February 28, 2020

[redacted], MS RAC
[redacted]

Dear [redacted]

Enclosed is Addendum #24 to EAY131-Q, *Molecular Analysis for Therapy Choice (MATCH): Ado-trastuzumab Emtansine in Patients with Tumors with HER2 Amplification (Except Breast and Gastric/Gastro-Esophageal Junction (GEJ) Adenocarcinomas).*

Please replace your current copy of the protocol and Informed Consent document with these updated versions. We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

IRB Review Requirements:

This addendum has been reviewed and approved by the Central IRB, which is the sole IRB of record for this study. Local IRB review and approval is unnecessary.

Implementation of this addendum must occur on the activation date. Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.

The following are ECOG-ACRIN's responses to the CTEP's Review of **Amendment # 24** of Protocol # EAY131-Q, entitled, "*Ado-trastuzumab Emtansine in Patients with Tumors with HER2 Amplification (Except Breast and Gastric/Gastro-Esophageal Junction (GEJ) Adenocarcinomas)"* dated December 16, 2019, from the disapproval of Addendum #24 first submission to CTEP. Please note that the Principal Investigator's comments appear in bold below:

I. Comments Requiring a Response– Administrative & Editorial Issues:

#	Section	Comments
1.	*Title page of Appendix III*	As a reminder, Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy requires all persons participating in any NCI-sponsored clinical trial to register. Protocol activation will be delayed until all investigators on the CS-MATCH-0012 title page are appropriately registered in RCR. These study contributors also need to be claimed on the ECOG-ACRIN roster. Our records indicate: • [redacted] has a person registration that expires January 17,

28 State Street, Suite 1100, Boston, MA 02109 p: 857.504.2900 f: 617. 589.0914 ecog-acrin.org

#	Section	Comments
		2020. Please renew as soon as possible. • [redacted], PhD has never been registered. Please register as person registration type of Associate Plus (AP) or higher. • [redacted], PhD [redacted] has a suspended person registration. Please re-register as soon as possible. **To re-register, please log into the NCI Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr/ using CTEP-IAM username and password and complete the required information.** If you need to update your **CTEP-IAM account** information, please visit: https://ctepcore.nci.nih.gov/iam . **For guidance** on registering via RCR, please visit: https://ctep.cancer.gov/investigatorResources/default.htm . If you have questions or encounter difficulties, please contact the CTEP Registration and Credential Repository (RCR) Team at RCRHelpDesk@nih.gov at any time. **PI Response: These registrations have been updated.**

Additional Changes by Principal Investigator:

The following revisions to EAY131-Q protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date.
2.	Appendix III	Inserted CS-MATCH-0012 correlative study.

The following revisions to EAY131-Q Informed Consent Document have been made in this addendum:

	Section	Change
1.	Page 1	Updated Version Date.

If you have any questions regarding this addendum, please contact aagu@ecog-acrin.org or 857-504-2900.

We request review and approval of this addendum to EAY131-Q so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

[redacted]

[redacted]

Enclosure

CC: [redacted], MD, FACP
[redacted], MD
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Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol Q: Ado-trastuzumab Emtansine in Patients with Tumors with HER2 Amplification (Except Breast and Gastric/Gastro-Esophageal Junction (GEJ) Adenocarcinomas)

ADO-TRASTUZUMAB EMTANSINE TREATMENT SUBPROTOCOL CHAIR: [redacted], MD, FACP

ADO-TRASTUZUMAB EMTANSINE TREATMENT SUBPROTOCOL CO-CHAIR: [redacted], MD

ADO-TRASTUZUMAB EMTANSINE TRANSLATIONAL CHAIR: [redacted], MD

Version Date: February 28, 2020
NCI Update Date: August 12, 2015

NOTE: This subprotocol (EAY131-Q) should be used in conjunction with the MATCH Master Protocol (EAY131).

Rev. Add16 **NOTE: As of 11/17, all protocol changes will be noted by addendum number. Please reference the activation memo for the addendum activation date**

SUBPROTOCOL ACTIVATION DATE

August 12, 2015 (Incorporated in Addendum #1)
Update #2 – 8/15
Addendum #2 – 2/16
Addendum #3 – 5/16
Addendum #5 – 12/16
Addendum #6 – 1/17
Addendum #7 – 3/17
Addendum #16
Addendum #17
Addendum #24

Agent		NSC#	Supply
Ado-trastuzumab emtansine		780263	NCI Supplied

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TREATMENT SUBPROTOCOL CHAIR

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Rev. 3/17

Schema

Cycle = 21 days
Accrual Goal: 70
***Please refer to sections 3.4 and 3.6**

1. Introduction

The National Cancer Institute (NCI) - Molecular Analysis for Therapy Choice (MATCH) is a broad-based genetic pre-screening study to assign patients whose tumors harbor specific molecular abnormalities to relevant targeted therapies, regardless of tumor type. This trial aims to establish whether patients with tumor mutations, amplifications or translocations in one of the genetic pathways of interest are likely to derive clinical benefit (defined as objective response) if treated with agents targeting that specific pathway in a single-arm design. It will also investigate whether agents proven or likely to have activity against a molecular alteration in one disease will exhibit similar activity in other diseases that have the same molecular alterations. This subprotocol focuses on evaluating ado-trastuzumab emtansine for patients with non-breast, non-gastric/gastro-esophageal junction (GEJ) adenocarcinomas with HER2 amplification.

The human epidermal growth factor receptor 2 (HER2) is a member of the HER or ErbB family of tyrosine kinases that consists of four members HER1 (ErbB1/EGFR), HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4). The HER receptors are transmembrane proteins with an extracellular domain, a hydrophobic membrane spanning region (except for HER3) and an intracellular tyrosine kinase domain[1]. Ligand binding to the receptor leads to conformational changes and dimerization thus activating the tyrosine kinase part of the receptor and stimulation of the downstream signaling pathways such as the Ras/Raf/mitogen-activated protein kinase (Ras/Raf/MAPK) and phosphatidylinositol-3 kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathways which ultimately leads to cell proliferation and survival[2]. In the case of HER2, activation is thought to occur predominantly in a ligand-independent manner, particularly when the receptor is found to be mutated or overexpressed. Of note, in normal cells there are 2 copies of the ERbB2 gene but in HER2 amplified cells, there may be as many as 100 gene copies per tumor cell[2-4]. This gene amplification leads to HER2 overexpression both at the mRNA and protein level enabling homo (HER2:HER2) and heterodimerization (HER2:HER3) finally causing constitutive activation of growth factor signaling pathways. In fact, HER2, the preferred partner for heterodimerization, has the strongest catalytic kinase activity among all four members and serves as an oncogenic driver[1]. HER2 therefore serves as a key target for HER2-directed therapy.

Around 20% of breast cancers exhibit HER2 amplification and/or overexpression, presenting with an aggressive breast cancer phenotype and prior to the introduction of trastuzumab (a humanized monoclonal anti-HER2 antibody), a poor prognosis[5,6]. Similarly, HER2 amplification has also been linked with chemoresistance and overall poor survival in cervical, endometrial and ovarian cancers[7]. On the contrary, while 20% of gastric cancers and cancers of the GEJ also exhibit HER2 amplification and/or overexpression, studies have yielded inconsistent results regarding the prognostic role of HER2 amplification/overexpression in gastric cancer[8,9].

HER2 is also overexpressed in several other human solid tumors including and not limited to, ovarian, endometrial, colon, bladder, prostate, colon, cervical and non-small cell lung cancer (Figure 1 and Table 1)[20]. Inhibition of this pathway can therefore have a potential therapeutic value in these tumors compared to tumors that lack HER2 amplification. It is therefore hoped that ado-trastuzumab emtansine, a novel antibody drug-conjugate will be active for this group of patients and is being investigated in this subprotocol of the NCI-MATCH trial.

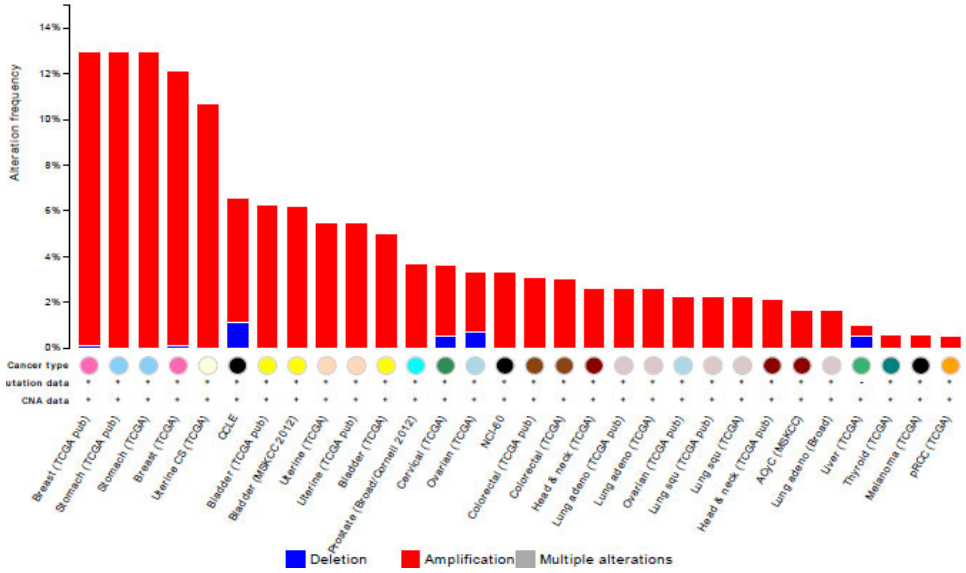

Figure 1: ERBB2 Alteration Frequency in Solid Tumors (www.cBioPortal.org)

Table 1: HER2 aberrations in cancer 20.

Cancer	Incidence of HER2 positivity (3+ immunohistochemistry and/or amplification)
Bladder	5–15%
Breast	~20%
Cervix	1–21%
Cholangio-carcinoma	1–8%
Colorectal	2–3%
Endometrium	8–35%
Esophagus	4–22%
Gastric	22%
Germ Cell	5–8%
Glioblastoma	7–15%
Head and neck	3%
Liver	2.40%
Melanoma	0–5%
Lung (NSCLC)	1–6%
Osteosarcoma	Uncommon
Ovary	6–7%
Pancreas	2–29%
Prostate	Uncommon
Renal cell carcinoma	Uncommon
Salivary duct	15–37%
Soft tissue sarcoma	Uncommon

1.1 Supporting Preliminary Data

Four HER2-directed therapies have been approved to date for HER2 amplified breast cancer. Trastuzumab was the first anti-HER2 directed therapy to be approved by the Food and Drug Administration (FDA) in the late 1990's based on improved clinical benefit and overall survival in patients with metastatic breast cancer. Later, in 2005 trastuzumab in combination with chemotherapy was approved in the adjuvant setting for early stage HER2-positive breast cancer. Despite these significant advances, both de novo and acquired trastuzumab resistance occurs. Approximately 15 percent of women develop metastatic breast cancer (MBC) despite trastuzumab-based adjuvant therapy[10]. This has led to the development of other HER2 directed therapies. Lapatinib, a potent small molecule dual tyrosine kinase inhibitor of HER2 and epidermal growth factor receptor (EGFR), was approved by the United States Food and Drug Administration (FDA) in 2007 either in combination with capecitabine or trastuzumab for patients with HER2 positive MBC following disease progression on trastuzumab[11-14]. In 2012, pertuzumab, a monoclonal antibody that binds sub-domain II of the HER2 extracellular domain and blocks HER2 dimerization and signaling, was approved in combination with trastuzumab and docetaxel in the first-line setting for HER2-positive MBC[15,16].

One novel approach in the development of new HER2 targeted therapies has been the development of HER2-directed antibody-drug conjugates (ADCs)[17]. ADCs are cytotoxic drugs that are connected by chemical linkers to monoclonal antibodies specific for a tumor-associated antigen. ADCs are designed to preferentially deliver a cytotoxic drug to cancer cells while minimizing exposure to normal tissues, thus improving the therapeutic index[18]. Ado-trastuzumab emtansine is an ADC that was approved by the FDA in 2013 based on the pivotal results of the phase III, second-line EMILIA trial that demonstrated a survival benefit in favor of ado-trastuzumab emtansine compared to FDA-approved comparator of capecitabine plus lapatinib[19].

1.2 Ado-trastuzumab emtansine

Ado-trastuzumab emtansine consists of trastuzumab covalently bound via a thioether linker, [N-maleimidomethyl] cyclohexane-1-carboxylate (MCC), to the cytotoxic agent, DM1, a derivative of maytansine. DM1 is a highly potent antimitotic drug that binds to microtubules in a similar way to that of vinca alkaloids [17,21,22]. Vinca alkaloids have demonstrated synergy with trastuzumab [23]. Ado-trastuzumab emtansine binds to the extracellular domain of HER2 and the complex is then internalized into the cell. The antibody is degraded by proteases and the active metabolite, lysine-N^{ε} –MCC-DM1 is released into the cytoplasm [21]. This metabolite is a charged molecule and is relatively membrane impermeable. This reduces the chance that DM1 can enter a neighboring cell and limits the possibility of non-specific toxicity [21]. Ado-trastuzumab emtansine also retains the effector functions of trastuzumab: inhibition of HER2-mediated signal transfusion and activation of antibody dependent cellular cytotoxicity [21,24].

1.2.1 Preclinical Studies

Preclinical trials initially demonstrated synergistic or additive interactions of trastuzumab with a variety of antimicrotubulin agents, including maytansines. Because initial trials with maytansine proved

to be associated with intolerable side effects such as nausea and peripheral neuropathy, cell culture and animal work were geared towards developing an ADC with trastuzumab and maytansinoids[25]. Maytansinoids, derivatives of maytansine, bind directly to microtubules in a manner similar to the vinca alkaloids. Trastuzumab linked to DM1 through a nonreducible thioether linkage (MCC), displayed superior activity compared with unconjugated trastuzumab or trastuzumab linked to other maytansinoids through disulfide linkers. Serum concentrations of trastuzumab-MCC-DM1 remained elevated compared with other conjugates, and toxicity in rats was negligible compared with free DM1 or trastuzumab linked to DM1 through a reducible linker. Potent activity was observed on all HER2-overexpressing tumor cells, whereas nontransformed cells and tumor cell lines with normal HER2 expression were unaffected. In addition, ado-trastuzumab emtansine was active in HER2-overexpressing, trastuzumab-refractory and lapatinib-refractory cell lines and tumors[24].

In vitro studies showed that ado-trastuzumab emtansine and trastuzumab have similar binding affinities for HER2. After binding, it is postulated that the ado-trastuzumab emtansine –HER2 complex is endocytosed and degraded in lysosomes, resulting in the release of an active metabolite, Lys-MCC-DM1 and induces a direct cytotoxic effect via direct release of adenylate kinase, PARP cleavage, and caspase 3/7 activation. ado-trastuzumab emtansine has also been shown to retain the same mechanisms of action of unconjugated trastuzumab. These include inhibition of the HER3/phosphoinositide 3-kinases (PI3K)/AKT signaling pathway, inhibition of HER2 shedding, and Fcy receptor-mediated engagement of immune cells, which may result in antibody-dependent cellular cytotoxicity[24,25].

In conclusion, because trastuzumab linked to DM1 through a nonreducible linker offered improved efficacy and pharmacokinetics and reduced toxicity over the reducible disulfide linkers evaluated, T-MCC-DM1 (ado-trastuzumab emtansine) was selected for clinical development.

1.2.2 Clinical Pharmacology of Ado-trastuzumab emtansine

The half-life of ado-trastuzumab emtansine is approximately 3.5-4 days and there is no significant accumulation of ado-trastuzumab emtansine when given every 3 weeks. The level of free DM1 in the plasma is very low (average of approximately 5 ng/mL) throughout the treatment cycle, which is likely related to the favorable toxicity profile of ado-trastuzumab emtansine. Pre-treatment residual levels of trastuzumab have not been shown to influence the pharmacokinetics (PK) or clinical efficacy of ado-trastuzumab emtansine [26,27].

Maximum distributions (Cmax) of the ado-trastuzumab emtansine and DM1 have been observed close to the end of the infusion. *In vitro* studies have indicated that DM1 undergoes metabolism by CYP 3A4/5. DM1 does not inhibit or induce major CYP450 enzymes *in vitro*. In human plasma, ado-trastuzumab emtansine catabolites MCC-DM1, Lys-MCC-DM1 and DM1 have been detected at low levels [28].

A population PK analysis on 671 patients revealed that body weight, sum of longest diameter of target lesions by RECIST, HER2 extracellular domain (ECD) concentrations, AST, albumin and baseline trastuzumab concentrations were identified as statistically significant covariates for ado-trastuzumab emtansine clearance. However, the magnitude of effect of these covariates on ado-trastuzumab emtansine exposure suggests that, with the exception of body weight, these covariates are unlikely to have a clinically meaningful effect on KADCYLA exposure. Therefore, the body weight based dose of 3.6 mg/kg every 3 weeks without correction for other covariates is considered appropriate [28]. The PK of ado-trastuzumab emtansine are not affected by mild to moderate renal impairment.

The effect of multiple doses of ado-trastuzumab emtansine (3.6 mg/kg every 3 weeks) on the QTc interval was evaluated in an open-label, single-arm study of 51 patients with HER2-positive MBC. No large changes in the mean QT interval (>20 msec) were observed in this study [28].

1.2.3 Clinical trials of ado-trastuzumab emtansine in the metastatic setting

1.2.3.1 Phase I Studies of ado-trastuzumab emtansine

Ado-trastuzumab emtansine was initially evaluated as a single agent in a phase I dose escalation study in 24 patients with trastuzumab-refractory HER2+ MBC (TDM3569g) [22]. Weekly and every-3-week dosing schedules were tested. The maximum tolerated dose (MTD) for the 3-week regimen was determined to be 3.6 mg/ kg. Ado-trastuzumab emtansine was well tolerated and the most common adverse events (AEs) were thrombocytopenia, elevated transaminases, fatigue, anemia, and nausea [22]. In the 3-week regimen, the objective response rate (ORR) was 44% in patients treated at the MTD and was comparable to patients treated on the weekly regimen (40%). Subsequently, the every-3-week schedule has been utilized in the majority of subsequent studies, largely due to the convenience for patients [22,26].

1.2.3.2 Phase II Studies of ado-trastuzumab emtansine

Ado-trastuzumab emtansine monotherapy has been studied in two single arm phase II trials (TDM4258g and TDM4374g). TDM4258g evaluated ado-trastuzumab emtansine at 3.6 mg/kg every 3 weeks for patients with HER2-positive MBC who had progressed on at least one line of HER2-directed therapy. A total of 112 patients with a median of 8 (range 2-19) prior anticancer agents in all settings were enrolled. The primary endpoint, ORR, was 25.9% (95% confidence interval [CI], 18.4% to 34.4%). Median PFS was 4.6 months (95% CI, 3.9 to 8.6 months), and median duration of response (DOR) was not reached. In a post hoc exploratory analysis, the ORR in patients who had received prior lapatinib and trastuzumab was not

significantly different than the overall ORR, suggesting that ado-trastuzumab emtansine has activity after progression on prior HER2-directed therapies [29].

TDM4374g enrolled 110 patients who had previously received trastuzumab, lapatinib, capecitabine, a taxane, and an anthracycline for HER2-positive breast cancer and had progressed on at least two HER2-directed agents in the metastatic or locally advanced setting[30]. This was in contrast to TDM4258g, which only required that patients had received and progressed on at least one prior HER2-directed therapy and had received at least one chemotherapy regimen in the metastatic setting [29]. In TDM4374g, all patients were heavily pretreated with a median of 7 (range 3-17) anticancer agents in the metastatic setting. The ORR was 34.5% (95% CI, 26.1% to 43.9%) with a median PFS of 6.9 months (95% CI, 4.2 to 8.4 months) and a CBR of 48.2% (95% CI, 38.8% to 57.9%). This confirmed the single agent activity of ado-trastuzumab emtansine in the metastatic setting [30] .

The TDM4450g study was a phase II trial in which 137 patients with previously untreated HER2-positive metastatic or locally advanced breast cancer were randomized to ado-trastuzumab emtansine or trastuzumab plus docetaxel. The primary endpoints were PFS and safety. PFS was significantly longer in patients receiving ado-trastuzumab emtansine compared with those receiving trastuzumab plus docetaxel (14.2 months vs 9.2 months, HR 0.59; 95% CI, 0.36 to 0.97; P=.035). Patients receiving ado-trastuzumab emtansine had fewer grade ≥3 AEs compared with the trastuzumab plus docetaxel group (46.4% vs 90%). Of note, only 27.1% of the patients in the trastuzumab plus docetaxel group and 17.9% of the patients in the ado-trastuzumab emtansine group had received trastuzumab in the neoadjuvant or adjuvant setting [31].

Encouraged by the synergistic activity noted in xenograft models, the combination of ado-trastuzumab emtansine plus pertuzumab was evaluated in a phase Ib/II clinical trial (TDM4373g). The safety and efficacy of ado-trastuzumab emtansine plus pertuzumab in 64 patients with HER2-positive locally advanced or MBC was assessed. Patients received the combination either in the first-line or relapsed setting (defined as progression on prior HER2 therapy for MBC). Patients with advanced MBC had received trastuzumab and a median of 6 prior nonhormonal treatments for MBC. 86% of patients receiving ado-trastuzumab emtansine in the first line MBC setting had receiving trastuzumab in the neoadjuvant or adjuvant setting. The ORR was 41% overall: 33% in patients with

advanced MBC and 57% in first line patients. Median OS was 6.6 months, 5.5 months and 7.7 months in the overall, advanced MBC and first line MBC settings, respectively. The combination was deemed to be safe and tolerable. The most common adverse events (AEs) were fatigue, nausea and diarrhea. The most frequent grade ≥3 AEs were thrombocytopenia, fatigue and liver enzyme elevations. One patient had a left ventricular ejection fraction (LVEF) of less than 40% after study drug discontinuation [32].

1.2.3.3 Phase III Studies of ado-trastuzumab emtansine

Ado-trastuzumab emtansine was subsequently evaluated in two large, randomized studies. The pivotal EMILIA study was a phase III, international trial in patients with locally advanced or metastatic, centrally confirmed, HER2-positive breast cancer. Patients had previously received a taxane and trastuzumab and had progressed on their most recent treatment in the locally advanced or metastatic setting or within 6 months of completion of adjuvant trastuzumab for early-stage disease. A total of 991 patients were randomized 1:1 to ado-trastuzumab emtansine (3.6 mg/kg every 3 weeks) or to lapatinib (1250 mg daily) and capecitabine (2000 mg/m2 days 1-14). The primary endpoints were PFS and OS. Treatment with ado-trastuzumab emtansine significantly improved median PFS compared with lapatinib plus capecitabine (9.6 vs 6.4 months; hazard ratio [HR] 0.65; 95% CI, 0.55 to 0.77; P<.001). OS also favored ado-trastuzumab emtansine (30.9 vs 25.1 months, HR 0.68; 95% CI, 0.55 to 0.85; P<.001). ORR and DOR were superior in patients treated with ado-trastuzumab emtansine. Serious AEs were reported for 18% of patients in the lapatinib-capecitabine group versus 15.5% in the ado-trastuzumab emtansine group. There were more grade ≥3 AEs in the lapatinib-capecitabine group versus in the ado-trastuzumab emtansine group (57% vs 40.8%). The most commonly reported grade 3 or 4 AEs were diarrhea and palmar-plantar erythrodysesthesia in the lapatinib-capecitabine group and thrombocytopenia and elevated transaminases in the ado-trastuzumab emtansine group [33]. The results of the EMILIA study led to the FDA approval of ado-trastuzumab emtansine in February 2013 for patients with HER2-positive MBC [22].

The TH3RESA trial evaluated the efficacy and safety of ado-trastuzumab emtansine in comparison with treatment of physician's choice (TPC) in 602 patients with MBC or unresectable locally advanced/recurrent HER2-positive breast cancer who had received at least two prior HER2-directed therapies, including trastuzumab and lapatinib.

602 patients were randomly assigned in a 2:1 ratio to ado-trastuzumab emtansine versus TPC. The PFS was significantly improved with ado-trastuzumab emtansine compared with TPC (6.2 months versus 3.3, months, stratified HR 0.528 [0.422-0.661], *P*<0.0001). Interim overall survival showed a trend favoring ado-trastuzumab emtansine (stratified HR 0.552 [95% CI 0.369-0.836], *P*=0.0034) but stopping boundary was not crossed. There was a lower incidence of grade ≥ 3 adverse events reported with ado-trastuzumab emtansine compared to TPC. Neutropenia, diarrhea and febrile neutropenia were more common in the TPC arm and thrombocytopenia was more common in the ado-trastuzumab emtansine arm [34].

1.2.3.4 Other Studies of ado-trastuzumab emtansine

Multiple trials of ado-trastuzumab emtansine in various combinations are ongoing. After the promising results of the TDM4373g study, the MARIANNE study is a randomized, 3-arm, multicenter, phase III study that is evaluating the efficacy and safety of ado-trastuzumab emtansine with pertuzumab in patients with HER2-positive progressive or recurrent locally advanced or previously untreated MBC (NCT01120184). Patients were randomized to one of the three cohorts: ado-trastuzumab emtansine with pertuzumab, ado-trastuzumab emtansine with pertuzumab-placebo (blinded for pertuzumab), or trastuzumab combined with a taxane. This trial has completed enrollment [35].

The KATHERINE Trial is a phase III trial evaluating adjuvant ado-trastuzumab emtansine versus trastuzumab in HER2+ breast cancer with residual tumor in breast or axillary lymph nodes following neoadjuvant therapy, with the primary endpoint being disease-free survival (DFS). The trial is currently recruiting [36].

1.2.4 Ado-trastuzumab emtansine in gastric cancer

National clinical trials of ado-trastuzumab emtansine in gastric cancer are available (NCT01641939, NCT01702558).

1.2.5 Safety of ado-trastuzumab emtansine

Overall, ado-trastuzumab emtansine is well tolerated with a relatively low rate of clinically significant AEs [26,37]. A pooled analysis of toxicity data from 884 patients treated in seven studies (six clinical 'parent' studies and one extension study) with single agent ado-trastuzumab emtansine at 3.6 mg/kg every 3 weeks found that the most commonly reported all-grade AEs were fatigue (46.4%), nausea (43.0%), thrombocytopenia (32.2%), headache (29.4%), and constipation (26.5%) [38,39]. The most common grade 3 to 4 AEs were the laboratory abnormalities of thrombocytopenia (11.9%) and increased AST serum concentration (4.3%). These were manageable and not generally

associated with clinical symptoms. Other grade ≥ 3 AEs occurring in ≥ 2% of patients included fatigue (3.2%), hypokalemia (3.3%), increased ALT (3.1%) and anemia (2.9%). There were 12 AE-related deaths (hepatic failure; hepatic failure and encephalopathy; hepatic function abnormal; bacterial sepsis; neutropenic sepsis; pneumonia (n=2); metabolic encephalopathy; respiratory failure (n=2); interstitial lung disease (ILD); and sudden death). AEs resulted in dose reductions in 17.2% of patients and drug discontinuations in 7.0% [38,39]. It is important to note that up to two dose modifications (3.0 mg/kg and 2.4 mg/kg) are allowed with ado-trastuzumab emtansine treatment. After two dose reductions, any further requirements for dose reductions should result in discontinuation of ado-trastuzumab emtansine [28,38,39].

Table 2: Most common AEs (> 20% incidence in single agent trials) reported in clinical trials of ado-trastuzumab emtansine.

	Trials and Incidence (%)													
	TDM3569g (n=24)[a]		TDM4258g (n=112)		TDM4374g (n=110)		TDM4450g (n=69)[b]		TDM4373g (n=64)[c]		EMILIA (n=490)[d]		TH3RESA (n=403)[e]	
Adverse Event	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All Grades	Grade 3/4	All Grades
Thrombo-cytopenia	3 (12.5)	13 (54.2)	9 (8)	NR	10 (9.1)	42 (38.2)	5 (7.2)	19 (27.5)	8 (12.5)	14 (21.9)	63 (12.9)	137 (28)	19 (4.7)	61 (15)
Increased AST	0	10 (41.7)	NR	NR	3 (2.7)	29 (26.4)	6 (8.7)	30 (43.5)	6 (9.4)	16 (25)	21 (4.3);	110 (22.4);	9 (2)	34 (8)
Increased ALT			NR	NR	3 (2.7)	15 (13.6)	7 (10.1)	18 (26.1)	6 (9.4)	15 (23.4)	14 (2.9)	83 (16.9)	NR	NR
Diarrhea	NR	NR	0	29 (25.9)	0	14 (12.7)	0	11 (15.9)	1 (1.6)	4 (6.3)	8 (1.6)	114 (23.3)	3 (<1)	40 (10)
Vomiting	0	3 (12.5)	1 (0.9)	27 (24.1)	0	18 (16.4)	2 (2.9)	17 (24.6)	2 (3.1)	5 (7.8)	4 (0.8)	93 (19)	NR	NR
Fatigue	0	9 (37.5)	5 (4.5)	73 (65.2)	5 (4.5)	68 (61.8)	3 (4.3)	34 (49.3)	7 (10.9)	24 (37.5)	12 (2.4)	172 (35.1)	8 (2)	109 (27)
Anemia	0	7 (29.2)	3 (2.7)	23 (20.5)	2 (1.8)	22 (20)	2 (2.9)	9 (13)	2 (3.1)	6 (9.4)	13 (2.7)	51 (10.4)	11 (2.7)	36 (9)
Nausea	0	6 (25)	1 (0.9)	57 (50.9)	1 (0.9)	41 (37.3)	2 (2.9)	34 (49.3)	2 (3.1)	11 (17.2)	4 (0.8)	192 (39.2)	NR	NR
Low potassium	0	1 (4.2)	10 (8.9)	27 (24.1)	1 (0.9)	23 (20.9)	NR	NR	NR	NR	11 (2.2)	42 (8.6)	NR	NR
Headache	0	2 (8.3)	0	45 (40.2)	0	24 (21.8)	0	28 (40.6)	0	2 (3.1)	NR	NR	NR	NR
Constipation	0	2 (8.3)	0	34 (30.4)	1 (0.9)	26 (23.6)	NR	NR	0	6 (9.4)	NR	NR	NR	NR
Neuropathy	0	2 (8.3)	NR	1 (1)[f]	0	20 (18.2)	NR	NR	2 (3.1)	12 (18.8)	NR	NR	NR	NR

a. Patients were treated with 0.3-4.8 mg/kg every 3 weeks. This trial also included a separate cohort of a weekly regimen, which is not reported here.

b. TDM4450g compared ado-trastuzumab emtansine (n=67) versus trastuzumab plus docetaxel (HT) (n=70). Only the ado-trastuzumab emtansine arm is reported here. 67 patients were enrolled in the ado-trastuzumab emtansine arm but two patients in the HT arm mistakenly received a dose of ado-trastuzumab emtansine and were included in the ado-trastuzumab emtansine safety analyses.

c. TDM4373g compared ado-trastuzumab emtansine with pertuzumab. The AEs reported here are of the combination regimen. This trial consisted of a dose escalation (n=9) and dose expansion

(n=58) phase. Data reported for the 6 out of 9 patients treated in dose escalation phase (3.0 mg/kg dose not included). Study only reports Grade ≥2 AEs and higher.

d. EMILIA compared ado-trastuzumab emtansine (n=490) versus lapatinib plus capecitabine (n=488). Only the ado-trastuzumab emtansine arm is reported here.

e. TH3RESA compared ado-trastuzumab emtansine (n=404) to treatment of physician's choice (N=198). Safety data for 403 patients provided. Only the ado-trastuzumab emtansine arm is reported here.

f. One patient required a dose reduction for neuropathy but exact grade is not known.

NR: Not reported

1.2.6 Adverse Events of Special Interest

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of ado-trastuzumab emtansine.

The trastuzumab emtansine Events of Special Interest are:

- Cardiac events (LVEF < 40% or symptomatic CHF, Grade ≥ 3 left ventricular systolic dysfunction._

  Cardiotoxicity has been carefully studied in patients receiving ado-trastuzumab emtansine because of the cardiac toxicity of trastuzumab, and a boxed warning for left ventricular dysfunction exists for ado-trastuzumab emtansine [26, 40]. In the pooled safety analysis, four patients (0.5%) had a baseline LVEF < 40%, and 16 patients (1.8%) had LVEF decline ≥ 15 percentage points from baseline to below 50%. A total of 4 patients discontinued ado-trastuzumab emtansine because of cardiac disorders (atrial fibrillation, n=1; left ventricular dysfunction, n=1; and decreased EF, n=2) [26, 38, 39]. The incidence of cardiac dysfunction may be underestimated as patients with cardiac toxicity secondary to trastuzumab or severe cardiac disease were excluded from enrollment [39]. The effect of multiple doses of ado-trastuzumab emtansine (3.6 mg/kg every 3 weeks) on the QTc interval was evaluated in an open label, single arm study in 51 patients with HER2-positive MBC. No large changes in the mean QT interval (i.e. > 20 msec) were detected in the study [28].

- Thrombocytopenia (Grade ≥ 3)

  Thrombocytopenia is typically grade 1 or 2 and rapidly reversible, and has generally not been associated with clinically significant bleeding [22, 26]. Platelet counts can start to decline as soon as 24 hours after dosing, nadir around day 8, and recover by day 15 [22]. In approximately 20% of patients, platelet counts do not completely recover to baseline after repeated dosing [26, 38].

- Hepatic events

  Serious hepatobiliary disorders, including fatal cases of severe drug-induced liver injury and associated hepatic encephalopathy, have been reported; as such, the prescribing information for ado-trastuzumab emtansine includes a boxed warning for hepatotoxicity [40, 41]. Rare cases of nodular regenerative hyperplasia (NRH) have also been described [26, 40]. NRH is a rare liver disorder characterized by a widespread transformation of

the hepatic parenchyma into small regenerative nodules and can result in noncirrhotic portal hypertension [42]. NRH can only be diagnosed by a liver biopsy and should be considered in any patient receiving ado-trastuzumab emtansine who develops signs and/or symptoms of portal hypertension but with normal transaminases and no manifestations of cirrhosis. [42]. Ado-trastuzumab emtansine should be discontinued if NRH develops [26, 42].

- Infusion Associated Reactions, Hypersensitivity
- Embryofetal Toxicity or Birth Defects
- Pregnancies

2. Selection of Patients

Each of the criteria in the checklist that follows must be met, along with the eligibility in the MATCH Master Protocol, in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 2 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 2 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.Execofficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

NOTE: All patients must have signed the relevant treatment consent form

2.1 Eligibility Criteria

Rev. 2/16

_____ 2.1.1 Patients must fulfill all eligibility criteria outlined in Section 3.1 of MATCH Master Protocol. (excluding Section 3.1.6) at the time of registration to treatment step (Step 1, 3, 5, 7).

_____ 2.1.2 Patients' tumor sample must have HER2 amplification > 7 based on targeted custom Ampliseq panel on the Ion Torrent PGM. See Appendix I for a list of the ERBB2 amplifications and corresponding Levels of Evidence.

_____ 2.1.3 Adequate hematologic function as defined by:

- Hemoglobin ≥ 9.0g/dL (which may be reached by transfusion)

  Hemoglobin level _____

  Date of Test: _____

_____ 2.1.4 Patients will be allowed if on anticoagulation (except warfarin and other coumarin derivatives) or on aspirin 81 mg by mouth daily. Additional monitoring while on anticoagulation will be based on institutional guidelines and/or physician discretion. However, patients will not be allowed if on long acting anti-platelet agents such as clopidogrel.

Rev. 2/16 _____ 2.1.5 Patients must have an electrocardiogram (ECG) within 4 weeks prior to treatment assignment and must have no clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g. complete left bundle branch block, third degree heart block).

Date: _____

Rev.2/16 _____ 2.1.6 Patients must have ECHO or nuclear study (MUGA or First Pass) within 4 weeks prior to registration to treatment and must not have a left ventricular ejection fraction (LVEF) < 50% to be eligible.

Date of ECHO/nuclear study: _____

_____ 2.1.7 Patients with a diagnosis of Breast cancer or gastric/GEJ cancer will be excluded.

_____ 2.1.8 Patients must not have known hypersensitivity to ado-trastuzumab emtansine or compounds of similar chemical or biologic composition.

_____ 2.1.9 Patients with current peripheral neuropathy of Grade 3 or greater (NCI-CTC, version 4.0) will be excluded.

Neuropathy assessment and grade assignment will be based on history (location, duration, balance and gait, effect on activity of daily living (ADLs)) and physical exam.

_____ 2.1.10 Patient must not have had any of the prior therapies:

- FDA approved:
  Trastuzumab
  Pertuzumab
  Ado-trastuzumab emtansine
- Investigational:
  Margetuximab
  PF-05280014 (Pfizer, Trastuzumab Biosimilar)
  CT-P6 (Celltrion, Trastuzumab Biosimilar)
  ABP-980 (Amgen, Trastuzumab Biosimilar)

Rev. 2/16 _____ 2.1.11 Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 7 months after completion of study.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

3. Ado-trastuzumab emtansine Treatment Plan

Rev.2/16
Rev.3/17

3.1 Administration Schedule

Ado-trastuzumab emtansine will be administered 3.6 mg/kg intravenously every 3 weeks (±3 days) on a 21 day schedule until toxicity or progression in an outpatient setting. The dose should be calculated based on the patient's weight (kg) as measured every cycle, prior to treatment.

3.2 Adverse Event Reporting Requirements

The Adverse Event Reporting Requirements for all EAY131 subprotocols are outlined in the MATCH MASTER protocol. Please refer to those guidelines when determining if an event qualifies as a Serious Adverse Event (SAE) and requires expedited reporting via CTEP's Adverse Event Reporting System (CTEP-AERS).

In addition, the following section outlines agent specific requirements and must be followed to ensure all reporting requirements are met.

3.2.1 Additional instructions, requirements and exceptions for EAY131 – Subprotocol Q

Additional Instructions

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

EAY131 – Subprotocol Q specific expedited reporting requirements:

- **Thrombocytopenia:** All ≥ grade 3 thrombocytopenia must be reported via CTEP-AERS according to the timeframes outlined in the AE table in section 5.3.6 of the MATCH Master protocol
- **Cardiac Changes:** All ≥ grade 3 cardiac events must be reported via CTEP-AERS according to the timeframes outlined in the AE table in section 5.3.6 of the MATCH Master protocol
- **Liver Chemistry Changes:** If any of the following circumstances occur, the event(s) must be reported via CTEP-AERS according to the timeframes outlined in the AE table in section 5.3.6 of the MATCH Master protocol
  - ≥ Grade 3 ALT or AST
  - ≥ Grade 3 total bilirubin
  - Any grade drug inducted liver injury
- **Infusion Associated Reactions, Hypersensitivity:** Any grade infusion associated reaction/hypersensitivity must be reported via CTEP-AERS according to the timeframes outlined in the AE table in section 5.3.6 of the MATCH Master protocol

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- **Pregnancies:** Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the female patient is on ado-trastuzumab emtansine, or within 7 months of the female patient's last dose of ado-trastuzumab emtansine, are considered immediately reportable events. A female partner of a male patient who becomes pregnant within 7 months of the male's last dose of ado-trastuzumab emtansine is also considered a reportable event. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix VIII in MATCH Master protocol for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

  NOTE: The timeframes and requirements for reporting pregnancies on this study is longer than the standard 28 days as stated in Appendix VIII of the MATCH Master Protocol. Please note on this study, pregnancies must be reported if they occur within 7 months of the subjects last dose of ado-trastuzumab emtansine.

EAY131 – Subprotocol Q specific expedited reporting exceptions:

For Subprotocol Q, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

3.2.2 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.

- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov
  3. Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  4. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  5. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

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3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Ado-Trastuzumab Emtansine (NSC 780263)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2009 patients*. Below is the CAEPR for ado-trastuzumab Emtansine.

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER.

Version 2.1, July 23, 2018[1]

Adverse Events with Possible Relationship to Ado-Trastuzumab Emtansine (CTCAE 5.0 Term) [n= 2009]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
		Atrial fibrillation	
		Left ventricular systolic dysfunction	
EYE DISORDERS			
		Blurred vision	
	Dry eye		
	Watering eyes		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		
		Gastrointestinal hemorrhage[2]	
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
	Edema limbs		
Fatigue[3]			***Fatigue[3] (Gr 2)***

Adverse Events with Possible Relationship to Ado-Trastuzumab Emtansine (CTCAE 5.0 Term) [n= 2009]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Fever[4]		***Fever[4] (Gr 2)***
		Infusion site extravasation	
		Multi-organ failure	
HEPATOBILIARY DISORDERS			
		Gallbladder pain	
		Hepatic failure[5, 6]	
		Hepatobiliary disorders - Other (nodular regenerative hyperplasia)[6]	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[7]	
INFECTIONS AND INFESTATIONS			
	Conjunctivitis		
	Infection[8]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		
		Infusion related reaction[4]	
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
		Blood bilirubin increased	
		Creatinine increased	
		Ejection fraction decreased	
	Neutrophil count decreased		
	Platelet count decreased		***Platelet count decreased (Gr 2)***
		White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hypokalemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
Myalgia			***Myalgia (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	

Adverse Events with Possible Relationship to Ado-Trastuzumab Emtansine (CTCAE 5.0 Term) [n= 2009]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		
		Encephalopathy[5]	
Headache			***Headache (Gr 2)***
		Intracranial hemorrhage	
	Nervous system disorders - Other (peripheral neuropathy)[9]		
		Seizure	
PSYCHIATRIC DISORDERS			
		Confusion	
	Insomnia		
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Vaginal hemorrhage	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough[3]		***Cough[3] (Gr 2)***
	Dyspnea[3,4]		
	Epistaxis		***Epistaxis (Gr 2)***
		Pleural effusion	
		Pneumonitis[3]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Bullous dermatitis	
		Palmar-plantar erythrodysesthesia syndrome	
	Rash maculo-papular		
		Stevens-Johnson syndrome	
VASCULAR DISORDERS			
	Hypertension		
		Thromboembolic event	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3]Symptoms of interstitial lung disease (ILD) may include cough, dyspnea, fatigue, and pulmonary infiltrates. ILD, including pneumonitis, with some cases leading to acute respiratory distress syndrome or fatal outcome, have been reported.

[4]Infusion related reaction, which may manifest as flushing, chills, fever, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia, have been observed.

[5]Encephalopathy has been only observed in clinical trials ado-trastuzumab as hepatic encephalopathy in the context of hepatic failure.

[6]Serious hepatobiliary disorders including nodular regenerative hyperplasia (NRH) of the liver, some resulting in fatal liver failure, have been observed.

[7]Allergic reactions (hypersensitivity) including serious anaphylaxis have been observed.

[8]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[9]Peripheral neuropathy includes Peripheral motor neuropathy and Peripheral sensory neuropathy under the NERVOUS SYSTEM DISORDERS SOC.

NOTE: Ado-trastuzumab emtansine in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

3.4 Dose Modifications

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

- Patients should be assessed for toxicity prior to each dose of ado-trastuzumab emtansine; dosing will occur only if the clinical assessment and laboratory values are acceptable.
- Dose reduction levels for ado-trastuzumab emtansine are described in Table 3 below. No re-escalation of ado-trastuzumab emtansine dose will be allowed. Patients requiring a dose reduction will be de-escalated one dose level with a maximum of two dose reductions allowed, following which further indication for dose reduction will result in the patient being taken off study as indicated below.

Table 3: Dose Reduction levels of ado-trastuzumab emtansine

DOSE LEVEL	Ado-trastuzumab emtansine Dose
0	3.6mg/kg
Dose -1	3 mg/kg
Dose -2	2.4mg/kg
Indication for further dose reduction	Off ado-trastuzumab emtansine

- In addition to the specific toxicities presented in the tables below, if a patient develops any other significant grade 3 or 4 toxicity thought to be related specifically to ado-trastuzumab emtansine, ado-trastuzumab emtansine will be held until the symptoms resolve to grade ≤ 1 or to the baseline grade. When treatment is resumed, the ado-trastuzumab emtansine dose should be modified according to the guidelines in Tables 4.1-4.5. If grade ≥ 3 toxicity persists for more than 14 days (with the exception of thrombocytopenia, refer to table 4.1) or recurs after the maximum dose reduction, the patient will discontinue ado-trastuzumab emtansine and come OFF STUDY.
- Ado-trastuzumab emtansine should be permanently discontinued in patients with interstitial lung disease (ILD) or pneumonitis.
- Dose modifications will be allowed only based on labs done on days 19-21 conducted prior to the next treatment cycle and not for any nadir found mid-cycle. See Study Calendar (Section 4.1) for protocol required lab schedule.

Table 4.1: Dose Modifications for Thrombocytopenia

Adverse Event	Ado-trastuzumab emtansine Dose
Grade 1 Thrombocytopenia (< Lower limit of normal-75,000 mm^3)	No change; continue ado-trastuzumab emtansine dose at same dose and schedule.
Grade 2 Thrombocytopenia (50,0000-< 75,000 mm^3)	
Grade 3 Thrombocytopenia (25,000-< 50,000 mm^3)	Hold ado-trastuzumab emtansine up to 21 days until platelet count recovers to Grade ≤ 1 (75,000 mm^3) and then treat at same dose level.
Grade 4 Thrombocytopenia (< 25,000 mm^3)	Hold ado-trastuzumab emtansine up to 21 days until platelet count recovers to Grade ≤ 1 (75,000 mm^3) before the next scheduled dose and then reduce to next lower dose level

Table 4.2: Dose Modifications for Hepatic Function

Adverse Event	Ado-trastuzumab emtansine Dose
Increased serum transaminases (AST/ALT)	
Grade 1 AST/ALT Elevation (> ULN-3x ULN)	No change; continue ado-trastuzumab emtansine at same dose and schedule
Grade 2 AST/ALT Elevation (> 3-5x ULN) without bilirubin elevation to > 2 x ULN	
Grade 3 AST/ALT Elevation (>5-20x ULN) without bilirubin elevation to > 2 x ULN	Hold ado-trastuzumab emtansine until AST/ALT recovers to ≤ Grade 2. If resolves in ≤ 14 days, then resume ado-trastuzumab emtansine at next lower dose level.
Grade 4 AST/ALT Elevation (>20x ULN) without bilirubin elevation to > 2 x ULN	Permanently discontinue ado-trastuzumab emtansine
Hyperbilirubinemia	
Grade 1 Hyperbilirubinemia (> ULN – 1.5x ULN)	No change; continue ado-trastuzumab emtansine at same dose and schedule
Grade 2 Hyperbilirubinemia (> 1.5 – 3x ULN)	Hold ado-trastuzumab emtansine until total bilirubin recovers to ≤ Grade 1, then resume treatment at the same dose.
Grade 3 Hyperbilirubinemia (> 3 – 10x ULN)	Hold ado-trastuzumab emtansine until total bilirubin recovers to ≤ Grade 1. If resolves in ≤14 days, then resume ado-trastuzumab emtansine at next lower dose level.
Grade 4 Hyperbilirubinemia (> 10x ULN)	Permanently discontinue ado-trastuzumab emtansine
Concomitant AST/ALT and hyperbilirubinemia	
AST/ALT > 3 x ULN and total bilirubin > 2 x ULN.	Permanently discontinue ado-trastuzumab emtansine

NOTE: Permanently discontinue ado-trastuzumab emtansine in patients diagnosed with nodular regenerative hyperplasia (NRH).

Table 4.3: Dose Modifications for Peripheral Neuropathy

Adverse Event	Ado-trastuzumab emtansine Dose
Grade 1 peripheral neuropathy	No change; continue ado-trastuzumab emtansine at same dose and schedule
Grade 2 peripheral neuropathy	
Grade 3 peripheral neuropathy	1st occurrence: Hold ado-trastuzumab emtansine until resolved to grade ≤ 2. If resolves in ≤14 days, resume ado-trastuzumab emtansine at next lower dose level. 2nd occurrence: Permanently discontinue ado-trastuzumab emtansine
Grade 4 peripheral neuropathy	Permanently discontinue ado-trastuzumab emtansine

Table 4.4 Dose Modifications for Left Ventricular Dysfunction

Symptomatic CHF	LVEF < 40%	LVEF 40% to ≤ 45% and decrease is ≥ 10% points from baseline	LVEF 40% to ≤ 45% and decrease is < 10% points from baseline	LVEF > 45%
Discontinue ado-trastuzumab emtansine	Do not administer ado-trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF <40% is confirmed, permanently discontinue ado-trastuzumab emtansine	Do not administer ado-trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to within 10% points from baseline, discontinue ado-trastuzumab emtansine.	Continue treatment with ado-trastuzumab emtansine. Repeat LVEF assessment within 3 weeks.	Continue treatment with ado-trastuzumab emtansine.

Table 4.5 Dose Modifications for other AEs

Other significant, related toxicities (aside from those described above) that have not recovered to grade 1 or baseline.	Dose may be delayed up to 14 days from the last dose. If dosing resumes, it may be at the same dose level or one dose level lower, per treating investigator's discretion.

3.5 Supportive Care

3.5.1 All supportive measures consistent with optimal patient care will be given throughout the study.

3.5.2 The use of erythropoietin or other specific red blood cell growth factors and red blood cell transfusions will be permitted as clinically indicated during the study after documentation of anemia secondary to the study treatment. These agents cannot be used prior to this occurrence.

3.5.3 The use of bone marrow colony stimulating factors (such as granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) is permitted as clinically indicated after documentation of neutropenia secondary to the study treatment. These agents cannot be used prior to this occurrence.

3.5.4 Other concomitant medications may be given as clinically indicated

3.6 Duration of Agent-specific treatment

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the MATCH Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Disease Progression

3.7 Duration of Follow-Up

Refer to the MATCH Master Protocol for specifics on the duration of follow-up.

4. Study Parameters

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4.1 Therapeutic Parameters for Ado-trastuzumab emtansine Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients receiving ado-trastuzumab emtansine treatment.

NOTE: All assessments required prior to registration to treatment should be done ≤ 4 weeks prior to registration to Steps 1, 3, 5, 7, excluding the radiologic evaluation.

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Test/Assessment	Prior to Registration to Treatment	Treatment		End of Treatment	Follow Up[F]
		Every Cycle, prior to treatment	Every 3 Cycles		
H&P, Weight, Vital signs[A]	X	X[H]			X
Performance status	X	X[H]			X
CBC w/diff, plts[B]	X	X[H]			X
Serum chemistry[B]	X	X[H]			X
Radiologic evaluation[D]	X		X[D]		X[F]
β-HCG[C]	X				
Rev.12/16 Toxicity Assessment		X[H]		X	X[F]
ECG[G]	X				
Echocardiogram or Nuclear Study[I]	X		X		
Rev.3/17 Tumor biopsy and blood sample for MATCH Master Protocol[E]			X	X	

A. History and physical, including neuropathy assessment and grade assignment, vital signs and weight at the start of each cycle (up to 3 days before start of new cycle).

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B. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, glucose, phosphorus, potassium, SGOT[AST], SGPT[ALT], sodium, magnesium and serum tumor markers (including LDH, PSA if appropriate). CBC w/diff, platelets and serum chemistries should be performed on cycle 1, day 1 (or up to 7 days prior), and at the start of each subsequent cycle (up to 3 days before start of new cycle). CBC with differential will be performed more frequently in patients with grade 4 neutropenia or thrombocytopenia until resolution to ≤ grade 3. CBC and serum chemistries are only required in follow-up until values return to pre-treatment levels or until progressive disease.

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C. Blood pregnancy test (women of childbearing potential) required prior to beginning treatment.

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D. Disease measurements are repeated every 3 cycles for the first 33 cycles, and every 4 cycles thereafter until PD or start of another MATCH treatment step. The baseline evaluation should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before registration to treatment step. For multiple myeloma patients, please refer to Section 6.4 of the MATCH Master Protocol for additional

information on myeloma response criteria and the required disease assessments. Documentation (radiologic) must be provided for patients removed from study for progressive disease.

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E. Additional blood specimens and/or biopsies are to be submitted from consenting patients per Section 9.3.2 of the MATCH Master Protocol. Submit at the following time points, as applicable:

- Blood specimens are to be submitted at the end of Cycle 2 (prior to start of Cycle 3 treatment). If patient progresses or treatment is discontinued prior to Cycle 3, collect the blood at that time instead. On-treatment kits for blood sample collections will be automatically shipped to sites upon registration to the treatment step.
- Screening biopsies for additional aMOI assessments after registration to appropriate screening step, if applicable (Step 2 or Step 4).
- At end of all MATCH study treatments, blood specimens and/or research biopsy after consent and registration to Step 8

Please refer to Section 4 of the MATCH Master Protocol to determine whether the patient proceeds to the next screening step or to follow-up (with a potential end of treatment biopsy for research purposes on Step 8). Samples are to be submitted as outlined in Section 9 of the MATCH Master Protocol. To order Step 2/4 Screening or Step 8 kits, complete the EAY131 Collection and Shipping Kit Order Form (See Appendix XII of the MATCH Master Protocol) and fax to 713-563-6506.

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F. Every 3 months if patient is < 2 years from study entry, and every 6 months for year 3. Toxicity assessments and radiologic evaluations are not required to be done during Follow Up if progression has been previously reported; however if an adverse event occurs post treatment that meets
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the SAE reporting requirements, it still must be reported via CTEP-AERS, even if progression has occurred.

G. ECG must be done at baseline (within 4 weeks of treatment assignment). Additional ECGs can be done as clinically indicated.

H. For Cycle 1, if the following tests/assessments occurred within 7 days of Day 1, they do not need to be repeated at this timepoint: H&P, Weight, Vital Signs; Performance Status; CBC w/diff, plts; Serum chemistry; Concomitant Medications. The Toxicity Assessment is not required prior to Cycle 1, but required every subsequent cycle.

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I. Echocardiogram/nuclear study must be done at baseline (within 4 weeks of treatment assignment), then every three cycles. Additional ECHOs/nuclear studies can be done as clinically indicated.

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5. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

Availability

NO STARTER SUPPLIES MAY BE ORDERED. Subjects must be enrolled and assigned to the treatment subprotocol prior to submitting the clinical drug request to PMB.

Drug Ordering: NCI supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained – see general information). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://ctepcore.nci.nih.gov/OAOP). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam/) and the maintenance of an “active” account status, a “current” password, and an active person registration status.

NCI Supplied Agent(s) – General Information

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time or email PMBAfterHours@mail.nih.gov anytime.

Drug Returns: All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

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Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of agent received from the PMB using the NCI Investigational Agent Accountability Record Form available on the NCI home page (http://ctep.cancer.gov). Maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator.

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Investigator Brochure Availability: The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status, a “current” password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator at IBCoordinator@mail.nih.gov.

5.1 Ado-trastuzumab Emtansine (NSC 780263)

5.1.1 Other Names

KADCYLA®, T-DM1, TRASTUZUMAB-MCC-DM1, PRO132365, RO5304020

5.1.2 Classification

Humanized monoclonal antibody (IgG1 isotype) directed against the extracellular region of HER2

5.1.3 Mode of Action

Ado-trastuzumab emtansine binds to HER2 with affinity similar to that of trastuzumab. After binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization, resulting in intracellular release of DM1 and subsequent cell death. DM1 is an inhibitor of tubulin polymerization.

5.1.4 Storage and Stability

Storage:

Intact vials should be refrigerated at 2ºC-8ºC (36ºF-46ºF). Do not freeze or shake.

Stability:

Reconstituted single-use vials should be used within 1 hour of reconstitution. If not used within this time frame, the reconstituted vials can be stored for up to 24 hours in a refrigerator at 2°C–8°C. Vials stored beyond this time period should be discarded.

The diluted solution should be used immediately. If not used immediately, the diluted solution may be stored at 2ºC-8ºC (36ºF-46ºF) for up to 24 hours. Diluted solutions stored past 24 hours should be discarded.

5.1.5 Dose Specifics

Ado-trastuzumab emtansine is provided as a lyophilized product in 20-mL single-use vials which contain enough product to deliver 160 mg of ado-trastuzumab emtansine. When reconstituted, each single-use vial contains ado-trastuzumab emtansine (20 mg/mL), polysorbate 20 [0.02% (w/v)], sodium succinate (10 mM), and sucrose [6% (w/v)] with a pH of 5.0 and density of 1.026 g/mL. Ado-trastuzumab emtansine vials will have either a white or purple flip cap.

Ado-trastuzumab emtansine will be administered on Day 1 of each cycle at 3.6 mg/kg IV.

RECONSTITUTION: Slowly inject 8 mL of Sterile Water for Injection into the 160 mg ado-trastuzumab emtansine vial to yield a solution containing 20 mg/mL. Swirl the vial gently until completely dissolved. Do not shake. Inspect the reconstituted solution for particulates and discoloration. The reconstituted solution should be clear to slightly opalescent and free of visible particulates. The color of the reconstituted solution should be colorless to pale brown. Do not use if

the reconstituted solution contains visible particulates or is cloudy or discolored.

DILUTION: To prepare the infusion solution from the reconstituted lyophilized product, remove the indicated volume of product from the vials, based on patient weight, and add to the IV bag. Gently invert the bag to mix the solution. Do not shake vigorously. Reconstituted ado-trastuzumab emtansine should be diluted into polyvinyl chloride (PVC), latex-free PVC-free polyolefin bags (PO), polypropylene (PP) or polyethylene (PE) bags containing 250 mL 0.9% NS.

5.1.6 Route of Administration

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Administer ado-trastuzumab emtansine as an intravenous infusion only with a 0.2 or 0.22 micron in-line polyethersulfone (PES) filter. Do not administer as an intravenous push or bolus.

Method of Administration:

First infusion: Administer infusion over 90 minutes. Patients should be observed during the infusion and for at least 90 minutes following the initial dose for fever, chills, or other infusion related reactions. Subsequent infusions: Administer over 30 minutes if prior infusions were well tolerated. Patients should be observed during the infusion and for at least 30 minutes after infusion.

5.1.7 Incompatibilities

Dextrose infusion solutions

Potential Drug Interactions: No formal drug-drug interaction studies with ado-trastuzumab emtansine have been conducted. In vitro studies indicate that DM1, the cytotoxic component of ado-trastuzumab emtansine, is metabolized mainly by CYP3A4 and to a lesser extent by CYP3A5. Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) with ado-trastuzumab emtansine should be avoided due to the potential for an increase in DM1 exposure and toxicity. Consider an alternate medication with no or minimal potential to inhibit CYP3A4. If concomitant use of strong CYP3A4 inhibitors is unavoidable, consider delaying ado-trastuzumab emtansine treatment until the strong CYP3A4 inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If a strong CYP3A4 inhibitor is coadministered and ado-trastuzumab emtansine treatment cannot be delayed, patients should be closely monitored for adverse reactions.

5.1.8 Side Effects

See Section 3.3 for side effects.

5.1.9 Nursing/Patient Implications

Follow procedures for proper handling and disposal of anticancer drugs

6. Translational Studies

Please refer to the MATCH Master Protocol for information on the Translational Studies.

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Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Q: Ado-trastuzumab Emtansine/HER2 Amplification

Appendix I

Actionable Mutations for Sub-Protocol EAY131-Q

Gene Name	Variant ID	Variant Type	Level of Evidence Code	aMOI
ERBB2	ERBB2	CNV	1	ERBB2 Amplification

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Q: Ado-trastuzumab Emtansine/HER2 Amplification

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Appendix II

Patient Drug Information Handout and Wallet Card

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

Rev. 12/16 The patient _____ is enrolled on a clinical trial using the experimental study drug, **Ado-trastuzumab emtansine**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Ado-trastuzumab emtansine is broken down by the CYP3A4 enzyme in your liver.

Some drugs interfere or inhibit the CYP3A4 enzyme and if taken in combination with **Ado-trastuzumab emtansine** may result in very high blood levels of **Ado-trastuzumab emtansine** which may make you sick.

There are also some drugs that make the CYP3A4 enzyme work harder (inducers) and if taken in combination with **Ado-trastuzumab emtansine** may result in low blood levels of **Ado-trastuzumab emtansine** which may make your treatment less effective.

Finally, other drugs, that are also broken down by the CYP3A4 enzyme, may interfere with removing **Ado-trastuzumab emtansine** from your body and when taken in combination with **Ado-trastuzumab emtansine** may cause **Ado-trastuzumab emtansine** to stay in your body longer and cause more side effects.

Strong inhibitors and inducers of CYP3A4 should not be used in combination with **Ado-trastuzumab emtansine**

Moderate inhibitors and inducers of CYP3A4 should be used with caution in combination with **Ado-trastuzumab emtansine**

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Ado-trastuzumab emtansine may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Ado-trastuzumab emtansine must be used very carefully with other medicines that use certain liver enzymes to be cleared from your system. Before you enroll onto the clinical trial, your study

doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered moderate or strong inducers/inhibitors or major substrates of CYP3A4.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is

  _____ and he or she can be contacted at

  _____

STUDY DRUG INFORMATION WALLET CARD You are enrolled on a clinical trial using the experimental study drug **Ado-trastuzumab emtansine.** This clinical trial is sponsored by the NCI. **Ado-trastuzumab emtansine** may interact with other drugs. Because of this, it is very important to: ➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➢ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	**Ado-trastuzumab emtansine** is broken down by the **CYP3A4** enzyme in your liver and must be used very carefully with other medicines that interact with **CYP3A4.** Strong inhibitors and inducers of CYP3A4 should not be used in combination with **Ado-trastuzumab emtansine** Moderate inhibitors and inducers of CYP3A4 should be used with caution in combination with **Ado-trastuzumab emtansine** Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that may interact with **Ado-trastuzumab emtansine** ➢ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Q: Ado-trastuzumab Emtansine/HER2 Amplification

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Appendix III

CS-MATCH-0012

An Explorative Analysis of the Roles of Tumor Intrinsic and Micro-Environmental Factors in the Clinical Response to TDM1 in the NCI-MATCH Q Arm

Principal Investigators:

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I. Introduction

TDM1 may soon join a growing list of cancer therapy that can function in a tissue agnostic manner, in particular for patients with HER-2 positive salivary gland cancer. Despite this exciting finding, only a minority of patients from the Q arm responded. Identification of biomarkers that can predict the response of therapy will allow us to better select patients that will more likely benefit from the treatment as well as elucidate the mechanism of resistance. Both microenvironmental and tumor intrinsic properties may modulate the response of breast cancer to the parental molecule: trastuzumab. In this proposal, we will focus on tumor HER-2 status.

The potential mechanism of resistance to TDM1 therapy was discussed in a recent review article (Barok et al., 2014). Breast and GE junction cancers with HER-2 protein over-expression, as defined by IHC 3+, or gene amplification, as defined by a HER-2 copy number greater than 6 or a HER-2/CEP17 ratio of greater than 2.0. Among these HER-2 positive tumors, whether higher levels of HER-2 gene amplification or protein over-expression predict better clinical outcome to anti-HER-2 therapy remains an open question. In this proposal, we will examine if a higher level of HER-2 gene amplification, as evaluated by FISH or NCI-MATCH assay, or over-expression, as evaluated by IHC or RNAseq, will correlate with improved clinical outcome with TDM1 treatment.

Both IHC and FISH have been routinely used for HER-2 status evaluation in breast cancer. According to the HER-2 scoring system put forth by the ASCO/CAP, uniform intense membrane staining in more than 10% of invasive tumor cells is considered positive for HER-2 protein over-expression (Wolff et al., 2014). However there are differences in HER-2 staining patterns between breast and gastric cancer cells (incomplete membrane staining in a basolateral pattern and greater tumor heterogeneity are more prominent in gastric cancer cells), a modified HER-2 scoring system specific for gastric cancer has been proposed and has been shown to be reproducible and adopted in the ToGA trial (Bang et al., 2010). NCCN guidelines recommend that assessment for HER-2 status by IHC should follow the modified scoring system used in the ToGA trial (NCCN Guidelines Version 2. 2017). These observations importantly indicate that though the same biomarker is being interrogated in both tissues, the technology involved may need to be individually optimized depending on the tissue origin). In order to assess the HER-2 status and the HER-2 protein expression status in the matched samples of the Q arm, we will apply both scoring systems independently. Since clinically validated scoring criteria for HER-2 IHC testing in non-gastric/GE or non-breast cancer have not been established, we will use both breast and gastric/GE HER-2 IHC scoring criteria to all samples independently and analyze according to either criteria separately.

HER-2 testing by FISH and IHC is a well-recognized and widely disseminated HER-2 testing strategy (Wolff et al., 2014). Its performance in selecting out patients whose tumors are more likely to respond to HER-2 targeted therapeutics, based on the HER-2 protein expression and/or gene amplification, is well established for breast and gastric cancers. HER-2 testing is done routinely in the community setting for both breast and GE junction cancers. FDA approved testing methodologies include IHC, FISH and CISH. HER-2 testing done by NGS, such as the Oncomine assay, is not routinely done in the community. Translating the finding from the Q arm study to a clinical scenario most familiar to the oncology community in general serves as additional rationale to perform HER-2 FISH and Her-2 IHC from Q arm patients that are tested positive for HER-2 amplification by the NCI-MATCH assay. Though this is not a formal concordance study,

this will at least answer the question if HER-2 testing by FISH or IHC can correctly identify most, if not all, of the patients that score positive by the MATCHBOX assay- i.e. sensitivity close to 100%.

Another important contribution of HER-2 FISH and IHC assays is direct histological assessment of the cancer cells and determine if there is tumor heterogeneity in terms of their HER-2 protein over-expression and/or gene amplification and if heterogeneity will correlate with response. Tumor heterogeneity in HER-2 status has been previously reported in breast cancer though at low incidence, relevant information for other tissue types is not available.

II. Objectives

A. Primary objective:

Determine if HER-2 gene copy number and HER-2 protein over-expression will correlate with response to TDM1.

III. Methodology

Both FISH and IHC tests will be performed with FDA approved testing kits in accordance with the ASCO/CAP 2013 guidelines. HER-2 IHC has generally speaking sensitivity of 70% and specificity close to 100%. HER-2 FISH has specificity and sensitivity in the high 90%. The concordance rate between HER-2 FISH and IHC is between 80-90+%. HER-2 FISH and HER-2 IHC will be performed at Dr. [redacted] Laboratory at MD Anderson.

IHC and FISH will be performed utilizing autostainers (Leica Bond Max, Leica Biosystems, Vista, CA). All antibodies have been optimized for IHC by examination of positive and negative controls and testing of the antibodies by Western blotting. Expression of the markers in cells will be detected using a Novocastra Bond Polymer Refine Detection kit (Leica Microsystems, Buffalo Grove, IL) with a diaminobenzidine reaction to detect antibody labeling and hematoxylin counterstaining. To perform quantitative image analysis of the expression of each marker, all IHC slides will be scanned into a digital image scanner (Aperio™ AT Turbo, Leica Biosystems, Buffalo Grove, IL), and analyzed using the Aperio Image Genie Toolbox™ software (Leica Biosystems, Buffalo Grove, IL). Five random 1-mm square areas within the tumor region will be selected for analysis. The expression of markers in malignant cells will be evaluated using the Aperio™ digital H-score system which includes the percentage of positive cells (0 to 100) and intensity (0 to 3+), with a total score ranging from 0 to 300. Quantification of markers expressed in immune cells will be expressed by cell density (number of cells per mm square).

Scoring will be as follows:

- C-erB-2 (Her2) IHC: DAKO #A0485, Polyclonal Rabbit anti-Human Oncoprotein. Dilute 1:800.
  - IHC 0+ and 1+ are negative (not over-expressed)
  - IHC 3+ are positive (over-expressed)
  - IHC 2+ are equivocal and reflex to HER-2 FISH is needed.
- Dual-probe HER2/cep17 FISH assay:
  - Ratio greater or equal to 2, positive (amplified)
  - Ratio less than 2 with an average HER-2 copy number greater than or equal to 6, positive (amplified).

- Ratio less than 2 with an average HER-2 copy number less than 4, negative (not amplified).
- Ratio less than 2 with an average HER-2 copy number greater than or equal to 4 but less than 6, intermediate and reflex to IHC is needed.

IV. Statistical Considerstions

A. Endpoints

Primary: HER-2 gene copy number and HER-2 protein over-expression

B. Case selection and Sample Size

All consenting cases with adequate biospecimens available from the MATCH-Q subprotocoal arm.

Sample size estimate: 35 patients for tissue analyses

C. Analysis plan:

We would like to examine if HER-2 gene amplification and/or protein over-expression status are associated with clinical outcome after treatment with TDM1. Specifically we will assess their association with overall response and progression-free survival (PFS).

HER-2 gene amplication will be assessed by FISH as binary (amplication or not) and continuous variable (normalized to chromosome 17 centromere). Protein expression will be evaluated by IHC. For breast and gastric cancer, it has been established that IHC 0+ and 1+ are negative, IHC 3+ are over-expressed and IHC 2+ are equivocal.

For association between PFS and HER2 amplification, log-rank test will be used to test for differences in PFS between amplification status. IHC categories may be combined into over-expressed vs. not over-expressed (0+ plus 1+ versus 3+). For PFS and continuous amplification level (FISH normalized against chromosome 17 centromere), spline-based method (Gray 1992) will be used to examine the relationship between hazard ratio and the continuous variable.

For overall response and amplification status or over-expression status, Fisher's exact test will be used to test for differences in proportion amplified or over-expressed between responders and non-responders. For overall response and amplification level, Wilcoxon test will be used to test for differences in amplification level between PRs and SDs, and between SDs and PDs.

Because of the small sample size, exploratory data analysis will be performed. Data will be visualized by boxplots or dotplots. Correlation between HER2 amplification and protein over expression will be examined by scatter plot. Response can be overlayed by color.

V. References

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