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Response to Consultation on the Proposal to Fund trastuzumab emtansine (T-DM1, KADCYLA) for HER-2 positive metastatic breast cancer from December 2019 (1)

This response to consultation is from Breast Cancer Aotearoa Coalition (BCAC), a coalition of more than 30 breast cancer-related groups, and an incorporated society with charitable status run by breast cancer survivors, established in 2004. BCAC's mission is to make world-class detection, treatment and care accessible to all those affected by breast cancer in Aotearoa, New Zealand; to provide information and support to empower those with breast cancer to make informed choices about their treatment and care; and to provide a voice for New Zealanders who have experienced breast cancer.

In summary

1. **BCAC supports the proposal to provide access to treatment with T-DM1.**
2. **BCAC urges earlier implementation of the proposal to fund T-DM1.**
3. **BCAC proposes an amendment to access criterion 5 so that women with LVEF 40-49% are not excluded from access to treatment with T-DM1.**
4. **BCAC proposes removal of access criterion 6 so that people with brain metastases are not excluded from treatment with T-DM1.**

Evidence and rationale for these proposals are outlined below.

1. BCAC supports the proposal to provide access to treatment

As we are all well aware, recent research has shown alarmingly poor survival for all New Zealanders with advanced breast cancer, compared to those in other countries. In New Zealand the median

survival for all breast cancer subtypes is 16 months, compared to 29.4 months in the Netherlands, 36.8 months in Germany, 25 - 54 months in the USA, 23.1 months in France, and 33 months in Sweden (2). In New Zealand, median survival for those with human epidermal growth factor receptor 2 (HER2) enriched breast cancer is only 13.3 months from metastatic diagnosis (2).

BCAC has received a strong message from members that the issue currently causing the greatest distress and hardship to breast cancer patients is the lack of access to effective medicines. Trastuzumab emtansine (T-DM1) is one of a number of treatments to which subsidised access for people with advanced breast cancer is both urgent and important.

2. BCAC urges earlier implementation of the proposal

BCAC supports the proposal for access to T-DM1 for patients with metastatic breast cancer previously treated with trastuzumab and/or a taxane, with minor changes, as proposed below. However, we would like to see implementation of this proposal as soon as possible, in view of the very urgent need for subsidised treatment, that is, before 1 December 2019. This treatment has already been under consideration for two years and denial of access to treatment for another three months is unwarranted. Providing funding for their own treatment is causing significant financial hardship to people with advanced breast cancer, and no access to treatment for those who cannot afford to pay is a matter of survival.

3. BCAC proposes an amendment to access criterion 5 so that women with LVEF 40-49% are not excluded from access to treatment with T-DM1

The phase 3 TH3RESA and EMILIA clinical trials in previously treated HER2+ metastatic breast cancer noted low rates of LVEF decrease for patients receiving T-DM1 or an alternate therapy (including trastuzumab or lapatinib plus chemotherapy or chemotherapy alone). The low rate of cardiac events was confirmed in a retrospective analysis of 250 patients receiving T-DM1 for metastatic disease in a real-world setting (3). The Medsafe datasheet for KADCYLA states that patients with left ventricular ejection fraction (LVEF) <50% have not been studied and advises that if, during therapy, LVEF falls below 40% or >10% from baseline during therapy, that treatment should be discontinued. Importantly, it does not recommend that people with LVEF <50% are excluded from treatment. As stated by Jerusalem et al. in their recent review (2019), “As cardiotoxicity due to HER2-targeted therapy is well recognized, patients at increased risk for

cardiac events are frequently excluded from trials, leaving little evidence for the treatment of patients with baseline cardiac disease, a common scenario in clinical practice. This underscores the need for studies such as the ongoing SAFEHEaRT trial in patients with mild reductions in LVEF."(4).

The SAFEHEaRt trial has recently been published, rendering the statement in the datasheet, that patients with LVEF <50% have not been studied, incorrect. The SAFEHEaRt trial was designed to prospectively evaluate cardiotoxicity of anti HER-2 therapies in patients with a baseline LVEF of 40-49% based on retrospective analyses that suggested that continuation of trastuzumab in the setting of symptomatic LV dysfunction may be safe with appropriate cardiac management (5). The objective of the SAFEHEaRt study was to evaluate the cardiac safety of HER2 targeted therapy in patients with HER2 positive breast cancer and mildly reduced LVEF with optimised cardiac therapy (6).

In this prospective trial, patients with stage I–IV HER2-positive breast cancer candidates for trastuzumab, pertuzumab or ado-trastuzumab emtansine (T-DM1), with LVEF 40–49% and no symptoms of heart failure were enrolled. All patients underwent cardiology visits, serial echocardiograms and received beta blockers and ACE inhibitors unless contraindicated. The primary endpoint was completion of the planned HER2-targeted therapies without developing either a cardiac event defined as heart failure, myocardial infarction, arrhythmia or cardiac death or significant asymptomatic worsening of LVEF. The study was considered successful if planned oncology therapy completion rate was at least 30%.

Results showed that, of 31 enrolled patients, 30 were evaluable. Fifteen patients were treated with trastuzumab, 14 with trastuzumab and pertuzumab, and two with T-DM1. Mean LVEF was 45% at baseline and 46% at the end of treatment. Twenty-seven patients (90%) completed the planned HER2-targeted therapies. Two patients experienced a cardiac event and one had an asymptomatic worsening of LVEF to ≤ 35%. It was concluded that this study provides safety data of HER2-targeted therapies in patients with breast cancer and reduced LVEF while receiving cardioprotective medications and close cardiac monitoring. It is important to note that although there were only two patients with T-DM1 in this study, reversible cardiotoxicity is considered a class effect, and lower rates of cardiotoxicity have been reported with T-DM1 versus trastuzumab. Based on this, BCAC proposes that patients with baseline LVEF 40%-50% be given access to treatment with T-DM1. This is expected to be only a handful of patients, who can be appropriately managed and who have no other effective treatment options. Patients who have severe symptomatic limitations

will be excluded from treatment via the requirement for ECOG status of 0-1, as has been proposed in the Special Authority criteria.

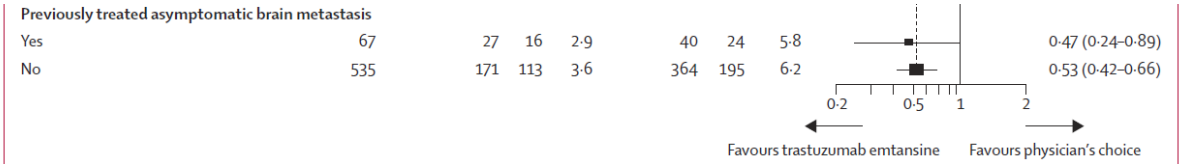
4. BCAC proposes removal of access criterion 6 so that people with brain metastases are not excluded from treatment with T-DM1

Monoclonal antibodies, such as trastuzumab and pertuzumab were traditionally thought not to cross the blood brain barrier (BBB), due to their relatively high molecular weights and the unlikely activation of antibody-dependent cell-mediated cytotoxicity process in the immuno-privileged brain microenvironment. However, preclinical evidence suggests that the integrity of BBB can be compromised in the presence of brain metastases and become increasingly permeable and this increased permeability is not always homogeneous, with a small subset of brain metastases (~10%) having sufficient permeability to show a response to common cytotoxic agents. Moreover, radiotherapy may further increase the BBB permeability. The proposal to deny access to patients with symptomatic brain metastases should be reconsidered. BCAC already raised this issue in response to CaTSoP minutes in early 2019.

Although the TH3RESA (7, 8), EMILIA (9), and KAMILLA studies excluded patients with symptomatic central nervous system (CNS) metastases, post hoc subgroup analyses showed improvement in patients with CNS metastases who were entered in these studies (8, 10, 11).
Results of the retrospective analyses of these studies are presented below. Access is all the more critical in New Zealand as lapatinib is not subsidised for this population.

- ***Analyses of TH3RESA (Progression Free Survival and Overall Survival) (7, 8)***

In the first publication of TH3RESA, subgroup analysis of the Progression Free Survival (PFS) benefit with trastuzumab emtansine was consistent across subgroups, including those defined by age, hormone receptor status, visceral involvement, number of previous regimens, and presence of asymptomatic or treated brain metastases – see figure below (7).



Final overall survival (OS) results of TH3RESA, published in 2017, also showed improved OS irrespective of the presence or absence of brain metastases (see figure from published paper below) (8).

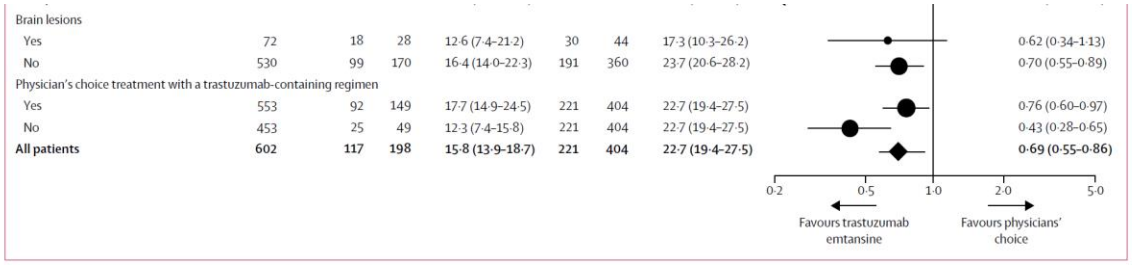


Figure 3: **Overall survival in prespecified and clinically relevant subgroups**

- ***Retrospective Analysis of EMILIA (10)***

This retrospective study characterised the incidence of CNS metastases after treatment with trastuzumab emtansine (T-DM1) versus capecitabine–lapatinib (XL), and treatment efficacy among patients with pre-existing CNS metastases in the phase III EMILIA study. In EMILIA, patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane were randomized to T-DM1 or XL until disease progression. Patients with treated, asymptomatic CNS metastases at baseline and patients developing post baseline CNS metastases were identified retrospectively by independent review; exploratory analyses were carried out. Among 991 randomized patients (T-DM1 = 495; XL = 496), 95 (T-DM1 = 45; XL = 50) had CNS metastases at baseline. CNS progression occurred in 9 of 450 (2.0%) and 3 of 446 (0.7%) patients without CNS metastases at baseline in the T-DM1 and XL arms, respectively, and in 10 of 45 (22.2%) and 8 of 50 (16.0%) patients with CNS metastases at baseline. Among patients with CNS metastases at baseline, a significant improvement in OS was observed in the T-DM1 arm compared with the XL arm [hazard ratio (HR) = 0.38; P = 0.008; median, 26.8 versus 12.9 months]. Progression-free survival by independent review was similar in the two treatment arms (HR = 1.00; P = 1.000; median, 5.9 versus 5.7 months). Multivariate analyses demonstrated similar results. Grade $\geq$3 adverse events were reported in 48.8% and 63.3% of patients with CNS metastases at baseline administered T-DM1 and XL, respectively; no new safety signals were observed. It was concluded that the rate of CNS progression in patients with HER2-positive advanced breast cancer was similar for T-DM1 and for XL, and higher overall in patients with CNS metastases at baseline compared with those without CNS metastases at baseline. In patients with treated, asymptomatic CNS metastases at baseline, T-DM1 was associated with significantly improved OS compared with XL (10).

- ***KAMILLA Observational Study (11)***

The largest cohort of patients with CNS metastases treated with T-DM1 was reported by Montemurro et al., who analysed a subgroup of 399 patients with CNS metastases at baseline from the KAMILLA trial, a phase IIIb study investigating T-DM1 in patients with HER2-positive metastatic breast cancer. Patients with untreated, asymptomatic CNS metastases or controlled CNS disease

previously treated with radiotherapy were also eligible. Of the 236 patients with disease progression in the brain, 65 (28%) continued treatment with T-DM1 post progression. The median duration of T-DM1 treatment post progression was 6.0 months. Median time to progression in the brain was 11.3 months (95% CI 8.6-13.7) (11) .

Prospective and retrospective cohort studies have also shown the benefits of T-DM1 in patients with brain metastases

- **Jacot et al.** studied breast cancer patients with brain metastases treated with T-DM1 in 5 French centres in this retrospective study. Clinical management was performed according to the product guidelines. Efficacy was evaluated recording tumour response rates, PFS and OS, treatment compliance, and safety. Thirty nine patients received T-DM1, among whom 82% presented with concomitant extra-cerebral disease. Median number of previous metastatic chemotherapy and HER2-directed targeted therapy regimens was 2 (range 0–8) and 1 (0–7), respectively. Thirty six patients had received brain metastasis loco-regional treatment (72 % whole-brain radiation therapy). After a median follow-up of 8.1 months (1.4–39.6), 24 patients had progressed (first site of progression: brain 14; meningeal 2; outside of the central nervous system 5; both intra- and extra-cerebral 3), 12 patients had died (disease progression), and 27 patients were still alive. Median number of T-DM1 cycles was 8 (1–43). There were 17 partial responses (44 %) and 6 patients achieved disease stabilisation (59 % clinical benefit rate). Median PFS was 6.1 months (95 %CI 5.2–18.3), with one- and two-year PFS rates of 33 and 17 %, respectively. Treatment was well tolerated, without unexpected toxicities, treatment delay, or dose reduction. In this retrospective study, T-DM1 appeared to be an effective and well-tolerated therapeutic option in unselected HER2+ BC patients with brain metastases (12).
- **McCabe et al.** reviewed case notes for 76 patients and identified 23 with CNS metastases, 10/23 who had actively progressing metastases. Of these 10 patients, 4 had an objective response in the CNS. Overall survival did not differ for those with and without CNS metastases. It was concluded that T-DM1 is active in CNS metastases (13).
- **Okines et al.** undertook a retrospective study of all patients treated with T-DM1 at the Royal Marsden Hospital from 2011 to 2016. Data collected included baseline characteristics, previous treatment for advanced breast cancer, sites of metastatic disease, duration of T-DM1, sites of progression, and treatment of CNS progression. Fifty-five patients were identified who had received a median of two prior lines of treatment (range 0-5). All were HER2 positive; 45 patients had IHC 3+ tumours and 10 were ISH positive.

Patients received a median of 12 cycles of T-DM1 (range 1-34), and six remained on treatment at the time of analysis. Before commencing T-DM1, 16/55 (29%) had known brain metastases (treated with whole brain radiotherapy [9], stereotactic radiotherapy [6] or both [1]). Brain was the first site of progression in 56% (9/16) patients, with a median time to brain progression of 9.9 months (95% CI 3.9-12.2). In patients without known baseline brain metastases, 17.9% (7/39) developed new symptomatic brain disease during T-DM1, after a median of 7.5 months (95% CI 3.8-9.6). Brain progression was isolated, with control of extra-cranial disease in 4/7 patients. Only one patient was suitable for stereotactic radiotherapy. Median time to extra-cranial progression in all patients was 11.5 months (95% CI 9.1-17.7), and median OS in all patients was 17.8 months (95% CI 14.2-22). In patients not screened for brain metastases at baseline, the brain was the first site of progression in a significant proportion. In this study, the development of new brain disease on T-DM1 was more common than previously reported, and survival from diagnosis with symptomatic progression was poor. It was concluded that larger, prospective studies are required to determine whether baseline brain imaging prior to commencing T-DM1 is indicated to identify asymptomatic brain disease that can be treated with stereotactic radiotherapy, or surgery. Residual disease may be treated effectively by T-DM1, potentially allowing avoidance or at least deferral of whole brain radiotherapy and its complications. (14)

- **Fabi et al.** conducted an Italian, multicentre, retrospective analysis involving 303 patients with advanced breast cancer treated with T-DM1 and analysed 87 patients with brain metastases (BM-group). The study sought to evaluate the efficacy of T-DM1 on brain metastases and to compare the BM-group with the remaining 216 patients without brain metastases (nBM-group) in order to study outcome of disease. MRI was used as assessment imaging. The number of extracranial metastatic sites in the BM-group and in the nBM-group was 1 for 10 (11.5%) and for 74 patients (34.3%), 2 for 23 (26.4%) and 93 (43%) patients, 3 for 25 (28.7% and 38 (17.6%) and 4 or more for 29 (33%) and 11 (5%), respectively. In the BM-group, 5 patients (5.7%) had received surgery alone as local treatment for brain metastases, 13 (14.9%) surgery plus stereotactic radio-surgery (SRS), 4 (4.7%) surgery plus whole-brain radiotherapy (WBRT), 23 (26.5%) SRS alone, 40 (45.9%) WBRT alone and 2 (2.3%) WBRT followed by SRS. Twenty-eight patients (32.9%) and 89 (42.4%) in the BM-group and nBM-group, respectively, received T-DM1 as second line, 24 (28.2%) and 49 (23.3%) as third line and 33 (38.8%) and 72 (34.3%) as fourth line. Mean number of cycles was 6 in both groups. Results showed that among BM-group, 53 patients

(60.9%) were evaluable for response. Two (3.8%) obtained brain complete response, 14 (26.4%) partial response and 13 (24.5%) stable disease [brain disease control rate: 54.7%); 24 (45.3%) progressed during T-DM1. Regarding extracranial metastases, overall response rate was 35.1% in the BM-group and 38.3% in the nBM-group; 6 months-clinical benefit was 50.6% and 52.3%, respectively. Median PFS was 7 months in the BM-group and 8 months in the nBM-group; when T-DM1 was given as second line, median PFS was 5 months in the BM-group and 11 months in nBM-group (p=0.01) while as third, line in which 76% of patients received lapatinib/capecitabine before TDM1, median PFS was 12 and 13 months (p=NS), respectively. It was concluded that T-DM1 showed a good activity on brain metastases in breast cancer patients. A better outcome was shown in patients previously treated with lapatinib. The identification of clinical and biological prognostic factors could be needed to better select more responder patients with brain metastases to T-DM1 (15).

- **Pizzuti et al.** retrospectively enrolled 194 HER2+ (IHC 3+ or 2+ amplified) metastatic breast cancer patients treated with T-DM1 in real-world practice in 20 Italian oncologic centres. Median follow up was 9.8 months (range, 2-37). T-DM1 treatment duration was 5 months (range, 1-30). Among 183 evaluable patients, 5.4% had a complete response and 35% a partial response, for an Overall Response Rate of 40% (95%CI, 33-47). A stable disease state was recorded in 26.8% patients, with a clinical benefit (defined as response or stable disease lasting ≥ 6 months) of 55% (95% CI, 47-62). No significant differences in responses have emerged according to disease sites. Median PFS was 6 months (95%CI, 5-7), median OS was 35 months (95% CI, 11-59). Patients who had previously carried out ≤3 lines for metastatic breast cancer had improved PFS (p = 0.006). At multivariate analysis, factors related to PFS benefit were lower ECOG performance status (p < 0.0001) and HER2+ status at first diagnosis (p = 0.03), while OS benefit was related with lower ECOG performance status (p = 0.01), absence of brain metastases (p = 0.08), other than ductal histology (p = 0.04) and clinical benefit (p < 0.0001). Central nervous system progression occurred in 10.4% of the patients without CNS metastases, and in 29.1% of the patients with CNS metastases at baseline. Patients with CNS metastases at baseline have a median PFS similar to that observed in the general population, whereas median OS was shorter (16 months, 95% CI, 12-21). Toxicity was manageable, with grade ≥3 adverse events reported in 5.6% of patients, most commonly thrombocytopenia and fatigue. Cardiac dysfunction was reported in 2 patients (1%) (16).
- **Bartsch et al**., evaluated the efficacy of T-DM1 in 10 patients with brain metastases of breast cancer and trastuzumab pre-treatment. An intracranial PFS of 5 months was

observed; 3 patients had partial remission of brain metastasis, 4 had stable disease, and 3 progressed under the treatment (17).

- **Case Reports in the Literature** report the use of T-DM1 in people with brain metastases (18-28).

Guidelines on HER2+ Patients with Brain Metastases

ASCO guidelines recommend that patients with advanced breast cancer and brain metastases should receive appropriate local therapy and systemic therapy, if indicated as shown in the recommendations below (29), published in 2018. Only patients with poor prognosis are not recommended for systemic therapy.

- For patients with poor prognosis, options include WBRT, best supportive care, and/or palliative care.
- For patients with progressive intracranial metastases despite initial radiation therapy, options include SRS, surgery, WBRT, a trial of systemic therapy, or enrollment in a clinical trial, depending on initial treatment. For patients in this group who also have diffuse recurrence, best supportive care is an additional option.
- For patients whose systemic disease is not progressive at the time of brain metastasis diagnosis, systemic therapy should not be switched.
- For patients whose systemic disease is progressive at the time of brain metastasis diagnosis, clinicians should offer HER2-targeted therapy according to the algorithms for treatment of HER2-positive metastatic breast cancer.

ESMO guidelines (30) recommendations for HER2+ patients with brain metastases are shown below

HER2-positive ABC and brain metastases		
Because patients with HER2-positive ABC and brain metastases can live for several years, consideration of long-term toxicity is important and less toxic local therapy options (e.g. stereotactic RT) should be preferred to WBRT, when available and appropriate (e.g. in the setting of a limited number of brain metastases).	I/A	89%
In patients with HER2-positive ABC who develop brain metastases with stable extracranial disease, systemic therapy should not be changed.	I/D	95%
For patients with HER2-positive ABC where brain metastases are the only site of recurrence, the addition of ChT to local therapy is not known to alter the course of the disease and is not recommended.	I/D	83%
It is recommended to re-start the anti-HER2 therapy (trastuzumab) if this had been stopped.	I/B	83%
For patients with HER2-positive ABC with progressive brain metastases as the predominant cause of disease burden, if no further relevant local therapy options are available, a change in systemic therapy is a reasonable option, preferably in clinical trials.	III/A	85%

In summary, BCAC proposes that this exclusion be deleted from the proposed Special Authority criteria for T-DM1.

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