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Qingchun Jin Date

Alternative Dosing Intervals of Denosumab and Effects on Clinical Outcomes and Safety in Patients with Solid Tumor Malignancies with Bone Metastases

By

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Degree to be awarded: Master of Public Health

Biostatistics and Bioinformatics Department

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By

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B.S.

Nanjing Tech University

2018

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An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Biostatistics and Bioinformatics Department

2020

Abstract

Alternative Dosing Intervals of Denosumab and Effects on Clinical Outcomes and Safety in Patients with Solid Tumor Malignancies with Bone Metastases

By Qingchun Jin

Background: Bone metastases are common in patients with solid tumor malignancies such as breast cancer. Bone metastases disrupt normal bone function, which leads to increased skeletal-related events (SREs). Denosumab is a human monoclonal antibody that can inhibit osteoclast function to decrease SREs. The FDA-approved dose for Denosumab is 120 mg every 4 weeks, however, other schedules have been clinically utilized. Existing literature suggest there is no difference in the incidence of SREs between Denosumab administration 180 mg every 4 weeks and 12 weeks in solid tumor patients with bone metastases. However, there is limited evidence regarding efficacy and safety of alternative dosing regimens.

Methods: This is a single-center retrospective study on solid tumor patients with bone metastases. Patients were grouped by an average Denosumab dosing interval of <5 vs. 5-11 vs. >12 weeks. The primary endpoint was a composite of first occurrence of SRE or all-cause death. The secondary objective was to compare safety outcomes. The cumulative event rate for the primary endpoint was estimated by Kaplan-Meier method. Hazard ratios were calculated to measure the degree of association between baseline covariates and composite outcome by fitting Cox proportional hazards model. Cochran-Armitage trend tests were used to analyze safety events.

Results: The 3-year cumulative composite event rate was approximately 27%, and the rates didn't differ by dosing intervals (p=0.37). From multivariable Cox proportional hazards regression, independent predictors included prior radiation for primary cancer (HR=0.47, p=0.001), prior surgery for primary cancer (HR=0.74, p=0.12), ECOG (HR=0.48, grade 2 and3 versus grade 0 and 1, p=0.01), presence of visceral metastases (HR=2.10, p=0.0004), Vitamin D supplementation (HR=0.78, p=0.18), creatinine clearance (HR=0.995 per ten mL/min increase, p=0.10) and previous skeletal-related events (HR=1.59, p=0.02). There were significantly more subjects with hospitalizations and hypocalcemia in <5 weeks group (55.0%, p<0.0001; 31.1%, p=0.02).

Conclusion: Extending Denosumab dosing intervals outside labeling recommendations does not appear to significantly affect the time to SRE (or all-cause mortality) among solid tumor patients with bone metastases. Dosing intervals consistent with labeled recommendations were associated with increased incidence of hospitalizations and hypocalcemia compared to less frequent dosing schedules.

KEYWORDS: Bone metastases, SREs, Denosumab, Dosing intervals

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ACKNOWLEDGEMENTS

I would like to thank the Department of Biostatistics of Rollins School of Public Health at Emory University, in which I systematically learned the statistical knowledge and reached my potential. I would also like to thank the staff there, who helped create a warm and enjoyable BIOS community.

I would like to thank my thesis advisor Prof. Nelson Chen who gave me a great help in guiding my thesis direction, methods and writing. I would also like to thank my thesis reader Neeta Shenvi, Kirk Easley, and Julia Silva Sobolik, who gave me detailed revision insights. Without their instruction and support, this thesis would not have been possible.

I would like to thank my master faculty advisor Prof. Yi-An Ko, who advised me through any time at Emory University RSPH. Without her help, I would not be able to get a lot of opportunities to engage a lot of relevant projects and work as a research assistant in Emory Clinical Cardiovascular Research Institute at School of Medicine of Emory. I would also like to express gratitude to my summer practicum advisor Chang Liu, who gave me a lot of favors whenever I have questions and always instruct and explain to me patiently. I enjoyed working with them and they would always be my great mentors.

I would like to thank all my fellow Biostatistics cohort, my classmates, and friends who helped created an effective learning space and help and encourage me whenever I came across difficulties in academic study.

Finally, I would sincerely thank my parents, who always provide me with huge support and encouragements as well as endless care through my whole studying years.

Thank you!

Contents

1.Introduction

Bone metastases are common among a majority of patients with advanced solid tumor malignancies such as prostate, breast and lung cancers.[1] Metastases occur when cancer cells from the original tumor site relocate to the bones and result in the disruption of normal bone metabolism and homeostasis between osteoclasts and osteoblasts.[2] These tumor cells in the bone lead to the increased expression of the receptor activator of nuclear factor-kappa B ligand(RANKL)[3], which is essential for osteoclast formation, function, survival[4], and the development of bone metastases.[5] Due to the disruption of normal bone functioning, patients with bone metastases are at high risk of skeletal-related events (SREs)[6] including spinal cord compression or pathological fracture that can result in paralysis, surgery to bone to prevent fractures, and radiation therapy to alleviate bone pain.[7] More than half of patients with bone metastases have evidence of SREs. SREs are frequently associated with functional declines in patient daily quality of life,[8] and decreased overall survival (OS). Therefore, national guidelines recommend the use of bone-modifying agents in cancer patients with bone metastases in order to prevent fractures and skeletal events.[9]

Denosumab is a human monoclonal antibody, which has high specificity for RANKL. Binding of Denosumab to RANKL can impede the osteoclast formation and function, therefore suppressing generalized bone resorption and decreasing SREs.[10] Denosumab has been shown to have superior efficacy in delaying time to SREs, improving pain palliation and reducing bone turnover markers among other osteoclast-targeting agents such as zoledronic acid.[11, 12] In 2010, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) approved Denosumab for SREs prevention in adults with bone metastases from solid tumors. The side effects of Denosumab administration include hypocalcemia, osteonecrosis of jaw, bone pain, renal toxicity, etc.[13]

Three recent clinical trials evaluating different dosing schedules found blank with the FDA-approved optimal dosing strategy as 120 mg subcutaneous administration every 4 weeks.[14] However, clinicians frequently utilize other schedules based on balancing patient convenience with their chemotherapy schedules and needing to balance treatment side effects. From a systematic review and meta-analysis comparing Denosumab administration every 4 weeks vs. every 12 weeks in patients with bone metastases from breast cancer, there was no difference in the incidence of SREs with extended interval dosing.[15] A small randomized phase II trial also examined Denosumab 180mg every 4 or 12 weeks in solid tumor patients who previously received bisphosphonates vs bisphosphonate continuation and found fewer SREs in Denosumab arm.[16] However, all of these studies failed to address a middle dosing interval such as 6 weeks or 8 weeks, which is often observed in clinical practice. There is a need to characterize the safety and clinical outcomes of alternative Denosumab dosing intervals in patients with solid tumor malignancies and bone metastases. The purpose of this study was to explore the impact of three different intervals of Denosumab dosing (<5, 5-11, and >12 weeks) on time to first SRE or death while on Denosumab, as well as patient reported side effects.

2. Methods

2.1 Study Population and Design

In this single-center retrospective study, electronic medical records were used to abstract data on patients who received Denosumab. All patients with solid tumor malignancies and bone metastases who received at least two doses of Denosumab 120 mg from November 1, 2010 to July 27, 2018 were included in this study. Patients who have received Denosumab for another indication such as hypercalcemia of malignancy, osteoporosis, giant cell neoplasm or multiple myeloma were excluded. Patients who received a dose other than 120 mg or changed frequencies during the Denosumab treatment were excluded. Patients who received a dose of Denosumab outside of the Emory Healthcare system were also excluded.

2.2 Endpoints

The primary objective of this study was to assess the outcomes in patients with solid tumor malignancies and bone metastases after receiving an average Denosumab dosing interval of <5 weeks (short interval) or 5-11 weeks (medium interval) or >12 weeks (long interval). The primary endpoint was the first SRE (or all-cause mortality) while on Denosumab. SREs are defined as pathologic fracture (exclusive of major inciting trauma), radiation or surgery to bone, or spinal cord compression.

The secondary objective was to compare safety outcomes including the incidence of hypocalcemia, osteonecrosis of the jaw (ONJ) and hospitalizations by Denosumab dosing interval.

2.3 Statistical Analysis

The baseline and clinical factors of the patients were compared by Denosumab dosing interval using chi-square test or Fisher's exact test for the categorical covariates and t test or ANOVA test for the numerical covariates when the covariates were normally distributed and Kruskal-Wallis test when they were not normally distributed.

The composite endpoint was defined as time from the date of first dose of Denosumab to the date of first occurrence of SRE or all cause death whichever came first. Patients were considered as censored if they were lost to follow-up and the time to censoring were defined as the time to the last follow up. The incidence of first SRE (or all-cause mortality) was estimated by the Kaplan-Meier method. Log-rank tests were used to compare cumulative event rates for the composite outcome according to baseline and clinical characteristics.

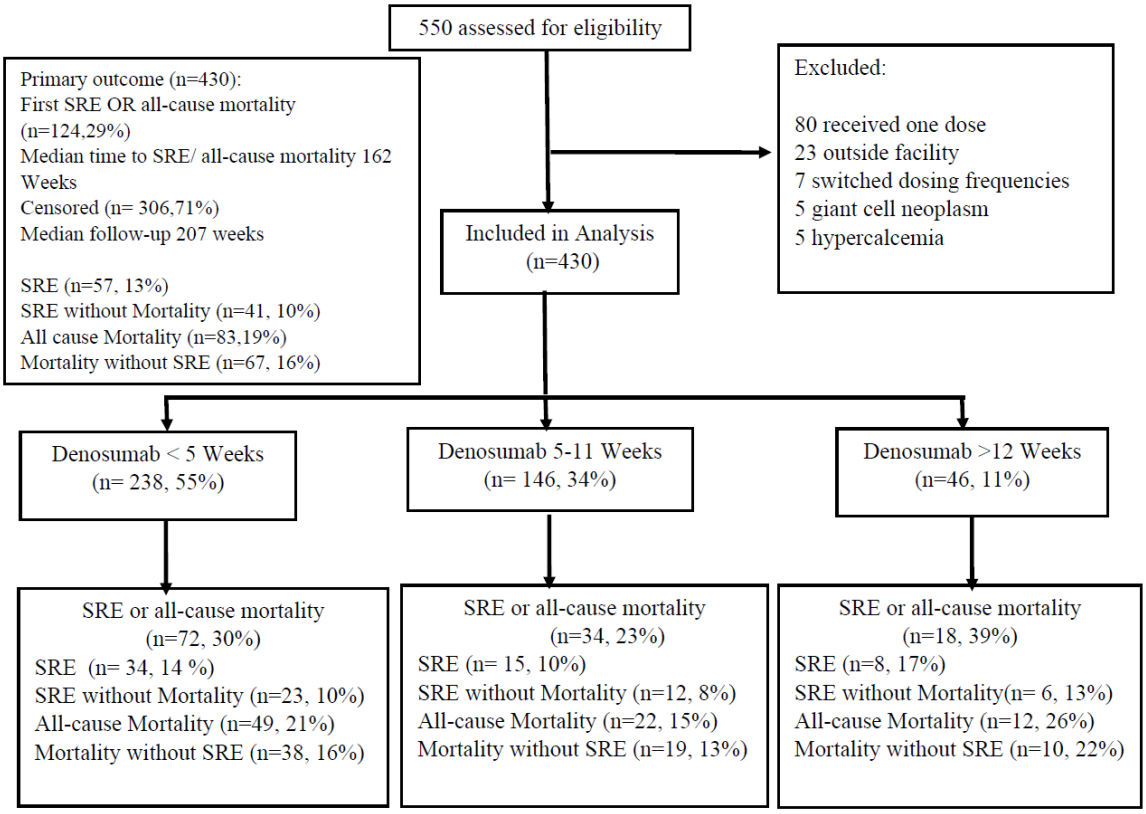
The univariate association of each covariate with the effects of Denosumab dosing schedules was estimated by using a Cox Proportional Hazards model. Furthermore, a multivariate association, adjusting for certain covariates was estimated by using the same model. The stepwise variable selection method with an alpha of removal level of 0.2 was used to identify the best predictive models. Cochran-Armitage trend tests were used to analyze safety events. Additionally, the assumption of the proportional hazards model was checked graphically with regression diagnostics. All of the analyses were conducted using SAS software (version 9.4, Cary, North Carolina) and R software version 3.6.1 (http://www.R-project.org).

3. Results

3.1 Demographic and Clinical Characteristics

There were 430 patients included in the analysis after applying the inclusion criteria. The most common reason for exclusion were patients who received only one dose of Denosumab. Out of 430 subjects who received 120mg Denosumab, 238 (55%) subjects received short dosing interval (<5 weeks), 146 (34%) patients received medium dosing interval (5-11 weeks) and 46 (11%) subjects in the long dosing interval (>12 weeks) (Figure 1). A total of 57(13%) subjects developed SRE, and 83(19%) subjects died (all cause). Median time to first SRE (or all-cause mortality) for all three groups was 162 Weeks. Median follow up time for censored subjects was 207 weeks.

Figure 1. Cohort Diagram



Demographic and clinical characteristics are presented in Table 1. Mean age was 65 years. Forty-four (44%) of subjects were males and 59% were white race. Twenty-six (26%) had breast cancer, 37% had prostate or other cancer.

Patient clinical characteristics were statistically significant for several covariates. Breast cancer was more common in the < 5 weeks group and there was a difference in prior lines of anti-cancer therapy for metastatic disease where the 5-11 weeks group represented a population that was not as heavily pretreated compared to the <5 weeks group and >12 weeks group. There was also greater prior bisphosphonate use and greater adherence to vitamin D supplementation in the > 12 weeks group. The number of prior systemic therapy for Primary Cancer was greater in < 5 weeks group and the number of visceral metastases was greater in the 5-11 weeks group. CrCl at start of Denosumab was higher in short dose group compared to other (87 ± 30; 72 (31.2); 74 (28.7)).

Table 1. Demographic and Clinical Characteristics, Overall and According to Denosumab Dosing Interval Among 430 Patients With Solid Tumor Malignancies and Bone Metastases

Risk Factor	Overall (n=430)	Denosumab Dosing Interval < 5 weeks (n=238)	5-11 weeks (n=146)	> 12 weeks (n=46)	P
Age, mean (SD)	64.71(12.2)	64.19(12.8)	64.84 (11.4)	66.96 (11.5)	0.37
Males, n(%)	191(44.4)	110 (46.2)	63 (43.2)	18 (39.1)	0.63
Race, White n(%)	255(59.3)	127 (53.4)	95 (65.0)	33 (71.7)	0.06
Cancer type					**<0.001**
Cancer (Breast), n(%)	112(26.0)	80 (33.6)	23 (15.8)	9 (19.6)	
Cancer (Prostate),n(%)	158(36.7)	83 (34.9)	54 (37.0)	21 (45.7)	
Cancer (Other),n(%)	160(37.2)	75 (31.5)	69 (47.3)	16 (34.8)	
Number of Prior Lines of Anti-Cancer Therapy for Metastatic Disease (≤ 2), n(%)	275(64.0)	138 (58.0)	106 (72.6)	31 (67.4)	**0.01**
Prior Surgery for Primary Cancer, n(%)	220(51.2)	129 (54.2)	69 (47.3)	22 (47.8)	0.37
Prior Radiation for Primary Cancer, n(%)	216(50.2)	117 (49.2)	75 (51.4)	24 (52.2)	0.88
Prior Systemic Therapy for Primary Cancer, n(%)	370(86.0)	213 (89.5)	121 (82.9)	36 (78.3)	**0.05**
Prior Bisphosphonate Therapy, n(%)	57(13.3)	36 (15.1)	9 (6.2)	12 (26.1)	**0.001**
Prior Denosumab Therapy, n(%)	5(1.2)	4 (1.7)	1 (0.7)	0 (0.00)	0.50
ECOG PS at Initiation of Denosumab (0-1),n(%)	349(81.2)	189(79.4)	123(84.3)	37(80.4)	0.50
Presence of Visceral Metastases (non-Brain),n(%)	274(63.7)	132(55.5)	111(76.0)	31(67.4)	**< 0.001**
Presence of Brain Metastases, n(%)	83(19.3)	42 (17.7)	30 (20.6)	11 (23.9)	0.55
Previous Skeletal-Related Events, n(%)	137(31.9)	81 (34.0)	44 (30.1)	12 (26.1)	0.49
Dietary Supplementation of Calcium, n(%)	224(52.1)	128 (53.8)	68 (46.6)	28 (60.9)	0.18
Dietary Supplementation of Vitamin D, n(%)	213(49.5)	123 (51.7)	61 (41.8)	29 (63.0)	**0.03**
Received ≤ 10 Doses of Denosumab, n(%)	290(67.4)	138 (58.0)	112 (76.7)	40 (87.0)	**<0.001**
CrCl at start of denosumab (mL/min), Mean(SD)	80.2(30.7)	86.6 (30.0)	71.9 (31.2)	73.9 (28.7)	**<0.001**

3.2 Description of Exposures and Outcomes

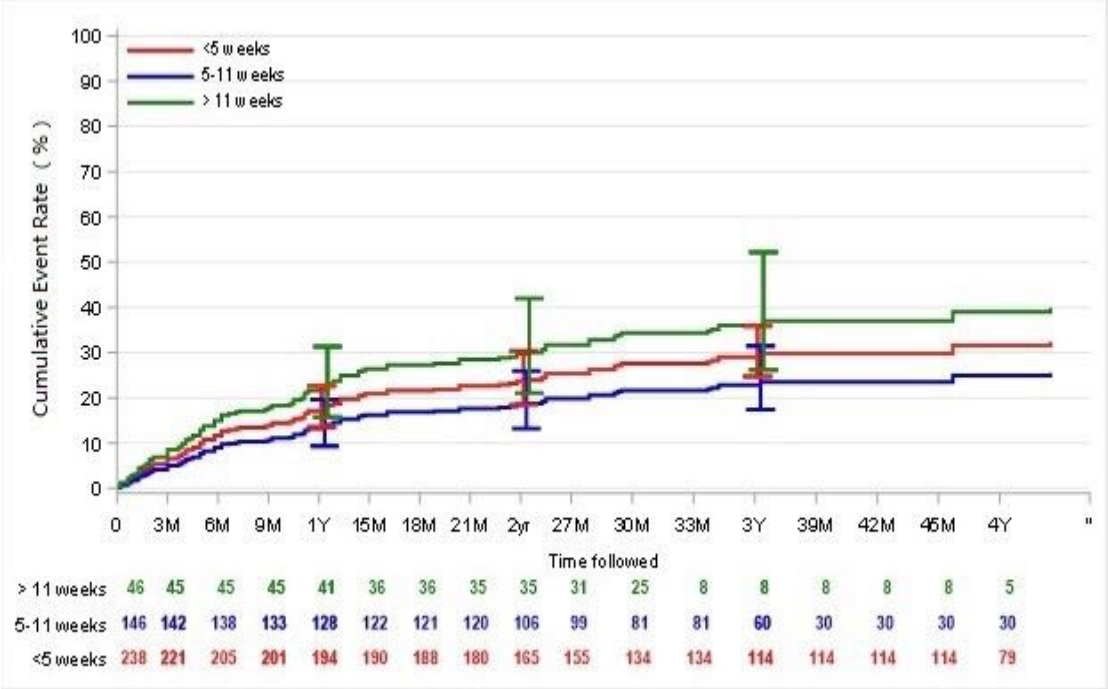
A total of 124 subjects developed SRE or death (27 subjects in <5 weeks of Denosumab, 34 subjects in 5-11 weeks of Denosumab and 18 in >12 weeks of Denosumab). Median time to first SRE (or all-cause mortality) was 162 Weeks. Median follow up time for censored subjects was 207 weeks.

The cumulative-incidence of First SRE (or all-cause mortality) was similar in 3 groups (P=0.15, Table 1) The overall cumulative incidence for first year was 16% (95%CI, 13% - 20%) and 22% (95%CI, 19% - 26%) and 27% (95%CI, 23% - 31%) for year 2 and year 3 respectively.

Table 2: Cumulative Event Rates for the Primary Outcome (a composite of the first occurrence of a skeletal-related event or all-cause death) by Denosumab Dosing Interval

	Overall (n=438)			< 5 weeks (n=238)			5-11 weeks (n=146)			> 12 weeks (n=46)			
	n	%	95%CI	n	%	95%CI	n	%	95%CI	n	%	95%CI	P
Number with SRE or all cause mortality	124	29	25-33	72	30	25-37	34	23	17-31	18	39	27-56	
Cumulative SRE or all cause mortality, year													0.15
1 year	70	16	13, 20	44	17	13, 23	19	13	10, 17	7	22	14, 33	
2 year	94	22	19, 26	54	23	18, 29	28	18	13, 25	12	29	21, 39	
3 years	111	27	23, 31	64	28	23, 34	33	22	16, 29	14	35	25, 49	
4 years	119	30	26, 35	70	32	25, 40	34	25	18, 35	15	39	28, 55	

Figure 2 Cumulative Event Rates for the Primary Outcome (a composite of the first occurrence of a skeletal-related event or all-cause death) by Denosumab dosing interval



3.3 Risk Factors for First SRE (or all-cause mortality)

In a bivariate analysis, factors associated with SRE and death were included. The unadjusted cumulative incidence of SRE (or all-cause mortality) was similar in three groups (At year 1: 17% (95% CI, 13%-23%) vs. 13%(95%CI,10%-17%) vs. 22% (95%CI,14%-33%)). Factors that increased the risk for first SRE (or all-cause mortality) included breast and prostate cancer, having Prior Radiation for Primary Cancer, and having presence of visceral metastases (no-brain).

The rate of first SRE (or all-cause mortality) who received <5 weeks compared with >12 weeks was (HR= 0.77 (95% CI, 0.46-1.29), P = 0.32) and who received 5-11 weeks compared with >12 weeks was (HR = 0.58 (95% CI, 0.33-1.03), P = 0.06). In multivariable analysis, prior radiation for primary cancer, prior surgery for primary cancer, ECOG scale of performance status at Initiation of Denosumab, presence of non-Brain visceral metastases, having Vitamin D dietary supplementation, creatinine clearance at start of Denosumab (mL/min), and previous skeletal-related events was associated with an increased rate of SRE (or all-cause mortality).

The adjusted analysis showed that the rate of first SRE (or all-cause mortality) was 47% lower for patients who had prior radiation for primary cancer (HR=0.47 (95% CI, 0.32 - 0.69), P=0.001), 74% lower for patients who had prior surgery for primary cancer (HR=0.74 (95% CI, 0.51 - 1.09), P=0.12), and 48% lower with ECOG scale of performance status with grade 2-3 at initiation of Denosumab verses 0-1 (HR=0.48 (95% CI, 0.28 -0.81), P=0.01). The rate of first SRE (or all-cause mortality) was 2.1 times higher for patients who had Visceral Metastases(non-Brain) compared with those didn't (HR=2.10 (95% CI, 1.39 -3.16), P= 0.0004). Having Previous Skeletal-Related Events is significantly associated with higher rate of first SRE (or all-cause mortality) (HR=1.59 (95% CI, 1.09-2.32), P =0.02). Having diet supplementation with Vitamin D is associated with lower rate of first SRE (or all-cause mortality) (HR=0.78 (95% CI, 0.55-1.12), P =0.18). CrCl at

start of Denosumab was also found associated with lower rate of first SRE (or all-cause mortality) (HR=0.995 per one mL/min increase, (95% CI, 0.99-1.00), P =0.10).

Table 3: Baseline Risk Factors for the Composite Outcome among 430 Patients with Solid Tumor Malignancies and Bone Metastases

Risk Factor	N	Number with SRE or death (%)	β ± SE	Hazard Ratio (95% CI)	P
A. Univariable Analyses					
OVERALL	430	124(28.8%)			
Denosumab Dosing Interval					0.15
< 5 weeks	238	72 (30.3%)	-0.27±0.26	0.77 (0.46-1.29)	0.32
5-11 weeks	146	34 (23.3%)	-0.54±0.29	0.58 (0.33-1.03)	0.06
> 12 weeks	46	18 (39.1%)		Reference	
Gender					0.33
Male	191	51(26.7%)	-0.18±0.18	0.84 (0.59-1.20)	0.33
Female	239	73(30.5%)		Reference	
Age (per one year increase)					
	430	1.72 (0.4%)	-0.004±0.01	1.00 (0.98-1.01)	0.15
Race					0.27
Black	144	38(26.4%)	0.34±0.44	1.41 (0.59-3.33)	0.44
White	255	80(31.4%)	0.56±0.42	1.75 (0.76-4.01)	0.19
Other	31	6(19.4%)		Reference	
Cancer					**0.03**
Breast	112	28(25.0%)	-0.50±0.23	0.61 (0.39-0.96)	**0.03**
Prostate	158	41(26.0%)	-0.45±0.21	0.63 (0.43-0.96)	**0.03**
Other	160	55(34.4%)		Reference	
Number of Prior Lines of Anti-Cancer Therapy for Metastatic Disease (<=2)					
<=2	275	78(28.4%)		Reference	
>2	155	46(29.7%)	0.04±0.19	1.05 (0.73-1.51)	0.81
Prior Surgery for Primary Cancer					
Yes	220	59(26.8%)	-0.23±0.18	0.80 (0.56-1.13)	0.21
No	210	65(31.0%)		Reference	
Prior Radiation for Primary Cancer					
Yes	216	46(21.3%)	-0.64±0.19	0.53 (0.37-0.76)	**<0.001**
No	214	78(36.5%)		Reference	
Prior Systemic Therapy for Primary Cancer					
Yes	370	107(28.9%)	-0.04±0.26	0.96 (0.57-1.60)	0.87
No	60	17(28.3%)		Reference	
Prior Bisphosphonate Therapy					
Yes	57	20(35.1%)	0.20±0.24	1.22 (0.75-1.96)	0.42
No	373	104(27.9%)		Reference	

Table 3 continued: Risk Factors for SRE or death using Cox regression models (n=430)

Risk Factor	N	Number with SRE or death (%)	β ± SE	Hazard Ratio (95% CI)	P
A. Univariate analysis continued					
Prior Denosumab Therapy					
Yes	5	2(40.0%)	0.49±0.71	1.64(0.40-6.63)	0.49
No	425	122(28.7%)		Reference	
ECOG PS at Initiation of Denosumab (0-1)					
0 to1	349	107(30.7%)		Reference	
2 to3	81	17(21.0%)	-0.49±0.26	0.61 (0.37-1.02)	0.06
Presence of Visceral Metastases (non-Brain)					
Yes	274	89(32.5%)	0.47±0.20	1.59 (1.08-2.36)	**0.02**
No	156	35(22.4%)		Reference	
Presence of Brain Metastases					
Yes	83	24(28.9%)	0.02±0.23	1.02 (0.65-1.59)	0.93
No	347	100(28.8%)		Reference	
Previous Skeletal-Related Events					
Yes	137	47(34.3%)	0.30±0.19	1.34 (0.93-1.93)	0.11
No	293	77(26.3%)		Reference	
Dietary Supplementation of Calcium					
Yes	224	63(28.1%)	-0.09±0.18	0.91 (0.64-1.30)	0.62
No	206	61(29.6%)		Reference	
Dietary Supplementation of Vitamin D					
Yes	213	59(27.7%)	-0.11±0.18	0.89 (0.63-1.27)	0.53
No	217	65(30.0%)		Reference	
Received <= 10 Doses of Denosumab					
<= 10	290	82(28.3%)		Reference	
> 10	140	42(30.0%)	-0.10±0.19	0.91 (0.63-1.32)	0.61
B. Multivariable Analysis					
Denosumab Dosing Interval					0.37
< 5 weeks			-0.10±0.27	0.91 (0.53 -1.55)	0.72
5-11 weeks			-0.23±0.18	0.80 (0.56 -1.13)	0.21
> 12 weeks					
Prior Radiation for Primary Cancer (Yes vs No)			-0.75±0.19	0.47 (0.32 - 0.69)	**0.001**
Prior Surgery for Primary Cancer (Yes vs No)			-0.30±0.19	0.74 (0.51 - 1.09)	0.12
ECOG PS at Initiation of Denosumab (2 to3 vs 0-1)			-0.74±0.27	0.48 (0.28 - 0.81)	**0.01**
Presence of Visceral Metastases(non-Brain) (Yes vs No)			0.74±0.21	2.10 (1.39 - 3.16)	**0.0004**
Dietary Supplementation of Vitamin D (Yes vs No)			-0.24±0.18	0.78 (0.55 - 1.12)	0.18
CrCl at start of denosumab (per 10 mL/min increase)			-0.01±0.003	0.995 (0.99 - 1.00)	0.1
Previous Skeletal-Related Events (Yes vs No)			0.46±0.19	1.59 (1.09 -2.32)	**0.02**

3.4 Safety Outcomes

Table 4 summarizes safety outcomes by Denosumab Dosing Interval. There were significantly more subjects with any hospitalizations in <5 weeks group (55.0% vs 34% vs 31%, p<0.0001). The number of subjects with hypocalcemia was higher in <5 weeks group (31% vs 23% vs 17%, p<0.02).

The three main reasons for hospitalizations in the <5 weeks group were abdominal pain, hematuria and fever. There was no statistically significant difference in presence of any episode of ONJ in three Denosumab groups.

Table 4. Safety outcomes by Denosumab Dosing Interval

Safety outcome	Overall (n=430)	Denosumab Dosing Interval: < 5 weeks (n=238)	5-11 weeks (n=146)	> 12 weeks (n=46)	P Trend Test
		n(%)	n(%)	n(%)	
Presence of Any Hospitalizations While on Denosumab	194 (45.1)	131 (55.0)	49 (34.3)	14 (31.1)	**<.0001**
Presence of Any Hypocalcemia While on Denosumab Based on Corrected Calcium	116 (27.0)	74 (31.1)	34 (23.3)	8 (17.4)	**0.02**
Presence of Any Episode of ONJ While on Denosumab or Reported	7 (1.6)	6 (2.5)	1 (0.7)	0	0.16
Any of the above three morbidities	244 (56.7)	159 (66.8)	66 (45.2)	19 (41.3)	**<.0001**

4. Discussion

The purpose of this study was to characterize the safety and clinical outcomes of alternative Denosumab dosing intervals in patients with solid tumor malignancies and bone metastases. Specifically, we explored the impact of three different intervals of Denosumab dosing (<5, 5-11, and >12 weeks) on time to first SRE (or all-cause mortality) while on Denosumab and patient reported side effects. Using a retrospective study design, we found that alternative dosing schedules of 120 mg subcutaneous Denosumab did not alter efficacy as it relates to time to first SRE (or all-cause mortality). However, there was a difference in safety with increased hospitalizations and hypocalcemia in the <5 weeks group.

Extending Denosumab dosing intervals outside of the current FDA approved label recommendation does not show a benefit for time to SRE (or all-cause mortality) among patients with solid tumor

malignancies and bone metastases. We used the average dosing frequency and excluded those patients who had ever switched their dosing frequency in order to eliminate potential confounding factors. Our findings are consistent with the previous literature which has shown that every 4 weeks Denosumab administration versus every 12 weeks has no difference in time to first SRE[15]. Importantly, our study provides additional information on time to first SRE (or all-cause mortality) for dosing frequencies between short and medium intervals.

Another key finding from this study is that there were more hospitalizations and hypocalcemia in the < 5 weeks group versus 5-11 weeks group and the > 12 weeks group. The most common complaints were abdominal pain, hematuria, and fever (Table 5). The 5-11 weeks group had similar hospitalization reasons (shortness of breath, abdominal pain and fever) as shown in Table 6. Of note, it is possible the chief complaints can be attributed to many different factors in cancer patients other than the dosing schedule. Moreover, the statistical significance could be skewed due to the limited number of patients in the > 12 weeks group and not meeting power when comparing across all three groups.

There are several limitations to this study. Due to the retrospective nature of this study, it is possible that the patients may not have received their dose at a precise frequency. This may have impacted why we did not find a difference between the three interval treatment groups. We also note that the baseline characteristics among the three different interval groups were different. For instance, the differences of cancer types among the three groups of patients may be due to the correlation between the cancer type and dose frequency. There was also a difference with presence of visceral metastases being higher in the 5-11 weeks group (76.0%) versus the <5 weeks group (55.5%) and the > 12 weeks group (67.4%), which indicates a potentially sicker patient population. However, this did not correlate to any differences in safety with more hospitalizations being found in the <5 weeks group. Renal function was also different among the three groups. The 5-11 weeks group was

found to have worse renal function. However, this did not correlate with safety. Dietary supplementation was determined based on whether patients had calcium or vitamin D in their medication history while receiving Denosumab doses. The accuracy of the dietary supplementation data might be flawed, because patients may not document their medication accurately and there was no documentation to assess for adherence. This could affect SRE risk and development of hypocalcemia while on Denosumab. Finally, while there were limited number of patients in the > 12 weeks group which could lead to reduced study power, there were sufficient numbers of patients when comparing the <5 weeks dosing interval group and the 5-11 weeks group. In this way we were able to expand fill the gaps in the literature on this middle interval dosing on the impact of first SRE (or all-cause mortality).

Moreover, although automated model selection procedures such as stepwise are popular for covariate selection, they do not account for model selection uncertainty based on a single sample, often tending to reject null hypotheses more often than the nominal levels would suggest, and to produce confidence intervals that are too narrow. In our future study, treating non-SRE mortality as competing risks may be an informative alternative analysis.

5. Conclusion

Clinical practice frequently uses middle dosing regimens of Denosumab to treat patients with solid tumor malignancies and bone metastases despite there being limited evidence to support these dosing schedules. As prior clinical trials have not assessed the clinical benefit of middle dosing intervals (6-8 weeks), there has been a need to characterize the safety and clinical outcomes of alternative Denosumab dosing intervals in patients with solid tumor malignancies and bone metastases. The purpose of this study was to explore the impact of three different intervals of Denosumab dosing (<5, 5-11, and >12 weeks) on time to first SRE (or all-cause mortality) while on Denosumab and patient reported side effects. We found that extending Denosumab dosing

intervals outside of the current FDA approved label recommendation does not show a benefit for time to SRE (or all-cause mortality) among patients with solid tumor malignancies and bone metastases. Moreover, in this studied population, Denosumab dosing within the recommended intervals was found to be associated with more hospitalizations and hypocalcemia than that with extended intervals. This work has implications on how patients and clinicians design treatment regimens for patients with solid tumor malignancies and bone metastases.

6. References

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APPENDIX

Table 5. Reason for Hospitalizations in < 5 Weeks Group

Chief Complaint	Number of Hospitalizations
Chest pain	8
Urinary retention	6
Fever	10
Nausea	4
Vomiting	4
Diarrhea	4
Constipation	1
Procedure	6
Altered mental status	6
Anemia	2
Abdominal pain	21
Edema	4
Hemoptysis	3
Hip pain	6
Bleed	6
Seizure	1
Respiratory distress	1
Hernia	1
Hip fracture	1
Deep vein thrombosis	6

Tachycardia	5	
Hematuria	16	
Acute kidney injury	4	
Dehydration	1	
Failure to thrive	1	
Brain met	1	
Hypotension	1	
Hyperkalemia	1	
Total		**131**

Table 6. Reason for Hospitalizations in 5-11 Weeks Group

Chief Complaint	Number of Hospitalizations	
Chest pain	4	
Pulmonary embolism	4	
Cough	4	
Fever	10	
Shortness of breath	14	
Anemia	2	
Abdominal pain	11	
Total		**49**

Table 7. Reason for Hospitalizations in >12 Weeks Group

Chief complaint	Number of hospitalizations
Sob	4
Hematuria	3
Constipation	2
Fever	4
Elevated total bilirubin	1
Total	**14**