

# Medication Related Osteonecrosis of the Jaw (MRONJ): prevention and management



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**2018**  
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**MASCC/ISOO**  
ANNUAL MEETING  
SUPPORTIVE CARE IN CANCER



MAKES EXCELLENT  
CANCER CARE POSSIBLE

## Faculty Disclosure

**Consultant for Amgen Corporation**



# Lecture outline



- Frequency of disease
- Pathophysiology
- Prevention strategies
- Treatment strategies and outcomes
- New areas of research



# Population at risk

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2004: > 3 million patients worldwide and 1/3 of all Americans with breast cancer had received IV Bp's

2009: sales of zoledronic acid nearly \$1.5 billion

2010-11: expanded role for IV Bp's (Db also!)

- ✓ survival benefits
- ✓ tumor suppression

2011: new medications (Db, AA) a/w MRONJ risk

# MRONJ Frequency

## IV Bisphosphonates

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- Durie (2005, NEJM): 12.8%
- Dimopoulos (2005, ASH): 6.7%
- Tossi (2005, ASH): 2.7%
- Pozzi (2005, ASH): 1.8%
- Cafo (2005, ASH): 12%
- Mavrokokki (2007, JOMS): 1.1-9.1%
- Hoff (2008, JBMR): 1.2-2.8%
- Ibrahim (2008, Oncologist): 1.5%
- Boonyapakorn (2008, Oral Oncol): 28%
- Morgan (2010 ASCO meeting): 3.5%

**“Among patients exposed to antiresorptive medications, what is the risk of developing ONJ following dentoalveolar procedures (tooth extraction, implant placement, etc.)”???**

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### **Oral BPs: best current estimate 0.5%**

- Kunchar (JOMS, 2009): prospective study (194 pts) exposed to oral BP that had extractions. 1 patient developed ONJ

### **IV BPs (cancer pt): best current estimate 1.6%-14.8%**

- Yamazaki (IJOMS, 2012): retrospective study cohort study (1,347 pts) 14.8%
- Mozzati (Oral Oncol, 2012): prospective cohort study (176 pts) 2.8%
- Scoletta (JOMS, 2013): prospective cohort study (63 pts) 1.6%

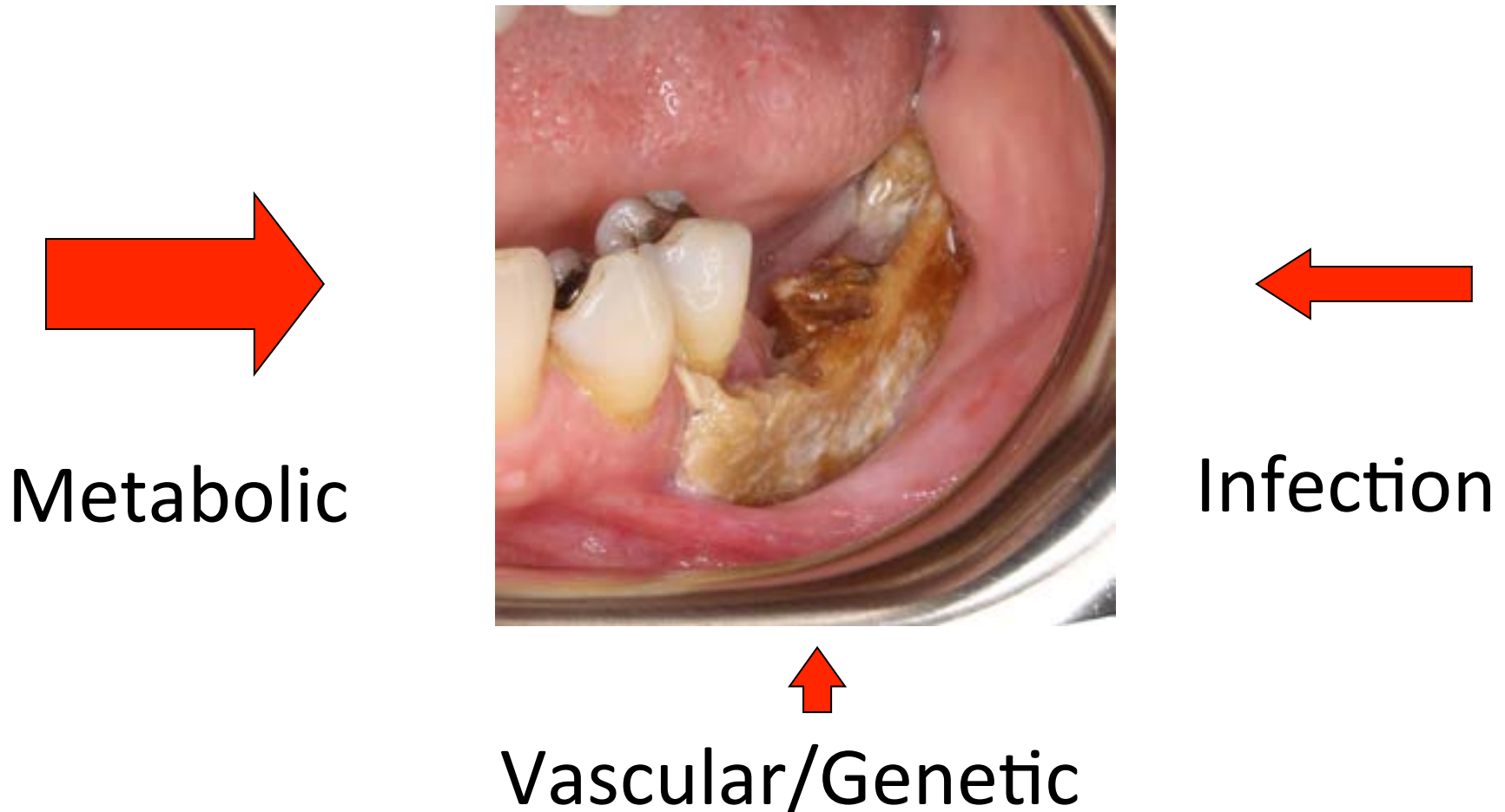
# ***“Combination of Bisphosphonates and Antiangiogenic Factors Induces Osteonecrosis of the Jaw More Frequently than Bisphosphonates Alone”***

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- Retrospective review of 116 patients receiving Bps +/- antiangiogenic therapy
- Bp duration / dose similar in both groups
- Frequency of ONJ:
  - ✓ 16% Bp, +antiangiogenic agent
  - ✓ 1.1% Bp alone (p=0.008)

# Pathogenesis of MRONJ (multifactorial)

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# MRONJ: Criteria for diagnosis

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- History of BP/DB/AA therapy
- No history of XRT to the maxillofacial region
- exposed bone or bone that can be probed in the maxillofacial area that occurred spontaneously or following dentoalveolar surgery
- no evidence of healing for more than 8 weeks following appropriate care

# MRONJ prevention strategies

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## Pre-treatment for cancer therapy (IV Bp/Db/AA)

- Measurable risk within a short period of time (1.6% - 15%)
- A delay in starting IV BP therapy should be considered in order to optimize the dental condition (if possible)
- May apply to select antiangiogenic medications
- Strategies similar to those for pre-irradiation dental treatment

# MRONJ prevention strategies

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Prophylactic treatment prior to initiating monthly IV BP/Db/AA therapy (ORN model)

- Pre-treatment dental exam to detect potential dental and periodontal infections
- Remove abscessed and non-restorable teeth and teeth with severe periodontal disease
- Remove teeth with poor long-term prognosis
- **Educate patients** on oral hygiene and signs of disease



# MRONJ prevention strategies

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Asymptomatic patients receiving monthly IV BP/Db/AA therapy

- Avoid invasive dental procedures when possible
- Maintain routine dental care, avoid soft-tissue injury (especially at lingual plate and tori)
- Aggressively manage dental infections non-surgically (root canal tx if possible, AAE position paper)
- Regular dental assessments after initiating BP therapy (frequency dependent upon risk)
- Consider antiangiogenic medications as well

# Drug holiday

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## Consider the following:

- 50% of serum BP eliminated in first pass
- Osteocytes have a low affinity for BP
- Osteoblasts incorporate BP into bone
- Osteoclast is the only cellular reservoir for BP
- Osteoclast life span is 2 weeks....
- Therefore: amount of free BP after a 2 month holiday (4x life span of osteoclast) should be extremely low.

# ***“Bp uptake in areas of tooth extraction or periapical disease”***

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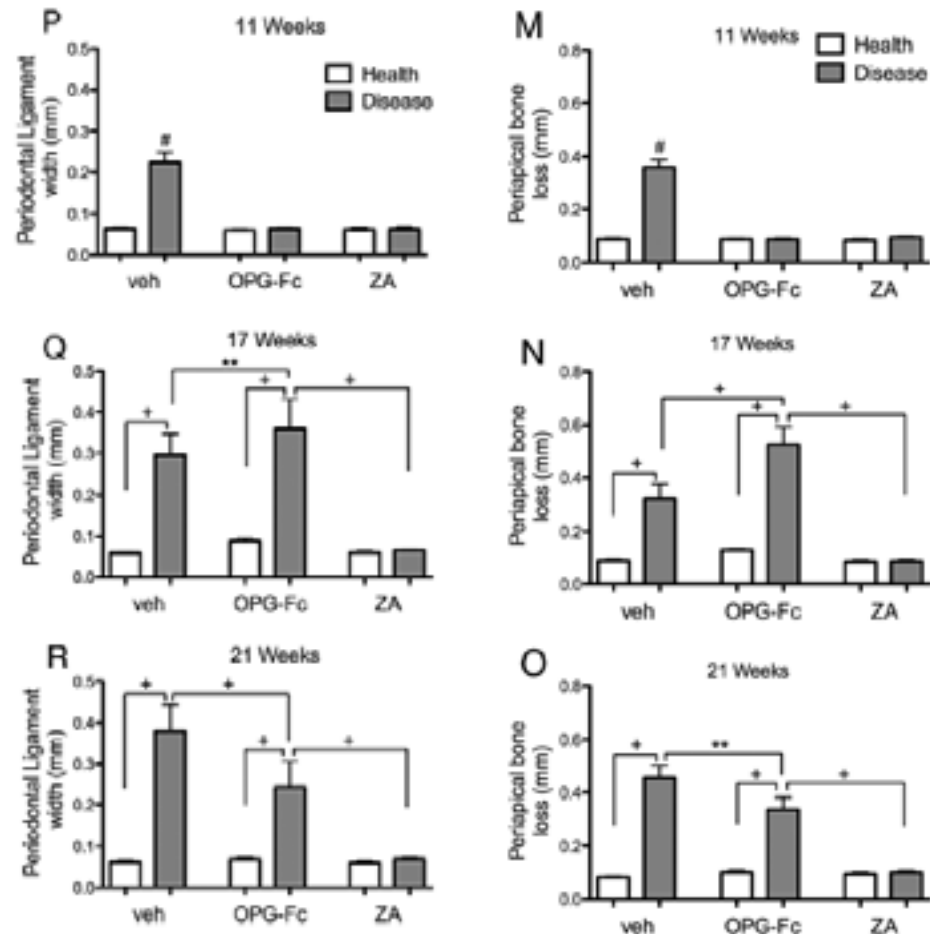
- Labeled Za administered to mice following exo or induced PA disease
- Significantly increased uptake in all exo sites and at alveolar ridge adjacent to PA defect
- Uptake maximized by 3 days
- Non-wounded site with minimal uptake
- High Bp content @ sites with increased bone turnover (exo)

## OPG-Fc but Not Zoledronic Acid Discontinuation Reverses Osteonecrosis of the Jaws (ONJ) in Mice

ONJ lesions created in mice exposed to OPG-Fc and ZA and then drugs stopped

- OPG-Fc but not ZA discontinuation reversed radiographic features of ONJ\*
- Serum TRACP-5b levels increased after OPG-Fc but not ZA discontinuation\*
- OPG-Fc not ZA discontinuation reverses histologic features of ONJ\*

\*statistically significant

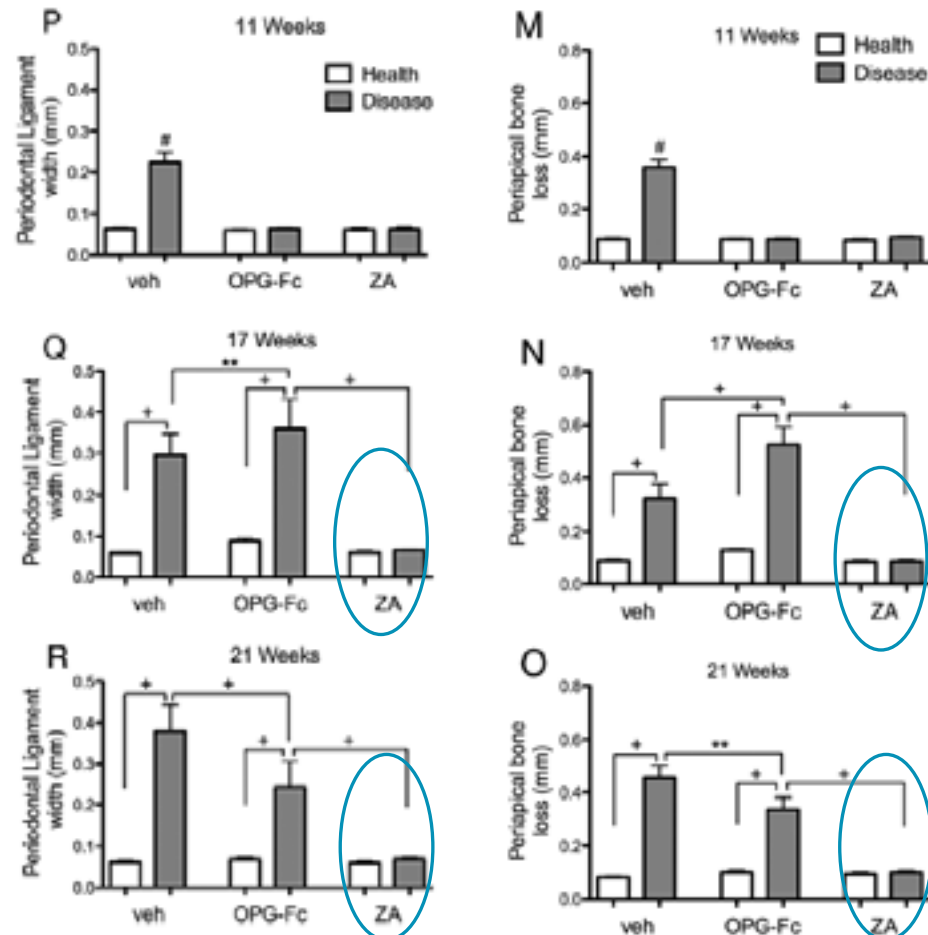


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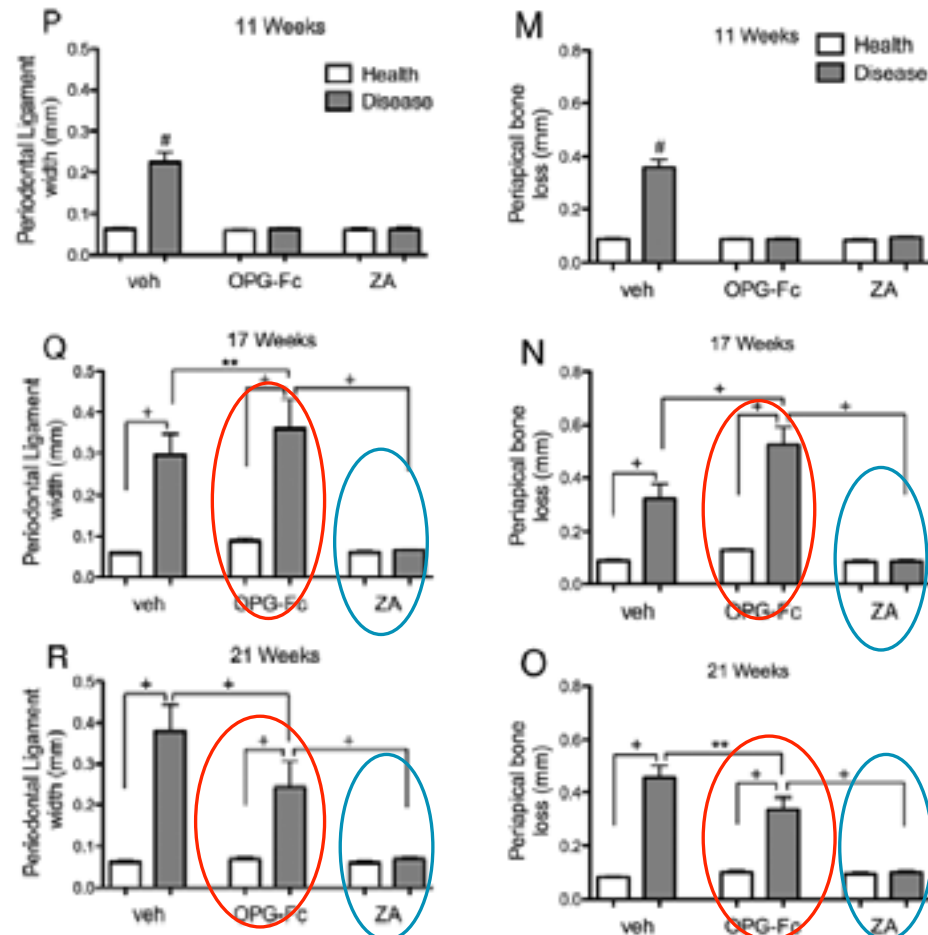


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\*statistically significant



# Drug holiday of at-risk medication therapy for prevention or management of ONJ

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- No studies that define “who”, “when” and for “how long” for pts with OP
- No data to support or refute that drug holidays alter ONJ risk
- ASBMR recommends a holiday for high risk pts and exposure h/o >4 yrs (2014)
- AAOMS recommends holiday for exposure h/o >4 yrs based on pharmacokinetics of oral BP therapy
- No clinical studies to support or refute the strategy of stopping monthly antiresorptive therapy (BP, denosumab) in pts with cancer
- No data for anti-angiogenic therapy

# Treatment objectives in the management of MRONJ

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- Eliminate pain
- Manage or eliminate infection
- Prevent additional exposure/necrosis
- Treatment with curative intent?
- Patient education



# Treatment recommendations

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*All patients (all stages) with established MRONJ*

- Consultation between oral surgeons, general dentists and the treating oncologist is strongly recommended
- **Superficial** bony debridement to reduce sharp surfaces prevent trauma to adjacent soft tissues
- Removal of mobile sequestrum
- A removable appliance or protective stent
- Avoid invasive dental procedures when possible



# Treatment recommendations

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## *Patients with established MRONJ*

- Elective dentoalveolar surgery should be avoided
- Biopsy is not recommended unless metastasis to the jaw is **strongly** suspected
- Decisions regarding stopping anti-resorptive or AA therapy should be made in consultation with the treating oncologist and oral surgeon, taking into account the potential risk of further osteonecrosis versus the risk of skeletal complications. **Benefit of anti-resorptives > Risk for most patients.**
- No specific data for AAs

# Treatment recommendations

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## Stage 1

- A non-surgical approach is recommended to prevent further osseous injury
- Daily irrigation/mechanical debridement and oral antimicrobial rinses (0.12% chlorhexidine)
- Clinical follow up every 3 months



# Treatment recommendations

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## Stage 2

- Culture-directed antibiotic therapy (long term and maintenance)
- Pain control
- Daily irrigations and oral antimicrobial rinses (0.12% chlorhexidine)
- Clinical follow up every 3 months



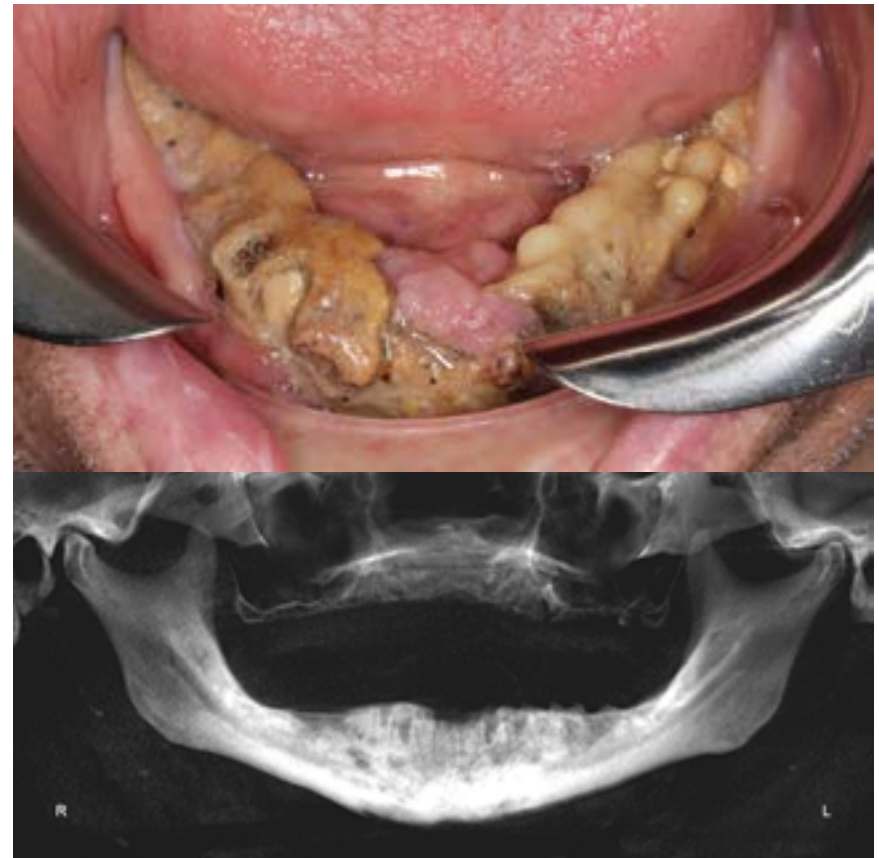


# Treatment recommendations

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## Stage 3

- Culture-directed antibiotic therapy (PO/IV, long term and maintenance)
- Pain control
- Daily oral antimicrobial rinses (0.12% chlorhexadine)
- Surgical debridement/resection to reduce the volume of necrotic bone





# Treatment strategies for mandibular MRONJ

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Non-operative  
therapies

Sequestrectomy

Resection

No reconstruction

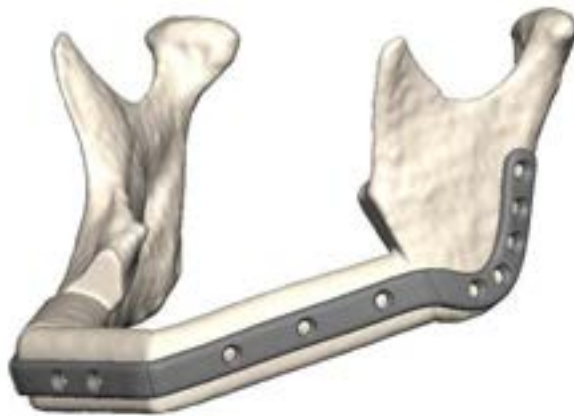
reconstruction with  
plate and vascularized  
bone/soft tissue

reconstruction with  
plate (+/- soft tissue)

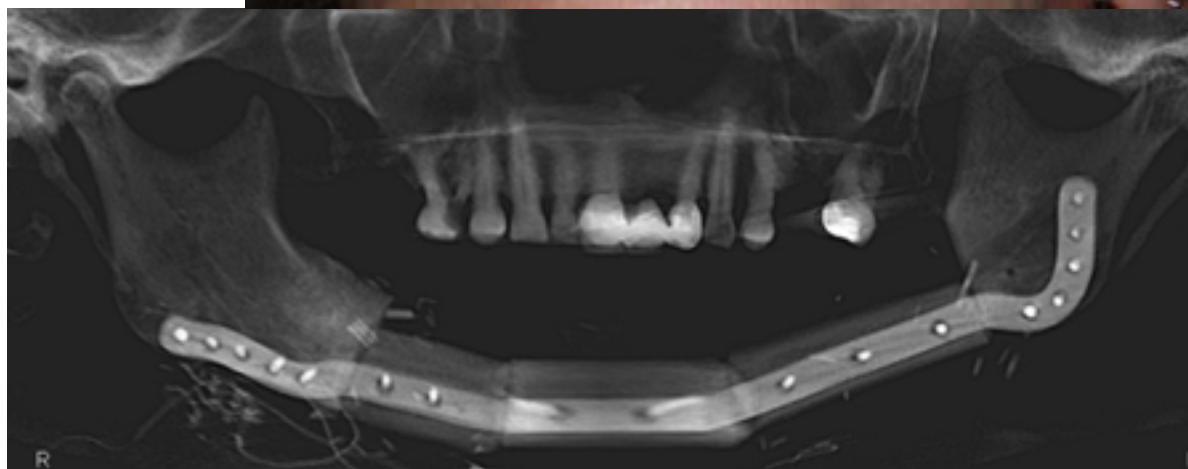
64 yo female with  
multiple myeloma  
and a 2 year  
history of  
monthly Zometa  
treatment

**Stage 3 MRONJ**

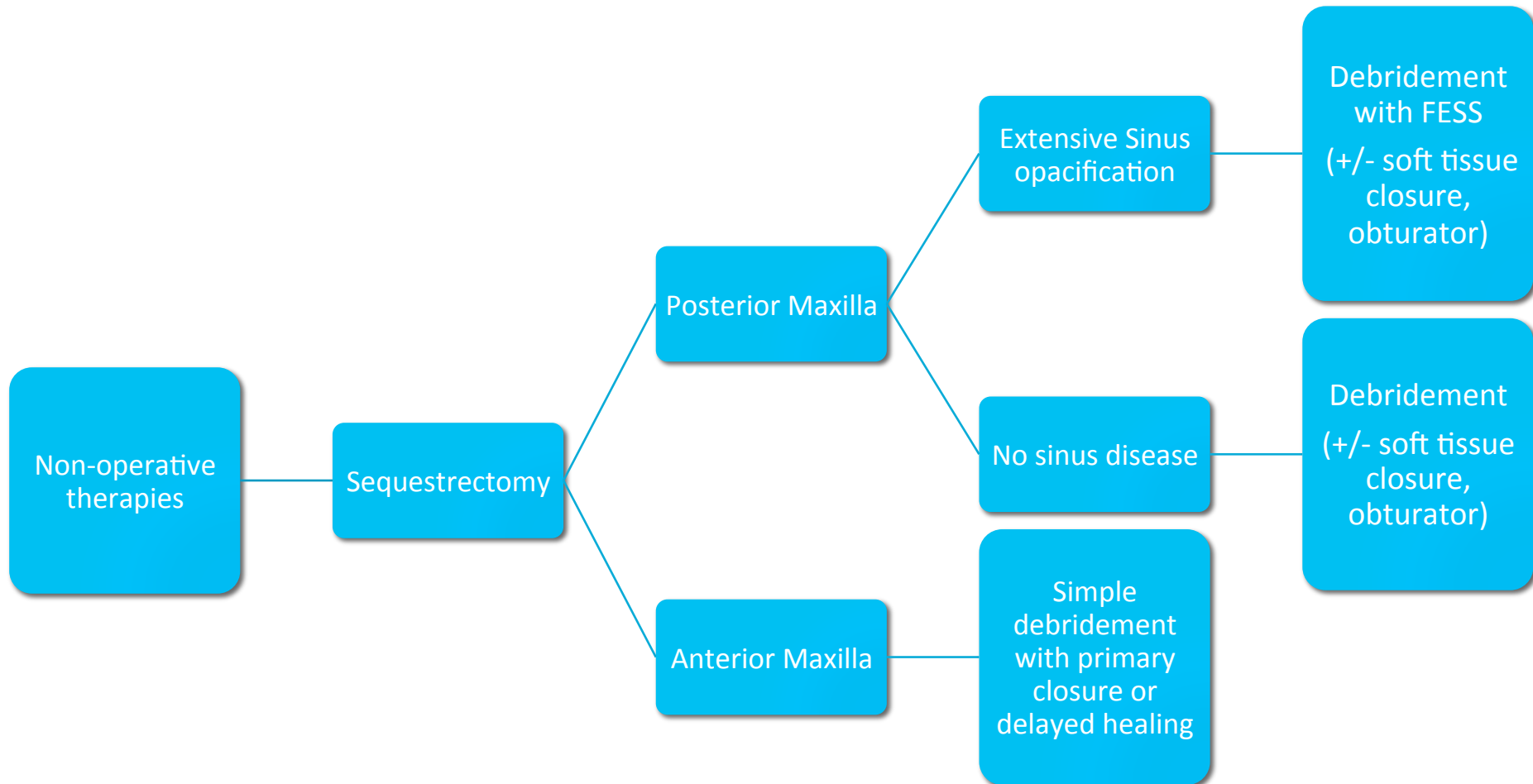




6 months  
post-op

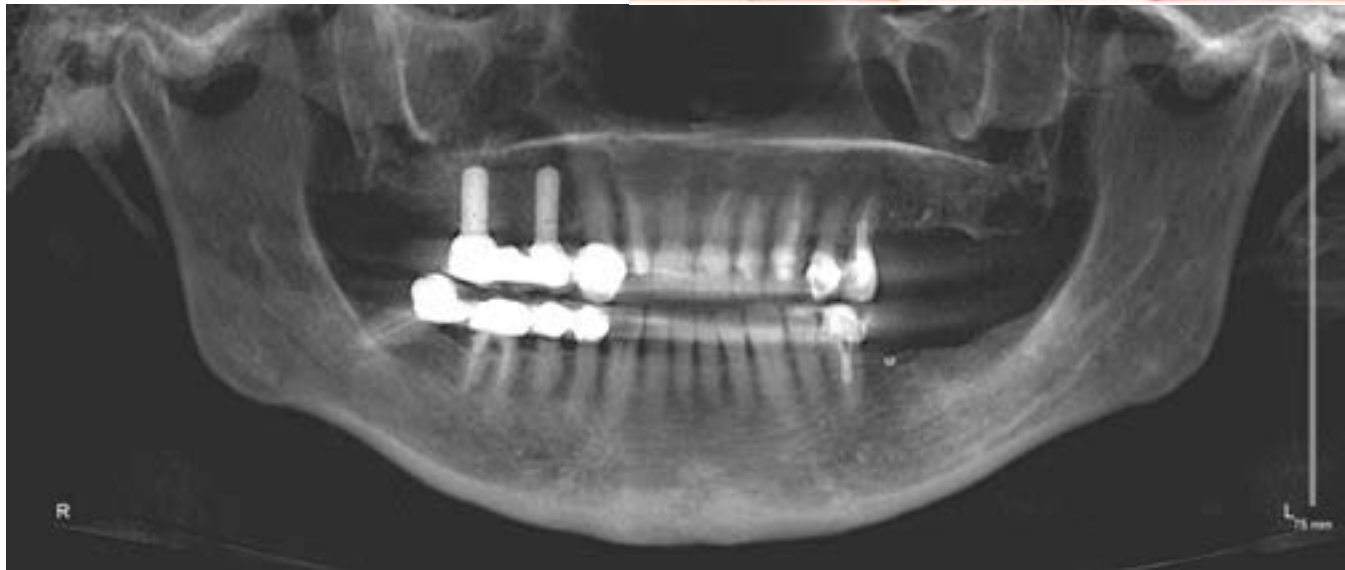


# Treatment strategies for maxillary MRONJ



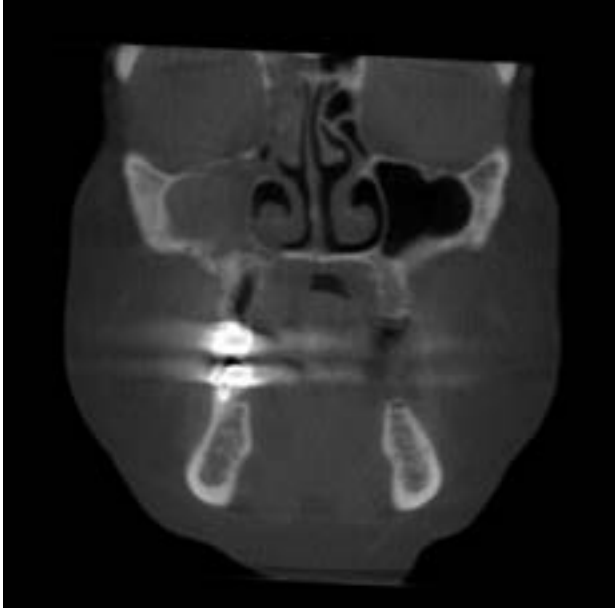
68 yo female with stage IV breast cancer who received monthly denosumab treatment for bone metastasis. Implants placed years prior to treatment.

**Stage 3 MRONJ**









1 month  
following right  
infra-structure  
maxillectomy



# Treatment Outcomes

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# Can modifying risk factors affect outcome or occurrence of disease?



# Dental treatment intervention

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Dimopoulos, et al. 2007 ASH meeting:

- 5 fold reduction of MRONJ in the group with increased dental surveillance and avoidance of dental surgery

Ripamonti, et.al. Ann Oncol. 2009

- RS/PS study 966 pt: 50% reduction in ONJ rate

Bonacina, et.al. JCDA. 2011

- PS 282 pts: 5-10% ONJ with no dental tx. 0% with care

Vandone, et.al. Ann Oncol. 2012

- PS study 211 pts: 50% reduction in ONJ rates in group with screening and preventive care

# Can modifying risk factors affect outcome or occurrence of disease?

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## Modification of BP therapy

- **Badros, et al. 2007 ASH meeting:**
  - ✓ MRONJ recurrence and # of non-healed patients linked to BP re- challenge
- **Corso, et al. 2007 Leukemia:**
  - ✓ ONJ risk 8x lower with reduced schedule ZA
  - ✓ Higher ONJ risk with ZA compared to pamidronate

# Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases

## A Randomized Clinical Trial

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- Open-label clinical trial in 269 academic and community sites across USA
- Pt with BC, MM, PC (n=1822)
- Randomized to receive zoledronic acid at a 4 or 12 week interval over 2 years
- No difference in SRE
- 18 cases (2%) ONJ in 4 wk group, 9 cases (1%) in 12 wk group (p=.08)

# new strategies for the treatment and management of MRONJ

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## Early surgical intervention

- Graziani, 2012 (JOMS): 68%
- Mucke, 2010 (J Cancer Res): 70%
- Carlson, 2009 (JOMS): 90%
- Stockman, 2009 (Cancer Care): 90%
- Stanton, 2007 (JOMS) 80%

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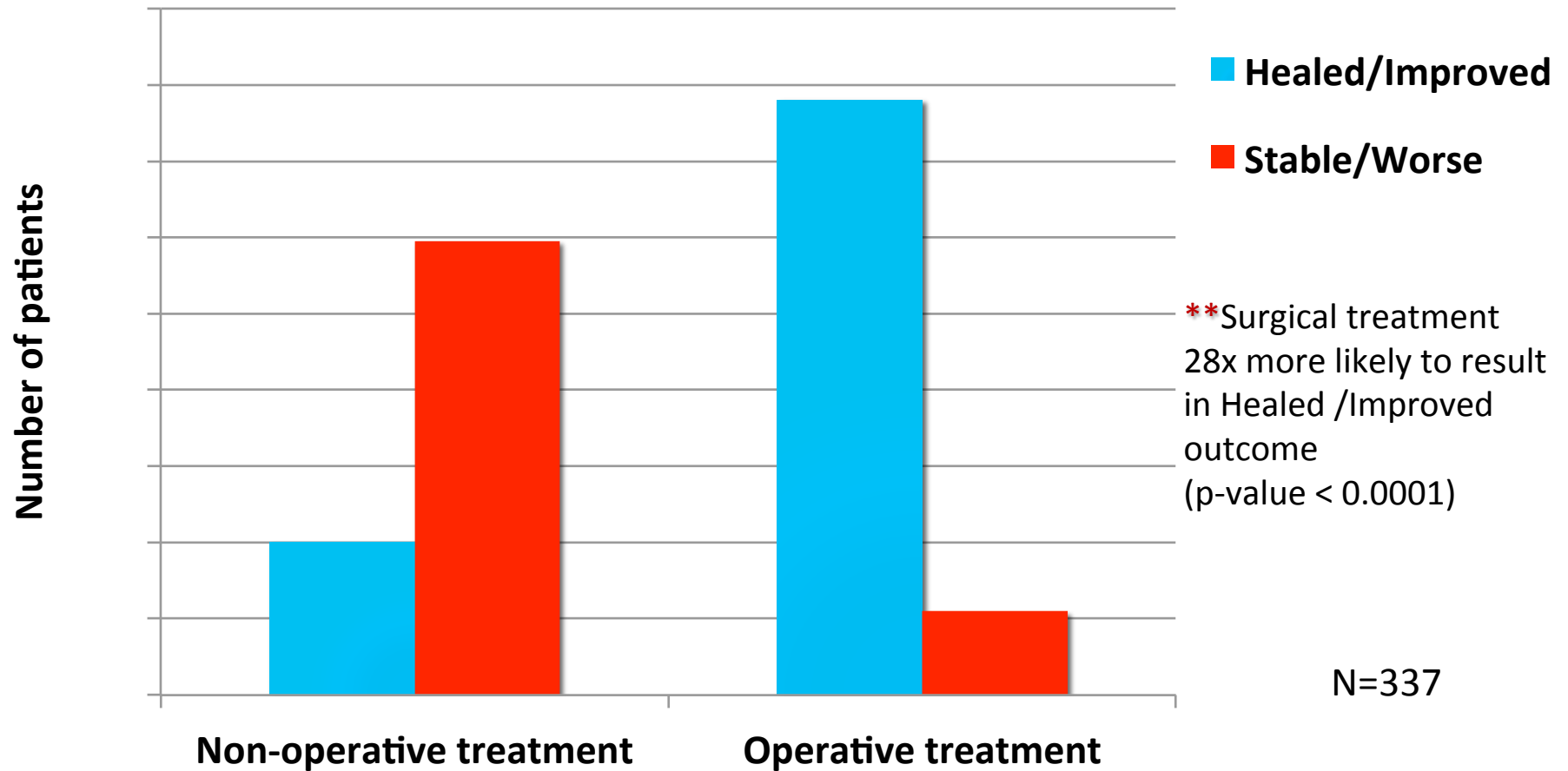
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# **Disease Stage and Mode of Therapy Are Important Determinants of Treatment Outcomes for Medication-Related Osteonecrosis of the Jaw**

*Salvatore L. Ruggiero, DMD, MD,\* and Nina Kohn, MBA, MA†*

# Outcome based on mode of therapy







Oral Surgery, Oral Medicine,  
Oral Pathology, Oral Radiology, and  
Endodontology

**ORAL MEDICINE**

*Editor: Craig S. Miller*

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**Management of bisphosphonate-associated osteonecrosis:  
pentoxifylline and tocopherol in addition to antimicrobial  
therapy. An initial case series**

Demonstrated efficacy in tx of RIF and ORN (Europe)

- ✓ Delanian S, et al: Head and Neck, 2005 (ORN)

Pentoxifylline: improves peripheral blood flow, inhibits dermal fibroblasts, increases collagenase activity

$\alpha$ - tocopherol: impairs tissue fibrosis, potent scavenger of oxygen radicals

- ✓ 6 cases prospectively reviewed
- ✓ No controls
- ✓ Decreased pain and smaller size of exposed bone

***“Pentoxifylline and tocopherol in the treatment of medication-related osteonecrosis of the jaw (MRONJ): a blinded, prospective, randomized controlled trial to evaluate a novel non-operative treatment study”***

- Aim: To determine if PTX-Vit E regimen in addition to the standard of care treatment significantly reduces the mean area (mm<sup>2</sup>) of exposed bone compared to standard of care alone
- Standard of care is defined as the clinical guidelines of the 2014 AAOMS Position Paper on Medication-Related Osteonecrosis of the Jaw (MRONJ)
- Multi-center study (UW, NYCOMS, UAB, UM)

# Management of MRONJ: points to consider in 2018

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- Emphasis on prevention
  - ✓ Dental, Medical
- Continued Education
  - ✓ Patients
  - ✓ Practitioners (Dental, Medical)
- Early surgical intervention?
  - ✓ Success rates 70-90%
- Rationale for drug holidays?

# Future research initiatives

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- Continued development and implementation of new, evidence-based strategies for the surgical and non-surgical management of ONJ
- Modification of antiresorptive therapy (dosing schedule changes)
  - ✓ Results from multicenter study
- Animal model systems directed at validating treatment strategies
- PTH and other anabolic agents in ONJ treatment
  - ✓ Systemic therapy for oncology patients?
  - ✓ Role for anti-sclerostin inhibitors (Romosozumab)?
- Risk assessment based on genetic profile
  - ✓ susceptibility, resistance
- Establish/evaluate the risk of ONJ related to new anti-angiogenic therapies
  - ✓ animal model?

**Thank You!!**

