Design and methods for a Scandinavian pharmacovigilance study of osteonecrosis of the jaw and serious infections among cancer patients treated with antiresorptive agents for the prevention of skeletal-related events

John Acquavella,1 Vera Ehrenstein,1 Morten Schiødt,2 Uffe Heide-Jørgensen,1 Anders Kjellman,3,4 Svein Hansen,5 Cecilia Larsson Wexell,2,5 Bente Brokstad Herlofson,5 Sven Erik Noerholt,9 Haijun Ma,10 Katarina Öhring,11 Rohini K Hernandez,12 Henrik Toft Sørensen1

1Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; 2Department of Oral and Maxillofacial Surgery, Rigshospitalet, Copenhagen, Denmark; 3Department of Urology, Karolinska University Hospital, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden; 4Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden; 5Cancer Registry of Norway, Oslo University Hospital, Oslo, Norway; 6Department of Oral and Maxillofacial Surgery, Södra Älvsborg Hospital, Borås, Sweden; 7Department of Biomaterials, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; 8Department of Oral Surgery and Oral Medicine, Faculty of Dentistry, University of Oslo, Oslo, Norway; 9Department of Oral and Maxillofacial Surgery, Aarhus University Hospital, Aarhus, Denmark; 10Global Biostatistical Science, Amgen Inc., Thousand Oaks, CA, USA; 11Clinical Development, Amgen Inc., Thousand Oaks, CA, USA; 12Center for Observational Research, Amgen Inc., Thousand Oaks, CA, USA

Objective: Osteonecrosis of the jaw (ONJ) is a recognized complication of potent antiresorptive therapies, especially at the doses indicated to prevent skeletal complications for cancer patients with bone metastases. This paper describes the rationale and methods for a prospective, post-authorization safety study of cancer patients treated with antiresorptive therapies.

Methods: As part of a comprehensive pharmacovigilance plan, developed with regulators’ input, the study will estimate incidence of ONJ and of serious infections among adult cancer patients with bone metastases treated with denosumab (120 mg subcutaneously) or zoledronic acid (4 mg intravenously, adjusted for renal function). Patients will be identified using routinely collected data combined with medical chart review in Denmark, Sweden, and Norway. Follow-up will extend from the first administration of antiresorptive treatment to the earliest of death, loss-to-follow-up, or 5 years after therapy initiation. Results will be reported for three treatment cohorts: denosumab-naive patients, zoledronic acid-naive patients, and patients who switch from bisphosphonate treatment to denosumab. ONJ cases will be identified in three newly established national ONJ databases and adjudicated by the committee that functioned during the XGEVA® clinical trials program.

Conclusion: This study will provide a real world counterpart to the clinical trial-estimated risks for ONJ and serious infections for cancer patients initiating denosumab or zoledronic acid. The establishment of ONJ databases in the three Scandinavian countries will have potential benefits outside this study for the elucidation of ONJ risk factors and the evaluation of ONJ treatment strategies.

Keywords: cohort study, osteonecrosis of the jaw, pharmacovigilance, postmarketing drug surveillance, denosumab, zoledronic acid

Introduction

Bone metastases and their clinical sequelae are frequent and debilitating complications for patients with advanced cancer.1–4 Bone metastases are associated with markedly increased osteoclast activity and skeletal-related events (SREs), including pathologic fractures, radiation to bone, spinal cord compression, and surgery to bone.5,6 Until approval of the first RANK ligand (RANKL) antibody (denosumab) in 2010, intravenous (IV) bisphosphonates were the only approved treatment to prevent SREs. Denosumab is a fully human IgG2 monoclonal antibody that inhibits RANKL, prevents
RANK activation, and thereby inhibits the formation, differentiation, and survival of osteoclasts.7

Efficacy results from three pivotal Phase 3 active-comparator studies of denosumab (120 mg subcutaneously [SQ] every 4 weeks [Q4W]) against the standard of care bisphosphonate (zoledronic acid, IV, 4 mg, adjusted for renal function, Q4W) established the efficacy of denosumab for the prevention of SREs.8-10 Accordingly, XGEVA® (denosumab 120 mg SQ Q4W) was approved in the United States (2010), Canada (2011), and the European Economic Area (2011) to prevent SREs in patients with bone metastases from solid tumors.

A serious complication observed for both treatment arms during the sponsor’s clinical trial program was osteonecrosis of the jaw (ONJ). ONJ is a recognized clinical entity, defined during the clinical trial program as an area of exposed alveolar or palatal bone associated with non-healing after 8 weeks of appropriate care in a patient without a prior history of radiation therapy to the jaws.11,12 Since then, the American Association of Oral and Maxillofacial Surgeons’ (AAOMS) definition for ONJ has broadened, as reflected in a recent position paper from AAOMS, to recognize that ONJ can manifest without exposed bone.13 Research suggests a strong association of ONJ with suppression of bone turnover.12,14,15 ONJ has been observed among 1% to 10% of cancer patients, followed for up to 36 months, treated with IV bisphosphonates for the prevention of SREs.16 In the pooled analysis of the three denosumab (120 mg SQ, Q4W) pivotal trials, at 3 years’ follow-up, the proportions of subjects with ONJ were 1.8% and 1.3% among subjects who received denosumab (median time on therapy 13 months) and IV zoledronic acid (median time on therapy 12 months), respectively (P=0.13).17 Based on common terminology criteria for adverse events grading,18 severity was mild to moderate for all but three of the 89 ONJ cases.

As part of the marketing authorization agreement in Europe, the sponsor was required to design and implement a post-authorization safety study (PASS) of cancer patients treated with antiresorptive agents. Two endpoints were stipulated: ONJ and serious infections. The latter endpoint was included based on theoretical concerns because RANKL is expressed on activated T and B cells and in the lymph nodes, although no evidence of immunosuppression or increased risk for infection was seen in denosumab-treated cancer patients during the clinical trial program.19 The study designed to fulfill this regulatory commitment is a prospective study of Danish, Swedish, and Norwegian cancer patients with bone metastases initiating treatment with denosumab or zoledronic acid from the first date of XGEVA® availability in the three countries (Denmark, September 2011; Sweden and Norway, October 2011) through the end of 2013 in Norway and Sweden, and through the end of 2014 in Denmark. The study includes three treatment cohorts: denosumab-naïve patients, zoledronic acid-naïve patients, and cancer patients who switch from bisphosphonate treatment to denosumab. The last cohort does not have a counterpart in the three pivotal clinical trials, but is of interest to European Union regulators based on the expectation that patients might switch from IV bisphosphonates to the new therapy when renal function deteriorates or when an SQ therapy is clinically preferable. Herein, we describe briefly the design and methods being employed in this study.

Methods

Cohort identification and follow-up

The Scandinavian national comprehensive health and administrative registries and databases are linkable on an individual level, within a setting of universal health care, and capture health-related data on all residents during their lifetime. A broad spectrum of health information is routinely registered, with only slight differences among the countries. Residents can be tracked in all databases from birth or immigration until death or emigration, providing virtually complete long-term follow-up. Completeness and accuracy of these records have been found to be high.20,21

Eligibility criteria for this study require that patients be at least 18 years old, diagnosed with cancer, and, subsequent to the development of bone metastases, initiated antiresorptive treatment for SRE prevention with denosumab or zoledronic acid. Patients could also have switched to denosumab after receiving up to 24 treatments with oral or IV bisphosphonates at doses for cancer indications. The exclusion criteria are a history of radiation therapy to the head and neck region or having hypercalcemia of malignancy as the sole indication for (usually short-term) treatment with an antiresorptive agent.

Patients are initially identified from diagnoses (Denmark, Norway, and Sweden) and treatments (Denmark only) recorded in the national patient registries (the Danish National Patient Register,20,22 the Norwegian Patient Register,23 and the National Patient Register of Sweden)24 and then verified to be eligible by medical chart review. Data on vital status and dates of death or emigration are to be obtained from the population registries of the participating countries: the Danish Civil Registration System,25 Statistics Norway,26 and the Swedish Total Population Register.27 Patients are followed annually through the relevant data systems from the first administration of antiresorptive...
treatment to the earliest of death, loss-to-follow-up, or 5 years after therapy initiation, regardless of the duration of therapy. The follow-up period ends in September 2019.

The study was approved by the Danish Data Protection Agency, Danish National Board of Health, the Norwegian Regional Committee for Medical and Health Research Ethics South-East, and the Swedish Regional Ethical Review Board. The www.clinicaltrials.gov identifier is: NCT01967160.

**Endpoint detection**

A key challenge in registry-based PASS can be the detection of clinical outcomes with completeness and validity comparable to that of randomized trials. Therefore, as part of the development of this study, extensive validation efforts were initiated for the co-primary endpoints.

**ONJ**

Unlike the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) classification system used in the United States, the version of the ICD-10 classification used in the three Scandinavian countries does not have a specific code for ONJ. Accordingly, based on expert opinion, we developed an algorithm of ICD-10 codes that could conceivably be used to code ONJ. This algorithm was used to identify patients in the Danish National Patient Register during the pre-approval period 2005 through 2010 who also had a cancer diagnosis and who had sought care in Departments of Oral and Maxillofacial Surgery (DOMS) in Denmark. Then, the expert ONJ adjudication committee (ONJAC) from the sponsor’s clinical trial program reviewed information abstracted from medical records for these potential cases to identify true positive cases.

Our validation efforts included 212 potential ONJ cases. Charts were available for 197 (93%) of these patients. Of these, 83 cases were adjudicated positive (positive predictive value [PPV] 42%, 95% confidence interval [CI] 35% to 49%). We also evaluated the sensitivity of the algorithm to identify known cases from a collection of ONJ cases maintained by two DOMS in Denmark. Based on 101 ONJ cases known to these two DOMS, we estimated sensitivity to be 73% (95% CI 64% to 81%). No additional ICD codes were identified that would have improved sensitivity appreciably.28

The PPV and sensitivity of the ONJ algorithm were judged unsuitable to accurately estimate the incidence of ONJ for this PASS. While adjudication can solve the false positive identification problem, additional steps were necessary to address the likely under-ascertainment of cases (viz low sensitivity). Accordingly, the study team consisting of leading oral and maxillofacial surgeons in Denmark, Sweden, and Norway established country-specific databases of ONJ cases that can be used for case identification. The process, challenges, and procedures for the establishment of these three national databases have been previously described.29 Thus, ONJ case detection will involve linkage with these newly established resources for ONJ, coupled with algorithm searches of national patient databases where improvement in coding of ONJ at the DOMS level can be expected. Potential cases identified through these procedures will be adjudicated by the ONJAC so that ONJ in this PASS is defined in a manner consistent with the sponsor’s clinical trials program.

**Serious infection**

Serious infections are common among patients with advanced cancer.30 We defined a serious infection as one that was recorded in the patient registries during inpatient hospitalization. Because validity of inpatient diagnoses for infection had not been studied previously for cancer patients, we conducted such an assessment during the 5 years immediately preceding our study period.31

Based on an algorithm of ICD-10 codes for infection and blinded physician review of medical records for a sample of 266 patients with infection diagnoses identified from the Danish National Patient Register, the PPV of our algorithm was 98% (95% CI 96% to 99%) for any infection (the study’s co-primary endpoint), supporting this approach of endpoint assessment. For specific infection subcategories that are of special interest for cancer patients, PPVs were 93% for sepsis, 84% for pneumonia, and 79% for skin infections. Sensitivity was not evaluable in this study, but clinical judgment suggests that infections leading to or associated with a hospitalization are unlikely to go unrecorded in patient databases, and that other common conditions among cancer patients are unlikely to be miscoded as infections.

**Statistical analysis**

The primary analytic approach chosen for this study is descriptive: to calculate cumulative year by year cohort specific incidence proportions (IPs) for the three treatment cohorts. The IP is calculated simply as the proportion of patients who manifested ONJ or a serious infection at yearly cumulative time points. In addition, incidence rates will be calculated for the cohorts after 3 and 5 years’ follow-up, respectively. Incidence rates will be calculated as the number of patients who manifest ONJ or a serious infection divided by the total person-years of observation in the respective cohorts when 3 or 5 years’ follow-up time has elapsed.
Comparative analyses were deemed unlikely to be valid because of the expected non-comparability of the naïve treatment cohorts to each other. In contrast to the XGEVA® clinical trial program where naïve patients were exchangeable at treatment assignment, exchangeability is not expected among naïve real world patients, especially for newly marketed medications.12 There is a contraindication for zoledronic acid, but not denosumab, for patients with severe or worsening renal impairment and the availability of an SQ therapy enables treatment with denosumab, but not zoledronic acid, by physicians who do not administer IV medications as part of their practices. In addition, there is also the potential for new physician adoption bias with a novel therapy like denosumab. Early adopting physicians are likely to be more comprehensive about pre-treatment oral evaluation to prevent initiation of antiresorptive therapy for patients with invasive dental treatment in the last 6 months, a strong risk factor for ONJ, and about ongoing evaluation of patients to identify oral lesions that should be referred for expert dental evaluation.33 This could bias comparative analyses to the extent that pre-treatment evaluation and comprehensiveness of evaluation during treatment may differ for denosumab and zoledronic acid.

ONJ, by consensus definition, is only diagnosed after 8 weeks of exposed or probed alveolar or palatal bone.12 Therefore, time at risk for ONJ will start 8 weeks after a patient receives his/her first antiresorptive treatment. Consequently, patients diagnosed with ONJ within 8 weeks of their first qualifying antiresorptive treatment will not contribute to numerators or denominators in ONJ IPs and incidence rates, and patients switching from zoledronic acid to denosumab will be at risk in the zoledronic acid cohort until 8 weeks after the switch.

There is no natural comparator for patients who switch from bisphosphonate treatment to denosumab. Switching is expected to be predominantly, though not exclusively, from zoledronic acid or other bisphosphonates to denosumab. This pattern of switching can cause some ambiguity in interpreting results for those who switch therapies to denosumab due to the long residence of bisphosphonate in the bone and the clinical experience that ONJ has been diagnosed months after bisphosphonate treatment ended.

The study was designed to include 700 to 900 patients in the denosumab-naïve cohort, all denosumab switch patients who meet eligibility criteria (expected to be at least 150), and one matched zoledronic acid patient for each denosumab patient. This study size would enable estimation of ONJ IPs with 95% CI half-widths of approximately 1% or less for the denosumab and zoledronic acid inception cohorts, and 3.7% or less for the denosumab switch cohort. The corresponding 95% CI half-widths for serious infection IPs would be approximately 2% or less for the denosumab and zoledronic acid inception cohorts. Based on the observed 3-year cumulative incidence of ONJ during the clinical trial program and the planned 5-year follow-up in this PASS, the three treatment cohorts would be expected to yield approximately 80 to 100 cases of ONJ. These cases will be followed to ascertain ONJ severity at diagnosis and during routine clinical care, treatment practices, and the proportion of ONJ cases that resolve.

Discussion
This PASS focuses on cancer patients with bone metastases, a population characterized by relatively short survival. Based on recent studies in Denmark, 99%, 80%, and 63% of patients with bone metastases who have lung, prostate, or breast cancer, respectively, died within 2 years of their bone metastasis diagnosis date.34-36 Antiresorptive therapies effectively reduce pain and the number of debilitating SREs during patients’ remaining lifespans.8-10,37

Recent legislation in the United States and the European Union gave regulatory agencies the authority to require sponsors to conduct PASS as a condition of approval. The regulatory intent behind these required studies is often the assessment of rare adverse events that might surface with greater numbers of patients under observation for longer time periods than would be possible during a clinical trial program. This is especially likely for medications used to treat conditions that are not associated with high near-term mortality rates. For patients whose median life expectancy is short, such studies often focus on providing a real world estimate of the frequency of serious adverse events observed during a clinical trial program. This addresses recognized limitations of clinical trials: underrepresentation of specific patient groups and treatment in a more controlled environment than routine clinical practice.38

The non-comparative analysis approach chosen in this study has as its primary utility providing a real world counterpart to the clinical trial ONJ risks for denosumab (120 mg Q4W) and zoledronic acid (4 mg Q4W). The study will also provide novel information on ONJ and serious infections for patients in routine clinical practice who switch therapies to denosumab. The fact that these treatment cohorts are likely to differ in ways that obviate comparative analyses does not reduce the value of the cohort-specific results as a measure of real world outcomes. For a condition like ONJ, which is exceedingly rare in the absence of antiresorptive therapy, the complement of a cohort-specific IP also addresses directly a question of primary interest for
practitioners and patients: viz what percent of patients can benefit from therapy without the adverse event of ONJ.

Frequently PASS may focus on adverse events that are exceedingly rare outside of patients treated with a specific class of therapeutic drug. Some of these adverse events may have low clinical awareness and be difficult to ascertain completely outside the clinical trial setting. Indeed, we established that detection of ONJ would be incomplete in the national patient registries, even with an algorithm developed to maximize sensitivity. This led to collaboration with oral and maxillofacial surgeons at centers in Denmark, Sweden, and Norway where virtually all suspected cases of ONJ are evaluated and, subsequently, to the establishment of three national databases of known ONJ cases for linkage with the treatment cohorts. Establishment of the ONJ database is therefore critical to ascertainment of ONJ risk, although the potential for underreporting of ONJ into the database remains. Potential cases identified with this approach will be adjudicated as in the denosumab clinical trial program. The establishment of these national ONJ databases will not only help to meet the requirements of the PASS for detection of ONJ, but also support broader studies of the clinical course of ONJ. Much remains to be learned about ONJ, including elucidation of risk factors that could serve as a basis for preventive activities and evaluation of treatment strategies.

Acknowledgment
This research was sponsored by Amgen Inc. The funding from Amgen Inc. received to conduct this study was issued to and administered by Aarhus University.

Disclosure
JA was formerly employed by Amgen Inc. and holds Amgen stock. VE, UHJ, and HTS are employed by the Department of Clinical Epidemiology at Aarhus University and Aarhus University Hospital. MS has consulted for Amgen Inc. as an educator and member of an expert panel on osteonecrosis. BBH has received a one-time lecture fee from Amgen Inc. CLW, AK, SEN, and SH have no conflicts of interest. HM, KÖ, and RKH are employees and stockholders of Amgen Inc.

References
1. Carlin BI, Andriele GL. The natural history, skeletal complications, and management of bone metastases in patients with prostate carcinoma. Cancer. 2000;88(12 Suppl):2989–2994.
2. Coleman RE. Skeletal complications of malignancy. Cancer. 1997;80(8 Suppl):1588–1594.
3. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006;12(20 Pt 2):6243s–6249s.
4. Viadana E, Cotter R, Pickren JW, Bross ID. An autopsy study of metastatic sites of breast cancer. Cancer Res. 1973;33(1):179–181.
5. Roodman GD. Mechanisms of bone metastasis. Disoc Med. 2004;4(22):144–148.
6. Yonou H, Ochiai A, Goya M, et al. Intraosseous growth of human prostate cancer in implanted adult human bone: relationship of prostate cancer cells to osteoclasts in osteoblastic metastatic lesions. Prostate. 2004;58(4):406–413.
7. Kearns AE, Khosla S, Kostenuik PJ. Receptor activator of nuclear factor kappaB ligand and osteoprotegerin regulation of bone remodeling in health and disease. Endocr Rev. 2008;29(2):155–192.
8. 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 randomised, double-blind study. Lancet. 2011;377(9768):813–822.
9. 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(9):1125–1132.
10. 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(35):5132–5139.
11. Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2007;22(10):1479–1491.
12. Ruggiero SL, Dobson TD, Assael LA, et al. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaw - 2009 update. J Endod. 2009;35(3):119–130.
13. Ruggiero SL, Dobson TD, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw-2014 update. J Oral Maxillofac Surg. 2014;72(10):1938–1956.
14. Cartsos VM, Zhu S, Zavras AI. Bisphosphonate use and the risk of adverse jaw outcomes: a medical claims study of 714,217 people. J Am Dent Assoc. 2008;139(1):23–30.
15. Van den Wyngaert T, Huizing MT, Vermorken JB. Bisphosphonates and osteonecrosis of the jaw: cause and effect or a post hoc fallacy? Ann Oncol. 2006;17(8):1197–1204.
16. Migliorati CA, Woo SB, Hewson I, et al. A systematic review of bisphosphonate osteonecrosis (BON) in cancer. Support Care Cancer. 2010;18(8):1099–1106.
17. Saad F, Brown JE, Van Poznak C, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol. 2012;23(5):1341–1347.
18. National Institutes of Health. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE); Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010). 2010. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed June 7, 2016.
19. Peddi P, Lopez-Olivo MA, Pratt GF, Suarez-Almazor ME. Denosumab in patients with cancer and skeletal metastases: a systematic review and meta-analysis. Cancer Treat Rev. 2013;39(1):97–104.
20. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449–490.
21. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sorensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin Pharmacol Toxicol. 2010;106(2):86–94.
Acquavella et al

22. Lyne E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39(7 Suppl):30–33.

23. Bakken IJ, Gystad SO, Christensen OO, et al. Comparison of data from the Norwegian Patient Register and the Cancer Registry of Norway. *Tidsskr Nor Laegeforen*. 2012;132(11):1336–1340.

24. Ludvigsson JF, Andersson E, Ekborn A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450.

25. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541–549.

26. Statistics Norway [homepage on the Internet]. Available from: http://www.ssb.no/en. Accessed May 7, 2016.

27. Skatteverket [homepage on the Internet]. Population Registration in Sweden. Available from: http://www.skatteverket.se/privat/sjalvservice/blanketterbroschyrer/broschyrer/info/717b.4.39f16f103821c58f6800008017.html. Accessed May 7, 2016.

28. Ehrenstein V, Gammelager H, Schiodt M, et al. Evaluation of an ICD-10 algorithm to detect osteonecrosis of the jaw among cancer patients in the Danish National Registry of Patients. *Pharmacoepidemiol Drug Saf*. 2015;24(7):693–700.

29. Schiodt M, Larsson Wexell C, Herlofsson BB, Giltvedt KM, Norholt SE, Ehrenstein V. Existing data sources for clinical epidemiology: Scandinavian Cohort for osteonecrosis of the jaw - work in progress and challenges. *Clin Epidemiol*. 2015;7:107–116.

30. Centers for Disease Control and Prevention [homepage on the Internet]. Preventing Infections in Cancer Patients. CDC; 2016. Available from: http://www.cdc.gov/cancer/dcp/resources/features/preventinfections/index.htm Accessed May 7, 2016.

31. Holland-Bill L, Xu H, Sorensen HT, et al. Positive predictive value of primary inpatient discharge diagnoses of infection among cancer patients in the Danish National Registry of Patients. *Ann Epidemiol*. 2014;24(8):593–597.e1–18.

32. Schneeweiss S, Gagne JJ, Glynn RJ, Ruhl M, Rassen JA. Assessing the comparative effectiveness of newly marketed medications: methodological challenges and implications for drug development. *Clin Pharmacol Ther*. 2011;90(6):777–790.

33. XGEVA® (denosumab) injection, for subcutaneous use [prescribing information]. California: Amgen Inc.; 2010.

34. Chia VM, Cetin K, Jacobsen JB, et al. The incidence and prognostic significance of bone metastases and skeletal-related events in lung cancer patients: A population-based cohort study in Denmark. *Journal of Clinical Oncology*. 2010;28(15 Suppl).

35. Norgaard M, Jensen AO, Jacobsen JB, Cetin K, Fryzek JP, Sorensen HT. Skeletal related events, bone metastasis and survival of prostate cancer: a population based cohort study in Denmark (1999 to 2007). *J Urol*. 2010;184(1):162–167.

36. Yong M, Jensen AO, Jacobsen JB, Norgaard M, Fryzek JP, Sorensen HT. Survival in breast cancer patients with bone metastases and skeletal-related events: a population-based cohort study in Denmark (1999–2007). *Breast Cancer Res Treat*. 2011;129(2):495–503.

37. Patrick DL, Cleeland CS, von Moos R, et al. Pain outcomes in patients with bone metastases from advanced cancer: assessment and management with bone-targeting agents. *Support Care Cancer*. 2015;23(4):1157–1168.

38. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol*. 2005;58(4):323–337.