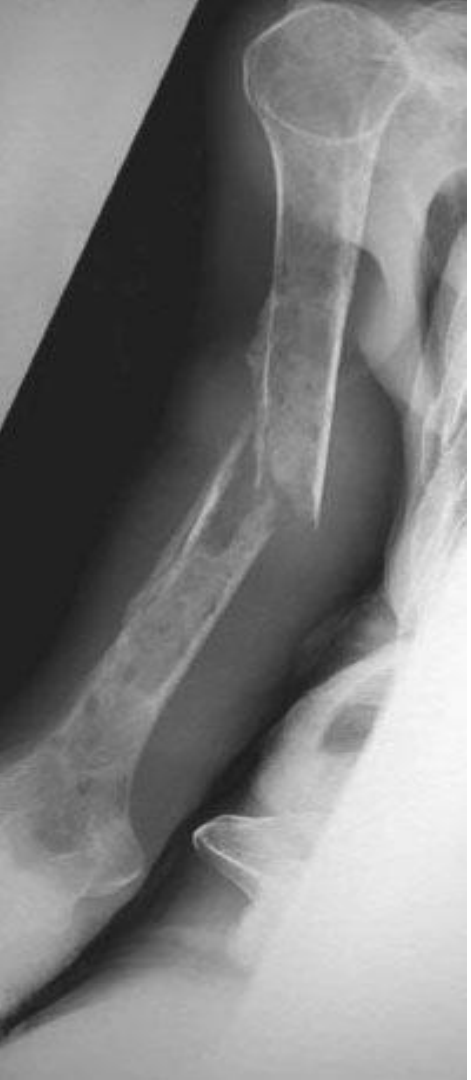
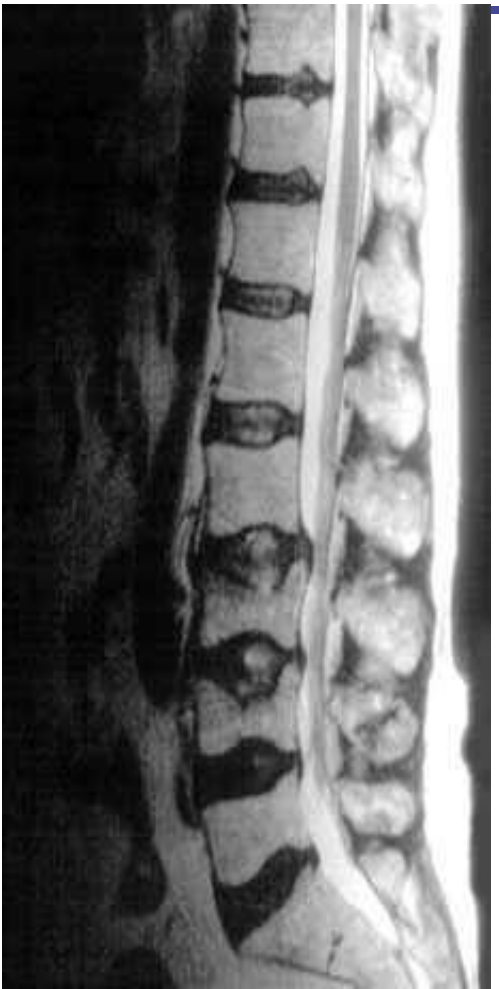


A Saúde Óssea no Mieloma Múltiplo: Porque é Importante

Prof. Dra. Vania Tietsche de Moraes Hungria

Professora Adjunta da Disciplina de Hematologia e Oncologia da Faculdade de Ciências Médicas da Santa Casa de São Paulo
Diretora Médica Clínica São Germano



Bone Disease in Multiple Myeloma

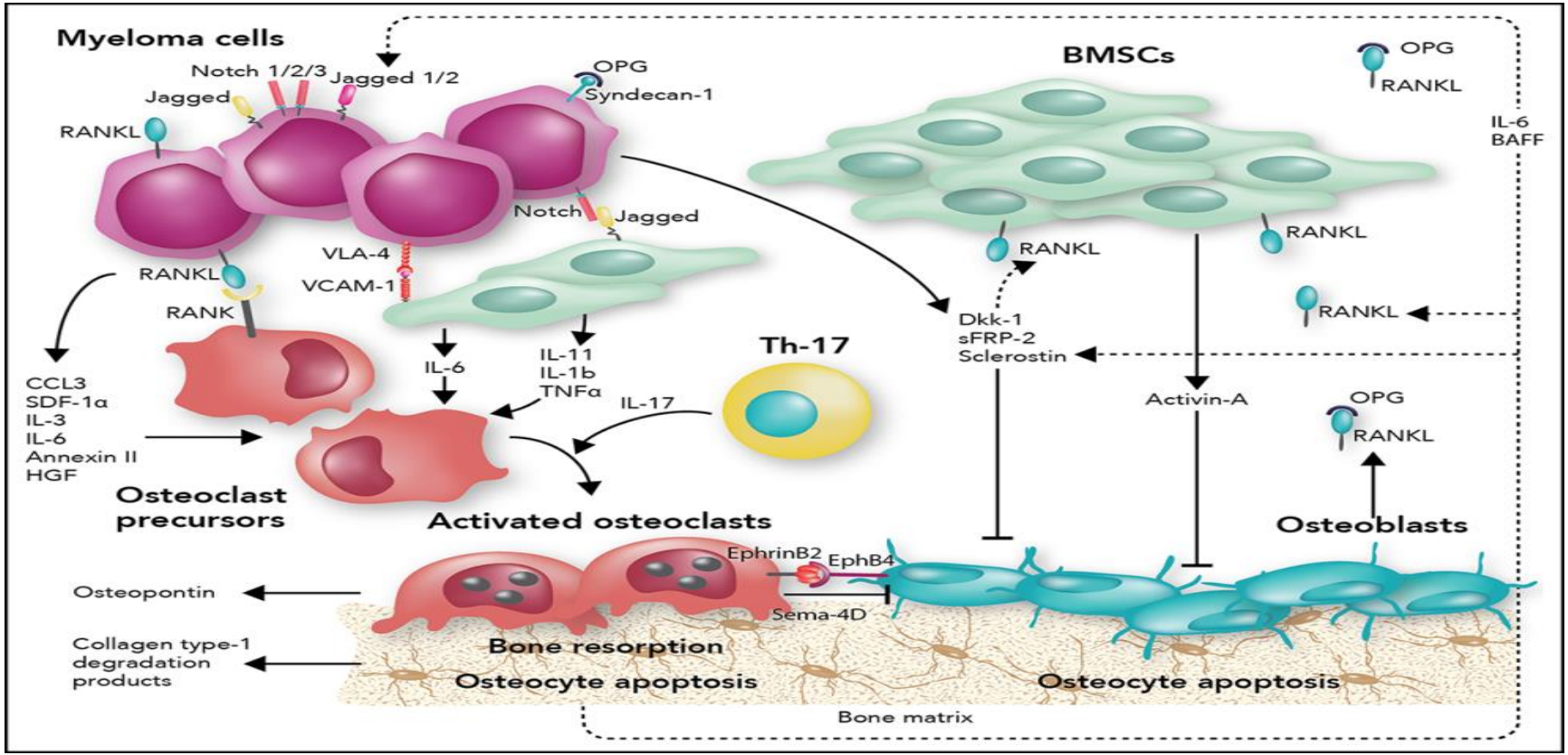
- **A burdensome and frequent complication in MM**
  - **Present in up to 80% of patients at diagnosis**
  - **Pathologic fractures 26% at diagnosis**
  - **Compression fracture 22% at diagnosis**
- **Characterized by osteolytic bone lesions secondary to increased bone resorption and impaired bone formation**

- **Sequelae**
  - Pathological fractures
  - Osteoporosis
  - Hypercalcemia
  - Bone pain
  - Spinal cord compression

- **At diagnosis, lytic lesions by WBXR:**
  - Vertebrae in 65% of patients
  - Ribs in 45%
  - Skull in 40%
  - Shoulders in 40%
  - Pelvis in 30%
  - Long bones in 25%

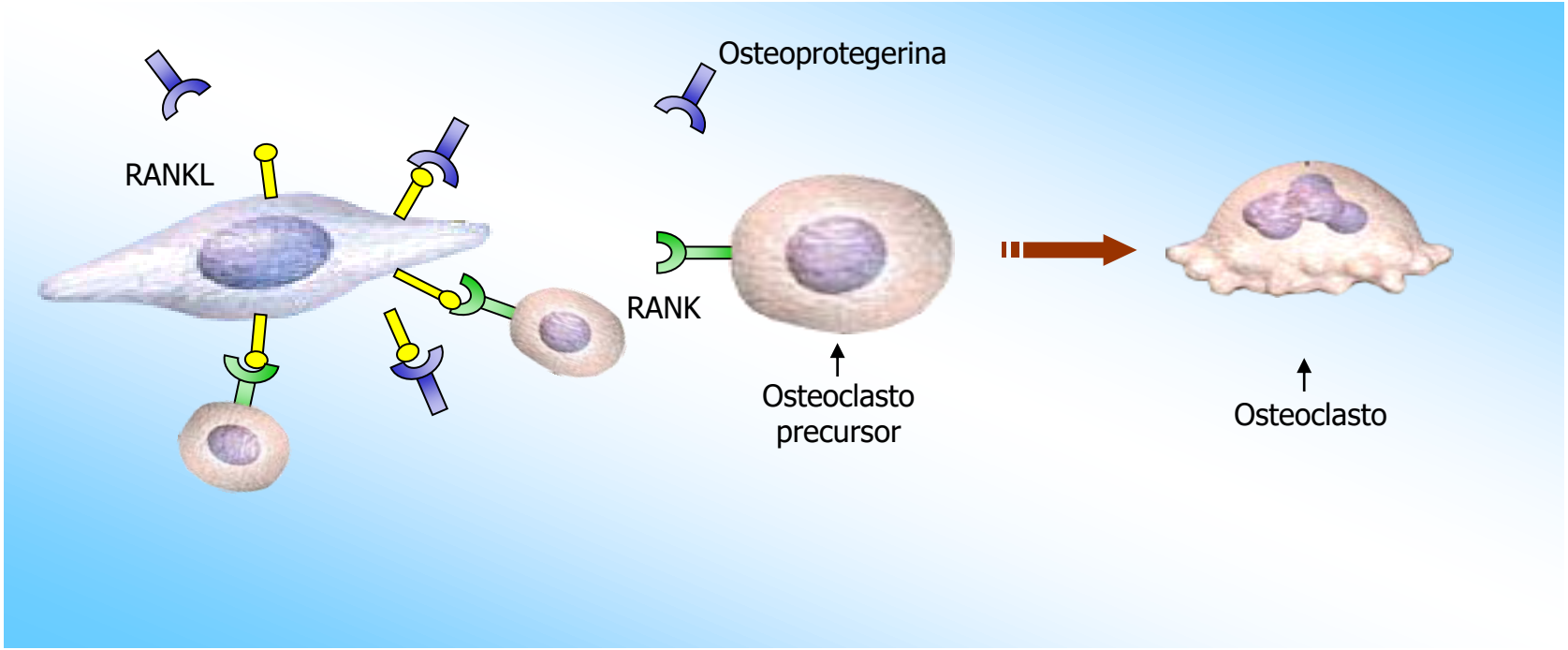
1. Terpos E, et al. J Clin Oncol. 2011;29:1907-1915; 2. Dimopoulos M, et al. Leukemia. 2009;23:1545-1556.

Myeloma Bone Disease: from biology findings to treatment



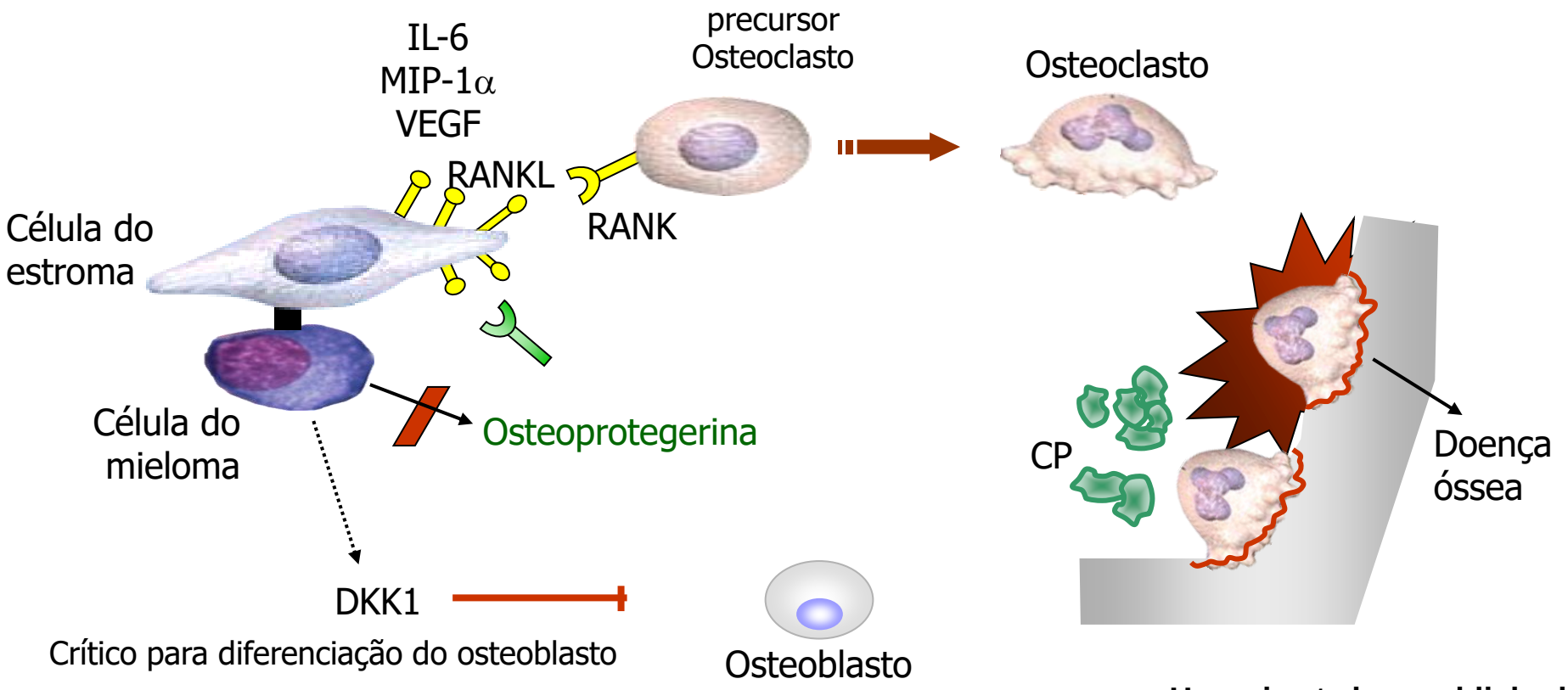
Terpos et al, Blood, 2019

Sistema RANKL/OPG

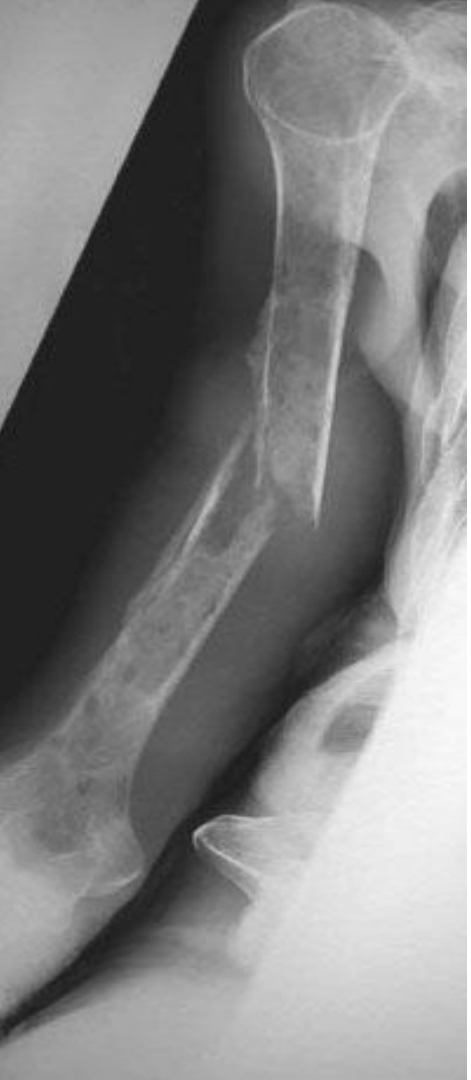


Hungria et al, unpublished

Doença Óssea



Hungria et al, unpublished



Tratamento da Doença Óssea do Mieloma Múltiplo

Bisfosfonatos

- Inibidores específicos da atividade osteoclástica
- Eficientes no tratamento da hipercalcemia
- Reduzem eventos esqueléticos
- Melhoram qualidade de vida

Table 1. Summary of major randomized clinical trials on bone-targeting agents for treatment of MBD

Study	Treatment drug	Treatment schedule	Patients, n	Median time to first SRE, mo	SRE incidence, %	ONJ incidence, %	Renal toxicity, %
52	Pamidronate vs placebo	90 mg of pamidronate every 4 wk for 9 cycles	196 vs 181	Shorter in placebo group ($P = .001$)	24 vs 41 ($P < .001$)	NR	NR
53	ZA vs pamidronate	4 or 8 mg of ZA IV or 90 mg of IV pamidronate every 3-4 wk for 12 mo	129 vs 65	12.5 vs 9.4	NR	NR	NR
54	Pamidronate	30 vs 90 mg of pamidronate	252 vs 252	10.2 vs 9.2 ($P = .63$)	33.7 vs 35.2	0.8 vs 3.2	NR
55,56	ZA vs clodronate	4 mg of ZA IV every 3-4 wk or 1600 mg of clodronic acid orally daily	981 vs 979	NR	27 vs 35 ($P = .0004$)	4 vs <1	Similar for 2 treatment groups ($P = .55$)
57	ZA	ZA every 12 vs every 4 wk	139 vs 139	NR	55 vs 60	NR	NR
58	Denosumab vs ZA	120 mg of denosumab sc plus placebo IV or ZA 4 mg IV plus placebo sc every 4 wk	859 vs 859	22.8 vs 24 ($P_{noninferiority} = .01$)	43.8 vs 44.6	4.1 vs 2.8	10 vs 17.1

NR, not reported; ONJ, osteonecrosis of the jaw; sc, subcutaneously; ZA, zoledronic acid.

First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial

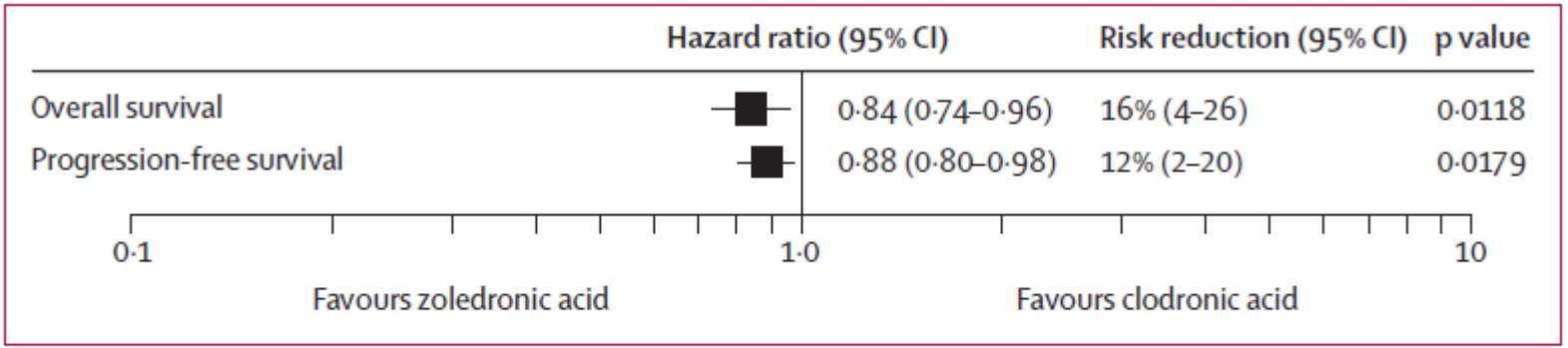


Figure 3: Hazard ratios for overall survival and progression-free survival for zoledronic acid versus clodronic acid during the full follow-up period

Morgan et al, Lancet 2010; 376:1989-99

MRC Myeloma IX Conclusões:

- Aumento da sobrevida global e sobrevida livre de progressão
- Benefício para pacientes sem lesão óssea
- Insuficiência renal similar
- Osteonecrose: ácido zoledrônico 4% vs clodronato 1%

Morgan et al, Lancet 2010; 376:1989-99

Bisfosfonatos - Dúvidas

- Quando iniciar?
- Por quanto tempo?
- Como manejar ONJ e alterações renais?

Bisphosphonates Choice: Cochrane Meta-Analysis[1,2]

- No evidence of superiority in any specific aminobisphosphonate (**zoledronate, pamidronate,** or ibandronate) for any outcome
- However, **zoledronate appears to be superior** to placebo and etidronate in **improving OS**

IMWG Recommendations for BPs Choice

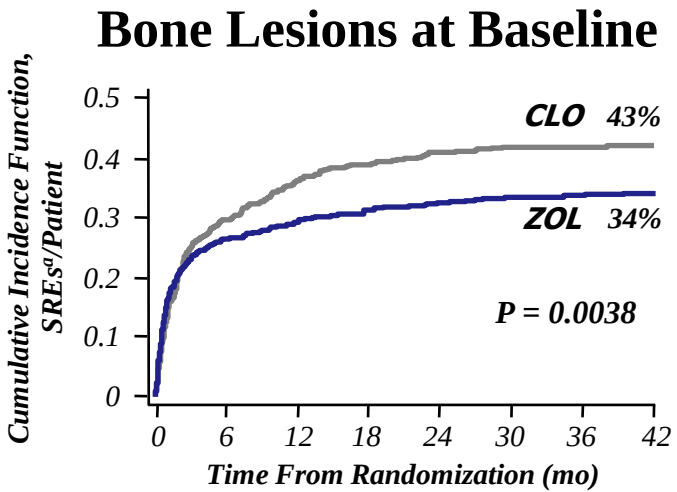
- **ZOL and PAM exhibit comparable efficacy in reducing SREs** in patients with MM and are recommended for preventing SREs in MM patients (grade A)
- IV **ZOL is recommended over oral CLO** because it is significantly more efficacious in preventing SREs (grade A)
- **ZOL is the only BP shown to increase survival** in the whole studied population of a prospective randomized trial

OS = Overall Survival; CLO = Clodronate; ZOL = Zolodrenic Acid, SREs = skeletal-related events

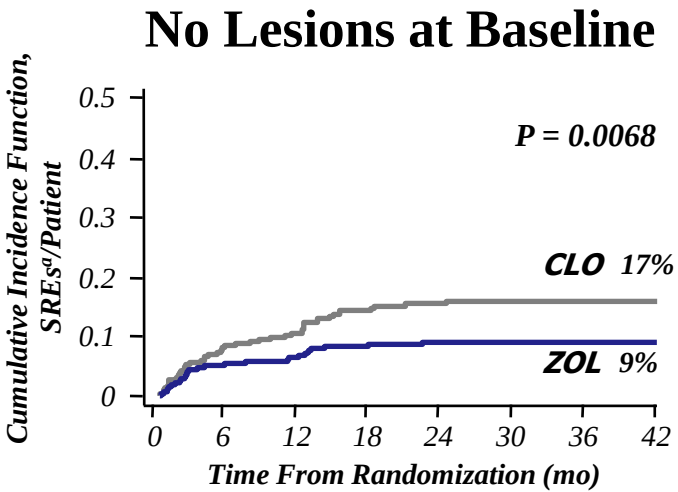
1. Mhaskar R, Redzepovic J, Wheatley K, et al. Bisphosphonates in multiple myeloma: a network meta-analysis. *Cochrane Database Syst Rev.* 2012(5):CD003188; 2. Terpos E, Morgan G, Dimopoulos MA, et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. *J Clin Oncol.* 2013;31(18):2347-2357.

When and how to start the treatment with BPs?

MRC Myeloma IX: ZOL ⬇ SREs vs CLO Regardless of Bone Lesions at Baseline



Graph 1. *Adapted from reference 1.*



Graph 2. *Adapted from reference 1.*

Highlights the importance of treating all patients regardless of skeletal morbidity at presentation

aSREs were defined as vertebral fractures, other fractures, spinal cord compression, and the requirement for radiation or surgery to bone lesions or the appearance of new osteolytic bone lesions.

BPs = Bisphosphonates; CLO = clodronate; MRC = Medical Research Council; SRE = skeletal-related event; ZOL = zoledronic acid.

1.Morgan GJ, Child JA, Gregory WM, et al. Effects of zoledronic acid versus clodronic acid on skeletal morbidity in patients with newly diagnosed multiple myeloma (MRC Myeloma IX): secondary outcomes from a randomised controlled trial. *Lancet Oncol.* 2011;12(8):743-752.

IMWG Recommendations: BPs Initiation and Treatment Duration

BPs Initiation

- BPs should be initiated in patients with MM, **with (grade A) or without (grade B) detectable osteolytic bone lesions on conventional radiography, who are receiving antimyeloma therapy** as well as patients with osteoporosis (grade A) or osteopenia (grade C) resulting from myeloma
- The **beneficial effect of ZOL** in patients **without detectable bone disease** by MRI or PET/CT is **unknown**

BPs Treatment Duration

- **ZOL** improves OS and reduces SREs over CLO in patients who received treatment for more than two years; **thus it should be given until disease progression in patients not in CR/VGPR and further continued at relapse (grade B)**
- For patients in **CR/VGPR**, the optimal treatment duration of BPs is unclear; **the panel agrees that BPs should be given for at least 12 months and up to 24 months and then at the physician's discretion** (grade D; panel consensus)

OS = Overall Survival; CLO = Clodronate; ZOL = Zolodrenic Acid, SREs = skeletal-related events, MM = Multiple Myeloma, MRI = Magnetic Ressonance Imaging; PET/CT = Positron Emission Tomography, CR = complete response; vgPR = very good partial response
BPs = Bisphosphonates

1. Terpos E, Morgan G, Dimopoulos MA, et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. *J Clin Oncol.* 2013;31(18):2347-2357.

IMWG Guidelines: BPs and ONJ

- Preventive strategies should be adopted to avoid ONJ
  - Patients should receive a comprehensive dental examination and be educated regarding optimal dental hygiene (grade C)
  - Existing dental conditions should be treated before initiating BP therapy (grade C; panel consensus)
  - After BP treatment initiation, unnecessary invasive dental procedures should be avoided
- Temporary suspension of BP treatment should be considered if invasive dental procedures are necessary (grade D). **The panel's consensus is to stop BPs for 90 days before and after invasive dental procedures** (tooth extraction, dental implants, and surgery to the jaw). BPs do not need to be discontinued for routine dental procedures including root canal
- **Initial treatment of ONJ should include discontinuation of BPs until healing occurs** (grade C)

BPs = Biphosphonates, ONJ = Osteonecrosis of the Jaw

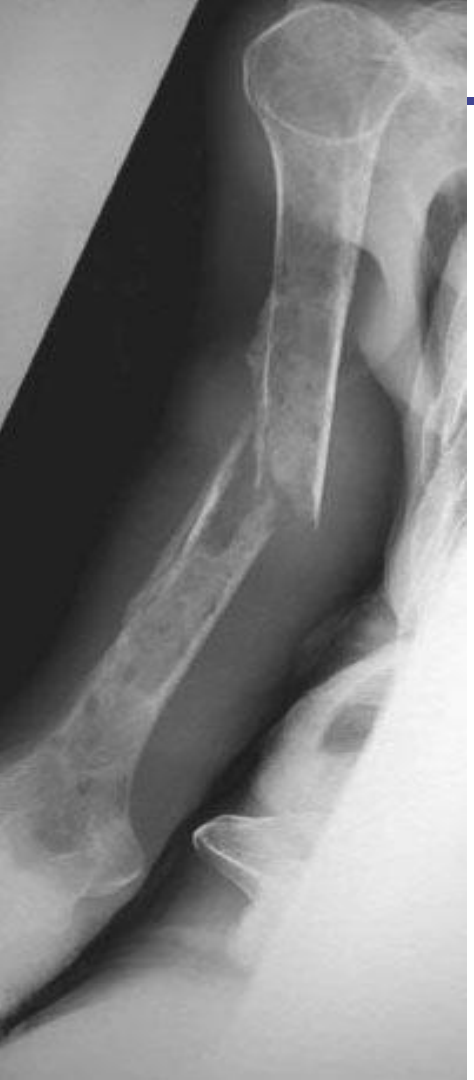
1. Terpos E, Morgan G, Dimopoulos MA, et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. *J Clin Oncol.* 2013;31(18):2347-2357.

Patients With Renal Failure

- Patients with mild to moderate renal impairment (CrCl 30–60 mL/min) should receive reduced doses of zoledronic acid and clodronate. No change to zoledronic acid infusion time is recommended
- Pamidronate should be administered via 4-hours infusion in patients with mild to moderate renal impairment
- **Pamidronate and zoledronic acid are not recommended for patients with CrCl < 30 mL/min**
- Bisphosphonate therapy should be discontinued in patients experiencing renal problems until CrCl returns to within 10% of baseline values

CrI = Creatinine clearance

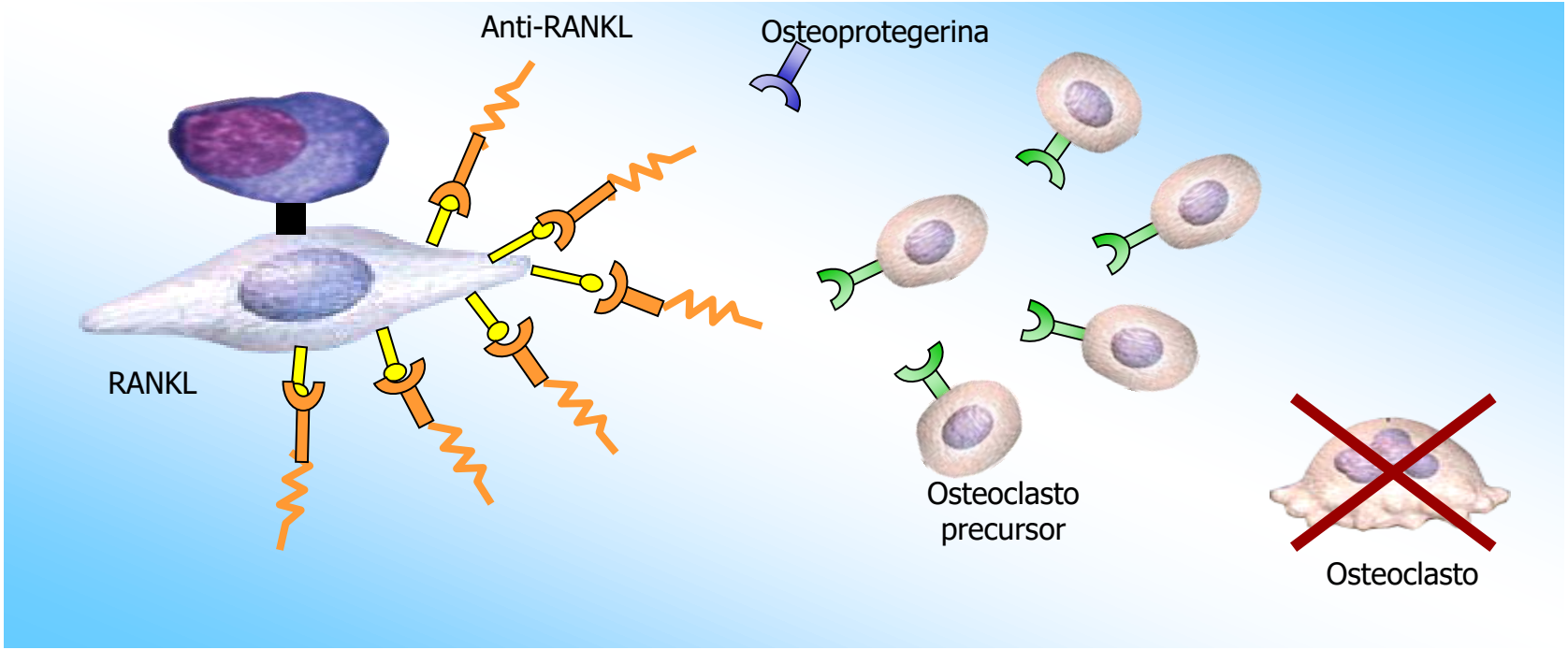
1. Terpos E, Morgan G, Dimopoulos MA, et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. *J Clin Oncol.* 2013;31(18):2347-2357.



Tratamento da Doença Óssea do Mieloma Múltiplo

Novos agentes

Sistema RANKL/OPG



Hungria et al, unpublished

Denosumab is the First Fully Human mAb Against RANKL in Clinical Use[1]

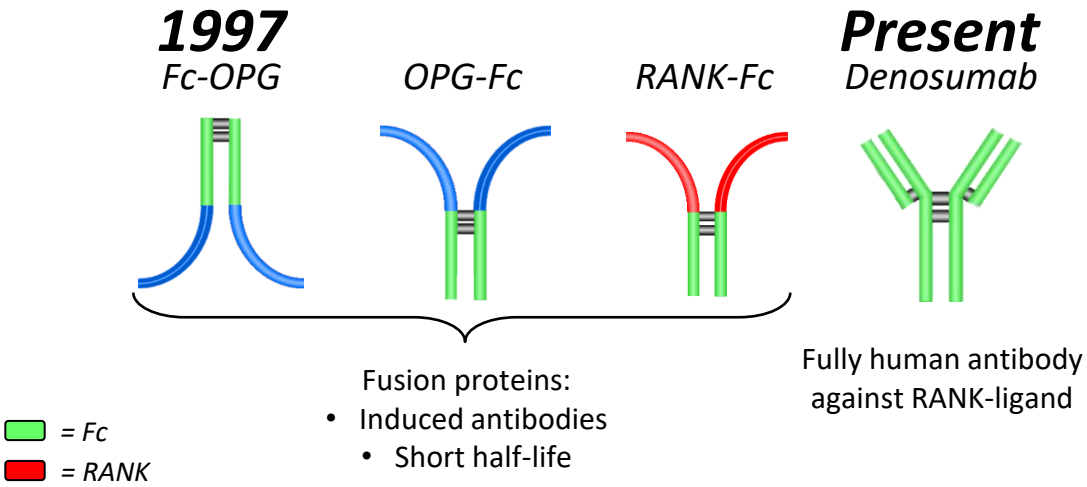
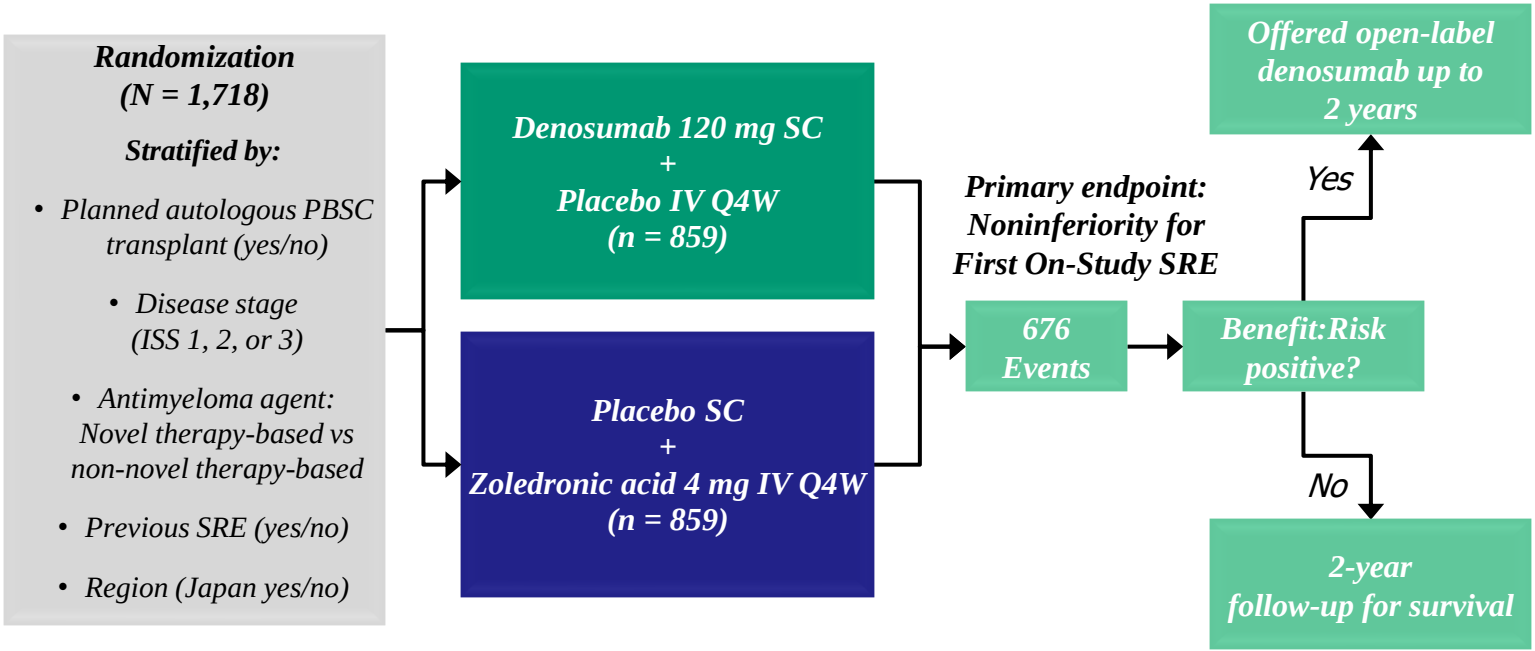


Figure 1. Adapted from reference 1.

1. Simonet WS, Lacey DL, Dunstan CR, et al. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. *Cell.* 1997;89(2):309-319.

Denosumab vs Zoledronic Acid in Myeloma: Study Design[1]



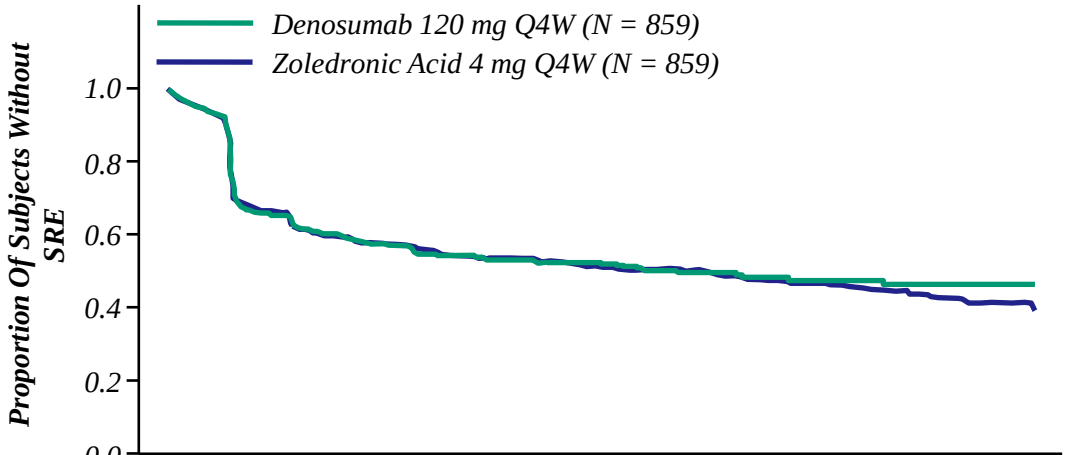
Graph 1. *Adapted from reference 1.*

SRE = Skeletal-related event

1. Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. *Lancet Oncol.* 2018;19(3):370-381

Results: First On-Study SRE

Primary Endpoint Met: Noninferiority for First On-Study SRE



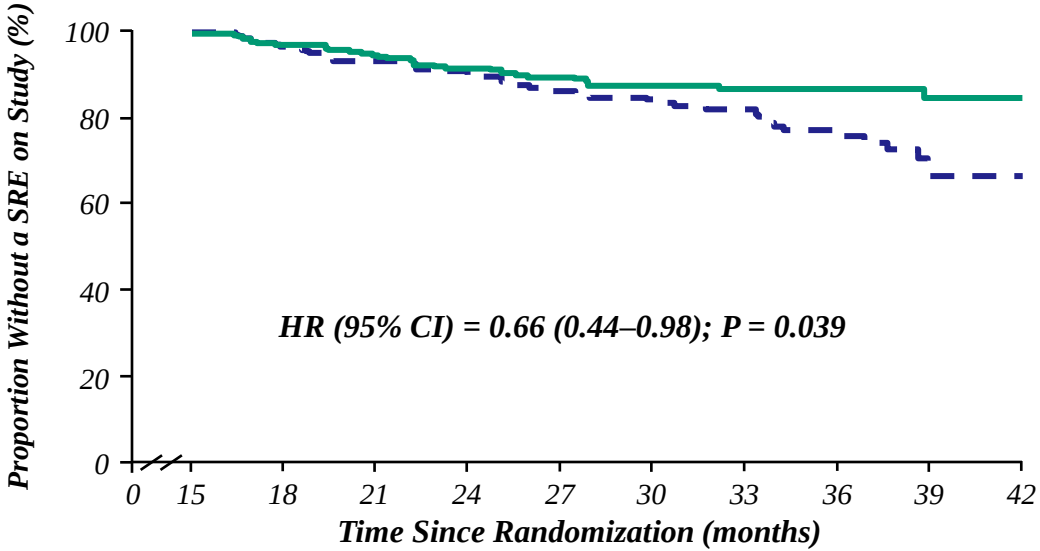
Denosumab 120 mg Q4W	859	583	453	370	303	243	197	160	127	99	77	50	35	22
Zoledronic Acid 4 mg Q4W	859	595	450	361	288	239	190	152	125	95	69	48	31	18

Graph 1. *Adapted from reference 1.*

1. Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. *Lancet Oncol.* 2018;19(3):370-381.

SRE = Skeletal-related event

Post-hoc Landmark Analysis at 15 Months



Graph 1. *Adapted from reference 1.*

Number at risk (censored)										
Denosumab:	450 (0)	366 (72)	300 (58)	238 (53)	183 (50)	143 (36)	98 (44)	68 (30)	41 (26)	16 (25)
Zoledronic Acid:	459 (0)	367 (78)	294 (61)	231 (54)	176 (46)	129 (43)	90 (36)	58 (26)	31 (22)	10 (21)

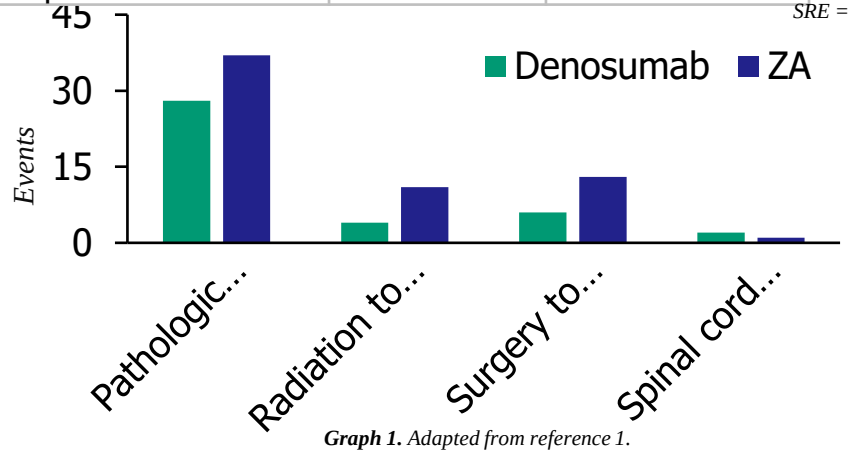
CI Confidence interval; HR Hazard ratio.

1. Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. *Lancet Oncol.* 2018;19(3):370-381.

Results: Type of SRE, Landmark Analysis

Total First SREs

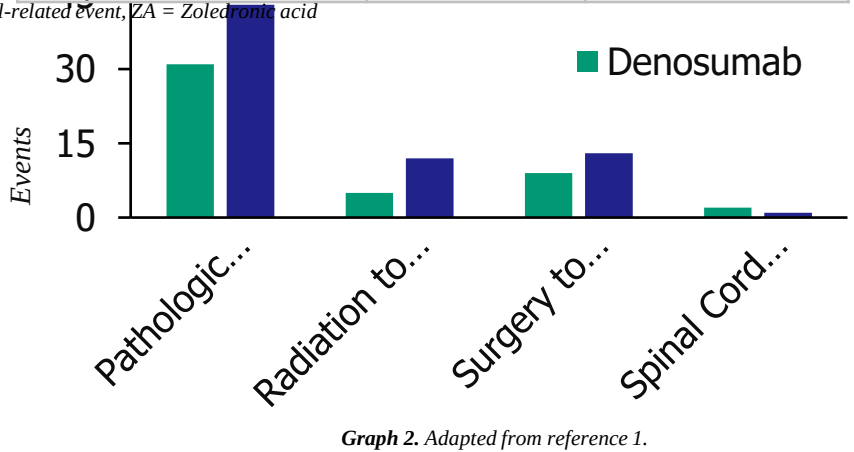
	Denosumab, n	Zoledronic acid, n
Fracture	28	37
Radiation to bone	4	11
Surgery to bone	6	13
Spinal cord compression	2	1



Graph 1. *Adapted from reference 1.*

Total SREs

	Denosumab, n	Zoledronic acid, n
Fracture	31	43
Radiation to bone	5	12
Surgery to bone	9	13
Spinal cord compression	2	1

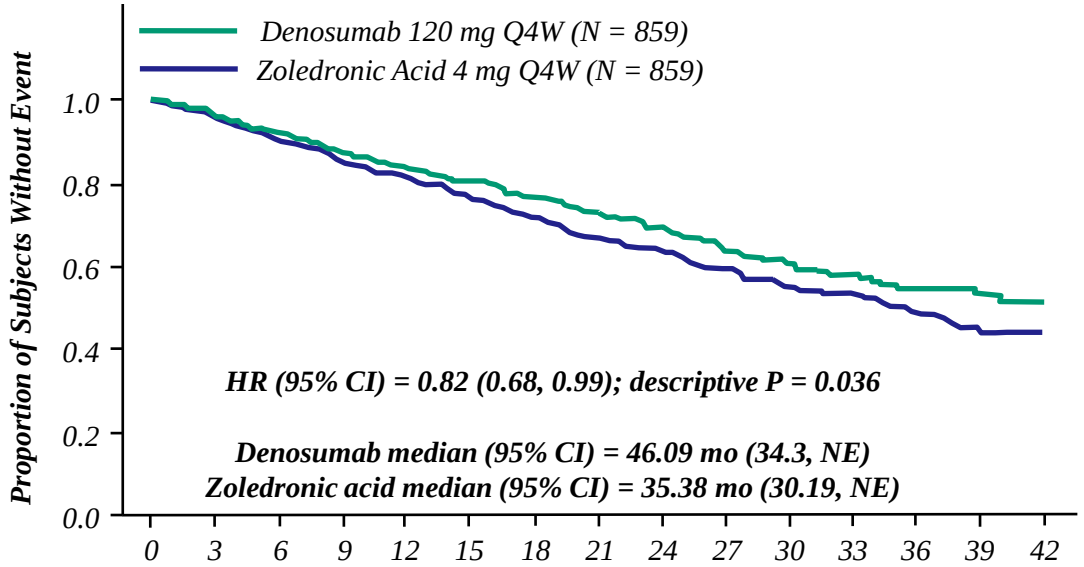


Graph 2. *Adapted from reference 1.*

SRE = Skeletal-related event, ZA = Zoledronic acid

1. Terpos E, Roodman GD, Willenbacher W, et al. Comparison of denosumab (dmb) with zoledronic acid (za) for the treatment of bone disease in patients (pts) with newly diagnosed multiple myeloma; an international, randomized, double blind trial. Haematologica. 2017;102(s1):318. Abstract S782.

Results: Progression-Free Survival



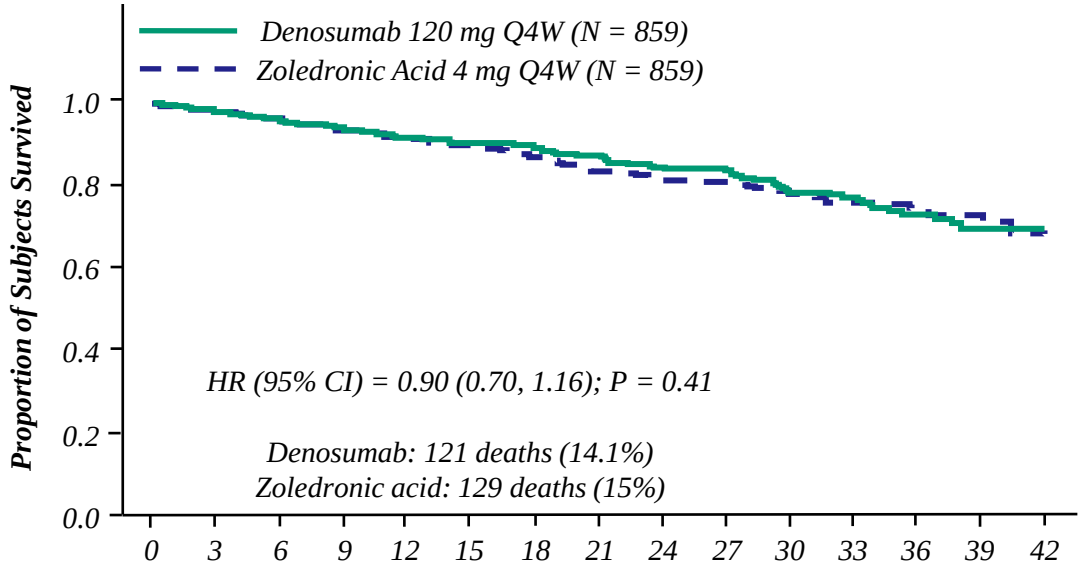
Graph 1. *Adapted from reference 1.*

CI Confidence interval; HR Hazard ratio.

Denosumab 120 mg Q4W	859	789	703	583	501	411	329	269	214	157	125	82	57	35	14
Zoledronic Acid 4 mg Q4W	859	806	690	584	495	404	324	252	206	159	112	78	53	30	9

1. Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. *Lancet Oncol.* 2018;19(3):370-381.

Results: Overall Survival



CI Confidence interval; HR Hazard ratio.

Denosumab 120 mg Q4W	859	809	737	640	565	477	395	344	288	229	175	130	85	48	19
Zoledronic Acid 4 mg Q4W	859	830	737	652	568	488	414	348	289	233	179	127	87	49	15

Graph 1. *Adapted from reference 1.*

1. Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. *Lancet Oncol*. 2018;19(3):370-381.

Results: Adverse Events of Interest[1]

	Zoledronic Acid (N = 852) n (%)	Denosumab (N = 850) n (%)
Hypocalcemia	106 (12.4)	144 (16.9)
Serious AEs of hypoglycemia	2 (0.2)	8 (0.9)
Adjudicated positive osteonecrosis of the jaw	24 (2.8)	35 (4.1)
Adjudicated positive atypical femur fracture	0	0
AEs potentially associated with hypersensitivity	189 (22.2)	219 (25.8)
Serious AEs potentially associated with hypersensitivity	9 (1.1)	5 (0.6)
Musculoskeletal pain	425 (49.9)	407 (47.9)
Infections and infestations	500 (58.7)	537 (63.2)
Serious AEs of infections and infestations	163 (19.1)	165 (19.4)
New primary malignancy	12 (1.4)	22 (2.6)
Renal toxicity TEAEs	146 (17.1)	85 (10.0)
in patients with baseline CrCl < 60 mL/min	58/220 (26.4)	30/223 (12.9)
Creatinine > 2 mg/dL	54/823 (6.6)	31/824 (3.8)
in patients with baseline CrCl < 60 mL/min	32/203 (15.8)	20/216 (9.3)
Creatinine doubled from baseline	55/840 (6.5)	28/841 (3.3)
in patients with baseline CrCl < 60 mL/min	16/220 (7.3)	6/233 (2.6)

Table 1. *Adapted from reference 1.*
CrCl = Creatinine clearance; TEAEs = treatment-related adverse events

1. Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. Lancet Oncol. 2018;19(3):370-381.

Conclusions for Denosumab

- **Non-inferiority was demonstrated for the primary endpoint of time to first SRE**
- **However, the 15-month landmark analysis demonstrated an improved delay in time to first skeletal-related events for patients treated with denosumab**
- **Progression-free survival for denosumab was longer (10.7 months) compared to zoledronic acid (ZA), with an HR (95% CI) = 0.82 (0.68, 0.99), descriptive *P* = 0.036**
- Safety data from this study were comparable to those seen in the previous SRE studies, with overall adverse events similar between the arms
  - There were 35 (4.1%) and 24 (2.8%) positively adjudicated events of osteonecrosis of jaw (ONJ) in the denosumab arm and ZA arm, respectively
  - Hypocalcemia events for denosumab and ZA were 144 (16.9%) and 106 (12.4%), respectively, with no grade 5 events
  - **Fewer AEs potentially related to renal toxicity occurred with denosumab than ZA (10% vs 17.1%), as with acute phase reactions (5.4% vs 8.7%)**
- **The bone-specific benefits and observed prolongation of progression-free survival in combination with a better renal toxicity profile provides denosumab is the new standard of care for multiple myeloma patients**

SRE = Skeletal-related event; CI Confidence interval; HR Hazard ratio; AE = adverse event.

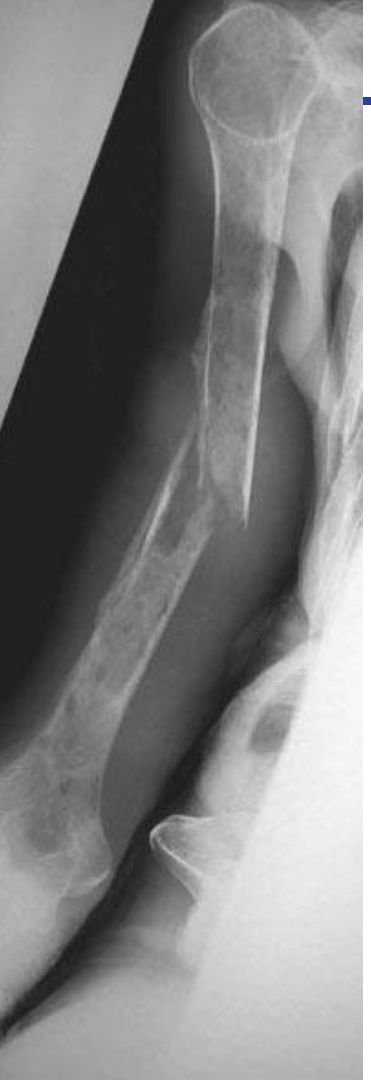
1. Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. Lancet Oncol. 2018;19(3):370-381.

Denosumab - Dúvidas

- Por quanto tempo? Debate em aberto!

  Não há dados em MM e tumores sólidos, apenas em osteoporose. Após 12 a 18 meses da descontinuação do denosumab, há aumento do risco de fraturas, que se deve há um efeito rebote com alteração da razão do RANKL/OPG, o que resulta em aumento da atividade osteoclástica. É recomendado uma dose de BP quando interromper o denosumab.

- Em Mieloma Múltiplo não há dados de como e quando parar o uso de Denosumab. São necessários estudos para definir esta recomendação.



Conclusões

- Melhor conhecimento da fisiopatologia da doença óssea
- Bisfosfonatos demonstram eficácia
- Denosumab demonstra eficácia
- Ambos demonstram importante melhora na qualidade de vida
- Novos agentes estão sendo testados

OBRIGADA!!!

hungria@dialdata.com.br

GBRAM
GRUPO BRASILEIRO DE MIELOMA