1. ABSTRACT

- **Title**

Title: Prospective Observational Study to evaluate the persistence of treatment with XGEVA® in patients with bone metastases from solid tumors for prevention of skeletal related events (SREs) in routine clinical practice

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Main authors:

Katja Björklöf
Therapeutic Area Head Oncology/Hematology, Europe North East – EU Medical
Amgen (Europe) GmbH
Dammstrasse 23
6301 Zug
Switzerland
Email: katja.bjorklof@amgen.com
Phone: +41413692592

Christine Jäger
Therapeutic Area Head Oncology/Hematology, Austria
Amgen GmbH
Franz-Josefs-Kai 47
1010 Wien
Austria
Email: cjaeger@amgen.com
Phone: +43150217878

- **Keywords**

Denosumab, persistence, bone metastases, real-world, observational study

- **Rationale and Background**

In three pivotal, phase 3 head-to-head trials that evaluated the efficacy of denosumab versus zoledronic acid at delaying SREs, denosumab demonstrated a clinically meaningful improvement in preventing SREs compared to zoledronic acid. Yet, suboptimal compliance and/or persistence with therapy for the prescribed duration may impact the therapeutic potential of denosumab treatment demonstrated in the clinical trials. Medication persistence refers to the act of conforming to a recommendation of continuing treatment for the prescribed length of time. Therefore, medication persistence is defined as “the duration of time from initiation to discontinuation of therapy” (http://www.ispor.org).

To date the availability of real life data assessing persistence of denosumab in health care settings in the countries of interest is limited. The convenience of a subcutaneous route of administration and the beneficial safety profile of denosumab compared to other available treatments may result in a high persistence not only in clinical trials, but also in

daily clinical practice. The objectives of the study are consistent with the need to obtain useful information on real-world practice conditions and persistence of denosumab use for planning subsequent observational trials and the support of regional reimbursement strategies.

- **Research Question and Objectives**

The aims were to provide statistical estimates of persistence at 24 weeks (primary objective) and persistence at 48 weeks, time to non-persistence, primary and secondary persistence outcomes by tumor type, demographics, disease characteristics, concomitant anticancer therapy, medical history, and calcium and vitamin D supplementation patterns(secondary objectives) in solid tumor patients with bone metastases treated with denosumab as per routine clinical practice.

- **Study Design**

This was a single-arm, prospective, observational (non-interventional), multi-center cohort study in patients with solid tumors and bone metastases in Austria and selected CEE countries. No laboratory, diagnostic, or therapeutic procedures other than those performed as part of the patient's routine care were required.

- **Setting**

This study was conducted in Austria (24 centers), Czech Republic (10 centers), Hungary (4 centers), Slovakia (8 centers), Bulgaria (5 centers) between October 2012 and May 2017.

- **Patients and Study Size, Including Dropouts**

This study analysed 598 patients: Austria (n=294), Bulgaria (n=130), Czech Republic (n=103), Slovakia (n=54), and Hungary (n=17). Of 598 patients in the FAS, 451 (75.4%) completed 24 weeks of observation and 147 (24.6%) discontinued. Reasons for discontinuation before week 24 were death (n=59, 9.9%), loss to follow-up (n=26, 4.3%), withdrawal of informed consent (n=5, 0.8%), discontinuation of denosumab (n=35, 5.9%; [S]ADRs [n=2, 0.3%]), other reasons (n=20, 3.3%). 387 (64.7%) completed 48 weeks of observation and 211 (35.3%) discontinued. Reasons for discontinuation before week 48 were death (n=80, 13.4%), loss to follow-up (n=35, 5.9%), withdrawal of informed consent (n=7, 1.2%), discontinuation of denosumab (n=56, 9.4%; [S]ADRs [n=5, 0.8%]), other reasons (n=28, 4.7%). Discontinuations before week 48 include those before week 24. Of patients who did not die and were nt lost to follow-up, 474 (79.3%) completed safety follow-up and 9 (1.5%) did not. Reasons for not completing safety follow-up were death (n=2, 0.3%), loss to follow-up (n=3, 0.5%), and other reasons (n=4, 0.7%).

54.2% of patients (n=324) had breast cancer, 24.4% (n=146) had prostate cancer, 9.9% (n=59) had lung cancer. 11.5% (n=69) had cancers summarized as "other" in the overall analysis; 62.9% of patients were female. The median age was 65.0 years (range: 24 – 91). 44.0% of patients (n=263) were diagnosed for cancer less than one year before baseline and in 86.6% of patients (n=518). Metastatic disease was diagnosed less then one year before baseline. Of patients, 46.7% (n=279) had bone metastases only, and 53.3% (n=319) had metastases in the bone and other sites. 10.9% of patients (n=65) had previous SREs: 7.5% (n=45) had pathological fractures, 2.2% (n=13) required radiation to the bone, 1.5% (n=9) had surgery to the bone, and 0.5% (n=3) had spinal cord compression. 3.2% of patients (n=19) received an intervention due to their SRE(s).

- **Variables and Data Sources**

Patient data was collected from medical charts (starting with first denosumab administration). No study-specific clinical tests were required, and no study-specific procedures (other than denosumab administration) apart from being asked to voluntarily complete one short questionnaire at baseline, at every 3rd visit and at the end of observation, and the handout of a diary card (prescription card) where applicable were required.

- **Results**

Patients received denosumab for a median (IQR) of 309 days (168.0, 319.0) and 11 doses (6.0, 12.0). The median (IQR) study duration was 48 weeks (27.3, 49.9). Persistence at week 24 was 62.6% (95% CI 58.4, 66.7) overall, and ranged between 26.1% for lung cancer and 69.5% for breast cancer,and between 56.0% for Austria and 84.8% for Slovakia. Persistence at 48 weeks was 40.1% (95% CI 35.9, 44.4). The Kaplan-Meier median (95% CI) time to non-persistence was 274.0 (232.0, 316.0) days, with 317.0 (263.0, 335.0) in breast cancer, 325.0 (271.0, 344.0) in prostate cancer, 118.0 (59.0, 144.0) in lung cancer, and 118.0 (57.0, 230.0) in other cancers. The most frequently documented reason for non-persistence at 24 weeks was the violation of time windows (77.2%, n=156 of 202 non-persistent patients). Of patients violating a time window (n=156), 75.6% (n=118/156) violated one time window. Violation of one time window was also the most frequently documented reason for non-persistence at week 48.

Overall, a steady proportion of approximately 60% of patients did not use analgesics. The proportion of patient receiving strong opiods at a dose <75 mg oral morphine equivalents (OME) per day ranged between 9% and 11%. The percentages are based on the number of subjects with available values.

Overall, 10.2% of patients (n=61) experienced an ADR. The most frequently reported ADR was hypocalcemia (7.4%, n=44). Eight patients (1.3%) experienced serious ADRs. Osteonecrosis was documented in 3 patients (0.7%), two with confirmed osteonecrosis of the jaw, one with unspecified osteonecrosis. The exposure-adjusted incidence of osteonecrosis was 0.012 (95% CI 0.004, 0.029) per patient year. No fatal ADRs occurred.

- **Discussion**

The majority of patients were persistent with treatment with denosumab every 4 weeks for over 24 weeks after initiation. The primary tumour type, previous chemo- or concomitant radiotherapy, and the number of metastases appeared to influence whether or not a patient was persistent. The most frequent reason for non-persistence was the violation of one time window. Most patients reported taking calcium and vitamin D supplementation as recommended in the Summary of Product Characteristics. The incidence adverse drug reactions, especially of osteonecrosis was not higher than expected from previouy studies.

- **Marketing Authorization Holder(s)**

Amgen Europe B.V.

- **Names and Affiliations of Principal Investigators**

Not applicable.

2. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
ADR	adverse drug reaction
AQA	clinician based 8-point scale analgesics score
CEE	Central and Eastern Europe
CRO	contract research organization
CI	confidence interval
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EQ-5D	European Quality of Life-5 Dimensions
FAS	full analysis set
FU	follow-up
HT	Hormonal therapy
HRU	Health resource utilization
ICF	Informed Consent Form
ID	Identification
IU	International units
NF-κB	nuclear factor kappa-B
NIS	Non-interventional study
OME	Oral Morphine Equivalent
ONJ	Osteonecrosis of the jaw
OPG	osteoprotegerin
PRO	patient-reported outcome
Q3W	Every three weeks
Q4W	Every four weeks
Q6M	Every 6 month
RANKL	Receptor activator of nuclear factor kappa-B ligand
SADRs	serious adverse drug reaction
SD	standard deviation
SmPC	summary of product characteristics
SoC	standard of care
SREs	skeletal related events
TNF	tumor necrosis factor
US	United States
Y/N	Yes/No

3. INVESTIGATORS

A list of all collaborating institutions and physicians will be made available upon request.

4. OTHER RESPONSIBLE PARTIES

2KMM Sp. Z.o.o., Al. Korfantigo 79, 40-161 Katowice, Poland, Phone: +48 32 2592390, was responsible for opening of sites in electronic data capture system, training of sites, safety reporting to Amgen, housing of electronic data capture, querying and cleaning of data, and transferal of data to Amgen.

2KMM and the study sponsor were jointly responsible for study start up activities and monitoring and source data verification. The study sponsor maintained the trial master file. Ethics and regulatory submissions were within the responsibility of the country responsible person of the study sponsor.

Quartesian, 42A Tobolskaya Street, Suite 504, Kharkov 61072, Ukraine, was responsible for the preparation of the statistical analysis plan and for statistical programming and analysis.

5. MILESTONES

Milestone	Planned Date	Actual Date	Comments
Start of data collection	Anticipated start is in Q4/2012	04.10.2012	FSE consent date (Austria)
End of data collection	Appr. Q1 2017	26.05.2017	EoS date (Hungary)
Final report of study results	13.04.2018	20.03.2018	none

6. RATIONALE AND BACKGROUND

Bone metastases are a frequent complication of solid tumors, occurring in more than 1.5 million patients with cancer worldwide (Coleman, 2005). Patients with metastatic bone disease frequently experience osteoclast-mediated bone destruction, resulting in clinically important skeletal complications such as fractures, need for radiation or surgery to bone, spinal cord compression, or hypercalcemia (Coleman 2004, Vogel, 2004). These complications, collectively known as skeletal-related events (SREs) often leads to pain and decreased quality of life (Weinfurt, 2005).

Denosumab is a fully human monoclonal antibody of IgG2 subtype, capable of inhibiting the receptor activator of nuclear factor κB ligand (RANKL) on bone cells. XGEVA® (denosumab) in Europe is indicated for prevention of SREs (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumors and for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity (European Medicines Agency 2017).

In 3 pivotal, phase 3 head-to-head trials that evaluated the efficacy of denosumab versus zoledronic acid at delaying SREs (studies 20050136, 20050103 and 20050244), denosumab demonstrated a clinically meaningful improvement in preventing SREs compared to zoledronic acid (Lipton, 2012). Yet, suboptimal compliance and/or persistence with therapy for the prescribed duration may impact the therapeutic potential of denosumab treatment demonstrated in the clinical trials.

- Medication Compliance: A synonym for adherence, compliance refers to the act of conforming to the recommendations made by the provider with respect to timing, dosage, and frequency of medication taking. Therefore medication compliance is defined as “the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen” (http://www.ispor.org).
- Medication Persistence: Refers to the act of conforming to a recommendation of continuing treatment for the prescribed length of time. Therefore, medication persistence is defined as “the duration of time from initiation to discontinuation of therapy” (http://www.ispor.org).

The exact extent to which poor compliance and persistence will affect clinical effectiveness is a complex issue. From a payer’s perspective the impact of medication compliance and persistence on medication costs and health resources utilization often works in two directions: poor compliance and persistence is likely to reduce medication costs, but increases subsequent health resource utilization. Although this relationship cannot be necessarily assumed in all settings, data on health resource utilization (HRU)

related to SREs shows that SREs lead to additional inpatient stays and to an increased use of procedures related to the treatment of SREs (Pereira, 2016).

To date the availability of real-life data assessing compliance or persistence of denosumab in health care settings in the countries of interest is limited. The convenience of a subcutaneous route of administration and the beneficial safety profile of denosumab compared to other available treatments may result in a high persistence not only in clinical trials, but also in routine clinical practice. From previous publications and clinical experience, it is anticipated that overall persistence of use for denosumab during a 24- to 48-week observation period might be as high as 60% (Stopeck, 2010, Fizazi, 2011, Henry, 2011, Lipton, 2012). The objectives of the study are consistent with the need to obtain useful information on real-world practice conditions and persistence of denosumab use for planning subsequent observational trials and the support of regional reimbursement strategies.

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this prospective observational study was to evaluate the persistence of treatment with denosumab in patients with bone metastases from solid tumors for prevention of SREs in routine clinical practice.

Primary objectives

The primary objective of this study was to estimate the persistence at 24 weeks in solid tumor patients with bone metastases treated with denosumab as per routine clinical practice.

Secondary objectives

- To estimate the persistence to denosumab at 48 weeks as per routine clinical practice.
- To estimate time to non-persistence to denosumab at the end of study.
- To describe the primary and secondary persistency outcomes by tumor type.
- To describe demographics, disease characteristics, concomitant anticancer therapy and medical history of patients treated with denosumab as per routine clinical practice.
- To describe calcium and vitamin D supplementation patterns of patients treated with denosumab as per routine clinical practice.

Exploratory objectives

- To describe usage of individual pain medication on monthly basis between baseline and end of observation.
- To collect patient-reported outcomes describing problems with mobility, self-care, daily activities, pain/discomfort, and anxiety/depression (EQ-5D) in countries where this is accepted by local authorities.
- To collect reasons for choice of denosumab as treatment for bone metastases from solid tumors.

8. AMENDMENTS AND UPDATES

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	06.12.2012	Header, Cover page, Investigator Agreement, Summary of observational plan, section 7, section9	Please review summary of changes for details	The new EU PV Directive which came into effect July 2, 2012, mandates new Safety reporting requirements for non-interventional observational studies. This applies to all studies involving products where Amgen is the MAH in the EU, and is not restricted to those with activities in EU only. Thus respective changes in Safety reporting requirements have been incorporated for respective study 20110240 (as outlined below), including the retrospective requirement to report those ADRs that the investigator had knowledge of as of Jul 2nd 2012. Such ADRs require completion of an Adverse Drug Reaction Report Form by investigator within 60 calendar days after the investigator has signed the protocol signature page for amendment 1 version 03 Dec 2012. In addition some typographic and formatting errors were corrected throughout the protocol.
2	07.03.2014	Header, Cover page, Investigator Agreement, Summary of observational plan, Section: 3.5.1 of section 3, Section: 10.2 of section 10, Section: 12.	Please review summary of changes for details	The protocol is being amended to allow-upon discretion of the sponsor- prolongation of enrolment (beyond 24 months) in a certain country in order to meet the planned enrollment target. Reaching the planned enrollment number is important, as the proposed sample size is based on the objective to estimate the 95% confidence interval (CI) around the proportion of persistence. The analysis is planned to be carried out by tumor types (breast cancer, prostate cancer and other solid tumors) as well as for the overall population, thus the sample size was planned sufficiently large to allow precision to be estimated for the subgroups. In addition a by country analysis can be performed for the country that enrolls a sufficient number of subjects for the analysis.
3	23.05.2016	Header, Cover page, Investigator Agreement; Section 9	Please review summary of changes for details	A statement has been added, why collection of adverse events (AEs) that are not related to XGEVA, is not required for this study. Updates have been implemented to align with the current template.

9. RESEARCH METHODS

9.1 Study Design

This was a single-arm, prospective, observational (non-interventional), multi-center cohort study in patients with solid tumors and bone metastases in Austria and selected CEE countries.

As per definition, apart from being asked to voluntarily complete one short questionnaire at baseline, every 3rd visit and at end of observation (in countries where accepted by local authorities) and the handout of a diary card (prescription card) where applicable, no laboratory, diagnostic, or therapeutic procedures other than those performed as part of the patient's routine care were required.

The overall study design is described by a study schema in Figure 1.

9.2 Setting

This study was conducted in Austria (26 centers), Czech Republic (10 centers), Hungary (7 centers), Slovakia (14 centers), Bulgaria (5 centers). The study centre selection was based on a balanced distribution of study sites with regard to geography and specialty. Enrolment of consecutive patients as they presented to each clinic was expected to result in a study population sample similar to a typical population of patients with solid tumors and bone metastases in similar health care settings. The first patient entered the study on 04 October 2012 (date of first informed consent signed), and recruitement ended on 28 June 2016 with the last patient entering the study. The last patient completed the study on 26 May 2017 (date of last patient-last visit). The period for assessing persistence for denosumab was aligned with Amgen´s clinical trial program, in which a median of 12 doses of denosumabwas administered. Therefore the patient observation period was defined as the time from the first until the last denosumab administration up to a maximum of 48 weeks plus 30 days safety follow-up or until death, loss to follow-up or withdrawal of consent, whichever occured first.

9.3 Patients

The decision to treat with denosumab was to be undertaken freely by the clinician prior to consideration of whether the patient was to be included into the observational study. Therefore, treatment administration was considered independent and dissociated from participation in the study and the availability for inclusion into this study did not affect the clinical practice decision for individual patients.

Patient criteria for inclusion

Patients with bone metastases from solid tumor treated with denosumab in accordance with the label (most current version of the SmPC at time of enrolment) and who meet the inclusion and exclusion criteria were eligible to participate in this study.

- Patients of at least 18 years of age at enrolment
- Diagnosis of breast, prostate, lung cancer or any other solid tumors with bone metastasis
- ECOG Performance Status 0-2
- Patients having received the first denosumab dose ever within 28 days prior to enrolment
- Appropriate written informed consent has been obtained

The participating physicians were expected to maintain a patient identification list of patients registered and documented in the study.

Patient criteria for exclusion

- Diagnosis of multiple myeloma
- Patient was previously treated for more than 6 months with bisphosphonates or other antiresorptive treatment for bone metastasis in clinical studies or clinical routine.
- Patients previously treated with radionuclides (eg, strontium-98, samarium-153, radium-223).
- Patients enrolled in an investigational drug trial for the treatment/prevention of bone metastases and SREs (Patients in a treatment trial related to their underlying cancer, or in long-term follow up studies were eligible for this observational study).
- Contraindications for the treatment with denosumab according to the most current SmPC at time of enrolment.

9.4 Variables

The objective of this prospective observational study was to evaluate the persistence of treatment with denosumab in patients with bone metastases from solid tumors for prevention of SREs in routine clinical practice.

Primary outcome measure

- Number of patients persistent for denosumab use at 24 weeks from 1st administration of denosumab – a patient was considered persistent for denosumab use at 24 weeks if he/she received at least 6 denosumab injections no more than 4 weeks plus 7 days apart.

Secondary outcome measures

- Number of patients persistent for denosumab use at 48 weeks from 1st administration of denosumab – a patient was considered persistent for denosumab use at 48 weeks if he/she received at least 12 denosumab injections no more than 4 weeks plus 7 days apart.
- Time to non-persistence was calculated as the time in days between the date of the first injection and the date of the last injection received during the period where the patient was still classified as persistent plus 4 weeks (28 days).
- Primary and secondary persistence outcomes by tumor type – The outcome tables were repeated for each tumor type.
- Patient characteristics at baseline assessed for description of patients treated with denosumab as per clinical routine and their association with persistence/non-persistence.
- The use (in terms of use y/n as per recommendation) and physician advice of usage (y/n) of calcium and vitamin D supplementation throughout treatment with denosumab was evaluated.

Exploratory outcome measures

- Type of pain medication used (in percent), clinician-reported results from the 8 point analgesics scale (AQA) was tabulated baseline and monthly until the end of observation.
- EQ-5D results at baseline and every 3rd study visit up to end of observation was tabulated.
- The rate and distribution of physicians' reasons for selecting denosumab as treatment for bone metastases from solid tumors

Safety outcome measures

- ADRs and serious ADRs

Covariates

- Country (if applicable/possible)
- Each of primary tumor types (breast cancer, prostate cancer and other)
- Previous antiresorptive therapy (y/n)
- Systemic antineoplastic therapy (by type)

9.5 Data Sources and Measurement

An electronic case report form (eCRF) was used for data collection; physicians were trained on the protocol and data entry using the eCRF during investigator meetings or individual site initiation visits. Patients were registered online.

Patient data was collected (starting with first denosumab administration) from enrollment until end of observation. For the patient the study ended 30 days after the last administered denosumab dose (safety follow-up only).

No study-specific clinical tests were required, and no study-specific procedures (other than denosumab administration) apart from being asked to voluntarily complete one short questionnaire at baseline, at every 3rd visit and at the end of observation, and the handout of a diary card (prescription card) where applicable were offered to support a better documentation of the denosumab applications out of the hospital'. The patient was observed from enrollment (having received the 1st dose of denosumab as per standard of care, i.e. local medical practice, within 28 days prior to enrollment) until the last denosumab dose administered up to a maximum of 48 weeks after the date of first denosumab administration. Safety data related to denosumab was collected up to 30 days after the date of administration of the last dose of denosumab within this study.

9.6 Bias

The study center selection process (based on a balanced distribution of study sites with regard to geography and specialty) combined with consecutive enrollment of patients, was expected to result in a patient sample similar to a typical population of patients with solid tumors and bone metastases in similar health care settings. However, potential selection bias may have ben introduced in several ways:

1. Participant drop-out may have lead to retention of a non-representative sample of patients (self-selection bias). Before developing any conclusion the analysis of characteristics and results for the drop-out population versus all enrolled population was made to assess the impact of early termination of treatment on the studied outcomes.
2. The study was not intended to compare outcomes for different patient groups, thus other selection bias concerns were considered to be limited to adequately representing the population of denosumab-treated patients at large. These concerns were addressed at the study center level and patient level.
    a. On the study center level, centers were selected to adequately represent the health care facilities of each country.
    b. On the patient level, consecutive enrollment of all eligible patients ensured that the study population adequately represented each center's patient population as they presented themselves for treatment during the observation intervals. Demographic information, disease characteristics, data on concomitant anticancer medications, and data on the medical history of these patients were used to address potential bias.

9.7 Study Size

Sites were selected to adequately represent the health care facilities of each country, based on their estimated number of patients, their experience in observational studies, the type of site and their geographical location to ensure geographical spread within each participating country. Sites were selected only after feasibility assessment was completed. Sites that did not enroll patients within 6 months of site initiation were closed.

Approximately 190 sites in Austria and CEE countries (ie.: Poland, Czech Republic, Hungary, Slovakia, Slovenia, Romania, Bulgaria) were planned to be selected. A total of approximately 1.500 patients were planned to be enrolled in order to minimizing bias of excluding difficult patients and to ensure the accuracy of estimates of the primary and secondary endpoints.

The following calculations provide information about the level of reliability for the proposed sample size for this descriptive observational study with respect to the described primary and secondary outcomes. As no prospectively formulated hypotheses was tested, the sample size calculation was not based on statistical power calculations. Instead the expected level of precision for the incidence of patients persisting with denosumab at any time point and by covariate value formed the basis for the sample size calculation.

- Based on different information from local sources (e.g., local market research, Amgen data on file) it was assumed that studied tumor types, i.e. breast cancer, prostate cancer and other solid tumors would take 40%, 40% and 20%, respectively, of the enrolled population.
- Different tumor type populations were expected to show different dropout rates on target time points (24 week and 48 week after initiation of the therapy)(Stopeck, 2010, Fizazi, 2011, Henry, 2011). For breast cancer the proportions would be 15% for 24 week and 30% for 48 week, for prostate cancer these would be 25% and 50%, for other solid tumors 50% and 90%, respectively.

The proposed sample size was based on the objective to estimate the 95% confidence interval (CI) around the proportion of persistence. The proportion of persistent patients was determined by taking all drop-outs related to denosumab into account.

These estimates employed an assumed proportion of 60% of patients' persistence to denosumab after 24 weeks for the 1st administration of treatment when an overall dropout rate of 26% after 24 weeks was taken into account (see Table below and Table 1 in the study protocol provided in Annex 2).The precision (half-width of the

95% CI) of maximum 15% was considered reasonable for describing the primary endpoint for the overall, by tumor type and by country analyses.

The sample size of ~1.500 patients confered the precision for the subgroup tumor types on the primary endpoint as follows: 4.3% (~600 patients), 4.5% (~600 patients) and 7.8% (~300 patients) respectively for breast cancer, prostate cancer and other solid tumor for an assumed proportion of 60% of patients persistence to denosumab after 24 weeks for the 1st administration of treatment when an overall dropout rate of 26% after 24 weeks was taken into account. With the assumption of the overall dropout rate of 26% after 24 weeks the sample size of ~1.500 patients the 15% margin of the 95% CI half-width for the countries with enrollment greater of equal to 100 patients would not be exceeded (95% CI half-width in this case was 11.2% according to Table 1 in the study protocol provided in Annex 2).

Number of Subjects Required Overall and by Tumor Type for Subjects with 24 Weeks and 48 Weeks Persistence to XGEVA® (Using Normal Approximation)

	Expected Prevalence in Enrolled Patient Population (%)	Proportion of Total Sample Size	Assume Dropout Rate	Expected Number of Evaluable Patients	Approximate Half-Width of 95% CI for 60% Persistence (%)	Approximate 95% CI
All Countries (N=1500)						
Breast Cancer	40	600	24w: 15% 48w: 30%	510 420	4.3 4.7	(55.7, 64.3) (55.3, 64.7)
Prostate Cancer	40	600	24w: 25% 48w: 50%	450 300	4.5 5.5	(55.5, 64.5) (54.5, 65.5)
Other Types	20	300	24w: 50% 48w: 90%	150 30	7.8 17.5	(52.2, 67.8) (42.5, 77.5)
Overall	100	1500	24w: 26% 48w: 50%	1110 750	2.9 3.5	(57.1, 62.9) (56.5, 63.5)

The proposed sample size would also allow the estimation of the key secondary endpoint proportion of patients' persistence to denosumab after 48 weeks from the 1st administration of treatment. The assumed proportion of 60% of patients' persistence to denosumab after 48 weeks with the dropout rate after 48 weeks of 30%, 50%, 90% for breast cancer, prostate cancer, and other tumor types could be estimated with a precision of 4.7%, 5.5%, and 17.5% respectively.

Enrollment of a minimum of 3 and maximum of 40 patients per site was recommended. Poland and Romania did not participate in the study, because denosumab was not

reimbursed. In Slovenia the minimum required number of sites and thus patients could not be reached.

9.8 Data Transformation

The analysis was carried out by tumor types (breast cancer, prostate cancer, lung cancer and other solid tumors) as well as for the overall population. In addition a by country analysis was performed for the countries that enrolled a sufficient number of patients for the analysis. The most recent registered values prior to the first dose of treatment with denosumab were treated as baseline data.

The data used in the planned analyses came from electronic web-based CRF forms. The data were transferred by 2kmm.

9.9 Statistical Methods

9.9.1 Main Summary Measures

No formal hypothesis was tested. Analyses were descriptive in nature. For continuous variables, descriptive statistics including the mean, standard deviation (SD), median, first and third quartiles, minimum and maximum values were presented along with 95% two-sided CIs, where appropriate. Missing values of continuous variables were counted as “Missing”. For categorical variables, the number and percentage of patients in each category were reported. For binary variables, the number and percentage of patients were reported, along with exact two-sided CIs, where appropriate. Missing results were excluded from the calculation of CI however number and percentage of patients with missing results were given for categorical data. The statistical analyses were based in general on the Full Analysis Set (FAS), which consisted of the enrolled patients who met inclusion/exclusion criteria and received at least one dose of denosumab. For the evaluation of the primary and the first secondary outcome measure the basis for the analysis were as was defined in the respective sections of this SAP.

Patient Accountability

The number of patients enrolled were tabulated by site, and the number of patients treated per year at each site. The number and percentage of patients who completed the planned observational period according to the observation plan and who discontinued the observational period prematurely were presented. Reasons for stopping the observation were summarised.

In addition, the number and percentages of patients in full analysis set population were given. The number of deaths along with the relationship to study product were calculated. Percentages were based on the FAS.

The number and percentages of patients who continued denosumab after the end of observation period were also calculated. The number of patients who were still on-treatment at 24 weeks and at 48 weeks were summarized. A time window of -7 days was allowed, ie, patients were counted as 'still on treatment at 24 weeks' if they had at least one injection at or after day 161 (week 23) and at or after day 329 (week 47) respectively. The study duration in weeks was summarized.

9.9.2 Main Statistical Methods

This was an observational study for which the analysis was descriptive in nature.

9.9.3 Missing Values

Missing and incomplete data were identified for investigation, and possible resolution, by Quartesian and Amgen OSS Management prior to database lock (or a data snapshot) through the review of ongoing data.

For adverse drug reactions if the start date was incomplete the following rules were applied:

- If the date was partial and the known part was the same as respective part of first dose date, the imputed date was set to the date of first dose.
- If the date was partial and the known part was greater than respective part of first dose date, the imputed date was set to first day of the month for missing day and to the 31st of January for missing month and day.
- As only related to denosumab events were analysed the situation where the date was partial and the known part was less than respective part of first dose date was not considered.

In case date of death, informed consent withdrawal or date when last information of alive patient was available was partial it was imputed to the earliest possible date provided it was not greater than the date of last dose.

Number of patients with missing findings was given for continuous and categorical data for each timepoint and analyzed endpoint where it was appropriate.

9.9.4 Sensitivity Analyses

In order to assess the impact of patients who died or were lost to follow-up before the appropriate study endpoint, additional sensitivity analyses were performed. For the analysis of persistence at 24 weeks, patients who died or were lost to follow-up prior to

week 24 were excluded in any case (in addition to patients who died or were lost to follow-up prior to week 24 and did not violate the persistence definition before the discontinuation date). The same was repeated for the endpoint at week 48.

Additionally, sensitivity analyses with extended time windows were performed. The analyses repeated the definition for persistence with the following exceptions:

1. Extended time window after 24 and 48 weeks endpoints:
   - a time window of +2 weeks was allowed after the 24 weeks endpoint.
   - a time window of +7 weeks was allowed after the 48 weeks endpoint.

2. Extended time window between the injections and after 24 and 48 weeks endpoints:
   - an additional time window of 14 days (instead of 7 days) was allowed for each injection relative to the previous injection for persistence to denosumab at 24 weeks and after 48 weeks.
   - a time window of +4 weeks was allowed after the 24 weeks endpoint.
   - a time window of +10 weeks was allowed after the 48 weeks endpoint.

9.9.5 Amendments to the Statistical Analysis Plan

The statistical analysis plan was amended to be aligned with the respective statistical analysis plans of the sister studies, the German X-TREME study (20101312) and the Greek XPERT study (20110277) to enable a pooled analysis. Details on the reasons for non-persistence (eg violation of 1 or more time windows), as well as some further sensitivity analyses around broadening the time window allowed for each injection relative to the previous injection for persistence (from 7 to 14 days) were added. Other changes/additions, e.g. further details on pain medication and pain scales analysis, time to ONJ analysis, and format of output tables have also been made to align the studies.

9.10 Quality Control

Outliers

Outliers were identified via the use of descriptive statistics and the review of the derived datasets, tables and graphics. Edit checks were created to specifically look for outlier data as indicated in the data management plan. There were no outliers excluded from the analysis.

Validation of statistical analysis

Programs were developed and maintained, and output was verified in accordance with current risk-based quality control procedures. Tables, figures and listings were produced with validated standard macro programs developed by Quartesian LLC, where standard macros were able to produce the specified outputs. The production environment for statistical analysis consisted the SAS System 9.4.

The results of the analysis was presented as a composition of tables, and figures.

10. RESULTS

10.1 Participants

A total of 634 patients were enrolled: 319 from Austria, 130 from Bulgaria, 109 from the Czech Republic, 58 from Slovakia, and 18 from Hungary. 598 patients were analyzed (full analysis set, FAS): 294 from Austria, 130 from Bulgaria, 103 from the Czech Republic, 54 from Slovakia, and 17 from Hungary. The reasons for exclusion from analysis were violation of inclusion or exclusion criteria, erroneous double entry, or entry by mistake. Of 598 patients in the FAS, 451 (75.4%) completed 24 weeks of observation and 147 (24.6%) discontinued. Reasons for discontinuation before week 24 were death (n=59, 9.9%), loss to follow-up (n=26, 4.3%), withdrawal of informed consent (n=5, 0.8%), discontinuation of denosumab (n=35, 5.9%; [S]ADRs [n=2, 0.3%]), other reasons (n=20, 3.3%). 387 (64.7%) completed 48 weeks of observation and 211 (35.3%) discontinued. Reasons for discontinuation before week 48 were death (n=80, 13.4%), loss to follow-up (n=35, 5.9%), withdrawal of informed consent (n=7, 1.2%), discontinuation of denosumab (n=56, 9.4%; [S]ADRs [n=5, 0.8%]), other reasons (n=28, 4.7%). Discontinuations before week 48 include those before week 24. Of patients who did not die and were not lost to follow-up, 474 (79.3%) completed safety follow-up and 9 (1.5%) did not. Reasons for not completing safety follow-up were death (n=2, 0.3%), loss to follow-up (n=3, 0.5%), and other reasons (n=4, 0.7%). The overall number of deaths was 82 (13.7%): 71 patients (11.9% of FAS) died of their underlying cancer and 11 (1.8% of FAS) died of other causes not related to denosumab. After the end of study-related observation, 370 patients (63.4%) continued denosumab treatment. 91 patients discontinued either during study or after the end of observation. The reasons for discontinuation of denosumab were the patient's decision (n=28, 4.7% of FAS), the physician's decision (n=29, 4.8%), (S)ADRs (n=8, 1.3%; [S]ADRs: peripheral edema, hypocalcemia, hypophosphatemia, osteonecrosis, cellulitis), switch to other antiresorptive drugs (n=5, 0.8%), or other reasons (n=21, 3.5%).

Of thirteen patients it is unknown, whether they continued denosumab after end of observation. Table T1.1 of the Tables, Listings and Figures (TFLs) provided in Annex 5 shows the patient disposition by tumor type and by country.

10.2 Descriptive Data

Patient demographics

In the FAS, 54.2% of patients (n=324) had breast cancer, 24.4% (n=146) had prostate cancer, 9.9% (n=59) had lung cancer. 11.5% (n=69) had cancers summarized as "other"

in the overall analysis; these were colon cancer (15.9%, n=11), renal cell cancer (11.6%, n=8), rectal cancer (5.8%, n=4), ovarian cancer (5.8%, n=4), head and neck cancer (5.8%, n=4), cervical cancer (4.3%, n=3), gastric cancer (2.9%, n=2), endometrial cancer (2.9%, n=2), thyroid cancer (1.4%, n=1), soft-tissue sarcoma (1.4%, n=1), and other cancers specified in free-text field, but not formally analyzed (42.0%, n=29). 62.9% of patients were female, owing to the large number of patients with breast cancer. The median age was 65.0 years (range: 24 – 91); 47.8% of patients (n=286) were younger than 65 years and 52.2% (n=312) were 65 years or older, and 16.9% (n=101) were 75 years or older. Patients with prostate cancer had the largest proportion of very old patients aged 75 or older (32.2% of patients with prostate cancer, n=47), patients with lung cancer had the fewest of very old patients (5.1% of patients with lung cancer, n=3). Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 52.5% of patients (n=314), 1 in 40.5% (n=242) and 2 in 7.0% (n=42). Table 1 shows patient demographics.

Disease characteristics

In Austria and Slovakia, the largest group of represented tumors was breast cancer, in Hungary, only prostate cancer patients were enrolled. In the Czech Republic and Bulgaria, breast and prostate cancer patients were approximately equally represented and formed the largest groups. 44.0% of patients (n=263) were diagnosed for cancer less than one year before baseline, with a median time since cancer diagnosis of 19 months (interquartile range [IQR] 2.2, 65.0). The median time since diagnosis ranged from 1.8 months in lung cancer patients to 35.9 months in breast cancer patients. In 86.6% of patients (n=518), metastatic disease was diagnosed less then one year before baseline, with a median time since diagnosis of one month (IQR 0.6, 4.4). In 93.0% of patients (n=556) bone metastases were diagnosed less than one year before baseline. Of patients, 46.7% (n=279) had bone metastases only, and 53.3% (n=319) had metastases in the bone and other sites, with 21.6% (n=129) having liver metastases, 20.2% (n=121) having lung metastases, 3.7% (n=22) having brain metastases, and 28.6% (n=171) showing metastases on other sites. Patient could have metastases in more than one site. Table 2 shows disease characteristics.

Prior treatments

In the metastatic setting, 35.3% of patients (n=211) had received previous chemotherapy, 32.8% (n=196) had received previous hormonal therapy, 14.4% (n=86) had received previous radiotherapy, 7.9% (n=47) had received previos surgery, and

7.7% (n=46) had received previous antiresorptive therapy. Previous antiresorptive therapies were zoledronic acid (6.2%, n=37), ibandronate (0.3%, n=2), pamidronate (0.3%, n=2), and others, not specified (0.8%, n=5), mainly via the intravenouy route (6.7%, n=40: Six patients (1.0%) received antiresorptive agents per os. All 46 patients received their antiresorptive therapy for 6 months or less. Reasons for not continuing previous antiresorptive therapies were intolerability in 1.5% (n=9), patient's wish (0.5%, n=3), and physician decision (5.7%, n=34). Physicians decided to stop previous antiresorptive agents because of the route of administration (3.3%, n=20), renal insufficiency (1.5%, n=9), or other, not-specified reasons reasons (1.2%, n=7).

Concomitant therapies

Concomitant therapies, i.e. therapies administered during study observation concomitantly with denosumab, were chemotherapy (52.3%, n=313), hormonal therapy (46.3%, n=277), radiotherapy (15.7%, n=94), and surgery (3.5%, n=21).

Prior skeletal-related events

10.9% of patients (n=65) had previous SREs; 7.5% (n=45) had pathological fractures, 2.2% (n=13) required radiation to the bone, 1.5% (n=9) had surgery to the bone, and 0.5% (n=3) had spinal cord compression. Figure 2 shows the proportions of patients with previous SREs overall and by tumor type. The time between SRE and diagnosis of cancer was <3 months in 7.4% of patients (n=44) and between 3 and 6 months in 2.3% (n=14); in 2 patients (0.3%) it was between 6 and 12 months, and in 5 patients (0.8%) it was longer than 12 months. 3.2% of patients (n=19) received an intervention due to their SRE(s), mostly other, not-specified interventions (2.8%, n=17); 0.5% (n=3) received bisphosphonates for their SRE(s). Multiple options per patient were possible.

Tables T2.1 to T2.6 of the TFLs provided in Annex 5 show details of data described in Section 10.2 by tumor type and by country.

10.3 Outcome Data

Outcomes were analyzed for each different tumor types, breast cancer (n=324), prostate cancer (n=146), lung cancer (n=59), other cancers (n=69), overall (n=598) and by participating country, Austria (n=294), Bulgaria (n=130), Czech Republic (n=103), Slovakia (n=54), and Hungary (n=17). Combined overall results are presented here. Major differences between tumor types or countries are highlighted as applicable and discussed in the Generalizability Section (Section 11.4). Tables T3.1.1 to T8.1 of the

TFLs provided in Annex 5 show details of data described in Section 10.4 to Section 10.6 by tumor type and by country.

10.4 Main Results

Persistence at 24 weeks

The primary outcome measure of this observational study was the number of patients persistent for denosumab use at 24 weeks from 1st administration of denosumab, excluding patients who died or were lost to follow-up before week 24. A patient was considered persistent for denosumab use at 24 weeks if he/she received at least 6 departially nosumab injections no more than 4 weeks plus 7 days apart. The denominator for the proportion was the number of patients in FAS excluding patients who died or were lost to follow-up before week 24 and did not violate the persistence definition before the discontinuation date. According to this definition, persistence at week 24 was 62.6% (95% CI 58.4, 66.7) overall, and ranged between 26.1% for lung cancer and 69.5% for breast cancer,and between 56.0% for Austria and 84.8% for Slovakia. Figure 3 and Figure 4 show persistence at 24 weeks by tumor type and by country, respectively. The sensitivity analysis showed that extending the definition of patients excluded did not change the results. However, extending the time window after week 24 to 4 weeks increased the proportion of patients persistent at week 24 by more than 10% (lower limit of 95% CI of time window extended to 4 weeks not overlapping upper limit of 95% CI of primary time window of 24 weeks plus one week and time window extended to 2 weeks). Figure 5 shows results of the sensitivity analysis of persistence at week 24.

Persistence at 48 weeks

The secondary outcome measure was persistence at 48 weeks from 1st administration of denosumab. By the primary definition excluding patients who died or were lost to follow-up before week 48 and did not violate the persistence definition before the discontinuation date, persistence at 48 weeks was 40.1% (95% CI 35.9, 44.4). Patterns by tumor type and by country were similar to the persistence results for week 24. Figure 6 and Figure 7 show persistence at 48 weeks by tumor type and by country, respectively. A similar sensitivity analysis was conducted. Results are shown in Tables T3.2.1 to T3.2.3a of the TFLs provided in Annex 5.

Time to non-persistence

The Kaplan-Meier (KM) method was used to estimate the proportion of patients who were still persistent at 24 weeks and 48 weeks. The KM median (95% CI) time to non-persistence was 274.0 (232.0, 316.0) days, with 317.0 (263.0, 335.0) in breast cancer, 325.0 (271.0, 344.0) in prostate cancer, 118.0 (59.0, 144.0) in lung cancer, and 118.0 (57.0, 230.0) in other cancers (Figure 8). Sensitivity analyses, in which patients who died or were lost to follow-up before Week 48 were always considered censored, irrespective of whether they violated the definition of persistence, and sensitivity analyses with time windows after end of week 48 were extended by 7 or 10 weeks were performed. Extension of time windows was shown to have considerable effects on time to persistence in lung cancer and other cancers. In breast and prostate cancers, none of the sensitivity analyses had strong effects on the results (Figure 9). An analysis of median time to non-persistence by previous antiresorptive therapy (y/n) showed a KM median (95% CI) of 294.0 days (168.0, 344.0) for 46 patients with previous antiresorptive therapy and 273.0 days (232.0, 316.0) for 552 patients with no previous antiresorptive therapy. Persistence at week 24 was influenced by tumor type (breast versus lung, prostate versus lung), previous chemotherapy (y/n), number of metastases (unknown versus multiple) and concomitant radiotherapy (y/n) (all factors with $p < 0.05$). Persistence at week 48 was influenced by tumor type (breast versus lung, prostate versus lung), previous chemotherapy (y/n), and number of metastases (unknown versus multiple) (all factors with $p < 0.05$). The most frequently documented reason for non-persistence at 24 weeks was the violation of time windows (77.2%, n=156 of 202 non-persistent patients). Of patients violating a time window (n=156), 75.6% (n=118/156) violated one time window. Violation of one time window was also the most frequently documented reason for non-persistence at week 48. Table 3 summarizes all reasons for non-persistence at week 24 and 48. The analysis of influence factors of time to non-persistence showed significance ($p < 0.05$) for cancer type, ECOG status, and previous anticancer therapy including chemotherapy, surgery, radiotherapy or hormonal therapy. For previous anticancer therapies, influencing factors were calculated including all of therapies and a separatly for each of them. A summary of time to non-persistence analysis using a proportional hazards model is shown in Tables T3.8.1 to T3.8.3a of the TFLs provided in Annex 5.

Denosumab exposure

Patients received denosumab for a median (IQR) of 309 days (168.0, 319.0) and 11 doses (6.0, 12.0). The median (IQR) study duration was 48 weeks (27.3, 49.9).

The most frequent physician-reported reasons for the selection of denosumab were the prevention of first SRE (63.5%, n=380; first most important), superior efficacy of denosumab (28.3%, n=169, second most important), and better safety provile of denosumab (15.6%, n=93; third most important).

Calcium and vitamin D supplementation

At baseline, 70.2% of patients (n=420) received calcium supplementation and 71.4% (n=427) received vitamin D supplementation. The baseline median (IQR) serum calcium was 2.35 (2.25, 2.44) mmol/L. At the second dose of denosumab, serum calcium was 2.26 (2.15, 2.37). Serum calcium remained above this lowest value from the third dose onwards throughout the study. Approximately 70% of patients received calcium and vitamin D supplements at baseline, increasing to approximately 80% at dose 2 and steadily decreasing thereafter. Figure 10 shows median (IQR) serium calcium levels over time and the proportions of patients receiving calcium and vitamin D supplementation. Calcium and vitamin D supplementation data are shown in Tables T4.1.1 to T4.1.3, and laboratory parameters are shown in Table T6.1 of the TFLs provided in Annex 5.

Pain management

The proportion of patients receiving or not receiving analgesics was calculated using the FAS as the denominator. In a post-hoc analysis, the number of patients with available data entries at each timepoint was used as the denominator. Overall, the proportion of patients not using analgesics remained constant at approximately 60% of patients with available values at the respective timepoints. Figure 11 shows both methods of calculation for patients not receiving analgesics. The proportion of patients receiving non-opiod analgesics increased from 20% of patients with available values at baseline to 29% (9th dose and thereafter). The proportion of patient receiving strong opiods at a dose <75 mg oral morphine equivalents (OME) per day ranged between 9% and 11%. The percentages are based on the number of patients with available values. The pain medication and clinician based 8-point scale analgesics score (AQA) showed a median (IQR) score at baseline of 0.0 (0.0, 1.0). It did not change over time. Pain management and pain scores are shown in Tables T4.2.1 to T4.3.3 of the TFLs provided in Annex 5.

10.5 Other Analyses

Not applicable.

10.6 Adverse Events/Adverse Reactions

Only denosumab-related adverse drug reactions (ADRs) were collected; adverse events not related to denosumab were not collected. Overall, 10.2% of patients (n=61) experienced an ADR. The most frequently reported ADR was hypocalcemia (7.4%, n=44). Ten patients (1.7%) experienced ADRs leading to discontinuation of denosumab (osteonecrosis including of the jaw, n=3; joint stiffness, n=1; myalgia, n=1; hypocalcemia, n=3; hypophosphatemia, n=1; peripheral edema, n=1; cellulitis, n=1). It was possible for a single patient to have more than one ADR and more than one event of a particular ADR. If a patient had more than one type of ADR, each ADR was counted; if one ADR occurred multiple times it was counted only once per patient. Eight patients (1.3%) experienced serious ADRs. Osteonecrosis was documented in 3 patients (0.7%). One patient (ID 28) experienced osteonecrosis in regio 48 lingualis after 4 injections of denosumab (1 event). Patient 473 experienced osteonecrosis of the jaw after 6 injections of denosumab. The patient complained about pain in the jaw and her cheek was swollen. An X-ray was ordered from the dentist. Osteonecrosis was diagnosed in regio 23+ 24. An antibiotic therapy with augmentin was started. For patient 473 this sequence of events was split into 3 terms and treated as 3 events. Patient 152 experienced osteonecrosis (not further characterized) after 10 injections of denosumab (1 event). The median (IQR) duration to first ONJ event based on these 3 patients was 165.0 days (105.0, 298.0). Other serious ADRs reported were costovertebral angle tenderness (n=1), pain (n=1), hypocalcemia (n=1), peripheral edema (n=1), dyspnea (n=1), swelling face (n=1), and cellulitis (n=1). No fatal ADRs occurred.

Overall, the exposure-adjusted incidence rate of ADRs per patient-years was 0.187 (95% CI 0.147, 0.235), for SADRs 0.027 (95% CI 0.014, 0.049), for fatal ADRs 0.000 (95% CI 0.000, 0.009), ADRs leading to discontinuation of denosumab 0.027 (95% CI 0.014, 0.049) and ONJ events 0.012 (95% CI 0.004, 0.029).

Other safety findings were 2 patients in the category medication error, overdose, misuse, or abuse. Summaries of safety findings are shown in Tables T5.1.1 to T5.3, T7.1 and T8.1 of the TFLs provided in Annex 5.

11. DISCUSSION

11.1 Key Results

This study analysed 598 patients: Austria (n=294), Bulgaria (n=130), Czech Republic (n=103), Slovakia (n=54), and Hungary (n=17). 54.2% of patients (n=324) had breast cancer, 24.4% (n=146) had prostate cancer, 9.9% (n=59) had lung cancer. 11.5% (n=69) had cancers summarized as “other” in the overall analysis; 62.9% of patients were female. The median age was 65.0 years (range: 24 – 91). 44.0% of patients (n=263) were diagnosed for cancer less than one year before baseline and in 86.6% of patients (n=518). Metastatic disease was diagnosed less then one year before baseline. Of patients, 46.7% (n=279) had bone metastases only, and 53.3% (n=319) had metastases in the bone and other sites. 10.9% of patients (n=65) had previous SREs: 7.5% (n=45) had pathological fractures, 2.2% (n=13) required radiation to the bone, 1.5% (n=9) had surgery to the bone, and 0.5% (n=3) had spinal cord compression. 3.2% of patients (n=19) received an intervention due to their SRE(s).

Patients received denosumab for a median (IQR) of 309 days (168.0, 319.0) and 11 doses (6.0, 12.0). The median (IQR) study duration was 48 weeks (27.3, 49.9). Persistence at week 24 was 62.6% (95% CI 58.4, 66.7) overall, and ranged between 26.1% for lung cancer and 69.5% for breast cancer,and between 56.0% for Austria and 84.8% for Slovakia. Persistence at 48 weeks was 40.1% (95% CI 35.9, 44.4). The Kaplan-Meier median (95% CI) time to non-persistence was 274.0 (232.0, 316.0) days, with 317.0 (263.0, 335.0) in breast cancer, 325.0 (271.0, 344.0) in prostate cancer, 118.0 (59.0, 144.0) in lung cancer, and 118.0 (57.0, 230.0) in other cancers. The most frequently documented reason for non-persistence at 24 weeks was the violation of time windows (77.2%, n=156 of 202 non-persistent patients). Of patients violating a time window (n=156), 75.6% (n=118/156) violated one time window. Violation of one time window was also the most frequently documented reason for non-persistence at week 48.

Overall, a steady proportion of approximately 60% of patients did not use analgesics. The proportion of patient receiving strong opiods at a dose <75 mg oral morphine equivalents (OME) per day ranged between 9% and 11%. The percentages are based on the number of patients with available values.

Overall, 10.2% of patients (n=61) experienced an ADR. The most frequently reported ADR was hypocalcemia (7.4%, n=44). Eight patients (1.3%) experienced serious ADRs.

Osteonecrosis was documented in 3 patients (0.7%), two with confirmed osteonecrosis of the jaw, one with unspecified osteonecrosis. No fatal ADRs occurred.

11.2 Limitations

This study was an observational study with all limitations inherent to the observational study design, as described in Section 9, applying, especially selection and reporting bias and lack of blinding and of a control group.

Persistence was estimated taking all drop-outs related to denosumab into account. Impact of bias was addressed in sensitivity analyses. The sensitivity analyses revealed that the different ways of handling drop-outs did not change the results of the primary and secondary outdome measure. The most important reason for non-persistence was missing one time window and the extension of the time windows for week 24 and week 48 persistence analysis were the only factors having an impact on results in the sensitivity analyses.

The study originally planned approximately 190 sites in Austria, Poland, Czech Republic, Hungary, Slovakia, Slovenia, Romania, Bulgaria and a total of approximately 1.500 patients in order to minimizing bias of excluding difficult patients and to ensure the accuracy of estimates of the primary and secondary endpoints. However, Poland and Romania did not participate in the study, because denosumab was not reimbursed, and in Slovenia the minimum required number of sites and thus patients could not be reached. The final number of enrolled patients was 634 patients. The sample size calculation, however, was done on the originally assumed number of 1500 patients. As per SAP the proposed sample size is based on the objective to estimate the 95% confidence interval (CI) around the proportion of persistence. Due to the lower actual number of patients the confidence interval will be wider than planned and the precision smaller. However, since the previously assumed proportion of patients persistent to denosumab at 24 weeks of 60% based on phase 3 studies (Stopeck, 2010, Fizazi, 2011, Henry, 2011, Lipton, 2012) is very similar to the actually observed persistence at 24 weeks found in this study (62.6%), it can be assumed that the primary outcome measure has been evaluated with an adequate level of precision.

Patients received a diary to report each administration of denosumab. Especially in countries where denosumab is distributed as a retail product and not exclusively administered in the hospital, patient self-reporting may be prone to inaccuracies.

11.3 Interpretation

This study is part of a group of similarly designed studies. The study protocol and statistical analysis plan has been aligned with the German X-TREME study (20101312) and the Greek XPERT study (20110277) to allow a pooled analysis.

In the present study, a patient was considered persistent for denosumab use at 24 weeks if he/she received at least 6 denosumab injections no more than 4 weeks plus 7 days apart and persistent for denosumab use at 48 weeks if he/she received at least 12 denosumab injections no more than 4 weeks plus 7 days apart. According to this definition, persistence at week 24 was 62.6% (95% CI 58.4, 66.7) and persistence at 48 weeks was 40.1% (95% CI 35.9, 44.4). In the German X-TREME study the final analysis on 1008 patients included in the persistence assessment, showed persistence for denosumab at week 24 of 61.5% (95% CI 58.5, 64.5). Persistence at week 48 was 37.7% (95%CI 34.6, 40.9). These findings are very similar to the results of the present study. For the Greek XPERT study, no results are available to date.

A retrospective analysis of a German sick-fund claims database including ~1156 adult patients with solid tumors (breast, prostate or lung cancer) newly diagnosed with bone metastases and no prior hypercalcemia, who initiated denosumab or bisphosphonates. Persistence was defined as continuous prescriptions with <90-days gaps. Of patients with breast, prostate, and lung cancer, respectively, 25%, 17% and 20% had prior SREs. For breast cancer, persistence at 1 year, according to the above definition, was 78% (95% CI 70-85) for denosumab and 58% (45-75), 56% (43-72) and 54% (47-61) for ibandronate, pamidronate and zoledronate, respectively. For prostate cancer, persistence with denosumab and zoledronate were 58% (48-71) and 50% (42-59), respectively. Finally for lung cancer persistence for denosumab, pamidronate and zoledronate were 68% (47-99), 34% (15-80) and 60% (50-73), respectively. Persistence was lower in a sensitivity analysis in which the definition of persistence was applying 60-day gaps/windows and was thus stricter. The definition of persistence differed between these studies and was substantially stricter in the present study, as the German sick-fund study did not take into account persistence for each of the individual once-monthly administrations and missing one time window was the most important reason for non-persistence.

The incidence of osteonecrosis was 0.5% in the present study (n=3), with two confirmed cases of osteonecrosis of the jaw and one with unspecified location. In the German X-TREME study 15 patients with suspected ONJ (1.3%) were reported. In randomized

controlled studies of denosumab, 2% of breast cancer patients, 2.3% of prostate cancer patients and 1.1% of patients with either a solid tumor or multiple myeloma experienced ONJ (Stopeck, 2010, Fizazi, 2011, Henry, 2011).

11.4 Generalizability

Data extractions were performed for interim analysis to review any inconsistencies within the data and minimise the effects of bias. Centre selection bias was a potential threat to representativeness of the patient population included in the study. Therefore a wide selection of hospitals were selected to adequately represent the health care facilities of each country, based on their estimated number of subjects, their experience in observational studies, the type of site and their geographical location to ensure geographical spread within each participating country. The fact that a site was participating in a trial may change how the clinicians routinely record information. Also, there may have been systematic differences in the patients who consent to participate in the prospective setting of this study. In addition, there may have been a potential for initially selecting more severe patients for this study thereby having a biased comparison with the general population of patients with bone metastases.

Sensitivity analyses and subgroup analyses taking confounding factors into account were performed. The subgroup analyses by tumor type and by country revealed some differences in persistence as outlined in Section 10.4, which limit generalizability of the results to other tumors, countries, and regions. An analysis of the distribution of tumor types by country revealed that differences between countries can at least in part be explained by the different distribution of tumors in each country. Another difference between countries is the method of dispensation of denosumab to the patients. In Austria denosumab is mainly dispensed as a retail product; in Hungary it is available as a retail product and reimbursed in prostate cancer only. In Czech Republic and Bulgaria, it is administered exclusively in hospitals. In Slovakia it was a retail product during the first part of the present study and a hospital product as of October 2016. For further subgroup analyses see the TFLs provided as standalone documents (see Annex 5).

12. OTHER INFORMATION

None.

13. CONCLUSION

The majority of patients were persistent with treatment with denosumab every 4 weeks for over 24 weeks after initiation. The primary tumour type, previous chemo- or concomitant radiotherapy, the number of metastases, appeared to influence whether or not a patient was persistent. The most frequent reason for non-persistence was the violation of one time window. Most patients reported taking calcium and vitamin D supplementation as recommended in the Summary of Product Characteristics. The incidence adverse drug reactions, expecially of osteonecrosis of the jaw was not higher than expected from previous studies.

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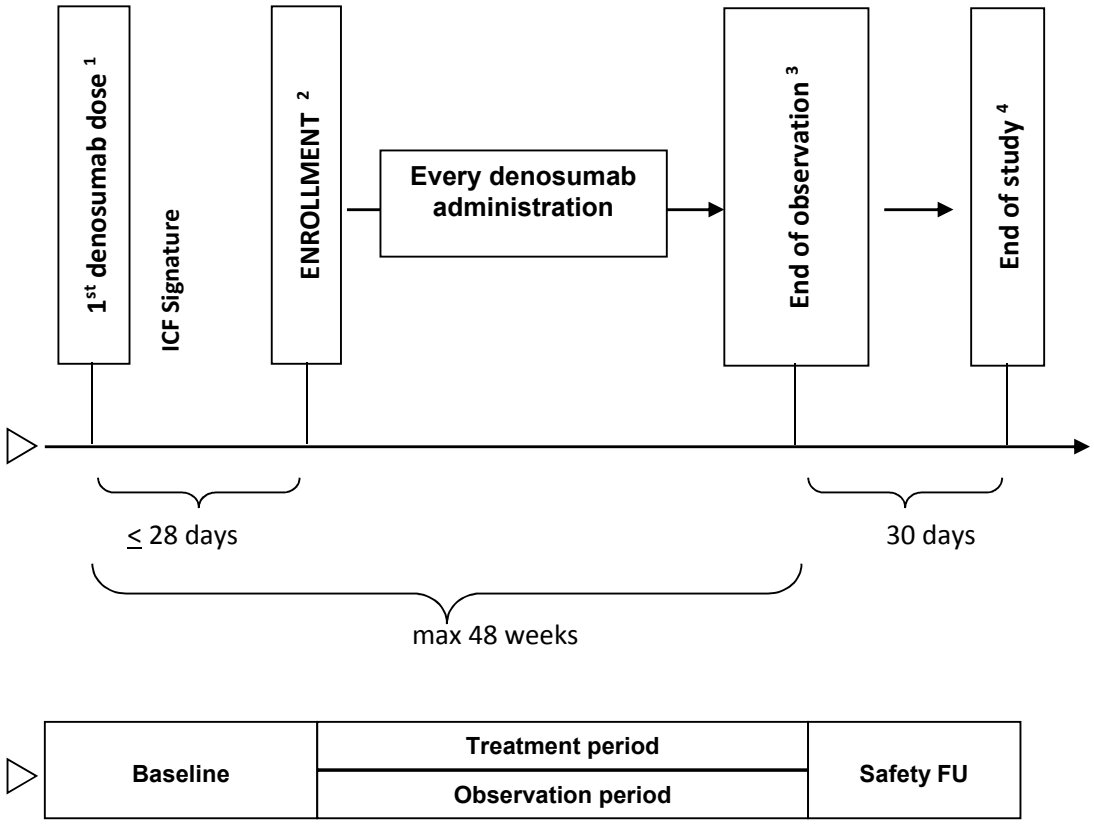
15. SUMMARY TABLES, FIGURES, AND LISTINGS

Figure 1. Study Design and Treatment Schema



Definitions:

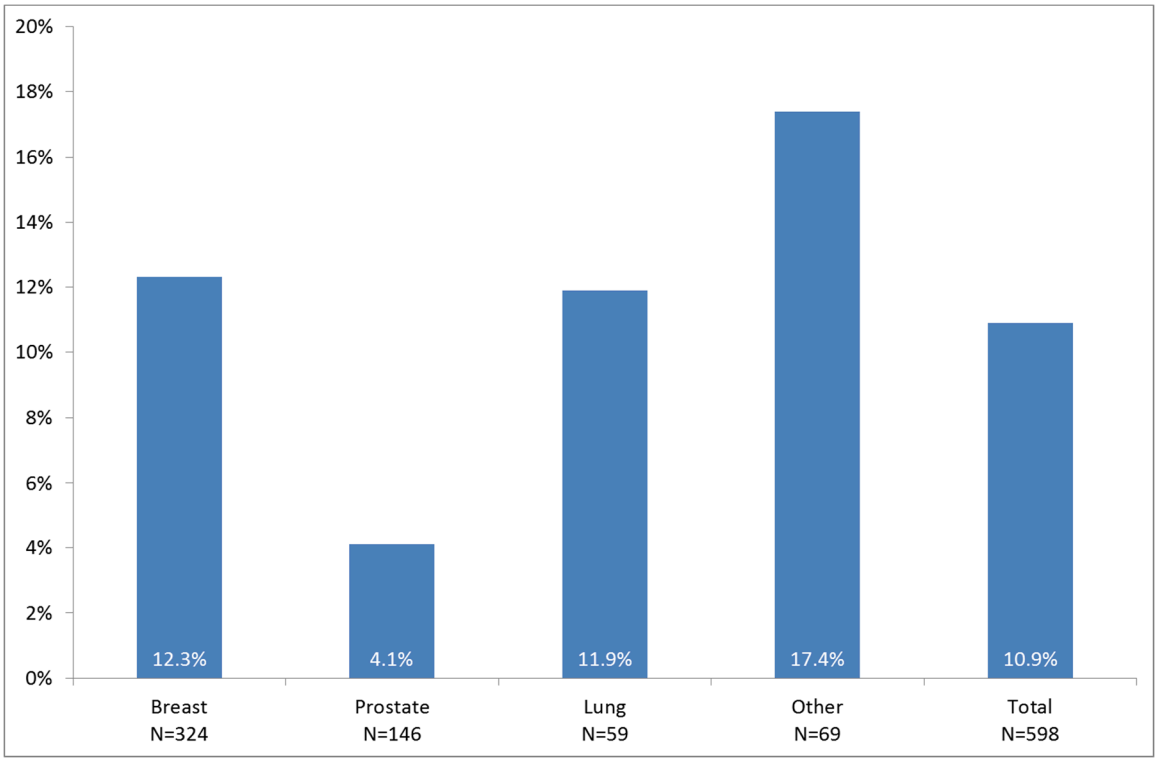
1 1st dose denosumab is defined as the first administration of denosumab as per standard of care (SoC) for a patient and will also be the first dose to be documented in this study.

2 Enrollment is defined as the day of eCRF registration (≤ 28 days post first denosumab dose but not later than the 2nd denosumab dose).

3 Observation period is defined as time from 1st administration until the last denosumab dose administered up to a max of 48 weeks.

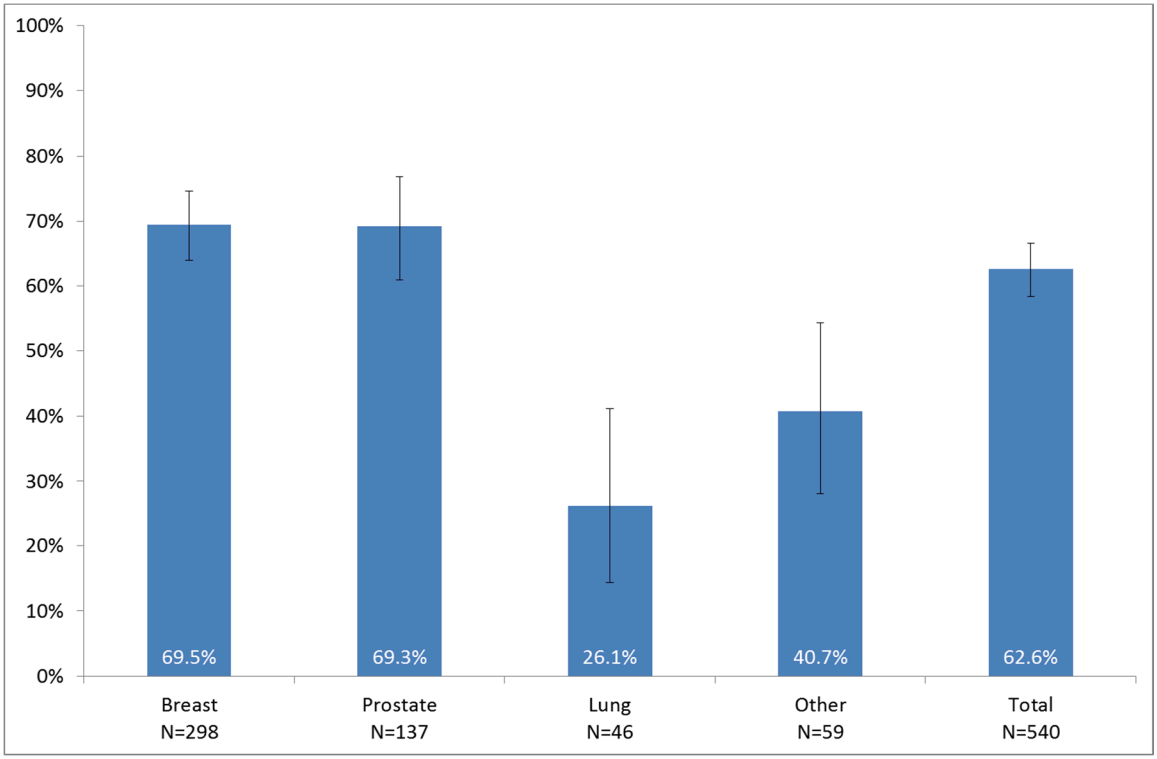
4 End of study is the end of the observation + 30 day safety follow-up.

Figure 2. Previous Skeletal-related Events, Overall and by Tumor Type



Note: percentages are based on the number of patients in Full Analysis Set.

Figure 3. Persistence for Denosumab at 24 Weeks, Overall and by Tumor Type (95% CI)

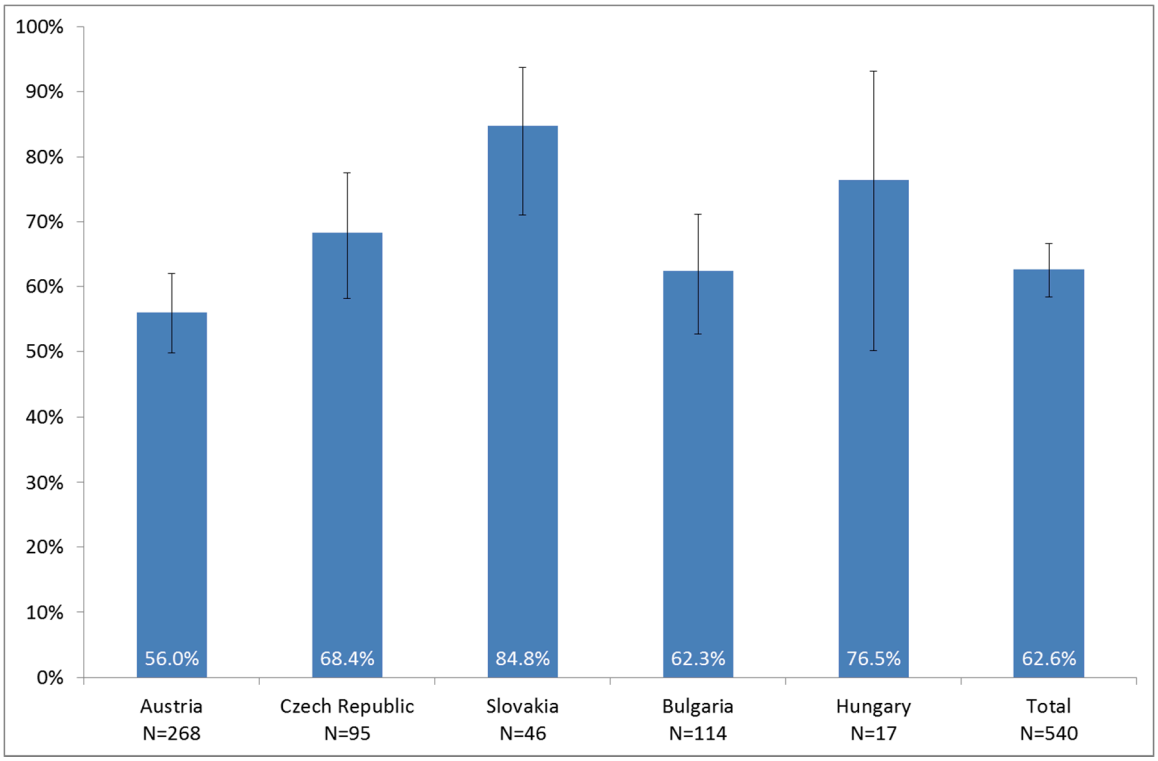


The analysis partially excluded patients who died or were lost to follow-up before week 24, i.e. the denominator for the proportion will be the number of patients in FAS excluding patients who died or were lost to follow-up before week 24 and did not violate the persistence definition before the discontinuation date.

A patient was considered persistent for denosumab use at 24 weeks if he/she received at least 6 denosumab injections no more than 4 weeks plus 7 days apart.

CI, confidence interval

Figure 4. Persistence for Denosumab at 24 Weeks, Overall and by Country (95% CI)

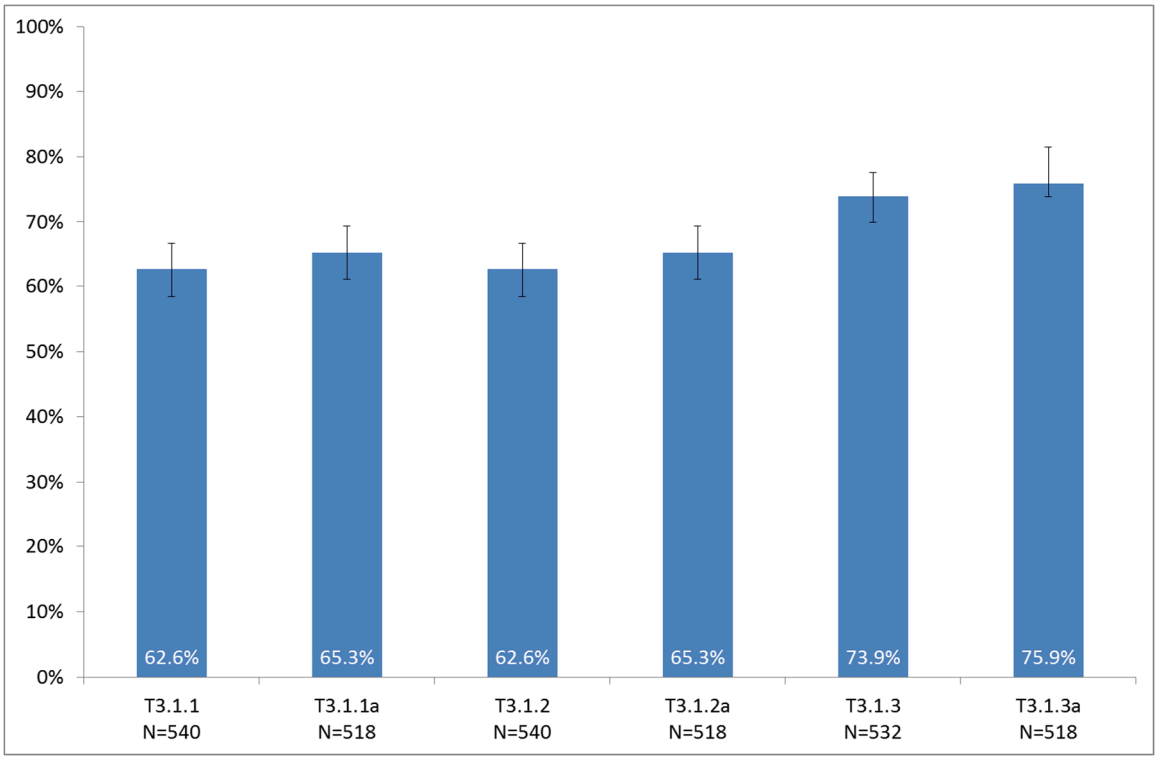


The analysis partially excluded patients who died or were lost to follow-up before week 24, i.e. the denominator for the proportion will be the number of patients in FAS excluding patients who died or were lost to follow-up before week 24 and did not violate the persistence definition before the discontinuation date.

A patient was considered persistent for denosumab use at 24 weeks if he/she received at least 6 denosumab injections no more than 4 weeks plus 7 days apart.

CI, confidence interval

Figure 5. Sensitivity Analysis of Persistence for Denosumab at 24 Weeks , Overall (95% CI)



The number and percentage of patients persistent to XGEVA at 24 weeks from 1st dose administration will be calculated along with exact 95% confidence limits.

A patient was considered persistent for denosumab use at 24 weeks if he/she received at least 6 denosumab injections no more than 4 weeks plus 7 days apart.

T3.1.1, T3.1.2, T3.1.3: The denominator for the proportion will be the number of patients in FAS excluding subjects who died or were lost to follow-up before week 24 and did not violate the persistence definition before the discontinuation date.

T3.1.1a, T3.1.2a, T3.1.3a: In order to explore the impact of dropouts on the persistence a sensitivity analysis identical to described above will be carried out on FAS further excluding subjects who died or were lost to follow-up before week 24 regardless of whether they violated the persistence definition before the discontinuation date

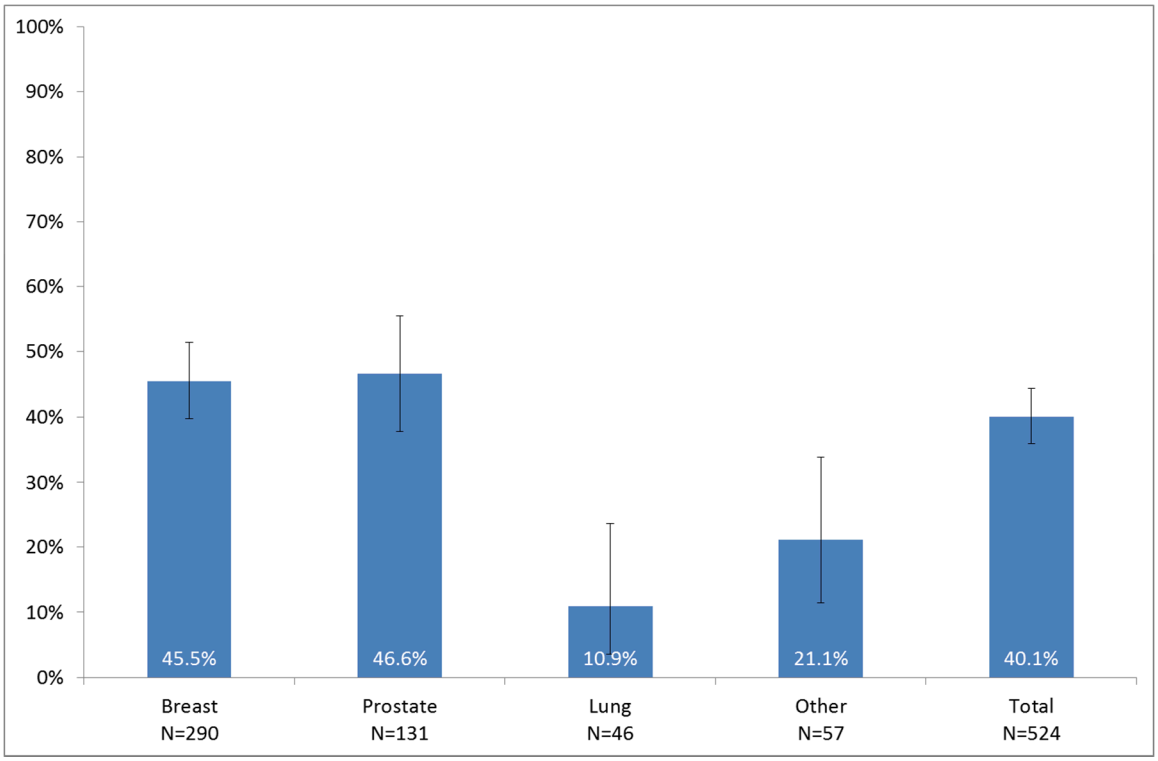
T3.1.1, T3.1.1a: Patients received at least 6 denosumab injections no more than 4 weeks plus 7 days apart.

T3.1.2, T3.1.2a: a time window of +2 weeks was allowed after the 24 weeks endpoint.

T3.1.3, T3.1.3a: a time window of +4 weeks was allowed after the 24 weeks endpoint.

CI, confidence interval

Figure 6. Persistence for Denosumab at 48 weeks, Overall and by Tumor Type (95% CI)

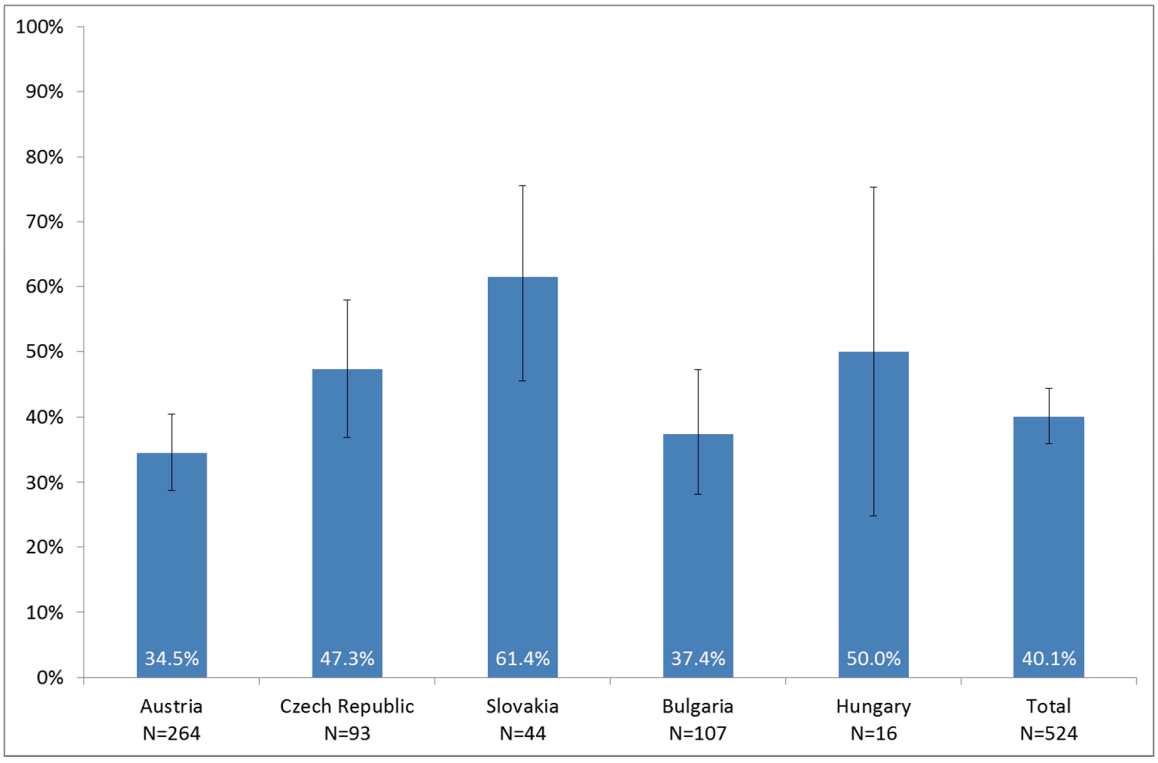


The analysis partially excluded patients who died or were lost to follow-up before week 48, i.e. the denominator for the proportion will be the number of patients in FAS excluding patients who died or were lost to follow-up before week 48 and did not violate the persistence definition before the discontinuation date.

A patient was considered persistent for denosumab use at 48 weeks if he/she received at least 12 denosumab injections no more than 4 weeks plus 7 days apart.

CI, confidence interval

Figure 7. Persistence for Denosumab at 48 Weeks, Overall and by Country (95% CI)



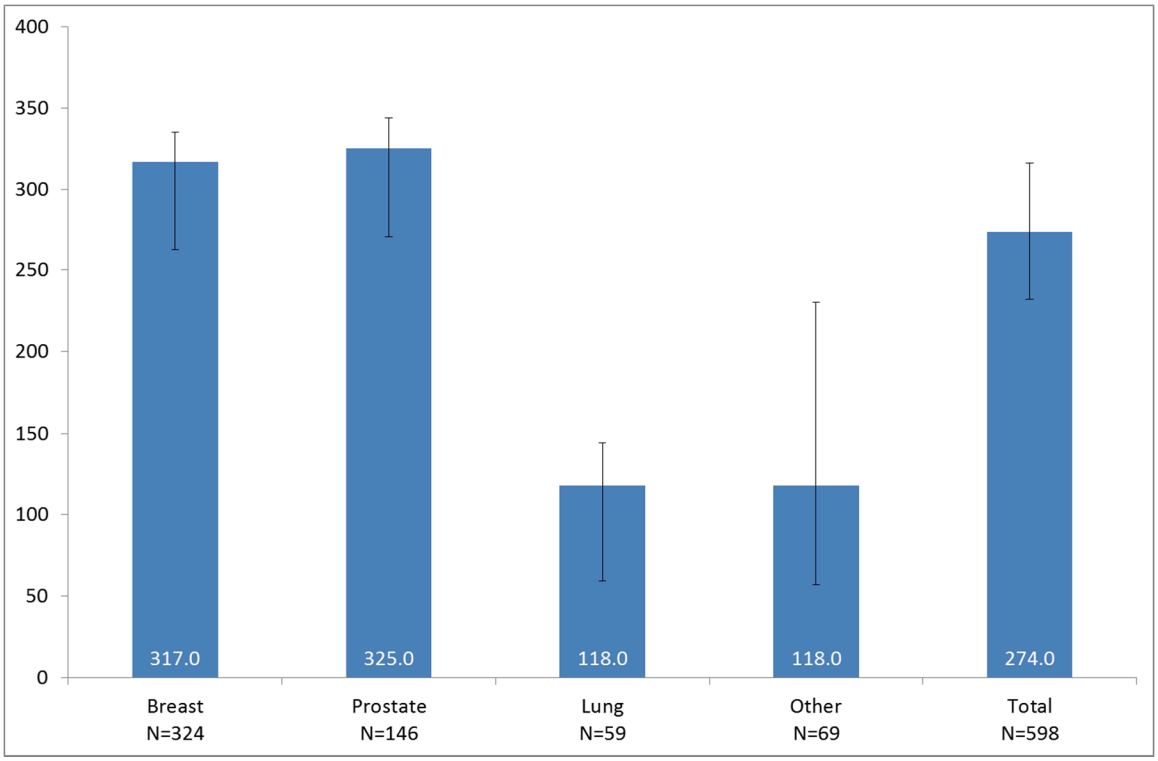
Note: percentages are based on the number of patients in Full Analysis Set.

The analysis partially excluded patients who died or were lost to follow-up before week 48, i.e. the denominator for the proportion will be the number of patients in FAS excluding patients who died or were lost to follow-up before week 48 and did not violate the persistence definition before the discontinuation date.

A patient was considered persistent for denosumab use at 48 weeks if he/she received at least 12 denosumab injections no more than 4 weeks plus 7 days apart.

CI, confidence interval

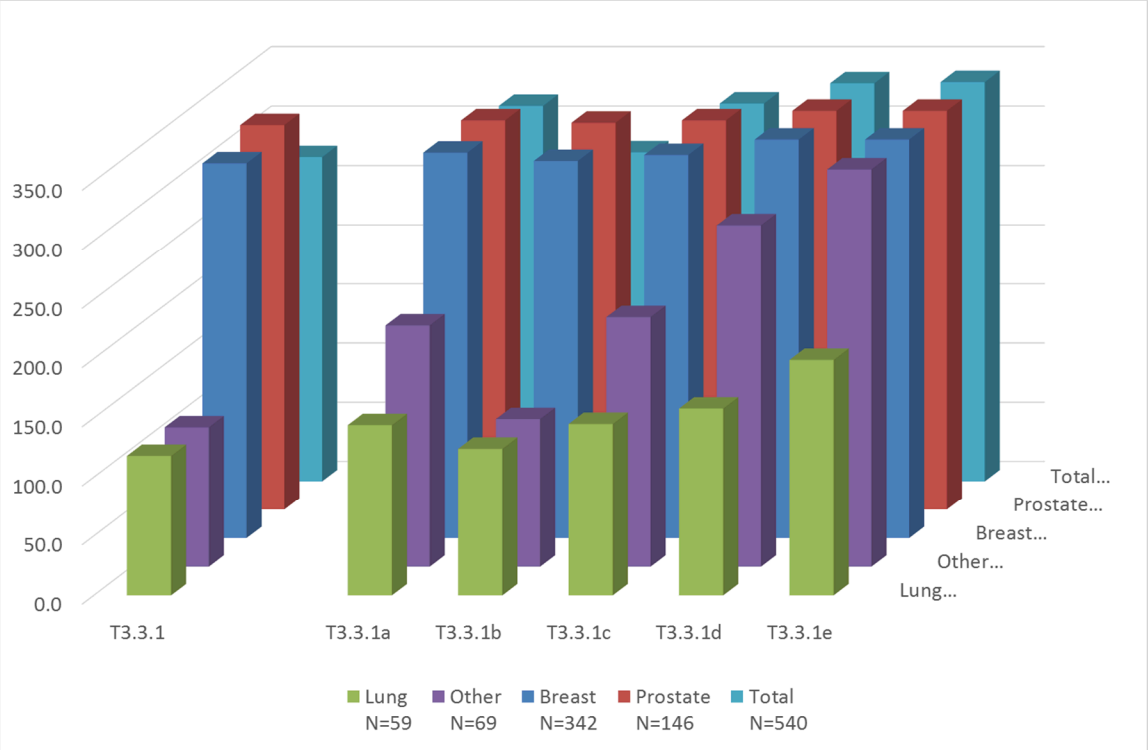
Figure 8. Time to Non-persistence (Days), Overall and by Tumor Type, Kaplan-meier Median (95% CI)



CI, confidence interval

Patients who died or were lost to follow-up before week 48 and did not violate the persistence definition before the discontinuation date were considered censored.

Figure 9. Sensitivity Analysis of Time to Non-persistence (days), Kaplan-meier Median



T3.3.1: Censors patients who died or were lost to follow-up before week 48 and did not violate the persistence definition before the discontinuation date (partial censoring).

T3.3.1a: Censors patients who died or were lost to follow-up before week 48, irrespective of whether they violated the definition of persistence before the discontinuation date (complete censoring).

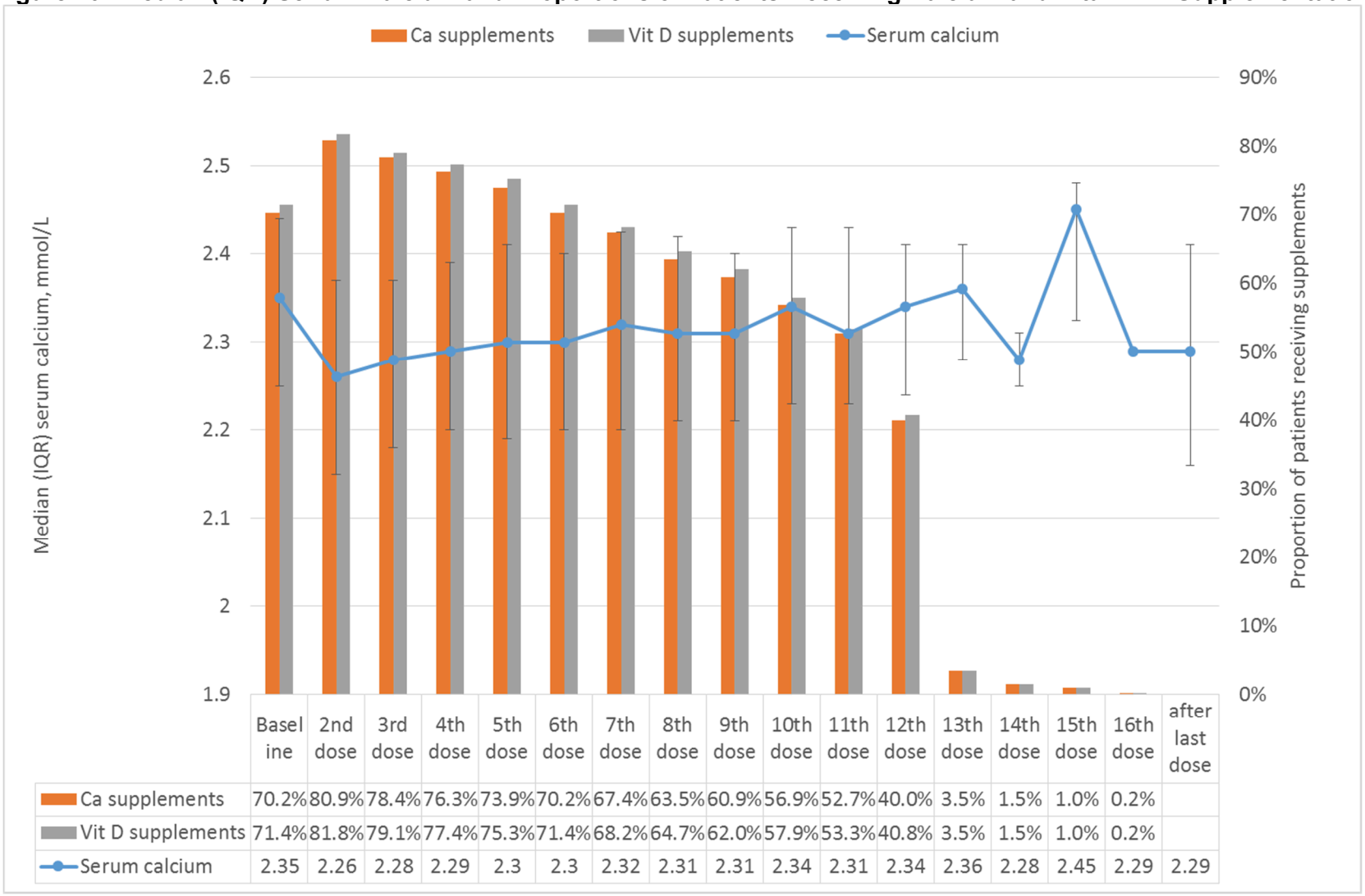
T3.3.1b: Partial censoring with time windows after end of week 48 were extended by 7 weeks.

T3.3.1c: Complete censoring with time windows after end of week 48 were extended by 7 weeks.

T3.3.1d: Partial censoring with time windows after end of week 48 were extended by 10 weeks.

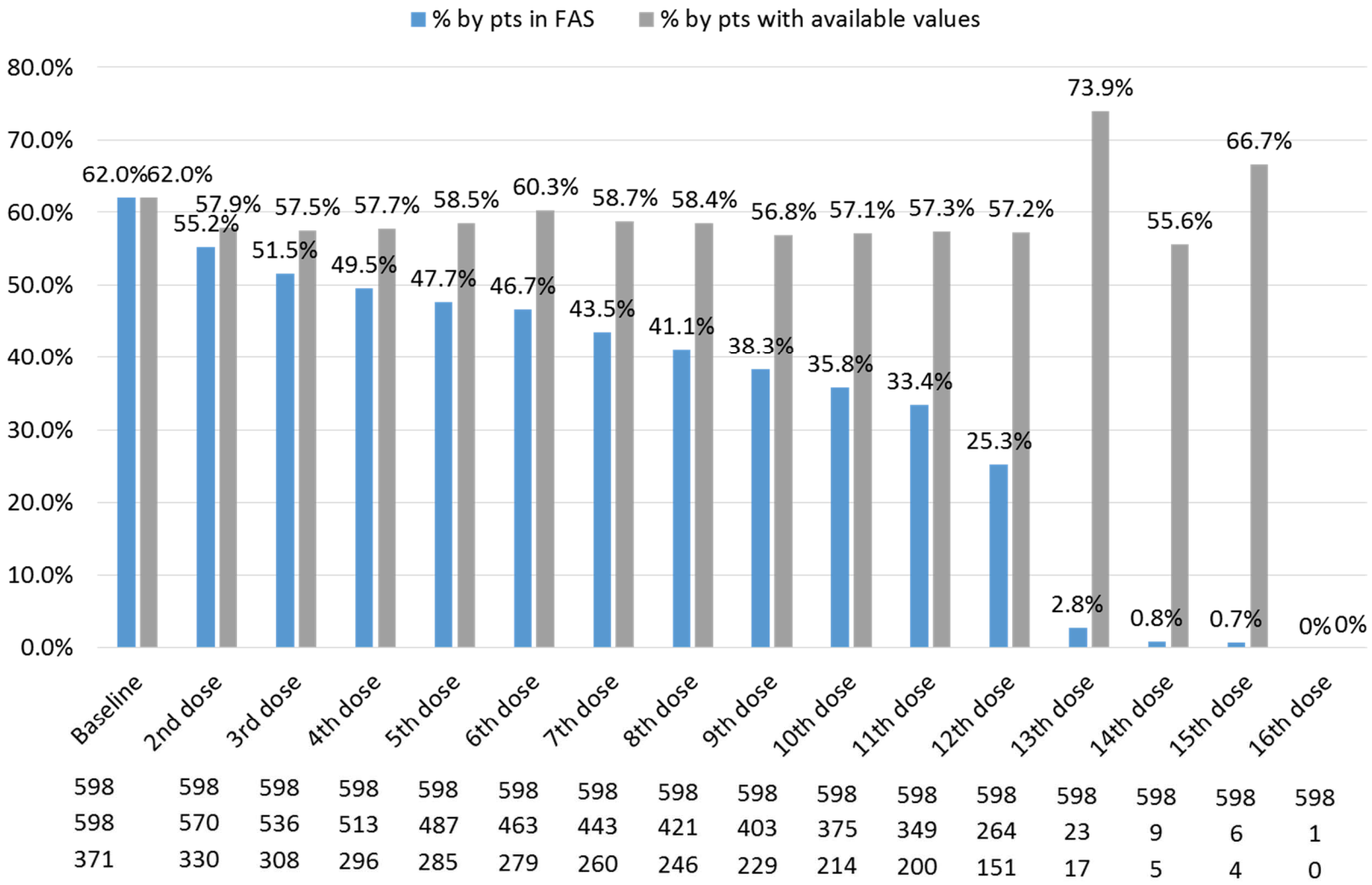
T3.3.1e: Complete censoring with time windows after end of week 48 were extended by 10 weeks.

Figure 10. Median (IQR) Serium Calcium and Proportions of Patients Receiving Calcium and Vitamin D Supplementation



	Baseline	2nd dose	3rd dose	4th dose	5th dose	6th dose	7th dose	8th dose	9th dose	10th dose	11th dose	12th dose	13th dose	14th dose	15th dose	16th dose	after last dose
Ca supplements	70.2%	80.9%	78.4%	76.3%	73.9%	70.2%	67.4%	63.5%	60.9%	56.9%	52.7%	40.0%	3.5%	1.5%	1.0%	0.2%	
Vit D supplements	71.4%	81.8%	79.1%	77.4%	75.3%	71.4%	68.2%	64.7%	62.0%	57.9%	53.3%	40.8%	3.5%	1.5%	1.0%	0.2%	
Serum calcium	2.35	2.26	2.28	2.29	2.3	2.3	2.32	2.31	2.31	2.34	2.31	2.34	2.36	2.28	2.45	2.29	2.29

Figure 11. Proportion of Patients not Using Analgesics



N_{FAS}=	598	598	598	598	598	598	598	598	598	598	598	598	598	598	598	598
N_{avail}=	598	570	536	513	487	463	443	421	403	375	349	264	23	9	6	1
n=	371	330	308	296	285	279	260	246	229	214	200	151	17	5	4	0

Footnotes defined on next page

N_{FAS}, number of patients in the full analysis set; the primary analysis used the FAS as the denominator for the percent of patients not using analgesics.

N_{avail}, number of patients with available values on analgesics use at a given timepoint; the post-hoc analysis used the number of patients with available values as the denominator for the percent of patients not using analgesics.

n, number of patients not using analgesics

Table 1. Patient Demographics

Characteristic	Breast Cancer (N=324)	Prostate Cancer (N=146)	Lung Cancer (N=59)	Other (N=69)	Total (N=598)
Age (years)					
n	324	146	59	69	598
Mean	60.6	70.5	62.8	66.3	63.9
SD	12.06	7.74	9.45	9.25	11.36
Q1	51.0	65.0	57.0	60.0	57.0
Median	61.0	72.0	65.0	66.0	65.0
Q3	70.0	76.0	69.0	74.0	72.0
Min	30	46	24	46	24
Max	91	87	77	89	91
<65	197 (60.8%)	32 (21.9%)	27 (45.8%)	30 (43.5%)	286 (47.8%)
>=65	127 (39.2%)	114 (78.1%)	32 (54.2%)	39 (56.5%)	312 (52.2%)
<75	286 (88.3%)	99 (67.8%)	56 (94.9%)	56 (81.2%)	497 (83.1%)
>=75	38 (11.7%)	47 (32.2%)	3 (5.1%)	13 (18.8%)	101 (16.9%)
18-<25	0	0	1 (1.7%)	0	1 (0.2%)
25-<35	4 (1.2%)	0	0	0	4 (0.7%)
35-<45	27 (8.3%)	0	1 (1.7%)	0	28 (4.7%)
45-<55	71 (21.9%)	4 (2.7%)	5 (8.5%)	6 (8.7%)	86 (14.4%)
55-<65	95 (29.3%)	28 (19.2%)	20 (33.9%)	24 (34.8%)	167 (27.9%)
65-<75	89 (27.5%)	67 (45.9%)	29 (49.2%)	26 (37.7%)	211 (35.3%)
75-<85	31 (9.6%)	46 (31.5%)	3 (5.1%)	12 (17.4%)	92 (15.4%)
>=85	7 (2.2%)	1 (0.7%)	0	1 (1.4%)	9 (1.5%)
Gender					
Male	2 (0.6%)	146 (100.0%)	34 (57.6%)	40 (58.0%)	222 (37.1%)
Female	322 (99.4%)	0	25 (42.4%)	29 (42.0%)	376 (62.9%)
ECOG Status					
0	194 (59.9%)	70 (47.9%)	22 (37.3%)	28 (40.6%)	314 (52.5%)
1	108 (33.3%)	67 (45.9%)	34 (57.6%)	33 (47.8%)	242 (40.5%)
2	22 (6.8%)	9 (6.2%)	3 (5.1%)	8 (11.6%)	42 (7.0%)

Note: percentages are based on the number of patients in Full Analysis Set.

Table 2. Patient and Disease Characteristics

Characteristic	Breast Cancer (N=324)	Prostate Cancer (N=146)	Lung Cancer (N=59)	Other (N=69)	Total (N=598)
Time since Cancer Diagnosis Category					
<1 year	105 (32.4%)	79 (54.1%)	54 (91.5%)	25 (36.2%)	263 (44.0%)
1-<2 years	25 (7.7%)	15 (10.3%)	3 (5.1%)	14 (20.3%)	57 (9.5%)
2-<5 years	77 (23.8%)	28 (19.2%)	2 (3.4%)	14 (20.3%)	121 (20.2%)
5-<10 years	60 (18.5%)	13 (8.9%)	0	11 (15.9%)	84 (14.0%)
10-<20 years	42 (13.0%)	8 (5.5%)	0	5 (7.2%)	55 (9.2%)
>=20 years	13 (4.0%)	2 (1.4%)	0	0	15 (2.5%)
Missing	2 (0.6%)	1 (0.7%)	0	0	3 (0.5%)
Time since Cancer Diagnosis (months)					
n	322	145	59	69	595
Mean	63.933	30.850	4.683	39.002	47.104
SD	77.6592	48.3438	7.5682	48.1873	67.0935
Q1	3.975	2.070	0.821	4.797	2.168
Median	35.893	8.772	1.774	17.511	19.318
Q3	94.489	34.431	4.632	58.973	64.953
Min[a]	0.00	-0.07	0.07	-0.13	-0.13
Max	400.36	258.60	42.32	219.40	400.36
Missing	2	1	0	0	3
Hormone Receptor Status[b]					
ER positive	86 (26.5%)				86 (14.4%)
PR positive	6 (1.9%)				6 (1.0%)
ER/PR positive	173 (53.4%)				173 (28.9%)
ER/PR negative	51 (15.7%)				51 (8.5%)
Unknown	8 (2.5%)				8 (1.3%)

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Table 2. Patient and Disease Characteristics

Characteristic	Breast Cancer (N=324)	Prostate Cancer (N=146)	Lung Cancer (N=59)	Other (N=69)	Total (N=598)
HER2 Status[b]					
Positive	57 (17.6%)				57 (9.5%)
Negative	243 (75.0%)				243 (40.6%)
Unknown	24 (7.4%)				24 (4.0%)
Current Disease Status[c]					
Castration-resistant		37 (25.3%)			37 (6.2%)
Hormone sensitive		85 (58.2%)			85 (14.2%)
Unknown		24 (16.4%)			24 (4.0%)
Lung Cancer Type[d]					
Non small cell			43 (72.9%)		43 (7.2%)
Small cell			11 (18.6%)		11 (1.8%)
Unknown			5 (8.5%)		5 (0.8%)
Type of Non-Small Cell Cancer[d]					
Adenocarcinoma			34 (57.6%)		34 (5.7%)
Squamous cell carcinoma			8 (13.6%)		8 (1.3%)
Unknown			1 (1.7%)		1 (0.2%)
Time since Metastasis Diagnosis Category					
<1 year	287 (88.6%)	124 (84.9%)	57 (96.6%)	50 (72.5%)	518 (86.6%)
1-<2 years	15 (4.6%)	6 (4.1%)	1 (1.7%)	9 (13.0%)	31 (5.2%)
2-<5 years	15 (4.6%)	10 (6.8%)	1 (1.7%)	6 (8.7%)	32 (5.4%)
5-<10 years	3 (0.9%)	2 (1.4%)	0	3 (4.3%)	8 (1.3%)
10-<20 years	4 (1.2%)	0	0	0	4 (0.7%)
>=20 years	0	0	0	0	0
Missing	0	4 (2.7%)	0	1 (1.4%)	5 (0.8%)

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Table 2. Patient and Disease Characteristics

Characteristic	Breast Cancer (N=324)	Prostate Cancer (N=146)	Lung Cancer (N=59)	Other (N=69)	Total (N=598)
Time since Metastasis Diagnosis (months)					
N	324	142	59	68	593
Mean	7.174	6.211	2.989	10.123	6.865
SD	22.4593	12.0365	6.1723	16.7841	18.6603
Q1	0.460	0.723	0.559	0.723	0.559
Median	1.068	1.676	1.380	2.661	1.314
Q3	3.450	5.848	3.318	12.107	4.402
Min	0.00	0.00	0.13	0.00	0.00
Max	214.70	74.18	42.32	78.82	214.70
Missing	0	4	0	1	5
Time since Bone Metastasis Diagnosis Category					
<1 year	306 (94.4%)	127 (87.0%)	58 (98.3%)	65 (94.2%)	556 (93.0%)
1-<2 years	10 (3.1%)	6 (4.1%)	1 (1.7%)	0	17 (2.8%)
2-<5 years	5 (1.5%)	9 (6.2%)	0	3 (4.3%)	17 (2.8%)
5-<10 years	0	0	0	0	0
10-<20 years	2 (0.6%)	0	0	0	2 (0.3%)
>=20 years	0	0	0	0	0
Missing	1 (0.3%)	4 (2.7%)	0	1 (1.4%)	6 (1.0%)

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Table 2. Patient and Disease Characteristics

Characteristic	Breast Cancer (N=324)	Prostate Cancer (N=146)	Lung Cancer (N=59)	Other (N=69)	Total (N=598)
Time since Bone Metastasis Diagnosis (months)					
N	323	142	59	68	592
Mean	3.307	4.823	1.901	3.213	3.520
SD	12.1725	9.0023	3.2933	6.8442	10.3510
Q1	0.329	0.657	0.427	0.296	0.427
Median	0.789	1.511	1.051	0.838	0.953
Q3	2.004	4.567	2.168	2.267	2.464
Min	0.00	0.00	0.00	0.00	0.00
Max	143.51	54.24	23.43	41.53	143.51
Missing	1	4	0	1	6
Metastasis Site					
Bone only	128 (39.5%)	113 (77.4%)	20 (33.9%)	18 (26.1%)	279 (46.7%)
Bone and other	196 (60.5%)	33 (22.6%)	39 (66.1%)	51 (73.9%)	319 (53.3%)
Number of Bone Metastasis					
1	39 (12.0%)	12 (8.2%)	13 (22.0%)	21 (30.4%)	85 (14.2%)
2-4	73 (22.5%)	27 (18.5%)	19 (32.2%)	20 (29.0%)	139 (23.2%)
>4	171 (52.8%)	94 (64.4%)	26 (44.1%)	20 (29.0%)	311 (52.0%)
Unknown	41 (12.7%)	13 (8.9%)	1 (1.7%)	8 (11.6%)	63 (10.5%)
Diagnosis Method of Bone Metastasis					
By symptoms	81 (25.0%)	35 (24.0%)	21 (35.6%)	17 (24.6%)	154 (25.8%)
Asymptomatic/imaging	237 (73.1%)	111 (76.0%)	38 (64.4%)	50 (72.5%)	436 (72.9%)
Unknown	6 (1.9%)	0	0	2 (2.9%)	8 (1.3%)

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Table 2. Patient and Disease Characteristics

Characteristic	Breast Cancer (N=324)	Prostate Cancer (N=146)	Lung Cancer (N=59)	Other (N=69)	Total (N=598)
Other than Bone Metastasis Site[e]					
Liver	81 (25.0%)	6 (4.1%)	16 (27.1%)	26 (37.7%)	129 (21.6%)
Lung	80 (24.7%)	6 (4.1%)	14 (23.7%)	21 (30.4%)	121 (20.2%)
Brain	11 (3.4%)	0	7 (11.9%)	4 (5.8%)	22 (3.7%)
Other	96 (29.6%)	28 (19.2%)	23 (39.0%)	24 (34.8%)	171 (28.6%)

Note: percentages are based on the number of patients in Full Analysis Set.
[a] Negative values are from the following patients:
Patientid 270, first XGEVA dose: 2014-07-16, Cancer Diagnosis Date: 2014-07-18
Patientid 544, first XGEVA dose: 2015-11-05, Cancer Diagnosis Date: 2015-11-09
[b] Only for patients with breast cancer.
[c] Only for patients with prostate cancer.
[d] Only for patients with lung cancer.
[e] Percentages in this section may add upp to more than 100% because one patient may have different metastasis sites.

Table 3. Reasons for non-persistence at week 24 and at week 48

	Breast Cancer n (%)	Prostate Cancer n (%)	Lung Cancer n (%)	Other n (%)	Total n (%)
Persistent at week 24?					
Yes	207/298 (69.5%)	95/137 (69.3%)	12/46 (26.1%)	24/59 (40.7%)	338/540 (62.6%)
No	91/298 (30.5%)	42/137 (30.7%)	34/46 (73.9%)	35/59 (59.3%)	202/540 (37.4%)
Reason for non-persistence					
ICF withdrawal	1/91 (1.1%)	1/42 (2.4%)	0/34	1/35 (2.9%)	3/202 (1.5%)
XGEVA discontinuation	10/91 (11.0%)	3/42 (7.1%)	5/34 (14.7%)	6/35 (17.1%)	24/202 (11.9%)
S(ADR)	0/91	1/42 (2.4%)	0/34	1/35 (2.9%)	2/202 (1.0%)
Other reason for ending the observation	9/91 (9.9%)	2/42 (4.8%)	3/34 (8.8%)	3/35 (8.6%)	17/202 (8.4%)
Not enough injections	0/91	0/42	0/34	0/35	0/202
Violation of time windows	71/91 (78.0%)	35/42 (83.3%)	26/34 (76.5%)	24/35 (68.6%)	156/202 (77.2%)
Violation of 1 time window	52/71 (73.2%)	27/35 (77.1%)	21/26 (80.8%)	18/24 (75.0%)	118/156 (75.6%)
Violation of 2 time windows	15/71 (21.1%)	7/35 (20.0%)	4/26 (15.4%)	4/24 (16.7%)	30/156 (19.2%)
Violation of 3 time windows	4/71 (5.6%)	1/35 (2.9%)	1/26 (3.8%)	2/24 (8.3%)	8/156 (5.1%)
Violation of more than 3 time windows	0/71	0/35	0/26	0/24	0/156
Persistent at week 48?					
Yes	239/296 (80.7%)	106/137 (77.4%)	17/43 (39.5%)	31/56 (55.4%)	393/532 (73.9%)
No	57/296 (19.3%)	31/137 (22.6%)	26/43 (60.5%)	25/56 (44.6%)	139/532 (26.1%)
Reason for non-persistence					
ICF withdrawal	3/57 (5.3%)	1/31 (3.2%)	0/26	1/25 (4.0%)	5/139 (3.6%)
XGEVA discontinuation	10/57 (17.5%)	3/31 (9.7%)	6/26 (23.1%)	6/25 (24.0%)	25/139 (18.0%)
S(ADR)	0/57	1/31 (3.2%)	0/26	1/25 (4.0%)	2/139 (1.4%)
Other reason for ending the observation	9/57 (15.8%)	2/31 (6.5%)	3/26 (11.5%)	3/25 (12.0%)	17/139 (12.2%)
Not enough injections	0/57	0/31	0/26	0/25	0/139
Violation of time windows	35/57 (61.4%)	24/31 (77.4%)	17/26 (65.4%)	14/25 (56.0%)	90/139 (64.7%)
Violation of 1 time window	29/35 (82.9%)	23/24 (95.8%)	15/17 (88.2%)	14/14 (100.0%)	81/90 (90.0%)
Violation of 2 time windows	5/35 (14.3%)	1/24 (4.2%)	2/17 (11.8%)	0/14	8/90 (8.9%)
Violation of 3 time windows	1/35 (2.9%)	0/24	0/17	0/14	1/90 (1.1%)
Violation of more than 3 time windows	0/35	0/24	0/17	0/14	0/90

[a] Subject may have had more than one different type of antineoplastic therapy.