Horizon Scanning in Oncology

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Agencja Oceny Technologii Medycznych (AOTM; Poland) and
The Italian Horizon Scanning Project, Dipartimento Farmaceutico, Azienda ULSS 20 (Italy)

Authors: Dr. Anna Nachtnebel, MSc (LBI-HTA)
Marta Polkowska MSc Pharm (AOTM)
Jadwiga Czeczot MSc Pharm (AOTM)
Dr. Roberta Joppi (Italian Horizon Scanning by Dipartimento Farmaceutico, Azienda ULSS 20, Verona/Italy)
Dr. Chiara Poggiani (Italian Horizon Scanning by Dipartimento Farmaceutico, Azienda ULSS 20, Verona/Italy)

External review: Prof. Dr. Martin Pecherstorfer
Head of Haemtalogic-Oncologic Service,
Landesklinikum Krems, Austria

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CONTACT INFORMATION

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Responsible for Contents:

Ludwig Boltzmann Institut für Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

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1 Drug descriptio

Generic/Brand name/ATC code:

Trastuzumab emtansine/Kadcyla™/not yet assigned

Developer/Company:

Genentech, Inc., Roche Group

Description:

T-DM1 (trastuzumab emtansine) consists of two components: trastuzumab, a human epidermal growth factor receptor 2 (HER2) targeted monoclonal antibody, conjugated to DM1, an anti-microtubule maytansinoid derivative [1]. The cellular cytotoxicity of trastuzumab is improved by the cytotoxicity of DM1. Trastuzumab binds to the surface of tumour cells, resulting in internalisation of DM1 and by distorting microtubule assembly in inhibition of cell division and proliferation of cancer cells that overexpress HER2 [1, 2]. Prior to initiation of T-DM1 therapy, HER2 positivity has to be confirmed.

T-DM1: HER2 targeted monoclonal antibody and maytansinoid derivative

The drug is administered intravenously at a dosage of 3.6 mg/kg every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Since thrombocytopenia is a common side-effect of T-DM1 therapy, platelet counts should be monitored before each cycle [3].

intravenous administration

2 Indication

Trastuzumab emtansine (Kadcyla™) is indicated for previously treated patients with HER2-positive advanced/metastatic breast cancer (BC).

for previously treated HER2 positive BC

3 Current regulatory status

In Europe, T-DM1 is not yet licensed, but the Marketing Authorisation Application has been accepted for review by the EMA in November 2012 [4].

not yet licensed in Europe but in the U.S. in February 2013

In the U.S., T-DM1 was licensed in February 2013. It is indicated as a single agent, for the treatment of patients with HER2-positive, metastatic BC who previously received trastuzumab and a taxane, separately or in combination [3].

Patients should have either:

- Received prior therapy for metastatic disease, or
- Developed disease recurrence during or within six months of completing adjuvant therapy.

4 Burden of disease

risk factors are age, nulliparity, early menarche, genetic factors

In 2010, about 5,000 women were newly diagnosed with and 1,500 died of BC in Austria [5] making BC the most common type of cancer in females. More than 80% of all cases occur in women aged over 50 years [6]. Risk factors associated with the development of BC are age, nulliparity, early menarche, genetic factors (e.g. genetic mutations such as of the BRCA1, BRCA2) or family history [7, 8]. Prognostic factors are age, menopausal status, tumour stage, histology and hormone receptor status [7].

hormone-receptor status, HER2 status, menopausal status and general health determine management strategy

Important factors to determine the best management strategy are oestrogen-receptor (ER) and progesterone-receptor (PR) status in the tumour tissue, HER2 status, menopausal status, and the general health of the patient [8]. In addition, the Tumor Node Metastasis (TNM) is also relevant for choosing the treatment strategy. This staging system reflects the extent of disease, which is used to inform treatment management decisions and to determine prognosis. Besides the primary tumour, the extent to which the regional lymph nodes are involved and the absence or presence of distant metastases are taken into account, leading to four main stage groupings (stage I to IV) [7]. Metastatic disease corresponds to stage IV. Metastases are most common in the bones, liver or the lungs [7].

metastatic disease in 10%, HER2 positivity in 20–25%

Metastatic disease at diagnosis is present in less than 10% of women [7] and evidence suggests that 20% to 25% of all women diagnosed with BC have tumours over-expressing HER2 [9-11]. HER2 positivity is determined either by immunohistochemistry (IHC) or by fluorescent in situ hybridization (FISH) [12]. Due to various methods for determining HER2 status it might be the case though that these numbers are slightly overestimated and that rather 15–20% overexpress HER2 [13]. However, applying these estimates to an Austrian context would result in about 100 women with HER2 positive advanced metastatic BC. Median survival of women with metastatic BC is about 18 to 24 months [8] and only 5–10% of women survive five or more years [7].

median survival: 18–24 months

HER2 overexpressing tumours more aggressive

BC with amplification and over-expression of HER2 are usually more aggressive [7, 11] corresponding to a reduced overall survival (OS) and a shortened time to relapse [10] and HER2 status is also used to predict response to drugs such as trastuzumab or lapatinib or T-DM1 [7]. Additionally, primary resistance to endocrine therapy might be associated with HER2 over-expression due to a cross-talk between ErbB1/ErbB2 and ER pathways and a link between responsiveness to chemotherapy and HER2 over-expression might exist [7].

HER2 status also for predicting response to e.g. T-DM1

5 Current treatment

factors for choosing therapy

Choice of therapy for BC is based on numerous factors like tumour histology, axillary node status, hormone and HER2 receptor status, presence of metastases as well as patient characteristics including menopausal status, age and co-morbidities [9, 14].

backbone for HER2 positive breast cancer are targeted therapies such as trastuzumab and lapatinib

Therapy of HER2 positive metastatic BC usually aims at symptom palliation, improvement of quality-of-life and extension of life [8]. Even though surgery and radiation therapy are indicated for symptom palliation in selected patients, the mainstay of therapy is systemic treatment. The backbone for the treatment of HER2 positive metastatic BC are HER2 targeted therapies (trastuzumab: preferably in combination with single-agent chemotherapy or endocrine therapy but also as single-agent; lapatinib in combination with chemotherapy (i.e. capecitabine) or in combination with endocrine therapy for HR positive tumours [2, 7, 8]; pertuzumab).

continuation of HER2 blockade indicated even after disease progression on HER2 targeted therapies

For patients progressing on HER2 targeted therapy, evidence has occurred in the last years that continuation of HER2 blockade still provides clinical benefit to patients [15-18]. Thus, treatment options include

- trastuzumab + chemotherapy
- lapatinib + trastuzumab (this combination is currently not licensed in Europe) or capecitabine
- pertuzumab + trastuzumab
- T-DM1 [15-18].

6 Evidence

literature search in 4 databases

1 phase III trial and

2 phase II trials included

A literature search was conducted on the 20th of February 2013 in 4 databases (Medline, Embase, CRD, Cochrane Central). Search terms were “breast cancer”, “human epidermal growth factor receptor 2”, “trastuzumab emtansine”, and “t dm1”. Overall 142 references were identified. Considered for inclusion were phase III studies (full text and abstracts) and phase II studies published as full text. If available, other study designs such as results from compassionate-use-programmes or meta-analysis were eligible. Overall, one phase III trial [19] and two phase II trials [20, 21] were included in this report.

6.1 Efficacy and safety – Phase III studies

Table 1: Summary of efficacy

Study title Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer [19, 22]			
Study identifier	NCT00829166, EMILIA trial		
Design	Randomized, open-label, international, multi-centre (213 centres in 26 countries), phase III; 1:1 randomisation, stratification according to world region, number of prior chemotherapies for unresectable, locally advanced or metastatic disease; disease involvement		
	Duration	*Enrolment:* February 2009 – October 2011 *Median follow-up:* 13 months (19 months for second interim analysis of OS) *Cut-off dates for analyses:* January 14, 2012 (for all endpoints except second interim analysis for overall survival); July 31, 2012: for second interim analysis of OS	
Hypothesis	Superiority 90% power to detect a hazard ratio of 0.75 for progression or death from any cause with T-DM1 as compared with lapatinib plus capecitabine and 80% power to detect a hazard ratio of 0.80 for death from any cause, with a two-sided alpha level of 0.05		
Funding	Hoffmann – La Roche/Genentech		
Treatment groups (n=991)	I(ntervention) (n=495)	3.6 mg/kg of body weight T-DM1 i.v. every 21 days	
	C(ontrol) (n=496)	1250 mg/d lapatinib orally + 1000 mg/m² BSA capecitabine of every 12 hours (maximum planned daily dose, 2000 mg/m²) on days 1 through 14 of each 21-day treatment cycle	
Endpoints and definitions	Progression-free survival assessed by independent review (primary outcome)	PFS	Time from randomization to progression (according to modified Response Evaluation Criteria in Solid Tumours (RECIST), version 1.0); or death from any cause
	Overall survival	OS	Time from randomization to death from any cause
	Progression-free survival (investigator-assessed)	PFS	Time from randomization to first documented investigator-assessed disease progression or death from any cause, whichever occurs earlier [22]
	Objective response rate	ORR	Determined according to modified RECIST on the basis of an independent review of patients with measurable disease at baseline; responses were confirmed at least 28 days after the initial documentation of a response [22]
	Duration of response	DOR	The period of time from the date of initial confirmed partial response (PR) or complete response (CR) until the date of progressive disease or death from any cause (whichever occurs earlier) [22]
	Time to symptom progression	TSP	Time from randomization to the first decrease of 5 points or more from baseline scores on the Trial Outcome Index of the patient-reported Functional Assessment of Cancer Therapy–Breast (FACT-B TOI, on which scores range from 0 to 92, with higher scores indicating a better quality of life) in women with a baseline score and at least one postbaseline score

Results and analysis				
Analysis description	ITT; two sided log-rank tests with stratification according to factors used for randomisation.			
Analysis population	Inclusion	• Documented progression of unresectable, locally advanced or metastatic centrally confirmed HER2-positive BC previously treated with a taxane and trastuzumab • HER2 positive status centrally confirmed and assessed by means of immunohistochemical analysis (with 3+ indicating positive status), fluorescence in situ hybridization (with an amplification ratio ≥2.0 indicating positive status), or both • Left ventricular ejection fraction of 50% or more determined by echocardiography or multiple-gated acquisition [MUGA] scanning • Eastern Cooperative Oncology Group PS ≤1		
	Exclusion	• Prior treatment with T-DM1, lapatinib, or capecitabine • Peripheral neuropathy of grade 3 or higher • Symptomatic central nervous system (CNS) metastases or treatment for these metastases within 2 months before randomization • History of symptomatic congestive heart failure or serious cardiac arrhythmia requiring treatment; and a history of myocardial infarction or unstable angina within 6 months before randomization		
	Characteristics	*Age* (years (range)): I 53 (25–84) vs C 53 (24–83) *ECOG* 0/1 (%): I 60/39 vs C 63/35 *Site of disease involvement* – visceral/non-visceral (%): I 67/33 vs C 68/32 *Hormone- receptor status* – ER, PR+/ER,PR-/unknown (%): I 57/41/2 vs C 53/45/2 *Prior systemic therapy* – anthracycline/other chemotherapy/biologic agent other than trastuzumab or pertuzumab/endocrine (%): I 61/78/3/41 vs C 61/77/4/41 *Prior chemotherapy regimens* for locally advanced or metastatic disease – 0 or 1/>1 (%): I 61/39 vs C 61/39 *Prior trastuzumab treatment* – metastatic or early BC or both/early BC only (%): I 84/16 vs C 84/16		
Descriptive statistics and estimated variability	Treatment group		Intervention (T-DM1)	Control (lapatinib + capecitabine)
	Number of subjects		N = 495	N = 496
	Median PFS (independent analysis), months		9.6	6.4
	Median PFS (investigator assessed), months		9.4	5.8
	Median OS (2nd interim analysis), months		30.9	25.1
	Survival rates, % (95% CI) 1-year 2- year		 85.2 (82.0–88.5) 64.7 (59.3–70.2)	 78.4 (74.6–82.3) 51.8 (45.9–57.7)
	ORR, % (95% CI) CR, % PR, %		43.6 (38.6–48.6) 1.0 42.6	30.8 (26.3–35.7)* 0.5 30.3
	Median DOR, months (95% CI)		12.6 (8.4–20.8)	6.5 (5.5–7.2)
	Median TSP, months		7.1	4.6

Effect estimate per comparison	*Comparison groups*		*I vs C*
	PFS (independent analysis)	HR	0.65
		95% CI	0.55–0.77
		P value	<0.001
	PFS (investigator assessed)	HR	0.66
		95% CI	0.56–0.77
		P value	<0.001
	OS (1^{st} interim analysis)	HR	0.62
		95% CI	0.48–0.81
		P value	0.0005
	OS (2^{nd} interim analysis)	HR	0.68
		95% CI	0.55–0.85
		P value	<0.001
	TSP	HR	0.80
		95% CI	0.67–0.95
		P value	0.012

** P<0.001*

Abbreviations: BC = breast cancer; BSA = body-surface area; C = control, CI = confidence interval, CR = complete response, DOR = duration of response, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, I = intervention, i.v. = intra-venously; kg = kilogram, ORR = objective response rate, OS = overall survival, PFS = progression- free survival, PR = partial response, TSP = time to symptom progression

Table 2: Adverse Events

Outcome n (%)	**I (N= 490)**		**C (N=488)**	
Grade (according to CTC version 3.0)	Any Grade	Grade 3 or 4 events	Any Grade	Grade 3 or 4
Any event	470 (95.9)	200 (40.8)	477 (97.7)	278 (57.0)
Diarrhoea	114 (23.3)	8 (1.6)	389 (79.7)	101 (20.7)
Palmar-plantar erythrodysesthesia	6 (1.2)	0	283 (58.0)	80 (16.4)
Vomiting	93 (19.0)	4 (0.8)	143 (29.3)	22 (4.5)
Neutropenia	29 (5.9)	10 (2.0)	42 (8.6)	21 (4.3)
Hypokalemia	42 (8.6)	11 (2.2)	42 (8.6)	20 (4.1)
Fatigue	172 (35.1)	12 (2.4)	136 (27.9)	17 (3.5)
Nausea	192 (39.2)	4 (0.8)	218 (44.7)	12 (2.5)
Mucosal inflammation	33 (6.7)	1 (0.2)	93 (19.1)	11 (2.3)
Anaemia	51 (10.4)	13 (2.7)	39 (8.0)	8 (1.6)
Elevated ALT	83 (16.9)	14 (2.9)	43 (8.8)	7 (1.4)
Elevated AST	110 (22.4)	21 (4.3)	46 (9.4)	4 (0.8)
Thrombocytopenia	137 (28.0)	63 (12.9)	12 (2.5)	1 (0.2)
Bleeding	NR (29.8)	NR (1,4)	NR (15.8)	NR (0,8)

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, NR = not reported

EMILIA trial with 991 patients comparing T-DM1 to lapatinib + capecitabine

The EMILIA trial, a phase III study, compared T-DM1 to lapatinib + capecitabine in overall 991 patients with HER positive advanced BC. All patients had been treated previously with trastuzumab and a taxane for their advanced/ metastatic disease. HER2 status was determined by FISH or IHC. 496 patients were randomised to lapatinib (1250 mg/d orally) + capecitabine (1000 mg/m^2 body surface area capecitabine orally every 12 hours on days 1–14 of each 21 day cycle) and 495 to T-DM1 (3.6 mg/kg every 21 days).

characteristics of study population

Median age of the study population was 53 years; the majority of women had ECOG status 0 and visceral involvement. In both groups, slightly more patients were hormone-receptor status positive (>53%) than negative (<45%). 61% in both groups were either treatment-naïve or had received a maximum of 1 chemotherapy for their metastatic disease, whereas the rest had received more than 1 regimen. Most patients (i.e. 84% in both groups) had been treated with prior trastuzumab for metastatic, for early BC or for both and 16% in each group had received trastuzumab for early disease only.

dose reductions and treatment discontinuation more frequent in lapatinib + capecitabine group

Dose-reductions were necessary in 27.3% of patients treated with lapatinib, in 53.4% treated with capecitabine and in 16.3% of the T-DM1 group respectively. Treatment discontinuation due to AEs were most frequently observed with capecitabine in the safety population (capecitabine: 9.4%, lapatinib: 7.6%, T-DM1: 5.9%).

primary outcome was PFS: + 3.2 months for T-DM1 group

OS:+ 5.8 months for T-DM1 treated patients

also better results for QoL

PFS as assessed by independent review, the primary outcome, was 9.6 months in the T-DM1 group in comparison to 6.4 months in the lapatinib group, yielding a HR of 0.65 (95%CI 0.55–0.77; p<0.001) after a median follow-up of 13 months. These findings were consistent across clinical relevant subgroups, with the exception of patients aged ≥75 years. After a median of 19 months follow-up, OS was 30.9 months in the T-DM1 group and 25.1 months in the lapatinib + capecitabine group (HR = 0.68; 95%CI 0.55–0.85; p<0.001). More favourable results for the T-DM1 group were also found for ORR (43.6% vs 30.8%, p<0.001) and DOR (12.6 months vs 6.5 months) and median time to symptom progression was also longer (7.1 months vs 4.6 months; HR = 0.80; 95%CI 0.67–0.95; p<0.012).

fewer side-effects in T-DM1 group

most frequent grade 3 or 4 AE in T-DM1 group: thrombocytopenia, elevated liver enzymes, anaemia

differences in side-effect profiles

Different profiles in adverse events (AEs) were seen for the two groups. Any AE of any grade occurred in nearly all patients in both groups. Any event of grade 3 or 4 was less frequent in patients treated with T-DM1 (40.8% vs 57.0%). The most common grade 3 or 4 AE in the T-DM1 group was thrombocytopenia, followed by elevated liver enzymes and anaemia, whereas patients treated with lapatinib + capecitabine experienced more often diarrhoea, palmar-plantar erythrodysaesthesia or vomiting. Overall 5 deaths due to AEs were seen in both treatment groups; 4 in the lapatinib + capecitabine group (coronary artery disease, multi-organ failure, coma and hydrocephalus) and 1 (metabolic encephalopathy after CNS progression) in the T-DM1 group. Reported cardiac side-effects, side-effects associated with trastuzumab therapy, were a decline in left ventricular ejection fraction to less than 40% from baseline in 3 patients in each group.

6.2 Efficacy and safety – further studies

single-arm phase II study with 112 heavily pre-treated women

A single-arm phase II study [21] encompassing 112 patients evaluated efficacy and safety of T-DM1 (3.6 mg/kg every 3 weeks) in heavily pre-treated women (median number of prior anticancer agents in all disease setting was 8) for a minimum of 12 months. For inclusion, HER2 positivity had initially been determined by local laboratories and was retrospectively confirmed by a central laboratory in 78%. The primary outcome ORR determined by an independent review facility was 25.9% only due to partial responses. Median DOR was not reached (95%CI 6.2 months – not estimable) and median PFS was 4.6 months (95%CI 3.9–8.6 months). More favourable results were found for these outcomes in patients with retrospectively confirmed HER2 positivity than in those with unconfirmed HER2 positive status. The most common AEs of all grades were fatigue (65.2%), nausea (50.9%) and headache (40.2%), but mainly of grade 1. Higher grade AEs (i.e. grade 3 or 4) were hypokalaemia (8.9%), thrombocytopenia (8.0%) and fatigue (4.5%).

confirmation of HER2 positivity in 78%

median PFS 4.6 months,

ORR 25.9%

better results for patients with confirmed HER2 positivity

T-DM1 evaluated in 110 patients with at least 2 prior HER2 targeted therapies

Krop et al. [20, 23] reported the results of a single-arm phase II study comprising 110 pre-treated and HER2 positive (assessed by local laboratory criteria) metastatic BC patients. T-DM1 (3.6 mg/kg every 3 weeks) was administered to patients who had been treated with at least two prior HER2 targeted therapies. Enrolled patients had received a median of 7 prior agents including trastuzumab, lapatinib, an anthracycline, a taxane and capecitabine for metastatic BC. Median follow-up was 17.4 months. ORR, the primary outcome, was assessed by an independent review facility, and was 34.5% (95%CI 26.1%–43.9%), all of these being partial responses. Median PFS was 6.9 months (95%CI 4.2–8.4 months) and median DOR was 7.2 months (95%CI 4.6 – not estimable). HER2 status was reassessed by central testing, and confirmed HER2 positivity in 84.2% of patients. For these patients, better results were obtained in ORR (HER2 positivity confirmed: 41.3% vs HER2 positivity not confirmed: 20.0%) and PFS (HER2 positivity confirmed: 7.3 months vs HER2 positivity not confirmed: 2.8 months). The most frequent AEs of any grade were fatigue (61.8%), thrombocytopenia (38.2%) and nausea (37.3%). Higher grade AEs were mainly of grade 3 with thrombocytopenia (7.3%) and fatigue (4.5%) being the most common ones. Side-effects of grade 4 were rare and included thrombocytopenia (1.8%), spinal cord compression (1.8%), cellulitis (0.9%) and abdominal pain (0.9%).The only grade 5 AE was pneumonia (0.9%).

retrospective confirmation of HER2 positivity in 84%

better outcomes for HER2 positive patients: PFS 7.3 months

most frequent AEs of any grade: fatigue, thrombocytopenia, nausea

grade 4 AEs rare: thrombocytopenia, spinal cord compression, cellulitis, abdominal pain

7 Estimated costs

no cost estimates for Austria

No cost estimates are available for Austria. In the U.S. monthly treatment costs of $ 9,800 (= € 7,660) are mentioned for T-DM1 only [24], totalling up to treatment costs of $ 94,000.

8 Ongoing research

2 ongoing phase III trials for indication assessed

At http://clinicaltrials.gov/ and at https://www.clinicaltrialsregister.eu/ctr-search/ 2 phase III studies for the investigated indication were found:

- *NCT01419197:* (TH3RESA): randomized, multicentre, two-arm, open-label study (TH3RESA) will evaluate T-DM1 in comparison with treatment of the physician's choice in patients with metastatic or unresectable locally advanced/recurrent HER2-positive BC. Estimated study completion date: October 2015.
- *NCT01702571:* multi-centre, single-arm study will assess the safety and the efficacy of T-DM1 in patients with HER2-positive locally advanced or MBC who have received prior anti-HER2 and chemotherapy-based treatment. Estimated study completion date: March 2017.

T-DM1 being tested for first-line, in combination with other agents and for gastric cancer

Moreover, phase III trials were found investigating T-DM1 for BC, for example, as first-line therapy in combination with pertuzumab (NCT01120184) or as adjuvant therapy in comparison to trastuzumab (NCT01772472). T-DM1 is also being assessed for gastric cancer.

9 Commentary

T-DM1 not licensed in Europe, but in the U.S., after trastuzumab and taxane therapy

T-DM1, currently not yet licensed in Europe but in the U.S., is a new drug combining the HER2 targeted agent trastuzumab with DM1 a cytotoxic maytansine derivative. This drug has been licensed in the U.S. for patients with HER2 positive metastatic BC who have previously received trastuzumab and a taxane.

+3.2 months in PFS for T-DM1 group, consistent across subgroups but not for patients ≥75 years

other outcomes such as OS, ORR also favoured T-DM1 and fewer side-effects

A phase III trial, the EMILIA trial, investigated this indication in overall 991 patients. Independently assessed PFS, the primary outcome, was extended by 3.2 months in comparison to patients treated with lapatinib + capecitabine (HR = 0.65; 95%CI 0.55–0.77), a regimen commonly used for patients with disease progression on trastuzumab therapy. This result was consistent across clinically relevant subgroups, with the exception of patients aged ≥75 years. For the whole study population, the difference in OS was 5.8 months (HR = 0.68; 95%CI 0.55–0.85; $p<0.001$). Also other outcomes such as ORR, DOR and time to symptom progression consistently favoured T-DM1. Side effects profiles differed between the two groups but were less frequent in patients receiving the trastuzumab conjugate than in those in the control group.

disease progression despite trastuzumab therapy necessitates new treatment options

Due to the fact that most patients treated with anti-HER2 therapy, mostly trastuzumab, have disease progression while on therapy, new treatment strategies were needed. In recent years, evidence has emerged that continuation of HER2 blockade, despite disease progression under HER2 targeted therapy, may still yield clinical benefit [25, 26]. This has led to the development of new therapeutic options including T-DM1. Since treatment options commonly used within this setting consist of combination therapies (trastuzumab + alternative chemotherapeutic regimen/other HER2 targeted therapy; lapatinib in combination with chemotherapy [27]), the rationale for developing an antibody-drug conjugate like T-DM1 was to increase the targeted delivery of chemotherapy while reducing toxicities associated with chemotherapy [27, 28]. Furthermore, use of single agent T-DM1 reduces the need of concomitant systemic chemotherapy and thus increases the ease of administration.

treatment options commonly used are combination therapies with continuation of HER2 blockade

single agent T-DM1 easier to administer than combination therapies

EMILIA trial showed consistent subgroup results for heterogeneous population

Even though the EMILIA trial comprised a rather heterogeneous study population favourable results for most subgroups were achieved (e.g. ER status, prior systemic therapy for metastatic BC, prior trastuzumab therapy). However, since mechanisms of resistance, either de-novo or acquired, to HER2 targeted therapies are diverse, HER2 status as the only criterion for selecting patients for costly therapies is increasingly challenged [27, 29]. A more refined characterisation of pathways involved in resistance development and of molecular predictors for choosing new treatment options is needed and will allow more tailored treatment approaches [29, 30] which is important since besides T-DM1 other agents such as tanespimycin or neratinib are under evaluation [30].

but due to resistance to HER2 targeted therapies further criteria needed

no improved outcomes for patients ≥75 years, but only small group; further investigation needed for elderly and frail patient

One of the subgroups for which no improved outcomes were found was for patients aged ≥75 years, but since this group comprised only 25 patients, no definite conclusions can be drawn. Thus efficacy of T-DM1 for elderly patients, and due to the fact that enrolled patients had a good performance status (i.e. 0 or 1) also for co-morbid patients, needs to be investigated further.

long-term data on T-DM1 therapy needed, foremost since it is being also tested in first-line setting

In addition, despite the fact that cardiac side-effects did not occur more frequently in the T-DM1 group than in the control arm, the FDA recommended placing cardiac toxicity in a boxed warning on the label, because cardiotoxicity is an AE known to be linked to HER2 targeted therapies [31, 32]. For this outcome, as well as all others, long-term data on T-DM1 therapy would be helpful, foremost since optimal duration of HER2 targeted therapies are unknown. This fact is of further importance, because T-DM1 is also under investigation in the adjuvant and neoadjuvant setting (NCT01196052) and also for previously untreated patients with metastatic BC (NCT01120184) [30].

costs unknown, but may be substantial when given as combination therapy

comparison to trastuzumab of interest, foremost since patent expires in July 2014

Furthermore, besides T-DM1 single-agent therapy, combinations with, for example, pertuzumab are being tested [30]. Even though cost estimates for Austria are not available yet, combination therapies with several expensive therapies for a long period of time will result in high treatment costs [33]. With respect to costs but also in terms of clinical outcomes, it can be questioned whether lapatinib + capecitabine was the most appropriate comparator. Since trastuzumab either in combination with lapatinib (currently not licensed in this combination in Europe) or with capecitabine are treatment options recommended by several guidelines [16, 18], the comparison to a trastuzumab containing therapy would have been of utmost interest, foremost, because both agents are manufactured by the same company. and the patent for trastuzumab will expire in July 2014 [34].

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