

Osteonecrosis of the Jaws in Myeloma

Time Dependent Correlation with AREDIA and ZOMETA Use

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Osteonecrosis of the Jaws – What Is It?



- ✚ Exposed bone in the maxilla or mandible
- ✚ Due to disruption of the resorption-remodeling cycle of bone and inhibition of endothelial cell proliferation
- ✚ Poor healing and secondary infection can lead to loss of teeth and segments of jaw bones.

Pictures courtesy Dr. Sal Ruggiero

How Frequent Is Osteonecrosis?

- ❖ Rare prior to 2001
- ❖ 2003 – Marx* reported 36 patients
- ❖ 2004 – Ruggiero** et al reported 63 patients diagnosed 2001-2003
 - Myeloma specialty groups report an increased frequency

* JOMF SURG 61:115 2003

** JOMF SURG 62:527 2004

Questions About Osteonecrosis

- Was the diagnosis missed prior to 2001?

Probably Not

It is an obvious dental problem

- What caused the increased frequency of ONJ?

Not Clear

Marx and Ruggiero et al proposed an association with bisphosphonate use

Important Current Questions/ Issues

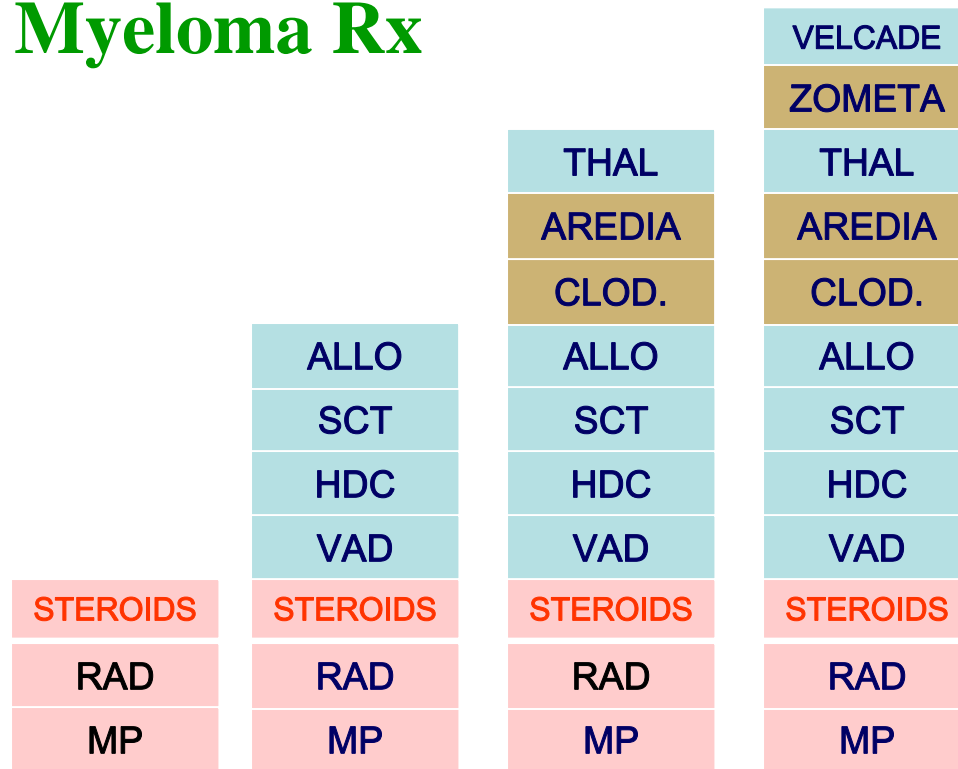
- **Is the likelihood of ONJ linked to use of Aredia and/or Zometa?**
- **To what extent do other therapies or disease processes have an impact?**
- **Are there identifiable risk factors?**
- **What is the magnitude/severity of the problem?**
- **Are myeloma patients particularly at risk for osteonecrosis (ONJ) e.g. versus breast cancer?**

OUR STUDY

- ❖ **Anonymous WEB Based Survey: Summer 2004**
- ❖ **Included 1203 Myeloma(904) and Breast Cancer (299) patients**
- ❖ **Recruited using IMF email lists/web site plus “ACOR” myeloma and breast Listservs (email), Nexcura (email) and Y-Me National Breast Cancer Organization (web site)**
- ❖ **Evaluates dates for diagnosis, treatments and complications including dental findings**

Increase in Treatment Options Over Time

Myeloma Rx



Bortezomib (Velcade)
Thalidomide
Bisphosphonates

Stem cell transplantation
High-dose chemotherapy

Vincristine, doxorubicin, dex

Radiation
Melphalan + Prednisone

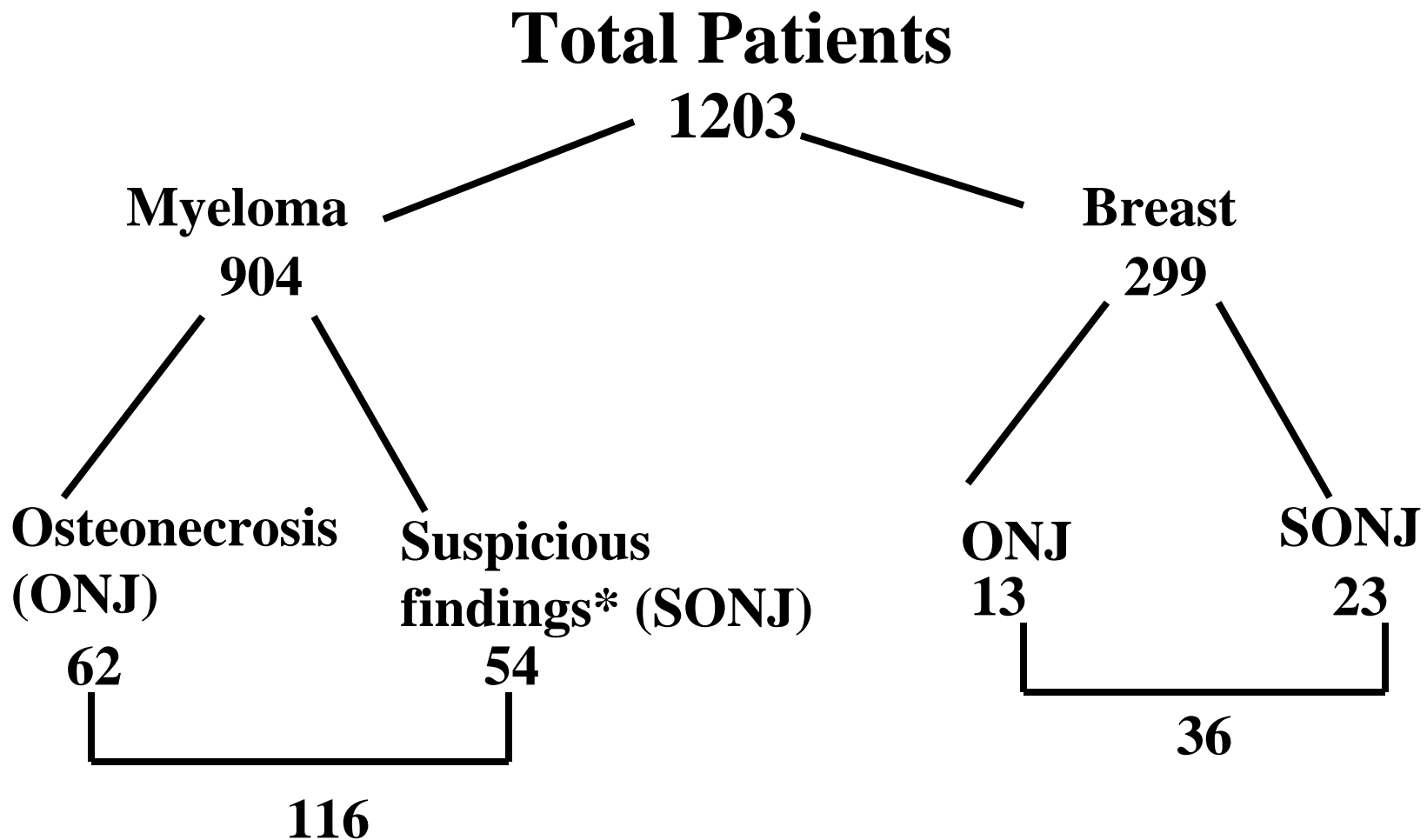
1950-1960s

1970-1980s

1990s

2000s

Numbers of Patients Responding to Survey

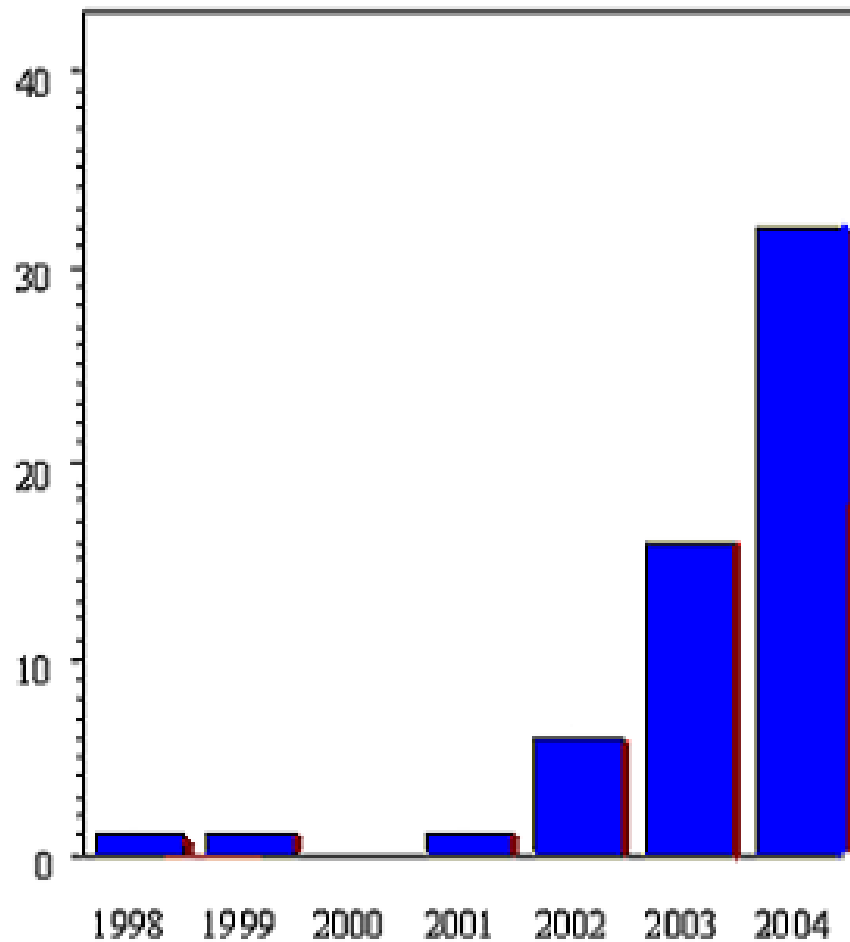


* SONJ: Suspicious findings: bone erosions; bone spurs; exposed bone

New Cases of ONJ Each Year Among Respondents

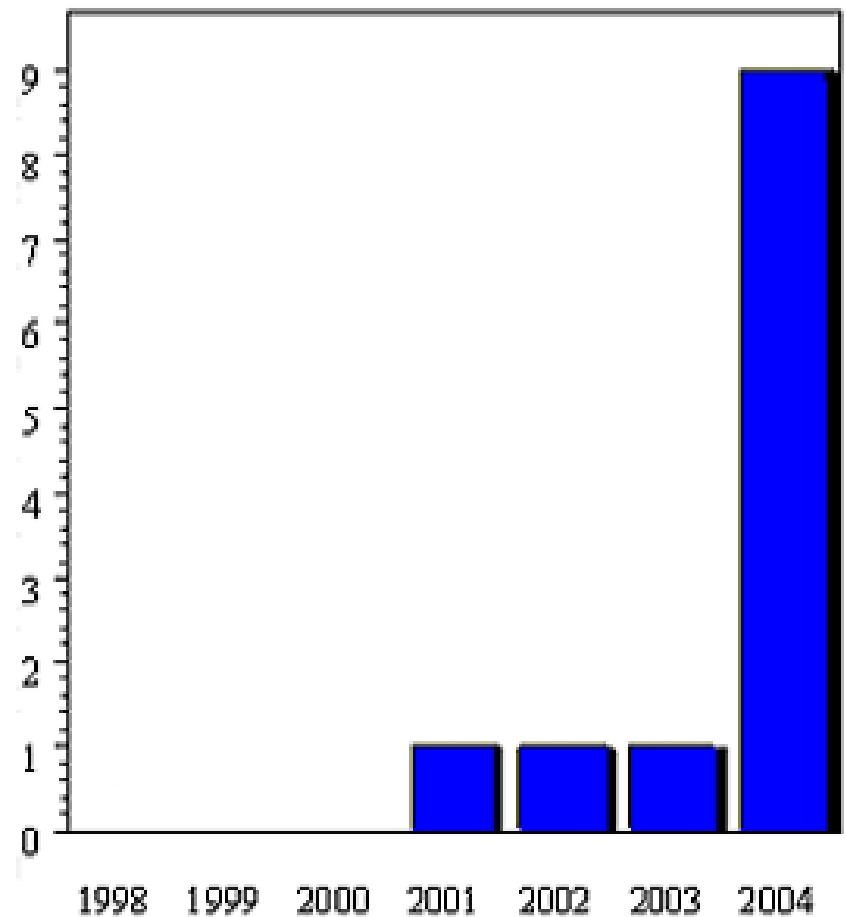
Myeloma

57 patients








Breast Cancer

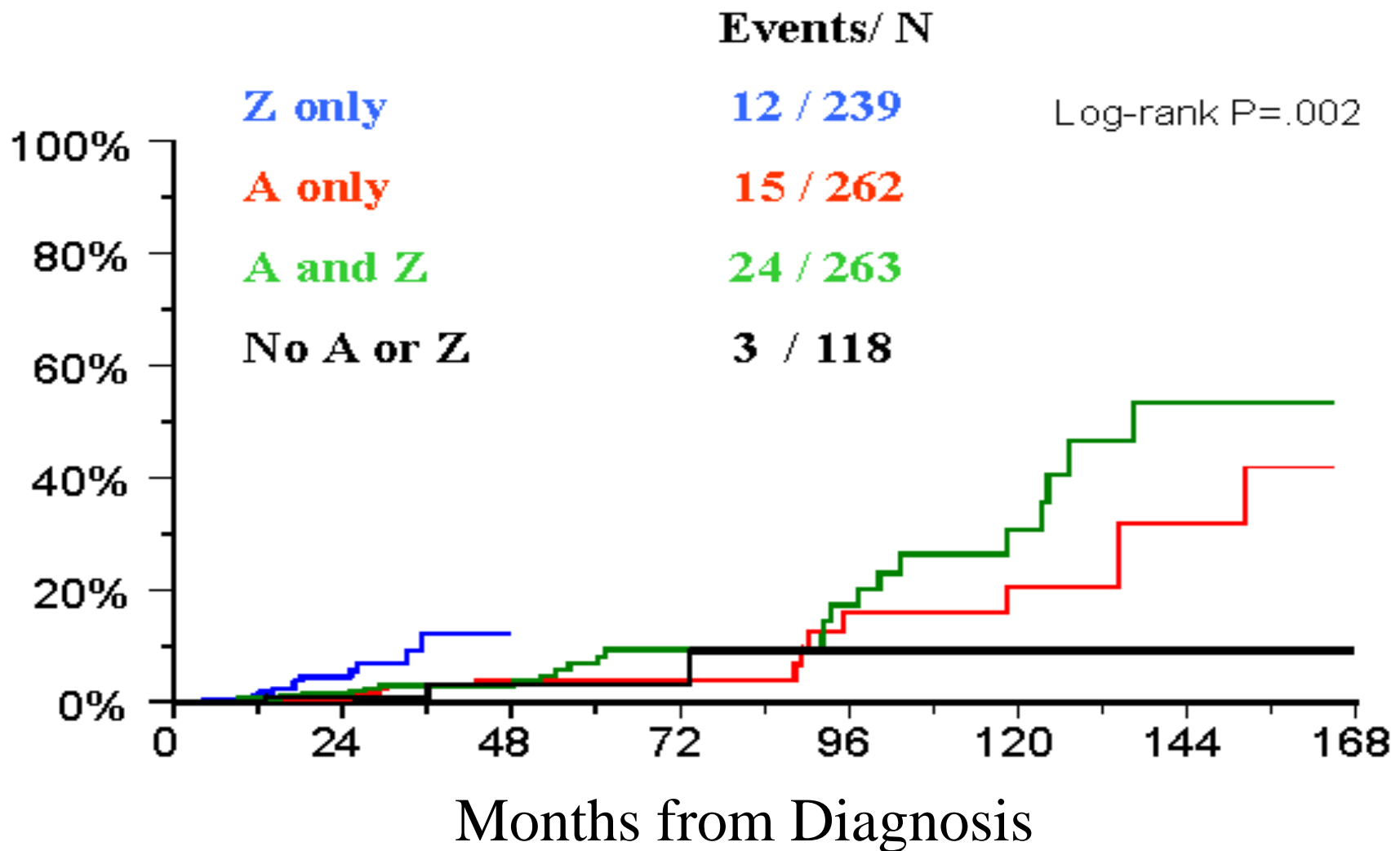
12 patients



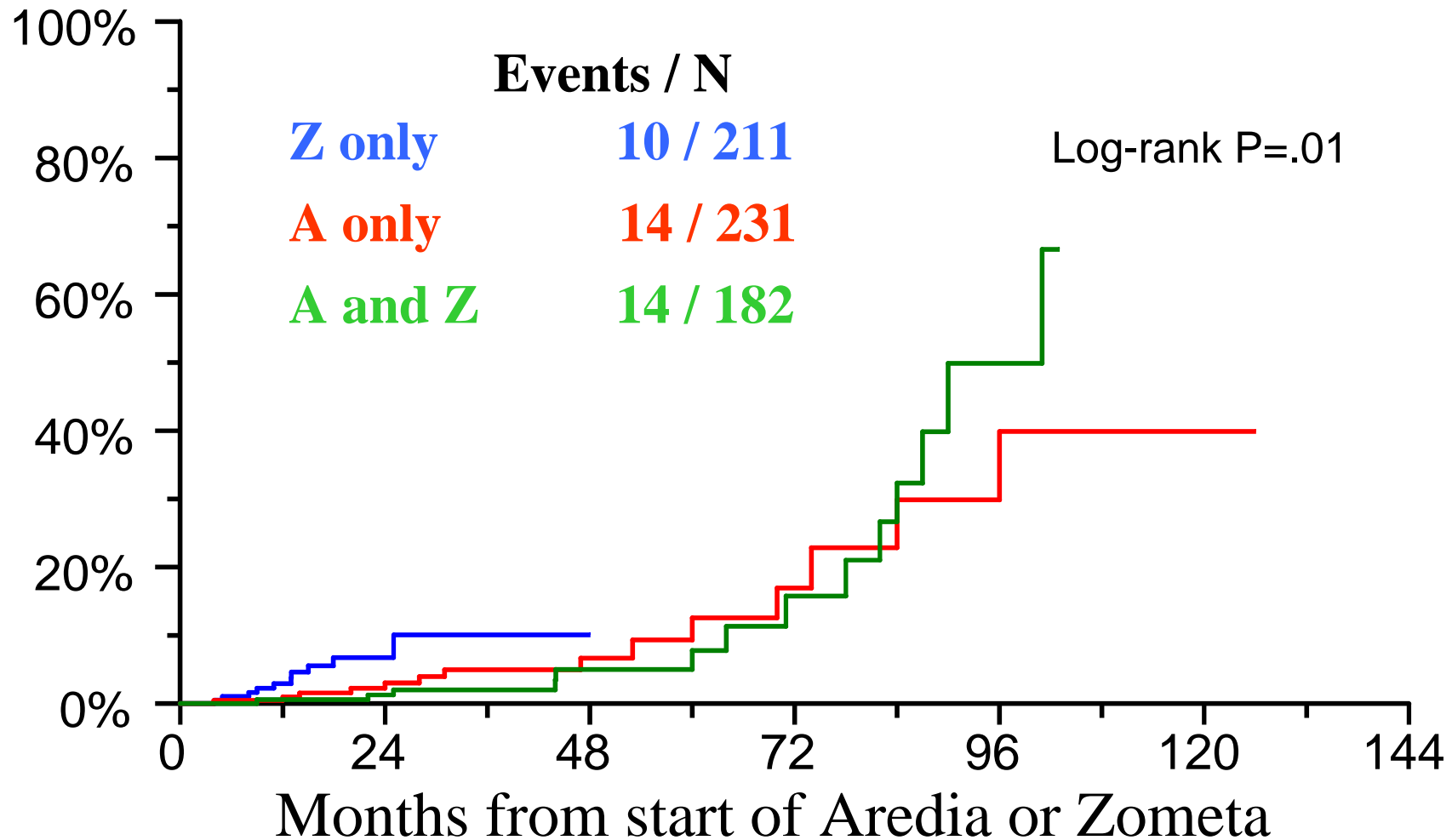
Frequency of Therapeutic Interventions in Myeloma Respondents

	Overall	ONJ
 Bisphosphonates	804/904 (89%)	57/62 (92%)
<ul style="list-style-type: none"> • AREDIA (ONLY) • ZOMETA (EVER) 	<ul style="list-style-type: none"> 267/904 (30%) 515/904 (57%) 	<ul style="list-style-type: none"> 17/62 (27%) 40/62 (65%)
 Steroids	738/904 (81%)	55/62 (89%)
<ul style="list-style-type: none"> • PREDNISON • DEXAMETHASONE 	<ul style="list-style-type: none"> 210/904 (23%) 525/904 (58%) 	<ul style="list-style-type: none"> 24/62 (39%) 64/62 (55%)
 Thalidomide	496/904 (55%)	37/62 (59%)
 Radiation to head/ neck	61/904 (7%)	3/62 (5%)
 Stem Cell Transplant	426/904 (47%)	26/62 (42%)

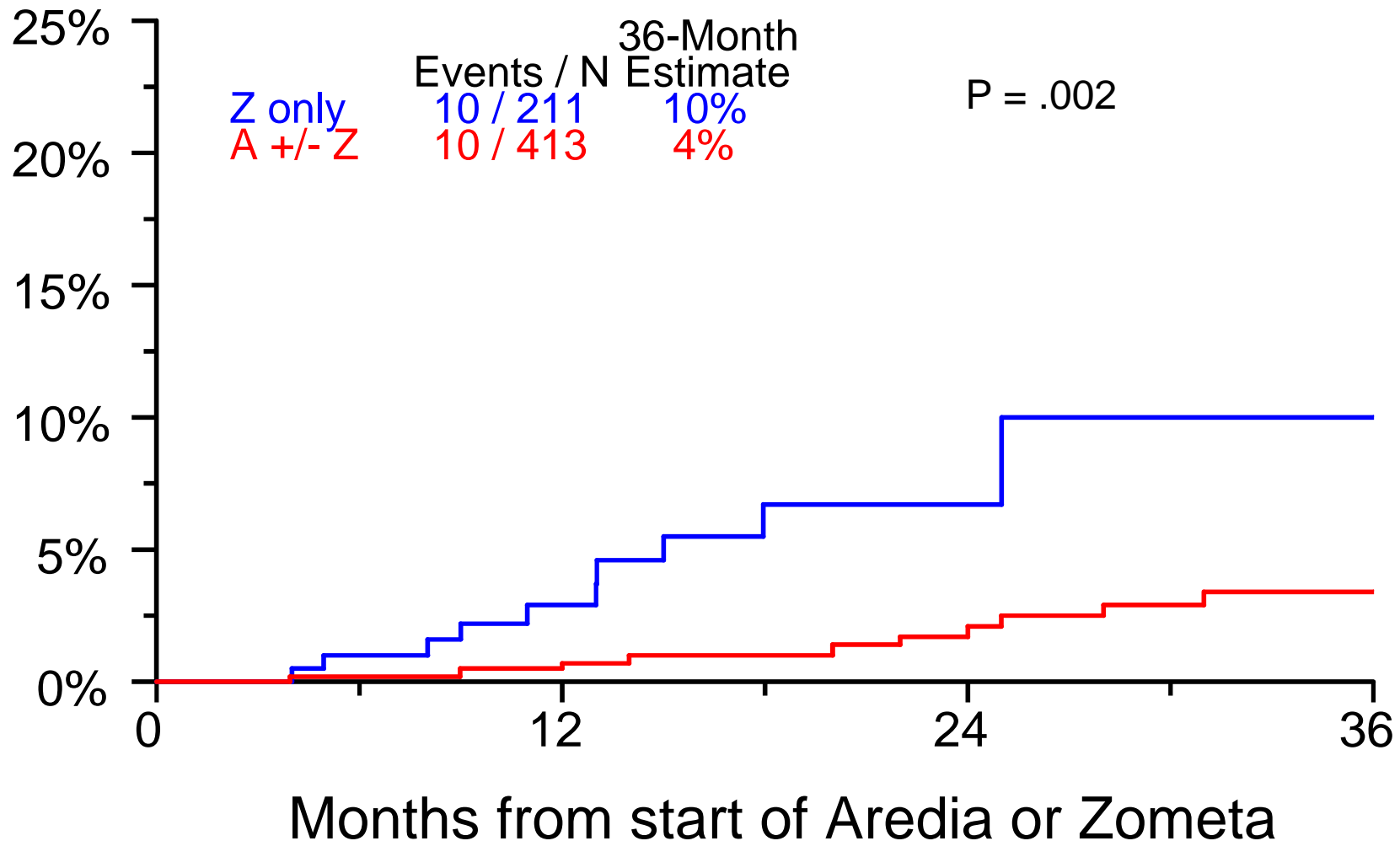
Increasing Incidence of ONJ Among Respondents from Date of Diagnosis



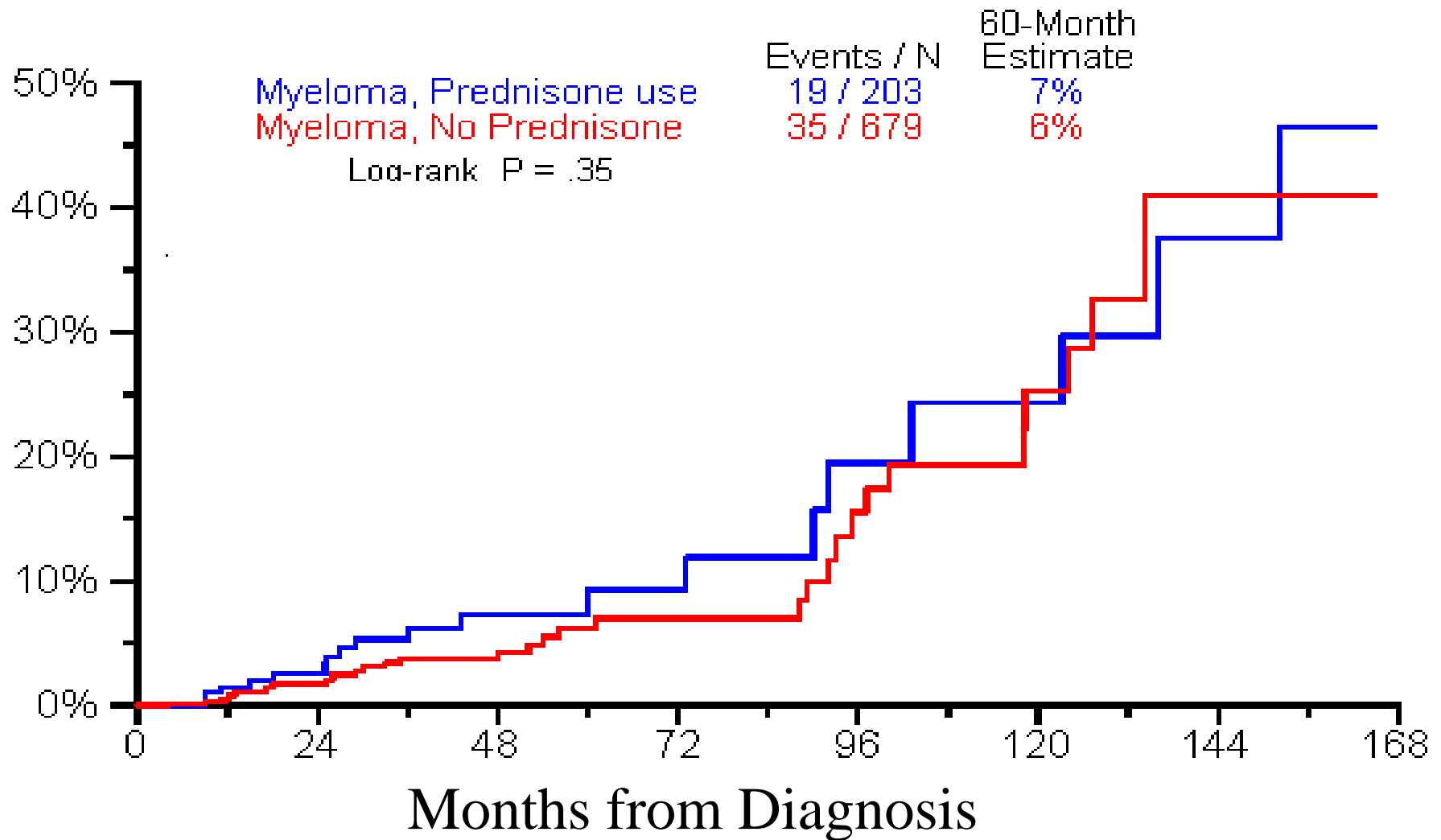
ONJ Among Respondents vs. Duration of Aredia or Zometa Treatment



Duration of Aredia and/or Zometa use censored at 3 years



Prednisone Does Not Increase the Likelihood of ONJ

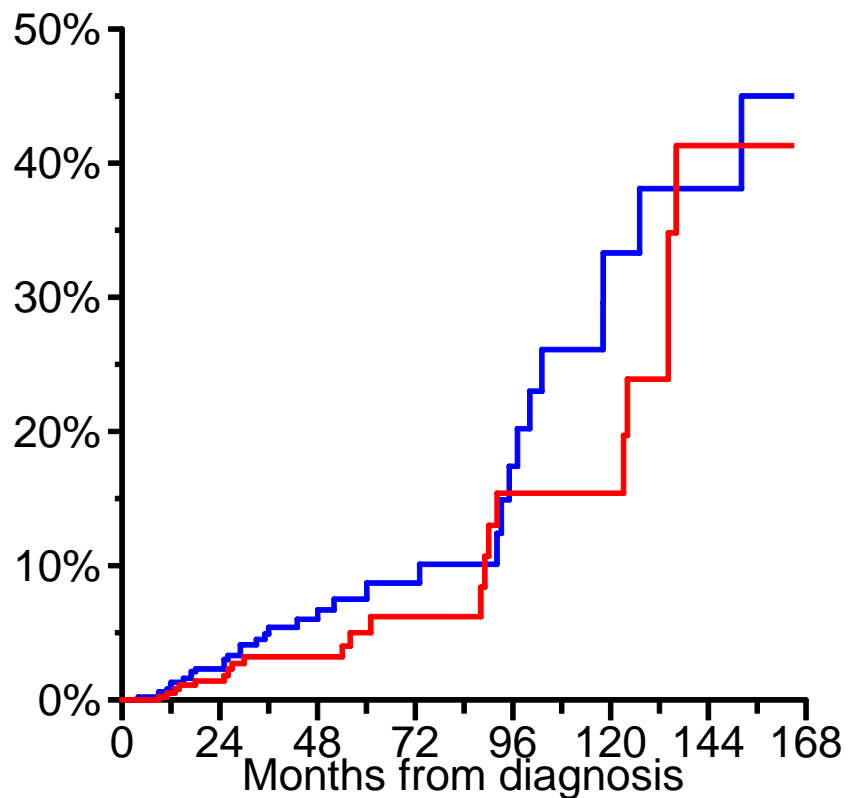


Thalidomide and Dexamethasone Do Not Increase the Likelihood of ONJ

Log-rank $P > 0.5$

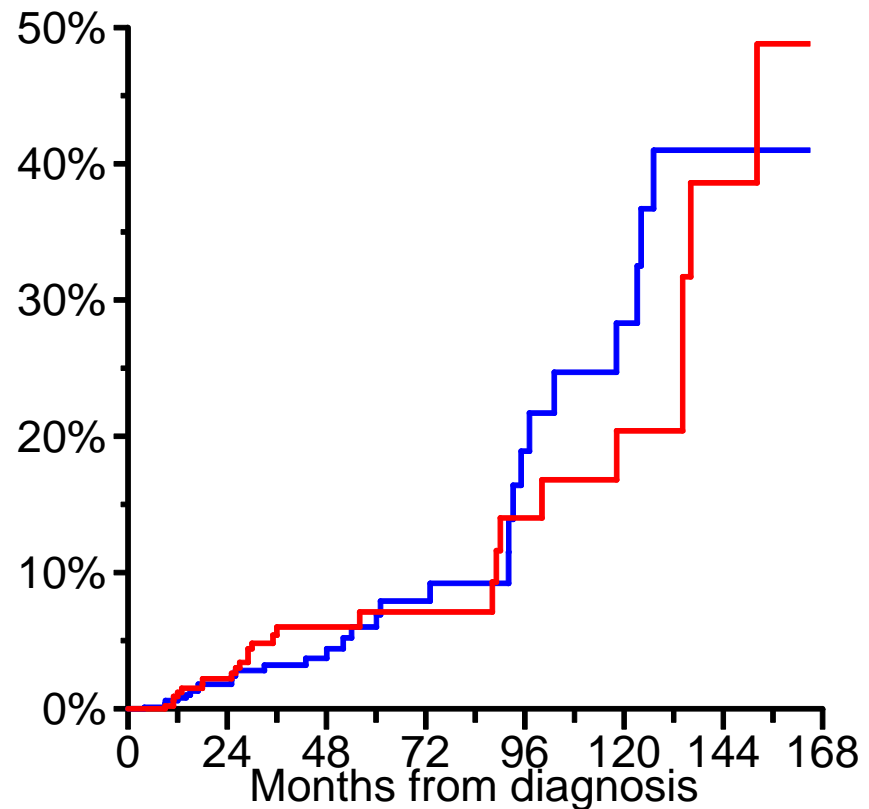
Thalidomide

	Events / N	60-Month Estimate
Myeloma, Thalidomide use	33 / 485	8%
Myeloma, No Thalidomide	21 / 397	5%



Dexamethasone

	Events / N	60-Month Estimate
Myeloma, Dex use	29 / 515	6%
Myeloma, No Dex	25 / 367	7%



*Frequency of Prior Dental Problems**

	Overall	ONJ Patients
⊕ Total Population	396/1203(33%)	59/75 (79%)
⊕ Myeloma	294/904 (32%)	50/62 (81%)
⊕ Breast Cancer	102/299 (34%)	9/13 (69%)

Two sided P-value for dental problems and osteonecrosis:

in Breast: 0.0129

in Myeloma: <0.0001

* Other than Suspicious ONJ findings

Conclusions

- **Amongst the respondents to this survey**
 - **Duration of bisphosphonate use in myeloma and breast cancer is associated with increased risk of Osteonecrosis (ONJ)**
 - **36 month estimates of ONJ are higher for Zometa versus Aredia**
 - **None of the other therapies analyzed were associated with increase risk of ONJ**
 - **Patients with prior dental problems have a higher risk of ONJ**
- **It is likely that precautions related to dental care and bisphosphonates use may reduce the likelihood of ONJ**

Other Implications and Future Research

- ➊ Further retrospective analysis will be important to better understand ONJ in the near-term
- ➋ Prospective evaluation for ONJ and investigation of causal factors in clinical trials should yield definitive answers in the long-term
- ➌ Evaluation of improved dental precautions will be important and could help determine to what extent ONJ is a preventable problem
- ➍ The oral surgery community has developed specific recommendations for physicians and patients relative to pre-ONJ elective surgery and the risks of further surgery in an ONJ setting

Acknowledgements



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