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Review Article

Trastuzumab Emtansine: Antibody-drug Conjugate in Treatment of Human Epidermal Growth Factor Receptor-2-Positive Metastatic Breast Cancer

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Abstract

The human epidermal growth factor receptor-2 (HER2)-targeted therapies have improved clinical outcomes for patients at any stage of HER2-positive breast cancer (BC). Trastuzumab, a monoclonal antibody that targets the HER2 receptor on BC cells, showed improved survival in metastatic BC (MBC). However, resistance to therapy arises in the majority of patients with advanced disease. Antibody–drug conjugate (ADC) is a relatively new development to deliver cytotoxic drugs specifically to cancer cells. Trastuzumab emtansine (T-DM1) is a HER2-targeted ADC, composed of trastuzumab, a stable thioether linker, and the potent cytotoxic agent, emtansine (DM1, derivative of maytansine). T-DM1 has been approved for use in patients with MBC who have failed prior therapy with trastuzumab and a taxane. Dose finding Phase I study established the maximum tolerated dose at 3.6 mg/kg every 3 weeks. Phase I and II studies of T-DM1 have shown clinical activity and a favorable safety profile in HER2-positive MBC patients. The Phase III randomized EMILIA and TR3RESA trials demonstrated that T-DM1 significantly improves progression-free and overall survival in pretreated HER2-positive MBC patients. Nausea and fatigue are most commonly reported adverse drug reactions with T-DM1 and cardiac toxicity comparable with standard of care therapies. The drug is well tolerated in most patients, with a predictable pharmacokinetic profile and minimal systemic exposure to free cytotoxic DM1. T-DM1 has emerged as an effective therapeutic option for the management of patients with HER2-positive MBC.

Keywords: *Drug conjugate, human epidermal growth factor receptor-2, metastatic breast cancer, Trastuzumab emtansine*

Introduction

Breast cancer (BC) is the second most common cancer worldwide and second leading cause of cancer-related death in women.[1] Research over the past 3 decades has led to a better insight into multifaceted molecular heterogeneity of the disease. The discovery of human epidermal growth factor receptor 2 (HER2) (also known as epidermal growth factor receptor or Erb-B), a membrane tyrosine kinase and oncogene, was one such important finding.[2,3] Slamon *et al*. showed that amplification of HER2 gene occurs relatively infrequently in BC, and that it is associated with disease relapse and reduced overall patient survival.[2] The HER2 proteins are involved in promoting cell growth through activation of the phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt)-mammalian target of rapamycin and Ras-Raf-MEK-Erk1/2 pathways, resulting in tumor growth and progression.[4,5]

BC cells can have up to 25–50 copies of the HER2 gene (HER2 amplification) and up to 40–100-fold increase in HER2 protein resulting in two million receptors expressed at the tumor cell surface (HER2 overexpression).[6] HER-2 is amplified in 15%–20% of human primary BC and is significant predictor of both overall survival (OS) and time to relapse in patients with BC.[7] The identification of HER2 in BC pathogenesis has led to the development of therapies targeting this receptor.[8]

Trastuzumab (Herceptin®; Genentech, South San Francisco, CA, USA), the first monoclonal antibody developed to target HER2, received US Federal Drug Authority approval in 1998 for the treatment of HER2-positive metastatic BC (MBC) in combination with paclitaxel for first-line treatment.[9] Trastuzumab was shown to significantly improve the time to progression and OS of patients with metastatic HER2-positive BC.[10,11]

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Despite the significant efficacy of trastuzumab-based therapy, 50% of patients progress within 1 year.[10,11] Lapatinib, an orally administered small molecule inhibitor of the HER1 and HER2 tyrosine kinases, was found to be superior in combination with capecitabine compared with capecitabine alone, in the treatment of HER2-positive MBC that had progressed after trastuzumab-based therapy.[12] Although this combination therapy provided patients with trastuzumab-resistant disease, an additional treatment option, only 29% of patients showed clinical benefit (complete response, partial response, or stable disease lasting at least 6 months), and half of patients had disease progression at 6.2 months.[13]

Diarrhea is a well-known side effect and a dose-limiting factor associated with lapatinib plus capecitabine treatment. Despite availability of treatment guidelines for the management of lapatinib–capecitabine-associated diarrhea, it still represents a significant limitation in the optimal regimen administration in many patients. This frequently has a negative impact on patients' quality of life and efficacy of drug in daily clinical practice.[14]

In 2013, the FDA approved the first successful HER2-targeted antibody–drug conjugate (ADC), trastuzumab emtansine (T-DM1; Kadcyla®; Genentech), for the treatment of HER2-positive trastuzumab-pretreated MBC.[15] In this review, we will discuss the pharmacology, efficacy, and tolerability of T-DM1 in HER2-positive MBC. A search of published medical literature was performed following the principles of evidence-based medicine. The search strategy included a search using the keywords: T-DM1, HER2+ve BC, HER2 targeted therapy, MBC in PubMed, Medscape, ClinicalTrials.gov, in addition to older studies identified by the literature reviews were reviewed.

Trastuzumab Emtansine-Human Epidermal Growth Factor Receptor-2-Targeted Antibody–Drug Conjugate

ADCs are relatively new drugs and are designed to deliver cytotoxic drugs specifically into cancer cells,[16] thereby creating a more favorable therapeutic window for cytotoxic agents than that would be achieved by a free cytotoxic agent.[17] The key components of an ADC are the cytotoxic agent, a monoclonal antibody targeting a tumor-enriched or tumor-specific antigen, and a linker; covalently binding these components together.[18]

T-DM1, first ADC targeting the HER2 receptor, is a conjugate of trastuzumab through a non-reducible thioether linker (N-succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate [SMCC]) and a cytotoxic moiety (emtansine, derivative of maytansine [DM1]).[19]

Trastuzumab

Trastuzumab component of T-DM1 binds to subdomain 4 of HER2 receptor and exerts its own antitumor effects. The HER2-DM1 complex is then endocytosed and ultimately fused with a lysosome where it undergoes proteolytic degradation with release of the active DM1.[20]

Derivative of maytansine

DM1 is the derivative of maytansine ($C_{34}H_{46}ClN_3O_{10}$), a benzoansamacrolide collected from plants and mosses. Maytansine is a potent microtubule-targeted compound, considered to have a high affinity for tubulin located at the ends of microtubules. The suppression of microtubule dynamics causes cells to arrest in the G2/M phase of the cell cycle, ultimately resulting in cell death by apoptosis.[21] *In vitro* studies demonstrate that on a molar basis across a range of cancer cell lines, DM1 is 24- to 270-fold more potent than paclitaxel, 180- to 4000-fold more potent than doxorubicin, and 100 fold more potent than vincristine (Vinca alkaloids).[22-24]

Maytansine had been extensively evaluated in Phase I and II clinical trials in humans, but side effects mainly gastrointestinal and neurologic toxicities and lack of tumor specificity have prevented its successful clinical development.[25-27] However, DM1, a derivative of maytansine, was selected for use in T-DM1, owing to high potency, excellent stability, in addition to the acceptable solubility of maytansine in aqueous solutions.[22,26]

Thioether linker

The linker should stabilize the ADC in circulation, and once the compound enters the cell, it should liberate the cytotoxic agent either in a pH-dependent manner or by disulfide reaction.[28] T-DM1 is the first clinically developed ADC that uses the noncleavable linker. The advantage of noncleavable linker is that it undergoes proteolytic degradation once internalized and has better stability while in circulation.[19]

The conjugation of linker to trastuzumab is multistep process, first step is reaction of SMCC with the amino side chain of a lysine residue to form an amide bond at pH 7–9. Subsequently, the maleimide moiety undergoes a Michael-type addition with thiols at pH 6.5–7.5 to form thioether bonds with the cytotoxic agent resulting in an average 3.5 molecules per trastuzumab antibody (different drug–antibody ratio).[21]

Trastuzumab Emtansine - Mechanisms of Action

The mechanism of action (MOA) of T-DM1 is twofold [Figure 1].

First, T-DM1 has been shown to retain the MOA of unconjugated trastuzumab including inhibition PI3K/AKT pathway, inhibition of HER-2 shedding, and Fcγ receptor mediated engagement of immune cells, which may result in antibody-dependent cellular cytotoxicity.[23] Moreover, trastuzumab-mediated effect should not be underestimated and is particularly of importance, when target cells do not undergo rapid apoptotic death caused by DM1.[18]

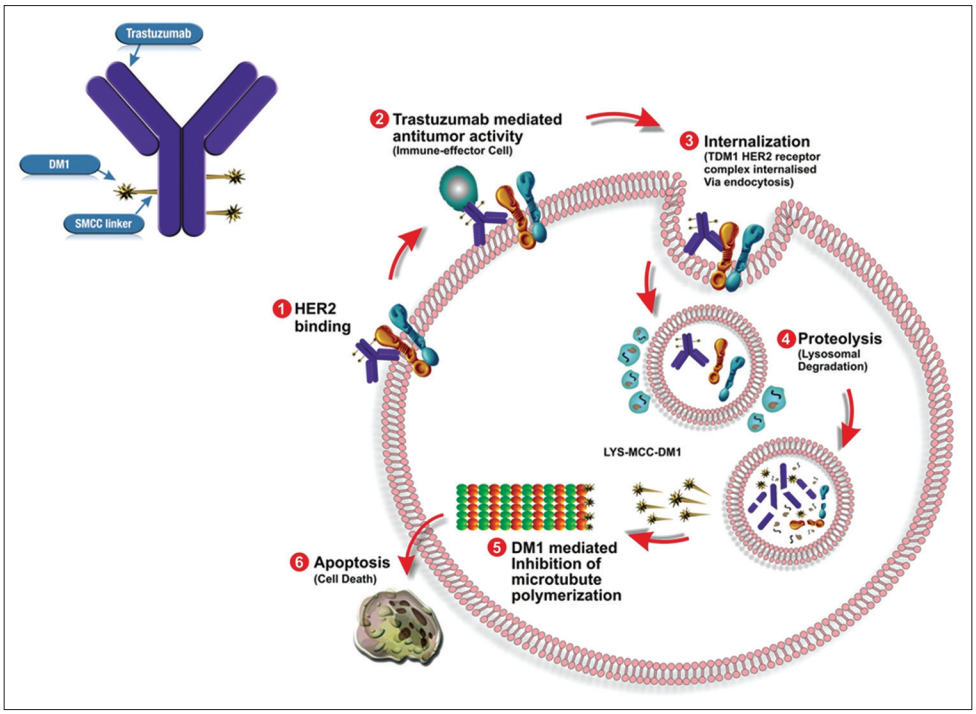

Figure 1: Trastuzumab emtansine - mechanism of action

Second, binding of T-DM1 to HER2 triggers entry of the HER2-T-DM1 complex into the cell through receptor-mediated endocytosis and ultimately fused with a lysosome where it undergoes proteolytic degradation.[29-31] As nonreducible linker is stable in the circulation and the tumor microenvironment, conjugates are efficiently degraded in lysosomes to yield metabolites consisting of the intact maytansinoid drug and linker attached to lysine.[19,31] Subsequent to release from lysosome, microtubule assembly is inhibited by DM1-containing metabolites, finally causing cell death.[32] The primary active metabolite, lysine–SMCC–DM1, is a charged molecule, and relatively membrane impermeable, reducing the possibility that the DM1 entering a neighboring cell.[22]

Trastuzumab Emtansine Pharmacokinetics

T-DM1 appears quite stable in circulation, as very low levels of free DM1 were reported to be present in plasma samples from patients treated with T-DM1.[32]

Lu *et al.* evaluated *s*erum samples collected from 671 patients with HER2-positive locally advanced or MBC who received single-agent T-DM1 in five Phase I to Phase III studies. The results from the study showed terminal half-life of 3.94 days, with clearance of 0.676 L/day and a central volume of 3.127 L. Age, race, region, and renal function had no influence on pharmacokinetic of T-DM1.[33] In Phase I study of HER2-positive MBC patients with normal or reduced hepatic function, Li *et al.* reported that no increase in the systemic concentration of DM1 was observed in patients with mild or moderate hepatic impairment, compared to patients with normal hepatic function.[34] T-DM1 is neither an inducer nor inhibitor of CYP isoform. There was no accumulation or tissue retention by day 14 and 80% of the drug was excreted in feces and a small fraction in urine.[35]

Clinical Efficacy

Dose finding studies

T-DM1 was initially evaluated as a single agent in a Phase I dose escalation study in patients with trastuzumab-refractory HER2-positive advanced BC. Both weekly and 3-weekly schedules were tested. The 3-weekly dosing cohort was enrolled first. A total of 24 patients received intravenous T-DM1 doses at 0.3 mg/kg to 4.8 mg/kg every 3 weeks.[18] Grade IV thrombocytopenia was dose limiting at 4.8 mg/kg. The investigators deemed the maximum tolerated dose (MTD) to be 3.6 mg/kg. Response rate in these heavily pretreated patients with measurable disease at MTD was 44%.[18]

Phase II studies

Burris *et al*. conducted a Phase II clinical trial (TDM 4258 g) [Table 1] in 112 patients with HER2-positive MBC with tumor progression after prior HER2-directed therapy. By independent review, the objective response rate (ORR) was 26%.[32]

A confirmatory single-arm Phase II study (TDM 4374 g) [Table 1] was subsequently conducted by Krop *et al*., on a more heavily pretreated HER2-overexpressing MBC patient with prior exposure to trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine with an ORR of 34.5%.[36]

Table 1: Summary of published trastuzumab emtansine Phase II studies

Trial and reference	Year	Study population	Patients (*n*)	Regimen/ treatment groups	End points		ORR	CR	CBR	Median (months)	
					Primary	Secondary				DOR	PFS
Burris *et al*. (TDM4258g)[32]	2011	Previously treated with chemotherapy and progressed on HER2-targeted therapy	112	T-DM1; 3.6 mg/kg IV, q3w	ORR by IRF, safety, and tolerability	ORR by investigator review, DOR, PFS by IRF	26%	3.6%	NR	9.4	4.6
Krop *et al*. (TDM4374g)[36]	2012	Previously treated with anthracycline, a taxane, and capecitabine, plus lapatinib, and T for MBC	110	T-DM1; 3.6 mg/kg IV, q3w	ORR by IRF, safety, and tolerability	CBR, DOR, PFS	34.5%	0%	48.2%[a]	7.2	6.9

[a]Defined as CR plus partial response plus stable disease≥6 months. CBR – Clinical benefit rate; CR – Complete response; DOR – Duration of response; HER2 – Human epidermal growth factor receptor 2; IRF – Independent radiologic facility; MBC – Metastatic breast cancer; NR – Not reported; ORR – Objective response rate; PFS – Progression-free survival; q3w – Every-3-week; T – Trastuzumab; T-DM1 – Trastuzumab emtansine; IV – Intravenous

Table 2: Summary of published trastuzumab emtansine Phase III studies

Trial and reference	Year	Study population	Patients (*n*)	Regimen/treatment groups	End points		ORR (%)	Median (months)		
					Primary	Secondary		OS	DOR	PFS
EMILA (NCT00829166)[37]	2012	Previously treated with T and a taxane with centrally confirmed HER2 + un-resectable, locally advanced or MBC	495	T-DM1 (3.6 mg/kg IV, q3w)	PFS by IRF, OS and safety	PFS by investigator and ORR	43.6	30.9	12.6	9.6
			496	X (1000 mg/m^2 PO BID, days 1-14 q3w) + L (1250 mg PO daily)			30.8	25.1	6.5	6.4
TH3RESA (NCT01419197)[41,42]	2015	HER2 + MBC previously treated with a taxane (any setting), and lapatinib plus T (advanced setting)	404	T-DM1 (3.6 mg/kg q3w)	PFS by investigator and OS	ORR by investigator and safety	31	22.7	NR	6.2
			198	TPC[a]			9	15.8		3.3
MARIANNE (NCT01120184)[43]	2015	Recurrent, locally advanced breast cancer or MBC, with no prior chemotherapy for metastatic disease	365	T + D (8 mg/kg LD then 6 mg/kg + 100 or 75 mg/m^2 q3w) or T + paclitaxel (4 mg/kg LD then 2 mg/kg + 80 mg/m2 qw)	PFS by IRF	OS, PFS by investigator, ORR, safety, patient-reported outcomes	67.9	NR	12.5	13.7
			367	T-DM1 + placebob (3.6 mg/kg + 840 mg LD then 420 mg q3w)			59.7		20.7	14.1
			363	T-DM1 + pertuzumab (3.6 mg/kg + 840 mg LD then 420 mg q3w)			64.2		21.2	15.2

[a]83% of the patients received HER2-targeted therapy and 17% received single-agent chemotherapy, as part of their regimen; [b]Pertuzumab placebo. BID – Twice daily; CBR – Clinical benefit rate; D – Docetaxel; DOR – Duration of response; HER2 – Human epidermal growth factor receptor 2; IRF – Independent radiologic facility; L – Lapatinib; LD – Loading dose; MBC – Metastatic breast cancer; NR – Not reported; ORR – Objective response rate; q3w – Every-3-week; PFS – Progression-free survival; PO – Oral; T – Trastuzumab; T-DM1 – Trastuzumab emtansine; TPC – Treatment of physician's choice; X – Capecitabine; IV – Intravenous

Phase III studies

EMILIA study

This pivotal trial was a Phase III randomized, multicenter global trial evaluating the safety and efficacy of T-DM1 compared with capecitabine + lapatinib in 991 HER2-positive, unresectable, locally advanced, or MBC patients previously treated with trastuzumab and a taxane. The progression was during or after the most recent treatment for locally advanced or metastatic disease or within 6 months of treatment for early-stage disease. Patients were randomly assigned 1:1 to receive either oral lapatinib 1250 mg once daily plus oral capecitabine 1000 mg/m^2 every 12 h on days 1–14 of a 21-day treatment cycle or T-DM1, 3.6 mg/kg, intravenous every 21 days).[37] The primary end points of this study were progression-free survival (PFS) (as assessed by independent review), OS, and safety [Table 2]. Key eligibility criteria for study are summarized in Table 3.[37]

Median PFS as assessed by independent review was 9.6 months with T-DM1 versus 6.4 months with lapatinib plus capecitabine (hazard ratio [HR] 0.65; 95% confidence interval [CI]: 0.55–0.77; $P < 0.001$), and median OS at the second interim analysis (30.9 vs. 25.1 months; HR, 0.68; 95% CI: 0.55–0.85; $P < 0.001$) crossed the stopping boundary for efficacy and was considered confirmatory OS. Recently, published final OS analysis (descriptive analysis) indicates that OS benefit with T-DM1 treatment was maintained despite 27% of patients crossing over to T-DM1 after second interim analysis [Table 4].[38]

The ORR was higher with T-DM1 as compared to lapatinib plus capecitabine (43.6%, vs. 30.8% $P < 0.001$). In addition, results for all additional secondary end points favored T-DM1. The median time to decrease of 5 points or more in the Functional Assessment of Cancer Therapy-Breast Trial Outcome Index score was delayed in the T-DM1-treated patients (7.1 vs. 4.6 months; HR, 0.80; 95% CI: 0.67–0.95; $P = 0.012$).[37]

In the subgroup of patients who had relapsed within 6 months of completing adjuvant therapy and had not received any prior systemic anticancer treatment in the metastatic setting ($n = 118$), the median PFS in T-DM1 recipients was 10.8 months compared with 5.7 months in lapatinib plus capecitabine recipients (HR, 0.51; 95% CI: 0.30–0.85); median OS was not reached in the T-DM1 group and was 27.9 months in the lapatinib plus capecitabine group (HR: 0.61; 95% CI, 0.32–1.16).[39]

In EMILIA study, patients with asymptomatic central nervous system (CNS) metastases previously treated with radiotherapy were eligible to enroll 14 days after last radiotherapy treatment. In retrospective, exploratory analysis of patients with treated, asymptomatic CNS metastases at baseline, T-DM1 was associated with significantly improved OS of 26.8 months versus 12.9 months with lapatinib and capecitabine.[40]

Other Phase III studies

TH3RESA study compared T-DM1 with treatment of physician's choice (TPC) in patients with HER2-positive MBC, previously treated with a taxane (any setting), and both trastuzumab and lapatinib (advanced setting). PFS and OS were significantly longer in the T-DM1 compared with in the TPC group.[41,42]

MARIANNE study evaluated the benefit of T-DM1 in the first-line setting. Treatment with T-DM1 – either with placebo or pertuzumab – was compared with trastuzumab plus either docetaxel or paclitaxel. Study was powered at 80% for both noninferiority (established if the upper limit of the 97.5% CI for the HR is below 1.1765) and superiority (target HR = 0.75 [T-DM1/T-DM1+P vs. HT] and target HR = 0.73 [T-DM1+P vs. T-DM1], established if $P \leq 0.025$) analyses of PFS.[39] The study met the PFS

Table 3: Patients eligibility criteria-EMILIA study

Inclusion criteria
Progression during or after the most recent treatment for locally advanced or metastatic disease or within 6 months after treatment for early-stage disease, and a centrally confirmed HER2-positive status, 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
Patients with measurable disease (according to modified RECIST) and those with nonmeasurable disease were included
Left ventricular ejection fraction of 50% or more (determined by echocardiography or multiple-gated acquisition scanning)
Eastern Cooperative Oncology Group performance status of 0 (asymptomatic) or 1 (restricted in strenuous activity but ambulatory and able to do light work)
Exclusion criteria
Prior treatment with T-DM1, lapatinib, or capecitabine
Peripheral neuropathy of Grade 3 or higher (according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0) 14
Symptomatic central nervous system metastases or treatment for these metastases within 2 months before randomization
History of symptomatic congestive heart failure or serious cardiac arrhythmia requiring treatment
History of myocardial infarction or unstable angina within 6 months before randomization

T-DM1 – Trastuzumab emtansine; HER2 – Human epidermal growth factor receptor 2; RECIST – Response evaluation criteria in solid tumor

noninferiority endpoint and interim OS and ORR were also similar across treatment arms. However, neither of the T-DM1 treatment arms achieved a superior PFS compared with the trastuzumab-containing regimen.[43]

Results of Phase III studies of T-DM1 are summarized in Table 2.

Safety and Tolerability

EMILIA study

Thrombocytopenia (14.3%) was the most frequently reported Grade 3 or above adverse events (AEs) in patients treated with T-DM1, followed by increased AST (4.5%) and anemia (3.9%). Thrombocytopenia was mostly reported during/after the first two cycles of treatment, and with dose reductions, most patients were able to continue treatment. Overall, 2% of all patients discontinued therapy due to thrombocytopenia and <1% discontinued it due to transaminitis. The incidences of cardiac dysfunction were similar between the T-DM1 and capecitabine + lapatinib arms (0.2% vs. 0.6%). Most deaths occurring in the study were attributed to disease progression (123 in the lapatinib + capecitabine and 91 in the T-DM1).[37,38] Summary of Grade 3 or above AEs at final OS analysis in EMILA study is presented in Table 5.[38]

Safety data of 1871 patients in T-DM1 clinical studies of were evaluated. The most commonly reported all-grade adverse drug reactions (ADRs) were nausea (40%), fatigue (36.8%), musculoskeletal pain (35.5%), hemorrhage (34.8%), headache (28.1%),

Table 4: Summary of overall survival analyses EMILIA study

OS	Cap + Lap	T-DM1	HR (95% CI)	*P*	Stopping boundary
First interim analysis[a]					
n (percentage OS events)	129 (26.0)	94 (19.0)	0.62 (0.48-0.81)	0.0005	*P*<0.0003 or HR <0.617
Median (months)	23.3	NE			
Second interim analysis[b]					
n (percentage OS events)	182 (36.7)	149 (30.1)	0.68 (0.55-0.85)	0.0006	*P*<0.0037 or HR <0.727
Median (months)	25.1	30.9			
Final analysis[c]					
n (percentage OS events)	333 (67.1)	303 (61.2)	0.75 (0.64-0.88)	0.0003	Boundary met at second IA/descriptive only
Median (months)	25.9	29.9			
Sensitivity analysis with crossover patients censored[c]					
n (percentage OS events)	278 (56.0)	303 (61.2)	0.69 (0.59-0.82)	<0.0001	Descriptive only
Median (months)	24.6	29.9			

[a]Data cutoff January 2012; [b]Data cutoff July 2012; [c]Data cutoff December 2014. Cap + Lap – Capecitabine plus lapatinib; CI – Confidence interval; HR – Hazard ratio; IA – Interim analysis; OS – Overall survival; T-DM1 – Trastuzumab emtansine; NE – Not estimable

Table 5: Summary of grade ≥3 adverse events with at least 2% incidence in either arm at the final overall survival analysis-EMILA study

Grade ≥3 AEs, *n* (%)	Second interim OS analysis[a]		Final OS analysis[b]		
	Cap + Lap (*n*=488)	T-DM1 (*n*=490)	Cap + Lap (*n*=488)	T-DM1 (*n*=491)	Crossover (*n*=136)
Diarrhea	102 (20.9)	9 (1.8)	103 (21.1)	9 (1.8)	1 (0.7)
PPE syndrome	86 (17.6)	0	87 (17.8)	0	0
Vomiting	22 (4.5)	4 (0.8)	24 (4.9)	5 (1.0)	1 (0.7)
Hypokalemia	21 (4.3)	11 (2.2)	22 (4.5)	11 (2.2)	0
Neutropenim	21 (4.3)	11 (2.2)	21 (4.3)	11 (2.2)	2 (1.5)
Fatigue	17 (3.5)	12 (2.4)	17 (3.5)	12 (2.4)	2 (1.5)
Nausea	12 (2.5)	4 (0.8)	13 (2.7)	4 (0.8)	0
Anemia	11 (2.3)	17 (3.5)	11 (2.3)	19 (3.9)	4 (2.9)
Mucosal inflammation	11 (2.3)	1 (0.2)	11 (2.3)	1 (0.2)	0
ALT increased	8 (1.6)	15 (3.1)	9 (1.8)	15 (3.1)	0
Asthenia	8 (1.6)	2 (0.4)	9 (1.8)	4 (0.8)	4 (2.9)
Rash	10 (2.0)	0	8 (1.6)	0	1 (0.7)
AST increased	6 (1.2)	22 (4.5)	7 (1.4)	22 (4.5)	2 (1.5)
Thrombocytopenia	2 (0.4)	68 (13.9)	2 (0.4)	70 (14.3)	6 (4.4)
GGT increased	0	4 (0.8)	0	6 (1.2)	3 (2.2)

[a]Data cutoff July, 2012; [b]Data cutoff December 2014. AEs – Adverse events; ALT – Alanine transaminase; AST – Aspartate transaminase; Cap + Lap – Capecitabine plus lapatinib; GGT – Gamma-glutamyl transpeptidase; OS – Overall survival; PPE – Palmar-plantar erythrodysesthesia; T-DM1 – Trastuzumab emtansine

and thrombocytopenia (24.9%). The most common Grade 3/4 ADRs were the laboratory abnormalities of thrombocytopenia (8.7%), increased transaminase (7.2%), and anemia (3.8%). The left ventricular dysfunction occurred 0.4% (grade 3–5).[44]

Real world experience

Yardley *et al*. evaluated safety profile of T-DM1 in the real-world setting. In this expanded-access, multicenter study of T-DM1 in US patients with pretreated HER2-positive locally advanced BC or MBC, the most commonly reported AEs were fatigue (50.7%) and nausea (38.1%). Grade 3 or greater AEs were reported by 46.5% patients. Thrombocytopenia and platelet count decrease (10.2%) were most commonly reported Grade 3 or greater AEs. Cardiac dysfunction (primarily asymptomatic LVEF decreases) was reported in 6.5% patients. Authors concluded that the safety profile of T-DM1 in this real-world setting of heterogeneous, HER2-positive, pretreated, locally advanced BC or MBC was comparable with that reported in Phases II and III studies of similar patient populations, with no new safety signals.[45]

Dosage and Administration

The recommended dose of T-DM1 is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle), until disease progression or unacceptable toxicity. Initial dose is administered as a 90 min infusion and patient observed for 90 min; if initial dose is well-tolerated subsequent doses of T-DM1 can be administered as 30 min infusions.[44] Monitoring of hematology parameters, serum transaminases, bilirubin, and LVEF in patients before and during treatment with T-DM1 is recommended. Dose reductions or interruptions may be required in cases of increased serum transaminases, hyperbilirubinemia, thrombocytopenia, decreased LVEF, or peripheral neuropathy.[44] Practitioners are advised to refer to local prescribing information of Kadcyla® (T-DM1) for guidance on dose reductions and interruptions in scenario of these AEs.

Clinical Practice Guidelines

Based on the results of the EMILIA trial, major international guidelines recommend T-DM1 for treatment of patients with HER2-positive MBC who have previously received a trastuzumab-based regimen.[46-49]

Future Directions

Ongoing Phase III trials KATHERINE (NCT01772472)[50] and KAITLIN (NCT01966471)[51] will define the role of T-DM1 plays in the treatment of patients with early-stage HER2-positive BC. In addition, understanding resistance to T-DM1 will be important, as some patients are primarily nonresponsive or minimal responsive drug or progress over time. This will help to develop treatment strategies for further improvement of its efficacy and possibly circumvent drug resistance.

Conclusion

T-DM1 represents a unique approach for the treatment of HER2-positive BC that has progressed during or after therapy with trastuzumab and a taxane. Its novel MOA allows targeted delivery of chemotherapy to HER2 overexpressing cells, thereby increasing antitumor effect and minimizing toxicity. The published Phase I and II studies, along with results of two large randomized Phase III trials, have demonstrated that T-DM1 significantly improves PFS and OS, amid lower incidence of Grade 3 or above AEs, as compared to standard of care therapies. In addition, localized treatment for stable CNS disease followed by T-DM1 improved clinical outcomes. To conclude, T-DM1 offers improved safety and efficacy both in the second as well as subsequent line treatment setting and after early relapse on adjuvant trastuzumab therapy. It will be interesting to view the outcomes of ongoing studies in early setting, which may further pave the way for improvement in disease-free survival, quality of life, and other treatment outcomes.

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Conflicts of interest

The authors have no conflicts of interest to declare except for Dr. Jagdish Nigade and Dr. Binay Swarup who are full–time employees of Roche Products (India) Pvt. Ltd.

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