Vraag 3a: Wat is - bij patiënten met castratie-resistent prostaatcarcinoom met botmetastasen - het effect van bisfosfonaten (clodronaat, pamidronaat of zoledronaat) en denosumab (in vergelijking met placebo) op preventie en reductie van 'skeletal related events', pijn, morbiditeit en mortaliteit?

Vraag 3b: Wat is - bij patiënten met castratie-resistent prostaatcarcinoom met botmetastasen - het effect van bisfosfonaten (alleen zoledronaat) – in vergelijking met denosumab - op preventie en reductie van 'skeletal related events', pijn, morbiditeit en mortaliteit?

Treatment

a. Primary studies

Clodronate
Evidence table clonodrate

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcome(s)	VII Critical appraisal of study quality
Adami 1989 [1]	• Randomized controlled trial • Support and conflicts of interest: Instituto Gentili SpA supplied the clodronate; not reported on • Setting: Italy • Sample size: N= 13 • Duration: not reported	• Inclusion: patients with bone metastasis due to prostatic carcinoma • Exclusion: not reported • Patient characteristics: not reported	Clodronate 300 mg iv/day during 2 weeks vs. placebo	Significant difference in the changes in mean pain scores and in analgesic consumption in favor of clodronate (data in graph, not reported; p<0.01)	-	• Randomisation method not described • Allocation concealment not described • Placebo control likely to ensure blinding of participants and outcome assessors • Treatment groups similarity not described • ITT analyses • The trial was not extended due to the ´striking´ difference in favour of clodronate between treatment groups at 2 weeks, according to the authors

						• The decision to abort the trial after only 2 weeks, with only 13 patients included, seriously undermines validity
Dearnaley 2003 [2, 3]	• Randomized controlled trial • Support and conflicts of interest: U.K. Medical Research Council and Boehringer Mannheim; not reported on • Setting: 33 centres in the United Kingdom and 1 centre in New Zealand • Sample size: N= 311 • Duration: June 1994 – July 1998	• Inclusion: prostate cancer patients with bone metastases commencing first-line hormone treatment or already responding to such treatment; commencing or showing a positive response to initial hormone therapy with orchidectomy, luteinizing hormone–releasing hormone analogs, cyproterone acetate, flutamide, or maximal androgen blockade; normocalcemia; WHO performance status ≤2; serum creatinine level less than twice the upper limit of the local normal range • Exclusion: concomitant or previous use of bisphosphonates; other active malignancy within the past 5 years; acute, severe inflammatory conditions of the gastrointestinal tract; serious concomitant physical or psychiatric disease; use of any investigational drug within 12 months of the first	Oral sodium clodronate 2080 mg/day vs. placebo for a maximum of 3 years after randomisation or up to development of symptomatic bone metastases or unacceptable toxicities	<u>Symptomatic bone progression-free survival at 2 y</u>: 49.3% vs. 41%: difference of 8% (95%CI:-1% to 18%) <u>Symptomatic bone progression-free survival at a median of 58 m</u>: • hazard ratio: 0.79 (95%CI: 0.61 to 1.02; p=0.07) • median time to event: 23.6m vs. 19.3m • difference: 4.3m (95% CI: 0.8 to 11.5m) <u>Overall survival at 2 y</u>: 66.5% vs. 60% (6.5% difference; 95%CI: -1% to 14% increase) <u>Overall survival at 59 m</u>: • hazard ratio 0.80 (95%CI: 0.62 to 1.03; p=0.08) • difference: 20% (95%CI: -3% to 38%)	<u>Subgroup analyses:</u> no evidence of differential effects with respect to age, WHO performance status, baseline blood markers (i.e., hemoglobin, serum creatinine, PSA), type of hormone therapy, time from diagnosis of bone metastases to randomization, time on long-term hormone therapy prior to randomization, or number of patients that were included in the trial from the clinical center <u>Time on trial medication</u>: hazard ratio: 1.08 (95%CI: 0.86 to 1.35; p=0.52)	• Randomisation method not described • Allocation concealment: central randomisation • Placebo control likely to ensure blinding of participants and outcome assessors • Treatment groups similar at trial start • ITT analyses

		dose; previous use of long-term hormone therapy • Patient characteristics: median age 71 y, range: 49-88 y		• median overall survival: 37.1 m vs. 28.4 m • difference: 8.7 m (95%CI: 3.3 to 14.2 m) <u>Overall survival at median 11.5 y</u>: hazard ratio 0.77 (95%CI: 0.60 to 0.98; p=0.03) <u>Estimated 5 y survival</u>: 30% vs. 21% <u>Estimated 10 y survival</u>: 17% vs. 9% <u>Hazard ratios (95%CI) disease events at 59 m</u>: • symptomatic bone progression: 0.80 (0.60 to 1.08) • prostate cancer death: 0.77 (0.58 to 1.02) • prostate cancer involved death: 0.77 (0.59 to 1.01) • any death: 0.80 (0.62 to 1.03) • symptomatic bone progression/prostate cancer involved death:		

				0.81 (0.63 to 1.04) • symptomatic bone progression/any death: 0.79 (0.62 to 1.01) <u>Time to first adverse event hazard ratio</u>: 1.71 (95%CI: 1.21 to 2.41); 71% increase (95%CI: 21% to 141%; p=0.002) <u>Time to the first dose-modifying adverse event hazard ratio</u>: 2.81 (95%CI: 1.78 to 4.44) ; 181% increase (95%CI: 78% to 344%; p<.0001) <u>Worsened WHO performance status by at least one grade</u>: hazard ratio 0.71 (95%CI: 0.56 to 0.92); -29% reduction (95%CI: -44% to -8%; p=0.008)		

Grade table clodronate vs. placebo

Quality assessment							No of patients		Effect (95%CI)			
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Clodronate**	**Placebo**	**Relative**	**Absolute**	**Quality**	**Importance**
Significant difference in the changes in mean pain scores and in analgesic consumption in favour of clodronate at two weeks												

1	Randomized controlled trial	Serious [1]	No serious inconsistency	No serious indirectness	Very serious [2]	No other considerations	6	7	Data in graph, not reported	Data in graph, not reported	Very low ⊕OOO	Critical
Skeletal related events												
0	-	-	-	-	-	-	-	-	-	-	-	Critical
Symptomatic bone progression-free survival at 2 years												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	Serious imprecision [3]	No other considerations	155	156	-	Difference 8% (-1 to 18%)	Moderate ⊕⊕⊕O	Critical
Symptomatic bone progression-free survival at a median of 58 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	155	156	-	Difference 4.3 m (0.8 to 11.5 m)	High ⊕⊕⊕⊕	Critical
Overall survival at 2 years												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	Serious imprecision [3]	No other considerations	155	156	-	Difference 6.5% (-1 to 14%)	Moderate ⊕⊕⊕O	Important
Overall survival at 59 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	Serious imprecision [3]	No other considerations	155	156	-	Difference 20% (-3% to 38%)	Moderate ⊕⊕⊕O	Important
Overall survival at median 11.5 years												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	155	156	Hazard ratio 0.77 (0.60 to 0.98)	-	High ⊕⊕⊕⊕	Important
First dose-modifying adverse event												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	155	156	-	181% increase (78% to 344%)	High ⊕⊕⊕⊕	Important
Worsened WHO performance status by at least one grade												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	155	156	-	Difference -29% (-44% to -8%)	High ⊕⊕⊕⊕	Critical
Overall quality of evidence: high [4]												

[1] Stopping early for benefit observed, in the absence of adequate stopping rules
[2] Serious risk of fragility because of the very low number of participants and danger of an initial trial with impressive results
[3] The 95% confidence interval around the best estimate of effect includes both no effect and an effect that, if it were real, would represent a benefit that would outweigh the downsides
[4] Critical outcomes point in the same direction — towards benefit— the highest quality of evidence for any of the critical outcomes determines the overall quality of evidence

Pamidronate

Evidence table pamidronate

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcome(s)	VII Critical appraisal of study quality
Small 2003 [4]	• Randomized controlled trial • Support and conflicts of interest: Novartis Oncology; several authors held stock of Novartis and/or received funding or acted as a consultant for Novartis • Setting: multicentre international trial • Sample size: N=378 • Duration: February 1998 – November 1999	• Inclusion: patients with bone pain due to metastatic prostate cancer with disease progression after first-line hormonal therapy; aged ≥18 y; skeletal or bone metastases confirmed by central radiology review; life expectancy of ≥ 6 m; progressive systemic disease despite androgen deprivation (an increase in serum prostate-specific antigen was not considered a sufficient indication of disease progression) • Exclusion: white blood cell count ≤3x10^9 cells/L; platelet count < 50x10^9/L; serum creatinine≥5.0 mg/dL, corrected serum calcium≥11.0 mg/dL or ≤8.4mg/dL; magnesium ≤0.9 mg/dL; total bilirubin > 2.5 mg/dL; untreated brain metastases; prior bisphosphonate therapy; clinically significant abnormal ECG; ascites; impending spinal cord compression or spinal	Intravenous pamidronate disodium (90 mg) vs. placebo every 3 weeks for 27 weeks	<u>Mean change BPI score at 27 weeks</u>: • worst BPI score group: -0.60 vs. -0.65 (p=0.89) • average BPI score group: -0.40 vs. -0.27 (p=0.71) • least BPI score group: -0.15 vs. 0.26 (p=0.19) <u>Oral morphine equivalent score change at 27 weeks</u>: 28.5 vs. 16.6 (p=0.31) <u>SRE at 9 weeks</u>: 12% vs. 11% (ns) <u>SRE at 27 weeks</u>: 25% vs. 25% (ns) No significant differences in change from baseline in <u>mobility measurements</u> for either treatment group to week 9 or week 27 (data not reported)	-	• Pooled analysis of two identical trials in either of which full enrollment was not achieved for undisclosed reasons • The pooled sample size had insufficient power for the secondary outcome SRE at 27 weeks in the à priori power calculations • Randomization procedure and allocation concealment not reported on • A SRE included hypercalcemia (corrected serum calcium ≥ 12.0 mg/dL), which seems clinically irrelevant. This happened in 3 patients only • Non-differential loss to follow-up, withdrawal or protocol violation • ITT analyses (last observation carried forward)

		orthosis; a skeletal event (pathologic fracture, radiation or surgery to bone) < 1 m before randomization; change in chemotherapy or hormone therapy regimen < 6 weeks before randomization • Patient characteristics: median age 71.5 y, range: 46-89 y		The percentages of patients who reported ≥1 adverse event, any serious adverse event, or treatment discontinuation due to an adverse event were similar for the pamidronate and placebo groups (data not reported)		

Abbreviations: BPI: brief pain inventory; CI: confidence interval; ITT: intention to treat; m: months; ns: non-significant; SRE: skeletal related event; y: years

Grade table pamidronate vs. placebo

Quality assessment							No of patients		Effect (95%CI)			
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pamidronate**	**Placebo**	**Relative**	**Absolute**	**Quality**	**Importance**
Mean change BPI score at 27 weeks												
1	Randomized controlled trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	169	181	-	• Worst BPI score group: -0.60 vs. -0.65 (p=0.89) • Average BPI score group: -0.40 vs. -0.27 (p=0.71) • Least BPI score group: -0.15 vs. 0.26 (p=0.19)	High ⊕⊕⊕⊕	Critical
Oral morphine equivalent score change at 27 weeks												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	169	181	-	28.5 vs. 16.6 (p=0.31)	High ⊕⊕⊕⊕	Important

SRE at 9 weeks												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	Serious [1]	No other considerations	169	181	-	12% vs. 11% (ns)	Moderate ⊕⊕⊕O	Critical
SRE at 27 weeks												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	Serious [1]	No other considerations	169	181	-	25% vs. 25% (ns)	Moderate ⊕⊕⊕O	Critical
Survival free from skeletal related events												
0	-	-	-	-	-	-	-	-	-	-	-	Critical
Change from baseline mobility measurements week 9 or week 27												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	Not assessable	Other considerations [2]	169	181	-	No significant differences (data not reported)	Moderate ⊕⊕⊕O	Critical
Percentages of patients who reported ≥1 adverse event, any serious adverse event, or treatment discontinuation due to an adverse event												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	Not assessable	Other considerations [2]	169	181	-	Similar (data not reported)	Moderate ⊕⊕⊕O	Important
Overall quality of evidence: moderate [3]												

Abbreviations: BPI: brief pain inventory; ns: not significant; SRE: skeletal related events
[1] The pooled sample size had insufficient power for the secondary outcome SRE in the à priori power calculations
[2] Primary data not reported
3 The balance of the benefits and downsides is uncertain, thus the grade of the critical outcome with the lowest quality grading was assigned

Zoledronic acid

Evidence table zoledronic acid

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcome(s)	VII Critical appraisal of study quality
Saad 2002 [5-8]	• Randomized controlled trial • Support and conflicts of interest: Novartis	• Inclusion: hormone-refractory prostate cancer and a documented history	Zoledronic acid 4 mg (N=214) vs.	Difference in proportion at 15 m (95%CI): • all SRE: −11.1 (−20.3	Differences at 24 m (95%CI): • proportion all SRE: -11.0	• Randomization was computer generated • Allocation concealment

	Pharmaceuticals Corporation; several authors conducted research sponsored by Novartis; the main author is a consultant on an advisory board • Setting: multicenter international trial • Sample size: N=643 • Duration: June 1998 – January 2001	of bone metastases (defined as more than three foci of increased activity on a bone scan); 3 consecutive increasing serum prostate-specific antigen measurements while on hormonal therapy; serum testosterone levels within the castrate range (<50 ng/dL); Eastern Cooperative Oncology Group performance status of 0, 1, or 2 • Exclusion: initiation of cytotoxic chemotherapy at the time of study entry; bone pain requiring strong narcotic therapy; were receiving cytotoxic chemotherapy (with the exception of estramustine); had received radiation therapy within 3 months; had received any previous bisphosphonate treatment; severe cardiovascular disease, refractory hypertension, symptomatic coronary artery disease; serum creatinine > 3.0 mg/Dl; a corrected (for albumin) serum calcium <8.0 mg/dL or > 11.6 mg/dL • Patient characteristics: mean age 59.8 y, range: 12-91 y; 72.5% had pain at study entry	8 mg (subsequently reduced to 4 mg (8/4 mg)(N=221) vs. placebo (N=208) every 3 weeks for 15 m or optional up to 24 m (N=122) In addition all patients received 500 mg calcium supplement and 400 500 IU of vitamin D daily	to −1.8; p=0.02) • all pathologic fractures: −9.0 (−16.3 to −1.8; p=0.02) • vertebral fractures: −4.4 (−8.9 to 0.1; p=0.05) • non-vertebral fractures: −5.6 (−12.0 to 0.8; p=0.09) • radiation therapy to bone: −6.4 (−14.8 to 1.9; p=0.14) • surgery to bone: −1.0 (−4.2 to 2.1; p=0.51) • spinal cord compression: −2.5 (−6.9 to 1.8; p=0.26) • change in antineoplastic treatment: −2.1 (−6.5 to 2.4; p=0.36) Mean increase from baseline pain score BPI at 15 m: 0.58 (95%CI: 0.29 to 0.87) vs. 0.88 (95%CI: 0.61 to 1.15) (p=0 .13) Chance of a favorable response in BPI (two points decline) at 60 w: 33% vs. 25%; difference 8% (95%CI: 0.5% to 15.6%; p=0.04) The mean ECOG performance scores increased from baseline	(-20.2 to -1.3; p=0.03) • median time to first SRE: 488 vs. 321 d; hazard ratio: 0.68 (0.51 to 0.91; p=0.01) • mean annual incidence SRE: 0.77 vs. 1.47 (p=0.01) • mean least-square change BPI from baseline value: 0.58 vs. 1.05; difference: -0.47 (-0.88 to -0.06; p=0.02) • mean change from baseline analgesic score: 1.04 vs. 1.17 (p=0.49) Adverse events (e.g., mild-to-moderate fatigue, myalgia, and fever) occurred more frequently in patients treated with zoledronic acid than with placebo during the core phase; the incidence of these adverse events was similar between the zoledronic acid and placebo groups during the extension phase (data not shown). Moreover, the rate of study discontinuation due to adverse events did not differ substantially among the three treatment groups In patients with pain at baseline zoledronic acid decreased the mean BPI composite pain scores	was unclear • The initial 5 minute infusion was amended to a 15 minute infusion; the 8 mg dose was lowered to a 4 mg dose. Both due to renal toxicity. Results of 4 mg vs. placebo reported here • SRE were prospectively defined as pathologic bone fractures (vertebral or nonvertebral), spinal cord compression, surgery to bone, radiation therapy to bone (including the use of radioisotopes), or a change of antineoplastic therapy to treat bone pain • ITT analysis • Subgroup analyses sometimes lacking actual data, 95%CI and/or p-values and

				to the last measurement, with no statistically significant difference among the three groups at 15 m (data not reported) The total FACT-G quality-of-life and the EURO-QoL scores decreased from baseline to the last measurement, with no statistically significant differences among the three groups at 15 m (data not reported) Overall death: 25 vs. 32 Similar proportions of patients who received zoledronic acid at 4 mg (9.8%), zoledronic acid at 8/4 mg (12.4%), and placebo (10.1%) discontinued the study drug because of a serious adverse event at 15 m Relative risk ratio first renal function deterioration at 15 m: 1.07 (95%CI: 0.46 to 2.47; P=0.88) 4 patients (2.0%) from the zoledronic acid-at-4-mg group experienced	compared with placebo during the entire study period (data in a figure) with a decrease from baseline by -10% at 3 m and by -1% at 9 m, vs. + 6% and +13% in the placebo group (post hoc subgroup analysis) Post hoc subgroup analyses in patients without pain at baseline vs. patients with pain at baseline: • median interval to the first SRE with pain at baseline: 17 vs. 11 months (p=0.09); no pain at baseline: not reached at 24 m vs 15 m (p=0.04) • difference in proportion ≥1 SRE -18% in patients with pain at baseline; -39%in patients without pain at baseline • mean annual incidence of SRE -39% in patients with pain at baseline and by-49% in patients without pain at baseline	

				grade 3 or 4 hypocalcemia at 15 m 9 (4.6%) patients from the zoledronic acid-at-4-mg and placebo groups had grade 3 or 4 decreases in hemoglobin concentration at 15 m 7 patients (3.3%) in the zoledronic acid-at-4-mg group and two (1.0%) in the placebo group had grade 3 serum creatinine increases, but no patient had a grade 4 increase		

Abbreviations: BPI: brief pain inventory; CI: confidence interval; d: days; ITT: intention to treat; m: months; SRE: skeletal related events; w: weeks; y: years

Grade table zoledronic acid

Quality assessment							No of patients		Effect (95%CI)			
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Zoledronic acid**	**Placebo**	**Relative**	**Absolute**	**Quality**	**Importance**
Mean increase from baseline pain score BPI at 15 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	221	208	-	0.58 (0.29 to 0.87) vs. 0.88 (0.61 to 1.15)	High ⊕⊕⊕⊕	Critical
Mean increase from baseline pain score BPI at 24 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	214	208	-	Difference -0.47 (-0.88 to -0.06)	High ⊕⊕⊕⊕	Critical
Chance of a favourable response in BPI (two points decline) at 60 weeks												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	221	208	-	Difference 8% (0.5 to 15.6%)	High ⊕⊕⊕⊕	Critical
Mean change from baseline analgesic score at 24 months												

1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	214	208	-	1.04 vs. 1.17 (p=0.49)	High ⊕⊕⊕⊕	Important
Difference all SRE at 15 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	221	208	-	−11.1% (−20.3 to -1.8)	High ⊕⊕⊕⊕	Critical
Difference all SRE at 24 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	214	208	-	-11.0 (-20.2 to -1.3)	High ⊕⊕⊕⊕	Critical
Median time to first SRE at 24 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	214	208	Hazard ratio: 0.68 (0.51 to 0.91)	488 vs. 321 days	High ⊕⊕⊕⊕	Critical
Mean annual incidence SRE at 24 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	214	208	-	0.77 vs. 1.47 (p=0.01)	High ⊕⊕⊕⊕	Critical
Difference all pathological fractures at 15 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	221	208	-	−9.0% (−16.3 to −1.8)	High ⊕⊕⊕⊕	Critical
Difference all vertebral fractures at 15 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	Serious imprecision [1]	No other considerations	221	208	-	−4.4% (−8.9 to 0.1)	Moderate ⊕⊕⊕O	Important
Difference all non-vertebral fractures at 15 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	Serious imprecision [1]	No other considerations	221	208	-	−5.6% (−12.0 to 0.8)	Moderate ⊕⊕⊕O	Important
Difference all radiation therapy to bone at 15 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	Serious imprecision [1]	No other considerations	221	208	-	−6.4% (−14.8 to 1.9)	Moderate ⊕⊕⊕O	Important
Difference surgery to bone at 15 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	Serious imprecision [1]	No other considerations	221	208	-	−1.0 % (−4.2 to 2.1)	Moderate ⊕⊕⊕O	Important
Difference spinal cord compression at 15 months												

1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	Serious imprecision [1]	No other considerations	221	208	-	−2.5 % (−6.9 to 1.8)	Moderate ⊕⊕⊕O	Important
Survival free from skeletal related events												
0	-	-	-	-	-	-	-	-	-	-	-	Critical
Mean ECOG performance scores, total FACT-G quality-of-life and the EURO-QoL scores at 15 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	Not assessable	Other considerations [2]	221	208	-	No statistically significant differences between groups (data not reported)	Moderate ⊕⊕⊕O	Critical
Difference in mortality at 15 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	Serious imprecision [1]	No other considerations	221	208	-	-4.1% (-10.5 to 2.4%)	Moderate ⊕⊕⊕⊕	Important
Proportion of patients who discontinued the study drug because of a serious adverse event at 15 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	221	208	-	9.8 vs. 10.1%	High ⊕⊕⊕⊕	Important
Overall quality of evidence: high [2]												

Abbreviations: BPI: brief pain inventory; m: months; w: weeks

[1] The 95% confidence interval around the best estimate of effect includes both no effect and an effect that, if it were real, would represent a benefit that would outweigh the downsides

[2] Primary data not reported

3 All outcomes point in the direction towards a benefit— the highest quality of evidence for a critical outcome that by itself would suffice to recommend an intervention determines the overall quality of evidence

Denosumab vs. zoledronic acid

Evidence table denosumab vs. zoledronic acid

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcome(s)	VII Critical appraisal of study quality
Fizazi 2009 [9, 10]	• Randomized controlled trial • Support and conflicts of interest: Amgen Inc; several	• Inclusion: ≥18 y, prostate cancer with radiographic evidence ≥1 bone lesions	denosumab 180 mg s.c. every 4 w (N=17) vs.	SRE at 25 w: 1 (3%) in the pooled denosumab group	-	• The prostate cancer patients formed a subset of a larger trial

	authors worked for, held stock, received funding and/or honoraria from Amgen • Setting: 26 centers in Europe and North America • Sample size: N=50 • Duration: December 2004 – January 2008	and an ECOG performance status ≤2; ≥8 w i.v. zoledronic acid with continuous evidence of excessive bone resorption (uNTx levels >50) • Exclusion: ≥2 prior SREs; osteonecrosis or osteomyelitis of the jaw (current or past); planned oral surgery; radiotherapy to bone <2 w before randomization; evidence of impending fracture in weight bearing bones • Patient characteristics: mean age 68 y; 78% of patients was considered castration resistant as they had evidence of bone metastases despite ongoing androgen deprivation therapy/antiandrogens	denosumab 180 mg s.c. every 12 w (N=16) vs. zoledronic acid 4mg i.v. every 4 w(N=16) all for 25 w All patients: daily supplements of calcium (500 mg) and vitamin D (400 or more IU)	vs. 3 (19%) (p=0.06) <u>Adverse events</u>: 31 (94%) vs. 16 (100%) (p=0.31) <u>Adverse events considered treatment related</u>: 9 (27%) vs. 2 (12%) (p=0.24) Similar low rates of <u>serious adverse events</u> considered potentially treatment related were reported in both treatment groups		• Randomisation procedure not described • Allocation concealment not described • Non-blinded study (risk of performance bias) • Blinding of outcome assessors not described (unclear risk of detection bias) • Patient groups differed: 52% of the patients randomized to the denosumab groups vs. 24% of those randomized to the zoledronic acid group experienced SREs before entering the study (a strong predictor of subsequent SREs) • SRE was defined as: pathological bone fracture, spinal cord compression, or surgery or radiation therapy to bone • Time from enrolment to first on-study SRE was a predefined outcome that was not reported for the prostate population (selective reporting of outcomes) • ITT analyses • p-values calculated by us in STATA
Fizazi 2011 [11 12 13]	• Randomized controlled trial • Support and conflicts of interest: Amgen; not reported	• Inclusion: histologically confirmed prostate cancer with existing or previous radiographic evidence of	Denosumab 120 mg s.c. + placebo i.v. (N=950) vs. zoledronic acid 4 mg i.v.	<u>Median time to first SRE</u>: 20.7m (95%CI: 18.8 to 24.9m) vs. 17.1 m	-	• Randomisation: computer generated • Allocation concealment: interactive voice response

	• Setting: 342 centers in 39 countries • Sample size: N=1904 • Duration: May 2006 – October 2009	≥1bone metastasis; documented failure of at least one hormonal therapy indicated by a rising prostate-specific antigen concentration, with a final concentration ≥ 0.4 µg/L within 8 weeks of randomisation; in the setting of castrate serum testosterone concentrations (<1.72 nmol/L by chemical or surgical castration); adequate organ function; albumin-adjusted serum calcium 2.0–2.9 mmol/L; ECOG performance status of 0, 1, or 2 • Exclusion: current or previous treatment with bisphosphonate for bone metastasis (previous oral bisphosphonate use for osteoporosis was allowed provided treatment was stopped before the first dose of investigational drug); planned radiation therapy or surgery to bone, life expectancy of <6 m; current or previous osteonecrosis or osteomyelitis of the jaw; planned invasive dental procedure during the study; malignancy other than prostate cancer within the past 3 years; creatinine clearance <0.5 mL/s	+ placebo s.c. (N=951) every 4 weeks All patients received supplemental calcium and vitamin D	(95%CI: 15.0 to 19.4m) <u>SRE at a median follow-up of 12.2 m</u>: 780 SREs/1,045 patient-years vs. 943 SREs/996 patient-years: hazard ratio 0.82 (95%CI. 0.71 to 0.95; p<0.01) • in patients with no prior SRE: hazard ratio 0.80 (95%CI: 0.67 to 0.95; p=0.01) • in patients with no/mild pain at baseline: hazard ratio 0.77 (95%CI: 0.63 to 0.95; p=0.01) Treatment of 5 patients with denosumab would prevent an additional SRE (first or subsequent) per year <u>Numbers with event: at a median of 12.2 m follow up</u>: • SRE: 341 vs. 386 (p=0.04); difference: -4.7% (95%CI: -9.1 to -0.3%)		system • Blinded outcome assessment • Treatment groups did not differ at baseline • ITT analysis • At the time of data analysis median time on study was 12.2 m (IQR 5.9–18.5) for the denosumab group vs. 11.2 months (IQR 5.6–17.4) for the zoledronic acid group • p-values, % differences with 95%CI for numbers with event were calculated by us using STATA

		• Patient characteristics: mean age 61 y, range: 64-77 y		• radiation to bone: 177 vs. 203 • pathological fracture: 137 vs. 143 • spinal cord compression: 26 vs. 36 • surgery to bone: 1 vs. 4 Survival: hazard ratio 1.03 (95%CI: 0.91 to 1.17; p=0.65) Disease progression: hazard ratio 1.06 (95%CI: 0.95 to 1.18; p=0.30) Adverse events occurred in 97% of patients in both groups Adverse event leading to treatment discontinuation: 17% vs. 15% (p=0.10) Adverse events grade 3 or 4: 72% vs. 66% (p=0.01) Osteonecrosis of the jaw: 2% vs. 1% (p=0.09)		

				Hypocalcemia: 13% vs. 6% (p<0.01)		

Abbreviations: CI: confidence interval; ITT: intention to treat; m: months; SRE: skeletal related events; w: weeks; y: years

Grade table denosumab vs. zoledronic acid

Quality assessment							No of patients		Effect (95%CI)			
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Denosumab**	**Zoledronic acid**	**Relative**	**Absolute**	**Quality**	**Importance**
Pain												
0	-	-	-	-	-	-	-	-	-	-	-	Critical
SRE at a median follow up of 12.2 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	950	951	Hazard ratio 0.82 (0.71 to 0.95)	780 SREs/1,045 patient-years vs. 943 SREs/996 patient-years	High ⊕⊕⊕⊕	Critical
Difference in SRE at a median follow up of 12.2 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	950	951	-	-4.7% (-9.1 to -0.3)	High ⊕⊕⊕⊕	Critical
Survival free from skeletal related events												
0	-	-	-	-	-	-	-	-	-	-	-	Critical
Difference in survival at a median follow up of 12.2 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	950	951	Hazard ratio 1.03 (0.91 to 1.17)	-	High ⊕⊕⊕⊕	Important
Quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	Critical
Difference in disease progression at a median follow up of 12.2 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations			Hazard ratio 1.06 (0.95 to 1.18)	-	High ⊕⊕⊕⊕	Important
Adverse events leading to treatment discontinuation at a median follow up of 12.2 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	Serious imprecision [3]	No other considerations	945	943	-	17% vs. 15% (p=0.10)	High ⊕⊕⊕⊕	Important
Adverse events grade 3 or 4 at a median follow up of 12.2 months												

1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	945	943	-	72% vs. 66% (p=0.01)	High ⊕⊕⊕⊕	Important
Osteonecrosis of the jaw at a median follow up of 12.2 months												
1	Randomized controlled trial	No serious bias	No serious inconsistency	No serious indirectness	Serious imprecision [1]	No other considerations	945	943	-	2% vs. 1% (p=0.09)	Moderate ⊕⊕⊕O	Important
Overall quality of evidence: high [2]												

Abbreviations: SRE: skeletal related events

[1] Serious risk of fragility because of the very low number of events

2 Critical outcomes point in the direction towards a benefit— the highest quality of evidence for a critical outcome that by itself would suffice to recommend an intervention determines the overall quality of evidence