ECOG-ACRIN
cancer research group
Reshaping the future of patient care

November 10, 2022

[redacted], MS RAC
[redacted]
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room [redacted]
Bethesda, MD 20892

Dear [redacted]:

Enclosed is Addendum #31 to EAY131-J, *MATCH Treatment Subprotocol J: Trastuzumab and Pertuzumab (HP) in Patients with Non-Breast, Non-Gastric/GEJ, and Non-Colorectal Cancers with HER2 Amplification.*

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 Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.

This addendum is in response to the Trastuzumab Rapid Request for Amendment (RRA) from Dr. [redacted] dated February 2, 2022.

Re: Review of **Amendment #44** of Protocol #**EAY131-J: "MATCH Treatment Subprotocol J: Trastuzumab and Pertuzumab (HP) in Patients with Non-Breast, Non-Gastric/GEJ, and Non-Colorectal Cancers with HER2 Amplification."** The following are ECOG-ACRIN's responses to the CTEP review comments dated 9/28/22. Please note that the Principal Investigator's comments appear in bold below.

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

#	Section	Comments
1.	ICD - Possible Side Effects of Trastuzumab	Possible Side Effects of Trastuzumab: The risk list table definition for **OCCASIONAL, SOME MAY BE SERIOUS** events was updated inappropriately. Change to: In 100 people receiving Trastuzumab (herceptin) and Herceptin Hylecta™ (SQ trastuzumab), from 4 to 20 may have:

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

#	Section	Comments
		PI Response: This change has been made.
2.	ICD - Possible Side Effects of Trastuzumab	Possible Side Effects of Trastuzumab: The risk list table definition for **RARE, AND SERIOUS** events was updated inappropriately. Change to: In 100 people receiving Trastuzumab (herceptin) and Herceptin Hylecta™ (SQ trastuzumab), 3 or fewer may have: **PI Response: This change has been made.**

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

	Section	Change
1.	Cover Page	Updated Version Date and addendum number.
2.	3.3	Updated CAEPR for Trastuzumab (Herceptin) to Version 2.6, December 14, 2021.

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

	Section	Change
1.	Cover Page	Updated Version Date.
2.	Possible Side Effects of Trastuzumab	Updated Risk List for Trastuzumab (Herceptin) to Version Date: December 14, 2021.

If you have any questions regarding this addendum, please contact [redacted] or [redacted].

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

Thank you.

Sincerely,

[redacted]

[redacted]

ECOG-ACRIN cancer research group
Reshaping the future of patient care

EAY131-J

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol J: Trastuzumab and Pertuzumab (HP) in Patients with Non-Breast, Non-Gastric/GEJ, and Non-Colorectal Cancers with HER2 Amplification

TRASTUZUMAB AND PERTUZUMAB TREATMENT SUBPROTOCOL CHAIR: [redacted], MB, BCh

Rev. Add25 TRASTUZUMAB AND PERTUZUMAB SUBPROTOCOL TRANSLATIONAL CHAIR: [redacted], MD, PhD

Version Date: November 10, 2022

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

Rev. Add13 Rev. Add25 **NOTE: As of 11/17, all protocol changes will be noted by addendum number.**

SUBPROTOCOL ACTIVATION DATE

March 13, 2017 (Incorporated In Addendum #7)
Addendum #10 – 5/17
Addendum #13
Addendum #18
Addendum #21
Addendum #22
Addendum #25
Addendum #31

Agent	IND#	NSC#	Supply
Trastuzumab	IND Sponsor: DCTD, NCI IND#: [redacted]	688097	NCI Supplied
Pertuzumab	IND Sponsor: DCTD, NCI IND#: [redacted]	740102	NCI Supplied

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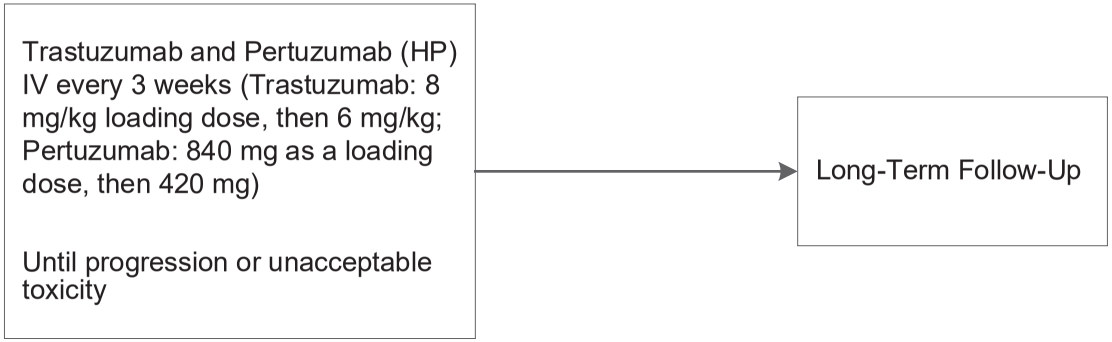
Schema



Cycle = 21 days
Accrual Goal: 35

1. Introduction

Amplification and/or overexpression of the human epidermal growth factor receptor 2 (HER2) gene is present in approximately 15-20% of breast cancers and has been associated with an aggressive breast cancer phenotype and a poor prognosis.(1) HER2 is a member of the epidermal growth factor receptor (EGFR or ErbB) family of receptor tyrosine kinases and is a key target for HER2-targeted therapy.(2) The humanized monoclonal antibody trastuzumab (Herceptin) was approved by the Food and Drug Administration (FDA) for use in the metastatic setting in the late 1990s based on improved clinical benefit and overall survival (OS). In 2005, trastuzumab was also approved in the adjuvant setting for patients with HER2-positive early breast cancer when combined with chemotherapy(3). Trastuzumab is also approved for the treatment of patients with HER2-overexpressing metastatic gastric/GEJ adenocarcinoma based on an observed survival advantage when combined with standard chemotherapy versus chemotherapy alone.(4)

Despite the advances noted above, resistance to trastuzumab is a common clinical dilemma. Dysregulation of downstream signalling pathways, alternative receptor tyrosine kinase signaling and accumulation of the truncated kinase active p95-HER2 have all been implicated in resistance to trastuzumab(5). Based on extensive preclinical and clinical development, additional HER2-targeted therapies are now available for patients with HER2-positive breast cancer and include the HER2/HER3 dimerization inhibitor pertuzumab (Perjeta). Pertuzumab is approved for treatment of patients with HER2-positive metastatic breast cancer, and recently received accelerated approval for use in the neoadjuvant setting in combination with trastuzumab and chemotherapy. Based on the information provided below, it appears that the combination of trastuzumab and pertuzumab is more effective than either agent alone, in a variety of settings in breast cancer.

A variety of tumor types other than breast and gastric/GEJ adenocarcinoma demonstrate amplification of the HER2 receptor (Figure 1), which may indicate a heavier dependence of these tumors on this pathway than in those tumors without amplification.(6,7) These patients are unlikely to have had prior trastuzumab. Thus, the combination of trastuzumab and pertuzumab may result in higher response rate and/or prolonged progression-free survival for this group of patients and is being investigated in this arm of the NCI MATCH trial.

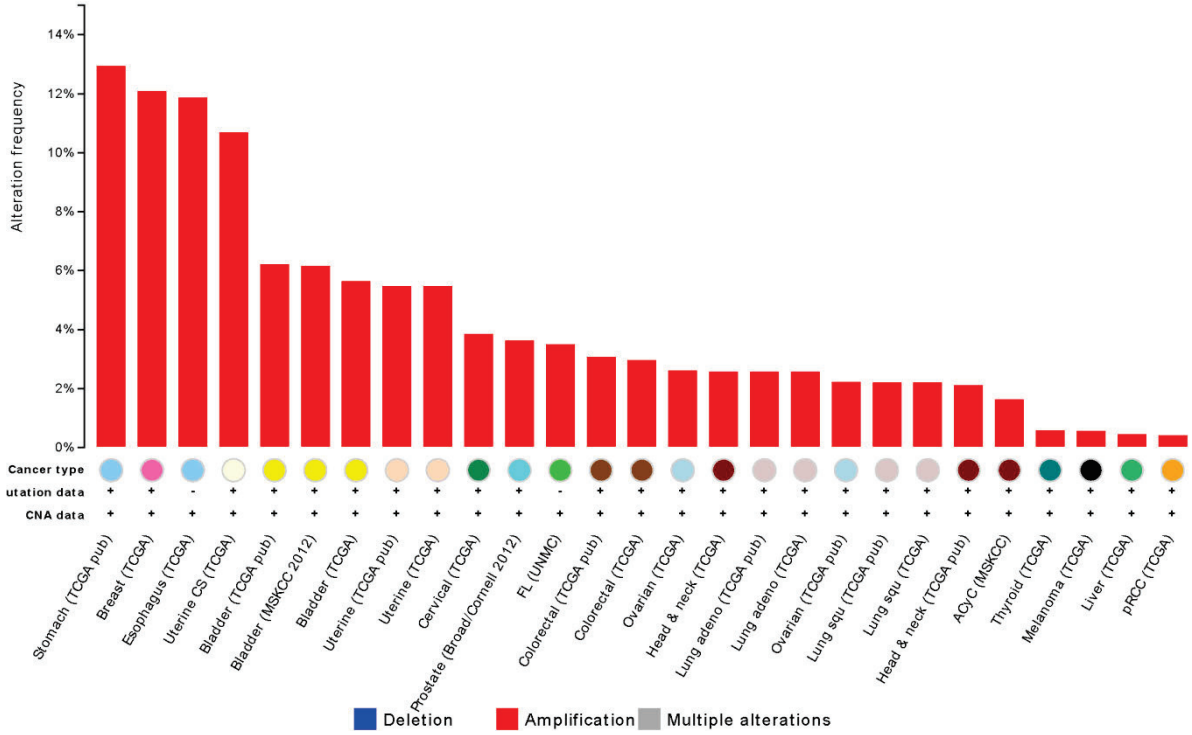


Figure 1: ERBB2 Alteration Frequency in Solid Tumors (www.cBioPortal.org)

1.1 Trastuzumab

Trastuzumab binds to extracellular domain IV of the HER2 receptor, inhibits downstream signaling and stimulates antibody-dependent cell-mediated cytotoxicity (ADCC)(*8*). It is becoming increasingly recognized that trastuzumab may also harness the immune system against HER2(*9*).

1.1.1 Preclinical Studies

Trastuzumab has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2. In vitro, trastuzumab mediated antibody-dependent cell-mediated cytotoxicity (ADCC) is preferentially exerted on HER2-overexpressing cancer cells compared with cancer cells that do not overexpress HER2.(10) Preclinical *in vivo* studies revealed no direct toxicity of trastuzumab via the intravenous, subcutaneous or intrathecal route. Reproductive toxicity studies in female monkeys did not reveal any impaired fertility, embryotoxicity, or effects on fetal development. An increased risk of cardiac dysfunction observed in clinical trials, particularly in combination with anthracycline therapy, was not predicted by preclinical safety studies. (Trastuzumab Investigator Brochure)

1.1.2 Clinical Studies

1.1.2.1 Breast Cancer

Single agent trastuzumab has been investigated as second- or third-line therapy for women with HER2-overexpressing metastatic breast cancer. Its use resulted in an objective response rate (ORR) of 15% and a median

survival of 13 months. (11) When used as monotherapy in the first-line setting, the ORR was 26%.(12) The use of trastuzumab in combination with chemotherapy as first-line treatment of women with metastatic breast cancer significantly prolonged median time to disease progression (TTP) and overall survival (OS), when compared with chemotherapy alone.(13)

Specifically, the combination of trastuzumab and docetaxel significantly increased ORR (61% versus 34%) and prolonged the median time to disease progression (by 5.6 months), compared with patients treated with docetaxel alone. Median survival was also significantly increased in patients receiving the combination, compared with those receiving docetaxel alone (31.2 months versus 22.7 months).(14) A number of clinical trials have indicated that the addition of 1 year of trastuzumab to adjuvant chemotherapy regimens in HER-2 positive breast cancer patients results in an approximately 50% reduction in breast cancer recurrence and 35% reduction in mortality.(15-17)

1.1.2.2 Gastric/GEJ adenocarcinoma

ToGA (Trastuzumab for Gastric Cancer) was an open-label, randomized, multicenter, Phase III study, which evaluated the efficacy of trastuzumab in combination with a fluoropyrimidine and cisplatin versus chemotherapy alone, as first-line therapy in patients with locally advanced or metastatic HER2-positive adenocarcinoma of the stomach including the gastroesophageal junction (GEJ).(4) Median overall survival was 13.8 months (95% CI 12-16) in those assigned to trastuzumab plus chemotherapy compared with 11.1 months (95% CI 10-13) in those assigned to chemotherapy alone (hazard ratio 0.74; 95% CI 0.60-0.91; p=0.0046).An exploratory post-hoc analysis found that the median OS in patients with high HER2-expressing tumors (IHC 2+/FISH+ and IHC3+) was extended from 11.8 months to 16 months (HR 0.65; 95% CI [0.51-0.83]). This study led to FDA approval of trastuzumab for this indication.

1.1.2.3 Other tumor types

A multicenter phase II single arm NCI trial included patients with advanced urothelial carcinoma selected based on HER2 overexpression by immunohistochemistry (IHC), gene amplification and/or elevated serum HER2, no prior chemotherapy for metastasis and adequate organ function.(18) Treatment consisted of trastuzumab, paclitaxel, carboplatin, gemcitabine, and was feasible. The overall response rate was 70% in 44 patients (five complete and 26 partial responses) with 57% confirmed response rate, which is considered meaningful, especially

in the absence of cisplatin. Median TTP and OS were 9.3 and 14.1 months, respectively.

The ECOG Group evaluated the combination of trastuzumab with carboplatin/paclitaxel, in patients with advanced NSCLC. (19) Toxicity was no worse than chemotherapy alone. Overall survival was similar to historical data with carboplatin/paclitaxel. However, patients with HER2 protein over-expression (+3) did well compared to historical data suggesting potential benefit with trastuzumab in a target-based selected subset of NSCLC patients.

In a report, two patients with HER2 over-expressing progressive or recurrent metastatic endometrial carcinoma were treated with trastuzumab after radiation treatment and/or salvage chemotherapy.(20) Clinical responses to trastuzumab alone or combined with chemotherapy were confirmed in both patients by imaging and serum CA-125 evaluations. These patients experienced symptomatic relief and had prolonged survival with no significant toxicity.

1.2 Pertuzumab

Pertuzumab is a humanized monoclonal antibody and is the first of a novel class of HER2-targeted agents known as HER2 dimerization inhibitors. This agent binds to a distinct epitope on the extracellular domain of the HER2 receptor (the domain II dimerization arm), blocking the interaction between HER2 and other HER family receptors.(21) Potent inhibition of HER-mediated intracellular signaling results in cancer cell growth inhibition and death.(22) Pertuzumab has a complementary mechanism of action to trastuzumab, in that it inhibits HER2/HER3 dimerization, inhibiting HER2-mediated cell signalling via the phosphatidylinositol 3-kinase (PI3K/Akt) pathway. Pertuzumab can also trigger ADCC-independent of trastuzumab, and with comparable efficacy. (23)

1.2.1 Preclinical Studies

The antitumor activity of pertuzumab and trastuzumab, a HER2-targeted monoclonal antibody, has been evaluated both as a single agent and in combination in HER2-positive breast cancer xenografts. The combination of trastuzumab and pertuzumab was found to have a greatly enhanced antitumor effect, a result not achieved with monotherapy. The enhanced efficacy of the combination was also observed after tumor progression during trastuzumab monotherapy and may relate to the different mechanisms of action of pertuzumab; inhibition of HER2 dimerization and prevention of p95HER2 formation. (22)

It was observed in in vitro studies that pertuzumab inhibits the heregulin-induced activation of the PI3K cell survival pathway, whereas trastuzumab does not (2). This implied that pertuzumab was more effective than trastuzumab in preventing HER2 signaling. Activity of single agent pertuzumab in breast, prostate, ovarian and lung cancer cell lines was observed in human tumor xenograft models

in mice (2). The combination of pertuzumab and trastuzumab was found to have a greatly enhanced antitumor effect in HER2-positive breast cancer in vitro studies as well as xenografts, a result not achieved with monotherapy (24).

The antitumor effects of HER2-directed combination therapy with trastuzumab and pertuzumab in ovarian cancer xenograft models have been demonstrated. (25) The combination of these antibodies showed enhanced anti-tumor activity compared to single agent therapy. High HER2 expression and increasing HER3 protein expression on treatment were associated with response.

In an in vitro study, pertuzumab and trastuzumab induced equally strong ADCC and CDC in FISH-positive uterine serous papillary adenocarcinoma cell lines.(26) Pertuzumab significantly increased tratuzumab-induced ADCC in uterine serous papillary adenocarcinoma with low HER2 expression, implying that it may represent a new therapeutic agent in patients with advanced, recurrent and/or refractory disease.

1.2.2 Clinical Studies

Pertuzumab was investigated initially as a single agent in metastatic breast cancer, with disappointing results. In a study that evaluated pertuzumab monotherapy in patients with progressive HER2-negative metastatic breast cancer, the ORR was 4.9% and the clinical benefit rate (CBR) was 9.8% (n=79). Pertuzumab was relatively well tolerated, with most adverse events being mild to moderate. Decline in left ventricular ejection fraction of ≥ 10% and/or to ≤ 50% was observed in eight patients, with one case of congestive heart failure.(27) In another study in HER2-positive patients with metastatic breast cancer progressing on trastuzumab, the ORR was 7.4% with a CBR of 11.1% (n=29). Interestingly, if the tumor failed to respond to pertuzumab monotherapy or responded and then progressed, trastuzumab could be added to pertuzumab. This strategy was undertaken in 14 patients, and 2 of these 14 achieved confirmed response when trastuzumab was added to the pertuzumab. This was the first clinical report providing evidence of an enhanced effect when the antibodies are combined.(28)

1.3 Dual anti-HER2 Therapy

Rev. Add13

1.3.1 Clinical Studies: Dual anti-HER2 Therapy without chemotherapy

The combination of pertuzumab and trastuzumab has yielded promising results in early phase clinical trials. A phase 2 trial in patients with HER2-positive metastatic breast cancer whose disease had progressed during prior trastuzumab-based therapy assessed the efficacy and safety profile of the combination of pertuzumab and trastuzumab (n=66). The ORR was 24.2%, and the CBR was 50%, with median PFS of 5.5 months. Cardiac dysfunction was minimal, and no patients needed to discontinue therapy as a result of cardiac-related adverse events.(29) More recently, preliminary results from the MyPathway clinical trial were presented at the 2016 ASCO GI Symposium, suggesting an ORR of 38% and CBR of 54% with

median time to progression 5.6 months in HER-2 overexpressing or amplified metastatic colorectal cancer without new safety signals with the anti-HER2 combination. (35) This promising response rate in the setting of dual anti-HER2 therapy without chemotherapy has also been shown with the combination of trastuzumab and lapatinib in the HERACLES trial, with a 30% ORR in patients with heavily pre-treated HER2-positive and RAS wild type metastatic colorectal cancer. (36)

1.3.2 Clinical Studies: Dual anti-HER2 Therapy and Chemotherapy

This combination of HER2-targeted agents has also been investigated in the neoadjuvant setting. NeoSphere was a Phase 2 randomized trial of preoperative systemic therapy comparing trastuzumab/docetaxel, trastuzumab/pertuzumab/docetaxel, trastuzumab/pertuzumab, and pertuzumab/docetaxel. The pCR rates were 29%, 46%, 17% and 24% respectively. When patients were analyzed based on ER status, a 63% pCR rate was observed in those with ER-negative disease treated with trastuzumab/pertuzumab/docetaxel and 27% in those with ER-negative disease treated with trastuzumab/pertuzumab.(30) Based on data from NeoSphere and other preoperative studies investigating pertuzumab in combination with chemotherapy, the FDA granted accelerated approval in late 2013 to pertuzumab for use preoperatively in combination with a complete chemotherapy regimen such as that investigated in NeoSphere.

A phase 3 trial in previously untreated HER2-positive metastatic breast cancer patients (CLEOPATRA), which randomized patients to trastuzumab/docetaxel vs trastuzumab/pertuzumab/docetaxel, has been presented.(31) The median PFS was 12.4 months in the control group compared with 18.5 months in the pertuzumab group (HR for progression or death, 0.62; 95% CI, 0.51 to 0.75; P<0.001). The interim analysis of overall survival showed a strong trend in favor of pertuzumab/trastuzumab/docetaxel.(31) Updated data indicated a median OS of 37.6 months (95% CI 34.3-NE [not estimable]) in the trastuzumab/docetaxel group but had not been reached (95% CI 42.4-NE) in the trastuzumab/pertuzumab/docetaxel group (HR 0.66, 95% CI 0.52-0.84; p=0.0008).(32) In addition, a phase 1 trial is ongoing investigating the combination of trastuzumab, pertuzumab, and paclitaxel in patients with metastatic breast cancer.

Rev. Add13

1.4 Summary

The management of HER2-positive breast cancer has been revolutionized by the development of anti-HER2 therapies such as trastuzumab, which is also approved for treatment of HER2-overexpressing metastatic gastric/GEJ adenocarcinoma. Recent studies indicate that dual anti-HER2 therapy is more efficacious than single anti-HER2 therapy, with recent promising data as above also suggesting a high ORR of 30-35% in patients with colorectal cancer. A variety of tumor types other than breast and gastric/GEJ adenocarcinoma demonstrate amplification of the HER2 receptor (Figure 1), which may indicate a heavier dependence of the tumor on this pathway than in those tumors without amplification. These patients are unlikely to have had prior trastuzumab or pertuzumab. Thus, the combination of trastuzumab and pertuzumab may result

in higher response rate and/or prolonged PFS for this group of patients and is being investigated in this arm of the NCI MATCH trial in patients with HER2 amplification.

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 Registration to Treatment

_____ 2.1.1 Patients must fulfill all eligibility criteria outlined in Section 3.1 of MATCH Master Protocol (excluding Sections 3.1.6, 3.1.7 and 3.1.11) at the time of registration to treatment step (Step 1, 3, 5, 7).

Rev. Add13

_____ 2.1.2 Patients must have HER2 amplification, or another aberration, as determined via the MATCH Master Protocol and according to Appendix I. See Appendix I for information on the targeted mutations and corresponding Levels of Evidence.

_____ 2.1.3 Patients must have an electrocardiogram (ECG) within 8 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 of ECG: _____

_____ 2.1.4 Patients must have ECHO or MUGA within 4 weeks prior to treatment assignment and must not have a left ventricular ejection fraction (LVEF) < institutional lower limit of normal (LLN). If the LLN is not defined at a site, the LVEF must be ≥ 50% for the patient to be eligible.

Date of ECHO/MUGA: _____

Rev. Add13

_____ 2.1.5 Patients must not have breast cancer, gastric/GEJ/esophageal adenocarcinoma or mixed histology, gastric/GEJ NOS tumors, or colorectal adenocarcinoma.

_____ 2.1.6 Patients must not have known hypersensitivity to trastuzumab or pertuzumab or compounds of similar chemical or biologic composition.

_____ 2.1.7 Patients must not have received prior anti-HER2 therapies, including trastuzumab, pertuzumab, T-DM1, lapatinib, afatinib, neratinib, dacomitinib, canertinib.

_____ 2.1.8 Women of childbearing potential (WOCBP) and men who are sexually active with WOCBP must agree to use adequate contraception (hormonal or double barrier method of birth control, abstinence) from one week prior to study treatment starting, during treatment, and for a period of 7 months after the last dose of study treatment.

_____ _____

Physician Signature Date

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

3. Trastuzumab and Pertuzumab (HP) Treatment Plan

Rev. Add13

3.1 Administration Schedule

3.1.1 Pertuzumab

Pertuzumab intravenous (IV) will be administered before trastuzumab on Day 1 every 3 weeks. Allow 60 minutes between drug administration for Cycle 1 and 30 minutes between drugs for subsequent cycles. Administer a loading dose of 840 mg on Day 1 Cycle 1 as a 60-minute intravenous infusion. Subsequent doses of 420 mg are administered every 3 weeks over 30 or 60 minutes if the initial infusion was well tolerated.

Repeat cycles until progression or unacceptable toxicity.

3.1.2 Trastuzumab

Trastuzumab intravenous (IV) will be administered after pertuzumab on Day 1 every 3 weeks. Allow 60 minutes between drug administration for Cycle 1 and 30 minutes between drugs for subsequent cycles. Administer a loading dose of 8 mg/kg on Day 1 Cycle 1 as a slow intravenous infusion. Subsequent doses of 6 mg/kg are administered every 3 weeks over 30 minutes if the initial infusion was well tolerated.

Repeat cycles until progression or unacceptable toxicity.

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 protocol EAY131 – Subprotocol J

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.

Rev. Add13
Rev. Add25

EAY131 – Subprotocol J specific expedited reporting requirements:

- **Cardiac toxicities:** Any grade congestive heart failure or asymptomatic decline in LVEF requiring treatment or leading to discontinuation of pertuzumab and trastuzumab 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.

- **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 Trastuzumab and Pertuzumab (HP), or within 7 months of the female patient's last dose of Trastuzumab and Pertuzumab (HP), are considered immediately reportable events. 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 Trastuzumab and Pertuzumab.

Rev. Add25

EAY131 – Subprotocol J specific expedited reporting exceptions:

For Subprotocol J, 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. Since this protocol uses multiple investigational agents, if an AE is listed on both SPEERs, use the lower of the grades to determine if expedited reporting is required.

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

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. 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.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

Rev. Add21
Rev. Add31

3.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Trastuzumab (Herceptin, NSC 688097)

The Comprehensive Adverse Events 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 4621 patients.* Below is the CAEPR for trastuzumab (Herceptin) and Herceptin Hylecta™ (SQ trastuzumab).

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. Since this protocol uses multiple investigational agents, if an AE is listed on both SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, December 14, 2021[1]

Adverse Events with Possible Relationship to Trastuzumab (Herceptin) (CTCAE 5.0 Term) [n= 4407]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	**Expected**
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Febrile neutropenia[2]		
CARDIAC DISORDERS			
	Heart failure		
	Left ventricular systolic dysfunction		***Left ventricular systolic dysfunction (Gr 3)***
	Palpitations		
	Pericardial effusion		
	Pericarditis		
	Restrictive cardiomyopathy		
	Sinus tachycardia[3]		***Sinus tachycardia (Gr 2)***
	Supraventricular tachycardia[3]		
EYE DISORDERS			
	Watering eyes		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Diarrhea		***Diarrhea (Gr 3)***
	Mucositis oral		***Mucositis oral (Gr 2)***
	Nausea		***Nausea (Gr 3)***
		Pancreatitis	
	Vomiting		***Vomiting (Gr 3)***

Adverse Events with Possible Relationship to Trastuzumab (Herceptin) (CTCAE 5.0 Term) [n= 4407]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	**Expected**
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[3]		***Chills[3] (Gr 2)***
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever[3]		***Fever[3] (Gr 2)***
	Flu like symptoms		***Flu like symptoms (Gr 2)***
	Injection site reaction[4]		***Injection site reaction[4] Gr 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 2)***
	Pain		***Pain (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	
		Allergic reaction[5]	
INFECTIONS AND INFESTATIONS			
	Infection[6]		***Infection[6] (Gr 3)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[7]		***Infusion related reaction[7] (Gr 2)***
INVESTIGATIONS			
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Cardiac troponin I increased		
		Ejection fraction decreased	***Ejection fraction decreased (Gr 3)***
	GGT increased		***GGT increased (Gr 2)***
	Neutrophil count decreased[2]		***Neutrophil count decreased[2] (Gr 4)***
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
	Bone pain		***Bone pain (Gr 2)***
	Muscle cramp		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Tumor Pain		***Tumor pain (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		
	Headache		***Headache (Gr 2)***

Adverse Events with Possible Relationship to Trastuzumab (Herceptin) (CTCAE 5.0 Term) [n= 4407]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	**Expected**
	Peripheral sensory neuropathy		
PSYCHIATRIC DISORDERS			
	Depression		
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Adult respiratory distress syndrome[3,5]	
	Allergic rhinitis		***Allergic rhinitis (Gr 2)***
		Bronchospasm	
	Cough		***Cough (Gr 2)***
	Dyspnea[3,5]		***Dyspnea (Gr 3)***
	Hypoxia[5]		***Hypoxia (Gr 2)***
		Pneumonitis[5]	
		Pulmonary edema[5]	
		Pulmonary fibrosis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Nail changes		
	Nail loss		
	Rash acneiform		***Rash acneiform (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria[3]		***Urticaria[3] (Gr 2)***
VASCULAR DISORDERS			
	Hot flashes		
	Hypertension[3]		
	Hypotension[3]		
	Lymphedema Vascular disorders - Other (vasodilation)		

[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]Fatal event when given in combination with Xeloda® (capecitabine) and Taxotere® (docetaxel).

[3]Associated with infusion-related reactions or administration-related reactions (ARRs).

[4]Injection site reaction was observed primarily in subjectes treated with Herceptin Hylecta™ SC formuation.

[5]Severe hypersensitivity reactions including angioedema and pulmonary adverse events (e.g., hypoxia, dyspnea, pulmonary infiltrates, pleural effusion, intersitial lung disease, wheezing, and acute respiratory distress syndrome) have been reported.

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

[7]Infusion related reaction was obseved primarily subjects treated with the trastuzumab IV formulation.

Adverse events reported on trastuzumab (Herceptin) and/or Herceptin HylectaTM (SQ trastuzumab) trials, but for which there is insufficient evidence to suggest that there was

a reasonable possibility that trastuzumab (Herceptin) and/or Herceptin HylectaTM (SQ trastuzumab) caused the adverse event:

CARDIAC DISORDERS - Asystole; Atrial fibrillation; Atrial flutter; Chest pain - cardiac; Myocardial infarction; Myocarditis; Sinus bradycardia; Ventricular arrhythmia; Ventricular tachycardia

EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo

EYE DISORDERS - Dry eye; Extraocular muscle paresis

GASTROINTESTINAL DISORDERS - Ascites; Colitis; Constipation; Duodenal ulcer; Dyspepsia; Enterocolitis; Esophagitis; Gastric hemorrhage; Gastritis; Gastrointestinal pain; Small intestinal perforation; Typhlitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Generalized edema; Sudden death NOS

HEPATOBILIARY DISORDERs - Cholecystitis

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Dermatitis radiation; Fracture; Injury, poisoning and procedural complications - Other (incision site pain); Injury, poisoning and procedural complications - Other (procedural pain)

INVESTIGATIONS - Alanine aminotransferase increased; Creatinine increased; Weight gain; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperkalemia; Hypoalbuminemia; Hypokalemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Chest wall pain; Flank pain; Generalized muscle weakness; Neck pain

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Treatment related secondary malignancy

NERVOUS SYSTEM DISORDERS - Amnesia; Depressed level of consciousness; Encephalopathy; Leukoencephalopathy; Muscle weakness left-sided; Paresthesia; Seizure; Syncope

PSYCHIATRIC DISORDERS - Anxiety; Confusion

RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Amenorrhea

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Epistaxis; Nasal congestion; Oropharyngeal pain; Pharyngolaryngeal pain; Pleural effusion[4]; Pulmonary hypertension; Respiratory failure; Wheezing[4]

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Eczema; Erythema multiforme; Hyperhidrosis; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Skin hyperpigmentation; Stevens-Johnson syndrome

VASCULAR DISORDERS - Hematoma; Thromboembolic event

NOTE: Trastuzumab (Herceptin) 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.

Rev. 5/17
Rev. Add22

3.4 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pertuzumab (NSC 740102)

The Comprehensive Adverse Events 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 9575 patients. Below is the CAEPR for Pertuzumab.

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. Since this protocol uses multiple investigational agents, if an AE is listed on both SPEERs, use the lower of the grades to determine if expedited reporting is required.

NOTE: Frequencies of AEs on this CAEPR are based on pooled clinical data from treatment arms, pivotal clinical trials using pertuzumab in combination with trastuzumab and docetaxel in patients with MBC (metastatic breast cancer), and pertuzumab in combination with trastuzumab and chemotherapy in patients with EBC (early stage breast cancer).

Version 2.4, July 6, 2019[1]

Adverse Events with Possible Relationship to Pertuzumab (CTCAE 5.0 Term) [n= 9575]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 2)***
CARDIAC DISORDERS			
		Heart failure	
EYE DISORDERS			
	Watering eyes		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***

Adverse Events with Possible Relationship to Pertuzumab (CTCAE 5.0 Term) [n= 9575]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	General disorders and administration site conditions - Other (mucosal inflammation)		
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[2]		***Allergic reaction[2] (Gr 2)***
		Anaphylaxis[2]	
INFECTIONS AND INFESTATIONS			
Infection[3]			***Infection[3] (Gr 3)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Dermatitis radiation		
	Infusion related reaction[4]		***Infusion related reaction[4] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Ejection fraction decreased	
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
	Paresthesia		
	Peripheral motor neuropathy		
	Peripheral sensory neuropathy		
PSYCHIATRIC DISORDERS			
	Insomnia		***Insomnia (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			

Adverse Events with Possible Relationship to Pertuzumab (CTCAE 5.0 Term) [n= 9575]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Cough		
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***
	Dry skin		
	Nail changes		***Nail changes (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		
	Pruritus		***Pruritus (Gr 2)***
	Rash[5]		***Rash[5] (Gr 2)***
VASCULAR DISORDERS			
	Hot flashes		

[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]Symptoms of allergic reaction and anaphylaxis may include bronchospasm.

[3]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC and may be due to concomitant chemotherapy.

[4]In pivotal studies adverse events that occurred during or within 24 hours after study drug administration and were judged to be related to the infusion of study drug were captured as associated signs and symptoms, not as a diagnosis (e.g., "infusion-related reaction").

[5]Rash includes the terms rash, exfoliative rash, rash popular, rash maculo-papular.

Adverse events reported on pertuzumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that pertuzumab caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Chest pain - cardiac; Left ventricular systolic dysfunction; Pericardial effusion

EYE DISORDERS - Blurred vision; Dry eye; Eye disorders - Other (diplopia)

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Dry mouth; Esophagitis; Gastroesophageal reflux disease; Hemorrhoids

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Flu like symptoms; Generalized edema; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Cholecystitis; Hepatobiliary disorders - Other (hepatitis fulminant); Hepatobiliary disorders - Other (hepatocellular injury)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture; Injury, poisoning and procedural complications - Other (post-procedural inflammation); Injury, poisoning and procedural complications - Other (procedural pain); Injury, poisoning and procedural complications - Other (skin toxicity); Wound complication; Wound dehiscence

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Creatinine increased; GGT increased; Investigations - Other (granulocytopenia); Lymphocyte count decreased; Platelet count decreased; Weight gain; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hypoglycemia; Hypokalemia; Hypomagnesemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (dermatomyositis syndrome); Musculoskeletal and connective tissue disorder - Other (spinal pain)

NERVOUS SYSTEM DISORDERS - Amnesia; Dysarthria; Lethargy; Nervous system disorders - Other (osmotic demyelination syndrome); Somnolence; Syncope

PSYCHIATRIC DISORDERS - Anxiety; Depression

RENAL AND URINARY DISORDERS - Acute kidney injury; Dysuria; Urinary frequency

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Amenorrhea; Breast pain; Irregular menstruation; Reproductive system and breast disorders - Other (metrorrhagia); Vaginal dryness

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm[4]; Nasal congestion; Oropharyngeal pain; Pleural effusion; Pneumonitis; Postnasal drip; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (painful respiration); Rhinorrhea

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Erythroderma; Hyperhidrosis; Nail discoloration; Pain of skin; Rash acneiform; Skin and subcutaneous tissue disorders - Other (onycholysis); Skin and subcutaneous tissue disorders - Other (onychomadesis); Skin hyperpigmentation; Urticaria

VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Lymphedema; Thromboembolic event; Vascular disorders - Other (hyperemia)

NOTE: Pertuzumab 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.

3.5 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).

Dose modification of pertuzumab and trastuzumab is not permitted.

If possible, symptoms should be managed with best supportive care. In case of toxicity, appropriate medical treatment should be used (including anti-emetics for nausea/vomiting, anti-diarrheals for diarrhea, etc.). No dose escalation is planned for this study.

A new cycle of treatment may begin when the following are met:

-All non-hematologic toxicity improved to Grade ≤ 2 (or to baseline)

-ANC ≥ 1,000/mm^3 and platelets ≥ 75,000/mm^3

For any event, which is apparent at baseline, the dose delays will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. (e.g. if a patient has grade 1 asthenia at baseline which increases to grade 2 during treatment, this will be considered as a shift of 1 grade and treated as a grade 1 toxicity for dose delay purposes).

A cycle may be delayed as noted below.

For delayed or missed doses, if the time between 2 sequential infusions is less than 6 weeks, the 420 mg IV dose of pertuzumab should be administered. Do not wait until the next planned dose. If the time between 2 sequential infusions is 6 weeks or more, the initial dose of 840 mg pertuzumab should be re-administered as a 60 minute IV infusion followed every 3 weeks thereafter by a dose of 420 mg IV administered over 30-60minutes.

Rev. Add13

Pertuzumab should be withheld or discontinued if trastuzumab treatment is withheld or discontinued. Trastuzumab may continue if pertuzumab is withheld or discontinued.

3.5.1 Toxicity Management for Trastuzumab and Pertuzumab

Dose delays and recovery windows refer to date of planned dose, not since last dose. For example: if cycle 2 was to start on January 1st, but is delayed due to grade 3 ANC; you may hold treatment up to additional 3 weeks from the originally planned cycle 2 day 1.

Figure 1: Actions to be Taken in Case of Trastuzumab and Pertuzumab Hematologic Toxicity

Hematologic toxicity related to study treatment	Action
ANC	Grade 1 or 2: Continue with study treatment Grade 3 or 4: Hold study treatment Toxicity resolves to Grade ≤2 within 3 weeks, resume study treatment Toxicity does NOT resolve to Grade ≤2 within 3 weeks, discontinue treatment, or discuss with Protocol Chair
Platelets	Grade 1: Continue with study treatment Grade 2: Consider holding treatment per grade 3 or 4 guidelines, or continue at treating physician discretion Grade 3 or 4: Hold study treatment Toxicity resolves to Grade ≤2 within 3 weeks, resume study treatment Toxicity does NOT resolve to Grade ≤2 within 3 weeks, discontinue treatment, or discuss with Protocol Chair
Hemoglobin	Grade 1 or 2: Continue with study treatment Grade 3 or 4: Hold treatment until resolution per below or consider transfusion Toxicity resolves to Grade ≤2 within 3 weeks, resume study treatment Toxicity does NOT resolve to Grade ≤2 within 3 weeks, discontinue treatment, or discuss with Protocol Chair.

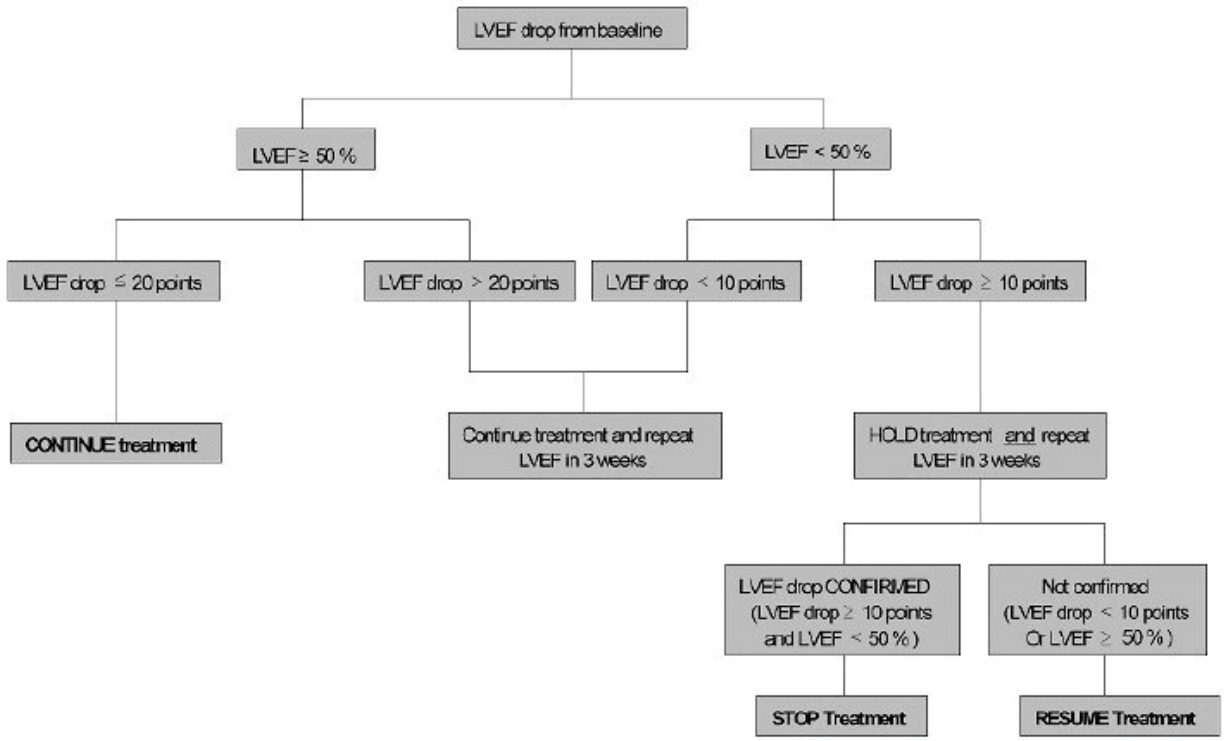
Figure 2: Actions to be Taken in Case of Trastuzumab and Pertuzumab Non-Hematologic Toxicity

Non-hematologic toxicity related to study treatment, excluding cardiac toxicity	Action
1. Grade 1 or 2	Continue with study treatment
2. Grade 3 or 4	Hold study treatment Toxicity resolves to Grade ≤2 within 3 weeks, resume study treatment Toxicity does NOT resolve to Grade ≤2 within 3 weeks, discontinue treatment, or discuss with Protocol Chair
3. Recurrence of Grade 3 or 4 toxicity upon re-challenge	Discontinue treatment

Figure 3: Actions to be Taken in Case of Trastuzumab and Pertuzumab Cardiac Toxicity

Cardiac toxicity related to study treatment	Action
1. Asymptomatic drop in LVEF	Hold study treatment. Monitor and continue per Figure 4
2. Left ventricular systolic dysfunction (grade 3 or 4) or heart failure (grade 2, 3 or 4)	Discontinue study treatment
3. Other cardiac toxicities not covered by this figure.	Follow rules 1 and 2 above for non-hematologic toxicity

Figure 4: Algorithm for Continuation/Discontinuation of Study Therapy in Asymptomatic Patients Based on LVEF Assessment



NOTE: The LVEF ≥ 50% and < 50% refers to the current LVEF. For example: if the current LVEF is < 50%, but did not drop at least 10 points from baseline, continue treatment and repeat LVEF in 3 weeks. If repeat LVEF still has not dropped at least 10 points, continue treatment and repeat LVEF at next scheduled time point. If LVEF has dropped ≥ 10 points on repeat, continue treatment and repeat LVEF in another 3 weeks. If LVEF at that time is confirmed as having dropped ≥ 10 points AND LVEF is < 50%, stop treatment.

NOTE: The Subprotocol Chair must be notified if an assessment of LVEF is performed prior to the planned assessment after 12 weeks of therapy so guidance can be given if necessary.

3.5.2 Important Toxicities for Trastuzumab and Pertuzumab

3.5.2.1 Infusion-Associated Reactions (IAR)

Like other monoclonal antibodies, pertuzumab has been associated with infusion associated reaction (such as chills, diarrhea, fatigue, headache, nausea, and pyrexia), and with hypersensitivity reactions. Close observation of the patient during and for 60 minutes after the first infusion and during and for 30 minutes following subsequent infusions is recommended following the administration of pertuzumab. If a significant IAR occurs, the infusion should be slowed down or interrupted and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should

be considered in patients with severe infusion reactions. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction.

3.5.2.2 Serious Infusion-Associated Events

Serious adverse reactions to trastuzumab infusion including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress have been reported infrequently. In rare cases (4 per 10,000), these events were associated with a clinical course culminating in a fatal outcome. Serious reactions have been treated with supportive therapy such as oxygen, beta-agonists, corticosteroids and withdrawal of trastuzumab as indicated.

3.5.2.3 Respiratory Symptoms

A low rate of respiratory events that are compatible with an IAR or hypersensitivity reaction/anaphylaxis has been reported. Although pertuzumab targets the HER2 receptor it inhibits heterodimerization with other members of the HER family (eg, EGFR [HER1]). Accordingly, it may cause toxicities associated with the use of EGFR inhibitors, such as interstitial lung disease (ILD). The few reports of ILD occurring in pertuzumab-treated patients received so far also had evidence of alternative causes, e.g., concomitant medication, preceding/concurrent neutropenia with potential infection or relevant medical history.

3.5.2.4 Left Ventricular Dysfunction

Decreases in LVEF have been reported with drugs that block HER2 activity. Trastuzumab and pertuzumab both target HER2, thus there is a risk of cardiac dysfunction with these agents. In the CLEOPATRA pivotal trial, pertuzumab in combination with trastuzumab and docetaxel was not associated with increases in the incidence of symptomatic LVSD or decreases in LVEF compared with placebo in combination with trastuzumab and docetaxel.(*31*) Pertuzumab combined with trastuzumab and chemotherapy did not result in any significantly greater incidence of symptomatic LVSD or decreases in LVEF than trastuzumab and chemotherapy in patients with early breast cancer.(*33*) However, in the pivotal MBC trial a greater proportion of patients who developed symptomatic LVSD had received prior anthracyclines and/or radiotherapy compared to the proportion of patients receiving prior anthracyclines and/or radiotherapy in the overall pertuzumab-treated population.(*31*) Therefore, patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of decreased LVEF.

Pertuzumab has not been studied in patients with: a pretreatment LVEF value of ≤ 50%; a prior history of CHF; decreases in LVEF to < 50% during prior trastuzumab adjuvant therapy; conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to > 360mg/m^2 of doxorubicin or its equivalent.

3.5.2.5 Management of Cardiac Safety

All patients must have a baseline evaluation of cardiac function including a measurement of LVEF by either MUGA or ECHO prior to entry into the study. Only patients with an LVEF ≥ 50% will be entered into this study.

It is recommended that patients should have cardiac monitoring at regular intervals (e.g., every three months) during treatment with pertuzumab and trastuzumab. As part of this study, cardiac monitoring will occur at baseline and at conclusion of study treatment (i.e., after about 3 months); or additionally if required to monitor toxicity. ECHO or MUGA scans should be scheduled at the same radiology facility where the patient's baseline ECHO or MUGA was conducted. When a cardiac event occurs, the Cardiac Report Form must be submitted within 14 days of learning of the event.

During the course of trastuzumab and pertuzumab therapy, patients should be monitored for signs and symptoms of CHF (i.e., dyspnea, tachycardia, new unexplained cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and rapid unexplained weight gain). The confirmation of the CHF diagnosis should include the same method used to measure LVEF at baseline (either ECHO or MUGA).

Pertuzumab and trastuzumab should be discontinued in any patient who develops clinical signs and symptoms suggesting CHF. CHF should be treated and monitored according to standard medical practice. At present, there are inadequate data available to assess the prognostic significance of asymptomatic drops in LVEF.

3.5.2.6 EGFR-Associated Toxicities

Although pertuzumab targets the HER2 receptor, it inhibits heterodimerization with other members of the HER family (e.g., EGFR [HER1]). Accordingly, it may cause toxicities associated with the use of EGFR inhibitors such as diarrhea, rash and other dermatologic toxicities (eg, dry skin, pruritus, nail disorders, mucositis).

3.5.2.7 Diarrhea

In the 7-week IV and 26-week toxicity studies in cynomolgus monkeys, there was a treatment-related increase in the incidence of diarrhea. Diarrhea has been observed in approximately 60% of patients (treatment-related diarrhea in 50% of patients) being treated with pertuzumab in phase 2 single-agent studies, and up to approximately 70% of patients in combination therapy studies. Diarrhea was CTCAE Grade 1 or 2 in the majority of cases. To prevent dehydration, early treatment of diarrhea with anti-diarrheal medication should be considered and patients treated with fluids and electrolyte replacement, as clinically indicated.

3.5.2.8 Rash

Rash has also been observed with EGFR inhibitors, mostly of mild to moderate intensity. Rash has been observed in approximately 17% of patients receiving pertuzumab in Phase 2 single-agent studies and up to 73% of patients in combination studies. The rash was generally of CTCAE Grade 1 or 2 in severity. Treatment recommendations for EGFR-associated rash include topical or oral antibiotics, topical pimecrolimus, topical or (for severe reactions) systemic steroids. These agents may be used in patients experiencing pertuzumab-related rash, as clinically indicated, although they have not been studied in this context.

3.6 Supportive Care

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

The administration of any other therapies intended to treat the primary cancer including endocrine therapy, chemotherapy, immunotherapy, radioactive and biologic/targeted agents is NOT permitted. However, patients with prostate cancer may continue on GnRH agonist (or antagonist) with approval by the Protocol Chair (oral anti-androgens [e.g. enzalutamide, bicalutamide, flutamide, nilutamide], abiraterone, ketoconazole, estrogen are not allowed for prostate cancer). Similarly, the use of other concurrent investigational drugs is not allowed. Local therapy to sites of disease may be allowed on study (e.g., radiation to bone metastases, stereotactic surgery) at the discretion of the Protocol Chair, as long as is not the only lesion being monitored for response.

3.6.1 Bone-modifying agents

Patients may be treated with bone modifying agents such as bisphosphonates or RANK-ligand agents (e.g. denosumab) per ASCO guidelines. Whenever possible, patients requiring bone modifying agents should start treatment 7 days prior to study therapy and should continue the same agent throughout study unless clinically compelled to change.

3.7 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

3.8 Duration of Follow-Up

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

4. Study Parameters

4.1 Therapeutic Parameters for Trastuzumab and Pertuzumab Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients receiving Trastuzumab and Pertuzumab 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 and electrocardiogram (ECG).

NOTE: The schedule should be followed as closely as is realistically possible; however, the schedule may be modified due to problems such as scheduling delays or conflicts (e.g., clinic closure, poor weather conditions, vacations, etc.) with the guidance of the Protocol Chair/designee, as appropriate, and will not be reportable as a deviation unless the endpoints of the study are affected.

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

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

B. Concomitant Medications will be collected up to 90 days from the end of study treatment.

C. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, glucose, phosphorus, potassium, SGOT[AST], SGPT[ALT], sodium (magnesium as clinically indicated). For eligibility purposes, participants with creatinine levels above institutional normal, Cockcroft-Gault will be used to calculate creatinine clearance, as clinically indicated. 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) if clinically indicated (see foot

note J). 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.

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.

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

F. Site personnel should evaluate for toxicity and discuss treatment compliance with the patient in order to ensure the medication is taken correctly; this evaluation may be conducted by telephone or in person. The Toxicity Assessment is not required prior to Cycle 1, but is required every subsequent cycle.

G. As clinically indicated.

Rev. Add13 H. ECHO/Nuclear Study should be repeated every 12 weeks from Cycle 1 Day 1 (±1 week) while on therapy and at discontinuation unless done in the prior 4 weeks.

Rev. Add13 I. 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.

J. Within 8 weeks of treatment assignment.

K. 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.

L. 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 the SAE reporting requirements, it still must be reported via CTEP-AERS, even if progression has occurred.

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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).

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 for Oral Agents 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.

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 Trastuzumab (NSC #688097)

5.1.1 Other Names

HERCEPTIN®; rhuMAb HER-2/NEU; MoAb HER2/NEU

5.1.2 Classification

Monoclonal antibody

5.1.3 Mode of Action

The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Trastuzumab has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.

Trastuzumab is a mediator of antibody-dependent cellular cytotoxicity (ADCC). In vitro, Herceptin-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

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5.1.4 How Supplied

Genentech supplies and the Pharmaceutical Management Branch, CTEP, NCI, distributes trastuzumab in a multi-use vial containing 440 mg trastuzumab as a lyophilized sterile powder, under vacuum. Each carton contains one vial Herceptin® and one vial (20 mL) of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative.

Trastuzumab is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous administration. Each multi-use vial of trastuzumab contains 440 mg trastuzumab, 400 mg α,α-trehalose dihydrate, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, and 1.8 mg polysorbate 20, USP.

In the first half of 2019, NCI will switch over to start supplying only single-use 150 vials of trastuzumab as a lyophilized preparation for parenteral administration. The commercially-labeled 150 mg vials are formulated in histidine/histidine-HCl monohydrate, α,α-trehalose dihydrate, and polysorbate 20. **NOTE: The 150 mg vials are not multi-use vials.**

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5.1.5 Storage and Stability

Storage: store at 2−8°C (36−46°F) prior to reconstitution.

Stability: Do not use beyond the expiration date stamped on the product label (440 mg kit box or 150 mg vial). The 440 mg vial of trastuzumab reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2−8°C (36−46°F). Discard any remaining multi-dose reconstituted solution after 28 days. A vial of trastuzumab reconstituted with unpreserved SWFI (not supplied) should be used immediately and any unused portion discarded. **Do Not Freeze** trastuzumab following reconstitution or dilution.

The solution of trastuzumab for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, should be stored at 2−8°C (36−46°F) for no more than 24 hours prior to use.

Either multi-dose or single dose handling is allowed at institutional discretion.

5.1.6 Dose Specifics

Trastuzumab intravenous (IV) will be administered after pertuzumab on Day 1 every 3 weeks. Allow 60 minutes between drug administration for Cycle 1 and 30 minutes between drugs for subsequent cycles. Administer a loading dose of 8 mg/kg on Day 1 Cycle 1 as a slow intravenous infusion. Subsequent doses of 6 mg/kg are administered every 3 weeks over 30 minutes if the initial infusion was well tolerated.

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5.1.7 Preparation

Reconstitute each 440 mg vial of trastuzumab with 20 mL of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multi-dose solution containing 21 mg/mL trastuzumab.

Reconstitute each 150 mg vial of trastuzumab with 7.4 mL of Sterile Water for Injection (SWFI), USP to yield a solution containing approximately 21 mg/mL trastuzumab at a pH of approximately 6.0. Use of other reconstitution solvents should be avoided. A volume overfill ensures that the labeled dose of 150 mg can be withdrawn from each vial.

Reconstitution

Use appropriate aseptic technique when performing the following reconstitution steps:

440 mg vials

- Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized cake of trastuzumab. The stream of diluent should be directed into the lyophilized cake.
- Swirl the vial gently to aid reconstitution. **DO NOT SHAKE.**
- Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for particulates and discoloration. The solution should be free of visible particulates, clear to slightly opalescent and colorless to pale yellow.
- Store reconstituted trastuzumab at 2−8ºC; discard unused trastuzumab after 28 days. If trastuzumab is reconstituted with SWFI without preservative, use immediately and discard any unused portion.

150 mg vials

- Using a sterile syringe, slowly inject the 7.4 mL of Sterile Water for Injection (SWFI), USP into the vial containing the lyophilized cake of trastuzumab. The stream of diluent should be directed into the lyophilized cake.
- Swirl the vial gently to aid reconstitution. **DO NOT SHAKE.**
- Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for particulates and discoloration. The solution should be free of visible particulates, clear to slightly opalescent and colorless to pale yellow.
- Single-use vial should be used immediately after reconstitution.

Dilution

- Determine the dose (mg) of trastuzumab. Calculate the volume of the 21 mg/mL reconstituted trastuzumab solution needed, withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. **DO NOT USE DEXTROSE (5%) SOLUTION.**
- Gently invert the bag to mix the solution.

5.1.8 Route of Administration

Intravenous infusion through standard IV tubing

5.1.9 Incompatibilities

The mean serum trough concentration of trastuzumab was consistently elevated approximately 1.5-fold, when administered in combination with paclitaxel as compared to trough concentrations of trastuzumab when administered in combination with an anthracycline and cyclophosphamide.

In other pharmacokinetic studies, where trastuzumab was administered in combination with paclitaxel, docetaxel, carboplatin, or doxorubicin, trastuzumab did not alter the plasma concentrations of these chemotherapeutic agents, or the metabolites that were analyzed. In a drug interaction substudy conducted in patients, the pharmacokinetics of cisplatin, capecitabine and their metabolites were not altered when administered in combination with trastuzumab.

5.1.10 Side Effects

See Section 3.3 for side effects.

5.1.11 Nursing/Patient Implications

The initial dose should be administered over approximately 90 minutes. If this is well tolerated, subsequent administration may be infused over approximately 30 minutes. DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.

Premedication regimens standard to each institution are suggested. This may include acetaminophen and diphenhydramine, for example. Each institution may employ the premedication regimens considered routine in their practices. The regimens used should be clearly noted in the medical record and research file.

See Section 3.5.2 for management of infusion-associated reactions (IARs) and other specific toxicities.

5.2 Pertuzumab (NSC #740102)

5.2.1 Other Names

PERJETA®

5.2.2 Classification

HER2/neu receptor antagonist

5.2.3 Mode of Action

Pertuzumab blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two major signal pathways, mitogen-activated protein (MAP) kinase, and phosphoinositide 3-kinase (PI3K). Inhibition of these signaling pathways can result in cell growth arrest and apoptosis, respectively. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

5.2.4 How Supplied

Pertuzumab is supplied by Genentech, Inc. and distributed by CTEP, DCTD, NCI. Pertuzumab is a sterile, clear to slightly opalescent, colorless to pale brown liquid for intravenous infusion. Each single use vial contains 420 mg of pertuzumab at a concentration of 30 mg/mL (14mL) in 20 mM L-histidine acetate (pH 6.0), 120 mM sucrose and 0.02% polysorbate 20.

5.2.5 Storage and Stability

Storage: Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep vial in the outer carton in order to protect from light. **DO NOT FREEZE. DO NOT SHAKE.**

Stability: If the diluted infusion solution is not used immediately, it can be stored at 2ºC to 8ºC for up to 24 hours. Dilute with 0.9% Sodium Chloride injection only.

Diluted pertuzumab has been shown to be stable for up to 24 hours at a temperature up to 30°C. However, since diluted pertuzumab contains no preservative, the diluted solution should be stored refrigerated (2°C–8°C).

5.2.6 Dose Specifics

Pertuzumab intravenous (IV) will be administered before trastuzumab on Day 1 every 3 weeks. Allow 60 minutes between drug administration for Cycle 1 and 30 minutes between drugs for subsequent cycles. Administer a loading dose of 840 mg on Day 1

Cycle 1 as a 60-minute intravenous infusion. Subsequent doses of 420 mg are administered every 3 weeks over 30 or 60 minutes if the initial infusion was well tolerated.

5.2.7 Preparation

Administer as an intravenous infusion only. Do not administer as an intravenous push or bolus. Do not mix pertuzumab with other drugs.

Prepare the solution for infusion, using aseptic technique, as follows:

- Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.
- Withdraw the appropriate volume of pertuzumab solution from the vial(s).
- Dilute into a 250 mL 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag.
- Mix diluted solution by gentle inversion. Do not shake.
- Administer immediately once prepared.

5.2.8 Route of Administration

Intravenous through standard IV tubing

5.2.9 Method of Administration

The initial pertuzumab dose is administered as an approximately 60-minute intravenous infusion. Subsequent doses are administered by intravenous infusion over approximately 30 or 60 minutes, depending on how the initial dose was tolerated.

5.2.10 Incompatibilities

Do not use dextrose (5%) solution.

5.2.11 Side Effects

See Section 3.4 for side effects.

6. Translational Studies

These may include, but not limited to, immunohistochemistry, fluorescent in situ hybridization (FISH) in tumor tissue, as well as assessment of correlation with gene amplification by sequencing, evaluation of other tissue biomarkers, additional collection of blood (e.g. circulating biomarkers, tumor cells, nucleic acids), others. Additional studies will be discussed with MATCH team and may require amendment to protocol.

Please also 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 J: HP in HER2 Amplification

Appendix I

Actionable Mutations for Sub-Protocol EAY131-J

Rev. Add25

ERBB2 Copy number ≥ 7 copies/cell as assessed by the central Oncomine® Assay which will be ≥15 copies per cell for those Designated Laboratories that correct for tumor content.

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol J: HP in HER2 Amplification

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

The patient _____ is enrolled on a clinical trial using the experimental study drugs, Trastuzumab and Pertuzumab. 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.

There are no expected interactions with other medications.

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

There are no expected interactions with other medications.

However, it is still 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:

- Your regular health care provider should 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 drugs Trastuzumab and Pertuzumab**.** This clinical trial is sponsored by the NCI. **There are no expected interactions with other medications.** However, it is still 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.

- 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 should be discontinued.
- Before prescribing new medicines, your regular health care providers should contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.