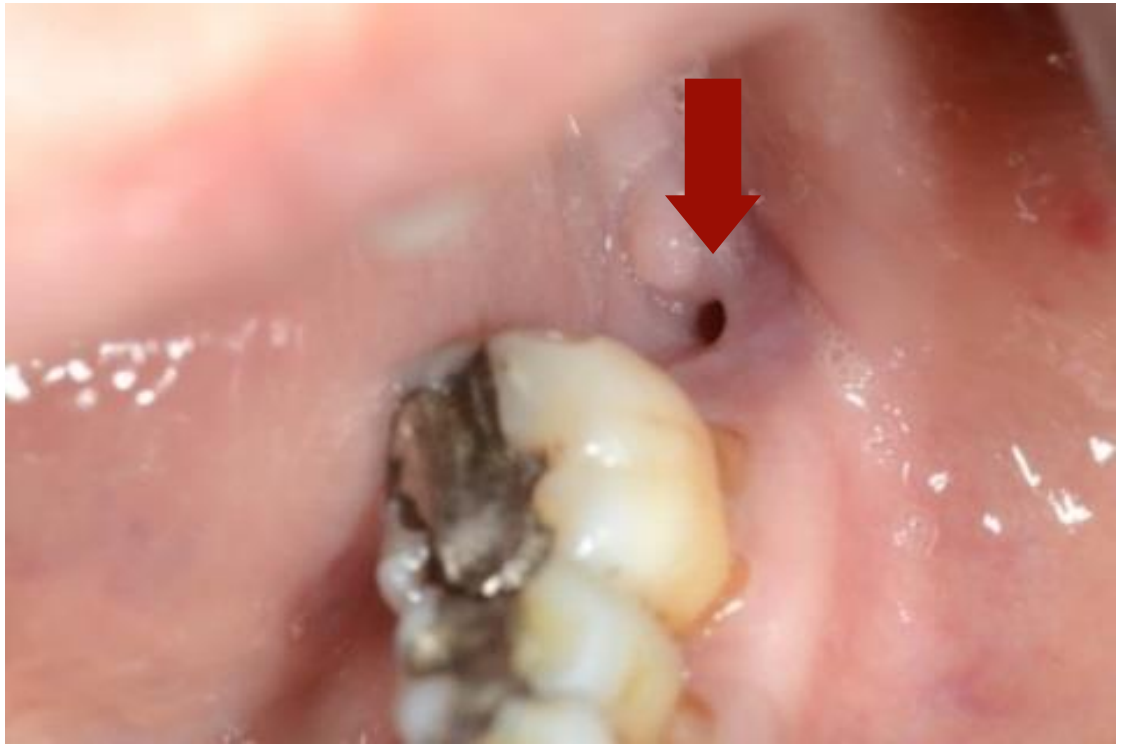
My personal tips for bone health management in patients with mHSPC

- Routine assessment of BMD (baseline, then annually or bi-annually)
- Refer patients with **osteopenia** (T-score −1.0 to −2.5) and osteoporosis (T-score <−2.5) to endocrinologist for specialized care
- Choice between different ARPIs
  - Direct androgen receptor antagonist preferred rather than CYP17A1 inhibitor
- Use of supplements (calcium and vitamin D) with BPA
- Patient education
  - Smoking cessation
  - Alcohol cessation
  - Oral hygiene

ARPI, androgen receptor pathway inhibitor; BMD, bone mineral density; BPA, bone-protecting agent; mHSPC, metastatic hormone-sensitive prostate cancer.
Speaker's own experience.

Case 2: mHSPC under BTA with ONJ

- Male, aged 77 years
- Height and weight: 170 cm and 70 kg
- Never smoker
- Alcohol consumption (+)
- Sudden back pain with walking/voiding difficulty
- Lumbar fusion surgery for spinal cord compression
- Diagnosed as mHSPC
- BMD T-score: −1.0
- FRAX 10-year probability of hip fracture: 4.2%
- Start ADT + enzalutamide + denosumab
- Left jaw pain with mild fever 18 months after systemic treatment



Slide content provided by the speaker. Patient permission has been obtained for all images.
ADT, androgen deprivation therapy; BMD, bone mineral density; BTA, bone-targeting agent; FRAX, Fracture Risk Assessment Tool; mHSPC, metastatic hormone-sensitive prostate cancer; ONJ, osteonecrosis of the jaw.
Speaker's own case.

Question for the audience

- What is the appropriate management for ONJ?

A Conservative treatments (antimicrobial rinses, systemic antibiotics, and pain management)

B Surgical treatment (debridement sequestrectomy, or other surgical interventions may be necessary by specialist)

C Denosumab interruption

D Teriparatide (a bone remodeling stimulator), may be used to promote bone healing and potentially enhance the effectiveness of other treatments in certain patients

ONJ, osteonecrosis of the jaw.

Conclusion

- Bone health is closely associated with the incidence of skeletal-related adverse events, quality of life, and overall survival across all stages of prostate cancer
- BPAs may be considered for patients with mHSPC based on individual risk stratification
- The FRAX risk score can be a useful tool to guide decisions regarding the use of bone-protecting agents in patients with mHSPC
- Modifiable risk factors for fracture should be routinely assessed in clinical practice, with an emphasis on patient education
- The use of BPAs requires careful consideration, and referral to a specialist may be warranted in certain cases

BPA, bone-protecting agent; FRAX, Fracture Risk Assessment Tool; mHSPC, metastatic hormone-sensitive prostate cancer.
Speaker's own experience.

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