

Ado-Trastuzumab Emtansine (Kadcyla®)**National Drug Monograph****December 2014****VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Ado-trastuzumab emtansine (T-DM1) is a HER2-antibody-drug conjugate (ADC) that incorporates a HER2-targeted antibody (trastuzumab) with a microtubule inhibitor conjugate (maytansine or DM1) through a linker which is a nonreducible thioether bond. Mechanistically, T-DM1 is internalized when binding to HER2-overexpressed tumor cells occurs. At that point, proteolytic degradation occurs, releasing maytansine within the cell.
Indication(s) Under Review in this document (may include off label)	FDA-approval is as a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer that have previously received trastuzumab and a taxane, separately or in combination. Patients should have either: <ol style="list-style-type: none"> 1) Received prior therapy for metastatic disease, or 2) Developed disease recurrence during or within 6 months of completing adjuvant therapy
Dosage Form(s) Under Review	Ado-trastuzumab 100mg or 160 mg of lyophilized powder in single-use vials for injection
REMS	<input type="checkbox"/> REMS <input checked="" type="checkbox"/> No REMS <i>See Other Considerations for additional REMS information</i>
Pregnancy Rating	Pregnancy Category D

Executive Summary

Efficacy	<ul style="list-style-type: none"> • EMILIA was a phase 3 trial comparing ado-trastuzumab emtansine to lapatinib/capecitabine in the second-line setting for patients with HER2-positive MBC. • Improvement in Progression-Free Survival (PFS) as well as OS was noted in the ado-trastuzumab emtansine arm.
Safety	<ul style="list-style-type: none"> • Boxed Warning: Do not substitute ado-trastuzumab emtansine for or with trastuzumab. Potential for medication errors due to Look Alike Sound Alike generic names. • Boxed Warning: Risk of hepatotoxicity. Monitoring at baseline and prior to each dose is recommended. • Boxed Warning: Risk of cardiac toxicity as reductions in Left Ventricular Ejection Fraction (LVEF) noted. Monitoring at baseline and throughout course of therapy is recommended. • Boxed Warning: Risk of embryo-fetal toxicity. Patients should be aware of this and the need for effective contraception during and post-therapy. • Patients at increased potential for bleeding due to concomitant conditions or medications, may further increase their risk for bleeding due to risk of hemorrhage as well as the risk of thrombocytopenia noted in the ado-trastuzumab emtansine arm of the clinical trial. Additional monitoring of these patients is suggested.

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Other Considerations	<ul style="list-style-type: none"> HER2 testing is essential to determine if patients are appropriate for ado-trastuzumab emtansine therapy. Selected laboratories need to be proficient with IHC and FISH technology to ensure reliable results. 								
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Potential Impact	<ul style="list-style-type: none"> Projected place in therapy. The American Society of Clinical Oncology (ASCO) Guidelines on Systemic therapy for patients with advanced HER2-positive breast cancer and latest update of National Comprehensive Cancer Network (NCCN) Guidelines include ado-trastuzumab emtansine as a second-line treatment recommendation for patients who have progressed during or after first-line HER2-targeted therapy. ASCO Guidelines also recognize that patients may not have received ado-trastuzumab emtansine as second-line therapy. In such cases, the Guidelines recommend that ado-trastuzumab emtansine be considered as subsequent therapy. Patient convenience. Ado-trastuzumab emtansine is an injectable therapy administered every 3 weeks. The logistics of an injectable therapy may make the lapatinib/capecitabine all-oral regimen a more convenient option for some patients. 								

Background

Purpose for review

Recent FDA approval

Issues to be determined:

- Does the use of ado-trastuzumab emtansine provide a benefit beyond the current standard?
- Should we expect this benefit in our Veteran population?
- What safety issues need to be considered?
- Does ado-trastuzumab emtansine have specific characteristics that are best managed by the non-formulary process, prior authorization or CFU?

Other therapeutic options for HER2-positive advanced or metastatic breast cancer with prior exposure to trastuzumab

Non-formulary Alternative	Other Considerations (For example efficacy, dosing regimen, safety concerns, storage limitations, etc.)
Lapatinib + Capecitabine	Oral; Oral
Trastuzumab (H) + Capecitabine	Injectable; Oral
H + Lapatinib	Injectable; Oral (cytotoxic-sparing regimen)

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to October 2014) using the search terms <ado-trastuzumab, T-DM1> and <Kadcyla >. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

Trial	Criterion	Intervention	Results
Verma (2012) EMILIA R, OL, P3 N=991 patients T-DM1 ado-trastuzumab emtansine L lapatinib C capecitabine	Inclusion PD during or after treatment with taxane and trastuzumab for Locally advanced (LA) or metastatic breast cancer; or within 6 months after treatment for early-stage disease; HER2 + via IHC 3+ or FISH amplification ratio ≥ 2 or both; LVEF $\geq 50\%$ via MUGA; ECOG PS 0 or 1	Randomized 1:1 T-DM1 vs. Lapatinib/capecitabine T-DM1 3.6 mg/kg IV every 21 days Lapatinib 1250 mg PO daily Capecitabine 1000 mg/m ² PO every 12 hours, days 1-14; repeat every 21 days Tumor assessments: baseline, q6 weeks LVEF: baseline, weeks 6, 12 and q12weeks until DC	T-DM1 vs. Lapatinib/capecitabine Primary endpoint: PFS, OS, safety Secondary: PFS (investigator-assessed), ORR, DOR, Time to symptom progression At 1 st interim analysis ~ 13 mos Median PFS 9.6 vs. 6.4 months; HR 0.65 (95% CI, 0.55-0.77); p<0.001 At 2 nd interim analysis ~ 19 mos Median OS 30.9 vs. 25.1 months; HR 0.68 (95% CI, 0.55-0.85); p< 0.001
Krop (2014) TH3RESA R, OL P3 N=602 patients 22 countries	Inclusion Age ≥ 18 years; LVEF $\geq 50\%$; ECOG PS 0-2; HER2-positive advanced br ca; s/p ≥ 2 HER2-directed regimens in the advanced setting (including both trastuzumab and lapatinib)	Randomized 2:1 T-DM1 vs. Physician's choice Stratified: Region (USA vs. western Europe vs. other); Number of previous regimens (2-3 vs. ≥ 3); Visceral disease (any vs. none)	T-DM1 vs. Physician's choice (PC) 83% PC included combo therapy with trastuzumab and/or lapatinib 17% PC included single-agent chemotherapy Co-primary endpoints: Investigator-assessed PFS; OS (ITT) PFS 6.2 vs. 3.3 mos HR 0.528 [95% CI, 0.422-0.661] p<0.0001 Consistent benefit across all subgroups OS trending to favor T-DM1, but did not meet stopping boundary

Metastatic Breast Cancer (MBC), second-line

- FDA-approval of ado-trastuzumab emtansine in MBC was supported by data from the EMILIA study group that compared ado-trastuzumab emtansine to the combination of lapatinib/capecitabine in patients who have been previously treated with trastuzumab and a taxane.
- The primary endpoint of median PFS, assessed by independent review, was greater in the ado-trastuzumab emtansine arm, compared to the lapatinib/capecitabine arm. At 13 months, median PFS was 9.6 vs. 6.4 months, respectively.
- Overall Survival (OS) was significantly greater in the ado-trastuzumab emtansine arm with a median OS of 30.9 vs. 25.1 months, respectively. This data was noted at the second interim analysis. Data at the first interim analysis did not meet the predefined stopping boundary.
- All prespecified secondary efficacy endpoints (i.e. investigator-assessed PFS, ORR and median DOR) favored the ado-trastuzumab emtansine arm.
- ASCO Clinical Practice Guideline recommends that ado-trastuzumab be considered as a second-line treatment in advanced HER2-positive breast cancer that has progressed during or after first-line HER2-targeted therapy. This recommendation is based upon data from the EMILIA trial: Evidence quality is high; Strength of recommendation is strong.
- NCCN Guidelines list ado-trastuzumab as a preferred therapy in the second-line setting of HER2-positive recurrent or stage IV breast cancer.

Advanced Breast Cancer, after multiple HER2-directed therapies

- The TH3RESA trial evaluated ado-trastuzumab emtansine vs. physician's choice regimens in patients with advanced breast cancer who have received at least two HER2-directed therapies that included trastuzumab and lapatinib.
- Physician's choice included combination regimens of trastuzumab and/or lapatinib and single-agent chemotherapy. The majority (83%) received combinations of prior HER2-directed therapies, while 17% received various single-agents with activity in breast cancer.
- The primary endpoint of PFS was statistically improved in the ado-trastuzumab emtansine arm compared to physician's choice. PFS was 6.2 vs. 3.3 months HR 0.528 [95% CI, 0.422-0.661] p<0.0001 in the ado-trastuzumab emtansine vs. physician's choice arm, respectively.
- Consistent benefit was noted with ado-trastuzumab emtansine across all subgroups, which included age, hormone receptor status, visceral involvement, number of prior regimens.
- A benefit in OS favored T-DM1, but did not meet the predefined stopping boundary (HR 0.37). Numerically higher values were noted with ado-trastuzumab emtansine vs. physician's choice, respectively: estimated 6-months survival 90.9 vs. 78.3% and 1-year survival 68.6 vs. 56.9 %.

Potential Off-Label Use

The following trials can be found in www.clinicaltrials.gov

- In the adjuvant or neoadjuvant setting for HER2-positive early stage breast cancer
- Treatment of metastatic HER2-positive breast cancer and have not received prior chemotherapy for metastatic disease. The MARIANNE study is a phase 3 trial to evaluate safety and efficacy of ado-trastuzumab emtansine combined with pertuzumab vs. ado-trastuzumab emtansine plus pertuzumab placebo vs. trastuzumab plus taxane as first-line therapy in HER2-positive advanced or metastatic breast cancer. Results are anticipated in 2016.
- Treatment of advanced HER2-positive gastric cancer

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	<ul style="list-style-type: none"> • Do not substitute ado-trastuzumab emtansine for or with trastuzumab. • Risk of hepatotoxicity, liver failure and death has occurred. Monitor hepatic function at baseline and prior to each dose. Dose-modify and/or permanently discontinue as appropriate. • Risk of cardiac toxicity, as ado-trastuzumab may lead to reductions in left ventricular ejection fraction (LVEF). Assess LVEF at baseline and monitor throughout therapy. Consider holding therapy or discontinue based upon significant decline in LV function. • Risk of embryo-fetal toxicity, as exposure can result in embryo-fetal death or birth defects. Advise patients of these risks and the need for effective contraception.
Contraindications	<ul style="list-style-type: none"> • None
Warnings/Precautions	<ul style="list-style-type: none"> • Do not substitute ado-trastuzumab emtansine for or with trastuzumab, they are not interchangeable. • Hepatotoxicity. In the clinical trial setting, ado-trastuzumab has been associated with asymptomatic, transient increases in serum transaminase concentrations. At least 2 fatal cases of severe drug-induced liver injury and hepatic encephalopathy have been reported. Monitor serum transaminases and bilirubin prior to initiation of ado-trastuzumab and each dose. Dose-reduce or discontinue drug as appropriate in setting of elevated LFTs. Permanent discontinuation of drug is recommended in patients with serum transaminases > 3x ULN and concomitant total bilirubin > 2x ULN. The drug has not been studied in patients with serum transaminases > 2.5x ULN or bilirubin > 1.5x ULN at baseline. Nodular Regenerative Hyperplasia (NRH) of the liver has been identified from liver biopsies. This condition can lead to non-cirrhotic portal hypertension. If NRH is diagnosed, ado-trastuzumab must be permanently discontinued. • Left Ventricular Dysfunction. A decrease in LVEF to < 40% has been observed in patients treated with ado-trastuzumab. LV decline was noted in 1.8 vs. 3.3% of the ado-trastuzumab vs. lapatinib/capecitabine-treated arms, respectively. LVEF should be assessed at baseline and at regularly scheduled intervals (e.g. every 3 months). If LVEF is < 40% or between 40-45% with a \geq 10% absolute decrease below baseline value, ado-trastuzumab should be withheld and LVEF repeated in approximately 3 weeks. Drug should be permanently discontinued if LVEF has not improved or declines further. Those with a history of symptomatic

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CHF, serious cardiac arrhythmia, history of MI, unstable angina within 6 months of start of study or baseline LVEF < 50% were excluded from the clinical trial.

- **Embryo-Fetal Toxicity.** There are no adequate and well-controlled trials of ado-trastuzumab in pregnant women. Treatment with trastuzumab, the antibody component, during pregnancy, has resulted in oligohydramnios, some associated with fatal pulmonary hypoplasia, skeletal abnormalities and neonatal death. Based upon the mechanism of action of the cytotoxic component of ado-trastuzumab emtansine, embryo-fetal toxicity can be expected. If used during pregnancy, or if the patient becomes pregnant while receiving drug, they should be informed of the potential hazard to the fetus. Pregnancy status should be verified prior to initiation of drug. Patients should be advised of the risks and need for contraception during and after treatment.
- **Pulmonary Toxicity.** Interstitial Lung Disease (ILD), including pneumonitis, has been reported in clinical trials with ado-trastuzumab emtansine. Some cases have led to acute respiratory distress syndrome or fatalities. Pneumonitis was reported in 0.8% (7/884 patients) with one grade 3 case. The overall frequency of pneumonitis was 1.2% in the randomized trial. Signs and symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates. Treatment with ado-trastuzumab emtansine should be permanently discontinued in patients with ILD or pneumonitis. Those with dyspnea at rest due to comorbidities or advanced disease may be at increased risk of toxicity.
- **Infusion-Related Reactions (IRR), Hypersensitivity Reactions.** Infusion-related reactions have been reported in clinical trials of ado-trastuzumab emtansine. Symptoms have included flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm and tachycardia. The overall frequency of IRR was 1.4%. Reactions typically resolved over a period of a few hours to a day after the infusion. Drug treatment should be interruption in the case of severe IRR and permanently discontinued in the case of life-threatening IRR. Observe patients closely for IRR, especially during the first infusion. Medication and emergency equipment to treat serious, allergic, anaphylactic-like reactions should be available for immediate use.
- **Hemorrhage.** The overall frequency of hemorrhage was 32.2 vs. 16.4% in the ado-trastuzumab emtansine vs. lapatinib/capecitabine groups, respectively. Grade 3 hemorrhage was reported in 1.8 vs. 0.8% of ado-trastuzumab emtansine vs. lapatinib/capecitabine groups, respectively. Use caution in patients with thrombocytopenia and/or receiving concomitant anticoagulation or antiplatelet therapy. Consider additional monitoring in these situations.
- **Thrombocytopenia.** The overall frequency of thrombocytopenia was 31.2 vs. 3.3% of ado-trastuzumab emtansine vs. lapatinib/capecitabine groups, respectively. Grade 3 thrombocytopenia was noted in 14.5 vs. 0.4% of ado-trastuzumab emtansine vs. lapatinib/capecitabine groups, respectively. Asian patients experienced greater incidence and severity of Grade 3/4 thrombocytopenia (45.1 vs. 1.3%, in ado-trastuzumab emtansine vs. lapatinib/capecitabine groups, respectively). Monitor platelet counts prior to initiation of ado-trastuzumab emtansine and prior to each dose. If platelet counts should fall to < 50,000/mm³, hold therapy

until recovery to $75,000/\text{mm}^3$. Patients with platelet count $< 100,000/\text{mm}^3$ with concomitant anticoagulant therapy should be monitored closely during therapy.

- Neurotoxicity. Peripheral neuropathy (primarily sensory) was reported in clinical trials. The incidence was 21.2% vs. 13.5% in the ado-trastuzumab emtansine vs. lapatinib/capecitabine arms, respectively. Grades 3 or 4 neuropathy were reported in 2.2 vs. 0.2%, respectively. Temporarily discontinue ado-trastuzumab emtansine until neuropathy resolves to Grade 2 or less. Monitor patients on an ongoing basis for signs or symptoms of neuropathy.
 - HER2 Testing. HER2 protein overexpression or gene amplification is necessary to determine if patients are appropriate for ado-trastuzumab emtansine therapy. Patients within the clinical trial were required to have evidence of HER2 overexpression defined as 3+ IHC by Dako Herceptest™ or evidence of overexpression defined as FISH amplification ratio ≥ 2.0 by Dako HER2 FISH PharmDx™ test kit. Assessment of HER2 status should be performed by laboratories with demonstrated proficiency in the technology utilized for reliable results.
 - Extravasation. Reactions secondary to extravasation have been observed. They are usually mild and include erythema, tenderness, skin irritation, pain or swelling at the infusion site and frequently occur within 24 hours of drug infusion. Monitor the infusion site closely for possible subcutaneous extravasation during administration. Specific treatment for extravasation is unknown.
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Safety Considerations

- HER2 testing is essential to determine if patients are appropriate for ado-trastuzumab emtansine therapy. Selected laboratories need to be proficient with IHC and FISH technology to ensure reliable results.
- Look Alike Sound Alike potential for medication errors due to similarity in names between ado-trastuzumab emtansine and trastuzumab.
- Potential for decline in LVEF needs to be considered prior to therapy initiation. Diligent monitoring should be performed throughout the course of therapy. Patients with a history of symptomatic CHF, serious cardiac arrhythmia, history of MI, unstable angina within 6 months of start of study or baseline LVEF $< 50\%$ were excluded from the clinical trial, therefore it is unknown how ado-trastuzumab emtansine may impact their cardiac function.
- Inform patients of the possibility of liver injury and potential signs/symptoms. Hepatotoxicity, liver failure and death have occurred. Monitor hepatic function at baseline and prior to each dose. Dose-modify and/or permanently discontinue as appropriate.
- Risk of embryo-fetal toxicity, as exposure can result in embryo-fetal death or birth defects. Advise patients of these risks and the need for effective contraception. Perform a pregnancy test before initiating therapy in women of childbearing potential and periodically throughout treatment if risk of pregnancy is questionable.
- Patients at increased potential for bleeding due to concomitant conditions or medications, may further increase their risk for bleeding due to risk of hemorrhage as well as the risk of thrombocytopenia noted in the ado-trastuzumab emtansine arm of the clinical trial. Additional monitoring of these patients is recommended.
- Sensory peripheral neuropathy was experienced at increased frequency among those treated with ado-trastuzumab emtansine. Recognition and holding drug doses can help to lessen the severity of neuropathy. Patients should be monitored for peripheral neuropathy and doses held as necessary.

Adverse Reactions

Common adverse reactions	Incidence \geq 25%: fatigue, nausea, musculoskeletal pain, hemorrhage, thrombocytopenia, headache, increased transaminases, constipation, epistaxis
Death/Serious adverse reactions	Most common events \geq Grade 3 were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy and fatigue; hepatic failure was observed in 2 patients (0.2%) with ado-trastuzumab emtansine as a single-agent.
Discontinuations due to adverse reactions	6.5% discontinued ado-trastuzumab emtansine, compared to 8.4% who discontinued lapatinib and 10.5% who discontinued capecitabine; the most common events leading to withdrawal include thrombocytopenia, increased transaminases

Drug Interactions**Drug-Drug Interactions**

- Although no formal drug-drug interaction studies with ado-trastuzumab emtansine have been conducted, the cytotoxic component (DM1) is thought to be metabolized by CYP3A4 and CYP3A5 (minor route). Concomitant use of strong CYP3A4 inhibitors should be avoided due to the potential for increased DM1 exposure and toxicity. Consider an alternative medication with no CYP3A4 inhibiting potential. If this is not possible, consider delaying ado-trastuzumab emtansine treatment until the CYP3A4 inhibitors have cleared the circulation (approximately 3 half-lives). If this interaction is unavoidable and treatment cannot be delayed, closely monitor patients for adverse reactions.

Risk Evaluation

As of October 24, 2014

Comments

Sentinel event advisories	<ul style="list-style-type: none"> None Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	<ul style="list-style-type: none"> Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

NME Drug Name	Lexi-Comp	First Data Bank	ISMP	Clinical Judgment
Ado-trastuzumab emtansine 100mg or 160mg IV	Pertuzumab Trastuzumab	None	Trastuzumab	Adalimumab Alemtuzumab
Kadcyla	None	None	None	Kalydeco Keytruda

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Other Considerations

- The American Society of Clinical Oncology (ASCO) Guidelines on Systemic therapy for patients with advanced HER2-positive breast cancer and the latest update of National Comprehensive Cancer Network (NCCN) Guidelines include ado-trastuzumab in their treatment recommendations for MBC. Cost analyses are not considered in their Guideline.
- The National Institute for Health and Care Excellence (NICE) Evidence Review Group (ERG) published their final appraisal determination August 2014. They concluded that ado-trastuzumab emtansine, for the treatment of HER2-positive, unresectable, locally advanced or MBC after treatment with trastuzumab and a taxane, did not represent a cost-effective use of resources.
- The Scottish Medicines Consortium (SMC) reviewed the use of ado-trastuzumab emtansine as a single agent for HER2-positive, advanced or MBC in patients who have previously received trastuzumab and a taxane. They do not recommend its use within NHS Scotland.
- The European Medicines Agency (EMA) publishes a European Public Assessment Report (EPAR) for every medicine granted a central marketing authorization by the European Commission following an assessment by the EMA's Committee for Medicinal Products for Human Use (CHMP). EPARs are full scientific assessment reports of medicines authorized at a European Union level. The Agency decided that the benefits of ado-trastuzumab emtansine outweigh its risks and recommends use in the European Union.

Outcome in clinically significant area	PFS 9.6 vs. 6.4 months (ado-trastuzumab emtansine vs. lapatinib/capecitabine, respectively)
Effect Size	HR 0.65 [95% CI: 0.55-0.85]; p<0.001
Potential Harms	All grades (> 20%): fatigue, musculoskeletal pain, peripheral neuropathy, hemorrhage, nausea Grade 3/4: Thrombocytopenia (14%); Anemia (4.1%)
Net Clinical Benefit	Substantial (high benefit with low risk of harm)

Definitions

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life

Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio

Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)

Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Dosing and Administration

- Refer to the package insert for full dosing information.

Special Populations (Adults)

	Comments
Elderly	<ul style="list-style-type: none"> • In the clinical trial, 13% were aged ≥ 65 years and 2% were aged ≥ 75 years. The hazard ratios for patients ≥ 65 years (n = 138 across both treatment arms) for PFS was 1.06 (95% CI: 0.68, 1.66) and for OS was 1.05 (95% CI: 0.58, 1.91). Population pharmacokinetic analysis indicates that age does not have a clinically meaningful effect on the pharmacokinetics of ado-trastuzumab emtansine.
Pregnancy	<ul style="list-style-type: none"> • Pregnancy Category D. Fetal harm may result when treating a pregnant woman. No adequate or well-controlled studies have been performed with ado-trastuzumab emtansine in pregnant women. The components of trastuzumab and DM1 are suspected to cause fetal harm. Consider performing a pregnancy test before initiating therapy in women of childbearing potential and periodically throughout treatment if risk of pregnancy is questionable. If given during

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	pregnancy or if a patient becomes pregnant while receiving drug, inform the patient of the potential hazard to the fetus. Advise patients to use effective contraception during treatment and for 6 months following the last dose of ado-trastuzumab emtansine.
Lactation	<ul style="list-style-type: none"> It is not known if ado-trastuzumab emtansine is specifically excreted in breast milk, but IgG is; a decision concerning the importance of the drug to the mother with the potential risk to the nursing infant should be addressed.
Renal Impairment	<ul style="list-style-type: none"> Based on population pharmacokinetics and analysis of Grade 3 or greater adverse drug reactions and dose-modifications, adjustments of ado-trastuzumab emtansine are not needed in patients with mild (defined as CrCl 60-89 ml/min) or moderate (CrCl 30-59 ml/min) renal impairment. No dose adjustment can be recommended in cases of severe renal impairment (CrCl < 30 ml/min).
Hepatic Impairment	<ul style="list-style-type: none"> <i>In vitro</i> data indicates that DM1 is metabolized by CYP3A4/5; the influence of hepatic insufficiency on pharmacokinetic variables has not been determined.
Pharmacogenetics/genomics	<ul style="list-style-type: none"> No data identified.

Projected Place in Therapy

- Approximately 200,000 new cases of breast cancer are expected to be diagnosed each year with about 40,000 deaths. Metastatic breast cancer is the initial diagnosis in ~ 5% of the population, while ~ 30% of those with early stage breast cancer will at some point, develop metastatic disease.
- It is estimated that 15-20% of patients with breast cancer have HER2-overexpression. HER2-overexpression is associated with shortened survival, decreased time to relapse and increased incidence of metastatic disease compared to breast tissue in which HER2 is not overexpressed.
- HER2-targeted therapy has improved outcomes in this population. The combination of trastuzumab and taxane-agent has increased OS and PFS in the first-line management of MBC. Unfortunately, resistance to trastuzumab is a common finding within a year of treatment initiation.
- The combination of lapatinib and capecitabine has improved time-to-progression in patients previously treated with trastuzumab, an anthracycline and a taxane and has become a second-line option in HER2-positive MBC.
- The American Society of Clinical Oncology (ASCO) Guidelines on Systemic therapy for patients with advanced HER2-positive breast cancer and latest update of National Comprehensive Cancer Network (NCCN) Guidelines include ado-trastuzumab emtansine as a second-line treatment recommendation for patients who have progressed during or after first-line HER2-targeted therapy.
- ASCO Guidelines also recognize that patients may not have received ado-trastuzumab emtansine as second-line therapy. If patients progress during or after second-line or greater HER2-targeted therapy, and have not yet received ado-trastuzumab emtansine, the recommendations from ASCO and NCCN are consistent in recommending that ado-trastuzumab emtansine be offered at that time. Evidence GRADE. Evidence quality: high ; strength of recommendation: strong
- EMILIA is a phase 3 trial comparing ado-trastuzumab emtansine to lapatinib/capecitabine in previously treated patients with HER2-positive MBC. Improvement in PFS as well as OS was noted in the ado-trastuzumab emtansine arm. Evidence GRADE. Evidence quality: high; strength of recommendation: strong
- Despite the improvement in overall survival, ado-trastuzumab emtansine is an injectable therapy administered every 3 weeks. The logistics of an injectable therapy may make the lapatinib/capecitabine all-oral regimen a more convenient option for some patients.

References

Kadcyla [prescribing information]. South San Francisco, CA: Genentech, Inc. July 2014.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation Description

High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.

Appendix B: Approval Endpoints (use for oncology NMEs)

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	<ul style="list-style-type: none"> • Randomized studies essential • Blinding not essential 	<ul style="list-style-type: none"> • Universally accepted direct measure of benefit • Easily measured • Precisely measured 	<ul style="list-style-type: none"> • May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	<ul style="list-style-type: none"> • Randomized blinded studies 	<ul style="list-style-type: none"> • Patient perspective of direct clinical benefit 	<ul style="list-style-type: none"> • Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Randomized studies essential • Blinding preferred • Blinded review recommended 	<ul style="list-style-type: none"> • Smaller sample size and shorter follow-up necessary compared with survival studies 	<ul style="list-style-type: none"> • Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended 	<ul style="list-style-type: none"> • Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history 	<ul style="list-style-type: none"> • Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended 	<ul style="list-style-type: none"> • Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies 	<ul style="list-style-type: none"> • Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression-Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Randomized studies essential • Blinding preferred • Blinded review recommended 	<ul style="list-style-type: none"> • Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment 	<ul style="list-style-type: none"> • Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.