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An International, Randomized, Double Blind Trial Comparing Denosumab With Zoledronic Acid for the Treatment of Bone Disease in Patients With Newly Diagnosed Multiple Myeloma

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Disclosures

- **NR** has consulted for Amgen Inc., BMS, Celgene, Merck, Novartis, Roche, Takeda; received research funding from AstraZeneca and Lilly.
- **ET** has consulted for Amgen Inc., BMS, Janssen, Takeda; received research grants from Amgen Inc., Celgene and Janssen-Cilag; honoraria by Amgen Inc., BMS, Celgene, Genesis, Janssen-Cilag, Novartis and Takeda.
- **WW** has consulted for Amgen Inc., BMS, Celgene, CTI, Gilead, Janssen, Novartis, Mundipharma, Pfizer, Roche, Sandoz, The Binding Site; received research grants from Amgen Inc., BMS, Celgene and Janssen-Cilag, Novartis, Roche, Takeda; honoraria by Amgen Inc., BMS, Celgene, Cephalon, Gilead, Janssen, Mundipharma, Myelom- und Lymphomselbsthilfe Österreich, Novartis, Roche, Sandoz, The Binding Site.
- **KS** has consulted for Daiichi-Sankyo, Fujimoto Pharma, Novartis; received research grants from Daiichi-Sankyo; honoraria by Amgen Inc.
- **RGS** has consulted for Amgen Inc., Takeda; received research grants from Pfizer, Takeda; honoraria by Amgen Inc., Celgene, Janssen, Takeda.
- **BD** has consulted for Amgen Inc., Bristol-Myers Squibb, Celgene, Johnson & Johnson, Millenium Pharmaceuticals, Takeda.
- **WL** and **MK** have no reported disclosures.
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- **LZ** and **DW** are Amgen Inc. employees and have received Amgen Inc. stocks.
- **PC** was an employee of Amgen Inc.
- **GDR** has consulted for Amgen Inc.

Introduction

- Multiple myeloma (MM) is a plasma cell malignancy typically characterized by bone disease, with approximately 80% of pts presenting with osteolytic lesions at diagnosis

- Myeloma related bone disease is consequent to bone destruction by osteoclasts and can be directly promoted by secreted MM cell factors, including RANK ligand (RANKL)[1]

- RANK ligand (RANKL) is a key driver of osteoclast-mediated osteolysis, increasing the risk of skeletal-related events (SREs; defined as: pathologic fractures, radiation therapy or surgery to bone, or spinal cord compression) and impacting morbidity, mortality and quality of life[2]

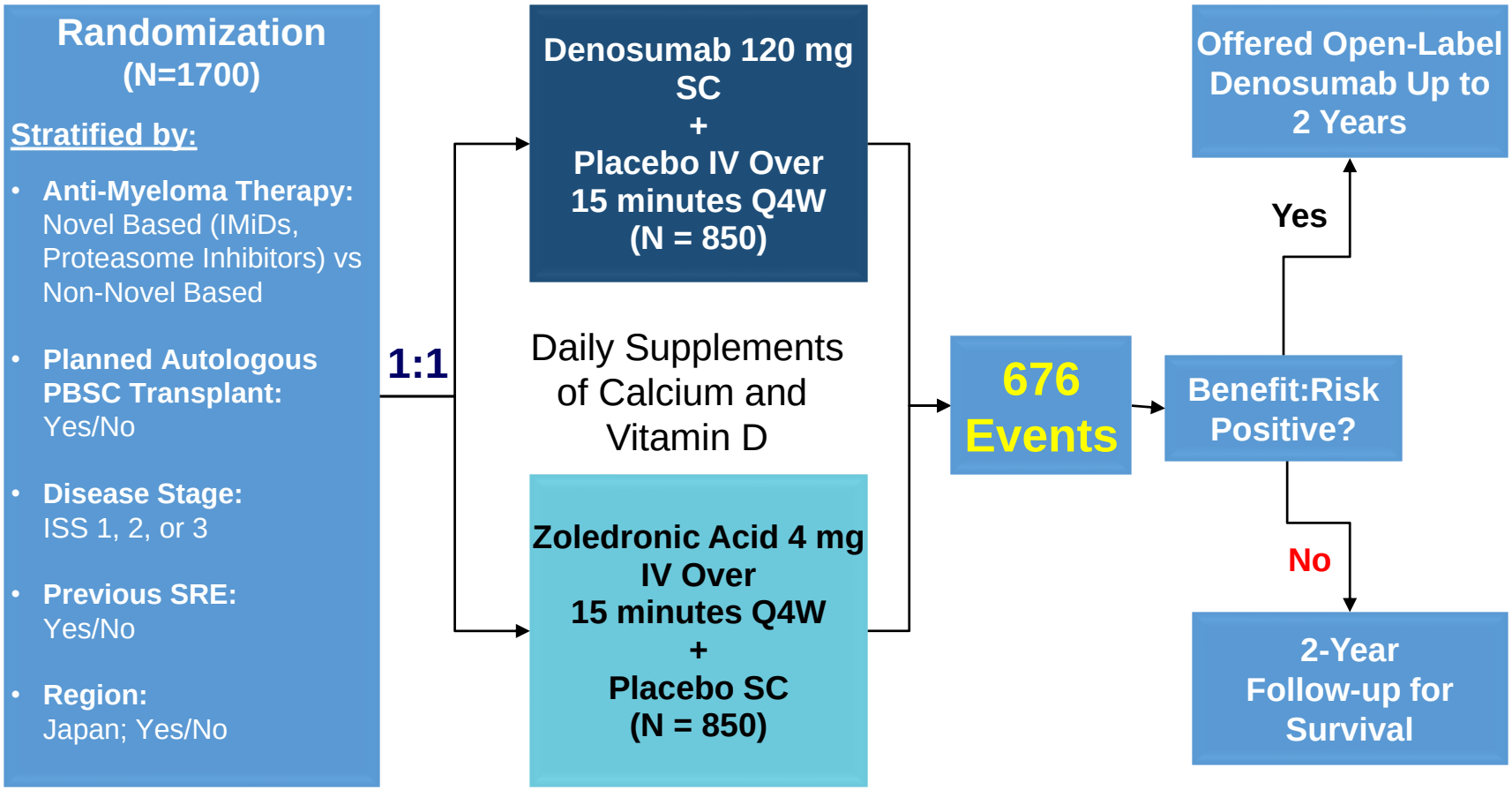
- Denosumab, a human monoclonal antibody that binds with high specificity and affinity to RANKL, may directly inhibit RANKL-mediated myeloma growth and reactivation of dormant myeloma cells[3]

This international, phase 3, randomized, double blind study evaluates the efficacy and safety of denosumab compared with zoledronic acid in newly diagnosed, myeloma patients

1. Spanoudakis et al., Overexpression of RANKL by invariant NKT cells enriched in the bone marrow of patients with multiple myeloma, *Blood Cancer J*, 2016.
2. Weinfurt et al., The significance of SREs for the HRQOL of patients with metastatic prostate cancer, *Ann Oncol*., 2005.
3. Lawson et al., Osteoclasts control reactivation of dormant myeloma cells by remodeling the endosteal niche, *Nat Commun*., 2015.

Methods

Study Design



*Per protocol and Zometa® label, IV product was dose adjusted for baseline creatinine clearance and subsequent dose intervals were determined by serum creatinine levels. No SC dose adjustments were required.

Methods

Key Inclusion Criteria

- Documented evidence of multiple myeloma per local assessment
- Radiographic (X-ray, or computer tomography) evidence of at least 1 lytic bone lesion or at least 1 focal lesion per magnetic resonance imaging
- Plan to receive or is receiving primary frontline anti-myeloma therapies
- ECOG ≤2 and adequate organ function
- Age ≥18 years and patient has provided written informed consent

Key Exclusion Criteria

- Nonsecretory multiple myeloma based upon standard M-component criteria (i.e., measurable serum/urine M-component) unless the baseline serum free light chains is elevated; POEMS syndrome; plasma cell leukemia
- More than 30 days of previous treatment (before screening) with anti-myeloma therapy
- Prior use of denosumab; use of oral bisphosphonates with a cumulative exposure of more than 1 year; more than 1 previous dose of IV bisphosphonate
- Prior history or current evidence of osteonecrosis/osteomyelitis of the jaw

Methods

Key Endpoints

Primary

- Time to the first on-study skeletal-related event (non-inferiority)

Secondary

- Time to the first on-study skeletal-related event (superiority)
- Time to the first-and-subsequent on-study skeletal-related event (superiority)
- Overall survival

Exploratory

- Progression-free survival

Results

Baseline Demographics and Characteristics

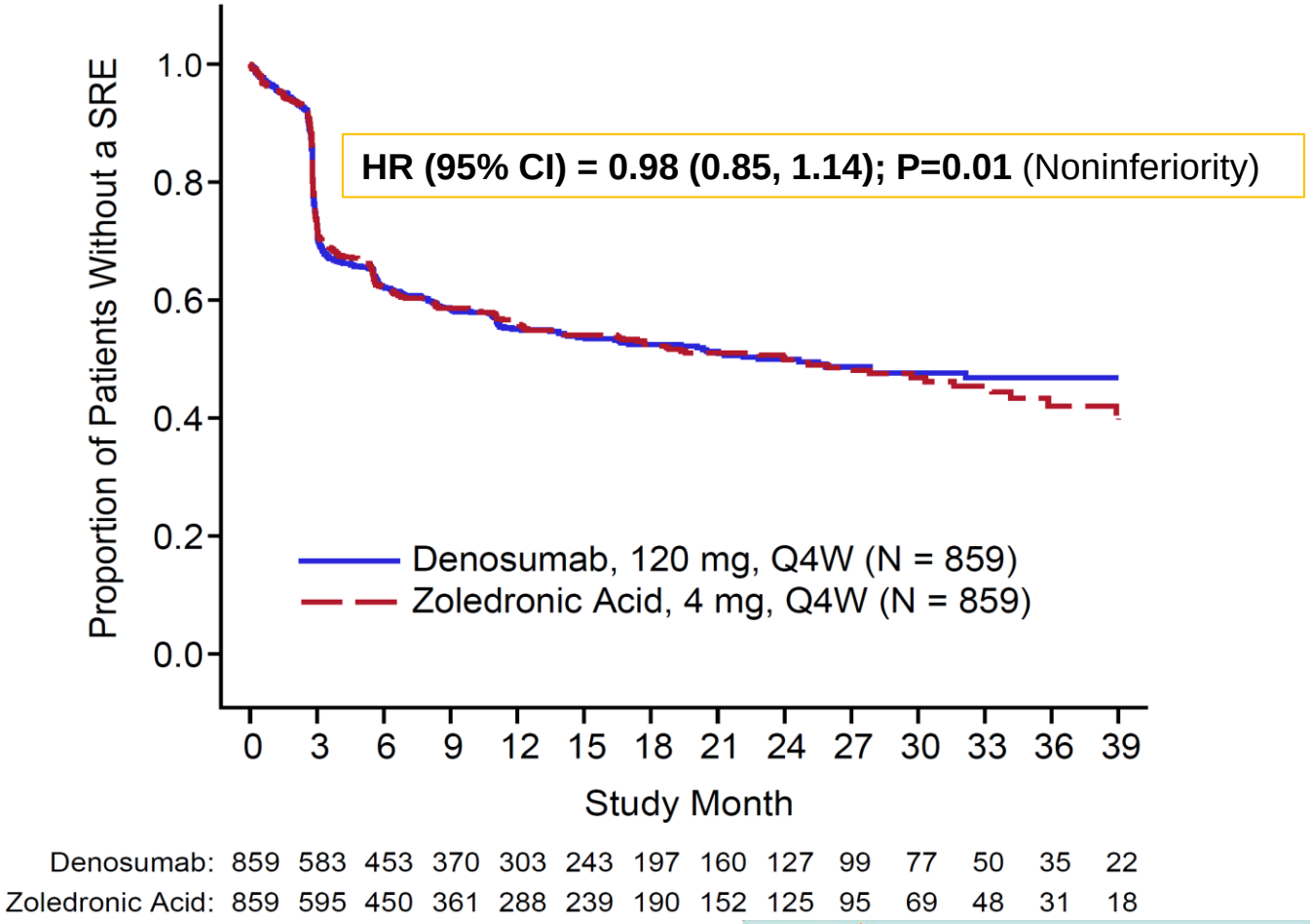
	Denosumab N = 859; n (%)	Zoledronic Acid N = 859; n (%)	All Patients N = 1718; n (%)
Male	462 (53.8)	473 (55.1)	935 (54.4)
Female	397 (46.2)	386 (44.9)	783 (45.6)
White	711 (82.8)	699 (81.4)	1410 (82.1)
Asian	107 (12.5)	101 (11.8)	208 (12.1)
Black or African American	29 (3.4)	36 (4.2)	65 (3.8)
Europe	509 (59.3)	513 (59.7)	1022 (59.5)
North America	218 (25.4)	227 (26.4)	445 (25.9)
Rest of the World	132 (15.4)	119 (13.9)	251 (14.6)
Prior SRE History (Yes)	567 (66.0)	577 (67.2)	1144 (66.6)
Mean Age (Years)	63.5	63.3	63.4
Median	63.0	63.0	63.0
Min, Max	29, 91	31, 89	29, 91
< 65 Years	472 (54.9)	464 (54.0)	936 (54.5)
≥ 65 Years	387 (45.1)	395 (46.0)	782 (45.5)
≥ 75 Years	141 (16.4)	132 (15.4)	273 (15.9)

- Enrollment started on May 17, 2012 and continued to March 29, 2016
- The primary analysis cutoff date was July 19th, 2016

Results

Primary Endpoint Met:

Noninferiority for Time to First On-Study Skeletal-Related Event



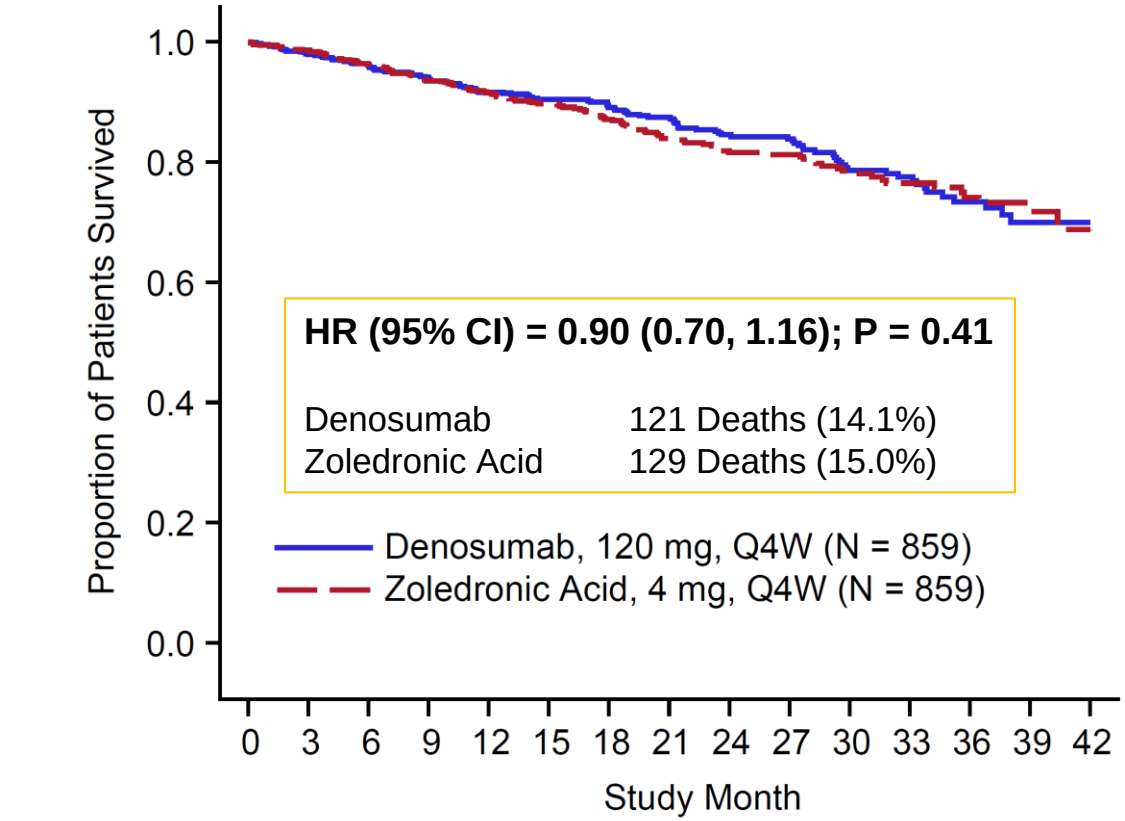
Results

Secondary Endpoints:

	Denosumab N = 859; n (%)	Zoledronic Acid N = 859; n (%)	Treatment Difference	P-Value
Time to First Skeletal-Related Event	• Crude Incidence: 376 (43.8%) • KM Median (95% CI): 22.83 (14.72, NE) Months	• Crude Incidence: 383 (44.6%) • KM Median (95% CI): 23.98 (16.56, 33.31) Months	HR (95% CI) = 0.98 (0.85, 1.14)	• Non-Inferiority: 0.01 • Superiority: 0.82 • Superiority(Adjusted): 0.84
Time to First-and-Subsequent Skeletal-Related Event (21-Day Window Applied)	• Number of Events: 565 • Mean Number of Events per Patient: 0.66	• Number of Events: 565 • Mean Number of Events per Patient: 0.66	RR (95% CI) = 1.01 (0.89, 1.15)	• Superiority: 0.84 • Superiority (Adjusted): 0.84

Results

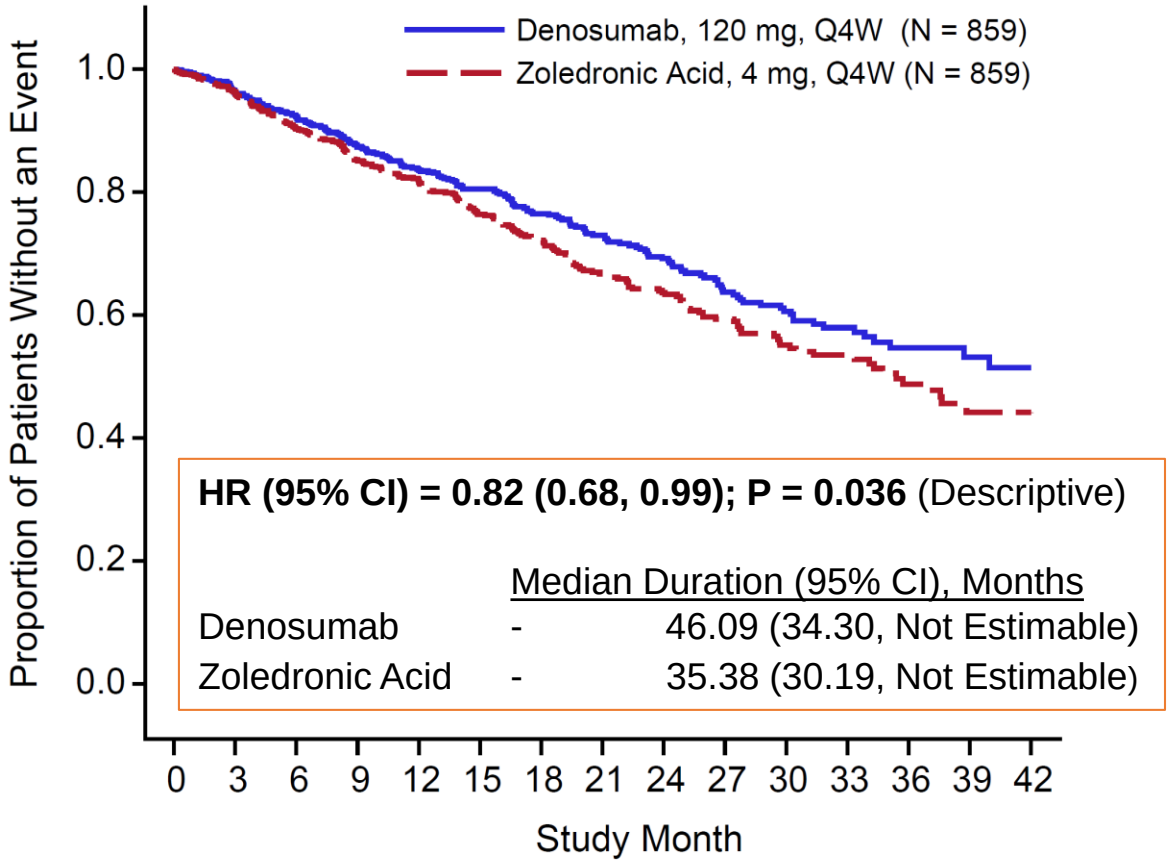
Additional Secondary Endpoint: Overall Survival



Denosumab:	859	809	737	640	565	477	395	344	288	229	175	130	85	48	19
Zoledronic Acid:	859	830	737	652	568	488	414	348	289	233	179	127	87	49	15

Results

Exploratory Endpoint: Progression-Free Survival



Results

Safety

	Denosumab N = 850; n (%)	Zoledronic Acid N = 852; n (%)
All Treatment-Emergent Adverse Events (AE)	816 (96.0)	825 (96.8)
AEs with Grade ≥ 3	562 (66.1)	575 (67.5)
Serious AEs	391 (46.0)	403 (47.3)
Fatal AEs	89 (10.5)	93 (10.9)
AEs Leading to IP Discontinuation	110 (12.9)	98 (11.5)
AEs Leading to Study Discontinuation	17 (2.0)	9 (1.1)
IP Related Treatment-Emergent AEs	217 (25.5)	222 (26.1)
AEs with Grade ≥ 3	44 (5.2)	49 (5.8)
Serious AEs	27 (3.2)	28 (3.3)
Fatal AEs	0 (0.0)	1 (0.1)
AEs Leading to IP Discontinuation	36 (4.2)	36 (4.2)
AEs Leading to Study Discontinuation	5 (0.6)	1 (0.1)
Most Frequent AEs (≥20% Denosumab Arm)		
Diarrhea	285 (33.5)	276 (32.4)
Nausea	268 (31.5)	259 (30.4)
Constipation	199 (23.4)	203 (23.8)
Anemia	189 (22.2)	180 (21.1)
Fatigue	187 (22.0)	203 (23.8)
Back pain	178 (20.9)	167 (19.6)
Pyrexia	176 (20.7)	206 (24.2)

Results

Adverse Events of Interest

	Denosumab N = 850, n (%)	Zoledronic Acid N = 852, n (%)
Hypocalcemia	144 (16.9)	106 (12.4)
Serious AEs of Hypocalcemia	8 (0.9)	2 (0.2)
Adjudicated Positive Osteonecrosis of the Jaw	35 (4.1)	24 (2.8)
Adjudicated Positive Atypical Femur Fracture	0	0
AEs Potentially Associated With Hypersensitivity	219 (25.8)	189 (22.2)
Serious AEs Potentially Associated With Hypersensitivity	5 (0.6)	9 (1.1)
Musculoskeletal Pain	407 (47.9)	425 (49.9)
Infections and Infestations	537 (63.2)	500 (58.7)
Serious AEs of Infections and Infestations	165 (19.4)	163 (19.1)
New Primary Malignancy	22 (2.6)	12 (1.4)
AEs Potentially Associated with Renal Toxicity	85 (10.0)	146 (17.1)
Acute Phase Reactions	46 (5.4)	74 (8.7)

- There were significantly lower incidences of adverse events potentially related to renal toxicity with denosumab therapy compared to zoledronic acid,10% vs 17.1%, P<0.001, particularly in those patients with baseline CrCl≤60mL/minute, 12.9% vs 26.4%, respectively

- The incidence of hypocalcemia events was 144 (16.9%) for denosumab and 106 (12.4%) for zoledronic acid, with the majority of events grade 1 or 2; there were no grade 5 events

Conclusions

- This study successfully demonstrated non-inferiority as the primary endpoint for time to first skeletal-related events between denosumab and zoledronic acid
- Superiority was not demonstrated for time to first and time to first-and-subsequent skeletal-related events between denosumab and zoledronic acid
- Overall survival was similar in both arms, HR (95% CI) = 0.90 (0.70, 1.16); P = 0.41
- Progression-free survival for denosumab was numerically longer compared to zoledronic acid, with a HR (95% CI) = 0.82 (0.68, 0.99), descriptive P = 0.036
- The median progression-free survival difference between treatment arms was 10.7 months
- Safety from this multiple myeloma, skeletal-related events study was comparable to those seen in the previous skeletal-related event studies, with overall adverse events similar between the treatment arms:
  - There was a significantly lower incidence of adverse events potentially related to renal toxicity with denosumab therapy compared to zoledronic acid
  - There were 35 (4.1%) and 24 (2.8%) positively adjudicated events of osteonecrosis of the jaw in the denosumab and zoledronic acid arms, respectively
  - A lower incidence of adverse events potentially related to acute phase reaction occurred with denosumab than zoledronic acid (5.4% vs 8.7%)

The bone specific benefits in combination with significantly fewer renal adverse events and possible prolongation of progression-free survival with denosumab therapy is promising

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