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Bisphosphonates therapy (BT) in Early Breast Cancer

&

Establishing BT locally

Acknowledgements

- **Dr Kate Scatchard** – Con Medical Oncologist RD&E/NDDH
- **Dr jenny Forrest** – Con Clinical Oncologist RD&E/NDDH
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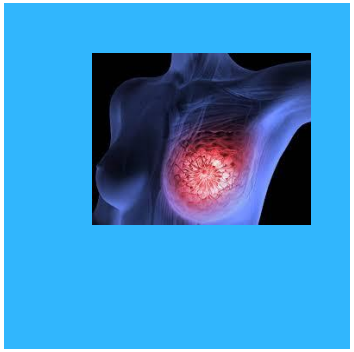
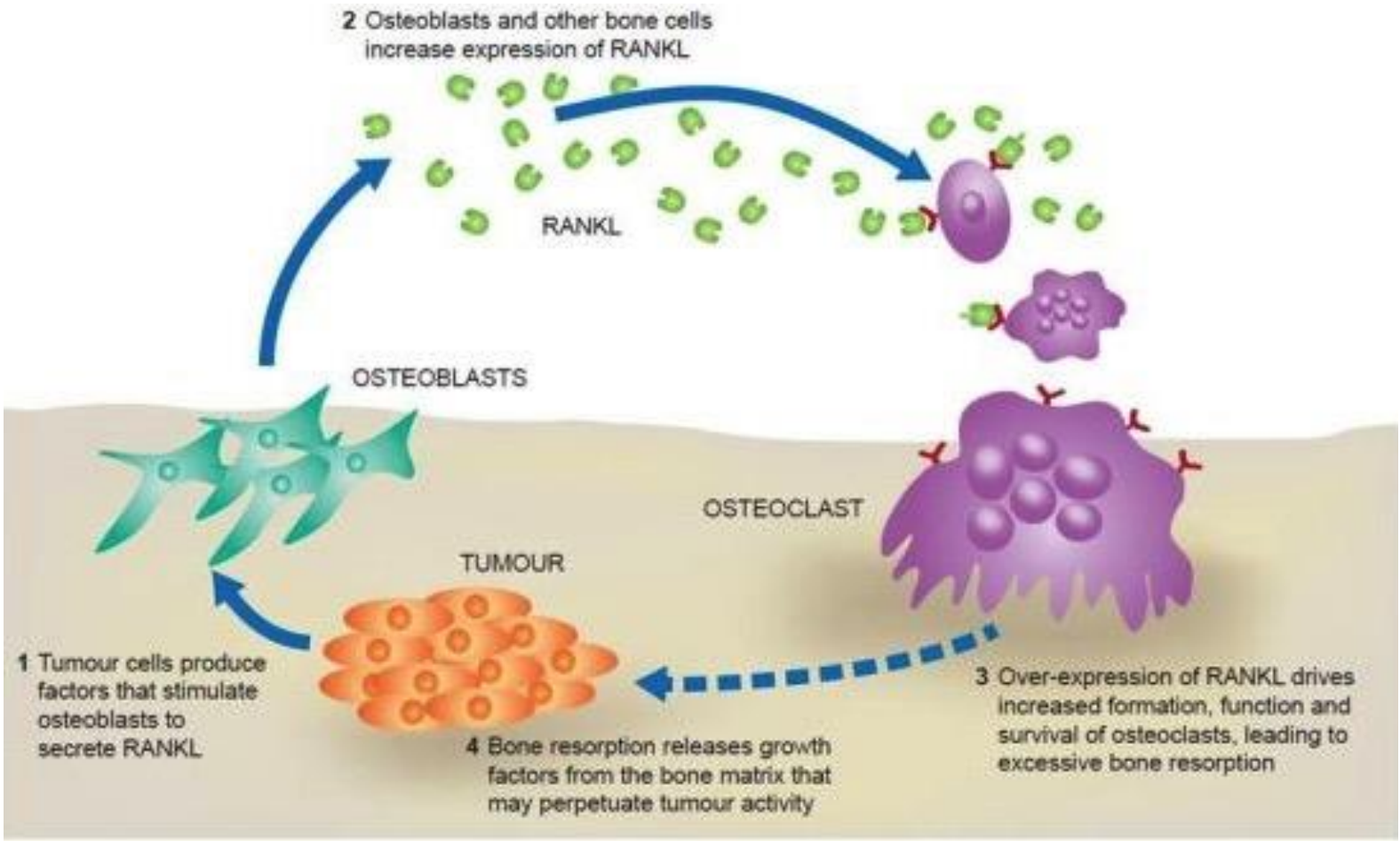
- **Dr Stuart Kyle** – Con Rheumatology & associate medical director NDDH
- **Ms Ann-Marie Whitehead** – lead Surgical pharmacist RD&E
- **Prof. Chris Holcombe** – Consultant Oncoplastic Surgeon & Breast Cancer Clinical Expert Group (CEG) Vice-chair. Royal Liverpool



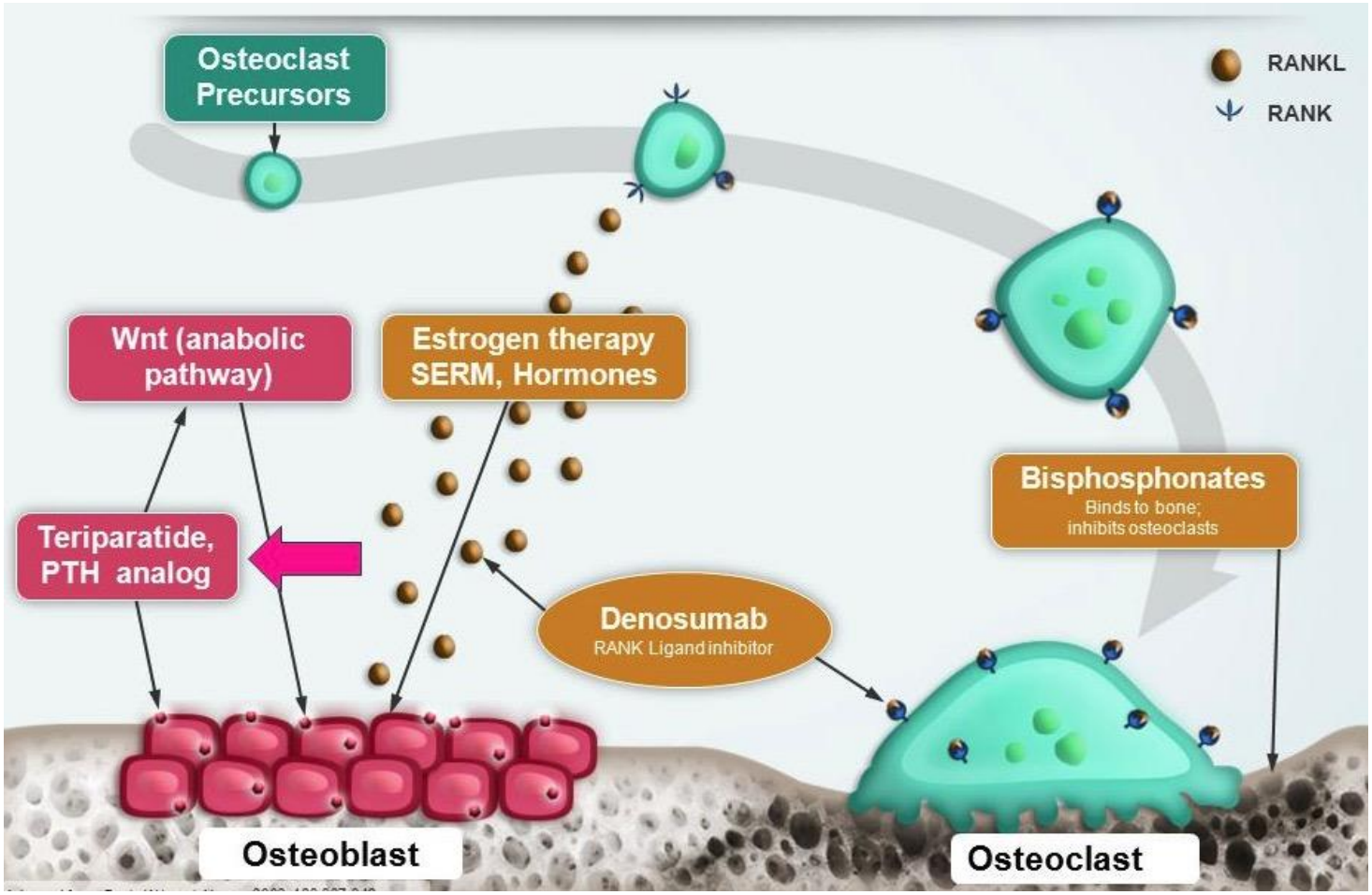
Introduction

- How bisphosphonates work
- Evidence for use Bisphosphonate Therapy (BT)
- Considerations when using BT
- Complications
- RD&E guidance on BT

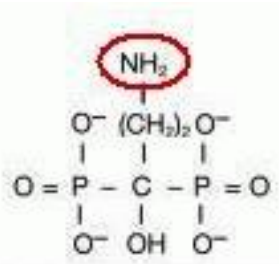
Bone mets; seed & soil



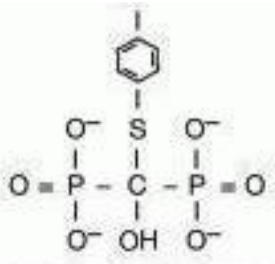
Bisphosphonates



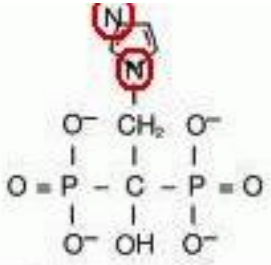
Bisphosphonates



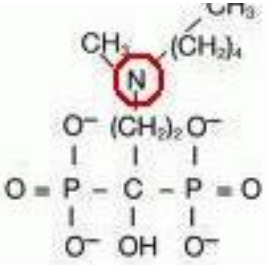
Pamidronat



Tiludronat



Zoledronat



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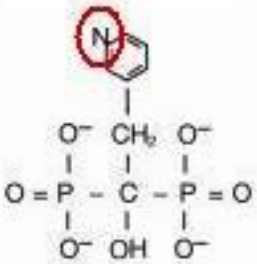
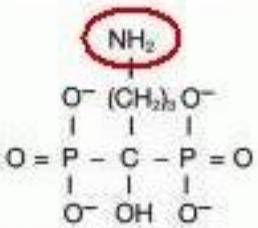
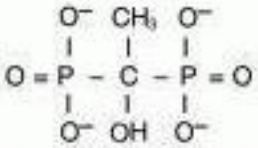


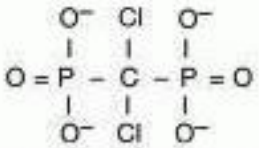
Risedronat



Alendronat



Etidronat



Clodronat

Evidence

Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

THE LANCET

www.thelancet.com

Published online July 24, 2015

http://dx.doi.org/10.1016/S0140-6736(15)60908-4

Evidence

- Trails started before 2008
- Randomised
- Any type of BT vs. Control of no BT
- Women
- Information was sought for individual patients through 2012-14

	Studies identified		Studies with data received			
	Trials (n)	Patients (n)	Trials (n)	Patients (n)	%*	Years†
Up to 1 year of treatment						
<1 year clodronate	2	120	1	72	60%	0·5
<1 year aminobisphosphonate	2	208	1	40	19%	0·1
1 year aminobisphosphonate	7	1088	3	448	41%	1·0
Total for ≤1 year of treatment	11	1416	5	560	40%	0·9
2–5 years of treatment						
2 years clodronate	4	3978	3	3912	98%	2·0
3–5 years clodronate	1	1069	1	1069	100%	3·0
2 years aminobisphosphonate	10	3654	8	3514	96%	2·0
3–5 years aminobisphosphonate	12	11 910‡	9	9711	82%‡	4·5
Total for 2–5 years of treatment	27	20 611‡	21	18 206	88%‡	3·5
Any clodronate regimen	7	5167	5	5053	98%	2·6
Any aminobisphosphonate§	31	16 860‡	21	13713	81%‡	3·8
Total, all regimens	38	22 027‡	26	18766	85%‡	3·4

*Number of patients with data received as a percentage of all randomised patients in identified studies. †Mean scheduled treatment duration (weighted in proportion to numbers of patients with data received). ‡Includes two trials (2116 patients) still in progress; excluding these, the total with data received is 94%. §The aminobisphosphonates in these trials were zoledronic acid (9290 patients with data received, 1582 recurrences [46% of all recurrences]), ibandronate (3072 patients, 380 recurrences [11%]), pamidronate (953 patients, 473 recurrences [14%]), risedronate (398 patients, 13 recurrences [0·4%]), and alendronate (no trials with data received); the only non-aminobisphosphonate in these trials was clodronate (5053 patients, 1005 [29%] recurrences).

Table: **Numbers of unconfounded randomised trials of an adjuvant bisphosphonate identified, and numbers with data received, by duration and type of bisphosphonate treatment**

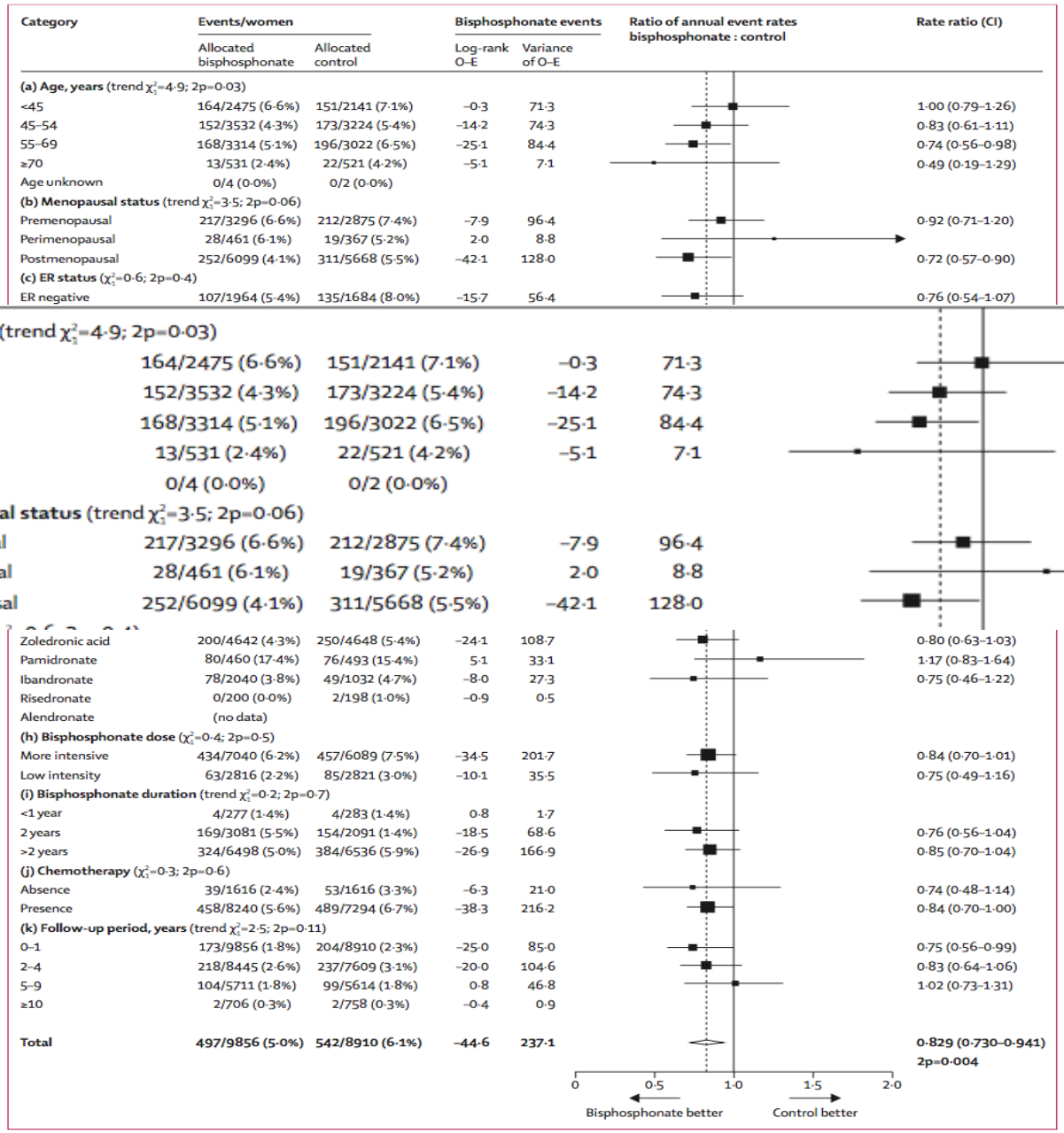
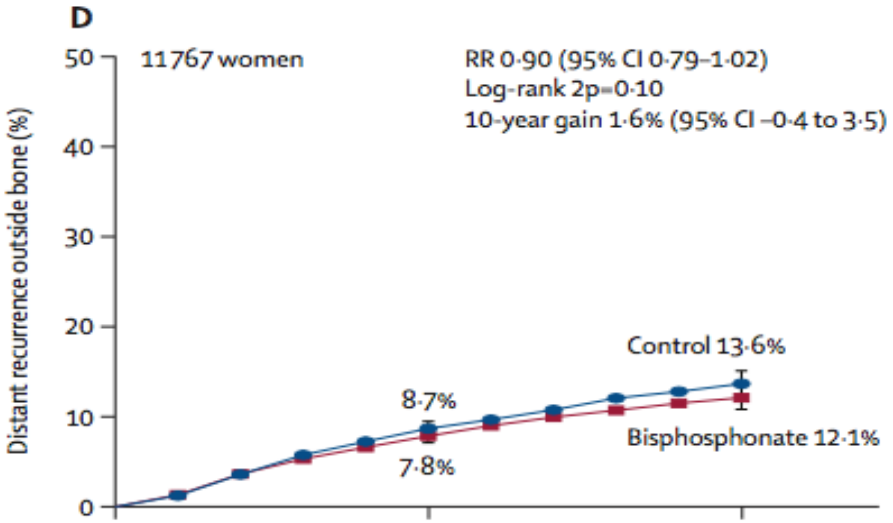


Figure 2: **Multiple subgroup analyses of effects on bone recurrence in trials of bisphosphonate versus no bisphosphonate (control)**
Results are plotted as black squares with horizontal lines that denote 99% rather than 95% CIs to allow for multiple hypothesis testing. Total is plotted as a white diamond that denotes 95% CI. ER=oestrogen receptor. O–E=observed minus expected.



Recurrence outside bone rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	1·67 (420/25 220)	1·04 (85/8157)	0·78 (4/513)
Control	1·98 (427/23 642)	1·17 (92/7870)	1·65 (8/484)
Rate ratio (95% CI)	0·90 (0·77–1·04)	0·89 (0·60–1·19)	0·38 (0·09–1·34)
from (O–E)/V	−18·4/182·4	−4·5/39·7	−1·7/1·8

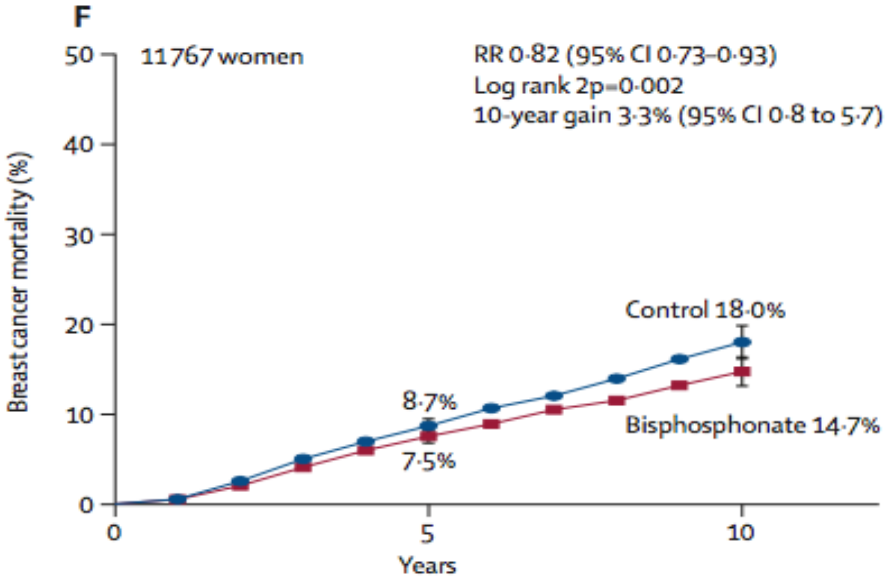


Figure 3: **Main outcon premenopausal (excl perimenopausal) a postmenopausal wom trials of bisphosph versus no bisphosph (co**

Kaplan-Meier graphs sh the effects of treat allocation on 10-year l cancer outc (A) Premenopaus (B) postmenopausal recurrence. (C) Premenop and (D) postmenop distant recurrence outsi bone. (E) Premenopaus (F) postmenopausal l cancer mor O-E=observed expected. V=variance o RR=rate ratio (exp[(O-E Error bars a

BT

- The EBCTCG meta-analysis provides high quality evidence for the use of adjuvant BT with:

- **Absolute survival benefit of 3.3% at 10 years**
- Reduced recurrence (RR 0.86, 2p = 0.002)
- Reduced distant recurrence (RR 0.82, 2p = 0.003)
- Reduced bone recurrence (RR 0.72, 2p=0.002)
- Reduced bone fractures (RR 0.85, 2p=0.02)

BT

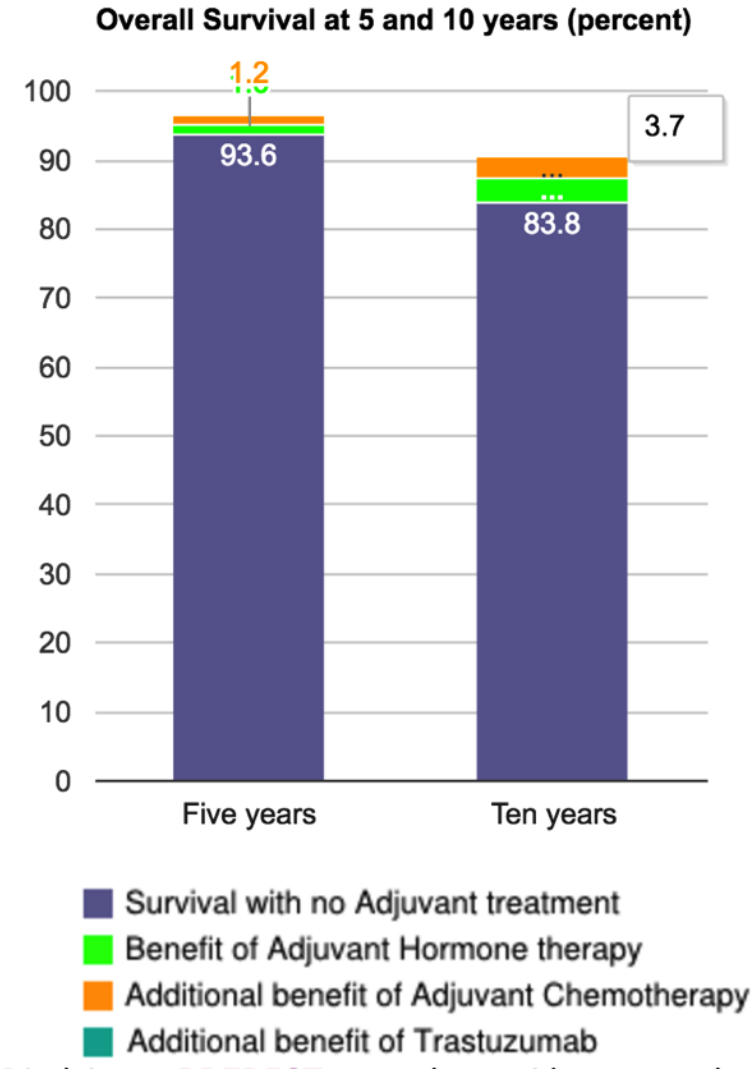
- Benefits were only confirmed in post-menopusal women, but this includes those who have induce menopause by ovarian suppression or ovarian radiation ablation
- The benefits are regardless of tumour type, receptor status or nodal status
- It was not possible to assess if the type of bisphosphonate and method of administration (IV vs. PO) used has an influence on the outcome – except pamidronate
- There is no evidence for the use in male breast cancer at present

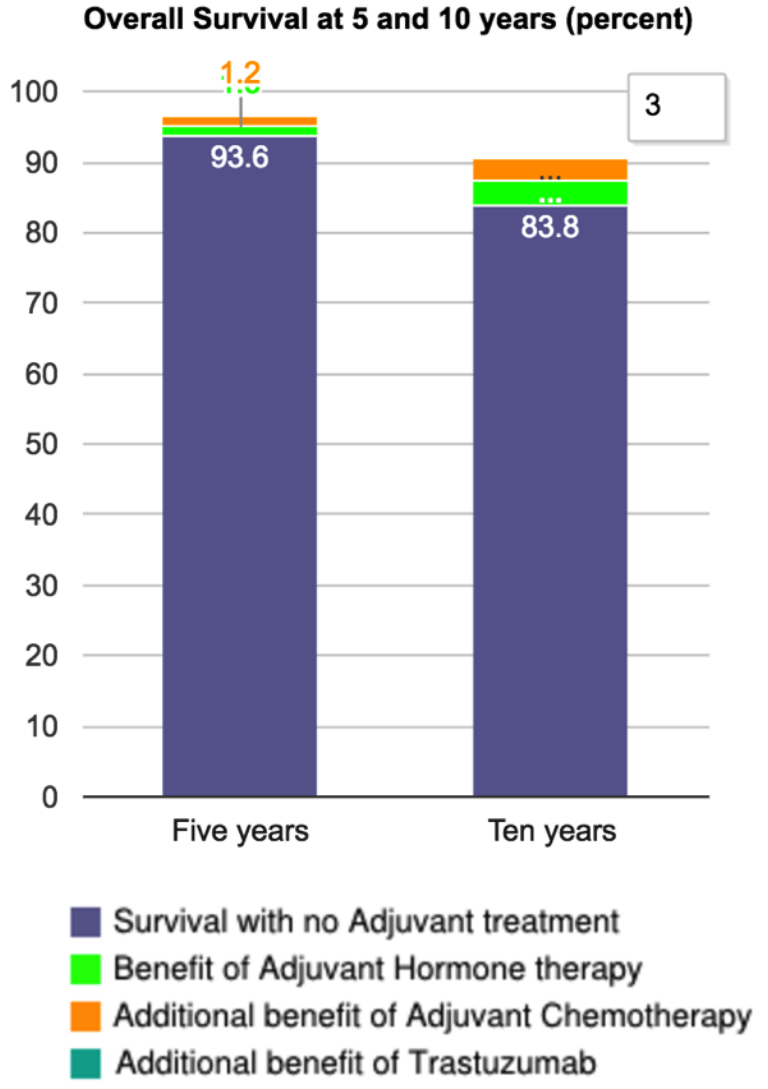
Small but significant benefits

PREDICT Tool Version 2.0: Breast Cancer Overall Survival; Input

Age at diagnosis:	50		
Mode of detection:	○ Screen-detected	◉ Symptomatic	○ Unknown
Tumour size in mm:	30		
Tumour Grade:	○ 1	◉ 2	○ 3
Number of positive nodes:	0		☐ Micromet
ER status:	◉ Positive	○ Negative	
HER2 status:	○ Positive	◉ Negative	○ Unknown
KI67 status:	○ Positive	○ Negative	◉ Unknown
Gen chemo regimen:	○ No chemo	○ Second	◉ Third

Predict Surviva | Clear All Fields | Print Results


Overall Survival at 5 and 10 years (percent)
100
90
80
70
60
50
40
30
20
10
0
1.2
93.6
3.7
83.8
Five years
Ten years
Survival with no Adjuvant treatment
Benefit of Adjuvant Hormone therapy
Additional benefit of Adjuvant Chemotherapy
Additional benefit of Trastuzumab


Overall Survival at 5 and 10 years (percent)
100
90
80
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50
40
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0
1.2
93.6
3
83.8
Five years
Ten years
Survival with no Adjuvant treatment
Benefit of Adjuvant Hormone therapy
Additional benefit of Adjuvant Chemotherapy
Additional benefit of Trastuzumab

PREDICT Tool Version 2.0: Breast Cancer Overall Survival; Input

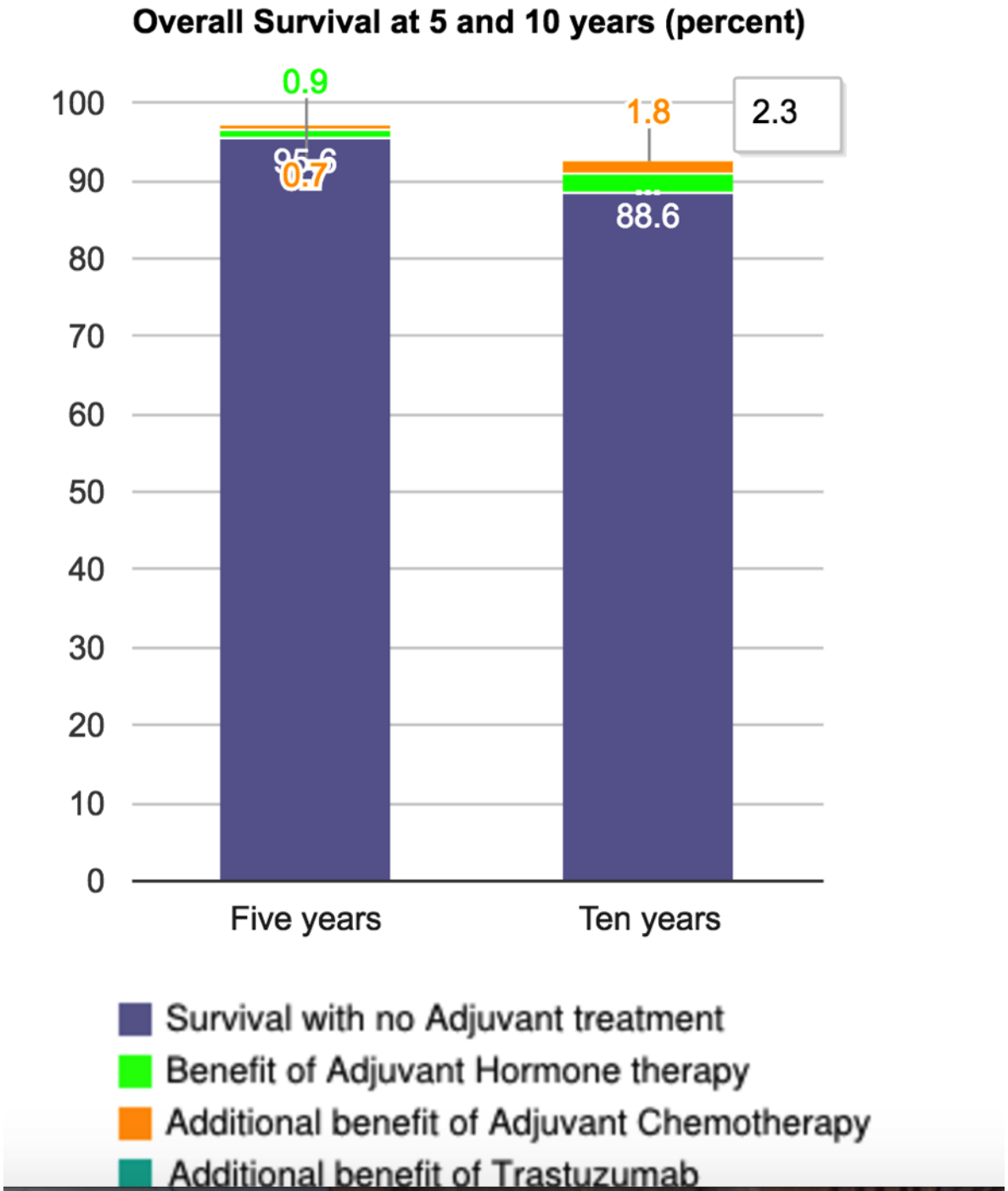
Age at diagnosis:	50		
Mode of detection:	(•) Screen-detected	( ) Symptomatic	( ) Unknown
Tumour size in mm:	20		
Tumour Grade:	( ) 1	(•) 2	( ) 3
Number of positive nodes:	0		[ ] Micromet
ER status:	(•) Positive	( ) Negative	
HER2 status:	( ) Positive	(•) Negative	( ) Unknown
KI67 status:	( ) Positive	( ) Negative	(•) Unknown
Gen chemo regimen:	( ) No chemo	( ) Second	(•) Third

[Predict Surviva] [Clear All Fields] [Print Results]

PREDICT Tool Version 2.0: Breast Cancer Overall Survival; Results

Five year survival
96 out of 100 women are alive at 5 years with no adjuvant therapy after surgery
An extra 1 out of 100 women treated are alive because of hormone therapy
An extra 2 out of 100 women treated are alive because of hormone therapy & chemotherapy
Ten year survival
89 out of 100 women are alive at 10 years with no adjuvant therapy after surgery
An extra 2 out of 100 women treated are alive because of hormone therapy
An extra 4 out of 100 women treated are alive because of hormone therapy & chemotherapy

To view the numbers in bars hover pointer over each bar segment


Overall Survival at 5 and 10 years (percent)
100
90
80
70
60
50
40
30
20
10
0
0.9
95.6
0.7
1.8
88.6
2.3
Five years
Ten years
Survival with no Adjuvant treatment
Benefit of Adjuvant Hormone therapy
Additional benefit of Adjuvant Chemotherapy
Additional benefit of Trastuzumab

PREDICT Tool Version 2.0: Breast Cancer Overall Survival; Input

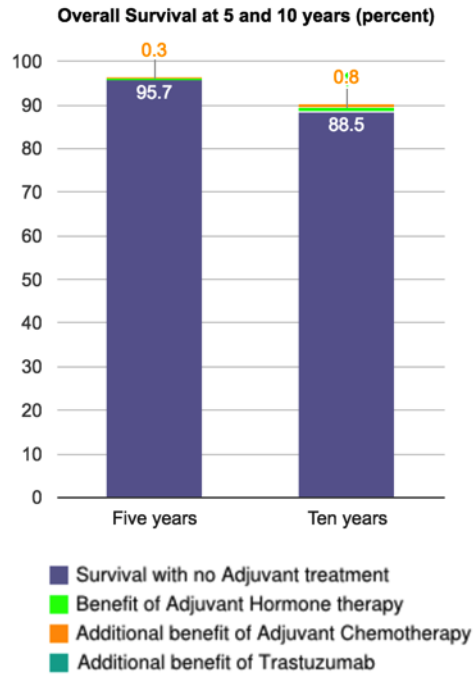
Age at diagnosis:	60		
Mode of detection:	(•) Screen-detected	( ) Symptomatic	( ) Unknown
Tumour size in mm:	15		
Tumour Grade:	(•) 1	( ) 2	( ) 3
Number of positive nodes:	0		[ ] Micromet
ER status:	(•) Positive	( ) Negative	
HER2 status:	( ) Positive	(•) Negative	
KI67 status:	( ) Positive	( ) Negative	
Gen chemo regimen:	( ) No chemo	( ) Second	

Predict Survival | Clear All Fields | Print Results

PREDICT Tool Version 2.0: Breast Cancer Overall Survival; Results

Five year survival
96 out of 100 women are alive at 5 years with no adjuvant therapy after surgery
An extra 0 out of 100 women treated are alive because of hormone therapy
An extra 1 out of 100 women treated are alive because of hormone therapy & chemotherapy
Ten year survival
88 out of 100 women are alive at 10 years with no adjuvant therapy after surgery
An extra 1 out of 100 women treated are alive because of hormone therapy
An extra 2 out of 100 women treated are alive because of hormone therapy & chemotherapy

To view the numbers in bars hover pointer over each bar-segment
(Or tap segment if using a mobile device)



Considerations with BT

- Ca2+
- Vit D
- Bone Health – (in general, on AI)
- Dental Health
- ?DEXA

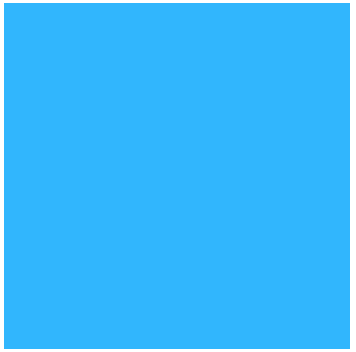
Side Effects

- Dyspepsia / GI Ulceration
- Muscle aches & pains
- Low Ca
- Atypical fracture
- OsteoNecrosis of the Jaw (ONJ)

Contraindications

- Allergy
- Delayed Gastric emptying/ UGI stricture
- Low Calcium
- On going dental surgery / jaw sepsis

Vit D



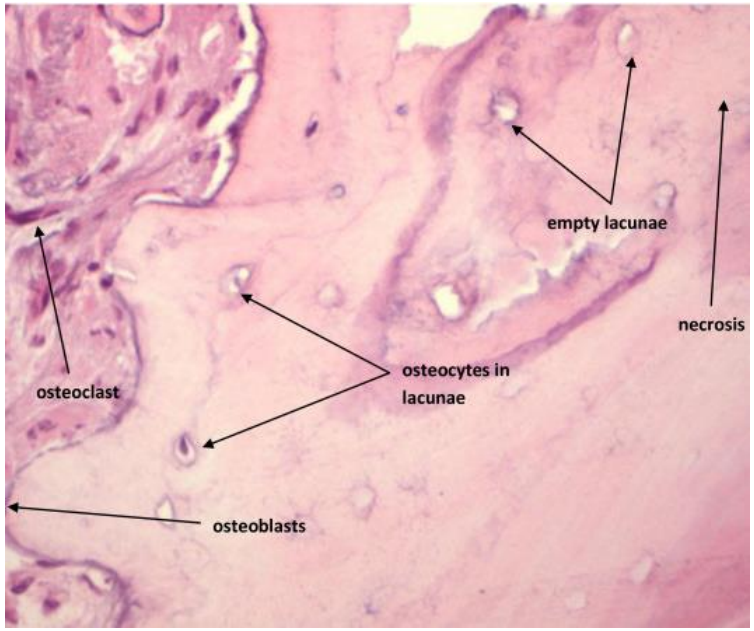
mL/minute/1.73m

Table 1: Liverpool Definition of Vitamin D status reported as Serum 25-Hydroxyvitamin D [25(OH)D] Total Concentrations			
nmol/L*	**ng/mL***	**Vitamin D Status**	**Health status**
≤30	<12	**Deficiency**	Associated with vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults
>30–50	12–20	**Insufficiency**	Generally considered inadequate for bone and overall health in healthy individuals
>50	>20	**Adequate**	Generally considered adequate for bone and overall health in healthy individuals. ***Remember levels may decrease over autumn/winter***
>75	>30	**Optimal**	Emerging evidence links potential adverse effects to high concentrations particularly >150 nmol/L (>60 ng/mL)

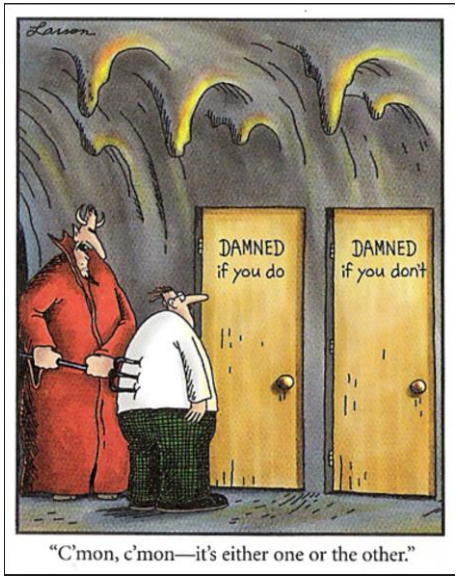
Please Note: Serum concentrations of 25(OH)D reported in either nanomoles per litre (nmol/L) or nanograms per millilitre (ng/mL). 1ng/mL = 2.5nmol/L
Since 2010 clinical chemistry laboratories should be reporting results in nmol/L.

MRONJ - Medication related osteonecrosis of the jaw

- **Pathology** — reduced osteoclastic bone turnover and blood supply can leads to bone death, bony dehiscence and mucosal breakdown overlying bone
- Can be spontaneous increased by
  - Poor dentures
  - Tooth extractions
  - Dental infections



Incidence (no-one really knows)

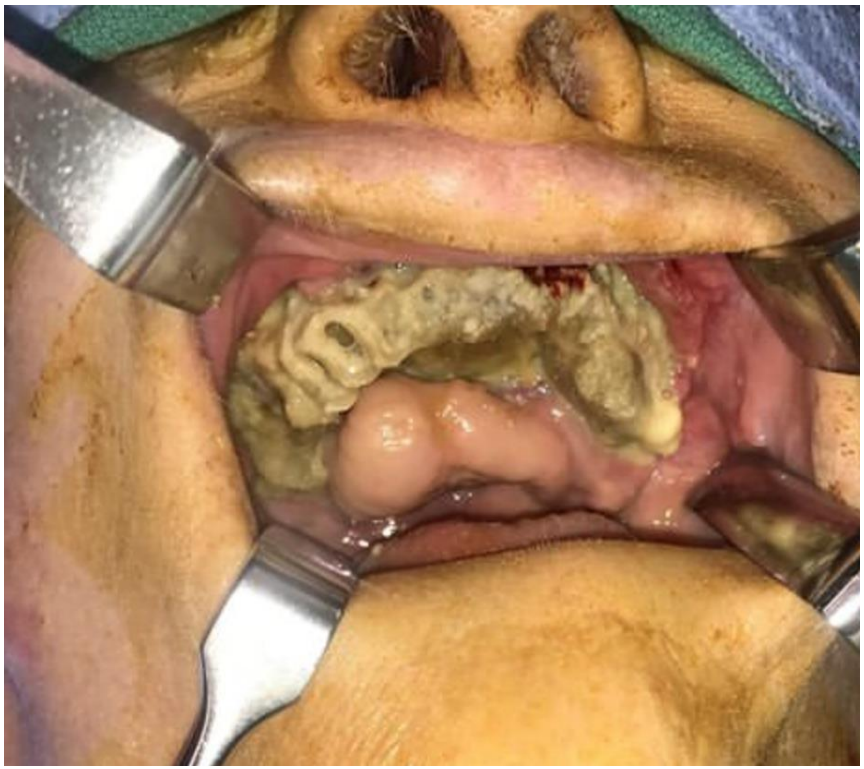


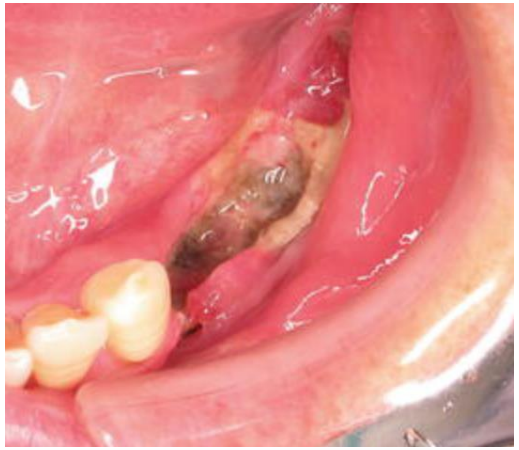
- 1.5%-28% ??
- Incidence of MRONJ in individuals with cancer exposed to IV zoledronic acid was between 0.3 and 5% (Coleman 2011; Lopez-Olivo 2012; Mauri 2009; Morgan 2010).
- Oral bisphosphonates to treat osteoporosis, 0.1 to 0.7 cases per 10,000 patient years of exposure (Chamizo Carmona 2013; Grbic 2010)
- Concurrent use of steroids increases risk

Importance

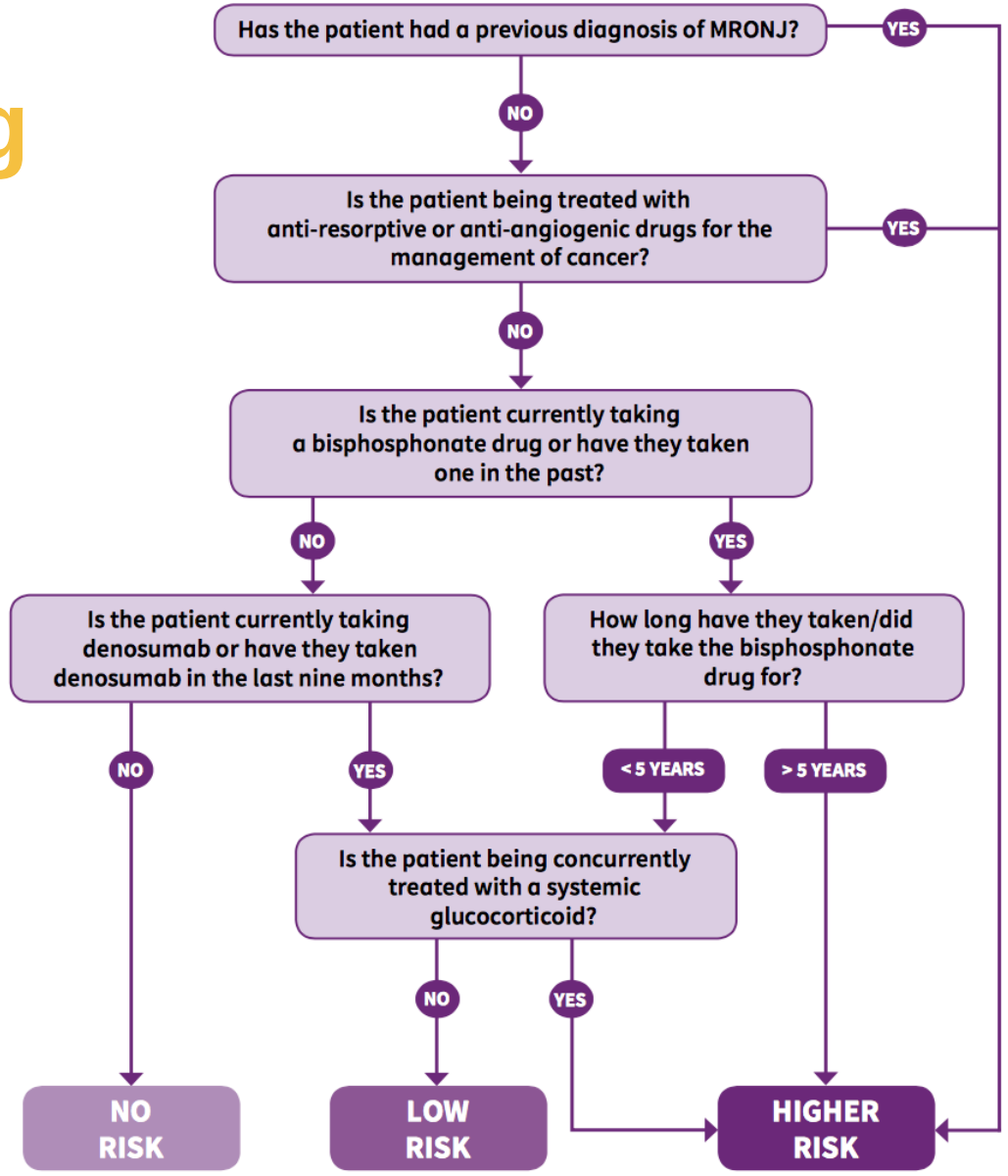
- **Intractable and difficult to treat**

Clinical presentation	Prevalence (*n*)	Percentage (%)
Exposed bone	62	93.9
Pain	52	78.8
Wound healing disturbances	45	68.2
Swelling	34	51.5
Inflammation	42	63.6
Fistula formation	27	40.9
Pathological mandibular fractures	3	4.5
Impairment of inferior alveolar nerve	6	9.1
Involvement of maxillary sinus	11	16.7
Sinusitis	(11)	(16.7)
Oroantral fistula formation	(5)	(7.6)





Risk stratifying

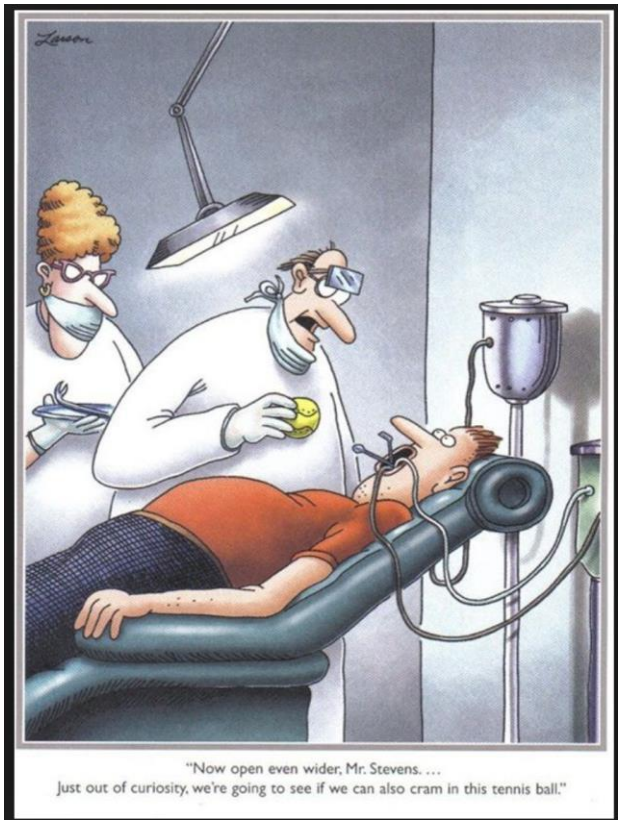


N.B. Be aware that any low risk patient who continues to take bisphosphonate drugs after their five-year medication review should be reclassified as higher risk.

Scottish Dental Clinical Effectiveness Program

Prevention

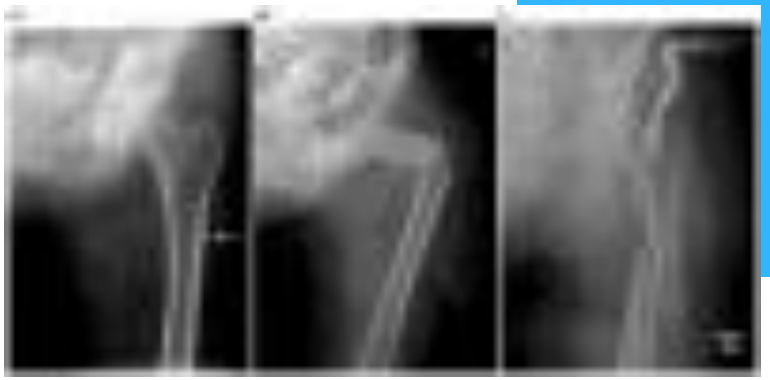
- Ideally start medication **after dental screening** and any remedial treatment
- **Dentist needs to be aware** of risk and modify treatment accordingly particularly risk reducing extraction protocols or referral to OMFS
- **Regular dental check ups** good oral hygiene
- **MHRA guidance** is that prescriber makes patient aware of above
- Consider referral pathway or network as per KCH and Welsh health boards as many barriers to access timely dental care in current NHS ?



“The risk of MRONJ should be discussed with patients but it is important that they are not discouraged from taking anti-resorptive or anti-angiogenic drugs or from undergoing dental treatment. “

Ref: SDCEP Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw

Atypical fractures



Risk of Atypical Femoral Fracture during and after Bisphosphonate Use

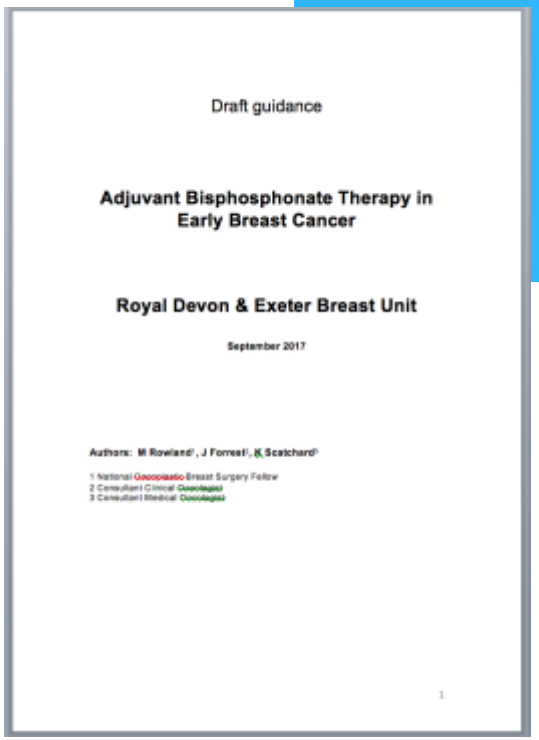
N Engl J Med 2014; 371:974-976September 4, 2014DOI: 10.1056/NEJMc1403799

- Rare (55 in 100,000 pts)
- Sweedish case control suggests only likely with longer term use (>3 yrs)
- Over all fracture risk reduced

Guidance on BT in early breast caner

- UK-CA'17 & ASCO'17 both advocate BT for post-men women (inc. OS)
- Both suggest it should be discussed with the pt. along with other adjuvant treatments
- Low/lowest risk pts. should be advised risks out weight the benefits
- No clear guidance in either documents on where to set the 'low risk' bar

Local guidance


Draft guidance

Adjuvant Bisphosphonate Therapy in Early Breast Cancer

Royal Devon & Exeter Breast Unit

September 2017

- Vit/Ca screening peri-op
- MDT discussion
- Dental Review - ? Develop 'advance warning to dentists ' leaflet
- **Issues:**
- when to use oral vs. IV ?
- Who is 'too low risk' to be offered it?
- Who to continue DEXA scanning?
- Do all pts need Adcal Supps. If VItD normal

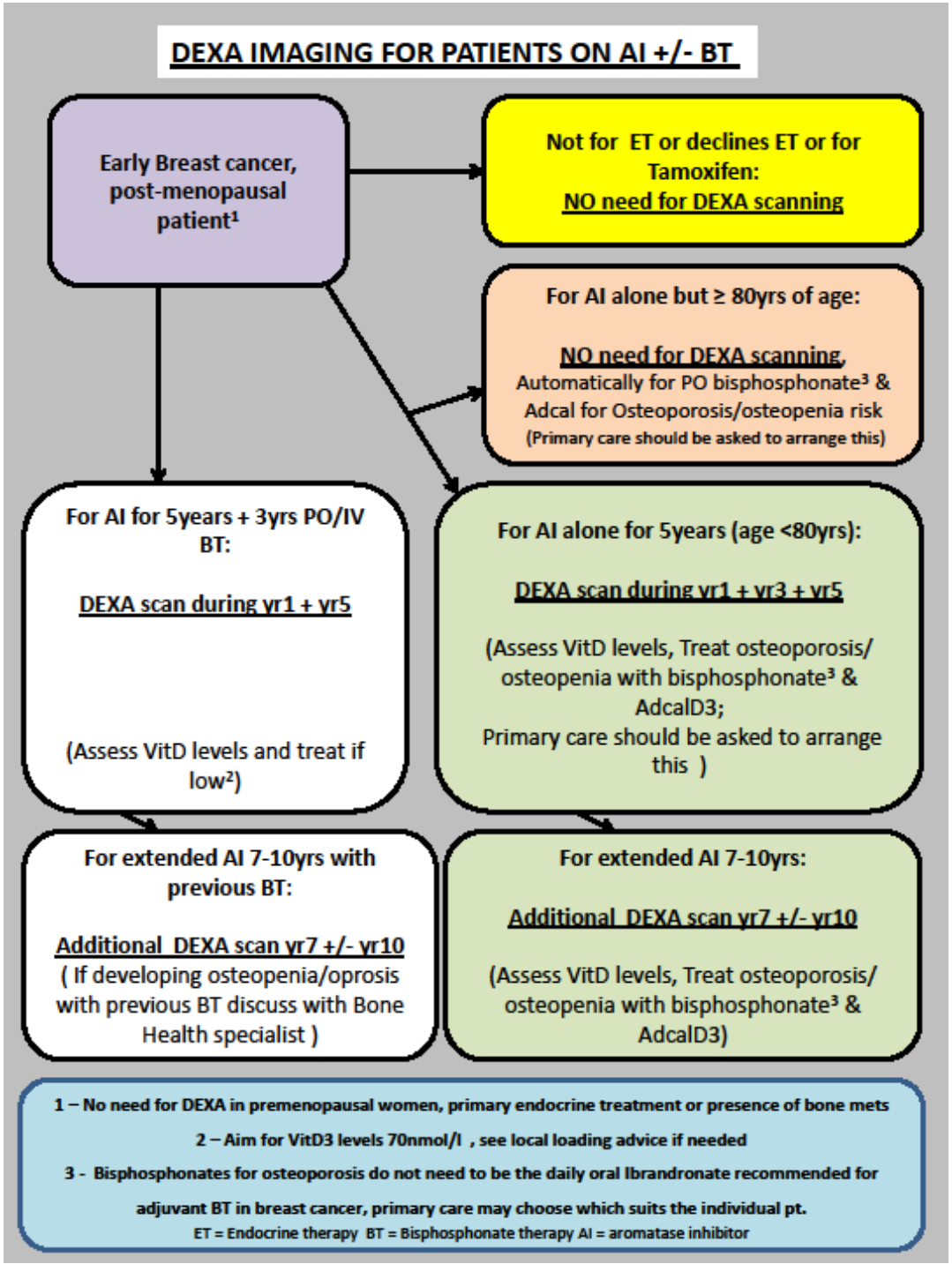
Diagnosis of Breast Cancer in post-menopausal patient consider:

Clinician / BCN to advise the patient to have U&Es/EGFR + Ca2+ & 25(OH)-Vit D3 levels taken before surgery
(Request card to be provided in OPC as Vit-D3 levels take at least a week to process)

Investigation	Result	Action
U&Es/EGFR	**If EGFR < 50ml/min**	**Discuss Vit D3 / BT dosing with pharmacist**
Ca^{2+}	**< 2.15**	**BT contraindicated , refer to endocrinology**
	>2.50	**Check PTH, consider exclusion of bone mets +/- referral to endocrinology**
2-(OH)-Vit D/ Vit D3 Levels	**<70nmols/l**	**Low –needs loading (see below)**
	70-100 nmols/l	**Ideal for bone health with breast cancer on AI or BT**
	>100nmols/l	**Excessive Vit D3 – stop any supplements**

For low Vit D levels Surgeons may prescribe on TTO post-op or ask GP to prescribe oral vitamin D replacement:

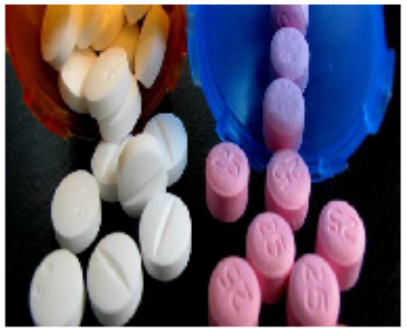
Vitamin D loading for BT	in early breast cancer
Colecalciferol (e.g. StexerolD3) 25,000IU orally <u>ONE daily for 12 days</u> (Hospital prescription)	**Then maintenance dose: Colecalciferol (e.g. (e.g. StexerolD3) 25,000 IU <u>ONE orally once a Month for 6 months</u>** (GP to prescribe)


DEXA IMAGING FOR PATIENTS ON AI +/- BT
Early Breast cancer, post-menopausal patient[1]
Not for ET or declines ET or for Tamoxifen:
NO need for DEXA scanning
For AI alone but ≥ 80yrs of age:
NO need for DEXA scanning,
Automatically for PO bisphosphonate[3] & Adcal for Osteoporosis/osteopenia risk
(Primary care should be asked to arrange this)
For AI for 5years + 3yrs PO/IV BT:
DEXA scan during yr1 + yr5
(Assess VitD levels and treat if low[2])
For AI alone for 5years (age <80yrs):
DEXA scan during yr1 + yr3 + yr5
(Assess VitD levels, Treat osteoporosis/ osteopenia with bisphosphonate[3] & AdcalD3;
Primary care should be asked to arrange this)
For extended AI 7-10yrs with previous BT:
Additional DEXA scan yr7 +/- yr10
(If developing osteopenia/oprosis with previous BT discuss with Bone Health specialist)
For extended AI 7-10yrs:
Additional DEXA scan yr7 +/- yr10
(Assess VitD levels, Treat osteoporosis/ osteopenia with bisphosphonate[3] & AdcalD3)
1 – No need for DEXA in premenopausal women, primary endocrine treatment or presence of bone mets
2 – Aim for VitD3 levels 70nmol/l , see local loading advice if needed
3 - Bisphosphonates for osteoporosis do not need to be the daily oral Ibrandronate recommended for adjuvant BT in breast cancer, primary care may choose which suits the individual pt.
ET = Endocrine therapy BT = Bisphosphonate therapy AI = aromatase inhibitor

breast cancer now

What are bisphosphonates?

How can bisphosphonate drugs help prevent some women's breast cancer spreading?



Information last reviewed: October 2016

Next review due: October 2019

Bisphosphonates are drugs which slow down the process that breaks down bone.

Bisphosphonates are drugs which protect your bones. They slow down the process that breaks down bone.

There are three groups of people for whom doctors often prescribe bisphosphonates as part of their standard practice:

- People with osteoporosis and other bone diseases – prescribed by their GP
- People taking an aromatase inhibitor who are at high risk of osteoporosis – prescribed by their breast care team
- People with cancer that has spread to their bone – prescribed by their oncologist

For about 20 years, people with different types of cancer (not just breast cancer) whose cancer has already spread to the bone have been prescribed bisphosphonates. Its purpose for these secondary cancer patients is to reduce bone damage caused by their cancer and to prevent fractures. Pamidronate, ibandronic acid, sodium clodronate and zoledronic acid are all currently used to help prevent this damage.

Who else might benefit from bisphosphonates?

In July 2015 a study was published which looked at the risks and benefits of giving women with early (or primary) breast cancer bisphosphonates after their main treatment (usually surgery) as well as standard chemotherapy and hormone treatments. It analysed the results of a large number of previous studies which looked at the role of bisphosphonates in reducing the spread of breast cancer to the bones.

This new study found that, for some women, bisphosphonates can lower the risk of their breast cancer spreading to the bone.

They can be effective for women who:

- have been diagnosed with early breast cancer of any type within the last six months, and
- have already gone through the menopause or have had treatment to stop their ovaries from functioning

For women who met these criteria, bisphosphonates prevented:

- 1 in 3 recurrences of breast cancer in the bone
- 1 in 6 deaths from breast cancer 10 years after diagnosis

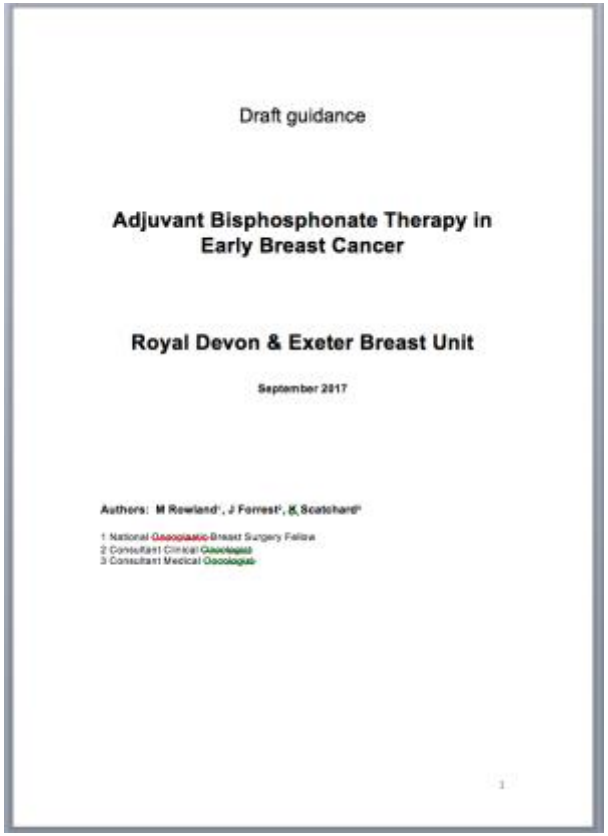
Do bisphosphonates help lower the risk of spread for women who have finished treatment?

We don't know yet whether women who have already finished surgery, radiotherapy and chemotherapy treatment would benefit from starting bisphosphonates too. All the women taking bisphosphonates whose results

Governance

- Assess who's getting it post-guidance
- Chemo unit to address IV BT complications
- Breast M&M for oral BT complications
- Rheumatology to audit atypical fractures in due course

The bottom line … it's progress for breast cancer patients !



Draft guidance

Adjuvant Bisphosphonate Therapy in Early Breast Cancer

Royal Devon & Exeter Breast Unit

September 2017

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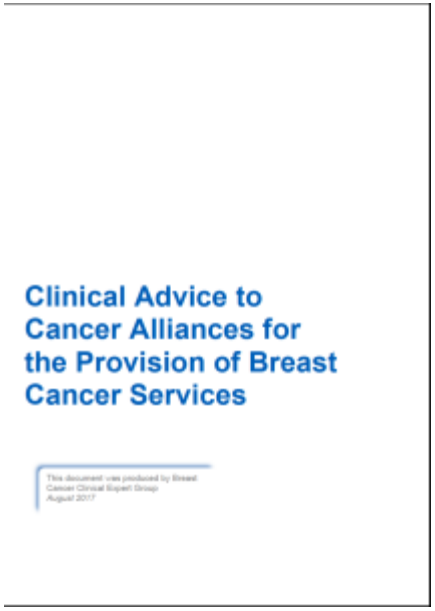

Clinical Advice to Cancer Alliances for the Provision of Breast Cancer Services

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Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline

Sukhminder Dhesy-Thind, Glenn G. Fletcher, Phillip S. Blanchette, Mark J. Clemons, Melissa S. Dillenburg, Elizabeth S. Fowler, Sonal Gandhi, Reena Gupta, Michaela Mates, Beverly Moy, Ted Vandenberg, and Catherine H. Van Poznak

ABSTRACT

Purpose
To make recommendations regarding the use of bisphosphonates and other bone-modifying agents as adjuvant therapy for patients with breast cancer.

Methods
Cancer Care Ontario and ASCO convened a Working Group and Expert Panel to develop evidence-based recommendations informed by a systematic review of the literature.

Results
Adjuvant bisphosphonates were found to reduce bone recurrence and improve survival in post-menopausal patients with nonmetastatic breast cancer. In this guideline, postmenopausal includes patients with natural menopause or that induced by ovarian suppression or ablation. Absolute benefit is greater in patients who are at higher risk of recurrence, and almost all trials were conducted in patients who also received systemic therapy. Most studies evaluated zoledronic acid or clodronate, and data are extremely limited for other bisphosphonates. While denosumab was found to reduce fractures, long-term survival data are still required.

Recommendations
It is recommended that, if available, zoledronic acid (4 mg intravenously every 6 months) or clodronate (1,600 mg/d orally) be considered as adjuvant therapy for postmenopausal patients with breast cancer who are deemed candidates for adjuvant systemic therapy. Further research comparing different bone-modifying agents, doses, dosing intervals, and durations is required. Risk factors for osteonecrosis of the jaw and renal impairment should be assessed, and any pending dental or oral health problems should be dealt with prior to starting treatment. Data for adjuvant denosumab look promising but are currently insufficient to make any recommendation. Use of these agents to reduce fragility fractures in patients with low bone mineral density is beyond the scope of the guideline. Recommendations are not meant to restrict such use of bone-modifying agents in these situations.

Additional information at www.asco.org/breast-cancer-adjuvant-bisphosphonates-guideline, www.asco.org/guidelineswiki, https://www.cancercareontario.ca/guidelines-advice/types-of-cancer/breast.

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