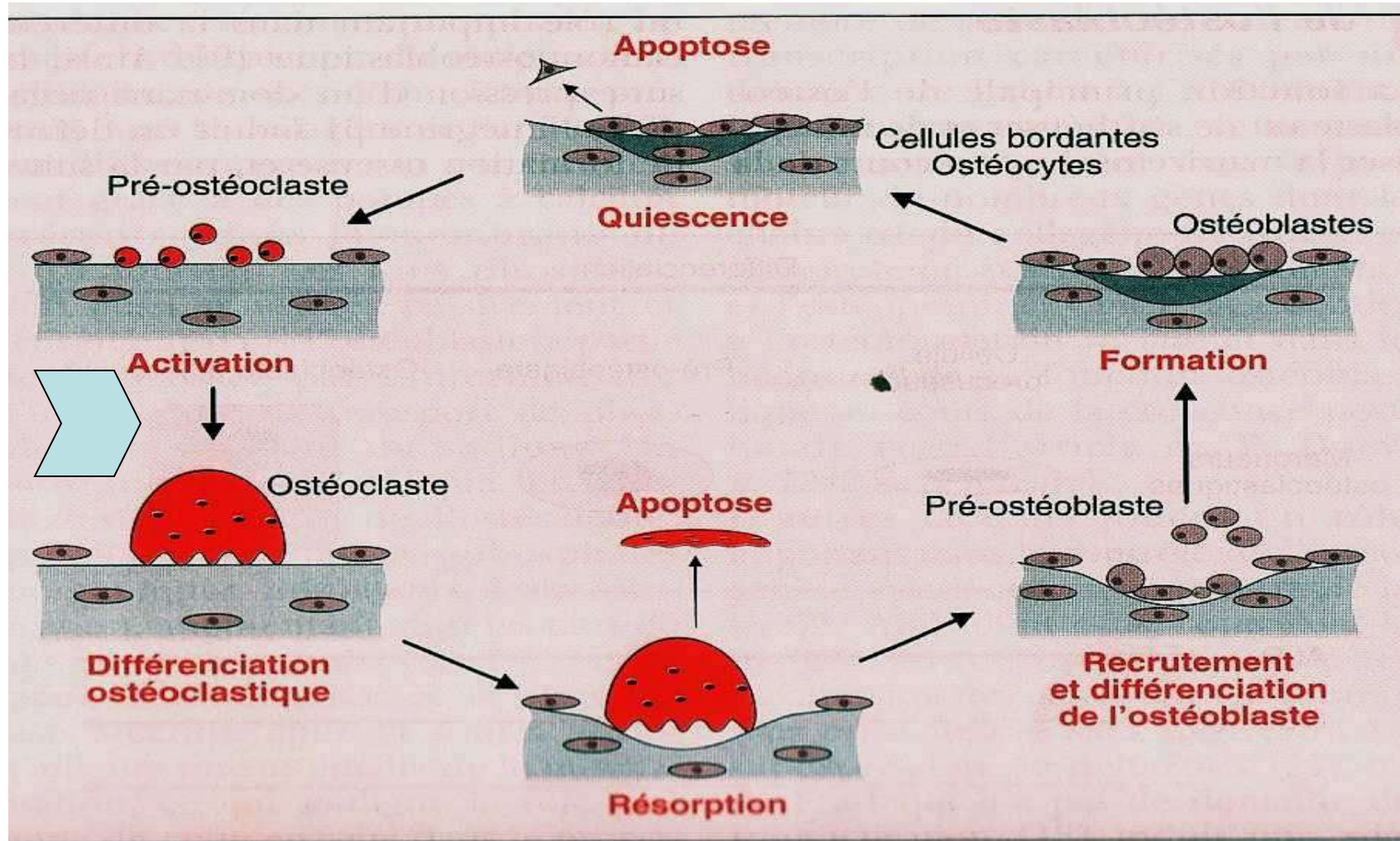




**Les Soins de Support Oncologiques
ASCO et MASCC 2010
prise en charge des métastases osseuses**

**Dr Mario DI PALMA
Institut Gustave Roussy**

cycle de remodelage osseux



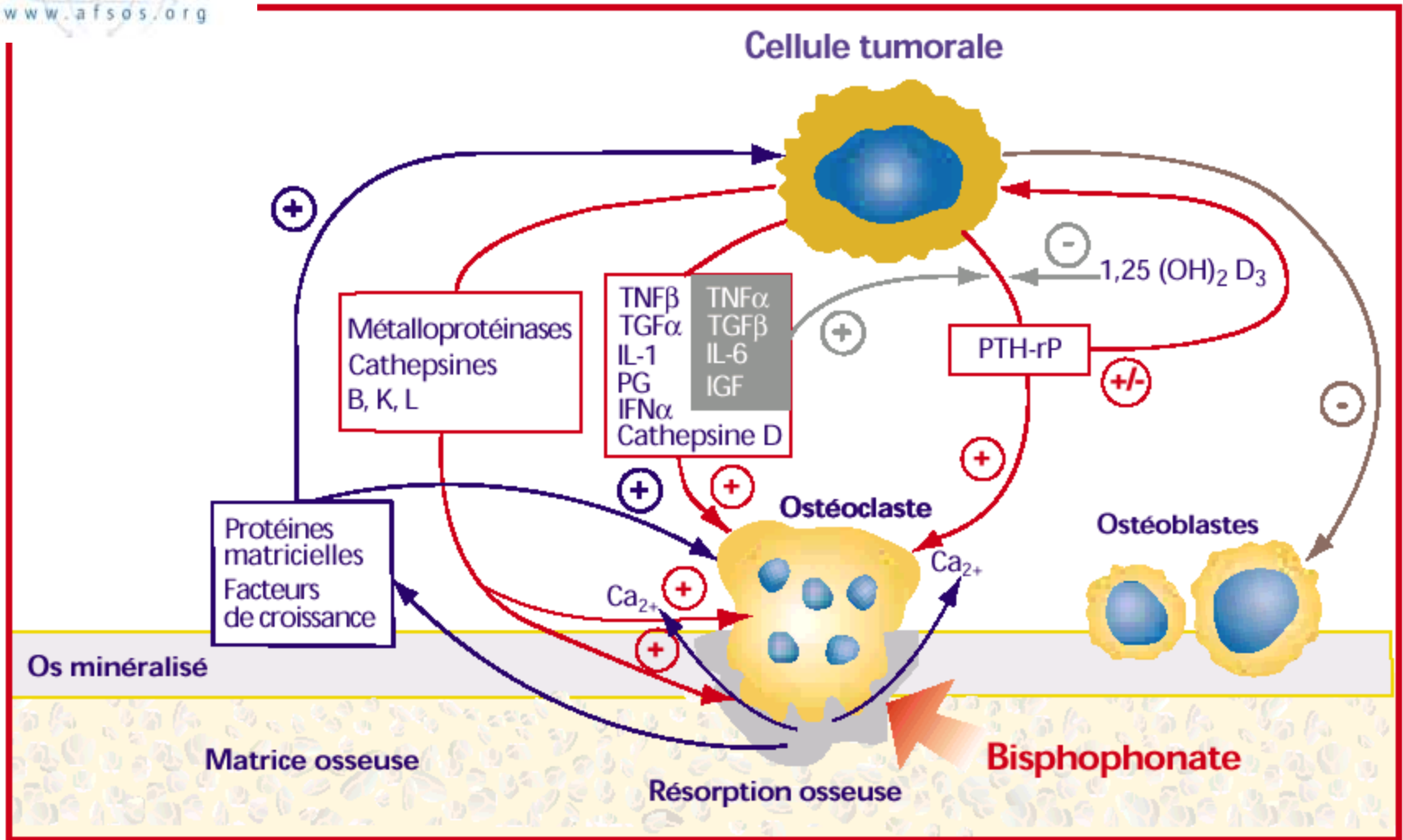


Schéma des interactions moléculaires entre ostéoclastes et cellules tumorales ⁽⁴⁾

Conséquences des métastases osseuses

- Complications mécaniques
 - Douleurs osseuses
 - Fractures pathologiques*
 - Tassements vertébraux
 - Compression médullaire*
- Hypercalcémie maligne*
- Recours chirurgie / radiothérapie*

évènements osseux* (SRE skeletal-related events)



Qualité de vie
Survie

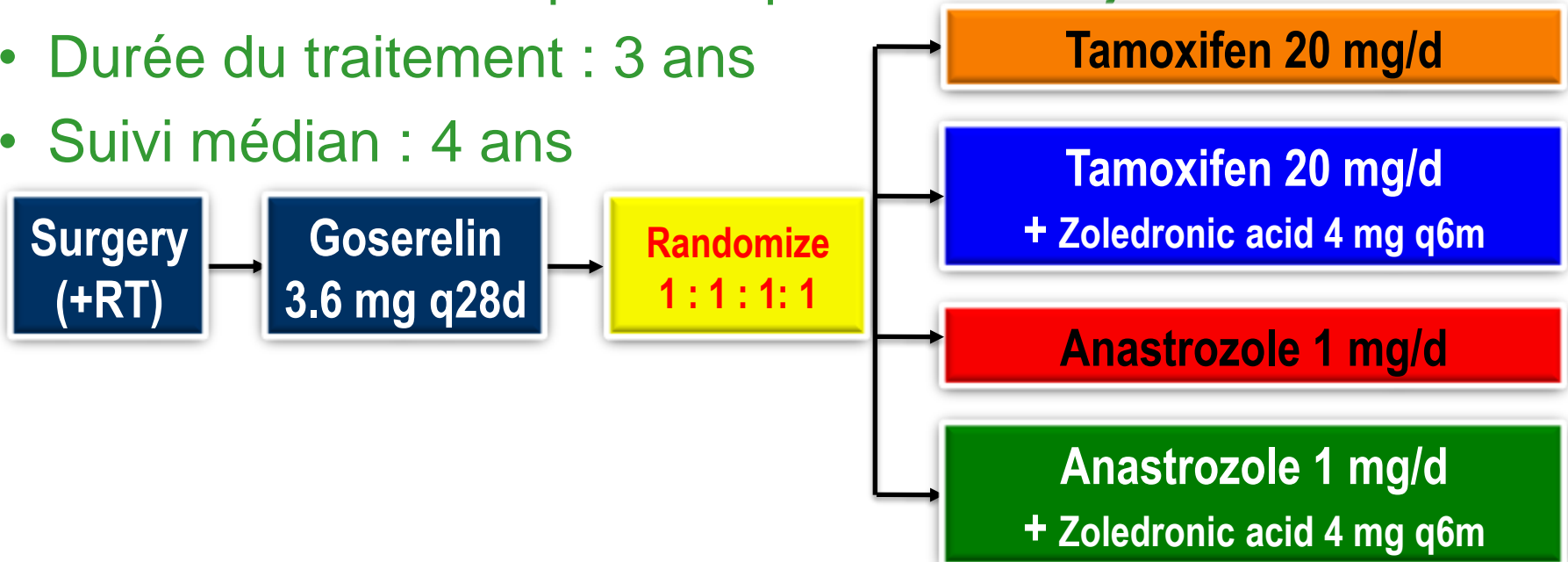


biphosphonates: intérêts établis

- **ttt hypercalcémie**
- **effet antalgique**
 - 50% des patients
 - réduction des ttt antalgiques rare
 - effet dose, voie IV
- **prévention des complications osseuses**
 - ↘ de 30 à 40% du taux de complications
 - ↗ du délai de survenue
- **ttt ostéoporose** (post ménopause, prostate)

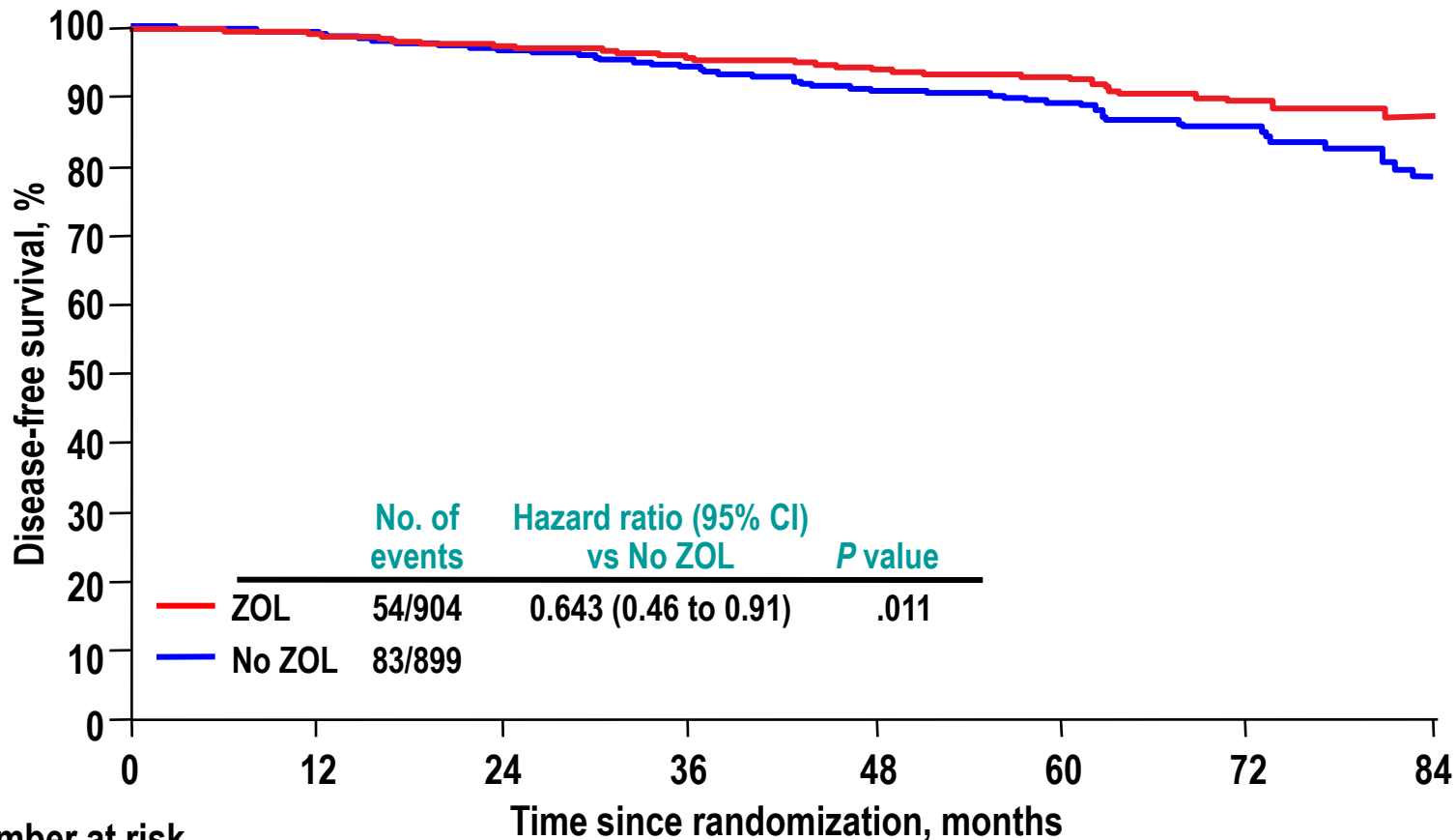
Etude ABCSG-12

- Phase III randomisé prospectif
- 1 803 patientes préménopausées
- cancer du sein hormonosensible (RE+ et/ou RP+)
- Stades I et II, <10 N+
- Pas de chimiothérapie excepté en néoadjuvant
- Durée du traitement : 3 ans
- Suivi médian : 4 ans



DFS Zol vs no Zol

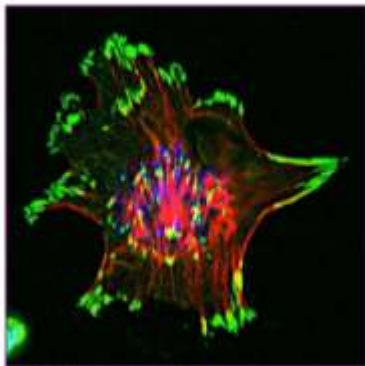
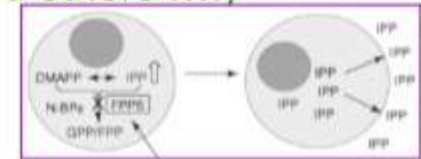
L'acide zolédronique diminue significativement de 36 % le risque de progression vs HT seule (p=0,01)



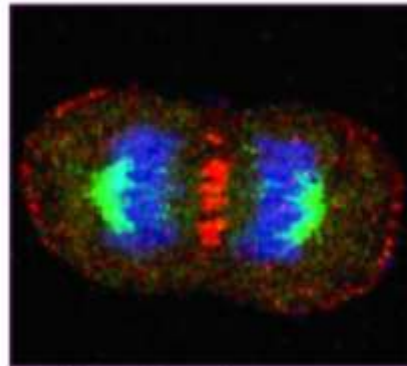
Number at risk		12	24	36	48	60	72	84
No ZOL	904	838	735	565	441	265	161	60
ZOL	899	851	744	573	434	270	131	59

Activité antitumorale propre *in vitro* de l'acide zolédronique

- Inhibition of cancer cell adhesion to extracellular matrix proteins (Pluijm *et al.*, J Clin Invest, 1996; Boissier *et al.*, Cancer Res, 1997; and others)
- Inhibition of cancer cell proliferation and induction of apoptosis (Shipman *et al.*, Br J Haematol, 1997; and others)
- Inhibition of cancer cell migration and invasion (Boissier *et al.*, Cancer Res, 2000; and others)
- Inhibition of angiogenesis (Fournier *et al.*, Cancer Res, 2002; Wood *et al.*, JPET, 2002; and others)
- Stimulation of the expansion of human $\gamma\delta$ T cells (Kunzmann *et al.*, Blood, 2000; and others)



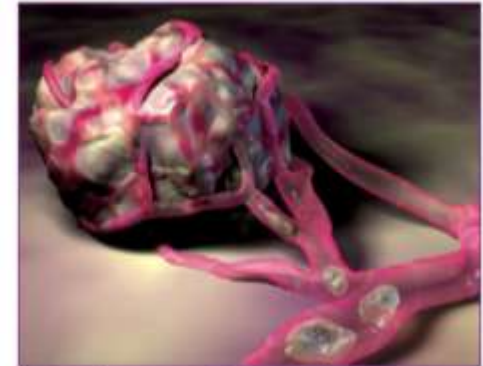
Cell adhesion



Cell proliferation



Apoptosis



Angiogenesis

Synergie avec CT (modèles murins)

- traitement séquentiel CT (doxo) puis d'acide zolédronique

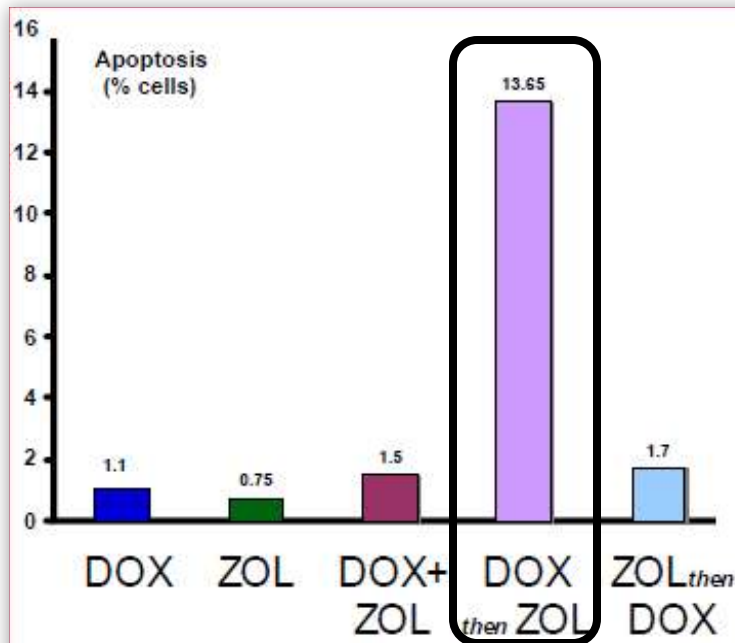


Figure 1: Synergistic enhancement of MCF-7 tumour cell apoptosis *in vitro* with sequential treatment with doxorubicin and zoledronic acid

Adapted and reproduced from Neville-Webbe et al. *Int J Cancer* 2005; 113:364-71 with permission of Wiley-Liss Inc., a subsidiary of John Wiley & Sons Inc. © Wiley-Liss Inc. 2004

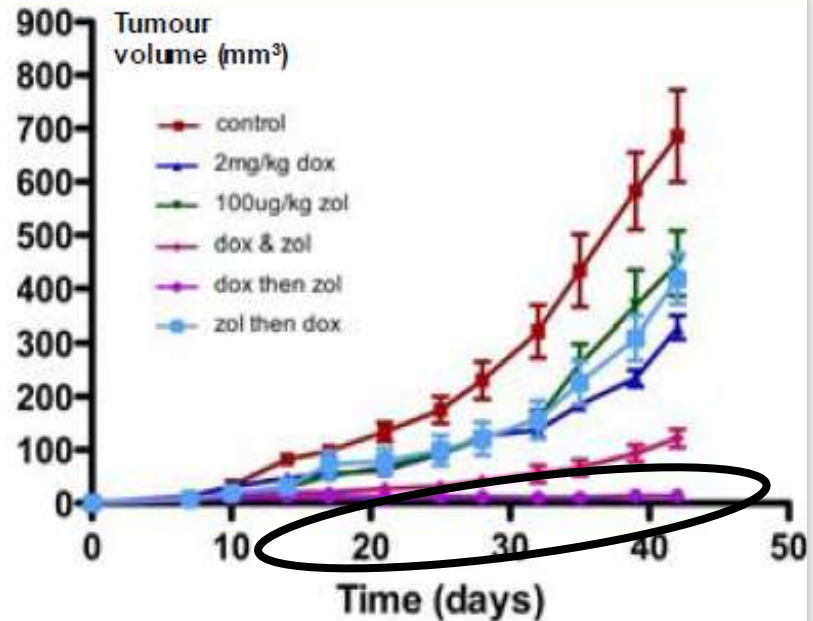


Figure 2: Effects of zoledronic acid and doxorubicin, administered alone, in combination, or in sequence, on subcutaneous MDA-G8 tumour growth

Adapted and reproduced from Ottewill et al. *J. Natl. Cancer Inst.* 2008 100(16):1167-1178 with permission of Oxford University Press © Oxford University Press 2008

ZOL réduit le taux de cellules tumorales osseuses

Rack et al.1 (N = 172)

■ ZOL q 4 wk vs
■ no ZOL for 6 mo

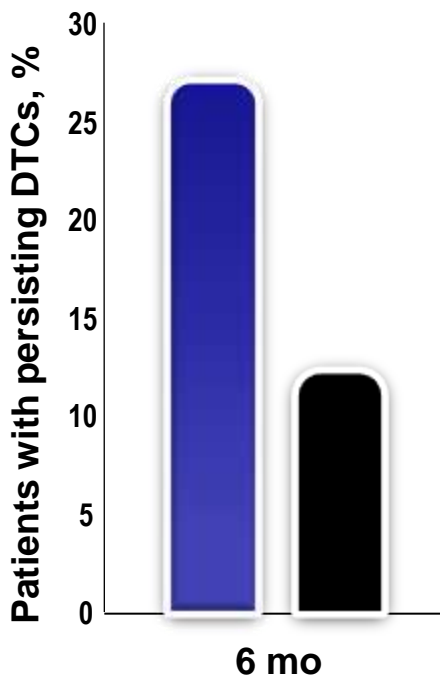
Aft et al.2 (N = 120)

■ ZOL q 3 wk vs
■ no ZOL

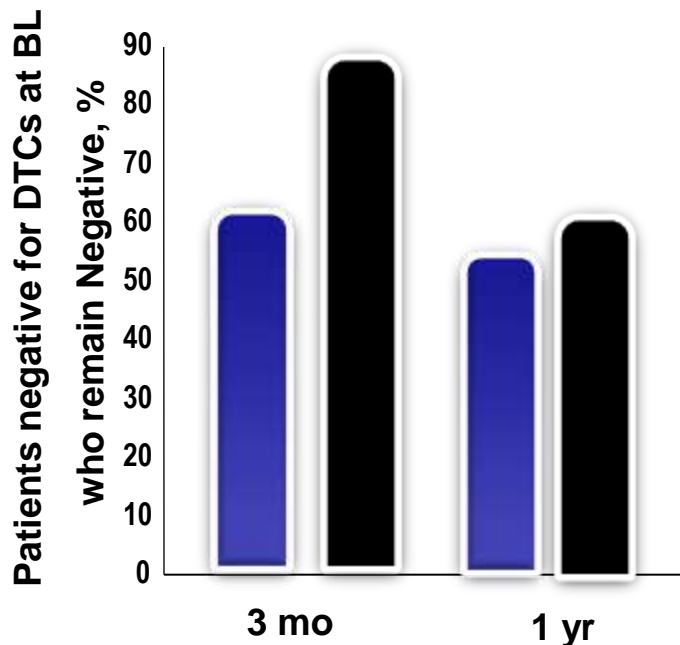
Lin et al.3 (N = 45)

■ ZOL q 4 wk (vs BL)

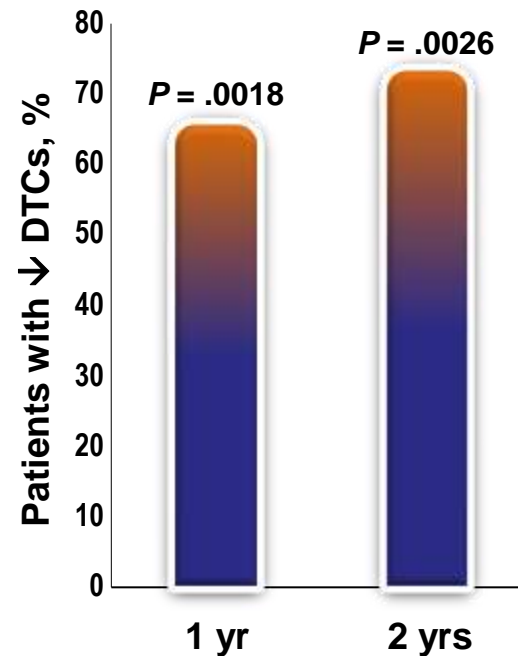
ZOL ↑ DTC CLEARANCE



ZOL KEEPS PATIENTS DTC-FREE



ZOL CONSISTENTLY ↓ DTCS OVER TIME

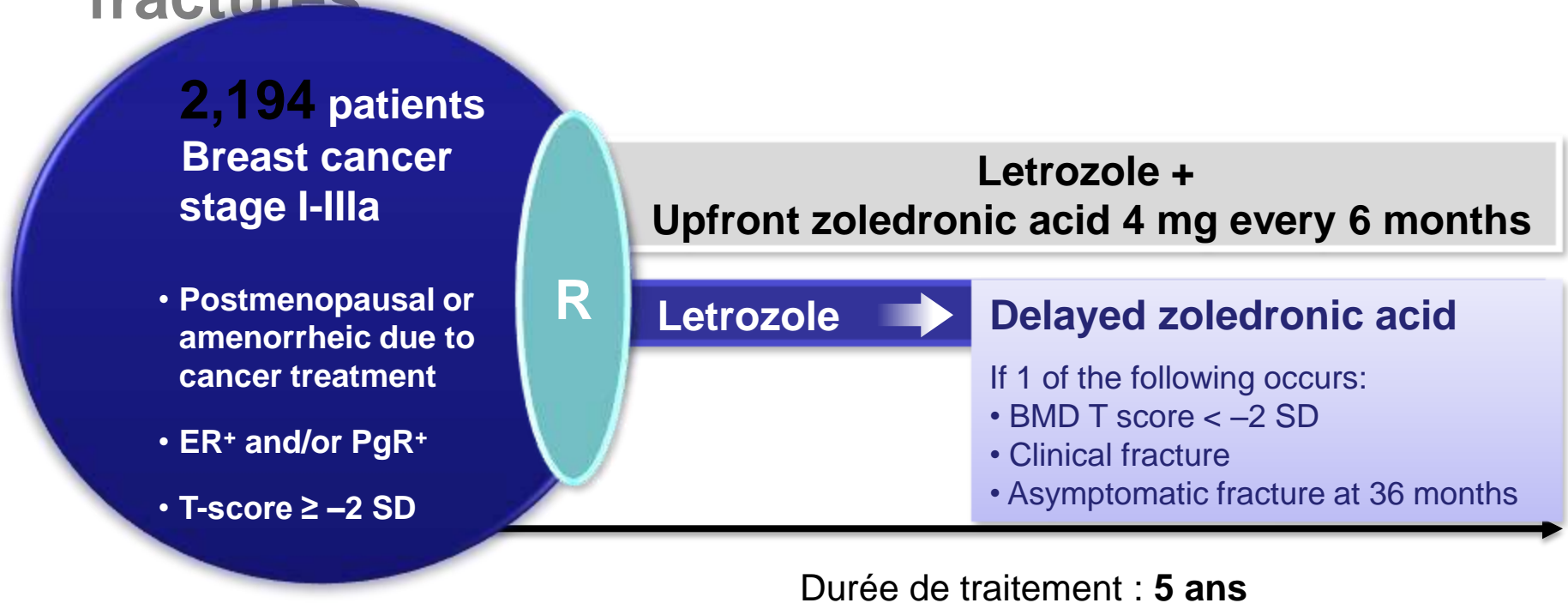


DTC = Disseminated tumor cells; BL = Baseline; ZOL = Zoledronic acid.

1. Rack BK, et al. *Dtsch Med Wochenschr* 2008;133:285-289;
2. Aft R, et al. Presented at: ASCO 2008. Abstract 1021;
3. Lin A, et al. Presented at: ESMO 2008. Abstract 559.

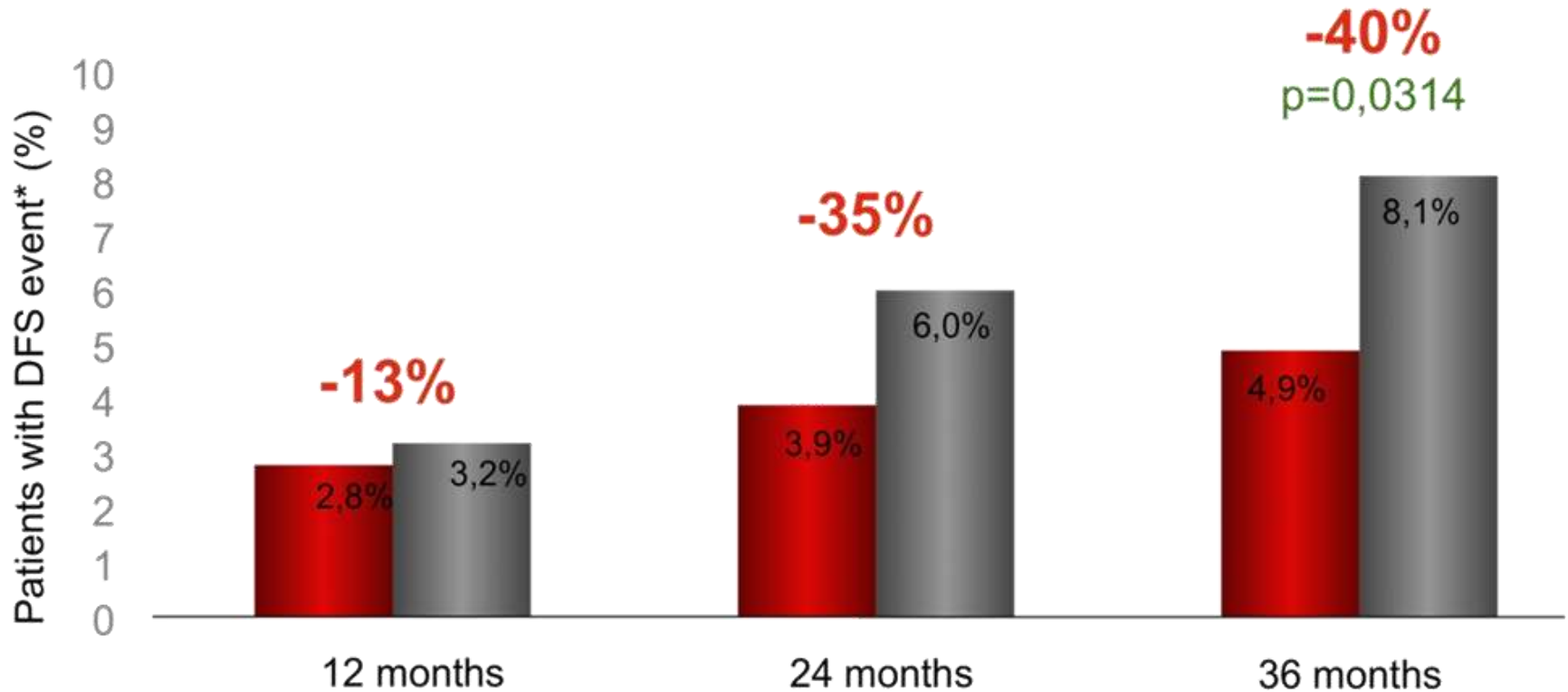
Z-FAST, ZO-FAST, E-ZO-FAST

- Critère **primaire** : DMO
- Critères **secondaires** : DFS, marqueurs osseux, fractures



BMD = Bone mineral density; CT = Chemotherapy; ER = Estrogen receptor; PgR = Progesterone receptor; SD = Standard deviation.

ZO-FAST: DFS

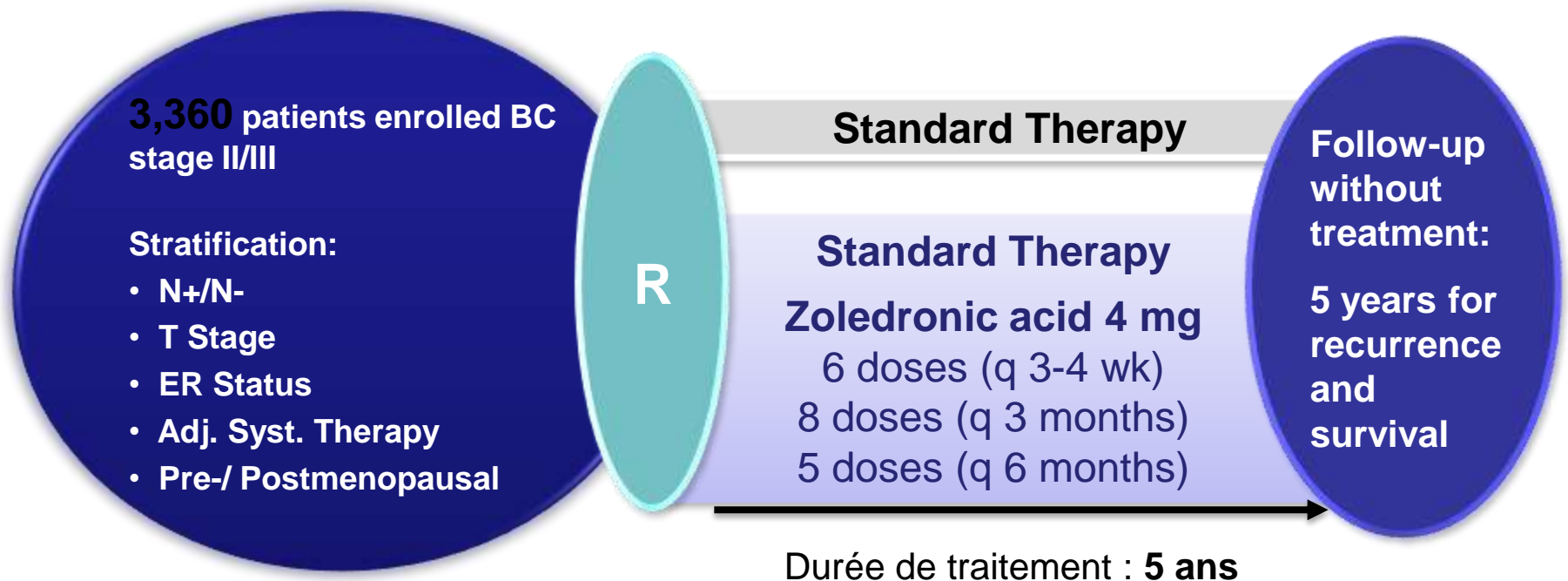


■ Upfront
 ■ Delayed

*DFS: Distant relapse, locoregional relapse, Death

AZURE : prévention des métastases osseuses dans le cancer du sein adjuvant

- Critère **primaire** : DFS
- Critères **secondaires** : Délai d'apparition métastases osseuses / métastases à distance, survie globale et sans récurrence



206 (6.1%) received neoadjuvant chemotherapy +/- ZOL

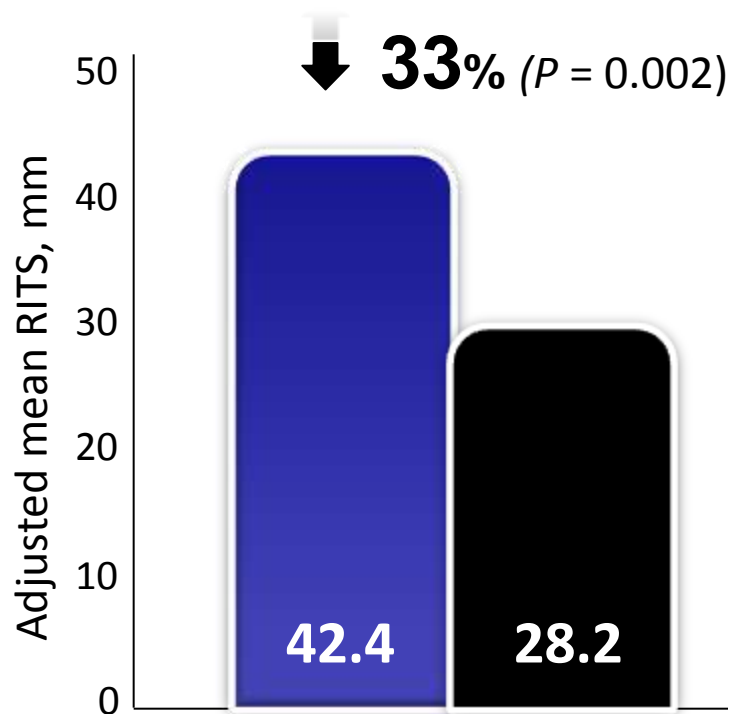
Well balanced for baseline characteristics

Tumour size, ER, HER2, menopausal status, chemotherapy type

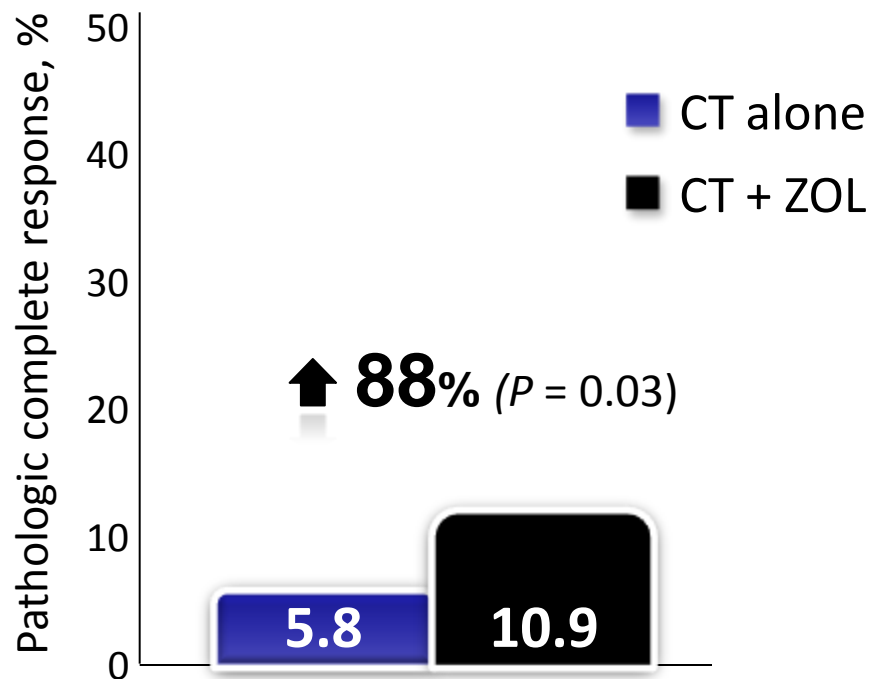
Residual invasive tumour size (RITS) and median number of residual nodes compared

AZURE: patientes CTnéo adjuvante

Taille de la tumeur résiduelle



Réponse pathologique complète



^a **Multivariate analysis (N=171 pts).**

CR=Complete response; CT = Chemotherapy;

IQR = Interquartile range; ZOL = Zoledronic acid.

Winter MC, et al. SABCS, 2008 (Abst #5101)



Zoledronate et myélome

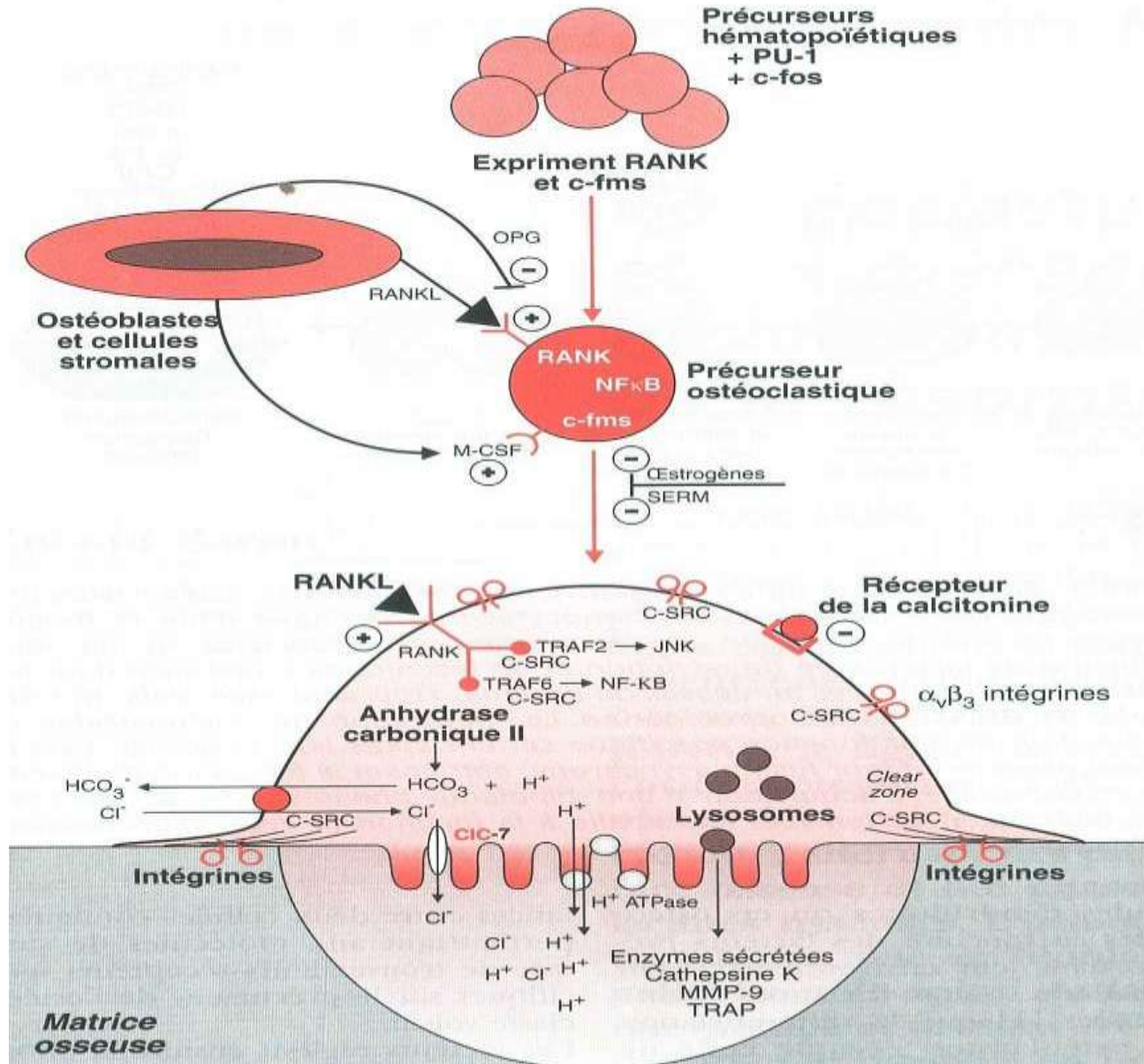
- **Evaluating the effects of zoledronic acid (ZOL) on overall survival (OS) in patients(Pts) with multiple myeloma (MM): Results of the Medical Research Council (MRC) Myeloma IX study. (Morgan et al, Abstract 8021)**



Zoledronate et myélome

- Newly diagnosed MM pts were randomised to ZOL (4 mg q 21-28 days) or CLO (1,600 mg q day) plus antimyeloma therapy. Treatment continued at least until disease progression.
- 1,970 pts randomised, 1,960 were evaluable,
- ZOL reduced the proportion of pts with an SRE vs CLO (27.0% vs 35.3%, respectively; P 0.0004).
- ZOL-treated pts showed 5.5 months' prolonged OS (50 vs 44.5 months, respectively; P 0.0118)
- Both BPs were generally well-tolerated, and deterioration in renal function was similar between treatment groups. The incidence of confirmed osteonecrosis of the jaw was also low (ZOL, 3.5%; CLO, 0.3%).

fonction ostéoclastes



Study Design: International, Randomized, Double-Blind, Active-Controlled Study

Key Inclusion

- Hormone-refractory (castration resistant) prostate cancer and bone metastases

Key Exclusion

- Current or prior IV bisphosphonate treatment

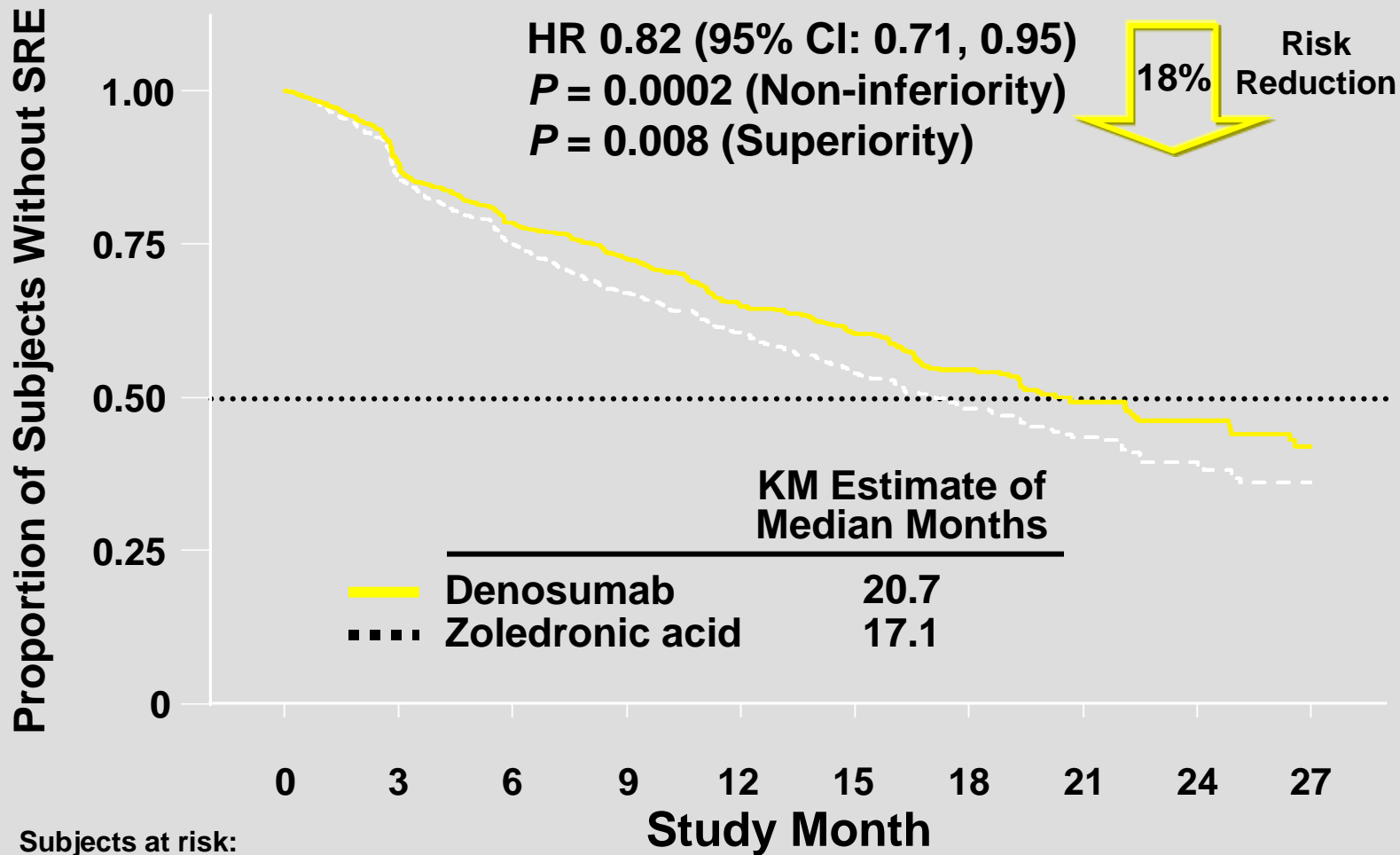
Denosumab 120 mg SC and Placebo IV* every 4 weeks (N = 950)

Zoledronic acid 4 mg IV* and Placebo SC every 4 weeks (N = 951)

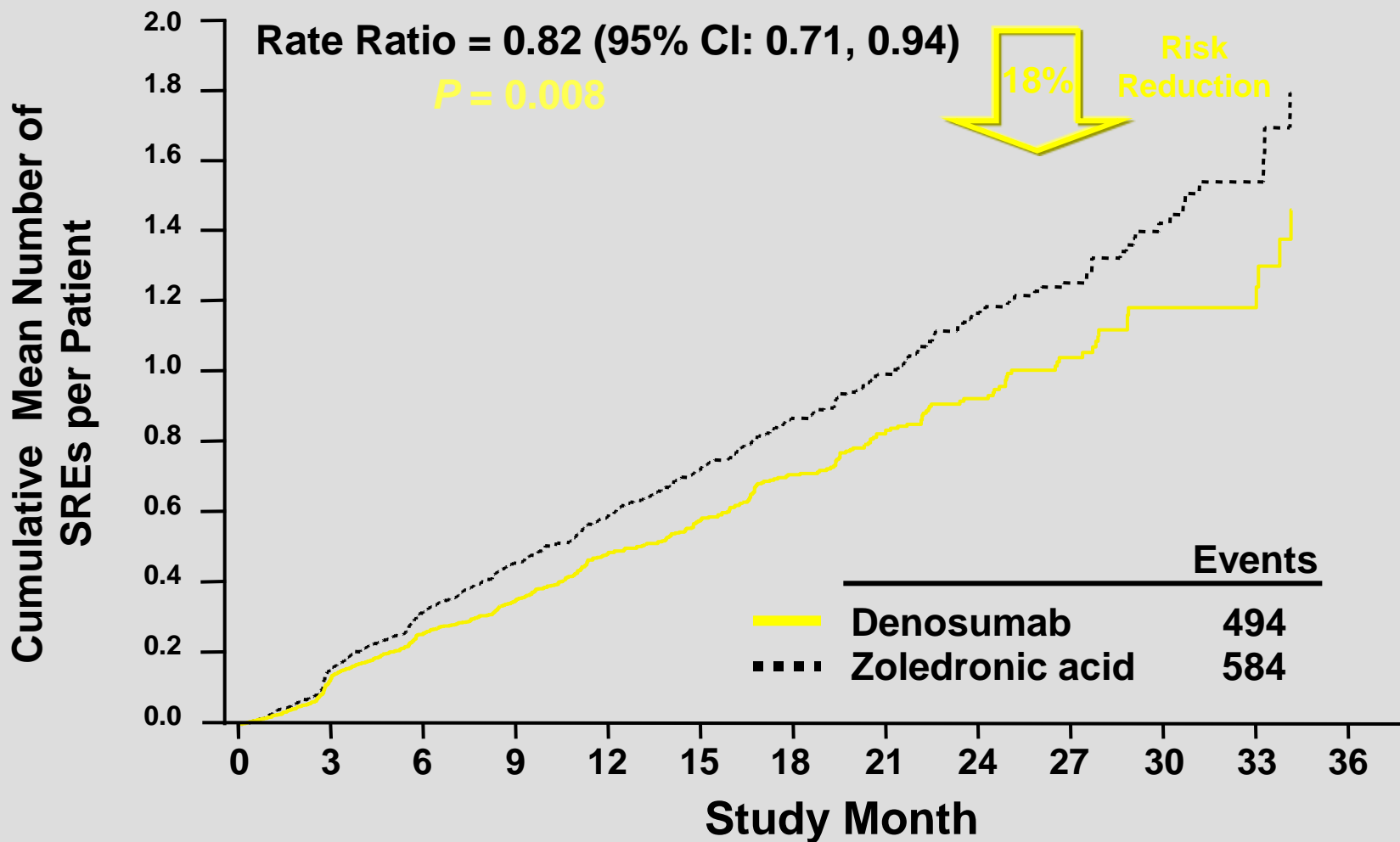
- Calcium and Vitamin D supplemented in both treatment groups
- Accrual period from May 2006 to December 2008

*IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine (per Zometa[®] label)

Time to First On-Study SRE



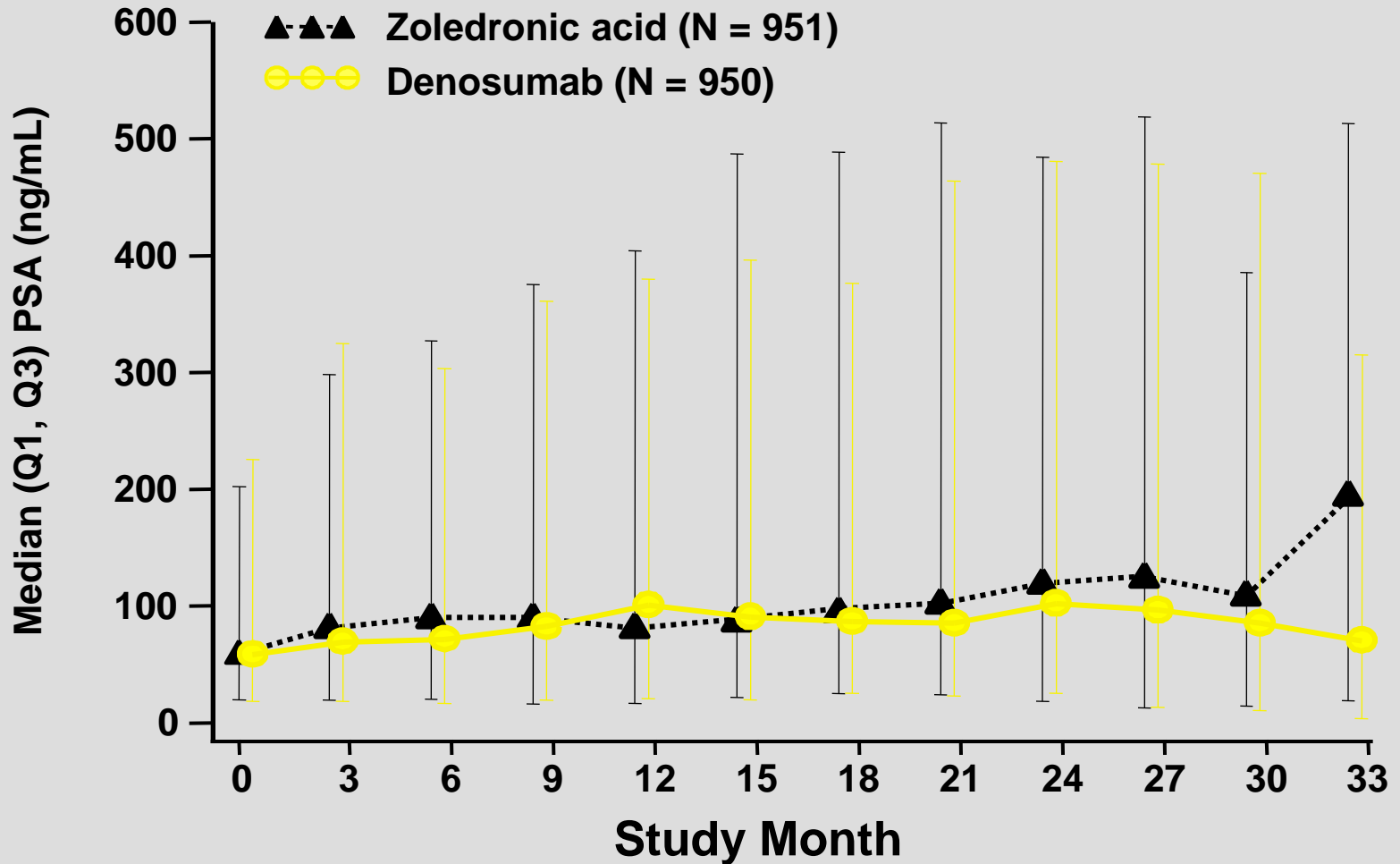
Time to First and Subsequent On-Study SRE* (Multiple Event Analysis)



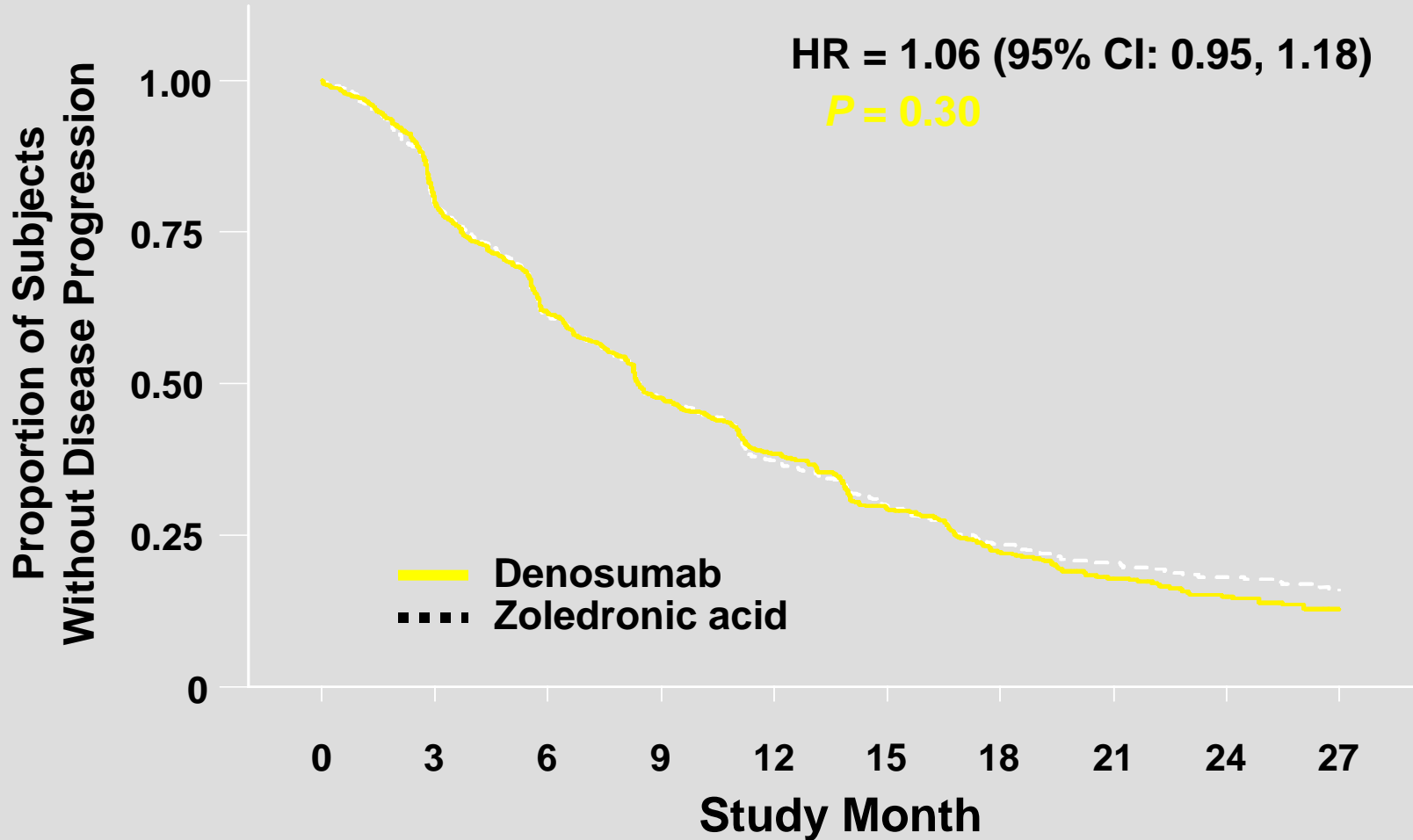
*Events occurring at least 21 days apart

K. Fizazi, ASCO 2010

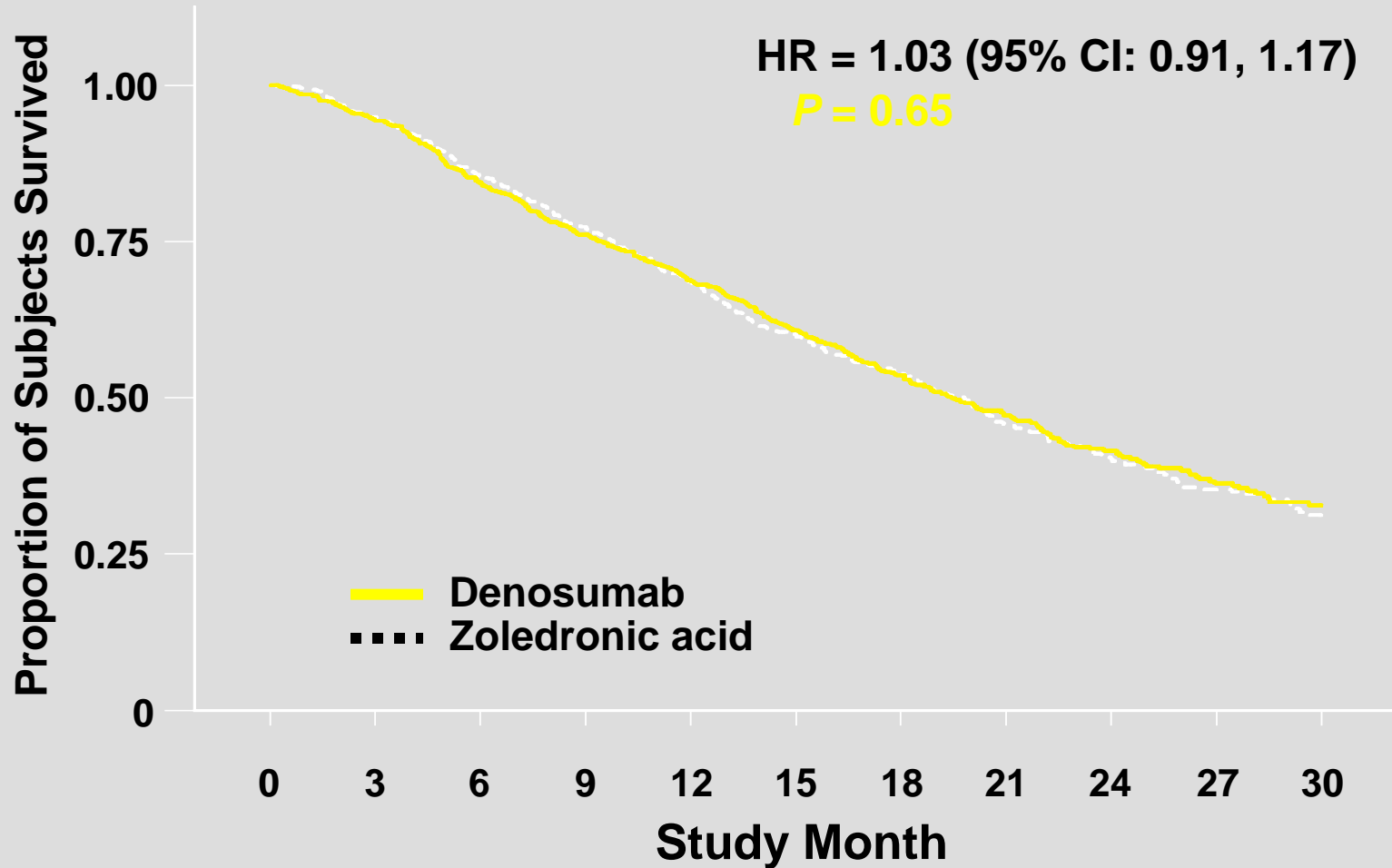
Prostate-Specific Antigen



Progression-free survival



Overall Survival



Adverse Events of Interest

Subject incidence, n (%)	Zoledronic Acid (N = 945)	Denosumab (N = 943)
Infectious AEs	375 (39.7)	402 (42.6)
Infectious serious AEs	108 (11.4)	130 (13.8)
Acute phase reactions (first 3 days)	168 (17.8)	79 (8.4)
Renal AEs*	153 (16.2)	139 (14.7)
Cumulative rate of Osteonecrosis of the Jaw (ONJ)†		
Year 1	12 (1.3)	22 (2.3)
Year 2	5 (0.5)	10 (1.1)
Year 2	8 (0.8)	22 (2.3)
Hypocalcemia	55 (5.8)	121 (12.8)
New primary malignancy	10 (1.1)	18 (1.9)

* Includes blood creatinine increased, hypercreatininemia, oliguria, renal impairment, proteinuria, renal failure, urine output decreased, creatinine renal clearance decreased, renal failure acute, renal function test abnormal, anuria, blood urea increased, renal failure chronic.

†*P* = 0.09

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Conclusion

- Zoledronate
- Denosumab
- Prévention des complications osseuses
- Prévention ostéoporose
- Effet anti-tumoral ?
- **Ratio bénéfique /tolérance / coût**