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Research Paper

Patterns of care for patients with metastatic bone disease in solid tumors: A cross-sectional study from Switzerland (SAKK 95/16)

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ABSTRACT

Background: Bone-targeted agents (BTAs) are widely used in the management of patients with bone metastases from solid tumors, but knowledge of their routine care use and the therapeutic implications remains limited. This non-interventional study aimed to characterize real-world BTA patterns of care in Switzerland.

Materials and methods: Non-interventional, cross-sectional study involving oncologists from across Switzerland who completed a Treating Physician questionnaire, providing data on their clinical setting and BTA-related practices, and a Patient Characteristics and Treatment questionnaire, providing data on their patients' disease status, risk of bone complications, BTA regimen and related outcomes. Eligible patients were aged ≥ 18 years, with solid tumors and at least one bone metastasis and were receiving routine management at the participating physician's center over the 3-month study period.

Results: A total of 86 oncologists recruited 417 patients from across 18 centers in Switzerland (80% public hospitals; 20% private clinics). The majority of physicians (70.9%) reported prescribing BTAs in line with international guidelines; denosumab was the treatment of choice in 78.5% of patients. BTAs were widely administered (94.2%) according to a 3–4-weekly dosing regimen; 33.7% of physicians reported extending intervals to 12 weeks after an initial 2 years of treatment. Physicians appeared to use clinical judgement, as well as formal risk assessment, to guide treatment for symptomatic skeletal events. No association was seen between either BTA use, or risk of complications, and incidence of skeletal complications. Only 4.3% of patients were reported to be experiencing severe bone pain at the time of the study.

Conclusions: This cross-sectional, non-interventional study found high implementation of guideline-recommended BTA prescribing, good pain control and low incidence of skeletal-related events. Long-term BTA randomized controlled trials have the potential to further optimize routine care outcomes for patients.

Abbreviations: BP, bisphosphonate; BTA, bone-targeted agent; HRQoL, health-related quality of life; IBCSG, International Breast Cancer Study Group; mCRPC, metastatic castration-resistant prostate cancer; RANKL, receptor activator of nuclear factor kappa-B ligand; RCT, randomized controlled trial; SAKK, Swiss Group for Clinical Cancer Research; SGMO, Schweizerische Gesellschaft für Medizinische Onkologie; SRE, symptomatic skeletal-related event; SSE, symptomatic skeletal event

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1. Introduction

The occurrence of bone metastases is common among patients with solid tumors and is associated with additional pain and fatigue, impaired quality of life and skeletal complications (skeletal-related events [SREs] and symptomatic skeletal events [SSEs]) [1–3].

A number of bone-targeting agents (BTAs) have been developed with the goal of restoring the healthy equilibrium between bone resorption and formation. Bisphosphonates (BPs) are a class of BTAs that act by binding to the surface of the bone and slowing down the bone resorption activity of osteoclasts, thereby allowing osteoblasts to work more effectively. Another class of BTAs are receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (e.g., denosumab), which help to control the differentiation, proliferation and survival of osteoclasts [4]. BPs and RANKL inhibitors have been shown to reduce the incidence, and to delay the onset, of SREs in patients with bone metastases in clinical trials [5].

BTAs are now widely used in clinical practice in Switzerland, increasingly in the form of the RANKL inhibitor denosumab since its introduction to the Swiss market in 2011. While the longer-standing BP options (zoledronic acid and pamidronate) require intravenous infusion every 34 weeks over a period of 1530 min, or 12 h (respectively), the monoclonal antibody denosumab is approved for convenient subcutaneous administration once every 4 weeks.

In clinical practice, BTAs are typically co-administered as add-on therapy to traditional systemic anticancer treatment, which is usually given every 2–4 weeks to allow the bone marrow to recover from cytotoxicity [6]. The pragmatic drivers of this BTA dosing regimen, however, do not take into consideration the pharmacokinetics of BTAs and their implications; BPs can have a half-life in bone of many years [7]. As a result, despite their widespread use in clinical practice, questions remain as to the optimal frequency and duration of BTA therapy over the longer term [8]. Data from randomized controlled trials (RCTs) suggest that less frequent dosing may be preferable over the longer term, with comparative trials of 12- versus 4-weekly dosing after the first 1–2 years of treatment reporting no significant difference in terms of SRE incidence in patients with metastatic breast cancer [9–11]. Similarly, a phase 2 trial of denosumab in patients with mCRPC found no difference in SREs, pain or bone turnover biomarkers between 12-weekly and 4-weekly dosing regimens [12].

Establishing the optimal dosing frequency of BTAs is not significant as evidence suggests that they are routinely prescribed beyond the 1–2-year evaluation period of most registration RCTs and that, once started, they are rarely discontinued [13–15]. Within this context, it is important to note that patients diagnosed with bone metastases limited to the skeleton often have a prolonged disease course [16,17] and up to 20% of patients with metastatic bone disease survive for more than 5 years [17]. Physicians must, therefore, consider the implications of cumulative BTA dosing, as the risk of BP-related adverse events (such as hypocalcemia, renal toxicity, osteonecrosis of the jaw, atypical fractures and vascular events [18–24]) have been shown to be directly proportional to both drug potency and cumulative dose [25]. To balance this, the potential implications of BTA discontinuation must also be taken into account, as multiple rebound fracture events have been reported following the cessation of denosumab [26].

A critical step in optimizing routine care use of BTAs in patients with bone metastases from solid tumors is not only the generation of RCT evidence of long-term therapeutic efficacy and safety, but also the characterization of current practices and identification of opportunities for practice refinement. To complement awaited RCT data on the long-term use of BTAs, therefore, this multicenter, observational study provides real-world insight into the routine care of BTA prescribing practices of physicians treating patients with bone metastases from solid tumors in Switzerland.

2. Methods

2.1. Physicians and patients

Eligible physicians were identified via the SAKK research network with the support of the Schweizerische Gesellschaft für Medizinische Onkologie (SGMO) oncologists, and could practice at either public hospitals or private clinics/practices within Switzerland.

Participating physicians accepted an invitation to take part in the study and confirmed that they were personally responsible for patient treatment decisions at their center. They then completed a Treating Physicians questionnaire that was designed to capture details of their clinical context (e.g., specialism, experience, type of center, case load) and BTA prescribing behaviors (preferred agent, dosing schedule and factors that influence BTA-related clinical decision-making) (Supplementary materials, Table S1).

The physicians then identified eligible patients under their treatment: those aged ≥18 years; with solid tumors and at least one bone metastasis; and who attended regular visits during the 3 months that the physician's center was participating in the study. All patients provided informed consent before participating. Any patient participating in the SAKK 96/12 study [22] was excluded.

For each eligible patient, physicians completed a Patient Characteristics and Treatment questionnaire (Supplementary materials, Table S2). The questionnaire consisted of three sections; the first captured data on the patient's demographic and socioeconomic status, medical history and current cancer status and management. The second section recorded data on the patient's duration and regularity of treatment, hospitalizations for bone metastases and life expectancy. The third section (which was completed only for patients who received BTA therapy) included questions related to: choice of agent; duration and frequency of treatment; rationale for selected treatment and dosing regimen; and instances and details of any BTA discontinuation and/or switches, including complications.

2.2. Outcomes

The key study outcomes were the real-world BTA prescribing patterns of this Swiss physician population (BTA use, preferred agent, dosing frequency and clinical drivers of BTA initiation) and related outcomes (bone complication incidence, bone pain and analgesia use).

2.3. Statistical analyses

As this is a cross-sectional descriptive study, no formal sample size calculation was required or performed. All eligible patients treated by participating physicians were included in the analysis. Categorical variables are reported as frequencies and percentages.

3. Results

3.1. Physician characteristics

A total of 86 oncologists from 18 sites across Switzerland participated in the study between November 2017 and May 2018. The overall study period extended beyond 3 months as the 3-month period of participation varied for each participating center. Eighty percent (69/86) of the participating physicians reported working in public hospitals and 20% (17/86) in private clinics. The majority of physicians participating in the study were Senior Consultants (34.9%), followed by Consultants (30.0%), Private practitioners (15.1%) and Residents (14.0%), with the remaining 5.8% being Head of Departments. Aligned with this, almost half (47.7%) had 10–20 years' medical expertise, 19.8% had between 5–10 years' experience, 17.4% had ≤5 years' experience, followed by 15.1% with >20 years' medical expertise.

Table 1
Bone metastases location at time of diagnosis (N = 471 patients).

Locations*	*n* (%)
Vertebrae	313 (75.1)
Hip/Pelvis	275 (65.9)
Ribs	175 (42.0)
Leg	81 (19.4)
Arm	68 (16.3)
Skull	43 (10.3)
Unknown	2 (0.2)

*Individual patients could have metastases in multiple locations.

3.2. Patient characteristics

Across the 18 centers, 417 patients with advanced solid tumors and bone metastases were recruited. The most common underlying tumor type was breast cancer (169/417, 40.5%), followed by prostate cancer (106/417, 25.4%) and lung cancer (62/417, 14.9%). The majority of breast cancer patients included in the study were endocrine-responsive (140/169, 82.8%); two-thirds of the prostate cancer patients were castration-resistant (68/106, 64.2%). Disease stabilization at the time of study assessment was found in 72.4% (302/417) of patients, while 26.9% (112/417) had progressive disease. As expected, the majority of patients had received hormone therapy (63.3%), chemotherapy (61.9%) and/or radiotherapy (60.2%). Other treatments received by patients included surgery (49.6%), targeted treatments (24.0%), immunotherapy (19.7%) and radioisotope therapy (8.2%). More than three-quarters of patients (328/417, 78.7%) had at least three bone metastases. The most common sites of bone metastases were vertebrae locations (71.1%) and in the hip/pelvis (65.9%) (Table 1). The frequency of co-morbidities was collected at study start, with the most common (>8%) conditions reported for patients being hypertension (38.4%), diabetes mellitus (10.1%), chronic obstructive pulmonary disease (8.6%), renal impairment (8.6%) and coronary heart disease (8.1%).

3.3. Physician survey: BTA practices

The majority of the participating physicians (61/86, 70.9%) reported initiating BTAs according to international treatment guidelines (i.e., by the American Society for Clinical Oncology, European Society for Medical Oncology or National Comprehensive Cancer Network).

Almost one-quarter of physicians (21/86, 24.4%) reported using patients' SRE risk (i.e., at high or low risk of pathological fractures, surgery or radiation to bone, or spinal cord compression) to guide their decision to initiate (or delay) BTA therapy. The factors that physicians reportedly felt contributed to a patient being categorized as being at high SRE risk are summarized in Table 2, with prior SRE events and presence of lytic bone metastases being the most frequently reported contributory risk factors (89.5% and 87.2% of physicians, respectively).

More than one-third of the treating physicians (30/86, 34.8%) reported initiating BTA therapy even in low-risk patients, while a similar proportion (31/86, 36%) indicated that they would only initiate BTA therapy in a low-risk patient if and when bone pain occurred.

3.4. Patient questionnaire: BTA treatment patterns

3.4.1. Clinical driver for initiation

Among the 417 included patients with solid tumors and bone metastases, 307 (73.6%) were receiving BTA therapy at the time of data capture. The proportion of patients receiving BTA therapy by tumor type was 80%) for breast cancer, 73%) for prostate cancer, and 65%) for lung cancer, with others being 69%). For prostate cancer, those receiving BTA therapy was split between 82%) of patients with castration-resistant disease and 53%) with hormone-sensitive disease.

Table 2
Factors reported by physicians as contributing to a high-risk of bone complications (N = 86 investigators).

Factors*	*n* (%)
Former SREs	77 (89.5)
Lytic bone metastases	75 (87.2)
High burden of metastatic disease	58 (67.4)
Pain score	53 (61.6)
Elevated alkaline phosphatase	38 (44.2)
Age	31 (36.0)
Elevated markers for bone turnover	17 (19.8)
Osteoplastic bone metastases	16 (18.6)
Elevated lactate dehydrogenase	15 (17.4)
There are no reliable factors to estimate the risk of SRE	3 (3.5)

*Physicians could indicate more than one factor that contributes to risk of bone complications.
SRE, skeletal-related events.

Among participating physicians, the most commonly reported drivers of BTA initiation were: 'high risk of bone complications' (132/307, 43.0%); 'bone pain' (67/307, 21.8%), and 'location of bone metastases' (31/307, 10.1%). Conversely, the most frequently reported reasons for not initiating BTA therapy were: 'low risk of bone complications' (44/110, 40.0%); 'focus on treating the primary tumor' (27/110, 24.5%); and 'very recent diagnosis' (19/110, 17.3%).

More than half of the patient population was considered to be at high risk of bone complications by their treating physicians (235/417, 56.3%). Despite this, 17% of these patients (40/235) were not receiving current BTA treatment. The reported reasons for non-initiation in these patients are summarized in Table 3; the most common being a 'very recent diagnosis' (35.0%), followed by 'focus on treating the primary tumor' (32.5%).

Conversely, among the 165 patients considered as being at low risk of bone complications, more than half (99/165, 60%) were receiving current BTA therapy. The clinical drivers for use of BTA therapy in this low-risk subgroup are summarized in Table 4, with 'bone pain' and 'long patient life expectancy' being the most commonly reported (38.4% and 17.2% of patients, respectively).

3.4.2. Dosing regimen

Among treated patients, the BTA of choice was reportedly denosumab, initiated in 78.5% of patients (241/307), followed by zoledronic acid (45/307, 14.7%) and ibandronate (17/307, 5.5%). BTA drug choice was not documented for four patients.

The vast majority of participating physicians reported administering BTAs every 3–4 weeks (81/86, 94.2%). Approximately one-third of physicians (31/86, 36.0%) reported implementing no change to BTA dosing frequency after an initial 2 years of treatment, while a further

Table 3
Physician-reported reasons for not initiating BTA treatment in patients at high risk of bone complications (N = 40 patients).

Reason for non-initiation*	*n* (%)
Very recent diagnosis, so no time to initiate	14 (35.0)
Focus on treating the primary tumor	13 (32.5)
Risk of osteonecrosis of the jaw	8 (20.0)
Patient refusal	5 (12.5)
Short life expectancy	3 (7.5)
Poor performance status	2 (5.0)
Poor renal function	1 (2.5)
Risk of hypocalcaemia	1 (2.5)
Costs	0 (0.0)
Pill burden	0 (0.0)

*Physicians could indicate a single reason for each patient.

Table 4
Physicia n-reported reasons for initiating BTA treatment in patients at low risk of bone complications (N = 99 patients).

Reason for initiation*	n (%)
Bone pain	38 (38.4)
Long life expectancy	17 (17.2)
Location of bone metastases	15 (15.2)
Number of bone metastases	15 (15.2)
Good performance status	12 (12.1)
Patient's request	1 (1.0)
Prior history of bone complications	1 (1.0)

*Physicians could indicate a single reason for each patient.
BTA, bone-targeting agent.

one-third (29/86, 33.7%) reported reducing dosing frequency to once every 12 weeks after 2 years and 16.2% (14/86) reported implementation of 12-weekly dosing after 1 year. A minority of the physicians reported implementing 12-weekly dosing after only 3 months of BTA therapy (7/86; 8.1%) and even fewer (3/86, 3.4%) reported initiating BTAs with a 12-weekly regimen.

3.5. Bone complications, pain and analgesic use

At the time of data collection, approximately half of the patients (220/417, 52.8%) were not experiencing bone pain due to bone metastases based on physician report; almost one-third (131/417, 31.4%) were reported to have mild bone pain, 11.5% (48/417) had moderate bone pain, and only 4.3% (18/417) had severe bone pain. Over the same assessment period, approximately half of the patients (197/417, 47.2%) were not receiving analgesics, 30% (125/417) were receiving non-opioid analgesics and 16.3% (68/417) were receiving strong opioids.

There was no apparent association between presence of bone pain and BTA treatment, or between presence of bone pain and perceived risk of bone complications (see Table 5). Incidence of current bone pain was similar in both the BTA-treated and untreated groups (16.0% and 14.2% of patients, respectively). Similarly, incidence of bone pain was similar in both patients categorized as high- and low-risk by their treating physicians (17.9% and 12.1%, respectively).

3.5.1. Bone complications and SREs

Treating physicians reported a similar incidence of bone complications in BTA-treated patients as in untreated patients (7.8% and 7.6%, respectively). Furthermore, no difference in SRE rate was found between patients categorized as high- versus low-risk by their treating physicians (7.7 vs 7.9%, respectively). Frequencies and percentages of patients with current complications by BTA treatment and by risk status are summarized in Table 5. The types of SRE experienced by patients with current complications for the overall group and for those with a given risk status are provided in Table 6.

Table 6
Incidence of SREs in patients with current complications for the overall patient group and those with known risk status.

Complication, n (%)	Overall sample, N = 34 Receiving BTA therapy		Known risk status, N = 31 Receiving BTA therapy	
	No (N = 8)	Yes (N = 26)	No (N = 8)	Yes (N = 23)
Bone radiation	4 (50.0)	15 (57.7)	4 (50.0)	13 (56.5)
Bone surgery	3 (37.5)	1 (3.8)	3 (37.5)	1 (4.3)
Hypercalcemia	0	1 (3.8)	0	1 (4.3)
Pathologic fracture	2 (25.0)	9 (34.6)	2 (25.0)	7 (30.4)
Spinal cord compression	0	2 (7.7)	0	2 (8.7)
Other bone complications	0	2 (7.7)	0	2 (7.7)

BTA, bone-targeting agent.

4. Discussion

This cross-sectional study provides valuable insights into real-world BTA treatment patterns in patients with solid tumors and bone metastases in Switzerland. Almost three-quarters (73.6%) of patients were receiving current BTA therapy during the study, which aligns with current guidelines recommendations to initiate BTAs at the time that bone metastases are diagnosed in patients with advanced breast cancer and mCRPC (the most frequent tumor entities in our study) [27].

The study also revealed that almost all participating physicians in Switzerland (94%) administer BTAs via a 3–4-weekly treatment schedule, one-third (33.7%) implement a 12-weekly dosing regimen after 2 years (16.2% after 1 year), and only a minority (3%) administer BTAs 12-weekly at time of initiation.

The published literature reports associations between increased SRE risk and a number of factors, such as: history of palliative radiation therapy, presence of extra-skeletal metastases, elevated serum calcium levels, or bone pain [28,29]. Although only a minority of participating physicians (24.4%) reported conducting a formal SRE risk assessment before initiating BTA therapy, a perceived 'high risk of bone complications' and 'bone pain' were the most common drivers of BTA initiation (43.0% and 21.8%, respectively). Together, these findings suggest that practicing physicians tend to use their clinical judgement and symptom reports, rather than formal assessments, to guide perceptions of SRE risk.

Interestingly, physician-assessed risk of bone complications was not associated with reported incidence of bone complications in patients treated with BTA therapy: bone complication incidence was 7% in both high- and low-risk groups. This finding might suggest that treating physicians were successfully able to identify patients at high risk of complications and to initiate BTA therapy accordingly. In patients who were prescribed BTA therapy despite being at low risk of bone complications, bone pain was the most commonly reported reason for BTA initiation. This may, again, suggest that practicing physicians perceive bone pain to be a marker of increased SRE risk and use SSEs (defined as: symptomatic fractures, surgery or radiation to bone, or spinal cord compression) to guide BTA initiation, or use BTA simply for bone-

Table 5
Incidence of current bone pain and current bone complications by BTA treatment, and bone complication risk for the overall patient group and those with known risk status.

	Overall sample, N = 417* Receiving BTA therapy		Known risk status, N = 400* Receiving BTA therapy		Bone complication risk	
	No (N = 110)*	Yes (N = 307)	No (N = 106)*	Yes (N = 294)	High (N = 235)*	Low (N = 165)
Patients with current bone pain, n (%)	15 (13.6)	51 (16.6)	15 (14.2)	47 (16.0)	42 (17.9	20 (12.1)
Patients with current bone complications, n (%)	8 (17.3)	26 (8.5)	8 (7.6)	23 (7.8)	18 (7.7)	13 (7.9)

Current bone pain was recorded if 'moderate-to-severe pain' was selected.
* Pain incidence was missing for one patient.
BTA, bone-targeted agent.

directed analgesia.

Among patients considered to be at high risk of developing bone complications, 17% (40/235) were not receiving BTA therapy. This is similar to the 12% of patients with breast cancer and bone metastases not receiving BTA therapy in a study assessing real-world practice across Europe [30]. Although this was reported to be partly due to a lack of time to initiate treatment in those patients whose diagnosis of bone metastases was very recent (35% of cases), the reason for non-initiation was reportedly because of a 'focus on treating the primary tumor' in another one-third of these cases (32%). In comparison, although 81% of patients had received BTA therapy within 3 months of diagnosis, the main reasons for not receiving a BTA in the cross-Europe study were: very recent BM diagnosis, perceived low risk of bone complications, and short life expectancy [30].

At the time of assessment, more than half of the patients (52.8%) were reported to be without bone pain due to bone metastases, 31.4% had only mild bone pain, and a minority (4.3%) had severe bone pain. Conversely, in the cross-Europe study, most patients with BMs (68%) were experiencing bone pain, with 20% reporting moderate-to-severe pain. If reflective of the current situation, data from our study would suggest that treating physicians are achieving adequate pain management for their patients, representing a marked improvement from the high incidence of bone pain events reported in the pivotal BTA registration trials [28,31]. The apparent use of appropriate analgesia in this study population is further supported by a lack of association between pain and BTA use, with pain reported in 16.0% of treated patients and 14.2% of untreated patients. The low incidence of bone pain was even evident in the cohort of patients categorized as being at high risk of bone complications. This may be due to more effective anti-cancer treatment use and improved pain management, including collaboration between pain specialists and palliative care specialists. This is, indeed, a promising finding for patients as inadequate pain management is common in advanced cancer, presenting in up to 55% of patients with bone metastases [32–34].

Although offering a unique insight into real-world patterns and perceptions of BTA use in Switzerland, there are some data limitations in this study that should be acknowledged. All data included in the analysis came direct from physician reports; patient records were not reviewed. However, data management was completed according to SAKK Coordinating Center Standard Operating Procedures. The cross-sectional nature of the study design provides only a snapshot of potential BTA outcomes, as pertinent to the patient's disease stage at the time of the study. It is not possible from a cross-sectional study to infer or deduce longitudinal and cumulative incidence of endpoints, thus the high rate of bone control should be interpreted with caution. Nevertheless, study design measures were taken to minimize some potential sources of selection within the physician and patient populations, for instance: the combined use of the SAKK research and SGMO networks to identify physicians helped to ensure that a representative sample of Swiss practitioners were invited to participate (albeit that participation was ultimately self-selecting from the invited group). In addition, the 3-month study period was determined and informed by current clinical practice guidelines for BTAs (and the administration cycles of commonly used chemotherapeutic agents) so as to ensure inclusion of all patients with bone metastases, whether or not they were treated with BTAs. Further, the observational, non-interventional nature of the study ensured that reported findings reflect true real-world practice and management decisions in patients with solid tumors and bone metastases.

5. Conclusion

This real-world study of BTA practice and perceptions suggests high implementation of guideline-recommended BTA prescribing by Swiss physicians [27,35,36] and high levels of pain control in patients with metastatic breast cancer and mCRPC. Denosumab appears to be the treatment of choice. The number of reported SREs was low in patients treated with BTAs, irrespective of their formal risk of bone complications. This low SRE rate may indicate the efficacy of systemic BTA therapy, irrespective of patients' risk profile, and/or the ability of treating physicians to use clinical judgement to assess bone complication risk and to treat appropriately.

Declarations

Ethics approval and consent to participate

The study protocol was written and the study conducted in accordance with the principles enunciated in the Declaration of Helsinki (2011), the Swiss Human Research Act and its associated Ordinances (OrgO-HRa) and from relevant Swiss regulatory bodies.

All relevant study documentation (including the protocol, patient information and consent form) were submitted to relevant ethics committees, in agreement with local legal requirements for formal authorization. Any amendment to the protocol or patient information and consent form was submitted for authorization to these institutions. The decision of the ethics committees with regards to the conduct of the study was provided in written form to the study Sponsor prior to study initiation. Any substantial amendments to the protocol (except for safety reasons) were only implemented after obtaining written authorization by the corresponding regulatory bodies, as required for affected sites.

Patient recruitment only commenced after the site was officially opened for accrual by the SAKK CC.

All participating sites had to adhere to the Swiss HRA and all applicable local regulatory guidelines.

Consent for publication

The results of the study are published in accordance with the current SAKK publication guidelines (https://www.sakk.ch/en/about-us/media-and-publications), which afford freedom of reporting to participating physicians.

Declaration of Competing Interest

Michael Mark, no conflict of interest to declare.

Beat Thürlimann, holds stock of Novartis and Roche, and has received consultation honoraria from Amgen, AstraZeneca, Novartis and Roche

Karin Ribi, no conflict of interest to declare

Corinne Schär, no conflict of interest to declare

Daniel Dietrich, no conflict of interest to declare

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

Ursina Zürrer-Härdi, no conflict of interest to declare

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Sandro Anchisi, has participated in advisory boards for Janssen-Lilly, Lilly and Novartis

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Philipp von Burg, no conflict of interest to declare

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CRediT authorship contribution statement

Michael Mark: Conceptualization, Visualization, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Beat Thürlimann:** Conceptualization, Visualization, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Karin Ribi:** Conceptualization, Visualization, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Corinne Schär:** Conceptualization, Visualization, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Daniel Dietrich:** Conceptualization, Visualization, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Richard Cathomas:** Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Ursina Zürrer-Härdi:** Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Thomas von Briel:** Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Sandro Anchisi:** Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Pierre Bohanes:** Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Veronika Blum:** Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Philipp von Burg:** Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Meinrad Mannhart:** Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Clemens B Caspar:** Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Roger von Moos:** Conceptualization, Visualization, Formal analysis, Data curation, Writing - original draft, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jbo.2019.100273.

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