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

Lawrence Drudge-Coates,1 Bruce Turner,2 Stacey Harrelson,3 Huei Wang,4 Carsten Goessl6

1Kings College Hospital NHS Foundation Trust, London, UK; 2Homerton Hospital NHS Trust, London, UK; 3Carolina Urologic Research Center, SC, USA; 4Amgen Inc., Thousand Oaks, CA, USA

BACKGROUND

• Bone metastases are common in men with advanced prostate cancer, and the associated complications – such as intraosseous pain, pathological fractures, spinal cord compression and need for radiation therapy to bone – present a significant burden to patients and healthcare services.

• 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 bisphosphonates, 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.1,2

• 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 osteoclasts and other cells, inhibiting osteoclast activity and resulting in bone destruction and SREs.3,4

• 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.1

KEY INCLUSION CRITERION

• Hormone-refractory (castration-resistant) prostate cancer and bone metastases

OBJECTIVES

• To evaluate the incidence of acute-phase reactions

• To compare denosumab with zoledronic acid for the treatment of bone metastases

• To evaluate the incidence of acute-phase reactions

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.

RESULTS

• Adequate organ function.

• Life expectancy > 2 years.

• 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 SREs (Cox proportional hazards model)

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• 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 initial treatment of denosumab or zoledronic acid, using 37 prespecified MedDRA version 12.1 preferred terms 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 prespecified Fisher’s exact test (the unadjusted p value was reported).

• One patient (0.1%) treated with denosumab (chest pain) and three patients (0.3%) treated with zoledronic acid (pyrexia [n = 2], asthma, 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.

• The safety analysis included data from all randomized patients who received at least one dose of denosumab or zoledronic acid.

• AEs occurring in the first 3 days.

• Calcium and vitamin D supplemented in both treatment groups.

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• Literature

• Intravenous administration of bisphosphonates, 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.1,2

• 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.

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