"Vascular Endothelial Growth Factor Antibody (anti-VEGF) Monotherapy Causes Destructive Advanced Periodontitis but Not Osteonecrosis of the Jaw in Rice Rats (*Oryzomys palustris*)"

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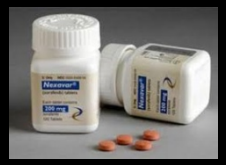
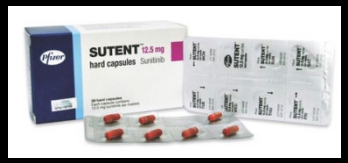
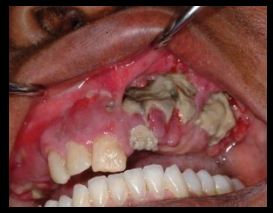
This research was supported by: NIH NIDCR (R01DE023783-01A), Genentech Inc., and Novartis

Background (1)

1. Angiogenesis inhibitors (AgIs) are a diverse group of drugs USFDA approved for use in combination with chemotherapy (CT) and/or powerful antiresorptive (pAR) drugs to treat certain types of cancer

2. Despite the significant benefits to cancer patients, AgIs have been associated with serious side effects including osteonecrosis of the jaw (ONJ)



3. ONJ is a severe condition characterized by exposed bone in the maxillofacial region that does not heal within eight weeks in patients with no history of radiation therapy or obvious metastatic disease in the jaws *(Ruggiero et. al., JOMS 2014; Khan et al., JBMR, 2015)*

Background (2)

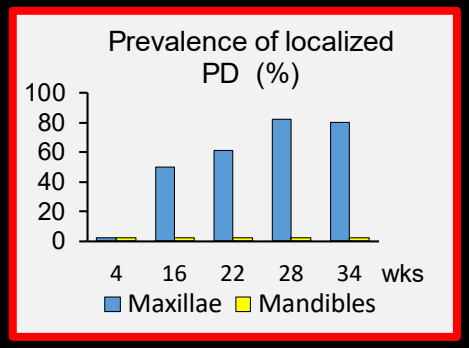
4. pARs, including N-BPs (e.g. zoledronic acid (*ZOL*)] and RANKL antibodies (e.g. denosumab), are causative agents for ONJ

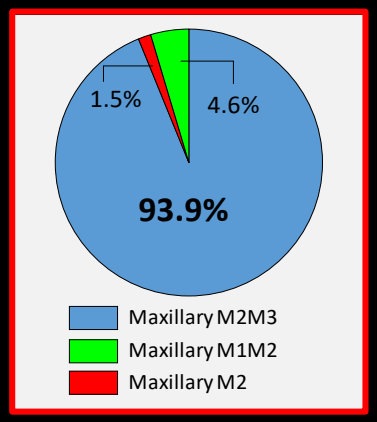
5. ONJ was also reported in pAR-naïve cancer patients receiving AgIs, including the *anti-VEGFA antibody bevacizumab* and receptor tyrosine kinase (RTK) inhibitors (e.g. *sunitinib*, *aflibercept*, etc.)

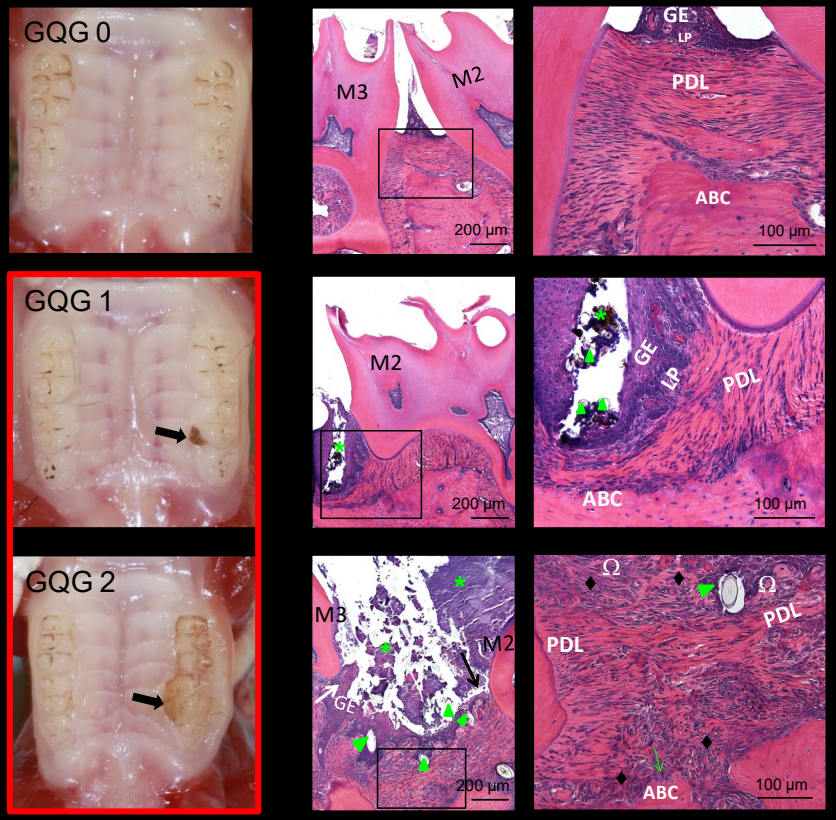
6. AgIs *are never given as monotherapy* but in combination with pARs, or with CTs (e.g. *docetaxel, paclitaxel, cisplatin, etc*.) and/or glucocorticoids

7. Oral risk factors, including dento-alveolar surgery (e.g. tooth extraction) and oro-dental infection /inflammation (e.g. *periodontitis*, periapical infection), play a critical role in the pathogenesis of ONJ

Rice rats fed a STD diet develop maxillary localized periodontitis at the M2M3 interdental area

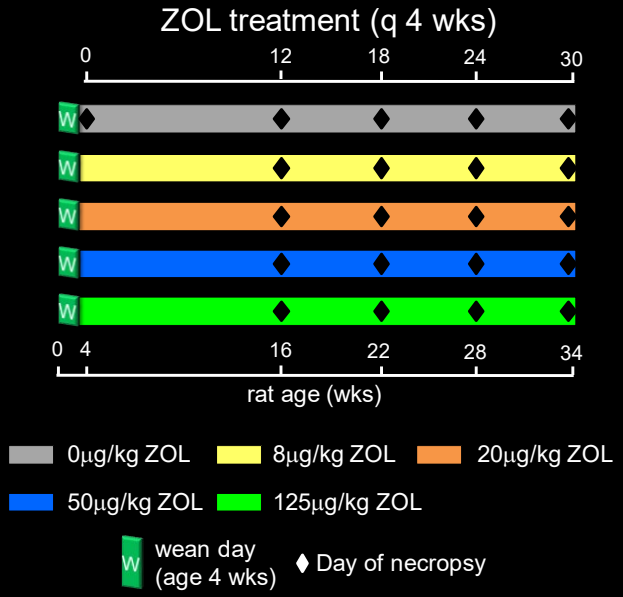




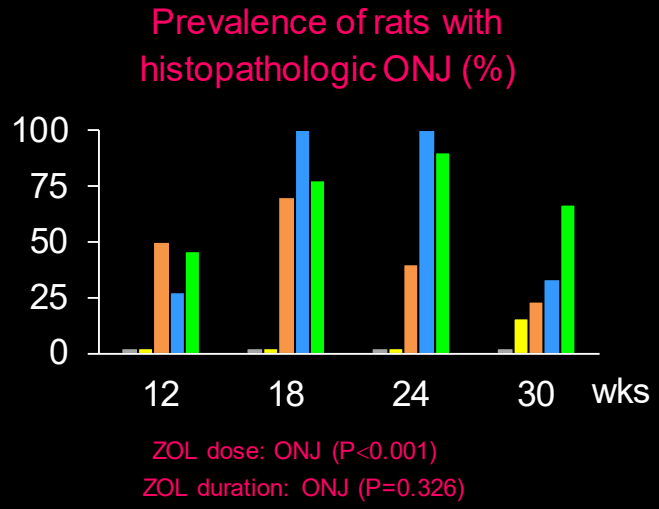


(Messer et al, 2017; Comp Med)

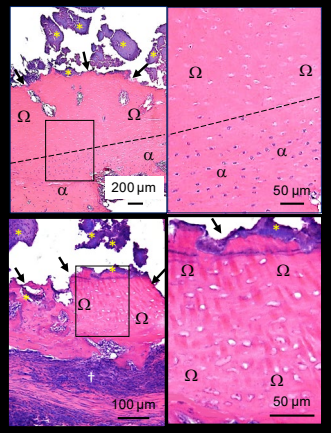
ZOL dose dependently induces ONJ in rice rats with localized periodontitis

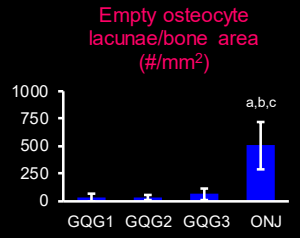


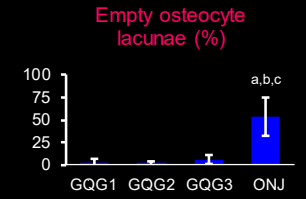
N=230 female rice rats; each subgroups (N=9-16)]

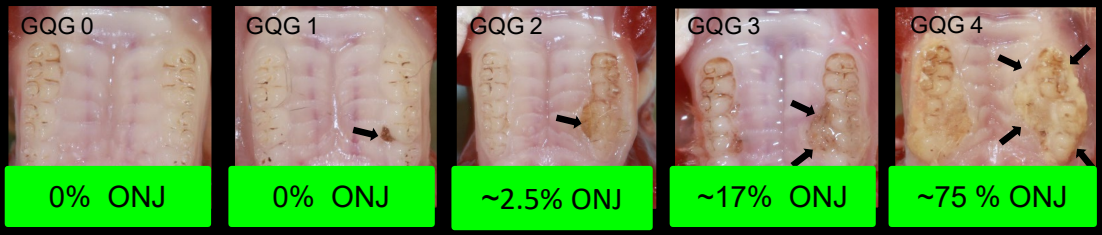


73% prevalence of ONJ with oncologic doses of ZOL (≥20 μg/kg)









GQG: gross quadrant grade

(Messer et al, 2018; Bone)

Rationale

*AgIs are never given as monotherapy but in combination with pARs, or with CTs and/or glucocorticoids in pAR-naïve cancer patients. Therefore, a causal relation between **AgIs and ONJ** cannot be established based on the current clinical data*

Hypothesis

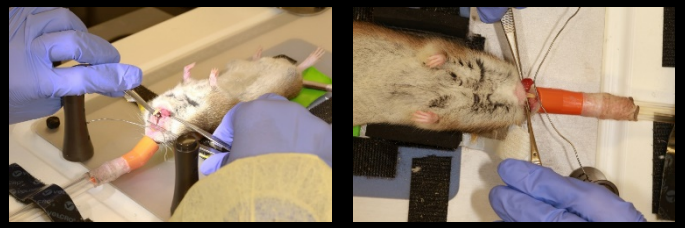
An anti-VEGF monotherapy treatment given to rice rats with maxillary localized PD will induce oral lesions that resemble ONJ, defined by exposed, necrotic alveolar bone

Methods

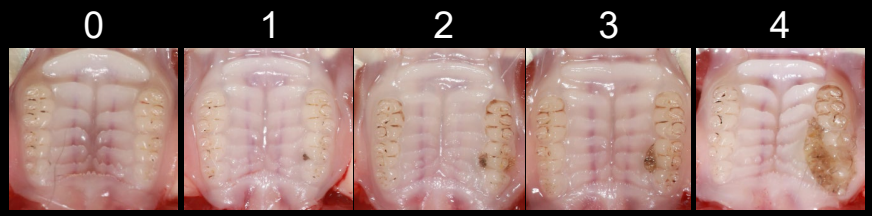
1) VEH (vehicle control)
2) 80 µg/kg ZOL (IV) q4wk (positive control)
3) 5 mg/kg anti-VEGF* (SC) 2/wk

*anti-VEGF: *cross-species rodent* anti-VEGF MAb [B20-4.1.1]), Genentech Corp.

- In vivo oral exams under isoflurane anesthesia (q2wks)

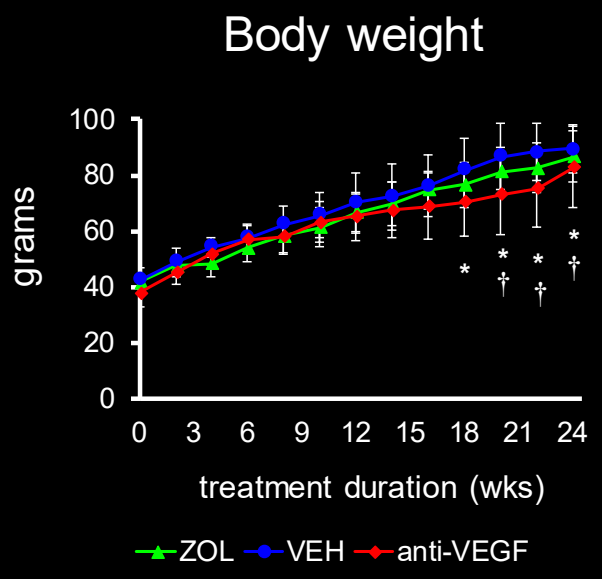


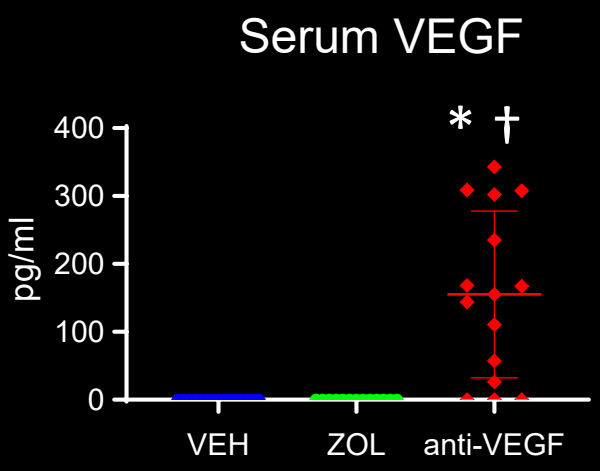
- High Resolution Photographs of Jaws (necropsy = 24 wks)
- Gross Quadrant Grade (GQG)

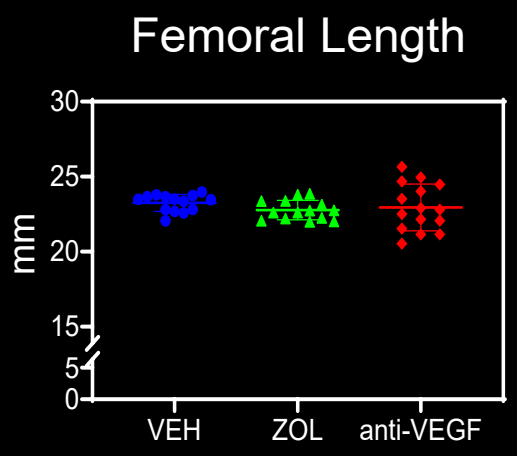


- MicroCT
- Histopathology of all quadrants with GQG ≥2 (decalcified, serially sectioned, and H&E stained)
- Immunocytochemistry

Evaluation of physiologic parameters in experimental groups

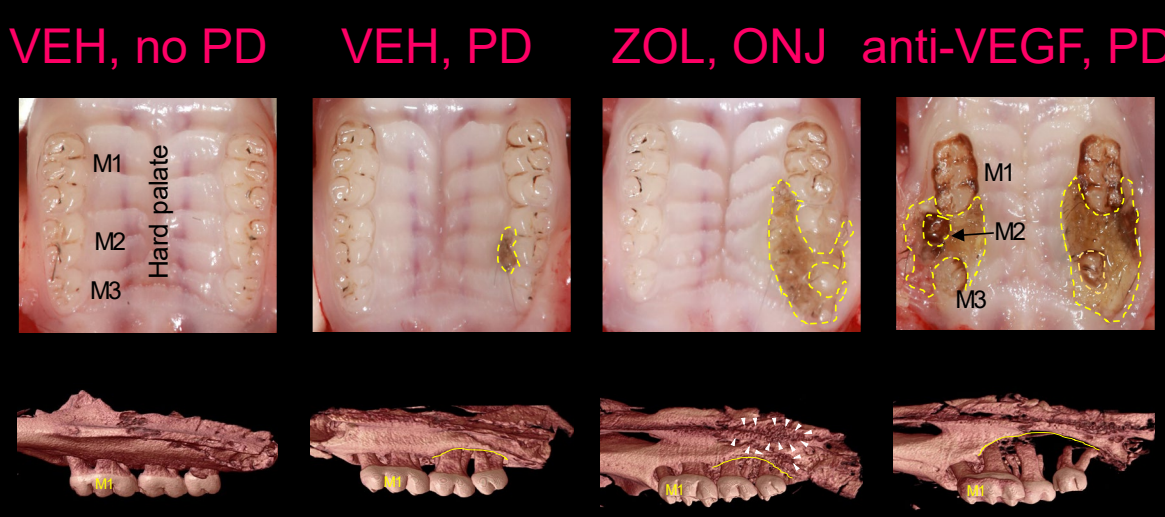


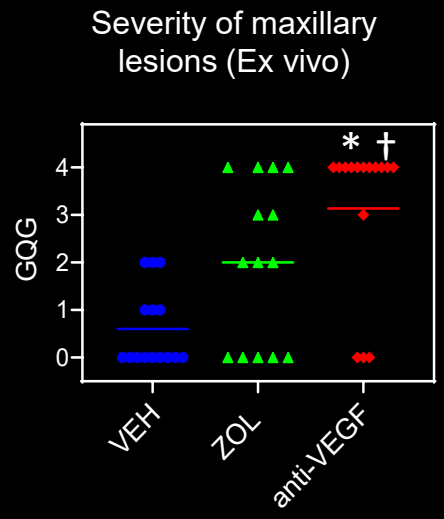




(Messer et al, 2019; under review)

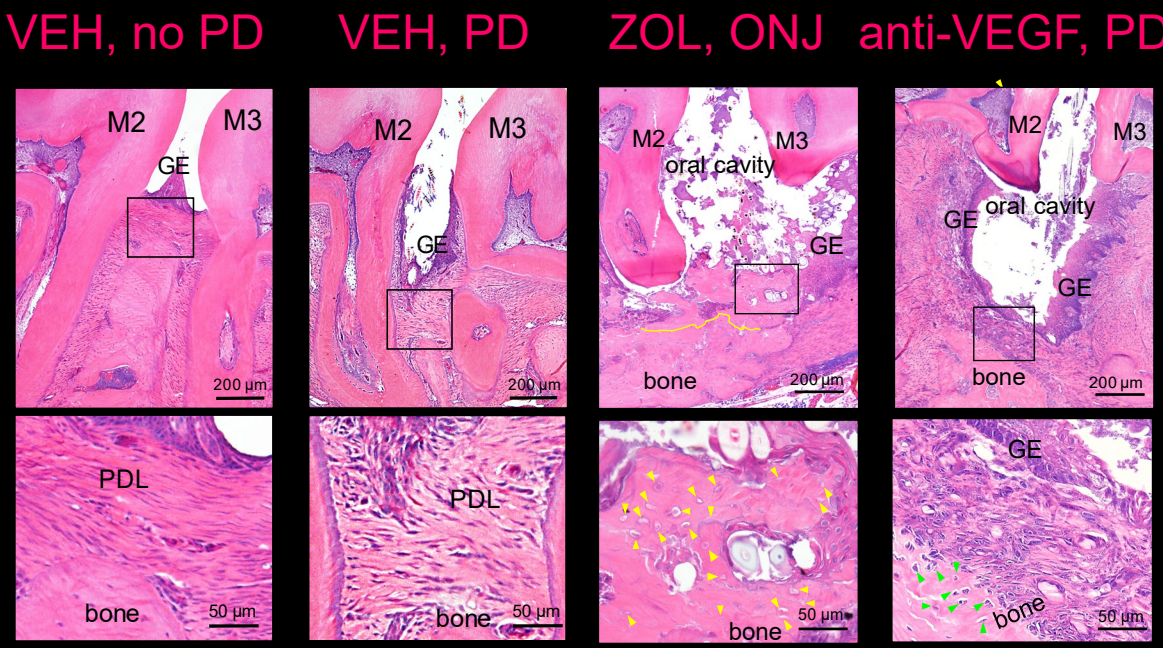
Greater severity and alveolar bone loss of maxillary oral lesions in rice rats treated with anti-VEGF antibody

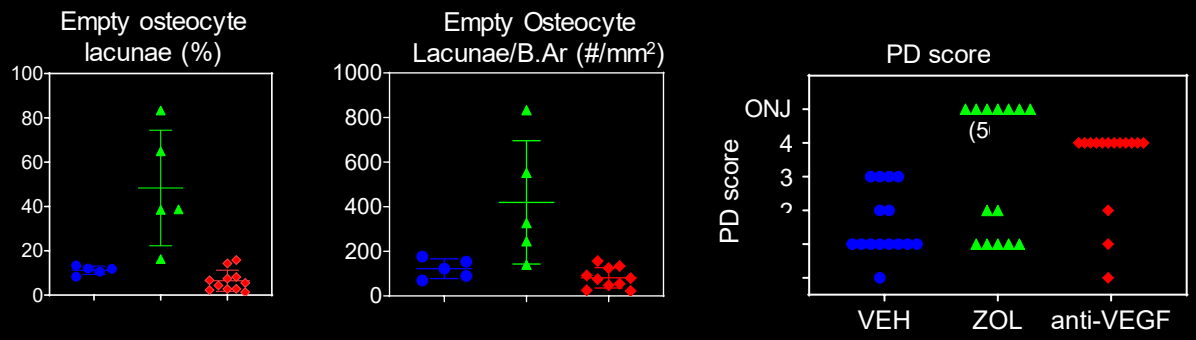




(Messer et al, 2019; under review)

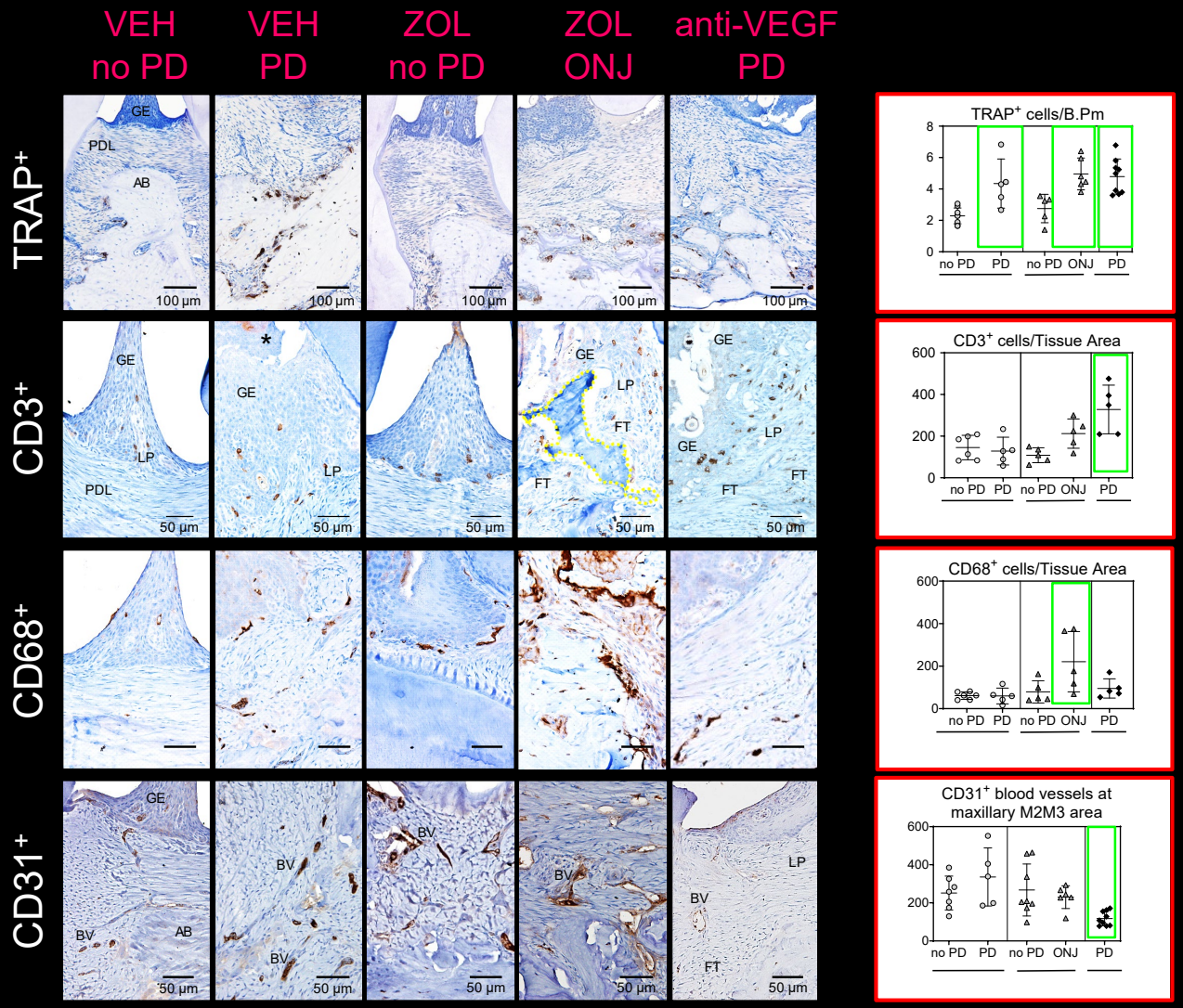
anti-VEGF rats with localized PD develop destructive advance PD but not ONJ





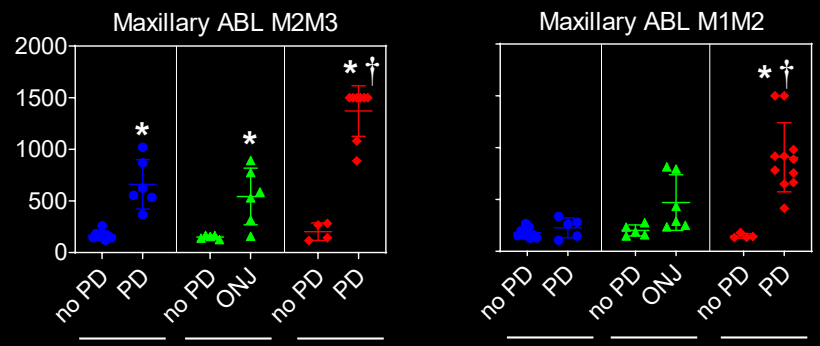
(Messer et al, 2019; under review)

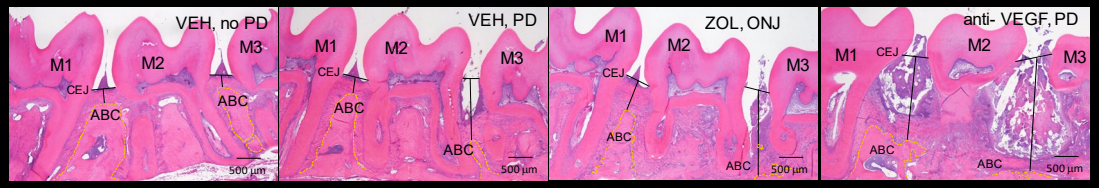
In situ analysis of cells that play an important role in PD and angiogenesis in maxillae

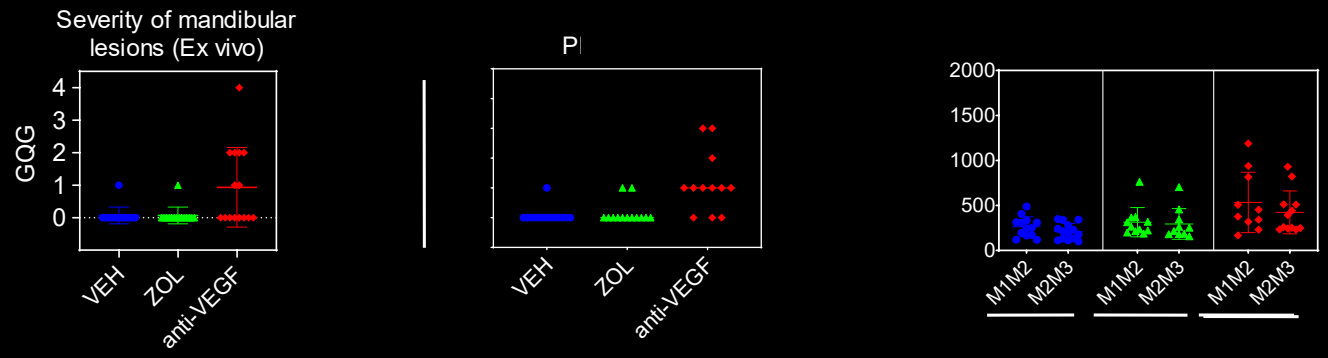


(Messer et al, 2019; under review)

anti-VEGF rats had increased alveolar bone loss and PD severity in all jaws







(Messer et al, 2019; under review)

Summary of Results

1. 40-80% of the rats in the three groups developed gross oral lesions and 50% of ZOL rats developed ONJ

2. In contrast, 80% of the anti-VEGF rats developed destructive advanced periodontitis, characterized by extreme alveolar bone loss and fibrosis. Anti-VEGF rats never developed exposed, necrotic bone

3. only anti-VEGF rats developed mild to severe mandibular periodontitis

4. Compared to VEH rats, more T-cells were found in periodontal lesions of anti-VEGF rats

Conclusions

1. anti-VEGF induces destructive advanced PD, but not ONJ in rice rats

2. This may suggest that concurrent therapies with pARs and/or anti-mitotic drugs are needed in addition to AgIs to induce ONJ in cancer patients

Acknowledgments

Dept. of Physiological Sciences

Physiological Sciences, UF

Donald Kimmel

Thomas Wronski

Jonathan Messer

Jessica Jiron

Evelyn Castillo

Jorge Mendieta Calle

H.Y. (Peter) Chen

Abel Abraham

Samantha Thomas

Ronnie Israel

Gabriella Gonzalez-Perez

Danae Wright

VA Medical Center &
UF College of Medicine

Joshua Yarrow

Michael Reynolds

Russell Wnek

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Catherine Van Poznak

Dep. Biology, Indiana University Southeast

Kent Edmonds

This research was supported by: NIH NIDCR (R01DE02378301A), Genentech Inc., and Novartis