1st March 2022

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Response to Consultation on Extension of Therapy with Zoledronic Acid for Early Breast Cancer

Thank you for the opportunity to comment on the proposed change to extend treatment with zoledronic acid from 2 years (4 treatments at 6-monthly intervals) to 3 years (6 treatments at 6-monthly intervals) for women with early breast cancer. I respond on behalf of the Breast Cancer Aotearoa Coalition (BCAC).

BCAC is a coalition of more than 30 breast cancer groups across Aotearoa run by breast cancer survivors and metavivors. BCAC is an incorporated society with charitable status providing an evidence-based voice for New Zealanders with breast cancer.

A number of international guidelines, including ESMO guidelines recommend bisphosphonate use for early breast cancer in women with low-oestrogen status (undergoing OFS or postmenopausal), especially if at high risk of relapse. Bisphosphonates are also recommended in patients with treatment-related bone loss. The treatment therefore has two key potential benefits for women with breast cancer: prevention of bone loss and prevention of disease recurrence.

A 2017 consensus statement by Hadji et al. (2017) concluded that bone-directed therapy should be given to all patients with a T-score<−2.0 or with a T-score of <−1.5SD with one additional RF, or with ≥2 risk factors (without BMD) for the duration of AI treatment. Patients with T-score>−1.5SD and no risk factors should be managed based on BMD loss during the first year and the local guidelines for postmenopausal osteoporosis. Compliance should be regularly assessed as well as BMD on treatment after 12 - 24 months. Furthermore, because of the decreased incidence of bone recurrence and breast cancer specific mortality, adjuvant bisphosphonates are recommended for all postmenopausal women at significant risk of disease recurrence. Various guidelines referred to by Hadji et al. (2017) are summarised in Table 1, below.

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Table 1 Guidelines on Antiresorptive Use in Women with Breast Cancer (Hadji et al., 2017)

Table 1
Summary of guidelines for antiresorptive use in women with breast cancer[a,b].

Source	Whom to treat	Antiresorptive	Dose	Duration of treatment
ESMO [5]	All women receiving AI therapy with ≥1 of the following T-score ≤ −2.0. Any 2 of the following risk factors T-score < −1.5, age > 65 yr,	Zoledronate Denosumab	4 mg IV q6mo	As long as AI therapy
SIOG [5]	low BMI (< 20 kg/m^2), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use > 6 mo, and smoking		60 mg SC q6mo	As long as AI therapy
ASCO [48]	Women with T-score ≤ −2.5 Women with T-score between −1.0 and −2.5 should receive individualized therapy	Alendronate Risedronate Zoledronate	Not given	Not given
St. Gallen [6]	No treatment for women with normal BMD	—	—	—
UK Expert Group [49]	Premenopausal women with ovarian suppression/failure and ≥1 of the following AI therapy and T-score < −1.0 T-score < −2.0 Vertebral fracture Annual bone loss > 4% at LS or TH	Alendronate Risedronate Ibandronate Zoledronate	70 mg/wk 35 mg/wk 150 mg PO/mo or 3 mg IV q 3 mo 4 mg IV q6mo	Follow-up at 2 yr to reassess
	Postmenopausal women receiving AI therapy with ≥1 of the following T-score < −2.0 Vertebral fracture Annual bone loss > 4% at LS or TH	Alendronate Risedronate Ibandronate Zoledronate	70 mg/wk 35 mg/wk 150 mg PO/mo or 3 mg IV q 3 mo 4 mg IV q6mo	Follow-up at 2 yr to reassess
Belgian Bone Club [47]	Women with T-score < −2.5 or history of fragility fracture Women with T-score between −1.0 and −2.5 plus other risk factors	Zoledronate Other BPs may be considered	4 mg IV q6mo	As long as AI therapy
International Expert Group (Hadji et al.) [5]	All women receiving AI therapy with ≥1 of the following T-score ≤ −2.0. Any 2 of the following risk factors T-score < −1.5, age > 65 yr, low BMI (< 20 kg/m^2), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use > 6 mo, and smoking	Zoledronate	4 mg IV q6mo	At least 2 yr, possibly as long as AI therapy
International Expert Panel (Aapro et al.) [46]	Women with ≥2 of the following risk factors: AI use, T-score < −1.5, age > 65 yr, corticosteroid use > 6 mo, family history of hip fracture, personal history of fragility fracture after age 50; T-score < −2.0	Zoledronate	4 mg IV q6mo	As long as AI therapy
ESCEO position paper (Rizzoli et al.) [50]	All women receiving AI therapy with (T-score hip/spine < −2.5 or ≥1 prevalent fragility fracture), to women aged ≥75 irrespective of BMD, and to patients with T-score < −1.5 + ≥1clinical risk factor or T-score < −1.0 + ≥2 clinical risk factors or FRAX-determined 10-year hip fracture probability ≥3%	Zoledronate Denosumab s.c., or possibly oral BP	4 mg IV q6mo 60 mg s.c. q6mo	As long as AI therapy

Abbreviations: AI, aromatase inhibitor; ASCO, American Society of Clinical Oncology; BMD, bone mineral density; BMI, body mass index; BP, bisphosphonate; GnRH, gonadotropin-releasing hormone; IV, intravenous; LS, lumbar spine; mo, month; NCCN, National Comprehensive Cancer Network; PO, oral; q, every; TH, total hip; UK, United Kingdom; wk, week; yr, year.

[a] Limited evidence for the use of other agents was available when these guidelines were written.

[b] Calcium and vitamin D supplements are to be used in conjunction with BPs, and exercise when appropriate is recommended by most panels.

Source: Consensus Guidelines (Hadji, Aapro et al. 2017)

More recently, updated guidance by Waqas et al. (2021) stated that extended use of AIs and persistent bone loss from recent data reinforce the need to evaluate fracture risk in EBC women initiated on AIs. Fracture risk should be assessed with clinical risk factors and BMD along with VFA, but FRAX is not adapted to CTIBL. Anti-resorptive therapy should be considered in those with a BMD T-score <-2.0 SD or with 2 clinical risk factors including a BMD T-score <-1.0 SD. In premenopausal women, intravenous zoledronate is the only drug reported to prevent bone loss and may have additional anticancer benefits. In postmenopausal women, either denosumab or BPs can be prescribed for fracture prevention with pertinent attention to the rebound phenomenon after stopping denosumab. Adjuvant BPs, in contrast to denosumab, have shown high level evidence for reducing breast cancer recurrence in high-risk post-MP women which should be taken into account when choosing between these two (Waqas, Lima Ferreira et al. 2021). Recent major studies of antiresorptive agents for bone loss and fracture prevention cited by Waqas et al. are outlined in Table 2 below.

Table 2 Recent Studies of Anti-Resorptive Agents in Women with Early Breast Cancer (Waqas et al. 2021)

Table 2
Major studies and updates from January 2017 to May 2020 regarding bone loss and fracture prevention of antiresorptive agents in women with EBC.

	Study	Population at study entry, N	Intervention, n	FU, M	Dose, route of administration	Mean BMD/T-score change from baseline, % LS	TH or FN	Fracture data
Bisphosphonates	Wilson *et al*, 2018, AZURE trial [50]	Stage II-III BC Adj AI (55.5%) Median age: NA N = 3359	ZOL = 1681 vs. Controls = 1678	84	4 mg, Q4W x6; 4 mg, Q3M x8; 4 mg, Q6M x5. IV	–	–	5y rate: 3.8% vs. 5.9%; Time to first fracture: HR 0.69, 95% CI = 0.53–0.90, p = 0.005
	Santa-Maria *et al*, 2018, ZAP trial [101]	Post-MP Stage 0-III BC Adj AI Median age: 59y N = 262	ZOL + L (ZAP trial) = 59 vs. L (ELPh trial) = 203	12	4 mg, Q6M. IV	T-score: +0.23, 95% CI = 0.13–0.33, p < 0.001 (12 M)	T-score: +0.12, 95% CI = 0–0.23, p = 0.046 (12 M)	–
	Sestak *et al*, 2019, IBIS-II Bone substudy [102]	Post-MP Osteopenic At high risk of BC Median age: NA N = 127	Risedronate = 68 vs. Placebo = 59	60	35 mg, Q1W. Oral	T-score: −0,4% vs. −4.2% p < 0.0001	T-score: −2.5% vs. −3.8%, p = 0.2	No difference in rate (20 vs. 18; RR = 0.91 (0.46 vs. 1.81)
	Livi *et al*, 2019, BONADIUV trial [99]	Post-MP Osteopenic HR + BC Adj AI Median age: 60y N = 171	Ibandronate = 89 vs. Placebo = 82	63	150 mg, Q4W. Oral	T-score: +0.35 vs. −0.24, p < 0.0001 (24 M)	T-score: +0.28 vs. −0.09, p = 0.0002 (24 M)	–
	Monda *et al*, 2017 [103]	Post-MP Osteopenic HR + EBC Adj AI Mean age: 56y N = 84	Risedronate = 42 vs. No treatment = 42	24	35 mg, Q1W. Oral	T-score: +6.86% vs. −4.8%, p < 0.0001	T-score: +2.8% vs. −3.5% p < 0.0001	Fractures: 0 vs. 3 (short FU and relatively young age)
Denosumab	Nakatsukasa *et al*, 2019 [65,67]	Post-MP Osteoporotic HR + I-IIIA BC Adj AI Mean age: 65y N = 103	Dmab = 93 (nonrandomized)	24	60 mg, Q6M. Subcutaneous	BMD: +7.0, 95% CI = 5.9–8.0 (24 M)	BMD: +3.4% to + 3.6% (24 M)	Any symptomatic clinical fractures (24 M)

Adj, adjuvant; AI, aromatase inhibitor; BC, breast cancer; BMD, bone mineral density; Dmab, denosumab; FN, femoral neck; FU, follow-up; HR, Hazard ratio; HR+, hormone-receptor positive tumours; IV, intravenous; LS, lumbar spine; M, month(s); NA, no available; Q, every; RR, relative risk; TH, total hip; W, week; y, years; ZOL, zoledronic acid.

Source: Waqas et al. 2021

In the AZURE trial, the duration of zoledronic acid therapy was 5 years, and this is the largest data collection of fracture incidence during adjuvant bisphosphonate use in breast cancer. The AZURE trial evaluated the addition of zoledronic acid (ZOL) 4 mg for 5 years to standard neo/adjuvant chemotherapy and/or endocrine therapy (control) in patients with stage II/III early breast cancer.

Two hundred forty-four patients reported ≥1 fracture, 140 (8.3%) in the control arm (171 fractures) and 104 (6.2%) in the ZOL arm (120 fractures). The 5-year fracture rate was reduced from 5.9% (95% confidence interval [CI] 4.8, 7.1%; control) to 3.8% (95%CI 2.9, 4.7%) with ZOL. ZOL significantly increased time-to-first fracture (hazard ratio [HR] 0.69, 95%CI 0.53–0.90; $P = 0.0053$) but the majority of fracture prevention benefit occurred after a disease-free survival event (HR 0.3; 95%CI 0.17, 0.53; $P < 0.001$) (Wilson, Bell et al. 2018).

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Therefore, although BCAC is supportive of the duration being extended beyond the current 2 years, the duration should be further extended to allow administration for the duration of AI therapy for women with early breast cancer. This gives optimal protection against bone loss and subsequent fracture.

A longer duration of therapy is also consistent with the BCSIG submission made in 2014 that requested treatment for 5 years for patients with early breast cancer based on 3 large randomised clinical trials (ABCSG-12, AZURE and ZO-FAST). This submission was mainly based on clinically significant benefits on cancer recurrence, rather than effects on bone. Your consultation implied that the proposed change (extension to 3 years therapy) was consistent with the BCSIG request, which does not seem to be the case.

Furthermore, based on the most recent results of clinical trials, denosumab should also be funded, particularly for patients with breast cancer who cannot tolerate zoledronic acid or who have high fracture risk. Waqas et al. (2021) concluded that denosumab is preferred when fracture prevention is a major concern with low breast cancer recurrence risk, while the need for sequential treatment after denosumab termination due to risk of the rebound effect should be considered in clinical decision making. Bisphosphonates are preferred when disease recurrence prevention is a major concern in high risk breast cancer women along with bone health, while denosumab failed to show a decline in breast cancer recurrence.

Given that the cost of zoledronic acid is minimal we suggest that the special authority could be removed altogether.

We look forward to your response.

Yours sincerely,

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