SINGAPORE 2015 ESMO ASIA

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

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10:10 - 10:20 371O - 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 371O

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


Annals of Oncology Advance Access published April 29, 2014

clinical practice guidelines

Bone health in cancer patients: ESMO Clinical Practice Guidelines†

- 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”

Coleman R et al. *Ann Oncol* 2014;00:1–14.

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

*European approval only (not US)
i.v. – intravenous; s.c. subcutaneous; p.o. per oral

Coleman R et al. *Ann Oncol* 2014;00:1–14.

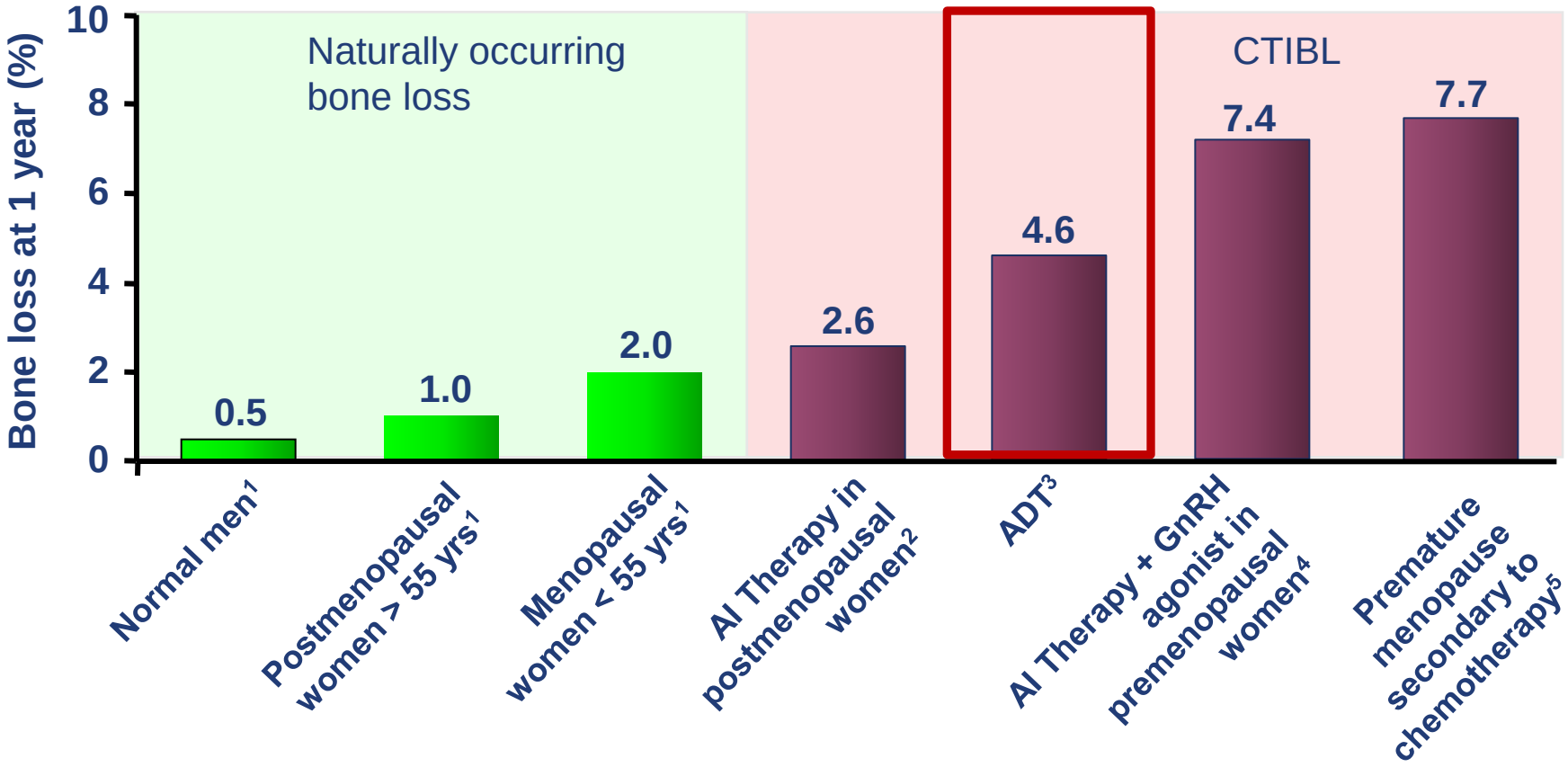
Treatment recommendations

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**

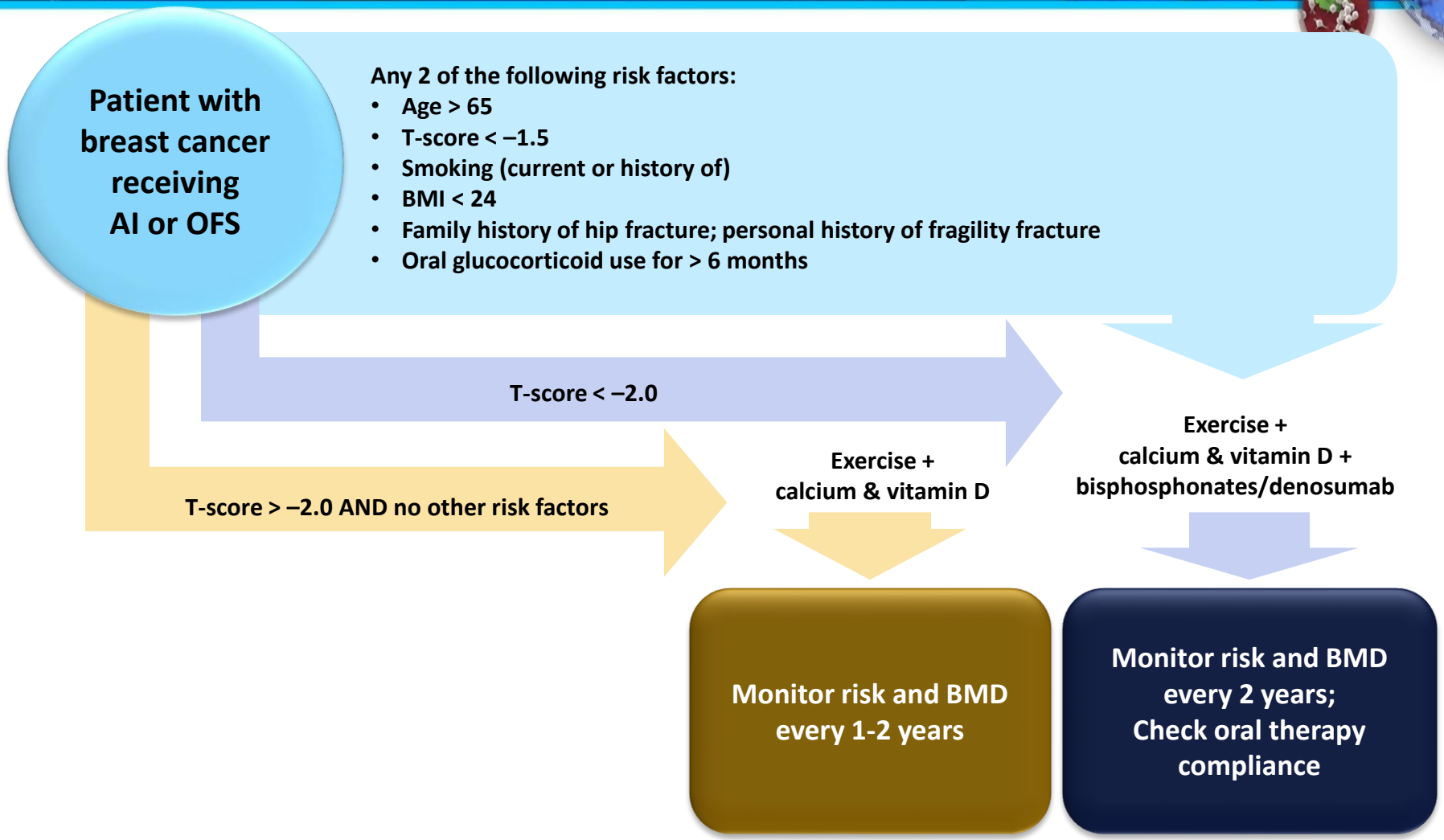
Coleman R et al. *Ann Oncol* 2014;00:1–14.

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

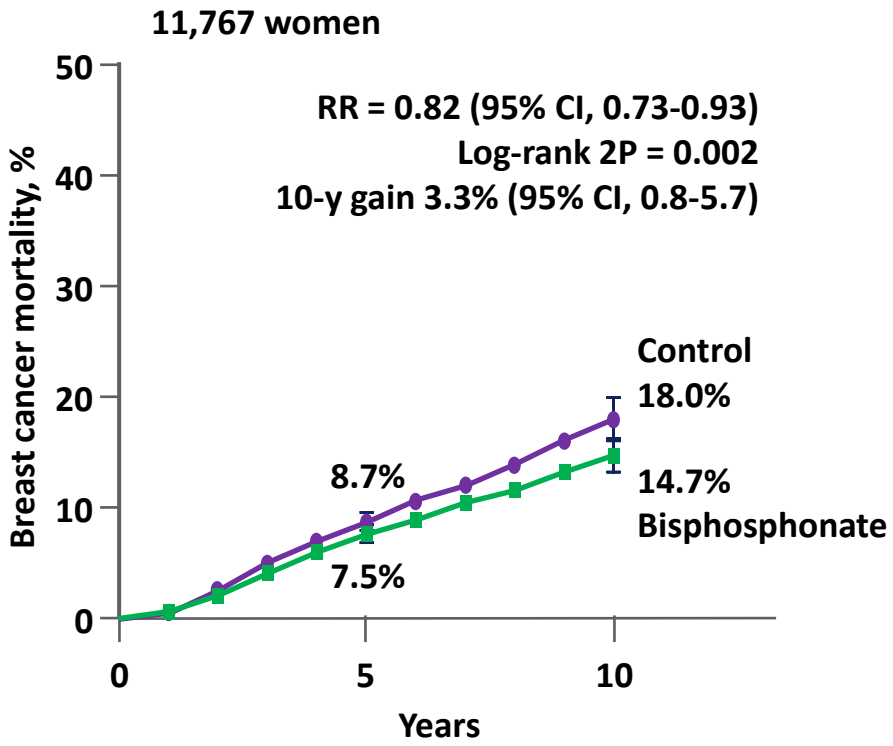
Lancet	Published online 24 July 2015

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

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

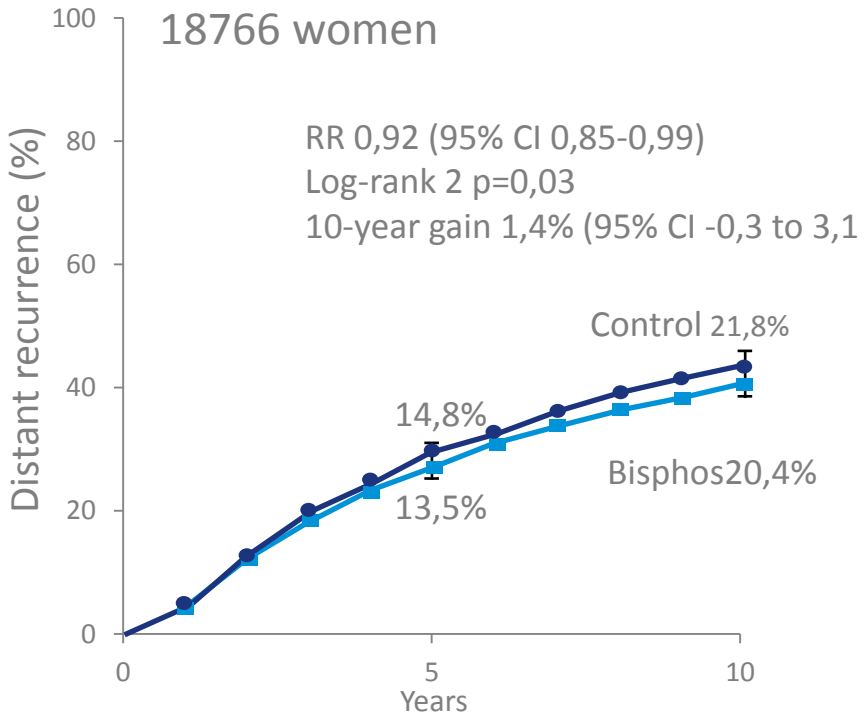
Adjuvant Bisphosphonates and Mortality in Postmenopausal Women



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

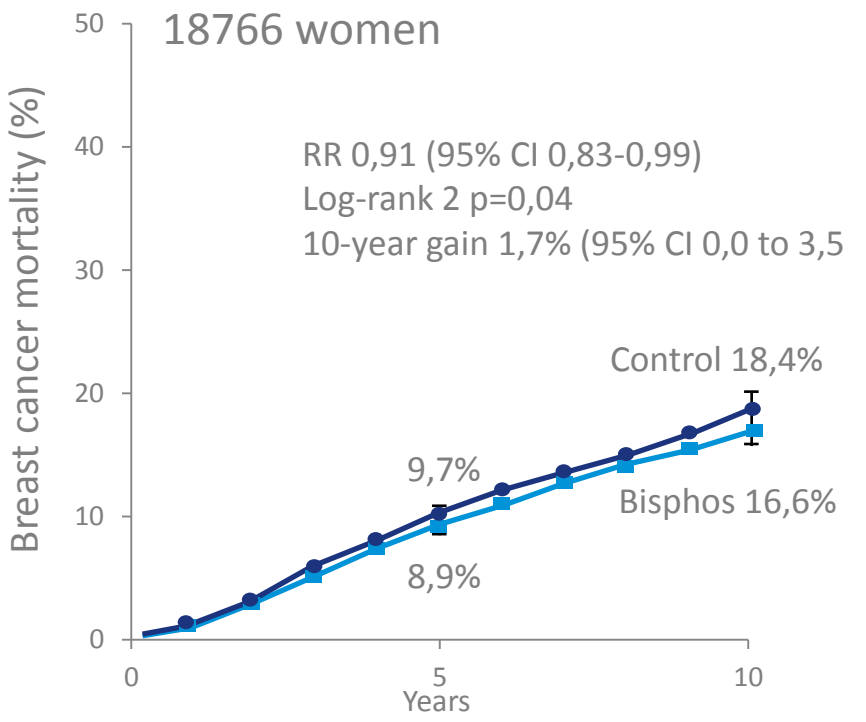
Error bars are standard error of the mean.
CI, confidence interval; OE, observed minus expected; RR, rate ratio; V, variance of O-E.
Reprinted from Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet*. 2015;386(10001):1353-1361.

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

EBCTCG, Lancet 2015

AND SOON IN ANNALS OF ONCOLOGY…

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

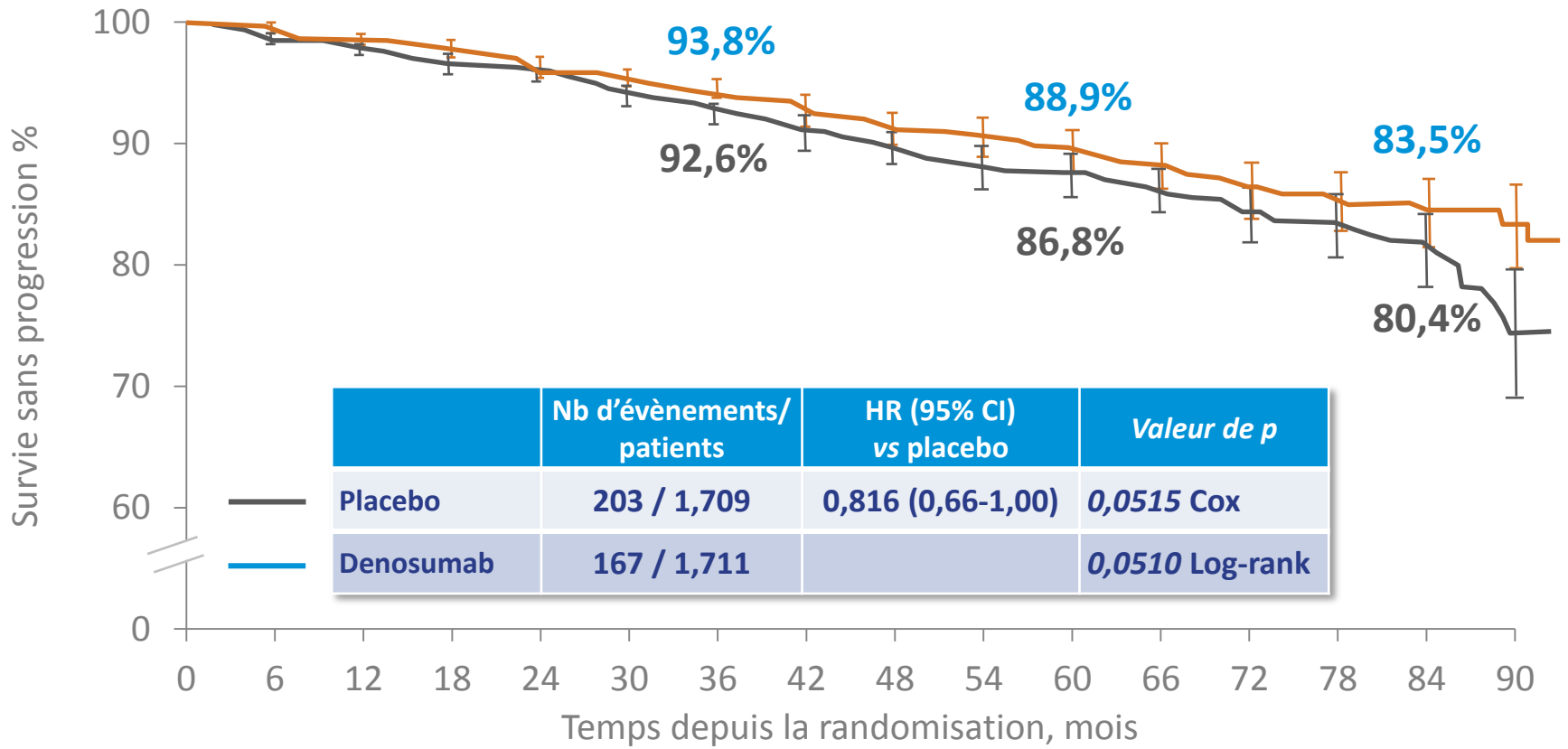
P. Hadji[1,*], R.E. Coleman[2,*], C. Wilson[2], T. J. Powles[3], P. Clézardin[4], M. Aapro[5], L. Costa[6], J-J. Body[7], C. Markopoulos[8], D. Santini[9], I. Diel[10], A. Di Leo[11], D. Cameron[12], D. Dodwell[13], I. Smith[14], M. Gnant[15], R. Gray[16], N. Harbeck[17], B. Thurlimann[18], M. Untch[19], J. Cortes[20], M. Martin[21], U-S. Albert[1], P-F. Conte[22], B. Ejlertsen[23], J. Bergh[24], M. Kaufmann[25], I. Holen[2]

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



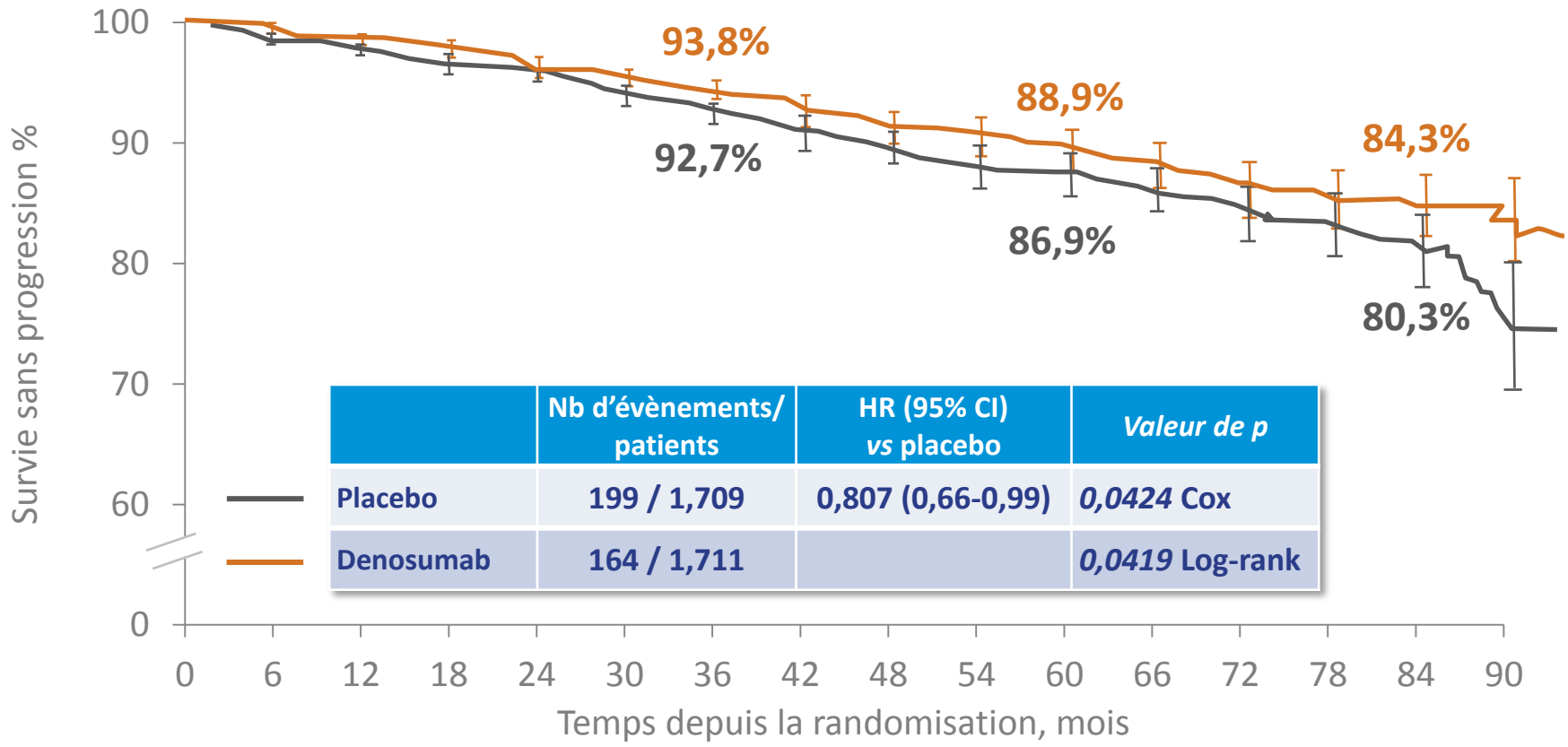
	Nb d'évènements/ patients	HR (95% CI) *vs* placebo	*Valeur de p*
Placebo	203 / 1,709	0,816 (0,66-1,00)	*0,0515* Cox
Denosumab	167 / 1,711		*0,0510* Log-rank

Patients à risque

Placebo	1709	1663	1626	1578	1443	1289	1086	958	779	693	534	454	289	241	115	73
Denosumab	1711	1676	1623	1584	1424	1296	1102	984	779	714	548	479	300	252	115	66

Gnant M. et al., SABCS 2015, S2-02

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



	Nb d'évènements/ patients	HR (95% CI) *vs* placebo	*Valeur de p*
Placebo	199 / 1,709	0,807 (0,66-0,99)	*0,0424* Cox
Denosumab	164 / 1,711		*0,0419* Log-rank

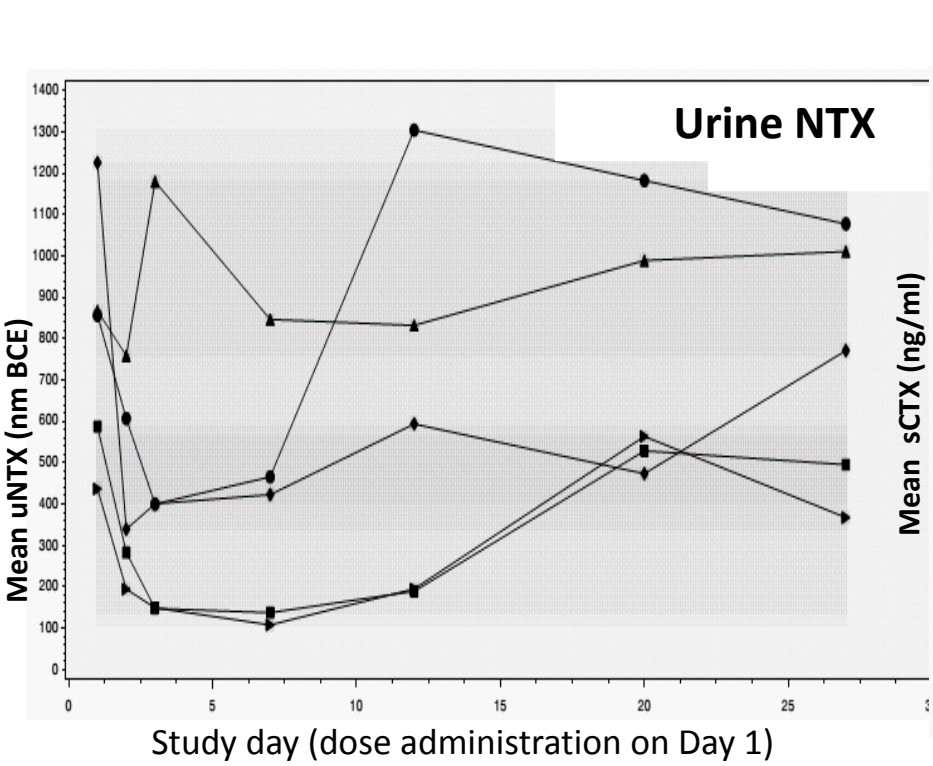
Patients à risque

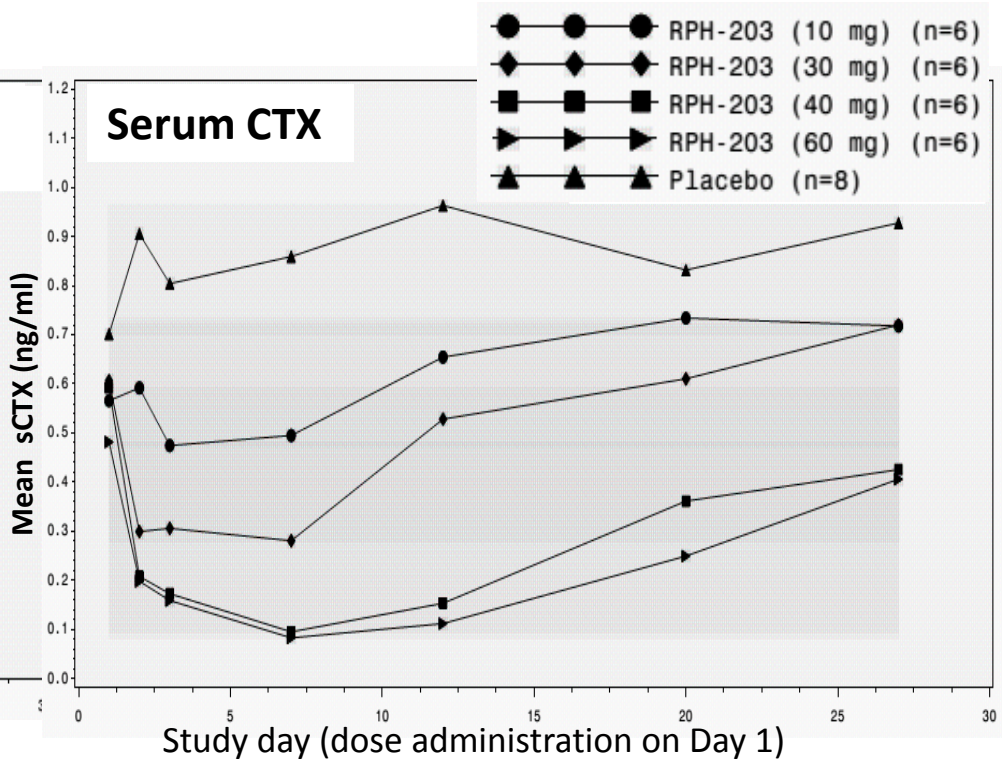
Placebo	1709	1661	1616	1562	1424	1269	1066	935	757	675	523	443	279	231	109	69
Denosumab	1711	1673	1619	1580	1418	1291	1095	976	773	708	543	475	296	250	115	66

Gnant M. et al., SABCS 2015, S2-02

AND HERE IN SINGAPORE…

PD parameters of RPH-203 by dose level
Mean levels of uNTX and sCTX (linear)

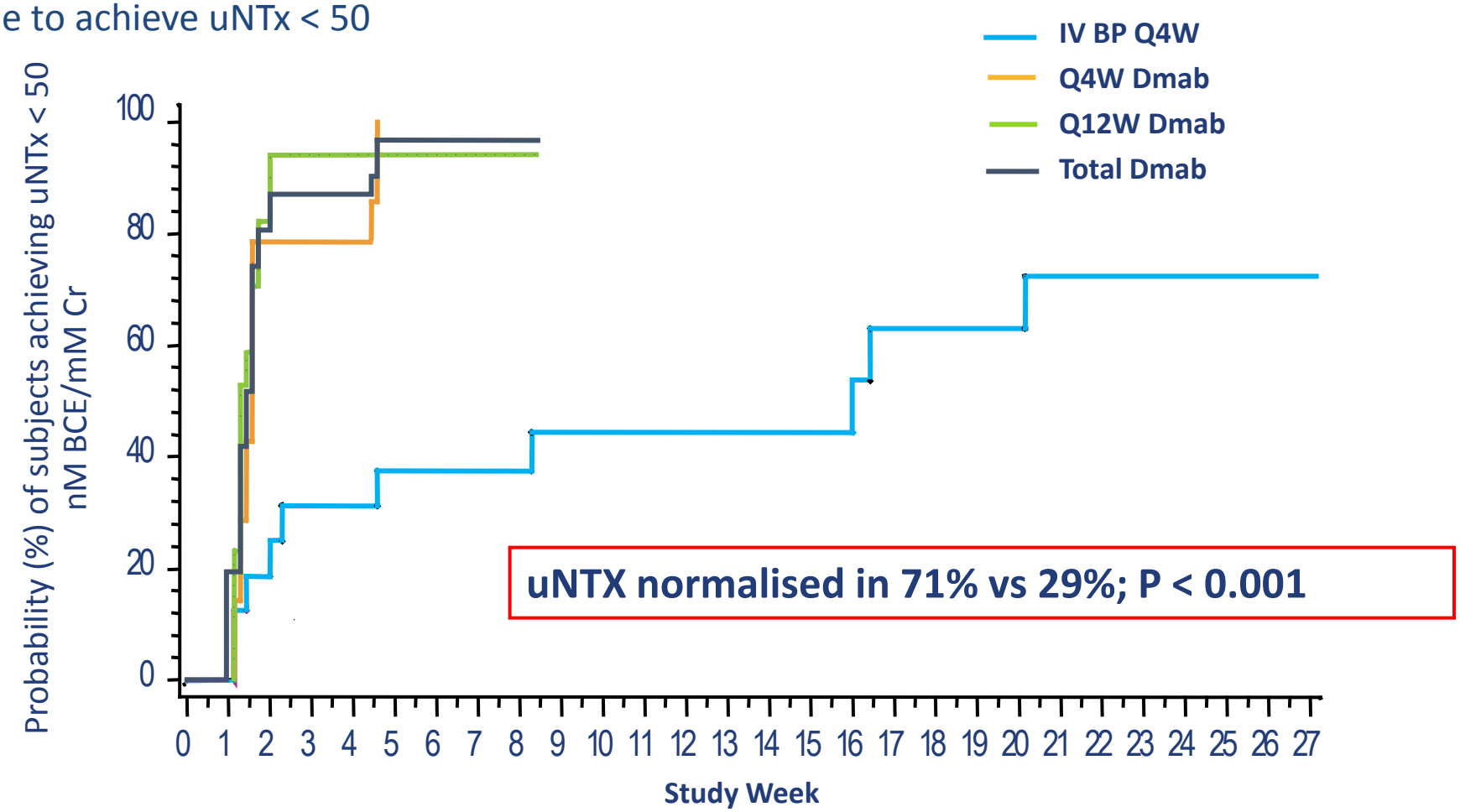




Single SC injection of RPH-203 resulted in dose-dependent decrease in uNTX and sCTX

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

Time to achieve uNTx < 50



Adapted from Fizazi K, et al. *J Clin Oncol* 2009;27:1564-71

RPH-203 safety

	Number (%) of Subjects with at least one TEAE [Number of TEAEs*]					
System Organ Class	**10 mg (N=6)**	**30 mg (N=6)**	**40 mg (N=6)**	**60 mg (N=6)**	**Placebo (N=8)**	**Total (N=32)**
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]

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

MASCC

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MASCC/ISOO 2016

International Symposium on Supportive Care in Cancer

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