European Journal of Cancer (2015) **51**, 1467–1475

Available at www.sciencedirect.com

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journal homepage: www.ejcancer.com

The role of denosumab in the prevention of hypercalcaemia of malignancy in cancer patients with metastatic bone disease ☆

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Received 19 March 2015; accepted 24 April 2015
Available online 11 May 2015

KEYWORDS
Hypercalcaemia of malignancy
Denosumab
Zoledronic acid
Breast cancer
Solid tumours
Multiple myeloma
Supportive care

Abstract ***Background:*** We compared the activity of denosumab with zoledronic acid for delaying or preventing hypercalcaemia of malignancy (HCM) in patients with advanced cancer and bone metastases or with multiple myeloma.
Methods: Patient-level data were combined from two identically designed, randomised, double-blind, active-controlled, phase III trials of advanced cancer patients with breast cancer and other solid tumours (excluding breast or prostate cancer) or multiple myeloma. End-points included time to first on-study HCM, time to first and subsequent on-study HCM, proportion of patients experiencing HCM and proportion of patients experiencing recurrent HCM.

Trial registration: This study is registered with ClinicalTrials.gov with the identifier NCT00321464 and NCT00330759.

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http://dx.doi.org/10.1016/j.ejca.2015.04.017

Results: Denosumab significantly delayed the time to first on-study HCM, representing a 37% reduction in the hazard ratio (HR) compared with zoledronic acid (HR, 0.63; 95% confidence interval (CI): 0.41–0.98; $P = 0.042$) and reduced the risk of developing recurrent HCM (time to first and subsequent on-study HCM) by 52% (rate ratio, 0.48; 95% CI: 0.29–0.81; $P = 0.006$). The median time on study was 12.9 months. Fewer patients receiving denosumab compared with zoledronic acid experienced an HCM event (1.7% versus 2.7%; $P = 0.028$). Of the 84 patients experiencing an HCM event, 40% of those receiving zoledronic acid experienced >1 event of HCM compared with 31% of those receiving denosumab.
Conclusion: Denosumab treatment was more efficacious than treatment with zoledronic acid in delaying or preventing HCM in advanced cancer patients with breast cancer, other solid tumours or multiple myeloma.

1. Introduction

During the course of cancer progression, hypercalcaemia of malignancy (HCM) affects 3–30% of all patients [1,2] and is often a sign of advanced malignancy with very poor prognosis [3]. Onset can be gradual or rapid, and clinical symptoms are a result of both the severity of hypercalcaemia and the rate of increase in serum calcium [3]. Multiple organ classes may be affected, including the renal, nervous and cardiovascular systems [4,5]. Left untreated, the median duration of survival is 2–6 months from HCM onset [3,6,7]. The prevalence of HCM varies depending on tumour type and is most often diagnosed in patients with advanced breast cancer, multiple myeloma, lung cancer and head and neck cancers [1,2]. Among advanced cancer patients with skeletal involvement, HCM is most common in metastatic breast cancer (30–65%) [1,8] and multiple myeloma (30–80%) [8] but is rare in both metastatic prostate cancer and osteosarcomas [4].

Serum calcium levels are mediated by physiological homoeostasis mechanisms involved in bone resorption/-formation and renal tubular reabsorption. Dysfunction of serum calcium homeostasis involves multiple pathologic mechanisms, several of which have been identified in HCM [9]. Osteolytic HCM involves cancer-directed, osteoclast-driven bone resorption while humoral HCM involves the systemic release of parathyroid hormone-related protein (PTHrP) by malignant tumours. More rarely, absorptive HCM involves tumour secretion of the active form of vitamin D which increases both osteoclastic bone resorption and gastrointestinal calcium absorption. It is important to note that in advanced cancer patients presenting with HCM, increases in serum calcium levels do not necessarily involve bone metastases or reflect increased bone resorption [1,4].

Treatment of HCM is aimed at lowering serum calcium concentration and treating the cancer. Historically, initial therapy has involved saline hydration followed by treatment with loop diuretics to increase urinary calcium excretion [3,10]. However, saline hydration therapy rarely results in normalisation of calcium levels, and the effects are limited and transient in nature [11]. Furthermore, constant and careful monitoring for fluid overload and electrolyte imbalances is required [2,3]. Advances in understanding bone physiology have led to more efficacious treatments with the availability of antiresorptives such as calcitonin, gallium nitrates and intravenous (IV) bisphosphonates, that specifically decrease tumour-induced osteoclast activity. However, treatment with calcitonin only exhibits modest efficacy in returning calcium levels to baseline [3,5] whereas gallium nitrates and IV bisphosphonates may be nephrotoxic [12,13]. More tolerable and effective therapies are required to prevent the onset and recurrence of all forms of HCM in cancer patients.

Recently, a combined analysis of three large, phase III clinical studies in patients with advanced cancer demonstrated that denosumab was superior to zoledronic acid in preventing skeletal-related events (SREs) [14]. In this report, we present the results of an exploratory analysis comparing denosumab with zoledronic acid for preventing or delaying HCM. The population for the current analysis was drawn from the two phase III clinical studies that included advanced cancer patients with breast cancer, other solid tumours or multiple myeloma. Prostate cancer patients were not included in the analysis due to the very low incidence of HCM [8], where the incidence of HCM in both treatment groups was less than 0.26% for this patient population [15].

2. Materials and methods

In this exploratory analysis, patient-level data were pooled and analysed from two identically designed, international, randomised, active-controlled, double-blind phase III trials. Denosumab 120 mg (XGEVA®, Amgen Inc., Thousand Oaks, CA) [15] was administered subcutaneously (SC), and zoledronic acid 4 mg (Zometa®, Novartis Pharmaceuticals, East Hanover, NJ) [16] was administered IV. Blinding was maintained by administering IV placebo to patients randomised to denosumab and

SC placebo to patients randomised to zoledronic acid. Both active study drugs and their placebo counterparts were administered every 4 weeks. IV product or placebo dosing was adjusted based on renal function (baseline creatinine clearance <60 mL/min, Cockcroft-Gault formula) [17]. If serum creatinine levels increased, subsequent dosing of IV zoledronic acid or placebo was withheld until serum creatinine levels returned to within 10% of the baseline levels, consistent with the zoledronic acid prescribing information [16]. SC denosumab or placebo was not dose adjusted in the trials.

2.1. Study design and patients

Eligible patients were randomised 1:1 by an interactive voice response system to receive either SC denosumab 120 mg and IV placebo every 4 weeks (Q4W) or IV zoledronic acid 4 mg (dose adjusted for renal impairment) and SC placebo Q4W. IV administration of either zoledronic acid or placebo was conducted as a single infusion over at least 15-min. Patients were stratified by tumour type, previous SRE (Yes or No), prior oral bisphosphonate use (Yes or No), as well as additional study specific factors [18,19]. Study sponsors and personnel, investigators and patients remained blinded to treatment assignment through completion of the primary analysis of each study.

Patient eligibility criteria and study methods have been previously reported [18,19]. Briefly, patients had a primary diagnosis of either breast cancer ($N = 2046$) [18], other solid tumours or multiple myeloma ($N = 1776$) [19] with radiographic evidence of at least one bone metastasis; an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 1 or 2; and adequate organ function. Patients were excluded from the study if creatinine clearance was <30 mL/min (per Zometa® prescribing information) [16], if they had received IV bisphosphonates for bone metastases, or if they had HCM. Eligible patients had albumin-adjusted serum calcium concentrations between ⩾2.0 mmol/L (8.0 mg/dL) and ⩽2.9 mmol/L (11.5 mg/dL), as determined by a central laboratory. All study participants were strongly advised to take at least 400 IU of vitamin D and 500 mg of calcium supplements daily unless HCM developed on study. Specific anticancer therapy and other concomitant medications or treatments were determined by the treating physician.

The study was approved by the institutional review board or equivalent ethics committee for each study site. All patients in the trials provided written informed consent before any study-specific procedures.

2.2. Assessment of hypercalcaemia of malignancy

HCM was defined as an albumin-adjusted serum calcium value of >2.9 mmol/L (11.5 mg/dL) or ionised calcium >1.5 mmol/L (grade ⩾2 per Common Terminology Criteria for Adverse Events [CTCAE v. 3.0]). Serum calcium levels were measured by a central laboratory.

2.3. End-points

The key end-points in this exploratory analysis included time to first on-study HCM, time to first and subsequent on-study HCM, proportion of patients experiencing HCM and proportion of patients experiencing recurrent events of HCM. Other end-points included on-study baseline calcium levels for patients who did or did not have an HCM event, adverse events (AEs) of hypercalcaemia resulting in hospitalisation, the number needed to treat (NNT) to prevent at least one SRE or event of HCM, the effect of an HCM event on overall survival time and overall survival time for patients who had an HCM event on study.

2.4. Statistical analysis

Time to first on-study HCM was analysed using the Cox proportional hazards model with treatment groups as independent variables, stratified by study and randomisation stratification factors. A multiple-events analysis utilising the Anderson-Gill model [20] was used to evaluate the time to first and subsequent HCM and was also stratified by study and the randomisation stratification factors. The Kaplan–Meier method was used to estimate the median time to first on-study HCM and overall survival time after developing an on-study HCM, along with the 95% confidence interval (CI). No adjustments for multiplicity were made. A Cox proportional hazards model with a time-dependent covariate (on-study HCM event) was used to assess the impact of an on-study HCM event on overall survival time. A Kaplan–Meier estimate was calculated for the overall survival time after an HCM event. Baseline calcium values were determined as the last recorded measurement on or prior to the day of the first dose of investigational product. The number of AEs of hypercalcaemia resulting in hospitalisation and percentage of patients experiencing an HCM event or multiple events of HCM were summarised with descriptive statistics. Based on the event-driven nature of the study, the NNT to determine a difference between denosumab and zoledronic acid was calculated as the inverse of the difference in the patient-year adjusted rates for the time to first or first and subsequent on-study SRE or HCM (or, for patients without an SRE or HCM, the time to the end of the study or primary analysis data cut-off date, whichever occurred first).

3. Results

3.1. Patients

A total of 3822 patients were enrolled and randomised between April 2006 and May 2008 ($N = 1912$ denosumab, $N = 1910$ zoledronic acid; Fig. 1). The median time (range) on-study was 12.9 months (0.0–34.2). The patient disposition categories were nearly identical between the treatment arms at the time of the primary analysis. Approximately 66% of patients for both the denosumab and zoledronic acid arms discontinued from this event driven study before the primary analysis data cut-off date. The most common reasons for discontinuation were death, followed by disease progression and withdrawal consent. Adverse events were recorded as the reason for discontinuation in approximately 3% of denosumab patients and 5% of zoledronic acid patients.

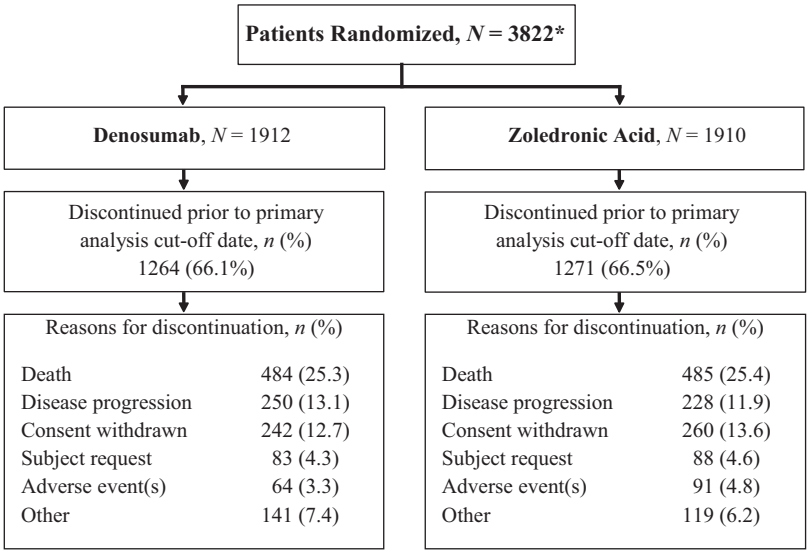
Patient characteristics were well balanced between treatment arms, including age, sex, ECOG status and distribution among the primary tumour types (Table 1). The median age for patients across treatment arms was 58 years. The majority of patients were female and had an ECOG performance status of 0 or 1. The median time from first bone metastasis to study randomisation was 1.9 months in each arm, and 43% of patients had experienced a previous SRE. Approximately 54% of patients from both arms had breast cancer as the primary diagnosis, followed by non-small cell lung cancer (NSCLC; 18%).

At baseline, the median (interquartile range) corrected calcium concentration for patients who had an HCM event in either the denosumab (10.20 mg/dL [9.70, 10.75]) or zoledronic acid arms (10.10 mg/dL [9.85, 10.45]) was slightly higher (not statistically significant) to those patients who did not have an HCM event in either the denosumab (9.80 mg/dL [9.50, 10.20]) or zoledronic acid arms (9.80 mg/dL [9.50, 10.10]).

3.2. Efficacy

A total of 84 patients experienced at least one HCM event while on antiresorptive therapy, including 32 patients in the denosumab arm (1.7%) and 52 patients in the zoledronic acid arm (2.7%; Table 2). For both treatment arms, HCM events occurred most frequently in patients with advanced breast cancer ($n = 50$; 1.3%), followed by NSCLC ($n = 20$; 0.5%), and multiple myeloma ($n = 7$; 0.2%). HCM events were infrequent in colon, cervical, liver and other types of cancers.

Denosumab treatment significantly delayed the time to first on-study HCM compared with zoledronic acid treatment (hazard ratio [HR], 0.63; 95% CI, 0.41 to 0.98; $P = 0.042$, representing a 37% reduction in the HR; Fig. 2). The greater efficacy of denosumab treatment was observed as early as 6 months and continued through the end of study. Denosumab also significantly reduced the risk of developing recurring HCM by 52% compared with zoledronic acid (time to first and subsequent on-study HCM: rate ratio) (0.48; 95% CI: 0.29 to 0.81; $P = 0.006$; Fig. 3). In both the denosumab and zoledronic acid arms, the majority of patients experienced a single HCM event during the course of therapy (Table 3). However, fewer patients treated with denosumab than zoledronic acid experienced CTCAE grade 2, 3 or 4 events (albumin-corrected calcium) or ⩾4



*Does not include 6 patients (inadequate informed consent or insufficient IRB oversight).

Fig. 1. Patient disposition. IRB, institutional review board. *Does not include six patients (inadequate informed consent or insufficient IRB oversight).

Table 1
Baseline demographics and characteristics.

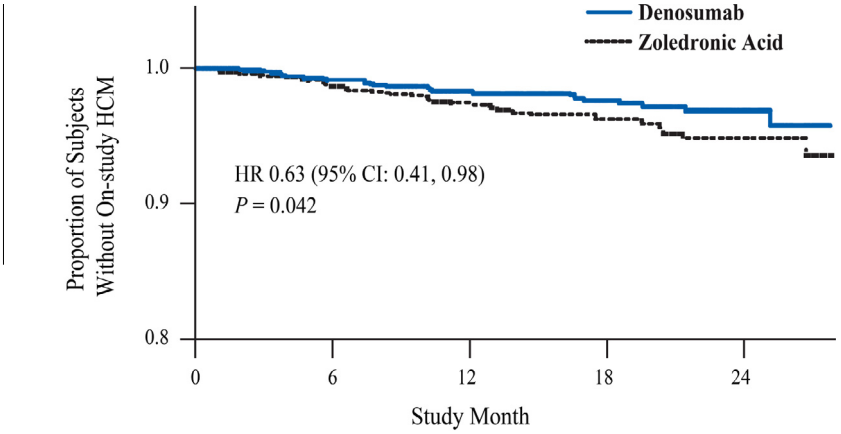
Characteristics *n* (%) or median (Q1, Q3)	Denosumab 120 mg Q4W (*N* = 1912)	Zoledronic acid 4 mg Q4W (*N* = 1910)
Women	1316 (69)	1349 (71)
Age, years	58	59
⩾65	574 (30.0)	602 (31.5)
ECOG status of 0 or 1	1703 (89)	1660 (87)
Prior SRE[a]	819 (43)	818 (43)
Months from first bone metastasis to randomisation, median (Q1, Q3)	1.9 (1.0, 4.6)	1.9 (1.0, 4.4)
Tumour type		
Breast	1026 (54)	1020 (53)
Non-small cell lung	350 (18)	352 (18)
Multiple myeloma	87 (5)	93 (5)
Renal	70 (4)	85 (4)
Small cell lung	61 (3)	48 (3)
Other	318 (17)	312 (16)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; Q4W, every 4 weeks; SRE, skeletal-related events.
[a] Prior SRE based on randomised stratum.

Table 2
Frequency of patients experiencing HCM by primary tumour type.

	Denosumab 120 mgQ4W (*N* = 1912)	Zoledronic acid 4 mg Q4W (*N* = 1910)
Patients experiencing HCM, *n* (%)	32 (1.7)	52 (2.7)
Primary tumour type		
Breast	19 (1.0)	31 (1.6)
Non-small cell lung	11 (0.6)	9 (0.5)
Multiple myeloma	1 (0.1)	6 (0.3)
Anal	0	1 (0.1)
Cervix	1 (0.1)	0
Liver	0	1 (0.1)
Renal	0	3 (0.2)
Other	0	1 (0.1)

Abbreviations: HCM, hypercalcaemia of malignancy; Q4W, once every 4 weeks.



Patients at risk:

Denosumab	1912	1298	952	544	167
Zoledronic acid	1910	1271	956	571	162

Fig. 2. Time to first hypercalcaemia of malignancy (HCM). CI, confidence interval; HR, hazard ratio.

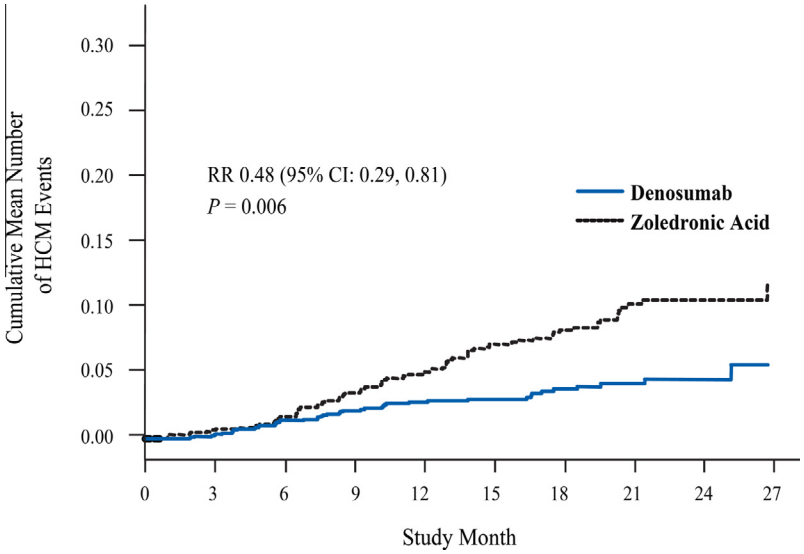


Fig. 3. Time to first and subsequent on-study hypercalcaemia of malignancy (HCM; multiple event analysis). CI, confidence interval; RR, rate ratio.

Table 3
Number of HCM patients by events and severity grade.

	Denosumab	Zoledronic acid
Number of HCM events[a]	$N = 32$	$N = 52$
	n (%)	*n* (%)
1 event	22 (69)	31 (60)
2 events	5 (16)	9 (17)
3 events	4 (13)	4 (8)
⩾4 events	1 (3)	8 (15)
Severity grade[b]	$N = 1898$	$N = 189$
	n (%)	*n* (%)
Grade 2	15 (0.8)	23 (1.2)
Grade 3	6 (0.3)	13 (0.7)
Grade 4	6 (0.3)	14 (0.7)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events (version 3.0); HCM, hypercalcaemia of malignancy.

[a] Based on the number of subjects having an albumin-adjusted serum calcium value of >2.9 mmol/L (11.5 mg/dL) or ionised calcium >1.5 mmol/L (grade ⩾2).

[b] Based on albumin-corrected calcium (CTCAE grade).

HCM events. No patients in either treatment group experienced a CTCAE grade 5 HCM event. In addition, the number of AEs of hypercalcaemia resulting in hospitalisation was lower in the denosumab arm (3/38; 7.9%) than in the zoledronic acid arm (10/71; 14.1%).

Fewer first SREs or HCM events occurred on-study in the denosumab arm than in the zoledronic acid arm (denosumab, 610 first SREs or HCM events in 1615.3 patient years; zoledronic acid, 719 first SREs or HCM events in 1567.4 patient years) resulting in an NNT of 12.3 patient years for denosumab compared with zoledronic acid.

For those patients who had an on-study HCM event, the median (range) for overall survival time was 4.1 (2.1–9.0) months. The time-dependent analysis showed that an on-study HCM event did not impact the overall survival time for this population ($P < 0.656$).

3.3. Safety

The overall rates of AEs and serious adverse events (SAEs) were similar between treatment arms for the full study population. Ninety-six percent of the patients treated with denosumab and 97% of those treated with zoledronic acid experienced AEs. Reported SAE rates were 53% for denosumab and 56% for zoledronic acid. Adverse events were primarily reflective of toxicities associated with the concomitant therapies (chemotherapy regimen) or complications related to the malignancy. In those patients experiencing ⩾1 HCM event, 2 (6.3%) denosumab patients and no zoledronic acid patients reported positively adjudicated osteonecrosis of the jaw (Table 4). There were no reported incidences of positively adjudicated atypical fractures for either group. Also, no patients developed detectable levels of neutralising anti-denosumab antibodies.

4. Discussion

HCM is a life-threatening complication in patients with advanced cancer. Evidence suggests that the primary mechanism responsible for humoral and osteolytic HCM is increased resorptive activity of osteoclasts leading to the release of calcium with a subsequent elevation of serum calcium levels. Current treatments focus on lowering serum calcium concentration by administering potent antiresorptives that inhibit osteoclast-driven bone resorption. Denosumab has demonstrated greater efficacy in the inhibition of osteoclast activity by reducing bone turnover marker levels (urinary

Table 4
Serious adverse events in patients experiencing ⩾1 HCM event.

Preferred term	Zoledronic acid 4 mg Q4W ($N = 52$) n (%)	Denosumab 120 mg Q4W ($N = 32$) n (%)
Number of patients reporting serious adverse events	41 (78.8)	24 (75.0)
Serious adverse events reported in ⩾5% of patients		
Hypercalcaemia	9 (17.3)	3 (9.4)
Anaemia	7 (13.5)	1 (3.1)
Dehydration	6 (11.5)	0 (0.0)
Hypoglycaemia	4 (7.7)	0 (0.0)
Malignant neoplasm progression	4 (7.7)	3 (9.4)
Vomiting	3 (5.8)	1 (3.1)
Hepatic failure	2 (3.8)	2 (6.3)
Thrombocytopenia	2 (3.8)	2 (6.3)
Metastasis	1 (1.9)	2 (6.3)
Pneumonia	1 (1.9)	4 (12.5)
Renal failure	1 (1.9)	2 (6.3)
Respiratory failure	1 (1.9)	2 (6.3)
Metastases to bone	0 (0.0)	2 (6.3)
Osteonecrosis	0 (0.0)	2 (6.3)
Dyspnoea	0 (0.0)	3 (9.4)
Metastases to central nervous system	0 (0.0)	3 (9.4)

N = Number of patients who received ⩾1 active dose of investigational product for subjects that have HCM.
n = Number of patients reporting at least one adverse event.
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product.
Preferred terms are sorted by descending order of frequency in the denosumab group.
Coded using MedDRA version 12.0.

N-telopeptide/creatinine and bone-specific alkaline phosphatase) and SREs compared with zoledronic acid [18,19,21]. In this combined analysis of advanced cancer patients with breast cancer, other solid tumours or multiple myeloma, denosumab therapy demonstrated greater efficacy in delaying the time to first HCM and time to first and subsequent HCM compared with zoledronic acid therapy. Further, fewer patients receiving denosumab experienced single or multiple event(s) of HCM compared with those receiving zoledronic acid. Although the original SRE trials [18,19] were not designed to evaluate HCM alone, combined data from these trials provide compelling evidence that denosumab provides greater suppression of osteoclast-driven, osteolytic activity compared with zoledronic acid. Fundamental differences in the antiresorptive mechanisms of denosumab and zoledronic acid may be responsible for the observed clinical responses from the combined trials.

Denosumab is a fully humanised monoclonal antibody that, similar to osteoprotegerin (OPG), interferes with the RANK/RANKL pathway and osteoclast-mediated bone resorption. Studies have demonstrated that OPG prevented experimentally induced HCM, rapidly restored normal calcium levels [22] and significantly delayed HCM onset in tumour-bearing mice with a 99% reduction in osteoclasts [23]. In addition, PTHrP-mediated bone resorption, the principal mechanism involved in humoral HCM, is also inhibited by interference with the RANK/RANKL pathway. Preclinical studies have shown that PTHrP requires functional RANK/RANKL interactions for osteoclast activation. When PTHrP was injected into RANK knockout mice [22], PTHrP failed to induce hypercalcaemia or the appearance of osteoclasts. Furthermore, when either PTHrP or recombinant RANKL was injected into wild-type mice, recombinant OPG successfully blocked the hypercalcaemic response [23]. PTHrP is also known to increase tubular calcium reabsorption and this effect is not modified by antiresorptive agents. In our analysis, denosumab therapy was more effective than ZA in preventing HCM across tumour types, with variations in between-group differences by tumour type (Table 2). Although data are not available by histological subtype for this dataset, the greater pathogenic significance of PTHrP for HCM in squamous cell tumours than in breast adenocarcinomas or in multiple myeloma [1,2,8] may have contributed to the observation.

Most advanced cancer patients with HCM respond favourably to bisphosphonate treatments, as shown by decreases in serum calcium concentrations to normal levels [11]. However, up to 25% of cancer patients who develop HCM do not respond or are inadequately controlled after receiving bisphosphonate therapy [23,24]. Studies have further suggested that resistant hypercalcaemia was a result of incomplete inhibition of bone

resorption [25,26] and/or increased renal calcium reabsorption driven by malignancy-increased PTHrP production [27,28]. Incomplete inhibition of bone resorption may be remediated with higher doses or use of stronger bisphosphonates such as IV zoledronic acid, but nephrotoxicity (including acute tubular necrosis) has been reported. Dosing must be adjusted and/or withheld in the setting of renal insufficiency (creatinine clearance <30 mL/min) [16] which is common in advanced cancer patients. Denosumab pharmacodynamics and pharmacokinetics are not affected by renal status, and therefore denosumab does not require dosing adjustment or scheduling based on kidney function. The reported rate of renal AEs in denosumab-treated patients in phase III studies [18,19] was lower than the background rate observed with placebo in a placebo-controlled study of zoledronic acid conducted in patients with metastatic cancer [29].

In recent years, the incidence of HCM has decreased, possibly as a result of increased bisphosphonate use in cancer patients with bone metastases [9]. In advanced cancer patients, long-term bisphosphonate therapy is often interrupted or discontinued to reduce the risk of known side effects and inconvenience to the patients. As a consequence, discontinuation of antiresorptive therapy may inadvertently increase the patient's risk of developing HCM. Risks and complications associated with antiresorptive therapy can be well controlled if guidelines are routinely followed, thereby minimising the number of patients who would need to interrupt or discontinue antiresorptive treatment [30]. The results from this combined study suggest that increased adoption of potent antiresorptive therapy in advanced cancer patients may contribute to the trend in the overall reduction of HCM incidence.

In conclusion, denosumab was more efficacious than zoledronic acid in preventing or delaying HCM in this post-hoc analysis of more than 3800 advanced cancer patients who were at risk for developing HCM.

Conflict of interest statement

I.J. Diel has been a speaker/consultant and received honoraria from Amgen, Novartis, and Roche. J.-J. Body has been a speaker/consultant and received honoraria from Amgen and Novartis. A.T. Stopeck has been a speaker/consultant and received honoraria from Amgen and Novartis. S. Vadhan-Raj has been a speaker/consultant, received honoraria and research funding for Amgen. A. Spencer has no financial disclosures to report. G. Steger has been a speaker/consultant, received honoraria and other remuneration from Amgen, Novartis, Eisai, Roche Austria, Hoffmann-La Roche, and AstraZeneca and has received research funding from Roche Austria. R. von Moos has been a speaker/consultant for Amgen, Novartis, and Hoffmann-La Roche; received honoraria from Amgen and Hoffmann-La Roche; and has received research grants from Amgen and Hoffmann-La Roche. F. Goldwasser has no financial disclosures to report. A. Feng and A. Braun are employed by and have received stocks/stock options from Amgen.

Acknowledgements

Funding was provided by Amgen Inc.

Medical writing assistance was provided by Albert Y. Rhee, an employee of Amgen Inc.

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