

SINGAPORE
2015



ESMO ASIA 2015

18-21 DECEMBER, SINGAPORE



SUNDAY, DEC 20
Hall 332

Supportive and palliative care

M. Dicato, LU; F. Scotté, FR; M. Aapro, CH

SINGAPORE
2015



ESMO ASIA 2015

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10:10 - 10:20 3710 - First in human study of RPH-203, a new potent RANKL blocker, for the treatment of bone Metastasis

S. Archuadze , S. Grishin , D. Koloda , G. Konopleva , M. Samsonov , Y. Lavrovsky , J. Lickliter

10:20 - 10:30

Dr M. Aapro

Invited discussant abstract 3710

COI

Dr Aapro is/was a consultant for
Amgen, BMS, Celgene, Clinigen, Eisai, Genomic Health,
GSK, Helsinn, Hospira, JnJ, Novartis, Merck, Merck Serono,
Pfizer, Pierre Fabre, Roche, Sandoz, Tesaro, Teva, Vifor

and has received honoraria for lectures at symposia of
Amgen, Bayer Schering, Cephalon, Chugai, Eisai, Genomic
Health, GSK, Helsinn, Hospira, Ipsen, JnJ OrthoBiotech,
Kyowa, Merck, Merck Serono, Novartis, Pfizer, Pierre Fabre,
Roche, Sandoz, Sanofi, Tesaro, Taiho, Teva, Vifor



No responsibility accepted for
involuntary errors or omissions.
The list may be incomplete, and does not reflect consultancy for
NGOs, Universities, Governmental agencies, and others

ESMO clinical practice guideline: Bone health in cancer patients

- Clinicians treating cancer patients need to be aware of:
 - Treatments to reduce skeletal morbidity in metastatic disease
 - Strategies to minimise cancer treatment-induced skeletal damage
- ESMO guidelines “provide a framework for maintaining bone health in patients with cancer”

The image shows the front cover of a clinical practice guideline document. At the top right, it says "Annals of Oncology Advance Access published April 23, 2014". Below that is the title "Bone health in cancer patients: ESMO Clinical Practice Guidelines". The authors listed are R. Coleman¹, J.J. Body², M. Aapro³, P. Hajdin⁴ & J. Hernanz⁵ on behalf of the ESMO Guidelines Working Group. The journal information includes "Volume 25 Number 6 June 2014" and "ISSN 0923-7536". The cover features a small graphic of a star and a cross.

Abstract

There are three distinct areas of cancer management that may have an impact on a patient's bone health: primary cancer, cancer treatment and cancer metastases. These three components working together can multiply the risk of bone loss. As a result, many cancer patients will have complex problems related to bone health. This document aims to provide a framework for managing patients with bone health problems. It is intended to help the clinician to identify the most appropriate treatment for the individual patient, which are often very different from those used in the management of primary bone diseases. The document also provides a framework for the management of bone metastases, which are frequently associated with cancer. Finally, the document highlights the importance of bone health in the prevention and treatment of cancer. The document is intended to help the clinician to manage bone health in patients with cancer, and to ensure that the best possible care is provided for cancer patients, and that they are informed about their condition and its treatment options.

Introduction

Cancer and the treatments applied can have profound effects on bone health. Advances in cancer treatment have led to significant improvements in survival, but these gains have been accompanied by increased incidence of secondary cancers and by increased rates of cancer treatment-related damage to normal tissue. These advances provide a framework for managing bone health in patients with cancer.

pathophysiology of bone metastases

The process of cancer metastasis involves tumor cell seeding, tumor colonization and growth within the host. The primary tumor releases cells that travel through the lymphatic system, blood vessels or bone marrow to distant organs. These secondary sites are often located in bones, lungs, liver and brain. The ability of cancer cells to colonize distant sites is determined by various factors, including the ability of cancer cells to bind to specific receptors on the surface of target cells, the ability of cancer cells to penetrate basement membranes and the ability of cancer cells to survive and grow in a new environment. These processes may result in a range of clinical outcomes, including local invasion, metastasis and death.

normal bone physiology and turnover

Bones have a constant rate of remodeling, as well as a capacity for proliferation. Normal bone remodeling is a process by which old bone is removed and new bone is deposited. This process is controlled by osteoclasts and osteoblasts. Osteoclasts are responsible for breaking down bone tissue, while osteoblasts are responsible for building new bone tissue. The balance between these two processes is important for maintaining bone health.

Conclusion

In conclusion, the ESMO Clinical Practice Guideline on Bone Health in Cancer Patients provides a framework for managing bone health in cancer patients. The guideline covers the pathophysiology of bone metastases, normal bone physiology and turnover, and the clinical presentation and management of bone health in cancer patients. The guideline is intended to help clinicians to provide the best possible care for cancer patients, and to ensure that they are informed about their condition and its treatment options.

Regulatory approval for anti-resorptive agents in cancer patients

Indication	Regulatory approval
Prevention of skeletal-related events	
Zoledronic acid 4 mg i.v. every 3–4 weeks Denosumab 120 mg s.c. every 4 weeks Pamidronate 90 mg i.v. every 3–4 weeks Clodronate 1600 mg p.o. daily Ibandronate 50 mg p.o. daily Ibandronate 6 mg i.v. monthly	All solid tumours and multiple myeloma All solid tumours Breast cancer and multiple myeloma Osteolytic lesions* Breast cancer* Breast cancer*
Prevention of breast cancer metastases	
Zoledronic acid 4 mg i.v. 6 monthly Zoledronic acid 4 mg i.v. monthly x 6, then 3–6 monthly Clodronate 1600 mg daily	None None None
Prevention of prostate cancer metastases	
Denosumab 120 mg s.c. monthly	None
Prevention of treatment-induced bone loss	
Denosumab 60 mg s.c. 6 monthly Zoledronic acid 4 mg i.v. 6 monthly Alendronate 70 mg p.o. weekly Risedronate 35 mg p.o. weekly Ibandronate 150 mg p.o. monthly Pamidronate 90 mg i.v. every 3 months	Prostate and breast cancer None None None None None

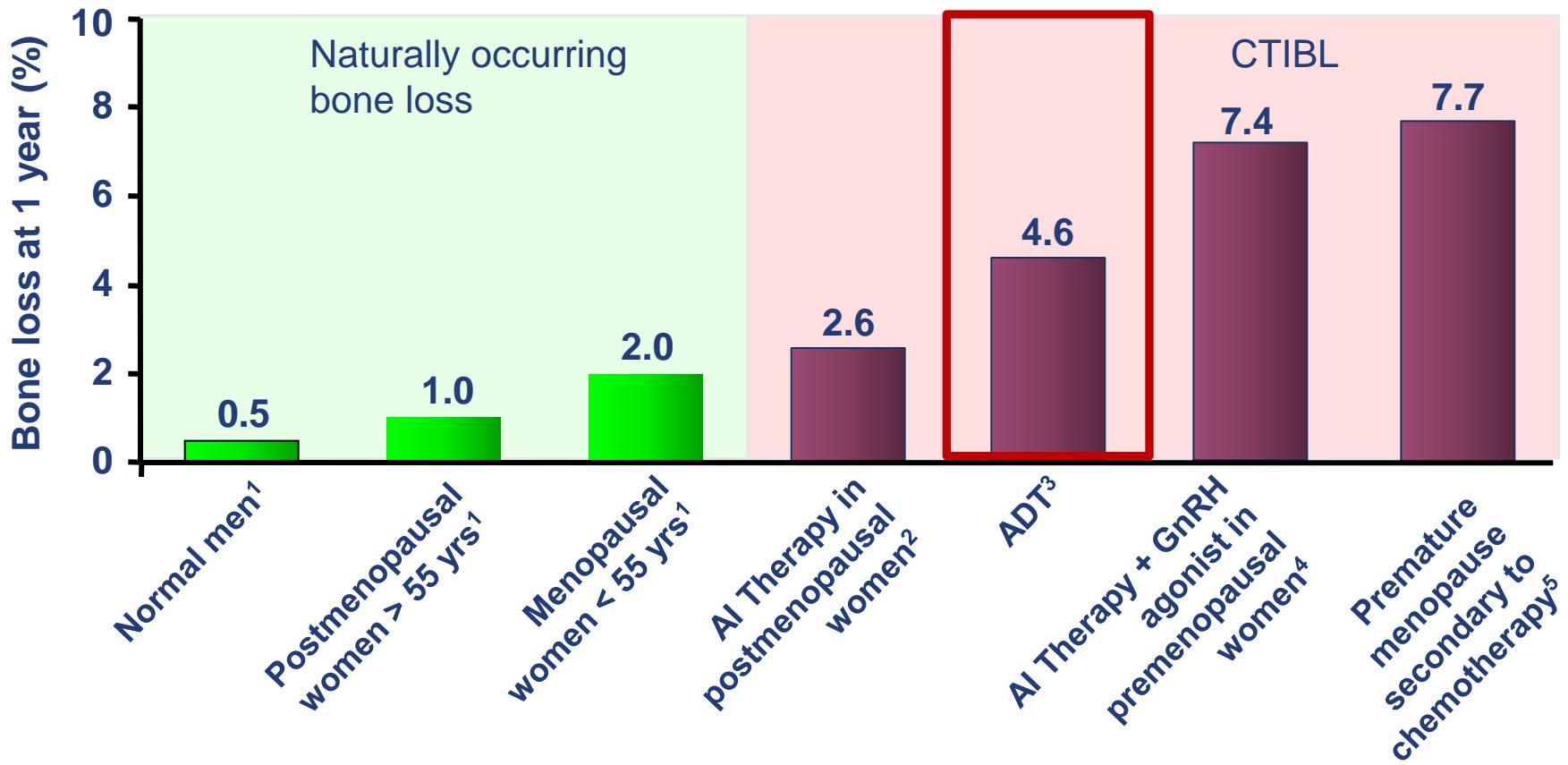
*European approval only (not US)

i.v. – intravenous; s.c. subcutaneous; p.o. per oral

Prevention of treatment- induced bone loss

- **Bisphosphonates** and **denosumab** prevent bone loss associated with ovarian suppression/aromatase inhibitors in **early breast cancer** and androgen deprivation therapy in **prostate cancer**

It is not only about women!

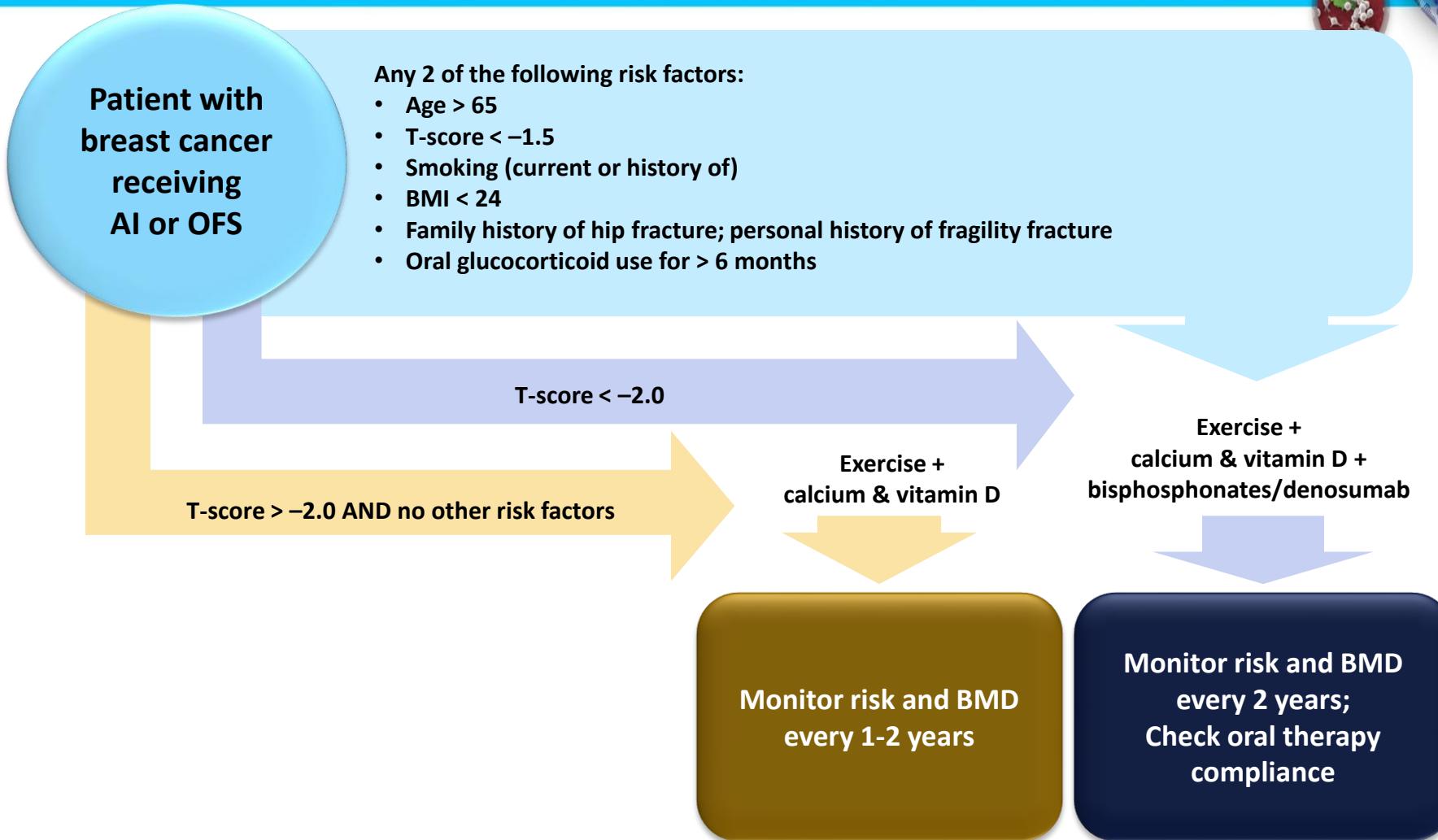


1. Higano CS. *Nat Clin Pract Urol* 2008;5:24-4; 2. Eastell R, et al. *J Bone Miner Res* 2006;21:1215-23;

3. Maillefert JF, et al. *J Urol* 1999;161:1219-22; 4. Gnant MF, et al. *Lancet Oncol* 2008;9:840-9;

5. Shapiro CL, et al. *J Clin Oncol* 2001;19:3306-11

ESMO Clinical Practice Guidelines on Bone Health in Cancer Patients



AI, aromatase inhibitor; BMD, bone mineral density; BMI, bone mineral density; OFS, ovarian function suppression.

Data from Coleman R, et al. Ann Oncol. 2014;25(suppl 3):iii124-iii137.

AND NOW...



Meta-Analysis of Adjuvant Bisphosphonate Trials

Lancet

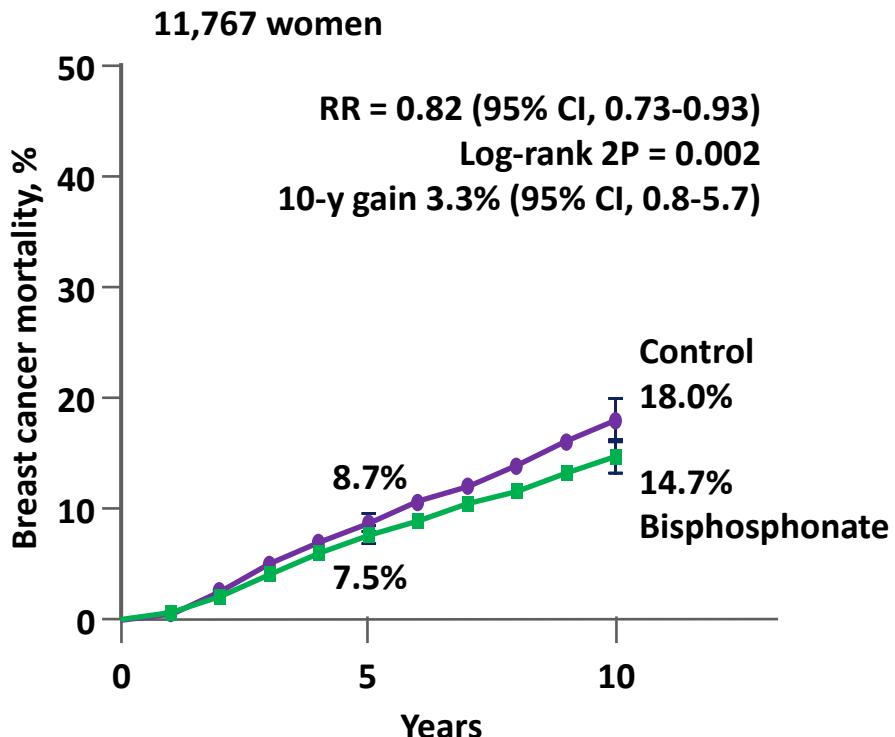
Published online 24 July 2015

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

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

Coleman R, Powles T, Paterson A, Gnant M, Anderson S, Diel I, Gralow J, von Minckwitz G, Moebus V, Bergh J, Pritchard KI, Bliss J, Cameron D, Evans V, Pan H, Peto R, Bradley R, and Gray R

Adjuvant Bisphosphonates and Mortality in Postmenopausal Women



Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

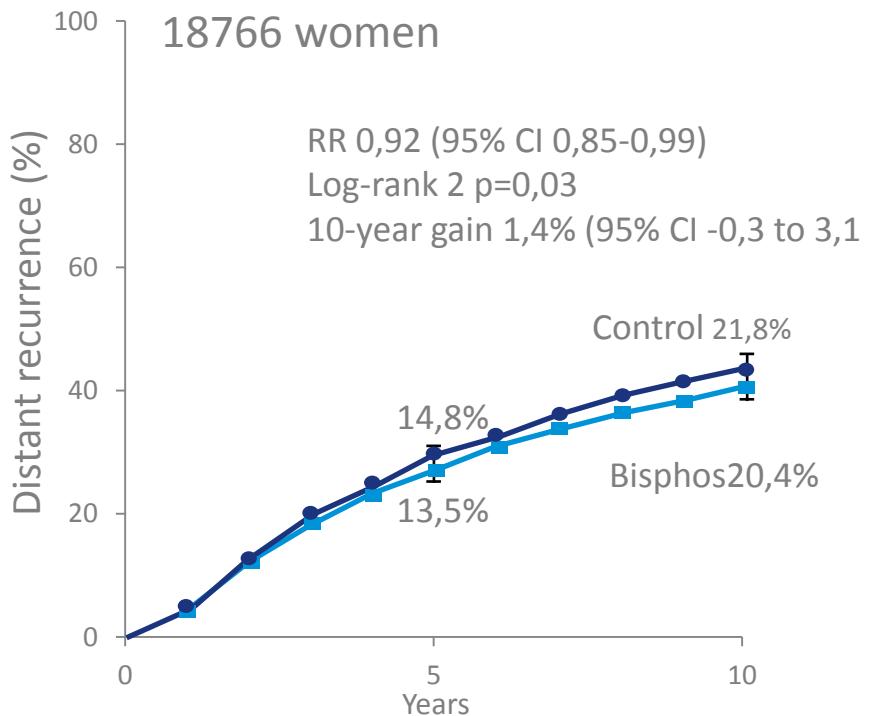
Allocation	Years 0-4	Years 5-9	Year ≥10
Bisphosphonate	1.56 (1.41-1.72)	1.57 (1.30-1.84)	1.30 (0.34-2.26)
Control	1.74 (1.58-1.91)	2.04 (1.74-2.35)	2.73 (1.30-4.16)
Rate ratio (95% CI)	0.86 (0.72-0.99)	0.76 (0.55-0.97)	0.52 (0.18-1.44)
from (O-E) / V	-27.1 / 174.9	-18.0 / 65.0	-2.4 / 3.6

Error bars are standard error of the mean.

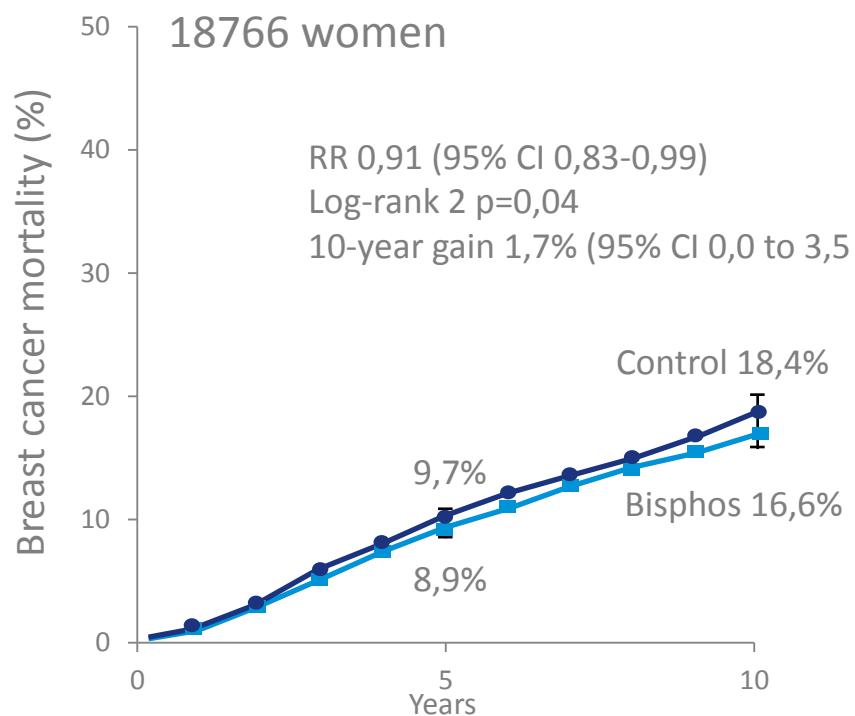
CI, confidence interval; O-E, observed minus expected; RR, rate ratio; V, variance of O-E.

Reprinted from Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet*. 2015;386(10001):1353-1361.

OVERALL EBCTCG ANALYSIS



Distant recurrence rate/year (%), events/woman-years and log-rank statistics			
Allocation	Years 0-4	Years 5-9	Years ≥ 10
Bisphosphonate	2,97 (1173/39559)	1,84 (253/13746)	0,67 (13/1932)
Control	3,20 (1170/36571)	1,82 (253/13931)	1,08 (21/1941)
Rate ratio (95% CI)	0,91 (0,83-0,99)	0,99 (0,81-1,18)	0,47 (0,21-1,03)
From (0-E)/V	-47,5/499,9	-0,7/114,3	-4,5/5,9



Death rates (%/year (%): total rate minus rate in women without recurrences) and log-rank statistics			
Allocation	Years 0-4	Years 5-9	Years ≥ 10
Bisphosphonate	1,83 (1,70-1,97)	1,81 (1,59-2,03)	1,21 (0,72-1,69)
Control	1,98 (1,84-2,12)	1,97 (1,75-2,20)	1,69 (1,12-2,25)
Rate ratio (95% CI)	0,91 (0,81-1,01)	0,92 (0,75-1,10)	0,66 (0,18-1,15)
From (0-E)/V	-30,5/321,7	-9,5/121,0	-4,5/10,9

AND SOON IN ANNALS OF ONCOLOGY...

Adjuvant bisphosphonates in early breast cancer: Consensus guidance for clinical practice
from a European Panel

P. Hadji^{1,*}, R.E. Coleman^{2,*}, C. Wilson², T. J. Powles³, P. Clézardin⁴, M. Aapro⁵, L. Costa⁶, J-J. Body⁷, C. Markopoulos⁸, D. Santini⁹, I. Diel¹⁰, A. Di Leo¹¹, D. Cameron¹², D. Dodwell¹³, I. Smith¹⁴, M. Gnant¹⁵, R. Gray¹⁶, N. Harbeck¹⁷, B. Thurlimann¹⁸, M. Untch¹⁹, J. Cortes²⁰, M. Martin²¹, U-S. Albert¹, P-F. Conte²², B. Ejlertsen²³, J. Bergh²⁴, M. Kaufmann²⁵, I. Holen²



BUT RECENTLY...

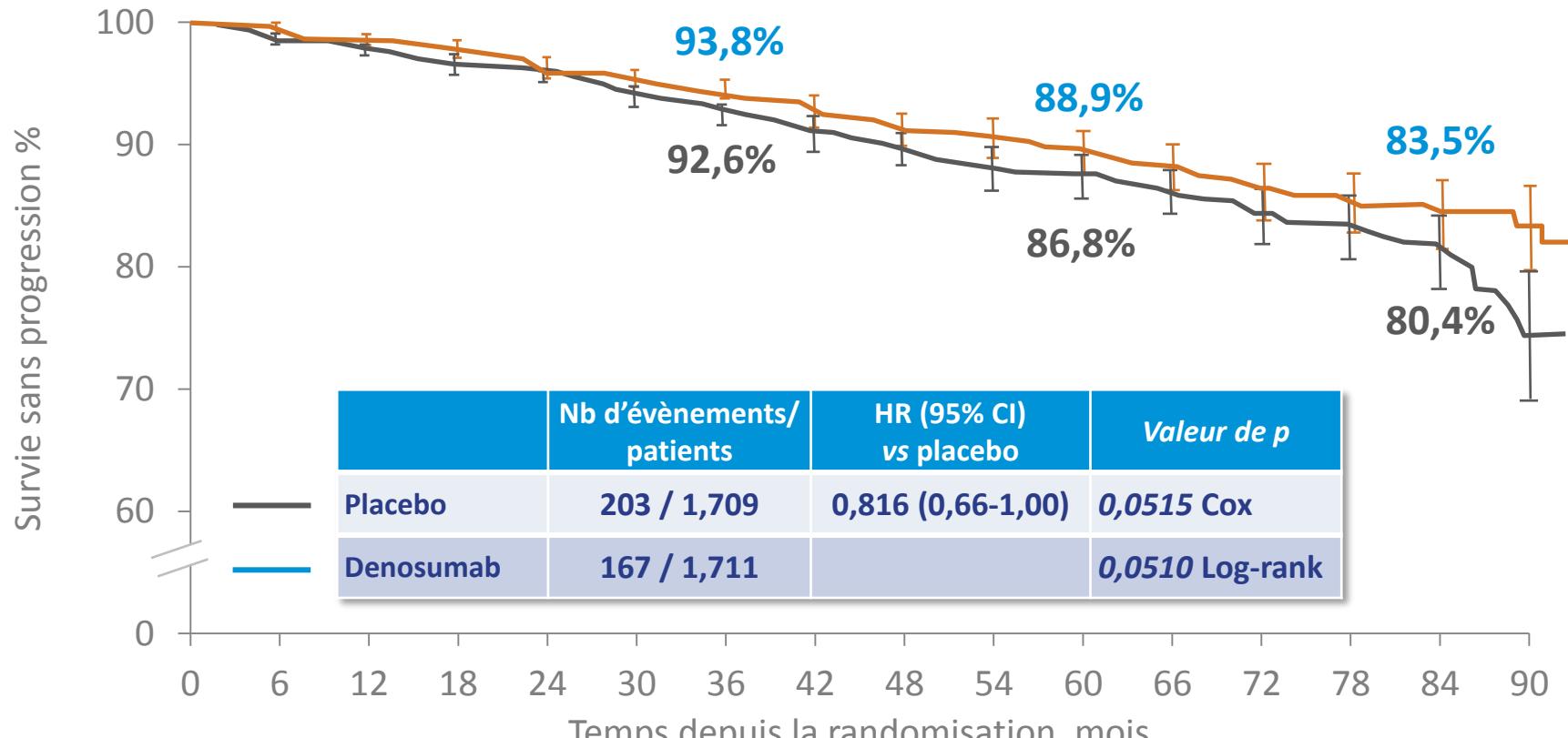




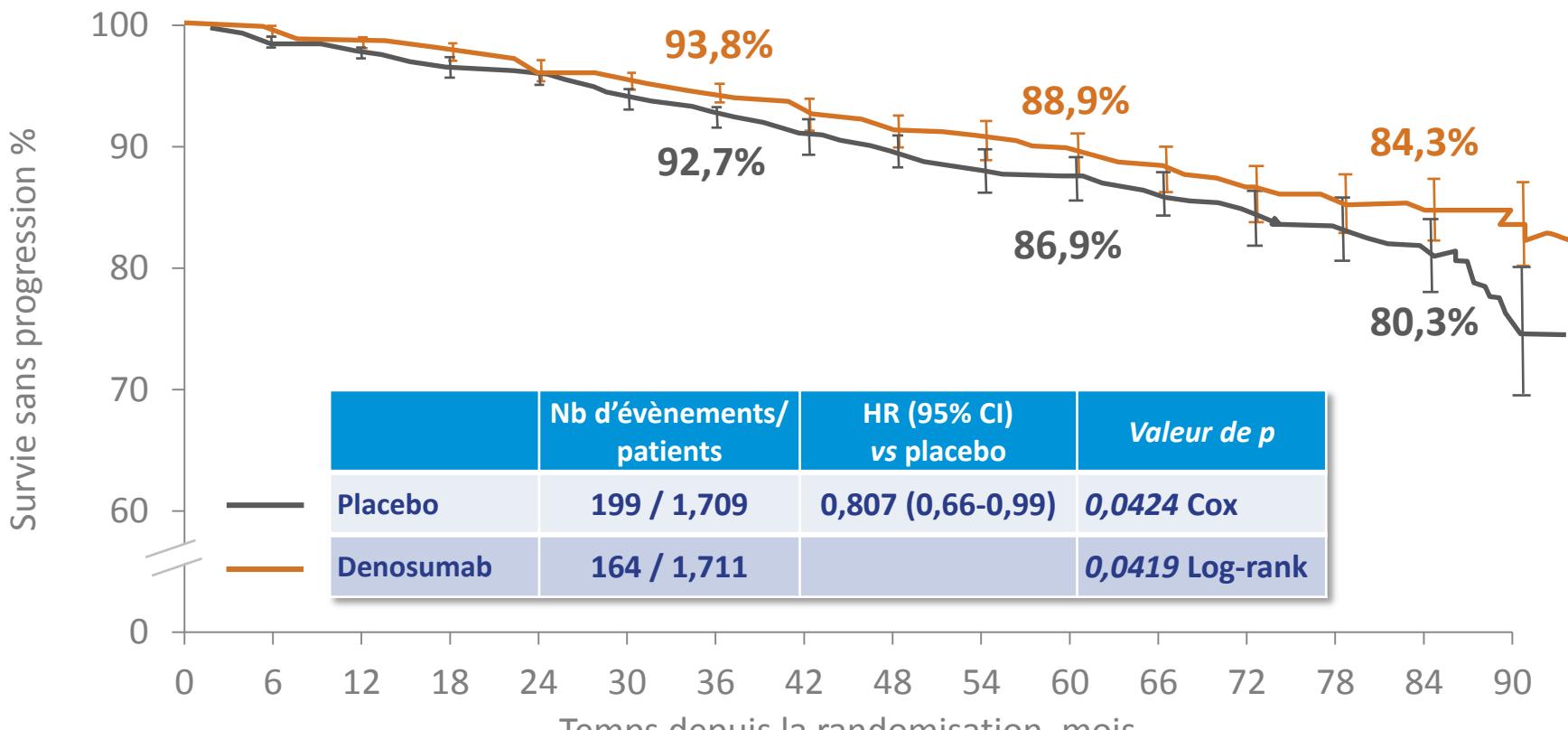
THE IMPACT OF ADJUVANT DENOSUMAB ON DISEASE-FREE SURVIVAL: RESULTS FROM 3,425 POSTMENOPAUSAL PATIENTS OF THE ABCSG-18 TRIAL

GNANT M. *et al.* – S2-02

ABCSG-18 PFS intent to treat



ABCSG-18 PFS after censoring some patients who received a BMA in the control arm



Patients à risque

Placebo	1709	1661	1616	1562	1424	1269	1066	935	757	675	523	443	279	231	109	69
Denosumab	1711	1673	1619	1580	1418	1291	1095	976	773	708	543	475	296	250	115	66

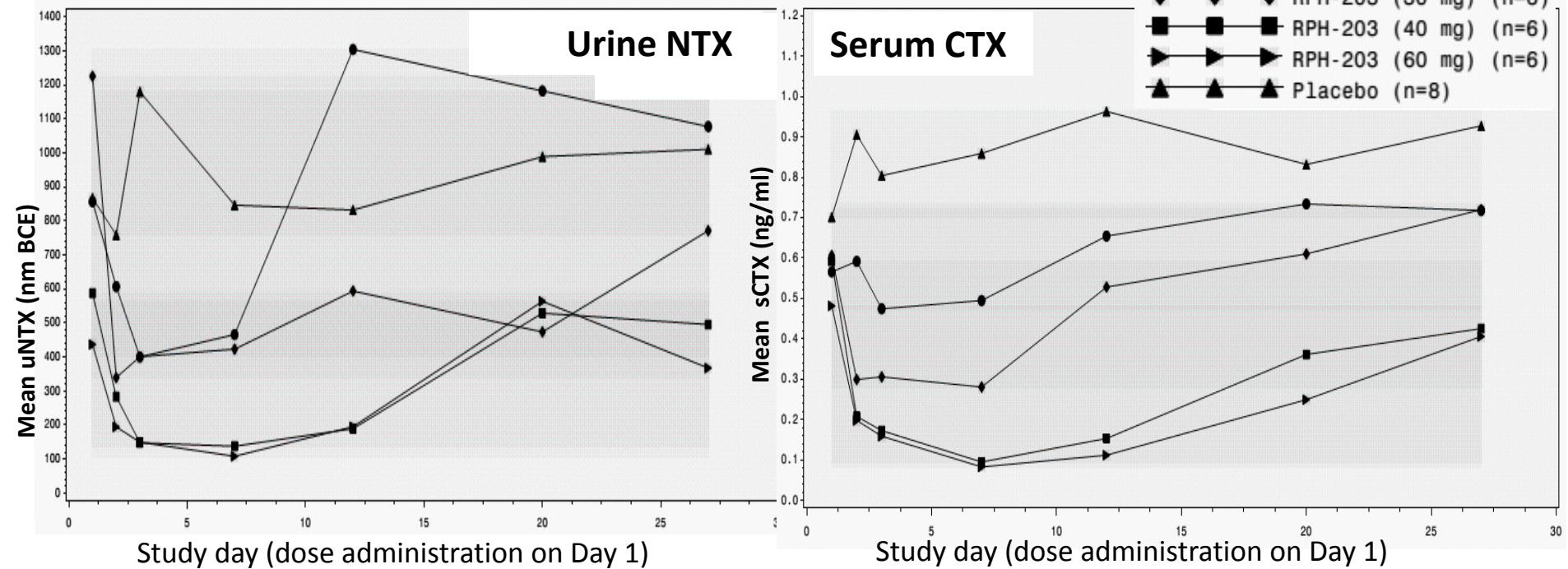
AND HERE IN SINGAPORE...





PD parameters of RPH-203 by dose level

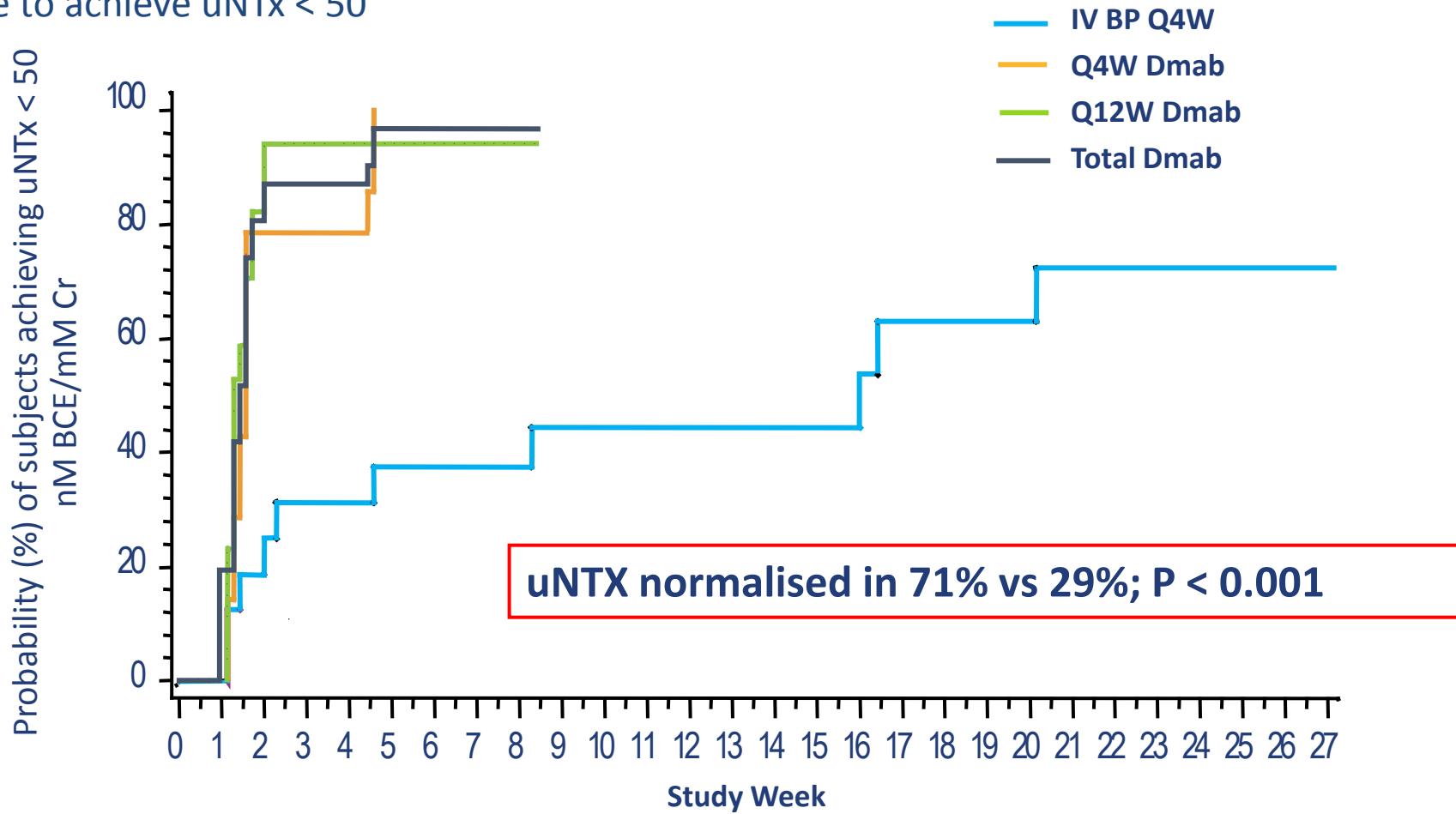
Mean levels of uNTX and sCTX (linear)



Single SC injection of RPH-203 resulted in dose-dependent decrease in uNTX and sCTX

Can we do better?: denosumab controls osteolysis better than ongoing bisphosphonates

Time to achieve uNTx < 50



RPH-203 safety



	Number (%) of Subjects with at least one TEAE [Number of TEAEs*]					
	10 mg (N=6)	30 mg (N=6)	40 mg (N=6)	60 mg (N=6)	Placebo (N=8)	Total (N=32)
System Organ Class						
Infections and infestations	2 (33%) [2]			1 (17%) [1]	1 (13%) [1]	4 (13%) [4]
Blood and lymphatic system disorders	1 (17%) [1]					1 (3%) [1]
Psychiatric disorders			1 (17%) [1]			1 (3%) [1]
Nervous system disorders	3 (50%) [4]	3 (50%) [4]	4 (67%) [5]	5 (83%) [6]	4 (50%) [4]	19 (59%) [23]
Vascular disorders	1 (17%) [1]					1 (3%) [1]
Gastrointestinal disorders	1 (17%) [1]		1 (17%) [1]	1 (17%) [1]	1 (13%) [2]	4 (13%) [7]
Skin and subcutaneous tissue disorders					2 (25%) [2]	2 (6%) [2]
Musculoskeletal and connective tissue disorders			1 (17%) [1]			1 (3%) [1]
General disorders and administration site reactions		1 (17%) [1]		2 (33%) [3]	2 (25%) [2]	5 (16%) [6]
Injury, poisoning and procedural complications	1 (17%) [1]					1 (3%) [1]
ALL TEAEs	5 (83%) [10]	3 (50%) [5]	5 (83%) [8]	6 (100%) [13]	6 (75%) [11]	25 (78%) [47]

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RPH- 203 s.c.

1. Does modify CTX and NTX levels at 40 mg in a way similar to 60 mg
2. Does have some side-effects at 60 mg which are...?
2 bis. No data shown for calcium levels...
3. Is being compared to denosumab for PK / PD properties
NB denosumab dose for bone mets is 120 monthly versus 60 every 6 months in “AI osteoporosis” trials
4. Development plan to take into account recent data on survival of patients receiving BMAs





ISOO

MASCC/ISOO 2016

International Symposium on Supportive Care in Cancer

Save The Date...Adelaide, Australia - June 23-25 2016



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