BUDGET IMPACT OF DENOSUMAB FOR BREAST CANCER IN BONE METASTASES

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ABSTRACT
This study reviews the existing evidences for denosumab usage for bone metastases therapy in breast cancer and evaluates its budget impact on the health care system in Bulgaria. Perspective of the analysis is from the third party payer that is the National Health Insurance fund. Desktop study of RCT for safety and efficacy of denosumab in comparison with zolendronic acid, as well as budget impact analysis were performed for breast cancer with metastases therapy. The results show that denosumab is effective and safe therapy for persons with breast cancer. The cost of administration of denosumab is higher in comparison with zolendronic acid, due to its high price but the administration cost of zolendroni acid as an infusion is higher. Administration costs are partly offset by the patients management cost and cost of skeletal events. Savings from denosumab utilization are increasing with the years even if the number of patients with metastases is very low in comparison with other countries. Savings are increasing from 79 to 240 thousands BGN in the 1st and 3rd year, respectively. Based on this study we can conclude that denosumab is effective, safe, and it is a good investment for the Bulgarian health care settings when treated breast cancer with metastases.

KEYWORDS: Denosumab, zolendronic acid, breast cancer, metastases, budget impact analysis.
INTRODUCTION
Bone metastases are one of the most common forms of metastatic disease among patients with cancer.\textsuperscript{[1]} A significant number of patients with advanced cancer suffer from bone metastases. In patients with advanced or metastatic solid tumors, 65\%-75\% with breast cancer, 90\% with prostate cancer, and 30\%-40\% with lung cancer develop bone metastases over the course of the disease.\textsuperscript{[2-5]} Skeletal related events (SREs) result from bone metastases secondary to advanced solid tumors and include pathologic fracture, spinal cord compression, radiation to bone, and surgery to bone.\textsuperscript{[6]}

Pain associated with bone metastases is often significant, debilitating, and difficult to treat.\textsuperscript{[7-12]} Depending on treatment status, between 38\%-68\% of patients experienced at least one on-study SRE over 21 to 24 months of follow-up.\textsuperscript{[13,14]}

Patients with bone metastases have consistently demonstrated reduced HRQOL compared with cancer patients without metastatic disease.\textsuperscript{[15-18]} Hospitalization costs due to SREs are substantial. The majority (59\%) of costs associated with SREs are due to inpatient hospitalization.\textsuperscript{[19]} Between 35\%-43\% of patients with an SRE require hospitalization during treatment.\textsuperscript{[20, 21]}

Bisphosphonates are bone-targeting agents used for bone metastases management. Intravenous (i.v.) zoledronic acid now a day is considered the standard of care for the treatment of bone metastases. However, clodronate, pamidronate, and ibandronate are also frequently used. Adverse drug reactions with bisphosphonates and zolendronic acid might cause stopping the therapy or development of SREs.\textsuperscript{[22, 23]} Therefore several new molecules are studied and entrance the markets to benefit the bone metastases therapy.

This study reviews the existing evidences for denosumab usage for bone metastases therapy in breast cancer and evaluates its budget impact on the health care system in Bulgaria. Perspective of the analysis is from the third party payer that is the National Health Insurance fund.

MATERIALS AND METHODS
Desktop study
Desktop study was performed for key randomized clinical trials (RCT) for safety and efficacy analysis of denosumab. It was searched PubMed, Scopus, and clinical trials registries with
key words denosumab, zolendronic acid, safety, efficacy, RCT. The works analyzing the safety and efficacy alone or in comparison with zolendronic acid were selected.

**Budget impact analysis**

The previously created and validated for Spain model were used for the purposes of this analysis. The model considers Bulgarian population and estimates the expected annual cost of treating eligible breast cancer patients with denosumab.

Budget impact of denosumab is compared to zoledronic acid for use in patients treated for bone metastases. The construction of the model reflects a trial-based approach using results provided in head to head studies (Figure 1) and follows the standard therapeutic approach. The patients with metastatic breast cancer that developed metastases and needs therapy to prevent the SREs are prescribed with one of the two treatment strategies (denosumab or zolendronic acid).

![Figure 1. Model Overview](image)

The model time horizon is three years. Due to the relatively short time frame and the variability in specific costs, the analyses do not consider discounting of costs. The model follows the recommendations of the guideline for good practice in budget impact modelling developed by Mauskopht et al. Input data in the model are presented on Table 1.

**Table 1. Input data in the model**

<table>
<thead>
<tr>
<th>Input data</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of breast cancer</td>
<td>1164 per 100 000</td>
<td>Cancer registry; <a href="http://ncpha.government.bg">http://ncpha.government.bg</a></td>
</tr>
<tr>
<td>Prevalence of metastatic breast cancer</td>
<td>6%</td>
<td>Cancer registry</td>
</tr>
<tr>
<td>Prevalence of bone metastases in metastatic cancer patients</td>
<td>70%</td>
<td>Error! Bookmark not defined.</td>
</tr>
<tr>
<td>Skeletal related events</td>
<td>64.4% pathologic fracture; 29.4% radiation to bone</td>
<td>RCT</td>
</tr>
</tbody>
</table>
The skeletal related event (SRE) rates in the models are derived from clinical trial data. Four distinct types of SREs were captured in the clinical trials: pathologic fracture, radiation to the bone, surgery to the bone, and spinal cord compression. The pooled distribution of each of these SREs varies by trial therefore the pooled analysis data were used (Table 2).

**Table 2: Pooled skeletal related events**

<table>
<thead>
<tr>
<th>SRE Type</th>
<th>Breast Cancer[29]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic Fracture</td>
<td>64.4%</td>
</tr>
<tr>
<td>Radiation to Bone</td>
<td>29.4%</td>
</tr>
<tr>
<td>Surgery to Bone</td>
<td>3.8%</td>
</tr>
<tr>
<td>Spinal Cord Compression</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

The step by step approach followed requires first to determine the number of patients that will be taking denosumab in each year of the model time horizon. Second is necessary to determine the costs of denosumab (120 mg) and zoledronic acid (4 mg) and third to determine the skeletal-related event outcomes and costs. At the end sensitivity analyses were performed on key variables through building a tornado diagram.

All costs are in national currency (BGN) with the ex-change rate of 1Euro=1,958BGN.

**RESULTS**

**Review of denosumab efficacy and safety studies for bone metastases therapy**

Stopeck et al.[30] in a RCT found that denosumab significantly increased the median time to first on-study SRE compared with i.v. zoledronic acid in patients with advanced breast cancer (median not reached vs 26.4 months, Hazard Ratio [HR] = 0.82, P = 0.01) and reducing the risk of first on-study SRE by 18% in advanced breast cancer (P = 0.01).[30] Denosumab decreased the proportion of patients who experienced a first on-study SRE compared with i.v. zoledronic acid in advanced breast cancer (30.7% vs 36.5%).[31]
Denosumab demonstrated superior efficacy in three head-to-head clinical trials against i.v. zoledronic acid, reducing the risk of first-and-subsequent SREs by 23% in advanced breast cancer (P = 0.001).\textsuperscript{[30, 31]}

Denosumab reduced the total number of SREs over the study period compared with i.v. zoledronic acid in patients with advanced breast cancer (474 vs 608).\textsuperscript{[30, 31]} The annualized rate of SREs was consistently lower with denosumab compared with i.v. zoledronic acid regardless of primary solid tumor type.\textsuperscript{[31-33]}

Across primary tumor types, fewer patients treated with denosumab experienced adverse events, serious adverse events, or adverse events leading to withdrawal of investigational product compared with those who received i.v. zoledronic acid.\textsuperscript{[32]} Overall survival was balanced between the denosumab and i.v. zoledronic acid treatment arms.

Unlike i.v. zoledronic acid, denosumab is not metabolized through the kidneys and does not require renal monitoring prior to or during treatment. Fewer patients experienced renal toxicity with denosumab compared with i.v. zoledronic acid across tumor types.\textsuperscript{[32]}

Denosumab delayed the progression to moderate or severe pain compared with i.v. zoledronic acid in patients with advanced breast cancer (9.7 vs 5.8 months, HR = 0.78, P = 0.0024).\textsuperscript{[30, 31, 34]} A lower proportion of denosumab-treated patients reported moderate or severe pain compared with i.v. zoledronic acid over the duration of each phase 3 clinical trial in patients with advanced solid tumors.

A greater proportion of patients with advanced breast cancer experienced clinically meaningful improvements in HRQOL with denosumab compared with i.v. zoledronic acid over 18 months on study. Additionally, fewer denosumab-treated patients experienced clinically meaningful worsening of HRQOL compared with i.v. zoledronic acid.\textsuperscript{[31, 35]} Denosumab maintains health utility in patients with bone metastases. In phase 3 clinical trials in patients with advanced solid tumors, mean EQ-5D index and VAS scores were similar between treatment groups across study visits.\textsuperscript{[31, 32]}

Denosumab was found to be cost-effective in preventing SREs in patients with bone metastases secondary to advanced breast cancer or CRPC compared with i.v. zoledronic acid in the US.\textsuperscript{[36]}
Results of the budget impact analysis for health care settings in Bulgaria

In Bulgaria both prevalence and incidence of neoplasms permanently shows an increase. In 2009 the prevalence increased to 3 229 for 100 000 population, while the incidence rose from to 393.3 for 100 000 inhabitants. Breast cancer is the leading cause for morbidity in women population also increasing from 1093.1 in 2009 to 1163.9 for 100 000 inhabitants in 2012.37, 38 The budget impact models present a comparison of the cost of treating bone metastases in all appropriate metastatic breast cancer patients with denosumab (120 mg) compared to zoledronic acid (4 mg). The breast cancer model estimates that within the Bulgarian population, there will be 5 098 metastatic breast cancer cases each year requiring treatment, of whom 6% will have bone metastases and 70% of them will be treated. 10% will try denosumab in Year 1 (n=63), 20.6% in Year 2 (n=127), and 30.9% in Year 3 (n=190). The average survival duration is expected to be 3.1 year and therefore the budget impact is evaluated at 3 years period.

Multiplying the expected number of denosumab patients for years 1, 2, and 3 respectively by the annual cost per patient results in the total three-year budget impact expected in Bulgaria. The total 3-year drug cost of denosumab treatment is offset by an incremental decrease in zoledronic acid drug use, patient management costs, and SRE costs.

Table 3: Presentation of Results – Drug Impact – Breast Cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>№ of Patients</th>
<th>Cost of Denosumab (BGN)</th>
<th>Zoledronic Acid Drug Savings Due to Denosumab Use (BGN)</th>
<th>Total Drug Impact (BGN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>573 030</td>
<td>92 609</td>
<td>480 421</td>
</tr>
<tr>
<td>2</td>
<td>127</td>
<td>1 155 155</td>
<td>186 688</td>
<td>968 467</td>
</tr>
<tr>
<td>3</td>
<td>190</td>
<td>1 728 185</td>
<td>279 297</td>
<td>1 448 888</td>
</tr>
<tr>
<td>Total:</td>
<td></td>
<td>3 456 370</td>
<td>558 594</td>
<td>2 897 776</td>
</tr>
</tbody>
</table>

Table 4: Presentation of Results – Total Budget Impact – Breast Cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>№ of Patients</th>
<th>Total Drug Impact</th>
<th>Additional Savings</th>
<th>Total Budget Impact of Denosumabin Bulgaria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patient Management Costs (Savings) per year</td>
<td>SRE costs (Savings) per year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>79 758</td>
<td>7 006</td>
</tr>
<tr>
<td>1</td>
<td>63</td>
<td>480 421</td>
<td>79 758</td>
<td>7 006</td>
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<tr>
<td>2</td>
<td>127</td>
<td>968 467</td>
<td>160 782</td>
<td>14 124</td>
</tr>
<tr>
<td>3</td>
<td>190</td>
<td>1 448 888</td>
<td>240 540</td>
<td>21 130</td>
</tr>
<tr>
<td>Total:</td>
<td></td>
<td>2 897 776</td>
<td>481 080</td>
<td>42 260</td>
</tr>
</tbody>
</table>
The total 3-year drug impact in Bulgaria is estimated to be 2 897 776 BGN for breast cancer (Table 3). The 3-year drug impact is offset by patient management costs and SRE costs for a total incremental 3-year budget savings of 2 374 436 for breast cancer (Table 4). The higher savings are due to patients’ management cost and less than the SRE therapy due to extremely lower costs of health care services in Bulgaria (Figure 1).

The expected annual cost per patient of treating bone metastases in metastatic breast cancer is 3 565.06 BGN when treated with zoledronic acid, and 9 813.58 BGN when treated with denosumab. These figures include drug costs, administration costs, patient management costs, and SRE costs (Table 5).

**Table 5. Cost of Denosumab per Patient Per Year – Breast Cancer**

<table>
<thead>
<tr>
<th>Total Drug Cost Per Patient (BGN)</th>
<th>Denosumab Cost</th>
<th>Zoledronic Acid Cost</th>
<th>Denosumab Incremental Cost (Savings) Per Patient Per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Cost</td>
<td>9 095.71</td>
<td>1469.98</td>
<td>7625.73</td>
</tr>
<tr>
<td>Patient Management Cost</td>
<td>325.00</td>
<td>1591.00</td>
<td>1266.00</td>
</tr>
<tr>
<td>SRE Cost</td>
<td>392.87</td>
<td>504.08</td>
<td>111.21</td>
</tr>
<tr>
<td><strong>Total Cost Per Patient Per Year</strong></td>
<td><strong>9813.58</strong></td>
<td><strong>3565.06</strong></td>
<td><strong>6248.52</strong></td>
</tr>
</tbody>
</table>

**SENSITIVITY ANALYSIS**

Sensitivity analyses were performed on key variables. Most analyses considered an increase or decrease in the variable of 25%. As expected, the most important cost drivers in the model are the drug cost per administration of denosumab and zoledronic acid, as well as the percent of breast cancer with metastases (Figure 2). Those are the variables that influence the total cost of therapy in a significant way.
DISCUSSION AND CONCLUSION

This is the first budget impact analysis for denosumab utilization in breast cancer women in Bulgaria. Most of the published economic models performed for the Bulgarian healthcare setting include diabetes, COPD, HIV infection, vaccination programs, etc.\[39-43\]

The performed budget impact analysis shows that denosumab is effective and safe therapy for persons with breast cancer. The cost of administration of denosumab is higher in comparison with that of zolendronic acid, due to its high price but the administration cost of zolendronic acid as an infusion is higher.

Administration costs are partly offset by the patients management cost and cost of skeletal events. Savings from denosumab utilization are increasing with the years even if the number of patients with metastases is very low in comparison with other countries.

The cost of skeletal related events is very low in comparison with other studies due to extremely low taxes for health care services. Due to that the cost of administration looks high but the prices of medicines in Bulgaria are the lowest from 17 EU countries at ex-manufacturing level.

Based on this study we can conclude that denosumab is effective, safe, and it is a good investment for the Bulgarian health care settings when treated breast cancer with metastases.

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