INCONTRI SARDO EUROPEI DI TERAPIA DEL DOLORE E CURE PALLIATIVE
Budoni, 3-5 ottobre 2008

I BISFOSFONATI NEL TRATTAMENTO E NELLA PREVENZIONE DELLE METASTASI OSSEE

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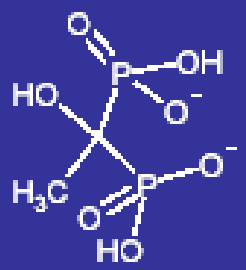
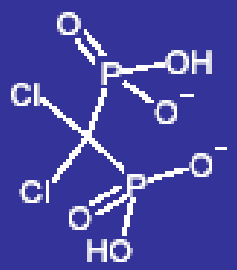
Chemical Structure of Bisphosphonates

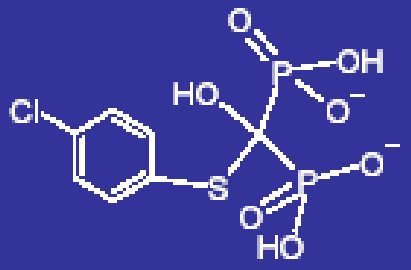
Etidronate (×1)



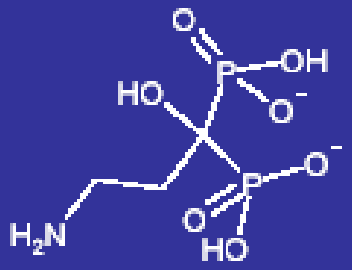
Clodronate (×10)



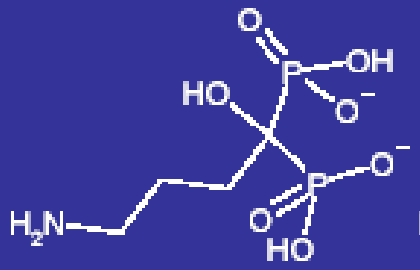
Tiludronate (×10)



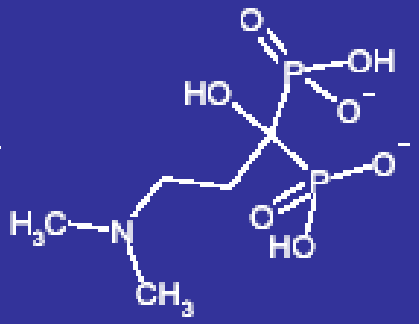
Pamidronate (×100)



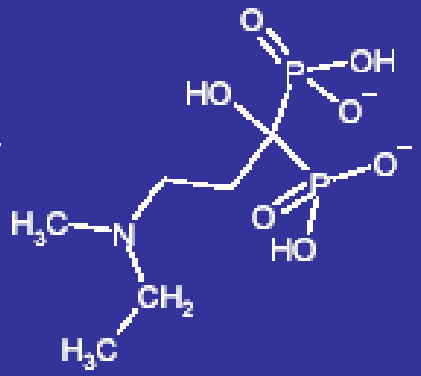
Alendronate (×1,000)



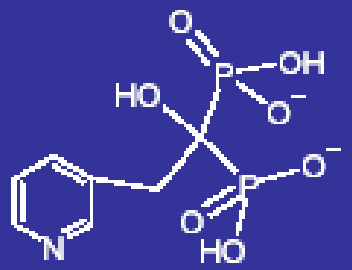
Olpadronate (×1,000)



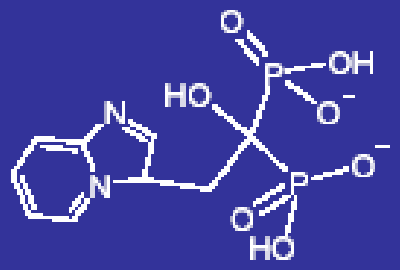
Ibandronate (×5,000)



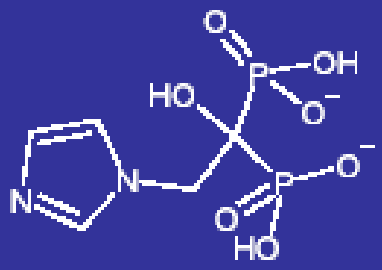
Minodronate (×5,000)



Risedronate (×5,000)



Zoledronate (×10,000)



Molecular Mechanisms of Action *(2)*

HMG-CoA

↓

Mevalonate

↓

Geranyl diphosphate

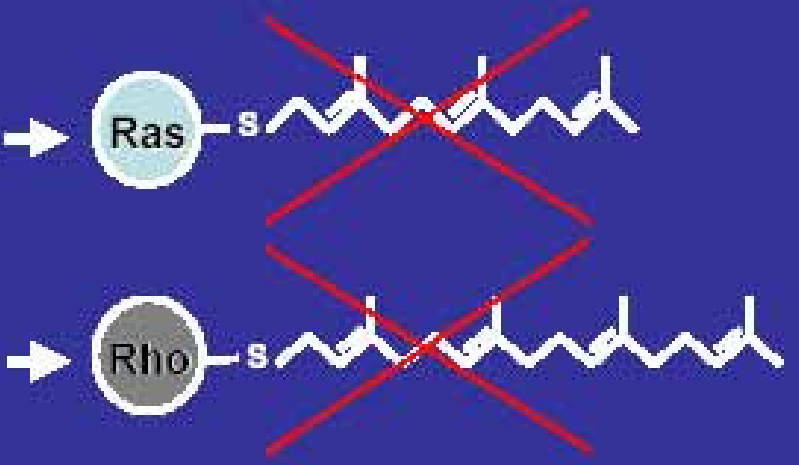
↓ FPP synthase

Farnesyl diphosphate (FPP)

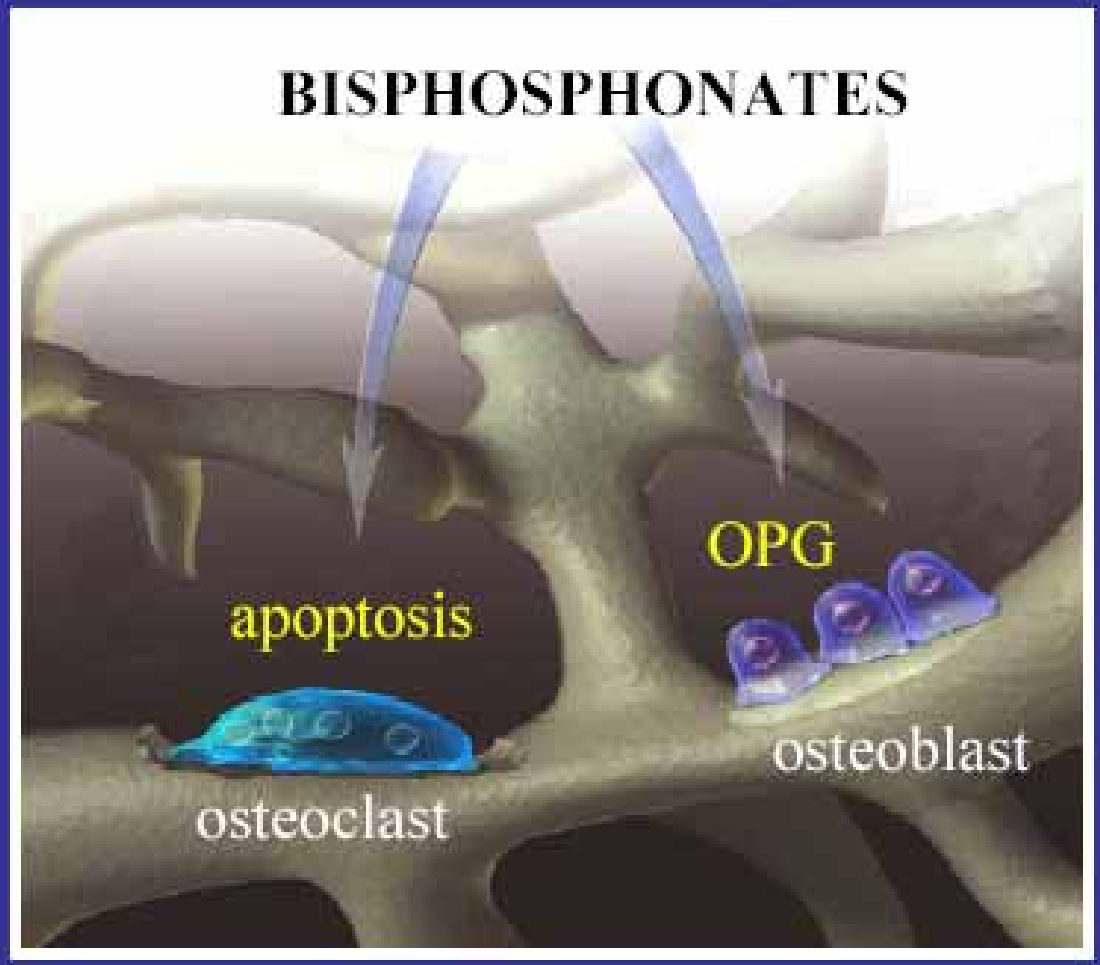
↓

Geranylgeranyl diphosphate (GGPP)

NBPs inhibits FPP synthase, thus blocking the prenylation of small signaling proteins required for cell function and survival



Mechanisms of Action of Bisphosphonates on Bone Cellular Elements



BISPHOSPHONATES MECHANISMS OF ACTION

- Inhibition of osteoclast maturation
- Inhibition of osteoclast recruitment to the site of bone resorption
- Suppression of mature osteoclast function
- Reduced production of cytokines (eg, IL-6)
- Direct antitumor activity (cytostatic and cytolytic)
- Inhibition of tumor-cell dissemination, invasion, and adhesion to the bone matrix
- Antiangiogenic effects

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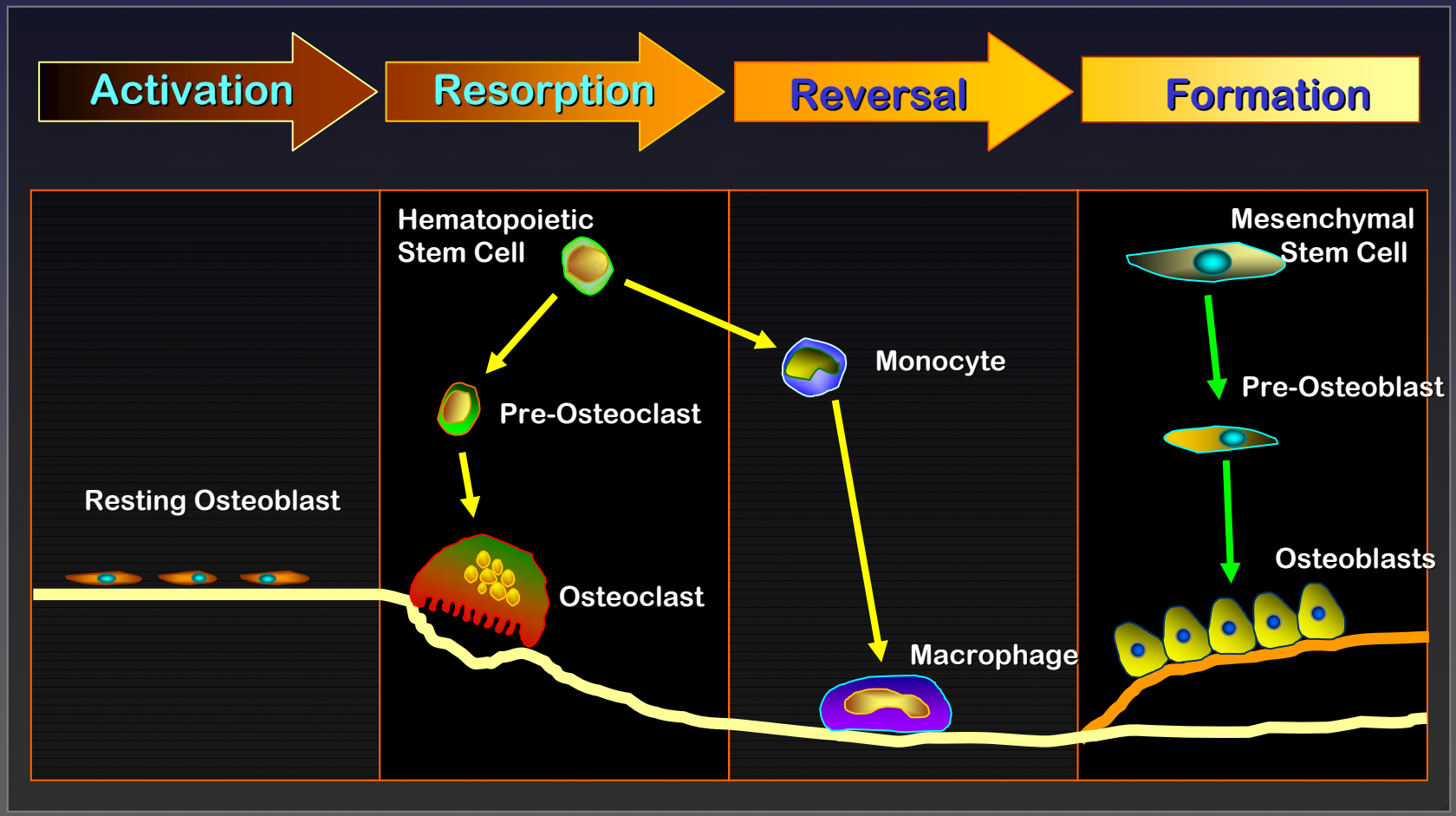
Bone Remodeling



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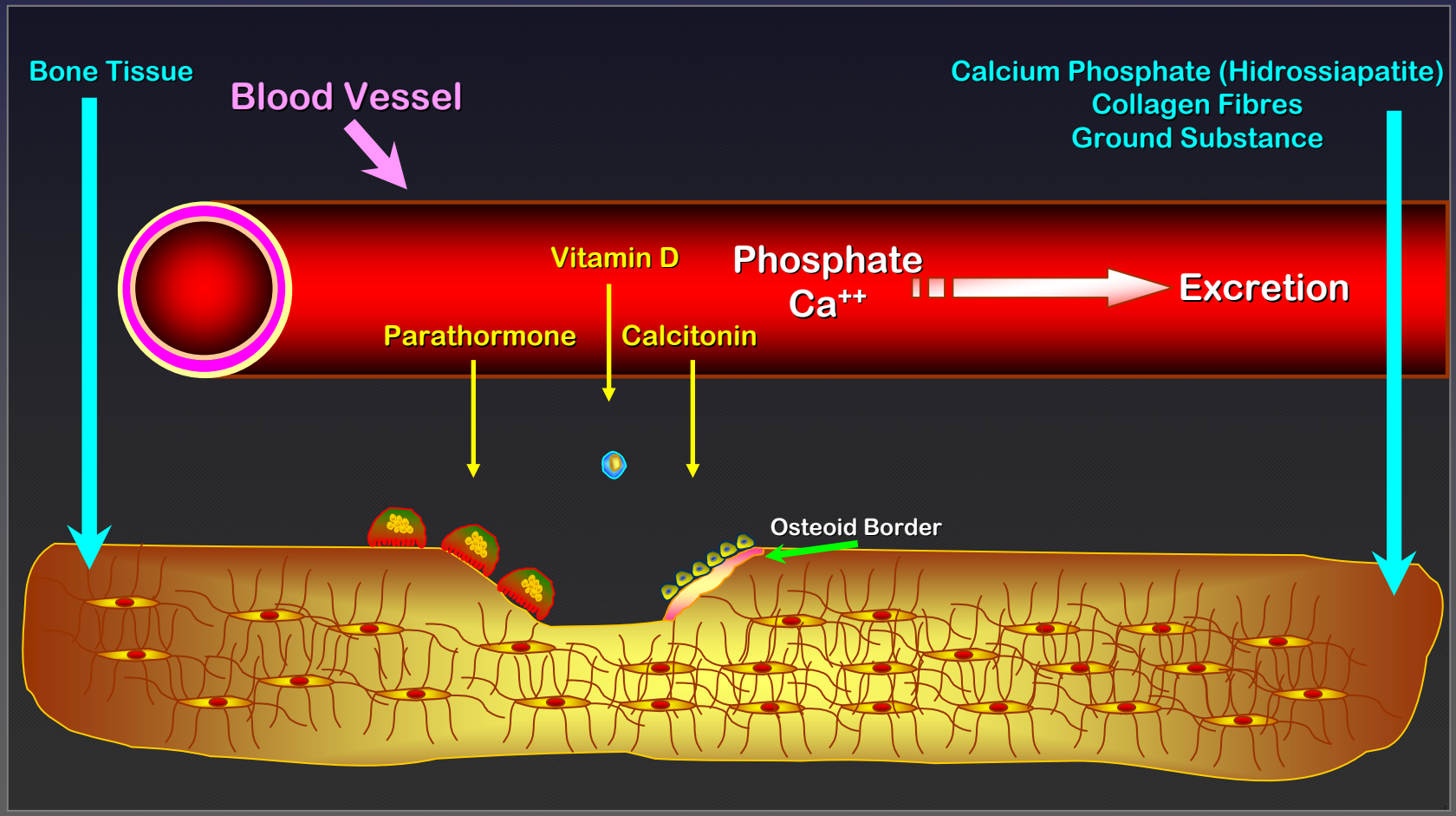
Hormonal Regulation of Bone Remodeling



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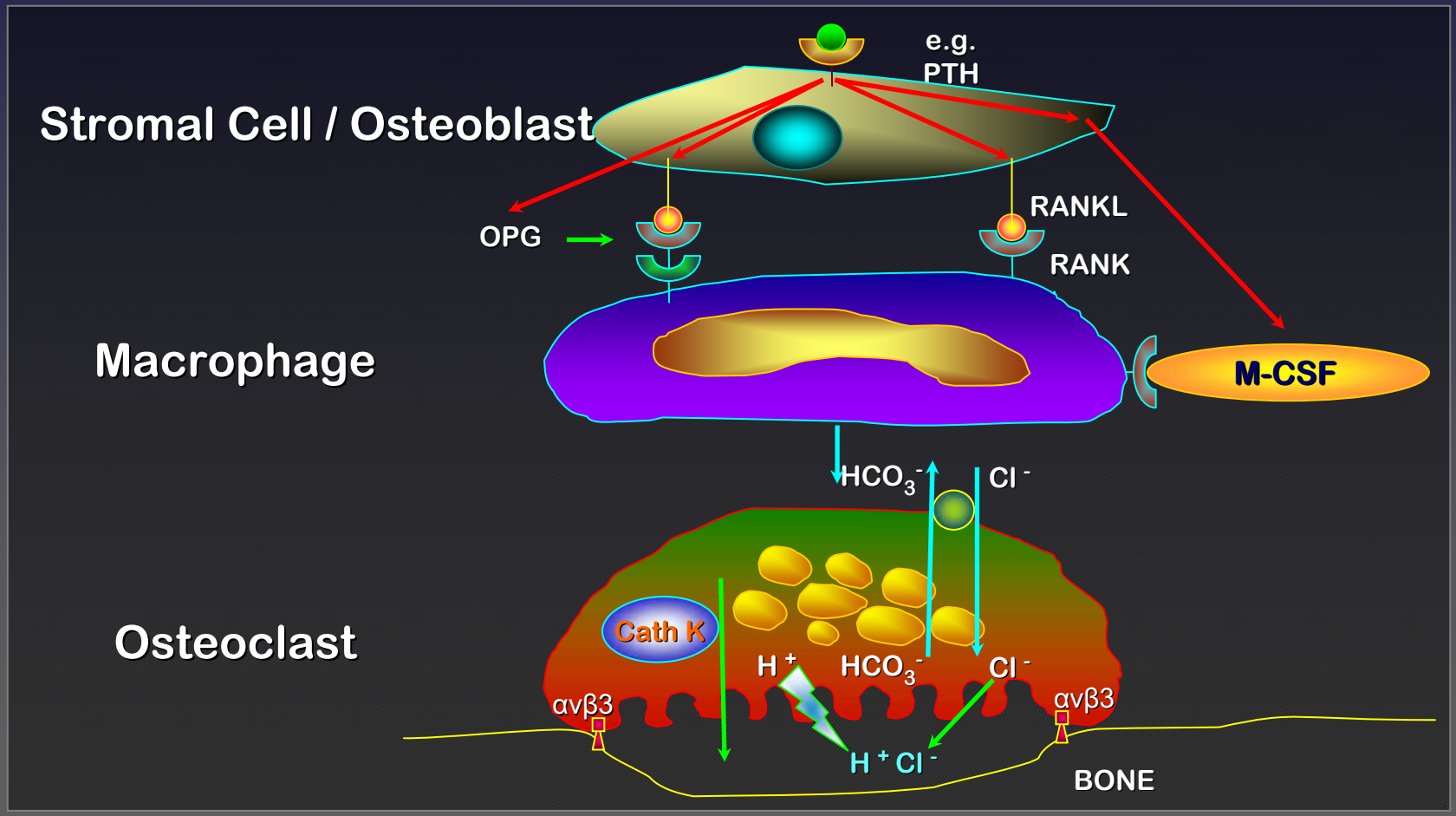
Osteoclastic Bone Resorption

- The three essential regulatory components of osteoclast action are:
  - *OSTEOPROTEGERIN* (OPG)
  - NF-KB LIGAND (RANKL)
  - RECEPTOR ACTIVATOR OF NF-KB (RANK)

Mechanisms of Osteoclastogenesis and Osteoclastic Bone Resorption



The RANKL/OPG System Plays a Key Role in Normal Bone Remodeling

- RANK and OPG are produced by bone marrow – derived stromal cells and osteoblasts
- RANKL expands the pool of active osteoclasts and increases bone resorption
- OPG reduces the active osteoclasts population and decreases bone resorption

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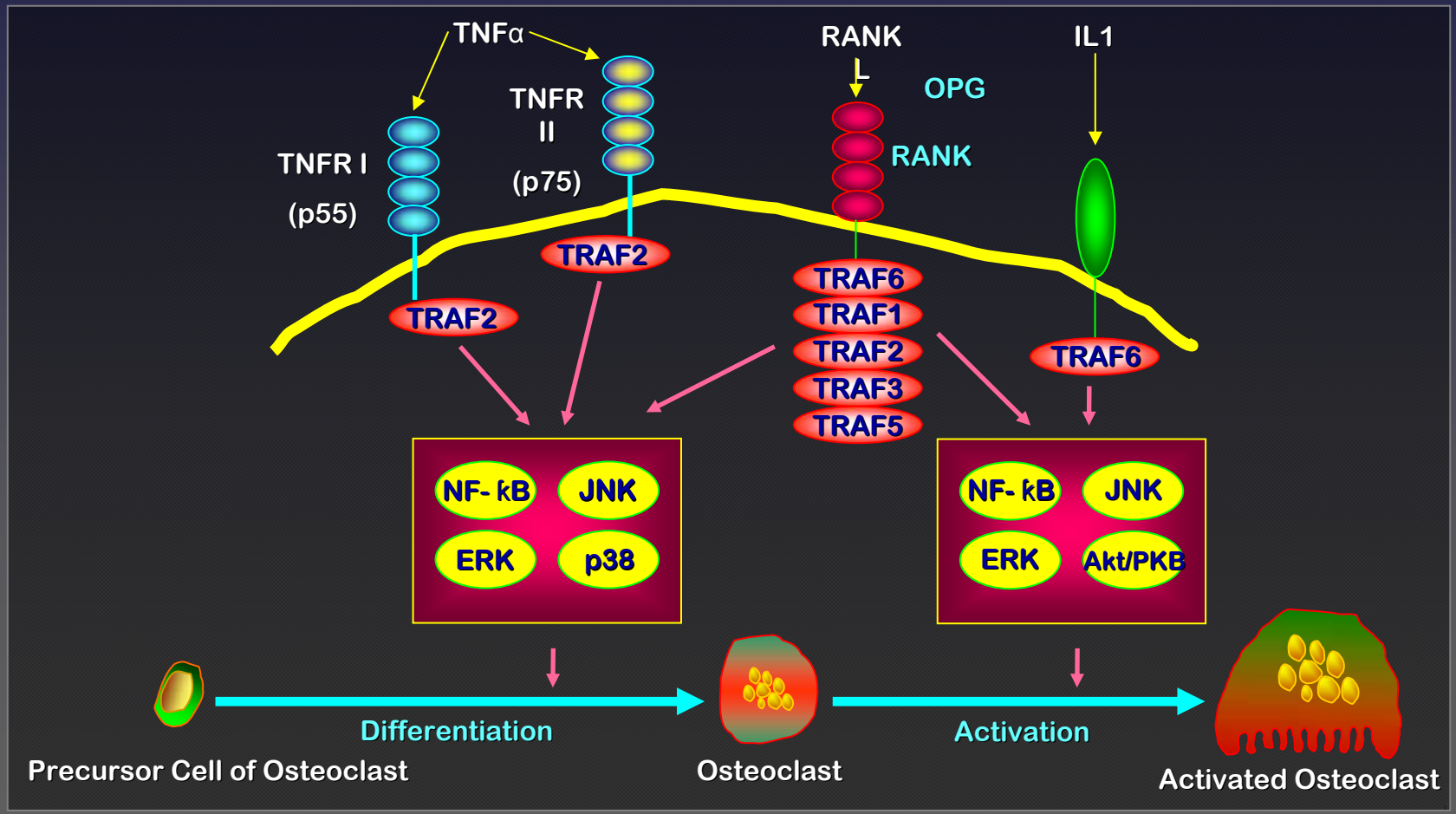
OPG / RANK-L
TNFα / IL1



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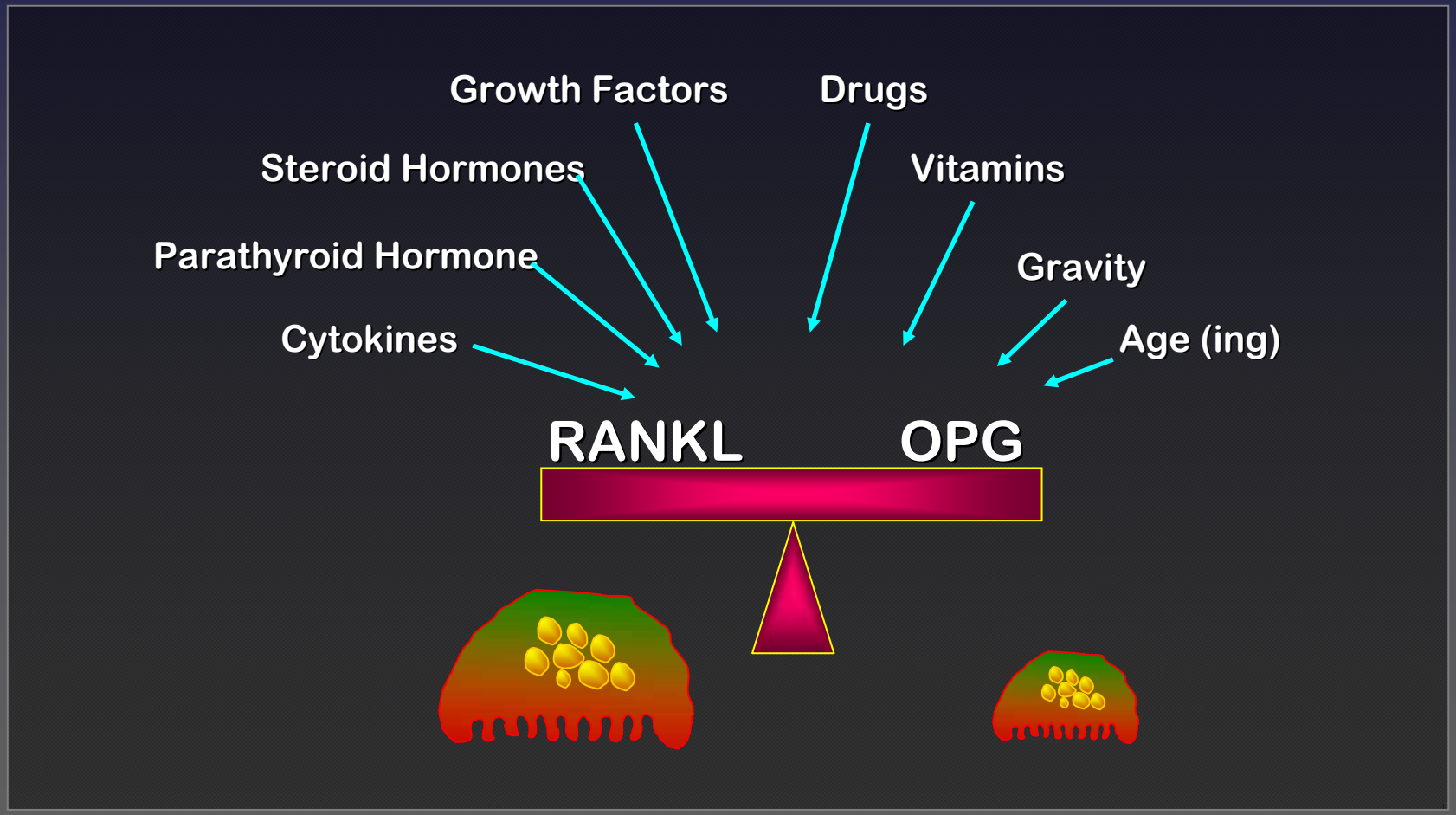
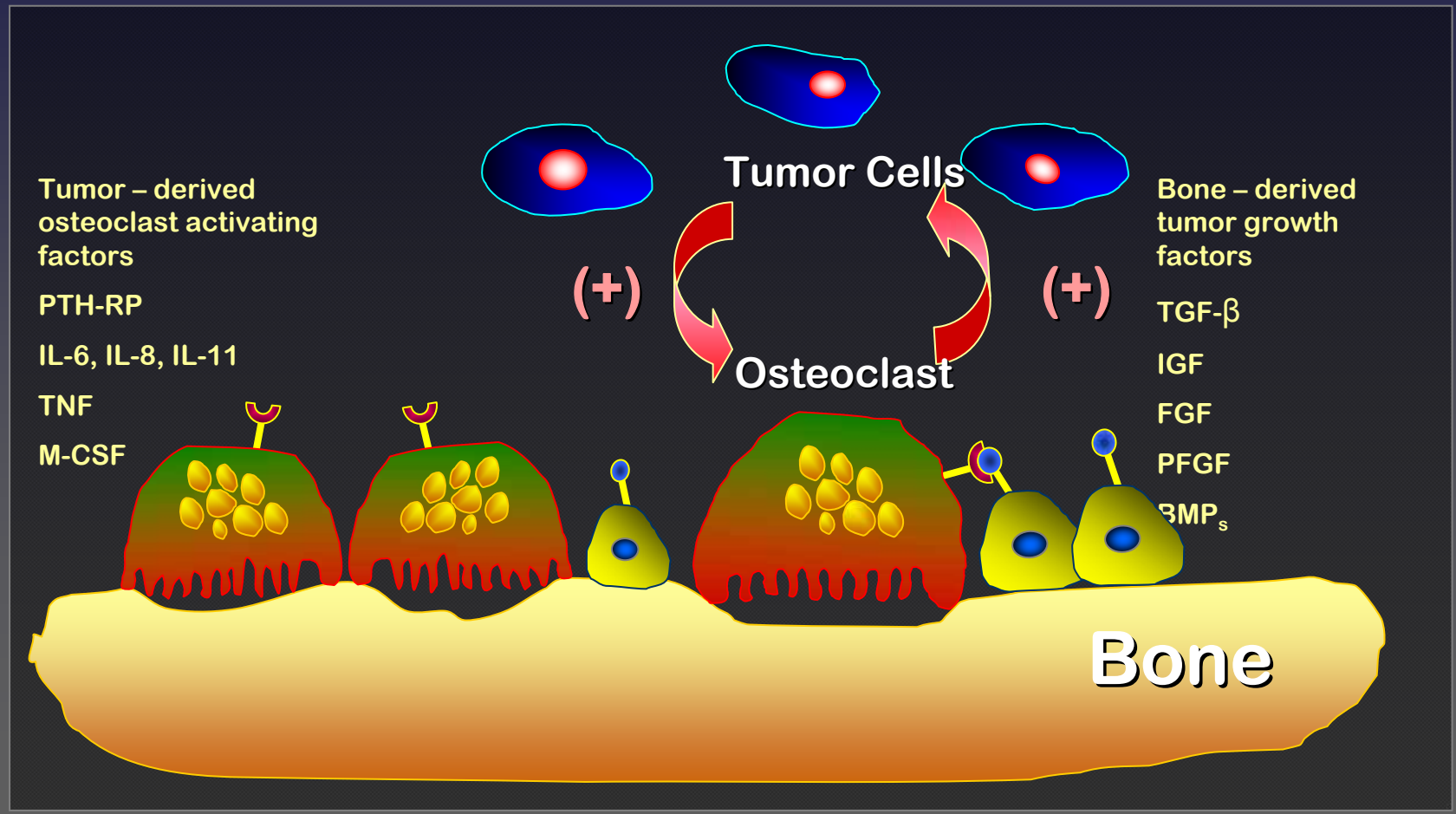
OPG / RANK-L System



Frequent Causes of Disruption of the OPG/RANKL

- ESTROGEN DEFICIENCY
- GLUCOCORTICOID EXPOSURE
- T-CELL ACTIVATION (Rheumatoid Arthritis)
- BONE METASTASES

Pathogenesis of Predominantly Osteoclastic Metastases



Adapted from Lipton A, Clin Cancer Res, 2006

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PTH-rP: a Local and Systemic Factor

- PTH-rP binds the same receptors and has biologic effects on bone similar to those of parathyroid hormone.
- Most studies suggest that PTH-rP is the major mediator of osteolytic bone destruction by solid tumors.

Francini G. J Cancer Res Clin Oncol, 1993
Francini G. Clin Exp Metastasis,1993

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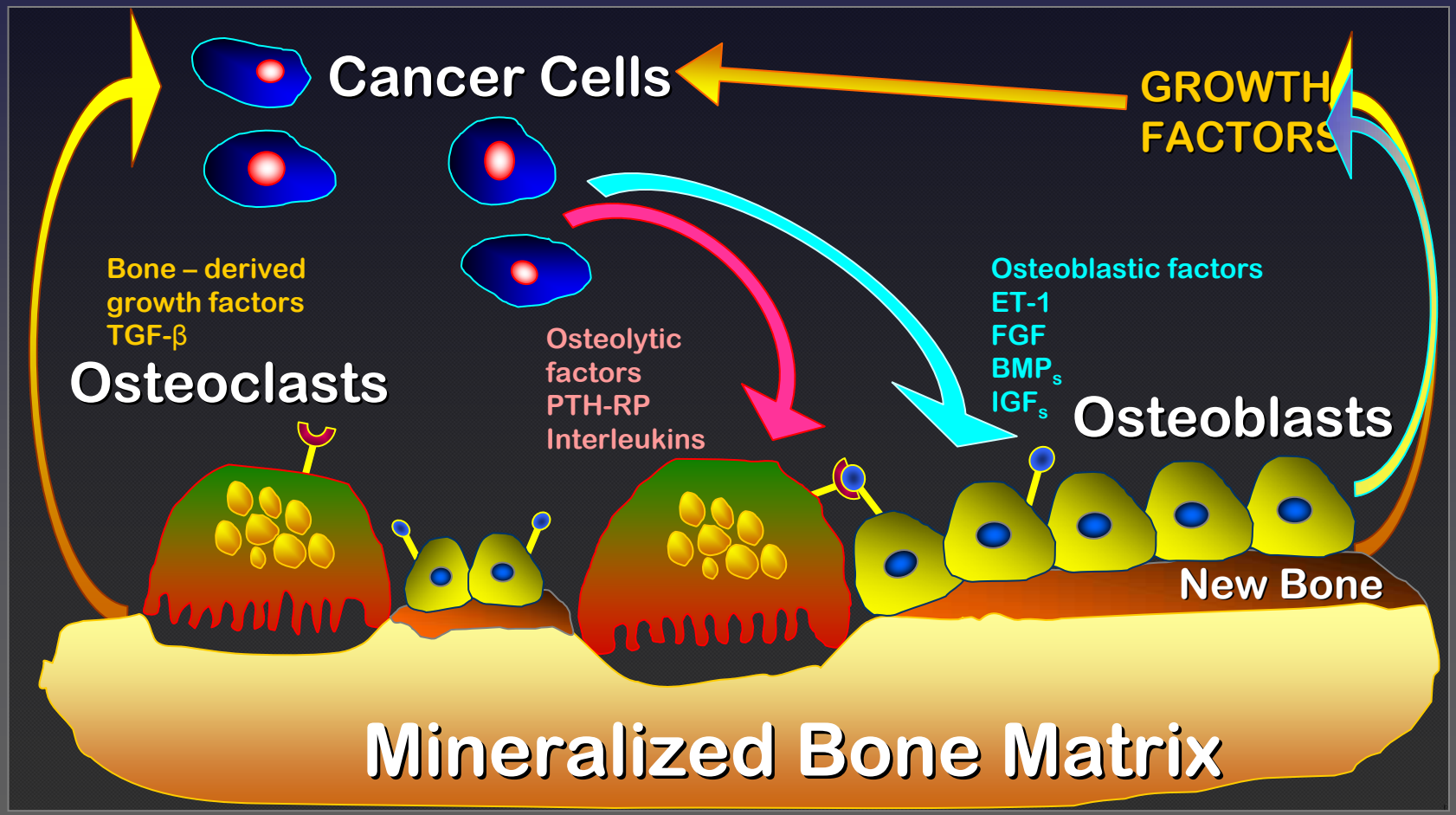
Pathogenesis of Predominantly Osteoblastic Metastases



Adapted from Lipton A, Clin Cancer Res, 2006

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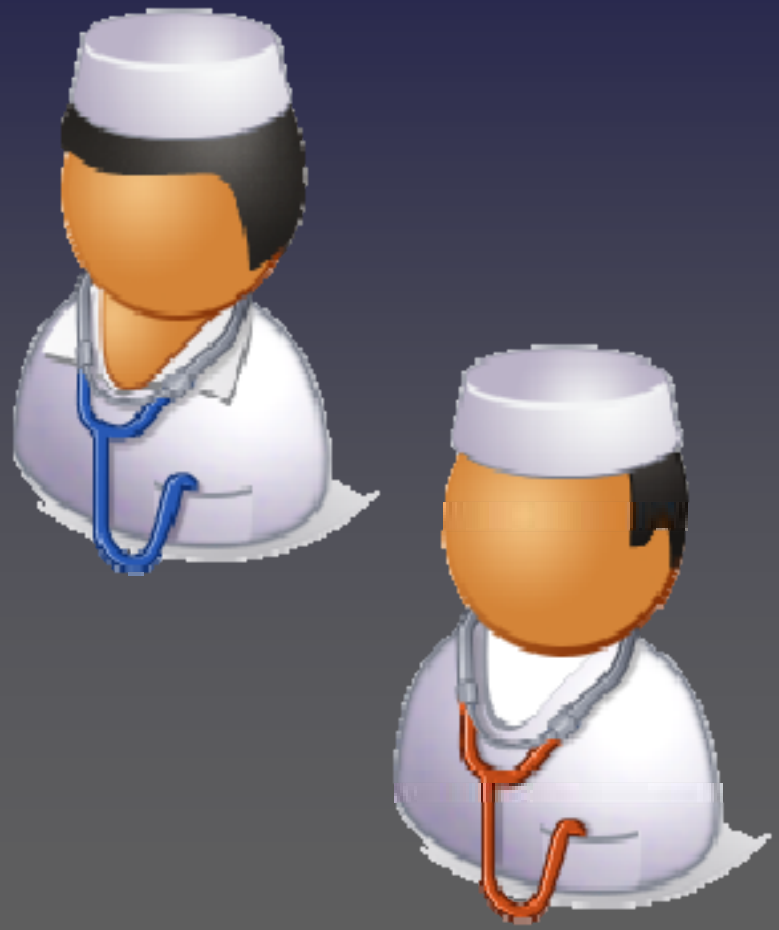
Conventional Management of Bone Metastases

- Chemotherapy
- Hormone Therapy
- Radiotherapy
- Surgery
  - Analgesics
  - Bisphosphonates

BISPHOSPHONATES

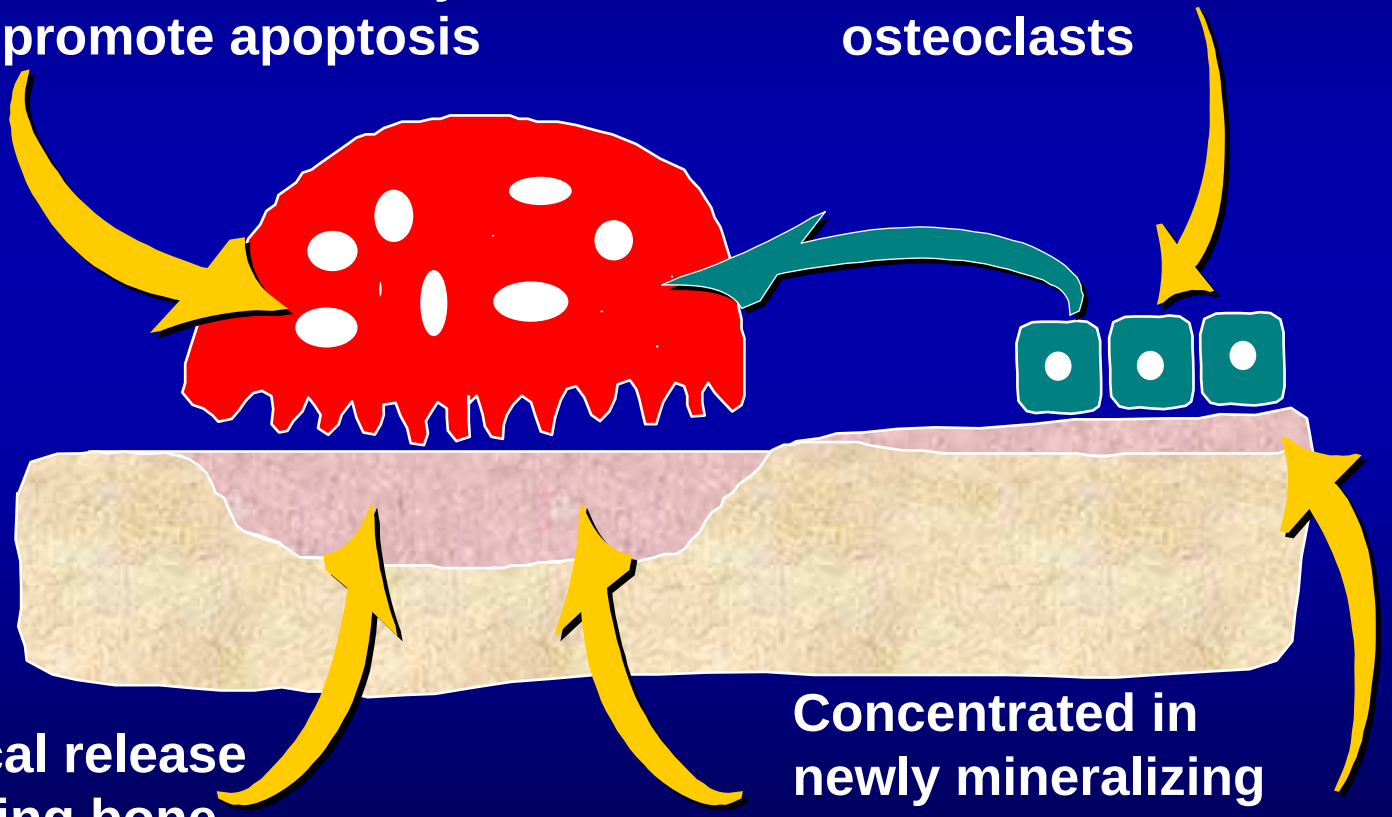
- Etidronate
- Clodronate
- Alendronate
- Pamidronate
- Ibandronate
- Risedronate
- Zoledronate



Mechanisms of Action of Bisphosphonates

Inhibit osteoclast formation and migration, and osteolytic activity; promote apoptosis

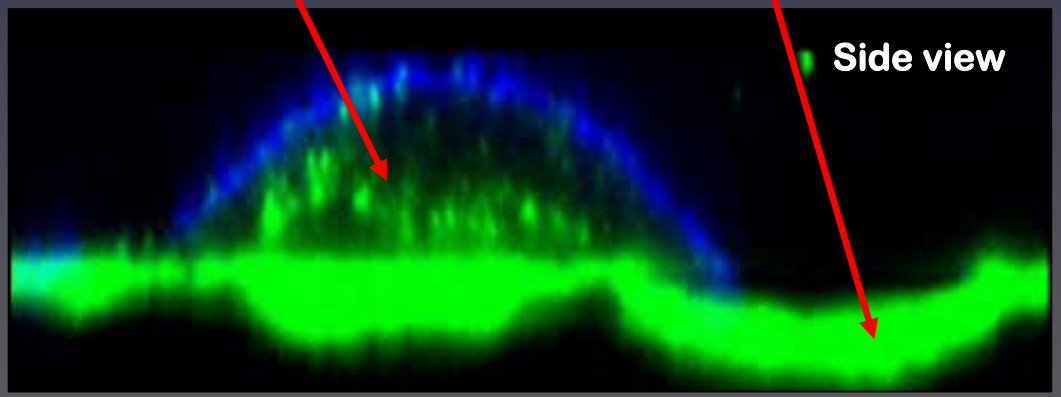
Modulate signaling from osteoblasts to osteoclasts



Local release during bone resorption

Concentrated in newly mineralizing bone and under osteoclasts

Bisphosphonates Are Internalised by Osteoclasts During Bone Resorption



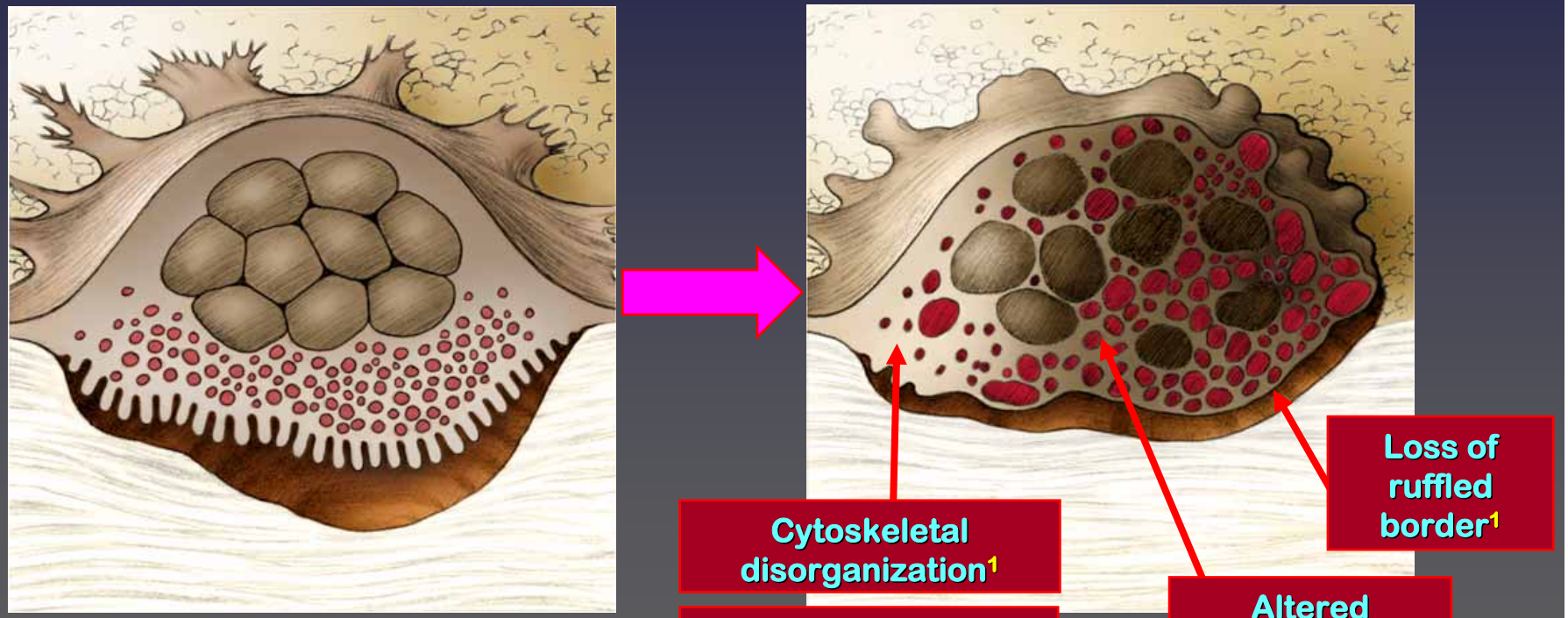
- Bisphosphonate (bone surface)
- Osteoclast membrane and nuclei
- Cytoskeleton

Courtesy of Dr Fraser Coxon, University of Aberdeen

Effects of Bisphosphonates on Osteoclast Function

Normal Osteoclast

Osteoclast Following Uptake of Bisphosphonate



1. Sato, M, et al. *J Clin Invest.* 1991;88:2095-2105. 2.
2. Hughes DE, et al. *J Bone Miner Res.* 1995;10:1478-1487.
3. Rogers M. *Curr Pharm Des.* 2003;9:2643-2658.

Effects of Bisphosphonates

" *Effects of disodium etidronate (EHDP) on the renal handling of electrolytes in man...*"
Francini G, Proc.1st. Int. Symp. Diphosph. Ther., Rome 1979

Our experience suggests that bisphosphonates are useful in reducing bone pain and the incidence of skeletal complications when they are administered in conjunction with standard anticancer therapy.

Francini G, J Clin Oncol, 1992
Conte P.F., Francini G et al, J Clin Oncol, 1996

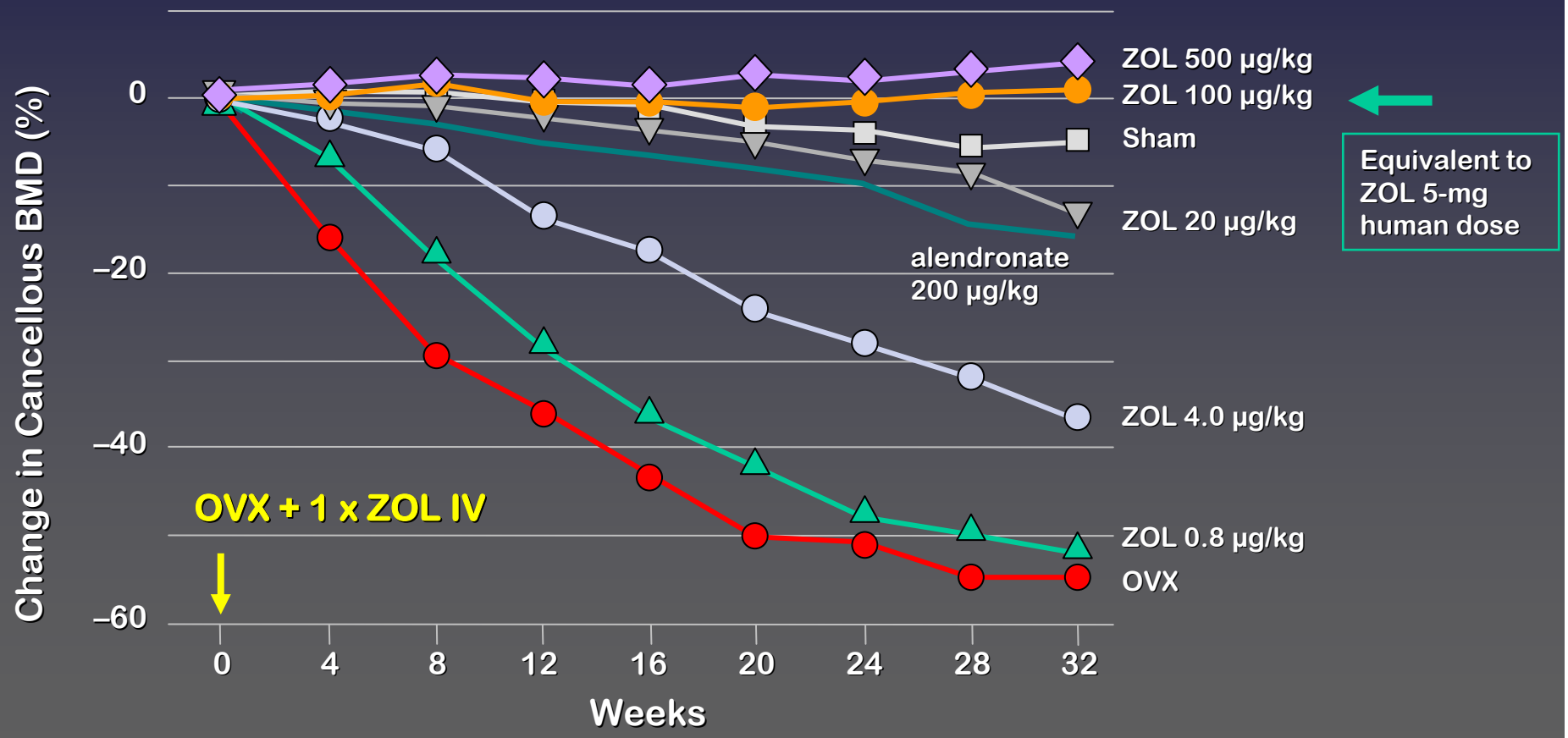
Guidelines for Patients Treated with Bisphosphonates

Timing

- At first diagnosis of bone metastases in solid tumors
- At first diagnosis of osteolytic bone disease in multiple myeloma
- Until patient is able to tolerate therapy

Prolonged Anti-resorptive Effect of a Single IV Injection of Zoledronic Acid in Adult OVX Rats

Proximal tibial metaphysis, pQCT



Gasser JA, Green J; *Bone,* 2002

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PTH-rP

- Cancer cells migrate to bone and overproduce PTH-rP.
- PTH-rP activates osteoblasts to produce RANKL and down regulate OPG, activating osteoclast precursors and leading to osteolysis.

BISPHOSPHONATES USE

ONCOLOGY

Metastatic setting

- treatment of metastases from primary tumor:

  osteolytic: breast, lung, myeloma, other sites

  osteoblastic / osteolytic: prostate cancer

in association with hormone / chemotherapy treatment

- paraneoplastic hypercalcemia

BISPHOSPHONATES USE

ONCOLOGY

Adjuvant setting

-In association with hormone treatment (AI) for the prevention of bone events (bone loss) secondary to hormone treatment (breast cancer);

- The trial of Gnant et al (ASCO 2008) has demonstrated ↑ of DFS and RFS with Zoledronate in association with adjuvant endocrine therapy (Goserelin + TAM or Goserelin + Anastrozole) in premenopausal breast cancer (possible antitumor direct action).

-In association with hormone therapy (LH-RH agonists) in early prostate cancer for the prevention of bone events.

BISPHOSPHONATES USE

Prevention Setting

-In association with hormone treatment (AI, LH-RH agonists) for the prevention of breast cancer.

Tumor progression effect in early breast cancer

- Gnant et al study (ASCO 2008);

- Lin et al study (ESMO 2008): Zoledronate administered after or together with adjuvant hormone therapy for two years decreases prevalence of disseminated tumor cells (DTC) in early breast cancer.

Other diseases

-Cure and/or prevention of post-menopausal osteoporosis (alternative to hormone replacement treatment), post-andropausal osteoporosis.

Breast Cancer

Abstract LBA4: M. Gnant, B. Mlineritsch, W. Schippinger, G. Luschin-Ebengreuth, S. Poestlberger, C. Menzel, R. Jakesz, E. Kubista, C. Marth, R. Greil, on behalf of the ABCSG

Adjuvant Ovarian Suppression Combined With Tamoxifen or Anastrozole, Alone or in Combination With Zoledronic Acid, in Premenopausal Women With Hormone-Responsive, Stage I and II Breast Cancer: First Efficacy Results From ABCSG-12

Michael Gnant

Professor of Surgery, Medical University of Vienna

Austrian Breast & Colorectal Cancer Study Group

ASCO 2008 Annual Meeting

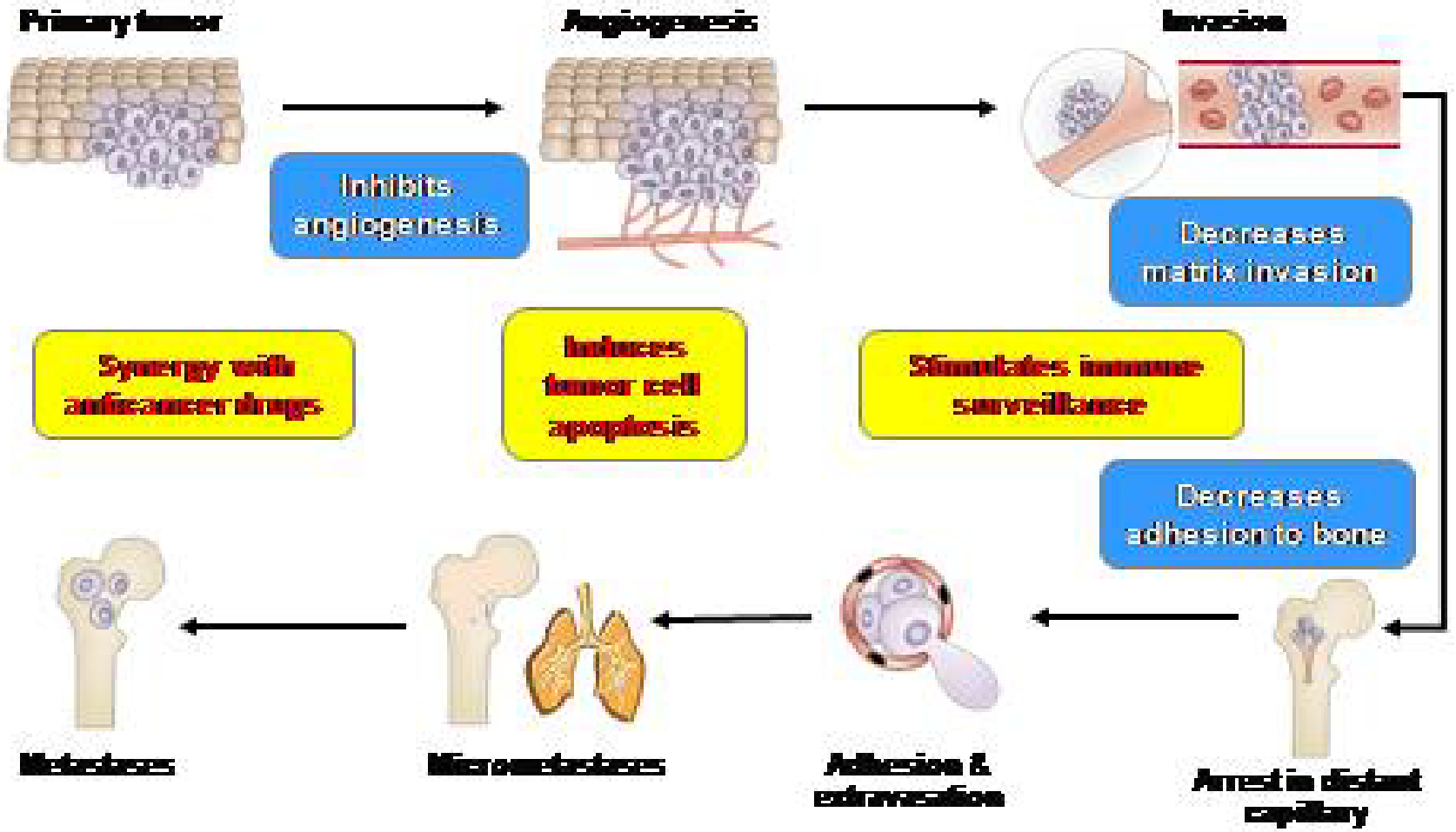
Chicago, Illinois; June 1, 2008

Questions to Be Answered

- **Can aromatase inhibitors (AIs) improve clinical outcome compared with tamoxifen?**

- **Can bisphosphonates added to endocrine therapy improve outcome beyond endocrine therapy alone?**

Can Zoledronic Acid Improve Outcomes?
Inhibition of Multiple Steps in Tumor Cell Metastasis

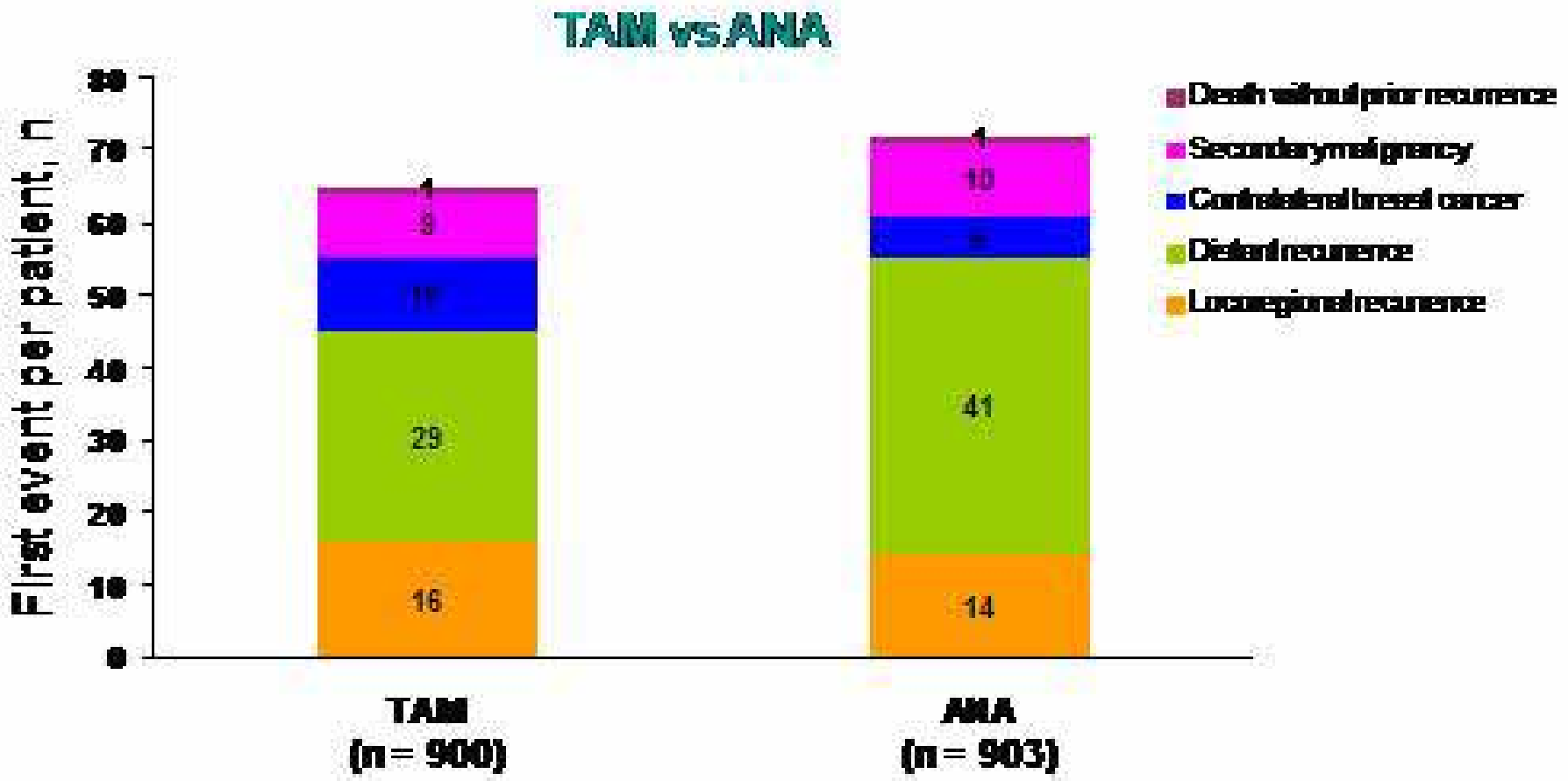


Adapted from Mundy GR, et al. Nat Rev Cancer. 2002;2:584-593.

Study Endpoints (TAM vs ANA; ZOL vs No ZOL)

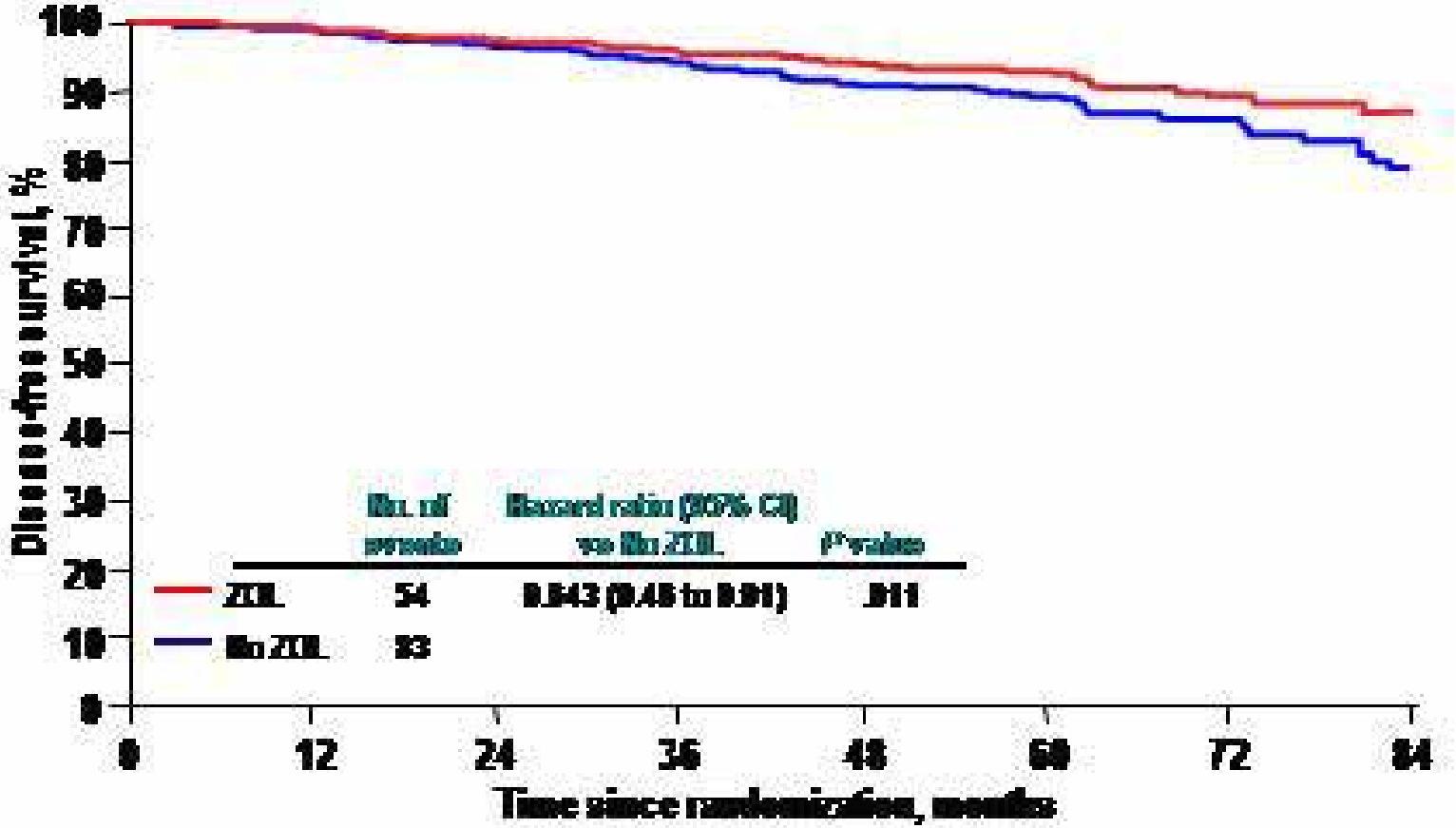
- **Primary endpoint**
  - Disease-free survival (DFS)
    - Local recurrence; contralateral breast cancer; distant metastasis; secondary carcinoma; death
- **Secondary endpoints**
  - Recurrence-free survival (RFS)
    - Local recurrence; contralateral breast cancer; distant metastasis; secondary carcinoma
  - Overall survival (OS)
  - Safety
- **Exploratory endpoint**
  - Bone-metastases–free survival

First DFS Events (ITT Population)



Primary Endpoint: Disease-Free Survival

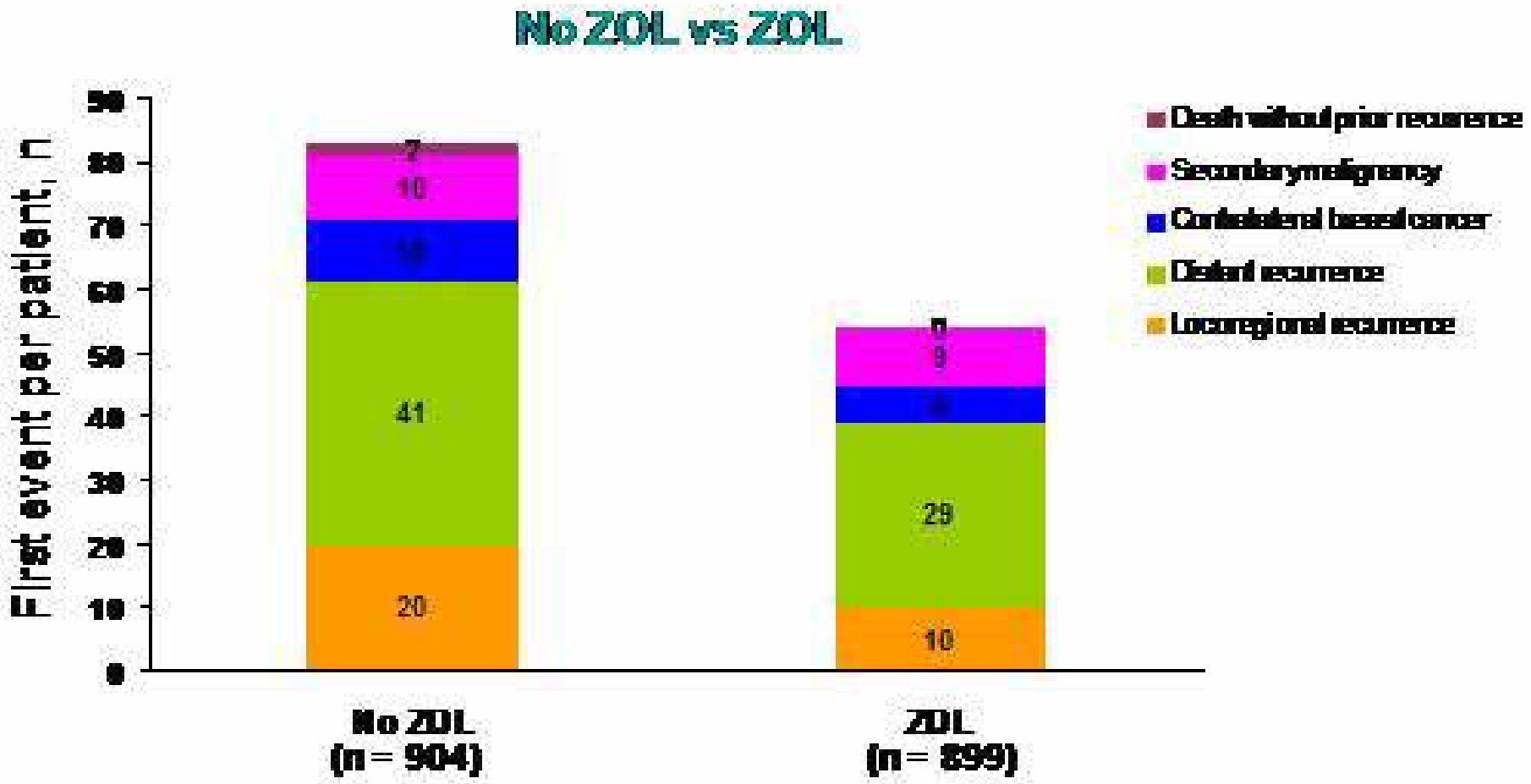
Zoledronic Acid Significantly Improves DFS Compared With Endocrine Therapy Alone



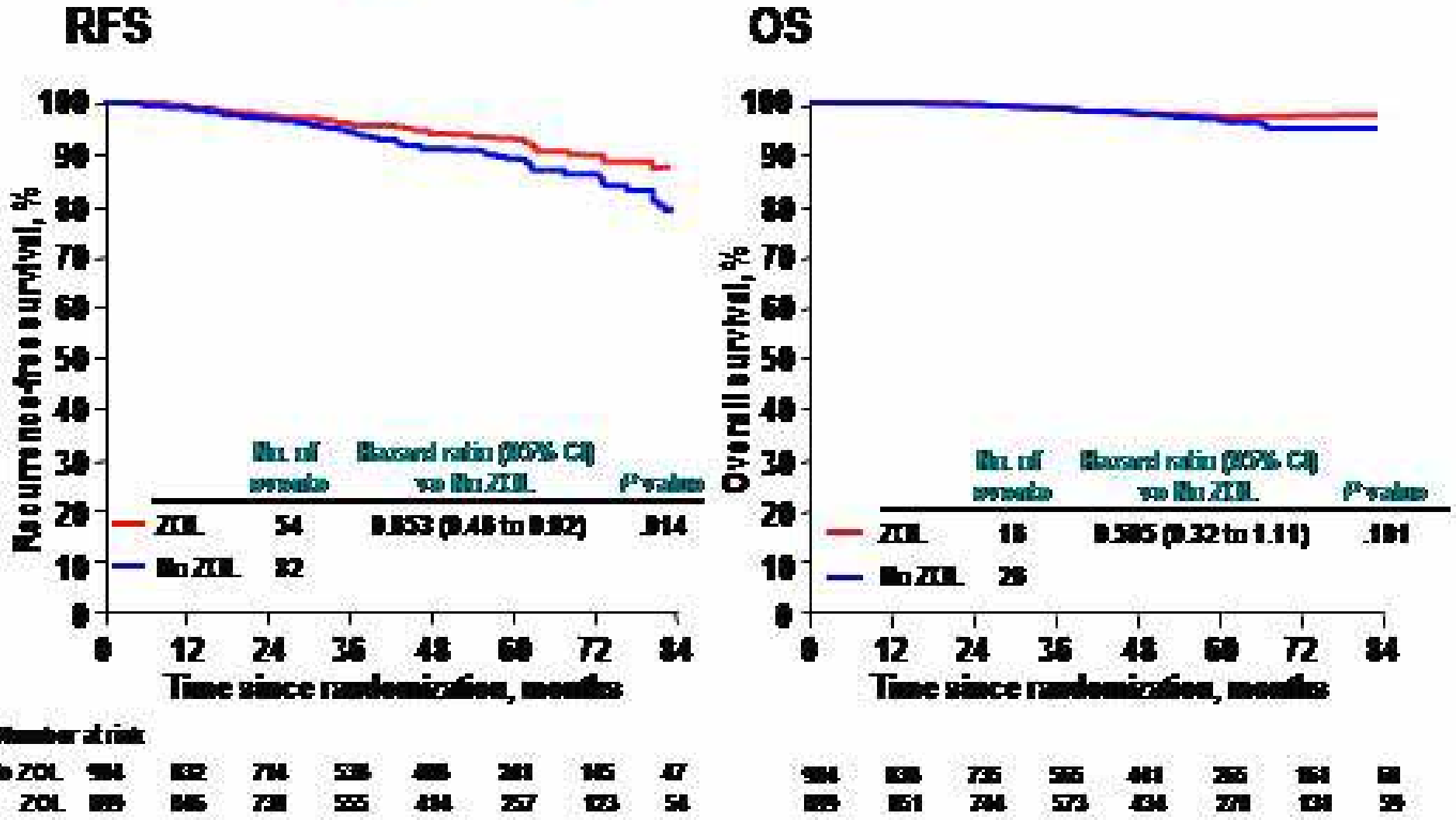
Number at risk

No ZOL	904	838	735	565	441	265	161	60
ZOL	899	851	744	573	434	270	131	59

First DFS Events (ITT Population)



Secondary Endpoints: ZOL vs No ZOL



Safety of Zoledronic Acid Treatment

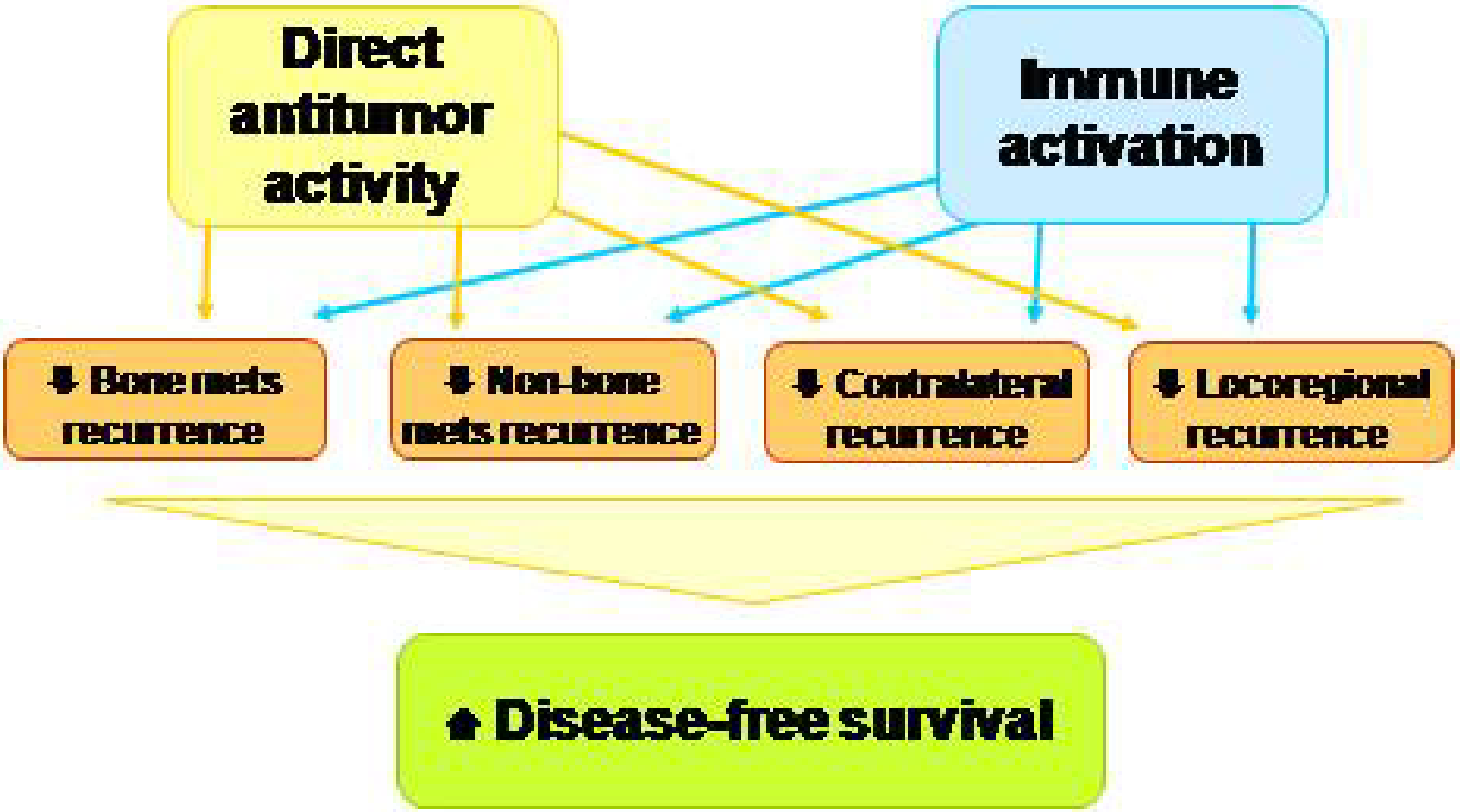
- Zoledronic acid has a well-established safety profile and is generally well tolerated
- The combination of adjuvant endocrine therapy and zoledronic acid was well tolerated
  - Side effects were as expected
  - Zoledronic acid therapy was not significantly associated with serious adverse events
  - No confirmed cases of ONJ
  - No renal toxicity

Summary: ZOL vs No ZOL

- **Adding zoledronic acid to endocrine therapy significantly prolonged DFS and RFS vs endocrine therapy alone**
  - ↓ Risk of DFS events by 36% (HR = 0.64; *P* = .01)
  - ↓ Risk of RFS events by 35% (HR = 0.65; *P* = .015)

- **Zoledronic acid produced a trend toward improved OS (HR = 0.60; *P* = .10)**

Zoledronic Acid-Mediated Mechanisms Contributing to Improved Disease-Free Survival



Bisphosphonates in Breast Cancer Patients With Bone Metastasis (1)

- Most available bisphosphonates have approval for a limited number of indications
- First-generation bisphosphonates (nonnitrogen containing)
  - Etidronate (no longer recommended)[1]
  - Clodronate (approved in some European countries)
    - Hypercalcemia of malignancy
    - Bone metastases from breast cancer
    - Multiple myeloma

[1]Hillner BE, et al. *J Clin Oncol*. 2003;21:4042-4057.

Bisphosphonates in Breast Cancer Patients With Bone Metastasis (2)

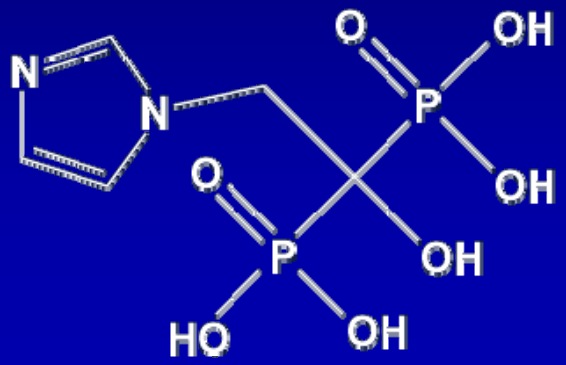
- Nitrogen-containing bisphosphonates (1 nitrogen group)
  - Pamidronate (approved in > 80 countries, including the United States and the European Union)
    - Hypercalcemia of malignancy
    - Osteolytic lesions in patients with breast cancer or multiple myeloma
  - Ibandronate (approved only in the European Union)
    - Hypercalcemia of malignancy
    - Bone metastases from breast cancer

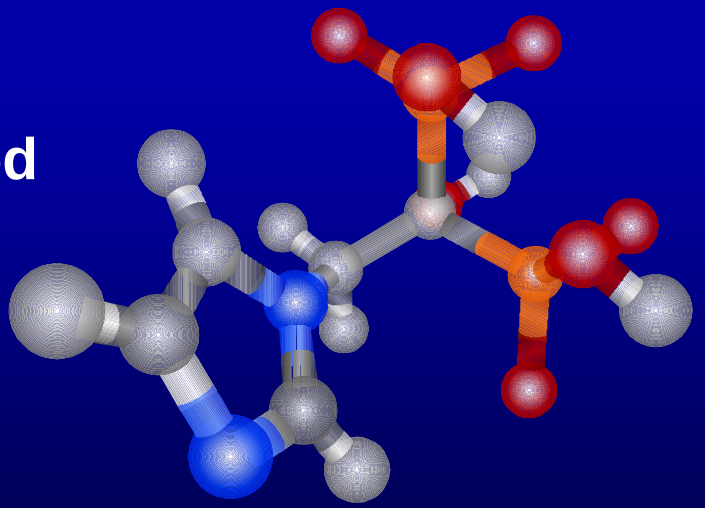
Bisphosphonates in Breast Cancer Patients With Bone Metastasis (3)

- Nitrogen-containing bisphosphonate (2 nitrogen groups)
  - Approved in > 80 countries (including the United States and the European Union)
    - Hypercalcemia of malignancy
    - Bone lesions or bone metastasis from
      - Multiple myeloma
      - Breast cancer
      - Prostate cancer
      - Lung cancer and other solid tumors

Zoledronic Acid (ZOMETA®)

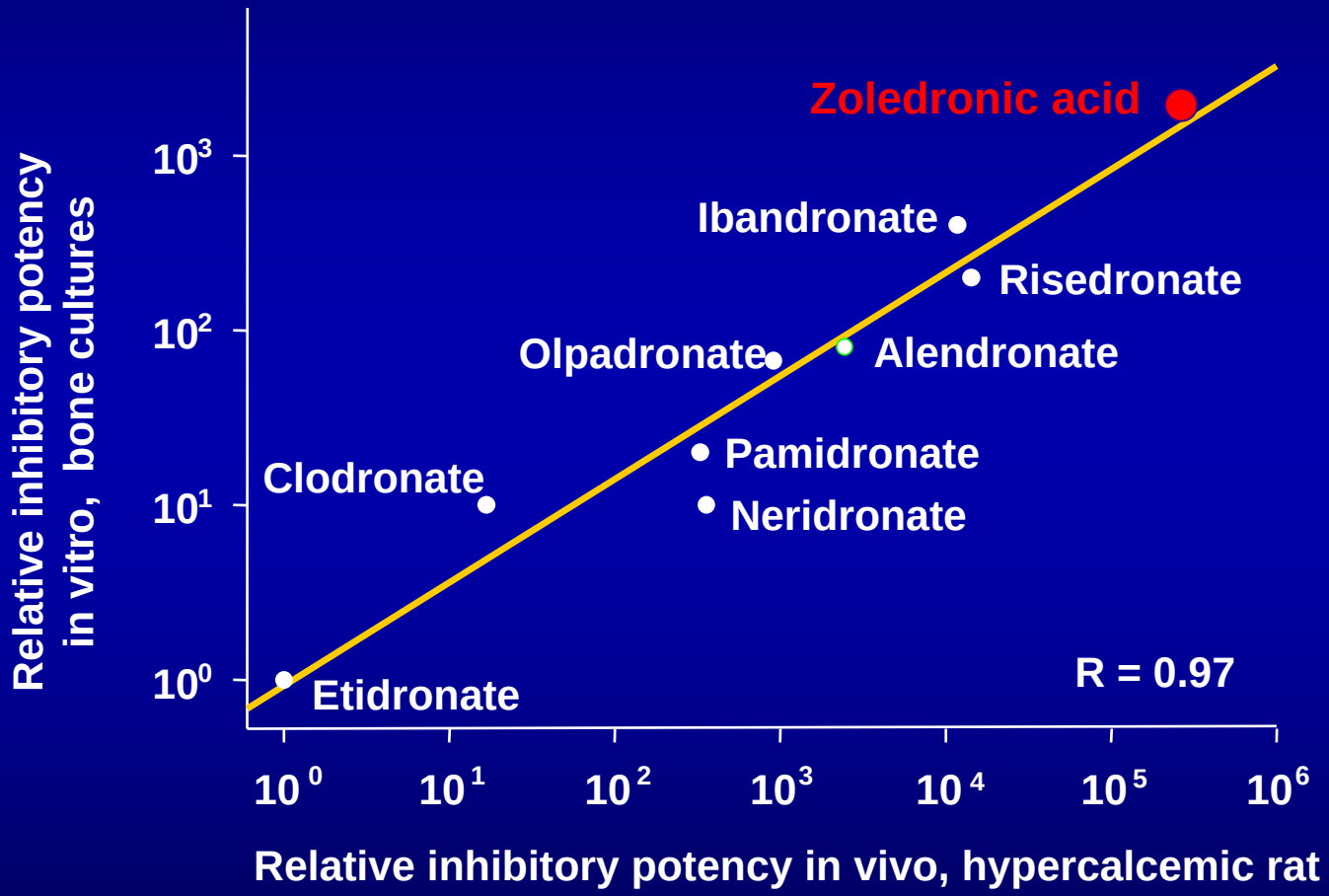
- Zoledronic acid is a third generation, highly potent bisphosphonate
- Heterocyclic, nitrogen-containing bisphosphonate composed of
  - A core bisphosphonate moiety
  - An imidazole-ring side chain containing 2 critically positioned nitrogen atoms





Green JR, et al. *J Bone Miner Res*. 1994;9:745-751.
Green JR, et al. *Pharmacol Toxicol.* 1997;80:225-230.

Zoledronic Acid Is the Most Potent Bisphosphonate Identified To Date



Green JR, et al. *J Bone Miner Res*. 1994;9:745-751.

Conclusions—Results of Bisphosphonates in Breast Cancer Patients With Bone Metastases

- Pamidronate, clodronate, and ibandronate have been compared with placebo
- Zoledronic acid is the only bisphosphonate that has been compared with pamidronate
  - Zoledronic acid was at least as effective as pamidronate in every endpoint
  - Zoledronic acid demonstrated a significant 20% reduction in the risk of developing an SRE beyond that produced by pamidronate†

†Andersen-Gill method.

Prostate Cancer

Treatment of Prostate Cancer Bone Metastases With 1st- and 2nd-Generation Bisphosphonates

Test drug	N	Result	Author
Etidronate	57	No benefit	Smith, 1989
Clodronate	99	No significant symptomatic benefit	Elomaa, 1992
Placebo-controlled trials			
Oral clodronate	311	No significant delay of symptomatic bone progression	Dearnaley, 2001
IV clodronate	204	No significant ↓ in pain or analgesic use	Ernst, 2002
IV pamidronate	378	No significant ↓ in mean pain score or incidence of SREs	Small, 2003

These bisphosphonates demonstrated transient palliation of bone pain but no objective clinical benefits in placebo-controlled trials

Oral Clodronate Versus Placebo for Metastatic Prostate Cancer

- Oral clodronate (2,080 mg/day)
- 311 men with hormone-responsive prostate cancer metastatic to bone
- Median follow-up = 3 years
- Primary endpoint was symptomatic bone progression or death

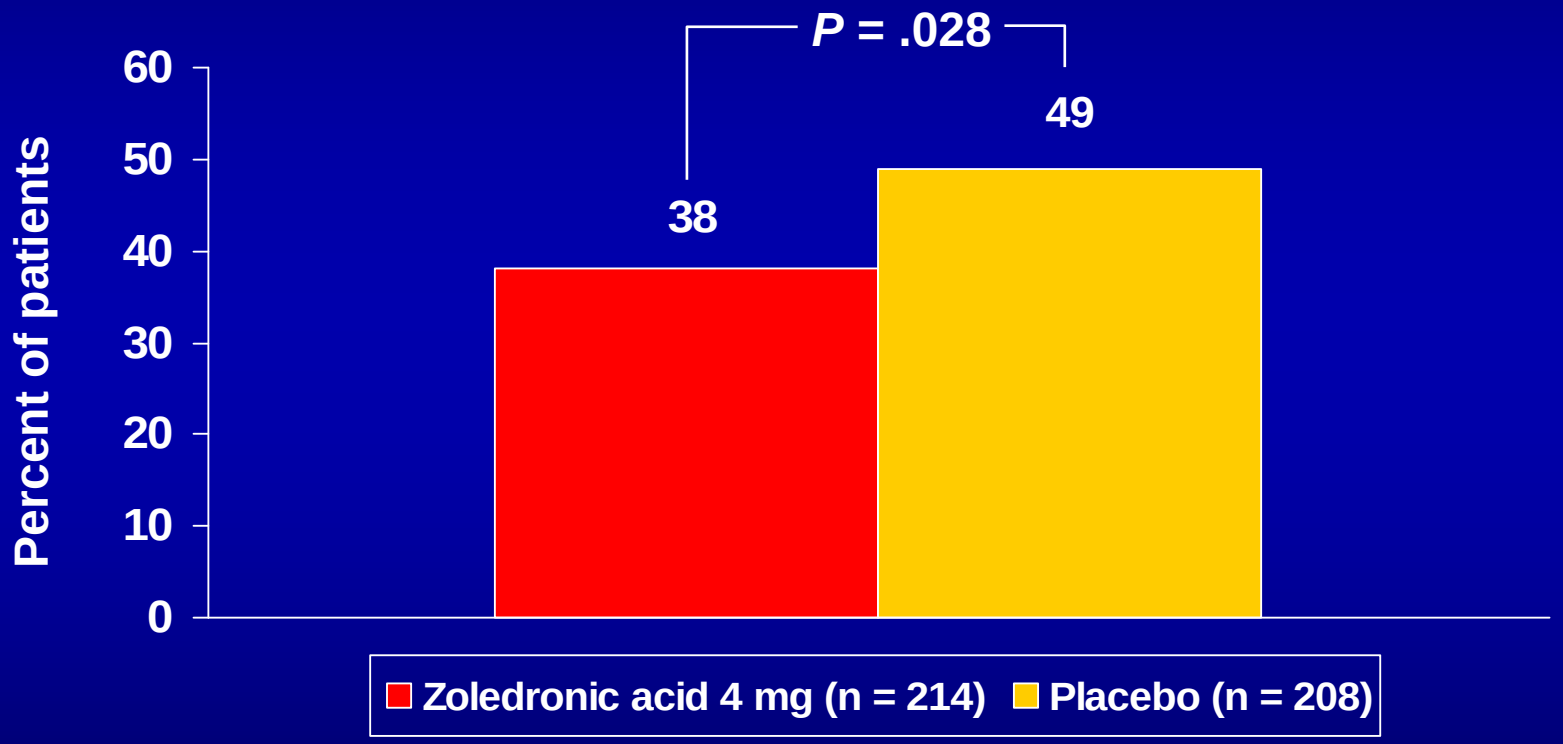
	Clodronate (n = 156)	Placebo (n = 155)	P value
Event-free survival, %	49	41	NS
Median event-free survival, months	23.6	19.3	NS
Deaths, n	82	94	.13

NS = Not significant; pts = Patients; RR = Relative risk for clodronate versus placebo.

Dearnaley DP, et al. *Proc Am Soc Clin Oncol*. 2001;20:174a. Abstract 693.

Prostate Cancer
Proportion (%) of Patients With an SRE

Significantly fewer patients experienced an SRE with zoledronic acid (22% relative reduction)



- **Zoledronic acid 4 mg versus placebo remained significant when asymptomatic fractures were excluded**

Saad et al. *J Natl Cancer Inst*. 2004 in press.

Non-Small Cell Lung Cancer and Other Solid Tumors

Randomized Placebo-Controlled Trial of Zoledronic Acid: Other Tumour Types

Tumor type	n	%
NSCLC	244	49
Renal cell carcinoma	46	9
Colon/Rectum/Intestinal	37	7
Small cell lung cancer (SCLC)	36	7
Cancer unknown primary	35	7
Bladder	26	5
Esophagus/Gastroesophageal	12	2
Head and neck	10	2
Melanoma	10	2
Thyroid	6	1
Other tumor types (n = 11)	39	8

Rosen et al. *Cancer*. 2004 in press.

Conclusions

- Skeletal complications from bone metastasis are an important healthcare problem
- Breast cancer
  - Pamidronate, clodronate, and ibandronate significantly reduce skeletal complications compared with placebo
  - Only pamidronate showed superiority vs placebo in all endpoints
  - Zoledronic acid is superior to pamidronate[1]
- Prostate cancer, NSCLC, RCC, and other solid tumours
  - Zoledronic acid is the only bisphosphonate proven effective in these tumour types

1. Rosen LS, et al. *Cancer*. 2003;98:1735-1744.

Conclusions cont.

- Zoledronic acid is the only bisphosphonate to
  - Significantly reduce skeletal complications across all tumour and lesion types
  - Demonstrate statistically significant clinical benefit compared with pamidronate in patients with breast cancer
  - Demonstrate statistically significant clinical benefit compared with placebo in patients with advanced prostate cancer
  - Reduce skeletal complications in poor prognosis patients with NSCLC, renal cell cancer, and other solid tumours

Criteria for Creatinine Increases in Zoledronic Acid Trials

- Notable serum increase was defined as:
  - Increase of 0.5 mg/dL in patients with normal baseline serum creatinine (< 1.4 mg/dL)
  - Increase of 1.0 mg/dL in patients with abnormal baseline serum creatinine (≥ 1.4 mg/dL)
  - Or doubling of serum creatinine from baseline value
  - If serum creatinine was notably increased, dose was withheld until serum creatinine returned to within 10% of baseline

Rosen LS, et al: *Cancer* 2003;98:1735-1744.

Handling serum creatinine elevation

- For patients with some level of nephropathy due to cancer, antitumour therapy
- General recommendation for i.v. BPs:
  - Prolong infusion time and add hydration (1L)
  - monitor serum creatinine
- Zoledronic acid and pamidronate
  - Not recommended for patients with baseline serum creatinine > 3.0 mg/dL unless potential clinical benefit outweighs the risk; caution recommended

*Defined as: Increase of 0.5 mg/dL in pts with baseline serum creatinine ≤ 1.4 mg/dL; an increase of 1.0 mg/dL in pts with baseline serum creatinine > 1.4 mg/dL; or any doubling of serum creatinine from baseline

Overview Oral vs IV Bisphosphonates

	Oral	IV
Pros	▪ Can be administered at home	▪ Efficacy (Pamidronate and Zoledronic acid recommended by ASCO guidelines) ▪ 1 dose every 3 - 4 weeks ▪ Compliance ▪ Long term safety
Cons	▪ Inconvenient therapeutic regimen ▪ GI adverse effects ▪ Reduced compliance ▪ Low absorption and bioavailability, which fluctuates with food intake ▪ Slow onset of action ▪ Not yet recommended by ASCO guidelines	▪ Need to be administered at the hospital/clinical center ▪ Requires renal function test (also recommended for oral Ibandronate)

Translation Into Daily Practice

- Ensure compliance by using IV bisphosphonates
- Renal monitoring recommended for all IV bisphosphonates
- For IV bisphosphonates, calcium + vitamin D supplementation are recommended (routinely practiced in clinical trials)

Conclusions (1)

- No report of negative interference between bisphosphonates and other cancer treatments
- IV bisphosphonates have good long-term safety
- IV bisphosphonates have acceptable renal safety profile
- IV bisphosphonates lack GI side effects

Conclusions (2)

- Patient compliance can be an issue with oral bisphosphonates (comorbidity, polytherapy)
- Zoledronic acid has a convenient 15-minute IV dosing schedule
  - 1 dose q 3-4 weeks in metastatic bone disease
  - 1 dose q 3-6 months for preventing cancer treatment induced bone loss

OSTEONECROSIS OF THE JAW:

A Maxillofacial Component of Systemic Effects of Bisphosphonates?

- Bisphosphonates remain active for many years
- Severe suppression of bone turnover

Osteonecrosis of the Jaw in Cancer Patients on Bisphosphonate Therapy

- Very rare adverse event (< 1 / 10,000 patients)
- No causal relationship between bisphosphonate use and osteonecrosis has been established
  - Osteonecrosis reported 4x more often in cancer patients than in the normal population
  - Multifactorial causes for osteonecrosis (trauma, infection, chemotherapy, radiotherapy, long-term glucocorticoid therapy)

Osteonecrosis of the Maxilla and Mandible in Patients Treated with Bisphosphonates: A Retrospective Study

C. L. Estilo, C.H. Van Poznak, T. Williams, E. Evtimovska, L. Tkach, J. L. Halpern, S. J. Tunick, J. M. Huryn

Memorial Sloan-Kettering Cancer Center, New York, NY

Objectives

- To identify risk factors for osteonecrosis in patients with breast cancer, multiple myeloma and prostate cancer
- To establish possible guidelines for management of osteonecrosis

Methodology

- The medical and dental records of all pts with multiple myeloma, breast cancer and prostate cancer who were treated in the Dental Service of Memorial Sloan-Kettering Cancer Center between 01/01/96-05/03/04 were reviewed.
- Pts who presented with exposed bone in the maxilla or mandible were further evaluated for various clinical and pathological characteristics.

Methodology

Patients and Methods:

- Time frame: 01/01/96 – 05/03/04
- Patients treated in the Dental Service, MSKCC
- Medical and dental chart review
- Evaluation for various clinical and pathological characteristics

Methodology

Clinical and Pathological Characteristics:

- Sex
- Age
- Primary tumor type
- Presence of bony metastasis
- History of BP therapy
- Duration of BP therapy
- History of corticosteroid use
- History of tobacco smoking
- Oral hygiene
- Presence of comorbid disease
- Symptomatology
- History of dental extraction in the area of ON
- Location of osteonecrosis

Results

- Total number of patients: 530
  - Breast cancer: 297
  - Multiple myeloma: 139
  - Prostate cancer: 83
- Patients who developed osteonecrosis: 23
  - Metastatic breast cancer: 15
  - Multiple myeloma: 6
  - Prostate cancer: 2

Results: Demographics

- Gender
  - Male: 6
  - Female: 17
- Age
  - Median: 63 years
  - Range: 25-90 years

Results: Bisphosphonate Therapy

- Intravenous bisphosphonate therapy (22/23)
  - Pamidronate alone: 8
  - Zoledronate alone: 2
  - Pamidronate + Zoledronate: 12
  - Median duration of bisphosphonate therapy at time of osteonecrosis discovery: 35 months
    - Range: 1-94 months

Results: Nature of Osteonecrosis

- Location of osteonecrosis
  - Maxilla: 7
  - Mandible: 15
  - Both: 1
- Nature of osteonecrosis
  - h/o dental extraction: 12
  - Spontaneous osteonecrosis: 10
  - Both related to dental extraction and spontaneous: 1
- Symptomatic
  - Yes: 9
  - No: 14

Results: Risk Factors and Comorbid Disease

- Oral Hygiene
  - Good: 9
  - Fair: 9
  - Poor: 2
- Corticosteroids: 15
- Tobacco: 10

Results: Risk Factors and Comorbid Disease

- Co-morbid disease: 19 (82.6 %)
  - * 2 or more comorbid diseases: 13 (56.5%)
  - – Diabetes: 6
  - – Asthma: 2
  - – Arthritis: 4
  - – Osteoporosis: 1
  - – Anemia: 3
  - – Renal disease: 4

Results: Management and Outcome

- Management
  - Chlorhexidine rinse and antibiotics: 16
  - Conservative sequestrectomy or curettage: 8
  - Surgical debridement: 1
- Outcome
  - Resolution: 4
    - Resolution without progression: 2
    - Resolution of ON, with subsequent development of draining neck fistula: 1
    - Resolution of tooth extraction-related, with subsequent development of spontaneous ON: 1
  - No change: 6
  - Ongoing follow-up: 4 (seen once)
  - Unknown: 4 (lost to follow-up)
  - Progression: 3
  - Deceased: 2

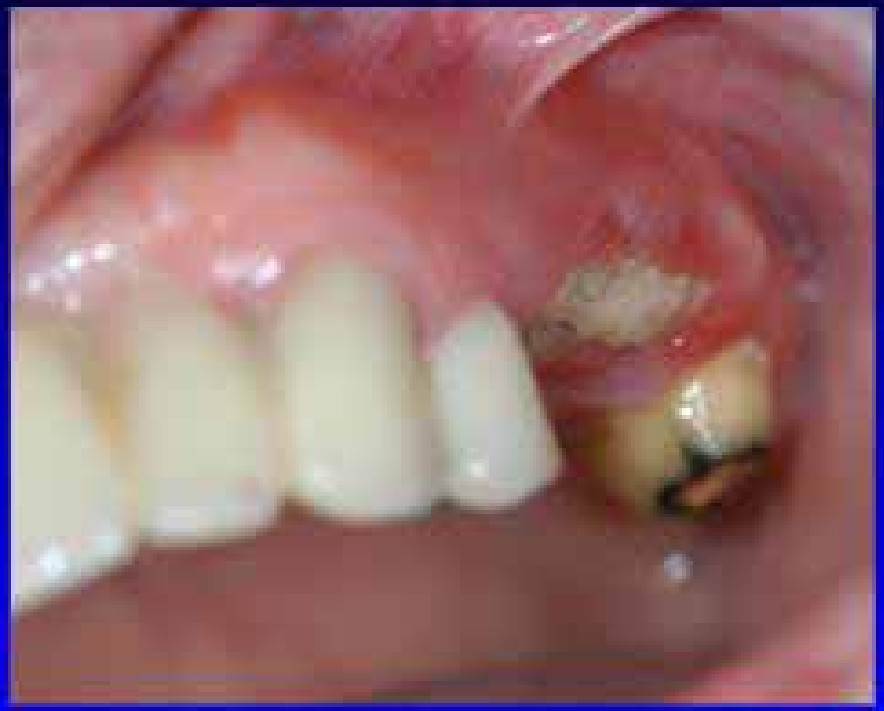


FIGURE 2. Incidental finding of osteonecrosis in a patient (Patient 6) complaining of a dislodged dental restoration. The patient underwent dental extraction in the region of the exposed bone one year prior to presentation. She has no symptoms.

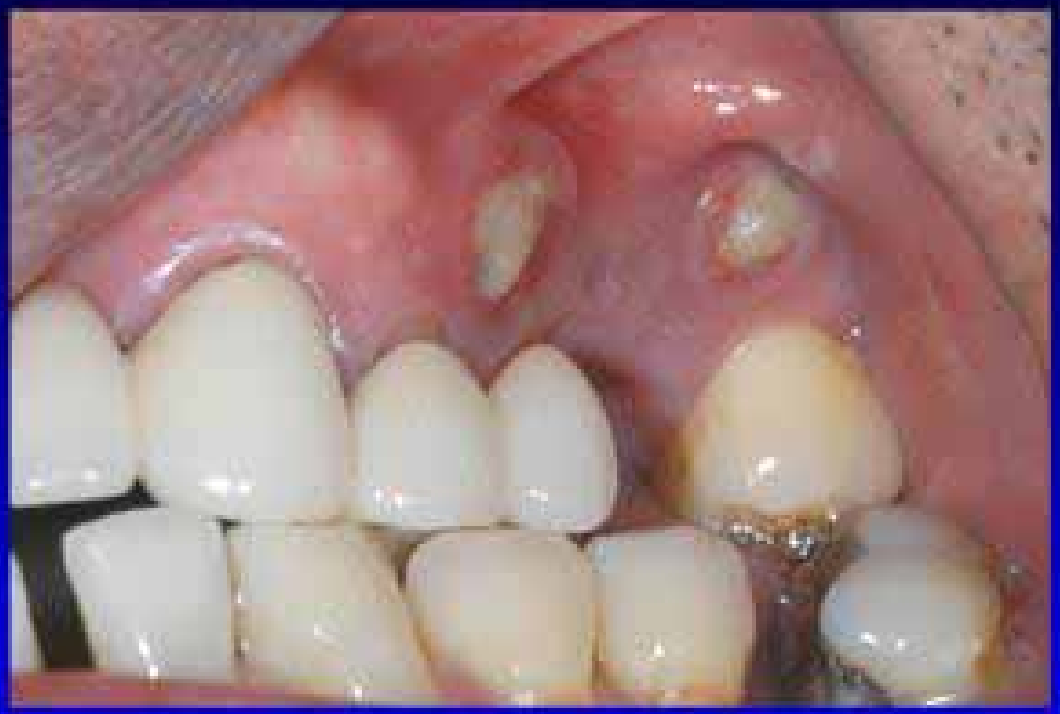


FIGURE 3. Spontaneous osteonecrosis in a patient (Patient 16) with multiple myeloma. Soft tissue dehiscence in two areas of exostoses resulted in exposed bone. An exostosis is a benign and innocuous condition representing overgrowth of normal bone. It is normally covered with mucosa and is asymptomatic. Osteonecrosis in this patient may have been precipitated by trauma (eg, tooth brushing).

FIGURE 4. Spontaneous osteonecrosis (Patient 3). Spontaneous osteonecrosis is most commonly seen in areas with thin mucosa such as the mylohyoid ridge of the lingual mandible. Trauma (eg, brushing) may have contributed to osteonecrosis in this patient.

Conclusions

- The clinically relevant literature on BPs is almost uniformly positive demonstrating a decrease in skeletal complications.
- We report herein 23 cases of ON in patients with breast cancer, multiple myeloma and prostate cancer, 22/23 of which have documented history of bisphosphonate therapy.
- The management of ON has proven to be challenging.
- Surgical intervention is not advocated since this may aggravate the condition.
- Conservative management consisting of close follow-up visits, chlorhexidine rinse and/or antibiotics is the current recommendation.
- Contributing causes of the ON may include: advanced cancer, chemotherapy, comorbid conditions, steroid uses, and possibly BP.
- Clinicians caring for patients with advanced cancer should be aware of ON as a possible treatment complication.

review

Annals of Oncology 19: 420–432, 2008
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Published online 28 September 2007

Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel

M. Aapro[1]*, P. A. Abrahamsson[2], J. J. Body[3], R. E. Coleman[4], R. Colomer[5], L. Costa[6], L. Crinò[7], L. Dirix[8], M. Gnant[9], J. Gralow[10], P. Hadji[11], G. N. Hortobagyi[12], W. Jonat[13], A. Lipton[14], A. Monnier[15], A. H. G. Paterson[16], R. Rizzoli[17], F. Saad[18] & B. Thürlimann[19]

Table 1. Measuring therapeutic benefit of bisphosphonates in patients with bone metastasis

Goal of therapy	Relevant end point
Prevent skeletal complications/bone events[a]	Percent of patients with ≥1 event
Delay onset of skeletal complications	Time to first event
Reduce the rate of occurrence of complications	SMR or SMPR[b]
Reduce the number of complications and/or delay the time to the first and subsequent complications, thereby reducing overall skeletal morbidity	Multiple event analyses[c]

[a]Definition of skeletal complications/bone events for different bisphosphonates to assess the efficacy: clodronate: Fractures, radiotherapy, hypercalcaemia of malignancies; pamidronate/zoledronic acid: fractures, surgery to bone, radiation to bone, spinal cord compression, HCM; IBA: fractures, radiation to bone, surgery to bone.
[b]SMR (events per year) or SMPR (number of 12-week periods on which a patient experiences new bone event divided by the number of periods on study) assess the number of events that occur during a defined time period.
[c]In contrast to the analysis of the proportion of patients with ≥1 skeletal events or the time to first event, which ignore all events after the first one, or skeletal morbidity (period) rates which fail to consider the timing of events, multiple event analyses are statistically robust methods accounting for all skeletal events and for the timing of events throughout the course of disease. The result is expressed as a hazard ratio indicating the reduction in the risk of skeletal events compared with control.
SMR, skeletal morbidity rate; SMPR, skeletal morbidity period rate.

summary of panel recommendations

- In breast cancer, an N-BP is preferably offered to patients with MBD. Generally, i.v. administration is preferable; however, oral administration should be considered for patients who cannot or do not have to attend regular hospital care.
- For patients with hormone refractory prostate cancer, ZOL therapy should be considered for preventing skeletal morbidity and improving QoL, based on evidence.

Aapro M et al. Annals of Oncology 19: 420–432, 2008

- Patients with lung, renal cell or solid tumours other than breast or prostate metastasizing to bone, ZOL therapy should be considered based on assessment of their general medical condition and expected survival time.
- BP therapy is a major factor contributing to control of pain due to MBD.

Aapro M et al. Annals of Oncology 19: 420–432, 2008

- Patients at risk of developing chemotherapy or hormone-deprivation therapy-induced or hormone deprivation therapy-induced (e.g. by AI or ADT) osteopenia or osteoporosis should be considered for preventative BP therapy. Presently the strongest evidence is on favour of ZOL.
- Dosing regimens of BP therapy should follow the scientific data and respective regulatory recommendations and adjustments due to preexisting medical conditions.

Aapro M et al. Annals of Oncology 19: 420–432, 2008

- Since the risk of SREs is continuous, the expert panel recommends continuing treatment until 2 years, even if a patient experiences a bone event. Continuation of therapy beyond 2 years based on an individual risk assessment is recommended.
- Transient acute-phase reactions are no reason for treatment discontinuation and can be managed with preventative or therapeutic analgesics (e.g. paracetamol or ibuprofen).

Aapro M et al. Annals of Oncology 19: 420–432, 2008

- In patients with renal impairment receiving i.v. BP, lower doses, longer infusion times, and selecting a BP with best possible renal tolerability (e.g. IBA) is recommended.
- To avoid renal toxicity with i.v. BP, patients should be adequately hydrated before treatment, and appropriate monitoring of serum creatinine is recommended.
- Calcium and vitamin D_3 should be considered from the start of therapy with BP.

Aapro M et al. Annals of Oncology 19: 420–432, 2008

- In case of oral administration, patients need to be instructed to comply well with the dosage prescriptions to prevent GI problems and maintain the adherence to therapy.
- Before starting N-BP treatment, patients should have a dental examination and appropriate treatment and should be advised to maintain good oral hygiene.
- For each patient with ONJ, an individual benefit/risk evaluation should be carried out to assess continuation or temporary discontinuation of BP therapy.

Aapro M et al. Annals of Oncology 19: 420–432, 2008

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Bone Metastases: New Targets

- RANKL / OPG
- Cathepsin K
- Endothelin-1
- Bone Morphogenetic Protein
- Wnt Proteins
- TGF-β
- Ca^{++}
- PTH-rP

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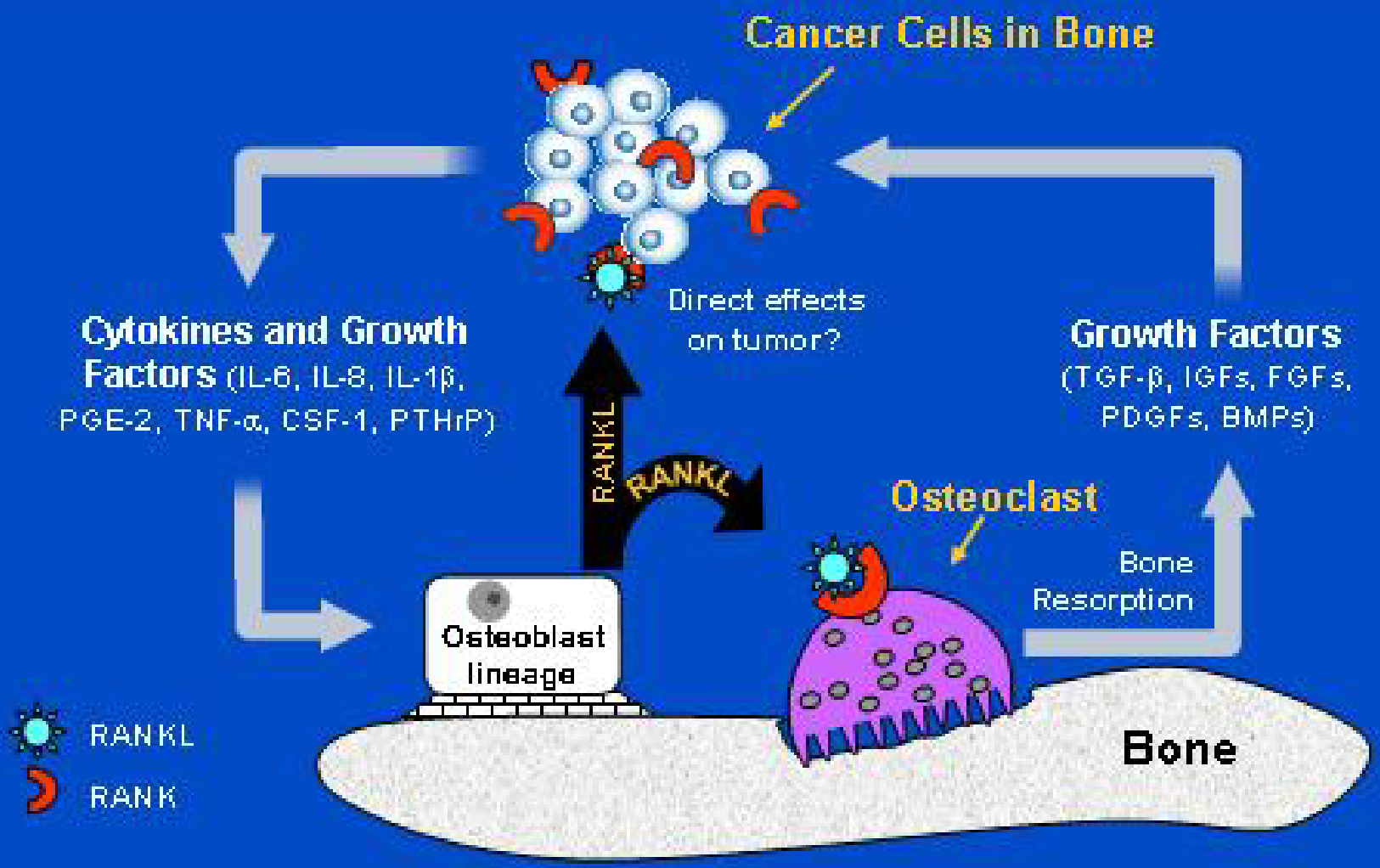
RANKL / OPG

- *Denosumab* is a monoclonal antibody that neutralizes RANK ligand and prevents osteoclast activity.

Zheng Y, Bone, 2007

RANK Ligand Is a Key Mediator in the "Vicious Cycle" of Bone Destruction in Metastatic Cancer



Adapted from Roodman G D. N Engl J Med. 2004;350:1655-64.

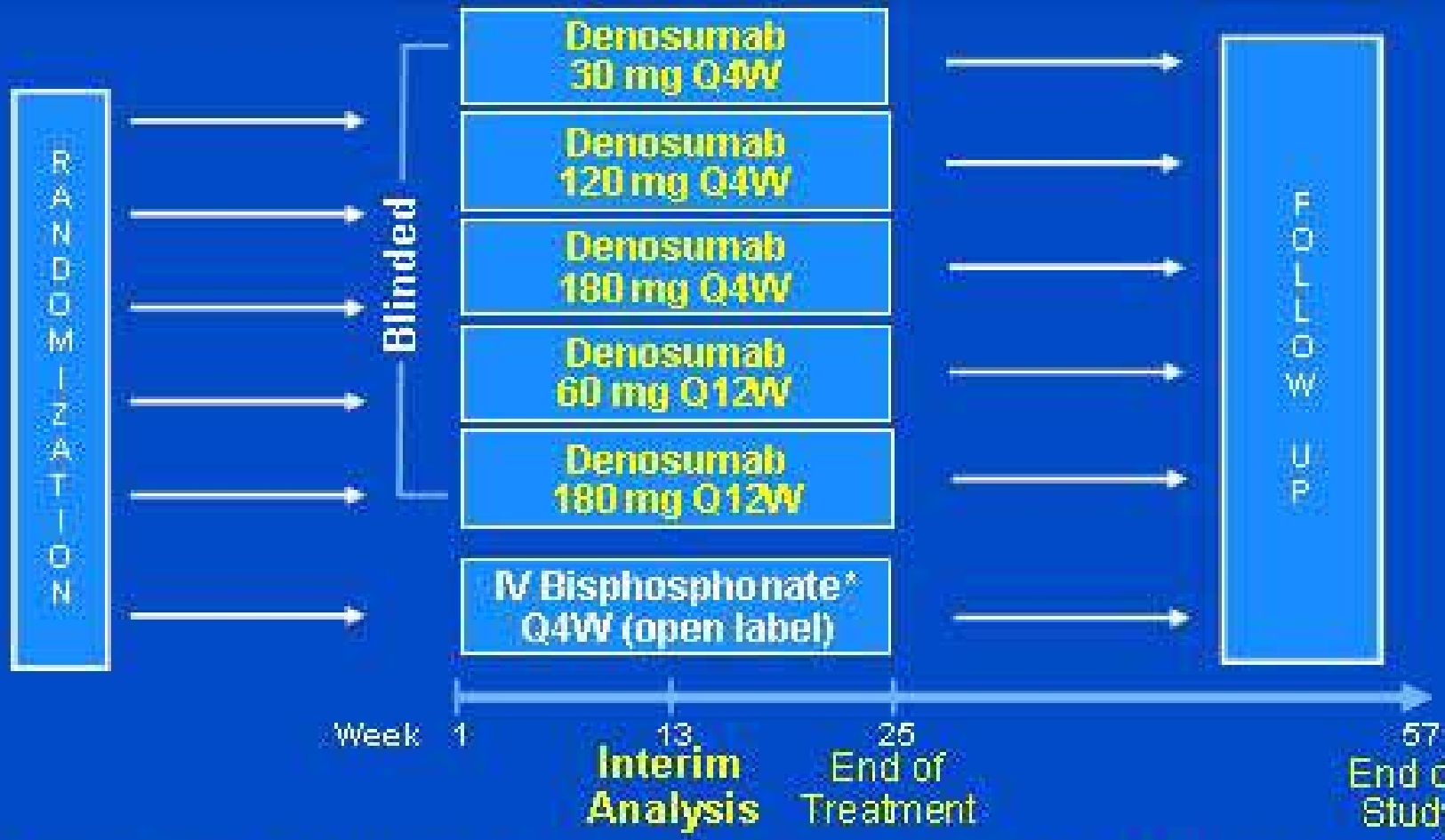
Denosumab Characteristics

- Fully human monoclonal antibody to RANKL
- High affinity IgG_2 antibody
- No binding to TNFα, TNFß, TRAIL, or CD40L
- Administration via subcutaneous (SC) injection

Key Eligibility Criteria

- Women aged ≥18 years with histologically or cytologically confirmed breast cancer
- Radiographic evidence of at least 1 bone metastasis
- ECOG score of 0, 1, or 2
- No prior IV bisphosphonates

Schema – Denosumab (SC) vs Bisphosphonate (IV)



All subjects were instructed to take 500 mg calcium and 400 IU Vitamin D daily

* IV bisphosphonates used in this study: zoledronic acid (n = 39), pamidronate (n = 3), or ibandronate (n = 1)

Safety - Laboratory Parameters

- No laboratory changes were observed in the denosumab treatment cohorts for:
  - Creatinine
  - Liver enzymes
  - Electrolytes
- In some subjects, transient decreases in serum calcium levels were observed without clinical sequelae

Summary of Interim Efficacy and Safety Analysis

- All tested denosumab doses caused rapid and sustained suppression of bone resorption in study subjects
- Denosumab appeared to be at least as effective in preventing SREs as IV bisphosphonates
- Safety results consistent with AE pattern expected in an advanced cancer population receiving chemotherapy or hormonal therapy
- Dose selected for phase 3 trials in metastatic breast and prostate cancer – 120 mg Q4W

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Cathepsin K

- The inibition of Cathepsin K, a protease expressed by osteoclasts, may reduce the osteoclastic action.

Chirgwin S M, J Cell Bioch, 2007

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Endothelin-1 (ET-1)

- Inhibitors of ET-1 may decrease the development of predominantly osteoblastic metastases.

Clines G A, MOC Endocrinol, 2007

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Bone Morphogenetic Proteins (BMP_s)

- Antagonists of BMP_s (a part of the TGF-β superfamily) may decrease osteolytic and osteoblastic activity.

Siclari V A, Breast Cancer Met, 2007

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Wnt Signaling Pathway

- Inhibitors of Wnt proteins such as *Dickkopf-1* (DKK1) reduce the osteoblast activation.

Hall C L, J Cell Bioch, 2006

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TGF-β

- Inhibitors of TGF-β Type I receptor kinase dramatically decrease bone metastases in breast cancer models.

Biswas S, Clin Cancer Res, 2006

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Extracellular Calcium (Ca^{++})

- Regulators of the extracellular calcium sensing receptor (Ca SR) have been developed and might be applied in bone metastases treatment .

Brown E M, Nat Clin Prat Endocrinol Metab, 2007

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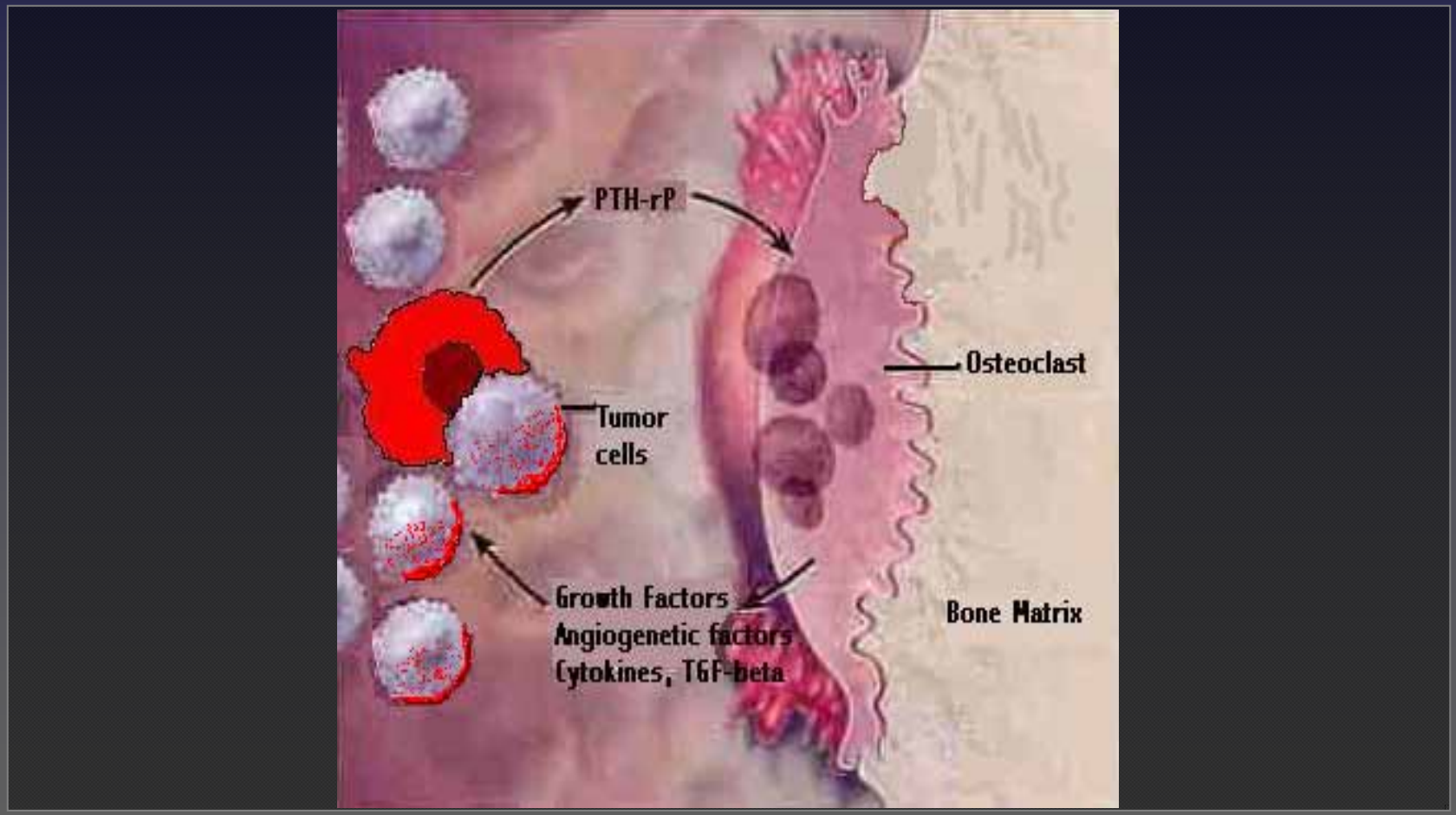
PTH-rP



Correale P and Francini G, Brit J Cancer, 2001.
Francini G, J Immunol, 2002.

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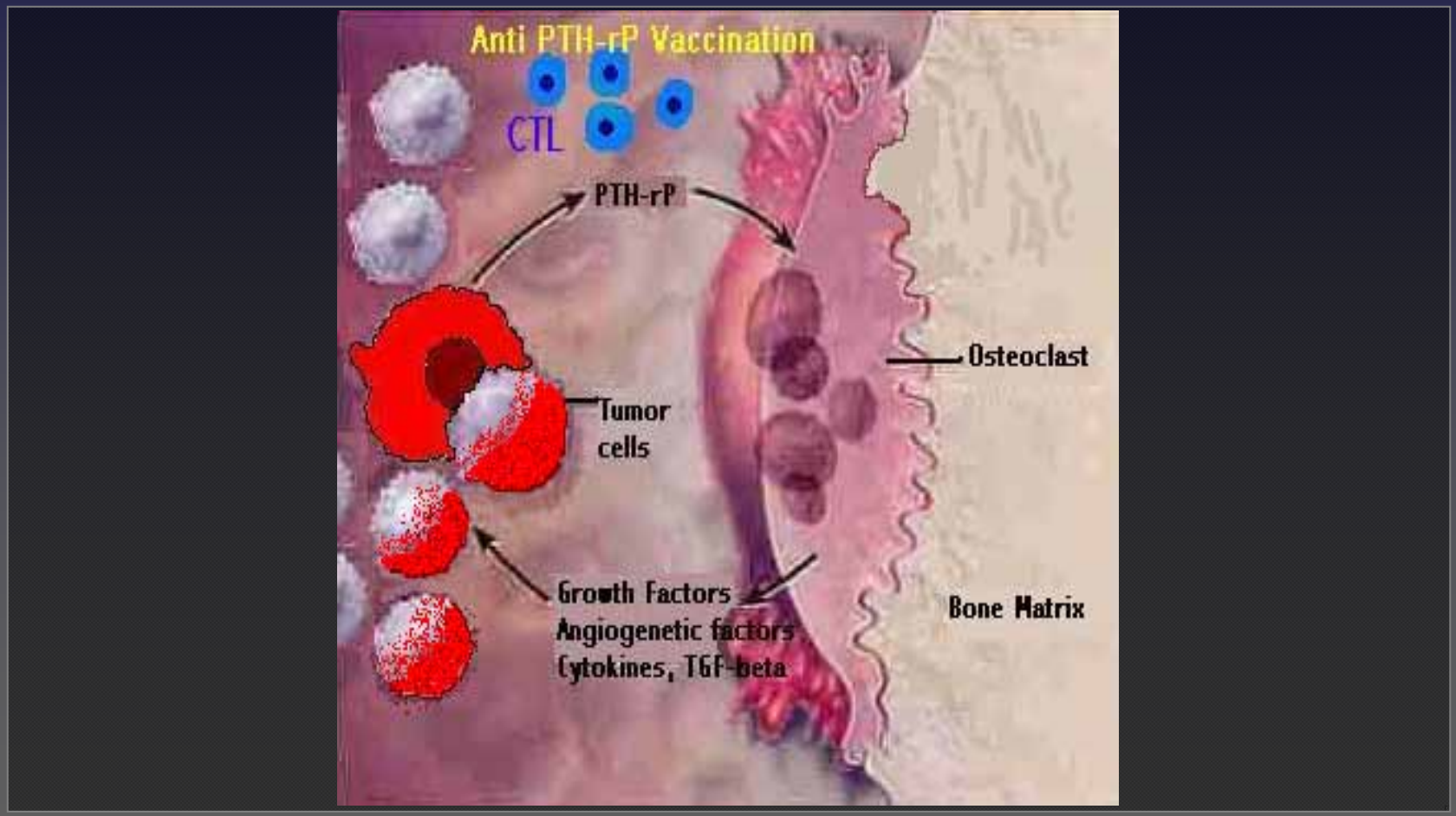

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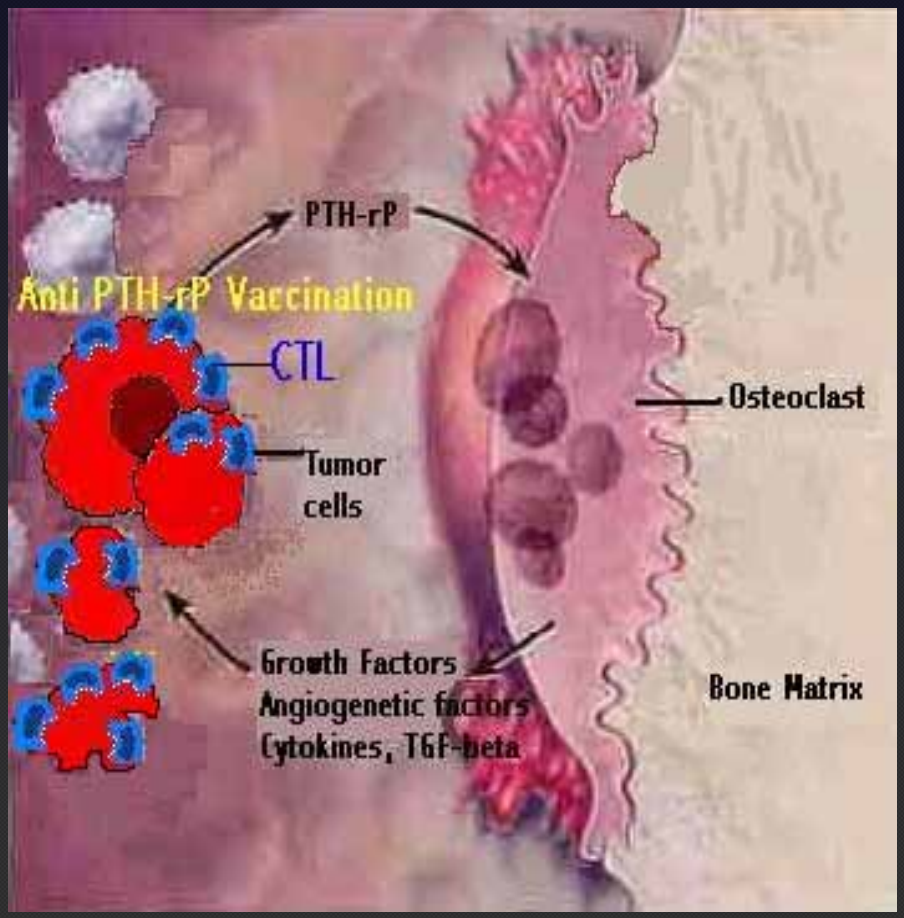

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Francini G, J Immunol, 2002.

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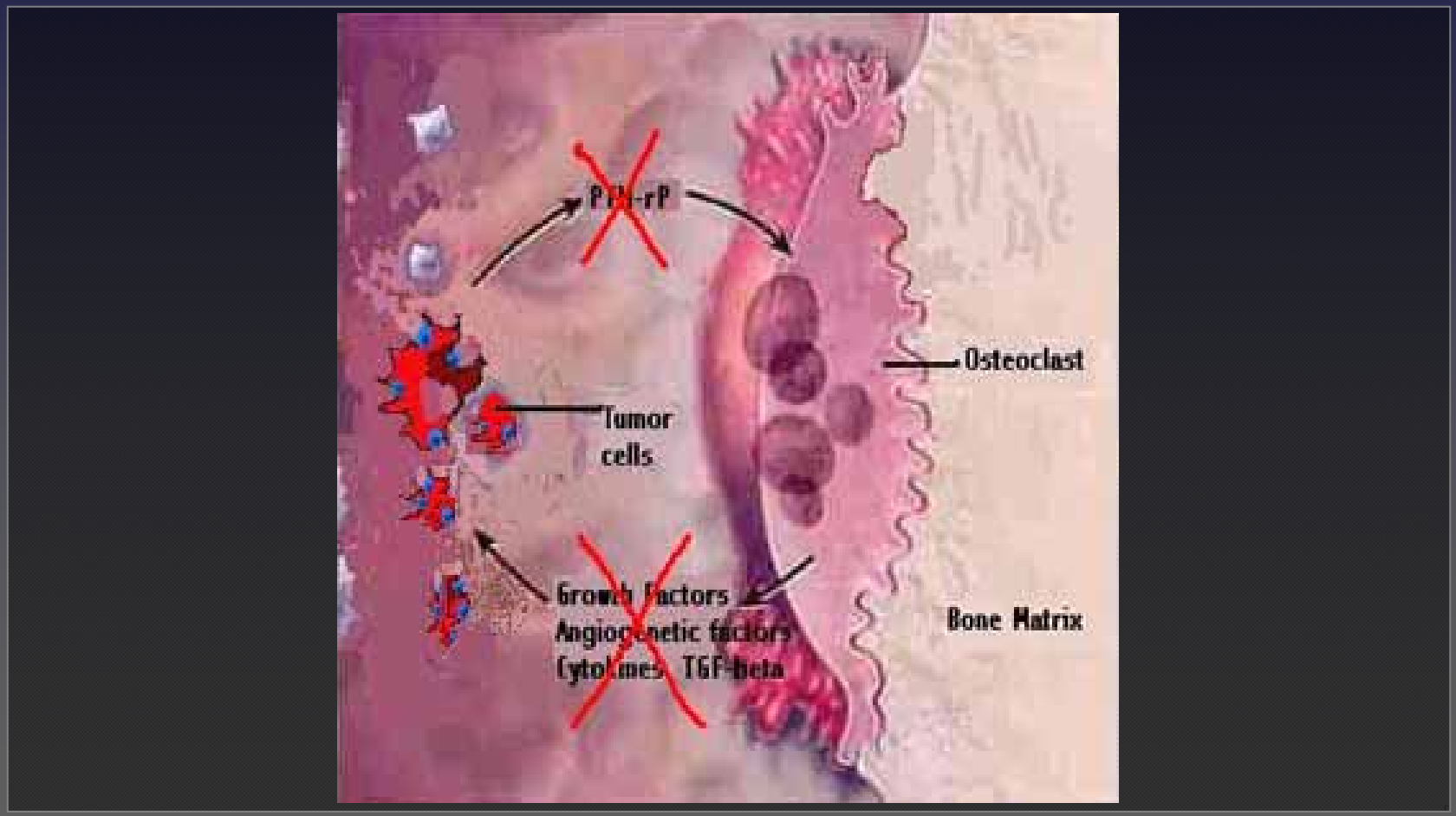
PTH-rP



Correale P and Francini G, Brit J Cancer, 2001.
Francini G, J Immunol, 2002.

Conclusions

- Ongoing research continues to expand our understanding of the molecular mechanisms that lead to bone metastases.
- A number of treatment options are now available, including systemic therapies that treat the underlying cancer and bisphosphonates that significantly reduce skeletal related events.

Casistica zoledronato
UOP ONCOLOGIA MEDICA AOU CAGLIARI

- Tra gennaio 2001 e aprile 2005 sono stati eseguiti 1746 RO recanti la diagnosi di dimissione metastasi ossee.
- La stima degli episodi clinici complessivi relativi è pari a 436 episodi/anno di cui circa il 20% è da riferirsi a nuove diagnosi. Circa 20 pazienti all'anno vengono ricoverati con diagnosi di metastasi ossee, cui si aggiungono in numero lievemente superiore quelli diagnosticati altrove.
- Circa 40 pazienti vengono trattati ogni anno generando per il trattamento medico delle metastasi ossee 480 ricoveri in DH per la somministrazione dell'acido zoledronico. Le neoplasie di origine sono prevalentemente : mammella, polmone, prostata, colon retto, stomaco, LNH, episodici MM.

Dolore da metastasi ossee

- Il dolore veniva misurato con il BPI. Dopo dodici mesi di trattamento è stato riscontrato un miglioramento del 60% degli score del BPI (anche se non si può ascrivere il beneficio esclusivamente a zoledronato in quanto i pazienti ricevevano terapia antalgica con oppioidi, ormonoterapia, chemioterapia)
- Nel periodo di osservazione il riscontro di eventi acuti scheletrici, anche con revisione della documentazione clinica, e' risultato <2%.

Dolore da metastasi ossee

- Dopo 12 mesi di somministrazione la risposta scheletrica al trattamento era cosi riassumibile : PD 42%, SD 44%, RP 18%: tale dato non e' ovviamente riconducibile unicamente al trattamento con zoledronato.
- Dopo 24 mesi i dati di risposta erano i seguenti : PD 56%, SD 33%, RP 11%.
- Non sono stati raccolti dati di osservazione più prolungata nel tempo

Eventi avversi e tossicità

- I pazienti sono stati trattati solo con livelli basali di creatinina normocompatibili. Non è stata rilevata alterazione dei parametri di funzionalità renale riferibile all'acido zoledronico.
- Gli effetti collaterali più frequenti erano costituiti da fatigue (20%), nausea (15%), artralgia (15%), dolori scheletrici (12%), febbre (14%)

Osteonecrosi della mandibola

- Non sono stati rilevati in retrospettiva , previa revisione critica della documentazione, episodi di osteonecrosi della mandibola.
- A partire da aprile 2005 i pazienti vengono selezionati attraverso il consulto clinico e l’esame OPT ad eventuale visita odontostomatologica per bonifica cavo orale prima di iniziare zoledronato.
- A partire dal giugno 2008 la visita odontostomatologica viene eseguita di routine.

University Hospital

Chair of Medical Oncology
University of Cagliari - Italy

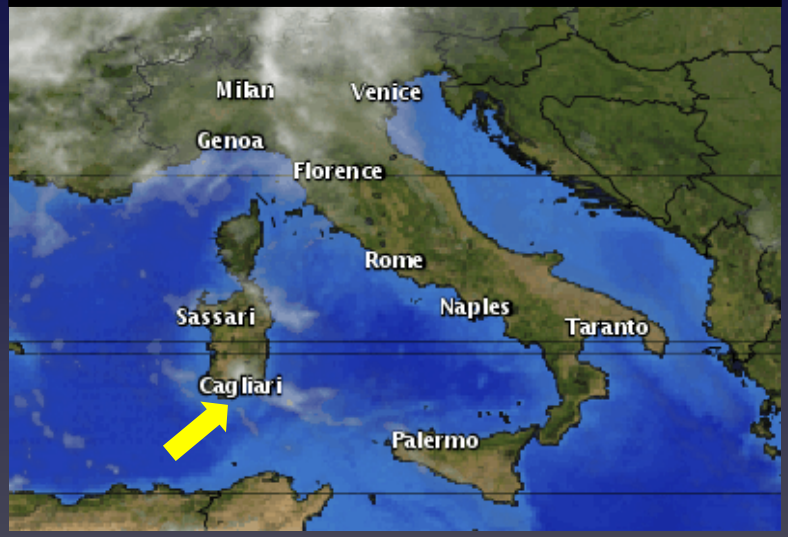
Prof. Giovanni Mantovani

and

Dr. Clelia Madeddu, M.D.
Dr. Elena Massa, M.D.
Dr. Giorgio Astara, M.D.
Dr. Mariele Dessì, M.D.
Dr. Roberto Serpe, M.Sc.
Ms. Anna Rita Succa B.A.

Dr. Francesca M. Tanca, M.D.
Dr. Elena Patteri, M.D.
Dr. Michela Pisano, M.D.
Dr. Laura Deiana, M.D.
Dr. Carla Spiga, M.D.
Dr. Federica Saba, M.D.
Dr. Valeria Cherchi, M.D.
Dr. Filomena Panzone, M.D.
Dr. Antonino Zarzana, M.D.
Dr. Laura Spano, M.D.

Thank you for your attention!




View of Cagliari


View of Cagliari


View of Cagliari


View of Cagliari


Baia Chia – South Western Sardinia


Sea sports in Cagliari


Villasimius – South Eastern Sardinia