**Summary Table of Study Protocol**

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|---|---|
| **Title** | Incidence of new Primary Malignancies Among Patients With Bone Metastases From Breast, Prostate, or Lung Cancer Treated With XGEVA or Intravenous Zoledronic Acid: a Retrospective Cohort Study |
| **Protocol version identifier** | 20170728 |
| **Date of last version of the protocol** | 05 April 2018 |
| **EU Post Authorisation Study (PAS) Register No** | <<*Insert Number*>> |
| **Active Substance** | N/A |
| **Medicinal Product** | XGEVA |
| **Product Reference** | N/A |
| **Procedure Number** | N/A |
| **Joint PASS** | No |
| **Research Question and Objectives** | The purpose of this study is to estimate the incidence of any new primary malignancy ( any haematologic or non-haematologic tumour, excluding non-melanoma skin cancer subsequent to the first primary malignancy) among patients with breast, prostate, or lung cancer and bone metastases following initiation of either XGEVA or zoledronic acid, and to describe the types of new primary malignancies that patients experience, as well as the characteristics of the patients who develop new primary malignancies.<br><br>The primary objective of this study is to estimate overall and by primary cancer site, the incidence rate and cumulative incidence proportion (for up to 4 years) of new primary maligancies among patients with solid tumours and bone metastases who were 1) newly treated with XGEVA (XGEVA exposure cohort), or 2) newly treated with zoledronic acid (zoledronic acid exposure cohort).<br><br>The secondary objectives, focused on each of the aforementioned exposure cohorts, will describe the demographic, clinical, and treatment characteristics of patients at XGEVA or zoledronic acid treatment initiation, and by NPM status, to estimate the time from first primary malignancy diagnosis to new primary malignancy diagnosis, and to describe the types of new primary malignancies patients experience. |

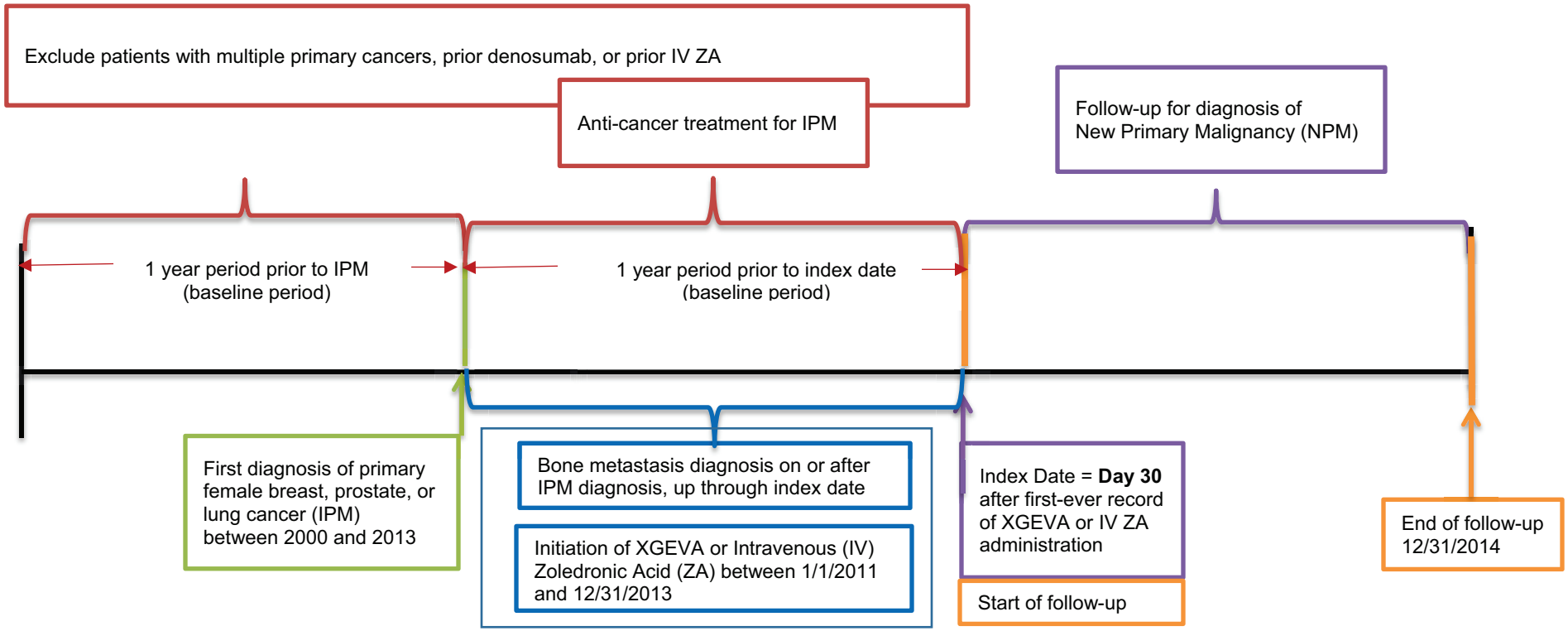
| | |
|---|---|
| **Country of Study** | United States |
| **Author** | PPD MHS, PhD<br>Outcomes Insights, Inc.<br>2801 Townsgate Road, Suite 330<br>Westlake Village, CA 91361<br>Tel : PPD<br>Email : PPD |

**Marketing Authorization Holder**

| | |
|---|---|
| **Marketing authorization holder(s)** | Amgen, Inc. |
| **MAH Contact** | PPD, PhD<br>Center for Observational Research, Amgen, Inc.<br>One Amgen Center Drive, MS 24-2-A<br>Thousand Oaks, CA 91320<br>Tel: PPD<br>Email: PPD<br><br>PPD, MBBS, MPH<br>Centre for Observational Research, Amgen Ltd.<br>1 Uxbridge Business Park, Sanderson Road;<br>Uxbridge UB8 1DH; England<br>Tel: PPD<br>Email: PPD |

## Confidentiality Notice

## Study Design Schematic




Patients who initiate therapy with XGEVA or IV ZA between 1/1/2011 and 12/31/2013 (inclusive), with no prior use of either agent, will be identified.
Patients will be required to have a first record of diagnosis of primary female breast, prostate, or lung cancer prior to XGEVA or IV ZA treatment initiation, and also to have a record of bone metastasis diagnosis on or after IPM, up through 30 days after treatment initiation (index date).
Patients with multiple primary cancers (including non-melanoma skin cancer, hematological malignancy) before index date will be excluded from the study.
Patients will be followed from index date through first occurrence of NPM, loss of Part B coverage, initiation of enrollment in Medicare Health Maintenance Organization, (HMO), death, or end of follow up (December 31, 2014).

## 1. Table of Contents

## List of Tables

## 2. List of Abbreviations

| Term | Definition |
|---|---|
| AJCC | American Joint Committee on Cancer |
| BM | Bone metastasis |
| CMS | Centers for Medicare and Medicaid Services |
| CI | Confidence interval |
| EMA | European Medicines Agency |
| EU | European Union |
| EUROCARE | European Cancer Registry based Study on Survival and Care of Cancer Patients |
| EAIR | Exposure-adjusted incidence rate |
| HMO | Health maintenance organization |
| IACR | International Association of Cancer Registries |
| IARC | International Agency for Research on Cancer |
| ICD | International Classification of Disease |
| IPM | Index primary malignancy |
| IV | Intravenous |
| MedPAR | Medicare Provider Analysis and Review |
| NCI | National Cancer Institute |
| NPM | New primary malignancy |
| PEDSF | Patient Entitlement and Diagnosis Summary File |
| RANKL | Receptor activator of nuclear factor kappa-B ligand |
| SEER | Surveillance, Epidemiology, and End Results |
| ST | Solid tumour |
| SRE | Skeletal-related event |
| TNM | Tumour, node and metastasis |
| ZA | Zoledronic acid |

## 3. Responsible Parties

Key Sponsor Contact

PPD PhD
Center for Observational Research, Amgen, Inc.
One Amgen Center Drive, MS 24-2-A
Thousand Oaks, CA 91320
Tel: PPD
Email: PPD

PPD MBBS, MPH
Center for Observational Research, Amgen Ltd.
1 Uxbridge Business Park, Sanderson Road;
Uxbridge UB8 1DH; England
Tel: PPD
Email: PPD

External Collaborators

PPD, MHS, PhD
Outcomes Insights, Inc.
2801 Townsgate Road, Suite 330
Westlake Village, CA 91361
Tel : PPD
Email : PPD

## 4. Abstract

- Study Title

  Incidence of new primary malignancies among patients with bone metastases from breast, prostate, or lung cancer treated with XGEVA or intravenous zoledronic acid: a retrospective cohort study

- Study Background and Rationale

  Patients with cancer are at increased susceptibility of developing a new primary malignancy (NPM) compared to the general population. This study will characterize the incidence and types of NPM experienced by patients treated with either XGEVA or intravenous zoledronic acid (ZA), as well as describe characteristics of patients who develop NPM.

- Research Question and Objective(s)
  - Primary Objective:

    To estimate, overall and by primary malignancy site, the incidence rate and cumulative incidence proportion (for up to 4 years) of any subsequent NPM (any haematologic or non-haematologic tumours, excluding non-melanoma skin cancer subsequent to the first primary malignancy) among patients with breast, prostate, or lung cancer and bone metastases (BM) who were newly treated with either XGEVA or intravenous (ZA

  - Secondary Objectives:

    Overall, and for each index primary malignancy (breast, prostate, lung),

    - To describe the type and sequence of anti-cancer treatment (including surgery, radiotherapy, chemotherapy) for the index primary malignancy (IPM) prior to initiation of XGEVA or ZA;
    - To describe the baseline characteristics and medications (including radiotherapy, chemotherapy, and other systemic agents) of patients at the time of XGEVA or ZA initiation;
    - To estimate the time from index primary malignancy diagnosis to NPM diagnosis in XGEVA- or ZA-treated patients;
    - To describe the types of NPM (hematologic malignancy; solid tumours; cutaneous malignancies; others) XGEVA- or ZA-treated patients experience; and
    - To describe the characteristics of patients by NPM status (no NPM or NPM during the follow-up period) within each exposure cohort.
  - Hypothesis/Estimation:
    This is an estimation study. No statistical hypothesis testing will be conducted.

- Study Design/Type

Retrospective cohort study of patients initiating therapy with either XGEVA or ZA between January 1, 2011 and December 31, 2013.

- Study Population or Data Resource

The study population will include patients diagnosed with breast, prostate, or lung cancer, and bone metastases who are newly treated with either XGEVA or ZA in the United States (U.S.). CCI [redacted]

All cancer patients with breast, prostate, or lung tumours and bone metastases initiating either XGEVA or ZA during the period that extends from January 1, 2011 through December 31, 2013 will be included in the cohort for analysis. Within each cohort, the index date will be 30 days after the first administration of XGEVA or ZA to allow for the identification of a bone metastasis diagnosis code within 30 days after treatment initiation.

- Summary of Patient Eligibility Criteria
  - New initiators of XGEVA or ZA
  - A diagnosis of a first, primary cancer, identified as a primary site code of female breast, prostate, or lung cancer (index primary malignancy, IPM) between 2000 and 2013
  - A diagnosis of bone metastasis, identified as a diagnosis code for secondary malignant neoplasm of bone or bone marrow (International Classification of Diseases (ICD)-9 198.5 or ICD-10 C79.5), on or after the primary cancer diagnosis and no later than 30 days after the first use of XGEVA or ZA; or a diagnosis of bone metastasis at the time of IPM diagnosis using tumour, node and metastasis (TNM) staging
  - Age 18 years or older at index date
  - Enrollment in Medicare Parts A (inpatient coverage) and B (outpatient and physician coverage) for at least 1 year before the IPM diagnosis and continuously until the index date
  - No record of a diagnosis of a second primary malignancy (including non-melanoma skin cancer, haematological malignancy, and others) prior to index date
  - No record of any denosumab (including Prolia) or intravenous zoledronic acid administration prior to the index administration.

- Follow-up

  Eligible patients will be identified during a period that extends from January 1, 2011 through December 31, 2013. Follow-up will begin 30 days after the date of XGEVA or ZA initiation and end on the date of first occurrence of NPM, loss of Part B coverage, enrollment in Medicare Health Maintenance Organization (HMO), death, or end of follow up (December 31, 2014), allowing the potential for a minimum of one year follow-up for each patient.

- Variables
  - *Outcome Variable*

    The primary outcome will be the first NPM subsequent to the index date

  - *Exposure Variable*
    The cohort definition is based on a first-ever record of XGEVA or ZA administration

  - *Other Covariates*: age, gender [lung cancer only], index primary malignancy type (female breast; prostate; lung), stage at IPM diagnosis, histology at IPM diagnosis, anti-cancer treatment for IPM (type, sequence, duration (for chemotherapy)), number of XGEVA/ZA administrations

- Study Sample Size

Based on the aforementioned eligibility criteria, the anticipated sample size is approximately 8,500 patients in the XGEVA initiation cohort, and approximately 6,500 patients in the ZA initiation cohort. In general, estimation studies are considered informative if the 95% confidence interval half-width is 5% or less. Assuming an incidence proportion of NPM of 0.5 - 2.5%, the anticipated half-width of the 95% confidence intervals will be 1% or less. Hence, the sample sizes anticipated for this study will be sufficient for informative analyses, both for the overall cohorts as well as the tumour-specific analyses.

- Data Analysis

The analytic focus will be descriptive and focus on exposure cohort-specific analyses. No hypotheses will be tested and no direct statistical comparisons will be made between the XGEVA and ZA cohorts.

- The primary analyses will estimate the incidence rate and cumulative incidence proportion of NPM in each exposure cohort using 95% confidence interval (CIs) as a measure of the uncertainty of the estimates. Cumulative incidence proportions will account for the competing risk of death. Analyses will be conducted both for index malignancy types combined and individually (breast, prostate, lung).
- Exposure cohorts will be characterized separately using descriptive statistics with regard to baseline demographic factors, cancer type, comorbid conditions, and medication use.
- Patients with and without NPM will be characterized separately using descriptive statistics with regard to demographic factors, cancer type, comorbid conditions, and medication use. The types of NPM patients experience (hematologic malignancy; solid tumour; cutaneous malignancy; other) will be described.
- Sensitivity analyses will be performed to address the issue of potential surveillance bias by examining time between IPM and NPM.

## 5. Amendments and Updates

None.

## 6. Milestones

| Milestone | Planned date |
|---|---|
| Draft study protocol | April 2018 |
| Start of data collection | Q3 2018 |
| End of data collection | Q4 2018 |
| Final report of study results | Q4 2019 |

## 7. Rationale and Background

### 7.1 Diseases and Therapeutic Area

Patients living with cancer are at increased risk (14%) for developing a new primary malignancy (NPM) compared with the general population (Curtis et al. 2006; Soerjomataram et al. 2005; Travis et al. 2006). Approximately one third of cancer survivors aged >60 years are diagnosed with another cancer (Soerjomataram et al. 2009). Generally, women have a slightly higher risk of an NPM compared with men (17% higher for women vs.11% for men), likely because common female cancers confer better survival chances compared with that of males (Curtis et al. 2006).

CCI [redacted] adjusting for the competing risk of death due to other causes, the cumulative incidence of developing any NPM among patients with primary lung cancer was 5.7% at 25 years (95% CI=5.5%-5.8%), which included an incidence of 1.7% (1.7%-1.8%) for second cancers of the lung or bronchus (Curtis et al. 2006). The cumulative incidence of developing NPM after breast cancer, in analyses accounting for the competing risk of death, was 17.6% at 25 years (95% CI=17.4%-17.8%), which included a 6.9% incidence of new primary breast cancers (Curtis et al. 2006). The cumulative incidence of developing any NPM following prostate cancer, adjusted for the competing risk of death due to other causes, was 15.2% at 25 years (95% CI=15.0%-15.4%) (Curtis et al. 2006). From 1995 to 2008, the percentage of multiple primary cancers at all sites CCI [redacted] increased by 25.4% CCI [redacted] (from 14.6% to 18.4%) (Weir et al. 2013). There are several factors related to the increased diagnosis of NPM, namely an increased awareness of the possibility of second malignancies, the frequent use and increased sensitivity of screening procedures during follow-up, and better treatment delivered to the initial malignancy with improved survival (Amer et al. 2014; Koubkova et al. 2014).

To examine the incidence of NPM in European countries, data from 2,919,023 malignant cancers from 69 European cancer registries participating in the European Cancer Registry based Study on Survival and Care of Cancer Patients (EUROCARE)-4 collaborative study were analyzed. A total of 183,683 multiple primary tumours were found, with an overall proportion of 6.3% over all the considered cancers. The proportion of multiple tumours ranged from 0.4% for the Naples registry (Italy), started in 1996, to 12.9% for the Icelandic registry, started in 1955. The proportion of multiple primary tumours varied greatly by type of tumour, being higher for those with high incidence and long survival (breast, prostate and colon-rectum) (Rosso et al. 2009). A key consideration is that NPM are generally recorded in European registries per the International Association of Cancer Registries and International Agency for Research on Cancer (IACR/IARC) criteria, which define tumours diagnosed in an interval of less than 6 months as synchronous, rather than new, primaries (IARC 2004). Additionally, IARC rules generally consider cancers that occur in paired organs, at the same anatomic site, or with the same/related histology as the same cancer, rather than separate primary cancers. The SEER definition is broader; second cancers diagnosed more than 2 months after the IPM may be considered separate primary cancers (Coyte et al. 2014).

Development of NPM is suspected to be a combination of risk factors, such as age, genetic predisposition, lifestyle, exposure to chemotherapy and radiation treatment, and environmental factors (Travis et al. 2006; Soerjomataram et al. 2009; Thomas et al. 2012). Studies report that NPM following chemotherapy arise within up to 9 years, while after radiation therapy or hormonal treatment, chronic sequelae usually develop after a longer latency period of 5–10 years (Soerjomataram et al. 2009). The role of cancer therapy in the development of NPM has been widely described in the published literature. According to the concept of field cancerization, exposure to carcinogens have to act on two independent organ systems and this would be reflected in the interval between the index primary tumour and the secondary primary tumour (Braakhuis et al. 2003).

### 7.2 Rationale

In completed controlled clinical studies with denosumab for skeletal-related events prevention versus intravenous zoledronic acid (ZA), and in placebo controlled studies, events of NPM were reported (Chen et al. 2016). Most events occurred within one year of treatment initiation, and there was no discernable pattern in the types of new primary malignancies observed. Given the increased susceptibility to NPM in patients with cancer, data on the incidence of NPM in XGEVA- and ZA-treated patients from routine clinical practice will provide further context in characterizing NPM in this patient population. Selection of the tumours of interest in the proposed study was driven by the tumour sites studied in the completed controlled clinical trials for denosumab for skeletal-related events prevention, and sample size considerations. The proposed study will employ a retrospective cohort design and data CCI [redacted] This study will help answer questions such as the following:

- What is the incidence of NPM following initiation of XGEVA or ZA, overall and by index primary malignancy type?
- What is the time between IPM diagnosis to NPM diagnosis in XGEVA or ZA treated patients?
- What are the types of NPM that XGEVA- or ZA- treated patients experience?
- What are the characteristics of patients who develop NPM, and who do not develop NPM, following initiation with XGEVA or ZA?

### 7.3 Statistical Inference (Estimation or Hypothesis)

This is an estimation study. No hypothesis will be tested.

## 8. Research Question and Objectives

### 8.1 Primary

The primary objective of this study is to estimate, overall and by index primary malignancy site (female breast, prostate, lung), the incidence rate and cumulative incidence proportion (for up to 4 years) of any subsequent, new primary malignancy (NPM; any haematologic or non-haematologic tumours, excluding non-melanoma skin cancer subsequent to the first primary malignancy) among patients with breast, prostate, or lung cancer and bone metastases who were newly treated with XGEVA or ZA.

### 8.2 Secondary

Overall, and for each index primary malignancy type,

- To describe the type and sequence of anti-cancer treatment (including surgery, radiotherapy, chemotherapy) for the IPM prior to initiation of XGEVA or ZA;
- To describe the baseline characteristics (including age, gender [lung cancer only], race/ethnicity) and medications (including radiotherapy, chemotherapy, and other systemic agents) at index date;
- To estimate the time from IPM diagnosis to NPM diagnosis in XGEVA- or ZA-treated patients who develop NPM;
- To describe the types (hematologic, solid tumour, cutaneous, other) of NPM XGEVA or ZA-treated patients experience; and
- To describe the characteristics of patients by NPM status (no NPM or NPM during the follow-up period) within each exposure cohort.

## 9. Research Methods

### 9.1 Study Design

Retrospective cohort study over the period of January 1, 2011 through December 31, 2014.

### 9.2 Setting and Study Population

This study will be conducted among patients diagnosed with female breast, prostate, or lung cancer and bone metastases who are newly treated with either XGEVA or ZA in the U.S between 2011 and 2013. CCI [redacted]

#### 9.2.1 Study Period

Eligible patients will be identified during the period that extends from January 1, 2011 through December 31, 2013. Follow-up will begin 30 days after the date of XGEVA or

ZA treatment initiation and end on the date of first occurrence of NPM, loss of Part B coverage or enrollment in Medicare HMO, death, or end of follow up (December 31, 2014). All patients will have the opportunity for at least one year of follow-up through December 2014, CCI [redacted]

### 9.2.2 Subject/Patient/Healthcare Professional Eligibility

#### 9.2.2.1 Inclusion Criteria

- Record of first ever use of XGEVA or ZA between 2011 and 2013 (index date)
- Age 18 years or older on the index date
- Diagnosis of a first primary cancer identified as a primary site code of female breast cancer, prostate cancer, or lung cancer (index primary malignancy, IPM) between 2000 and 2013
- Diagnosis of bone metastasis on or after their IPM and no later than 30 days after the first use of XGEVA or ZA, identified as a diagnosis code for secondary malignant neoplasm of bone or bone marrow (ICD-9 198.5 or ICD-10 C79.5)
- Medicare Parts A and B enrollment for at least 1 year before the IPM and continuously through the index date

#### 9.2.2.2 Exclusion Criteria

- Record of prior treatment with denosumab (Prolia) or ZA prior to index administration.
- Record of a diagnosis of a second primary malignancy (including non-melanoma skin cancer, haematological malignancy) prior to index date

### 9.2.3 Matching

Not applicable.

### 9.2.4 Baseline Period

Patients are required to have at least one year of history in the database prior to the diagnosis of the IPM. For the first secondary objective (describe the type and sequence of anti-cancer agents), the 1-year baseline period, as well as the active cancer treatment period after IPM, will be examined. For the second secondary objective (to describe characteristics of XGEVA- and ZA- treated patients at index date) and the last secondary objective (to describe baseline characteristics of patients who do and do not experience NPM), a baseline period of at least one year prior to the index date will be examined. The baseline period will include data collected on demographics, medications, comorbid conditions, and disease characteristics. CCI [redacted] variables are only identified at the time of

IPM (eg, stage, histology, behavior, etc.). The remainder of the variables will be extracted from the Medicare files.

#### 9.2.5 Study Follow-up

Day 30 after the first-ever record of XGEVA or ZA administration will be used to define the index date. The 30-day period will allow for bone metastases to be identified in the claims data after the XGEVA/ZA exposure. Follow up will begin the day after the index date, and end on the date of first occurrence of NPM, loss of Part B coverage or the initiation of enrollment in Medicare HMO, death, or end of follow up (December 31, 2014). The end of the follow-up period allows the potential for at least 1 year of follow-up for all patients (up to December 31, 2014).

### 9.3 Variables

#### 9.3.1 Exposure Assessment

Two cohorts will be identified: patients newly treated with XGEVA, and patients newly treated with ZA. All patients will have a minimum of one year lookback prior to treatment initiation to identify new users; patients with any history of prior denosumab or intravenous zoledronic acid use will be excluded.

#### 9.3.2 Outcome Assessment

The primary outcome for this study will be the date of the first NPM subsequent to the index date.

NPM is defined as any haematologic or non-haematologic tumour, excluding non-melanoma skin cancer, subsequent to the first primary malignancy. The CCI rules for classifying multiple primary cancers depend on the cancer site of origin, date of diagnosis, histology, tumour behavior (ie, in situ versus invasive), and laterality of paired organs (NCI 2009). In general, all cancers occurring 2 or more months after initial diagnosis are considered as separate primaries unless the medical record states that the tumour is recurrent or metastatic. Exceptions to this rule are multiple adenocarcinomas of the prostate and multiple transitional cell carcinomas of the bladder, which are reported as single primaries. Multiple tumours occurring on both sides of paired organs, such as the breast and testes, are generally considered to be independent cancers.

For the purpose of use in sensitivity analyses, NPM will be further categorized based on the chronology of presentation from Warren and Gates (Warren and Gates 1932):

- **Synchronous NPM**, defined as second primaries diagnosed within 6 months of the IPM
- **Metachronous NPM**, defined as secondary primaries occurring at/after 6 months of the IPM. These NPMs may be further subdivided to events that occur between 6 months and 5 years, and events that occur greater than five years after IPM

NPM will be identified CCI [redacted]. NPM will be further characterized by type of NPM according to clinical criteria (hematologic, solid tumours, cutaneous, others), CCI [redacted]

### 9.3.3 Covariate Assessment

Patient characteristics, comorbidities, and medications will be described, including (but not limited to):

- Demographic (age, gender [lung cancer only], race/ethnicity)
- American Joint Committee on Cancer (AJCC) cancer stage at IPM diagnosis
- Histology at IPM diagnosis
- Type of anti-cancer treatment (including surgery, radiotherapy, chemotherapy) received for the IPM
- Duration of treatment with chemotherapy after IPM diagnosis
- Sequence of anti-cancer treatment for IPM (eg, neoadjuvant followed by adjuvant chemotherapy)
- Time from anti-cancer treatment following IPM diagnosis to index date
- Time between bone metastasis diagnosis and index date
- Number of XGEVA or ZA administrations received in each cohort

### 9.3.4 Validity and Reliability

CCI [redacted] is conducted by NCI and CMS, based on a validated matching algorithm including Social Security number, name, sex, and date of birth (Warren et al. 2002). Previous studies have examined the validity and reliability of the data linkage, with positive results (Earle et al. 2002).

CCI [redacted] High rates of microscopic

confirmation for NPM cases, and the use of precise rules to ascertain and code first and subsequent primary cancers, are strengths of the data source.

### 9.4 Data Sources

This study will be conducted among patients diagnosed with female breast, prostate, or lung cancer and bone metastases who are newly treated with either XGEVA or ZA in the U.S. CCI

CCI

CCI [redacted]

### 9.5 Study Size

Based on the aforementioned eligibility criteria, the anticipated sample size is approximately 8,500 patients in the XGEVA initiation cohort, and 6,500 patients in the ZA initiation cohort. In general, estimation studies are considered informative if the 95% confidence interval half-width is 5% or less. Assuming an incidence proportion of NPM of 0.5 - 2.5%, the anticipated half-width of the 95% confidence intervals will be 1% or less. Hence, the sample sizes anticipated for this study will be sufficient for informative analyses, both for the overall cohorts as well as the tumour-specific analyses.

**Table 1. Half Width of Confidence Intervals Around Estimated NPM Probabilities**

| Sample Size | Expected Proportion (%) | Half Width of 95% CI (%) |
|---|---|---|
| **XGEVA Cohort** | | |
| 8500 | 0.5 | 0.15 |
| 8500 | 1.0 | 0.21 |
| 8500 | 1.5 | 0.26 |
| 8500 | 2.0 | 0.30 |
| 8500 | 2.5 | 0.33 |
| **Zoledronic Acid Cohort** | | |
| 6500 | 0.5 | 0.17 |
| 6500 | 1.0 | 0.24 |
| 6500 | 1.5 | 0.30 |
| 6500 | 2.0 | 0.34 |
| 6500 | 2.5 | 0.38 |
| **XGEVA Breast / Prostate Cohort** | | |
| 3400 | 0.5 | 0.24 |
| 3400 | 1.0 | 0.33 |
| 3400 | 1.5 | 0.41 |
| 3400 | 2.0 | 0.47 |
| 3400 | 2.5 | 0.52 |
| **Zoledronic Acid Breast / Prostate Cohort** | | |
| 2600 | 0.5 | 0.27 |
| 2600 | 1.0 | 0.38 |
| 2600 | 1.5 | 0.47 |
| 2600 | 2.0 | 0.54 |
| 2600 | 2.5 | 0.60 |
| **XGEVA Lung Cohort** | | |
| 1700 | 0.5 | 0.34 |
| 1700 | 1.0 | 0.47 |
| 1700 | 1.5 | 0.58 |
| 1700 | 2.0 | 0.67 |
| 1700 | 2.5 | 0.74 |
| **Zoledronic Acid Lung Cohort** | | |
| 1300 | 0.5 | 0.38 |
| 1300 | 1.0 | 0.54 |
| 1300 | 1.5 | 0.66 |
| 1300 | 2.0 | 0.76 |
| 1300 | 2.5 | 0.85 |

### 9.6 Data Management

All analyses will be conducted using Jigsaw version 2.0 and R version 3.4.5.

#### 9.6.1 Obtaining Data Files

Data will be queried CCI [redacted] using the inclusion criteria listed in Section 9.2.2.1. The data will be further limited using the exclusion criteria listed in Section 9.2.2.2, providing the full analytic dataset available for analysis.

#### 9.6.2 Linking Data Files

Data CCI [redacted] Medicare have already been linked; linkage is performed by NCI and CMS based on an algorithm involving a match of Social Security number, name, sex, and date of birth.

#### 9.6.3 Review and Verification of Data Quality

Data will be reviewed by the statistician at the time of the initial data pull for analysis. The data will be assessed for completeness and accuracy, and any variables with significant (>20%) missingness or with unlikely or impossible values will be assessed further in conjunction with the study team. Variables may be excluded from analysis if found to be incomplete or inaccurate at the time of data query.

### 9.7 Data Analysis

#### 9.7.1 Planned Analyses

The analyses will be descriptive and focus on estimation of cohort-specific incidence proportions and rates. No formal statistical comparisons or significance testing are planned due to likely unresolvable confounding by indication bias. Descriptive analyses include standard descriptive statistics for continuous and categorical measures.

##### 9.7.1.1 Primary Analysis

The primary analysis will begin after protocol approval and any other necessary approvals are finalized. The primary objective of the study is to estimate the incidence of NPM within the two exposure cohorts; the secondary objectives include describing the two exposure cohorts, describing patients with and without NPM, evaluating time from IPM to NPM, and describing the types of NPM patients experience.

#### 9.7.2 Planned Method of Analysis

##### 9.7.2.1 General Considerations

This is a descriptive study and will focus on exposure cohort-specific analyses. No formal statistical comparisons or significance testing are planned.

Patients may discontinue treatment or switch between treatment cohorts during follow-up. Published descriptive studies of XGEVA/ ZA treatment patterns in the U.S.

indicate that patients treated with XGEVA have better compliance and longer duration of therapy than patients treated with ZA, therefore cumulative exposure to XGEVA is anticipated to be higher than cumulative exposure to ZA (Hernandez et al. 2015; Qian et al. 2017). Therefore, treatment intensity (including both number of administrations and total duration of therapy) will be described for each exposure group.

#### 9.7.2.2 Missing or Incomplete Data and Loss to Follow-up

Data will be reviewed by the statistician at the time of the initial data pull for analysis. The data will be assessed for completeness and accuracy, and any variables with a significant amount of missingness (>20%) or with unlikely or impossible values will be assessed further in conjunction with the study team. Variables may be excluded from analysis if found to be incomplete or inaccurate at the time of data query. No imputations will be conducted for missing data.

#### 9.7.2.3 Descriptive Analysis

##### 9.7.2.3.1 Description of Study Enrollment

Patients newly treated with either XGEVA or zoledronic acid between January 1, 2011 and December 31, 2013 will be identified. Patients will be required to have a diagnosis of breast, prostate, or lung cancer prior to XGEVA or ZA initiation, and also required to have a bone metastasis diagnosis either prior to or within 30 days after treatment initiation. Patients with evidence of multiple primary cancers, or denosumab / zoledronic acid use, prior to the index date will be excluded. Additionally, patients will be required to have a minimum of one year of history prior to their initial primary malignancy, and continuous Medicare Parts A and B enrollment during the one year baseline period through the index date.

##### 9.7.2.3.2 Description of Patient and Treatment Characteristics

Patients' baseline characteristics (age, gender [lung cancer only], race/ethnicity), will be described within each treatment cohort (XGEVA and ZA) and within each NPM outcome (NPM and no NPM during follow-up period), including medians and interquartile ranges for continuous covariates and frequency tabulations for categorical variables.

Clinical details of the IPM, including stage at diagnosis and histology, will be described. Additionally, for each exposure cohort separately, and within index primary malignancy types (female breast, prostate, lung), the following will be described:

- Time from IPM to bone metastases
- Time from IPM to index date
- Time from bone metastases to index date
- Time from bone metastasis diagnosis to first recorded NPM

Standard descriptive analysis techniques will be used to describe the treatment patterns within each treatment cohort (XGEVA and ZA) and within each NPM outcome (NPM and no NPM during follow-up period):

- treatment history for IPM (including surgery (curative, palliative), radiotherapy, chemotherapy, and other systemic agents) prior to initiation of XGEVA or ZA
- concomitant treatment (including radiotherapy, chemotherapy, and other systemic agents) at the time of XGEVA or ZA initiation
- treatment (including surgery, radiotherapy, chemotherapy, and other systemic agents) following XGEVA or ZA initiation
- treatment sequence, based on the order in which anti-cancer treatment for IPM were administered (ex., adjuvant vs. neoadjuvant chemotherapy)
- Number of XGEVA and ZA administrations
- Duration of treatment with the administered XGEVA or ZA

#### 9.7.2.4 Analysis of the Primary and Secondary Endpoints

The index date for the XGEVA and IV zoledronic acid cohorts will be 30 days after treatment initiation. This 30-day window will allow for any potential data lag in recording of bone metastases in the Medicare administrative claims database that may occur shortly after treatment initiation. To avoid immortal person time bias that could arise from beginning follow-up on treatment initiation date, the index date will be 30 days after treatment initiation for all patients (Suissa 2008). Follow-up will end on the earliest of NPM, loss of Part B coverage, enrollment in Medicare Health Maintenance Organization (HMO), death, or end of follow-up (December 31, 2014).

For the primary endpoint, the following measures will be used to estimate the incidence of NPM. All estimates will be conducted for each exposure group separately, as well as by index primary malignancy type (female breast, prostate, or lung):

- The cumulative incidence proportions of NPM over follow-up time (up to 4 years) will be calculated accounting for the competing risk of death (Andersen et al 2012). 95% confidence intervals will be measured as an estimate of precision.

  Incidence rate calculated as total number of patients with NPM divided by total person-years at risk. 95% confidence intervals will be measured as an estimate of precision.

We will also describe the types of NPM (hematologic, solid tumour, cutaneous, others) within the XGEVA and ZA cohorts separately using frequency tabulations. The remaining secondary objectives are focused on describing patient and treatment characteristics and are detailed above.

#### 9.7.2.5 Sensitivity Analysis

To assess the extent of potential misclassification of the primary outcome of NPM (ie, synchronous vs. metachronous tumours), sensitivity analyses will be performed and will include the following:

- Excluding NPM cases diagnosed within the first 2, 4 or 6 months of IPM (synchronous NPM) to address the issue of surveillance bias within the 2, 4, or 6 months of a primary cancer diagnosis

In addition, to account for treatment discontinuation or switching, the incidence of NPM (primary objective) will also be calculated within the exposure cohorts censoring at treatment discontinuation, plus an applicable medication-specific washout period to account for residual drug activity. Given the relatively short overall survival of the patients included in the study, the potential for multiple treatment switches is limited.

### 9.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

Not applicable for this analysis of secondary data.

## 9.8 Quality Control

Data in the CCI [redacted] Medicare databases are managed and reviewed regularly by NCI and CMS for accuracy and completeness. Data will also be reviewed by the statistician at the time of the initial data pull for analysis. The data will be assessed for completeness and accuracy, and any variables with significant (>20%) missingness or with unlikely or impossible values will be assessed further in conjunction with the study team. Variables may be excluded from analysis if found to be incomplete or inaccurate at the time of data query.

## 9.9 Limitations of the Research Methods

### 9.9.1 Internal Validity of Study Design

CCI [redacted]. A number of previous studies have shown these data to be reliable, particularly when using data where billing accuracy is required (Earle et al. 2002). The diagnosis and treatment of cancer are expensive and require billing; therefore, the data present in Medicare claims are expected to be accurate and reliable.

#### 9.9.1.1 Measurement Error/Misclassification

CCI [redacted] rely on histopathologic confirmation of the NPM; however, misclassification of NPM is still possible, particularly when new malignancies arise at the same anatomic site and with the same histology as the first tumour, particularly in paired or contiguous organs. Additionally, cancer patients are often under closer medical

surveillance than persons in the general population which may lead to an ascertainment bias in the early detection of asymptomatic cancers that otherwise might not have been clinically evident for several years. On the other hand, under ascertainment of NPM is possible as subsequent cancers are not recorded for patients who migrate from their original CCI geographic area. Finally, misclassification of bone metastases is possible as bone metastases coding has been shown to be highly specific but with moderate sensitivity. We may miss childhood cancers due to the duration of time or movement out of CCI catchment area, and therefore we may include people at the time of a second or later primary cancer, instead of at the time of their first.

#### 9.9.1.2 Selection Bias

We expect to include all eligible patients initiating treatment with XGEVA or ZA during the study period, so selection bias is not a validity consideration for most analyses. Selection bias due to differential loss to follow-up is possible.

#### 9.9.1.3 Confounding

The ability to compare the incidence of NPM between patients treated with XGEVA and patients treated with zoledronic acid in this study will be limited by confounding by indication bias. In regular clinical practice, treatment decisions are influenced by patient characteristics that often predict ensuing morbidity and mortality. This is the root cause of the confounding-by-indication bias that plagues non-interventional pharmacoepidemiology studies (Strom, 2005). Even in the most comprehensive medical systems, there is unlikely to be enough information on relevant risk factors to enable control of this patient selection bias by statistical methods; some of these risk factors include smoking, body mass index, genetic markers and family history of cancer, which are unavailable in the CCI database. As a result, descriptive analyses will be provided.

### 9.9.2 External Validity of Study Design

The CMS-sponsored Medicare program is the primary health insurer for 97% of the US population aged ≥65 years. The linked database contains information on more than 94% of Medicare enrollees diagnosed with cancer in the SEER 18 reporting regions and will provide detailed information about patient demographics, characteristics, treatments, and outcomes (Potosky et al. 1993). The comprehensive nature of these data increases the generalizability and external validity of the current study.

### 9.9.3 Analysis Limitations

The analyses are limited in follow-up time, to a maximum of 4 years. It is possible that the XGEVA and ZA groups might differ substantially in either size or duration of follow up.

### 9.9.4 Limitations Due to Missing Data and/or Incomplete Data

Limitations inherent in using CCI [redacted] for analysis are discussed above.

## 10. Protection of Human Subjects

### 10.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

No IRB review is necessary for this analysis of secondary, de-identified data. There are no patient identifiers present in these data.

### 10.2 Patient Confidentiality

No patient identifiers are present in the CCI [redacted]. All data are de-identified, stripped of any identifying information.

### 10.3 Subjects Decision to Withdraw

Not applicable for this analysis of secondary, de-identified data.

## 11. Collection, Recording and Reporting of Safety Information and Product Complaints

CCI [redacted] The safety outcomes that are listed in section 9.3.2 will be analyzed in this study. These will be reported in aggregate in the final study report as cumulative incidence proportions and incidence rates. See section 9.3.2 for safety outcomes and definitions. Submission of safety outcomes as individual safety reports to Amgen is not required. Safety events suspected to be related to any medicinal product should be reported to the local authority in line with the local country requirements.

## 12. Administrative and Legal Obligations

### 12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement.

## 13. Plans for Disseminating and Communicating Study Results

A final report to regulatory agencies will be submitted in the fourth quarter of 2019. The final report will be comprehensive for all objectives and for the specific outcomes of interest. No interim reports are planned.

### 13.1 Publication Policy

The results of this analysis will be summarized in abstract and manuscript form, and submitted to a peer-reviewed journal for publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications based on this study will be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

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