Alessandria
24 GIUGNO 2015

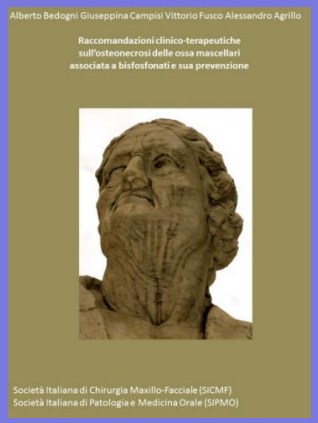
EPIDEMIOLOGIA:
ONJ da bifosfonati e altri farmaci

Vittorio Fusco **SC Oncologia**
Az. Ospedaliera di Alessandria

RACCOMANDAZIONI CLINICO-TERAPEUTICHE su L'OSTEONECROSI DELLE OSSA MASCELLARI ASSOCIATA A FARMACI

Basato su
RACCOMANDAZIONI PER PREVENZIONE E CURA DELLA OSTEONECROSI DELLE OSSA MASCELLARI
Bedogni A, Campisi G, Fusco V, Agrillo A.
CLEUP ed. (vers. 1.1 marzo 2013)

e **successive fonti della Letteratura**



**Speakers dichiarano: nessun conflitto di interesse*

SICMF Società Italiana Chirurgia Maxillo-Facciale

Comitato di Esperti delle
***Società Italiana di Chirurgia Maxillo-Facciale* (SICMF) e**
***Società Italiana di Patologia e Medicina Orale* (SIPMO)**

SPMO

ONJ : quanto è frequente ?

INCIDENZA : ?

PREVALENZA : ?

“FREQUENZA” : ?

tra <0.5% e >12%

Numeri assoluti : ?

(epidemiologia; carichi di lavoro…)

Rischio individuale : ?

(rischio nel tempo…; costi-benefici)

Epidemiologia: ONJ da bifosfonati e altri farmaci

V. Fusco

Quali sono i farmaci che possono determinare la ONJ ?

Epidemiologia: ONJ da bifosfonati e altri farmaci *V. Fusco*

Quali sono le categorie di pazienti a maggior rischio di ONJ?

Esistono ad oggi "nuovi" sottogruppi di popolazione ad alto rischio?

Fonti di dati epidemiologici

1. *Studi randomizzati (bracci con/senza farmaci in studio)*
2. *Studi osservazionali, case series (bias di selezione …)*
3. *Studi sistematici di popolazione (registro tumori, ecc).*
4. *Studi retrospettivi su database (assicurazioni, dimissioni ospedaliere, utenti sistema sanitario)*
5. *Surveys di specialisti o unità spec. (odonto / maxillofacciali) o di centri oncologici (Rete Oncologica Piemonte –VdA)*

ONJ
FARMACI RELATI

Comitato di Esperti delle
Società Italiana di Chirurgia Maxillo-Facciale (SICMF) e
Società Italiana di Patologia e Medicina Orale (SIPMO)

In collaborazione con **FNMOCeO-CAO**

Con il patrocinio del **COLLEGIO DEI DOCENTI DI ODONTOIATRIA**

BP

STRUTTURA CHIMICA

AMINOBISFOSFONATO Presenza di un gruppo amminico	Non AMINOBISFOSFONATO Assenza di un gruppo amminico
Alendronato	Clodronato
Ibandronato	Etidronato
Neridronato	Tiludronato
Pamidronato	
Risedronato	
Zoledronato	

Gli **Amino-BP** hanno maggiore affinità per l'osso, e una potenza da 10 a 1000 volte maggiore rispetto ai non BP

FARMACO	INDICAZIONI	NOMI COMMERCIALI
DENOSUMAB	• Osteoporosi postmenopausale • Osteoporosi negli uomini ad elevato rischio di fratture per terapia ormonale ablativa • Prevenzione di complicazioni a carico dell'apparato scheletrico in adulti con tumori solidi diffusi alle ossa	PROLIA XGEVA
SUNITINIB	• Metastasi ossee del Carcinoma a cellule renali (RCC) • Tumori stromali gastrointestinali (GIST) • Tumore primitivo ectodermale (pNET)	SUTENT
SORAFENIB	• Epatocarcinoma (HCC) • Carcinoma a cellule renali (RCC)	NEXAVAR
BEVACIZUMAB	• Carcinoma mammario metastatico • Carcinoma colon-rettale metastatico (mCRC) • Carcinoma polmonare a piccole cellule (NSCLC) • Glioblastoma (Glio) • Carcinoma renale metastatico (mRCC)	AVASTIN

2003-2005 "New" BP toxicities
(rarely or not reported on first trials)

- eye toxicity
- renal toxicity
- osteonecrosis of jaw (ONJ)

review

Annals of Oncology 17: 897–907, 2006
doi:10.1093/annonc/mdj105
Published online 17 March 2006

Management of the adverse effects associated with intravenous bisphosphonates

T. Tanvetyanon[1]* & P. J. Stiff[2]

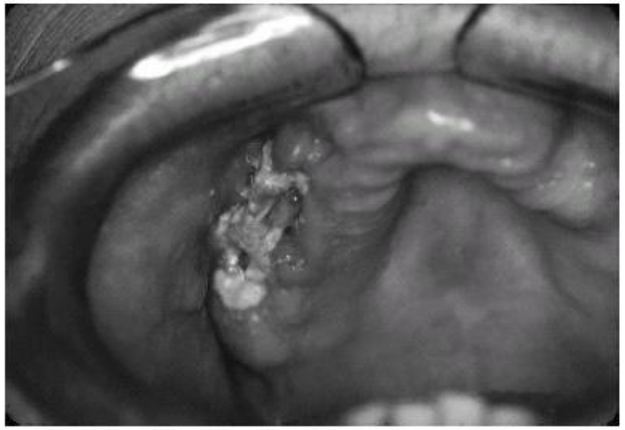


FIGURE 1. Exposed necrotic bone in the mandible in a patient who was taking pamidronate (Aredia). Exposed bone initiated by a tooth removal.

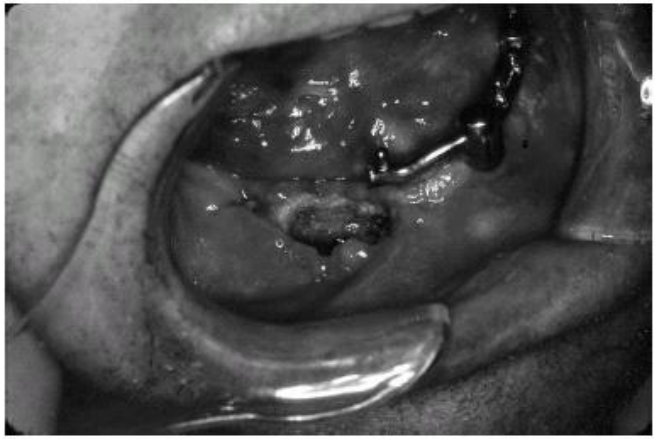


FIGURE 2. Exposed necrotic bone in the maxilla in a patient who was taking pamidronate (Aredia). Exposed bone occurred spontaneously.

Marx (Miami University) JOMS 2003-2004

36 cases

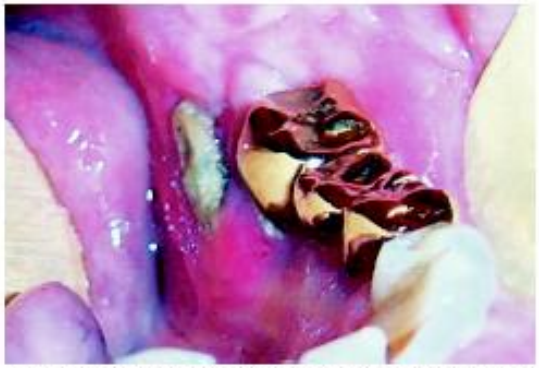


Fig 1. Bone necrosis of the mandible on a female patient with metastatic breast cancer to bone under treatment with zoledronic acid.

Migliorati, JCO 2003

5 cases

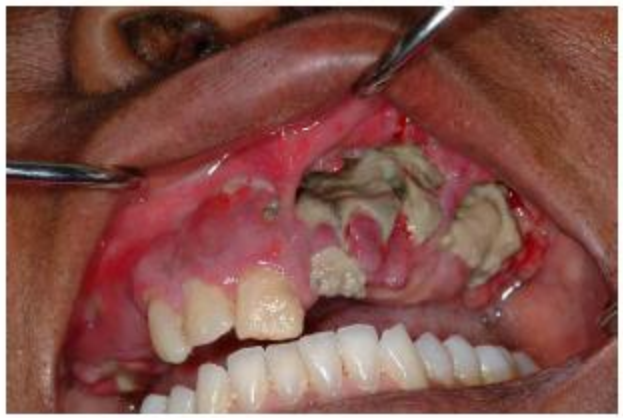
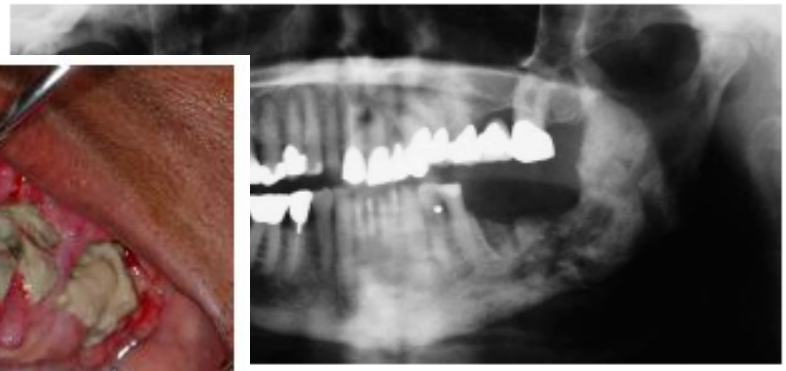


FIGURE 1. Exposed necrotic maxillary bone in a patient receiving zolendronic acid for 6 months. The patient had posterior maxillary extractions performed 4 months earlier. (Courtesy of Dr Jay Neugarten, New Hyde Park, NY.)



nic radiograph of the mandible following extrac-
teeth in a patient receiving pamidronate. The
lled bone in the region of the nonhealing extrac-

Ruggiero et al (NY) JOMS 2004 63 cases

2008: new guidelines and recommendations

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

Aapro M. et al, Annals of Oncology mar 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.

- 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.

Utilizzo attuale dei BP in Oncologia ed Ematologia

-Riduzione delle prescrizioni
- "Tailoring"

Ridotti i nuovi casi di ONJ ?

-Effetto delle misure "preventive" ?
-Effetto della ridotta esposizione ?
-Di entrambi ?

ONJ in Oncologia/Ematologia: Rischi presenti e futuri

- ONJ dopo denosumab (e shift)

- ONJ dopo agenti biologici, cd "target" (con/senza BP o denosumab)

ONJ in pazienti NON oncologici: Rischi presenti e futuri

-ONJ dopo BP orali (alendronato, risedronato, ibandronato) (RA !)

-ONJ dopo BP ev (zoledronato=Aclasta, ibandronato=Bonviva)

-ONJ dopo denosumab sc (Prolia)

-ONJ dopo clodronato (?) (in Italia: anche im)

DENOSUMAB

- **Different pathway (RANK-L inhibition)**
- **Subcutaneous injection (not IV infusion)**
- **Less toxic ?**
- **More active ?**

PROLIA (60 mg *q 6 months*) - osteoporosis

XGEVA (120 mg *q 28 days*) - bone metastases

Zol vs DENOSUMAB : 3 trials

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

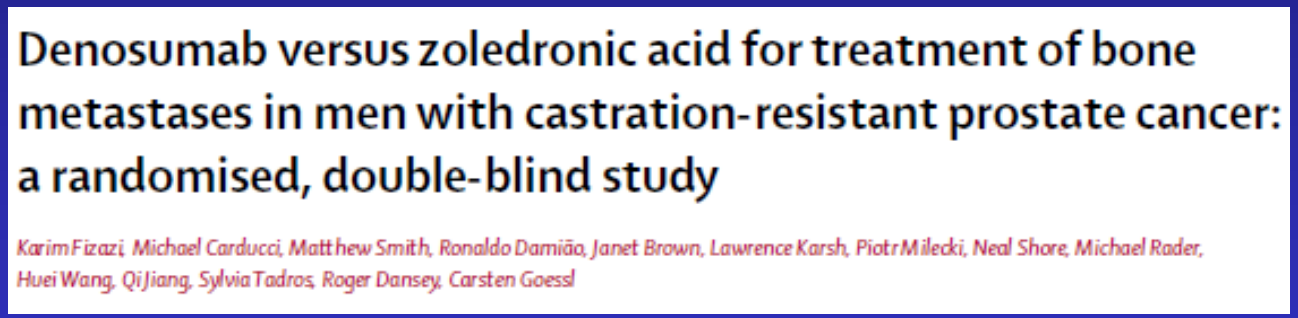
Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study

Alison T. Stopeck, Allan Lipton, Jean-Jacques Body, Guenther G. Steger, Katia Tonkin, Richard H. de Boer, Mikhail Lichinitser, Yasuhiro Fujiwara, Denise A. Yardley, Maria Viniegra, Michelle Fan, Qi Jiang, Roger Dansey, Susie Jun, and Ada Braun

See accompanying editorial doi: 10.1200/JCO.2010.31.0128

Stopeck, JCO 2010
2046 pts

First on-study SRE : HR 0.82
(26.4 months vs not reached)

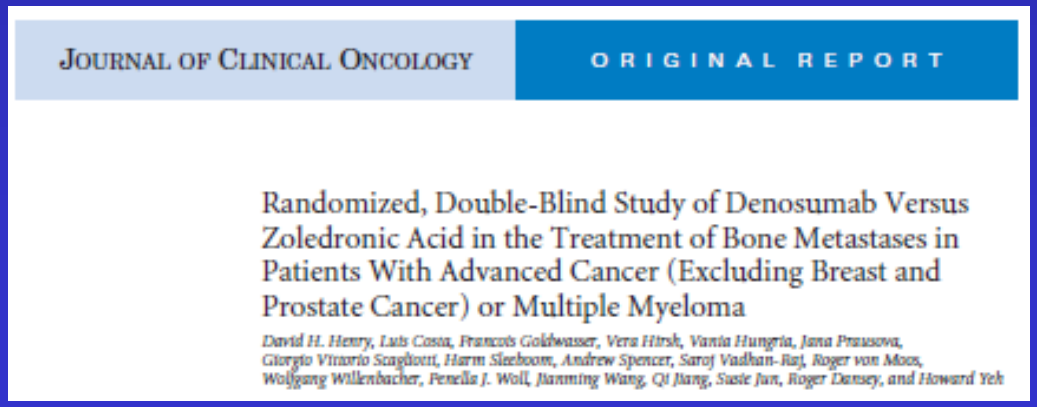


Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study

Karim Fizazi, Michael Carducci, Matthew Smith, Ronaldo Damião, Janet Brown, Lawrence Karsh, Piotr Milecki, Neal Shore, Michael Rader, Huei Wang, Qi Jiang, Sylvia Tadros, Roger Dansey, Carsten Goessl

Fizazi, Lancet 2011
1904 pts

First on-study SRE :
HR 0.82
(17.1 vs 20.7 months)



JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Randomized, Double-Blind Study of Denosumab Versus Zoledronic Acid in the Treatment of Bone Metastases in Patients With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma

David H. Henry, Luis Costa, Francois Goldwasser, Vera Hirsh, Vania Hungria, Jana Prausova, Giorgio Vittorio Scagliotti, Harm Sleeboom, Andrew Spencer, Saroj Vadhan-Raj, Roger von Moos, Wolfgang Wilkenbacher, Penella J. Woll, Jianming Wang, Qi Jiang, Susie Jun, Roger Dansey, and Howard Yeh

Henry, JCO 2011
1776 pts

First on-study SRE :
HR 0.8 (non inferiority)
(16.3 vs 20.6 months)

Zol vs DENOSUMAB trials : ONJ


JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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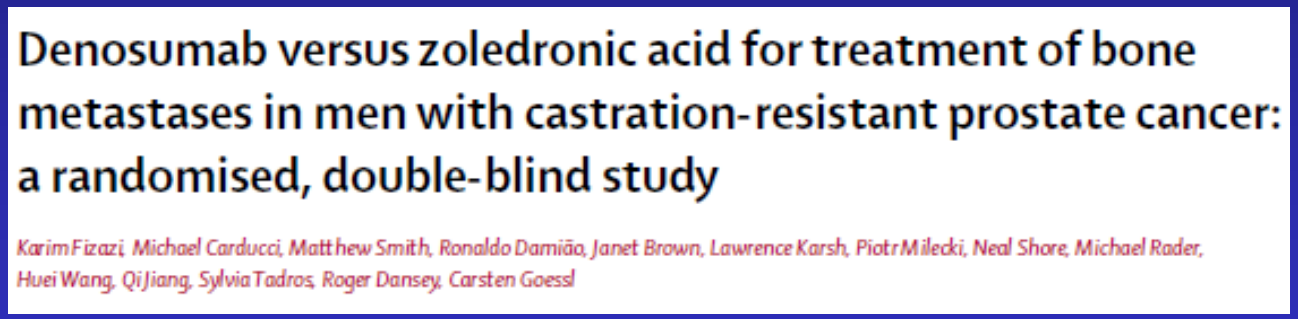
See accompanying editorial doi: 10.1200/JCO.2010.31.0128

Stopeck, JCO 2010

ONJ :
2% (DEN) vs 1.4% (ZA)


Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study

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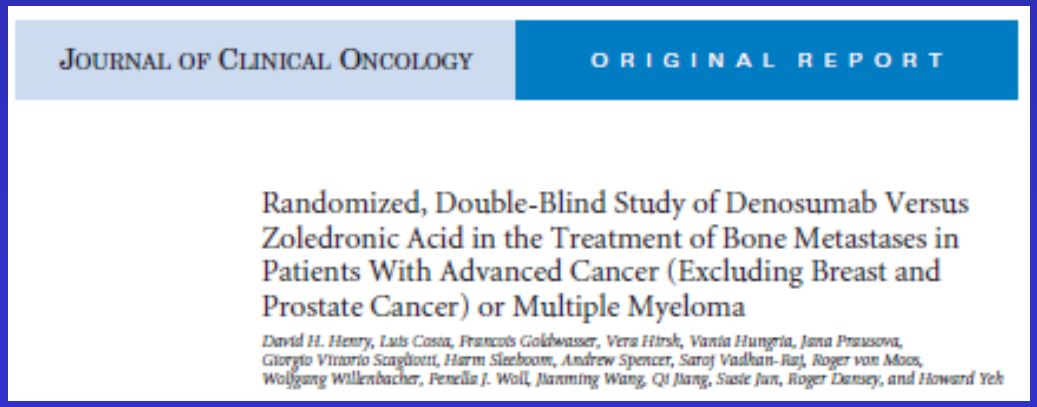
Fizazi, Lancet 2011

ONJ :
2% (DEN) vs 1% (ZA)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Henry, JCO 2011

ONJ :
1.1% (DEN) vs 1.3% (ZA)

V.Fusco et al - JCO 2011 (letter)

JOURNAL OF CLINICAL ONCOLOGY | CORRESPONDENCE

Osteonecrosis of the Jaw After Zoledronic Acid and Denosumab Treatment

Case Adjudication

Patient selection

Short follow-up

No cumulative incidence

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Giovannino Ciccone
Centro di Prevenzione Oncologica, Azienda Ospedaliera San Giovanni Battista, Torino, Italy

Saad et al - Ann Oncol 2012

Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases

Results: Of 5723 patients enrolled, 89 (1.6%) patients were determined to have ONJ: 37 (1.3%) received zoledronic acid and 52 (1.8%) received denosumab ($P = 0.13$). Tooth extraction was reported for 61.8% of patients with ONJ. ONJ treatment was conservative in >95% of patients. As of October 2010, ONJ resolved in 36.0% of patients (29.7% for zoledronic acid and 40.4% for denosumab).

5723 pts

Event as potential ONJ 276 (4.8%)

Adjudicated ONJ cases 89 (1.5%)

ONJ resolved in 36.0% (29% zoledronic acid, 40% denosumab)

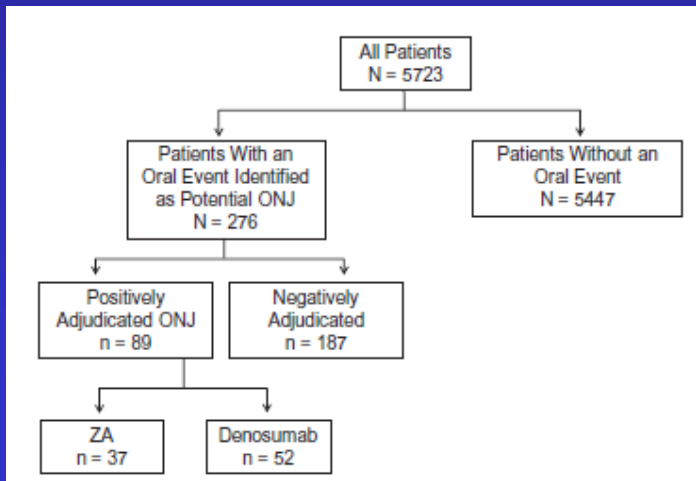


Figure 1. CONSORT diagram. Outcome of ONJ adjudication process. CONSORT, Consolidated Standards of Reporting Trials; ONJ, osteonecrosis of the jaw.

Breast cancer : new ASCO Guidelines 2011

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology 2003 Update on the Role of Bisphosphonates and Bone Health Issues in Women With Breast Cancer

Hillner BE, et al. *J Clin Oncol*. 2003

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Executive Summary of the Clinical Practice Guideline Update on the Role of Bone-Modifying Agents in Metastatic Breast Cancer

Catherine H. Van Poznak, Sarah Temin, Gary C. Yee, Nora A. Janjan, William E. Barlow, J. Sybil Biermann, Linda D. Bosserman, Cindy Geoghegan, Bruce E. Hillner, Richard L. Theriault, Dan S. Zuckerman, and Jamie H. Von Roenn

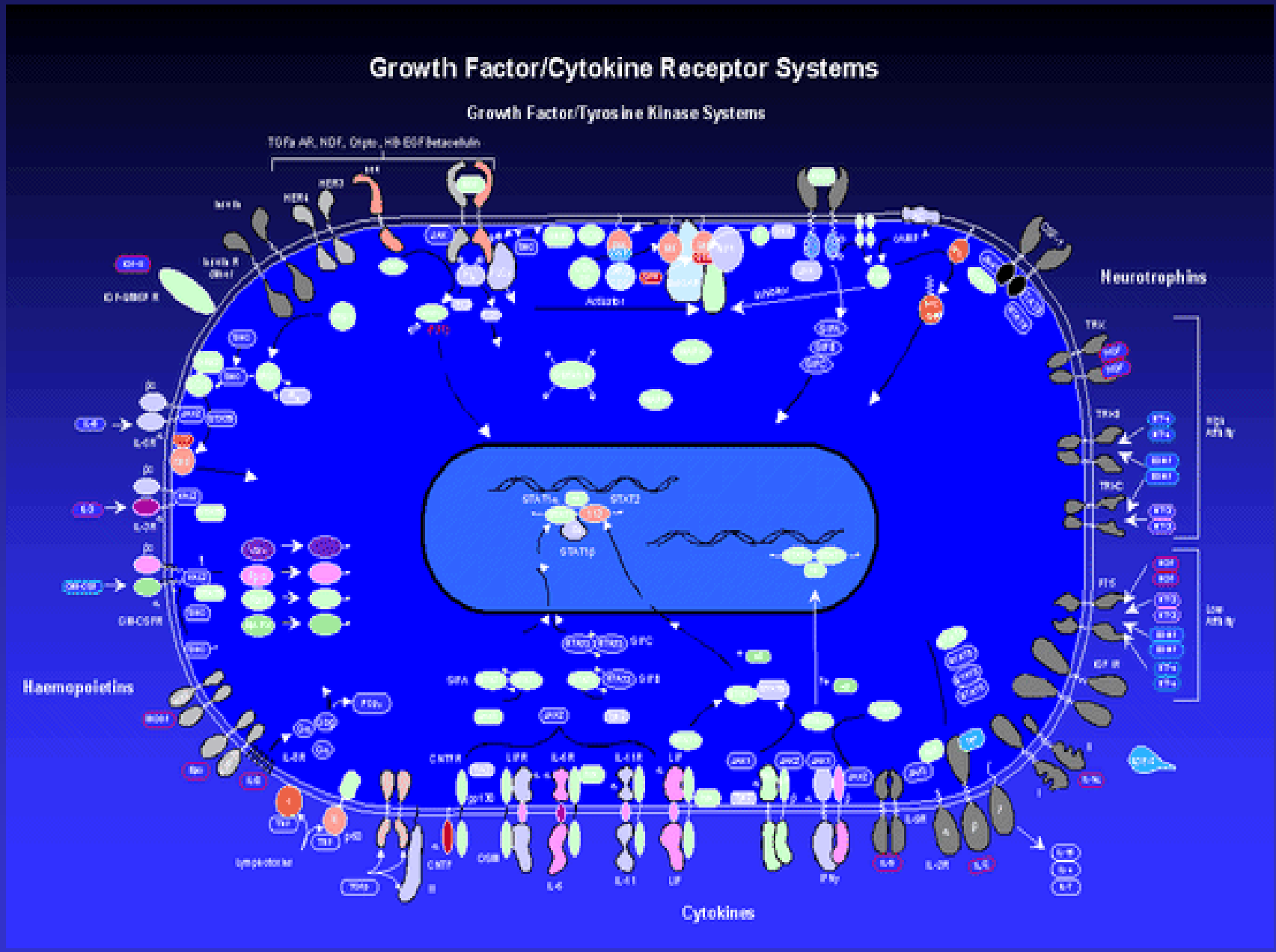
Van Poznak, et al. *J Clin Oncol*. 2011

Smith et al, Lancet Oncology 2011

Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial

- 1432 patients (716 denosumab, 716 placebo) without bone metastases, treated for > 24 months

- ONJ in 33 pts receiving denosumab (5%) vs 0 receiving placebo


Growth Factor/Cytokine Receptor Systems
Growth Factor/Tyrosine Kinase Systems
Neurotrophins
Haemopoietins
Cytokines

MEDICAL ONCOLOGY

- Chemotherapy
- Endocrine therapy
- Immunotherapy
- Bone modifying agents
- "Target therapy" (biological agents): antiangiogenic, mTOR inhibitors, antiEGFR, etc

Recent “targeted” agents : solid tumours

AFINITOR (Everolimus)

AVASTIN (Bevacizumab)

ERBITUX (Cetuximab)

GLIVEC (Imatinib)

HERCEPTIN (Trastuzumab)

IRESSA (Gefitinib)

NEXAVAR (Sorafenib)

PERJETA (Pertuzumab)

STIVARGA (Regorafenib)

SUTENT (Sunitinib)

TARCEVA (Erlotinib)

TORISEL (Temsirolimus)

TYVERB (Lapatinib)

VECTIBIX (Panitumumab)

VOTRIENT (Pazopanib)

YERVOY (Ipilimumab)

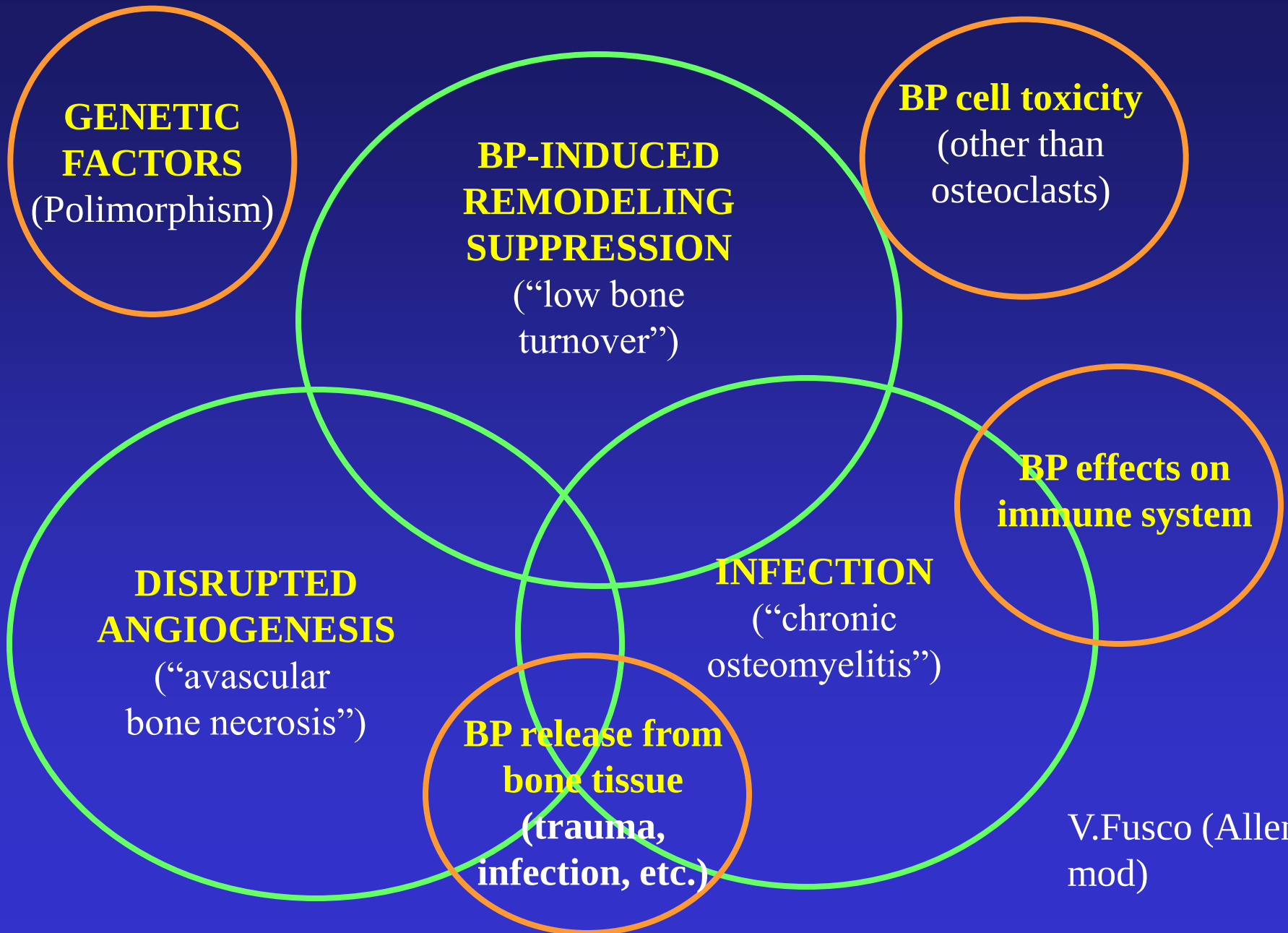
ZALTRAP (Aflibercept)

ZELBORAF (Vemurafenib)

Etc.

Etc.

ONJ : WHY ?



V.Fusco (Allen mod)

Bevacizumab

Aflibercept

Sunitinib
Sorafenib
Pazopanib
Regorafenib
Imatinib
etc.

Erlotinib
Gefitinib

Temsirolimus
Everolimus

Ipilimumab

Cetuximab
Panitumumab

Trastuzumab
Pertuzumab
Lapatinib

Vemurafenib
Dabrafenib
etc.

ONJ after BPs + biological "targeted" agents

Ayllon, Ann Oncol 2009	**1 case after BP + Bevacizumab (breast cancer)** **1 case after BP + Sunitinib (renal cell cancer)**
Brunello, Bone 2009	**1 case after BP + Sunitinib (renal cell cancer)**
Christodoulou, Oncology 2009	**3 cases after BP + Bevacizumab (2 breast, 1 colon cancer)** **1 case after BP + Sunitinib (renal cell cancer)**
Mc Arthur , ASCO 2008 (abs)	**8 cases after BP + Bevacizumab**

V.Fusco 2009

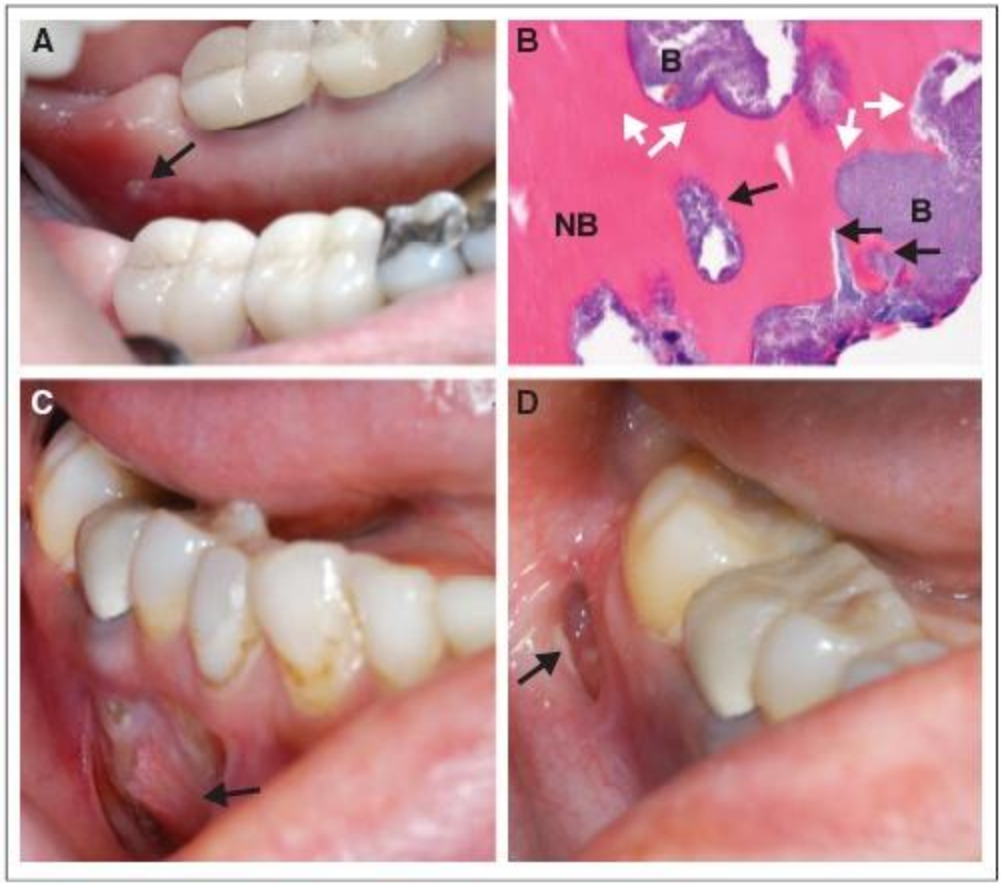
ONJ after Bevacizumab alone (without BP)

VOLUME 26 · NUMBER 24 · AUGUST 20 2008

JOURNAL OF CLINICAL ONCOLOGY

DIAGNOSIS IN ONCOLOGY

Osteonecrosis of the Jaw Related to Bevacizumab



1 breast cancer,
1 glioblastoma

Estilo et al, JCO 2008

V.Fusco

Brunello et al, Bone 2009

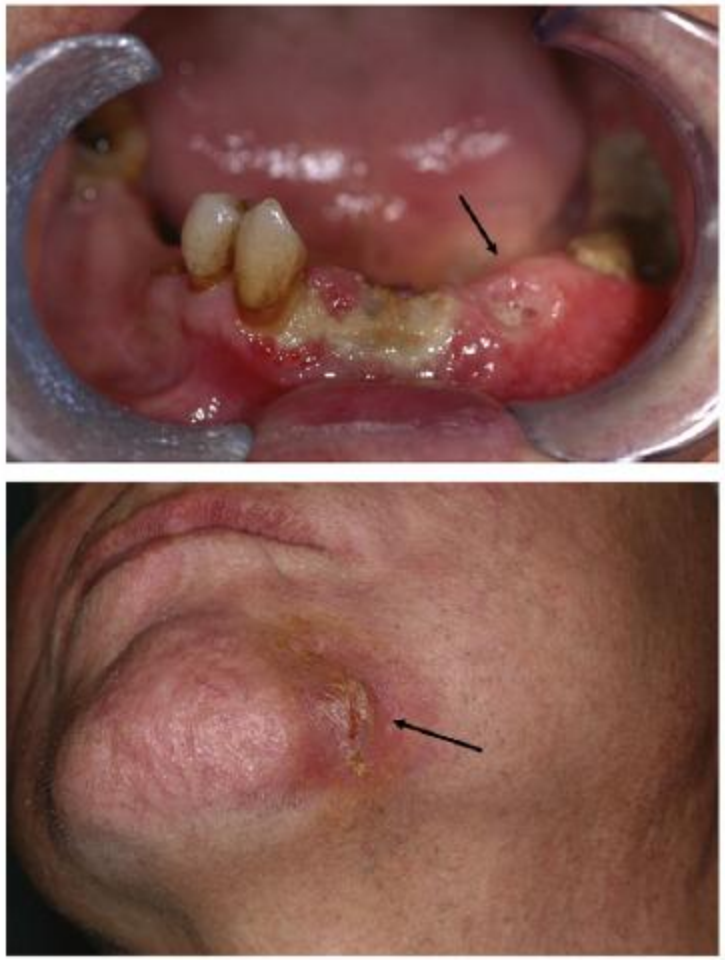


Fig. 2. Situation after resumption of sunitinib: increased exposure of bone, loss of a canine tooth and cervical cutaneous sinus-track formation.

(Fig. 4). The bone infection improved with another cycle of oral amoxicillin–clavulanic acid and metronidazole, and gingival repair occurred.

This is the first report of osteonecrosis of the jaw in a patient receiving a novel antiangiogenic drug who had been previously treated with i.v. bisphosphonates. The consecutive episodes of painful jaw infection with cutaneous fistula and bone sequestration in our patient were likely correlated with sunitinib therapy, occurring during active treatment, significantly improving after sunitinib discontinuation and antibiotic therapy, then rapidly worsening with resumption of treatment.

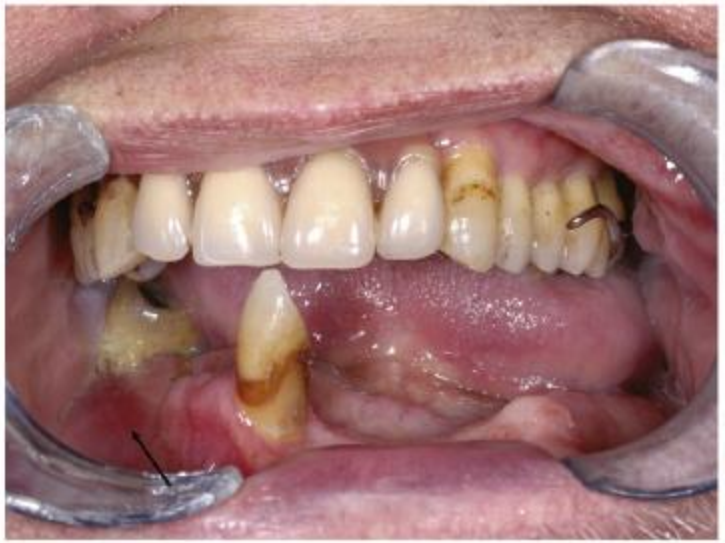


Fig. 4. At sunitinib re-challenge: painful swelling, bone exposure in the right body of the mandible with spontaneous tooth loss.

Bisphosphonate- Related ONJ

2002- 2003 : first cases (Marx, Ruggiero, Migliorati, etc.)

Disbelief / sceptisism

- refusal of major journals
- Tarassoff (Novartis) J Oral Max Surg oct 2003 : criticism

2009 : thousands of cases; need of prevention

Target therapy-related ONJ

Estilo 2008, ecc

?

raccomandazioni EMA - AIFA

NOTA INFORMATIVA IMPORTANTE CONCORDATA CON LE AUTORITA' REGOLATORIE EUROPEE E L'AGENZIA ITALIANA DEL FARMACO (AIFA)

Novembre 2010

Osteonecrosi della mascella in pazienti oncologici trattati con bevacizumab (Avastin ®), e che abbiano ricevuto contemporaneamente o precedentemente bifosfonati

Dicembre 2010

Nota Informativa Importante sull'osteonecrosi della mascella in pazienti oncologici trattati con sunitinib (Sutent) e concomitante o precedente uso di bifosfonati

ASCO 2011

ONJ in patients with metastatic Renal Cell Cancer receiving Sunitinib (Sutent)

Bozas (UK) (abs e15116) :
ONJ in pts receiving SUT+BP : **5/21 (24%) (HR 36% at 24 mo)**

Fusco (Italy) (abs e15182) :
ONJ in pts receiving SUT (or other target therapy) : 19 cases

Self-assessment of buccodental toxicity : comparison of patients with metastatic renal cell carcinoma (RCC) treated with sunitinib with patients treated with chemotherapy

Gilabert (F) (abs e15021) : higher incidence of dental and gingival toxicity in the first group (not dipendent on eventual BP treatment)

Beuselinck et al – BJC dec 2012

Concomitant oral tyrosine kinase inhibitors and bisphosphonates in advanced renal cell carcinoma with bone metastases.

Seventy-six patients were included in the outcome analysis:
49 treated with concomitant bisphosphonates, 27 with TKI alone.

The **incidence of ONJ** was **10% (5/49)**
in patients treated with TKI and bisphosphonates.

Projected ONJ incidence of 17% at 24 months

Conclusion: Concomitant use of bisphosphonates and TKI
in renal cell carcinoma patients with bone involvement
probably improves treatment efficacy, (…),
but is associated with a high incidence of ONJ.

V.Fusco et al ECCO 2013

Osteonecrosis of the jaw (ONJ) in patients with renal cell cancer (RCC) treated with bisphosphonates and sunitinib or other biological agents: characteristics of 39 cases in a multicenter survey

39 ONJ patients

Administered BPs : 34 receiving Zoledronic Acid only, 1 Ibandronate, 2 Pamidronate, 2 switching from Pamidronate to Zoledronic Acid

Administered biological agents at time of ONJ diagnosis : 27 Sunitinib, 3 Sorafenib, 1 Bevacizumab, 1 Deforolimus, 7 two or more of these agents in sequence.

BP treatment duration at ONJ onset: median 12 months (range 1-48).

Latest biological treatement was Sunitinib on 34/39 cases (87%).

Treatment duration of latest biological agent at ONJ onset: median 8 months (range 1-26). Site of ONJ: 20 in mandible, 14 in maxilla, 4 in both (1 unspecified).

Possible risk factors or precipitating events (teeth extraction, oral surgery, dental implants, ill-fitting denture, infections, etc.) have been reported on 28/39 cases (72%).

Smidt-Hansen et al - JOMS 2013

Combination of Zoledronic Acid and Targeted Therapy Is Active But May Induce Osteonecrosis of the Jaw in Patients With Metastatic Renal Cell Carcinoma

Torben Smidt-Hansen, MD, Troels B. Folkmar, DDS,† Kirsten Fode, MD,‡ Mads Agerbaek, MD,§ and Frede Donskov, MD, DMSc‖*

ONJ : 6/21 (29%) if no pretherapy oral examination
1/9 (11%) with pretherapy oral examination

Conclusion: The combination of ZA and TT resulted in high, clinically meaningful activity. ONJ may be exacerbated by concomitant ZA and sunitinib. Regular OM examinations before and during treatment are recommended.

October 2013

Case report

Osteonecrosis of the jaw related to everolimus: a case report

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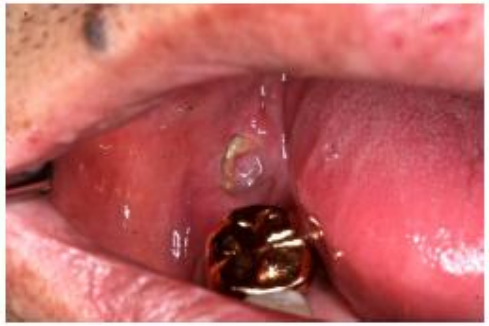


Fig. 1. Photograph of exposed necrotic bone on the right mandibular edentulous area.

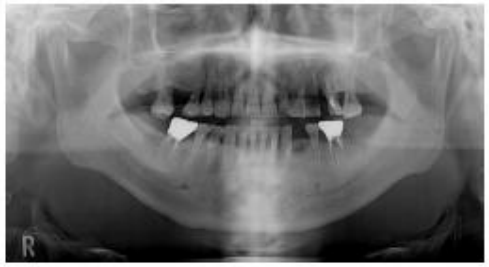


Fig. 2. Panoramic radiograph showing increased radiopacity in the right mandibular area.

BRITISH Journal of Oral and Maxillofacial Surgery
www.bjoms.com

Medullary thyroid carcinoma

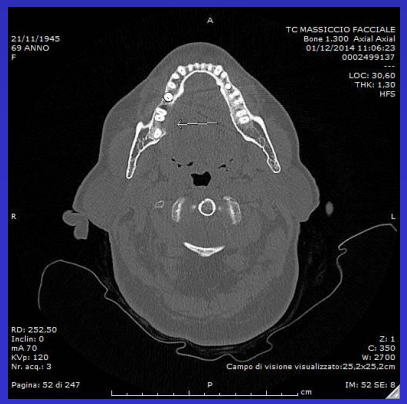
Zoledronic acid (5 years) in the past

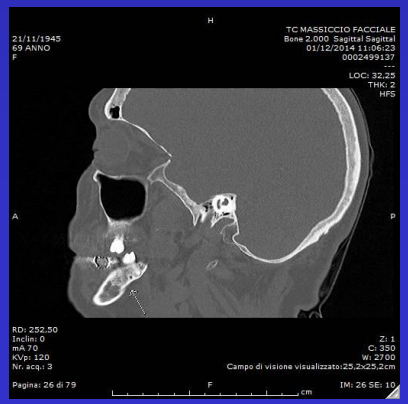
Everolimus (3 years)

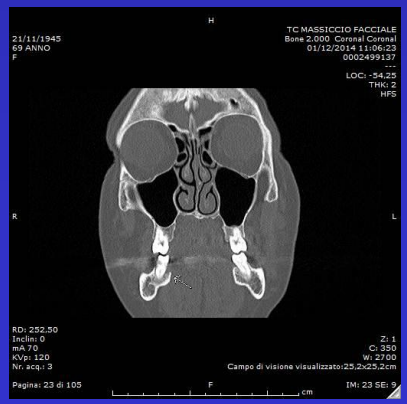
Aprile 2015

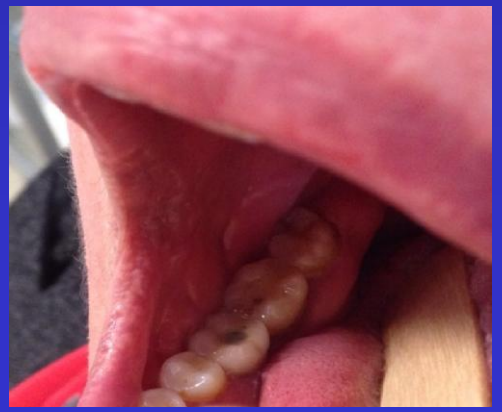
bevacizumab (Avastin) in pazienti con carcinoma ovarico :

- **Trattamento prolungato (oltre 12-18 mesi)**
- **Alte dosi (15 mg/kg ogni 21 giorni)**
- **Sopravvivenza attesa non breve (anni)**









ONJ in Oncologia : Remarks

- i BP e il denosumab hanno un ruolo centrale nel trattamento dei paz con metastasi ossee
- ONJ è "uncommon" (non "rara") e potenzialmente severa
- ONJ può essere "prevenuta" (riduzione del rischio)
- alert per i pazienti trattati con biologici ("target")
- aggiornare e seguire raccomandazioni e LG

ONJ in pazienti NON oncologici: Alert !!

-Pazienti con Artrite Reumatoide !

-ONJ dopo BP ev
(zoledronato=Aclasta 5 mg ogni 12 mesi
ibandronato=Bonviva 3 mg ogni 3 mesi)

-ONJ dopo denosumab sc (Prolia 60 mg)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 March 2015
EMA/169618/2015

Aclasta è usato per il trattamento di malattie che colpiscono le ossa, tra cui l'osteoporosi e il morbo di Paget. Il PRAC ha concluso che il rischio di osteonecrosi della mandibola/mascella con questo medicinale rimane molto basso, ma ha raccomandato altre misure per ridurre al minimo ulteriormente questo rischio.

La carta raccomandata dal PRAC ricorderà ai pazienti:

- il beneficio del trattamento dell'osteoporosi;
- il rischio di osteonecrosi della mandibola/mascella durante il trattamento con Aclasta;
- la necessità di evidenziare eventuali problemi dentali ai loro medici/infermieri, prima di iniziare il trattamento;
- la necessità di garantire una buona igiene orale durante il trattamento;
- la necessità di informare il loro dentista del trattamento con Aclasta e di contattare il medico e il dentista in caso di problemi alla bocca o ai denti durante il trattamento.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 March 2015
EMA/206916/2015

Ulteriori misure per la minimizzazione del rischio di osteonecrosi della mandibola/mascella con i bifosfonati

Misure da considerare per altri bifosfonati endovenosi e denosumab nelle revisioni future

L'Agenzia Europea de
zoledronico), uno dei
mandibola/mascella. L'Age
osseo) nella mandibola/masc
per ridurre al minimo il risc
l'introduzione di una carta di p

L'EMA sta pianificando misu
utilizzati per l'osteoporosi o p
sono associati ad un rischi
considerazione misure per qu
che sono previste nel corso del 2015/2016.

Il comitato EMA per i medicinali per uso umano (CHMP) ha ora adottato le raccomandazioni per Aclasta, a seguito di un riesame da parte del Comitato di valutazione dei rischi per la farmacovigilanza (PRAC).

Gli operatori sanitari devono seguire le seguenti raccomandazioni per Aclasta:

- Ritardare l'inizio della terapia o un nuovo ciclo di terapia in pazienti con lesioni dei tessuti molli della bocca non cicatrizzate che possono richiedere procedure odontoiatriche o orali.
- Assicurarsi che i pazienti abbiano un esame dentale e una valutazione individuale del beneficio-rischio prima di iniziare il trattamento nei pazienti con fattori di rischio concomitanti.

I CASI NON ONCOLOGICI STANNO SORPASSANDO numericamente I CASI ONCOLOGICI ?

Bisphosphonates-related osteonecrosis of the jaw in Korea: a preliminary report

JK Lee, J Korean Ass Oral Max Surg 2013

New ONJ diagnosis, in 15 teaching centers
January 2010-December 2010
Korea: 600.000 patients treated ?

254 cases
oral BP (78.7%) > iv BP (21.3%)

Alendronate	59.2 %
Risedronate	14,3%
Zoledronate	17.0%

GRAZIE

per l'attenzione !