

## Patterns of care and economic consequences of using bone-targeted agents for castration-sensitive prostate cancer patients with bone metastases to prevent skeletal-related events in Switzerland – the SAKK 95/16 prostate study

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### Summary

**BACKGROUND:** International guidelines state that bone-targeted agents such as denosumab or zoledronic acid at doses used for bone metastasis are not indicated for patients with metastatic castration-sensitive prostate cancer (mCSPC) with bone metastases. Whereas denosumab has never been studied in this patient population, zoledronic acid has been shown to be ineffective in decreasing the risk for skeletal-related events. This study estimates the prevalence and economic consequences of real-world use of bone-targeted agents for mCSPC patients in Switzerland.

**METHODS:** To estimate the frequency of bone-targeted agent administration and skeletal-related events, data from a non-interventional, cross-sectional survey involving oncologists across Switzerland (SAKK 95/16) was combined with data from the Swiss National Institute for Cancer Epidemiology and Registration (NICER). Economic parameters were calculated from the perspective of the healthcare system over the median time to prostate-specific antigen (PSA) progression for the extrapolated patient group, using data from NICER. The cost calculation covered costs for bone-targeted agents, their administration and skeletal-related events. The time to PSA progression

(33.2 months), as well as the probability and cost of skeletal-related events were derived from the literature.

**RESULTS:** The survey was answered by 86 physicians treating 417 patients, of whom 106 (25.4%) had prostate cancer, with 36 (34.0%) of these mCSPC. The majority of mCSPC patients (52.8%, n = 19) received bone-targeted agents monthly. Denosumab was the treatment of choice in 84.2% of patients (n = 16). Extrapolation using data from NICER indicated that 568 mCSPC patients may be treated with bone-targeted agents at doses used for bone metastasis every year in Switzerland, leading to estimated total costs of more than CHF 8.3 million over 33.2 months. Because of its more frequent prescription and higher price, it appears that almost 93% of the total costs can be attributed to denosumab. For both denosumab and zoledronic acid, the most expensive components were the cost of administration and the drug cost, making up more than 90% of the total costs, with the rest being costs of skeletal-related events.

**CONCLUSIONS:** This study found that the administration of bone-targeted agents in doses used for bone-metastatic diseases to prevent skeletal-related events is frequent in the setting of mCSPC and results in significant costs for the healthcare system.

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## Introduction

Skeletal-related events are a major concern for cancer patients with bone metastases [1]. They can pose a significant health burden, in the form of pathological fractures and spinal cord compression, which negatively influence emotional, functional and physical well-being [2]. Bone-targeted agents (BTAs) are used to reduce the risk of skeletal-related events as well as for cancer treatment-related bone loss induced by androgen deprivation therapy [3].

BTAs include bisphosphonates, drugs with a phosphorus-carbon-phosphorus backbone which decrease the risk of fracture by minimising bone resorption [4]. Alternatively, denosumab has emerged as a clinically effective human monoclonal antibody reducing osteoclast formation and preventing skeletal-related events caused by bone metastases from solid tumours [5]. Denosumab was originally developed for the treatment of osteoporosis, is injected subcutaneously after a calcium level check and does not require renal monitoring [6].

In a randomised phase III clinical trial in patients with metastatic castration-resistant prostate cancer (mCRPC) with bone metastases, denosumab (120 mg every 4 weeks) performed better than zoledronic acid (4 mg every 4 weeks) regarding prevention of skeletal-related events [7]. Based on this study, the European Society of Medical Oncology (ESMO) recommends the use of denosumab or bisphosphonates for mCRPC patients with bone metastases at high risk for clinically significant skeletal-related events [8]. The trial leading to approval of denosumab exclusively included patients with metastatic castration-resistant disease and not castration-sensitive disease. In the case of metastatic castration-sensitive prostate cancer (mCSPC) with bone metastases, no clinical trials have investigated the clinical benefit of denosumab [9]. In contrast, zoledronic acid has been tested in this setting in two randomised trials and did not reduce skeletal-related event risk [10, 11]. Thus, the American Society of Clinical Oncology (ASCO) and ESMO recommend that BTAs in the bone metastasis dose should not be part of the standard of care for patients with mCSPC [12, 13]. Use of BTAs is, however, indicated for patients on androgen deprivation treatment to prevent cancer treatment-induced bone loss and ultimately osteoporotic fractures. The dose in this indication is 10–13 times lower, denosumab 60 mg every 6 months or zoledronic acid 5 mg once per year.

Despite the lack of evidence in the mCSPC setting, denosumab at the dose of 120 mg (Xgeva<sup>®</sup>) is currently approved by Swissmedic and the European Medicines Agency (EMA) for the treatment of patients with bone metastases from solid tumours in conjunction with standard antineoplastic therapy, irrespective of castration status for prostate cancer patients [14, 15]. Similarly, zoledronic acid can be administered for the treatment of bone metastases in patients with solid tumours, including prostate cancer [16, 17].

We found widespread implementation of guideline-recommended BTA prescribing in Switzerland [17], but little is

known about the prevalence and health economic consequences of BTA use for mCSPC patients. Health spending in Switzerland is among the highest in the world. The total cost of cancer per capita in Switzerland was EUR 578 in 2018, corresponding to more than EUR 4000 million [18]. To address this gap in the literature, we used data from a recent pattern of care study. The study estimated the costs of administering denosumab and zoledronic acid based on marketing approval by Swissmedic for mCSPC patients. To our knowledge, this is the first study that investigates the economic consequences of administering BTAs for bone metastases to mCSPC patients.

## Methods

Information about the prevalence of BTA administration to mCSPC patients was taken from the SAKK 95/16 study [19]. This cross-sectional survey study was conducted between November 2017 and May 2018, and included 86 oncologists from 18 sites across Switzerland. Oncologists were recruited through the Swiss Group for Clinical Cancer Research (SAKK) network with the support of the Schweizerische Gesellschaft für Medizinische Onkologie (SGMO). Eligible oncologists could practice at either public hospitals or private clinics within Switzerland. These were asked about their BTA prescribing patterns for patients with solid tumours and bone metastases in a total of 417 patients, for whose treatment decisions they were personally responsible at their centre. Study details have been described elsewhere [19]. Briefly, included patients were at least 18 years old, with solid tumours and at least one bone metastasis, and were receiving routine management at the participating physician's centre over the 3-month study period. The most common underlying solid tumour type was breast cancer (169/417, 40.5%), followed by prostate cancer (106/417, 25.4%) and lung cancer (62/417, 14.9%). Almost one third of the prostate cancer patients were castration-sensitive (36/106, 34.0%).

### mCSPC population and survival

As the incidence of mCSPC in Switzerland is unknown, we estimated the size of the mCSPC population based on the total number of annual prostate cancer cases obtained from the Swiss National Agency for Cancer Registration (NACR) and the estimated development of bone metastases. Specifically, mCSPC patients who had either stage IV prostate cancer, or stage I–III prostate cancer with prostate-specific antigen (PSA) progression and development of metastases were considered. For this, we extracted the total number of incident prostate cancer cases in stages I to IV for the latest available year (2016) from NACR. We then multiplied the stage I–III prostate cancer patients by the probability of developing metastases (5.2%), taken from a US study, and added them to the stage IV patients [20]. Finally, we multiplied the number of metastatic prostate cancer patients by the probability (90.1%) that these metastases are present in the bone [21].

To get an estimate of how many new mCSPC patients are treated each year with BTAs, we combined the information from the survey about the proportion of mCSPC patients receiving BTAs from their oncologist with the estimated size of the Swiss mCSPC patient population.

The time to PSA progression of mCSPC patients treated with BTAs was based on a US trial, which reported a median time to PSA progression of 33.2 months (144.26 weeks) with 75th percentile of 12.1 months (52.58 weeks) in mCSPC patients on continuous treatment with abiraterone acetate and prednisone [22]. As the trial did not reach the time to measure the 25th percentile, we used the sum of the median time and the difference to the 75th percentile (33.2 months + (33.2 months – 12.1 months) = 54.3 months (235.95 weeks)) as an upper value in the sensitivity analysis.

#### Cost related to BTA administration

To estimate the health-economic consequences of administering BTAs to mCSPC patients in Switzerland, we calculated the costs of administering BTAs and the costs of osteonecrosis of the jaw (ONJ) as a treatment-related bone complication for the estimated number of treated mCSPC patients. The analysis used the perspective of the health-care system and combined information about BTA administration and reported health complications from the SAKK 95/16 cross-sectional study with above-described estimates about the mCSPC population in Switzerland. All costs were calculated in Swiss francs (CHF). The cost of administering BTAs was based on the 2020 Swiss tariffs for outpatient physician services TARMED [23]. Specifically, it included a physician visit with blood extraction, a short physical examination and the cost of calcium and albumin analyses and subcutaneous injection of Xgeva<sup>®</sup> in the case of denosumab. The resulting total costs were CHF 132.28. For zoledronic acid, the administration cost was CHF 183.77 and included a short examination by the physician with blood extraction and the cost of creatinine analysis and the intravenous infusion of zoledronic acid. Drug costs were based on 2020 public prices from the “Spezialitätenliste” [24]. In the case of denosumab, we assumed that Xgeva<sup>®</sup> was used, i.e., denosumab at a dose of 120 mg every 4 weeks, as it was the only drug with an administration interval fitting the intervals reported by the oncologists in SAKK95/16. Its public price was CHF 478.05 for one dose [24]. For zoledronic acid, there were seven different products available for treating metastases. The least expensive was Zoledronat Fresenius Onco<sup>®</sup> (CHF 129.45 for one dose of 5 ml) and the most expensive Zometa<sup>®</sup> (CHF 212.25 for one dose of 5 ml) [24]. For the analysis, we used an average price of CHF 170.35 per dose. Thus, total costs for each administration of denosumab and zoledronic acid were estimated at CHF 545.67 (CHF 478.05 + CHF 47.62) and CHF 314.16 (CHF 170.35 + CHF 143.81), respectively. To simplify the calculation, we assumed that for patients whose administration was recorded to be between 3–4 weeks, BTAs were given every 4 weeks [8].

#### Treatment-related complications

We consider ONJ as the main treatment-related bone complication. Our survey contained two questions asking oncologists whether they stopped BTA treatment or changed the administration interval in the event of ONJ, no oncologist treating mCSPC patients stated any occurrences. Thus, the frequencies of ONJ were calculated from a phase III trial that compared denosumab with zoledronic acid in patients with metastatic prostate cancer [8]. The extension of

the trial found that 12 out of 147 patients (8.2%) treated with denosumab and 7 out of 118 patients (5.9%) using zoledronic acid developed ONJ [25]. For the costs of ONJ treatment, we used estimates from a detailed US study, and adjusted for inflation to 2020 prices [26, 27]. The costs covered the pharmacological management (e.g., steroid injections, antibiotics), simple incision and drainage biopsies, dental extraction, root canal treatment, non-surgical sequestrectomy, debridement, and surgical resection and reconstruction [26]. For the conversion of the costs in US dollars (USD), we used the purchase power parity of 1.148 from the OECD [28]. The resulting median cost of treating ONJ in one prostate cancer patient used for the analysis was CHF 4299.05 (USD 3744.82) with 25th percentile CHF 2682.69 (USD 2336.84) and 75th percentile CHF 7623.88 (USD 6641.01).

#### Yearly costs of administering BTAs

The cost analysis reports the costs of one cohort of mCSPC patients over the median time to PSA progression of 33.2 months (2.78 years). Assuming a constant incidence of mCSPC over time, one can assume that each year a new cohort of the same size would start BTA treatment. Thus, in each year, there would be a cohort of patients in their first year of treatment and other cohorts of the same size in the second year and the third year of treatment. The total costs of administering BTAs in a given year can therefore be approximated by the cost of treating one cohort until PSA progression.

#### Sensitivity analyses

Because of the many uncertainties associated with the estimation of the health economic consequences of administering BTAs to mCSPC patients, univariate sensitivity analyses were used to test the robustness of the calculations. The following variables were varied:

- the percentage of mCSPC patients relative to all incidence patients,
- the frequency of BTA administration to mCSPC patients,
- the percentage of cases of ONJ with denosumab and zoledronic acid,
- the share of denosumab,
- the cost of administering BTAs,
- the cost of denosumab and zoledronic acid,
- the cost of ONJ, and
- the median time to PSA progression of mCSPC patients.

While the first five variables were subjected to  $\pm 30\%$  variation, the cost of zoledronic acid used the lowest and highest Swiss product prices. Further, the 25th and 75th percentiles were used for the cost of ONJ and the time to PSA progression of the patients. A summary of the model variables used is shown in table 5 in the results section “Sensitivity analyses”.

## Results

### Physician characteristics

Of the 86 oncologists participating in the survey, 20 treated 36 patients with mCSPC. Overall, 11 of these 20 oncologists (55.0%) prescribed BTAs such as denosumab and zoledronic acid. Eight (72.7%) oncologists reported initiating BTAs with all their mCSPC patients, and 3 (27.3%) administered them to some of their mCSPC patients. Table 1 summarises the demographic characteristics of these oncologists. Most of the oncologists who prescribed BTAs to at least some mCSPC patients were senior consultants (45.4%), followed by consultants (36.4%), residents (9.1%) and department heads (9.1%). None of them were private practitioners. Almost half (45.4%) had between 10 and 20 years of medical experience, 27.3% had between 5 and 10 years' experience, 18.2% had more than 20 years' experience, followed by 9.1% with up to 5 years' experience. The table also shows that the vast majority worked at a cantonal hospital (72.7%).

### Patient characteristics

Table 2 shows the demographic characteristics of the sample of mCSPC patients covered by the survey. Of the 36 patients physicians reported on, 19 (52.8%) were treated

with BTAs. Their median age of those who received BTAs was 73 years (25th percentile 80 years and 75th percentile 68 years) and most (79%) were retired. More than four fifths (84.2%) had three or more bone metastases. The most common sites of these bone metastases were vertebrae (79.0%), the hip/pelvis (63.2%) and/or ribs (42.1%). The most frequently reported co-morbidities were hypertension (47.4%), diabetes mellitus (26.3%), chronic obstructive pulmonary disease (8.6%), renal impairment (8.6%) and coronary heart disease (8.1%).

### Reported BTA administration and bone consequences in the sample

Of the 19 mCSPC patients receiving BTAs, the vast majority (84.2%) received denosumab and few (15.8%) zoledronic acid. At the time of the survey, more than four fifths of the mCSPC patients (84.2%) were still receiving BTAs. In the case of denosumab, almost half (43.8%) of the 16 patients received it every 3–4 weeks, 31.3% received it every 3–4 weeks for the first two years and then once every 12 weeks, 12.5% received it every 24 weeks, 6.2% every 3–4 weeks unless there was a substantial deterioration in the patient's performance status, and 6.2% every 3–4 weeks for the first year and then once every 12 weeks. Of the three mCSPC patients who received zole-

**Table 1:** Characteristics of oncologists treating patients with metastatic castration-sensitive prostate cancer (n = 20) in SAKK 95/16.

	No BTAs administered (n = 9)		BTAs administered (n = 8)		BTAs sometimes administered (n = 3)		Overall (n = 20)	
	n	(%)	n	(%)	n	(%)	n	(%)
<b>Experience in years</b>								
0–5 years	1	(12.5)	0	(0.0)	1	(33.3)	2	(10.5)
5–10 years	0	(0.0)	3	(37.5)	0	(0.0)	3	(15.8)
10–20 years	5	(62.5)	4	(50.0)	1	(33.3)	10	(52.6)
>20 years	2	(25.0)	1	(12.5)	1	(33.3)	4	(21.1)
<b>Expertise</b>								
Resident	1	(11.1)	1	(12.5)	0	(0.0)	2	(10.0)
Consultant	1	(11.1)	3	(37.5)	1	(33.3)	5	(25.0)
Senior consultant	2	(22.2)	4	(50.0)	1	(33.3)	7	(35.0)
Department head	1	(11.1)	0	(0.0)	1	(33.3)	2	(10.0)
Practitioner	3	(33.3)	0	(0.0)	0	(0.0)	3	(15.0)
Not answered	1	(11.1)	0	(0.0)	0	(0.0)	1	(5.0)
<b>Number of patients with bone metastases</b>								
>10	0	(0.0)	1	(12.5)	0	(0.0)	1	(5.0)
10–25	2	(22.2)	1	(12.5)	1	(33.3)	4	(20.0)
26–50	3	(33.3)	4	(50.0)	1	(33.3)	8	(40.0)
>50	3	(33.3)	2	(25.0)	1	(33.3)	6	(30.0)
Not answered	1	(11.1)	0	(0.0)	0	(0.0)	1	(5.0)
<b>Number of pat. with newly diagnosed bone metastases</b>								
>10	0	(0.0)	2	(25.0)	0	(0.0)	2	(10.0)
10–25	6	(66.1)	3	(37.5)	2	(66.7)	11	(55.0)
26–50	2	(22.2)	3	(37.5)	0	(0.0)	5	(25.0)
>50	0	(0.0)	0	(0.0)	1	(33.3)	1	(5.0)
Not answered	1	(11.1)	0	(0.0)	0	(0.0)	1	(5.0)
<b>Place of work</b>								
Cantonal hospital	5	(55.6)	6	(75.0)	2	(66.7)	13	(65.0)
Private clinic	1	(11.1)	1	(12.5)	0	(0.0)	2	(10.0)
Private practice	2	(22.2)	0	(0.0)	0	(0.0)	2	(10.0)
Regional hospital	0	(0.0)	1	(12.5)	1	(33.3)	2	(10.0)
University hospital	0	(0.0)	1	(12.5)	0	(0.0)	1	(5.0)

The table shows descriptive statistics for physicians who reported treating metastatic castration-sensitive prostate (mCSPC) cancer patients. The first group contains the nine physicians who did not treat their mCSPC patients with bone-targeted agents (BTAs). The second group contains the eight physicians who treated all their mCSPC cancer patients with BTAs. The third group shows the three physicians who treated some of their mCSPC patients with BTAs.

tronic acid, one received it continuously every 3–4 weeks, one every 24 weeks, and for the third there was no information about the administration available. Bone complications were reported for four patients treated with denosumab (25%); two had bone radiation (12.5%), one had a pathological fracture (6.3%), and one had another bone complication not specified further (5.3%). No complica-

tions were reported for patients treated with zoledronic acid. No BTA treatment was interrupted because of ONJ.

The most frequently mentioned reasons for administering BTAs to mCSPC patients were bone pain, high risk of bone complications, number of bone metastases, and the patient's prior history of bone complications (table 3).

**Table 2:** Characteristics of metastatic hormone-sensitive prostate cancer patients in study SAKK95/16 (n = 36).

	No BTAs (n = 17)		BTAs (n = 19)	
	n	(%)	n	(%)
Age (mean and SD)	76.8	7.9	72.5	8.3
<b>Education</b>				
Compulsory schooling	6	(35.3)	4	(21.1)
High school degree	2	(11.8)	4	(21.1)
University degree	2	(11.8)	3	(15.8)
Vocational school	6	(35.3)	7	(36.1)
Unknown	1	(5.8)	1	(5.9)
<b>Employment status</b>				
Retired	16	(94.1)	15	(79.0)
Working part-time	1	(5.9)	1	(5.2)
Working full time	0	(0.0)	3	(15.8)
<b>Smoking status</b>				
Never smoker	8	(47.0)	12	(63.1)
Ex-smoker	7	(41.2)	5	(26.3)
Current smoker	1	(5.9)	1	(5.3)
Unknown	1	(5.9)	1	(5.3)
<b>Location of bone metastases</b>				
Arm	3	(17.7)	5	(26.3)
Hip/pelvis	12	(70.6)	12	(63.2)
Leg	5	(29.4)	5	(26.3)
Ribs	8	(47.1)	8	(42.1)
Skull	3	(17.7)	3	(15.8)
Vertebrae	12	(70.6)	15	(79.0)
<b>Current number of bone metastases</b>				
Three or fewer	1	(5.9)	3	(15.8)
More than three	16	(94.1)	16	(84.2)
<b>Treatments received</b>				
Chemotherapy	9	(52.9)	8	(42.1)
Hormone therapy	16	(94.1)	18	(94.7)
Immunotherapy	0	(0.0)	0	(0.0)
Radiotherapy	6	(35.3)	8	(42.1)
Radioisotope therapy	0	(0.0)	2	(10.5)
Surgery	5	(29.4)	6	(31.6)
Targeted treatments	0	(0.0)	2	(10.5)
<b>Supportive treatments</b>				
Antidepressants	0	(0.0)	4	(21.1)
Antiemetics	1	(5.9)	1	(5.3)
Corticosteroids	3	(17.7)	6	(31.6)
Nonopioid analgesics	3	(17.7)	8	(42.1)
Opioid analgesics	1	(5.9)	4	(21.1)

BTA = bone-targeted agent; SD = standard deviation

**Table 3:** Reasons for administering bone-targeted agents to metastatic hormone-sensitive prostate cancer patients (n = 19).

Reason	Most important		Second most important		Third most important		Not mentioned	
	n	(%)	n	(%)	n	(%)	n	(%)
1 Bone pain	7	(36.8)	1	(5.3)	3	(15.8)	8	(42.1)
2 High risk of bone complications	4	(21.1)	5	(26.3)	2	(10.5)	8	(42.1)
3 Number of bone metastases	3	(15.8)	3	(15.8)	1	(5.2)	12	(63.2)
4 Prior history of bone complications	2	(10.5)	0	(0.0)	0	(0.0)	17	(89.5)
5 Long life expectancy	1	(5.3)	2	(10.5)	7	(36.8)	9	(43.4)
6 Good performance status	1	(5.3)	3	(15.8)	1	(5.3)	14	(73.7)
7 Location of bone metastases	0	(0.0)	3	(15.8)	3	(15.8)	13	(68.4)
8 Patient's request	0	(0.0)	0	(0.0)	0	(0.0)	19	(100.0)

### mCSPC population

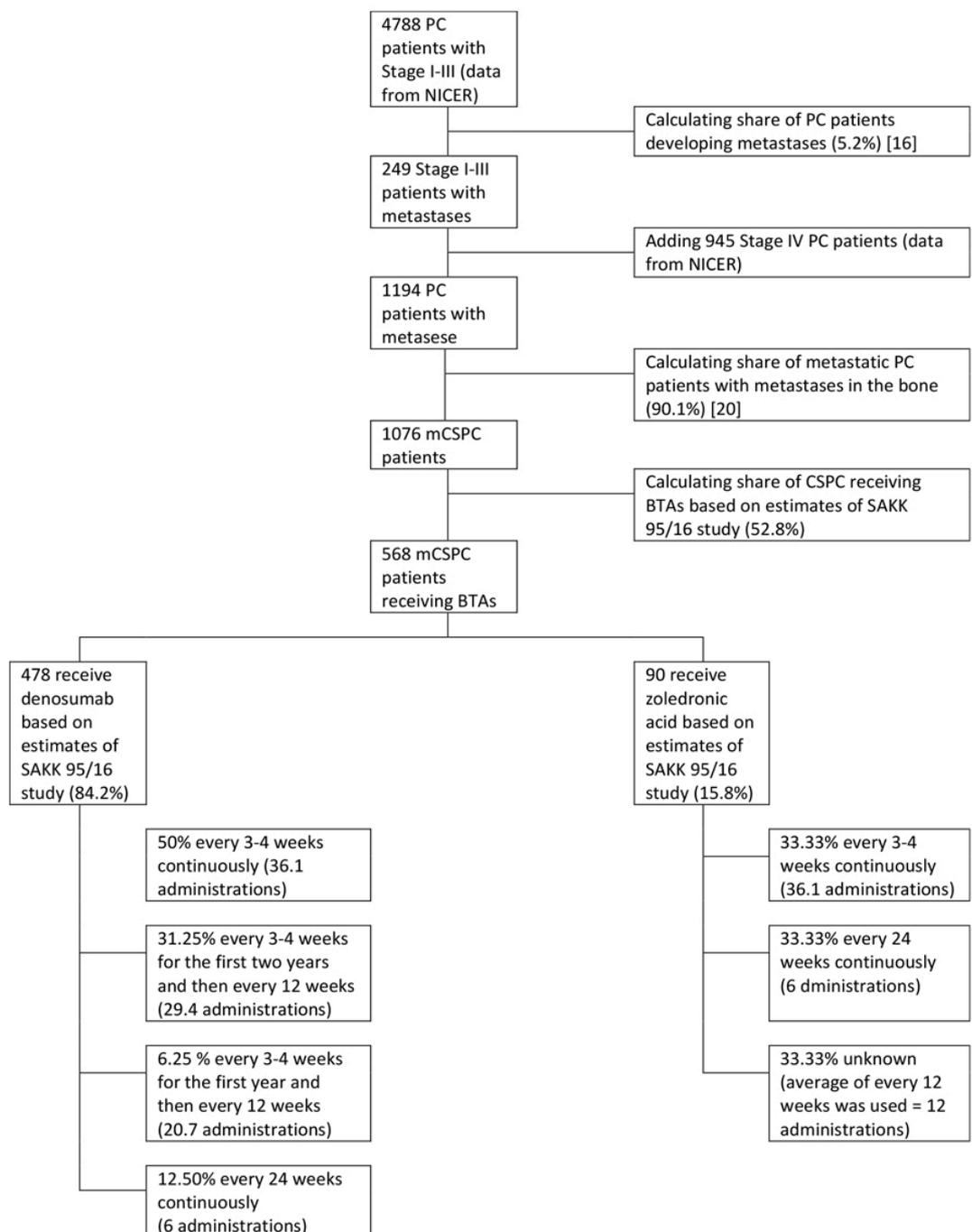
NACR estimated that there were 6120 new prostate cancer cases in 2016. This number was based on extrapolated data from nine Swiss population-based cancer registries covering 64.9% of the Swiss population. In the estimation, almost four fifths (n = 4788, 78.3%) were in stages I–III, 15.5% were in stage IV (n = 945) and for 6.3% (n = 386) no information about the stage was available.

Multiplying the number of stage I–III prostate cancer patients with the probability of developing bone metastases

and adding the stage IV patients led to an estimate of 1076 new mCSPC patients (17.58%) for the year 2016.

Combining the information from the survey about the frequency of BTA administration with estimates of the Swiss mCSPC patient population, we estimated that 568 new mCSPC patients (52.78% of 1076) may have been treated with BTAs in 2016 (see [fig. 1](#)). Furthermore, the estimates about the BTA of choice based on our study suggest that 478 patients may have received denosumab and 90 patients zoledronic acid.

**Figure 1:** Estimation of the Swiss metastatic hormone-sensitive prostate cancer (mCSPC) population that received bone-targeted agents (BTAs) in 2016. PC = prostate cancer



### Cost of BTA administration

Table 4 shows an estimated cost of CHF 7,843,301 for administering denosumab and CHF 535,840 for zoledronic acid over an estimated time to PSA progression of 33.2 months for 568 mCSPC patients (84.2% denosumab and 15.8% zoledronic acid), given the observed administration intervals from the oncologist survey. The resulting total cost estimate of this practice in the base case is CHF 8,379,141 over the median time of PSA progression of mCSPC patients or over 1 year, assuming constant incidence over time. Because of the more frequent prescription, higher price and higher probability of treatment-related consequences, more than 93% of this total cost can be attributed to denosumab. Administering denosumab every 4 weeks over 33.2 months costs CHF 11,006 per patient (CHF 3967 per year). In contrast, administering zoledronic acid at the same interval and over the same time costs CHF 4253 (CHF 1533 per year). Costs of ONJs are marginal. For both denosumab and zoledronic acid, the most expensive components are the cost of administering BTAs and the cost of the drug. For both drugs, these costs account for more than 96% of their total costs.

### Sensitivity analyses

The univariate sensitivity analyses in table 5 show the impact on the results of varying uncertain parameters. The largest impacts were seen when we varied the time to PSA progression, the percentage of mCSPC patients receiving

BTAs and the number of mCSPC patients. Compared with the base case, total costs would increase by more than 50% (CHF 12,599,460 vs CHF 8,379,141) when the time to PSA progression and the duration of the BTA treatment of mCSPC patients was assumed to be 54.3 months instead of 33.2 months. The assumption that the percentage of mCSPC patients is 30% higher than the base case (22.86% instead of 17.58%) increases total cost by CHF 2,516,602 to CHF 10'895'743. The table also shows that while variations in the cost and proportional use of denosumab were also influential, the probability and cost of ONJ had little impact.

### Discussion

This study provides insights into the economic consequences of administering BTAs to mCSPC patients. Using the example of Switzerland, we found that BTA use in mCSPC patients is frequent, as more than half of the mCSPC patients in our survey received BTAs from their treating oncologist. Importantly, international guidelines from ESMO and ASCO do not recommend the use of BTAs in this subgroup of prostate cancer patients since zoledronic acid has been shown to have no benefit and added toxicity in two randomised trials and denosumab has never been evaluated in this setting [12, 13]. Despite this fact, the marketing approval for denosumab issued by Swissmedic does not exclude the treatment of mCSPC in conjunction with

**Table 4:** Estimated total cost of BTA use for a cohort of 568 mCSPC patients.

	Denosumab (n = 478)*		Zoledronic acid (n = 90)*	
	(%)†	CHF	(%)†	CHF
<b>Cost of continuous BTA administration‡</b>				
Every 4 weeks (36.1 administrations)	(50.0%)		(33.33%)	
– Drug cost		CHF 4,085,811		CHF 181,819
– Administration cost		CHF 1,130,574		CHF 196,143
– Sum of drug and administration costs		CHF 5,216,385		CHF 377,962
Every 4 weeks for the first 2 years than once every 12 weeks (29.4 administrations)	(31.25%)		(0.0%)	
– Drug cost		CHF 2,078,521		CHF 0
– Administration cost		CHF 575,142		CHF 0
– Sum of drug and administration costs		CHF 2,653,663		CHF 0
Every 4 weeks for the first year than once every 12 weeks (20.7 administrations)	(6.25%)		(0.0%)	
– Drug cost		CHF 292,973		CHF 0
– Administration cost		CHF 81,068		CHF 0
– Sum of drug and administration costs		CHF 374,041		CHF 0
Every 12 weeks (12 administrations)	(0.0%)		(33.33%)	
– Drug cost		CHF 0		CHF 60,606
– Administration cost		CHF 0		CHF 65,381
– Sum of drug and administration costs		CHF 0		CHF 125,987
Every 24 weeks (6 administrations)	(12.5%)		(33.33%)	
– Drug cost		CHF 170,242		CHF 30,303
– Administration cost		CHF 47,107		CHF 32,690
– Sum of drug and administration costs		CHF 217,349		CHF 62,994
Total drug and administration costs		CHF 8'461'439		CHF 566'943
<b>Cost of ONJ§</b>		CHF 167,084		CHF 22,542
<b>TOTAL COSTS</b>		CHF 8,628,524		CHF 589,485

BTA = bone-targeted agent; mCSPC = metastatic castration-sensitive prostate cancer; ONJ = osteonecrosis of the jaw The table shows the total cost of administering BTAs to 568 mCSPC patients over 33.2 months (144.26 weeks). \* Indicates the number of mCSPC patients receiving the respective BTA, estimated from the oncologist survey. † Indicates the proportion of patients in the specific administration interval, according to the oncologist survey. ‡ Calculated for median time to PSA progression of 33.2 months (144.26 weeks) using administration costs of CHF 132.29 for denosumab and CHF 183.77 for zoledronic acid and the prices of CHF 478.05 for denosumab (Xgeva®) and CHF 170.35 for zoledronic acid. § Costs for treatment-related complications were based on the probability of ONJ and its costs. Note that while the probabilities differ between denosumab (8.2%) and zoledronic acid (5.9%), they are independent of the administration interval.

standard antineoplastic treatment [14]. A letter of Swiss opinion leaders was sent to Swissmedic in 2012, highlighting the lack of clinical data to support the approval of denosumab for prevention of skeletal-related events in mCSPC, but this letter did not lead to a change in the approval text [29].

This non-recommended treatment leads to estimated costs to the Swiss healthcare system of more than CHF 8.3 million over the time to PSA progression of 33.2 months in mCSPC patients or over 1 year. Almost all of these costs can be attributed to drug costs and administration costs. The health economic burden of this practice at the European level may also be quite substantial, as the administration of BTAs to mCSPC patients is also approved by the EMA [15]. Even more importantly, these drugs can produce relevant side effects, such as hypersensitivity reactions, musculoskeletal events and symptomatic hypocalcaemia [30]. Furthermore, ONJ is of substantial concern as it often leads to painful oral surgical procedures and relevant impairment of quality of life. Also, it is a side effect whose frequency increases with cumulative doses [31, 32]. In addition, administering BTAs in the mCSPC setting, before PSA progression under castration therapy and thus before a treatment phase where the benefit is really shown, makes the decision for how long to continue with the treatment at the time-point of castration-resistance more difficult. Note that in this study, we used a median time to PSA progression of 33.2 months, according to a trial including only patients with high risk mCSPC [22]. A more recent study allowing patients to be included irrespective of their risk situation found a much better survival outcome, with more than 60% of the patients being PSA progression-free at 3 years [33]. Although median progression-free survival from this trial has not been reported yet, this suggests that the true economic consequences may be substantially higher than in our estimation. The impact on the budget estimates – more than 8 million every year – is significant. Although only 0.2% of the cancer budget is being essentially wasted by this non-evidence-based, contraindicated and potentially harmful pharmacological intervention, this accounts for only one subtype of one cancer diagnosis.

With the nowadays growing armamentarium of systemic treatment options for mCSPC, patients, even though in a metastatic setting, have good long-term outcomes lasting for many years. In the absence of evidence supporting BTA use for mCSPC patients and knowing the aforementioned

risks, side effects and substantial costs of this non-recommended practice in times of constrained resources, the licensing of BTAs in Switzerland and Europe should be revisited.

To our knowledge, this is the first study that investigated the patterns of care and economic consequences of administering BTAs to mCSPC patients in a real-world setting. We note several strengths and limitations of the study, which influence the interpretation of the findings. The strength of this study lies in the physician sample of the oncologist survey, which featured oncologists from several hospitals in the French-, German- and Italian-speaking parts of Switzerland, enhancing the generalisability of the findings.

The present study also has several limitations. First, the small sample of mCSPC patients included may not be representative and therefore limit the generalisability. Second, prescription patterns were reported by the physician and not reviewed. Third, the survey did not collect information about the drug names but rather the compounds. For denosumab it was assumed that Xgeva<sup>®</sup> was administered, and not Prolia<sup>®</sup>, as the administration intervals of the latter do not fit those reported in the survey. Fourth, we estimated the mCSPC patient population through prostate cancer stages to be around 17.6% of all prostate cancer patients. Note that this estimate is in line with US studies, which suggest that around 14.1% of prostate cancer patients have a radical prostatectomy and then develop metastases afterwards [34, 35]. Finally, while oncologists were asked about patient-related reasons for engaging in the practice of prescribing BTAs to mCSPC patients, it is unclear whether oncologists were aware of the current international guidelines. In future studies it would be important to analyse whether BTA prescription decisions could be explained by physician's intrinsic determinants (such as knowledge, attitudes and individual characteristics), or external factors (at individual levels, e.g., patient requests, time constraints and financial incentives, and also at institutional levels, e.g., organisational culture such as shared values and behaviours among employees).

## Conclusion

BTAs are not recommended for mCSPC patients owing to the lack of clinical data supporting the benefit of these drugs for this population. This study found that, irrespec-

**Table 5:** Sensitivity analysis for total costs, performed by varying certain model parameters.

	Base case value	Min	Max	Result min compared with base case	Result max compared with base case
Time to PSA progression in weeks	144.26	52.58	235.95	-CHF 4,219,858	CHF 4,220,319
Percentage of mCSPC patients	17.58%	12.31%	22.86%	-CHF 2,511,836	CHF 2,516,602
Percentage of BTA administration	52.78%	36.94%	68.61%	-CHF 2,514,695	CHF 2,513,107
Cost of denosumab	CHF 478.05	CHF 334.64	CHF 621.47	-CHF 1,807,263	CHF 1,807,389
Share of denosumab	84.21%	58.95%	100.00%	-CHF 1,495,503	CHF 934,837
Cost of denosumab administration	CHF 132.28	CHF 92.60	CHF 171.96	-CHF 500,050	CHF 500,050
Cost of ONJ	CHF 4299.05	CHF 2682.69	CHF 7623.88	-CHF 64,808	CHF 133,308
Cost of zoledronic acid administration	CHF 183.77	CHF 128.64	CHF 238.90	-CHF 80,230	CHF 80,230
Cost of zoledronic acid	CHF 170.35	CHF 129.45	CHF 212.25	-CHF 59,522	CHF 60,977
Percentage of ONJ with denosumab	8.20%	5.74%	10.66%	-CHF 45,564	CHF 45,564
Percentage of ONJ with zoledronic acid	5.90%	4.13%	7.67%	-CHF 6147	CHF 6147

BTA = bone-targeted agent; mCSPC = metastatic castration-sensitive prostate cancer; max = maximum; min = minimum; ONJ = osteonecrosis of the jaw; PSA = prostate specific antigen Note: the table shows the difference in total costs of administering BTAs compared to the base case of CHF 8,379,141.

tive of this, they are frequently administered by oncologists in Switzerland. This practice leads to substantial healthcare costs and also increases the risk of side effects due to added toxicity.

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#### Potential competing interests

Roger von Moos has participated in advisory boards with Amgen, GlaxoSmithKline, Novartis and Roche. Beat Thürlimann holds stock of Novartis and Roche and received consultation fees from Amgen and Roche. Richard Cathomas has participated in advisory boards for Amgen, Astellas, AstraZeneca, Bayer, BMS, Janssen, MSD, Novartis, Pfizer and Roche, and has received speaker honoraria from Astellas, BMS, Debiopharm and Janssen. Silke Gillissen received honoraria from Janssen Cilag and has a consulting or advisory role for Astellas, Amgen, Roche, Pfizer, AAA International, Janssen, Innocein, Sanofi, Bayer, Orion Pharma, Clovis Oncology, Menarini Silicon Biosystems, Tolero Pharmaceuticals and MSD. Ursina Zürcher-Härdi received travel support from Gilead, Lilly, Pfizer, Bayer, Celgene and MSD. Sandro Anchisi has participated in advisory boards for Janssen-Lilly, Lilly and Novartis. Matthias Schwenkglens has received research funding from Amgen, MSD and Novartis, has received honoraria from Pfizer, and has participated in advisory boards for Amgen and BMS. Michael Mark received advisory fees from BMD, MSD, AstraZeneca, Roche, Takeda and institutional research grants from AstraZeneca and Amgen. The other authors report that they have no conflict of interest in relation to this article.

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