Myeloma Bone Disease and Physical Exercise in Myeloma

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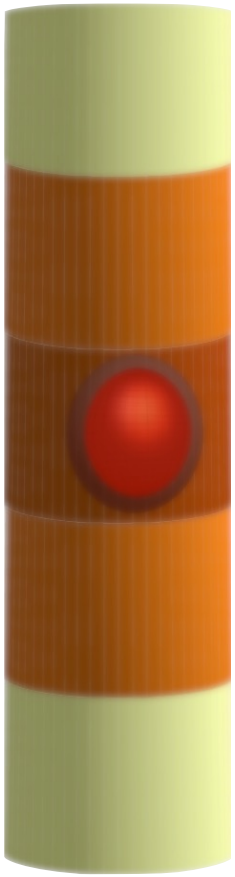
Malignant Bone Destruction in Multiple Myeloma

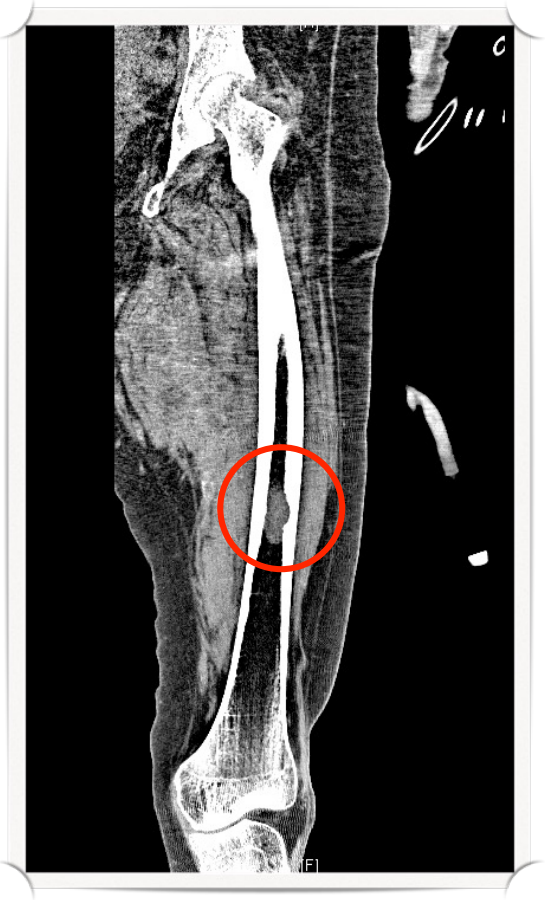


increased **cellularity** and **angiogenesis**

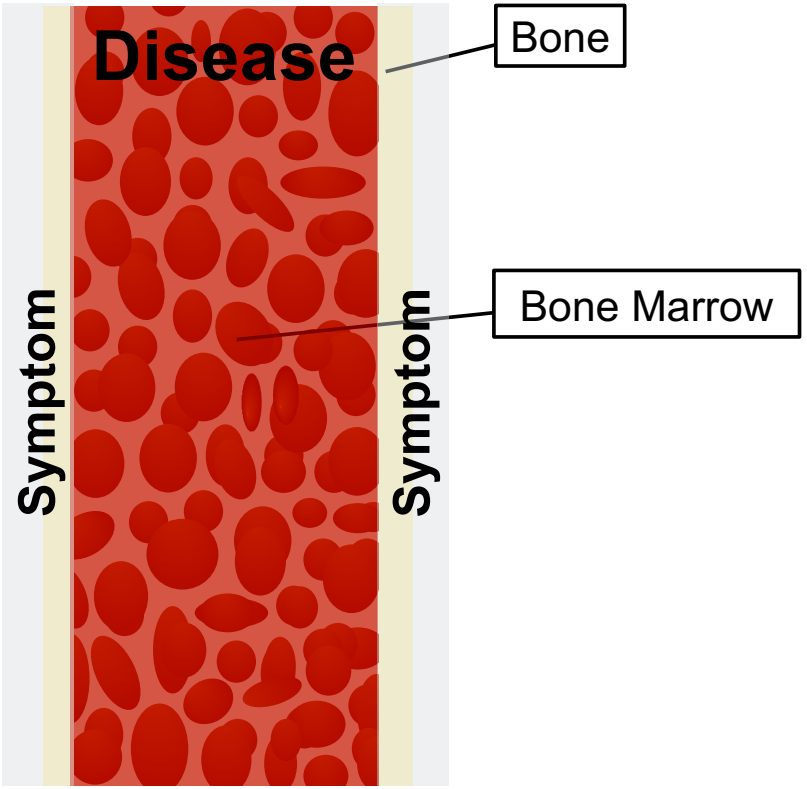
replacement of **fatty tissue**

impairment of **mineralized bone**

impairment of **bone metabolism**



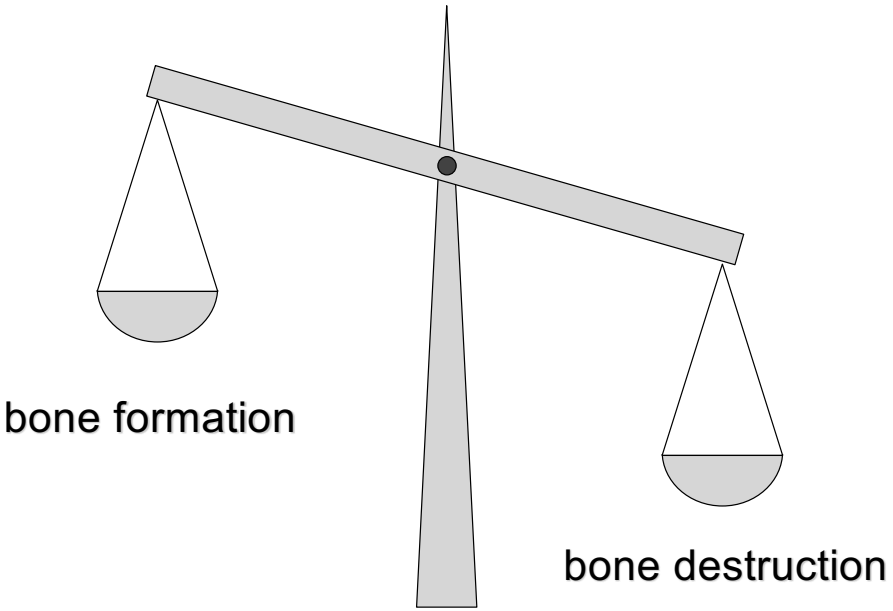
Multiple Myeloma



Pathophysiology of Bone disease

Initiating Factor:

- Imbalance of Osteoclasts and Osteoblasts



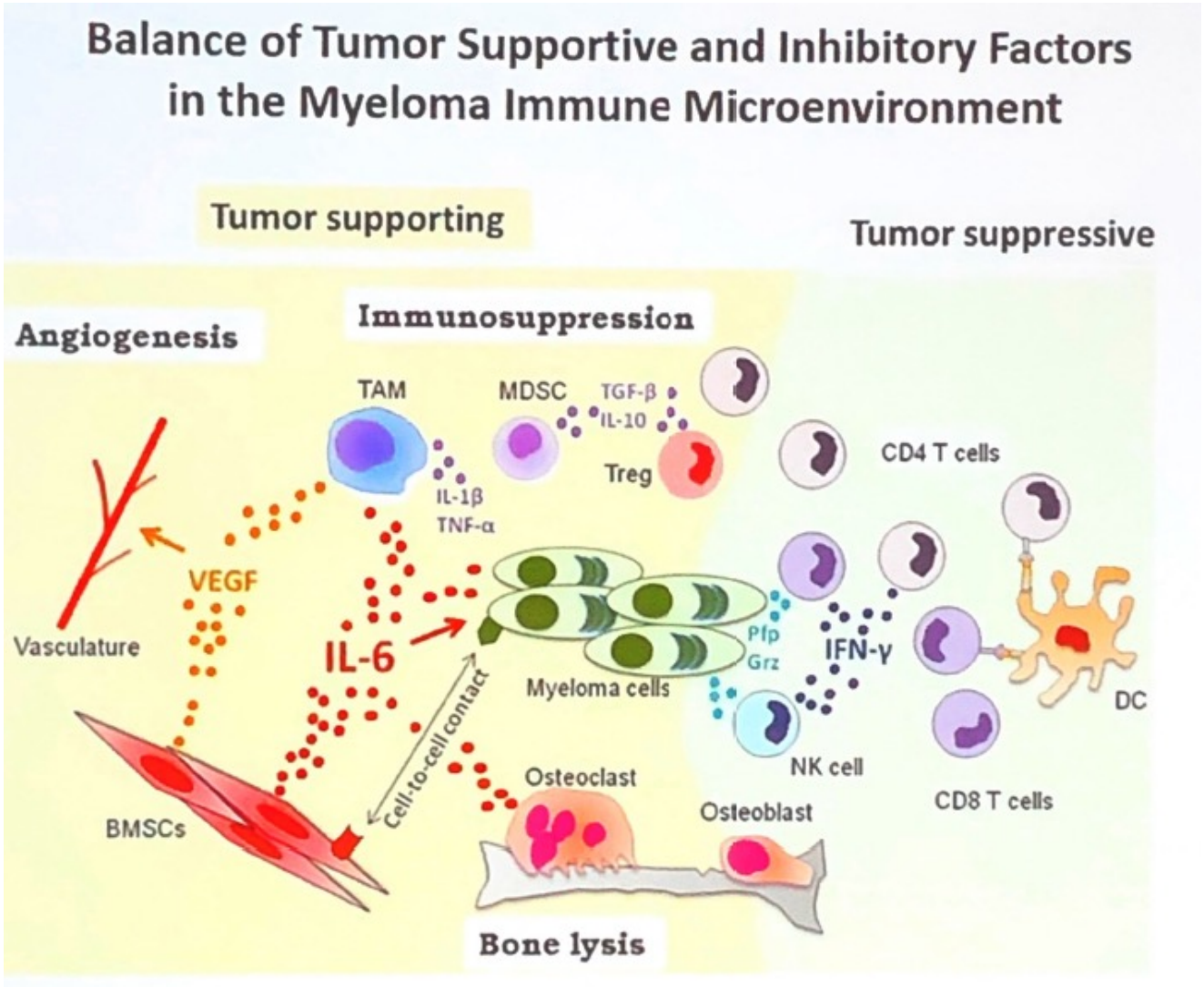
Pathophysiology of Bone disease

- **Osteoclasts:**
  - **Increased Number** of osteoclasts and **-activity** especially in proximity of myeloma cells
- **Osteoblasts:**
  - **reduced** osteoblast activity in proximity of myeloma cells
  - Normal to **increased** osteoblast activity in other regions

=> bone destruction by myeloma leads to formation of a „scar“

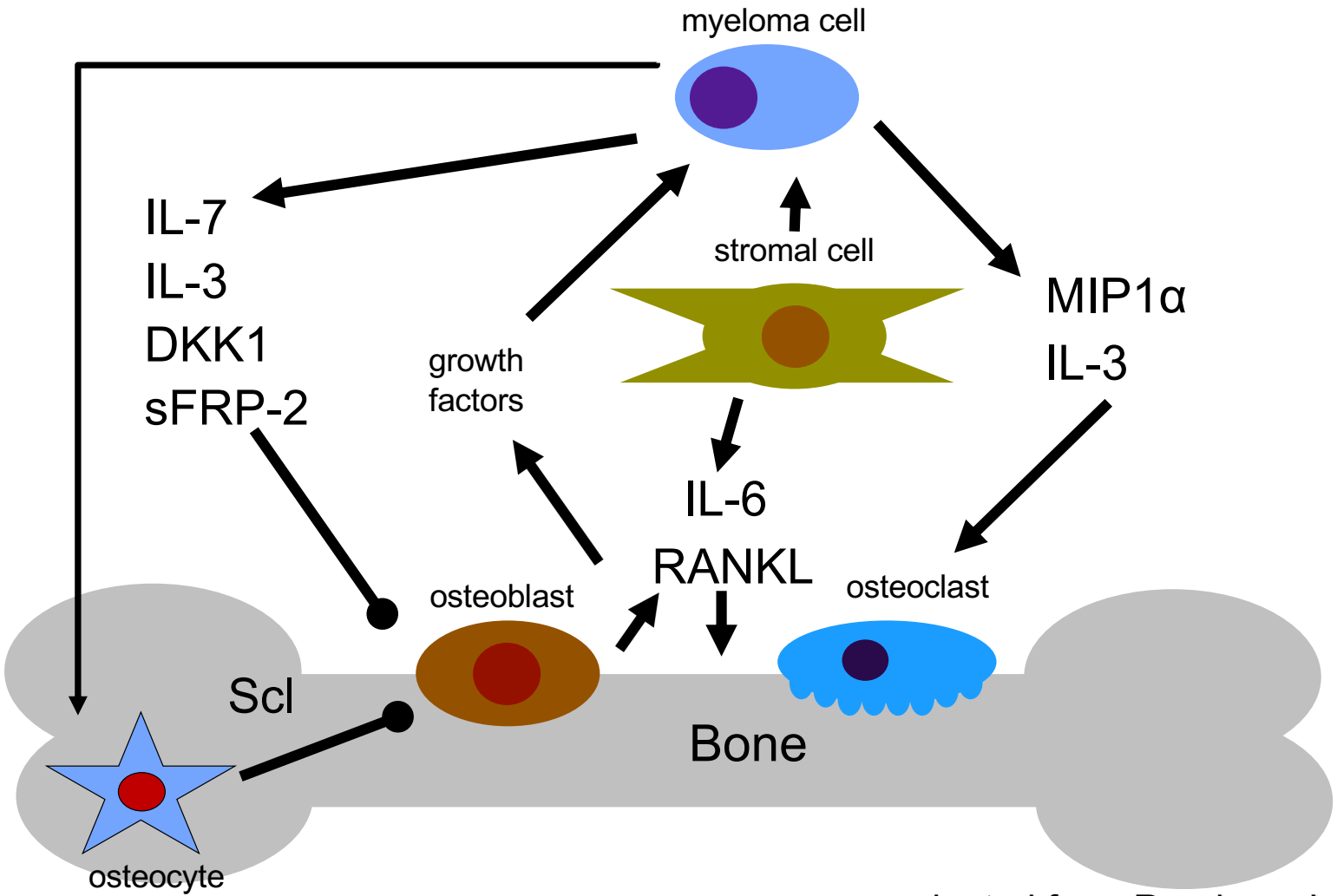
Valentin-Opran Br. J Haematol 1982

Bone Marrow Microenvironment



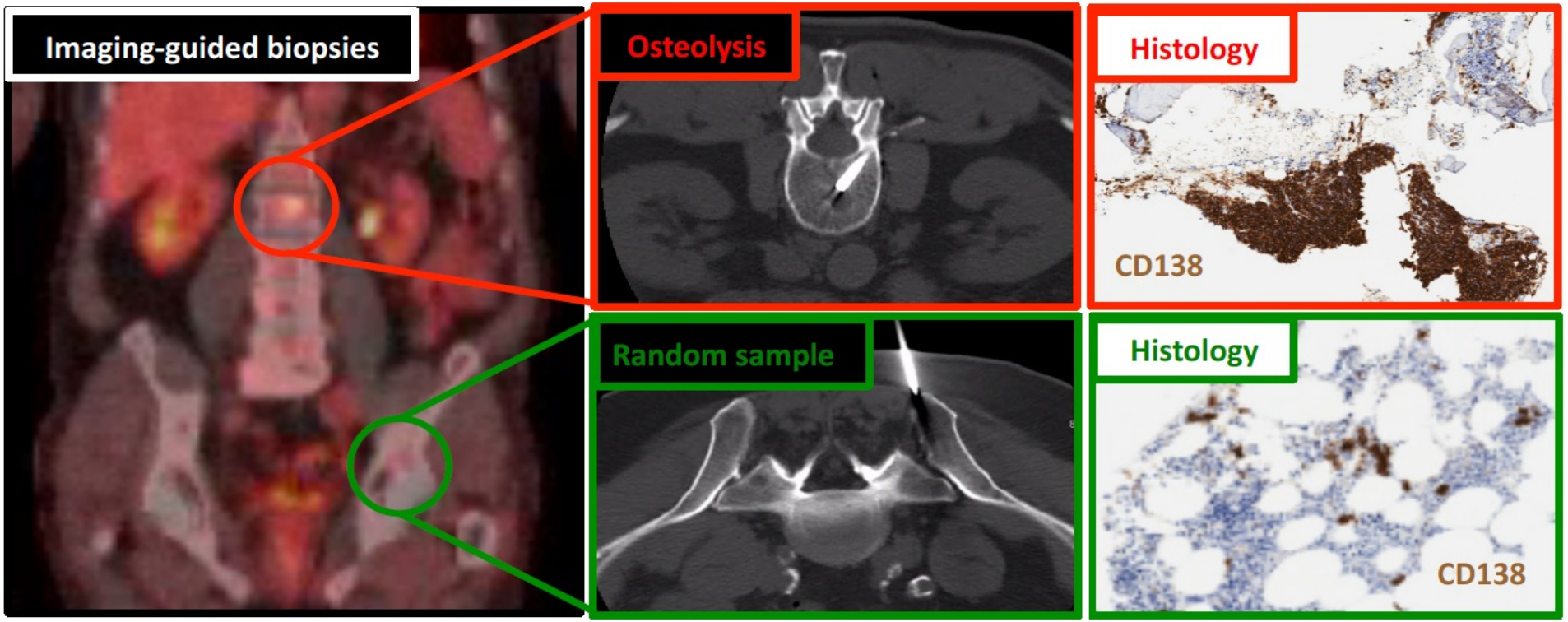
Guillerey CellMolLifeSci 2016

Pathophysiology of Bone disease



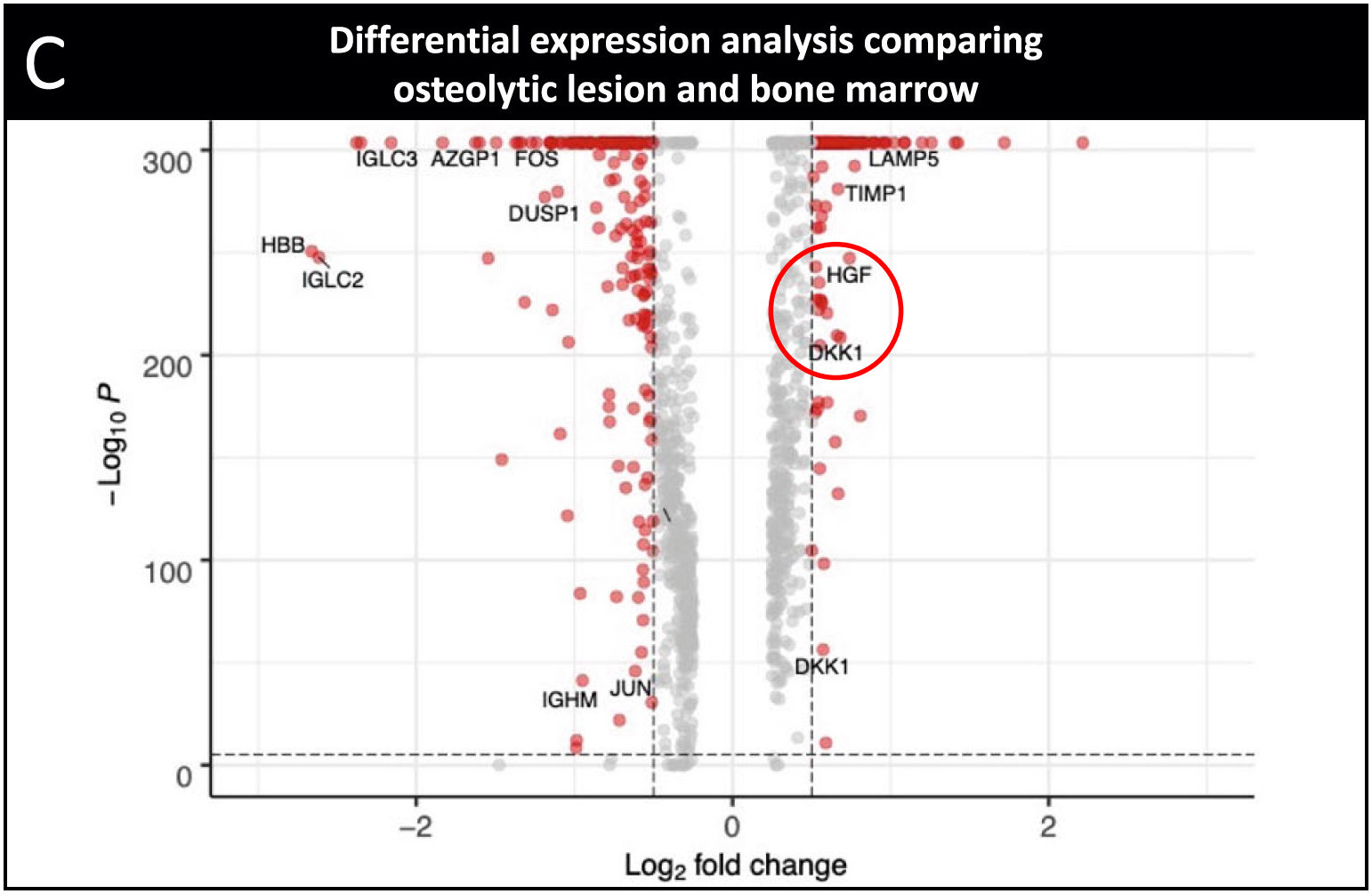
adapted from Roodman Leukemia 2009

Overexpression of Genes of Bone Turnover



Merz unpublished

Overexpression of Genes of Bone Turnover



Merz 2022 Nature Comm

Clinical Significance of Bone Disease in MGUS

- **Predictors of fracture risk:**
  - previous fracture
  - oral corticosteroid-intake
  - serum calcium
  - drugs

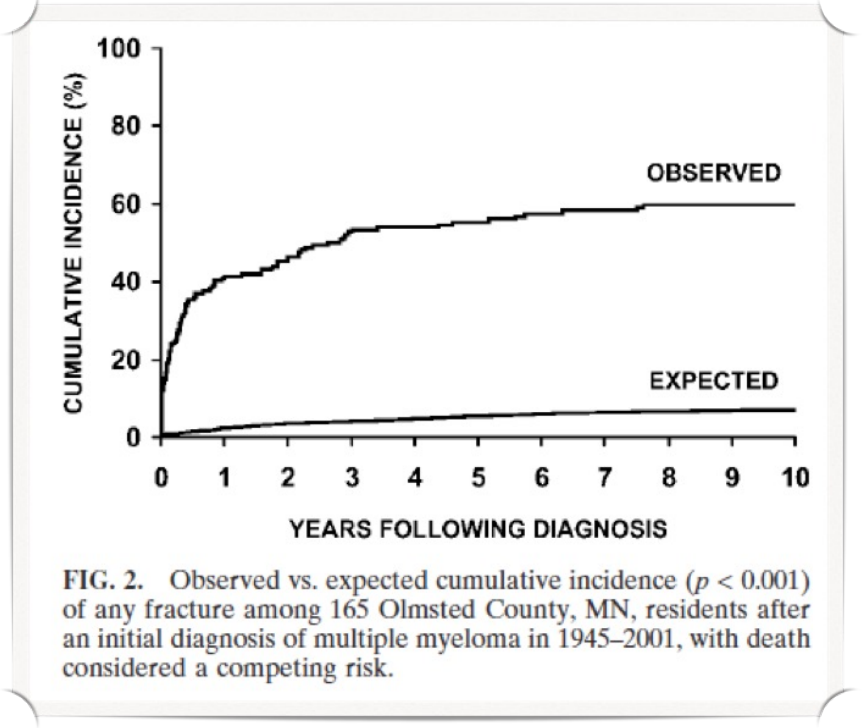


FIG. 2. Observed vs. expected cumulative incidence ($p < 0.001$) of any fracture among 165 Olmsted County, MN, residents after an initial diagnosis of multiple myeloma in 1945–2001, with death considered a competing risk.

Melton 2005 J Miner Res

Clinical Significance of Bone Disease in Multiple Myeloma

- Approx. 90% of patients show lytic changes
- Patienten with bone disease show a by 20% increased mortality
- Approx. 80% of all myeloma patients suffer

from a pathological fracture

=> important reasons of morbidity:

- bone pain
- pathological fractures
- hypercalcemia

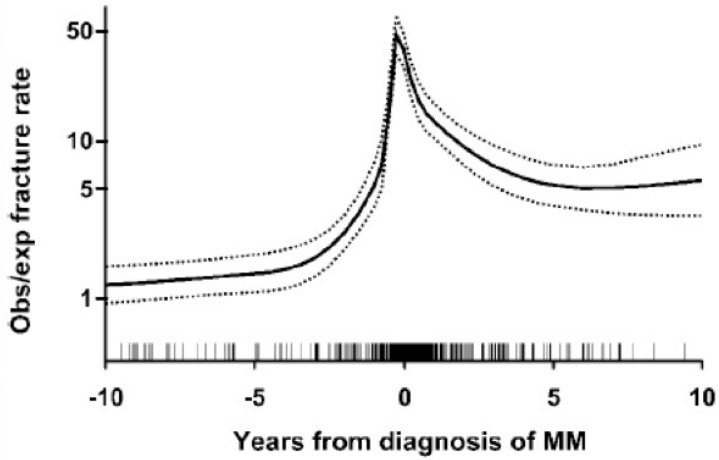


FIG. 1. Ratio of observed to expected fracture incidence (and 95% CI) by time before and after the diagnosis of multiple myeloma among 165 Olmsted County, MN, residents initially diagnosed in 1945–2001 (lines at the bottom of the figure indicate the occurrence of fractures).

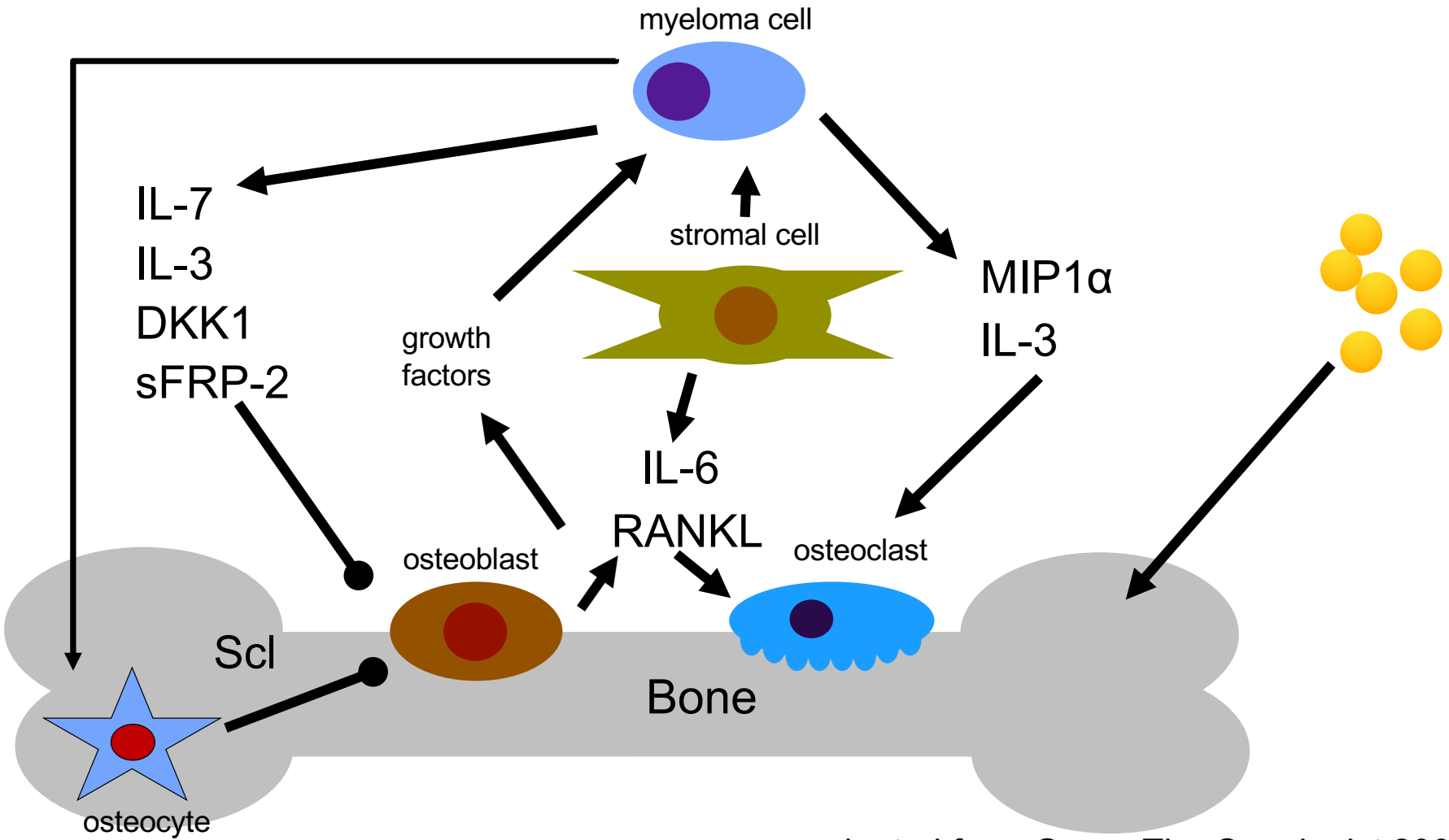
Saad 2007 Cancer, Melton 2005 J Miner Res

Treatment of Bone Disease

- **Bisphosphonates**
  - Inhibition of osteoclasts (no stimulation of osteoblasts)
  - Problems in case of longterm use:
    - Osteonecrosis of the Jaw
    - Nephrotoxicity
- **RANKL inhibitors**
- **Vertebroplasty and kyphoplasty**
- **Analgesia**
- **Controlling the underlying disease**

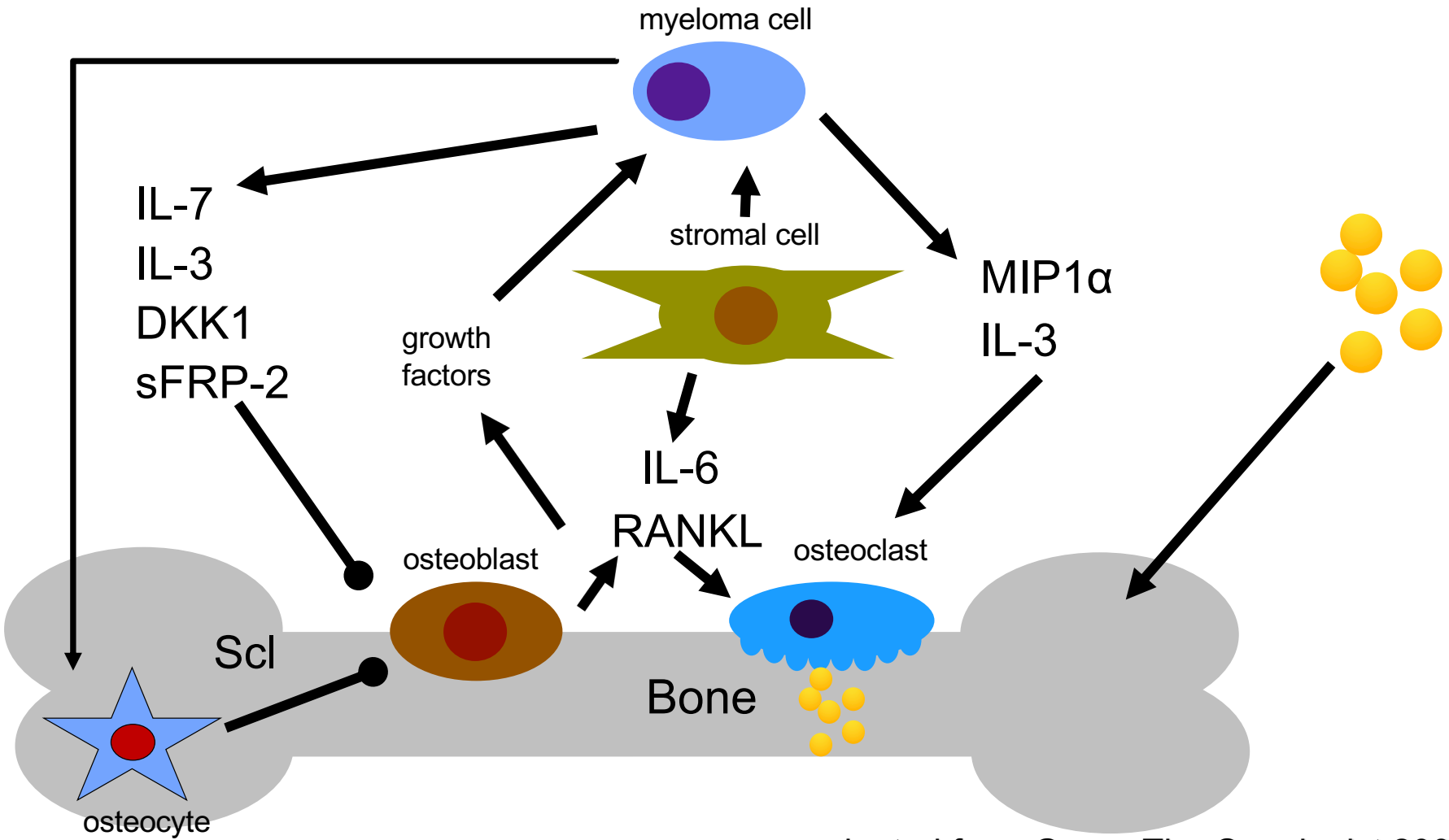
Kyle 1975 Mayo Clin Proc
Yeh 2006 Eur J Cancer
Roodman 2008 Hematology

Bisphosphonates – Mechanisms of Action



adapted from Green The Oncologist 2004

Bisphosphonates – Mechanisms of Action



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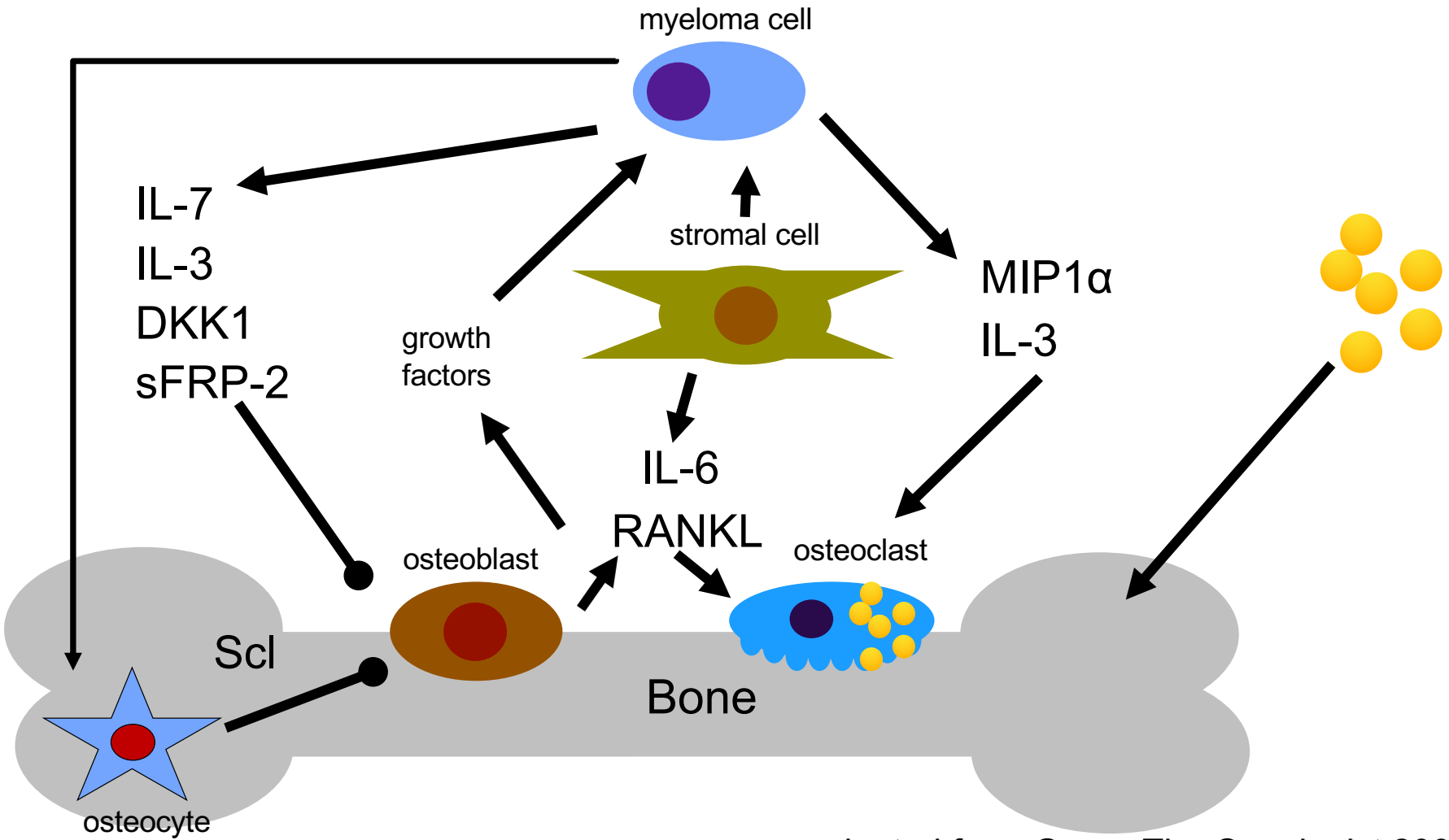
Bisphosphonates – Mechanisms of Action



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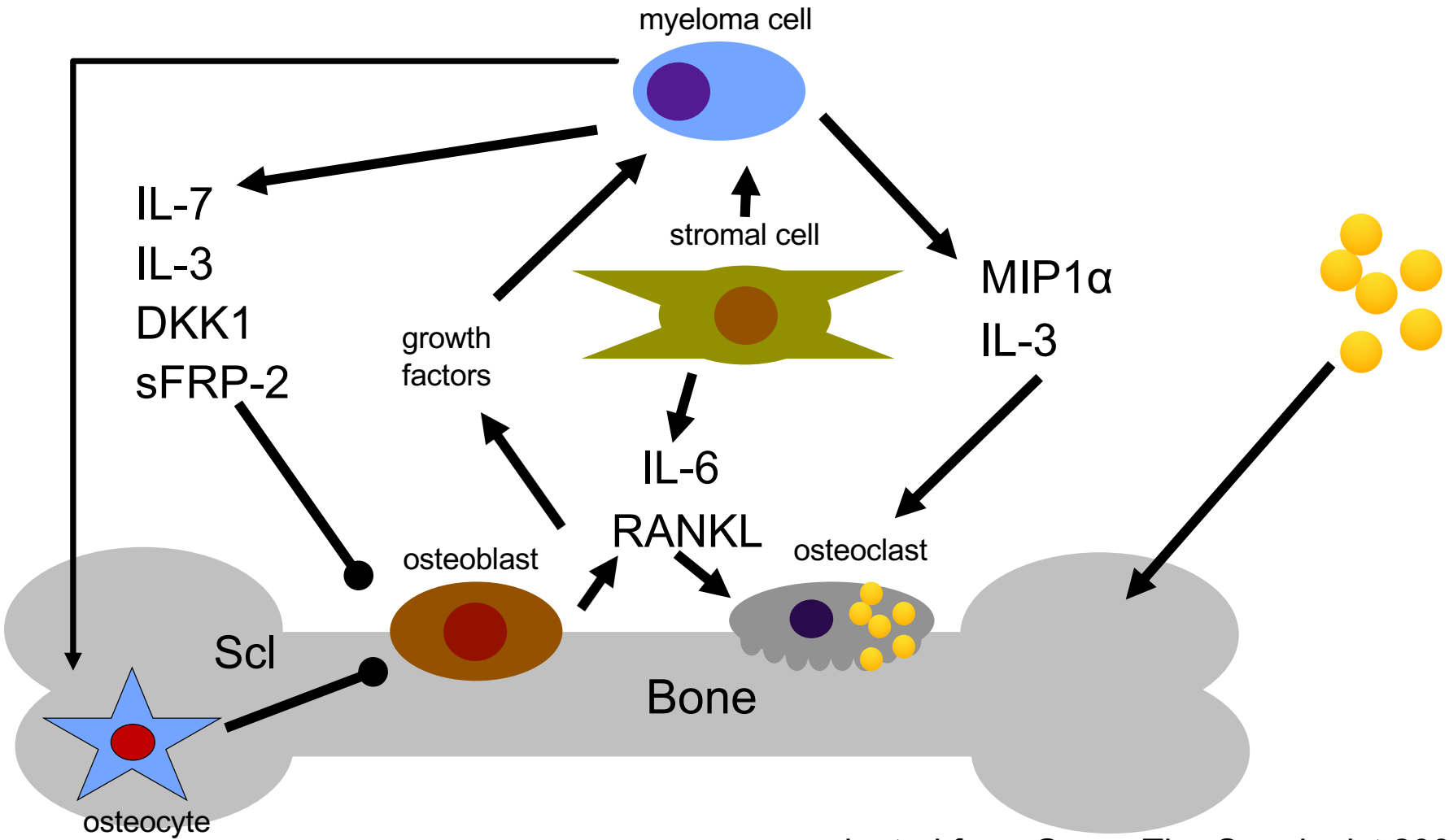
Bisphosphonates – Mechanisms of Action

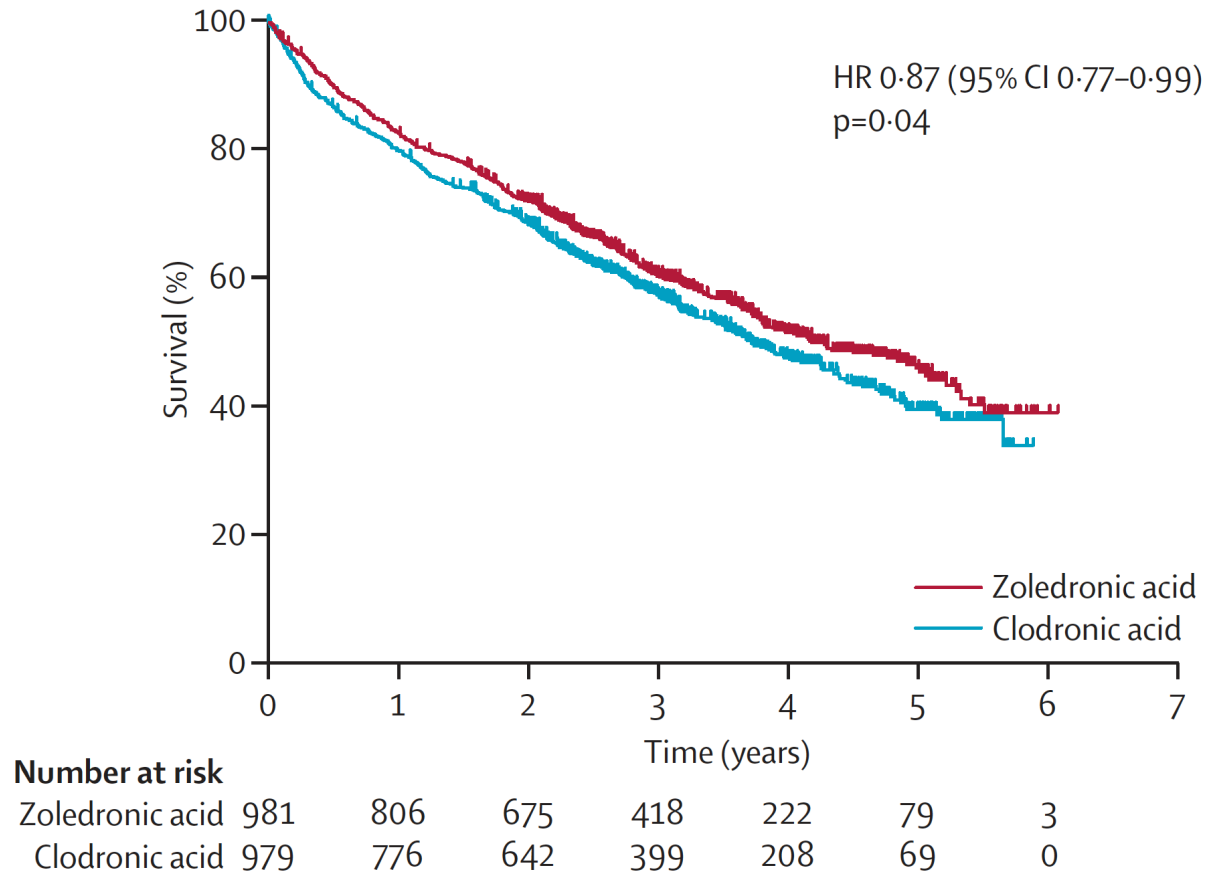


adapted from Green The Oncologist 2004

Bisphosphonates

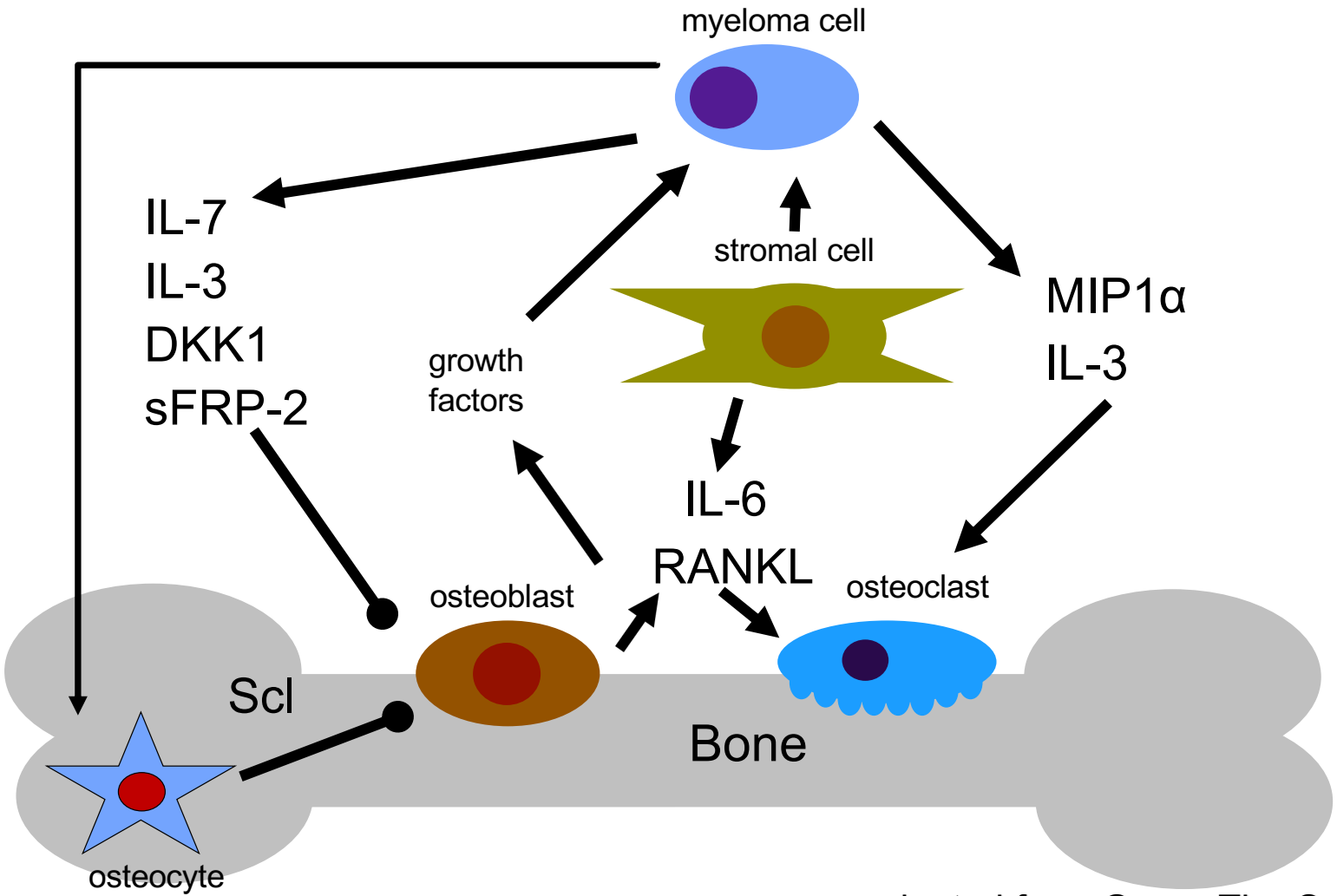
Zoledronic acid versus
Clodronic acid - 1 : 1

N = 1960



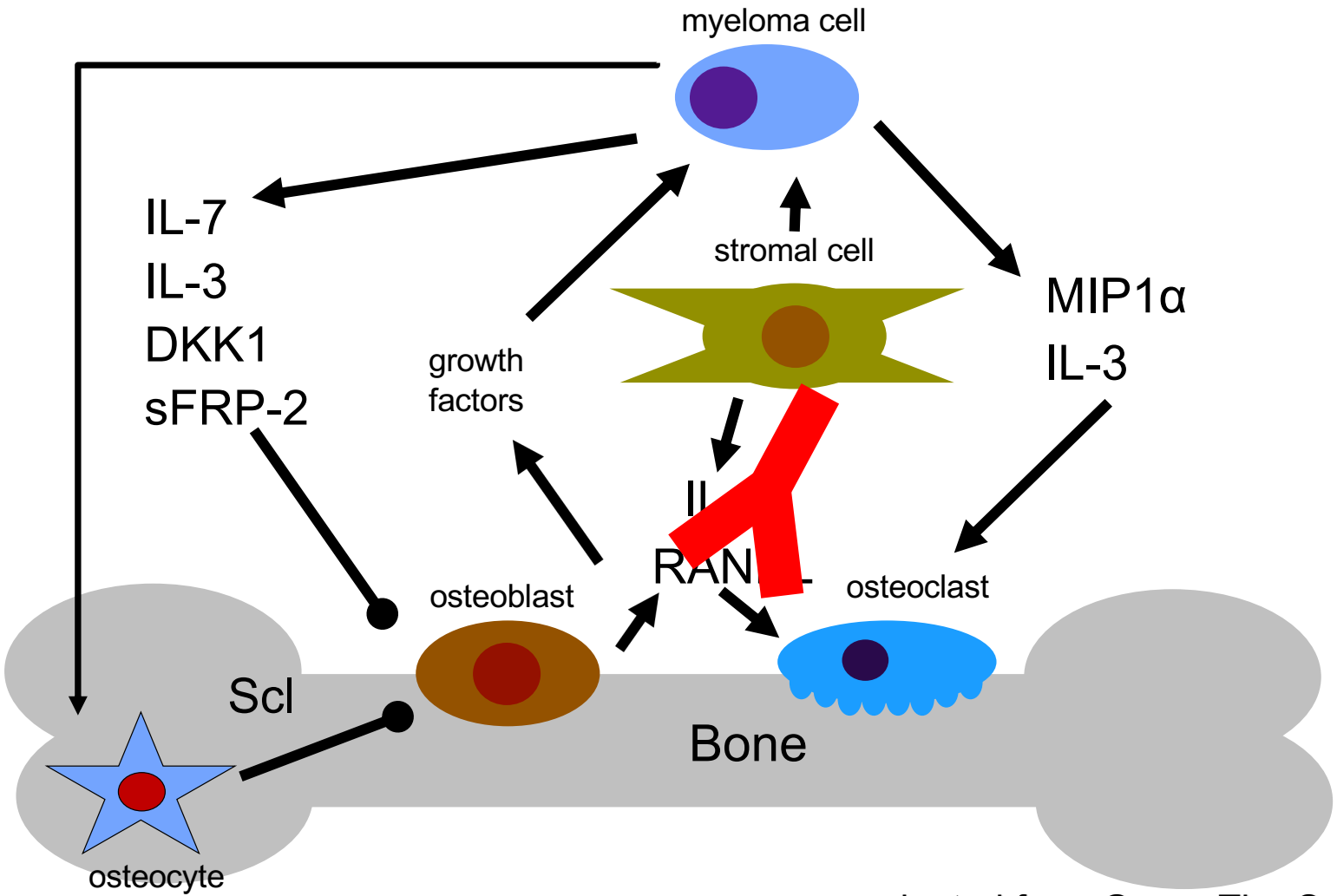
Morgan 2013 Lancet

RANKL Inhibitors – Mechanisms of Action



adapted from Green The Oncologist 2004

RANKL Inhibitors – Mechanisms of Action

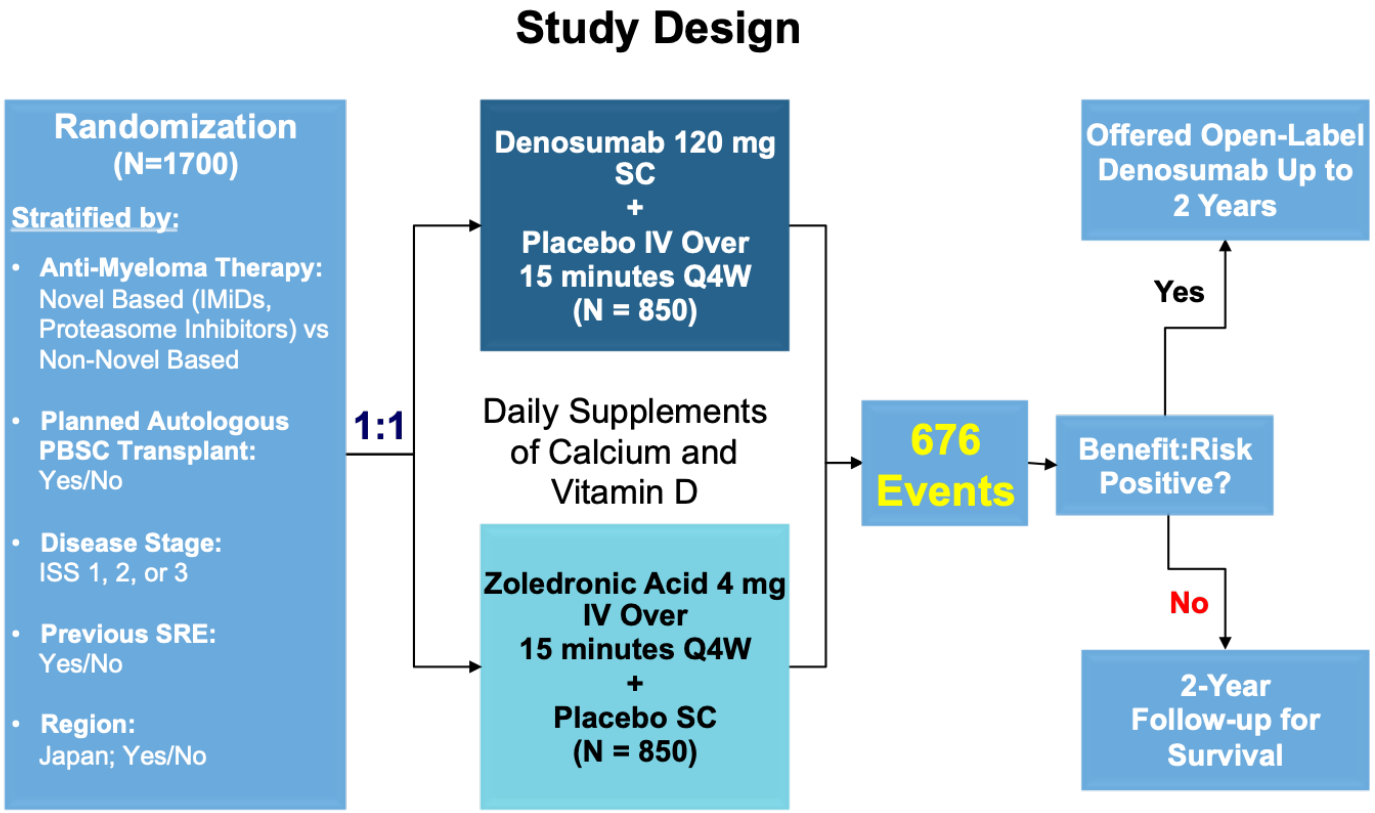


adapted from Green The Oncologist 2004

Denosumab

Denosumab acid versus zoledronic acid - 1 : 1

N = 1700

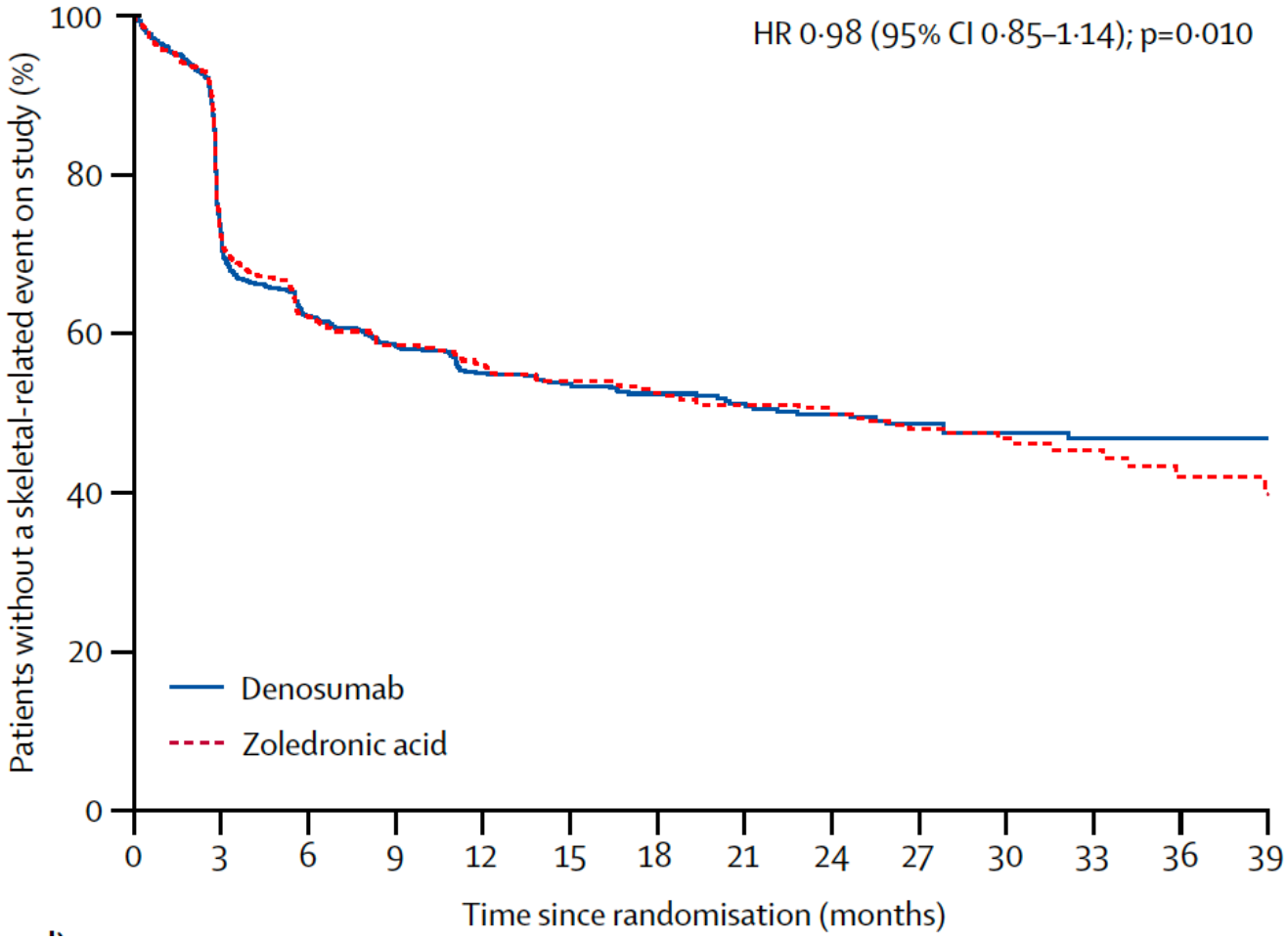


Raje 2017 IMW

Denosumab – Time to SRE

Denosumab acid versus zoledronic acid - 1 : 1

N = 1700

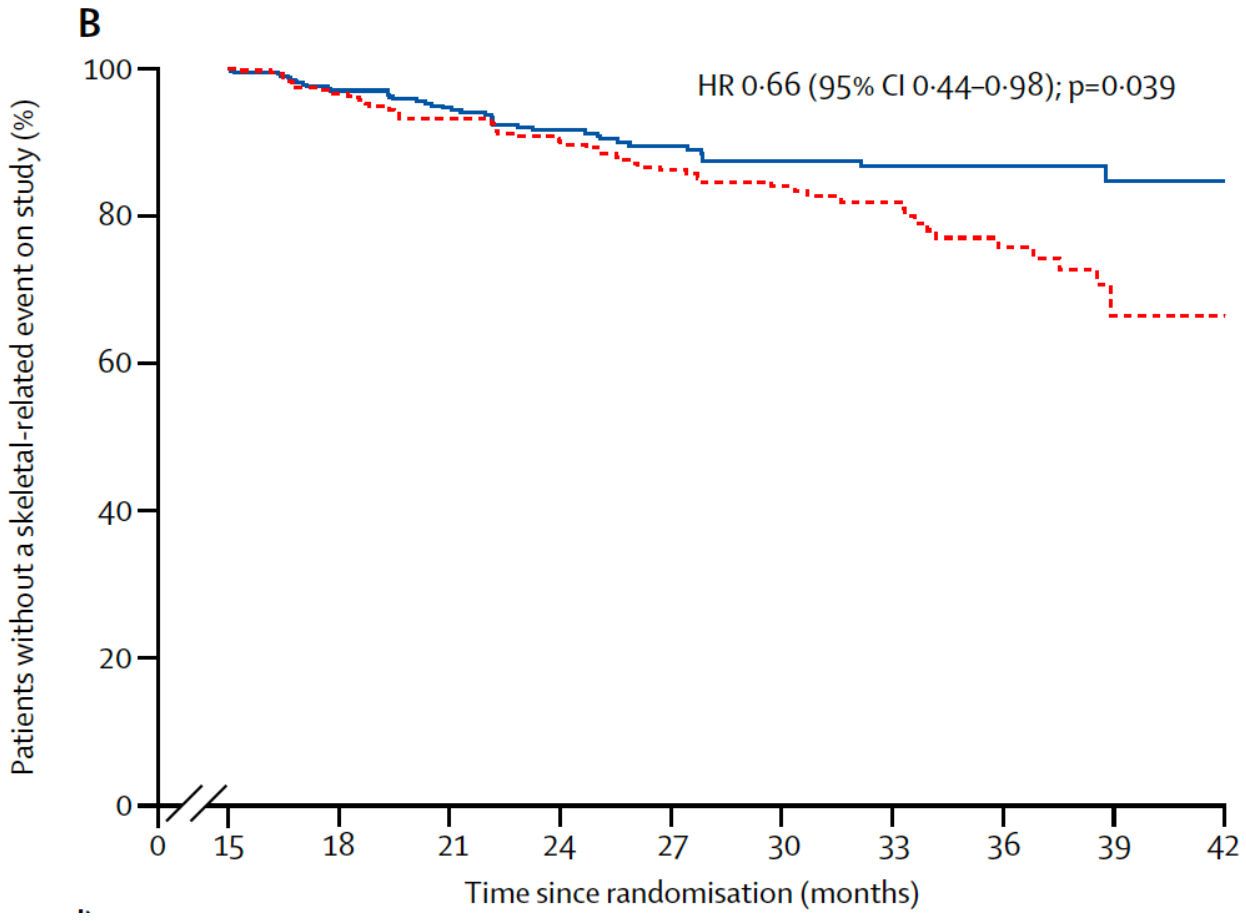


Raje 2018 Lancet Oncol

Denosumab – Time to SRE (after month 15)

Denosumab acid versus zoledronic acid - 1 : 1

N = 1700

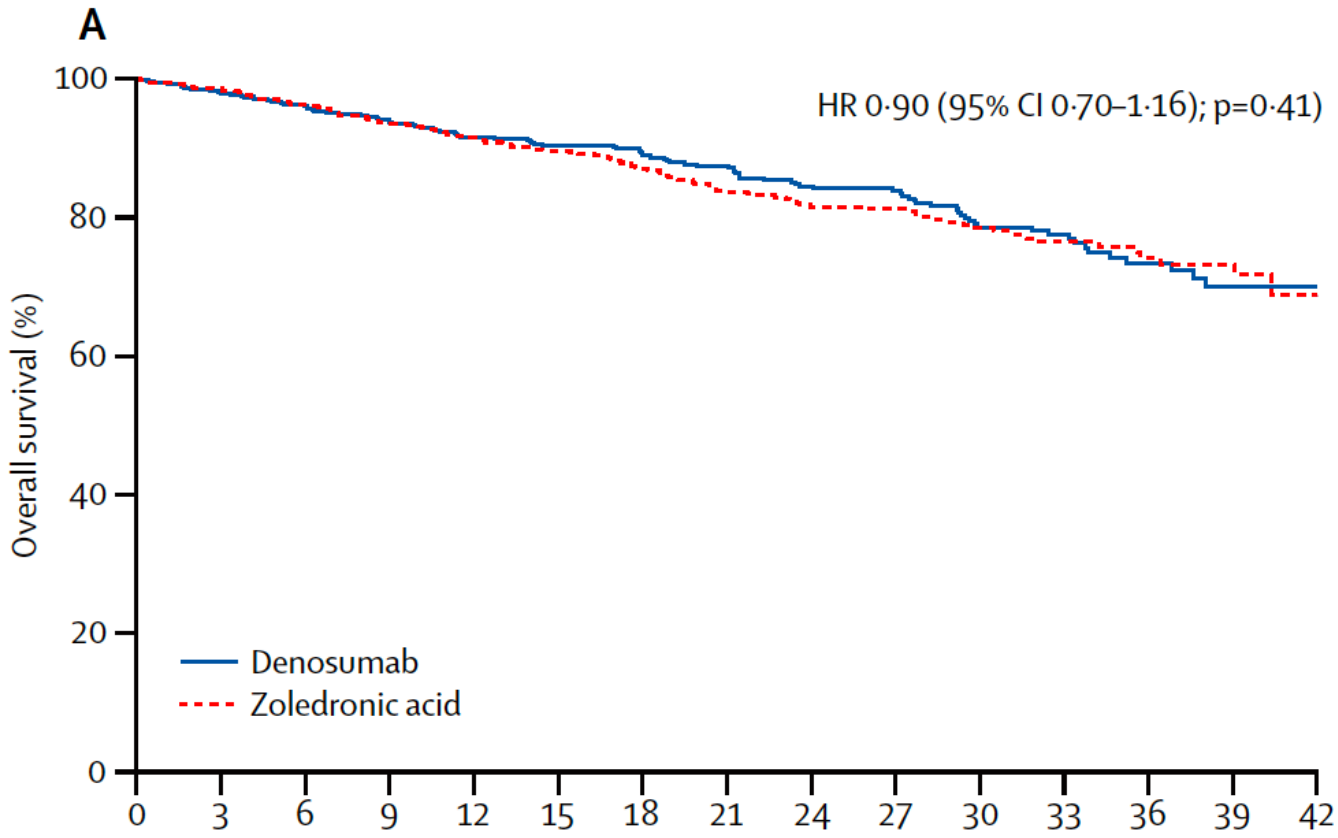


Raje 2018 Lancet Oncol

Denosumab – OS

Denosumab acid versus zoledronic acid - 1 : 1

N = 1700



Raje 2018 Lancet Oncol

Guidelines

	ASCO	IMWG	EMN	ESMO	NCCN
Initial duration	2 years	1 year	continuous	1-2 years in CR/VGPR	2 years
Long term	Resume at relapse	Decrease frequency		Continue if <PR	According to clinical judgement

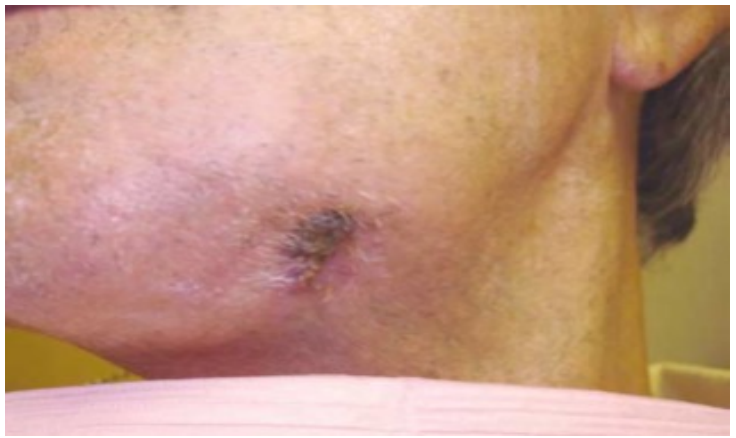
Adapted from Hussain 2022 Blood Rev

Osteonecrosis of the Jaw

Definition
Loss or Destruction of jaw bone by avascular necrosis

Incidence:
1-10 %

Symptoms:
Pain, ulcerations at the gingiva, loosening of teeth, impaired wound healing

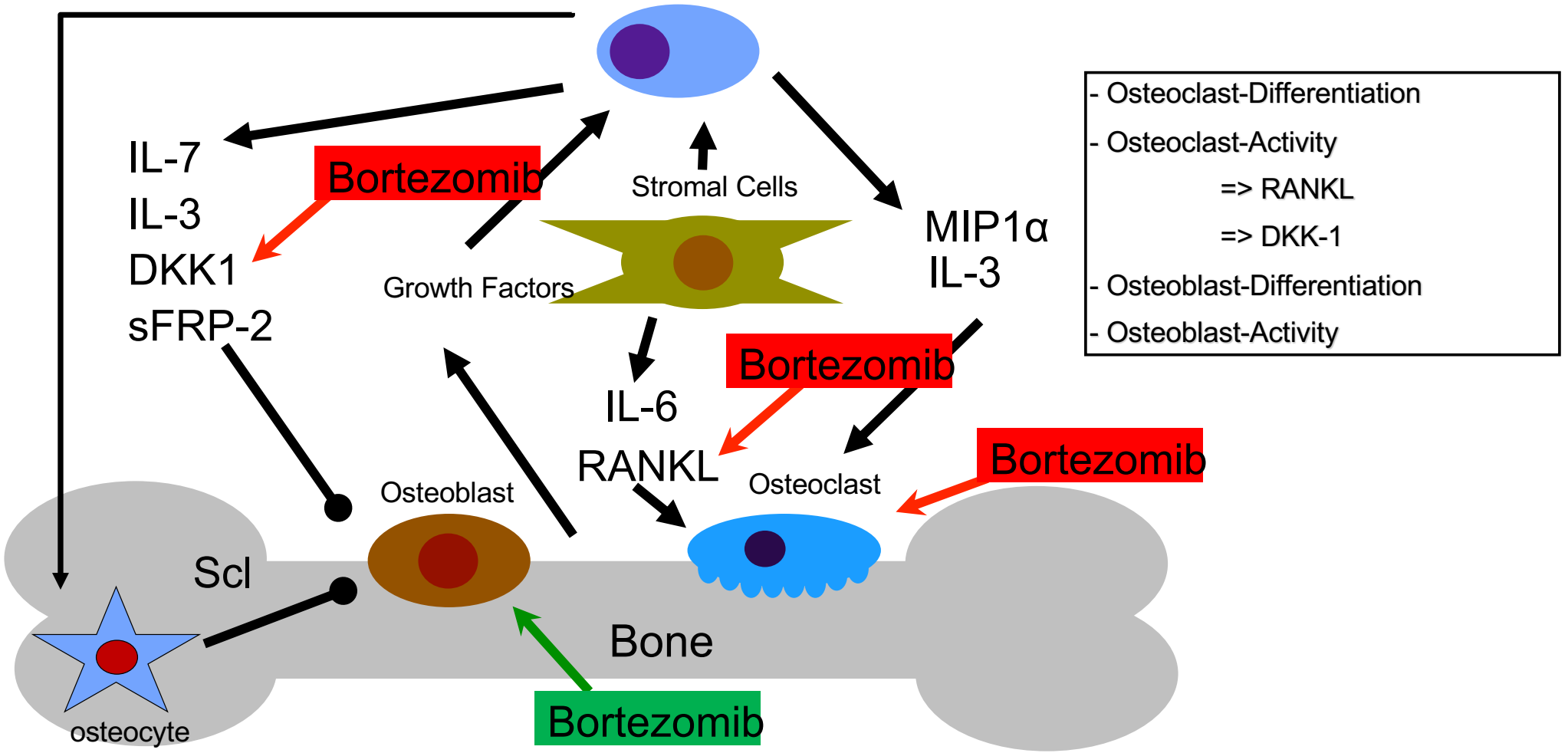


Osteonecrosis of the Jaw

Type of risk	Risk factors
Drug related	**Potency** of antiresorptive agent Higher **dose** (denosumab 120 mg Q4W) **Intravenous** bisphosphonates > oral bisphosphonates **Corticosteroid** therapy **Chemotherapy** **Antiangiogenic** therapy **Duration** of exposure to antiresorptive treatment
Local	Dentoalveolar **surgery** Concomitant **oral disease** Poor oral **hygiene** Intraoral **trauma** **Poor fitting** dentures
Other	Increased **age** **Race** (Caucasian) Cancer **diagnosis**: multiple myeloma > breast cancer > others **Comorbid** conditions (i.e. malignancy)

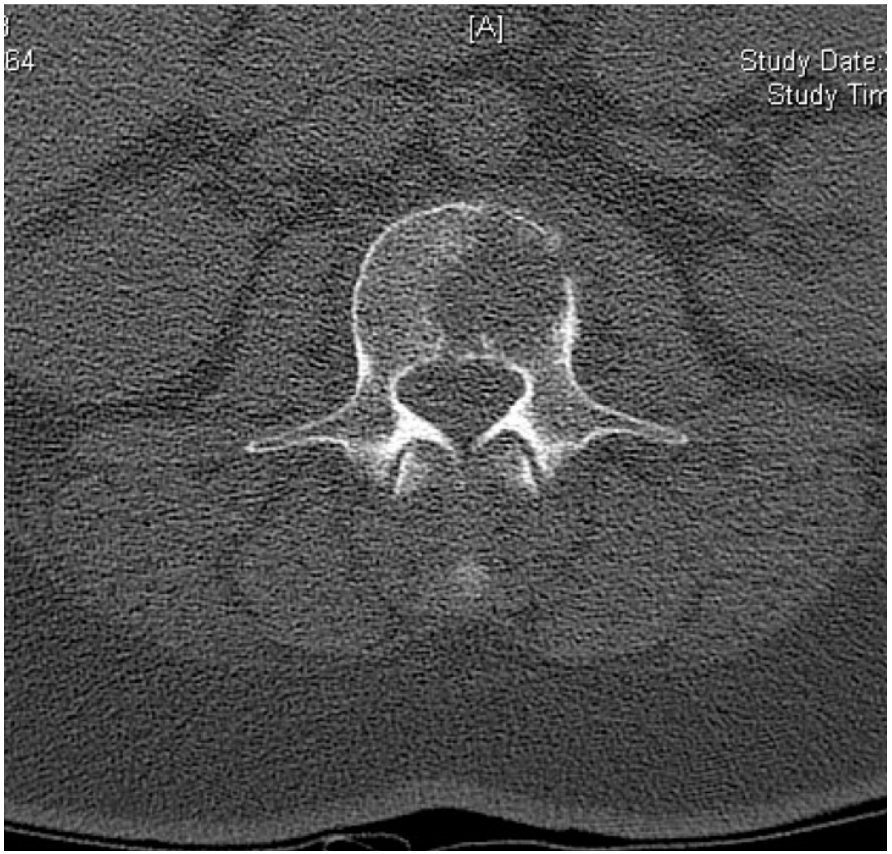
Adapted from: Yamashita J Evid Base Dent Pract 2012.

Influence of Bortezomib

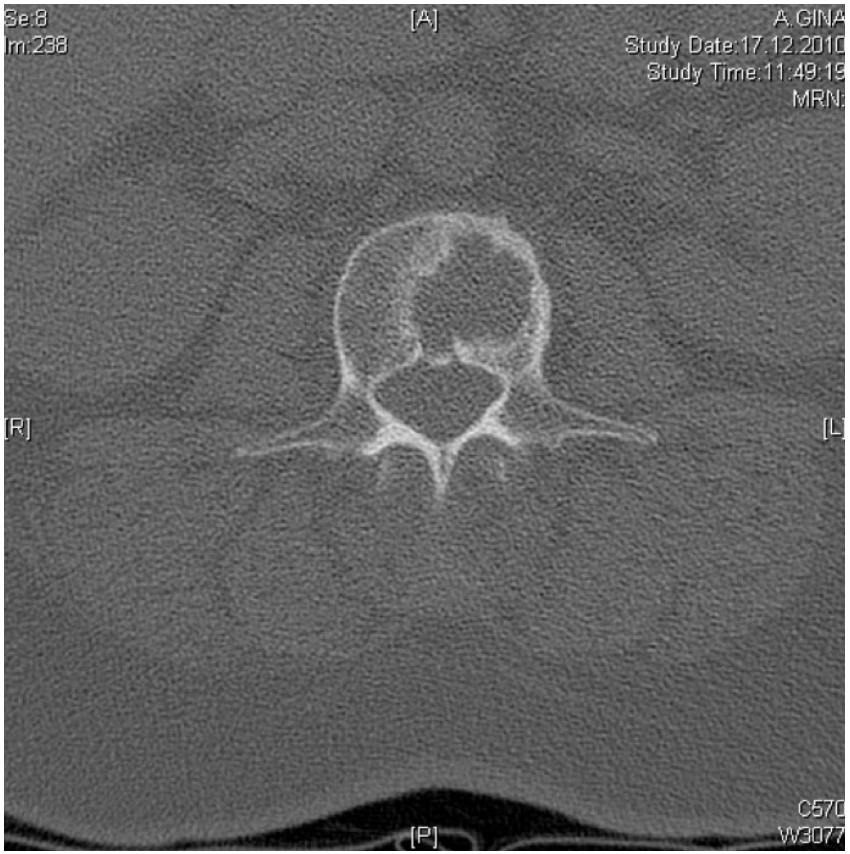


Breitkreutz 2008 Leukemia

Remineralization in Imaging



initial



after end of treatment

Local versus Systemic Treatment

- Pro local:
  - Pain reduction
  - Prevention of permanent disability
  - improved mobility, therefore:
    - lower risk for infections
    - lower risk for thrombo-embolic events
- Pro systemic:
  - Prevention of further end organ damage
  - Pain reduction without side effects of local therapy
  - Lower tumor burden

Local versus Systemic Treatment

- local treatment options:
  - Radio therapy
  - Surgery
  - Kyphoplasty/ vertebroplasty

Surgical Therapy

before

after

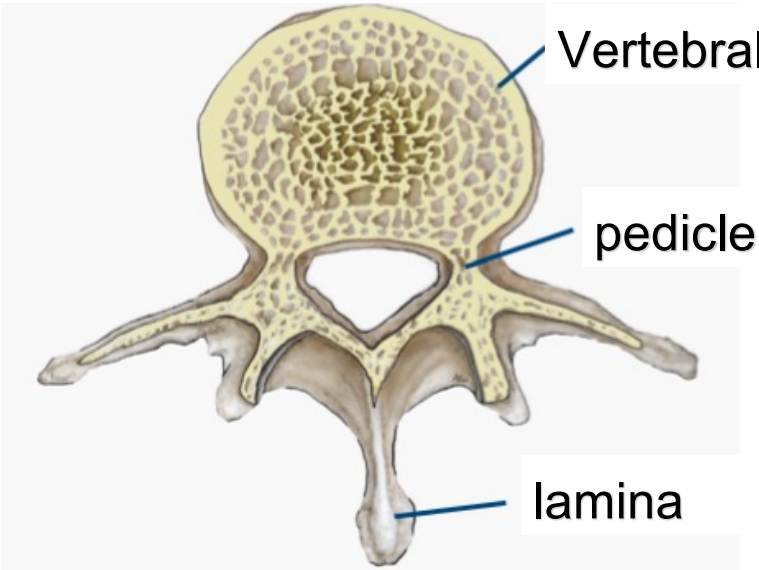
In case of increased fracture risk or after fracture adequate endoprothetic or osteosynthetic treatment is necessary.

Kyphoplasty/ Vertebroplasty

Filling of vertrebral bodies with bone substitute material

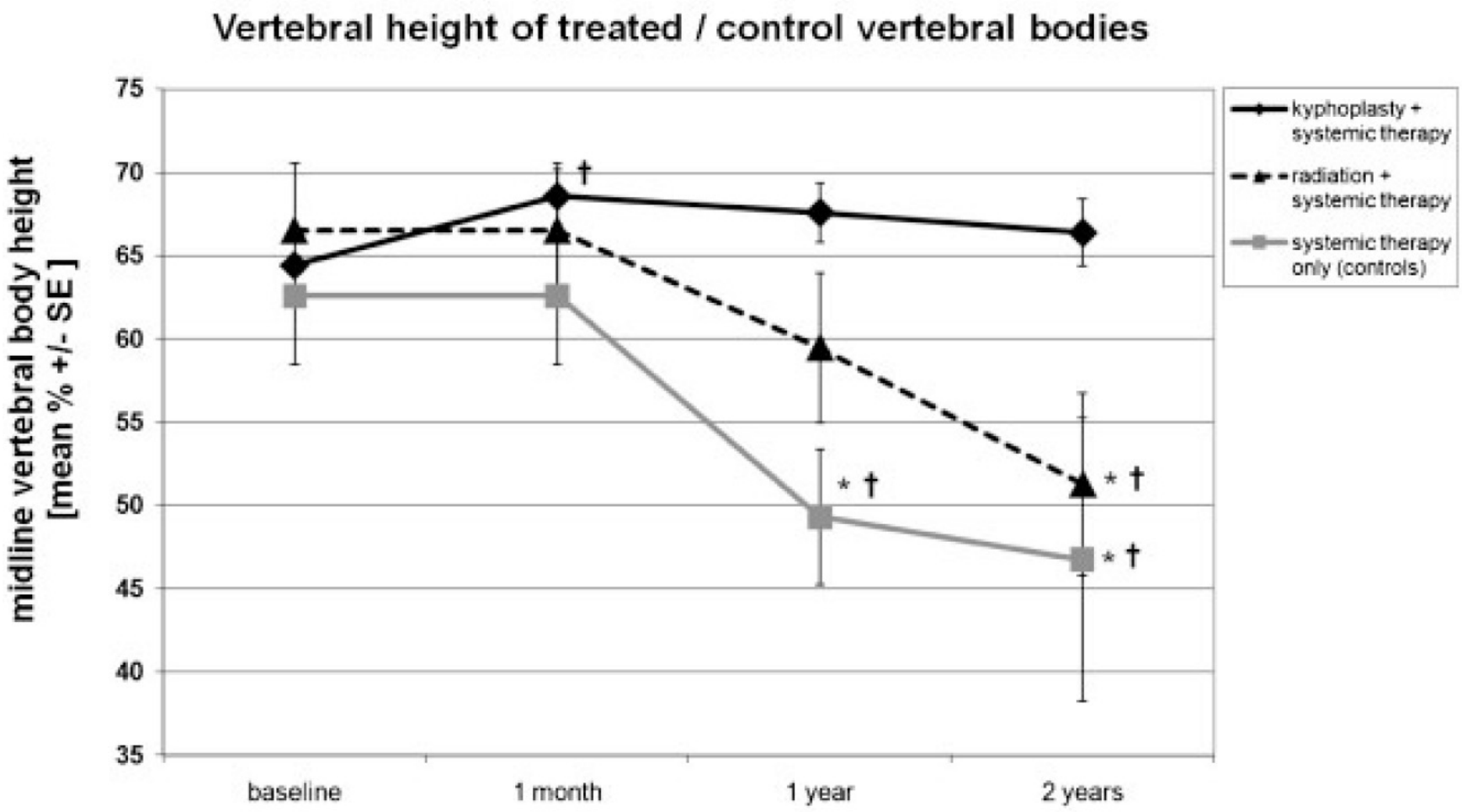
=> Because of increased stability

decrease of pain and fractures



Kyphoplasty

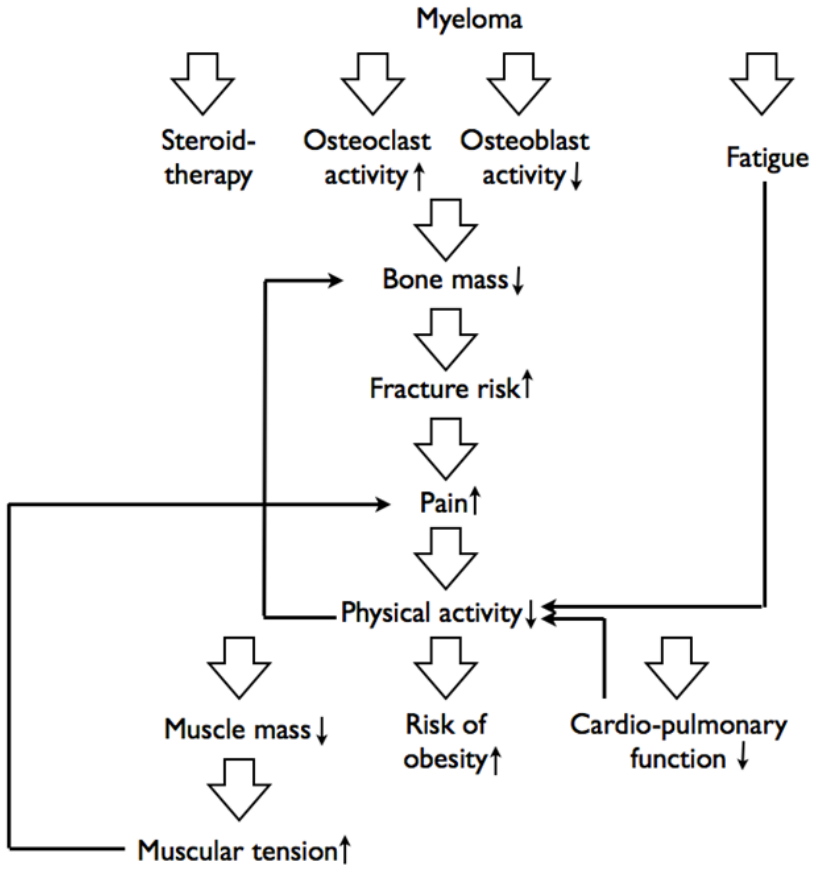
Kyphoplasty



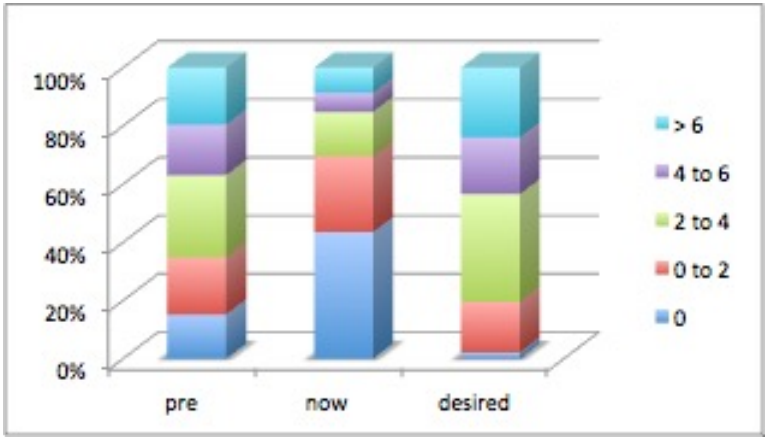
Kasperk J Surg Oncol 2012

Physical Exercise in Myeloma

Physical Exercise

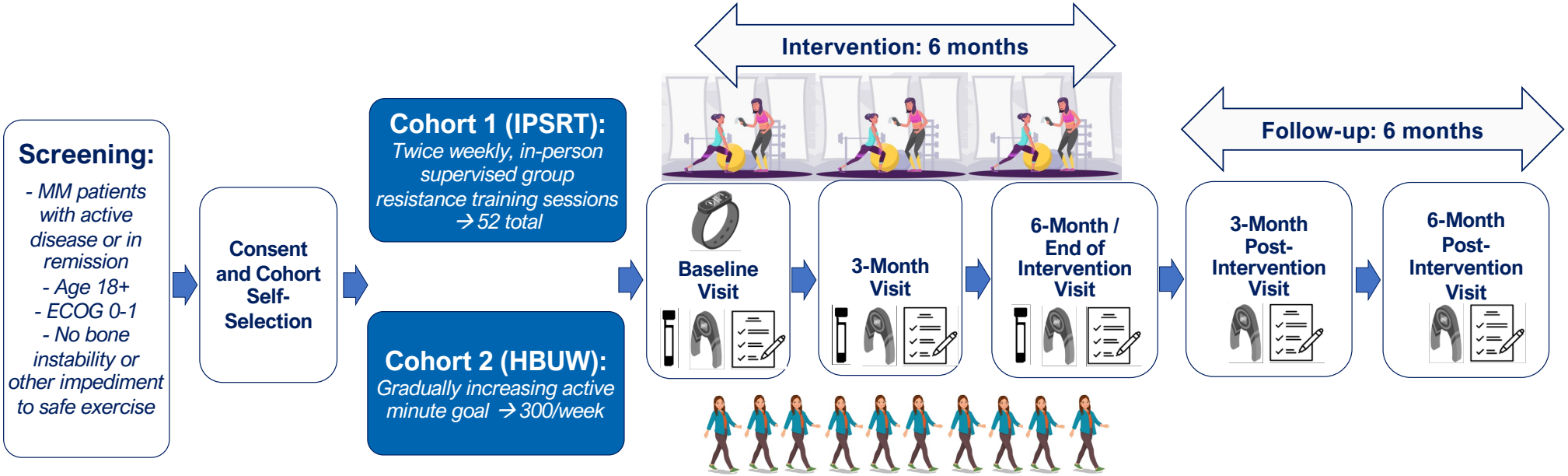


Hours of Physical Activity per Week



Hillengass 2017 IMW

Effects of Exercise on the Immune System



- **Primary endpoint:** Feasibility
- **Secondary endpoint:** Adherence
- **Exploratory endpoints:** Changes in immune fitness[1], physical function[2], patient-reported outcomes (psycho-oncological, pain, fatigue), lab parameters, clinical performance, physical activity level, polyneuropathy, opioid and other drug consumption

Joseph,…, Hillengass 2024 Clin Lymphom Myeloma Leuk

Physical Exercise

- For all patients in remission/after ASCT
- No acute bone fractures/instabilities
- No major comorbidities
- 2 times a week for 6 months
- Combination of cardiovascular and strength training
- Individualized after PT assessment
- Patients get Fitbit to track heartrate, moving habits, sleep patterns

Courtesy Michaela Hillengass

Physical Exercise

Exercise training

- Cardiovascular training:
- 10 min.warm up/cool down
- Strength training:
- Major muscle groups
- 2-4 sets
- w/without weights

Courtesy Michaela Hillengass

Effects of Exercise on the Immune System

Intervention

- 6 months
- Walking arm: 12 patients - activity promptings - Fitbit
- Strength training arm: 12 patients – in person resistance training twice weekly

Endpoints

- Effects on immune cells in the peripheral blood by flow cytometry

Joseph 2024 Clin Lymphom Myeloma Leuk

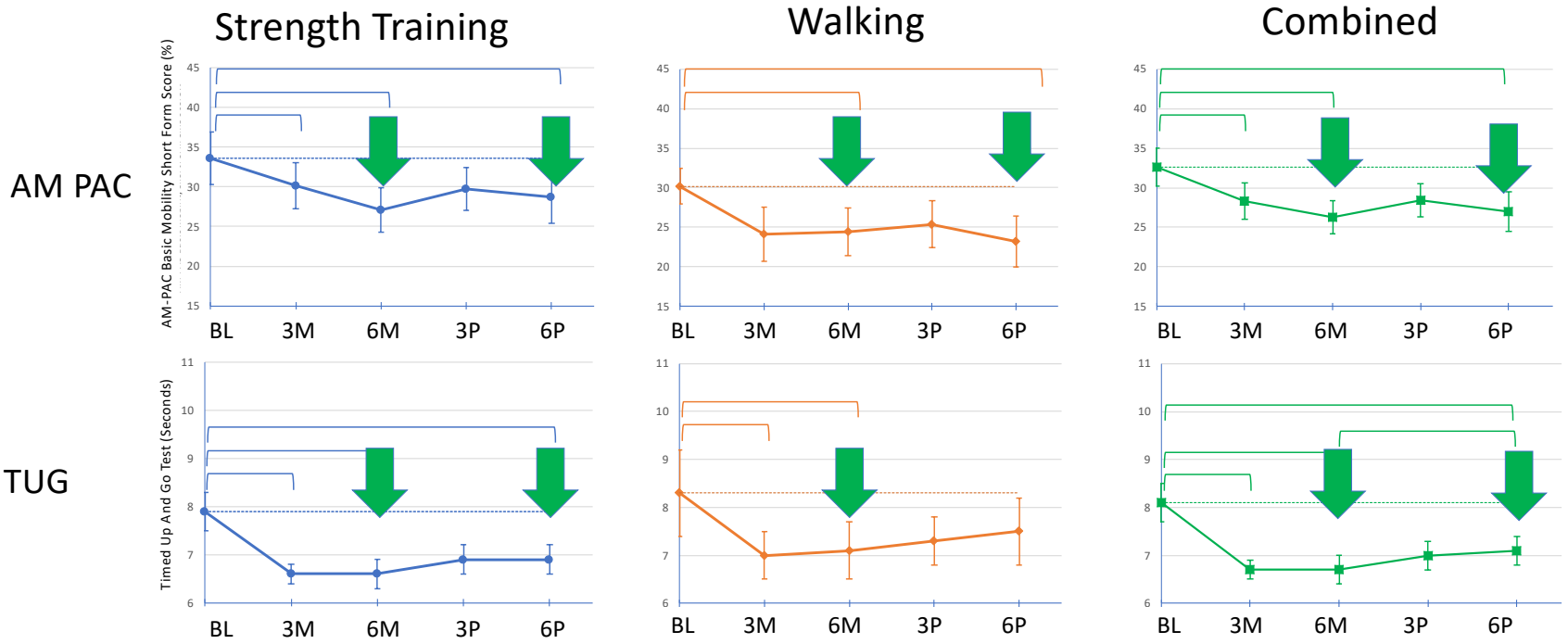
Effects of Exercise on the Immune System

Results (significant findings only)

Table 1. Changes in ratios of exhausted to non-exhausted T cell populations of 24 participants with multiple myeloma who completed at least three months of physical activity intervention (2020-2022)			
	Baseline	Final	p-value [b]
$CD4^+$ T cell markers [a]	All Subjects (n=24)		
$CD4^+$ $TIGIT^+$: Non-exhausted $CD4^+$	**0.7 (0.6)**	**0.6 (0.4)**	**0.04**
$CD8^+$ T cell markers [a]	All Subjects (n=24)		
Total exhausted $CD8^+$: Non-exhausted $CD8^+$	**2.5 (4.7)**	**2.2 (2.7)**	**0.03**
	Strength Training (n=12)		
$CD8^+$ $TIM3^+$: Non-exhausted $CD8^+$	**0.1 (1.2)**	**0.0 (0.1)**	**0.03**

Joseph 2024 Clin Lymphom Myeloma Leuk

Effects of Exercise on the Immune System

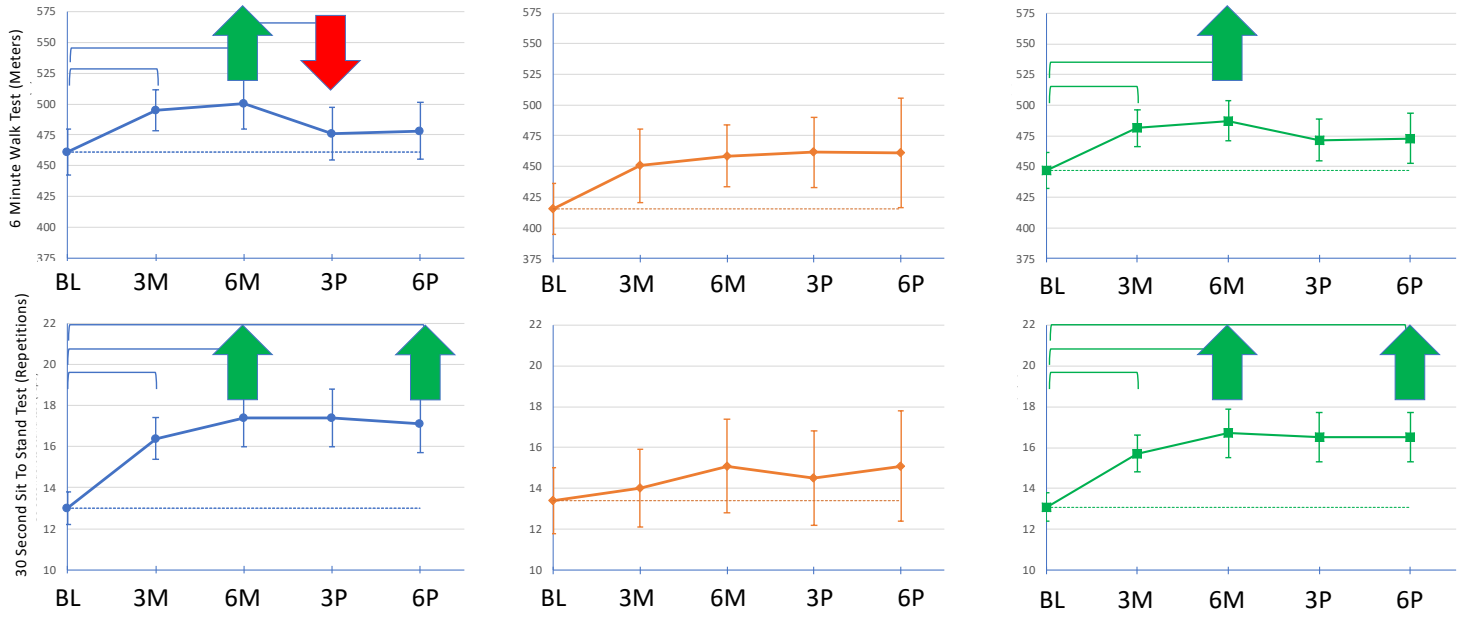


Hillengass 2024 in Remission

Effects of Exercise on the Immune System

6MWT

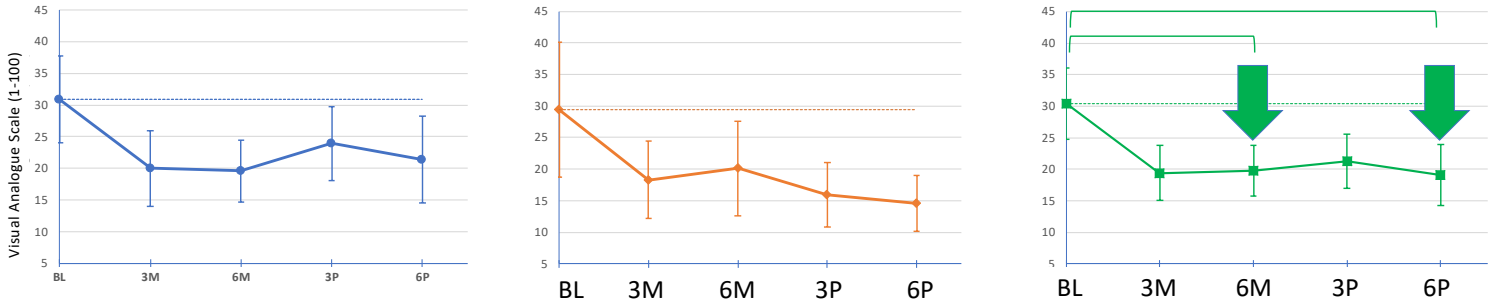
30SST



Hillengass 2024 in Remission

Effects of Exercise on the Immune System

VAS



Hillengass 2024 in Remission

Thank you

S.D.G.