

# Results From a Fifteen-Year Postmarketing Drug Safety Surveillance Study of Adult Osteosarcoma and Teriparatide in the US

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## ABSTRACT

**Background:** This study was initiated in 2003 at Forteo's time of approval in the United States (US) to monitor for a potential association between teriparatide (an osteoporosis treatment) and osteosarcoma, which occurs in the US in adults aged 40 years or older at a background incidence rate of approximately 2.5 cases per million per year.

**Objective:** To provide final study results, including descriptive characteristics of patients with osteosarcoma aged 40 years or older.

**Methods:** All state cancer registries, plus targeted regional and comprehensive cancer registries in the US, were invited to participate in this patient-contact study. Incident cases of osteosarcoma diagnosed between January 1, 2003, and December 31, 2016, identified through cancer registries were reported to RTI once all requirements for releasing patient-identifying information were met. Exposure to teriparatide was ascertained during telephone interview. Information about demographics, medication use prior to osteosarcoma diagnosis, and other possible risk factors for osteosarcoma were ascertained. Requirements necessary for contacting patients (patient access pathways) varied among cancer registries from passive notification to active permission from the patient and/or physician.

**Results:** As of September 30, 2018, 3,809 incident cases of osteosarcoma in patients aged 40 years or older were identified by 30 cancer registries. After cancer registries completed individual requirements to release contact information, 2,545 patients were available to be interviewed. Of these, interviews were completed for 1,165 patients (46%). The mean age at the time of diagnosis was 61 years of age, and more than half were men (53%). The most common ICD-O-3 morphology codes were for osteosarcoma not otherwise specified (NOS) (71%) and chondroblastic osteosarcoma (13%). Of those interviewed, 3 patients reported use of teriparatide prior to diagnosis of osteosarcoma, which is within the expected range assuming no increased risk with treatment.

**Conclusions:** Drug safety surveillance studies that involve both a rare drug exposure and a rare cancer outcome require participation by many cancer registries. Results from this study indicate that, while resource-intensive, patient-contact studies with multiple cancer registries are feasible. Data from this study contributed to evidence about the long-term safety of teriparatide that is valuable to patients and physicians considering treatment with this product.

## METHODS

Incident cases of osteosarcoma (12 ICD-O-3 codes; no restriction on primary site of tumor) diagnosed from 2003 to 2016 were identified through participating cancer registries in the US. Data collection concluded in September 2018, and all interviews were completed by December 31, 2018.

Various registry requirements had to be met before RTI could contact patients ("patient access pathways") regarding the interview.

- Study "notification," whether for the physician or patient, was considered a passive process in which RTI could contact the patient if refusal was not received.
- "Release" was considered an active process in which the physician or patient was required to provide permission before RTI could contact the patient.

The interview rate for each category of patient access pathway is defined as the number of patients interviewed by RTI divided by the number of osteosarcoma cases identified by the registries for each patient access pathway category. Table 1 shows the interview rate by patient access pathway from the least restrictive (green) to the most restrictive (red).

After receipt of consent, case information (including demographics, treatment with medications, and exposure to possible risk factors) was ascertained from the patient or proxy via a 25- to 30-minute telephone interview.

### Data Collected From Cancer Registries

- Patient demographics: age, sex, race, and vital status
- Cancer information: date of diagnosis, cancer site, and morphology

### Data Collected From Patient (or Proxy) by Telephone Interview

- Drug exposure: prior use of teriparatide and other medications for osteoporosis
- Lifestyle exposures: alcohol and tobacco use
- Potential risk factors for osteosarcoma:
  - Exposure to radiation
  - History of Paget disease of bone
  - History of other cancers
  - Injury or infection at the tumor site
  - Agricultural or occupational pesticide exposure
  - Petrochemical exposure
  - Family history of osteosarcoma

## RESULTS

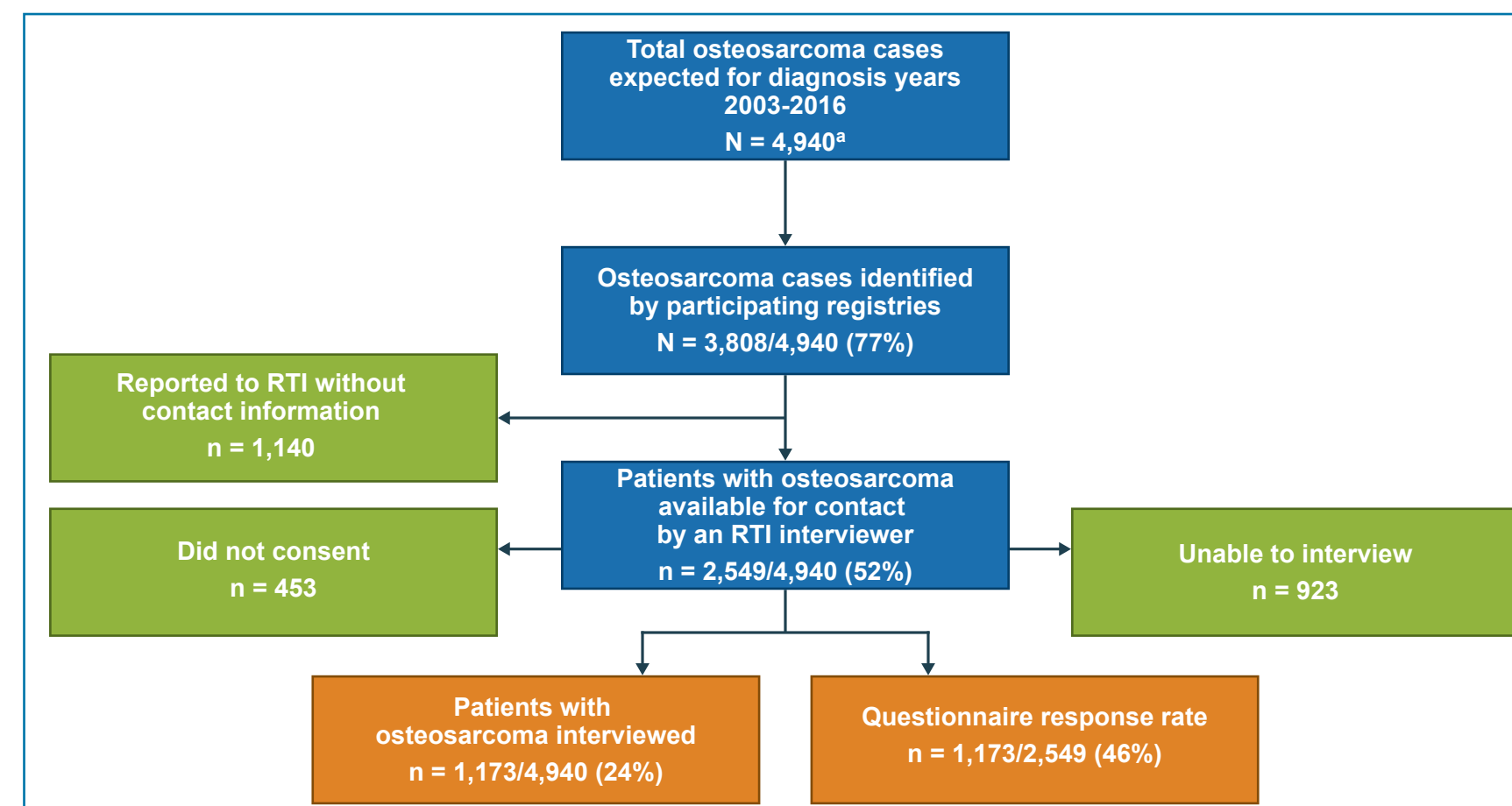
As of December 31, 2018, 3,808 incident cases of osteosarcoma diagnosed from 2003 to 2016 in patients aged 40 years or older had been identified by 30 participating cancer registries (Figure 1).

- 2,549 of these patients were reported to RTI with contact information and had met all requirements to allow RTI to contact them.

As of December 31, 2018, interviews were completed with 1,173 patients or their proxies (Figure 2) for a questionnaire response rate of 46% and a study interview rate of 24%.

Three reports of teriparatide use prior to diagnosis were identified.

Figure 2. Study Accrual for Patients Diagnosed From 2003 to 2016



\* Estimated using the Surveillance, Epidemiology, and End Results rate of osteosarcoma of 2.5 per million population per year<sup>3</sup> applied to Annual Estimates of the Resident Population by Age and Sex for States from 2003 to 2016.<sup>4</sup>

Table 1. Interview Rate by Patient Access Pathway

Patient Access Pathway	Number of Registries	Interview Rate <sup>a</sup>
Physician and/or patient notification	8	36%
Patient release	8	30%
Physician notification and patient release	10	28%
Physician release and patient notification	4	20%

<sup>a</sup>Interview rate defined as # interviewed by RTI / # identified by registries.

Table 2. Self-Reported Prevalence of Exposures (and Characteristics) Among Interviewed Patients and Proxies (N = 1,173)

Exposure/Characteristic	n (%)
<b>Lifestyle exposures</b>	
Drank alcohol during 12 months before diagnosis	763 (63%)
Smoked ≥ 100 cigarettes in their lifetime	577 (49%)
<b>Treatment, injury, and infection exposures</b>	
Previous injury or infection at tumor site	181 (15%)
Prior radiation treatment	226 (19%)
<b>Environmental exposures</b>	
Agricultural pesticide exposure	246 (24%)
Occupational petrochemical exposure	121 (12%)
Occupational radiation exposure	72 (7%)
<b>Personal and family history</b>	
Personal history of other cancers	314 (27%)
Family history of osteosarcoma	52 (4%)
Personal history of Paget disease of bone	46 (4%)

Table 3. Distribution of Morphology Among Interviewed Cases (N = 1,173)

Morphology	n (%)
9180 Osteosarcoma NOS	832 (71%)
9181 Chondroblastic osteosarcoma	148 (13%)
9182 Fibroblastic osteosarcoma	77 (7%)
9192 Parosteal osteosarcoma	34 (3%)
9186 Central osteosarcoma	25 (2%)
9183 Telangiectatic osteosarcoma	21 (2%)
9184 Osteosarcoma in Paget disease	16 (1%)
9185 Small cell osteosarcoma	8 (1%)
9193 Periosteal osteosarcoma	7 (1%)
9194 High-grade surface osteosarcoma	3 (< 1%)
9187 Intraosseous well-differentiated osteosarcoma	2 (< 1%)
9195 Intracortical osteosarcoma	0 (0%)

Figure 4. Osteosarcoma Site For Interviewed Patients (N = 1,173) as of December 31, 2018

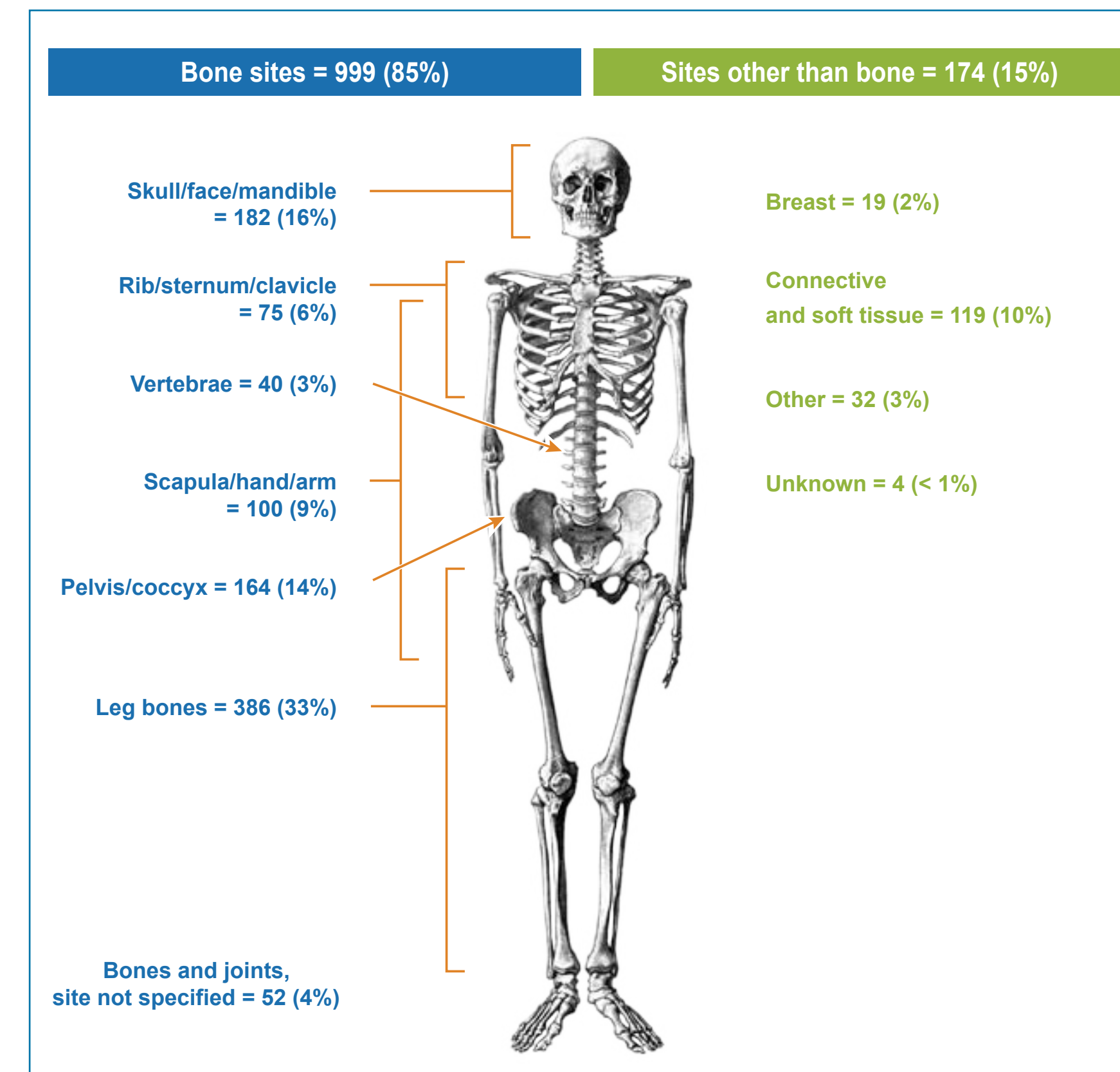
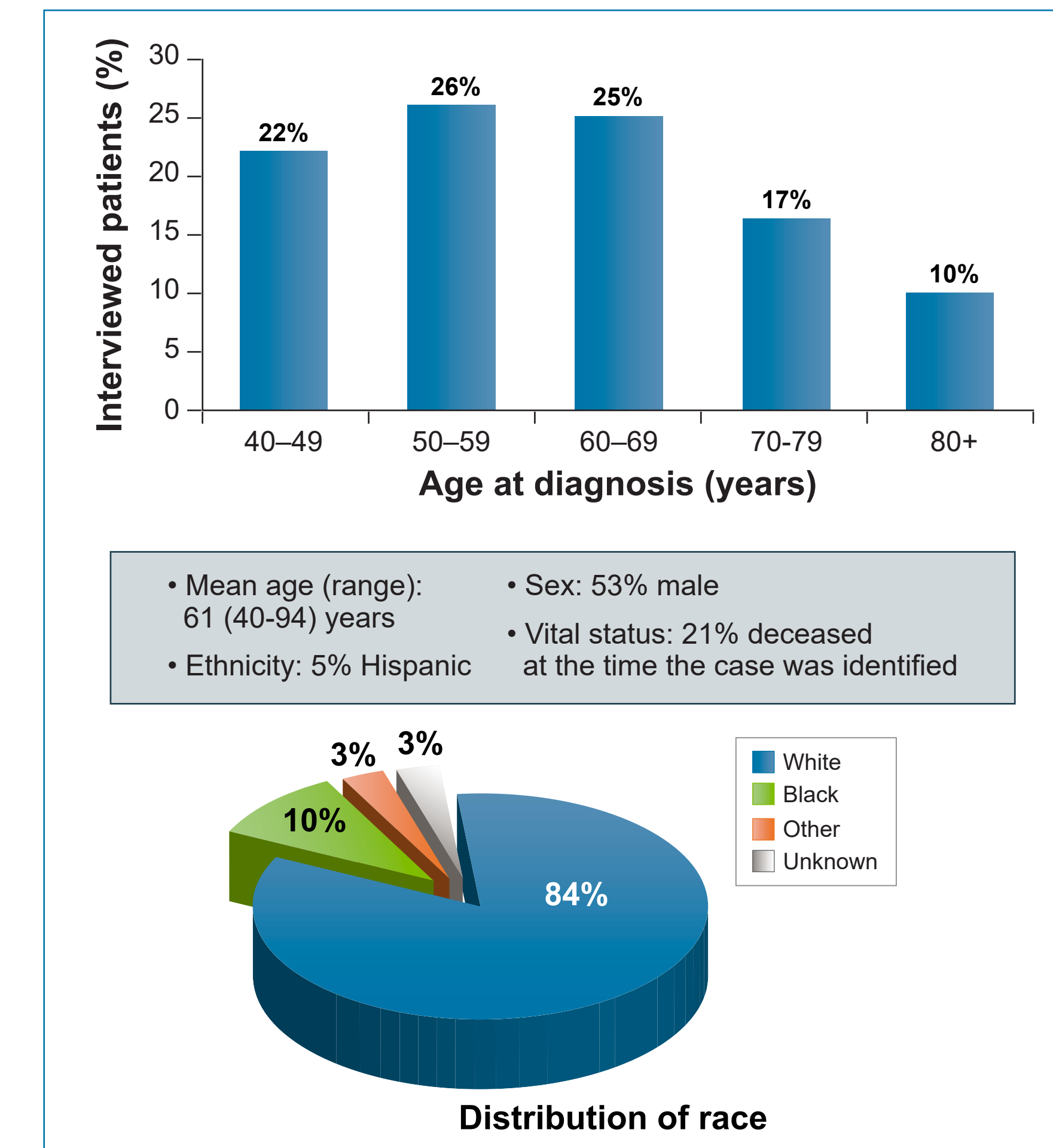


Figure 3. Demographic Characteristics of Adult Patients With Osteosarcoma Interviewed for the US Adult Osteosarcoma Surveillance Study (N = 1,173)



## DISCUSSION AND CONCLUSIONS

- Of those interviewed, 3 patients reported use of teriparatide prior to diagnosis of osteosarcoma, which is within the expected range assuming no increased risk with treatment.
- Drug safety surveillance studies that involve both a rare drug exposure and a rare cancer outcome require participation by many cancer registries.
- Results from this study indicate that, while resource intensive, patient contact studies with multiple cancer registries are feasible.

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## BACKGROUND

Teriparatide is a recombinant human parathyroid hormone analog (PTH 1-34)

- Approved in 2002 (with expanded indication in 2009) in the US for patients at high risk for fracture:
  - To treat postmenopausal women with osteoporosis
  - To increase bone mass in men with primary or hypogonadal osteoporosis
  - To treat men and women with glucocorticoid-induced osteoporosis

In preclinical studies in rats, teriparatide caused a dose-dependent increase in the incidence of osteosarcoma.

Osteosarcoma is a rare bone cancer in humans, with an estimated background incidence in adults aged 40 years and older of 2.5 cases per million population per year.<sup>1</sup> Standardized to the age-sex distribution of patients receiving teriparatide,<sup>2</sup> the estimated incidence rate of osteosarcoma is 3.2 cases per million per year.

As a condition of approval, the US Food and Drug Administration requested that the Forteo Post-Approval Surveillance Study: Case Series ("Osteosarcoma Surveillance Study") be conducted. The study was a 15-year surveillance study initiated in 2003. Data collection and patient interviews concluded in 2018.<sup>3,4</sup>

## OSTEOSARCOMA SURVEILLANCE STUDY

A surveillance study initiated in 2003 to monitor for a signal of a possible association between teriparatide, an injectable treatment for osteoporosis, and adult osteosarcoma.

Primary objectives: (1) to identify incident cases of osteosarcoma, if any, with a history of treatment with teriparatide, and (2) to identify and interview 33% of adults aged 40 years and older with a newly diagnosed cases of osteosarcoma in the US.

Secondary objective: To systematically collect additional patient information, including demographics and data related to other risk factors for osteosarcoma, for descriptive epidemiology purposes.

## OBJECTIVE

To provide final study results, including descriptive characteristics of patients with osteosarcoma aged 40 years or older.

Figure 1. Participating US Registries and Residence of Patients Identified in the Osteosarcoma Surveillance Study as of December 31, 2018 (n = 3,808)

