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Activation Date: October 9, 2017

SWOG

A RANDOMIZED PHASE II STUDY OF TRASTUZUMAB AND PERTUZUMAB (TP) COMPARED TO CETUXIMAB AND IRINOTECAN (CETIRI) IN ADVANCED/METASTATIC COLORECTAL CANCER (MCRC) WITH HER-2 AMPLIFICATION

NCT #03365882

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AGENTS:

IND-Exempt Agents:
Cetuximab (Erbitux) (NSC-714692)
Irinotecan (CPT-11, Camptosar) (NSC-616348)

SWOG-Held IND Agents:
Pertuzumab (Perjeta) (NSC-740102)
(IND-132527)
Trastuzumab (Herceptin) (NSC-688097)
(IND-132527)

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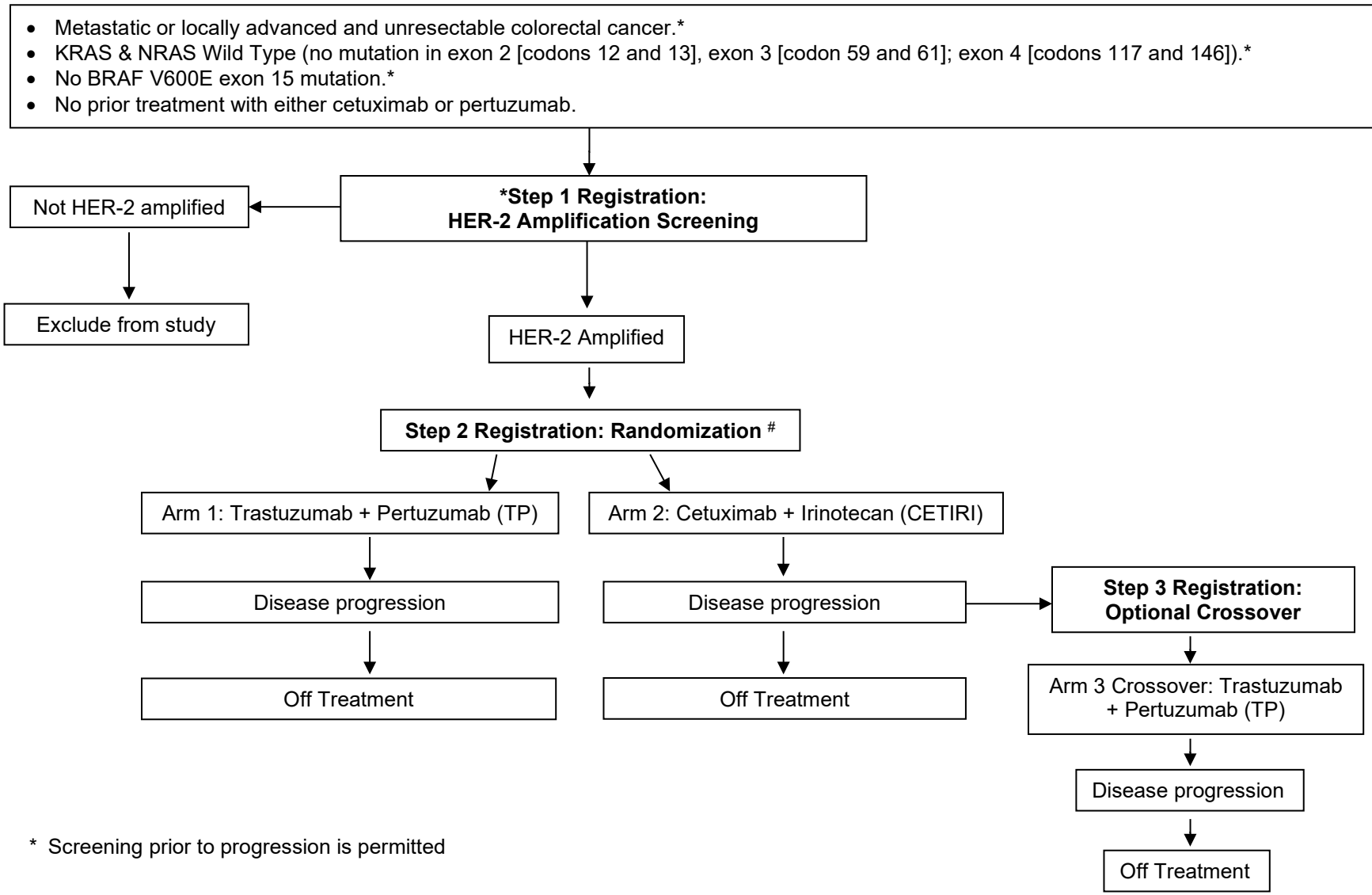
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation can be submitted to the CTSU via: **ONLINE**: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) **EMAIL**: CTSURegulatory@ctsu.coccg.org (regulatory documentation only) **FAX**: 215-569-0206 **MAIL**: CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 For regulatory questions call the CTSU Regulatory Help Desk at 1-866-651-CTSU	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM userid and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For patient eligibility questions contact the SWOG Statistics and Data Management Center by phone or email: 206-652-2267 giquestion@crab.org **For treatment or toxicity related questions** contact the Study PI of the Coordinating Group.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line: 888-823-5923 ctsucontact@westat.com All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

SCHEMA



* Screening prior to progression is permitted

[#] Randomization can be performed after progression on at least one line (or maximum 2 lines) of chemotherapy.

1.0 OBJECTIVES

1.1 Primary Objective

a. To evaluate the efficacy of trastuzumab and pertuzumab (TP) in HER-2 amplified metastatic colorectal cancer (mCRC) by comparing progression-free survival (PFS) on TP compared to control arm of cetuximab and irinotecan (CETIRI).

1.2 Secondary Objectives

a. To evaluate the overall response rate (ORR), including confirmed complete and partial response per RECIST 1.1, in the TP and CETIRI treatment arms.

b. To evaluate the overall survival (OS) in the TP and CETIRI treatment arms.

c. To evaluate the safety and toxicity of TP compared to CETIRI.

1.3 Additional Objectives

a. To estimate the rates of PFS, OS, and ORR in patients who crossover to TP after disease progression on CETIRI.

b. To bank images for future retrospective analysis.

1.4 Translational Objective

a. To evaluate if the following are prognostic of clinical efficacy (PFS and ORR) in patients receiving TP or CETIRI:

1. HER-2/CEP17 signal ratio

2. HER-2 gene copy number (GCN)

b. To bank tissue and blood samples for other future correlative studies from patients enrolled on the study.

2.0 BACKGROUND

Scope of the Problem: Colorectal cancer (CRC) is a major global burden and accounts for over 1.36 million new cancer cases and about 700,000 deaths as per 2012 estimates, worldwide. *(1)* Despite advances in systemic therapy, median survival in metastatic disease with current available regimens is about 30 months. *(2)* Options for systemic therapy are limited and include both cytotoxics (5-fluorouracil, capecitabine, oxaliplatin and irinotecan) and targeted agents (bevacizumab, cetuximab, pertuzumab, aflibercept, ramucirumab and regorafenib). (3) Therefore, a large unmet need for novel strategies targeting novel pathways involved in colorectal carcinogenesis and therapeutic resistance exists. The HER-2 (human epidermal growth factor 2) pathway is emerging as one such unique potentially drug-targetable pathway in CRC through comprehensive molecular characterization and recurrent copy number alterations specifically amplifications of HER-2 have been identified. *(4,5)*

HER-2 Amplification/Overexpression in CRC: HER-2 is amplified and/or overexpressed in a small but distinct subset (3-4%) of all unselected cases of mCRC. *(6,7,8,9)* As is the case with breast cancer, strong concordance exists between gene amplification and protein overexpression. *(10)* While low level of gene amplification and protein overexpression suggests that this oncogene plays an infrequent role in development and progression of unselected mCRC, recent data has

emerged showing enrichment for HER-2 amplification in cetuximab-resistant KRAS wild type subset (13.6%) and in quadruple negative (wild type KRAS, NRAS, BRAF and PIK3CA) xenopatients (36.4%) demonstrating its key role in a select subset of mCRC and in development of resistance to anti-EGFR therapy in mCRC. *(11)* The largest prospective experience regarding the prevalence of HER-2 amplification in mCRC patients comes from the HERACLES study in which HER-2 amplification (by IHC and FISH) was seen in 4.8% (total patients with KRAS wild-type tumors screened = 913). *(12) T*his also forms the basis of HER-2 testing strategy in mCRC. (2) In a retrospective analysis of 1,342 patients in stage IV trials (FOCUS and PICCOLO), HER-2-overexpression was associated with KRAS/BRAF-wild type status (5.2% in wild type versus 1.0% in mutated tumors (P < 0.0001). (13) HER-2 amplification will be tested using the principles of ASCO/CAP guidelines for breast cancer and TOGA criterion for gastric cancer. *(14,15)* Patients will be tested for HER-2 using immunohistochemistry (IHC) and dual-probe in-situ hybridization (Dual-ISH). The following criteria will be used:

- HER-2 IHC
    - Patients with HER-2 IHC 0 (no reactivity) and HER-2 IHC 1+ (faint or barely perceptible membranous reactivity) will be considered as HER-2 non-amplified.
    - Patients with HER-2 IHC 2+/3+ (weak to moderate complete basolateral or lateral membranous reactivity in > 10% of cancer cells) will undergo Dual ISH.
- Dual-ISH
    - HER-2 amplification testing will then be performed on HER IHC 2+/3+ cases and will be considered positive if HER-2/CEP17 ratio ≥ 2.0. These cases will be reported as HER-2 amplified. Cases with HER-2/CEP17 ratio < 2.0 will be reported as non-amplified.

HER-2 and Anti-EGFR Resistance: Extensive cross-talk between EGFR and HER-2 signaling links HER-2 in development of resistance to anti-EGFR therapy (cetuximab or pertuzumab). Although, EGFR expression is seen in about 50% of mCRC, anti-EGFR monotherapy results in low response rates and minimal clinical benefit even after appropriate selection of patients for RAS mutations, the single most important negative predictive biomarker, and other alterations in one or more downstream effectors of EGFR pathway (BRAF, AKT, PIK3CA). (16) In a molecularly annotated platform of patient derived xenografts, HER-2 amplification was shown to be an important mechanism of cetuximab resistance in mCRC patients. *(17)* This blunted response to anti-EGFR therapy was demonstrated clinically in a small retrospective study (N = 170) of mCRC patients. *(18)* In this study 4% patients with HER-2 gene amplification (HER-2/CEP17 ratio ≥ 2) compared to non-amplified patients showed poorer progression-free survival (median PFS in months: 2.5 vs 6.7; P = 0.0026) and overall survival (median OS in months: 4.2 vs 13.0; P = 0.0002). *(19)* In another cohort (n = 233) of mCRC patients with 13 (5.5%) HER-2 amplified tumors treated with cetuximab alone or in combination with chemotherapy, Yoneska et al. showed similar results with median PFS for HER-2 amplified patients being 2.9 months (0/23 responses to prior anti-EGFR therapy) compared to 5.0 months for patients without HER-2 amplification. (20*)*

HER-2 Inhibition in CRC (Pre-clinical and Clinical Data): In patient derived xenografts of HER-2 amplified mCRC, dual inhibition of HER-2 with lapatinib and pertuzumab resulted in significant tumor volume reduction. *(21)* A Phase II study of trastuzumab in combination with irinotecan in HER-2 overexpressed mCRC refractory to first-line therapy was performed by Ramanathan et al. and showed HER-2 overexpression was present in 11 of 138 (8.0%) of screened tumors. *(22)* Partial responses were seen in 70% cases (5/7 evaluable patients). *(23)* In another Phase II study of trastuzumab and lapatinib in HER-2-amplified, KRAS exon 2 wild-type, mCRC patients (n = 44 [total screened 913]) resistant to standard therapies (HERACLES Trial) an overall response rate of 35% (8 of 23 evaluable) was observed. *(24)* Median time to progression was 5.5 months (95% CL 3.7-9.8) and toxicity was limited to Grade 2 diarrhea, fatigue, and rash. *(25)* Preliminary experience from the My Pathway study which enrolled 13 HER-2 amplified mCRC patients refractory to standard lines of therapy and treated with trastuzumab and pertuzumab, showed partial responses in 3 and stable disease in 6 patients of 11 evaluable patients. *(26)*

Rationale for Control Arm: Addition of anti-EGFRab such as Cetuximab to a cytotoxic chemotherapy backbone is considered the standard of care for RAS wild-type patients. Irinotecan based regimen is considered the standard of care for patients who have progressed on an oxaliplatin based regimen. *(27)* Although both FOLFIRI and irinotecan can be used in patients after progression on FOLFOX based therapy, in a meta-analysis, no overall survival benefit of irinotecan and fluoropyrimidine treatment over irinotecan alone was seen and therefore both regimens remain reasonable options in treating patients with advanced or metastatic CRC, especially in patients who have progressed on a prior 5FU based regimen. *(28)* Since there were higher risks of toxicity outcomes Grade 3 or 4 diarrhea and Grade 3 or 4 neutropenia in combination, we choose irinotecan as the chemotherapy backbone. *(29)* The EPIC trial of second line cetuximab and irinotecan after oxaliplatin progression showed improved PFS and ORR with combined therapy. *(30)* Similarly, the BOND trial compared irinotecan plus weekly cetuximab versus cetuximab alone in patients with irinotecan-refractory mCRC and showed that combined therapy was associated with a significantly better response rate and TTP. *(31)*

Summary: Recognizing that HER-2 amplification adversely influences the clinical response to therapy with anti-EGFR-antibody, cetuximab (negative predictor of response to EGFR inhibition), and is predictive of response to dual anti-HER-2 therapy (positive predictor of response to HER-2-targeting agents), in HER-2 amplified mCRC patients, we hypothesize that dual anti-HER-2 inhibition using monoclonal antibodies, trastuzumab and pertuzumab, will result in enhanced tumor suppression in irinotecan-refractory mCRC patients thereby resulting in improved progression-free survival outcomes compared to standard of care therapy with cetuximab and irinotecan.

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

Note: We estimate that approximately 296 patients will be screened for HER-2 amplification in order to enroll the 62 patients necessary for the study. This table represents only the patients with HER-2 amplification who register to Step 2 (randomization).

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	1	0	0	2
Asian	2	2	0	1	5
Native Hawaiian or Other Pacific Islander	1	1	0	0	2
Black or African American	2	2	0	0	4
White	23	24	1	1	49
More Than One Race	0	0	0	0	0
Total	29	30	1	2	62

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study, cetuximab and irinotecan are commercially available; therefore, Investigator Brochures are not applicable to this/these drug/s. Information about commercial drugs is publicly available in the prescribing information and other resources.

For this study, pertuzumab and trastuzumab are investigational and are being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

3.1 Cetuximab (IMC-C225, Erbitux®) (NSC-714692)

a. PHARMACOLOGY

Mechanism of Action: Cetuximab, a chimerized antibody of the IgG1 subclass, was originally derived from a mouse myeloma cell line. Cetuximab was genetically engineered by cloning the heavy and light chains of cetuximab and adapting them for expression together with the constant regions of the human kappa light chain and human gamma 1 heavy chain. The chimerization resulted in an antibody with binding affinity to epidermal growth factor receptors (EGFR) greater than the natural ligand epidermal growth factor (EGF). Cetuximab blocks binding of EGF and transforming growth factor alpha (TGFα) to EGFR and inhibits ligand-induced activation of this tyrosine kinase receptor. Cetuximab also stimulates EGFR internalization, effectively removing the receptor from the cell surface for interaction with ligand.

b. PHARMACOKINETICS

1. Absorption: When cetuximab was administered as monotherapy or in combination with chemotherapy or radiation therapy it exhibited nonlinear pharmacokinetics. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner while the clearance decreased from 0.08 to 0.02 L/h/m^2 as the dose increased from 20 to 200 mg/m^2. The clearance seemed to plateau at doses greater than 200 mg/m^2.

2. Distribution: The volume of distribution of cetuximab is independent of the dose and is approximately the plasma volume (2 to 3 L/m^2). When administered at the recommended dose regimen of 400 mg/m^2 initial dose followed by 250 mg/m^2 weekly dose, the concentration of cetuximab reached steady-state levels by the third weekly infusion with mean peak and trough concentrations in the range of 168 to 235 and 41 to 85 mcg/mL, respectively.

3. Metabolism: Cetuximab is eliminated via the EGFR binding/internalization on hepatocytes and skin in a saturable manner.

4. Elimination: At the recommended dose regimen, the mean half-life of cetuximab was approximately 112 hours (range 63–230 hours).

3.2 Irinotecan (Camptosar ®) (NSC-616348)

a. PHARMACOLOGY

Mechanism of Action: Irinotecan and its metabolite SN-38 inhibit topoisomerase I. Topoisomerase I relieves torsional strain in the DNA helix during replication and RNA transcription by inducing single-strand breaks. By binding with the topoisomerase I—DNA complex, irinotecan or SN-38 prevents the relegation of the single-strand breaks. Irreversible DNA damage occurs when a DNA replication fork encounters the irinotecan or SN-38/topoisomerase I complexes resulting in double-strand DNA breaks. Camptothecins are highly S-phase specific in their activity due the requirement of DNA synthesis.

b. PHARMACOKINETICS

1. Absorption: N/A

2. Distribution: Protein binding of irinotecan is 30-70%, whereas SN-38 shows a higher protein binding of 95%. Both irinotecan and SN-38 are primarily bound to albumin. Volume of distribution of irinotecan is approximately 110-234 L/m^2.

3. Metabolism: Irinotecan is metabolized primarily in the liver by carboxylesterase to SN-38, and via hepatic cytochrome P450 (CYP) 3A4 to aminopentane carboxylic acid (APC). SN-38 is conjugated to form a glucuronide metabolite by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1). Genetic polymorphisms exist in the enzyme UGT1A1, leading to different levels of exposure and toxicity among patients. In addition, both irinotecan and SN-38 undergo plasma hydrolysis between their active (lactone) and inactive forms (carboxylate). Finally, a small amount of irinotecan is metabolized by the intestinal wall.

4. Elimination: Approximately 10-25% of irinotecan is recovered unchanged in urine whereas only small amounts of SN-38 have been found. Clearance is approximately 13.5 L/hr/m^2. In addition, irinotecan has approximately 25% biliary excretion.

c. ADVERSE EFFECTS

1. Possible Side Effects of irinotecan*:*
Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in >20% to 100% of subjects treated with irinotecan include: diarrhea and cholinergic reaction (may be severe), constipation, nausea, vomiting, asthenia, infection, leukopenia, neutropenia, alopecia, anorexia, weight loss, anemia, fatigue, fever, pain, dizziness, cough, dyspnea, mucositis, rash, thrombocytopenia.

Adverse effects reported in 4% to 20% of subjects include: gastrointestinal perforation, hypersensitivity reaction, cardiovascular events, thromboembolic events, interstitial lung disease.

2. Pregnancy and Lactation: Pregnancy Category D. It is not known whether irinotecan or its derivatives are excreted in human milk. Women should avoid pregnancy while taking irinotecan (in combination with cetuximab) and for at least 6 months after the last dose and men should avoid potential partner's pregnancy for at least 3 months after the last dose.

3. Drug Interactions: Irinotecan and its active metabolite SN-38 may be substrates for CYP3A4, CYP2B6, OATP1B1/SCLO1B1, P-glycoprotein/ABCB1 and UGT1A1. Inducers or inhibitors may affect serum concentrations of irinotecan. Due to potential drug interactions, a complete patient medication list, including irinotecan, should be screened prior to initiation of and during treatment with irinotecan. Refer to the current FDA-approved package insert. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Irinotecan is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

3.3 Pertuzumab (Perjeta®, RO4368451) (NSC-740102, IND-132527)

a. PHARMACOLOGY

Mechanism of Action: Pertuzumab is a HER2/neu receptor antagonist that 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).

Description: Pertuzumab is a recombinant humanized monoclonal antibody that targets the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2). Pertuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture. **M.W.:** 148 kDa.

b. PHARMACOKINETICS

1. Absorption: steady state concentration is reached after the first maintenance dose

2. Distribution: two-compartment linear model

3. Metabolism: Does not appear to undergo renal or hepatic metabolism

4. Elimination: first-order elimination; total body clearance 0.24 L/day; elimination half-life 18 days.

c. ADVERSE EFFECTS: Pertuzumab (Perjeta) (NSC-740102, IND 132527)

1. Adverse Effects:

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: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different 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 neutronpenia		***Febrile neutropenia (Gr 2)***
CARDIAC DISORDERS			
		Heart failure	
EYE DISORDERS			
	Watering eyes		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation***

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%)**	
			(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)***
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)***

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%)**	
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			
	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 papular, 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.

2. Pregnancy and Lactation: Pregnancy Category D

   Based on its mechanism of action and findings in animal studies, Perjeta can cause fetal harm when administered to a pregnant woman. No studies of Perjeta use during pregnancy have been performed. Cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported with use of Herceptin during pregnancy. Monitor women who received Perjeta and Herceptin during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and is consistent with community standards of care.

   Additional information on any pertuzumab- and/or trastuzumab-exposed pregnancy and infant will be requested by Roche Drug Safety at specific time points until 12 months of the infant's life. In case of a report of a congenital abnormality, a guided questionnaire will be sent out by Roche Drug Safety.

   It is unknown whether pertuzumab is excreted into human milk. Published literature suggests human IgG is present in all milk, but does not enter the neonatal and infant circulation in substantial amounts. However, due to the potential for adverse effects on the infant from nursing, it is advisable to discontinue breast-feeding during treatment with pertuzumab (in combination with trastuzumab) and for 7 months after the last dose.

3. Drug Interactions: No drug-drug interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

- Route of Administration: intravenous.
  Method of Administration: The initial pertuzumab dose is administered as

a 60-minute intravenous infusion. Subsequent doses are administered by intravenous infusion over 30 or 60 minutes, depending on how the initial dose was tolerated.

e. HOW SUPPLIED

Pertuzumab is supplied by Genentech, Inc. and distributed by Biologics, Inc. 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.

f. STORAGE, PREPARATION & STABILITY

1. Storage:
   - Keep vials in the outer carton in order to protect from light.
   - Store vials in a refrigerator at 2˚C to 8˚C (36˚F to 46˚F) until time of use.
   - Contact supplier for temperature excursion information.
   - Do not freeze.
   - Do not shake.

2. 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).

3. 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.

4. Compatibility:
   - 0.9% sodium chloride only.
   - Do not use dextrose (5%) solution.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering and shipping

   a. Pertuzumab may be requested by the principal investigator (or their authorized designee) at each participating site by completing the Biologics Drug Order Request Form for **S1613** once the patient has been randomized and faxing to the number listed on the order form. Authorized and completed orders will be processed and shipped "same day" of receipt if received before 2:00 p.m. EST Monday through Thursday. Authorized and completed orders received after 2:00pm EST Monday through Thursday or on Friday will be processed and shipped the next business morning. All drug orders are shipped via FedEx Priority Overnight delivery. Biologics distribution team monitors packages throughout duration of transit via FedEx One Call Solution (live support) and delivery exceptions are managed at the highest level of urgency to ensure therapy start date adherence. Packing slips with the shipment tracking number included will be faxed to the designated site coordinator.

   Drug deliveries are restricted during weekends and holidays. Biologics, Inc. observes the following holidays: New Year's Day, Memorial Day, Independence Day, Labor Day, Thanksgiving Day, the Friday following Thanksgiving Day, Christmas Eve, and Christmas Day. Sites should plan ahead to accommodate patients being treated during restricted times.

   Sites must allow up to 5 business days for study drug to arrive once the Drug Order Request Form is submitted to Biologics. The Drug Order Request Form should be faxed to 919-256-0794.

   b. Once a patient is randomized, the site will fax a completed Drug Order Request Form to Biologics at 919-256-0794. Upon receipt of completed and faxed Drug Order Request Form, Biologics Inc. will:

      - Check to confirm site has an active registration and approval for shipment.
      - Place a call or email to the site confirming the Drug Order Request Form was received, while providing the estimated day and time of arrival for the study drug.
      - Prepare an initial shipment supply for the patient's loading dose and subsequent 4 cycles.
      - Each vial of pertuzumab is 420 mg. Drug will be labeled by Genentech for Investigational Use Only. Drug supply will be dispensed by Biologics with patient-specific labeling.
        - Initial shipments will include approximately 6 vials of pertuzumab to complete a loading dose of 840 mg and 4 subsequent cycles at 420 mg.

c. If additional drug is required, the site will fax a completed Drug Order Request Form to Biologics at 919-256-0794.

- Check to confirm site has an active registration and approval for shipment.
- Place a call or email to the site confirming the Drug Order Request Form was received, while providing the estimated day and time of arrival for the study drug.
- Prepare a subsequent shipment supply for the patient's subsequent 4 cycles.
- Drug will be labeled by Genentech for Investigational Use Only. Drug supply will be dispensed by Biologics with patient-specific labeling.
    - Subsequent shipments will include approximately 4 vials of pertuzumab to complete 4 subsequent cycles at 420 mg.

d. Each shipment includes a patient-specific label on the outer packaging with the following information:

- Study Number and Date Dispensed
- Drug Identification, Lot number, Expiration Date
- Patient ID Number
- Patient Initials
- Storage Instructions
- Dosing Instructions
- IND Caution statement

e. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return or disposal of all drugs received from the supplier using the NCI Drug Accountability Record Form (DARF) available at http://ctep.cancer.gov.

f. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF. If the trial is a placebo control trial – indicate that separate DARFs are needed for each patient to also include the placebo drug supply.

2. Drug return and/or disposition instruction (include forms if needed)

a. Drug Returns: Unused drug supplies should NOT be returned. Unused drug should be disposed of per local institutional guidelines.

b. Drug expiration: Indicate drug expiration date on the DARF under Manufacturer and Lot # and use the drug lots with shorter expiration date first.

3. Contact Information

Questions about drug orders, transfers, returns, or accountability should be addressed to Clinical Research Services at Biologics, Inc. at 800-693-4906 or clinicaltrials@biologicsinc.com.

3.4 Trastuzumab (Herceptin®, rhuMAb HER-2/NEU; MoAb HER2/NEU) (NSC-688097, IND 132527)

a. PHARMACOLOGY

Mechanism of Action: Trastuzumab is a monoclonal antibody. 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. Herceptin has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2. Herceptin 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.

Description: Herceptin (trastuzumab) is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. Trastuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

b. PHARMACOKINETICS

1. Absorption: Time to steady state is 9 weeks in patients with metastatic gastric cancer and 12 weeks in patients with breast cancer

2. Distribution: Distributed in tissues and fluids; Vd: 44 mL/kg

3. Metabolism: Does not undergo renal or hepatic metabolism

4. Elimination: clearance increases with decreasing concentrations due to parallel linear and non-linear elimination pathways; elimination half-life 5.8 days

c. ADVERSE EFFECTS

1. Adverse Effects:

Comprehensive Adverse Events and Potential Risks list (CAEPR) For Trastuzumab (Herceptin, NSC 688097 and Herceptin HylectaTM (SQ trastuzumab, NSC 827797)

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*

4407 patients. Below is the CAEPR for Trastuzumab (Herceptin) and Herceptin Hylecta™ (SQ trastuzumab)

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different 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)***
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)***

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**
	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)***

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**
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		
	Headache		***Headache (Gr 2)***
	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 Hylecta™ (SQ trastuzumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that trastuzumab (Herceptin) and/or Herceptin Hylecta™ (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

2. Pregnancy and Lactation: Exposure to trastuzumab during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Use effective contraception during treatment and for 7 months following the last dose of trastuzumab.

   It is unknown whether trastuzumab is excreted into human milk. Published literature suggests human IgG is present in all milk, but does not enter the neonatal and infant circulation in substantial amounts. Trastuzumab was present in the milk of lactating Cynomolgus monkeys but not associated with neonatal toxicity. However, due to the potential for adverse effects on the infant from nursing, it is advisable to discontinue breast-feeding during treatment with trastuzumab and for 7 months after the last dose of trastuzumab 3. Drug Interactions:

   Avoid concomitant anthracycline-based therapy and use with caution for 7 months after stopping trastuzumab due to increased risk of cardiac dysfunction.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

Route of Administration: intravenous infusion.

Method of Administration: Trastuzumab is given by slow intravenous infusion only. The typical dosing schedule is 4mg/kg as a loading dose, followed by weekly doses of 2mg/kg. The loading dose is infused over 90 minutes. If this is well tolerated, subsequent infusions may be given over 30 minutes. *Please consult the protocol document for specific dosing/schedule instructions as doses/schedules may be different between tumor types.*

Drug-Drug Interactions: 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 Herceptin was administered in combination with paclitaxel, docetaxel, carboplatin, or doxorubicin, Herceptin 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 Herceptin.

e. HOW SUPPLIED

Trastuzumab (Herceptin) will be supplied free of charge. It will be provided by Genentech and distributed by McKesson Specialty Pharmacy, LP in a 150 mg/vial in a single-dose vial as a lyophilized sterile powder, under vacuum.

f. STORAGE, PREPARATION & STABILITY

1. Storage:
   - Store at 2°C to 8°C (36°F to 46°F) prior to reconstitution
   - Contact supplier for temperature excursion information

2. Preparation:

   Reconstitute each 150 mg vial of trastuzumab with 7.4 mL of Sterile Water for Injection (SWFI) (not supplied) to yield a single-dose solution containing 21 mg/mL trastuzumab that delivers 7.15 mL (150 mg trastuzumab).

Reconstitution: Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject 7.4 mL of Sterile Water for Injection (SWFI) into the vial containing the lyophilized powder of Herceptin. The stream of SWFI should be directed into the lyophilized powder. The reconstituted vial yields a solution for single use, containing 21 mg/ml trastuzumab.
- 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.
- Use the Herceptin solution immediately following reconstitution with SWFI, as it contains no preservative and is intended for single-dose only. If not used immediately, store the reconstituted Herceptin solution for up to 24 hours at 2◦C to 8◦C (36◦F to 46◦F); discard any unused Herceptin after 24 hours. **Do not freeze.**

Dilution:

- Determine the dose (mg) of Herceptin. Calculate the volume of the 21 mg/mL reconstituted Herceptin 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.

3. Stability:

The solution of Herceptin for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, should be stored at 2°C to 8°C (36°F to 46°F) for no more than 24 hours prior to use. Discard after 24 hours. This storage time is additional to the time allowed for the reconstituted vials. Do not freeze.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug order and shipping

a. Trastuzumab may be requested by the principal investigator (or their authorized designee) at each participating site by completing the Biologics Drug Order Request Form for **S1613** once the patient has been randomized and faxing to the number listed on the order form. Authorized and completed orders will be processed and shipped “same day” of receipt if received before 2:00 p.m. EST Monday through Thursday. Authorized and completed orders received after 2:00pm EST Monday through Thursday or on Friday will be processed and shipped the next business morning. All drug orders are shipped via FedEx Priority Overnight delivery. Biologics distribution team monitors packages throughout duration of transit via FedEx One Call Solution (live

support) and delivery exceptions are managed at the highest level of urgency to ensure therapy start date adherence. Packing slips with the shipment tracking number included will be faxed to the designated site coordinator.

Drug deliveries are restricted during weekends and holidays. Biologics, Inc. observes the following holidays: New Year's Day, Memorial Day, Independence Day, Labor Day, Thanksgiving Day, the Friday following Thanksgiving Day, Christmas Eve, and Christmas Day. Sites should plan ahead to accommodate patients being treated during restricted times.

Sites must allow up to 5 business days for study drug to arrive once the Drug Order Request Form is submitted to Biologics. The Drug Order Request Form should be faxed to 919-256-0794.

b. Once a patient is randomized, the site will fax a completed Drug Order Request Form to Biologics at 919-256-0794. Upon receipt of completed and faxed Drug Order Request Form, Biologics Inc. will:

- Check to confirm site has an active registration and approval for shipment.
- Place a call or email to the site confirming the Drug Order Request Form was received, while providing the estimated day and time of arrival for the study drug.
- Prepare an initial shipment supply for the patient's loading dose and subsequent 4 cycles.
- Each vial of trastuzumab is 150 mg. Drug will be labeled by Genentech for Investigational Use Only. Drug supply will be dispensed by Biologics with patient-specific labeling.
    - Initial shipments will include approximately 16 vials of trastuzumab to complete a loading dose of 8 mg/kg and 4 cycles at 6 mg/kg.

c. If additional drug is required, the site will fax a completed Drug Order Request Form to Biologics at 919-256-0794.

- Check to confirm site has an active registration and approval for shipment.
- Place a call or email to the site confirming the Drug Order Request Form was received, while providing the estimated day and time of arrival for the study drug.
- Prepare a subsequent shipment supply for the patient's subsequent 4 cycles.
- Each vial of trastuzumab is 150 mg. Drug will be labeled by Genentech for Investigational Use Only. Drug supply will be dispensed by Biologics with patient-specific labeling.

- Subsequent shipments will include approximately 12 vials of trastuzumab to complete 4 subsequent cycles at 6 mg/kg.

d. Each shipment includes a patient-specific label on the outer packaging with the following information:

- Study Number and Date Dispensed
- Drug Identification, Lot number, Expiration Date
- Patient ID Number
- Patient Initials
- Storage Instructions
- Dosing Instructions
- IND Caution statement

2. Drug Handling and Accountability

a. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return or disposal of all drugs received from the supplier using the NCI Drug Accountability Record Form (DARF) available at http://ctep.cancer.gov.

b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF. If the trial is a placebo control trial – indicate that separate DARFs are needed for each patient to also include the placebo drug supply.

3. Drug return and/or disposition instruction

a. Drug Returns: Unused drug supplies should NOT be returned. Unused drug should be disposed of per local institutional guidelines.

b. Drug expiration: If packaging has expiration date, indicate drug expiration date on the DARF under Manufacturer and Lot # and use the drug lots with shorter expiration date first.

4. Contact Information

Questions about drug orders, transfers, returns, or accountability should be addressed to Clinical Research Services at Biologics, Inc. at 800-693-4906 or clinicaltrials@biologicsinc.com.

4.0 STAGING CRITERIA

Staging criteria are not applicable to this study.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Section 5.1 must be met prior to initial registration for HER-2 testing, while Section 5.2 must be met prior to randomization. Consider all criteria before enrolling a patient to

Step 1. Section 5.3 must be met prior to crossover registration (optional). For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG Statistics and Data Management Center in Seattle at 206/652-2267 or giquestion@crab.org prior to registration.

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 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14, 28, 30, or 60 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Step 1 Initial Registration: HER-2 Testing

Disease Related Criteria

a. Patients must have histologically or cytologically documented adenocarcinoma of the colon or rectum that is metastatic or locally advanced and unresectable.

b. Mutation results:

1. All patients must have molecular testing performed in a CLIA certified lab which includes KRAS and NRAS gene and exon 15 of BRAF gene (BRAF V600E mutation). Patients with any known activating mutation in exon 2 [codons 12 and 13], exon 3 [codons 59 and 61] and exon 4 [codons 117 and 146]) of KRAS/NRAS genes and in exon 15 (BRAFV600E mutation) of BRAF gene are not eligible.

Prior/Concurrent Therapy Criteria

c. Patients must not have been treated with any of the following prior to Step 1 Initial Registration:

- Cetuximab, or any other monoclonal antibody against EGFR or inhibitor of EGFR.
- HER-2 targeting for treatment of colorectal cancer. Patients who have received prior trastuzumab or pertuzumab for other indications such as prior history of adjuvant or neoadjuvant breast cancer treatment prior to the development of advanced colorectal cancer are eligible.

d. Patients must not have had history of severe toxicity and intolerance to or hypersensitivity to irinotecan or any other study drug. Patients must not have had a severe infusion-related reaction during any prior therapy with pertuzumab or trastuzumab.

Specimen and Data Submission Criteria

e. Patients must have tumor slides available for submission for HER-2 testing as described in Section 15.1. HER-2 testing must be completed by the central lab prior to Step 2 Randomization. The central lab will perform HER-2 tests in accordance with instructions provided separately.

Regulatory Criteria

f. Patients must be informed of the investigational nature of this study and must sign and give informed consent in accordance with institutional and federal guidelines.

For Step 1 Initial Registration, the appropriate consent form is the Step 1 Consent Form.

g. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

5.2 Step 2 Randomization

Results of HER-2 testing will be available on the SWOG Specimen Tracking Website and sites will be notified by e-mail within 14 calendar days from submission of the tissue specimen to the central lab.

Disease Related Criteria

a. Patients must have HER-2 amplification as determined by central testing (3+ or 2+ by immunohistochemistry and HER-2 gene amplification by in situ hybridization with a ratio of HER-2 gene signals to centromere 17 signals ≥ 2.0).

b. Patients must have measurable disease that is metastatic or locally advanced and unresectable. Imaging used to assess all disease per RECIST 1.1 must have been completed within 28 days prior to Step 2 Randomization. All disease must be assessed and documented on the Baseline Tumor Assessment Form.

Prior/Concurrent Therapy Criteria

c. Patients must have had at least one prior regimen of systemic chemotherapy for metastatic or locally advanced, unresectable disease. Patients must have progressed following the most recent therapy. Prior treatment with irinotecan is allowed. For patients that received adjuvant chemotherapy: Prior treatment for metastatic disease is not required for patient who experienced disease recurrence during or within 6 months of completion of adjuvant chemotherapy. If the patient received one line of adjuvant treatment and had disease recurrence after 6 months of completing chemotherapy, patients will only be eligible after failing one additional line of chemotherapy used to treat the metastatic or locally advanced, unresectable disease. Patients who have received ≥3 lines of systemic chemotherapy for metastatic or locally advanced, unresectable disease are not eligible.

NOTE: See Section 5.2e for criteria related to treatment for brain metastases.

d. Patients must have completed prior chemotherapy, immunotherapy, or radiation therapy at least 14 days prior to Step 2 Randomization and all toxicity must be resolved to CTCAE v4.0 Grade 1 (with the exception of CTCAE v4.0 Grade 2 neuropathy) prior to Step 2 Randomization.

Clinical/Laboratory Criteria

e. Brain metastases are allowed if they have been adequately treated with radiotherapy or surgery and stable for at least 30 days prior to Step 2 Randomization. Eligible patients must be neurologically asymptomatic and without corticosteroid treatment for at least 7 days prior to Step 2 Randomization.

f. Patients must have a Zubrod Performance Status of 0 or 1. (See Section 10.4)

g. Patients must be ≥ 18 years of age.

h. Patients must have a complete physical examination and medical history within 28 days prior to Step 2 Randomization.

i. Patients must have adequate hematologic function as evidenced by all of the following within 14 days prior to Step 2 Randomization: ANC ≥ 1,500/mcL; platelets ≥ 75,000/mcL; and hemoglobin ≥ 9 g/dL.

j. Patients must have adequate hepatic function as evidenced by all of the following within 14 days prior to Step 2 Randomization: AST and ALT both ≤ 5 x institutional upper limit of normal (IULN); bilirubin ≤ 1.5 mg/dL.

k. Patients must have adequate kidney function as evidenced by calculated creatinine clearance > 30 ml/min within 14 days prior to Step 2 Randomization.

$$\text{Calculated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$$

l. Patients who have had an echocardiogram performed within 6 months prior to Step 2 Randomization, must have ventricular ejection fraction (LVEF) ≥ 50% or ≥ within normal limits for the institution.

m. Patients must have magnesium, potassium, calcium, sodium, bicarbonate, and chloride performed within 14 days prior to Step 2 Randomization. Results of these tests do not determine eligibility, but the tests are required to establish baseline values. Additional timepoints are noted in Section 9.0.

n. Patients must not have an uncontrolled intercurrent illness including, but not limited to diabetes, hypertension, severe infection, severe malnutrition, unstable angina, Class III-IV New York Heart Association (NYHA) congestive heart failure (see Section 18.1), ventricular arrhythmias, active ischemic heart disease, or myocardial infarction within 6 months prior to Step 2 Randomization.

o. Patients must not have any known previous or concurrent condition suggesting susceptibility to hypersensitivity or allergic reactions, including, but not limited to: known hypersensitivity to any of the study treatments or to excipients of recombinant human or humanized antibodies. Patients with mild or seasonal allergies may be included after discussion with the Study Chairs.

p. Patients must not be planning treatment with other systemic anti-cancer agents (e.g., chemotherapy, hormonal therapy, immunotherapy) or other treatments not part of protocol-specified anti-cancer therapy including concurrent investigational agents of any type.

q. No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, ductal carcinoma in situ, other low grade lesions such as incidental appendix carcinoid, or any other cancer from which the patient has been disease and treatment free for two years. Prostate cancer patients on active surveillance are eligible.

r. Patients must not be pregnant or nursing due to risk of fetal or nursing infant harm. Females of child-bearing potential must have a negative serum pregnancy test within 7 days prior to registration. Women/men of reproductive potential must have agreed to use an effective contraceptive method while on study and for at least 7 months after the last dose of study treatment. A woman is considered to

be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

Specimen Submission Criteria

s. Patients must be given the opportunity to consent to the optional submission of tissue and blood for future research as outlined in Section 15.2.

Regulatory Criteria

t. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines. The appropriate consent form for this registration is the Step 2 Consent Form.

u. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

5.3 Step 3 Crossover Registration (Optional)

Clinical/Laboratory Criteria

a. Patients must have documented disease progression as defined in Section 10.2d while on CETIRI (Arm 2) on this protocol. The Follow-up Tumor Assessment Form documenting disease progression must be submitted to SWOG prior to Step 3 Crossover Registration. Registration to Step 3 Crossover must be within 28 days of discontinuation of CETIRI protocol treatment. Patients going off treatment for any other reason are not eligible.

b. Patients must have a Zubrod Performance Status of 0 or 1. (See Section 10.4)

c. Patients must have adequate hematologic function as evidenced by all of the following within 14 days prior to Step 3 Crossover Registration: ANC ≥ 1,500/mcL; platelets ≥ 75,000/mcL; and hemoglobin ≥ 9 g/dL.

d. Patients must have adequate hepatic function as evidenced by all of the following within 14 days prior to Step 3 Crossover Registration: AST and ALT both ≤ 5 x institutional upper limit of normal (IULN); bilirubin ≤ 1.5 mg/dL.

e. Patients must have adequate kidney function as evidenced by calculated creatinine clearance > 30 ml/min within 14 days prior to Step 3 Crossover Registration.

$$\text{Calculated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$$

f. Patients must have left ventricular ejection fraction (LVEF) ≥ 50% or ≥ lower limit of normal for the institution by echocardiogram within 14 days prior to Step 3 Crossover Registration.

g. Patients must have a magnesium, potassium, calcium, sodium, bicarbonate, and chloride performed within 14 days prior to Step 3 Crossover Registration. Additional timepoints are noted in Section 9.0.

Regulatory Criteria

h. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines. The appropriate consent form for this registration is the Step 2 Consent Form.

i. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

Patients will be assigned to treatment arms using block randomization with stratification based on prior use of irinotecan (yes vs. no) and HER-2/CEP17 ratio (> 5 vs ≤ 5) *(32)*

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Kanwal Raghav at 917/733-0356 (or kpraghav@mdanderson.org) or Dr. Marwan Fakih at 626/471-4673 (or mfakih@coh.org). For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Pre-Medication

a. Arm 1: Trastuzumab + Pertuzumab (TP)

Patients randomized to this arm do not need any premedication unless deemed necessary by treating physician.

Note: Patients who experience infusion-associated symptoms, while receiving pertuzumab on-study, may subsequently be pre-medicated as per standard institutional practice.

b. Arm 2: Irinotecan + Cetuximab (CETIRI)

Patients randomized to this arm should receive:

- Diphenhydramine (or other H1-antagonist) 50 mg intravenously, given once 30-60 minutes prior to the first dose of cetuximab.
- Dexamethasone 10 mg intravenously, given 30-60 minutes prior to irinotecan.
- Patients may receive institutional recommended management for nausea.
- Institutional standard pre-medication (including atropine for irinotecan) is allowed.

NOTE: These may be modified at the discretion of the treating physician.

7.2 General considerations

a. Similar to other monoclonal antibodies, pertuzumab has been associated with infusion-related reactions, such as chills, diarrhea, fatigue, headache, nausea, and

pyrexia, and with hypersensitivity reactions including anaphylaxis. Pertuzumab is contraindicated in patients with known hypersensitivity to pertuzumab or any of its excipients. Since there is the potential for delayed onset infusion related reactions (IRRs), patients should be warned of this possibility and instructed to contact the treating physician with any concerns.

b. For the first infusion of trastuzumab (Cycle 1), patients should be observed for 60 minutes from the end of the infusion for fever and chills, or other infusion-related reactions. If Cycle 1 is tolerated, then Cycle 2 and subsequent Q 21 day doses of 6 mg/kg of trastuzumab may be administered over 30 (± 10) minutes, and patients will be observed as shown in Table 1 below.

Table 1: Infusion Time and Post-Infusion Observation Period for Trastuzumab

Infusion	Trastuzumab Dose (mg/kg)	Infusion Time (min) [a]	Post-Infusion Observation Period (min) [a]
1st infusion	8	90	60
2nd and subsequent infusions	6	30	30

[a] After Cycle 1, ONLY shorten infusion and post-infusion observation times if the prior dose was well-tolerated. If patient has tolerated first 2 infusions, post infusion observation can be omitted for 3rd and subsequent infusions as per institutional guidelines and at discretion of treating physician.

c. All infusion-related symptoms must have resolved before pertuzumab (if trastuzumab was given first) is given or the patient is discharged. Patients who experience infusion-related symptoms may be premedicated as per standard institutional practice for subsequent infusions.

d. The Administration of pertuzumab should be performed in a setting with emergency equipment and staff who are trained to monitor medical situations and respond to medical emergencies. The initial dose of pertuzumab will be administered over 60 minutes and patients will be monitored for a further 60 minutes following the completion of the infusion for any adverse effects. The infusion should be slowed or interrupted if the patient experiences infusion-related symptoms. If infusion-related symptoms occur, patients will be monitored until complete resolution of signs and symptoms. If the infusion is well tolerated, subsequent doses may be administered over 30 minutes, and patients will be observed for a further 30 minutes (as shown in Table 2) for infusion-related symptoms. All infusion-related symptoms must have resolved before the patient is discharged. Patients who experience infusion-associated symptoms may subsequently be pre-medicated as per standard institutional practice.

Table 2: Infusion Time and Post-Infusion Observation Period for Pertuzumab

Infusion	Pertuzumab Dose (mg)	Infusion Time (min) [a]	Post-Infusion Observation Period (min) [a]
1st infusion	840	60	60
2nd infusion and subsequent infusions	420	30	30

[a] After Cycle 1, ONLY shorten infusion and post infusion observation times if the prior dose was well tolerated. If patient has tolerated first 2 infusions, post

infusion observation can be omitted for 3rd and subsequent infusions as per institutional guidelines and at discretion of treating physician.

e. Irinotecan/Cetuximab doses omitted during a cycle will not be made up. Trastuzumab/Pertuzumab doses missed during a cycle should be made up as soon as possible. If patient has missed a dose of trastuzumab by one week or less, then the usual maintenance dose of 6 mg/kg should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent trastuzumab maintenance doses should be administered 21 days later according to the three-weekly schedule. If the patient has missed a dose of trastuzumab by more than one week, a re-loading dose of 8 mg/kg should be administered over approximately 90 minutes as soon as possible. Subsequent Trastuzumab maintenance doses (three-weekly schedule 6 mg/kg) should be administered 21 days later according to three-weekly schedules.

7.3 Treatment – Arm 1: Trastuzumab + Pertuzumab (TP) [a]

Patients assigned to TP will receive the following treatment until meeting one of the criteria in Section 7.6.

Agent	Dose	Route	Day	Schedule
Pertuzumab	840 mg	IV over 60 min	1	**Cycle 1 only** (21 days) given prior to trastuzumab
Trastuzumab	8 mg/kg	IV over 90 min	1	**Cycle 1 only** (21 days)
Pertuzumab	420 mg	IV over 30 min	1	**Cycles 2+** (q 21 days) given prior to trastuzumab
Trastuzumab	6 mg/kg	IV over 30 min [b]	1	**Cycles 2+** (q 21 days)

[a] Patients must be monitored for infusion reactions for 30-60 minutes after infusion of trastuzumab and/or pertuzumab for at least 2 cycles.
[b] Only if patient tolerates the initial 90 minute infusion. If patient does not tolerate the initial 90 minute infusion, subsequent infusions may be given over 120 minutes.

7.4 Treatment – Arm 2: Irinotecan + Cetuximab (CETIRI)

Patients assigned to CETIRI will receive the following treatment until meeting one of the criteria in Section 7.6.

Agent	Dose	Route	Day	Schedule
Cetuximab	500 mg/m^2	IV over 120 min	1	**Cycle 1 only** (14 days) given prior to irinotecan
Cetuximab	500 mg/m^2	IV over 60 min*	1	**Cycles 2+** (q 14 days) given prior to irinotecan
Irinotecan	180 mg/m^2	IV over 90 min	1	All cycles (q 14 days)

* Only if patient tolerates the initial 120 minute infusion.

7.5 Crossover Following Disease Progression on CETIRI

a. Following radiographic documentation by RECIST 1.1 (in Section 10.2d) of disease progression, patients initially randomized and treated with CETIRI may register to Step 3 Crossover Registration to be treated with trastuzumab and pertuzumab per the schedule and doses below. Patients must be eligible for Step 3 Crossover Registration per Section 5.3. Patients must be re-staged at time of progression on CETIRI prior to registration to Step 3 Crossover Registration. Follow-up for these patients after crossover will be the same as those patients initially randomized to TP.

b. Treatment – Arm 3: Trastuzumab + Pertuzumab (TP) [a]

Patients who are registered to Step 3 Crossover Registration will receive the following treatment until meeting one of the criteria in Section 7.6.

Agent	Dose	Route	Day	Schedule
Pertuzumab	840 mg	IV over 60 min	1	**Cycle 1 only** (21 days) given prior to trastuzumab
Trastuzumab	8 mg/kg	IV over 90 min	1	**Cycle 1 only** (21 days)
Pertuzumab	420 mg	IV over 30 min	1	**Cycles 2+** (q 21 days) given prior to trastuzumab
Trastuzumab	6 mg/kg	IV over 30 min [b]	1	**Cycles 2+** (q 21 days)

[a] Patients must be monitored for infusion reactions for 30-60 minutes after infusion of trastuzumab and/or pertuzumab for at least 2 cycles.
[b] Only if patient tolerates the initial 90 minute infusion. If patient does not tolerate the initial 90 minute infusion, subsequent infusions may be given over 120 minutes.

7.6 Criteria for Removal from Protocol Treatment

a. TP: Progression of disease (as defined in Section 10.2).

b. CETIRI: If patient progresses per RECIST 1.1 (see Section 10.2d), patient has the option to register to Step 3 Crossover. Patients who choose not to crossover will be removed from protocol treatment.

c. Symptomatic deterioration.

d. Unacceptable toxicity.

e. Treatment delay for any reason > 3 weeks.

f. The patient may withdraw from the study at any time for any reason.

7.7 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.8 Follow-Up Period

Patients who are randomized to a treatment arm will be followed while on treatment and until death or 3 years after Step 2 Randomization, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 **Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study**

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 will be utilized **for SAE reporting only**. The CTCAE Version 5.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 4.0 for routine toxicity reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

c. Where several toxicities with different grades or severity occur at the same time, the dose modification applied should be the greatest reduction applicable.

d. The maximum dose delay for any reason is 3 weeks.

e. If treating investigator feels an event is attributable to another drug or cause, then, after conversation with the Study Chair, other modification may be considered.

f. Patients on CETIRI (Arm 2) may continue protocol treatment if either cetuximab or irinotecan (but not both) must be stopped.

8.3 Dose Modifications

a. Dose reductions for TP are not permitted. For toxicity management see Sections 8.4 and 8.5.

b. Dose Levels for Treatment Modifications for CETIRI. For dose reductions and toxicity management, see Sections 8.4 and 8.6.

Agent	Starting Dose	Level -1	Level -2*
Irinotecan	180 mg/m^2	150 mg/m^2	125 mg/m^2

Cetuximab	500 mg/m^2	375 mg/m^2	250 mg/m^2

*Patients who require dose reductions below the values listed above will be removed from protocol treatment.

8.4 Dose Modifications and Toxicity Management for TP and CETIRI

a. Nausea and/or vomiting despite optimal medical management

Institute the recommended management at first occurrence, if reoccurs despite optimal medical management, follow dose modification guidelines below. If symptoms do not improve, then other alternatives like aprepitant, prochlorperazine, or metoclopramide may be considered.

Toxicity Grade	Dose Modification CETIRI	TP
2	Hold all treatment until recovery to ≤ Grade 1. Resume at same dose level.	No change.
3 or 4	Hold all treatment until recovery to ≤ Grade 1. Reduce irinotecan by one dose level.	If Grade 3-4 toxicity attributed to trastuzumab occurs, further dosing should be held until the toxicity improves to ≤ Grade 1. Trastuzumab should be restarted at full dose. If Grade 3-4 toxicity recurs, trastuzumab should be discontinued. If Grade 3-4 toxicity attributed to pertuzumab occurs, further dosing should be held until the toxicity improves to ≤ Grade 1. Pertuzumab should be restarted at full dose. If Grade 3-4 toxicity recurs, pertuzumab should be discontinued.

b. Fatigue

Toxicity Grade	Dose Modification CETIRI	TP
2 (first occurrence)	Continue at same dose	No change.
2 (second occurrence)	Hold all treatment until recovery to ≤ Grade 1.	No change.

Toxicity Grade	Dose Modification CETIRI	TP
	Resume at same dose level.	
3 or 4	Hold all treatment until recovery to ≤ Grade 1. Reduce irinotecan by one dose level.	If Grade 3-4 toxicity attributed to trastuzumab occurs, further dosing should be held until the toxicity improves to ≤ Grade 1. Trastuzumab should be restarted at full dose. If Grade 3-4 toxicity recurs, trastuzumab should be discontinued. If Grade 3-4 toxicity attributed to pertuzumab occurs, further dosing should be held until the toxicity improves to ≤ Grade 1. Pertuzumab should be restarted at full dose. If Grade 3-4 toxicity recurs, pertuzumab should be discontinued.

c. Hypersensitivity Reaction [a,b], Cytokine Release [b]

Toxicity Grade	Dose Modification
1	Decrease infusion rate by 50% until symptoms resolve, then resume at the initial planned rate.
2	Stop infusion. Administer H_1 and/or H_2 blockers, and/or steroids according to institutional policy. Restart the infusion at 50% lower rate when symptoms resolve and pretreat before all subsequent doses. All subsequent doses should be administered at the lower infusion rate.
3 or 4	Stop the infusion. Discontinue treatment.

[a] Similar to other monoclonal antibodies, pertuzumab has been associated with infusion-related reactions, such as chills, diarrhea, fatigue, headache, nausea, and pyrexia, and with hypersensitivity reactions including anaphylaxis. Pertuzumab is contraindicated in patients with known hypersensitivity to pertuzumab or any of its excipients. Since there is the potential for delayed onset infusion related reactions (IRRs), patients should be warned of this possibility and instructed to contact the treating physician with any concerns.

[b] For reporting these events: NCI CTCAE 4.0 defines these reactions differently: “Cytokine release syndromes/acute infusion reactions are different from allergic/hypersensitivity reactions, although some of the manifestations arecommon to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological

agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion." See the "Syndromes" section of the CTCAE version 4.0 for a complete list of signs and symptoms of "Cytokine release syndrome/acute infusion reaction;" and see the "Allergy/Immunology" section for a description of hypersensitivity.

d. Infusion Reactions

1. **Mild-Moderate Infusion-Associated Events with Trastuzumab:** During the first infusion with trastuzumab, a symptom complex consisting of chills and/or fever is observed in approximately 40% of patients. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. These symptoms are usually mild to moderate in severity, and occur infrequently with subsequent trastuzumab infusions. These symptoms may be treated as per standard institutional practice.

2. **Serious Infusion-Associated Events with Trastuzumab:** Serious adverse reactions to trastuzumab infusion, including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress, can be serious and/or potentially fatal. Most of these events have occurred either during or shortly after the start of the first trastuzumab infusion. Severe or moderate infusion-related symptoms may be managed by slowing or stopping the trastuzumab infusion, and implementing supportive therapy with oxygen, beta agonists, antihistamines, or corticosteroids.

   - If Grade 3 or Grade 4 toxicity occurs during the post-trastuzumab infusion observation period, the patient must be evaluated for a minimum of 1 hour from the time the toxicity was first observed until the resolution of any severe symptoms.

3. **Subsequent Pre-medication:** Patients who have an infusion-associated adverse event with trastuzumab should receive prophylactic treatment with antihistamines and/or corticosteroids before all subsequent trastuzumab infusions. Please refer to the Herceptinâ USPI for specific prophylactic pre-medications that are recommended.

4. **Pertuzumab Infusion-Associated Events:** Observe patients closely for 60 minutes after the first infusion and for 30 minutes after subsequent infusions of pertuzumab. If a significant infusion-associated reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies as per standard institutional practice. Monitor patients carefully until complete resolution of signs and symptoms. Consider permanent discontinuation in patients with severe infusion reactions.

e. Hypomagnesemia

Toxicity Grade	Dose Modification
1 or 2	Supplement with magnesium and closely monitor patient for appropriate magnesium levels.

3 or 4	Despite maximal medical management with magnesium, reduce cetuximab by one dose level. At second occurrence, discontinue cetuximab therapy.

f. Other clinically significant non-hematologic toxicities

Toxicity Grade	Dose Modification
3 or 4	Hold all treatment and monitor toxicity at least weekly. If toxicity resolves to ≤ Grade 1 within 3 weeks, reduce irinotecan by one dose level and resume treatment. If Grade 3-4 toxicity attributed to trastuzumab or petruzumab occurs, further dosing should be held until the toxicity improves to ≤ Grade 1. Trastuzumab and pertuzumab should be restarted at full dose. If Grade 3-4 toxicity recurs, trastuzumab and pertuzumab should be discontinued.

8.5 Toxicity Management for TP Only

a. Cardiac Disorders

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

Management of Symptomatic Cardiac Changes. Patients who develop signs and symptoms of heart failure NCI CTCAE v4.0 Grade 2, 3, or 4 should have trastuzumab and pertuzumab held and should receive treatment for heart failure (NYHA Class III or IV) as prescribed by the HFSA (e.g., ACE inhibitors, angiotensin-II receptor blockers, beta blockers, diuretics, and cardiac glycosides, as needed). Consideration should be given to obtaining a cardiac consultation. LVEF should be reassessed after 3 weeks (using the same method of measurement).

If the symptoms of heart failure resolve with treatment, and cardiac function (as measured by ECHO or MUGA) improves, trastuzumab and pertuzumab may be restarted after discussion with the patient concerning the risks and benefits of continued therapy. If the patient is benefiting clinically from HER-2-targeted treatment, the benefit of continued treatment may outweigh the risk of cardiac dysfunction. If trastuzumab and pertuzumab are restarted, continued surveillance with noninvasive measures of LVEF (MUGA or ECHO) will continue per protocol.

b. **Management of Asymptomatic Decreases in LVEF**. If routine LVEF measurements document asymptomatic LVEF decreases during treatment, patient management should follow guidelines outlined below.

Toxicity	Management
LVEF ≥ 50% and drop > 10% OR LVEF < 50% and drop < 5%	Continue treatment and repeat LVEF in 3 weeks.
LVEF < 50% and drop ≥ 5%	Hold treatment and repeat LVEF in 3 weeks. If LVEF drop is < 5% or LVEF is ≥ 50% continue treatment. If LVEF drop is ≥ 5% and LVEF is < 50% discontinue protocol treatment.

c. Diarrhea

Toxicity Grade	Dose Modification
1 or 2	No. change. 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 or 4	Hold further dosing until toxicity improves to </= Grade 1. Pertuzumab should be restarted at full dose. If Grade 3-4 toxicity recurs, pertuzumab should be discontinued.

8.6 Dose Modifications and Toxicity Management for CETIRI Only

a. Diarrhea despite optimal medical management

Recommended management: Loperamide 4 mg at first onset, followed by 2 mg with each loose movement until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours).

Toxicity Grade	Dose Modification
2	Hold irinotecan until recovery to ≤ Grade 1. Resume at same dose level.
3 or 4	Hold irinotecan until recovery to ≤ Grade 1. Reduce irinotecan by one dose level.

b. Neutropenia

Toxicity Grade	Dose Modification
2	Hold irinotecan until recovery to ≤ Grade 1. Resume at same dose level.
3 or 4	Hold all treatment until recovery to ≤ Grade 1. Reduce irinotecan by one dose level. Use of G-CSF (or PEGylated G-CSF) may be considered.*

* G-CSF or pegylated G-CSF may be utilized per ASCO guidelines (http://jop.ascopubs.org/cgi/content/full/2/4/196).

c. Thrombocytopenia

Toxicity Grade	Dose Modification
2	Hold irinotecan until recovery to ≤ Grade 1. Resume at same dose level.
3 or 4	Hold all treatment until recovery to ≤ Grade 1. Reduce irinotecan by one dose level.

d. Blood Bilirubin Increased

Toxicity Grade	Dose Modification
2	Hold irinotecan until recovery to ≤ Grade 1. Resume at same dose level.
3 or 4	Hold irinotecan until recovery to ≤ Grade 1. Reduce irinotecan each by one dose level.

e. Mucositis

Toxicity Grade	Dose Modification
2	Hold irinotecan until recovery to ≤ Grade 1. Resume at same dose level.
3 or 4	Hold all treatment until recovery to ≤ Grade 1. Reduce irinotecan by one dose level.

f. Pneumonitis

Toxicity Grade	Cetuximab Dose Modification
2	Hold cetuximab until recovery to ≤ Grade 1. Resume at same dose level.
3 or 4	Hold cetuximab until recovery to ≤ Grade 1 and until interstitial lung disease has been ruled out. Reduce cetuximab by one dose level. Discontinue protocol treatment if interstitial lung disease is confirmed by CT scan.

g. Rash

Toxicity Grade	Dose Modification
3 or 4	At the first occurrence of rash, hold cetuximab until recovery to Grade ≤ 2. If there is improvement in the rash upon holding therapy. Then, resume at same dose. At second occurrence of rash, hold cetuximab until recovery to Grade ≤ 2. If there is improvement in the rash upon holding therapy, reduce cetuximab by one dose level and resume. At third occurrence, remove patient from cetuximab treatment.

8.7 White Blood Cell Growth Factors

If used, white blood cell growth factors, including biosimilars, must be used per ASCO guidelines (http://jco.ascopubs.org/content/24/19/3187.full) and NCCN Guidelines® Myeloid Growth Factors (http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf).

8.8 Dose Modifications Contacts

For treatment or dose modification questions, please contact Dr. Kanwal Raghav at 917/733-0356 (or kpraghav@mdanderson.org) or Dr. Marwan Fakih at 626/471-4673 (or mfakih@coh.org).

8.9 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 **Arm 1:** Trastuzumab and Pertuzumab (TP)

			Cycle 1			Cycle 2			Cycle 3+				Ω	%
REQUIRED STUDIES	Step 1	Step 2	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Every	FU prior to prog	FU after prog
	Initial Reg	Rand	1	2	3	4	5	6	7	8	9	3 m		
PHYSICAL ∑														
History and Physical Exam		X	X			X			X				X	X
Weight and Performance Status		X	X			X			X				X	X
Toxicity Notation						X			X				X	X
Disease Assessment †		X							X				X	
LABORATORY ∑														
CBC/Differential/Platelets		X				X			X					
"KRAS/NRAS/BRAF status" for Step 1	X													
AST and ALT		X				X			X					
Serum creatinine/Calculated creatinine clearance		X				X			X					
Total bilirubin		X				X			X					
Magnesium/Potassium/ Calcium/Sodium/Bicarb/ Chloride §		X				X			X					
Pregnancy Test ɣ		X	X									X		
SPECIMEN SUBMISSION														
Tissue for HER2 Testing £	X													
Tissue for Banking Δ		X												
Blood for Banking ¤			X			X			X				X	
X-RAYS AND SCANS														
Images for Disease Assessment †		X							X				X	
Image Submission β		X							X				X	
ECHO Scan δ			X									X		
TREATMENT ∑														
Trastuzumab			X			X			X					

Pertuzumab			X			X			X					

Click here for Footnotes.

9.2 **Arm 2:** Cetuximab + Irinotecan (CETIRI)

			Cycle 1		Cycle 2		Cycle 3		Cycle 4+		Ω	%
REQUIRED STUDIES	Step 1	Step 2	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	FU prior to prog	FU after prog
	Initial Reg	Rand	1	2	3	4	5	6	7	8		
PHYSICAL ∑												
History and Physical Exam		X	X		X		X		X		X	X
Weight and Performance Status		X	X		X		X		X		X	X
Toxicity Notation					X		X		X		X	X
Disease Assessment †		X							X		X	
LABORATORY ∑												
CBC/Differential/Platelets		X			X		X		X			
"KRAS/NRAS/BRAF status" for Step 1	X											
AST and ALT		X			X		X		X			
Serum creatinine/Calculated creatinine clearance		X			X		X		X			
Total bilirubin		X			X		X		X			
Magnesium/Potassium/ Calcium/Sodium/Bicarb/ Chloride §		X			X		X		X			
Pregnancy Test ¥		X	X									
SPECIMEN SUBMISSION												
Tissue for HER2 Testing £	X											
Tissue for Banking Δ		X										
Blood for Banking ΠΙ			X		X				X		X	
X-RAYS AND SCANS												
Images for Disease Assessment †		X							X		X	
Image Submission β		X							X		X	
TREATMENT ∑												
Cetuximab			X		X		X		X			
Irinotecan			X		X		X		X			

Click here for footnotes.

9.3 Arm 3: Trastuzumab and Pertuzumab (TP)

		Cycle 1			Cycle 2			Cycle 3+				Ω	%
REQUIRED STUDIES	Step 3 Crossover Reg	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Every 3 m	FU prior to prog	FU after prog
PHYSICAL ∑													
History and Physical Exam	X	X			X			X				X	X
Weight and Performance Status	X	X			X			X				X	X
Toxicity Notation					X			X				X	X
Disease Assessment †	X							X				X	X
LABORATORY ∑													
CBC/Differential/Platelets	X				X			X					
AST and ALT	X				X			X					
Serum creatinine/Calculated creatinine clearance	X				X			X					
Total bilirubin	X				X			X					
Magnesium/Potassium/ Calcium/Sodium/Bicarb/ Chloride §	X				X			X					
Pregnancy Test ɣ	X	X									X		
Blood for Banking π		X			X			X				X	
X-RAYS AND SCANS													
Images for Disease Assessment †	X							X				X	
ECHO Scan δ	X										X		
TREATMENT ∑													
Trastuzumab		X			X			X					
Pertuzumab		X			X			X					

Click here for footnotes.

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://swog.org/Visitors/Download/QA/Best%20Practices%20upddate.pdf.

Footnotes:

∑ Protocol treatment and parameters will continue at these intervals until progression of disease or until patient has met any of the guidelines in Section 7.6.

ɣ Females of child bearing potential must have a negative serum pregnancy test within 7 days of C1/D1, If pregnancy test completed at time of registration was completed within 7 days of C1/D1, it does not need to be repeated. Subsequently, a serum or urine pregnancy test must be completed every 3 months for Arms 1 and 3 (TP). If urine pregnancy test is subsequently utilized and is positive, confirm with serum pregnancy test.

† Disease assessment and CT/MRI/PET-CT must be performed every 6 weeks through Week 12 and then every 8 weeks until progression.

§ Results of these tests do not determine eligibility but are performed prior to registration in order to obtain baseline measurements.

Ω After off treatment prior to disease progression, scans for disease assessment and physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 8 weeks until progression.

β Submit scans as outlined in Section 14.0 and Section 15.3.

% After off treatment following disease progression, physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 6 months for three years from the time of Step 2 Randomization as clinically indicated.

¥ Must be done within 28 days prior to registration.

£ Required specimen submission for patients. See Section 15.1 for additional information.

Δ Optional specimen submission for patients. See Section 15.2 for additional information.

δ All patients in treatment Arms 1 and 3 must have baseline ECHO prior to starting treatment and must have LVEF ≥ 50% or ≥ lower limit of normal for the institution by echocardiogram. Baseline ECHO for Arm 1 patients must be performed within 3 months prior to randomization or after randomization prior to starting treatment. Baseline ECHO for Arm 3 patients must be performed within 14 days prior to Step 3 Crossover Registration. ECHOs must then be performed once every 3 months (Arms 1 and 3) while on treatment with trastuzumab and pertuzumab.

π Collect 20 mL of blood in lavender top (EDTA) tubes after randomization and prior to C1D1 (+/- 3 days), on C2D1 (+/- 3 days), at each restaging (including restaging during treatment on crossover arm), and off treatment. Process plasma from samples per the guidelines in Section 15.2b.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

This study will use the RECIST 1.1 guidelines. *(33)*

10.1 Measurability of Lesions

a. **Measurable disease**

Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as ***non-target*** lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Best Response

This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status:

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	**DESCRIPTION**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Progression-Free Survival

From date of randomization to date of first documentation of progression or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact.

10.6 Time to Death

From date of randomization to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Sample Size and Primary Analysis

We estimate the median PFS of patients treated with cetuximab and irinotecan to be 3 months in this select population with HER-2 amplification. *(34,35)* Assuming dual anti-HER-2 therapy offers an increase in PFS to 5.1 months (HR 0.59, for results to be considered clinically significant), we will need 122 eligible patients, based on a two-sided type I error of 5% and 80% power. Assuming a 6% ineligibility rate, we will need to randomize 130 patients. We expect 33 months of accrual and 7 months of follow-up.

All potentially eligible patients will be registered (Step 1 Registration) and screened for HER-2 amplification status per ASCO/CAP guidelines and HERACLES criteria. *(36,37)* Patients who meet those criteria are then eligible for randomization (Step 2 Randomization) to treatment with trastuzumab and pertuzumab, or cetuximab and irinotecan. We estimate that approximately 2381 patients will be screened in order to enroll the 130 HER-2-amplified patients necessary for the study.

From activation on October 9, 2017 until May 28, 2021, 47 patients were randomized to this study. Given this slow accrual rate, it was determined that a smaller sample size will be targeted. Assuming a HR of 0.5 (median PFS of 6 months in the TP arm), 7 months of follow-up, 90% power and a 1-sided alpha of 0.10, the new design requires 62 eligible patients. Given the likelihood of continued slow accrual, the trial will be closed to enrollment when 62 patients have been randomized or on December 31, 2021, whichever occurs first.

The primary analysis of PFS will be conducted in all eligible patients according to the intent-to-treat principle, using the stratified log rank test with stratification by prior use of irinotecan and by HER-2/CEP17 ratio. No interim futility analysis will be performed since an early closure is planned.

11.2 Other Analyses

Secondary endpoints will include overall survival, response, and toxicity. Distributions of overall survival in each arm will be estimated using the method of Kaplan-Meier and compared using the stratified log-rank test. The overall response rate (ORR), including confirmed complete and partial responses per RECIST 1.1, will be compared using the Cochran-Mantel-Haenszel test. With 31 patients per arm, overall survival at a particular timepoint and ORR can be estimated to within 18% (95% confidence interval) in each treatment arm.

Patients receiving at least one dose of drug on any arm will be included in the assessment of adverse events. Adverse event monitoring is conducted by the study coordinators, disease committee chair, and Adverse Event Coordinator and study statistician on an

ongoing basis, with notification to the DSMC and CTEP should any concerns arise. Any events reported through the CTEP-AERS system are reported immediately, and reports are sent to the above group for all other AEs on a monthly basis. Thirty-one eligible patients in each arm are sufficient to estimate the probability of a particular toxicity to within 18% (95% confidence interval). Any toxicity occurring with at least 7% probability is likely (90% chance) to be seen at least once.

Patients progressing on CETIRI will be provided the opportunity to cross over to the experimental intervention. This will facilitate enrollment in the protocol in a competitive landscape for study enrollment. PFS, OS, and ORR among patients who register to Arm 3 will be summarized using descriptive statistics.

11.3 Translational Medicine

The associations between each biomarker and PFS will be explored via Kaplan-Meier curves and Cox regression. The associations between biomarker and response will be explored via Logistic regression. Power calculations are based on associations between biomarker and outcomes separately by treatment arm. We assume a median PFS of 3 months and a response rate of 15% in the control arm.

Objectives

a. To evaluate if the following biomarkers are prognostic of clinical efficacy in patients receiving TP or CETIRI.

    1. We hypothesize that higher HER-2/CEP17 signal ratio values are associated with improved outcomes. Dichotomizing by a median split (low vs high), 31 patients provide 80% power to detect a hazard ratio of 2.6 for PFS by HER-2/CEP17 signal ratio (corresponding to a median PFS of 7.8 months for the HER-2/CEP17-high subgroup) using a two-sided alpha of 0.10. With 31 patients evaluable for response in each treatment arm, we will have 80% power to detect a difference in response of 42% (corresponding to a response rate of 57% in the HER-2/CEP17-high subgroup) using a two-sided alpha of 0.10. We will also evaluate HER-2/CEP17 signal ratio as a continuous variable.

    2. We hypothesize HER-2 gene copy number (GCN) ≥ 20 is associated with improved outcomes. Assuming 60% of patients have GCN ≥ 20, 31 patients in each arm provides 80% power to detect a hazard ratio of 2.65 for PFS by GCN (corresponding to a median PFS of 7.95 months for the GCN-high subgroup) using a two-sided alpha of 0.10. With 31 patients evaluable for response in each treatment arm, we will have 80% power to detect a difference in response of 43% (corresponding to a response rate of 58% in the GCN-high subgroup) using a two-sided alpha of 0.10.

11.4 Data and Safety Monitoring

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistics and Data Management Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

Discipline Review is not applicable to this study

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

a. Specimens must be submitted as described in Section 15.1 on the day of Step 1 Registration. If tumor is HER-2 amplified, patient must be registered to Step 2 Randomization prior to initiation of treatment (no more than ten working days prior to planned start of treatment).

b. Patients must be registered to Step 3 Optional Crossover prior to initiation of treatment (no more than ten days prior to planned start of treatment and within 28 days of discontinuation of CETIRI treatment).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>.

For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

b. CTEP Associate Registration Procedures

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at ctepreghelp@ctep.nci.nih.gov.

c. CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

1. IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

2. Downloading Site Registration Documents:

Site registration forms may be downloaded from the **S1613** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on LPO Documents, select the Site Registration documents link,

and download and complete the forms provided.
- Click on the By Lead Organization folder to expand
- Click on the SWOG link to expand, then select **S1613**. Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

3. Requirements for **S1613** *S*ite Registration:

   - CTSU Transmittal Sheet (optional)
   - •IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4. Submitting Regulatory Documents:

   Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

   ONLINE: www.ctsu.org (members' section) → Regulatory Submission Portal
   EMAIL: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)
   FAX: 215/569-0206
   MAIL: CTSU Regulatory Office
   1818 Market Street, Suite 1100
   Philadelphia, PA 19103

5. Checking Your Site's Registration Status:

   You can verify your site registration status on the members' section of the CTSU website.

   - Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
   - Click on the Regulatory tab at the top of your screen
   - Click on the Site Registration tab
   - Enter your 5-character CTEP Institution Code and click on Go

   Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-

ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander

- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 888/823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, you must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU help Desk at 888/823-5923 or by e-mail at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

Step 1 Submission (required for all patients)

a. WITHIN 48 HOURS OF STEP 1 INITIAL REGISTRATION:

Submit the following per Section 15.1:

Tissue specimens for central HER-2 testing (directly to Protean BioDiagnostics, Inc.).

Pathology report with specimens to Protean BioDiagnostics, Inc.

14.5 Data Submission **FOR PATIENTS WHO WILL NOT ENROLL TO STEP 2 RANDOMIZATION:**

a. WITHIN 7 DAYS OF DECISION NOT TO RANDOMIZE PATIENT:

Submit the **S1613** Notice of Intention Not to Randomize form

14.6 **Step 2 Submission (required for patients randomized to a treatment arm)**

a. WITHIN 7 DAYS AFTER STEP 2 RANDOMIZATION:

Submit the following:

S1613 Onstudy Forms

Baseline Tumor Assessment Form (RECIST 1.1)

Pathology Report (NOTE: Upload reports via the Source Documentation: Baseline form in Rave®. This submission is in addition to the pathology report submission to Protean BioDiagnostics, Inc. that is required by Section 15.1).

Molecular testing reports for KRAS, NRAS, and BRAF (NOTE: Upload reports via the Source Documentation: Baseline form in Rave®.)

Submit radiology reports from all scans performed to assess disease at baseline. (NOTE: Upload reports via the Source Documentation: Baseline form found in the Randomization Disease Assessment Folder in Rave®)

Submit images from scans performed to assess disease to AG Mednet for Image Banking (see Section 15.3).

b. WITHIN 28 DAYS AFTER STEP 2 RANDOMIZATION:

If the patient consents, submit tissue specimens (including pathology report) as described in Section 15.2.

c. WITHIN 14 DAYS AFTER EACH CYCLE OF TREATMENT (INCLUDING BOTH ON INITIAL TREATMENT ARM AND CROSSOVER TREATMENT ARM):

Submit the following:

S1613 Treatment Form

S1613 Adverse Event Form

d. WITHIN 14 DAYS AFTER EACH DISEASE ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF TREATMENT PRIOR TO DISEASE PROGRESSION)*:

Submit the following:

Follow Up Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans used to assess disease (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®)

Submit images from scans performed to assess disease to AG Mednet for banking as specified in Section 15.3.

*For patients on CETIRI who continue to TP, submit disease assessments (in the Crossover Disease Assessment Folder) until second progression. However, submission of images to AG Mednet are not required for Arm 3.

e. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT (INCLUDING BOTH ON INITIAL TREATMENT AND CROSSOVER TREATMENT):

Submit the following:

Off Treatment Notice

S1613 Treatment Form

S1613 Adverse Event Form

f. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit the following:

Follow-up Tumor Assessment Form (RECIST 1.1)

Radiology Reports (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®.)

Off Treatment Notice (if the patient was still on protocol treatment)

Final **S1613** Treatment Form (if the patient was still on protocol treatment)

Final **S1613** Adverse Event Form (if the patient was still on protocol treatment)

Follow-Up Form (if the patient was off protocol treatment) documenting date, site and method for determining progression/relapse.

NOTE: For patients on CETIRI (Arm 2) who continue to TP (Arm 3), submit disease assessments until second progression.

Submit images from scans performed to assess disease to AG Mednet for banking as specified in Section 15.3. Image submission may be batched.

g. **WITHIN 7 DAYS AFTER STEP 3 CROSSOVER REGISTRATION:**

Submit the following:

Baseline Tumor Assessment Form (RECIST 1.1)

S1613 Crossover Eligibility Form

Radiology reports (NOTE: Upload reports via the Source Documentation: Baseline form found in the Crossover Disease Assessment Folder in Rave®)

h. AFTER OFF ALL PROTOCOL TREATMENT, EVERY 6 MONTHS FOR 3 YEARS FROM STEP 2 RANDOMIZATION:

Submit the following:

Follow Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported)

i. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death **and final S1613** Treatment Form and **S1613** Adverse Event Form (if the patient was still on protocol treatment) or Follow-Up Form (if the patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 Specimens for HER-2 testing (required for patients)

All patients must submit specimens for central HER-2 testing on the day of Step 1 Registration.

a. Collection instructions are outlined in Section 15.1c and submission instructions are outlined in Section 15.1e.

b. Specimens to be submitted (see Sections 9.1 and 9.2):

1. 1 H&E tumor tissue slide (an additional unstained slide may be submitted if unable to obtain H&E locally)

2. 6 unstained paraffin-embedded tissue charged slides (4-5 microns thick)

NOTE: If patient is registered on a Friday, sites should hold tissue shipment until Monday. If tissue is received at lab and HER-2 status cannot be obtained, the site will be notified and additional tissue may be submitted for testing.

c. Paraffin-embedded tissue must be fixed per the instructions on the SWOG Specimen Submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures#Formalin-Fixed%20Paraffin) and submitted to the lab in Section 15.1e.

d. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

e. SHIPPING SAMPLES

1. SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA

Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on using your SWOG roster ID number and password, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Non- SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://spectrack.crab.org select the option "SWOG – SWOG – CTSU"). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. The Specimen Submission Form is NOT required when the online system is used.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://spectrack.crab.org/Instructions) or contact the SWOG Statistics and Data Management Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of tissue samples for HER-2 testing is identified as follows:

Lab #237: Dry Lab
Attention: Catherine Wilson
Protean BioDiagnostics, Inc.
6555 Sanger Road
Suite 225
Orlando, FL 32827
Phone: 754/946-4309
E-mail: catherine.wilson@proteanbiodx.com

Hannah Park
E-mail: hannah.park@proteanbiodx.com

2. Institutions will be notified by e-mail with the patient's HER-2 testing results within 14 calendar days after specimen submission. A formal lab report will be FAXed on request. If the patient's HER-2 results are NOT received by e-mail within 14 calendar days of submitting the specimen, please contact the SWOG Statistics and Data Management Center at 206/652-2267.

15.2 Submission of Specimens for Banking (optional for patients registered to Step 2 Randomization)

Specimens for translational medicine and banking (submitted to the SWOG Biospecimen Bank– Solid Tissue, Myeloma and Lymphoma Division, Lab #201):

a. With patient's consent, the following baseline specimens must be submitted after Step 2 Randomization and after crossover (Step 3) prior to beginning treatment on C1D1 (+/- 3 days) (see Sections 9.1 and 9.2):

   1. FFPE block or 10 unstained slides (10-micron on charged slides preferred; if not available, 5-micron and/or uncharged slides acceptable). Biopsy may be from either the primary or metastatic tumor site.

   2. Collect 20 mL of blood in lavender top (EDTA) tubes on C1D1 (+/- 3 days), , on C2D1 (+/- 3 days) and at each restaging (including restaging during treatment on crossover arm), and off treatment. Process blood for plasma, aliquot, and store in a -70°C to -80°C freezer until shipment per the guidelines in Section 15.2b. Plasma may be frozen and batch shipped at least every 3 months (maximum 5 patients per shipment).

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures#Formalin-Fixed%20Paraffin)

c. Specimen collection kits are not being provided for this protocol; sites will use institutional supplies.

d. Shipping Samples

   1. SWOG Specimen Tracking System (STS)

      All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on using your SWOG roster ID number and password, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Non- SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://spectrack.crab.org select the option "SWOG – SWOG – CTSU"). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

      A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. The Specimen Submission Form is NOT required when the online system is used.

      ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

      To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://spectrack.crab.org/Instructions) or contact the SWOG Statistics and Data Management Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of tissue samples for HER-2 testing is identified as follows:

Lab #201:

SWOG Biospecimen Bank
Solid Tissue, Myeloma & Lymphoma Division
Nationwide Children's Hospital
700 Children's Drive, WA1340
Columbus, OH 43205

Phone: 614-722-2865
Email: bpcbank@nationwidechildrens.org

Plasma will be shipped frozen, on dry ice. Complete packaging and shipping instructions for both the plasma and the blocks or slides can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures#Formalin-Fixed%20Paraffin).

15.3 Submission of Images for Banking (required for patients on TP [Arm 1] and CETIRI [Arm 2])

All patients will undergo imaging at baseline and every 6 weeks through Week 12 and then every 8 weeks until progression. Images must be locally read and interpreted by the local site radiology service. Imaging exams must then be submitted through AG Mednet for image banking. Image submission may be batched. Any imaging that is used for progression detection must be submitted. In addition, if imaging done for other reasons detects progression, it must also be submitted. Banked images may be used in future retrospective analysis.

a. **Instructions for Electronic Submission of Digital Images via AG Mednet to SWOG**

Digital images must be submitted electronically via the AG Mednet service provided by SWOG. (Please note that while AG Mednet service is provided by SWOG, SWOG will not be responsible for the cost of the exams).

b. **Electronic Submission Set-Up**

Upon IRB approval, you can begin the process to use the AG Mednet Desktop Agent. To request access, email agmednetadmin@swog.org and provide the following information:

- Contact Name
- Email Address
- Phone Number
- Site Name
- NCI Site Code
- Address
- Trial Name
- Trial ID
- Date

c. **Registration via the AG Mednet Portal**

1. If your site is qualified to participate in the trial, the SWOG Trial Administrator will invite you to the trial via the AG Mednet Portal. When you are added, you will receive a welcome email notification prompting you to register in the portal: https://portal.agmednet.net.

2. Complete the 3 pages of registration information. This includes creating your own username and password and a challenge question and answer.

3. When you are finished with registration, the portal will display a "Registration Complete" page. At this point you now have access to the trial. After you download the Desktop Agent, you will be able to login with your new username and password. You will also receive a registration confirmation email notification.

d. **Download the Desktop Agent and Login**

All participating sites need to download the AG Mednet Desktop Agent. The AG Mednet Desktop Agent can be accessed from a networked PC with *Java 6 plugin* installed. This plug-in ensures AG Mednet will run within the web browser. It is likely that you already have Java 6 installed. If you do not have Java 6 installed, downloading the Desktop Agent automatically downloads Java 6.

1. Launch your web browser and type in the following URL. This will download the AG Mednet Desktop Agent to your system: https://portal.agmednet.net/Desktop-Agent.

2. Type in your user name and password.

3. Click "Launch"

NOTE: This will place an icon on your desktop so, for future submissions, you can click on the "AG Mednet" icon, and it will automatically launch and request your user name and password when clicked.

e. **Submission (DICOM Exam)**

1. Click on the tab "DICOM Import" (top of screen).

2. For CD/DVD, load a disc into your machine.

3. A normal directory tree will be visible (close any DICOM viewers that may pop-up). Select the location of your DICOM files (i.e., the CD/DVD drive) or your PACS server. (NOTE: if sending from a PACS or Modality, use the DICOM Query or DICOM Receive Tab. Further details are available in the user guide on the Welcome Tab).

4. Find the time-point you wish to submit and select the "DICOMDIR" file and click "Import Exam." Click "Close" when complete*.

5. Click the "Exam List" tab (top of screen).

6. Select the exam you want to submit from “Available Exams” by clicking on a row within the table. In the image preview, you will see a picture of the data selected. Please check this is what you intend to submit. If not, select a different exam or go back to step A or E and select a different exam from the exam list.

7. In “Available Tasks for Selected Exam” (bottom left of screen), click “Assign Exam to Trial.” In pop-up box, select **S1613** from drop-down list and click “Assign Trial.”

8. In “Available Tasks for Selected Exam” (bottom left of screen), click “Deidentification” and click “Do Task.”.

9. In the pop-up box, click into the first blank cell under “De-identified Value.” Follow the on screen guidance and enter required data. Then click the next blank cell below the first and repeat until all blank cells are populated. As you complete these cells, the red cross will turn into blue checks. If a red cross remains after data has been entered, please check that the data is correct and change if applicable.

10. Click out of the cells and click “De-identify” (bottom of pop-up). AG Mednet will then remove any personal patient information from the DICOM metadata fields and replace this information with the study-specific data you entered in the table. Click close when complete.

11. In “Available Tasks for Selected Exam” (bottom left of screen), click “Transmittal Form” and click “Do Task.” The Data Transmittal Form will open. Complete all mandatory fields according to the study protocol. If you attempt to save the form without completing all mandatory fields, an alert will appear, prompting you to complete the remaining fields. If you want to print the form, click the “Print” button prior to saving. When the form is complete, click the “Save” button.

12. In “Available Tasks for Selected Exam” (bottom left of screen), click “Upload Exam” and click “Do Task.”.

13. Data will now be transmitted. Upload time is variable (depending on network connection and the size and number of images), but AG Mednet can be left running in the background and the computer used for other work. Once the data has been transmitted, a message will pop-up and AG Mednet can be closed.

14. You can import new exams and process them during the upload.

15. After 15 minutes of inactivity, the Desktop Agent will lock out. However, this does not interfere with the upload. You only need to log back in if you want to import another exam. *In most cases, a DICOMDIR file will be generated by scanners. However, if this is not the case, please select “All Files” from the dropdown box at the bottom of the “DICOM Import” screen. Data can then be selected manually from the directory tree and “Import Exam” clicked. The process is then the same as where a DICOMDIR file exists.

    Note: The person responsible for activating the desktop agent should be involved in submitting the exams as the Desktop Agent requires specific log-in verification. All questions regarding AG

Mednet use should be directed to 888-9AGMEDNET, and hit 2 for the support option.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Definition and Purpose

Definition: Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. (FDA, 21 CFR 312.32). See Table 16.1 for definition of a Serious Adverse Event (SAE) and reporting requirements.

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of

patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported to SWOG Operations Office using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to SWOG by telephone at 210-614-8808 or by email adr@swog.org. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

When the adverse event requires expedited reporting, submit the report via CTEP-AERS within the number of calendar days of learning of the event specified in Table 16.1 or 16.2, as applicable.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent(s) used in Arms 1 and 3 of this study are pertuzumab and trastuzumab. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used or if internet connectivity is disrupted please telephone or email the SAE Program Manager at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse events that Occur on Studies under an Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] – Trastuzumab and Pertuzumab (Arm 1 and Arm 3)

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or Section 16.1f.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 and Early Phase 2 Studies Utilizing an Agent under a non-CTEP-IND:**

1. **Group-specific instructions.**

Supporting Documentation Submission – Within **5 calendar days** submit documentation supporting the CTEP-AERS report to the SWOG Operations Office by fax 210-614-0006. Specific instructions will be sent by email to the reporting site by the SAE Program Manager.

2. The adverse events listed below also require expedited reporting via CTEP-AERS for this trial:
   - Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of pertuzumab and/or tratuzumab
   - Congestive Heart Failure

3. The adverse events listed below do **not** require expedited reporting via
   - The following events are to be monitored and carefully recorded, however these do not require expedited reporting for **non-serious cases**:
     - Infusion-related reactions/ARRs including anaphylactic deformities, hypersensitivity/anaphylaxis,
     - Infections,
     - Medication error,
     - Severe skin reactions,
     - Hepatobiliary toxicity,
     - Exacerbation of chemotherapy-associated neutropenia/febrile neutropenia,
     - Diarrhea Grade ≥ 3,
     - Mucositis,
     - Rash

g. Expedited reporting for commercial agents

Commercial reporting requirements are provided in Table 16.2. The commercial agent(s) used in Arm 2 of this study are cetuximab and irinotecan. If there is any question about the reportability of an adverse event or if Internet connectivity is disrupted please telephone or email the SAE Program Manager at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.2

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event[b].

[a] This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

h. Reporting Secondary Malignancy, including AML/ALL/MDS

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

   SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

   - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
   - Myelodysplastic syndrome (MDS)
   - Treatment-related secondary malignancy

   Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

   Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

   For more information see:
   http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. Supporting documentation must also be submitted to SWOG Operations Office by fax to 210-614-0006.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

i. **Reporting Pregnancy, Pregnancy Loss, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study OR within 7 months of the last dose of study agent(s); that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Pregnancy Loss** Pregnancy loss is defined in CTCAE as "Death in utero." Pregnancy loss should be reported expeditiously as **Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions** SOC.

   A Pregnancy loss should **NOT** be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

3. **Death Neonatal** "Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth. A neonatal death should be reported expeditiously as **Grade 4 "Death neonatal"** under the **General disorders and administration** SOC.

   Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERS recognizes this event as a patient death.

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 210-614-0006. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

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18.0 APPENDIX

18.1 New York Heart Association Criteria

18.2 Receipt, Processing, and Distribution Instructions for the SWOG Biospecimen Bank

18.1 New York Heart Association Criteria

Class	Cardiac Symptoms	Need for Limitations	Physical Ability Additional Rest*	To Work**
I	None	None	None	Full Time
II	Only moderate	Slight or occasional	Usually only slight	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
** At accustomed occupation or usual tasks

18.2 Receipt, Processing, and Distribution Instructions for the SWOG Biospecimen Bank

Formalin-Fixed Paraffin-Embedded (FFPE) Tumor Tissue

The SWOG Biospecimen Bank will receive 1 FFPE tumor tissue block or 10 unstained slides. Upon receipt, the FFPE specimens will be barcoded and banked at room temperature for long-term storage.

Frozen Plasma from EDTA

The SWOG Biospecimen Bank will receive frozen plasma aliquots from up to 6 time points. Upon receipt, these frozen vials will be barcoded and banked in a -80°C freezer for long-term storage.