Acute-phase reactions following treatment with zoledronic acid or denosumab: results from a randomized, phase 3 study in patients with castrate-resistant prostate cancer and bone metastases

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BACKGROUND

- Bone metastases are common in men with advanced prostate cancer, and the associated complications – such as intractable pain, pathological fractures, spinal cord compression and need for radiation therapy to bone – present a significant burden to patients and healthcare services.[1,2]
- Since the late 1990s, agents for the treatment of bone metastases have been evaluated based on skeletal-related events (SREs), a composite measure that includes pathological fracture, spinal cord compression, radiotherapy to bone and surgery on bone.
- Intravenous (i.v.) bisphosphonates are commonly used to treat bone metastases and prevent SREs in men with castration-resistant prostate cancer (CRPC).
- Intravenous administration of aminobisphosphonates, such as zoledronic acid, is associated with development of an acute-phase reaction in up to 30% of patients who receive treatment for the first time.[3,4]
  - Such reactions are distressing for the patient and can lead to treatment withdrawal.
  - Symptoms generally resolve within 48 hours and may require treatment with non-steroidal anti-inflammatory drugs and antipyretics.
- Denosumab is a fully human monoclonal antibody that binds to human RANK ligand, produced by osteoblasts and other cells, inhibiting osteoclast activity and the resulting bone destruction and SREs.[5]
- In a randomized, active-controlled study, it was reported that denosumab inhibited osteoclast-mediated bone destruction in men with advanced prostate cancer to a higher degree than ongoing therapy with i.v. bisphosphonates.[6]

METHODS

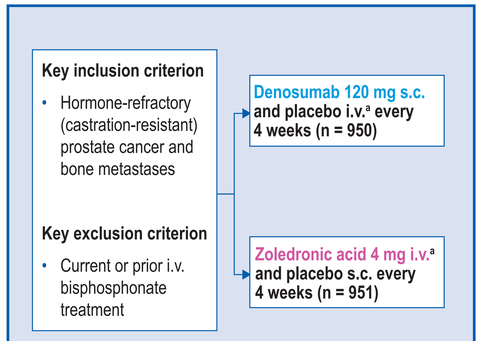
Objectives

- To compare denosumab with zoledronic acid for the prevention of SREs in men with bone metastases from CRPC.
- To evaluate the incidence of acute-phase reactions (influenza-like syndrome including pyrexia, chills, flushing, bone pain, arthralgia and myalgia) during the first 3 days after initial treatment in the study, according to a prespecified analysis.

Patient eligibility criteria

- Men ≥ 18 years of age with histologically confirmed prostate cancer and radiographic evidence of at least one bone metastasis.
- Documented failure of at least one hormonal therapy.
- Albumin-adjusted serum calcium 2.0–2.9 mmol/L (8.0–11.5 mg/dL).
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.

Figure 1. Study design: international, randomized, double-blind, double-dummy, active-controlled study



[a]Per protocol and Zometa® label, i.v. dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine.
No s.c. dose adjustments made owing to increased serum creatinine.

- Adequate organ function.
- Life expectancy ≥ 6 months.
- No current or previous use of i.v. bisphosphonates.

Endpoints and analysis

- Primary endpoint (non-inferiority):
  - time to first on-study SRE (Cox proportional hazards model).
- Secondary endpoints (superiority):
  - time to first on-study SRE (Cox proportional hazards model)
  - time to first-and-subsequent on-study SRE (multiple events; Andersen–Gill model with robust variance estimate).
- The safety analysis included data from all randomized patients who received at least one dose of denosumab or zoledronic acid.
- Patient records were searched for adverse events (AEs) and serious AEs that occurred during the first 3 days after the initial administration of denosumab or zoledronic acid, using 37 prespecified MedDRA version 12.1 preferred terms potentially indicating acute-phase reactions (Table 1).
- As per the study protocol, AEs were considered serious if they were fatal, life-threatening, required or prolonged inpatient hospitalization, resulted in a persistent or significant disability, or were considered to present a significant medical hazard.
- Acute-phase reaction AEs for the denosumab and zoledronic acid groups were compared using a two-sided Fisher's exact test (the unadjusted *p* value was reported).

Table 1. MedDRA version 12.1 preferred terms used to define adverse events potentially associated with acute-phase reactions

- Headache
- Musculoskeletal stiffness
- Asthenia
- Chest pain
- Bone pain
- Pain in extremity
- Decreased activity
- Discomfort
- Arthralgia
- Decreased appetite
- Fatigue
- Flank pain
- Myalgia
- Hyperthermia
- Lethargy
- Inflammatory pain
- Myalgia intercostal
- Chills
- Listless
- Non-cardiac chest pain
- Myofascial pain syndrome
- Feeling cold
- Malaise
- Pain
- Muscle tightness
- Feeling hot
- Sluggishness
- Tenderness
- Back pain
- Feeling of body temperature change
- Flushing
- Musculoskeletal discomfort
- Hyperpyrexia
- Influenza-like illness
- Musculoskeletal pain
- Pyrexia
- Acute-phase reaction

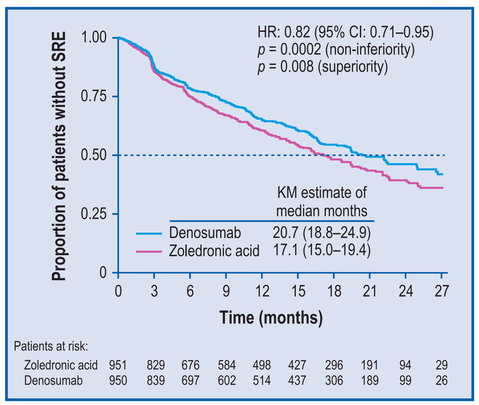
RESULTS

Table 2. Baseline characteristics

	Zoledronic acid (n = 951)	Denosumab (n = 950)
Median (Q1, Q3) age, years	71 (66, 77)	71 (64, 77)
ECOG status 0–1, n (%)	886 (93.2)	882 (92.8)
Recent chemotherapy, n (%)[a,b]	132 (13.9)	132 (13.9)
PSA at randomization, n (%)[a]		
< 10 ng/mL	145 (15.2)	145 (15.3)
≥ 10 ng/mL	806 (84.8)	805 (84.7)
Previous SRE, n (%)[a]	231 (24.3)	232 (24.4)

[a]Based on stratification at randomization.
[b]In the 6 weeks before randomization.
ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; Q, quartile; SRE, skeletal-related events.

Figure 2. Time to first skeletal-related event (SRE)

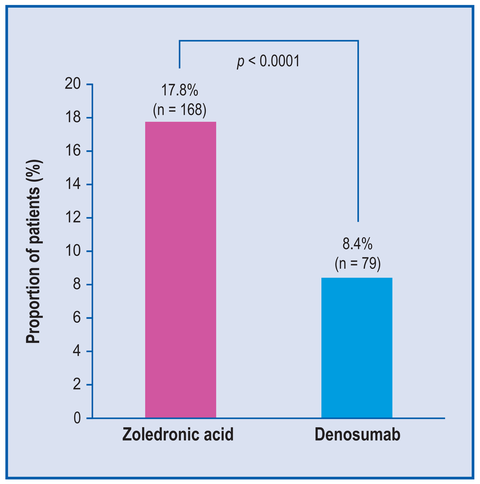


p values were adjusted for multiplicity.
HR, hazard ratio; KM, Kaplan–Meier.

Table 3. Adverse events (AEs) in patients receiving at least one dose of study treatment

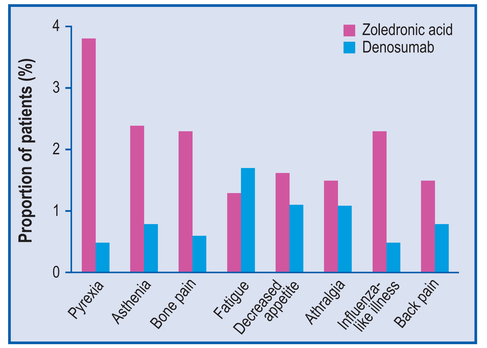
	Zoledronic acid (n = 945)	Denosumab (n = 943)
Any AE, n (%)	918 (97.1)	916 (97.1)
AEs occurring with ≥ 20% frequency in either treatment group, n (%)		
Anaemia	341 (36.1)	337 (35.7)
Back pain	287 (30.4)	304 (32.2)
Decreased appetite	274 (29.0)	267 (28.3)
Nausea	245 (25.9)	272 (28.8)
Fatigue	222 (23.5)	257 (27.3)
Constipation	251 (26.6)	236 (25.0)
Bone pain	245 (25.9)	235 (24.9)
Asthenia	239 (25.3)	239 (25.3)
Arthralgia	202 (21.4)	194 (20.6)
Pain in extremity	196 (20.7)	197 (20.9)
Peripheral oedema	174 (18.4)	192 (20.4)
AEs leading to treatment discontinuation, n (%)	138 (14.6)	164 (17.4)
CTCAE grade 3 or 4 AEs, n (%)	628 (66.5)	678 (71.9)
Serious AEs, n (%)	568 (60.1)	594 (63.0)

Figure 3. Patients experiencing acute-phase reactions occurring in the first 3 days after initial treatment



- One patient (0.1%) treated with denosumab (chest pain) and three patients (0.3%) treated with zoledronic acid (pyrexia [n = 2], asthenia, musculoskeletal pain) experienced serious AEs associated with acute-phase reactions during the first 3 days.
- None of the acute-phase reactions in the denosumab group were considered to be related to treatment.

Figure 4. Most common symptoms of acute-phase reactions[a]



[a]The most common symptoms that occur in the first 3 days after initial treatment.

SUMMARY

- In this head-to-head study of denosumab versus zoledronic acid for the treatment of men with CRPC and bone metastases, time to first SRE was significantly prolonged with denosumab.
  - As SREs can have a marked impact on patients' well-being, this benefit of denosumab is likely to make a major difference to patients as well as healthcare resources.
- Acute-phase reaction AEs were significantly more frequent with zoledronic acid than with denosumab ($p < 0.0001$).
  - The rate observed in the denosumab arm is likely to reflect the background level of such events, rather than being a result of denosumab treatment.
- The most common acute-phase reaction AEs were pyrexia, asthenia, bone pain, fatigue, decreased appetite, arthralgia, influenza-like illness and back pain.
- Serious AEs associated with acute-phase reactions occurred in one patient receiving denosumab and three patients receiving zoledronic acid.
- An excess of acute-phase reactions during zoledronic acid therapy creates an additional burden for patients and necessitates closer monitoring and may require treatment.
- Nurses play a key role in helping patients to manage symptoms of acute-phase reactions, and the reduced number of these AEs with denosumab may improve patient comfort and reduce nursing time.
- Patient education, which forms part of the nursing role, is important to prepare patients for possible onset of symptoms associated with acute-phase reactions and their management.

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