



SPMO

OSTEONECROSI

**DELLE OSSA MASCELLARI (ONJ)
DA BIFOSFONATI E ALTRI FARMACI :
PREVENZIONE, DIAGNOSI,
FARMACOVIGILANZA, TRATTAMENTO
UPDATE 2014**

ONJ : AGENTI ANTIANGIOGENETICI E TARGET THERAPY

IL CARCINOMA RENALE

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CANCER AND BONE METASTASES

Tumor type	5-year worldwide prevalence (× 1,000) ^a	Incidence of bone metastases in patients with advanced metastatic disease (%) ^b	Median survival from diagnosis of bone metastases (months) ^c
Breast cancer	3,860	65-75	19-25
Prostate cancer	1,555	65-75	12-53
Lung cancer	1,394	30-40	6-7
Bladder cancer	1,000	40	6-9
Renal cell carcinoma	480	20-25	12
Thyroid	475	60	48
Melanoma	533	14-45	6

Coleman R.E. The Oncologist 2004

Ten years ago ...

Bisphosphonates: approved indications

	Indications				
	HCM	Breast Cancer	Multiple Myeloma	Prostate Cancer	Other Solid Tumors
CLOD	✓	✓	✓		
PAM	✓	✓	✓		
ZOL	✓	✓	✓	✓	✓
IBAN	✓	✓			

✓ = European registration

✓ = Global registration

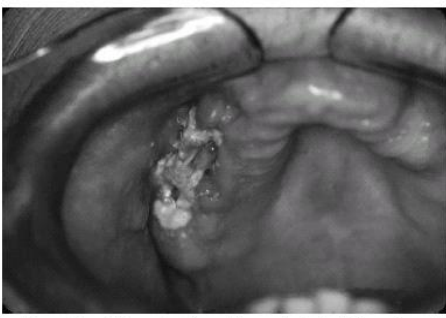


FIGURE 1. Exposed necrotic bone in the mandible in a patient who was taking pamidronate (Aredia). Exposed bone initiated by a tooth removal.



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 ONJ 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 ONJ cases



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

Ruggiero et al (NY) JOMS 2004 63 ONJ cases



E 4. Panoramic radiograph of the mandible following extraction of left posterior teeth in a patient receiving pamidronate. The shows the mottled bone in the region of the nonhealing extractions.

Woo (Ann Int Med 2006) : first systematic review . **No RCC cases**

Just few ONJ cases in RCC patients have been described in following years [Bamias 2005, Zarychansky 2006, Mignogna 2006, Cavanna 2007].

www.aiom.it

Attività scientifiche
Linee Guida

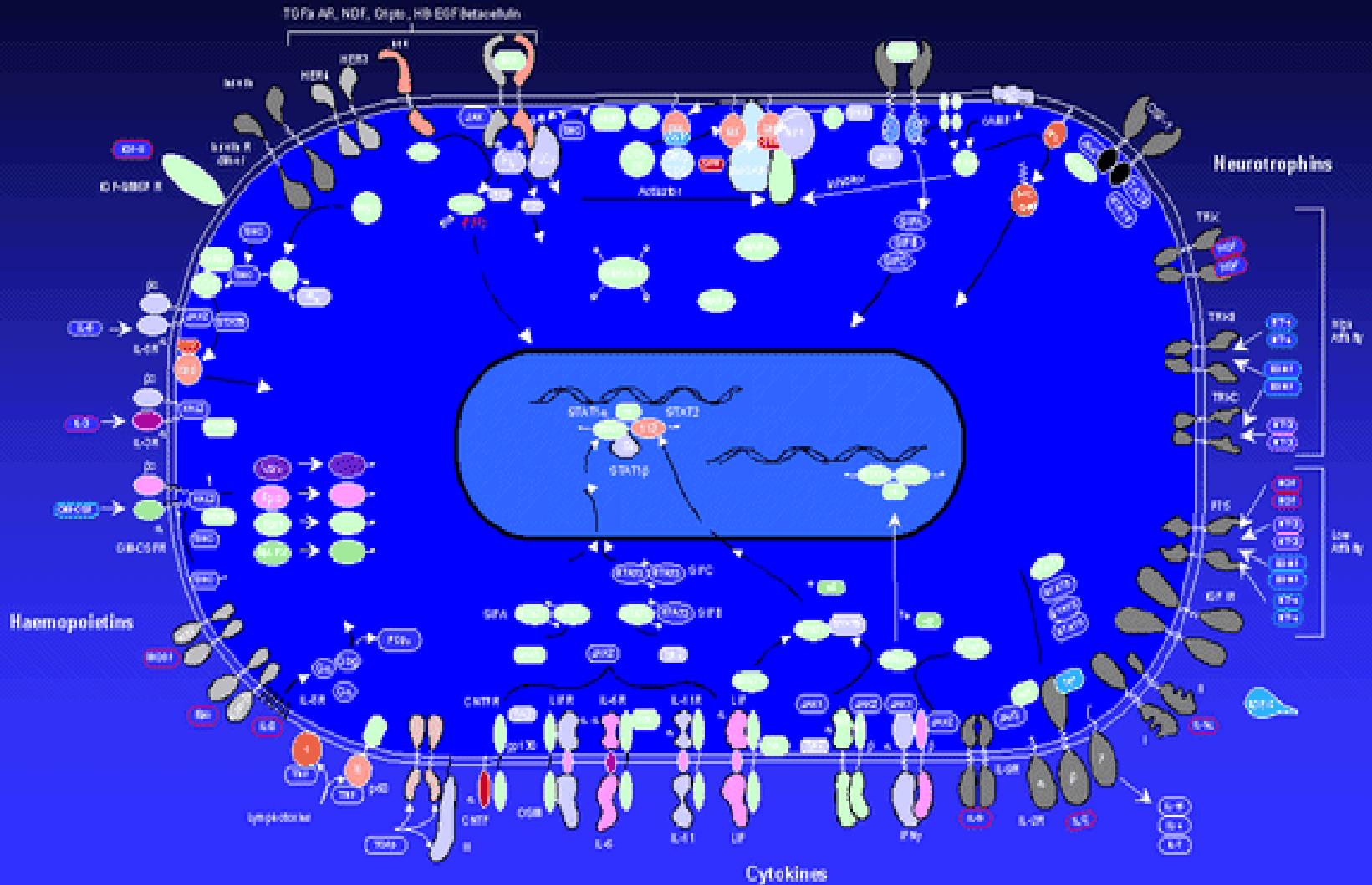
TUMORI DEL RENE

TRATTAMENTO DELLE METASTASI OSSEE

Edizione: 2013

Growth Factor/Cytokine Receptor Systems

Growth Factor/Tyrosine Kinase Systems



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.

Bevacizumab

Aflibercept

Sunitinib
Sorafenib
Pazopanib
Regorafenib
Imatinib
etc.

Erlotinib
Gefitinib

Temsirolimus
Everolimus

Ipilimumab

Cetuximab
Panitumumab

Trastuzumab
Pertuzumab
Lapatinib

Vemurafenib
Dabrafenib
etc.

Metastatic Renal Cell Cancer (RCC)

... THANKS TO 7 TARGETED AGENTS APPROVED TO DATE

	Treatment setting	Prognostic groups (MSKCC)	OS (months)	PFS (months)	ORR (experimental arm)
Sorafenib vs placebo	second-line	good: 52% intermediate: 48%	17.8 vs 15.2	5.5 vs 2.8	CR: <1% PR: 10% SD: 74%
Sunitinib vs IFN	first-line	good: 38% intermediate: 56% poor: 6%	26.4 vs. 21.8	11 vs 5.1	CR: 0% PR: 31% SD: 48%
Temsirolimus vs IFN	first-line (poor risk)	intermediate: 31% poor: 69%	10.9 vs 7.3	5.5 vs 3.1	CR: 0% PR: 9% SD: 46%
Bevacizumab + IFN vs IFN (AVOREN)	first-line	good: 29% intermediate: 56% poor: 8%	23.3 vs 21.3	10.2 vs 5.4	CR: 1% PR: 30%
Everolimus vs placebo	after TKIs failure	good: 29% intermediate: 56% poor: 15%	14.8 vs 14.4	4.6 vs 1.8	PR: 1% SD: 63%
Pazopanib vs placebo	first- and second-line	good: 39% intermediate: 54% poor: 3%	22.9 vs 20.5	11.1 vs 2.8	ORR: 30%
Axitinib vs Sorafenib	second-line	good: intermediate: poor:		6.7 vs 4.7	

Zol vs DENOSUMAB : 3 trials



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, Hwei Wang, Qi Jiang, Sylvia Tadros, Roger Dansey, Carsten Goessl

Fizazi, Lancet 2011
1904 pts

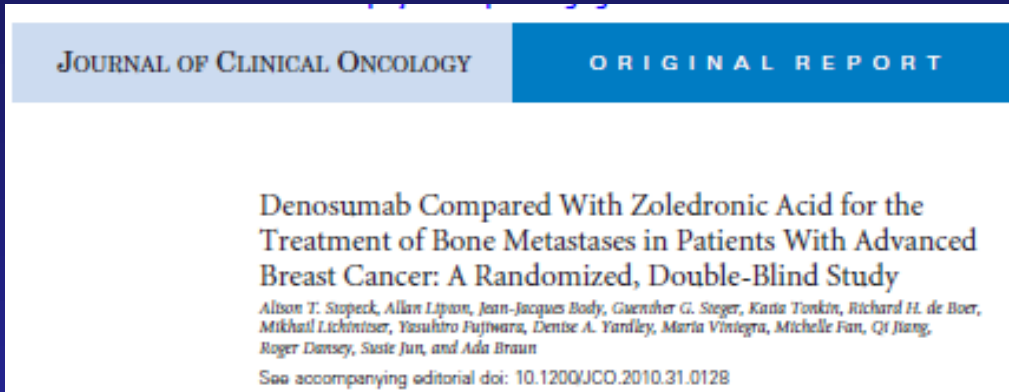
First on-study SRE :
HR 0.82
(17.1 vs 20.7 months)



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



Stopeck, JCO 2010

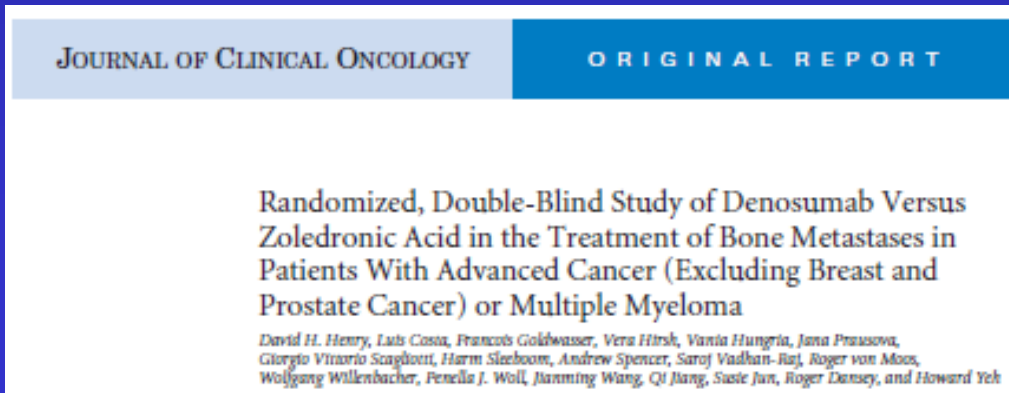
ONJ :
2% (DEN) vs 1.4% (ZA)

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)



Henry, JCO 2011

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

ONJ in carcinoma renale

-Aumento dei casi di RCC nelle casistiche più recenti di ONJ

Dall'1% al 4.5% di tutti i casi di ONJ

- Segnalazione di casi di ONJ in pazienti trattati con associazione di Bifosfonati e target therapy

Ayllon 2009 , Brunello 2009 , Christodolou 2009 , Wolter 2009, Bozas 2010 , Hoefert 2010 , Agostino 2010 , Agrillo 2012

- Segnalazione di casi di ONJ dopo sola target therapy, senza Bifosfonati

Koch 2011, Flessig 2012 , Nicolatou-Galitis 2012

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



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 / scepticism

- 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)**

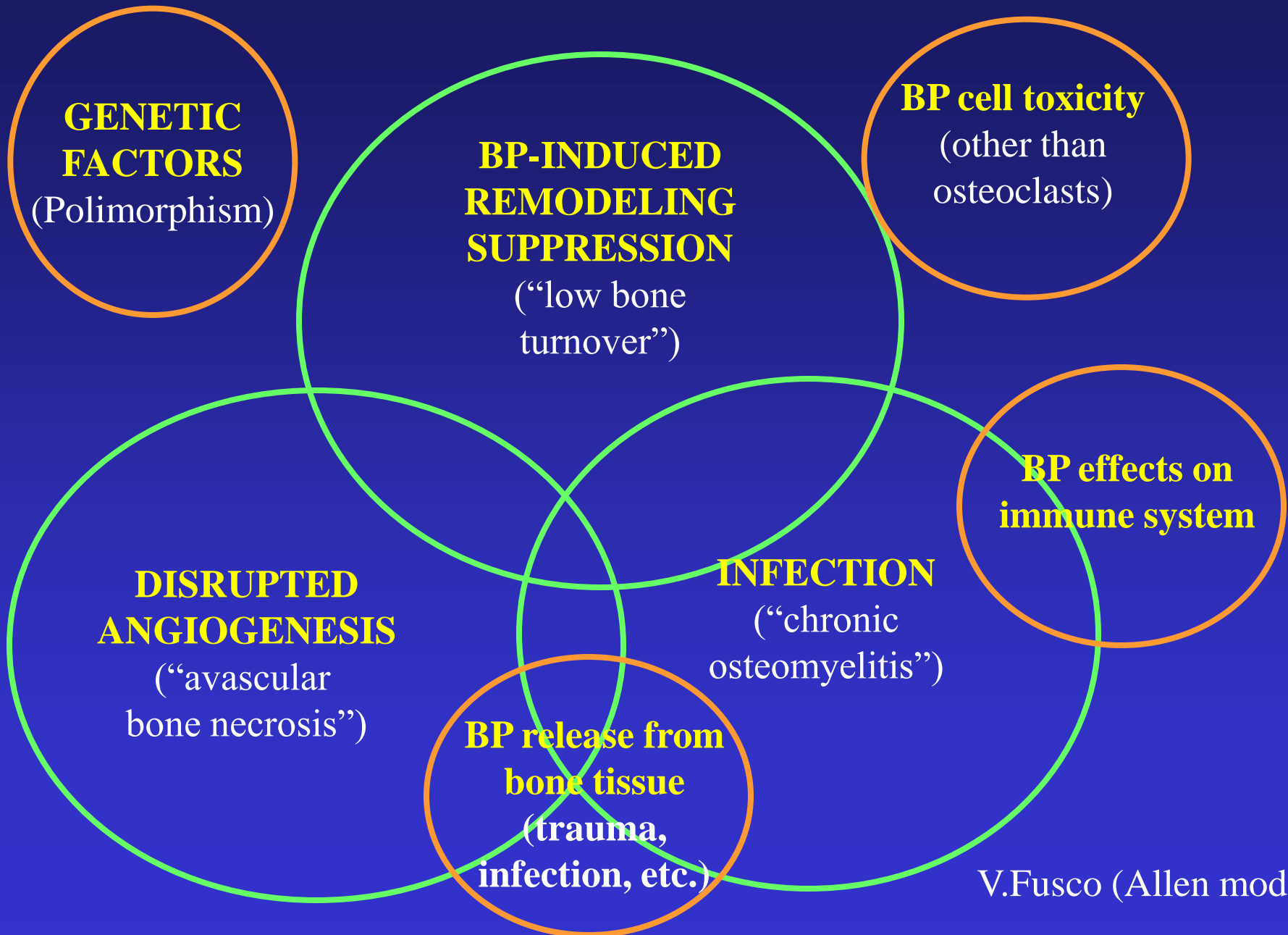
Novembre 2010

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

ONJ : WHY ?



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 dependent 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.

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 treatment 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%).

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.

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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%)

RCC pts : 155 (both arms)

Adjudicated ONJ : 6/155 (3.9%)

(Fusco et al, letter to Supp Care Cancer 2014)

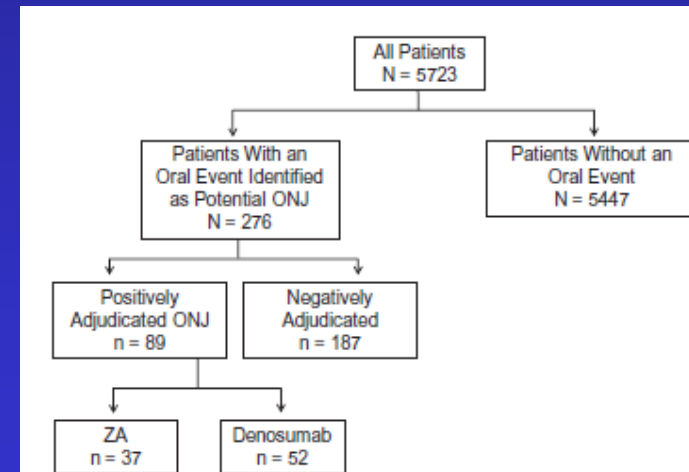


Figure 1. CONSORT diagram. Outcome of ONJ adjudication process. CONSORT, Consolidated Standards of Reporting Trials; ONJ, osteonecrosis of the jaw.

October 2013

Osteonecrosis of the jaw related to everolimus and bisphosphonate: a unique case report ?

Giancola F, Campisi G, Lo Russo L, Lo Muzio L, Di Fede O.
University of Palermo & Foggia

SIPMO Congress

Annali di Stomatologia (suppl 2) 2013

Remarks... also in RCC patients

- BPs and denosumab have a pivotal role in the treatment of bone metastatic patients
- ONJ is "uncommon" (not rare) and potentially severe
- alert for patients receiving biologicals
- ONJ must be prevented
- updated guidelines have to be followed

GRAZIE

per l'attenzione!