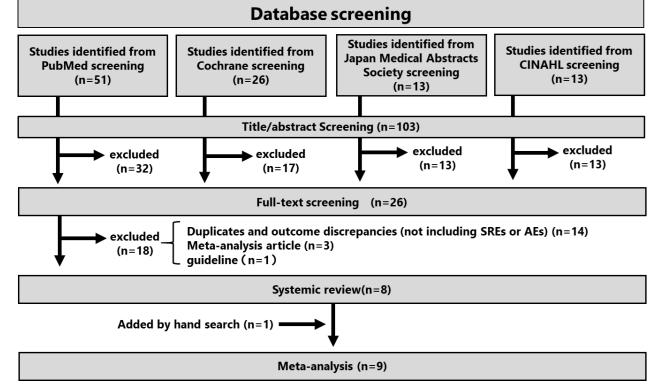
# Efficacy and Safety of Bone Management Agents Administered at 12 Weeks vs. 4 Weeks in Patients with Bone Metastases: A Systematic Review

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Background: Bone Modifying Agents (BMAs) have been used to prevent skeletal-related events (SRE) in cancer patients with bone metastases. In this meta-analysis, efficacy and adverse events (AEs) were studied based on a de-escalation strategy in which the BMA dosing interval was prolonged from 4 to 12 weeks.

## **Selection process for articles**



### **Key Results**

- The meta-analysis included three randomized controlled studies (RCTs) of Zoledronic acid hydrate (ZA) (n = 2,663) and six RCTs (n = 141) on BMA other than ZA.
- There was no difference in the incidence of SREs when comparing the dosing frequency of 12 versus 4 weeks for BMA (RR = 1.21, 95% CI [0.82-1.78], p = 0.33).
- AEs related to treatment discontinuation were significantly less frequent with ZA given every 12 weeks than when given every 4 weeks (RR = 0.51 [0.30-0.89], p = 0.02).
- Renal dysfunction leading to grade ≥3 or discontinuation of treatment with ZA occurred significantly less frequently with every 12-week dosing (RR = 0.33 [0.12-0.91], p = 0.03).

### **Details of studies included in the meta-analysis**

Study	Design	N	Disease (history of	ВМА	Study	Primary	Secondary	SRE or SSE*	AEs	Renal dysfunction	ONJ	Hypocalcemia	Others
CALGB	RCT	1,822	BMA use) Prostate, Multiple	ZA	period	endpoints SRE	endpoints BPI, ECOG-PS,	260/911(29%)	Treatment discontinuation AE:	Increased serum creatinine of ≥0.5	18/911(2.0%)		Others
-70604 <sup>1)</sup>	non- inferiority trial		myeloma (8-9% patient used any BMA)	ZA	2 year	SKE	ONJ, Renal dysfunction, SMR	vs 253/911(28%)	42/911(5%) vs 18/911(2%)	mg/dL: 174/875(20%) vs 137/882(16%) Severe renal dysfunction ( Grade ≥3 elevated serum creatinine level): 10/852(1.2%) vs 4/837(0.5%)	vs 9/911(1.0%)	Any grade: 329/866(38%) vs 298/851(35%) Grade4: 8/866(1%) vs 5/851(1%)	
OPTIMIZE-2 <sup>2)</sup>	RCT non- inferiority trial		Breast (All patient used ZA and/or PA)	ZA	1 year	SRE	Bone pain, BPI, analgesic consumption), metabolic bone markers, Safety	44/200(22%) vs 47/203(23%)	Any grade: 189/198(96%) vs 189/202(94%) Grade 3-4: 94/198(47%) vs 86/202(43%) Serious AE: 50/198(25%) vs 51/202(25%) Treatment discontinuation AE: 23/198(12%) vs 18/202(9%)	Any grade: 19/198(10%) vs 16/202(8%) Treatment discontinuation: 6/198(3%) vs 1/202(1%)	2/198(1%) vs 0/202(0%)		Nausea: 59/198(30%) vs 53/202(26%) vomiting: 32/198(16% vs 34/202(17%) Bone pain: 49/198(25%) vs 48/202(24%)
ZOOM <sup>3)</sup>	RCT non- inferiority trial	425	Breast (All patient used ZA)	ZA	1 year	SRE	Bone pain, analgesic use, NTx, safety	33/216(15%) vs 31/209(15%)	Any grade: 184/216(85%) vs 159/209(76%) Grade 3-4:95/216(44%) vs 92/209(44%) Serious AE: 29/216(13%) vs 21/209(10%) Treatment discontinuation AE: 9/216(4%) vs 2/209(1%)	Any grade: 2/216(1%) vs 1/209(<1%)	3/216(1%) vs 4/209(2%)		Nausea: 33/216(15%) vs 24/209(11%) vomiting: 23/216(11%) vs 14/209(7%) Bone pain: 65/216(31%) vs 56/209(27%)
REFORM <sup>4)</sup>	RCT	30	Breast (All patient used PA)	PA	2year	CTx, BSAP	BPI, FACT-BP	3/13(23%) vs 4/17(24%)					
REaCT <sup>5)</sup>	RCT non- inferiority trial	263	Breast, Prostate(48% patient used any BMA)	Dmab(56 <sup>%</sup> ) ZA(24 <sup>%</sup> ) PA(20 <sup>%</sup> )	2year	HRQoL, QLQ- C30	Pain, SSE, tSSE	12/133(9%) vs 44/130(34%) *	Treatment discontinuation AE: 22/133 (17%) vs 31/130 (24%)	Any grade: 4/133 <sup>(3%)</sup> vs 4/130 <sup>(3%)</sup>	1/133(1%) vs 1/130(1%)	Any grade: 3/133(2%) vs 3/130(2%)	
Fizazi.k <sup>6)</sup>	RCT	111	Breast, Prostate (82% patient used ZA)		13W-25W	NTx(13W)	CTx, NTx (25W)	6/35(17%) vs 4/35(11%)					
Lipton (2007) <sup>7)</sup>	RCT	255	Breast cancer (No use BP)		13W	NTx	Patient with -65% decrease in NTx, SRE, safety		Any grade: 155/169(92%) vs 76/85(89%) Serious AE: 28/169(17%) vs 12/85(14%) Treatment discontinuation AE: 41/169(24%) vs 13/85(15%)				
Lipton (2008) <sup>8)</sup>	RCT	255	Breast cancer (No use BP)	Dmab(q4w or q12w), BP(ZA, PA, IN)(q4w)	13W	NTx	NTx (25W)		Any grade: 41/43(95%) vs 82/85(96%) Serious AE: 15/43(35%) vs 29/85 (34%) Treatment discontinuation AE: 1/43(2%) vs 4/85(5%)				
REDUCE <sup>9)</sup>	RCT	101	Prostate cancer		3.5years (interim analysis)	SSE	hypocapnia					Any grade: 23/57(40%) vs 15/44(34%)	

Methods: PubMed, Cochrane, ICHUSHI, and CINAHL were searched for articles on BMA dosing intervals from outcomes measured were the incidence of SRE and related various AEs. A quantitative meta-analysis was performed using a random-effects model to calculate relative risk ratios (RR) and 95% confidence intervals (CI).

### Forest plot of studies including ZA only or BMA other than ZA comparing 4-weeks vs 12-weeks dosing schedule

	q12v	/	q4w			Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI Y	'ear	M-H, Random, 95% CI	
2.1.1 Only ZA									
ZOOM(2013)	31	209	33	216	20.0%	0.97 [0.62, 1.53] 20	013	<del>-</del>	
CALGB-70604(2017)	253	911	260	911	26.6%	0.97 [0.84, 1.13] 20	017	*	
OPTIMIZE-2(2017)	47	203	44	200	22.3%	1.05 [0.73, 1.51] 20	017	<del>-</del>	
Subtotal (95% CI)		1323		1327	68.9%	0.98 [0.86, 1.12]		<b>♦</b>	
Total events	331		337						
Heterogeneity: Tau <sup>2</sup> = 0	0.00; Chi <sup>2</sup>	= 0.16,	df = 2 (P	= 0.92	); $I^2 = 0\%$				
Test for overall effect: 2	Z = 0.26 (F	r = 0.79	))						
2.1.2 BMA other than	ZA								
Fizazi(2009)	4	35	6	35	7.7%	0.67 [0.21, 2.16] 2	009	<del></del>	
Addison(2014)	4	17	3	13	6.6%	1.02 [0.27, 3.78] 20	014		
REaCT(2020)	44	130	12	133	16.8%	3.75 [2.08, 6.77] 20	020		
Subtotal (95% CI)		182		181	31.1%	1.51 [0.46, 4.97]			
Total events	52		21						
Heterogeneity: Tau <sup>2</sup> = 0	0.84; Chi <sup>2</sup>	= 8.42,	df = 2 (P	= 0.01	); I <sup>2</sup> = 76%				
Test for overall effect: 2	Z = 0.67 (F	9 = 0.50	))						
Total (95% CI)		1505		1508	100.0%	1.21 [0.82, 1.78]		•	
Total events	383		358						
Heterogeneity: Tau <sup>2</sup> = 0	0.14; Chi <sup>2</sup>	= 19.74	, df = 5 (F	P = 0.00	01); I <sup>2</sup> = 75	%	0.04	0.1 1 10	100
Test for overall effect: 2	Z = 0.97 (F	= 0.33	3)				0.01	Favours [q12w] Favours [q4w]	100
Test for subgroup differ	rences: Ch	i <sup>2</sup> = 0 4	8. df = 1	(P = 0.4)	49) $I^2 = 0\%$			ravours [q 12w] Tavours [q4w]	

	q12v	V	q4w	,		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	l Year	M-H, Random, 95% C
4.1.1 Only ZA								
ZOOM(2013)	2	209	9	216	11.9%	0.23 [0.05, 1.05]	2013	-
CALGB-70604(2017)	18	911	42	911	26.9%	0.43 [0.25, 0.74]	2017	
OPTIMIZE-2(2017)	18	202	23	198	26.1%	0.77 [0.43, 1.38]	2017	<del>_</del>
Subtotal (95% CI)		1322		1325	64.9%	0.51 [0.30, 0.89]		•
Total events	38		74					
Test for overall effect:	-		•	- 0.19	); I <sup>2</sup> = 40%	)		
Test for overall effect:	Z = 2.40 (F		•	- 0.19	); 1² = 40%	)		
Test for overall effect: 4.1.2 BMA other than	Z = 2.40 (F	P = 0.02	•				0000	
Test for overall effect: 4.1.2 BMA other than Lipton(2008)	Z = 2.40 (F ZA 4	P = 0.02	2) 1	43	7.2%	2.02 [0.23, 17.55]		
Test for overall effect: 4.1.2 BMA other than	Z = 2.40 (F	P = 0.02	•		7.2%			•
Test for overall effect:  4.1.2 BMA other than Lipton(2008) REaCT(2020)	Z = 2.40 (F ZA 4	85 130	2) 1	43 133	7.2% 27.9%	2.02 [0.23, 17.55] 1.44 [0.88, 2.35]		•
Test for overall effect:  4.1.2 BMA other than Lipton(2008) REaCT(2020) Subtotal (95% CI)	Z = 2.40 (F ZA 4 31	85 130 <b>215</b>	1 22 23	43 133 176	7.2% 27.9% 35.1%	2.02 [0.23, 17.55] 1.44 [0.88, 2.35]		•
Test for overall effect:  4.1.2 BMA other than Lipton(2008) REaCT(2020) Subtotal (95% CI) Total events	Z = 2.40 (F 1 ZA 4 31 35 0.00; Chi <sup>2</sup>	85 130 <b>215</b> = 0.09,	2) 1 22 23 df = 1 (P	43 133 176	7.2% 27.9% 35.1%	2.02 [0.23, 17.55] 1.44 [0.88, 2.35]		•
Test for overall effect:  4.1.2 BMA other than Lipton(2008) REaCT(2020) Subtotal (95% CI) Total events Heterogeneity: Tau² =	Z = 2.40 (F 1 ZA 4 31 35 0.00; Chi <sup>2</sup>	85 130 <b>215</b> = 0.09,	2) 1 22 23 df = 1 (P	43 133 <b>176</b> = 0.76	7.2% 27.9% 35.1%	2.02 [0.23, 17.55] 1.44 [0.88, 2.35]		•

### Renal dysfunction (grade≥3 or treatment discontinuation)

Test for subgroup differences: Chi<sup>2</sup> = 8.04, df = 1 (P = 0.005),  $I^2$  = 87.6%

	q12v	v	q4w			Risk Ratio			Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Ran	dom, 95% CI	
Only ZA											
CALGB-70604(2017)	4	837	10	852	76.9%	0.41 [0.13, 1.29]	2017		_	+	
OPTIMIZE-2(2017)	1	202	6	198	23.1%	0.16 [0.02, 1.34]	2017		•	+	
Total (95% CI)		1039		1050	100.0%	0.33 [0.12, 0.91]			•	-	
Total events	5		16								
Heterogeneity: Tau <sup>2</sup> = 0	0.00; Chi <sup>2</sup>	= 0.56,	df = 1 (P	= 0.45	); I <sup>2</sup> = 0%			0.01	0.1	1 10	400
Test for overall effect: 2	Z = 2.15 (F	P = 0.03	3)					0.01		Favours [q4w]	100

#### Nausea

	q12v	/	q4w	,		Risk Ratio				Risk Ratio		
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	Year		M-H, I	Random, 9	5% CI	
ZOOM(2013)	14	209	23	216	39.3%	0.63 [0.33, 1.19]	2013		-	-		
OPTIMIZE-2(2017)	34	202	32	198	60.7%	1.04 [0.67, 1.62]	2017			-		
Total (95% CI)		411		414	100.0%	0.85 [0.53, 1.39]				•		
Total events	48		55									
Heterogeneity: Tau <sup>2</sup> =	0.05; Chi <sup>2</sup>	= 1.63	, df = 1 (F	= 0.20	); I <sup>2</sup> = 39%	, D		0.01	0.1		10	100
Test for overall effect:	Z = 0.64 (	P = 0.5	2)					0.01	Favours [q1	2w] Favo		100

#### **AEs(any grade)**

	q12v	V	q4w	,		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% C	Year	M-H, Random, 95% CI
3.1.1 Only ZA								
ZOOM(2013)	159	209	184	216	18.9%	0.89 [0.81, 0.98]	2013	•
OPTIMIZE-2(2017)	189	202	189	198	36.2%	0.98 [0.93, 1.03]	2017	•
Subtotal (95% CI)		411		414	55.1%	0.94 [0.84, 1.05]		•
otal events	348		373					
leterogeneity: Tau² =	0.00; Chi <sup>2</sup>	= 4.40	, df = 1 (F	P = 0.04	$I_{1}$ ); $I_{2} = 77\%$			
Test for overall effect:	Z = 1.08 (	P = 0.2	8)					
3.1.2 BMA other tha	n ZA							
Lipton(2007)	76	85	155	169	21.1%	0.97 [0.89, 1.06]	2007	•
.ipton(2008)	82	85	41	43	23.8%	1.01 [0.94, 1.09]	2008	•
Subtotal (95% CI)		170		212	44.9%	1.00 [0.94, 1.05]		•
otal events	158		196					
Heterogeneity: Tau² =	0.00; Chi <sup>2</sup>	= 0.46	, df = 1 (F	P = 0.50	)); $I^2 = 0\%$			
Test for overall effect:	Z = 0.17 (	P = 0.8	7)					
Total (95% CI)		581		626	100.0%	0.97 [0.92, 1.02]		•
Total events	506		569					
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 5.80	, df = 3 (F	P = 0.12	2); I <sup>2</sup> = 48%		<u> </u>	.01 0.1 1 10 10
Test for overall effect:	Z = 1.20 (	P = 0.2	3)				0.	.01
Test for subgroup diff	erences: C	$hi^2 = 0.7$	77, df = 1	(P = 0.	.38), $I^2 = 0$	%		i avoaio [q izw] Tavoaio [q+w]

#### **Renal dysfunction (any grade)**

	q12v	V	q4w			Odds Ratio			Odds Ratio			
Study or Subgroup	<b>Events</b>	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	Year		M-H, Random, 95% CI			
6.1.1 Only ZA												
ZOOM(2013)	1	209	2	216	0.9%	0.51 [0.05, 5.72]	2013		- <u>-</u>			
CALGB-70604(2017)	137	882	174	875	85.7%	0.74 [0.58, 0.95]	2017					
OPTIMIZE-2(2017) Subtotal (95% CI)	16	202 <b>1293</b>	19	198 <b>1289</b>	10.8% <b>97.4</b> %	0.81 [0.40, 1.63] <b>0.75 [0.59, 0.94]</b>	2017		•			
Total events	154		195									
Heterogeneity: Tau <sup>2</sup> = 0	.00; Chi <sup>2</sup>	= 0.15,	df = 2 (P	= 0.93	); $I^2 = 0\%$							
Test for overall effect: Z	= 2.49 (F	P = 0.01	)									
6.1.2 BMA other than 2	ZA											
REaCT(2020) Subtotal (95% CI)	4	130 <b>130</b>	4	133 <b>133</b>	2.6% <b>2.6%</b>	1.02 [0.25, 4.18] <b>1.02 [0.25, 4.18</b> ]	2020					
Total events	4		4									
Heterogeneity: Not appl	icable											
Test for overall effect: Z	= 0.03 (F	P = 0.97	<b>'</b> )									
Total (95% CI)		1423		1422	100.0%	0.75 [0.60, 0.94]			<b>♦</b>			
Total events	158		199									
Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z	-		•	= 0.95	); $I^2 = 0\%$			0.01	0.1 1 10	100		
Test for subgroup differ	•		,	(P = 0.6	66), I <sup>2</sup> = 0%	<b>%</b>			Favours [q12w] Favours [q4w]			

#### **Bone pain**

	q12v	/	q4w	,		Risk Ratio		Risk Ratio	
Study or Subgroup	<b>Events</b>	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI Ye	ear	M-H, Random, 95% CI	
ZOOM(2013)	56	209	65	216	56.7%	0.89 [0.66, 1.20] 20	)13	-	
OPTIMIZE-2(2017)	48	202	49	198	43.3%	0.96 [0.68, 1.36] 20	)17	*	
Total (95% CI)		411		414	100.0%	0.92 [0.73, 1.16]		•	
Total events	104		114						
Heterogeneity: Tau <sup>2</sup> = 0	0.00; Chi <sup>2</sup>	= 0.10	, df = 1 (F	P = 0.75	$5); I^2 = 0\%$		0.01	0.1 1 10	100
Test for overall effect: 2	z = 0.72 (I	P = 0.4	7)				0.01	Favours [q12w] Favours [q4w]	100



Each incidences were shown to q4w vs q12w. ZA: zoledronic acid, Dmab: denosumab, PA: pamidronic acid, N: Number of patients, AEs: Adverse events, HRQoL: Health-related quality of life, QLQ-C30: The European Organization for Research and Treatment of Cancer QLQ-C30, CTx: crosslinked N-terminal telopeptide type I collagen, BSAP: bone-specific alkaline phosphatase, BPI: brief pain inventory, NTx: type I collagen N-terminal telopeptide, BMA: bone modifying agents; FACT-BP: Functional Assessment of Cancer Therapy Bone Pain, SMR: Skeletal events, SSE: symptomatic skeletal events, tSSE: time to symptomatic skeletal events, ON. osteonecrosis of the jaw, RCT: randomized controlled trial, BP: bisphosphonates

1)JAMA 2017;317:48-58., 2)JAMA Oncol 2017;3:906-12, 3)Lancet Oncol 2013;14:663-70, 4)Springerplus 2014;3:577, 5)Eur J Cancer 2021;142:132-40, 6)J Clin Oncol 2009;27:1564-71, 7)J Clin Oncol 2007;25:4431-7, 8)Clin Cancer Res 2007;14:6690-6, 9)Eur Soc Med Oncol 2014;25(Suppl 4):540

Conclusion: This meta-analysis showed no influence of BMA de-escalation on the incidence of SRE, nevertheless, AEs appeared to reduce with the de-escalated usage of ZA. Prolonging the BMA dosing interval from 4 to a maximum of 12 weeks is a beneficial treatment strategy that reduces the risk of renal dysfunction without increasing SRE.