ASCO GU25 Utility of extended interval dosing of Denosumab in patients with metastatic prostate cancer.

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Utility of extended interval dosing of denosumab in patients with metastatic prostate cancer

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ABSTRACT # 68

- **For correspondence:** Stephanie Schneck, PharmD, BCOP
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- **Session Title:** *Prostate Cancer*

Background

- Bone modifying agents, such as zoledronic acid and denosumab, are commonly used in patients (pts) with metastatic solid tumors to reduce the incidence of skeletal-related events (SREs).
- The FDA-approved administration schedule for both agents is every 4 weeks, however less frequent administration (i.e. every 12 weeks) is commonly observed in practice due to patient convenience.
- The efficacy and safety of these extended interval regimens is well-established for zoledronic acid, however there is little evidence available supporting this practice with denosumab.

Methods

- Pts with metastatic prostate cancer were evaluated for development of SREs during treatment with extended intervals of denosumab.
- 103 pts evaluated and treated at Indiana University Health between September 2019 and September 2024 were included in this analysis.
- A historical control group of pts receiving every 4-week dosing was used as comparison[1].
- SREs were defined as pathologic fracture, spinal cord compression, operation, or radiation to bone.
- Extended interval dosing is defined as an administration schedule >4 weeks apart on a consistent basis.
- Statistical analysis: P-value comparisons across Tables 1 & 2 are based on Chi-Square or Fisher's Exact test for categorical variables and Wilcoxon (Normal Approximation) for continuous variables. Comparisons of incidence of SREs between the extended interval and historical dosing groups were performed by Chi-Square test. Time to SRE were estimated with the Kaplan-Meier method and compared using the 1-sided test from the Brookmeyer and Crowley method
- For the time to SRE, the time from initiation of bone preserving agent until the date of SRE was calculated. If a patient did not have an SRE, they were censored at the last follow up date.

Results

Table 1: Patient Characteristics of Extended Interval Dosing Group

	Castration-resistant (N=72)	Hormone-sensitive (N=31)	Total (N=103)	p-value
Age at diagnosis, median (range)	63.17 (46.63, 87.22)	67.19 (47.23, 82.99)	63.84 (46.63, 87.22)	0.2779
Age at start of denosumab, median (range)	70.50 (49.48, 90.00)	68.68 (51.30, 83.38)	70.16 (49.48, 90.00)	0.1641

- Median age at starting bone preserving agent was 70.16 years (range, 48.48-90.00).
- 72 pts (69.9%) had metastatic castration-sensitive prostate cancer, and 31 pts (30.1%) had metastatic castration-resistant prostate cancer (mCRPC) at time of initiation of denosumab.

Table 2: SREs & Safety Data for Extended Interval Dosing Group

	Castration-resistant (N=72)	Hormone-sensitive (N=31)	Total (N=103)	p-value
Patients experiencing ≥1 SRE, n(%)	16 (22.2%)	8 (25.8%)	24 (23.3%)	0.6931
Skeletal-related events, n(%)				
Pathologic fracture	3 (4.2%)	0 (0%)	3 (2.9%)	0.5520
Spinal Cord Compression	1 (1.4%)	0 (0%)	1 (1.0%)	1.0000
Surgery	2 (2.8%)	0 (0%)	2 (1.9%)	1.0000
Radiation Therapy	14 (19.4%)	8 (25.8%)	22 (21.4%)	0.4699
# of denosumab doses received, median (range)	4.00 (2.00, 17.00)	7.00 (2.00, 18.00)	5.00 (2.00, 18.00)	0.0027
Hypocalcemia (Corr. Ca <8mg/dL), n(%)	12 (16.7%)	5 (16.1%)	17 (16.5%)	0.9462
Dental Complications, n(%)	4 (5.6%)	2 (6.5%)	6 (5.8%)	1.000

Table 3: SRE Comparison of Historical vs Extended Interval Dosing in mCRPC Patients

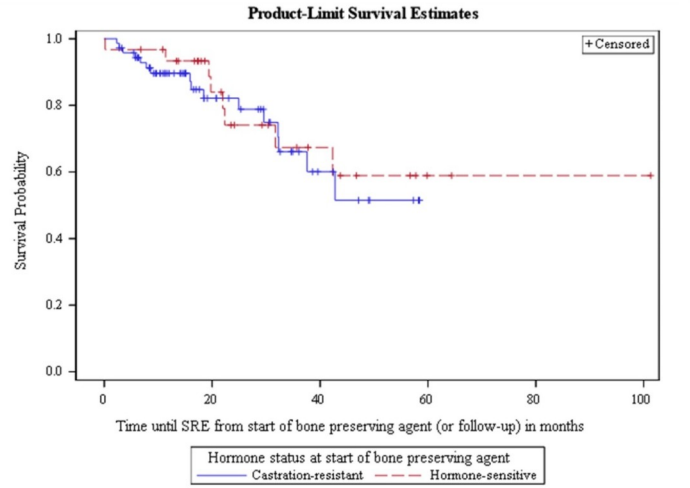
SRE development?	Historical Group	Extended Interval Group
No	609	56
Yes	341	16

- Incidence of SREs in all patients receiving extended interval denosumab was 23.3%.
- The incidence of SREs in patients with mCRPC status at time of initiating denosumab in the extended interval dosing was 22.2%. This compares favorably to historical data with incidence of SRE in the every 4 weeks dosing group at 35.9% (p=0.02).
- The incidence of SREs in patients with mCRPC status at time of last follow-up receiving extended interval dosing was 26.6%. This compares favorably to historical data with incidence of SRE in the every 4 weeks dosing group at 35.9% (p=0.10).
- SREs identified for all patients receiving extended dosing interval denosumab were pathologic fracture (3, 2.9%), spinal cord compression (1, 1.0%), surgery (2, 1.9%), and radiation to bone (22, 21.4%).

RESULTS (CONTINUED)

- The lower 99% confidence interval for time to SRE in patients with mCRPC at time of denosumab initiation in the extended interval dosing group was 32.2 months. This compared favorably to the median of 20.7 months in the historical every 4-week dosing group (p<0.01).

Figure 1: Time to SRE with Extended Dosing Intervals



CONCLUSIONS

- Extended interval dosing of denosumab in patients with metastatic prostate cancer is not associated with an increased risk of development of SREs and may offer convenience for pts.
- Larger prospective studies are needed to validate these findings

Reference: Fizazi K, Carducci M, Smith M, et al. Lancet 2011; 377: 813–822

BONE MODIFYING AGENTS

- ZOLEDRONIC ACID

- DENOSUMAB- fully human monoclonal antibody that binds to and neutralizes RANKL on osteoblasts and their precursors.

BACKGROUND DATA

Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study

Karim Fizazi, Michael Carducci, Matthew Smith, Ronaldo Damião, Janet Brown, Lawrence Karsh, Piotr Milecki, Neal Shore, Michael Rader, Huei Wang, Qi Jiang, Sylvia Tadros, Roger Dansey, Carsten Goessl

- In this phase 3 study, men with castration-resistant prostate cancer and no previous exposure to intravenous bisphosphonate were enrolled from 342 centres in 39 countries. An interactive voice response system was used to assign patients (1:1 ratio)
- 120 mg subcutaneous denosumab plus intravenous placebo, or 4 mg intravenous zoledronic acid plus subcutaneous placebo, every 4 weeks
- The primary endpoint was time to first on-study skeletal related event (pathological fracture, radiation therapy, surgery to bone, or spinal cord compression), and was assessed for non-inferiority.

Fizazi et al. Lancet 2011; 377: 813–22

	Zoledronic acid (n=951)	Denosumab (n=950)
Age (years)	71 (66–77)	71 (64–77)
<65	216 (23%)	253 (27%)
≥65	735 (77%)	697 (73%)
Race		
White	810 (85%)	829 (87%)
Other	141 (15%)	121 (13%)
ECOG performance status 0–1	886 (93%)	882 (93%)
Time from diagnosis of prostate cancer to randomisation (months)	41·2 (18·3–82·0)	37·5 (18·1–75·4)
Time from diagnosis of bone metastases to randomisation (months)	5·19 (1·31–16·10)	3·94 (1·22–15·67)
Presence of visceral metastases	181 (19%)	161 (17%)
Recent chemotherapy*†	132 (14%)	132 (14%)
Haemoglobin concentration (g/L)	126 (16)	125 (16)
Creatinine clearance of ≥1·5 mL/s	333 (35%)	331 (35%)
PSA at randomisation (μg/L)*	60·0 (19·8–202·2)	58·5 (18·2–225·6)
<10	145 (15%)	145 (15%)
≥10	806 (85%)	805 (85%)
Gleason score at diagnosis		
2–6	180 (19%)	175 (18%)
7	280 (29%)	273 (29%)
8–10	408 (43%)	394 (41%)
Missing	83 (9%)	108 (11%)
Bone turnover markers		
Bone-specific alkaline phosphatase (μg/L)	31·8 (17·2–82·2)	34·3 (17·5–90·0)
Urinary N-telopeptide (nmol/mmol)	49·7 (27·4–112·0)	53·9 (28·4–111·9)
Previous skeletal-related event*	231 (24%)	232 (24%)

Data are median (IQR), number (%), or mean (SD). ECOG=Eastern Cooperative Oncology Group. PSA=prostate-specific antigen. *Based on stratification at randomisation. †Within 6 weeks before randomisation.

Table 1: **Baseline demographic and clinical characteristics**

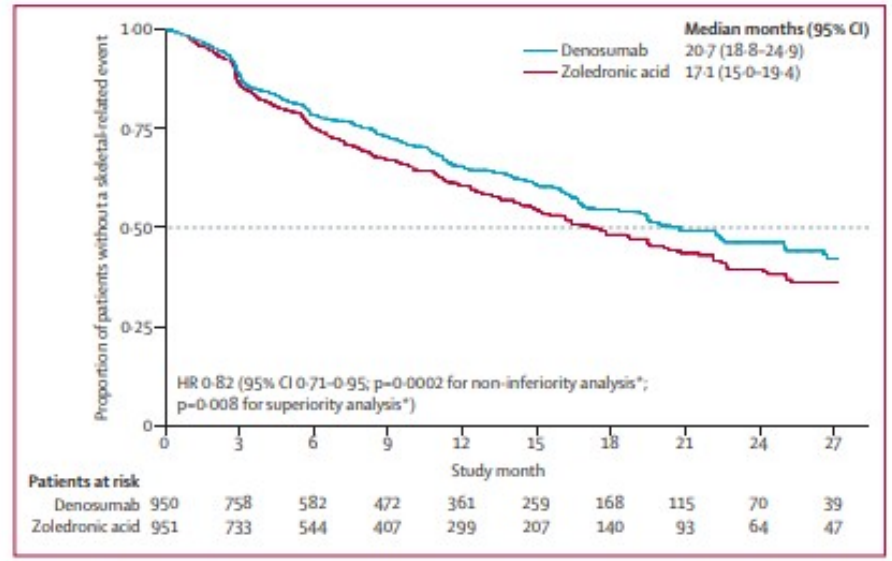


Figure 2: **Kaplan-Meier estimates of time to first on-study skeletal-related event**
Patients were assessed from baseline to the primary analysis cutoff date. HR=hazard ratio. *p values were adjusted for multiplicity.

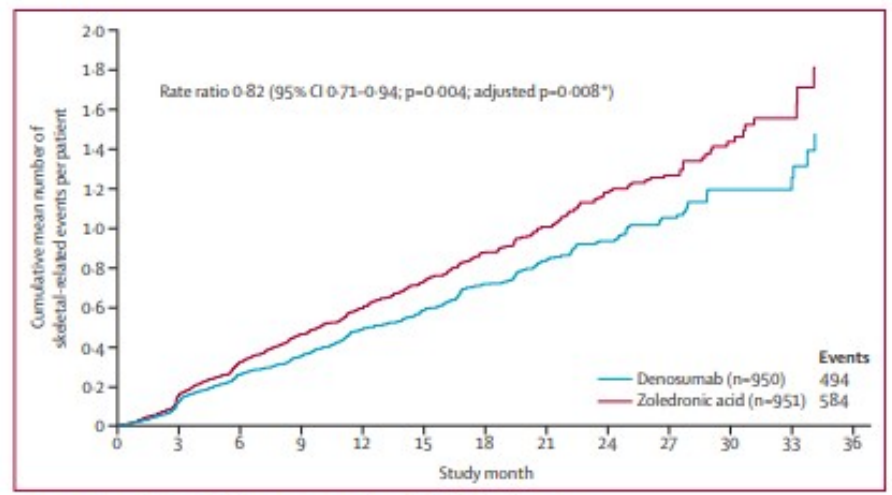


Figure 3: **Time to first and subsequent on-study skeletal-related events**
Events occurred at least 21 days apart. *Adjusted for multiplicity.

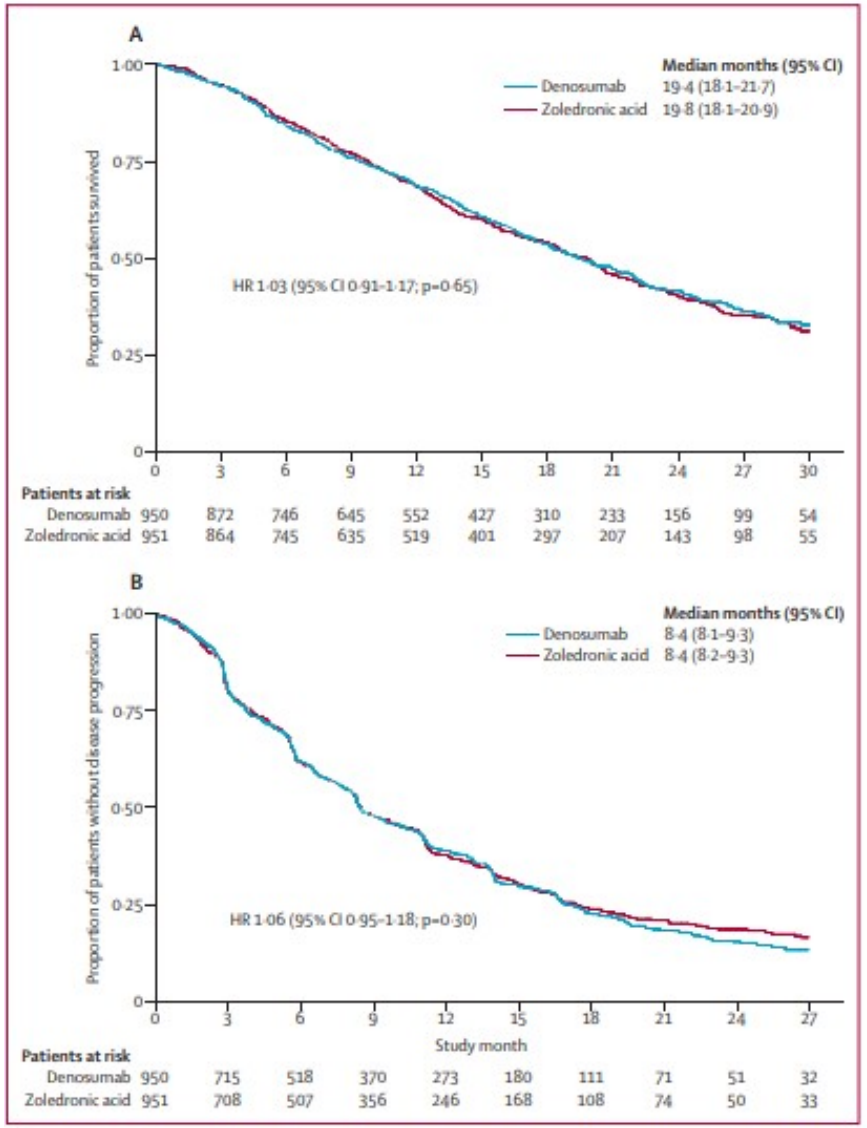


***Figure 4*: Kaplan-Meier estimates of (A) overall survival and (B) time to disease progression**
Patients who were no longer on study, but who were still in the survival follow-up, were included along with those remaining on study in the risk set for the survival analysis. HR=hazard ratio.

	Zoledronic acid (n=951)	Denosumab (n=950)
Total confirmed events	386 (41%)	341 (36%)
Radiation to bone	203 (21%)	177 (19%)
Pathological fracture	143 (15%)	137 (14%)
Spinal cord compression	36 (4%)	26 (3%)
Surgery to bone	4 (<1%)	1 (<1%)

Data are number (%).

Table 2: Patients with first on-study skeletal-related events by type

- The FDA-approved administration schedule for both agents is every 4 weeks, however less frequent administration (i.e. every 12 weeks) is commonly observed in practice due to patient convenience.
- The efficacy and safety of these extended interval regimens is well-established for zoledronic acid, however there is little evidence available supporting this practice with denosumab.

Extended dosing data: zoledronic acid

29.5% with 4-wekly schedule versus
28.6% with 12 weekly schedule had atleast 1 SRE

Research

JAMA | Original Investigation

Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases
A Randomized Clinical Trial

Andrew L. Himelstein, MD; Jared C. Foster, PhD; James L. Khatcheressian, MD; John D. Roberts, MD; Drew K. Seisler, BS; Paul J. Novotny, MS; Rui Qin, PhD; Ronald S. Go, MD; Stephen S. Grubbs, MD; Tracey O'Connor, MD; Mario R. Velasco Jr, MD; Douglas Weckstein, MD; Ann O'Mara, PhD, RN, MPH; Charles L. Loprinzi, MD; Charles L. Shapiro, MD

IMPORTANCE Zoledronic acid, a third-generation aminobisphosphonate, reduces the incidence of skeletal-related events and pain in patients with bone metastases. The optimal dosing interval for zoledronic acid is uncertain.

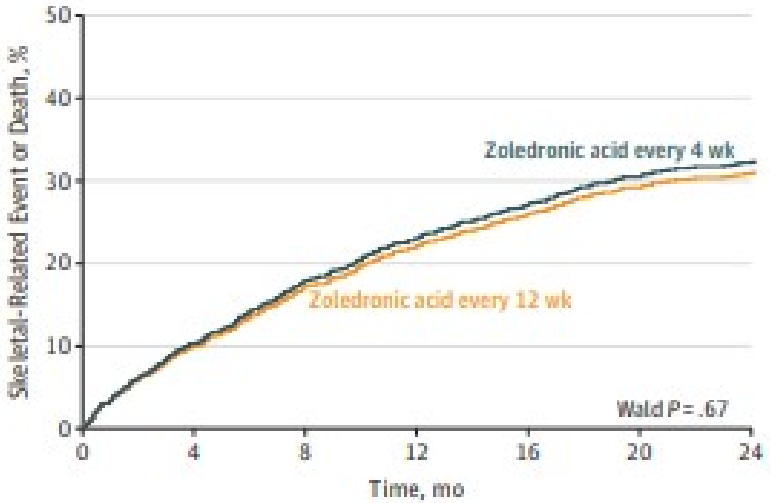
OBJECTIVE To determine whether zoledronic acid administered every 12 weeks is noninferior to zoledronic acid administered every 4 weeks.

DESIGN, SETTING, PARTICIPANTS Randomized, open-label clinical trial conducted at 269 academic and community sites in the United States. Patients (n = 1822) with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma who had at least 1 site of bone involvement were enrolled between May 2009 and April 2012; follow-up concluded in April 2014.

INTERVENTIONS Patients were randomized to receive zoledronic acid administered intravenously every 4 weeks (n = 911) vs every 12 weeks (n = 911) for 2 years.

The primary end point was the proportion of patients having at least 1 skeletal-related event (defined as clinical fracture, spinal cord compression, radiation to bone, or surgery involving bone) within 2 years after randomization and a between-group absolute difference of 7% as the noninferiority margin.

Figure 2. Cause-Specific Cumulative Incidence of Skeletal-Related Events



No. at risk

Every 4 wk	911	882	703	586	467	367	245
Every 12 wk	911	884	726	576	484	392	244

There were 256 patients with skeletal-related events in the zoledronic acid every 4-week dose group and 246 patients in the every 12-week dose group (hazard ratio, 0.96 [95% CI, 0.81-1.15]). The median follow-up was 15.7 months (interquartile range, 6.4-24.1 months) in the zoledronic acid every 4-week dose group and 16.8 months (interquartile range, 6.4-24.0 months) in the every 12-week dose group. There were 122 patients who died in the zoledronic acid every 4-week dose group and 118 in the every 12-week dose group.

JAMA. 2017;317(1):48-58.doi:10.1001/jama.2016.19425

EJMO

DOI: 10.14744/ejmo.2023.34433
EJMO 2023;7(3):220–226

Systematic Meta Analysis

Interval Comparison of Zoledronic Acid Treatment in Patients with Metastatic Bone Disease, Is 4-Weekly or 12-Weekly More Effective?: A Systematic Review and Meta-analysis

I Gede Eka Wiratnaya, Putu Astawa, Sherly Desnita Savio, Agus Suarjaya Putra, I Gusti Agung Wiksa Astrayana, I Made Arditya Dwi Yudhistira, Putu Angga Dharmayuda

Department of Orthopaedics and Traumatology, Faculty of Medicine Uday
Denpasar, Bali, Indonesia

Abstract

Objectives: The aim of bisphosphonate treatment in patients with metastatic bone disease is to prevent metastatic skeletal morbidity and prevent cancer treatment-induced skeletal damage. The classical recommendation of Zoledronic acid treatment is to be given indefinitely as intravenous infusion every 3 to 4 weeks until patients' health deteriorates. Data on zoledronic acid's long-term effectiveness and safety are insufficient, and some recent literatures start to consider 12-weekly administration as a reasonable alternative in order to minimize the adverse effects.

Methods: A systematic search was conducted based on PRISMA guideline to identify relevant studies through PubMed, Google Scholar, and Cochrane database. A total of 5 studies (2867 patients) were included, divided into outcome analysis, processed using Review Manager 5.3.

Results: The search of electronic databases yielded a total of 299 entries. Five studies were included in the qualitative and quantitative synthesis following the steps of identifying, screening, determining eligibility, eliminating duplicates, and excluding studies. Out of a total of 2.867 patients, 1.427 received ZA for 12 weeks and 1.440 received ZA for 4 weeks, making up the total number of patients included in this meta-analysis. Each trial had a comparable one-year follow-up duration after ZA was given. We discovered that the incidence of adverse effects varied significantly between the two groups. In contrast, there is no statistically significant difference in the rates of SRE, ONJ, renal dysfunction, or death between the two groups.

Conclusion: Our systematic review and meta-analysis reveals that 12-week intervals of zoledronic acid is as effective as the standard 4-week interval in terms of skeletal related event, jaw osteonecrosis, renal dysfunction, and mortality rate. However, the standard 4-week intervals led to higher rate of adverse effects.

Extended dosing schedule: Denosumab- limited data

Therapeutic Advances in Medical Oncology *Original Research*

Safety and efficacy of extended dosing intervals of denosumab in patients with solid cancers and bone metastases: a retrospective study

Ther Adv Med Oncol
2020, Vol. 12: 1–10
DOI: 10.1177/1758835920982859

Aseala I. Abousaud, Meagan S. Barbee, Christine C. Davis, Sarah E. Caulfield, Zeyuan Wang, Alexa Boykin, Bradley C. Carthon and Keerthi Gogineni

- Patient & Methods: Adult patients with solid cancers and bone metastases who received at least two doses of denosumab 120mg were reviewed. Patients were grouped based on an average denosumab dosing interval of dosing interval of <5weeks (short-interval) versus 5–11weeks (mediuminterval) versus ⩾12weeks (long-interval).
- The primary outcome was the time to first SRE while on denosumab between the short- and medium-interval groups.
- The secondary outcomes were overall survival (OS), efficacy comparisons between the other groups, and safety events.

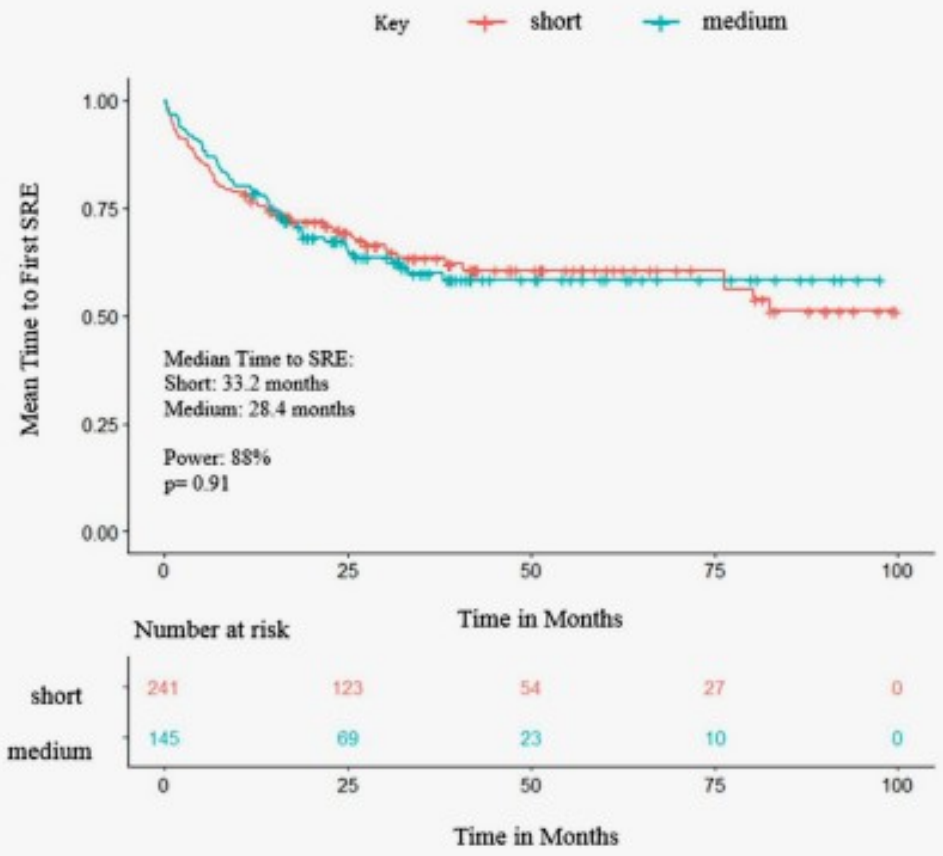


Figure 2. Kaplan–Meier-estimate time to first SRE short interval *versus* medium interval.
SRE, skeletal-related event.

Table 2. Efficacy outcomes.

	Overall population ($n=432$)	Short-interval <5 weeks ($n=241$)	Medium-interval 5–11 weeks ($n=145$)	Long-interval ⩾12 weeks ($n=46$)
Median time to first SRE (months)	–	33.2	29.1	32.2
HR (95% CI), *p* value	–	1.13 (0.66–1.92) $p=0.91$[a]	1.15 (0.66–2.01) $p=0.62$[b]	$p=0.66$[c]
mOS (months)		34.2	28.4	32.9
HR (95% CI), *p* value	–	1.05 (0.60–1.82) $p=0.2$[a]	1.33 (0.75–2.34) $p=0.28$[b]	$p=0.86$[c]

[a]For the comparison between the short- and medium-interval groups, power = 88%.
[b]For the comparison between the medium- and long-interval groups, power = 84%.
[c]For the comparison between the short- and long-interval groups, power = 45%.
CI, confidence interval; mOS, median overall survival.

ABSTRACT

- Bone modifying agents, such as zoledronic acid and denosumab, are commonly used in patients (pts) with metastatic solid tumors to reduce the incidence of skeletal-related events (SREs).
- The FDA-approved administration schedule for both agents is every 4 weeks, however less frequent administration (i.e. every 12 weeks) is commonly observed in practice due to patient convenience.
- The efficacy and safety of these extended interval regimens is well established for zoledronic acid, however there is little evidence available supporting this practice with denosumab.

Methods

- Pts with metastatic prostate cancer were evaluated for development of SREs during treatment with extended intervals of denosumab.
- 103 pts were evaluated and treated at Indiana University Health between September 2019 and September 2024 were included in this analysis.
- A historical control group of pts receiving every 4-week dosing was used as comparison. (Fizazi et al. Lancet 2011; 377: 813–22)
- SREs were defined as pathologic fracture, spinal cord compression, operation, or radiation to bone.
- Extended interval dosing is defined as an administration schedule 4 weeks apart on a consistent basis.

Statistical analysis

- Chi square or FISHER extract test for categorial variables
- Wilcoxon for continuous variable
- comparision of incidence of SREs between extended dosing and historical data
- Time to SRE were estimated with Kaplan-mayer method and compared 1 sided test from brookmeyer and crowlell method

Results

- Median age at starting bone preserving agent was 70.6 years (range, 49.5-90). 31 pts had metastatic castration-sensitive prostate cancer and 72 pts had metastatic castration-resistant prostate cancer (mCRPC) at time of last follow-up.

Table 1: Patient Characteristics of Extended Interval Dosing Group

	Castration-resistant (N=72)	Hormone-sensitive (N=31)	Total (N=103)	p-value
Age at diagnosis, median (range)	63.17 (46.63, 87.22)	67.19 (47.23, 82.99)	63.84 (46.63, 87.22)	0.2779
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Patients experiencing ≥1 SRE, n(%)	16 (22.2%)	8 (25.8%)	24 (23.3%)	0.6931
Skeletal-related events, n(%)				
Pathologic fracture	3 (4.2%)	0 (0%)	3 (2.9%)	0.5520
Spinal Cord Compression	1 (1.4%)	0 (0%)	1 (1.0%)	1.0000
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Radiation Therapy	14 (19.4%)	8 (25.8%)	22 (21.4%)	0.4699
# of denosumab doses received, median (range)	4.00 (2.00, 17.00)	7.00 (2.00, 18.00)	5.00 (2.00, 18.00)	0.0027
Hypocalcemia (Corr. Ca <8mg/dL), n(%)	12 (16.7%)	5 (16.1%)	17 (16.5%)	0.9462
Dental Complications, n(%)	4 (5.6%)	2 (6.5%)	6 (5.8%)	1.000

- Incidence of SREs in all patients receiving extended interval denosumab was 23.3%.
- The incidence of SREs at the last follow up in patients with mCRPC receiving extended interval dosing was 26.6%.
- This compares favorably to historical data with incidence of SRE in the every 4 weeks dosing group at 35.9% (p=0.10)

Table 3: SRE Comparison of Historical vs Extended Interval Dosing in mCRPC Patients

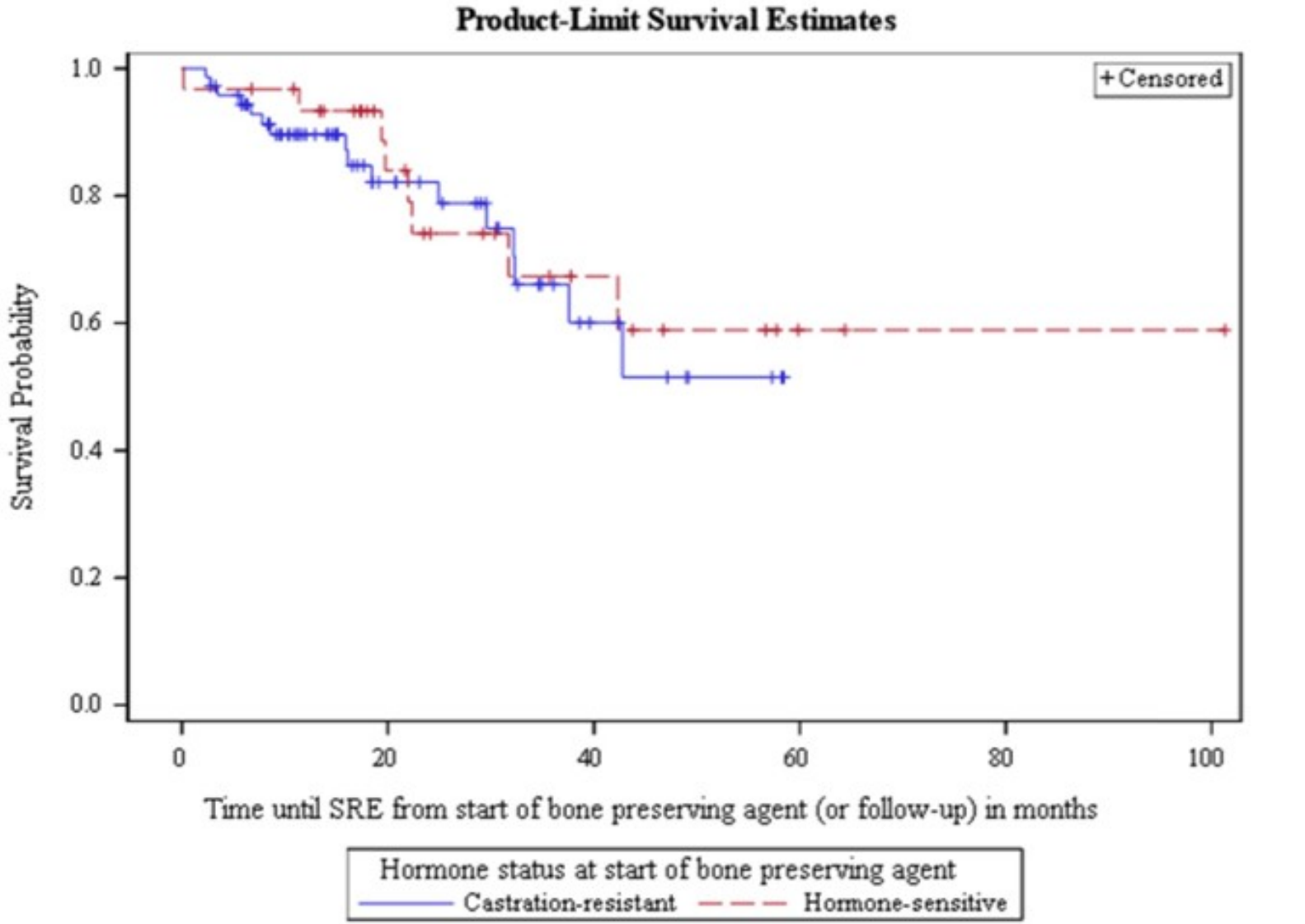
SRE development?	Historical Group	Extended Interval Group
No	609	56
Yes	341	16

- Median time to development of SRE was not estimable when all patients in the denosumab extended interval group were included in analysis.

- Median time to SRE in the mCRPC extended interval dosing group was 42.8 months and 20.7 months in the historical every 4-week dosing group (p,0.01).

- SREs identified for all patients receiving extended dosing interval denosumab were pathologic fracture (3, 2.9%), spinal cord compression (1, 1.0%), surgery (2, 1.9%), and radiation to bone (22, 21.4%).

Figure 1: Time to SRE with Extended Dosing Intervals



CONCLUSIONS

- Extended interval dosing of denosumab in patients with metastatic prostate cancer is not associated with an increased risk of development of SREs and may offer convenience for pts.
- Larger prospective studies are needed to validate these findings

THANKS FOR YOUR ATTENTION

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