# Prospective observational study to evaluate the persistence of treatment with denosumab in patients with bone metastases from solid tumors in routine clinical practice: interim analysis

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## BACKGROUND

- In an integrated analysis of three phase 3 head-to-head trials in patients with bone metastases from advanced solid tumors, denosumab demonstrated superiority versus zoledronate in preventing SREs.[1-3]
- Persistence in the real-world is undetermined and would affect clinical efficacy.

## OBJECTIVES

- This study aims at estimating treatment persistence with denosumab at week 24 and 48 and its relationship with baseline characteristics in patients with bone metastases secondary to solid tumors who received denosumab in routine clinical practice.

## METHODS

### *Study design*

- This is a single-arm, prospective, non-interventional study in patients with bone metastases from solid tumors, such as breast, prostate, lung, or other tumors, treated with denosumab in real-world clinical practice.
- The total enrolment for final analysis was 634 patients from 62 centers; the study is ongoing.
- Participating countries: Austria, Bulgaria, Czech Republic, Hungary, and Slovakia.
- The study was initiated in 08/2012. The data cut-off date for the present interim analysis was 12/2014.

### *Inclusion criteria*

- ≥18 years of age at enrollment
- Diagnosis of breast, prostate, lung cancer or any other solid tumors with bone metastases
- ECOG Performance Status 0-2
- Initiation of first denosumab dose ever within 28 days prior to enrollment
- Appropriate written informed consent.

### *Exclusion criteria*

- Previously treatment with bisphosphonates or other antiresorptive agents for bone metastasis in clinical studies or clinical routine for >6 months
- Previous treatment with radionuclides
- Parallel enrollment in an investigational drug trial for the treatment/prevention of bone metastases and SREs
- Contraindications for the treatment with denosumab according to the label approved at time of enrolement.[4]

### *Primary objective*

- Persistence at 24 weeks (=6 denosumab subcutaneous injections; permissible intervals: 4±1 weeks).

### *Secondary objectives*

- Persistence at 48 weeks
- Time to non-persistence
- Primary and secondary persistence outcomes by tumor type.
- Demographics, disease characteristics, concomitant anticancer therapy and medical history
- Calcium and vitamin D supplementation patterns.

### *Exploratory objectives*

- Usage of individual pain medication on monthly basis between baseline and study end.
- 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.
- Reasons for choice of denosumab as treatment for bone metastases from solid tumors.

## RESULTS

- A total of 158 patients were included and 121 completed 24 weeks of treatment.
- 76 patients discontinued prematurely: 37 died, 19 discontinued denosumab, including 2 due to serious adverse drug reactions; 11 were lost to follow-up, 2 withdrew consent, other (n=7).

## RESULTS (continued)

### *Patient characteristics*

- Table 1 describes the patient population included in the study.
- Median age was 65 years and differed by the site of the primary cancer.
- The largest group were patients with breast cancer, followed by prostate cancer.
- Most patients had two or more bone metastases and had received previous therapies in the metastatic setting.
- Bone metastases were diagnosed by imaging in 75.9% of patients (n=120) and by symptoms in 22.2% (n=35); the diagnostic method was unknown in 1.9% (n=3).

*Table 1. Patient characteristics and demographics*

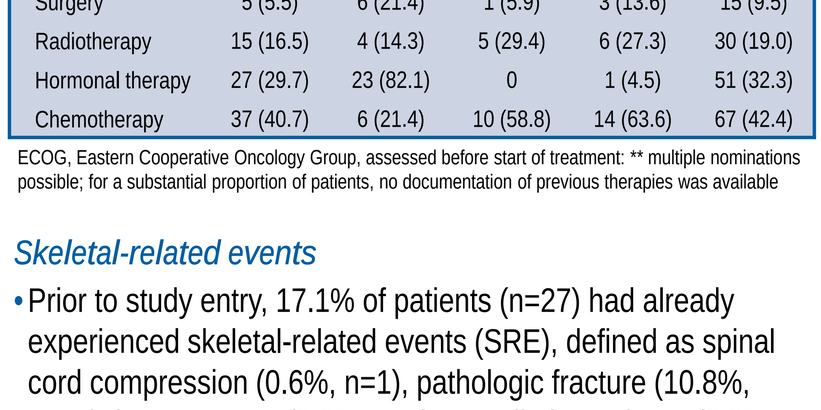
| | Breast *N=91* | Prostate *N=28* | Lung *N=17* | Other *N=22* | Total *N=158* |
|---|---|---|---|---|---|
| Gender, n (%) | | | | | |
| Male | 1 (1.1) | 28 (100) | 11 (64.7) | 16 (72.7) | 56 (35.4) |
| Female | 90 (98.9) | 0 | 6 (47.1) | 6 (27.3) | 102 (64.6) |
| Age | | | | | |
| <65 years, n (%) | 56 (61.5) | 7 (25.0) | 9 (52.9) | 22.7% | 48.7% |
| ≥65 years, n (%) | 35 (38.5) | 21 (75.0) | 8 (47.1) | 77.3% | 51.3% |
| Median, years | 61 | 73 | 59 | 69 | 65 |
| ECOG status, n (%) | | | | | |
| 0 | 53 (58.2) | 13 (46.4) | 6 (35.3) | 8 (36.4) | 80 (50.6) |
| 1 | 34 (37.4) | 9 (32.1) | 10 (58.8) | 10 (45.5) | 63 (39.9) |
| 2 | 4 (4.4) | 6 (21.4) | 1 (5.9) | 4 (18.2) | 15 (9.5) |
| Time since cancer diagnosis (years) | | | | | |
| Mean | 5.38 | 3.98 | 0.37 | 2.01 | 4.12 |
| Median | 3.33 | 2.49 | 0.22 | 1.18 | 1.92 |
| Range | 0.03-27.50 | 0.07-15.42 | 0.04-1.16 | 0.10-7.07 | 0.03-27.50 |
| Time since metastasis diagnosis (years) | | | | | |
| Mean | 0.91 | 0.73 | 0.19 | 0.87 | 0.80 |
| Median | 0.14 | 0.24 | 0.11 | 0.48 | 0.17 |
| Range | 0.01-17.94 | 0.00-6.22 | 0.01-0.82 | 0.06-3.07 | 0.00-17.94 |
| Metastasis site, n (%) | | | | | |
| Bone only | 26 (28.6) | 19 (67.9) | 5 (29.4) | 4 (18.2) | 54 (34.2) |
| Bone and other* | 65 (71.4) | 9 (32.1) | 12 (70.6) | 18 (81.8) | 104 (65.8) |
| *Liver | 32 (35.2) | 2 (7.1) | 7 (41.2) | 10 (45.5) | 51 (32.3) |
| *Lung | 27 (29.7) | 1 (3.6) | 5 (29.4) | 7 (31.8) | 40 (25.3) |
| *Brain | 5 (5.5) | 0 | 2 (11.8) | 1 (4.5) | 8 (5.1) |
| *Other | 31 (34.1) | 7 (25.0) | 6 (35.3) | 12 (54.5) | 56 (35.4) |
| Number of bone metastases, n (%) | | | | | |
| 1 | 14 (15.4) | 2 (7.1) | 4 (23.5) | 13 (59.1) | 33 (20.9) |
| 2-4 | 22 (24.2) | 7 (25.0) | 6 (35.3) | 4 (18.2) | 39 (24.7) |
| >4 | 45 (49.5) | 18 (64.3) | 6 (35.3) | 2 (9.1) | 71 (44.9) |
| Unknown | 10 (11.0) | 1 (3.6) | 1 (5.9) | 3 (13.6) | 15 (9.5) |
| Previous therapies in the metastatic setting**, n (%) | | | | | |
| Antiresorptives | 9 (9.9) | 2 (7.1) | 0 | 2 (9.1) | 13 (8.2) |
| Surgery | 5 (5.5) | 6 (21.4) | 1 (5.9) | 3 (13.6) | 15 (9.5) |
| Radiotherapy | 15 (16.5) | 4 (14.3) | 5 (29.4) | 6 (27.3) | 30 (19.0) |
| Hormonal therapy | 27 (29.7) | 23 (82.1) | 0 | 1 (4.5) | 51 (32.3) |
| Chemotherapy | 37 (40.7) | 6 (21.4) | 10 (58.8) | 14 (63.6) | 67 (42.4) |

ECOG, Eastern Cooperative Oncology Group, assessed before start of treatment: ** multiple nominations possible; for a substantial proportion of patients, no documentation of previous therapies was available

### *Skeletal-related events*

- Prior to study entry, 17.1% of patients (n=27) had already experienced skeletal-related events (SRE), defined as spinal cord compression (0.6%, n=1), pathologic fracture (10.8%, n=17), bone surgery (3.2%, n=5), or radiation to bone (3.8%, n=6), as reported by the investigators from medical charts (Figure 1). The frequency of previous SRE differed by tumor type.
- Overall, 5.1% (n=8) had received any intervention due to SRE.

*Figure 1. Frequency of previous skeletal-related events*




### *Denosumab exposure*

- The median (interquartile range; IQR) duration of exposure to denosumab was 326 (116.0, 346.0) days.
- The median (IQR) number of denosumab doses received within the observed duration of exposure was 10 (4.0, 12.0).

### *Persistence*

- Full persistence at 24 weeks was defined as receiving 6 denosumab subcutaneous injections with a permissible interval between injections of 4 ± 1 weeks.
- Persistence at 24 weeks was calculated on 121 patients completing 24 weeks, excluding those who died, were lost to follow-up, or discontinued for any other reason.
- The number of patients reaching 48 weeks at the time of this interim analysis was insufficient to calculate persistence.
- Overall, persistence at 24 weeks was 61% (95% confidence interval [CI]: 51.9—69.9).
- Persistence varied between cancer types and participating countries (Figures 2 and 3).
- The median (IQR) time to non-persistence was 142 (33.0, 308.0) days

*Figure 2. Persistence (95% CI) at 24 weeks, by tumor type*

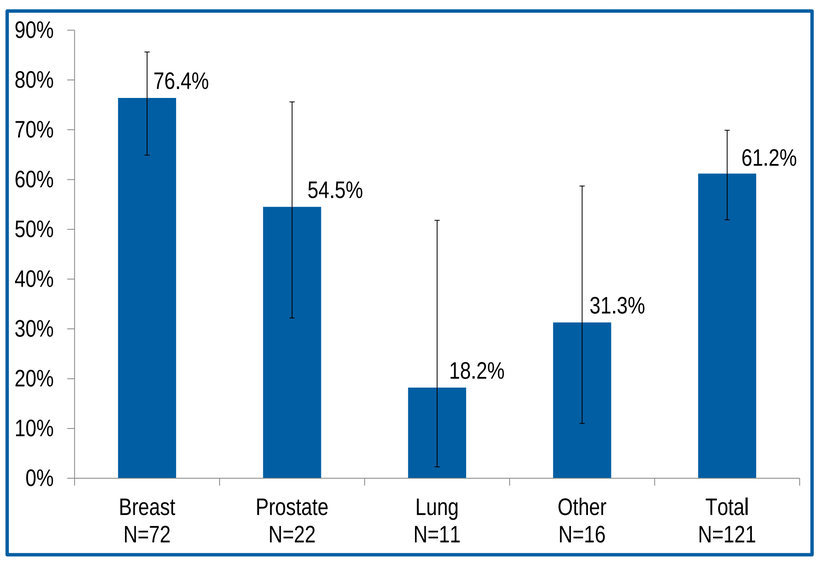
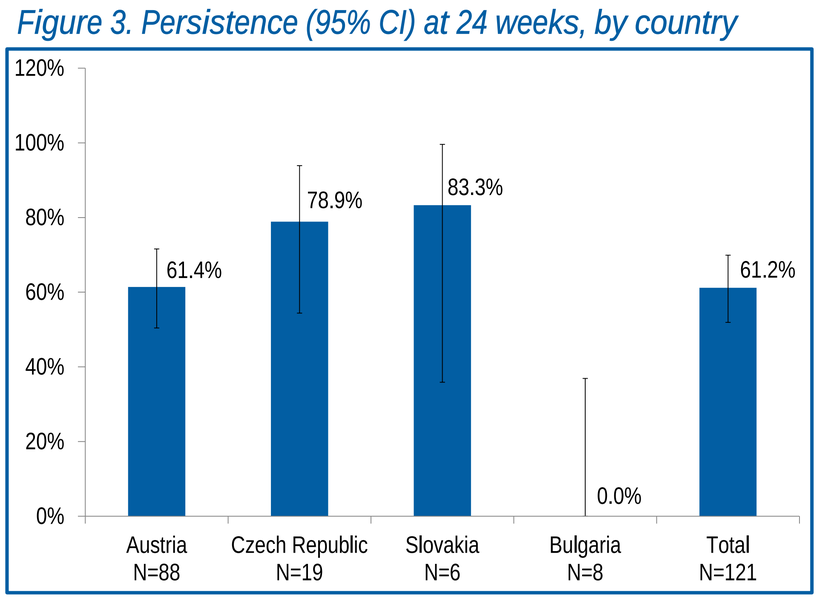



*Figure 3. Persistence (95% CI) at 24 weeks, by country*




- Persistence was significantly influenced by cancer type (lung or other versus breast cancer), presence of metastasis other than bone, and presence of previous skeletal-related events (Table 2).

*Table 2. Analysis of influence factors on persistence*

| | Odds ratio | 95% CI | P-value |
|---|---|---|---|
| Cancer type | | | |
| Lung versus breast | 0.037 | 0.003, 0.462 | 0.0104 |
| Other versus breast | 0.112 | 0.023, 0.551 | 0.0070 |
| Prostate versus breast | 0.672 | 0.148, 3.050 | 0.6065 |
| Presence of metastasis other than bone | | | |
| Bone only versus bone and other | 0.237 | 0.059, 0.951 | 0.0423 |
| Type of care | | | |
| Practice versus clinic | 2.858 | 0.886, 9.219 | 0.0788 |
| Previous SRE | | | |
| Yes versus no | 0.178 | 0.044, 0.719 | 0.0155 |

Stepwise regression models were applied to select the variables in the logistic regression model.
Variables: cancer type, presence of previous antiresorptive therapy in metastatic setting, previous SREs.

### *Calcium and vitamin D supplementation*

- The initial median serum calcium range was 2.19-2.34 mmol/L.
- After week 5 median calcium ranged at 2.22-2.28 mmol/L.
- ~60% of patients received calcium and vitamin D supplements, decreasing to ~50% by dose 6.

### *Serious adverse events*

- 2 patients (1%; 1 breast cancer, 1 prostate cancer) experienced osteonecrosis of the jaw (not adjudicated).
- Cellulitis occurred in 1 patient (1%).

## CONCLUSIONS

- Persistence was 61% in the 121 patients completing 24 weeks of study. There was a wide variation between tumor types and countries.
- Calcium remained within the normal range. Only 50-60% of patients received calcium and/or vitamin D supplementation throughout denosumab treatment.
- The rate of osteonecrosis of the jaw was comparable with previous reports and SmPC.[4,5]
- The identically designed German study X-TREME found very similar results with a persistence of 64.7% at 24 weeks.[6]

References: [1]Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomized, double-blind study. *Lancet* 2011;377:813-22. [2]Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized double-blind study. *J Clin Oncol* 2010;28:5132-9. [3]Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol* 2011;29:1125-32. [4]XGEVA® (Denosumab) Summary of Product Characteristics. Accessed April 2017, available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002173/WC500110381.pdf. [5]Stopeck AT, Fizazi K, Body JJ, et al. Safety of long-term denosumab therapy: results from the open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer. Supp Care Cancer 2016;24:447-55. 6Diel I, Hecker D, Hesse T., et al. X-TREME: Interim analysis from a German open-label, observational study for treatment persistence with denosumab in routine use in adults with bone metastases secondary to solid tumors. ESMO 2015; abstract 1522 and poster. Conflicts of interest: ZB, AT, FH, DK, MP, MS declare no conflicts of interest. DN and CJ are Amgen employees and hold Amgen stock. AP and RG are members of the Amgen Advisory Board. AP received speaker honoraria from Amgen. Acknowledgements and disclosures: Funding for this research was provided by Amgen (Europe North East) GmbH. Study design, data analysis and statistical support were provided by Quartesian, Kharkov, Ukraine, and were funded by Amgen (Europe North East) GmbH. Medical writing support was provided by Margit Hemetsberger of hemetsberger medical services, Vienna, Austria, and was funded by Amgen (Europe North East) GmbH.