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Comparative Treatment Persistence with Bone Targeting Agents among Asian Patients with Bone Metastases from Solid Tumors: a multinational retrospective cohort study.

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Running head: Comparative Persistence of Bone-targeting Agents in Asia

Abstract

Background: The efficacy of bone-targeting agents (BTAs) has been confirmed, but the results' generalizability to Asia is in question.

Objective: To evaluate and compare treatment persistence and re-initiation with different BTAs among patients with bone metastases from solid tumors.

Patients and Methods: This population-based cohort study included bone metastasis patients with breast, lung or prostate cancer who initiated BTAs, including denosumab (D), zoledronic acid (Z), and pamidronate (P) in Taiwan (2013-2017), Hong Kong (2013-2017) and Korea (2012-2016). We described the patients' persistence with BTAs, by evaluating the interruption probability, and compared risks of treatment interruption. The rates of re-initiation with index BTAs were evaluated.

Results: We included 5127 patients (D: 3440, Z: 1210, P: 477) from Taiwan, 883 patients (D: 458, Z: 357, P: 68) from Hong Kong and 4800 patients (Z: 4068, P: 732) from Korea. Compared with zoledronic acid, denosumab had lower risk of interruption in Taiwan (adjusted hazard ratio: 0.44; 95% CI, 0.40-0.48) and Hong Kong (0.36; 0.28-0.45). However, pamidronate was more likely to be interrupted than zoledronic acid in Taiwan (1.31; 1.11-1.54) and Korea (2.06; 1.83-2.32), but not in Hong Kong (1.13; 0.71-1.78). After discontinuation, original treatments with denosumab in Taiwan and zoledronic acid in Hong Kong were more likely to be resumed, while in Korea the rates were similar among the bisphosphonates.

Conclusions: Denosumab was associated with lower risk of interruption than bisphosphonates in patients with bone metastases in Taiwan and Hong Kong. Further investigations may be required to verify patients' actual reasons for discontinuation.

Keywords: bone-targeting agents, treatment interruption, solid tumor, bone neoplasms/secondary

Key Points:

- This multinational population-based cohort study using three nationwide databases from Taiwan, Hong Kong and Korea provided the utilization patterns of bone-targeting agents (BTAs), including treatment interruption- and re-initiation patterns.
- We found the risk of treatment interruption was lower for patients receiving denosumab compared to patients receiving bisphosphonates in Taiwan and Hong Kong, suggesting that denosumab may have composite benefits including better effectiveness, safety and cost of drugs.
- The re-initiation rates among patients who discontinued BTA regimens varied among the three countries, which may be related to country-specific factors such as healthcare systems or reimbursement guidelines.

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1. INTRODUCTION

Bone metastases are common in patients with advanced stage solid tumors [1]. Reports indicate that more than 65% of breast cancer and prostate cancer patients and more than 35% of lung cancer patients have bone metastases [2]. Bone metastases are associated with skeletal-related events (SREs) due to dysregulation of the osteoclast and osteoblast activities, and the remodeling of bone structure [3]. SREs, such as pathological fracture, the need for radiotherapy to the bone, the need for bone surgery, spinal cord compression and hypercalcemia, can greatly decrease patients' quality of life and increase mortality [4-6]. These complications increase the consumption of healthcare resources, leading to financial burden on society [7, 8].

Randomized clinical trials (RCT) have demonstrated the efficacy of bone targeting agents (BTAs), including bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, denosumab, in the prevention of SREs in patients with bone metastases [9-14]. Even though the optimal treatment duration with BTAs remains controversial, the American Society of Clinical Oncology (ASCO) has recommended the use of BTAs until general performance status of patients has substantially declined [15]. However, adverse reactions to BTAs, e.g. osteonecrosis of the jaw, hypocalcemia and renal toxicity, may hamper BTA treatment, and thus affect patients' persistence with BTAs [16-18].

RCTs involve highly selected patients under close monitoring and clinical attention to their treatment, raising the question of applicability of the efficacy results from RCTs to real-world practices [19]. Moreover, current RCTs on the topic of BTAs predominantly focused on populations from Western countries, and the results' generalizability to Asian countries is uncertain. Although BTA utilization in patients with bone metastases has been described in the United States and Europe, there has been no comparison of use persistence between the BTAs [20-23]. Good persistence indicates that patients consistently stay on the regimens, integrating patients' and clinicians' evaluations of effectiveness and safety, and reflecting their judgement of therapeutic benefits in relation to undesirable drug effects [24]. Therefore, persistence has come to be seen as a global measurement for real-world effectiveness in some pragmatic trials [25] and observational studies [24, 26]. In this study, we evaluated the utilization patterns of different BTAs in patients with bone metastases from solid tumors, analyzing three population-based, nationwide databases from Taiwan, Hong Kong and Korea in order to increase the generalizability of our results. Specifically, we compared the risk of treatment interruption between the BTAs among the three databases.

2. MATERIALS & METHODS

2.1 Study Design & Data Sources

This is a multi-database retrospective cohort study using data from Taiwan, Hong Kong and Korea. The National Health Insurance Databases (NHID) of Taiwan and Korea are claims databases which cover 99% (approximately 25 million individuals) [27] and 97% of their populations (approximately 50 million individuals) [28], respectively. Hong Kong's electronic medical records database, named Clinical Data Analysis and Reporting System (CDARS), covers about 80% of all hospital admissions and more than 90% of cancer patients (approximately 7 million individuals) [29]. The three databases provide anonymized, patient-level data on demographics, drug information, diagnosis and procedures administered during hospitalization or at outpatient departments.

To maintain data confidentiality, we used a distributed network approach and executed the analysis independently from each site on the basis of common protocol [30]. The coordinating center, National Cheng Kung University, Taiwan, only collected summary results from each site without access to the individual data. The study was

approved by the institutional review board of each site, i.e. National Cheng Kung University of Taiwan [A-ER-107-387], University of Hong Kong/Hospital Authority, Hong Kong West Cluster [UW18-691], and Sungkyunkwan University of Korea [SKKU 2019-06-008].

2.2 Study Population and Exposure

We included patients aged 18 years and above with bone metastases from the three major solid tumors of breast, prostate and lung cancer from 2013 to 2017 in Taiwan and Hong Kong, and from 2012 to 2016 in Korea. Patients also needed to have some record of BTAs use, including 120mg denosumab, 4mg zoledronic acid or any intravenous formulation of pamidronate. Newly diagnosed bone metastases patients were defined based on a two-year washout period prior to the first diagnosis of bone metastases, and new users of BTAs were defined as patients with no BTAs records within a one-year washout period before the first record of BTAs prescription. Patients who used more than two types of BTAs at the first BTAs prescription date (index date) were excluded. We also excluded patients who received only one BTA or re-administered BTAs within 14 days because they may have been prescribed for hypercalcemia. BTAs exposure was based on the first BTAs used at index date (index BTAs) including denosumab, zoledronic acid or pamidronate. All comorbidities and co-medications records were retrieved by ICD/drug codes, as listed in ***Supplementary Tables 1 - 3***.

2.3 Outcomes

We followed patients from the index date to death or the end of the study period. The primary outcome was persistence with the BTAs, based on evaluation of probability and risk of treatment interruption, including discontinuation and switching. Discontinuation was defined as patients failing to refill BTAs within 90 days of the last date of previous BTAs prescription. Switching was defined as patients receiving a BTA other than the index drug within the 90-day period following the last BTA prescription. The secondary outcome was the probability of patients re-initiating the index BTA after discontinuation. The timeframe for re-initiation was from the discontinuation date to the end date of the study period for each database.

2.4 Statistical Analysis

The covariates included patients' sex and age at index date, original cancer types, comorbidities and co-medications within the one-year baseline period before the index date. Continuous variables are presented as the mean with standard deviation and categorical variables are shown as numbers and percentages. We have presented the interruption probabilities and re-initiation rates during the follow-up period, whereby the probabilities of patients interrupting and re-initiating BTAs were assessed by cumulative incidence function. We compared the risk of treatment interruption among BTAs within the observation period by Cox-proportional hazard models with adjustments for aforementioned covariates, as listed in ***Table 1*** and ***Supplementary Table 4***. We also performed cause-specific hazard modeling and sub-distribution hazard modeling to evaluate effects from competing mortality risk [31]. Stratification analyses by different cancer types were conducted to examine possible confounding by indication while evaluating the risk of treatment interruption. We considered statistical significance based on alpha level 0.05. We used R version 3.5.2 in Hong Kong and SAS version 9.4 in Taiwan and Korea for statistical analyses.

3. RESULTS

There were 5127, 883 and 4800 patients in Taiwan, Hong Kong and Korea, respectively, who met the inclusion criteria. The denosumab, zoledronic acid and pamidronate users were 3440 (67.1%), 1210 (23.6%) and 477 (9.3%) patients, respectively, in Taiwan and 458 (51.9%), 357 (40.4%) and 68 (7.7%) patients in Hong Kong. Denosumab was not available during the study period in Korea. The zoledronic acid and pamidronate users were 4068 (84.8%) and 732 (15.3%) patients, respectively, in Korea ***(Figure 1)***. BTAs were primarily used for lung or breast cancer in all included countries. However, in Taiwan and Korea, a higher proportion of zoledronic acid was used for prostate- than for lung cancer. ***Table 1*** presents patients' characteristics and ***Supplementary Table 4*** presents the detailed comorbidities and co-medications of patients.

3.1 Probability of BTAs Interruption by the 12th month

The probabilities of interruption by the 12th month in Taiwan were 43% for denosumab, 65% for zoledronic acid and 86% for pamidronate. In Hong Kong, denosumab also had the lowest probability, followed by pamidronate and zoledronic acid (denosumab: 32%, pamidronate: 62% and zoledronic acid: 63%). In Korea, 67% of zoledronic acid use and 87% of pamidronate use had been interrupted by the 12th month, with zoledronic acid showing lower rates during the follow-up period. ***Figure 2*** presents the cumulative incidence of BTA treatment interruption among countries.

3.2 Risk of Treatment Interruption

The incidence rates of treatment interruption were 55, 113 and 178 per 100 person-year for denosumab, zoledronic acid and pamidronate users in Taiwan, and 39, 101 and 119 in Hong Kong, respectively**.** In Korea, the incidence rates of treatment interruption were 67 and 138 per 100 person-year for zoledronic acid and pamidronate users, respectively. Compared to zoledronic acid users, the risk of treatment interruption was lower in denosumab users in Taiwan (adjusted hazard ratio, 0.44; 95% CI, 0.40-0.48) and Hong Kong (0.36; 0.28-0.45). We found the risk of treatment interruption was higher in pamidronate users compared with zoledronic acid users in Taiwan (1.31; 1.11-1.54) and Korea (2.06; 1.83-2.32). There was no difference in the risk of interruption between the two bisphosphonates (1.13; 0.71-1.78) in Hong Kong ***(Table 2)***. The results of risk comparisons of treatment interruption remained consistent throughout causal-specific hazard models and sub-distribution hazard models. The results from stratification analyses by cancer types were generally consistent with the main analyses ***(Table 2 and Figure 3)***.

3.3 Probability of BTA Re-initiation

Figure 4 presents the probability of re-initiation of BTAs after discontinuation among the three countries. In Taiwan, we found more patients re-initiating denosumab (68%) within 12 months, compared to pamidronate (47%) and zoledronic acid (31%). However, in Hong Kong, a higher proportion of patients re-initiated zoledronic acid (62.5%) than denosumab (27%), with a rapid re-uptake within the first 90 days after discontinuation. In Korea, about 35% of patients re-initiated zoledronic acid within 12 months, which was similar to patients re-initiating pamidronate (30%).

4. DISCUSSION

Good persistence with BTA treatment may reflect the determination of clinicians and patients to integrate therapeutic benefits, side effects, availability, and affordability of the drugs in real-world practice [24]. In this international study, we found the risk of treatment interruption was lower for patients receiving denosumab compared to patients receiving bisphosphonates in Taiwan, with consistent results in Hong Kong. The findings may indicate a more favorable real-world effect of denosumab, compared to other BTAs in patients with solid tumor bone metastases. We also found a consistent trend toward lower risk of treatment interruption for zoledronic acid users, compared to pamidronate users across Taiwan and Korea. Moreover, comparing drug re-initiation between BTAs, we found patients in Taiwan who discontinued denosumab were more likely to re-initiate the treatment, compared to patients who discontinued pamidronate or zoledronic acid. However, in Hong Kong, zoledronic acid users had a higher rate of re-initiation compared to the other two BTAs. In Korea the re-initiation rate of zoledronic acid users was higher than that of pamidronate users.

4.1 Lower Interruption in Denosumab

A longitudinal cohort study conducted on US claims data found the rate of interruption was 23% in the denosumab group, compared to 36% in the zoledronic acid group at 12 months among a study population including 33%, 26% and 26% breast, prostate, and lung cancer patients, respectively [23]. Diel et al. [32] also found a similar result, with the risk of interruption lower in denosumab compared to zoledronic acid, regardless of patients' cancer types. Our study, based on Asian nationwide databases, supported the finding that the risk of interruption was lower in denosumab users, compared with the other two types of BTA users. This may be due to a few different reasons. First, the efficacy of denosumab in preventing SREs is superior to zoledronic acid in breast or prostate cancer patients with bone metastases, as shown by RCTs [9, 10, 33]. A meta-analysis including 6 clinical trials demonstrated denosumab users had favorable outcomes compared to bisphosphonate users in delaying the time to SREs and in the incidence of radiation treatment for bone events [34]. Second, because subcutaneous denosumab is more convenient to administer compared to intravenous infusion of bisphosphonates, clinicians and patients may prefer to use denosumab, leading to a better treatment adherence [16, 17, 35]. Third, renal impairment has remained a great safety concern when using bisphosphonates. Close monitoring of the bisphosphonate dosage and patient's renal function is mandatory. By contrast, denosumab is eliminated through nonspecific catabolism in the reticuloendothelial system [36], regardless of renal and hepatic functions of patients, and has been shown to reduce renal impairment or toxicity by 25% in comparison to zoledronic acid [34]. A better renal function safety profile affects clinicians' decisions [16-18].

4.2 Different Re-initiation Rates among Countries

Re-initiation of BTAs may reflect the fact that decisions by clinicians and patients are guided not only by the effects of drugs but also reimbursement guidelines or healthcare policies of the country. The rates of re-initiation vary in different studies. For example, the re-initiation rate of BTAs within one year is about 74% in the US [37], but only approximately 2-17% in Germany [32]. We also found the re-initiation rates of BTAs varied among Asian countries. We found the re-initiation rates were low for zoledronic acid (22%) in Korea, possibly because, based on the reimbursement guidelines in Korea, patients who developed SREs are not able to reuse zoledronic acid. The re-initiation rate of denosumab was 68% in Taiwan compared to only 27% in Hong Kong, because the copayments are relatively low in Taiwan. Since the price of denosumab is approximately 30 times higher than zoledronic acid in Hong Kong, patients may decide to switch to zoledronic acid in order to reduce medication cost. In addition, some patients in Hong Kong may

decide on a regimen with intermittent dosing of zoledronic acid to minimize medication costs, based on the results from a recent trial that showed that the use of zoledronic acid every 12 weeks provided similar effects to the standard treatment interval of every 4 weeks [38]. This may explain why we observed a high rate of patients reinitiating zoledronic acid in Hong Kong, but not other BTAs, within the first 90 days after discontinuation, as stated above. Other factors which may be related to re-initiation are listed in ***Supplementary Table 5***.

Possibly due to the heterogeneity of patients and varying effectiveness outcomes of the drugs in previous studies, optimal treatment duration with BTAs for patients with bone metastases is currently not well determined. The ASCO recommends patients should continue BTA treatment until the effect of the drugs has deteriorated [15]. Accumulated evidence from prospective trials or observational studies suggests continuous use of BTAs is associated with better outcomes in the prevention of SREs [39, 40]. Our study analyzed 5 years of BTA utilization patterns from population-based databases in three countries, and the findings could provide strong grounds for future investigations into optimal BTA regimens, balancing the trade-off between drug effectiveness, safety and affordability for patients.

4.3 Study Limitations

There are some limitations in our study. First, because laboratory data was not available in the databases, we were not able to confirm patients' serum calcium to differentiate the use of bisphosphonates for hypercalcemia from use as BTAs. To minimize possible misclassification bias, we removed patients who used only one administration of bisphosphonate or used bisphosphonates intensively within 14 days from the analysis. Second, because the reason for interruption of BTAs was unknown, no inference comparing BTA efficacy can be made from our analysis. However, on the basis of our clinical experience, the primary reason for the discontinuation of BTAs was the occurrence of adverse reactions to the drugs. Another reason was that patients' health had deteriorated so much that controlling SRE was no longer a clinical priority. We suggest further investigations to confirm the actual reasons for the discontinuation of BTAs. Third, we found that, in Hong Kong, 61.8 % of pamidronate users died in the first 90 days after drug initiation, but only 10.4% of zoledronic acid users died. The analyses in Hong Kong may therefore be subject to bias from competing risk of mortality. Patients with very poor cancer conditions are more likely to discontinue BTAs or die, leaving the comparison between BTAs indeterminate. Therefore, we considered competing risk models, including cause-specific hazard model and sub-distribution hazard model to address these issues. Fourth, we only included databases from Taiwan, Hong Kong and Korea. Because the populations and healthcare systems are diverse across the Asia-Pacific region, the generalizability of our results to other Asian countries should be further discussed. Fifth, the different characteristics among the countries could be due to the nature of our databases. That is, the databases from Taiwan and Korea were claims-databases and had issues of overestimation of the comorbidities, while the issue of overestimation should be less in EHR data (i.e., CDARS in Hong Kong). Therefore, any comparisons across the countries must be made carefully.

5. CONCLUSIONS

From this multinational population-based cohort study using three nationwide databases from Taiwan, Hong Kong and Korea, we found that in Taiwan and Hong Kong, denosumab was associated with lower risk of treatment interruption, compared to zoledronic acid and pamidronate in patients with solid tumor bone metastases. The re-initiation rates among patients who discontinued BTA regimens varied among the three countries. The drug utilization patterns may reflect the outcomes of patients receiving BTAs, but future investigations may be required to verify patients' actual reasons for discontinuing the treatment.

Declarations

Funding

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Conflicts of interest/Competing interests

CL Cheung reports receipt of funding from Amgen and Abbott outside the submitted work. J-Y Shin reports receipt of research funding from the Ministry of Food and Drug Safety, Ministry of Health and Welfare, and the National Research Foundation of the Republic of Korea; grants from pharmaceutical companies including Amgen, Pfizer, Hoffmann-La Roche, Dong-A ST, and Yungjin outside the submitted work. EC-C Lai reports receipt of research funding from the Ministry of Science and Technology and the Ministry of Health and Welfare of Taiwan, and grants from pharmaceutical companies including Amgen and Taketa outside the submitted work. T-C Lin is currently employed by Amgen Inc. Amgen Asia Holdings was an affiliate of NJ Kleinman at the time of the conducting of the study. The remaining authors have declared no conflicts of interest.

Author's Contributions

Study concept and design: all authors; data acquisition: EC-C Lai (Taiwan NHID), C-L Cheung (Hong Kong's CDARS) and J-Y Shin (Korea's NHID); statistical analysis: PC-M Au, Y-H Baek, JH Kim, T-C Liao, C-Y Shen, and C-W Sing; data interpretation: all authors; drafting of the manuscript: C-Y Shen; review and revision of the manuscript: all authors.

Ethics approval

The authors complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. The study was approved by the institutional review board of each site, i.e. National Cheng Kung University of Taiwan [A-ER-107-387], University of Hong Kong/Hospital Authority, Hong Kong West Cluster [UW18-691], and Sungkyunkwan University of Korea [SKKU 2019-06-008].

Consent

Not applicable. The study used secondary data with encrypted patient identification at all study sites. No specific patients could be identified during the whole study process.

Availability of Data and Material

We used a distributed network approach and executed the analysis independently from each site on the basis of a common protocol. The coordinating center, National Cheng Kung University, Taiwan, only collected summary results from each site without access to individual data. The datasets analyzed in the current study will not be available to the

public due to data privacy regulations in each participating country. Qualified researchers may request data from the corresponding author.

Code availability

Not applicable.

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TABLES

Table 1: Patient Characteristics

	Taiwan			Hong Kong			Korea	
	Denosumab	**Zoledronic acid**	**Pamidronate**	**Denosumab**	**Zoledronic acid**	**Pamidronate**	**Zoledronic acid**	**Pamidronate**
Patients, n	3440	1210	477	458	357	68	4068	732
Age mean, years (sd)	62.6 (13.2)	62.3 (14.1)	62.8 (12.2)	61.3 (12.5)	61.3 (11.7)	65.0 (12.6)	56.5 (12.5)	60.1 (12.3)
Age group, n (%)								
<54 years	955 (27.8)	384 (31.7)	113 (23.7)	130 (28.4)	105 (29.4)	17 (25.0)	1911 (47.0)	244 (33.3)
55 – 64 years	1011 (29.4)	304 (25.1)	164 (34.4)	157 (34.3)	119 (33.3)	19 (27.9)	1054 (25.9)	210 (28.7)
65 – 74 years	758 (22.0)	237 (19.6)	108 (22.6)	103 (22.5)	87 (24.4)	15 (22.1)	716 (17.6)	177 (24.2)
75 – 84 years	540 (15.7)	206 (17.0)	80 (16.8)	51 (11.1)	40 (11.2)	12 (17.6)	350 (8.6)	92 (12.6)
85 years and older	176 (5.1)	79 (6.5)	12 (2.5)	17 (3.7)	6 (1.7)	5 (7.4)	37 (0.9)	9 (1.2)
Sex, n (%)								
Male	1319 (38.3)	477 (39.4)	250 (52.4)	163 (35.6)	121 (33.9)	34 (50.0)	833 (20.5)	364 (49.7)
Calendar year, n (%)								
2012	N/A	N/A	N/A	N/A	N/A	N/A	695 (17.1)	116 (15.8)
2013	131 (3.8)	362 (29.9)	120 (25.2)	28 (6.1)	41 (11.5)	9 (13.2)	800 (19.7)	168 (23.0)
2014	357 (10.4)	314 (26.0)	124 (26.0)	87 (19.0)	49 (13.7)	14 (20.6)	818 (20.1)	149 (20.4)
2015	566 (16.5)	234 (19.3)	139 (29.1)	124 (27.1)	53 (14.8)	16 (23.5)	896 (22.0)	156 (21.3)
2016	1121 (32.6)	172 (14.2)	56 (11.7)	121 (26.4)	106 (29.7)	18 (26.5)	859 (21.1)	143 (19.5)
2017	1265 (36.8)	128 (10.6)	38 (8.0)	98 (21.4)	108 (30.3)	11 (16.2)	N/A	N/A
Original Cancer Type, n (%)								
Lung cancer	1300 (37.8)	132 (10.9)	411 (86.2)	192 (41.9)	114 (31.9)	38 (55.9)	57 (1.4)	336 (45.9)
Prostate cancer	750 (21.8)	393 (32.5)	27 (5.7)	86 (18.8)	65 (18.2)	9 (13.2)	785 (19.3)	129 (17.6)
Breast cancer	1464 (42.6)	700 (57.9)	27 (5.7)	180 (39.3)	178 (49.9)	21 (30.9)	3226 (79.3)	267 (36.5)

N/A: Not applicable

Table 2: Evaluation of Risk of Treatment Interruption between Bone Targeting Agents

	Event (N)	Total Time (person-year)	Incidence Rate (per 100 person-year)	Hazard Ratio (95% CI)			
				Crude	Adjusted*	Cause-specific hazard model*	Sub-distribution hazard model*
Taiwan							
Zoledronic acid	893	789.54	113.10	Reference	Reference	Reference	Reference
Denosumab	1386	2517.47	55.06	0.48 (0.44, 0.52)	0.44 (0.40, 0.48)	0.44 (0.39, 0.48)	0.49 (0.45, 0.54)
Pamidronate	334	187.41	178.22	1.65 (1.45, 1.87)	1.31 (1.11, 1.54)	1.31 (1.11, 1.54)	1.26 (1.06, 1.48)
Hong Kong							
Zoledronic Acid	212	210.086	100.91	Reference	Reference	Reference	Reference
Denosumab	155	397.544	38.99	0.38 (0.31, 0.47)	0.36 (0.28, 0.45)	0.36 (0.28, 0.45)	0.38 (0.31, 0.48)
Pamidronate	24	20.099	119.41	1.39 (0.91, 2.12)	1.13 (0.71, 1.78)	1.13 (0.71, 1.78)	0.42 (0.25, 0.71)
Korea							
Zoledronic Acid	2483	3732.32	66.53	Reference	Reference	Reference	Reference
Pamidronate	467	338.25	138.06	2.44 (2.21, 2.70)	2.06 (1.83, 2.32)	2.06 (1.83, 2.33)	1.50 (1.29, 1.74)

* Adjusted variables: cataract, cerebrovascular disease, chronic obstruction pulmonary disease, congestive heart failure, dementia, depression, diabetes mellitus, dyslipidemia, glaucoma, hypertension, ischemic heart disease, liver disease, macular degeneration, osteoarthritis, osteoporosis, Parkinson's disease, pneumonia, renal failure, anti-dementia, anti-depressant, anti-Parkinson's, anti-psychotics, hypnotics and anxiolytics, alpha blocker, anti-platelet, anti-thrombotic, beta blocker, calcium channel blockers, diuretic, renin-angiotensin system inhibitors, hypoglycemic agents, lipid lowering agents, non-steroidal anti-inflammatory drugs, opioids, bronchodilators.

FIGURES

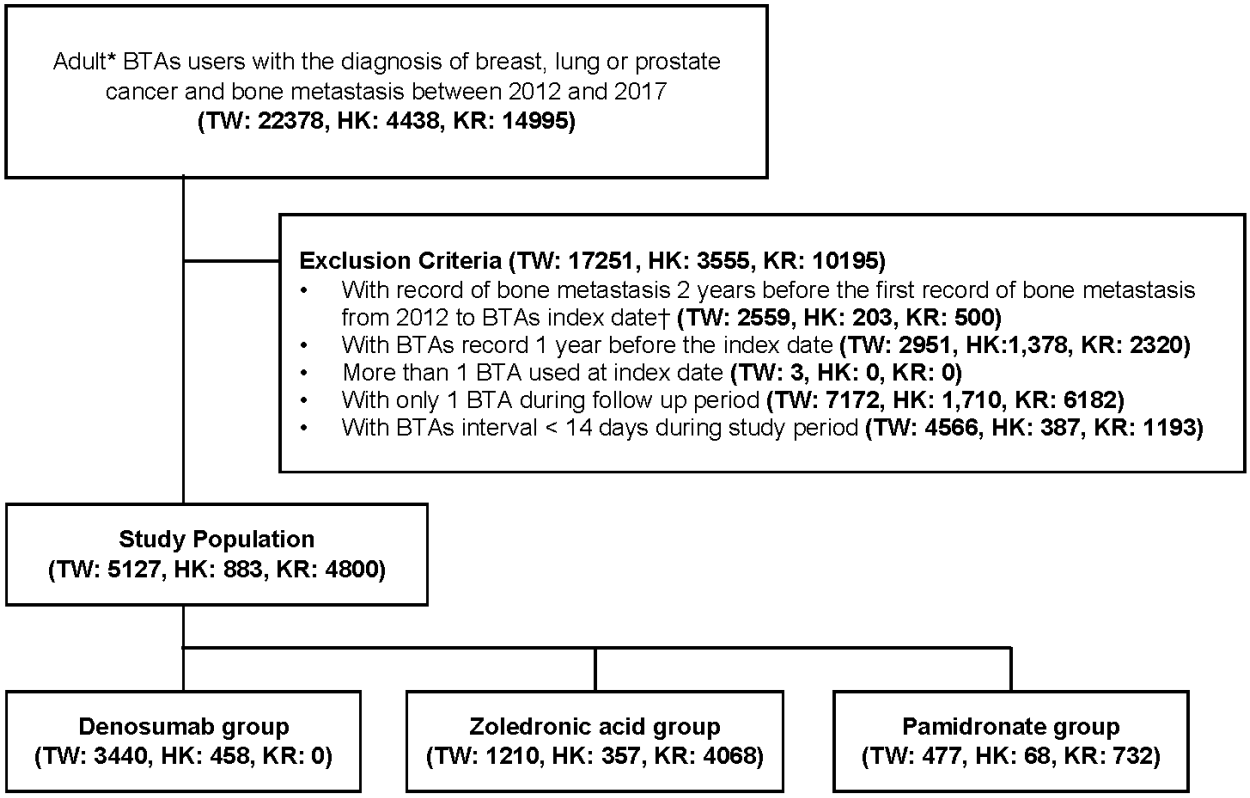


Figure 1: Flow Chart of the Study Cohort Assembly. * >18 y/o; † index date: first record of BTAs use; TW: Taiwan; HK: Hong Kong; KR: Korea

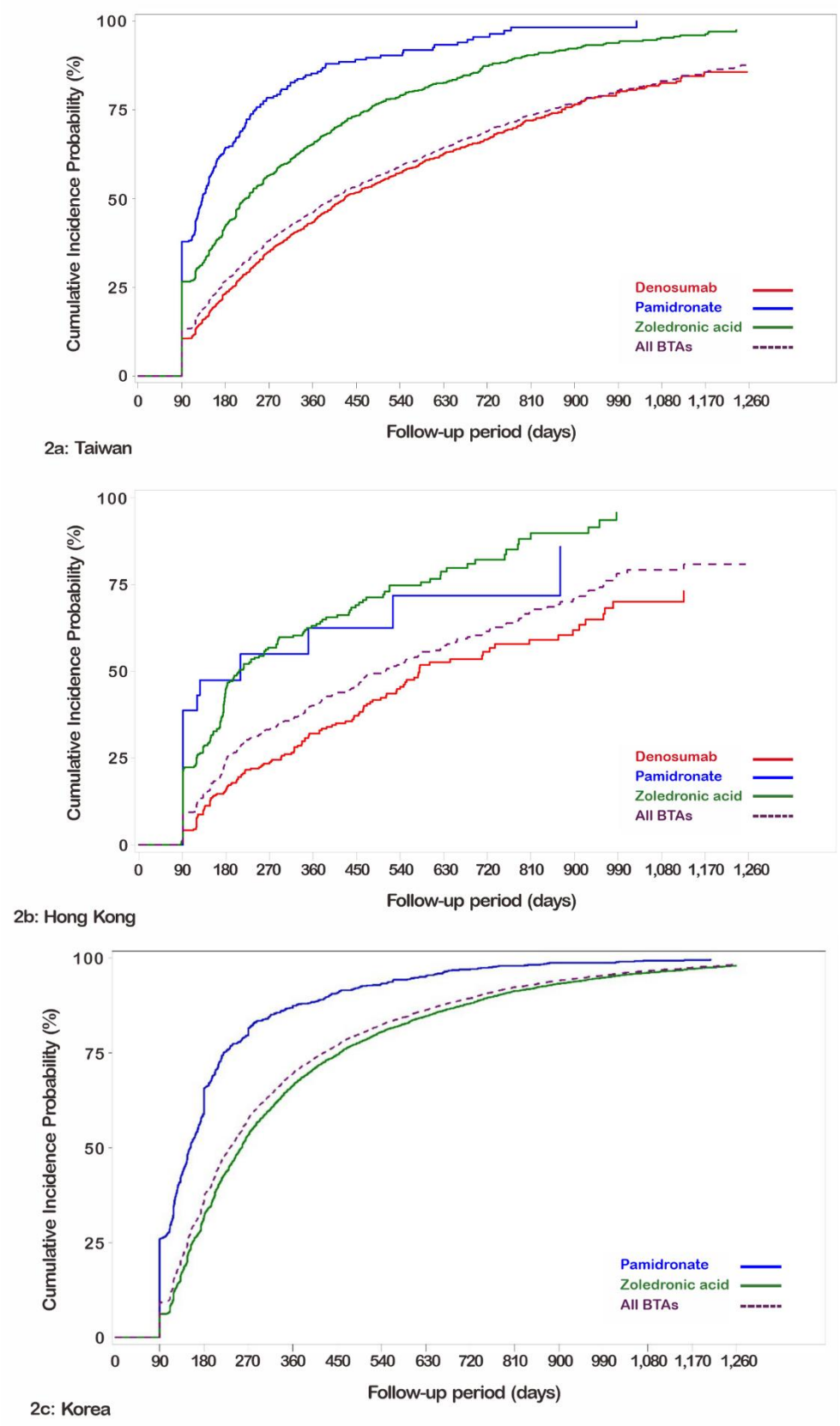
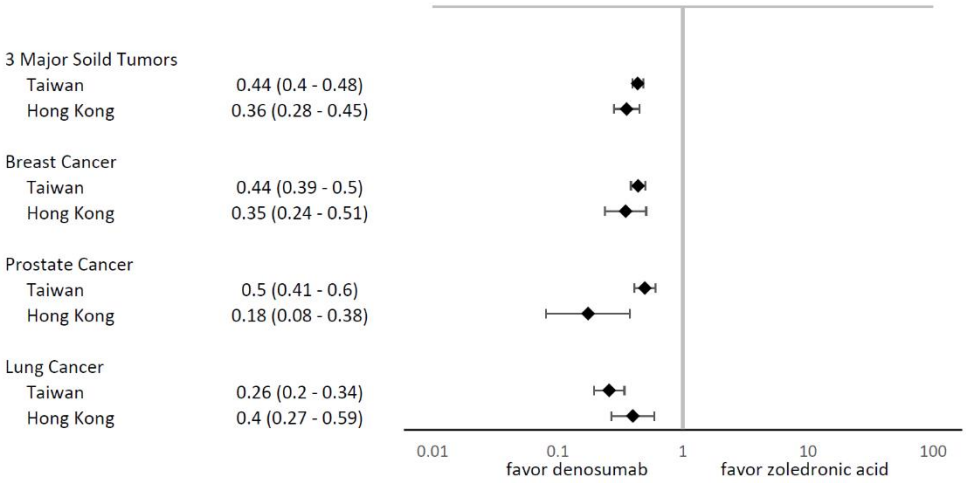
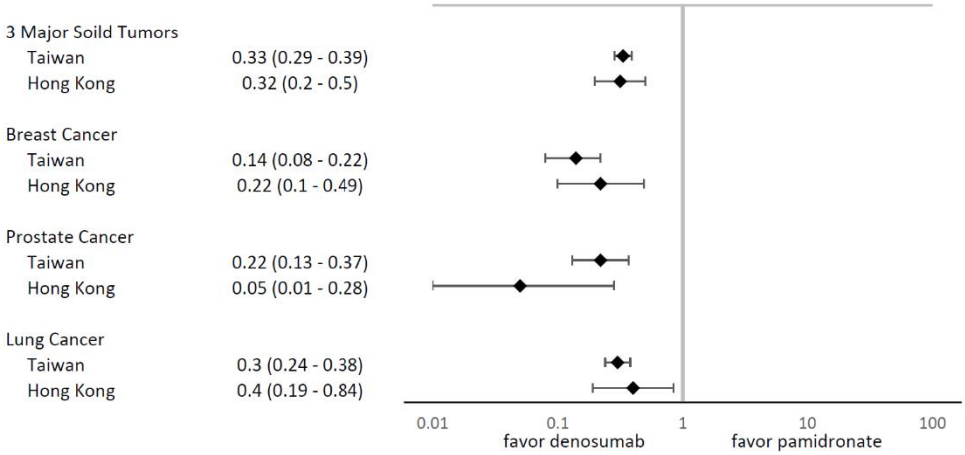


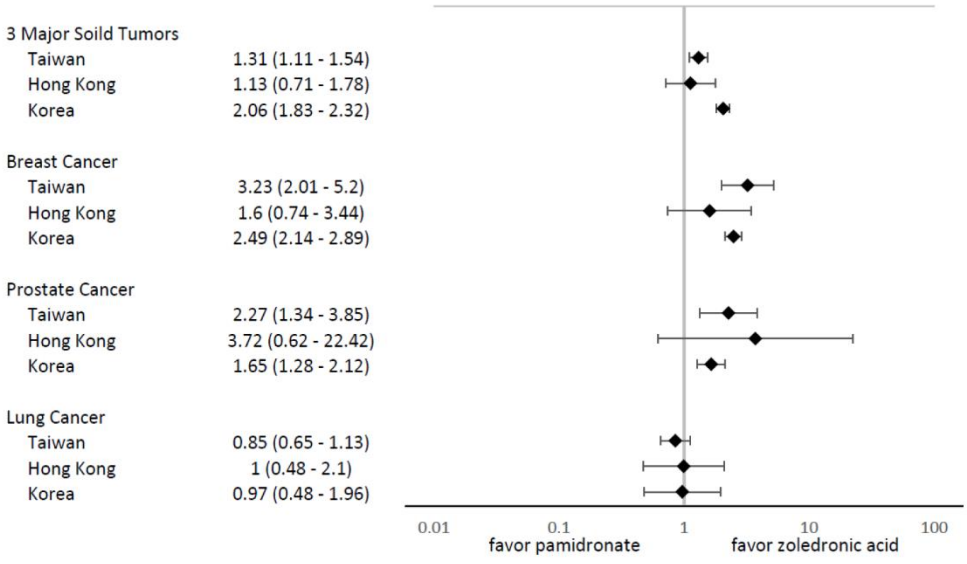
Figure 2: Cumulative Probability of Treatment Interruption by Different Bone Targeting Agents (2a: Taiwan, 2b: Hong Kong, 2c: Korea). Lower percentage of cumulative incidence probability indicates longer persistence with the BTAs.



3a: Denosumab vs Zoledronic acid

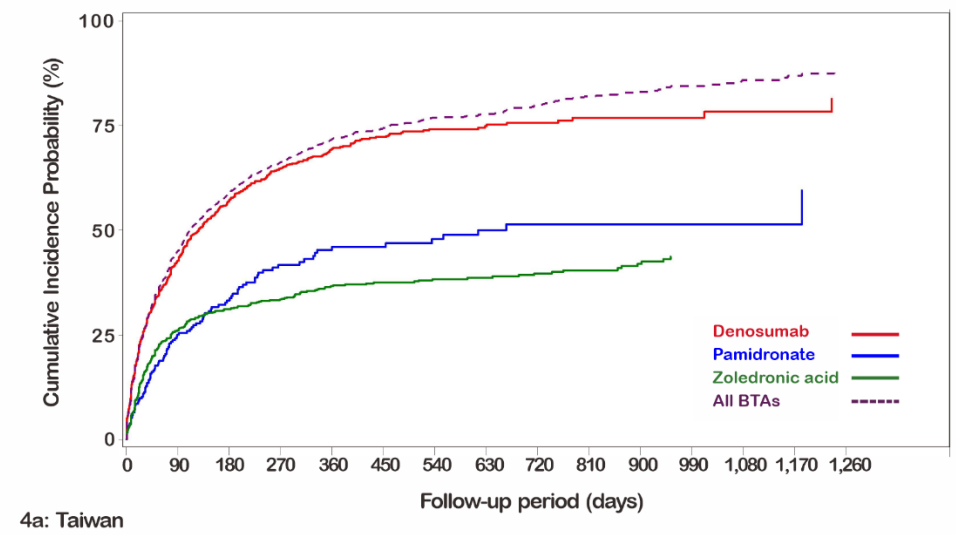


3b: Denosumab vs Pamidronate

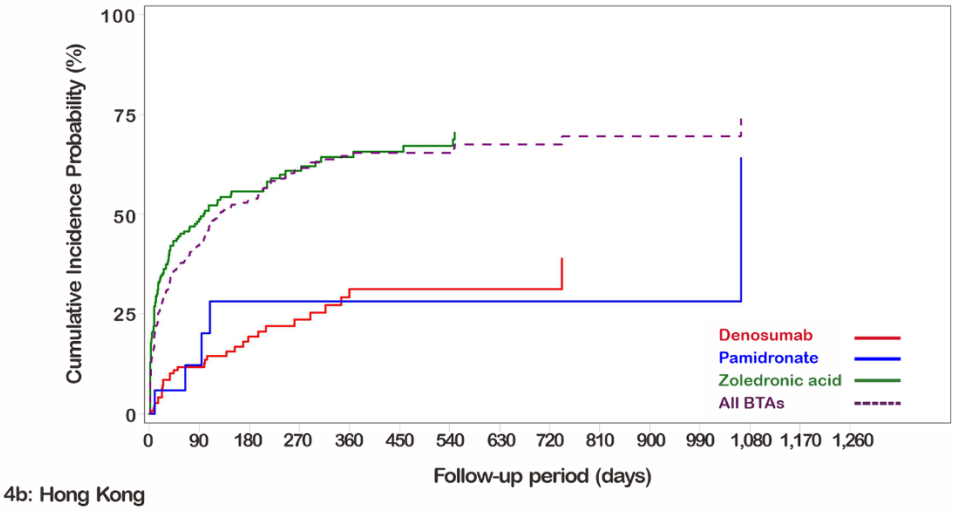


3c: Pamidronate vs Zoledronic acid

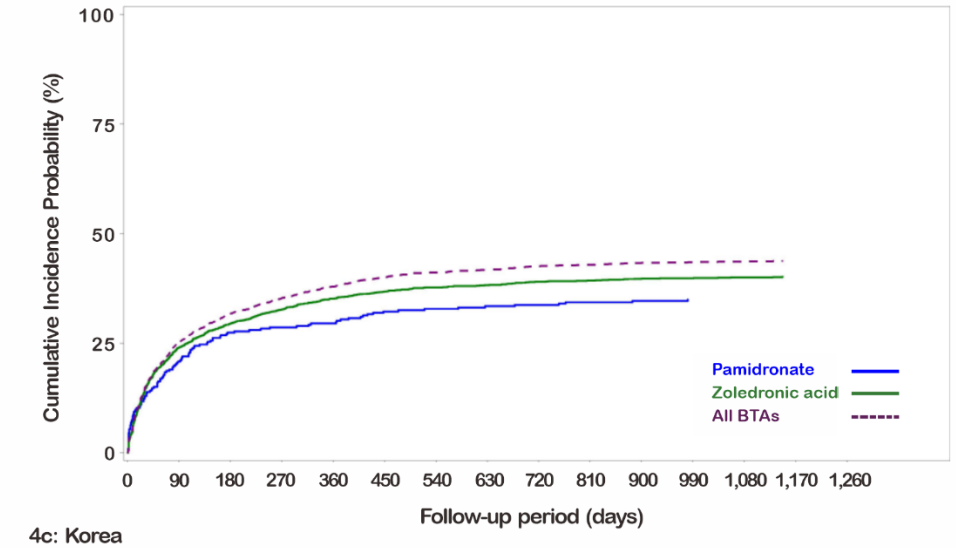
Figure 3: Risk of Treatment Interruption between Different Bone Targeting Agents (Stratified by Cancer Types).
The figure shows the adjusted hazard ratios and 95% confidence intervals of the BTA comparison.



4a: Taiwan



4b: Hong Kong



4c: Korea

Figure 4: Cumulative Probabilities of BTAs Re-initiation after Discontinuation (4a: Taiwan, 4b: Hong Kong, 4c: Korea). Higher percentage of cumulative incidence probability indicates a higher re-initiation rate of the BTAs.