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

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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.[1] 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.[2] 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.[2] 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].[1]

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.[3]

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.[4] 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.[5] 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.[6] 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.[7] 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

[1] Global Burden of Disease Cancer Collaboration et al. The Global Burden of Cancer 2013. JAMA Oncol. 2015 Jul;1(4):505-27.
[2] Stewart BW, Wild CP. World Cancer Report 2014. International Agency for Research on Cancer, WHO
[3] Joensuu H. Escalating and de-escalating treatment in HER2-positive early breast cancer. Cancer Treat Rev. 2016 Nov 10;52:1-11.
[4] King CR, Kraus MH, Aaronson SA. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. Science. 1985 Sep 6;229(4717):974-6.
[5] Schettini F, Buono G, Cardalesi C, Desideri I, De Placido S, Del Mastro L. Hormone Receptor/Human Epidermal Growth Factor Receptor 2-positive breast cancer: Where we are now and where we are going.Cancer Treat Rev. 2016 May;46:20-6.
[6] Martin M, López-Tarruella S. Emerging Therapeutic Options for HER2-Positive Breast Cancer. Am Soc Clin Oncol Educ Book. 2016;35
[7] Hideko Yamauchi, Daniel F Hayes. HER2 and predicting response to therapy in breast cancer. UpToDate. (Accessed on November 2016).

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 prefered 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, succinimidyl trans- 4-(maleimidylmethyl) cyclohexane-1-carboxylate (SMCC), to a cytotoxic agent, a maytansine derivative (DM1).[13] On average, each antibody moity 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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[8] Perez EA, Cortés J, Gonzalez-Angulo AM, Bartlett JM. HER2 testing: current status and future directions. Cancer Treat Rev. 2014 Mar;40(2):276-84.

[9] Mahtani RL, Vogel CL. When Can a Salvage Therapy (T-DM1) Take the Lead? J Clin Oncol. 2016 Jul 18.

[10] Luque-Cabal M, García-Teijido P, Fernández-Pérez Y, Sánchez-Lorenzo L, Palacio-Vázquez I.Mechanisms Behind the Resistance to Trastuzumab in HER2-Amplified Breast Cancer and Strategies to Overcome It. Clin Med Insights Oncol. 2016 Mar 28;10

[11] Nahta R, Esteva FJ.Trastuzumab: triumphs and tribulations.Oncogene. 2007 May 28;26(25):3637-43.

[12] Burnett JP, Korkaya H, Ouzounova MD, Jiang H, Conley SJ, Newman BW, Sun L, Connarn JN, Chen CS, Zhang N, Wicha MS, Sun D. Trastuzumab resistance induces EMT to transform HER2(+) PTEN(-) to a triple negative breast cancer that requires unique treatment options.Sci Rep. 2015 Nov 2;5:15821.

[13] Martínez MT, Pérez-Fidalgo JA, Martín-Martorell P, Cejalvo JM, Pons V, Bermejo B, Martín M, Albanell J, Lluch A. Treatment of HER2 positive advanced breast cancer with T-DM1: A review of the literature. Crit Rev Oncol Hematol. 2016 Jan;97:96-106.

[14] Junttila TT, Li G, Parsons K, Phillips GL, Sliwkowski MX. Trastuzumab-DM1 (T-DM1) retains all the mechanisms of action of trastuzumab and efficiently inhibits growth of lapatinib insensitive breast cancer.Breast Cancer Res Treat. 2011 Jul;128(2):347-56.

[15] Albanell J, Codony J, Rovira A, Mellado B, Gascón P. Mechanism of action of anti-HER2 monoclonal antibodies: scientific update on trastuzumab and 2C4. Adv Exp Med Biol. 2003;532:253-68.

cytotoxic part from being released back into extracellular space that would cause damage to healthy cells.[16] 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 release, 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.[17] As such, thioether-linked DM1 are slower to clear than those in conjugates linked through to regular disulfide bonds.[18] 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.[19]

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)

Dose Reduction Schedule	Dose Level
Starting dose	3.6 mg/kg

[16] Lewis Phillips GD, Li G, Dugger DL, Crocker LM, Parsons KL, Mai E, Blättler WA, Lambert JM, Chari RV, Lutz RJ, Wong WL, Jacobson FS, Koeppen H, Schwall RH, Kenkare-Mitra SR, Spencer SD, Sliwkowski MX. Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. Cancer Res. 2008 Nov 15;68(22):9280-90.

[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

[18] Erickson HK, Lewis Phillips GD, Leipold DD, Provenzano CA, Mai E, Johnson HA, Gunter B, Audette CA, Gupta M, Pinkas J, Tibbitts J. The effect of different linkers on target cell catabolism and pharmacokinetics/pharmacodynamics of trastuzumab maytansinoid conjugates. Mol Cancer Ther. 2012 May;11(5):1133-42.

[19] Yun Luo , Jérôme J. Lacroix, Sunil Prabhu, Chapter 12 Ado-Trastuzumab Emtansine,Antibody-Drug Conjugates ,Volume 17 of the series AAPS Advances in the Pharmaceutical Sciences Series pp 203-223

First dose reduction	3 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

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 the 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. Infact only 2 published meta-analysis for T-DM1 treatment in breast cancer were found.[20,21] 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.

[20] Shen K1, Ma X1, Zhu C1, Wu X1, Jia H1. Safety and Efficacy of Trastuzumab Emtansine in Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: a Meta-analysis. Sci Rep. 2016 Mar 16;6:23262.
[21] Ma B, Ma Q, Wang H, Zhang G, Zhang H, Wang X. Clinical efficacy and safety of T-DM1 for patients with HER2-positive breast cancer. Onco Targets Ther. 2016 Feb 29;9:959-76.

11.2 Summary of available data

11.2.1 Locally Advanced and Metastatic Breast cancer.

The EMILA 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).[22] Between February 2009 and December 2001, 991 patients were randomised 1:1 into 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. Cl 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.[23] PRO was measured with Trial Outcome Index Physical/Functional/Breas't (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].[23]

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.[24] 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

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[22] Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, Pegram M, Oh DY, Diéras V, Guardino E, Fang L, Lu MW, Olsen S, Blackwell K; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012 Nov 8;367(19):1783-91.

[23] Welslau M, Diéras V, Sohn JH, Hurvitz SA, Lalla D, Fang L, Althaus B, Guardino E, Miles D. Patient-reported outcomes from EMILIA, a randomized phase 3 study of trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib in human epidermal growth factor receptor 2-positive locally advanced or metastatic breast cancer. Cancer. 2014 Mar 1;120(5):642-51.

[24] Krop IE, Kim SB, González-Martín A, LoRusso PM, Ferrero JM, Smitt M, Yu R, Leung AC, Wildiers H; TH3RESA study collaborators.Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial.Lancet Oncol. 2014 Jun;15(7):689-99.

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].[25] 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.[25]

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.[20] 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

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

[25] Hans Wildiers et al. Trastuzumab emtansine improves overall survival versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer: Final overall survival results from the phase 3 TH3RESA study. 2015 San Antonio Breast Cancer Symposium. Abstract S5-05

NCT01419197, TH3RESA	A/MBC	III	T-DM1	Physician's choice	602 (404, 198)	2014, Krop

(A/MBC= advanced or metastatic breast cancer, p= pertuzumab)

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).

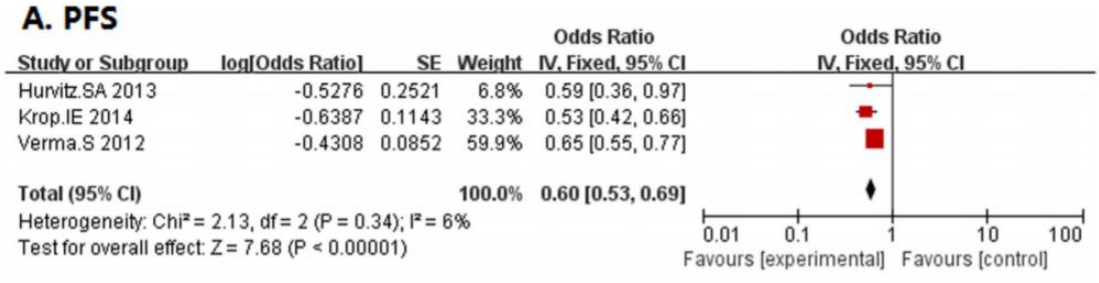

Figure 11-1: Forest plot for progression free survival in controlled trials (from Kai Shen *et al.*)

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.

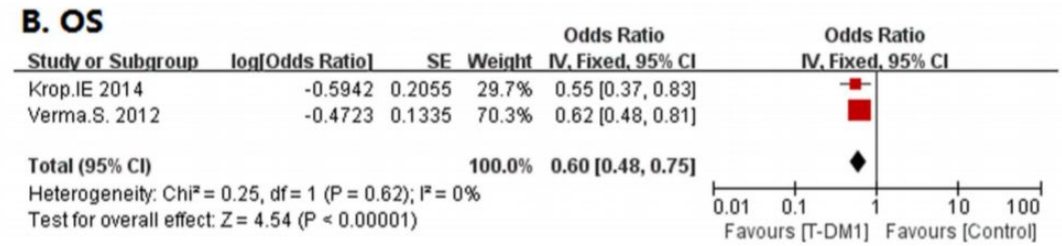

Figure 11-2: Forest plot for overall survival in EMILIA and TH3RESA (from Kai Shen *et al.*)

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%.

Table 11-2: Adverse events in controlled trials (from Kai Shen *et al.*)

Control-arm trials:						
	All grade			Grade ≥3		
Adverse events	Odds Ratio with 95% CI	Model	I^2	Odds Ratio with 95% CI	Model	I^2
Anemia	0.847(0.457,1.571)	Random Model	67.184	1.220(0.643,2.316)	Fixed Model	0.000
Fatigue	1.288(1.041,1.593)	Fixed Model	0.000	0.774(0.427,1.402)	Fixed Model	0.000
Increased Transaminases	4.040(1.429,11.427)	Random Model	87.995	3.2007(0.828,10.912)	Random Model	65.316
Nausea	0.843(0.664,1.069)	Fixed Model	29.670	0.862(0.067,11.046)	Random Model	62.427
Thrombocytopenia	8.500(3.964,18.226)	Random Model	59.033	7.271(1.098,48.133)	Random Model	75.811

The National Institute for Health and Care Excellence (NICE) is an 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.[26] 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:

[26] Squires H, Stevenson M, Simpson E, Harvey R, Stevens J. Trastuzumab Emtansine for Treating HER2-Positive, Unresectable, Locally Advanced or Metastatic Breast Cancer After Treatment with Trastuzumab and a Taxane: An Evidence Review Group Perspective of a NICE Single Technology Appraisal.Pharmacoeconomics. 2016 Jul;34(7):673-80.

[27] Elsada A, Doss S, Robertson J, Adam EJ. NICE guidance on trastuzumab emtansine for HER2-positive advanced breast cancer. Lancet Oncol. 2016 Feb;17(2):143-4.

[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=6344851232016101194953

Below is a summary of notable clinical trials studying T-DM1 in early and advanced settings (from Recondo *et al.*). [29]

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

Study name/ sponsor	Phase	ClinicalTrials.gov identifier	Study description	Comparison	No of patients	Primary end point
KATHERINE	III	NCT01772472	Adjuvant in patients with residual disease following neoadjuvant therapy for HER2+ BC	H q 3 wks × 14 T-DM1 q 3 wks × 14	1,484	IDFS
KAITLYN	III	NCT01966471	Adjuvant in patients with resected HER2+ BC following anthracycline-based chemotherapy	AC/FEC→T-DM1 + P × 1 yr AC/FEC→H + T + P × 1 yr	2,500	IDFS
KRISTINE	III	NCT02131064	Neoadjuvant in patients with HER2+ BC followed by surgery and adjuvant treatment	T + Cb + P + H→Surgery→P + H T-DM1 + P→Surgery→ T-DM1 + P	444	PCR
moTHER	IV	NCT00833963	Observational study. Pregnant women treated with T-DM1 ± P	Observational T-DM1 ± P	N/A	Pregnancy outcomes/ complications
PREDIX-HER2	II	NCT02568839	Neoadjuvant therapy with switch option after two cycles if no response achieved	scH + P + T→Surgery→ EC + H T-DM1→Surgery→EC + H	200	PCR
TEAL	II	NCT02073487	Neoadjuvant study	T-DM1 + P→Ab H + P→Pa	30	PCR

[29] Recondo G Jr, de la Vega M, Galanternik F, Díaz-Cantón E, Leone BA, Leone JP. Novel approaches to target HER2-positive breast cancer: trastuzumab emtansine.Cancer Manag Res. 2016 May 19;8:57-65.

Study name/ sponsor	Phase	ClinicalTrials.gov identifier	Study description	Comparison	No of patients	Primary end point
NSABP FB-10	I/II	NCT02236000	Dose-escalation trial of neratinib in combination with T-DM1 in MBC Adjuvant treatment for stage I HER2+ BC	N + T-DM1	63	Safety/ORR
ATEMPT	II	NCT01853748	Combination of T-DM1, lapatinib, and nab-paclitaxel in HER2+ MBC	T-DM1 H + Pa	500	DFS
STELLA	IB	NCT02073916	Neoadjuvant combination trial HER2+ EBC	T-DM1 + Ab + L	45	MTD
Dana-Farber Cancer Institute	II	NCT02326974	Combination of T-DM1 with PI3KCA inhibitor in MBC	T-DM1 + P	160	PCR
Northwestern University	I	NCT02038010	Adjuvant study in patients aged >65 years	T-DM1 + BYL719	28	MTD
Academic and Community Cancer Research United	II	NCT02414646	Thrombokinetic study of T-DM1, unresectable breast cancer or MBC	T-DM1	200	IDFS
University of Washington	I	NCT01816035	Combination of T-DM1 with anti-PD1 checkpoint inhibitor pembrolizumab in HER2+ MBC	T-DM1	20	Platelet function
PembroMab	Ib/II	NCT02318901	Combination study of capecitabine and T-DM1 for HER2+ MBC and gastric cancer	T-DM1 + pembrolizumab	90	Recommended Phase II doses
Hoffmann-La Roche	II	NCT01702558	T-DM1 in patients with HER2-amplified CTCs in peripheral blood of HER2 + MBC	T-DM1 + capecitabine	235	MTD/ORR
Institut Curie	II	NCT01975142	Combination of HER2 TKI in combination with T-DM1 in HER2+ MBC	T-DM1	480	Tumor response rate
Oncothyreon Inc	Ib	NCT01983501	Neoadjuvant T-DM1 or trastuzumab plus endocrine therapy in operable HER2/HR+ for 12 wks	T-DM1 + ONT-380	57	Safety
ADAPT	II	NCT01745965	First-line treatment with trastuzumab and pertuzumab randomized with or without chemotherapy and T-DM1 in the second line	H+ endocrine therapy T-DM1 + endocrine therapy	380	PCR
Swiss Group for Clinical Cancer Research	II	NCT01835236	T-DM1 in combination with nonpegylated liposomal doxorubicin in MBC	H+P+ chemotherapy→ T-DM1 H + P→T-DM1	208	OS
MedSIR	I	NCT02562378	Combination study of T-DM1 with cyclin-dependent kinase 4/6 inhibitor in advanced HER2+ BC	T-DM1 + nonpegylated liposomal doxorubicin	24	Dose-limiting toxicities
University of Texas Southwestern Medical Center	I	NCT01976169		T-DM1 + PD-0332991	17	MTD

Abbreviations: A, doxorubicin; Ab, nab-paclitaxel; BC, breast cancer; C, cyclophosphamide; Cb, carboplatin; CTCs, circulating tumor cells; DFS, disease-free survival; E, epirubicin; EBD, early breast cancer; F, 5-FU; H, 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, neratinib; ORR, overall response rate; OS, overall survival; P, pertuzumab; Pa, paclitaxel; PCR, pathological complete response; scH, subcutaneous trastuzumab; T, docetaxel; T-DM1, trastuzumab emtansine; TKI, tyrosine-kinase inhibitor; wks, weeks; yr, year.

(table 11-3 continued)

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,

respectively)."[30] 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".[30] 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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Company name, Country	Product name	Stage of development
Allergan/Amgen/Actavis/Synthon USA/The Netherlands	ABP-980	Phase III trial expected to be completed in December 2016 [2], "positive top line reports" were released in July [3]
Biocad, Russia*	BCD-022	Phase III trial completed in November 2014.[4] Non-originator biologic approved in Russia in January 2016 [5], being exported to developing country markets
Biocon/Mylan, India*	CanMab	'Similar biologic' launched in India in October 2013 [6]
	Hercules (Myl-1401O)	Phase III trial in metastatic breast cancer expected to be completed in December 2018 [7]. Positive data reported June 2016 [8]
BioXpress Therapeutics, Switzerland	BX2318	Biosimilar early in pipeline
Celltrion, South Korea	Herzuma	Marketed in South Korea following approval in January 2014 [9]. Application for approval in EEA Oct 2016 [10]. Phase I clinical trial for breast cancer in U.S. completed in April 2016. [11] Partnered with Teva for U.S. and Canada markets [12]
Hanwha Chemical, South Korea	HD201	Phase I study in Europe as of 2013.
Oncobiologics/Viropro, USA	ONS 10-50	Pre-phase 1. Companies are collaborating on six biosimilars [13]
Pfizer/Hospira, USA	PF-05280014	Phase I study completed [14]. Phase III study ongoing, expected to be completed March 2018 [15]
PlantForm, Canada	-	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]
Samsung Bioepis, South Korea	SB3	Applications for approval in S Korea Sept 2016, EEA Oct 2016 [7]
Stada Arzneimittel/Gedeon Richter, Germany/Hungary	-	Collaborating on biosimilars of trastuzumab and infliximab since 2011 [17]. Bought DM Bio from S Korea 2016, who is leading preclinical research

Table 12-1 References:

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3. Study finds Amgen, Allergan's proposed biosimilar ABP 980 comparable to Roche's Herceptin. First Word Pharma, 21 July 2016; Available from: https://www.firstwordpharma.com/node/1401504?tsid=33
4. Amgen and Pfizer seek deal with Russian biosimilars firm. Pro Pharma Communications International; Available from: www.gabionline.net/Pharma-News/Amgen-and-Pfizer-seek-deal-with-Russian-biosimilars-firm
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17. Stada and Richter to collaborate on biosimilar development. Pro Pharma Communications International; Available from: www.gabionline.net/Biosimilars/News/Stada-and-Richter-to-collaborate-on-biosimilar-development

DM1

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:

> Ulrich Storz, Antibody-drug conjugates: Intellectual property considerations, 2015. mAbs, Volume 7, Issue 6.

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