Accepted: 5 December 2016

DOI: 10.1111/ecc.12638

ORIGINAL ARTICLE

WILEY European Journal of Cancer Care

# Long-term safety of monthly zoledronic acid therapy beyond 1 year in patients with advanced cancer involving bone (LoTESS): A multicentre prospective phase 4 study

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**Funding information**
This research was supported by Novartis Pharmaceuticals Australia Pty Ltd. Novartis employee-authors were involved in the writing of this manuscript; however, Novartis had no role in the decision to submit this manuscript for publication.

Malignant bone disease can cause significant morbidity. Monthly zoledronic acid (ZOL) reduces skeletal complications; however, limited data are available regarding long-term safety. We aimed to assess efficacy and safety of ZOL beyond 1 year of treatment. We prospectively evaluated 73 patients; breast cancer ($n$ = 29), castrate-resistant prostate cancer ($n$ = 13), multiple myeloma ($n$ = 31) from 2006 to 2008 in 19 cancer centres. All patients were diagnosed with bone disease and had completed 1–2 years of monthly ZOL (4 mg) and received a further 1–2 years of therapy following contemporary guidelines for managing risks of osteonecrosis of the jaw (ONJ) and renal toxicity. Overall rates of skeletal-related events (SREs), renal impairment and ONJ were assessed. Over the additional 1 year of treatment, only 5.5% ($n$ = 4) of patients developed a new SRE. The overall Kaplan–Meier estimate for SRE incidence after 48 weeks on study was 6.75% (95 CI: 2.5–17.3). Although 51% of patients reported serious adverse events, only two cases were suspected as ZOL related. No patients had confirmed ONJ. The observed incidence of new renal impairment was 11% (none due to ZOL). Our study confirms the benefit over risk of continuing monthly ZOL for at least 2 years in patients with advanced cancer involving bone.

**KEYWORDS**
bone metastasis, long-term safety, osteonecrosis of the jaw, renal impairment, zoledronic acid

## 1 | INTRODUCTION

Bone disease associated with different types of cancer can cause a significant burden on patients, often resulting in disability that compromises cancer treatment (Berenson, 2005; Hillner et al., 2003; Morgan et al., 2012). It remains a major challenge for clinicians to control malignant disease, while at the same time offering an effective supportive treatment to reverse, prevent or at least slow the progression of the bone disease or skeletal events associated with different types of cancer (Crawford, McNulty, Kraut, & Turowski, 2009; Hillner et al., 2003; Theriault et al., 1999; Vogel et al., 2004).

An important approach for those patients who have been diagnosed with, or developed bone disease as part of their underlying cancer, is to offer bisphosphonate therapy to alter bone metabolism and

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control bone remoulding and hence, prevent further episodes of bone disease progression (Lacy et al., 2006; Morgan et al., 2012; van Poznak et al., 2011).

Many guidelines and consensus agreements recommend the use of bisphosphonate therapy for patients with bone involvement secondary to their malignant disease (Berenson, 2005; Brantus et al., 2011; Cassinello Espinosa, Gonzalez Del Alba Baamonde, Rivera Herrero, & Holgado Martin, 2012; Kyle et al., 2007; Lacy et al., 2006).

Zoledronic acid (ZOL) is a well-recognised supportive treatment for patients with bone disease associated with haematological malignancies such as multiple myeloma (MM), as well as in non-haematological malignancies such as metastatic breast and prostate cancers (Gnant et al., 2011; Kohno et al., 2005; Morgan et al., 2010; Rosen et al., 2003; Saad et al., 2004).

Zoledronic acid (4 mg) reduces skeletal-related events (SREs) in patients with bone involvement from breast cancer (BrCa), MM or castrate-resistant prostate cancer (CRPC) (Kohno et al., 2005; Rosen et al., 2003; Saad et al., 2004). Regular ZOL treatment has also been shown to prolong survival in MM patients (Morgan et al., 2010). However, patients in pivotal trials in advanced cancer settings were often not treated beyond 1 year (Rosen et al., 2003; Saad et al., 2004), and uncertainties remained over prolonged use of ZOL. Consequently, most treatment guidelines recommend the use of ZOL for at least 1 year with continuation at the physician's discretion (Hillner et al., 2003; Kyle et al., 2007; Lacy et al., 2006; van Poznak et al., 2011). In addition, increases in the incidence of osteonecrosis of the jaw (ONJ) and renal impairment were reported in patients receiving ZOL for time periods longer than 2 years (Bamias et al., 2005; Oh et al., 2007). These concerns prompted some oncologists to cease ZOL therapy after 1 or 2 years, despite the possible benefits in reducing SREs with longer therapy (Lacy et al., 2006).

Since 2003, guidelines have been instituted to reduce the risks of renal impairment and ONJ in patients treated with ZOL (Berenson, 2005; Brantus et al., 2011; Cassinello Espinosa et al., 2012; Hillner et al., 2003; Kyle et al., 2007; Marx, Sawatari, Fortin, & Broumand, 2005). Currently, serum creatinine is monitored for renal function before each dose, with an initial dose reduction from the standard 4 mg based on pre-treatment creatinine clearance, or treatment interruption based on the level of serum creatinine increase during treatment. A dental exam and all invasive procedures should be performed before initiating ZOL treatment, and prophylactic antibiotics are recommended for necessary dental procedures during treatment (Marx et al., 2005). Implementation of these guidelines should allow for the safe use of ZOL beyond 1 or 2 years, without increased risks of ONJ or renal impairment. Furthermore, patients would continue to have a reduced risk of SREs.

### 1.1 | Aims of the study

This prospective, safety, observational, multicentre study was conducted in patients with bone involvement from BrCa, CRPC or MM who had already been treated with ZOL for 12–24 months. Treatment on study would continue every 4 weeks for an extra year. The incidences of ONJ, new renal impairment and SREs in this patient population were determined to guide safe clinical practices in this setting.

## 2 | SUBJECTS AND METHODS

### 2.1 | Patient population

Eligible patients were ≥18 years of age, with a confirmed diagnosis of BrCa, CRPC or MM with bone involvement verified by imaging. All patients had to have received at least 12 months (defined as a minimum of nine doses) of ZOL and could have received up to 24 months (defined as a minimum of 18 doses) of ZOL. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients who received treatment with a bisphosphonate other than ZOL, and had impaired renal function (creatine clearance <30 ml/min), active dental problems (infection of the teeth or jaw, exposed bone, or dental or fixture trauma), recent (<6 weeks) or planned dental/jaw surgeries, a current or prior diagnosis of ONJ, or a history of slow healing after dental procedures were excluded. All patients provided written informed consent before the initiation of any study procedure in accordance with the Declaration of Helsinki, and the study was approved by the Independent Ethics Committee or Institutional Review Board for each Centre.

A total of 19 cancer treatment centres enrolled 73 patients from 2006 to 2008; BrCa ($n$ = 29; 40%), CRPC ($n$ = 13; 18%) and MM ($n$ = 31; 42%) (Table 1). Most patients were Caucasian, and there were a similar number of men and women overall, although all BrCa patients were women, CRPC patients were men, and the majority of patients with MM were men (74%).

### 2.2 | Study design and treatment

This phase 4, multicentre, single-arm study was conducted in Australia. During the study period of 1 year, all patients continued on ZOL 4 mg intravenous infusion every 4 weeks (−7/+14 days) at the discretion of their treating physician. In patients with renal impairment, any adjustments to ZOL dosage made previous to study entry were continued. It was recommended that all patients also be supplemented with daily oral Vitamin D (400 IU) and calcium (500 mg). Patients were managed with the latest guidelines on oral and renal safety for bisphosphonates.

The study number is CZOL446EAU22 and was prospectively registered in the clinicaltrials.gov with the identifier number NCT00434447.

### 2.3 | Study objectives

The objectives of this safety study were to define the incidence of ONJ, new renal impairment, and SREs. In addition, overall safety was monitored. New renal impairment was defined as an increase in serum creatinine levels of greater than 44 μmol/L for patients with baseline creatinine less than 125 μmol/L, or an increase in greater than 88 μmol/L for patients with baseline creatinine greater or equal to

**TABLE 1** Patient demographics and baseline disease characteristics

| Demographic variable | BrCa (*n* = 29) | CRPC (*n* = 13) | MM (*n* = 31) | Overall (*N* = 73) |
|---|---|---|---|---|
| Age, mean years (*SD*) | 57 (9.7) | 71 (9.6) | 61 (10.6) | 61 (11.1) |
| Male sex (%) | 0 | 100 | 74.2 | 49.3 |
| Race (%) | | | | |
| Caucasian | 96.6 | 100 | 100 | 98.6 |
| Indian | 3.4 | 0 | 0 | 1.4 |
| Prior antineoplastic therapy, *n* (%) | | | | |
| Chemotherapy | 25 (86.2) | 10 (76.9) | 24 (77.4) | 59 (80.8) |
| Radiotherapy | 21 (72.4) | 3 (23.1) | 10 (32.3) | 34 (46.6) |
| Surgery | 26 (89.7) | 4 (30.8) | 2 (6.5) | 32 (43.8) |
| Prior skeletal-related event, *n* (%) | | | | |
| 0 | 12 (41.4) | 7 (53.8) | 7 (22.6) | 26 (35.6) |
| 1 | 7 (24.1) | 2 (15.4) | 8 (25.8) | 17 (23.3) |
| 2 | 5 (17.2) | 1 (7.7) | 10 (32.3) | 16 (21.9) |
| 3 | 3 (10.3) | 3 (23.1) | 3 (9.7) | 9 (12.3) |
| 4 | 2 (6.9) | 0 | 0 | 2 (2.7) |
| ≥5 | 0 | 0 | 3 (9.7) | 3 (4.1) |
| Mean creatinine clearance,[a] (mL/min) | 96.8 | 90.8 | 92.3[c] | 93.8 |
| Renal impairment,[b] *n* (%) | 5 (17.2) | 5 (38.5) | 8 (26.7)[c] | 18 (25.0) |

BrCa, breast cancer; CRPC, castrate-resistant prostate cancer; MM, multiple myeloma; *SD*, standard deviation.
[a]Calculated by Cockcroft–Gault formula.
[b]Creatinine clearance <60 ml/min.
[c]One patient had unknown creatinine clearance and renal impairment.

125 μmol/L. SREs were defined as presence of pathologic bone fractures, spinal cord compression, surgery to bone, the need for radiation therapy to bone, hypercalcemia, or change in antineoplastic treatment.

## 2.4 | Study assessments

At each infusion visit, patients had a physical (including oral hygiene) assessment of vital signs, SREs, and performance status (ECOG criteria), and a blood sample for serum creatinine, calcium, magnesium and potassium levels. Every 6 months, patients also had a haematology assessment (erythrocytes, leucocytes, platelets and haemoglobin). Patients had routine assessments for bone disease (yearly bone scans for BrCa and CRPC and a yearly skeletal survey for MM). Suspected or symptomatic SREs were confirmed by imaging (bone scan or X-ray). Disease progression and deaths from all causes were also documented.

Adverse events (AEs) were continuously monitored and graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 3.0. Possible cases of ONJ were defined by exposed bone in the maxillofacial area that occurred either spontaneously or was induced by dental surgery with no evidence of healing for more than 3–6 weeks after appropriate care. The possible ONJ cases did not have to be associated with infection or pain, but must have developed in the absence of prior radiation to the head or neck. A diagnosis of ONJ was considered medically significant (jeopardised the patient or may have required medical or surgical intervention) and was followed as a serious AE.

## 2.5 | Populations analysed

The entry criteria required only that the patients had bone metastatic disease from an indicated setting of BrCa, PCa or MM and that they had already been receiving ZOL for 12 months, hence screen fails *per se* were low.

Based on the available information, all 73 patients were screened and attended the baseline visit. Two patients were deemed as protocol violations due to lack of bone involvement.

Seven (9.6%) of 73 patients had protocol deviations noted, and one patient withdrew consent as they did not wish to receive the full recommended dose of ZOL. Protocol violations included dose change/reduction (*n* = 2), insufficient doses (*n* = 1), screening failure (*n* = 2) lack of bone involvement (*n* = 1) and use of another bisphosphonate (*n* = 1). No patient was excluded from analysis with regard to efficacy (SREs) or ONJ due to protocol deviations. A patient who did not have a baseline serum creatinine value was excluded from analysis with regard to renal impairment, since changes from baseline could not be calculated.

As the trial was an open-label observational study, all 73 (100%) patients were included in the intent to treat and safety populations. All patients attended the screening and baseline visits.

At week 12, 88% of the overall group, and 93%, 85% and 84% for BrCa, CRPC, and MM cancer subgroups, respectively, remained on study medication. The continuation rates for BrCa, CRPC, and MM subgroups were at week 28 (77%, 83%, 62% and 77%), week 44 (66%, 69%, 39% and 74) and end of study (96%, 100%, 69% and 97%) respectively.

### 2.6 | Statistical methods

Descriptive statistics were used for patient demographics and exposure to ZOL. Kaplan–Meier estimates were used for the rate of ONJ, new renal impairment and SREs. The incidence of renal impairment was calculated as the total number of events divided by the total patient-years on study.

## 3 | SAMPLE SIZE CALCULATION

Several hypotheses were developed regarding rates of ONJ and renal impairment in patients receiving ZOL for longer than 12 months. Rate of ONJ was considered to be less than 5%; consistent with the approximately 3% rate estimated at 3 years in patients with BrCa or MM treated with ZOL for up to 2 years (Hoff et al., 2008). Rate of renal impairment was also considered to be less than 5% based on the rates of increases in serum creatinine levels among patients receiving ZOL reported from an open-label study in community centres (Vogel et al., 2004). Rate of SRE incidence was considered to be similar to those observed in the large phase 3 studies (Rosen et al., 2003; Saad et al., 2004).

Assumptions were made for a 25% dropout rate and having a majority of enrolled patients with BrCa or MM. Based on the available data, an estimated 200 patients were necessary to allow for statistical analyses of ONJ, renal impairment, and SREs with 95% confidence intervals (CI). However, because of slow enrolment the study was closed after 73 patients had enrolled.

## 4 | RESULTS

### 4.1 | Patients

At study entry, 25% of patients had some degree of renal impairment (defined as serum creatinine above the institutional upper limit of normal). All patients had a performance status of 0 (51%) or 1 (49%). Mean prior duration of ZOL therapy was 16 (standard deviation [*SD*], 3.5) months, which was similar for all disease types. Most patients (78%) had received at least 12 infusions of ZOL prior to study entry.

Early withdrawal (before completing the additional 1 year of ZOL therapy on study) occurred in 37% (*n* = 27) of patients: BrCa 31% (*n* = 9); CRPC 69% (*n* = 9); MM 29% (*n* = 9). Of these patients, 26% had disease progression, 26% had AEs and 26% had a protocol violation. Six patients (8%) died while on study: disease progression the cause in four patients (2 CRPC, 1 BrCa, and 1 MM), myocardial infarction in one patient with CRPC, and pneumonia in one patient with MM. These deaths were not considered linked to the study drug. In total, 46 (63%) patients completed the study.

### 4.2 | Exposure and safety

The mean number of infusions of ZOL received on study was 9.4 per patient (*SD*, 4.4): 10.5 infusions for each BrCa patient, 6.4 infusions for CRPC and 9.7 infusions for MM. The median overall exposure to ZOL on study was 365 days (95 confidence interval [CI], 302–370 days): 353 days for BrCa, 197 days for CRPC, and 370 days for MM. Treatment compliance with ZOL infusions ranged from 96% at Visit 3 to 73% at Visit 15. Patients with CRPC tended to show lower compliance compared with BrCa and MM.

A total of 60 (82%) patients experienced at least 1 non-serious AE (Table 2). The most common overall AEs (≥5%) were gastrointestinal (55%) and musculoskeletal (52%). However, infections were most common in patients with MM. A total of 37 (51%) patients experienced at least one serious AE (SAE; ≥5%) on study: 45% of BrCa patients; 77% of CRPC patients; and 45% of MM patients (Table 3). Two patients had SAEs considered as possibly related to ZOL by the investigator; a patient with jaw pain (not found to be ONJ) and a patient with periorbital cellulitis. No patient developed symptomatic hypocalcaemia and no patient had confirmed ONJ while on study. The binomial upper 95 CI for incidence of ONJ on study was 4.9%.

The incidence of new renal impairment was 11% (*n* = 6), but with considerable variation among tumour types (13% [*n* = 3] in BrCa, 38% [*n* = 3] in CRPC, and 0% for MM). Because the incidence of new renal impairment was low and patients with renal impairment at baseline improved, the mean and median creatinine clearance values over the course of the study were not affected (Table 4). The overall Kaplan–Meier estimate of new renal impairment at 336 days on study was 16% (95 CI; 8.6–28.7). Among eight patients with rises in serum creatinine judged clinically significant, the maximum creatinine level observed was 212 μmol/L. No cases of renal impairment were suspected to be due to ZOL.

### 4.3 | Efficacy

On study, only 5.5% (*n* = 4) of patients developed at least one new confirmed SRE: one patient with BrCa and three patients with MM (Table 5). Two patients with MM had more than one confirmed SRE during the study; however, no patient had more than three confirmed SREs on study. The overall Kaplan–Meier estimate for SRE incidence at 336 days on study was 6.75% (95 CI; 2.5–17.3). The median time to first on study SRE could not be determined because there were too few events.

### 4.4 | Treatment compliance

Details of the number and timing of doses of ZOL were recorded on the case report form (CRF). Concomitant medications and significant non-drug therapies prior to study start and during the study, were also recorded on the relevant CRF. Compliance was assessed by the investigator and/or study personnel at each visit by recording the number and timing ZOL doses received by each patient and this information was recorded on the CRF. Early termination in the study occurred in 31% of the BrCa, 69% of the HRPC and 29% of the MM groups.

### 4.5 | Concomitant treatments

All medications were coded using a hierarchical coding dictionary (WHO DRUG). The most frequently used concomitant medications included;

**TABLE 2** Non-serious adverse events (≥5%) by system organ class

| | Patients, *n* (%) | | | |
|---|---|---|---|---|
| | BrCa (*n* = 29) | CRPC (*n* = 13) | MM (*n* = 31) | Overall (*n* = 73) |
| Any AE | 26 (89.7) | 13 (100) | 21 (67.7) | 60 (82.2) |
| Blood and lymphatic | 4 (13.8) | 5 (38.5) | 4 (12.9) | 13 (17.8) |
| Gastrointestinal | 18 (62.1) | 10 (76.9) | 12 (38.7) | 40 (54.8) |
| General and administration site | 14 (48.3) | 7 (53.8) | 8 (25.8) | 29 (39.7) |
| Infections/infestations | 11 (37.9) | 6 (46.2) | 14 (45.2) | 31 (42.5) |
| Injury, poisoning, procedural | 3 (10.3) | 0 | 2 (6.5) | 5 (6.8) |
| Metabolism and nutrition | 7 (24,1) | 5 (38.5) | 9 (29.0) | 21 (28.8) |
| Musculoskeletal and connective tissue | 18 (62.1) | 7 (53.8) | 13 (41.9) | 38 (52.1) |
| Neoplasms | 2 (6.9) | 1 (7.7) | 1 (3.2) | 4 (5.5) |
| Nervous system | 13 (44.8) | 3 (23.1) | 11 (35.5) | 27 (37.0) |
| Psychiatric | 4 (13.8) | 4 (30.8) | 5 (16.1) | 13 (17.8) |
| Renal and urinary | 3 (10.3) | 2 (15.4) | 3 (9.7) | 8 (11.0) |
| Respiratory, thoracic, and mediastinal | 9 (31.0) | 2 (15.4) | 5 (16.1) | 16 (21.9) |
| Skeletal related | 8 (27.6) | 2 (15.4) | 2 (6.5) | 12 (16.4) |
| Skin and subcutaneous tissue | 8 (27.6) | 2 (15.4) | 5 (16.1) | 15 (20.5) |
| Vascular | 6 (20.7) | 1 (7.7) | 2 (6.50 | 9 (12.3) |

AE, adverse event; BrCa, breast cancer; CRPC, castrate-resistant prostate cancer; MM, multiple myeloma.

**TABLE 3** Serious adverse events (≥5%) by system organ class

| | Patients, *n* (%) | | | |
|---|---|---|---|---|
| | BrCa (*n* = 29) | CRPC (*n* = 13) | MM (*n* = 31) | Overall (*n* = 73) |
| Any SAE | 13 (44.8) | 10 (76.9) | 14 (45.2) | 37 (50.7) |
| Blood and lymphatic | 2 (6.9) | 1 (7.7) | 1 (3.2) | 4 (5.5) |
| Gastrointestinal | 2 (6.9) | 0 | 2 (6.5) | 4 (5.5) |
| General and administration site | 0 | 3 (23.1) | 4 (12.9) | 7 (9.6) |
| Infections/infestations | 4 (13.8) | 3 (23.1) | 8 (25.8) | 15 (20.5) |
| Pneumonia | 0 | 1 (7.7) | 4 (12.9) | 5 (6.8) |
| Metabolism and nutrition | 1 (3.4) | 2 (15.4) | 3 (9.7) | 6 (8.2) |
| Musculoskeletal and connective tissue | 6 (20.7) | 1 (7.7) | 4 (12.9) | 11 (15.1) |
| Nervous system | 2 (6.9) | 1 (7.7) | 1 (3.2) | 4 (5.5) |

BrCa, breast cancer; CRPC, castrate-resistant prostate cancer; MM, multiple myeloma; SAE, serious adverse event.

pain medications such as paracetamol, acetylsalicylic acid, oxycodone hydrochloride, steroids such as dexamethasone; antiemetics such as metoclopramide hydrochloride; and finally laxative therapy with coloxyl.

## 5 | DISCUSSION

Several guidelines have incorporated bisphosphonate treatment for patients with cancer associated with bone disease, until there is either a significant decline in their performance status or where no discontinuation criteria has been provided (Hillner et al., 2003; Kyle et al., 2007; Lacy et al., 2006; van Poznak et al., 2011). However, the majority of bisphosphonate studies only evaluated treatment for 2 years or less, with approximately 11%–36% of patients completing the studies and considered eligible for further treatment (Morgan et al., 2010; Rosen et al., 2003; Saad et al., 2004; Theriault et al., 1999). Few prospective and retrospective studies have reported on the efficacy and safety of bisphosphonate treatment beyond 2 years (Crawford et al.,

**TABLE 4** Assessment of renal function on study[a]

| | BrCa (*n* = 29) | CRPC (*n* = 13) | MM (*n* = 31) | Overall (*n* = 73) |
|---|---|---|---|---|
| Day 28 | | | | |
| Creatinine clearance (ml/min) | | | | |
| Mean (*SD*) | 97.4 (30.62) | 88.8 (53.45) | 95.3 (51.64) | 95.0 (44.06) |
| Median (range) | 98.4 (50.9–167.0) | 60.8 (36.1–188.0) | 82.3 (39.1–252.0) | 86.6 (36.1–252.0) |
| Renal impairment, *n* (%) | 4 (14.3) | 6 (50.0) | 7 (24.1) | 17 (24.6) |
| Day 56 | | | | |
| Creatinine clearance (ml/min) | | | | |
| Mean (*SD*) | 91.5 (27.61) | 86.6 (48.41) | 92.8 (39.16) | 91.2 (36.05) |
| Median (range) | 94.9 (41.7–131.0) | 78.8 (35.3–174.0) | 86.5 (38.5–199.0) | 88.2 (35.3–199.0) |
| Renal impairment, *n* (%) | 5 (18.5) | 5 (45.5) | 5 (19.2) | 15 (23.4) |
| Day 84 | | | | |
| Creatinine clearance (ml/min) | | | | |
| Mean (*SD*) | 90.9 (28.27) | 98.8 (64.01) | 95.0 (47.34) | 93.7 (42.4) |
| Median (range) | 96.4 (32.7–149.0) | 100.8 (39.8–241.0) | 95.2 (31.7–252.0) | 95.8 (31.7–252.0) |
| Renal impairment, *n* (%) | 5 (19.2) | 4 (44.4) | 5 (21.7) | 14 (24.1) |
| Day 112 | | | | |
| Creatinine clearance (ml/min) | | | | |
| Mean (*SD*) | 95.6 (27.21) | 101.4 (61.06) | 96.2 (45.6) | 96.6 (40.2) |
| Median (range) | 104.1 (39.5–141.0) | 87.7 (41.9–192.0) | 92.3 (37.1–239.0) | 96.6 (37.1–239.0) |
| Renal impairment, *n* (%) | 3 (12.0) | 3 (42.9) | 5 (20.0) | 11 (19.3) |
| Day 140 | | | | |
| Creatinine clearance (ml/min) | | | | |
| Mean (*SD*) | 97.7 (31.59) | 95.2 (68.48) | 93.69 (40.78) | 95.6 (41.23) |
| Median (range) | 105.6 (39.9–154.0) | 74.1 (38.4–246.0) | 92.3 (29.2–191.0) | 94.2 (29.2–246.0) |
| Renal impairment, *n* (%) | 4 (16.0) | 4 (50.0) | 7 (28.0) | 15 (25.9) |
| Day 196 | | | | |
| Creatinine clearance (ml/min) | | | | |
| Mean (*SD*) | 95.6 (30.89) | 118.1 (74.51) | 98.7 (40.14) | 100.2 (43.00) |
| Median (range) | 103.0 (30.6–141.0) | 120.7 (31.3–241.0) | 88.8 (30.7–173.0) | 100.4 (30.6–241.0) |
| Renal impairment, *n* (%) | 3 (12.5) | 3 (37.5) | 3 (14.3) | 9 (17.0) |
| Day 224 | | | | |
| Creatinine clearance (ml/min) | | | | |
| Mean (*SD*) | 96.0 (29.07) | 106.3 (70.67) | 95.7 (44.21) | 97.0 (41.14) |
| Median (range) | 99.2 (39.2–141.0) | 94.1 (46.2–235.0) | 97.3 (33.4–207.0) | 97.3 (33.4–235.0) |
| Renal impairment, *n* (%) | 3 (12.5) | 2 (33.3) | 6 (26.1) | 11 (20.8) |
| Day 252 | | | | |
| Creatinine clearance (ml/min) | | | | |
| Mean (*SD*) | 94.6 (32.33) | 106.7 (57.15) | 102.6 (43.39) | 99.5 (39.99) |
| Median (range) | 96.6 (39.2–163.0) | 114.0 (41.5–176.0) | 101.1 (34.5–214.0) | 97.8 (34.5–214.0) |
| Renal impairment, *n* (%) | 4 (17.4) | 2 (33.3) | 3 (13.6) | 9 (17.6) |
| Day 280 | | | | |
| Creatinine clearance (ml/min) | | | | |
| Mean (*SD*) | 103.8 (29.02) | 124.5 (77.07) | 104.1 (46.92) | 106.1 (43.71) |
| Median (range) | 109.5 (48.4–149.0) | 113.4 (44.2–252.0) | 90.8 (33.0–227.0) | 105.5 (33.0–252.0) |
| Renal impairment, *n* (%) | 2 (10.0) | 1 (20.0) | 5 (22.7) | 8 (17.0) |

BrCa, breast cancer; CRPC, castrate-resistant prostate cancer; MM, multiple myeloma; SD, standard deviation.
[a]Creatinine clearance was calculated by Cockcroft–Gault formula, and renal impairment was defined by creatinine clearance <60 ml/min.

**TABLE 5** Incidence of confirmed new SREs on study

| Number of SRE events | Patients, *n* (%) | | | |
|---|---|---|---|---|
| | BrCa (*n* = 29) | CRPC (*n* = 13) | MM (*n* = 31) | Overall (*n* = 73) |
| 1 | 1 (3.4) | 0 | 1 (3.2) | 2 (2.7) |
| 2 | 0 | 0 | 1 (3.2) | 1 (1.4) |
| 3 | 0 | 0 | 1 (3.2) | 1 (1.4) |

BrCa, breast cancer; CRPC, castrate-resistant prostate cancer; MM, multiple myeloma; SRE, skeletal-related event.

2009; Dearnaley, Mason, Parmar, Sanders, & Sydes, 2009; Gnant et al., 2011; La Verde et al., 2008; Morgan et al., 2012). This small, prospective, observational study helps to confirm the safety and ongoing efficacy of monthly treatment with ZOL for 2–3 years in patients with malignant disease involving bone, in the era of new safety guidelines.

In recent years, it has become clear that a small percentage of patients being treated with ZOL may develop ONJ, but this was not formally documented when the study was conceived.

At that time, concerns had been expressed that up to 30% of patients receiving ZOL for more than 1 year would develop ONJ, based initially, on an internet survey of myeloma patients. As a consequence, several institutions either stopped ZOL therapy for (particularly) myeloma patients, or limited its duration to 1 year out of concern that longer therapy might be associated with a relatively high risk of ONJ (Durie, Katz, & Crowley, 2005). Furthermore, at the time of analysis, there was no data available pertaining to extending the use of ZOL beyond 1 year. Therefore, this study was conceived to document more precisely the rate of ONJ in patients receiving ZOL for more than 1 year. The relatively small study size was ample to verify if ONJ occurred in 10%–30% of patients, as had been suggested. Certainly, the results of our study showed a much lower incidence of ONJ than was previously anticipated.

In this study, no cases of ONJ were reported in patients managed according to contemporary guidelines; the 95% upper CI estimate for ONJ incidence was <5%. These results are consistent with the low incidence of ONJ in patients continuing with monthly ZOL in recent long-term studies (≤5%) and in studies implementing the new safety guidelines (≤6.7%) (Dimopoulos et al., 2009; Gnant et al., 2011; Morgan et al., 2012; Ripamonti et al., 2009). Among patients with MM who received ZOL treatment before preventive dental measures, in one study (*n* = 38), the incidence of ONJ (albeit not adjudicated) was 26% (Dimopoulos et al., 2009). Thus, prevention of ONJ during bisphosphonate treatment appears effective with these guidelines.

Patients on ZOL therapy also require regular renal monitoring. While the Kaplan–Meier estimate of incidence of new renal impairment in this study was 16% during the additional 12 months, this complication was mild to moderate in all affected patients and may not have been due to ZOL. Compared with the large bisphosphonate studies, which had renal AE rates of 2.3% in CRPC (*N* = 643) to 10.7% in BrCa and MM (*N* = 1,648) (Rosen et al., 2003; Saad et al., 2002), the renal AE incidence rate of 11% in this study with primarily BrCa and MM patients was reasonable. However, in other long-term studies, the incidence of renal effects ranged from none in patients with BrCa (*N* = 1,803) to 7% in patients with MM experiencing acute renal failure (*N* = 1,960) (Gnant et al., 2011; Morgan et al., 2012). Differing patient baseline characteristics and definitions for renal endpoints may account for the wide variations reported for renal impairment. Nevertheless, the results from this study showed no increasing renal toxicities with long-term ZOL treatment.

Efficacy of ZOL treatment in this study was determined by the event rate of SREs, which was <7% by Kaplan–Meier estimate. However, it should be noted that assessments of bone disease beyond the yearly scan or survey were at the discretion of the treating physician and the event rate of SREs was low. Hence, the strength of ZOL efficacy may be diluted. In other long-term studies, SRE rates were not an endpoint; therefore, there is no basis for a comparison of continuing efficacy (Dearnaley et al., 2009; Gnant et al., 2011; Morgan et al., 2012). In the large bisphosphonate study in patients with BrCa and MM evaluating treatment for the first 2 years, the SRE rates were approximately 1 event per year for ZOL in the overall population and in patients with BrCa (Rosen et al., 2003). In patients with CRPC receiving ZOL, the SRE rate was 0.8 per year (Saad et al., 2004). Thus, the event rate in this study is consistent with an ongoing benefit of ZOL in reducing SREs in this high-risk population.

Although our study had a small number of patients, it is worth noting that there is a lack of data regarding long-term safety of ZOL in this cohort of patients. Furthermore, our study was prospectively designed and conducted at multiple centres to ensure the diversity and quality of the source of data. The patient population constitutes a sample of patients relevant to clinical practice, in that a decision needs to be made at 2 years whether to continue bisphosphonate treatment. This decision is based, in part, on balancing the risks of renal and dental AEs, with the expected benefits. Nonetheless, we acknowledge some limitations of our study, inherent with the observational nature of the trial and the relatively small number of patients. In addition, physician discretion governed further assessments of bone disease that possibly may or may not add some bias to the results.

In conclusion, this prospective multicentre study helps to confirm the benefit over risk of continuing monthly ZOL for 2–3 years in patients with advanced cancer involving bone, managed according to ONJ and renal safety guidelines.

## ACKNOWLEDGMENTS

We acknowledge the contribution of the following LoTESS study investigators and their patients: Dr K. Briscoe (North Coast Cancer

Institute, QLD Australia), Dr L. Catley (Mater Hospital, Brisbane, QLD, Australia), Dr J. Chirgwin (Box Hill Hospital & Maroondah Breast Hospital, VIC, Australia), Dr P. Craft (Canberra Hospital, ACT, Australia), Dr M. Frydenberg (Monash Medical Centre, Melbourne, VIC, Australia), Dr K. Hamilton (Ballarat Hospital, VIC, Australia), Dr J. Hill (Wagga Wagga Hospital, NSW, Australia), Dr I. Irving (Townsville Hospital, QLD, Australia), Prof R. Lowenthal (Royal Hobart Hospital, TAS, Australia), Dr A. Sullivan (Concord Repatriation Hospital, NSW, Australia), Dr J. Thompson (Frankston Hospital, VIC, Australia), Dr A-M. Watson (Liverpool Hospital, NSW, Australia), Dr N. Woodward (Princess Alexandra Hospital, QLD, Australia). We gratefully acknowledge the contribution of Dr Kevin Lynch, Ms Gillian Ryan and Dr Annie Solterbeck (Statistical Revelations). We thank the participating patients, their families, research coordinators, and nurses; and Tamalette Loh (ProEd Communications, Inc.®) for providing editorial assistance with a previous version of the manuscript.

## CONFLICTS OF INTEREST

Prof Khalafallah, Prof Abdi and Drs Slancar, Cosolo, and Chern report no conflicts of interest. Dr Woodfield is an employee of Novartis Oncology, and Dr Copeman is a consultant to Novartis Oncology.

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**How to cite this article:** Khalafallah AA, Slancar M, Cosolo W, et al. Long-term safety of monthly zoledronic acid therapy beyond 1 year in patients with advanced cancer involving bone (LoTESS): A multicentre prospective phase 4 study. *European Journal of Cancer Care*. 2017;00:e12638. doi:10.1111/ecc.12638