Denosumab Dose Selection for Patients with Bone Metastases from Solid Tumors

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Abstract

**Purpose:** To quantitatively characterize the longitudinal dose exposure–response [urinary N-telopeptide normalized to urinary creatinine (uNTx/Cr) suppression] relationship for denosumab in patients with bone metastases from solid tumors.

**Experimental Design:** Data from 373 patients who received denosumab as single or multiple subcutaneous doses ranging from 30 to 180 mg (or 0.01 to 3 mg/kg) administered every 4 or 12 weeks for up to 3 years were used in this analysis. An inhibitory sigmoid $I_{\text{Max}}$ model was used to characterize the time course of uNTx/Cr as a function of serum denosumab concentrations and the M3 method was used to analyze the 52% of uNTx/Cr values below the limit of quantification in the context of a mixed-effects model. Age, weight, sex, race, and cancer type were evaluated as potential covariates for model parameters. Model-based simulations were undertaken to explore and predict the role of denosumab dose and dosing intervals on uNTx/Cr suppression.

**Results:** The typical value (between-subject variability; %) for uNTx/Cr at baseline was 49.2 nmol/L/mmol/L (76.8%), denosumab maximal uNTx/Cr suppression (efficacy) was 93.7% (127%), and the denosumab concentration providing half-maximal uNTx/Cr suppression (potency) was 31.8 ng/mL (287%). No effect of covariates on denosumab efficacy and potency was identified. Simulations indicated that a s.c. denosumab dose of 120 mg administered every 4 weeks provides more than 90% suppression of uNTx/Cr in the maximum proportion of patients relative to other every 4- and 12-week doses evaluated.

**Conclusions:** Over the wide range of dosing regimens examined, a s.c. denosumab dose of 120 mg administered every 4 weeks is the optimal dosing regimen to suppress uNTx/Cr in patients with bone metastases from solid tumors. Clin Cancer Res; 18(9); 1–10. ©2012 AACR.

Introduction

The most common metastatic site for breast cancer, prostate cancer, and other solid tumors such as lung, thyroid, and kidney cancers is bone (1). Bone metastases can result in skeletal-related events (SRE) including pathologic fractures, spinal cord compression, and the need to undergo radiation to or surgery of the bone (2–4). The pathophysiology of bone metastases includes locally increased osteoclast-mediated bone breakdown, which results in elevated levels of bone turnover markers (BTM) such as urinary N-telopeptide normalized to urinary creatinine (uNTx/Cr). BTMs are not only indicative of excessive bone resorption but also have been associated with disease progression and death (5–8).

Receptor activator of NF-κB ligand (RANKL) plays a critical role in bone remodeling (9). By binding to its receptor, RANK, on osteoclast precursors and mature osteoclasts, it promotes the terminal differentiation, activation, and survival of osteoclasts, which in turn stimulate bone resorption and increase BTM levels, including uNTx/Cr (10–12). By secreting cytokines and growth factors that induce osteoblasts to release RANKL into the microenvironment, tumor cells in bone contribute to an imbalance that favors increased bone resorption and elevated BTMs. This is reflected clinically as an increased risk of fractures or other SREs (5) and a potentially increased susceptibility of the bone microenvironment to implantation and proliferation of circulating tumor cells (13, 14).

Denosumab (AMG 162, XGEVA, PROLIA) is a fully human IgG2 monoclonal antibody with high affinity ($K_D = 3 \times 10^{-12}$ mol/L; ref. 15) and specificity for RANKL (16) that neutralizes the activity of human membrane-bound or soluble RANKL by blocking its binding to RANK (17, 18). In clinical studies, denosumab has consistently reduced uNTx/Cr levels in patients with bone metastases from solid tumors, reflecting its antiresorptive effect (19–23).
patients with breast cancer–related bone metastases or multiple myeloma, levels of uNTx/Cr decreased within 1 day after a single s.c. dose of denosumab, and the duration of maximal uNTx/Cr suppression generally increased with dose and persisted for up to 12 weeks following a 3.0 mg/kg dose (21). Similarly, in patients with bone metastases from breast cancer (22) or bone metastases from solid tumors (including breast and prostate cancers; ref. 23), denosumab showed a rapid, sustained, and consistent suppression of uNTx/Cr levels over the dose range of 30 to 180 mg s.c. administered every 4 weeks, or 60 to 180 mg s.c. administered every 12 weeks. The reversibility of the effects on BTMs was observed after stopping the denosumab treatment (21, 22).

Three phase III studies also assessed suppression of uNTx/Cr levels along with prevention of SRE in patients with bone metastases from breast cancer, prostate cancer, or other solid tumors (19–20, 24). In these studies, denosumab 120 mg s.c. administered every 4 weeks was more effective in preventing SREs and suppressing uNTx/Cr compared with monthly intravenous zolendronic acid, the prior standard-of-care in this indication. Currently, denosumab 120 mg s.c. administered every 4 weeks is approved in the United States, European Union, and other countries for the prevention of SRE in patients with bone metastases from solid tumors.

Denosumab pharmacokinetics (PK) and the time course of uNTx/Cr suppression have been extensively investigated in multiple clinical studies in patients with cancer with bone metastases. Following s.c. denosumab administration, the absolute bioavailability was 61% (25) and the absorption was slow, reaching peak serum concentrations (C_{max}) within 4 weeks postdose. After reaching C_{max}, serum denosumab concentrations decline over 4 to 5 months with a mean half-life of approximately 25 to 30 days, with sustained concentrations higher than 2,000 ng/mL, at which the RANKL-mediated clearance pathway is almost fully saturated (25, 26). Following repeat monthly administration, approximately 2.7-fold accumulation at steady state and no evidence of time-dependent PK was observed under the dosage regimens examined.

This article aims to quantitatively characterize the time course of uNTx/Cr following denosumab administration in patients with bone metastases from solid tumors using a mixed-effect model that accounts for uNTx concentrations below the lower limit of quantification (BLQ). The objectives are 4-fold: (i) to characterize the efficacy and potency of denosumab in suppressing uNTx/Cr following s.c. administration; (ii) to quantify the degree of between-subject variability (BSV) of denosumab pharmacodynamic (PD) parameters; (iii) to evaluate patient-related variables as potential sources of PD variability; and (iv) to assess the activity of the 120 mg every 4 weeks dosing regimen relative to other dose levels and regimens in suppressing uNTx/Cr.

Materials and Methods

Clinical data

Data collected from the 6 clinical development studies of denosumab conducted in patients with bone metastases from solid tumors were used in this analysis. The data set included 2,013 uNTx/Cr samples from 373 patients treated with single s.c. doses of denosumab ranging from 0.1 to 3.0 mg/kg or multiple s.c. doses of denosumab ranging from 30 to 180 mg and administered every 4 or 12 weeks for up to 3 years. The relevant patient characteristics of each clinical study are summarized in Table 1. Additional details of these clinical trials are reported elsewhere (19–22, 24, 27). All studies were conducted in accordance with principles for human experimentation as defined in the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines and were approved by the respective Investigational Review Boards. Informed consent was obtained from each subject after being told the potential risks and benefits, as well as the investigational nature of the study.

Bioanalysis of uNTx and creatinine

A modified commercial ELISA, Osteomark NTx Urine (Wampole Laboratories) was used to measure uNTx concentrations. The assay is a solid phase competitive-inhibition ELISA where the microtiter plate is coated with NTx. Any NTx present in a standard, quality control, or unknown sample competed with the bound NTx for binding sites of a monoclonal antibody specific for NTx and labeled with horseradish peroxidase (HRP). After incubation and washing, a tetramethylbenzidine solution was added to react with HRP and create a colorimetric signal that was inversely proportional to the amount of NTx in the sample.
Table 1. Summary of patient’s characteristics and clinical studies design

<table>
<thead>
<tr>
<th>Study</th>
<th>N&lt;sup&gt;a&lt;/sup&gt; (% male)</th>
<th>Study population</th>
<th>Subcutaneous doses (regimen)</th>
<th>Sampling</th>
<th>Age,&lt;sup&gt;b&lt;/sup&gt; y</th>
<th>Weight,&lt;sup&gt;b&lt;/sup&gt; kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>20010123</td>
<td>(21) 22 (0)</td>
<td>Breast cancer</td>
<td>0.1, 0.3, 1, 3 mg/kg (single dose)</td>
<td>Intensive for 12 wk</td>
<td>55 (10) and 35–73</td>
<td>73 (15) and 56–104</td>
</tr>
<tr>
<td>20040176</td>
<td>(27) 11 (0)</td>
<td>Japanese breast cancer</td>
<td>60, 180 mg (single dose) 180 mg (Q4W × 3)</td>
<td>Intensive for 12 wk</td>
<td>53 (11) and 28–67</td>
<td>60 (14) and 46–86</td>
</tr>
<tr>
<td>20040113</td>
<td>(22) 164 (0)</td>
<td>Breast cancer</td>
<td>30, 120, 180 mg (Q4W × 6) 60, 180 mg (Q12W × 2)</td>
<td>At 1 wk and monthly for 24 wk</td>
<td>57 (11) and 31–82</td>
<td>69 (14) and 43–127</td>
</tr>
<tr>
<td>20050103</td>
<td>(20) 66 (100)</td>
<td>Prostate cancer</td>
<td>120 mg (Q4W)</td>
<td>Wk 13 and EOS</td>
<td>73 (8) and 53–88</td>
<td>87 (14) and 53–135</td>
</tr>
<tr>
<td>20050136</td>
<td>(24) 73 (3)</td>
<td>Breast cancer</td>
<td>120 mg (Q4W)</td>
<td>Wk 13 and EOS</td>
<td>56 (11) and 27–79</td>
<td>64 (15) and 40–121</td>
</tr>
<tr>
<td>20050244</td>
<td>(19) 37 (70.3)</td>
<td>Solid tumors&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>120 mg (Q4W)</td>
<td>Wk 13 and EOS</td>
<td>61 (12) and 35–82</td>
<td>76 (16) and 40–113</td>
</tr>
<tr>
<td>Total</td>
<td>373 (24.7)</td>
<td></td>
<td></td>
<td></td>
<td>60 (12) and 27-88</td>
<td>72 (17) and 40–135</td>
</tr>
</tbody>
</table>

NOTE: Total uNTx/Cr values (including baseline measurements): 2,013 from 373 patients, 1,615 were postdose samples, 840 (52%) of 1,615 postdose samples were BQL.
Abbreviations: EOS, end of study; kg, kilograms; Q4W, every 4 weeks; Q12W, every 12 weeks; wk, weeks; y, years.

<sup>a</sup>Number of patients with both pharmacokinetic and pharmacodynamic sampling.

<sup>b</sup>Numbers are mean (SD) and range.

<sup>c</sup>Excluding breast and prostate cancer.

<sup>d</sup>Cancer patients with bone metastases.
limit of quantification (LOQ) was 30.0 nmol/L bone collagen equivalents (BCE) for study 2001023 and 62.5 nmol/L BCE for all other studies. The upper LOQ was 2,857 nmol/L BCE. Creatinine was measured photometrically using a modification of the Jaffe reaction on Roche Modular Analyzers, with a linear range of the assay between 0.00884 and 2.21 mmol/L (0.1–25.0 mg/dL).

Software
Nonlinear mixed-effects modeling for the population pharmacodynamic analysis of denosumab was conducted using NONMEM Version 7.1.0 (ICON Development Solutions) with gfortran 4.4 compiler. The stochastic approximation of the expectation maximization (SAEM) method was used for parameter estimation. Graphical data visualization, evaluation of NONMEM outputs, construction of goodness-of-fit plots, and graphical model comparisons were conducted using S-Plus Version 8 (TIBCO Software Inc.).

Pharmacokinetic and pharmacodynamic model
The development of the pharmacokinetic and pharmacodynamic (PKPD) model was conducted using a sequential process described previously (28). Therefore, individual Bayesian estimates of PK parameters obtained from the denosumab population PK (25) model and the available individual serum concentration data were used to predict the individual denosumab serum concentration–time profile, which in turn was used as an input function into the PD model. Complete details about development of the denosumab PK model have been reported elsewhere (25).

A sigmoid maximum inhibition ($I_{\text{Max}}$) model was selected as the structural PD model that best characterized the time course of uNTx/Cr as a function of denosumab serum concentrations. The structure of the inhibitory sigmoid $I_{\text{Max}}$ model is as follows:

$$ \frac{uNTx}{Cr} = \frac{uNTx_0}{Cr_0} \left( 1 - \frac{I_{\text{Max}} \times C}{IC_{50} + C} \right) $$

where $uNTx_0/Cr_0$ represents the baseline $uNTx/Cr$; $C$ represents the predicted denosumab concentration; $I_{\text{Max}}$ represents the maximal denosumab inhibition of $uNTx/Cr$ (efficacy), $IC_{50}$ represents the denosumab serum concentration that produces half-maximal inhibition of $uNTx/Cr$ (potency), and $\lambda$ is the Hill coefficient accounting for the sigmoidicity of the concentration–response relationship. The predicted fractional RANKL inhibition as estimated from the population PK model was also tested as a predictor of $uNTx/Cr$ suppression, instead of denosumab serum concentration.

Statistical model
BSV in model parameters was assumed to follow an independent log-normal distribution. However, as $I_{\text{Max}}$ represents the fraction of maximal suppression, an additive error model in the logit domain was used to constrain the individual $I_{\text{Max}}$ values to be between 0 and 1. As $uNTx/Cr$ are distributed log-normally rather than normally, all measured $uNTx/Cr$ values and corresponding individual model predictions were converted into natural logarithms, and the magnitude of residual variability (RV) in the log domain was modeled using an additive error model.

Because the proportion of $uNTx$ values BLQ was high (52%) and was related to the predicted denosumab concentration (Fig. 1A), $uNTx$ values BLQ could not be ignored in this analysis and strategies for handling measurements reported as BLQ were needed. In previous denosumab studies, $uNTx$ concentrations BLQ were substituted by the LOQ. However, common approaches for handling of concentrations BLQ, such as data exclusion or substitution by LOQ, 0, or LOQ divided by 2, have been shown to introduce bias in parameter estimates (29, 30). Thus, methods based on simultaneous modeling of continuous and categorical data, where the BLQ observations are treated as censored data, are preferred from a statistical point of view. Therefore, simultaneous modeling of the continuous $uNTx$ observations and the $uNTx$ values BLQ treated as a categorical variable was conducted. In this analysis, the $uNTx$ values BLQ were treated as censored data, and the likelihood for BLQ observations was maximized with respect to the model parameters (M3 method) to minimize the impact of the $uNTx$ values BLQ on the efficacy and potency estimates (31–34).

The improvement in the fit obtained for each model evaluated was assessed by the likelihood ratio test ($P = 0.005$), the reduction in the BSV and RV, the precision in parameter estimates, the examination of diagnostic plots, and the shrinkage (35).

Model evaluation
Two predictive checks (36) were conducted to evaluate the model predictive performance. The first predictive check evaluated the relationship between $uNTx/Cr$ and denosumab concentration. In this case, $uNTx/Cr$ values of 10,000 patients were simulated on the basis of the model parameters and a range of denosumab concentrations, encompassing the expected concentrations of the patients included in the analysis data set. At each denosumab concentration, the 5th, 50th, and 95th percentiles of the simulated $uNTx/Cr$ values were computed and plotted. The observed data were then overlaid and visually compared with the model-based prediction. A similar analysis was conducted to assess the relationship between the proportion of $uNTx/Cr$ BLQ and denosumab concentration by simulating 500 replicates of the analysis data set.

The second predictive check evaluated the time course of changes in quantifiable $uNTx/Cr$ and the proportion of $uNTx$ concentrations BLQ following s.c. administration of 120 mg denosumab every 4 weeks. A total of 500 replicates of the analysis data set containing the patients with $uNTx/Cr$ time course following 120 mg denosumab every 4 weeks were simulated. The median (and 90% prediction interval) of the simulated $uNTx/Cr$ values for $uNTx$ concentrations
above the LOQ and the proportion of uNTx concentrations BLQ (and the 90% confidence interval [CI]) were computed and compared with observed data. Baseline concentrations were excluded for evaluation of the proportion of uNTx concentrations BLQ.

Model-based simulations
On the basis of the final estimates of model parameters, simulations were conducted to explore the role of denosumab dose level and dosing regimen on uNTx/Cr suppression. In this context, simulations were conducted to
evaluate: (i) the proportion of patients with at least 90% uNTx/Cr suppression as a function of denosumab serum concentration and (ii) the proportion of patients with at least 90% suppression of uNTx/Cr levels at the trough level achieved at week 25 of treatment across doses ranging from 0 to 180 mg and every 4 and 12-week dosing regimens. Using the final parameters of the population PK model, individual trough denosumab concentrations at steady state (week 25) were simulated for each dose level and dosing regimen (N = 5,000/dose/regimen) and were used to calculate the subsequent suppression of uNTx/Cr based on the model developed, which was summarized by dose and dosing regimen. Furthermore, to investigate the influence of denosumab weight-based dosing versus fixed dosing, model-based simulations comparing the time course of uNTx/Cr following 6 consecutive denosumab doses of 2 mg/kg or 120 mg every 4 weeks were conducted (n = 1,000 per group). Individual body weights and uNTx0/Cr0 were sampled from the analysis data set.

Results

The inhibitory sigmoid $I_{\text{max}}$ model was suitable to describe the time course of uNTx/Cr in patients with bone metastases from solid tumors following denosumab s.c. at different dosing schedules. The model parameter estimates and their relative standard error are presented in Table 2. Both fixed- and random-effects were estimated with acceptable precision. The typical value of uNTx0/Cr0 was 49.2 nmol/L/mmol/L and its associated BSV was 77%. Given the sample from the analysis data set, IC50 were estimated directly from the data. Furthermore, the model-predicted incidence of denosumab weight-based dosing versus fixed dosing, model-based simulations comparing the time course of uNTx/Cr following 6 consecutive denosumab doses of 2 mg/kg or 120 mg every 4 weeks were conducted (n = 1,000 per group). Individual body weights and uNTx0/Cr0 were sampled from the analysis data set.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (%RSE)</th>
<th>Variability (%RSE)</th>
<th>Shrinkage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{\text{max}}$ (%)</td>
<td>93.7 (4.28)</td>
<td>127 (14.1)</td>
<td>24.4</td>
</tr>
<tr>
<td>$I_{\text{50}}$, ng/mL</td>
<td>31.8 (37.5)</td>
<td>287 (30.0)</td>
<td>40.8</td>
</tr>
<tr>
<td>$\lambda$, ng/mL</td>
<td>0.806 (2.92)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Correlation between $I_{\text{max}}$ and $I_{\text{50}}$ is 0.675. RV, 70.1% (RSE, 1.05).

Abbreviation: RSE, relative SE.

* RSE value is for the logit-transformed value.

Table 2. Estimated population PD parameters of denosumab

Both models provided similar efficacy estimates ($I_{\text{max}} > 90\%$), the model based on fractional RANKL inhibition estimated a higher potency ($IC_{50} = 3.49\% \sim 7.52$ ng/mL) compared with the model based on denosumab concentration ($IC_{50} = 31.8$ ng/mL). Table 2 also shows that the variability in the denosumab efficacy and potency is high and evidenced a certain degree of shrinkage. Age, sex, race, and body weight had no notable effect on denosumab $I_{\text{max}}$ and $IC_{50}$.

The predictive checks shown in Fig. 1 indicate excellent predictive ability of the model to describe uNTx/Cr suppression following single and multiple s.c. doses of denosumab. Figure 1A indicates that, at steady state, serum denosumab concentrations during the entire dosing interval following 120 mg every 4-week dosing in patients with bone metastases from solid tumors are associated with greater than 95% of patients achieving uNTx/Cr values below 50 nmol/L BCE/mmol/L, a cutoff value that has been associated with a 2-fold increased risk for SRE and disease progression (10). Furthermore, the model-predicted incidence of uNTx/Cr values BLQ was 54.3% (90% CI, 50.9%–57.5%), consistent with the observed value (52%) in the analysis data set. The model-predicted incidence of uNTx/Cr values BLQ as a function of the predicted denosumab concentration (Fig. 1B) support the adequacy of the model to describe the uNTx/Cr values BLQ, an indirect marker of maximal suppression. In fact, the percentage of uNTx/Cr values BLQ following 120 mg every 4-week dosing is 14% higher than in 30 mg every 4-week dosing (63.7% vs. 55.9%). The predictive check results for uNTx/Cr in those patients who received 120 mg denosumab every 4 weeks are summarized in Fig. 1C and D and show that the model-based predictions are appropriate to describe the overall distribution of the time courses for uNTx/Cr following denosumab 120 mg s.c. every 4-week administration. Overall, the model has adequately characterized the time course of uNTx/Cr suppression following different denosumab schedules and was deemed appropriate to explore the effect of denosumab dose and dosing regimen on the uNTx/Cr suppression through model-based simulations.

Simulations illustrating the relationship between denosumab trough concentration at steady state and the proportion of patients who achieve at least 90% of uNTx/Cr suppression (Fig. 2A) show that the proportion of patients with maximal suppression increases steadily as denosumab concentrations increase with approximately 60% of patients achieving at least 90% suppression at the upper range of trough concentrations following s.c. denosumab dosing at 120 mg administered every 4 weeks. This level of uNTx suppression is higher than that achieved following a denosumab 30 mg every 4-week dose regimen (area between vertical dotted lines in Fig. 2A). To further establish the relationship between denosumab dosing regimen and proportion of patients with at least 90% suppression of uNTx/Cr at the trough level achieved at week 25 of treatment, model-based simulations were conducted across the range of doses and dosing regimens evaluated in the
analysis data set. Figure 2B shows that, for a given dose or a given cumulative dose, the proportion of patients achieving at least 90% of uNTx/Cr suppression is greater for every 4-versus 12-week dosing across the entire dose range and continues to increase until it starts to plateau at 120 mg every 4 weeks. While every 4-week dosing regimens with doses higher than 120 mg provide limited additional benefit in terms of the proportion of patients with at least 90% of uNTx/Cr suppression, the 120 mg every 4-week dosing regimen provides approximately 14.0% and 13.7% increases in the proportion of patients achieving the target uNTx inhibition as compared with 30 mg every 4-week and 180 mg every 12-week dosing, respectively. In addition, model-based simulations of uNTx/Cr time courses are presented in Fig. 2C for denosumab weight–based dosing (2 mg/kg every 4 weeks) and fixed dosing (120 mg every 4 weeks). At week 25, uNTx/Cr values are similar for both regimens with median (25th–75th percentile, Q1–Q3) concentrations of 4.91 (2.26–10.16) and 5.21 (2.31–12.01) nmol/L BCE/mmol/L, for 2 mg/kg and 120 mg, respectively. The suppression of uNTx/Cr as related to the proportion of observations BLQ was also consistent across both dosing regimens. When comparing dosing regimens at the upper and lower quartiles of body weight, both weight-based and fixed dosing resulted in similar uNTx/Cr values. For the lower quartile of body weight (≤59.7 kg), median (Q1–Q3) uNTx/Cr values at weeks 25 were 6.10 (2.58–13.17) nmol/L BCE/mmol/L for 2 mg/kg and 6.39 (2.54–13.0) nmol/L BCE/mmol/L for 120 mg. For the upper quartile of body weight (≥83 kg), median (Q1–Q3) values were 4.75 (2.17–10.1) nmol/L BCE/mmol/L for 2 mg/kg and 5.67 (2.54–12.48) nmol/L BCE/mmol/L for 120 mg. Overall, the difference in denosumab dosing (weight-based vs. fixed dose) did not translate to any relevant difference in uNTx/Cr values or their variability over time.

**Discussion**

Elevated BTMs have been associated with disease progression and poor prognosis in breast cancer, prostate cancer, and other solid tumors with bone metastases (38). After a single s.c. dose, denosumab caused rapid and sustained suppression of bone turnover in postmenopausal women with low bone mass and in patients with breast cancer or multiple myeloma (16, 21). A direct effect of denosumab on bone resorption was evidenced by a decrease in bone resorption markers such as uNTx/Cr (22). Therefore, the primary objective of this analysis was to characterize the time course of uNTx/Cr as a function of denosumab serum concentration following s.c. administration in patients with bone metastases from solid tumors and to quantify the degree of unexplained BSV on denosumab PD efficacy and potency.

In patients with bone metastases from solid tumors, the uNTx/Cr suppression induced directly by denosumab serum concentration was characterized by 2 parameters, $I_{\text{Max}}$ and $I_{\text{C}20}$, which were estimated to be 93.7% and 31.8 ng/mL, respectively. As expected from the method used to handle uNTx/Cr values BLQ, the estimates of $I_{\text{Max}}$ and $I_{\text{C}20}$ are different from the values previously reported that did not use such methods (22). The strategy of assigning uNTx/Cr values BLQ to the LOQ led to a model misspecification and suggested that an indirect response model, instead of
direct effect model, was the best structural model to describe uNTx/Cr suppression following denosumab treatment (22). The high incidence of uNTx/Cr values BLQ in the current data set and its correlation with the predicted denosumab concentration (Fig. 1B) precludes assigning uNTx/Cr values BLQ to the LOQ and justifies the joint analysis of the continuous uNTx/Cr observations and the uNTx/Cr values BLQ conducted. In addition, instead of conditioning the uNTx/Cr observations that were greater than 0 (M4 method), a log transformation of the uNTx/Cr was used within the M3 method. This approach has been proven to provide unbiased estimates of model parameters in analyzing BLQ data (29–34). Upon incorporating the BLQ data using the M3 method, an indirect response model did not provide as good a fit as the direct-effect model. In the previous analysis, the turnover rate of uNTx/Cr was estimated to be 1.26 days, which is significantly shorter than the absorption half-life for denosumab (2.71 days) and, therefore, denosumab absorption would be the rate-limiting step of suppressing the production rate of uNTx/Cr. In this situation, a direct-effect model is expected to perform at least equally well, if not better, than an over-parameterized indirect response model, in particular if one considers that only data from a sparse uNTx/Cr sampling schedule were available for these analyses.

The 2 methods used to handle uNTx/Cr values BLQ, acknowledging the uNTx concentrations BLQ versus the previously reported model fixing the uNTx concentrations BLQ to LOQ, allow us to compare the differences in \( I_{\text{max}} \) and IC\(_{50} \) estimates between the 2 methods (22). Previous results suggest that denosumab would have a 17% lower intrinsic efficacy and 2.6-fold higher potency with respect to the values reported here. In the current analysis, the RSE of \( I_{\text{max}} \) and IC\(_{50} \) estimates were reduced by 64.6% and 42.7%, respectively, compared with the analysis conducted by Lipton and colleagues. In contrast, the magnitude of the BSV and the RV were similar or slightly lower to that previously reported (22). These differences led to inaccuracies in the predicted proportions of patients with trough serum denosumab concentrations producing 90% of maximal uNTx/Cr suppression and therefore discrepancy with the results of the current simulations. For example, as the previous estimate of \( I_{\text{max}} \) was 17% lower than the current estimate, the predicted proportions of patients with more than 90% of maximal uNTx/Cr suppression in the previous analysis is approximately equivalent to the proportions of patients with approximately more than 70% uNTx/Cr suppression in the current analysis, which is less likely to reflect an effective and maximal suppression of the bone resorption marker. In addition, for a given range of denosumab serum concentrations, a 2.6-fold higher potency estimate in the previous analysis leads artificially to a higher proportion of patients achieving a certain target at the doses tested and explains the apparent lack of dose–response reported previously (22).

Taken together, the results of the comparisons between different methodologic approaches in handling uNTx/Cr values BLQ highlight the importance of analyzing the uNTx/Cr values BLQ as censored data and maximizing the likelihood for BLQ data with respect to the model parameters. Therefore, the implications derived from the previous analysis should be interpreted with caution. Notably, the results of the current analysis confirm the high efficacy and potency of denosumab in suppressing uNTx/Cr. However, the high BSV in denosumab efficacy and potency suggests that the serum concentrations required to effectively suppress uNTx/Cr levels vary substantially among patients with bone metastases from solid tumors. These empirical observations indicating that denosumab 120 mg s.c. every 4-week dosing suppresses bone resorption (uNTx/Cr) maximally in patients with bone metastases from solid tumor patients are supported by model-based simulations displayed in Fig. 2A and B. Consistent with the population PK analysis, the larger fluctuations in denosumab serum concentrations following every 12-week dosing resulted in larger fluctuations of uNTx/Cr levels during the dosing interval than in every 4-week dosing, which translated to less effective uNTx/Cr suppression and higher probability of “escape” from bone resorption suppression with extended dosing intervals. Moreover, while every 4-week dosing regimens with doses higher than 120 mg provide limited additional benefit in terms of bone resorption suppression, the 120 mg every 4-week dosing regimen provides higher increases in the proportion of patients achieving the target inhibition as compared with the other dosing regimens evaluated, such as 30 mg every 4 weeks and 180 mg every 12 weeks.

Notably, age, sex, weight, and race had no discernable effect on denosumab efficacy and potency. Given the limited magnitude of the effect, none of the covariates associated with statistically significant differences in denosumab PK parameters in patients with cancer (namely, race and cancer type) are expected to manifest clinically relevant variations in uNTx/Cr suppression. In fact, the population PK analysis indicated that a denosumab dosing regimen of 120 mg every 4 weeks provides at least 98% reduction of free RANKL in the vast majority of patients, regardless of the covariates affecting denosumab PK. Moreover, as body weight represents the covariate with the highest effect on denosumab PK parameters, simulations were undertaken to compare the time course of uNTx/Cr following a denosumab weight–based dose of 2 mg/kg and fixed dose of 120 mg. Both regimens provide comparable uNTx/Cr suppression over the every 4-week dosing interval with respect to both the median and distribution of uNTx/Cr model predictions (Fig. 2C), regardless of patient body weight. Therefore, dose adjustments on the basis of body weight and the covariates affecting the PK of denosumab are not warranted.

In summary, this analysis indicates that the denosumab 120 mg every 4-week dose regimen results in (i) a greater proportion of patients with normalized uNTx/Cr levels (<50 nmol/L BCE/mmol/L) relative to 30 mg every 4- and every 12-week dosing regimens; (ii) a greater proportion of patients with more than 90% uNTx/Cr suppression relative to every 12-week dosing; and (iii) the lowest every 4-week dose with the maximal proportion of patients with uNTx/Cr suppression more than 90%. Collectively, these results...
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indicate that the denosumab dosing regimen of 120 mg s.c. every 4 weeks is the optimal dosing regimen to maximally suppress bone resorption (uNTX/ Cr) during the entire dosing interval, to minimize uNTX/Cr variability, and to avoid "escape" from suppression of bone resorption associated with longer dosing intervals.

Disclosure of Potential Conflicts of Interest

S. Doshi, I. Sutjandra, J. Zheng, W. Sohn, G. Jang, A.T. Chow, and J.I. Pérez-Ruixo are employees of Amgen Inc. and own stock in Amgen Inc. M. Peterson is a former employee of Amgen Inc.

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