PROPOSAL
FOR THE INCLUSION OF TRASTUZUMAB EMTANSINE (T-DM1)
IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES
FOR THE TREATMENT OF HER2-POSITIVE LOCALLY
ADVANCED OR METASTATIC BREAST CANCER

List of Contributors

Knowledge Ecology International

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1. Name of the focal point in WHO submitting or supporting the application

N/A

2. Name of the organization(s) consulted and/or supporting the application

Knowledge Ecology International (KEI)

3. International Nonproprietary Name (INN, generic name) of the medicine

Trastuzumab emtansine, ado-trastuzumab emtansine, abbreviated as T-DM1

4. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

Trastuzumab emtansine (T-DM1) is currently distributed in two vial sizes: 160mg and 100mg as a lyophilized drug to be reconstituted in sterile water for injection (SWFI) and administered as intravenous infusion.

5. International availability - sources, if possible manufacturers and trade names

T-DM1 is sold internationally under the brand name Kadcyla, a product of Genentech/F. Hoffmann-La Roche Ltd., as well as through arrangements with other companies.

There are currently no biosimilars of T-DM1 on the market. However, in November 2016, the Coalition for Affordable T-DM1 requested a compulsory licence on T-DM1 patents from the British government. The Coalition indicated that “four potential suppliers have held confidential discussions with the petitioners and have indicated an interest and willingness to supply a biosimilar product to patients in the UK” (Letter is attached).

A discussion of the challenges in obtaining a biosimilar product are further elaborated in section 12 below.

6. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Individual medicine

7. Information supporting the public health relevance
Cancer is the second leading cause of mortality worldwide, responsible for 8.2 million deaths globally with an incidence of 14.9 million in 2013. Over 60% of the global cancer cases occur in Africa, Asia, and Central and South America, and these regions generally experience a higher mortality relative to incidence rates due to higher proportions of poor prognosis cancer and the impact of clinical care. High income countries have benefited from newer generations of neoplastic inhibitors and antibody based targeted treatments, however, drug cost remains a significant burden and block to access in both developed and developing countries.

Breast cancer is the primary cancer among women and the second most common cause of cancer overall. In 2013, Breast cancer incidence reached 1.8 million, where mortality and morbidity are higher in developing countries than in developed countries [8,257.05 thousand DALY (95%CI, 7,517.37-8,998.96) for developing countries vs. 4,811.57 thousand DALY (95%CI, 3,838.96- 5,490.48) for developed countries].

Over the past three decades, our understanding of the molecular mechanisms and phenotypic expression profiles of cancer has allowed scientist to develop highly targeted and effective systemic treatments. Breast cancer is a heterogeneous disease whose response can differ based on individual genotype. Up to 25 % of breast cancer are HER2- positives and with at least 450,000 (1.8X10^6 * 0.25) women worldwide newly diagnosed with HER2-positive breast cancer in 2013.

8. HER2 receptor as a target for breast cancer therapy

The human epidermal growth factor receptor 2 (HER2) is a 185 kDa transmembrane tyrosine kinase receptor encoded by the ERBB2 breast cancer oncogene. Its overexpression leads to constitutive activation MAPK and AKT signaling pathways that results in elevated metabolic function, increased proliferation and enhanced invasiveness of the tumor cells. The natural history and prognosis of breast cancer cells expressing high levels of HER2 is associated with more aggressive tumors and poor sensitivity to standard chemotherapeutic agents. Since HER2 status is predictive of outcomes and treatment response, routine HER2 testing is important and included on many guidelines such as that of the American Society of Clinical Oncology (ASCO), the College of American Pathologists (CAP), the National Comprehensive Cancer Network (NCCN), and the UK NICE guidelines. The ASCO recommends that HER2 testing of breast cancer specimens should be conducted using a validated immunohistochemical (IHC) assays. Inconclusive IHC results should undergo confirmatory testing using a Fluorescent In-situ Hybridization (FISH). As newer

QRT-PCR HER2 assays are being validated with improvements in IHC/ FISH concordance rates we can look forward to more affordable and automated alternatives for HER2 test in the near future.8

Currently, trastuzumab containing therapies are considered the preferred first line treatment for HER2-positive metastatic breast cancers and a standard part of earlier stage adjuvant therapy. However, most metastatic breast cancer patients will progress under such therapy and require newer HER2 directed therapies that are well tolerated in treatment experienced patients.9 Unfortunately the mechanism behind primary and acquired resistance to trastuzumab still remain elusive but most patient will develop resistance within one to two years.10,11,12

9. Trastuzumab emtansine

T-DM1 is biologic drug used to treat HER2-positive breast cancer. In 2013, the FDA approved its use based on the pivotal EMILIA clinical trial. The EMA also approved T-DM1 in 2013. T-DM1 is an innovative systemic treatment that combines the targeting properties of antibodies to deliver a highly potent anticancer agent directly to the neoplasm, thus minimising the damage to nearby healthy cells.

T-DM1 is an antibody-drug conjugate (ADC) consisting of the monoclonal antibody trastuzumab covalently bonded via a synthetic linker, succinimidy trans-4-(maleimidylmethyl) cyclohexane-1-carboxylate (SMCC), to a cytotoxic agent, a maytansine derivative (DM1).13 On average, each antibody moiety bind to 3.5 DM1. The trastuzumab part is a humanized anti-HER2 antibody that seeks out cells that overexpress the HER2 receptors. In addition to delivering the cytotoxic DM1 payload to target cells, trastuzumab itself also exhibits anti-tumor activity by inhibiting angiogenesis and recruiting NK cells through antibody-dependent cell mediated cytotoxicity (ADCC).14 Additionally, upon binding to the receptor, the antibody moiety induces an antiproliferative effect by down-modulating HER2 growth signaling pathways.15

The non-reducible crosslinker SMCC is bound to trastuzumab lysine residues via an amide bond and to DM1 through a thioether bond. Importantly, the chemical properties of SMCC keeps the ADC stable in the extracellular environment and once in the cells it prevents the

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cytotoxic part from being released back into extracellular space that would cause damage to healthy cells. Once T-DM1 selectively binds to the HER2 receptor, it is internalized via endocytosis and undergoes lysosomal proteolytic degradation, slowly releasing linker bound DM1 into the cell. DM1 is a highly toxic antimitotic agent that disrupts microtubule assembly. However once released, because thiols are resistant to reduction in the lysozyme, the linker, still covalently bonded to DM1, prevents it from crossing the plasma membrane thus, keeping levels in blood plasma initially low.

DM1 was shown to be metabolized through CYP34A4 and its clearance rate is link to the chemical properties of its chemical linker. As such, thioether-linked DM1 are slower to clear than those in conjugates linked through to regular disulfide bonds. Pharmacokinetic studies showed that T-DM1 clearance rates, when taken at the 3.6mg/kg every 21 days, range between 6 to 13 ml/ day/kg with a half-life of 3 to 4.5 days and no observable accumulation after multiple doses.

10. Treatment details

T-DM1 is typically used in a second line setting, for locally advanced or metastatic breast cancer, although, it could be an alternative first-line treatment in patients who cannot receive trastuzumab plus pertuzumab plus taxane. Based on the EMILIA trial, T-DM1 should also be given to patients who relapse within 6 month of completing adjuvant trastuzumab based therapy.

For an adult population: T-DM1 can be given intravenously at 3.6 mg/kg every 3 weeks until disease progression or unacceptable toxicity. Infusion protocol requires the monitoring of infusion-related reaction and further precautions and warning related to this can be found in the FDA label (section 5.5).

Adverse drug reactions should be closely monitored and dose reduction or treatment interruption/cessation may be required as indicated in regulatory guidelines (ie: FDA label, section 2.2).

**Table 10-1: Recommended Dose Reduction Schedule for Adverse Events** (adapted from FDA label)

<table>
<thead>
<tr>
<th>Dose Reduction Schedule</th>
<th>Dose Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>3.6 mg/kg</td>
</tr>
</tbody>
</table>

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17 D Lu, S Modi, AD Elias, P Agarwal, J-H Yi, AE Guardino, BL Althaus and S Girish. Pharmacokinetics (PK) of Trastuzumab Emtansine and Paclitaxel or Docetaxel in Patients with HER2−Positive MBC Previously Treated with a Trastuzumab-Containing Regimen. 34th Annual CTRC-AACR San Antonio Breast Cancer Symposium- Dec 6-10, 2011; abstract

5 of 17
Hepatotoxicity and Thrombocytopenia were the most commonly reported grade 3 and 4 adverse events associated with T-DM1 in clinical trials. Platelet counts, serum transaminases and bilirubin levels should be measured before each administration of T-DM1.

The EMILIA trial reported 1.8% of T-DM1 treated patients developed left ventricular dysfunction, therefore left ventricular ejection fraction (LVEF) should be monitored prior to treatment and every 3 months.

Other notable adverse events include pulmonary toxicity, hemorrhaging and neurotoxicity and should be monitored accordingly.

T-DM1 is contraindicated for pregnant women based on trastuzumab related embryo-fetal toxicity.

11. Summary of comparative effectiveness in a variety of clinical settings:

11.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

We searched systematic reviews, technology assessment reports, and meta-analyses of controlled clinical trials involving T-DM1 in at least one arm were searched on the Database of Abstracts of Reviews of Effectiveness. Additional searches for relevant reviews were undertaken in Clinical Evidence (CE), PubMed, and the Cochrane Database of Systematic Reviews. T-DM1 is still a relatively new medical technology and there is a paucity of meta-analysis or systematic reviews. In fact, only 2 published meta-analysis for T-DM1 treatment in breast cancer were found. Upon future assessment, we chose to focus on the analysis from Kai Shen et al., since inconsistencies were found in the review from Bo Ma et al. We supplemented the summary with the recent December 2015 technology appraisal from NICE since meta-analysis used in the assessment was published. Two notable clinical trials (EMILIA, TH3RESA) examining TDM-1 in the treatment experienced advanced stage breast cancer population were central to the various reviews due to their completion and statistical power. Therefore, we deemed it important to also summarized them below. We also provide a brief overview of pertinent ongoing clinical trials relating to T-DM1 in the context of advanced and earlier stages of breast cancer.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose reduction</td>
<td>3 mg/kg</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>2.4 mg/kg</td>
</tr>
<tr>
<td>Requirement for further dose reduction</td>
<td>Discontinue treatment</td>
</tr>
</tbody>
</table>

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11.2 Summary of available data

11.2.1 Locally Advanced and Metastatic Breast cancer.

The EMILIA clinical trial (NCT00829166) was the first phase III randomized clinical trial (RTC) to show efficacy and was the basis for FDA approval in February 2013 as a second-line treatment. The pivotal EMILIA study was a phase III, international open-label, randomised clinical trial comparing T-DM1 (3.6mg/kg every 3 weeks) with lapatinib (1250 mg daily) plus capecitabine [2000mg/m^2] (LC) in women who had unresectable, locally advanced or metastatic HER2-positive breast cancer and who were previously treated with trastuzumab and a taxane (ie: paclitaxel, docetaxel). Between February 2009 and December 2001, 991 patients were randomised 1:1 into treatment and control arms that went on for 32 months with median follow up of 19 months. Patients with grade≥ 3 peripheral neuropathy and untreated CNS metastases were excluded from the study. Two coprimary outcome measures were progression free survival (PFS) and overall survival (OS) and significant improvement in PFS and OS favored T-DM1 with less toxicity. T-DM1 patients experience an increase in median OS 30.9 months compared to 25.1 months of LC treated patients [HR 0.68, 95%CI 0.55-0.85, p<0.001]. PFS was assessed by an independent review and found to be significantly improved for T-DM1 at 9.6 months compared to 6.4 months for LC [HR 0.65, 95%CI 0.55-0.77, p<0.001]. Safety was also better for T-DM1 with decreased rates of serious adverse events [41% for T-DM1, 57% for CL]. Safety and tolerability were better for T-DM1 vs. CI since Grade 3 and 4 adverse event rates were 41% for T-DM1 and 57% for CL. The most common grade≥ 3 adverse reaction for T-DM1 was thrombocytopenia at 12.9 vs 0.2% and elevated transaminase at 7.2% vs 2.2%. Patient reported outcomes (PRO) that evaluate the subjective impact of the treatment on patient quality of life was shown to be superior for T-DM1. PRO was measured with Trial Outcome Index Physical/Functional/Breast (TOI-PFB) subset of the Functional Assessment of Cancer Therapy–Breast (FACT-B) questionnaire and showed a statistically significant delay in predefined symptom worsening secondary endpoints for T-DM1 compared to LC [7.1 months versus 4.6 months; HR 0.796, 95% CI 0.667-0.951; p=0.0121].

The second important phase III RTC, TH3RESA (NCT01419197), aimed to study T-DM1 in more heavily pretreated metastatic breast cancer patients with previous exposure to lapatinib. In this randomized, open-label, phase III clinical trial, TDM-1 (3.6 mg/Kg IV, every 21 days) was compared to a treatment of physician’s choice (TPC) in patients with advanced or metastatic breast cancer who had progressed after two or more HER2-directed regimens. In the TPC arm, 85% of patients were given trastuzumab plus another agent, 3% Lapatinib plus chemotherapy and 17% were treated with a single-agent chemotherapy. Randomization of 602 patients occurred in a 2:1 ratio for T-DM1 and 44 patients who had progressed on TPC crossed over to the T-DM1 arm, only once EMILIA data was reported. Coprimary

Endpoints included PFS and OS. The PFS was significantly greater with TDM-1 at 6.2 months vs. 3.3 months for the control arm [HR 0.528, 95%CI 0.422-0.661, p<0.0001]. At the time of the initial 2014 report, OS was still immature. However, final OS was presented at the December 2015 San Antonio Breast Cancer Symposium and showed a significant increase in survival with T-DM1 at 22.7 months vs. 15.8 months for TPC [HR 0.68, p=0.0007].

Overall serious adverse events of grade 3 or higher were 11% more common in TPC compared to T-DM1. Grade 3 or higher adverse events more often seen in the TPC were diarrhea (4.3% vs. 0.7%), neutropenia (15.8% vs. 2.5%), and febrile neutropenia (3.8% vs. 0.2%). Grade 3 or worse thrombocytopenia (6.0% vs. 2.7%) was seen in the T-DM1 arm.

In a 2016 meta-analysis conducted by Shen et al., the authors searched PubMed for studies reporting on clinical trials with T-DM1 published until June 2015. The nine eligible studies (summarized in table 11-1) that were evaluated using Comprehensive Meta-Analysis (CMA) program 2 and Review manager 5.2, included three phase I clinical trials, four phase II clinical trials and two phase III clinical trials. The nine trials included 2050 total patients with advanced or metastatic breast cancer in either controlled or single-arm clinical trials. Single arm trials were pooled to determine adverse event rate whereas controlled trials were used to calculate adverse events odds ratio. Similarly, odds ratio for PFS and OS were calculated using three (EMILIA, TH3RESA, BO21976) and two (EMILIA, TH3RESA,) controlled trials respectively.

Table 11-1: Studies analyzed in Shen et al meta-analysis

<table>
<thead>
<tr>
<th>Name/ Sponsor/ NCT#</th>
<th>Description</th>
<th>Phase</th>
<th>Treatment</th>
<th>Control</th>
<th># of patients</th>
<th>year, 1st author</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRO132365, NCT00932373</td>
<td>1st in human, dose escalation, MBC</td>
<td>I</td>
<td>T-DM1 single -arm</td>
<td>24</td>
<td>2010, Krop</td>
<td></td>
</tr>
<tr>
<td>TDM3569g, NCT00932373.</td>
<td>Dose escalation, MBC</td>
<td>I</td>
<td>T-DM1 single -arm</td>
<td>28</td>
<td>2012, Beeram</td>
<td></td>
</tr>
<tr>
<td>Chugai Pharmaceutical, Roche</td>
<td>Determine MTD in japanese patients</td>
<td>I</td>
<td>T-DM1 single -arm</td>
<td>10</td>
<td>2015, Yamamoto</td>
<td></td>
</tr>
<tr>
<td>TDM4258g, NCT00509769</td>
<td>Safety/efficacy</td>
<td>II</td>
<td>T-DM1 single -arm</td>
<td>112</td>
<td>2011, Burris</td>
<td></td>
</tr>
<tr>
<td>TDM4374g, NCT00679211</td>
<td>ORR</td>
<td>II</td>
<td>T-DM1 single -arm</td>
<td>110</td>
<td>2012, Krop</td>
<td></td>
</tr>
<tr>
<td>BO21976, TDM4450g, NCT00679341</td>
<td>1st line MBC</td>
<td>II</td>
<td>T-DM1 Trastuzumab+ docetaxel</td>
<td>137 (67, 70)</td>
<td>2013, Hurvitz</td>
<td></td>
</tr>
<tr>
<td>NCT00875979</td>
<td>Previous Herceptin, A/MBC, Combo w P</td>
<td>Ib/Ila</td>
<td>T-DM1+Per single -arm</td>
<td>64</td>
<td>2014, Miller</td>
<td></td>
</tr>
<tr>
<td>EMILIA</td>
<td>2nd line HER2+ unresectable/ MBC</td>
<td>III</td>
<td>T-DM1 Lapatinib+ capecitabine</td>
<td>991 (495, 496)</td>
<td>2012, Verma</td>
<td></td>
</tr>
</tbody>
</table>

T-DM1 was found to be more effective than therapies given in control arms. The median PFS in metastatic or advanced breast cancer in controlled trials significantly favored T-DM1 ranging from a difference in 2.9 months to 5 months with a total odds ratio of 0.60 [95% CI 0.53, 0.69] and heterogeneity coefficient $I^2$ as 6% (figure 11-1).

**Figure 11-1: Forest plot for progression free survival in controlled trials** (from Kai Shen et al.)

Only the EMILIA and TH3RESA clinical trial reported OS and showed an improved survival for T-DM1 taking patients over CL and TPC prescribed patients [OR 0.60, 95% CI 0.48, 0.75] with a heterogeneity $I^2$ of 0% (figure 11- 2). However, the published OS TH3RESA data used only included the first interim analysis where stopping boundary was not crossed.

**Figure 11-2: Forest plot for overall survival in EMILIA and TH3RESA** (from Kai Shen et al.)

Pooled analysis of all trial evaluated revealed that the most common adverse events were anemia, fatigue, increased transaminases, nausea, thrombocytopenia, arthralgia and headache, although severe events (grade ≥ 3) were relatively rare. In controlled studies only, the highest odds ratio (OR) associated with T-DM1 was for thrombocytopenia at 8.5 OR [95% CI 3.964, 18.224] for all grades and 7.271 OR [95% CI 1.098, 48.113] for grade 3 or greater. Other significant AE were all grade fatigue at 1.288 OR [95%CI 1.041, 1.593] and all grade increased transaminases at 4.040 [95%CI 1.429, 11.427] but heterogeneity for $I^2$ was 87.995%.
The National Institute for Health and Care Excellence (NICE) is a non-departmental public body that published guidance documents for the English and Welsh National health Services (NHS). In December 2015, NICE published its technology appraisal for T-DM1 to assess efficacy and cost-effectiveness. As part of the review process, the Institute reviewed evidence submitted by Roche, clinical experts, and other stakeholders. The University of Sheffield School of Health and Related Research Technology Appraisal group acted as the independent Evidence Review Group (ERG) to critically reviews the submission presented by the manufacturer. Clinical evidence came primarily from EMILIA and TH3RESA clinical trials. Because head-to-head treatment comparisons was only available for CL, the company conducted a Bayesian network meta-analysis using a fixed-effect model involving 5 clinical trials (EMILIA, CEREBEL, EGF100151, NCT00777101 and GBG26, table X). The ERG assessed it would be unlikely for there to be no heterogeneity between trials and repeated the meta-analysis using a random effect model. They found that, compared to CL, T-DM1 was associated with a 32% decrease in hazard of death [HR 0.68, 95% Credible Interval (CrI) 0.37-1.25] and a 35% reduction to the hazard of tumor progression or death [HR 0.65, 95%CrI 0.35-1.20]. However, the authors report that the CrI “do not rule out the possibility that T-DM1 is less efficacious than comparators”.27

More robust data came from the two clinical trials as the ERG concluded that there was a low risk of bias, and reported there to be a “statistically significant advantage” in PFS and OS for T-DM1 over CL.26 After the review process, NICE had indeed concluded that T-DM1 was a clinically effective for treatment for HER2+ unresectable, locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane, but it ultimately did not find it to be cost effective based on the current price that Roche was offering at the time.28

11.2.2 Upcoming clinical trials:

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28 Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane. NICE. Dec 2015. www.nice.org.uk/guidance/ta371?unlid=63448512320161011194953
Below is a summary of notable clinical trials studying T-DM1 in early and advanced settings (from Recondo et al.).

### Table 11-3: Ongoing T-DM1 clinical trials as of December 2016 (from Recondo et al.)

<table>
<thead>
<tr>
<th>Study name/sponsor</th>
<th>Phase</th>
<th>ClinicalTrials.gov identifier</th>
<th>Study description</th>
<th>Comparison</th>
<th>No of patients</th>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>KATHERINE II</td>
<td>NCT01772472</td>
<td>Adjuvant in patients with residual disease following neoadjuvant therapy for HER2+ BC</td>
<td>H q 3 wks × 14 T-DM1 q 3 wks × 14</td>
<td>1,484</td>
<td>IDFS</td>
<td></td>
</tr>
<tr>
<td>KAITLYN III</td>
<td>NCT01966471</td>
<td>Adjuvant in patients with resected HER2+ BC following anthracycline-based chemotherapy</td>
<td>AC/EC→T-DM1 + P × 1 yr AC/EC→H + T + P × 1 yr</td>
<td>2,500</td>
<td>IDFS</td>
<td></td>
</tr>
<tr>
<td>KRISTINE III</td>
<td>NCT0211306</td>
<td>Neoadjuvant in patients with HER2+ BC followed by surgery and adjuvant treatment</td>
<td>T + Cb + P + H→Surgery→P + H T-DM1 + P→Surgery→T-DM1 + P</td>
<td>444</td>
<td>PCR</td>
<td></td>
</tr>
<tr>
<td>moOTHER IV</td>
<td>NCT00833963</td>
<td>Observational study; Pregnant women treated with T-DM1 + P</td>
<td>Observational T-DM1 + P</td>
<td>N/A</td>
<td>Pregnancy outcomes/ complications PCR</td>
<td></td>
</tr>
<tr>
<td>PREDIX-HER2 II</td>
<td>NCT02568329</td>
<td>Neoadjuvant therapy with switch option after two cycles if no response achieved</td>
<td>scH + P + T→Surgery→EC + H T-DM1→Surgery→EC + H</td>
<td>200</td>
<td>PCR</td>
<td></td>
</tr>
<tr>
<td>TEAL II</td>
<td>NCT02073487</td>
<td>Neoadjuvant study</td>
<td>T-DM1 + P→Ab H + P→Ab</td>
<td>30</td>
<td>PCR</td>
<td></td>
</tr>
</tbody>
</table>

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11.2.3 Comparison with trastuzumab (Herceptin)

Trastuzumab is a monoclonal antibody that targets HER2 receptors expressed on breast cancer cells. Upon binding to the HER2 receptor, trastuzumab disrupts the cell signaling and activates the antibody-dependent cell-mediated cytotoxicity (ADCC). This biologic drug is indicated for treatment against HER2 positive in breast cancer, metastatic gastric or gastroesophageal junction adenocarcinoma. The Moja et al. systematic review analysed 8 studies totaling 11,991 patients. It reported that "a combined HRs for overall survival (OS) and disease-free survival (DFS) significantly favoured the trastuzumab-containing regimens (HR 0.66; 95% CI 0.57 - 0.77, P < 0.00001 and HR 0.60; 95% CI 0.50 - 0.71, P < 0.00001,

<table>
<thead>
<tr>
<th>Study name/ sponsor</th>
<th>Phase</th>
<th>ClinicalTrials.gov identifier</th>
<th>Study description</th>
<th>Comparison</th>
<th>No of patients</th>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAPAB FU-10</td>
<td>III</td>
<td>NCT02236000</td>
<td>Dose-escalation trial of neratinib in combination with T-DM1 in MBC</td>
<td>N + T-DM1</td>
<td>63</td>
<td>Safety/orr</td>
</tr>
<tr>
<td>ATEMPT</td>
<td>II</td>
<td>NCT01353748</td>
<td>Combination of T-DM1, lapatinib, and nab-paclitaxel in HER2+ MBC</td>
<td>T-DM1</td>
<td>500</td>
<td>DFS</td>
</tr>
<tr>
<td>STELLA</td>
<td>II</td>
<td>NCT02013916</td>
<td>Neoadjuvant combination trial HER2+ ESC</td>
<td>T-DM1 + Ab + L</td>
<td>45</td>
<td>MTD</td>
</tr>
<tr>
<td>Dana-Farber</td>
<td>II</td>
<td>NCT02336794</td>
<td>Combination of T-DM1 with NPICA inhibitor in MBC</td>
<td>T-DM1 + P</td>
<td>160</td>
<td>PCR</td>
</tr>
<tr>
<td>Northwestern</td>
<td>I</td>
<td>NCT02008010</td>
<td>Adjuvant study in patients aged &gt;65 years</td>
<td>T-DM1 + BYL719</td>
<td>20</td>
<td>MTD</td>
</tr>
<tr>
<td>University of</td>
<td>II</td>
<td>NCT02414646</td>
<td>Thrombosis study of T-DM1, unresetable breast cancer or MBC</td>
<td>T-DM1</td>
<td>300</td>
<td>IDFS</td>
</tr>
<tr>
<td>Washington</td>
<td>I</td>
<td>NCT01816035</td>
<td>Combination of T-DM1 with anti-PD1 checkpoint inhibitor pembrolizumab in HER2+ MBC</td>
<td>T-DM1</td>
<td>20</td>
<td>Platelet function</td>
</tr>
<tr>
<td>PembroMab</td>
<td>I/II</td>
<td>NCT02319001</td>
<td>Combination study of cetuximab and T-DM1 for HER2+ MBC and gastric cancer</td>
<td>T-DM1 + pembrolizumab</td>
<td>90</td>
<td>Recommended Phase II doses</td>
</tr>
<tr>
<td>Hoffmann-La Roche</td>
<td>II</td>
<td>NCT01702558</td>
<td>T-DM1 in patients with HER2- amplified CTCs in peripheral blood of HER2 + MBC</td>
<td>T-DM1 + cetuximab</td>
<td>335</td>
<td>MTD/ora</td>
</tr>
<tr>
<td>Institut Curie</td>
<td>II</td>
<td>NCT01975142</td>
<td>Combination of HER2 TKI in combination with T-DM1 in HER2+ MBC</td>
<td>T-DM1</td>
<td>400</td>
<td>Tumor response</td>
</tr>
<tr>
<td>Onclotherape</td>
<td>II</td>
<td>NCT01983561</td>
<td>Neoadjuvant T-DM1 or trastuzumab plus endocrine therapy in operable HER2HR+ for 12 wks</td>
<td>T-DM1 + ONT380</td>
<td>57</td>
<td>Safety</td>
</tr>
<tr>
<td>ADAPT</td>
<td>II</td>
<td>NCT01745965</td>
<td>First-line treatment with trastuzumab and pertuzumab randomized with or without chemotherapy and T-DM1 in the second line</td>
<td>H+ endocrine therapy</td>
<td>300</td>
<td>PCR</td>
</tr>
<tr>
<td>Swis Group for</td>
<td>II</td>
<td>NCT0183526</td>
<td>T-DM1 in combination with nonpegylated liposomal doxorubicin in MBC</td>
<td>H+H+ chemotherapy + T-DM1</td>
<td>200</td>
<td>OS</td>
</tr>
<tr>
<td>MedIRC</td>
<td>I</td>
<td>NCT02562378</td>
<td>Combination study of T-DM1 with cyclin-dependent kinase 4/6 inhibitor in advanced HER2+ BC</td>
<td>T-DM1 + nonpegylated liposomal doxorubicin</td>
<td>24</td>
<td>Dose-limiting toxicities</td>
</tr>
<tr>
<td>University of Texas</td>
<td>I</td>
<td>NCT01976169</td>
<td>T-DM1 + DO-333991</td>
<td>T-DM1 + PO-333991</td>
<td>17</td>
<td>MTD</td>
</tr>
</tbody>
</table>

Abbreviations: A, adrenocortic; Ab, ab-paclitaxel; BC, breast cancer; C, cyclophosphamide; Os, carboplatin; CTCs, circulating tumor cells; DFS, disease-free survival; E, epirubicin; ER, early breast cancer; P, S-FLI, PL, trastuzumab; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease-free survival; L, lapatinib; MBC, metastatic breast cancer; MTD, maximum tolerable dose; N, neoadjuv; ORR, overall response rate; OS, overall survival; P, pertuzumab; Ps, paclitaxel; PCR, pathological complete response; wh, weeks; yr, year.

(table 11-3 continued)
respectively). Currently Trastuzumab in combination with a taxane, is considered standard of care against metastatic breast cancer. Furthermore, trastuzumab or pertuzumab can be given as neoadjuvant and adjuvant therapy. Unfortunately, "most patients with metastatic breast cancer will develop progressive disease". This fact alone highlights the importance of the availability of 2nd line treatment such as T-DMI. Furthermore, trastuzumab based therapies carried with it an 4-6 fold increased risk of incidences of cardiomyopathy. The Phase 3 clinical trial MARIANNE, studied untreated HER2+ MBC patients receiving either T-DM1 plus pertuzumab, T-DM1 plus placebo and the combination of trastuzumab plus a taxane (paclitaxel or docetaxel). T-DM1 containing therapies were found to have noninferior PFS to trastuzumab and taxane treatments. Importantly, T-DM1 was better tolerated contributing to a better quality of life secondary endpoints and less adverse events related treatment discontinuation thus presenting a viable treatment option in first line settings.

12. Summary of available data on comparative cost** and cost-effectiveness within the pharmacological class or therapeutic group

At present, there is no biosimilar version of T-DM1, and the current prices from Roche are high and not affordable in many settings. In the UK, T-DM1 is considered medically effective, but not cost effective, for example.

For the WHO to consider a recommendation on T-DM1, it is important to consider the possibility of biosimilar products, of which there are none at present.

T-DM1 can be thought of as a combination of trastuzumab, DM1, and the SMCC linker. There are currently competitive suppliers for each of the two APIs and the SMCC linker, enhancing the prospects of a biosimilar supply.

trastuzumab

Roche’s Herceptin (trastuzumab), was approved by the US Food and Drug Administration (FDA) in September 1998 and by the European Medicines Agency (EMA) in August 2000.

Currently there are 3 biosimilar versions of trastuzumab that are commercially available in India and Iran for the treatment of breast cancer, plus a fourth in Russia. There are at least 4 biosimilars in Phase-III trials. The first biosimilar was developed by Biocon and Mylan, and received market authorization in India in 2013. In January 2015, BIOCAD announced the first trastuzumab biosimilar approved by the Ministry of Health of the Russian Federation. Iran also approved its own version of the monoclonal antibody in January 2016, and announced its readiness to export the drug to other countries in the Middle-East and Central Asia when trade sanctions were lifted.

Table 12-1 Biosimilars and non-originator biologicals* of trastuzumab approved or in development.

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<table>
<thead>
<tr>
<th>Company name, Country</th>
<th>Product name</th>
<th>Stage of development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergan/Amgen/Actavis/Synthone USA/The Netherlands</td>
<td>ABP-980</td>
<td>Phase III trial expected to be completed in December 2016 [2], “positive top line reports” were released in July [3]</td>
</tr>
<tr>
<td>Biocad, Russia*</td>
<td>BCD-022</td>
<td>Phase III trial completed in November 2014.[4] Non-originator biologic approved in Russia in January 2016 [5], being exported to developing country markets</td>
</tr>
<tr>
<td>Biocon/Mylan, India*</td>
<td>CanMab</td>
<td>‘Similar biologic’ launched in India in October 2013 [6]</td>
</tr>
<tr>
<td></td>
<td>Hercules (Myl-1401O)</td>
<td>Phase III trial in metastatic breast cancer expected to be completed in December 2018 [7]. Positive data reported June 2016 [8]</td>
</tr>
<tr>
<td>BioXpress Therapeutics, Switzerland</td>
<td>BX2318</td>
<td>Biosimilar early in pipeline</td>
</tr>
<tr>
<td>Hanwha Chemical, South Korea</td>
<td>HD201</td>
<td>Phase I study in Europe as of 2013.</td>
</tr>
<tr>
<td>Oncobiologics/Viropro, USA</td>
<td>ONS 10-50</td>
<td>Pre-phase 1. Companies are collaborating on six biosimilars [13]</td>
</tr>
<tr>
<td>Pfizer/Hospira, USA</td>
<td>PF-05280014</td>
<td>Phase I study completed [14]. Phase III study ongoing, expected to be completed March 2018 [15]</td>
</tr>
<tr>
<td>PlantForm, Canada</td>
<td>-</td>
<td>Pre-phase one. Clinical trials in humans expected to begin in 2014. Launch, in partnership with a pharmaceutical company, in world markets expected in 2016 [16]</td>
</tr>
<tr>
<td>Stada Arzneimittel/Gedeon Richter, Germany/Hungary</td>
<td>-</td>
<td>Collaborating on biosimilars of trastuzumab and infliximab since 2011 [17]. Bought DM Bio from S Korea 2016, who is leading preclinical research</td>
</tr>
</tbody>
</table>
DM1 was first manufactured in the 1970s, and the API is available from a number of manufacturers. A recent survey of price quotes from DM1 suppliers indicated prices of $1600 to $2000 per gram. In the current market, most purchases are for experimental use,
and prices would fall dramatically for use in larger quantities for commercial sales of a drug. However, even at these high prices, the amount of DM1 API used in treatment is quite small, making the costs very manageable. At $2000 per gram, the amount of DM1 required for a 100 mg vial of T-DM1 would cost just $0.84. For a patient requiring two vials, every three weeks, that would work out to about $0.08 per day.

**SMCC Linker**

The required SMCC linker is also available from a variety of suppliers. Even at the high prices associated with use in experiments, the cost per 100 mg vial of T-DM1 would be about $1.

**Intellectual Property, Regulatory and Financial Barriers**

In order to make T-DM1 cost effective, intellectual property right barriers may have to be overcome, certainly for the patents, and for the test data in some countries.

We are attaching a November 25, 2016 request for a compulsory license for patents and other intellectual property associated with T-DM1 in the United Kingdom. The attached letter to Jeremy Hunt MP, the current Secretary of State for Health, addresses a number of legal mechanisms to overcome the intellectual property barriers. We are also attaching a copy of this article:


Governments could speed up the process of manufacturing a biosimilar by requiring disclosures of know-how, and in some cases, certain materials. One model for such policies, in a somewhat different context, is the CREATES Act, proposed in the United States (S.3056, 114th Congress).

Biosimilar products require clinical trials. KEI proposes that entities that reimburse T-DM1 finance those trials, in exchange for low cost supplies of T-DM1, when regulators approve the biosimilar drugs.

There are challenges in obtaining affordable biosimilar drugs, including but not limited to T-DM1. Health advocates must find ways to meet these challenges, in order to protect the rights of the patients that need these drugs. In the case of T-DM1, there is an opportunity to expand access to a relatively new and important cancer fighting technology — antibody-drug conjugates (ADC).

13. Summary of regulatory status of the medicine

T-DM1 is approved for use in various jurisdictions as follows:

**EU (EMA)**

T-DM1 is licensed in the EU for the treatment of:

Advanced and Metastatic Breast Cancer
“adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:
• Received prior therapy for locally advanced or metastatic disease, or
• Developed disease recurrence during or within six months of completing adjuvant therapy”

**US (FDA)**
T-DM1 is licensed in the USA for the treatment of:
"single agent for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within six months of completing adjuvant therapy."

**Australia (TGA)**
"Kadcyla, as a single agent, is indicated for the treatment of patients with HER2 positive metastatic (Stage IV) breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:
Received prior therapy for metastatic disease or, Developed disease recurrence during or within six months of completing adjuvant therapy."

**Japan (PMDA)**
HER2-positive inoperable or recurrent breast cancer