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

ONJ: PAST AND FUTURE

GENVABO study:

preliminary GWAs result
and phenotypic analyses on time to event and risk factors

***Gen**etic **Va**riants as **B**iomarkers of*
*jaw **O**steonecrosis associated with bisphosphonates*

UCLH/UCL Comprehensive Biomedical Research Centre
Translational research for patient benefit
University College London Hospitals NHS
UCL

UCLPartners
Academic Health Science Partnership

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BDS (Hons) HKU, MSc Oral Medicine (Distinction) UCL
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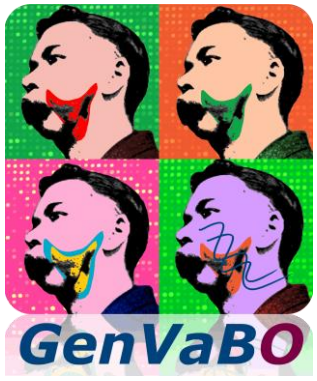

International
SAE Consortium

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Outline

I. GENVABO 2014 update

II. 2 parts: genetic, phenotypic analyses

III. Past, Present, Future

Past: background

Present: GENVABO

Future: further work, impact on clinical and research work

Structure:
GWAS: Past – Present – Future
Time to event: Past – Present – Future

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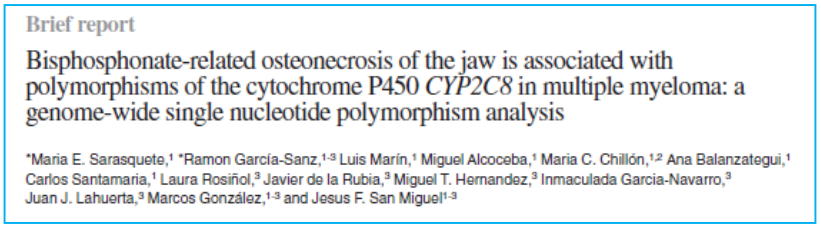
GWAS – Past – Scenario

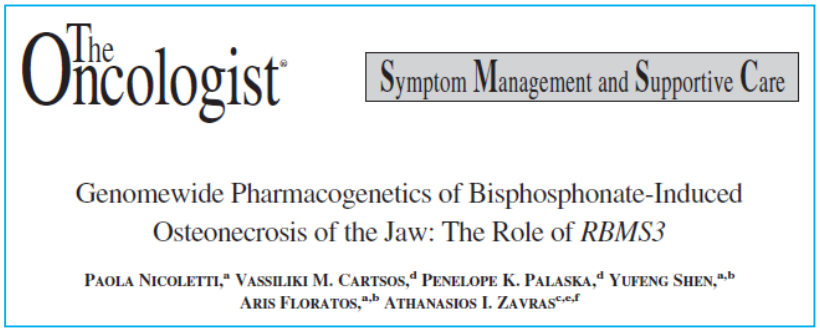
- **First GWAS in BONJ in 2008**
  - *N*=22
  - rs1934951, *CYP2C8*
  - $p = 1.07 \times 10^{-6}$
- **Second GWAS in 2010**
  - *N*=30
  - rs17024608, *RBMS3*
  - $p = 7.4 \times 10^{-8}$



Brief report

Bisphosphonate-related osteonecrosis of the jaw is associated with polymorphisms of the cytochrome P450 *CYP2C8* in multiple myeloma: a genome-wide single nucleotide polymorphism analysis

*Maria E. Sarasquete,[1] *Ramon García-Sanz,[1-3] Luis Marín,[1] Miguel Alcoceba,[1] Maria C. Chillón,[1,2] Ana Balanzategui,[1] Carlos Santamaria,[1] Laura Rosiñol,[3] Javier de la Rubia,[3] Miguel T. Hernandez,[3] Inmaculada Garcia-Navarro,[3] Juan J. Lahuerta,[3] Marcos González,[1-3] and Jesus F. San Miguel[1-3]



The Oncologist

Symptom Management and Supportive Care

Genomewide Pharmacogenetics of Bisphosphonate-Induced Osteonecrosis of the Jaw: The Role of *RBMS3*

PAOLA NICOLETTI,[a] VASSILIKI M. CARTSOS,[d] PENELOPE K. PALASKA,[d] YUFENG SHEN,[a,b] ARIS FLORATOS,[a,b] ATHANASIOS I. ZAVRAS[c,e,f]

1. Why do we study genetics in BONJ?
2. Why GWAS?
3. Why do we need another GWAS?

GWAS – Why do we study genetics in BONJ?

- "One size fits all"
- **Personalised medicine**
- Pharmacogenomics
  - Study of variations of DNA and RNA characteristics as related to drug response

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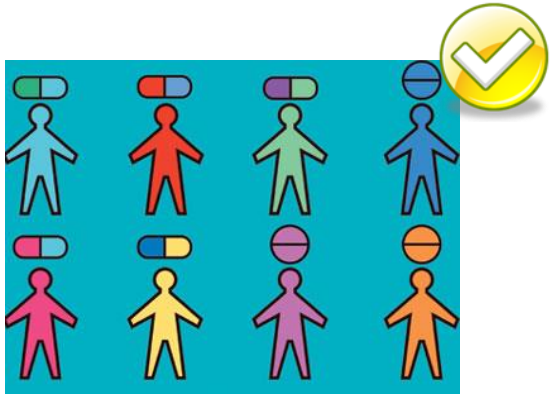


GWAS – Why study genetics? Personalised Medicine.

Drug Safety Update

Latest advice for medicines users

Carbamazepine: genetic testing recommended in some Asian populations

MHRA
Regulating Medicines and Medical Devices

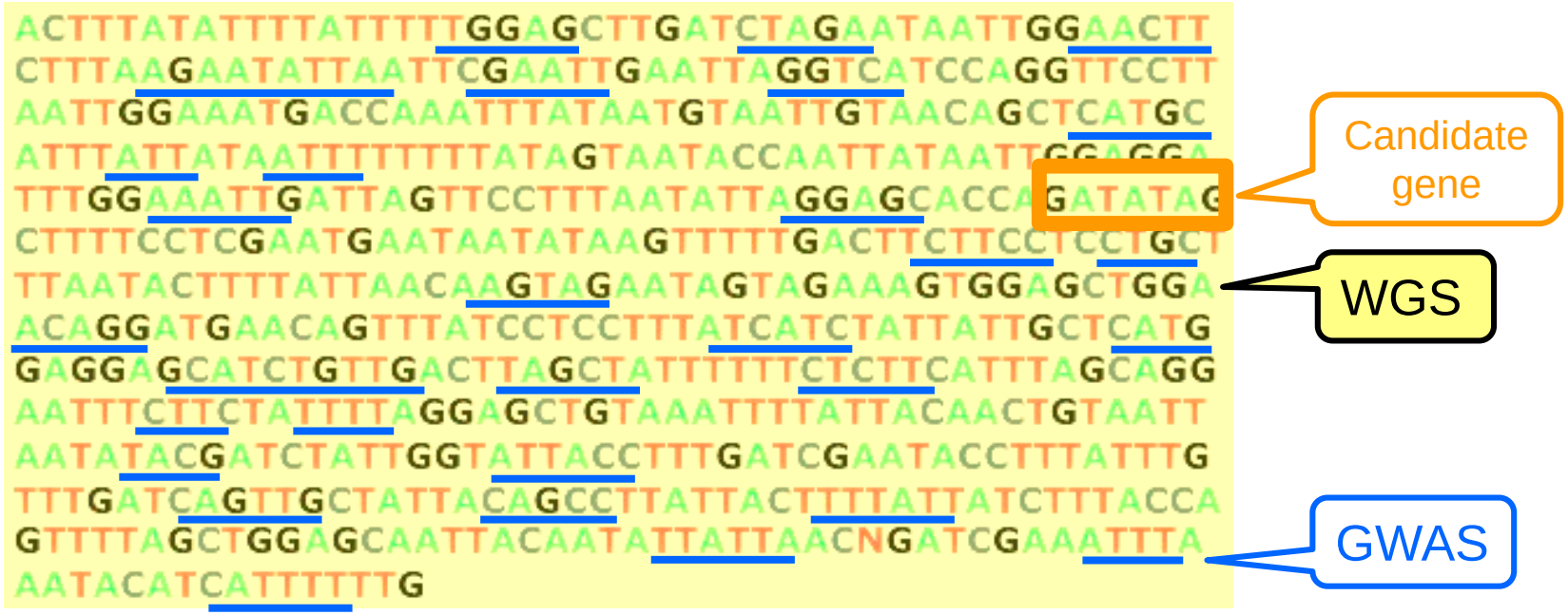
Article date: April 2008

Summary

The risk of carbamazepine-induced Stevens-Johnson syndrome is strongly associated with presence of the *HLA-B*1502* allele in individuals of Han Chinese, Hong Kong Chinese, or Thai origin. It is recommended that these individuals should be screened for *HLA-B*1502* before prescription of carbamazepine. Those who test positive should not start carbamazepine unless the benefits clearly outweigh the risks of Stevens-Johnson syndrome

GWAS – Why GWAS?

- Candidate gene study
- Whole genome sequencing: ~10M SNPs
- Genomewide association study: 0.5-1M SNPs



GWAS – Why GENVABO?

Genomewide significance level:
$p < 5 \times 10^{-8}$

- **First GWAS in BONJ in 2008**
  - *N*=22
  - 500,568 SNPs screened
  - rs1934951, *CYP2C8*
  - $p = 1.07 \times 10^{-6}$
- **Second GWAS in 2010**
  - *N*=30
  - 731,442 SNPs screened
  - rs17024608, *RBMS3*
  - $p = 7.4 \times 10^{-8}$
- **GENVABO**
  - Larger cohort: *N*=358
  - More SNPs screened: 951,117

Brief report

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Genomewide Pharmacogenetics of Bisphosphonate-Induced Osteonecrosis of the Jaw: The Role of *RBMS3*

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GENVABO

***Gen**etic **Va**riants as **B**iomarkers of*

*jaw **O**steonecrosis associated with bisphosphonates*

- Genome-wide association study (GWAS)

International SAE Consortium

Columbia University in the City of New York

University of Liverpool

Azienda Ospedaliera Nazionale Alessandria Santi Antonio e Biagio e Cesare Arrigo S.S.N. - Regione Piemonte

IRCCS CROB Istituto di Ricovero e Cura a Carattere Scientifico

Sapienza Università di Roma

SUN Seconda Università degli Studi di Napoli

Università degli Studi di Milano

Università degli Studi di Palermo

Università degli Studi di Torino Alma Universitas Taurinensis

Servizo Galego de Saúde

Xunta de Galicia Consellería de Sanidade

Uppsala Universitet

Rigshospitalet

Aintree University Hospital NHS Foundation Trust — Where quality matters

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

King's College London

Queen Mary University of London

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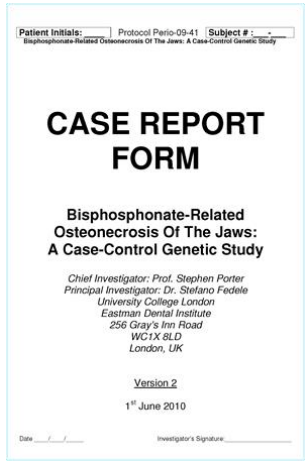
GWAS – Present – GENVABO

- **Automated DNA extraction**
  - QIAamp DNA Blood Mini Kit
  - Chemagic Magnetic Separation
- **Genotyping**
  - HumanOmniExpressExome-8v1 (Illumina Infinium II)
- **Statistical analysis**
  - Logistic regression and Fisher's Exact test, PLINK

ONJ/Healthy = SNP1 + SNP2 + SNP3……


Patient Initials: Protocol Perio-09-41 Subject #:
Bisphosphonate-Related Osteonecrosis Of The Jaws: A Case-Control Genetic Study

CASE REPORT FORM

Bisphosphonate-Related Osteonecrosis Of The Jaws: A Case-Control Genetic Study

Chief Investigator: Prof. Stephen Porter
Principal Investigator: Dr. Stefano Fedele
University College London
Eastman Dental Institute
256 Gray's Inn Road
WC1X 8LD
London, UK

Version 2

1st June 2010

Date ___/___/___ Investigator's Signature:_____

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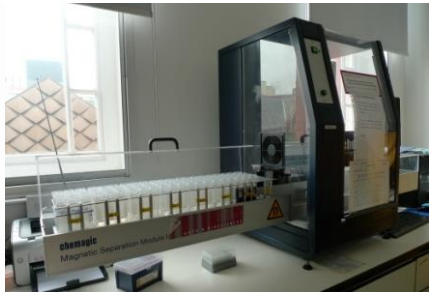

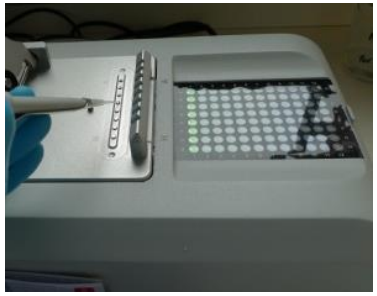

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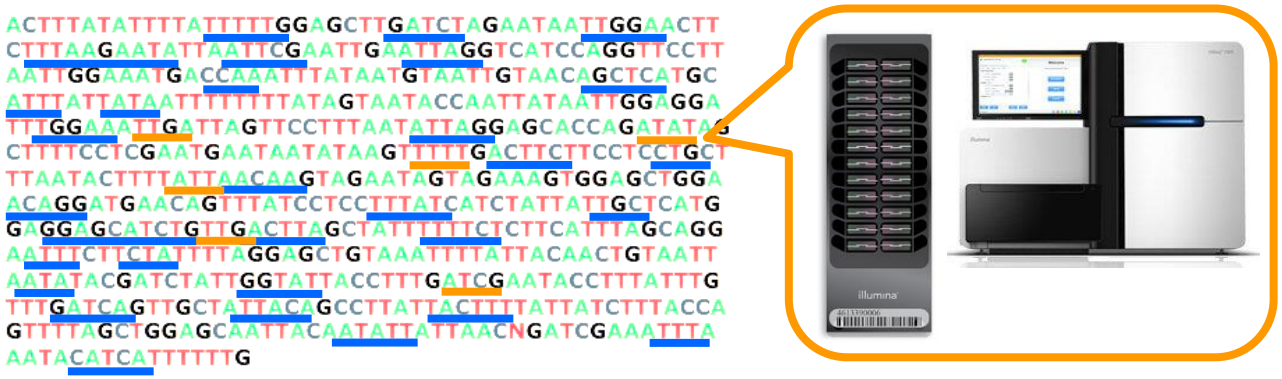
GWAS – Present – GENVABO

GWAS – Future – GENVABO validation, replication

- **Validation**

  Test the imputed SNPs in the same discovery cohort



- **Replication**

  Test the SNPs in a different yet phenotypically similar cohort

FRONTIERS IN ORAL MEDICINE
ORLANDO 2014
in Conjunction with the
World Workshop on Oral Medicine

NIH National Institutes of Health

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GENVABO – GWAS

I. GENVABO is the largest GWAS to date in BONJ

II. GENVABO identified the first GW significant SNP

III. Validation is ongoing; new funding for replication; hopeful of personalised medicine in BONJ

FRONTIERS IN ORAL MEDICINE
ORLANDO 2014
in Conjunction with the
World Workshop on Oral Medicine

Time to BONJ* Diagnosis: Results from a Large Multicentre Study

*** Bisphosphonate-associated osteonecrosis of the jaw**

Fung PPL [1], Petrie A [1] , Porter SR [1] , Fedele S [1,2]

on behalf of the GENVABO Consortium

1. University College London/University College London Hospital Eastman Dental Institute and Hospital
2. NIHR University College London Hospitals Biomedical Research Centre

UCLH/UCL Comprehensive Biomedical Research Centre
Translational research for patient benefit
University College London Hospitals NHS
UCL

UCLPartners
Academic Health Science Partnership

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Time to event – Past – Scenario

Doctor, I have been on Fosamax for 6 years.

Can I still have ONJ?

How long do I still need to come back for review?

A prospective study on ONJ amongst individuals on BPs /

Incidence of ONJ in antiresorptives trials

Activities	Time Fra											onths
	1	2	3	4	5	6			9	10	11	12
Planning and recruitment												
Pilot testing												
Data collection												
Final analysis												
Report writing and submission												

Figure: Example of Gantt Chart: Time Frame of Proposed Activities.

1. How long should we follow-up our patients?
2. How long should be the study period?

Time to event – Past – Previous work

- Important to clinical vigilance and research design
- Lack of robust evidence

Oncologist. 2009 Nov;14(11):1154-66. doi: 10.1634/theoncologist.2009-0115. Epub 2009 Nov 8.

Bisphosphonates and time to osteonecrosis development.

Palaska PK[1], Cartsos V, Zavras AI.

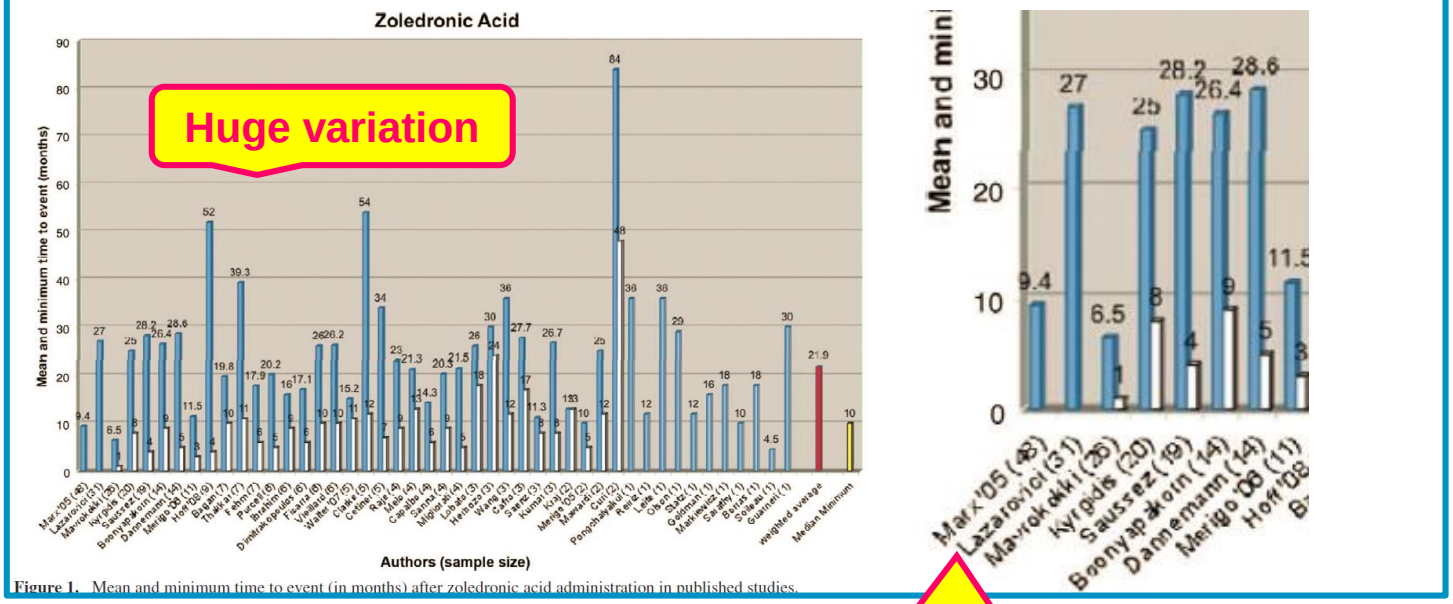


Figure 1. Mean and minimum time to event (in months) after zoledronic acid administration in published studies.

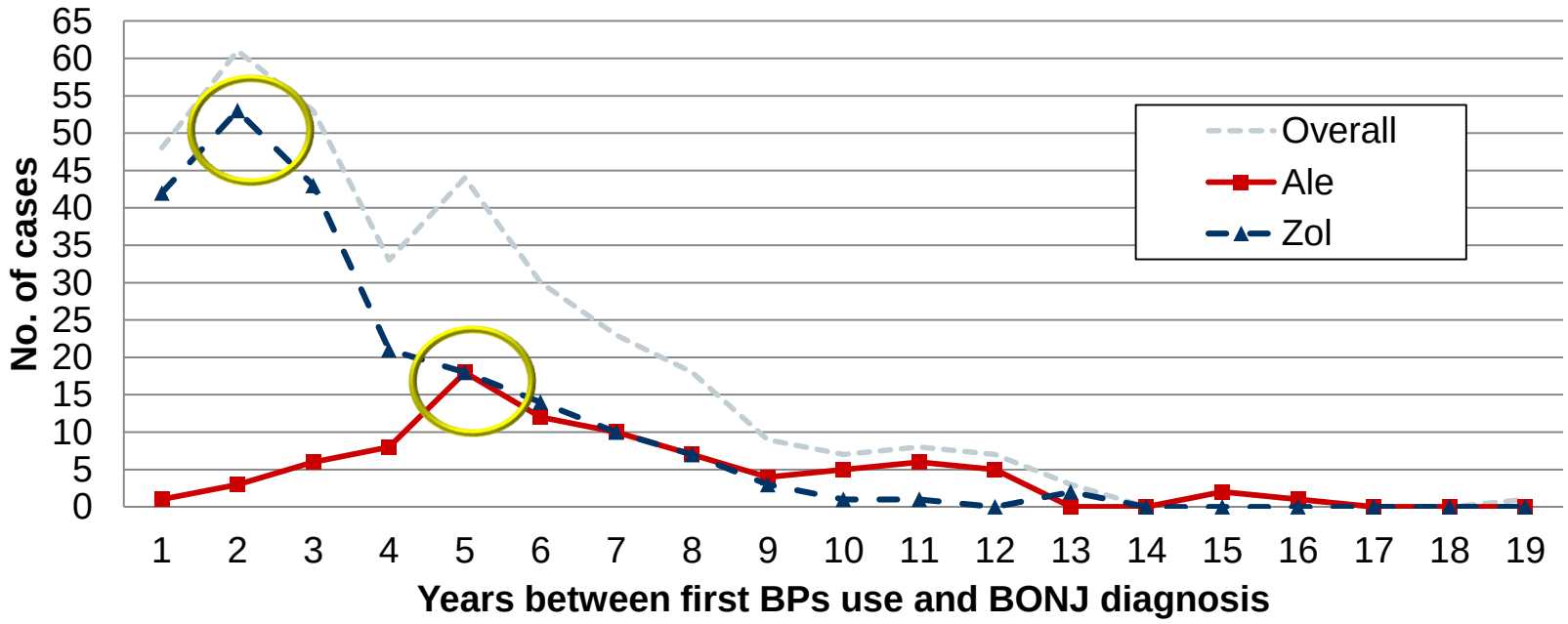
Time to event – Present – GENVABO

- Large, homogeneous cohort of 348 BONJ cases
- Well-defined time to BONJ: **time elapsed between the initiation of bisphosphonates (BPs) therapy and BONJ diagnosis**

- **Median time to BONJ**
  - Overall: median 39.5 months;
    95% CI 34.0 to 47.0
  - Alendronate: median 69.5 months;
    95% CI 59.3 to 74.7 months
  - Zoledronate: median 26 months
    95% CI 23.0 to 29.8 months

Time to event – Present – GENVABO

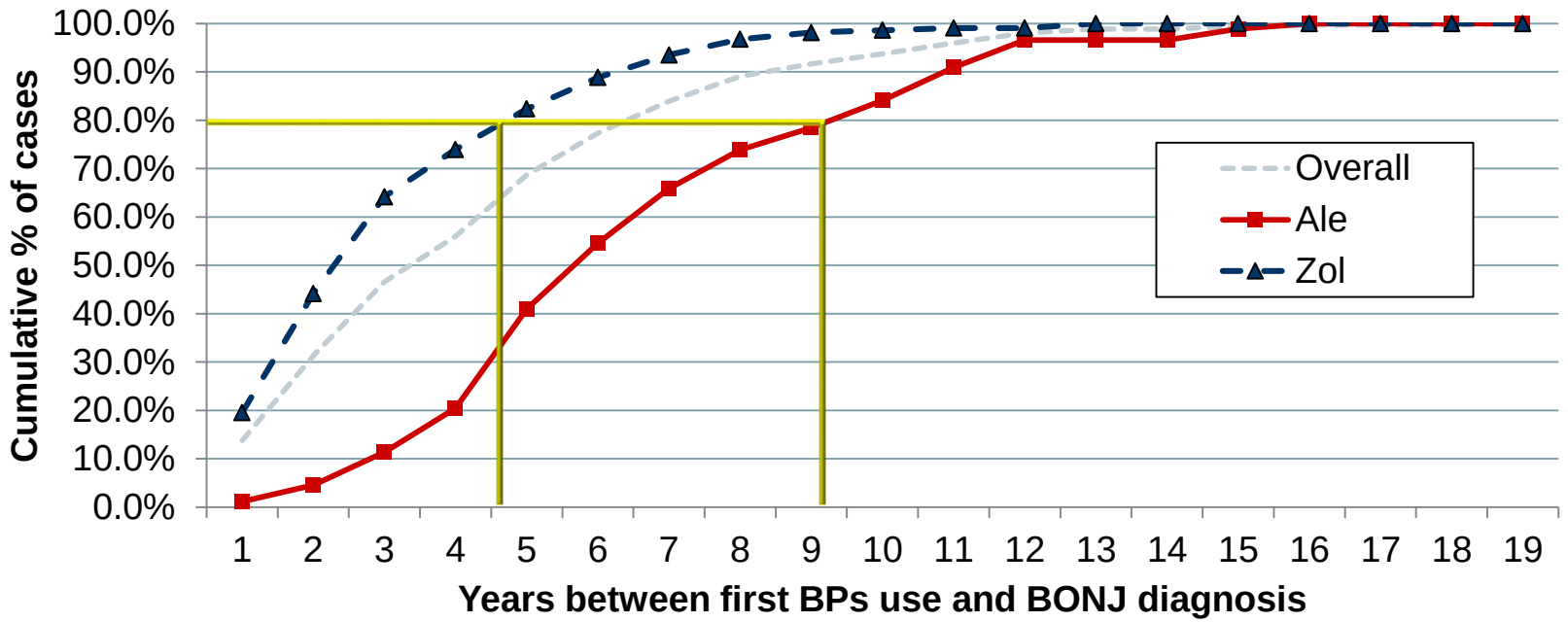
Number of cases being diagnosed at different lengths of time



Year, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Overall, N=348	48	61	53	33	44	30	23	18	9	7	8	7	3	0	2
Ale, n=88	1	3	6	8	**18**	12	10	7	4	5	6	5	0	0	2
Zol, n=215	42	**53**	43	21	18	14	10	7	3	1	1	0	2	0	0

Time to event – Present – GENVABO

Cumulative % of cases being diagnosed at different lengths of time



Year, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Overall, %	13.8	31.3	46.6	56.0	68.7	77.3	83.9	89.1	91.7	93.7	96.0	98.0	98.9	98.9	99.4
Ale, %	1.1	4.5	11.4	20.5	40.9	54.5	65.9	73.9	78.4	**84.1**	90.9	96.6	96.6	96.6	98.9
Zol, %	19.5	44.2	64.2	74.0	**82.3**	88.8	93.5	96.7	98.1	98.6	99.1	99.1	100.0	100.0	100.0

Time to event – Present – GENVABO

Factors for time, not disease risk

Secondary outcome

Association between time (outcome variable) and 13 potential risk factors (explanatory variables)

Univariable GEE linear regression	
	Variable
1	Age
2	**Gender***
3	**Underlying disease***
4	**BPs type***
5	Smoking
6	Diabetes
7	Systemic steroids
8	**Antiangiogenics***
9	Antiresorptives
10	**Dentoalveolar surgery***
11	**Denture***
12	BONJ type
13	BONJ site

***p*<0.1**

Multivariable GEE linear regression					
Variable	**Adjusted Coefficient**	**95% CI**			**p-value**
Gender (M=0, F=1)	-0.75	-10.90	to	9.41	0.885
Underlying disease	Reference: Multiple myeloma				
Osteoporosis	14.56	-2.87	to	31.99	0.102
Metastatic breast cancer	6.21	-4.26	to	16.67	0.245
Metastatic prostate cancer	-8.66	-22.16	to	4.85	0.209
Other cancers	-4.13	-17.90	to	9.63	0.556
Other benign diseases	-10.96	-57.02	to	35.09	0.641
BPs type	**Reference: Zoledronate**				
Risedronate	**60.22**	26.24	to	94.20	**0.001***
Ibandronate	-16.79	-35.76	to	2.19	0.083
Alendronate	**25.75**	9.45	to	42.05	**0.002***
Pamidronate	**33.06**	18.53	to	47.59	**<0.001***
Clodronate, Etidronate	**35.24**	6.86	to	63.63	**0.015***
Antiangiogenics	-6.90	-16.98	to	3.17	0.179
Dentoalveolar surgery	5.33	-1.35	to	12.01	0.118
Denture	5.65	-2.57	to	13.87	0.178

***significant results, *p*<0.05**

Time to event – Future – Clinical

ONJ still possible, especially accurate testing like genetics still unavailable; dental review for >4-6 years advised.

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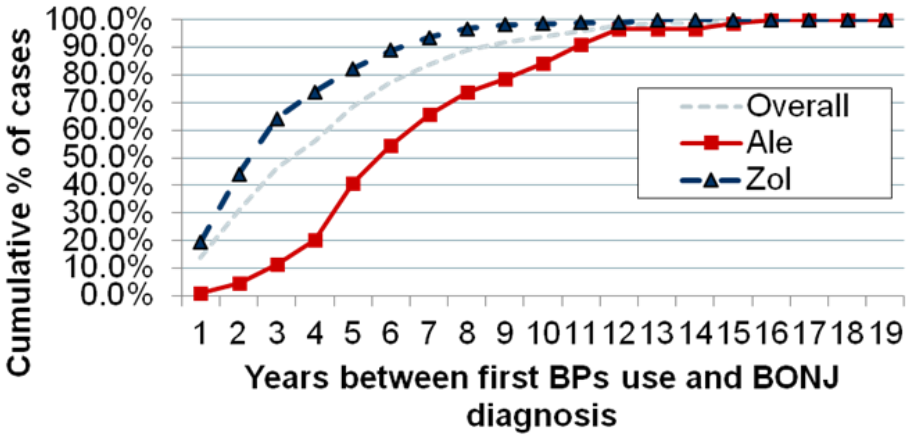
How long do I still need to come back for review?



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Zol, %	19.5	44.2	64.2	74.0	**82.3**	88.8	93.5	96.7	98.1	98.6	99.1	99.1	100.0	100.0	100.0

Time to event – Future – Research

Osteoporos Int. 2014 Mar;25(3):1131-9. doi: 10.1007/s00198-013-2575-3. Epub 2013 Dec 17.

Risk of osteonecrosis in patients taking bisphosphonates for prevention of osteoporosis: a systematic review and meta-analysis.

Lee SH[1], Chang SS, Lee M, Chan RC, Lee CC.

lute risks. Except for the study by Lapi, all included studies had a follow-up duration of more than 3 years (median 7 years, range 3–12 years; see Table 1), which is sufficient for most cases to be observed. When applying the summary relative risk

Alendronate:
7 years: 65.9%
Zoledronate:
3 years: 64.2%
➔ ONJ incidence 1.3%

European Journal of Cancer (2012) 48, 3082–3092

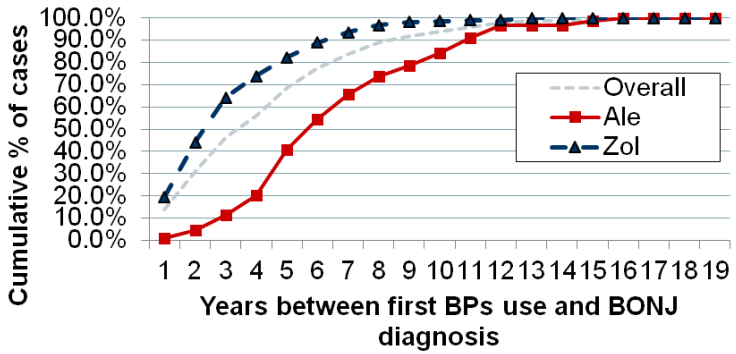
Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.info

Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: A combined analysis of 3 pivotal, randomised, phase 3 trials ☆

Allan Lipton[a,*], Karim Fizazi[b], Alison T. Stopeck[c], David H. Henry[d], Janet E. Brown[e], Denise A. Yardley[f], Gary E. Richardson[g], Salvatore Siena[h], Pablo Maroto[i], Michael Clemens[j], Boris Bilynskyy[k], Veena Charu[l], Philippe Beuzeboc[m], Michael Rader[n], Maria Viniegra[o], Fred Saad[p], Chunlei Ke[q], Ada Braun[q], Susie Jun[q]



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Zol, %	19.5	44.2	64.2	74.0	**82.3**	88.8	93.5	96.7	98.1	98.6	99.1	99.1	100.0	100.0	100.0

GENVABO – Time to event

I. At least 10 years required to capture the majority of ONJ cases amongst alendronate patients

II. At least 5 years required to capture the majority of ONJ cases amongst zoledronate patients