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

January 20, 2023

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #9 to EA1181, *EA1181 (CompassHER2 pCR): Preoperative THP and postoperative HP in patients who achieve a pathologic complete response*.

There are revised case report forms as a result of this amendment.

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

IRB Review Requirements:

This addendum has been reviewed and approved by the Central IRB, which is the sole IRB of record for this study. The protocol and/or informed consent form changes must be activated within 30 days of the CIRB posting of this notice.

The below comments were received on September 13, 2022 from CTEP's review of Amendment #8. PI responses to each comment appear in bold below.

I. Recommendations:

#	Section	Comments
1.	4	**In Section 4 *CTEP Registration Procedures,* please revise as shown.** Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). RCR utilizes five person registration types. • IVR — MD, DO, or international equivalent; • NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);

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<table>
<tr><th>#</th><th>Section</th><th>Comments</th></tr>
<tr><td></td><td></td><td>

AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

~~In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.~~

~~Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.~~

RCR requires the following registration documents:
<table>
<tr><th>Documentation Required</th><th>IVR</th><th>NPIVR</th><th>AP</th><th>A</th><th>AB</th></tr>
<tr><td>FDA Form 1572</td><td>✔</td><td>✔</td><td></td><td></td><td></td></tr>
<tr><td>Financial Disclosure Form</td><td>✔</td><td>✔</td><td>✔</td><td></td><td></td></tr>
<tr><td>NCI Biosketch (education, training, employment, license, and certification)</td><td>✔</td><td>✔</td><td>✔</td><td></td><td></td></tr>
<tr><td>GCP training</td><td>✔</td><td>✔</td><td>✔</td><td></td><td></td></tr>
<tr><td>Agent Shipment Form (if applicable)</td><td>✔</td><td></td><td></td><td></td><td></td></tr>
<tr><td>CV (optional)</td><td>✔</td><td>✔</td><td>✔</td><td></td><td></td></tr>
</table>
An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

Added to a site roster
Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
Act as the site-protocol Principal Investigator (PI) on the IRB approval.

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization. ~~In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).~~
Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.
PI Response: This has been completed.
</td></tr>
</table>

#	Section	Comments
2.	4	**In Section 4 *Downloading Site Registration Documents,* please add the text in BLUE.** **Downloading Site Registration Documents** Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms: • Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password; • Click on *Protocols* in the upper left of the screen: ○ Enter the protocol number in the search field at the top of the protocol tree; or ○ Click on the By Lead Organization folder to expand, then select *ECOG-ACRIN*, and protocol number *EA1181*. Click on *Documents, Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration to* download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.) **PI Response: This has been completed.**
3.	4.2.10	**In Section 4.2.10, please delete the text in RED as this language is from a previous CTSU logistical language template version.** The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics. The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Forms Status and DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms. The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP. To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms, DQP Form Status, and DQP Reports modules. ~~**NOTE:** Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.~~ **PI Response: This has been completed.**
4.	9.4.1	The power computed for the NPV may not be entirely correct as this is a cross-validated estimate. Since AUC is the primary endpoint of these imaging objectives and NPV is secondary, it is fine if power calculations for NPV are not included in the protocol. **PI Response: The power calculations for NPV have been removed.**

The following revisions to EA1181 protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated version date.
2.	1.8	Included rationale for assessing tumor infiltrating lymphocytes.
3.	2.2	Included secondary objectives for tumor infiltrating lymphocytes.
4.	2.3	Included exploratory objectives for tumor infiltrating lymphocytes.
5.	5.11	Updated the duration of follow-up.
6.	7.1	Updated footnote 1 regarding physical exams. Updated footnotes 2 and 4 regarding drawing labs. Updated the duration of follow-up in footnote 12.
7.	9.5	Included the statistical considerations for tumor infiltrating lymphocytes objectives.
8.	10.1.1.2	Updated information regarding archived tumor tissue from clinical biopsy.
9.	10.1.1.3	Updated information residual disease surgical tumor tissue specimen.
10.	10.3	Administrative edit.
11.	15	Added new references.
12.	Appendix I	Updated information regarding archived tumor tissue from clinical biopsy and residual disease surgical tumor tissue specimen.

The following revisions to EA1181 Informed Consent Document have been made in this addendum:

	Section	Change
1.	Cover Page	Updated version date.
2.	Why is this study being done	Included “or FDA approved biosimilar”.

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

We request review and approval of this addendum to EA1181 so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director, Protocol Development

Rev. Add3

EA1181 (CompassHER2 pCR): Preoperative THP and postoperative HP in patients who achieve a pathologic complete response

Part 1 Component of:

The CompassHER2 Trials (COMprehensive use of Pathologic response ASSessment to optimize therapy in HER2-positive breast cancer)

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Version Date: January 20, 2023

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Rev. Add2

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ACTIVATION DATE

February 11, 2020
Addendum #1
Addendum #2
Addendum #3
Addendum #4
Addendum #5
Addendum #6
Addendum #7
Addendum #8
Addendum #9

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Agents	IND#	NSC#	Supply
Paclitaxel	Study Exempt from IND Requirements per 21 CFR 312.2(b)	673089	Commercial
Docetaxel		628503	Commercial
Trastuzumab		688097	Commercial
Trastuzumab-hyaluronidase		827797	Commercial
Pertuzumab		740102	Commercial
Pertuzumab-trastuzumab-hyaluronidase		827796	Commercial
Nab-paclitaxel		736631	Commercial

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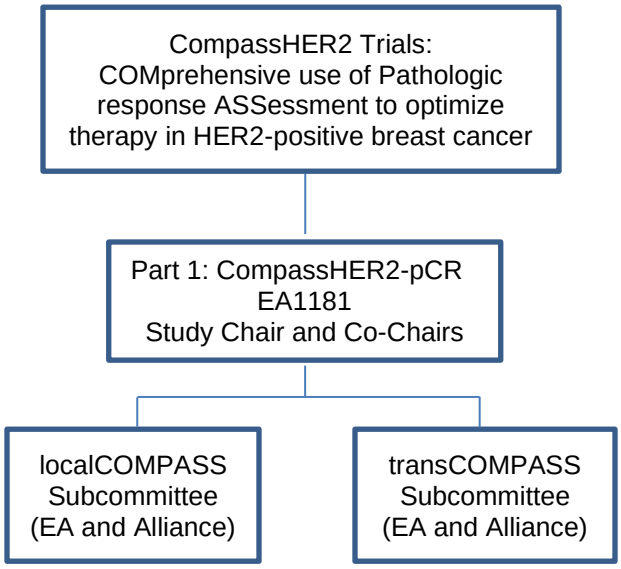
Rev. Add2



Rev. Add8

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at https://www.ctsu.org, and select the Regulatory > Submission Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	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 by phone or email : 1-888-823-5923, or 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.
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 clinical questions (i.e., patient eligibility or treatment-related) Contact EA1181team@jimmy.harvard.edu.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or 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		

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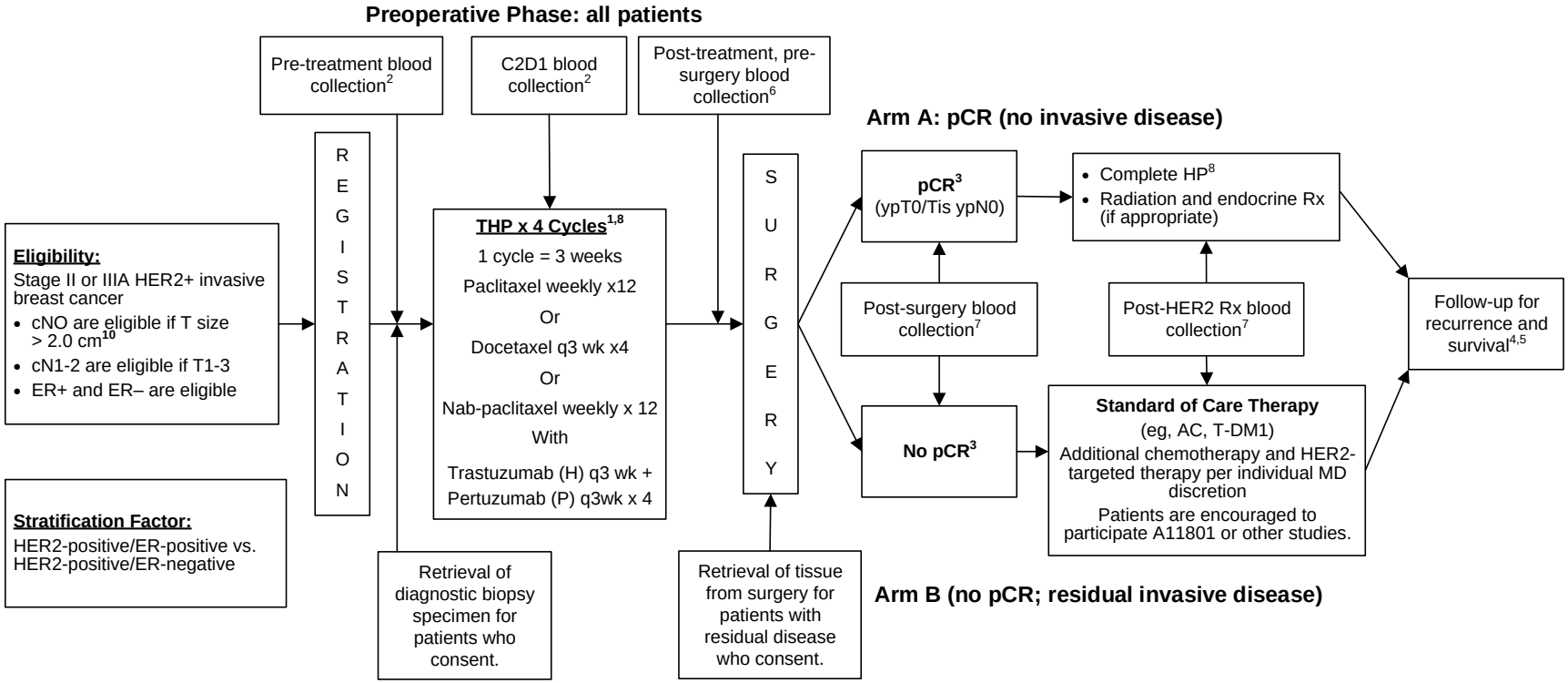
Schema (CompassHER2 pCR; EA1181; Compass Part 1)



1. The choice of taxane is up to the treating MD. For patients who develop hypersensitivity to paclitaxel or docetaxel, nab-paclitaxel is recommended.
2. 2 streck tubes for CTCs (mandatory); 2 additional streck tubes for cfDNA for patients who consent.
3. Isolated tumor cells (ITCs) or immunohistochemistry (IHC) evidence of cancer in nodes will be classified as “no pCR” (Arm B); IHC of nodes is not required. DCIS is allowed in Arm A.
4. Follow-up: Patients will be followed every 3 months for first 2 years after surgery, then every 6 months if the patient is 2-5 years from surgery, and then every 12 months if the patient is 5-15 years from date of surgery.
5. Primary objective is 3y RFS for patients who achieve pCR. Secondary objectives include 3 yr RFS for those without pCR and (for all patients): EFS, iDFS, DDFS, RFI, OS.
6. Research blood collection: 2 streck tubes for CTCs.
7. 2 streck tubes for CTCs (mandatory); 2 additional streck tubes for cfDNA in patients with pCR who consent.
8. 17 cycles **total** of HP will be administered to patients in Arm A including both pre- and post-surgery cycles. HP should be continued every 3 weeks until surgery, even when taxane therapy has been completed.
9. Trastuzumab-hyaluronidase SC may be substituted for trastuzumab; or pertuzumab-trastuzumab-hyaluronidase SC may be substituted for both trastuzumab and pertuzumab, following the dosing instructions in the US Package Inserts for Herceptin Hylecta® or Phesgo®.
10. As of July 28, 2022, for patients with HER2-positive/ER-positive disease with clinically negative nodes (cN0), tumor size(T) must be > 3.0 cm. Cohort for patients with 2-3 cm, ER+ and node negative HER2-positive/ER-positive disease closed on July 27, 2022.

1. Introduction

1.1 Rationale for neoadjuvant approach to de-escalate (and escalate) therapy in Stage II-IIIa HER2-postive breast cancer

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer represents about 15% of invasive breast cancers (Figueroa-Magalhaes et al, 2014). The first generation trials, including NSABP B31, N9831, and BCIRG 006, established the role of trastuzumab as standard adjuvant therapy in combination with cytotoxic chemotherapy, demonstrating significant improvement in outcomes (~50% reduction in recurrence and ~30% improvement in survival) Romond et al, 2005; Perez et al, 2014; Slamon et al, 2011). These trials primarily enrolled patients with node-positive and higher risk node-negative disease, and tested a range of adjuvant regimens, including anthracycline and cyclophosphamide followed by a taxane or docetaxel and carboplatin.

Further improvements in outcome were achieved by the addition of pertuzumab in both the neoadjuvant and adjuvant settings. This was demonstrated in the second-generation APHINITY trial, which enrolled about 5,000 patients to test the incremental benefit of adding pertuzumab to trastuzumab in the adjuvant setting. In the primary intent-to-treat analysis, there was a statistically significant improvement in 3-year IDFS with the addition of pertuzumab (94.1% vs 93.2%) with a hazard ratio (HR) of 0.81 (95% confidence interval (CI) 0.66-1.00). However, this absolute improvement of 0.9% was of marginal clinical relevance when all patients were considered; and the clinical benefit offered by pertuzumab was more apparent in estrogen receptor (ER)-negative tumors and in the node-positive population, where there was a 1.8% improvement in 3-year IDFS (92% vs 90.2%; HR 0.77, 95% CI 0.62-0.96) (von Minckwitz et al, 2017). Pertuzumab received accelerated approval in September 2013 for use as neoadjuvant therapy, based on a new regulatory path established by the FDA in 2012 (Prowell et al, 2012), and received regular (full) approval in December 2017 based on the results of APHINITY. Pertuzumab therefore secured a role in patients with clinical stage II and III disease who would accept additional therapy for marginal benefit (Miller, 2017).

However, given the excellent overall outcomes, and in view of significant toxicities/costs and the modest overall benefit, the APHINITY data also highlight the practical impossibility of attempting further improvements in early stage HER2-positive breast cancer when patients are grouped simply by surgical anatomic staging immediately after diagnosis (Miller, 2017). Further improvements in clinical outcome would require prohibitively large sample size, cost and time. And importantly, trials are unable to identify prospectively the patients with sufficiently high risk to require additional therapy. Consequently, it is now accepted that APHINITY was the last trial of its generation, and biological and functional information must be pursued and integrated into clinical trial designs to help further stratify patients in groups with different absolute risks.

The neoadjuvant setting can serve as a platform for risk stratification in therapeutic development. It is now clear that pathologic response is a patient-level functional prognostic marker for long term recurrence outcomes, wherein patients achieving a pathologic complete response (pCR) after neoadjuvant therapy have very low recurrence risk. The CTNeoBC pooled analysis obtained patient-level data from 12 trials and almost 12,000 patients (Cortazar et al, 2014).

While it could not validate pCR as a surrogate endpoint for improved event-free survival (EFS) and OS at a trial level, there was a strong and robust association between pCR and long-term outcomes at an individual patient level, particularly for those with triple negative and HER2-positive disease (Cortazar et al, 2014). Many patients in the preoperative studies included in the CTNeoBC analysis still received chemotherapy after surgery. However, its findings suggest that patients with an excellent response to preoperative therapy may do quite well. Also, it raises the possibility that these patients could receive less intensive/less toxic regimens after surgery (therapeutic "de-escalation"), especially if those therapies primarily focus on specific targets like HER2 and ER. Conversely, the CTNeoBC analysis suggests that patients with residual disease at surgery have a greater risk of future recurrence and could be candidates for new therapeutic strategies in addition to standard of care (therapeutic "escalation"). In the KATHERINE trial, 1,486 patients with HER2–positive early-stage breast cancer who had residual invasive cancer after preoperative chemotherapy plus trastuzumab were randomized to continue adjuvant trastuzumab or to switch to trastuzumab emtansine (T-DM1). Patients who received T-DM1 had a 50% relative reduction in the risk of breast cancer recurrence or death with an absolute difference of 11.3 % in 3-year IDFS (von Minckwitz et al, 2019). Prowell et al advocate that rather than adding new agents to conventional regimens preoperatively, patients with residual cancer after preoperative therapy have a high risk of recurrence and an unmet need. Trials evaluating new agents in this more selected group of high risk patients would produce results more quickly than conventional adjuvant trials, resulting in better patient outcomes and a more efficient use of research resources (Prowell et al, 2019).

Based on these data, we now have the opportunity to use the neoadjuvant setting to design studies in which pCR can be used as a "functional biomarker" to identify patients with excellent outcome, and refine treatment to maximize benefit and minimize toxicity, "de-escalating" toxic, unnecessary therapy for highly responsive tumors and "escalating" therapy for those that demonstrate some measure of resistance to standard therapy.

The neoadjuvant approach will also enable us to identify biological factors that can aid in the selection of escalated/de-escalated regimens for newly diagnosed patients. Data from the CALGB 40601 trial suggest that a further subsetting of HER2-positive disease by molecular profiling may identify a group of patients with more sensitive disease and greater likelihood of pCR, who may be particularly appropriate for "de-escalation" strategies. Approximately 50% of all HER2-positive breast cancer can be sub-classified as HER2E based on intrinsic subtyping (Prat et al, 2014). Previous smaller studies have demonstrated that these tumors appear to be the most responsive to HER2-targeted therapies based on pCR rates (Llombart-Cussac et al, 2017; Prat et al, 2014; Carey et al, 2016; Dieci et al, 2016). If pCR can serve as a functional biomarker to identify those patients with HER2-positive breast cancer who can successfully de-escalate chemotherapy without compromising outcomes, understanding which patients are most likely to achieve pCR in a larger, prospective trial becomes an important research goal. Likewise, being able to identify patients with HER2-positive breast cancer who are unlikely to achieve pCR will enable clinicians and patients to make informed decisions about the best therapy for individual patients.

Therefore, EA1181 will also assess pCR rate based on a clinically validated tumor-based biomarker (molecular intrinsic subtype) measured by an available commercial assay, enabling translation of tumor biology to diagnostic and therapeutic strategies.

Rev. Add3

1.2 The CompassHER2 Trials: A research program testing targeted escalation/de-escalation in HER2-positive breast cancer

The CompassHER2 ("COMprehensive use of Pathologic response ASSessment to escalate or de-escalate therapy in HER2-positive breast cancer") Trial Program represents a collaborative effort between the NCI NCTN Cooperative Groups ECOG-ACRIN and Alliance for Clinical Trials in Oncology (ALLIANCE) to further investigate the optimization of therapy in patients with HER2-positive breast cancer. The trials within CompassHER2 Program address clinical therapeutic objectives, as well as those that address translational questions [transCOMPASS], patient-reported outcomes [proCOMPASS] and outcomes measuring loco-regional recurrence [localCOMPASS]. The CompassHER2 organizational structure (outlined on page 5) includes these subcommittees with members from both ECOG-ACRIN and Alliance to align the various research objectives within and between trials. Each subcommittee will be responsible for coordinating, monitoring, and analyzing the clinical and correlative objectives within their purview. The first trial to open within the CompassHER2 Program is EA1181 (also known as "Part 1" or "CompassHER2 pCR).

Rev. Add3

1.3 EA1181 ("Part 1" or "CompassHER2 pCR")

1.3.1 Rationale for a single-arm design

EA1181 is a single-arm trial. The design of de-escalation trials poses certain challenges. Given the overall excellent outcomes in HER2-positive patients who achieve pCR, event rates are low. Randomized trials to demonstrate non-inferiority of a de-escalation strategy would be prohibitively large, and have the added disadvantage of exposing a group of patients to more toxic treatment than is necessary. Thus, it is appropriate to consider a single arm design of de-escalated therapy and the Adjuvant Paclitaxel and Trastuzumab (APT) trial serves as a precedent for a single-arm "de-escalation" approach that changed clinical practice. APT treated 410 patients with early stage, node negative, HER2-positive breast cancer in the adjuvant setting with 12 doses of weekly paclitaxel plus one year of trastuzumab, and demonstrated the ability to use anatomic information to identify patients expected to do well with a less intensive trastuzumab-based chemotherapy regimen (Tolaney et al, 2019). Patients have had an excellent outcome at 7 years with a DFS of 93.3%, RFI of 97.5%, and OS of 95% (Tolaney et al, 2017). This was a single arm, phase II study that changed clinical practice, and most investigators agree that it would have been difficult, expensive, and likely unnecessary to study this in a formal randomized phase III study.

The success of the APT trial and its impact in clinical practice provides the rationale to test a de-escalation strategy in appropriately selected patients. EA1181 attempts to expand this approach to a group of patients with higher initial anatomic risk, namely those with clinical Stage II and IIIa HER2-positive disease. EA1181 will use

pathological response to preoperative single-agent taxane plus dual HER2-targeted therapy as a functional biomarker and will test whether omission of adjuvant chemotherapy in those who achieve a pCR (ypT0 ypN0 or ypT0/is ypN0) reduces toxicity without compromising long-term survival outcomes.

1.3.2 Rationale for neoadjuvant THP

In the neoadjuvant setting, the addition of pertuzumab to taxane-based chemotherapy and trastuzumab has been shown to improve pCR as well as long-term outcomes. NeoSphere was a phase II trial that randomized 417 patients with early-stage HER2-positive breast cancer to one of four treatment arms. In one arm, patients received trastuzumab, docetaxel and pertuzumab, and in a second arm patients received trastuzumab plus docetaxel. Following surgery, all patients received 3 cycles of anthracycline-based chemotherapy (i.e., FEC [5-fluorouracil/epirubicin/cyclophosphamide]) and completed one year of trastuzumab. Compared with docetaxel and trastuzumab alone, the addition of pertuzumab significantly improved the pCR rate (45.8% vs 29.0%; p=0.0141) and the 5-year progression-free survival (PFS) from 81% to 86%, which reduced the risk of disease recurrence or death by 31% (HR, 0.69) (Gianni et al, 2012). TRYPHENA was a phase II trial with cardiac safety as the primary endpoint. All 225 participants received dual HER2 targeting with trastuzumab and pertuzumab and were randomly assigned to also receive either FEC for three cycles followed by docetaxel, or six cycles of docetaxel and carboplatin. In this trial, pCR (breast) was a secondary endpoint, with rates ranging between 57.3% and 66.2% (Schneeweiss et al, 2013).

In September 2013, based on results from the NeoSphere and TRYPHAENA trials, the FDA granted approval to pertuzumab for use in the neoadjuvant setting in combination with trastuzumab and chemotherapy for patients with locally advanced, inflammatory or early-stage breast cancer (tumors >2 cm in diameter or with positive lymph nodes) (Gianni, 2016).

The addition of pertuzumab in the adjuvant setting resulted in a modest benefit in IDFS in the APHINITY trial. APHINITY was a phase III, randomized, placebo-controlled study that enrolled 4,800 women with operable HER2-positive breast cancer to standard adjuvant chemotherapy and trastuzumab (6-8 cycles of AC-TH or TCH), or to the same therapy plus pertuzumab. After 45 months of follow-up, 3-year IDFS for all patients was 94.1 percent (with pertuzumab) versus 93.2 percent (without pertuzumab) (HR 0.81, p=0.045). Preplanned subgroup analysis demonstrated that in patients with nodal involvement, there was a significant improvement in 3-year IDFS: 92 versus 90.2 percent (HR 0.77, p=0.02) (von Minckwitz et al, 2017).

While the degree of benefit with the addition of pertuzumab to standard chemotherapy and trastuzumab was modest in APHINITY, the benefit of pertuzumab may be more discernible in patients who de-escalate chemotherapy or with disease that is more dependent on the HER2 pathway. The CompassHER2 trial (EA1181) will investigate whether pertuzumab in combination with a taxane and trastuzumab

allows further de-escalation of chemotherapy for some patients (i.e., those who achieve pCR) without compromising long-term outcomes, and confirm exploratory results reported in the KRISTINE trial (Hurvitz et al, 2019) (Hurvitz et al, 2019; Wolff et al, 2019).

1.3.3 Rationale for de-escalation in patients who achieve pCR

Pathologic response to neoadjuvant chemotherapy is prognostic in all breast cancer subtypes (Cortazar et al, 2014). In a meta-analysis by Cortazar et al, pCR was associated with improved long-term outcomes in the HER2-positive subgroup irrespective of ER status (EFS [event-free survival]: HR 0.39, 95% CI 0·31–0·50; OS: 0.34,0·24–0·47), and was even more predictive of good outcomes in those who achieved pCR after trastuzumab-based therapy (EFS HR 0.15, 0.09-0.27; OS HR 0.08, 0.03–0.22) (Cortazar et al, 2014). Symmans et al. showed that pCR achieved after trastuzumab, anthracycline and taxane based chemotherapy resulted in excellent relapse-free survival (95% at 5 and 10 years) in patients with HER2-positive breast cancer treated at a single institution (Symmans et al, 2017). Other studies that administered trastuzumab with standard chemotherapy in the neoadjuvant setting (without further chemotherapy after surgery) have also reported excellent secondary results with 3-year DFS and EFS rates of ≥88% and overall survivals ranging from 92-96% (Untch et al, 2011; van Ramshorst et al, 2017; Gianni et al, 2014). If additional, larger studies that allowed chemotherapy after pCR are also included, 3- to 5-year DFS/EFS rates range from 85-95%. Possible explanations for the varied results include differences in study populations, chemotherapy administered and specific outcomes measured (Tolaney et al, 2017; Gianni et al, 2012; Schneeweiss et al, 2013) (de Azambuja et al, 2014; Gianni et al, 2016). EA1181 is designed to address survival as a primary clinical objective.

Trial	Neoadjuvant Tx	pCR (# pts)	Adjuvant Tx	Outcomes for those with pCR
TECHNO[1] Phase 2 n=217	ECx4→Tx4+H	84	H Q 3 wk. to finish 1 year	HR for DFS 2.5; p=0.013 (i.e., improved DFS with pCR) 3-yr DFS 88%, 3-yr OS 96.3%
NOAH[2] Phase 3 n=235	AT q3wk X3→T q3wk X4→ CMF q28d X3 With or without H	68	H Q 3wk to finish 1 year	HR for EFS 0.29 (95%, 0.11-0.78) 3-yr EFS 87% for those who achieved pCR after chemo and Herceptin
TRAIN[3] Single arm Phase 2 N=108	Weekly Taxol/carbo/H x 24 wks.	47	H to finish 1 year	3-yr EFS 88% 3-yr OS 92%
Symmans[4] Cohort study N=203	H + T/FEC	95	H to finish 1 year	HR RFS 0.23; (95% CI: 0.06-0.90) 5-year relapse free survival 95%
NeoSphere[5] Phase 2 n=417	1: TH q3wk x4 2: THP q3wk x4 3: HP q3wk x4 4: TP q3wk x4	94	Arms 1,2,4: FEC x3→H q3wk to finish 1yr Arm 3: T q3wk x4→FEC x3→H to finish 1yr	HR PFS: 0.54 (0.29-1.0) 5-yr PFS 85%
NeoALLTO[6] Phase 3 N=455	1: L x6wks→L+TX12 wks. 2: H x6wks→H+TX12 wks. 3: H+L x6wks→ H+L+T x12wks	137	FEC q3wk X3→anti-Her2 tx as per original arm x 34 wks. (Total 52 wks)	HR EFS: 0.38 (0.22-0.63) ; p=0.0003 HR OS: 0.35 (0.15-0.70): p= 0.005 3-year EFS 86% 3-year OS 94%
CALGB 40601[7]	1. THL x 16 wks 2. TH x 16 wks 3. TL x 16 wks (closed)	139	AC q 3wk x 4→H x 32 wks	HR EFS 0.28 (0.12-0.66); p=0.003 5-yr EFS 92%

A-Adriamycin (doxorubicin); **C**-cyclophosphamide; **Carbo**-carboplatin; **T –**taxanes (either docetaxel or paclitaxel)l; **E**-epirubicin; **F**-fluorouracil; **M**-methotrexate; **L**-lapatinib; **P-** pertuzumab; **H-** trastuzumab; **pCR**-complete pathologic response defined as **ypT0/is ypN0**-no invasive cancer (in-situ allowed) in the breast or lymph nodes; **EFS**-event-free survival; **RFS**-recurrence-free survival; **DFS**-disease free survival; **PFS**-progression free survival; **OS**-overall survival.

References: **1**: Untch et al, 2011**;**
2: Gianni et al, 2014**;**
3: van Ramshorst et al, 2016**;**
4: Symmans et al, 2017**;**
5: Gianni et al, 2016**;**
6: de Azambuja et al, 2014**;**
7: Dieci et al, 2016; Prat, 2014

Rev. Add3

1.4 Rationale for restricting eligibility to patients with less ambiguous HER2 test results

There is consensus that tumors with HER2 immunohistochemical (IHC) staining result of 3+ or in-situ hybridization (ISH) results demonstrating HER2/CEP17 ratio ≥2.0 represent tumors with HER2 amplification that are sensitive to HER2-targeted therapy (Wolff et al, 2018).

However, there are limited data about the clinical response to HER2-targeted therapy for tumors with ISH results demonstrating a HER2/CEP17 ratio <2.0 and mean HER2 signals per cell ≥ 6.0 (Wolff et al, 2018). These tumors are uncommon, representing between 0.4% and 3.0% of cases sent for dual-probe FISH testing. These ISH cases have increases in both HER2 and control centromere signals, resulting in ratio results of <2.0. At the time of the pivotal HER2 trials, cases with these results were considered to have duplication of CEP17 (polysomy) and were most often excluded because they were considered negative for HER2 gene amplification. Breast Cancer International Research Group (BCIRG 006; Clinicaltrials.gov identifier: NCT00021255) allowed patients to be enrolled, but only if the HER2 copy number was ≥10 **and** central IHC testing was 3+. Subsequent studies examining multiple regions of chromosome 17 supported that the majority of cases with these results have HER2 amplifications that include regions encompassing the centromere rather than true polysomy for the entire chromosome 17 (coamplification of control and HER2 signals). Based on these data, the 2013 Guideline Update clarified that cases with an average HER2 copy number of ≥6.0 HER2 signals per cell ISH results (by either single- or dual-probe assays) should be reported as HER2-positive by gene amplification (Hanna et al, 2014; Tse et al, 2011; Troxell et al, 2006; Moelans, 2010; Marchio et al, 2009; Yeh et al, 2009; Vranic et al, 2011). However, it was acknowledged that data on the clinical response of this group to HER2-targeted therapies were limited.

Since the 2013 update, additional data have been published including concurrent IHC results for this ISH category, and they show that this group is heterogeneous. Data from a reanalysis of the HERA trial identified a small number of cases (21 total) originally considered negative due to ratios of <2.0 but with an average of ≥6.0 HER2 signals per cell (Stoss et al, 2015). 75% of them (15 of 20) had HER2 overexpression by IHC. In a combined study of three major academic medical centers performing HER2 FISH and IHC, similar results were seen with 63 cases in this ISH category; 31.7% were IHC 3+ for HER2 by IHC, 55% were IHC 2+, and 13.7% were IHC 0 or 1+ (Ballard et al, 2017). Published data from a reference laboratory at the University of Southern California described 48 cases with the same ISH characteristics and found that only 8.3% were IHC 3+, while 14.6% were IHC 2+ and 77% were IHC 0 or 1+ (Press et al, 2016). Additional analysis of these cases identified a highly amplified subgroup (eight total cases) with an average of 12.3 HER2 signals per cell that correlated well with HER2 IHC 2+ or 3+ (75%). This subgroup differed significantly from the other subgroup (40 total cases) that had a lower average of 6.8 HER2 signals per cell and 87.5% IHC negative (0 or 1+) results. Similarly, in the Breast Cancer International Research Group central testing clinical trial data, of the limited cases (nine total) with IHC data and ISH results in this category from BCIRG 005/006/007, one was IHC 3+ positive, one was IHC 2+, and seven were IHC negative. Taken together, these results suggest that cases in this ISH category

form a heterogeneous group that is best discriminated by the combination of IHC and ISH (Press et al, 2016).

Due to the rarity of cases with HER2/CEP17 ratio <2.0 and HER2 copy number ≥6.0, there is still limited clinical evidence regarding benefit from HER2-targeted therapy. The few cases enrolled in the BCIRG 006 adjuvant trastuzumab trial with these ISH results were insufficient to assess whether there was benefit from HER2-targeted therapy, and statistical analysis was not attempted.

Overall, the absence of robust clinical data to guide decisions for this group of patients with dual ISH probe Group 3 results and their observed heterogeneity raises concerns that some of these patients may not have disease that is biologically HER2-driven. The Expert Panel working in the ASCO/CAP 2018 guidelines ultimately favored continuing to classify these cases as HER2-positive unless the concurrent IHC result is clearly negative (IHC 0 or 1+), but the expectation then was the patients receiving routine care would receive combination chemo (doublet or triplet) plus HER2-targeted therapy. Therefore, some of these patients could potentially receive insufficient chemotherapy if ultimately treated with just one cytotoxic drug plus HER2 targeted therapy, especially if a tumor is both ER-negative and not HER2-driven.

CompassHER2 pCR is a chemotherapy optimization study for patients with HER2-positive breast cancer. The rationale for reducing chemotherapy exposure (single agent taxane) is based on the expected excellent responsiveness to a combination regimen with a single taxane agent plus dual HER2-targeted antibodies.

Given limited data on benefit from HER2-targeted therapy in tumors that are not clearly HER2-amplified by ISH or overexpressed by IHC, EA1181 investigators ultimately opted to limit eligibility to patients whose tumors have unambiguous patterns of HER2 positive status. These include tumors that are positive by immunohistochemistry (IHC 3+) or positive by ISH with appropriate IHC test if needed (e.g., HER2 ISH ratio ≥2.0 with HER2 copy number ≥4.0 regardless of IHC [dual probe ISH Group 1] or HER2 ISH ≥2.0 with HER2 copy number <4.0 and IHC 3+ [dual probe ISH Group 2). Patients whose tumors fall under ASCO/CAP dual ISH probe Group 3 (HER2 ISH ratio <2.0 with HER2 copy number ≥6.0) that have IHC test result 0, 1+, or 2+ are not eligible.

1.5 Rationale for Assessing Primary Outcomes in Estrogen Receptor-Positive/HER2-Positive and Estrogen Receptor-Negative/HER2-Positive Disease Separately

Several reported trials that described survival outcomes in patients with HER2+ breast cancer after pCR with standard chemotherapy and HER2-antibody therapy as secondary objectives also explored outcomes by ER status. However, these studies were underpowered to provide definitive evidence, especially according to ER status, as all those studies were powered for short-term outcomes like pCR and not for long-term outcomes. Therefore survival outcomes like (IDFS, EFS, PFS, and RFS) were mostly descriptive in nature and lack precision. Some of those data when analyzed by ER status are also conflicting (see Table below).

Data from the Early Breast Cancer Trialists' Collaborative Group meta-analysis of trastuzumab for early stage breast cancer (PMID 34339645) showed that recurrence rates in the first two years were higher for ER-negative than for ER-positive tumors while they were higher for ER-positive than for ER-negative in

years 5–9. As such, ultimately, the average overall absolute reductions in 10-year recurrence risk were similar for women with ER-negative (10.1%, 95% CI 7.7−12.5%) and ER-positive disease (7.8%, 5.5−10.1). These patterns according to ER status recapitulate in HER2-positive disease what had previously been reported in early-stage breast cancer overall, and emphasizes the importance of long-term follow-up and reporting of outcomes beyond the initial primary objective analysis.

EA1181 was initially designed to assess 3-year RFS among all patients who achieve a pCR after preoperative THP, regardless of ER status. However, should the original primary objective be met (3y RFS >92%), we expect some clinicians to wonder if the results equally apply to all patients regardless of ER status. EA1181 was initially designed to analyze outcomes according to ER status as secondary outcomes. However, the ability to report outcomes by ER status with greater precision will generate more robust data with immediate impact in the dissemination of EA1181 findings and the implementation of a HER2-based regimen with less chemotherapy for patients who achieve pCR after preoperative single-agent taxane with dual HER2-antibody therapy.

Study	# pts with pCR	Outcome	ER+ HER2+	ER- HER2+
NSABP B41[1]	294 (156 ER+ 138 ER-)	4.5y RFS	91.1%	89.2%
GeparSepto[2]	229 (153 ER+ 76 ER-)	3y iDFS 4y iDFS	94.4% 94.4%	88.6% 88.6%
I-Spy2[3]	131 (70 ER+ 61 ER-)	3y EFS	97%	93%
C40601[5]	141 (69 ER+ 72 ER-)	5 y RFS 7y RFS	89% 84.9%	97% 94.1%
NeoALTTO[6,7]	137	3y EFS 6y RFS	87% 78%	85% 77%
NeoSphere[8]	94 (22 ER+ 72 ER-)	3y PFS 5 y PFS	90% 90%	91% 84%
TRAIN[9]	46 (21 ER+ 25 ER-)	5y EFS	~95% (derived from Fig 1)	~88% (derived from Fig 1)
CHERLOB[10]	37	5y RFS	100%	94.7%
MDAnderson[11] (retrospective)	92 (34 ER+, 58 ER-)	10 y RFS	95%	95%

1) Robidoux et al. Journal of Clinical Oncology 34, no. 15_suppl (May 20, 2016) 501-501.
2) Sibylle Loibl- personal communication
3) I-SPY2 trial Consortium. JAMA Oncol. 2020;6(9):1355-1362
5) Lisa Carey and Aranzazu Fernandez- personal communication- 7yr
6) Azambuja et al. Lancet Oncol 2014; 15: 1137–46
7) Huober et al. Eur Journal Cancer 118 (2019) 169-177
8) Gianni et al. [ASCO abstract 505]. J Clin Oncol. 2015;33(15)(suppl)- 5 yr
9) van Ramshorst et al. European Journal of Cancer 74 (2017) 47e54
10) Guarneri et al. European Journal of Cancer 153 (2021) 133e141
11) Symmans et al. JCO 2017

1.6 EA1181 Correlative Science: Blood-Based Biomarkers

1.6.1 Circulating Tumor Cells (CTCs)

Several assays are available that may detect clinically-occult tumor burden or minimal residual disease (MRD) by assessment of CTCs, but their clinical utility has not been established. Enumeration of CTCs in the blood (≥ 1 CTC in 7.5 ml blood) has also shown to be associated with recurrence when detected in patients with operable breast cancer who have not yet had surgery particularly amongst those who have residual disease after neoadjuvant therapy (Kelemen, et al, 2016).

In EA1181, CTC detection before protocol therapy, after protocol therapy, and change (i.e., clearance of CTCs after study therapy (in those harboring these biomarkers pre-therapy) will be correlated with pathologic response and subsequent RFS. CTC detection after completion of chemotherapy will be coded as a binary variable (present versus absent). Two Streck tubes for CTC analysis will be collected at the following time points: (1) baseline (prior to study therapy); 2) after 1 cycle of pre-operative THP; 3) after 4 cycles of THP; 4) post-operatively and 5) after completion of HER2-targeted therapy (e.g., HP), CTC results will not be provided to the clinician or patient for clinical decision making.

Blood specimens will be forwarded to Epic Sciences, where they will be prepared for subsequent sequencing and analyses for the corresponding mutations detected in matched primary breast tissue.

We hypothesize that:

- (a) patients whose specimens are negative for CTC detection before protocol therapy will have a better RFS after surgery than patients with positive CTC detection at baseline;
- (b) patients whose specimens are negative for CTC detection after 3 weeks of THP, after 12 weeks of THP (before surgery), after surgery before any additional therapy, or after completion of HER2-targeted therapy will have a better RFS than patients with positive CTC detection at these time points.

We expect that the large-scale serial CTC detection will provide an important intermediate biomarker that will help identify patients with HER2-positive breast cancer at a higher risk of relapse after surgery, identify those most likely to benefit from additional adjuvant therapy, and identify alterations that could have clinically actionable potential.

Rev. Add8

1.7 EA1181 Correlative Science: Imaging Markers

1.7.1 MRI Functional Markers and Radiomics Signatures

The overall goal of this research is to leverage new computational tools to extract valuable biomarkers from routine imaging to improve risk stratification and treatment selection of HER2+ breast cancer.

Recent advances in the fields of artificial intelligence (AI) and computational image analysis have given rise to the new field of “radiomics”, where high dimensional, quantitative imaging features are

extracted from routine diagnostic radiology studies reflecting underlying tumor architecture and function (Gillies et al, 2016; Saltz et al, 2017). Studies suggest that these features are influenced by variables such as tumor mutational burden, histologic subtype, degree of cellular differentiation, mitotic rate, and superimposed biological processes such as apoptosis, tumoral edema, and lymphocytic infiltration. Radiologic imaging uniquely allows for comprehensive assessment of tumors intact in their de novo environment. Breast MRI in particular provides exceptional anatomic resolution and sensitivity for identifying breast cancer, and therefore commonly used for preoperative assessment. Advanced dynamic contrast-enhanced MRI (DCE-MRI) analyses have revealed distinct features related to intra-tumor heterogeneity, enhancement kinetics, functional tumor volume and other metrics, which individually show prognostic and predictive value in a variety of clinical applications (Li et al, 2020; Kuhl et al, 1999; Li et al, 2008; Esserman et al, 2001; Hylton et al, 2001). Extending on this, a growing number of breast MRI radiomics studies demonstrate significant associations with prognostic factors including treatment response and genomic assays of recurrence risk (Li et al, 2016; Reig et al, 2019; Ashraf et al, 2014; Wu et al, 2018; Braman et al, 2019; Jahani et al, 2019). One radiomics study also found DCE-MRI-derived breast tumor features were associated with level of immune activation reflected by tumor-infiltrating lymphocytes (TILs) and complementary to molecular markers for predicting recurrence free survival after treatment (Wu et al, 2018).

Specific to HER2-positive disease, most of the prior studies have not identified any predictive baseline MRI markers useful for stratification but were also not adequately powered for subanalysis by cancer subtype or investigated only select tumor imaging features. On the other hand, the Braman study identified baseline DCE-MRI radiomics signatures to predict TILs levels and pCR in HER2-positive disease (Braman et al, 2019), but requires further validation. Our study will seek to validate and refine this radiomics-based approach for predicting treatment response in a large cohort of women with HER2-positive breast cancer, and to determine whether reliable breast MR markers can be derived from standard of care breast MRIs.

We hypothesize that:

- Radiomics based on routine breast MRI can non-invasively characterize multiple aspects related to the tumor microenvironment including heterogeneity and immune activation to provide unique predictive value in women undergoing HER2-targeted breast cancer treatment.

We anticipate that these imaging-based biomarkers may facilitate up-front treatment selection and personalization (to escalation or de-escalation regimens) by improved prediction of treatment response and outcome for patients with early stage HER2-positive breast cancer.

Rev. Add9

1.8 Rationale for assessing tumor infiltrating lymphocytes (TILs)

Investigator: Dr. Sunil Badve at Emory University

1.8.1 Rationale for assessing TILs in the baseline tumor

The association of baseline tumor-infiltrating lymphocytes (TILs) and outcomes among patients with HER2+ breast cancer was assessed in 213 patients from the Tryphaena study who randomly received trastuzumab/pertuzumab with an anthracycline-containing or anthracycline-free regimen (Ignatiadis et al, 2018). At a median follow-up of 4.7 years, for every increase in baseline TILs of 10%, there was a 25% reduction in the hazard for an EFS event (aOR = 0.75, 95% CI = 0.56 to 1.00, P = .05). Kim et al. evaluated the association of stromal TILs (sTILs) with clinical outcomes in 1581 patients from NSABP B-31 (Kim et al, 2019). In patients receiving standard chemotherapy alone or in combination with trastuzumab, increases in sTILs (combined arms HR = 0.42, 95% confidence interval = 0.27 to 0.64, two-sided P < .001) or as lymphocyte-predominant breast cancer with more than 50% sTILs (combined arms HR = 0.65, 95% confidence interval 0.49 to 0.86, two-sided P = .003) were statistically significantly associated with improved disease-free survival. In NeoALTTO, with a median follow-up time of 3.77 (3.50-4.22) years, every 1% increase in TILs was associated with a 3% decrease in the rate of an event (adjusted hazard ratio, 0.97 [95% CI, 0.95-0.99]; P = .002) across all treatment groups (Salgado et al, 2015).

Studies assessing whether an increased level of TILs predicts benefit to trastuzumab have provided mixed results. Perez et al evaluated the prognostic and predictive value of stromal TILs in the adjuvant North Central Cancer Treatment Group (NCCTG)–N9831 trial that compared chemotherapy with adriamycin, cyclophosphamide, and paclitaxel with or without trastuzumab (Perez et al, 2016). Surprisingly, higher level of TILs was associated with better recurrence-free survival only in patients receiving chemotherapy alone, but not in patients who also received chemotherapy and trastuzumab. In contrast, Loi et al demonstrated better outcomes for patients with higher TIL levels receiving trastuzumab in the FinHER trial (Loi et al, 2014). It is not clear why these two studies have discrepant results, but differences in populations (i.e., tumor molecular intrinsic subtype, hormone receptor status, tumor grade) and treatment (i.e., duration of trastuzumab therapy) may contribute to these contradictory findings.

The predictive value of TILs for pCR in breast cancer patients receiving neoadjuvant therapy was evaluated in a pooled analysis for patients with breast cancer who were treated with neoadjuvant combination chemotherapy from six randomized trials done by the German Breast Cancer Group (Denkert et al, 2018). The level of stromal TILs (sTILs) in pretreatment core biopsies was assessed by standardized methodology according to the International TIL working group guidelines (Salgado et al, 2015). In patients with HER2+ breast cancer, pCR was experienced in 194 (32%) of 605 patients with low TILs (0-10%) 198 (39%) of 512 patients with intermediate TILs (11-59%), and 127 (48%) of 262 with high TILs (≥60%) (p<0.0001). A second meta-analysis, that included a total of 5 studies (N = 1256 patients) found that high sTIL at baseline was associated with a

significantly increased pCR rate (OR 2.46; 95% CI 1.36–4.43; P = 0.003) (Solinas et al, 2017).

However, the data regarding the predictive value of baseline tumor sTIL level and pCR in patients with HER2+ breast cancer have been mixed. Neither the NeoSPHERE nor TRYPHAENA study showed an association between baseline TILs and pCR after neoadjuvant chemotherapy alone or in combination with HER2-targeted therapy (Bianchini et al, 2015, Ignatiadis et al, 2018). However, in NeoALTTO, a baseline level of TILs greater than 5% was associated with higher pCR rates independent of treatment group (i.e., paclitaxel plus trastuzumab, lapatinib or both) (adjusted odds ratio, 2.60 [95% CI, 1.26-5.39]; P = .01) (Salgado et al, 2015). The median level of TILs among 350 patients with available samples was 12.5%, with levels lower in hormone receptor-positive (10.0%) vs hormone receptor-negative (12.5%) tumors (P = .02). Angelis et al found that a baseline sTILs level of $\geq$ 60% was marginally associated with higher pCR rate than tumors with < 60% sTILs in HER2+ breast cancer after a chemotherapy-free regimen of trastuzumab and lapatinib (Angelis et al, 2019).

Confirmation of the prognostic and predictive value of baseline TILs in patients with HER2+ breast cancer is now required. In CompassHER2 pCR (EA1181) trial, we plan to validate as a secondary outcome the association of TILs in the baseline tumor with 3-year RFS and with pCR.

1.8.2 Rationale for assessing TILs in residual tumor after THP

Among patients with HER2-positive breast cancer, data evaluating the prognostic significance of TIL levels in residual cancer after neoadjuvant chemotherapy and HER2-directed therapy are scant. Available evidence on TILs in RD after NACT has mainly focused on TNBC.

Data have shown that the level of TILs in residual tumor after neoadjuvant chemotherapy appears to be prognostic for long-term outcomes and may be predictive of outcomes independent of residual cancer burden score (Asano et al, 2017). Asano et al. found that on multivariable analysis TIL level > 10% (vs $\leq$ 10%) in the residual cancer was an independent factor for recurrence after NAC in 36 patients with HER2-positive breast cancer (p = 0.036, hazard ratio = 0.134). Kurozumi et al. found that among 45 patients with HER2+ breast cancer, recurrence-free survival was significantly better for the 20% of patients with residual disease demonstrating high level of TILs (> 40%) than for the 27% of patients with residual disease and low level of TILs (< 10%; p=0.33) (Kurozumi et al, 2019). In addition, Ladoire et al. found that the CD8+/FOXP3+ ratio was strongly associated with better RFS and overall survival in univariate analysis, and remained, together with the AJCC pathological stage, the only parameter independently associated with RFS and overall survival in multivariate analysis. Most interestingly, CD8+/FOXP3+ ratio had a greater predictive value for RFS and overall survival in the HER2-positive cohort than that of pCR (Ladoire et al, 2011).

Some patients on the CompassHER2 pCR trial who do not have a pCR will survive long-term, whereas other patients will relapse. The identification of biomarkers to refine risk stratification among patients with HER2-positive breast cancer who do not have a PCR with neoadjuvant THP is critically needed in order to enable better identification of high-risk patients eligible for additional systemic treatments and of those who can be spared the toxicity of additional therapy. TILs evaluated in residual disease after neoadjuvant chemotherapy have been suggested as a potentially useful and reliable marker for this purpose. For this reason, we propose to evaluate TILs in residual disease for patients in CompassHEr2 pCR who do not have a pCR.

2. Objectives

Rev. Add5 2.1 Independent Primary Objective

2.1.1 To determine if 3-year recurrence-free survival (RFS) is greater than 92% among clinical stages II or IIIa patients (by AJCC cancer staging manual anatomic staging table, 8th edition) with **HER2-positive/ER-positive** breast cancer who achieve pCR (ypT0/is ypN0) after preoperative therapy with 12 weeks of a taxane, trastuzumab (or FDA approved biosimilar) and pertuzumab (THP x 12). Post-operatively, patients will receive standard of care adjuvant locoregional therapy, plus completion of 12 months of HER2-targeted therapy (and standard adjuvant endocrine therapy for patients with estrogen receptor-positive disease).

Rev. Add2

Rev. Add4

Rev. Add5 2.1.2 To determine if 3-year recurrence-free survival (RFS) is greater than 92% among clinical stages II or IIIa patients (by AJCC cancer staging manual anatomic staging table, 8th edition) with **HER2-positive/ER-negative** breast cancer who achieve pCR (ypT0/is ypN0) after preoperative therapy with 12 weeks of a taxane, trastuzumab (or FDA approved biosimilar) and pertuzumab (THP x 12). Post-operatively, patients will receive standard of care adjuvant locoregional therapy, plus completion of 12 months of HER2-targeted therapy (and no adjuvant endocrine therapy for patients with estrogen receptor-negative disease).

2.2 Secondary Objectives

2.2.1 Secondary Clinical Objectives

2.2.1.1 To determine 3-year IDFS (invasive disease-free survival), DDFS (distant disease-free survival), DRFS (distant relapse-free survival), RFI (recurrence-free interval), OS (overall survival) and Breast Cancer-Specific Survival in patients who achieve pCR (and by pretreatment clinical stage).

2.2.1.2 To determine 3-year EFS (event-free survival) in all patients from time of study registration.

2.2.1.3 To evaluate safety and tolerability for all patients during the pre-operative phase and for patients who attain pCR and de-escalate therapy (Arm A) until the completion of post-surgery protocol assigned therapy (i.e., until the end of HP therapy).

2.2.2 Secondary Correlative Objectives

2.2.2.1 To evaluate the association of ER status in the untreated primary tumor with pathologic response and with long-term survival outcomes (including RFS, EFS, IDFS, DDFS, DRFS, RFI, OS, and Breast Cancer-Specific Survival).

2.2.2.2 To evaluate the associations of detection of CTCs in the blood at baseline with pCR.

2.2.2.3 To evaluate the association of detection of CTCs in the blood at baseline, after 3 weeks of THP, after 12 weeks of THP (before surgery), after surgery before any additional therapy, and after completion of HER2-targeted therapy with RFS in patients who achieve pCR or not.

Rev. Add8

2.2.2.4 To determine if breast MRI radiomics signatures reflecting intratumor heterogeneity and microenvironment at baseline are predictive of pCR.

Rev. Add9

2.2.2.5 To evaluate the association between tumor infiltrating lymphocytes (TILs) in the baseline tumor and 3-yr RFS in all patients.

2.2.2.6 To evaluate the associations between TILs in the baseline tumor with pCR in all patients.

2.3 Exploratory Objectives

2.3.1 Exploratory Clinical Objectives

2.3.1.1 To determine 3-year RFS, IDFS (invasive disease-free survival), DDFS (distant disease-free survival), DRFS (distant relapse-free survival), RFI (recurrence-free interval), OS (overall survival) and Breast Cancer-Specific Survival in patients who do **not** achieve pCR (and by pretreatment clinical stage).

2.3.1.2 To determine the pathologic response to THP neoadjuvant therapy, as assessed by Residual Cancer Burden (RCB).

2.3.1.3 To determine the association between residual cancer burden (RCB) and all described STEEP criteria outcomes.

2.3.1.4 To determine the false negative rate (FNR) of limited staging procedures (defined as SLNB plus removal of clipped node) in patients who undergo such procedures with a planned ALND.

2.3.1.5 To determine axillary pCR rates as a function of the burden of disease at presentation as determined on pre-treatment US and the axillary staging technique (SLNB plus ensuring removal of clipped node versus ALND).

2.3.2 Exploratory Correlative Objectives

2.3.2.1 To evaluate the associations between plasma tumor cell-free DNA (cfDNA) tumor-specific mutations (baseline and after therapy) with pathologic response and long-term outcomes (including RFS, EFS, IDFS, DDFS, DRFS, RFI, OS, and Breast Cancer-Specific Survival).

Rev. Add5
Rev. Add7

2.3.2.2 To evaluate the associations between tumor infiltrating lymphocytes (TILs) in the baseline tumor with pathologic response and long-term outcomes (including RFS, EFS, IDFS, DDFS, DRFS, RFI, OS and Breast Cancer-Specific Survival), and in the residual tumor with long-term outcomes.

Rev. Add5

2.3.2.3 To evaluate the associations between immune activation gene signatures in the baseline tumor and pathologic response as well as outcomes (including RFS, EFS, IDFS, DDFS, DRFS, RFI, OS and Breast Cancer-Specific Survival).

Rev. Add5

2.3.2.4 To evaluate the association of intrinsic subtype at baseline with outcomes (pathologic response and survival).

Rev. Add5

2.3.2.5 To determine the frequency of change in intrinsic subtype between pretreatment tumor specimen and residual disease at the time of surgery and to evaluate any association with survival.

2.3.2.6 To evaluate the associations between DNA copy number, DNA mutations, RNA expression and protein expression in the baseline tumor and changes from baseline to post-THP therapy with pathologic response and long-term outcomes (including RFS, EFS, IDFS, DDFS, DRFS, RFI, OS, and Breast Cancer-Specific Survival).

Rev. Add8

2.3.2.7 To determine if functional DCE-MRI markers (e.g., functional tumor volume, signal enhancement ratio) reflecting tumor vascularity at baseline are predictive of treatment outcome (pCR and EFS).

2.3.2.8 To determine if breast MRI radiomics signatures at post-treatment/presurgery are predictive of treatment outcome (pCR and EFS).

2.3.2.9 To investigate the performance of combined modeling incorporating radiomics and other prognostic markers (e.g., ER, PR, intrinsic subtype, tumor infiltrating lymphocytes [TILs] levels) to predict treatment response in women with HER2+ breast cancer.

Rev. Add9

2.3.2.10 To evaluate the association between TILs in the baseline tumor with pCR and 3-yr RFS in patients with HER2-positive/ER-positive breast cancer and in patients with HER2-positive/ER-negative breast cancer, separately.

2.3.2.11 To evaluate the association between TILs in the baseline tumor with 3-yr RFS in patients in Arm A (i.e., patients who have pCR) and those in Arm B (i.e., no pCR), separately.

2.3.2.12 To evaluate the associations between TILs in the residual tumor with 3-yr RFS in patients in Arm B.

2.3.2.13 To evaluate the association between TILs in the baseline tumor with other long-term outcomes (including EFS, IDFS, DDFS, DRFS, RFI, OS and Breast Cancer-Specific Survival) in all patients and separately in patients with HER2-positive/ER-positive disease and in patients with HER2-positive/ER-negative disease. This association will also be evaluated separately for patents in Arm A and Arm B.

2.3.2.14 To evaluate the associations between changes in TILs in the baseline tumor and residual cancer at surgery with long-term outcomes (including RFS, EFS, IDFS, DDFS, DRFS, RFI, OS and Breast Cancer-Specific Survival), for patients in Arm B.

2.3.2.15 To evaluate the associations between TILs in the baseline tumor and RCB score in all patients, and separately in patients with HER2-positive/ER-positive disease and in patients with HER2-positive/ER-negative disease.

3. Selection of Patients

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

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

ECOG-ACRIN Patient No. _____

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

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

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

3.1 Eligibility Criteria

_____ 3.1.1 Patient must be ≥ 18 years of age.

_____ 3.1.2 Patients must have an ECOG performance status of 0 or 1.

_____ 3.1.3 Patient must have histologically confirmed HER2-positive primary invasive breast carcinoma, determined by local testing. **The tumor must have either HER2 IHC result of 3+ or HER2/CEP17 ratio ≥ 2 with ≥ 4.0 HER2 signals per cell by ISH.** Tumors with HER2/CEP17 ISH ratio < 2 are ineligible, even if HER2 copy number is > 6, unless HER2 IHC result is 3+.

Rev. Add3
Rev. Add8

_____ 3.1.4 Patients hormone receptor (ER and PR) status must be known and will be determined by local testing. Patients with either hormone receptor–positive or hormone receptor- negative HER2-positive breast cancer are eligible.

Rev. Add2

_____ 3.1.5 Patients must have AJCC 8th Edition stage II or IIIa according to anatomic staging table at diagnosis.

- Patients without nodal involvement (cN0) are eligible if T size >2.0 cm (T2-3)

NOTE: Cohort for patients with 2-3 cm, ER+ and node negative HER2-positive/ER-positive disease closed on July 27, 2022.

Rev. Add8

- Patients with HER2-positive/ER-negative disease without nodal involvement (cN0) are eligible if T size > 2.0 cm (T2-3)
- Patients with HER2-positive/ER-positive disease without nodal involvement (cN0) are eligible if T size > 3.0 cm
- Patients with nodal involvement (cN1-2) are eligible if T1-3
- Patients with clinical T4 or N3 disease are not eligible

_____ 3.1.6 Patient must be willing and able (i.e., have no contraindication) to receive standard adjuvant therapy, consisting of HER2-directed therapy, radiation (if indicated) and endocrine therapy (if ER+) if achieving pCR at surgery.

Rev. Add2

_____ 3.1.7 Patient with bilateral invasive breast cancers are eligible if both cancers are HER2-positive (as defined in 3.1.3) at least one meets protocol eligibility and neither cancer renders the patient ineligible (i.e., per eligibility 3.1.5).

Rev. Add2 _____ 3.1.8 Patients with multiple ipsilateral invasive tumors are eligible as long as all tumors are HER2-positive, and at least one tumor focus meets eligibility criteria (per eligibility 3.1.5).

Rev. Add3

Multiple lesions that appear part of the same index tumor do not require additional biopsy/HER2 testing.However, even if biopsy is not deemed necessary, consideration must be given to placing a clip in any lesion that is 1 cm or further from the primary tumor to ensure that all tumor is removed at surgery AND that the pathologist can locate all primary sites of tumor to assess pathologic response at surgery.

_____ 3.1.9 Patients must not have impaired decision-making capacity.

_____ 3.1.10 Patient must not have a history of any prior (ipsilateral or contralateral) invasive breast cancer.

One exception: a patient with a history of T1N0 triple negative breast cancer diagnosed more than 10 years earlier, who remains disease free is eligible.

_____ 3.1.11 Patient must not have prior ipsilateral DCIS. Patients with prior LCIS, atypical hyperplasia, other high-risk benign lesions or contralateral DCIS (without evidence of microinvasion) are eligible. Current ipsilateral or contralateral DCIS (diagnosed at the time of the current invasive cancer) is permitted.

Rev. Add4

NOTE: Patients currently receiving endocrine therapy for prior contralateral DCIS are eligible.

Rev. Add2 _____ 3.1.12 Patient must not have Stage IV (metastatic) breast cancer.

Staging Studies (CT Chest/abdomen/pelvis and a bone scan or PET-CT scan) are required for Stage III disease (according to AJCC cancer staging manual anatomic staging table, 8th edition) or those with abnormal baseline LFTs, symptoms (e.g., new bone pain) or abnormal physical exam findings (NCCN guidelines V1.2019).

_____ 3.1.13 Patient must not have T4 and/or N3 disease, including inflammatory breast cancer.

_____ 3.1.14 Patient must not have any prior treatment for the current breast cancer, including surgery, chemotherapy, hormonal therapy, radiation or experimental therapy.

_____ 3.1.15 Patients with a history of other non-breast malignancies are eligible if they have been disease-free for at least 5 years, and are deemed by the investigator to be at low risk for recurrence of that malignancy.

Patients with the following cancers are eligible if diagnosed and treated within the past 5 years: cervical cancer in situ, basal cell or squamous cell carcinoma of the skin, melanoma-in-situ and localized papillary or follicular thyroid cancer who have completed recommended treatment including surgery. Patients with any other cancers within the last 5 years are ineligible.

Rev. Add2 _____ 3.1.16 Patients must have a left ventricular ejection fraction (LVEF) within normal institutional parameters (or ≥ 50%).

_____ 3.1.17 Patients must not have > grade 1 peripheral neuropathy of any etiology.

Rev. Add2
Rev. Add3
Rev. Add7 _____ 3.1.18 Patients must have a bilateral mammogram and a diagnostic breast ultrasound [on the side of the cancer(s)] (with or without breast MRI) performed at screening. An axillary ultrasound on the side of the cancer(s) is also required. Comprehensive breast and axillary imaging must be performed within 60 days of registration (i.e. the patient's mammogram/ breast ultrasound /axillary ultrasound OR their breast MRI). Either mammogram/ultrasound (including imaging of the ipsilateral axilla) or breast MRI must be performed within 60 days of registration.

Rev. Add3 _____ 3.1.19 Baseline imaging of the ipsilateral axilla by ultrasound is mandatory. For subjects with axillary lymph node(s) suspicious on clinical exam or imaging, patient must be willing to have a needle aspiration or core biopsy to determine the presence of metastatic disease in the lymph nodes. A clip must be placed in the involved axillary lymph node. (If there are more than 1 suspicious axillary nodes, only one clipped node is required). Alternatives to a clip that reliably mark the involved node for removal at surgery are acceptable (e.g., carbon tattooing, Savi scout, RFID etc.)

_____ 3.1.20 Patient must not have a concurrent serious medical condition that would preclude completion of study therapy. For example, uncontrolled hypertension (systolic >180 mm Hg and/or diastolic >100 mm Hg) or clinically significant (i.e., active) cardiovascular disease: cerebrovascular accident/stroke or myocardial infarction within 6 months prior to registration, unstable angina, congestive heart failure (CHF) or serious cardiac arrhythmia requiring medication and other concurrent serious diseases that may interfere with planned treatment.

_____ 3.1.21 Patient must not be pregnant or breast-feeding due to the potential harm to an unborn fetus and possible risk for adverse events in

nursing infants with the treatment regimens being used. Patients must also not expect to conceive from the time of registration, while on study treatment, and until at least 7 months after the last dose of study treatment.

Rev. Add8

All patients of childbearing potential must have a blood test or urine study within 14 days prior to registration to rule out pregnancy. If the pregnancy test (e.g., HCG level) is abnormal but is felt to represent a false positive test for pregnancy (e.g., due to treatments being administered for egg harvesting, or because of recent miscarriage), a note by the treating gynecologist explaining why the team is confident the woman is not pregnant is required.

A patient of childbearing potential is anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Patient of childbearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.1.22 Patient of childbearing potential and sexually active patients must use accepted and effective method(s) of contraception or to abstain from sexual intercourse for the duration of their participation in the study and for 7 months after the last dose of study treatment.

_____ 3.1.23 Patient must be willing and able to sign informed consent.

_____ 3.1.24 Patients must have adequate organ and marrow function as defined below (these must be obtained ≤ 28 days prior to protocol registration).

_____ Leukocytes ≥ 3,000/mcL

Leukocytes:_____ Date of Test:_____

_____ Absolute neutrophil count ≥ 1,500/mcL

ANC:_____ Date of Test:_____

_____ Platelets ≥ 100,000/mcL

Platelet:_____ Date of Test:_____

_____ Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)

Bilirubin:_____ Institutional ULN:_____

Date of Test:_____

_____ AST(SGOT)/ALT(SGPT) ≤ 2.5 x institutional ULN

ALT:_____ Institutional ULN:_____

Date of Test:_____

AST:_____ Institutional ULN:_____

Date of Test:_____

_____ Creatinine ≤ 1.5 x institutional ULN

Serum creatinine_____ Date of Test:_____

_____ 3.1.25 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

_____ 3.1.26 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

_____ 3.1.27 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

_____ _____

Physician Signature Date

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

4. Registration Procedures

Rev. Add8

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr).

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol Principal Investigator (PI) on the IRB approval.

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization. Additional

information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

CTSU Registration Procedures

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

Rev. Add8

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an active CTEP status;
- Active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Rev. Add8

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

Rev. Add8

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password
- Click on *Protocols* in the upper left of your screen:
- Enter the protocol number in the search field at the top of the protocol tree; or
- Click on the By Lead Organization folder to expand, then select *ECOG-ACRIN*, and protocol number *EA1181*.
- Click on *Documents, Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration to* download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Submitting Regulatory Documents

Rev. Add8

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

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
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go
- Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

NOTE: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance

with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

Patient Enrollment

Patients must not start protocol treatment prior to registration.

Treatment should start within seven working days after registration.

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

A valid CTEP-IAM account;

To perform enrollments or request lot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;

Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Registration

4.1.1 Protocol Number

4.1.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number

- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.2 Additional Requirements

4.2.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.2.2 Archived tumor tissue specimens from the clinical biopsy are to be submitted for future undefined research studies (per patient consent) as outlined in Section 10.

4.2.3 From patients with no pCR: Tumor tissue specimen is to be submitted from the residual disease on the definitive surgical specimen for future undefined research studies (per patient consent) as outlined in Section 10.

Rev. Add3

4.2.4 Blood specimens are to be submitted for defined laboratory research studies (mandatory) and/or future undefined research studies (per patient consent) as outlined in Section 10.

Rev. Add8

4.2.5 Routine breast MRIs should be submitted for the secondary radiomics objectives, as outlined in Section 12. We expect most participants will undergo a baseline breast MRI for pretreatment assessment, and that many will also undergo post-treatment MRI prior to surgery, depending on institutional standard of care and physician preference.

4.2.6 Eligibility Verification

Patient must meet all of the eligibility requirements listed in Section 3.1.

Rev. Add7

4.2.7 Stratification Factors

4.2.7.1 HER2-positive/ER-positive vs. HER2-positive/ER-negative

4.2.8 Medidata Rave

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Rev. Add8

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management > Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff 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 eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

Rev. Add8

4.2.9 TRIAD 4 Access Requirements

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) (CTEP-IAM) account.
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the

CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.

- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

Rev. Add8

4.2.10 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Forms Status and DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

4.3 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient is registered but does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the EA1181 Forms Completion Guidelines.

5. Treatment Plan

5.1 Pre-treatment tumor evaluation (see Study Calendar in Section 7.1)

Rev. Add2

5.1.1 If a clip was not placed in the breast primary tumor at the time of the diagnostic clinical biopsy, then a clip MUST be placed prior to initiation of pre-operative THP. In the event of multiple HER2-postive breast cancers, a clip MUST be placed in each primary.

5.1.2 Imaging (Tumor staging)

Rev. Add3

5.1.2.1 Breast and axillary imaging

Rev. Add3

All patients are required to have a bilateral mammogram and a diagnostic breast ultrasound [on the side of the cancer(s)] as well as imaging of the ipsilateral axilla (by ultrasound) performed at baseline. Any suspicious breast lesions must be biopsied (See Section 5.1.4 for axillary assessment). Either mammogram/ultrasound (including imaging of the ipsilateral axilla) or breast MRI must be performed within 60 days of registration.

Rev. Add7
Rev. Add2

*Breast MRI is strongly recommended, especially for patients in whom breast conserving therapy is being considered, and must be performed as clinically indicated, although not required.

5.1.2.2 Staging scans

Patients with AJCC 8th Edition Anatomic Stage III disease or with abnormal liver function tests, new symptoms (e.g., new bone pain) or abnormal physical exam findings must have CT scans of chest, abdomen and pelvis plus a bone scan or a PET/CT scan performed at baseline screening to rule out metastatic disease.

Staging scans for all other patients are at the discretion of the treating oncologists.

5.1.3 Surgical Assessment

All patients must be seen and examined by the treating surgeon at baseline and at the Pre-Operative Visit.

Each visit must include a clinical breast and lymph node examination and review of the imaging studies. Eligibility for breast-conserving therapy must also be assessed.

5.1.4 Axillary Assessment Pre-therapy

Rev. Add3

An axillary assessment must be performed as part of screening. Ipsilateral axillary lymph nodes must be assessed as clinically normal or clinically suspicious by physical examination. In all patients, ipsilateral axillary lymph nodes must also be assessed as normal or suspicious independently by dedicated axillary ultrasound. Axillary ultrasound and/or biopsy do not need to be repeated if performed prior to the screening period. **Patients with suspicious nodes**

documented by physical exam OR by imaging must have a biopsy of the nodes (fine needle aspirate or core needle biopsy). If clinical evaluation and biopsy results are discordant, the biopsy may be repeated at the discretion of the Investigator.

Rev. Add2

The number of suspicious nodes identified by ultrasound at baseline must be recorded.

Clip placement in the involved positive node is mandated. (If there are more than 1 suspicious axillary nodes, only one clipped node is required).

Rev. Add2

5.2 Pre-Operative/Neoadjuvant THP [Taxane, Trastuzumab (or FDA approved biosimilar), Pertuzumab)]

Administration Schedule

Doses are based on actual body weight at baseline. Weight must be obtained on Day 1 of each preoperative cycle, however no dose change is required unless the patient's weight change (higher or lower) is ≥10% from baseline weight. (i.e.,

Rev. Add3

equivalent to CTCAE V5 Grade 2).

Treatment must be administered within a ±3 day window (to allow for holidays, vacations and scheduling issues).

The choice of taxane in the THP therapy is up to the treating oncologist (see options outlined below). Three weeks of paclitaxel or nab-paclitaxel will be considered equivalent to one dose of docetaxel.

Each cycle is 3 weeks (21 days)

Every attempt to administer all 12 weeks of THP must be made (i.e., 12 weekly doses of paclitaxel or nab-paclitaxel, or 4 doses of docetaxel). If during the 4 cycles of THP neoadjuvant therapy, a dose of taxane is missed, every attempt must be made to administer that dose within 16 weeks of starting pre-operative therapy. If by week 16 (i.e., 15 weeks after C1D1) 12 weeks of taxane have not been administered, no further chemotherapy must be administered. Therefore, weekly paclitaxel or nab-paclitaxel must not be administered after week 15 (week 15 is permitted). Docetaxel must not be administered after week 13 (week 13 is permitted).

Trastuzumab (or FDA approved biosimilar) and pertuzumab must be administered if taxane is being held. Patients must receive all 4 doses of trastuzumab (or FDA approved biosimilar) and pertuzumab before surgery. Patients must continue to receive trastuzumab (or FDA approved biosimilar) and pertuzumab every 3 weeks without interruption if surgery is delayed.

Trastuzumab-hyaluronidase SC (Herceptin Hylecta®) may be substituted for intravenous trastuzumab following the same schedule. Pertuzumab-trastuzumab-hyaluronidase SC (Phesgo®) may be substituted for both intravenous

Rev. Add3

trastuzumab and intravenous pertuzumab, following the same schedule. See correct dosing information below for trastuzumab-hyaluronidase (Hylecta®) or trastuzumab-pertuzumab-hyaluronidase (Phesgo®).

Patients receiving IV therapy may switch to the subcutaneous product. The switch must take place on Day 1 of the next cycle. Dosing must follow the protocol-specified dosing and regimen for the selected product.

Rev. Add3 A biosimilar may be used in place of the originator, following the same dose and regimen, as long as that biosimilar product carries the same FDA-approved indication.

Surgery must occur before week 19 (i.e., no later than 126 days from C1D1).

Rev. Add7 Ovarian function suppression (e.g., leuprolide) is allowed during pre-operative THP therapy if this is desired for fertility preservation.

5.2.1 Pre-Operative/Neoadjuvant – THP (Taxane, Trastuzumab (or FDA approved biosimilar), Pertuzumab) Therapy

It is expected that most patients will receive option 1 (weekly paclitaxel). However, option 2 (docetaxel every three weeks) is an acceptable alternative if desired or if a patient develops neuropathy
Rev. Add2 from paclitaxel. Option 3 (weekly nab-paclitaxel) is also an acceptable alternative if desired or if patient has a hypersensitivity reaction to paclitaxel or docetaxel.

5.2.1.1 **Option 1:** Paclitaxel, Trastuzumab (or FDA approved biosimilar), Pertuzumab

Paclitaxel: 80mg/m^2 IV days 1, 8, and 15 of each cycle x 4 cycles.

Trastuzumab (or FDA approved biosimilar)**:**

- Initial loading dose of 8 mg/kg IV day 1 cycle 1, then 6 mg/kg IV day 1 cycle 2-4; or,
- Rev. Add3 Initial loading dose of 4 mg/kg IV on cycle 1 day 1, then 2 mg/kg IV weekly thereafter

Pertuzumab: Initial loading dose of 840mg IV on day 1 cycle 1, then 420 mg IV day 1 cycle 2-4.

Repeat cycles every 21 days for a total of 4 cycles.

Rev. Add2 *However, if surgery occurs later than 21 days after the fourth cycle of HP is administered, a 5th (or 6th) cycle of HP (without taxane) must be administered before surgery.*

NOTE:

- The order of infusion for the three medications may be performed per local institutional guidelines.
- Preparation and administration of paclitaxel, including premedications (e.g., dexamethasone), must follow institutional guidelines.
- Anti-emetics typically should not be administered prophylactically before initial treatment with study drug, though this may be modified based on the treating oncologist's discretion for a given patient.
- Rev. Add3 If substituting trastuzumab-hyaluronidase SC for IV trastuzumab, administer a fixed dose of 600mg/10,000units/5mL SC over 2-5 minutes on Day 1 of each cycle, following the US Package Insert for Herceptin Hylecta®.

- If substituting pertuzumab-trastuzumab-hyaluronidase SC for both IV pertuzumab and IV trastuzumab, administer a fixed loading dose of 1200mg/600mg/30,000units/15mL SC over 8 minutes on Day 1 of Cycle 1, followed by a fixed maintenance dose of 600mg/600mg/20,000units/10mL SC over 5 minutes on Day 1 of Cycles 2-4, following the US Package Insert for Phesgo®.

If a patient switches from docetaxel to weekly paclitaxel, one three-week dose of docetaxel is considered equivalent to three weekly doses of paclitaxel for the purposes of this protocol.

5.2.1.2 **Option 2:** Docetaxel, Trastuzumab (or FDA approved biosimilar), Pertuzumab (and prophylactic growth factor). At the discretion of the treating oncologist, docetaxel may replace paclitaxel (see Section 5.2.1). Oral steroids to prevent hypersensitivity and fluid retention reactions as well as other supportive care must be administered per package insert and institutional standards.

Rev. Add2

Prophylactic growth factor support is required for patients receiving docetaxel to maximize the likelihood of receiving docetaxel every 21 days, and to avoid febrile neutropenia. The recommended dose for prophylactic growth factor, Neulasta (pegfilgrastim; Granulocyte Colony-Stimulating Factor (G-Csf)) is 6 mg/0.6 mL. This may be given either subcutaneously or Onpro (On Body Injector). Neulasta biosimilar may be given.

Rev. Add4

Docetaxel: 75mg/m^2 IV-day 1 Cycle 1-4.

Trastuzumab (or FDA approved biosimilar)**:**

- Initial loading dose of 8 mg/kg IV day 1 cycle 1, then 6 mg/kg IV day 1 cycle 2-4; or,

Rev. Add3

- Initial loading dose of 4 mg/kg IV Cycle 1 Day 1, then 2 mg/kg IV weekly x 4 cycles

Pertuzumab: Initial loading dose of 840mg IV day 1 cycle 1, then 420 mg IV day 1 cycle 2-4.

Repeat cycles every 21 days for a total of 4 cycles.

However, if surgery occurs later than 21 days after the fourth cycle of HP is administered, a 5th (or 6th) cycle HP (without taxane) must be administered before surgery.

NOTE:

- The order of infusion for the three medications may be performed per local institutional guidelines.
- Preparation and administration of docetaxel including premedications (e.g., dexamethasone), must follow institutional guidelines.

Rev. Add3

- If substituting trastuzumab-hyaluronidase SC for IV trastuzumab, administer a fixed dose of 600mg/10,000units/5mL SC over 2-5 minutes on Day 1 of each cycle, following the US Package Insert for Herceptin Hylecta®.
- If substituting pertuzumab-trastuzumab-hyaluronidase SC for both IV pertuzumab and IV trastuzumab, administer a fixed loading dose of 1200mg/600mg/30,000units/15mL SC over 8 minutes on Day 1 of Cycle 1, followed by a fixed maintenance dose of 600mg/600mg/20,000units/10mL SC over 5 minutes on Day 1 of Cycles 2-4, following the US Package Insert for Phesgo®.

If a patient switches from paclitaxel to docetaxel, one three-week dose of docetaxel is considered equivalent to three weekly doses of paclitaxel for the purposes of this protocol.

5.2.1.3 **Option 3:** Nab-Paclitaxel, Trastuzumab (or FDA approved biosimilar), Pertuzumab

Rev. Add2

If a patient experiences hypersensitivity to paclitaxel or docetaxel or needs to avoid steroid premedications or clinician prefers nab-pacitaxel, Abraxane (nab-paclitaxel) can be substituted for paclitaxel or docetaxel.

Nab-Paclitaxel: 125 mg/m^2 IV on days 1, 8, and 15 of each cycle x 4 cycles.

Trastuzumab (or FDA approved biosimilar)**:**

- Initial loading dose of 8 mg/kg IV day 1 cycle 1, then 6 mg/kg IV day 1 cycle 2-4; or,
- Initial loading dose of 4 mg/kg IV day 1, then 2 mg/kg IV days 8 and 15 of each cycle x 4 cycles

Pertuzumab: Initial loading dose of 840mg IV day 1 cycle 1, then 420 mg IV day 1 cycle 2-4.

Repeat cycles every 21 days for a total of 4 cycles.

However, if surgery occurs later than 21 days after the fourth cycle of HP is administered, a 5th (*or 6th*) cycle of HP (without taxane) must be administered before surgery

NOTE:

- The order of infusion for the three medications may be performed per local institution guidelines.
- Preparation and administration of nab-paclitaxel including premedications must follow institutional guidelines.

Rev. Add3

- If substituting trastuzumab-hyaluronidase SC for IV trastuzumab, administer a fixed dose of 600mg/10,000units/5mL SC over 2-5 minutes on Day 1

of each cycle, following the US Package Insert for Herceptin Hylecta®.

- If substituting pertuzumab-trastuzumab-hyaluronidase SC for both IV pertuzumab and IV trastuzumab, administer a fixed loading dose of 1200mg/600mg/30,000units/15mL SC over 8 minutes on Day 1 of Cycle 1, followed by a fixed maintenance dose of 600mg/600mg/20,000units/10mL SC over 5 minutes on Day 1 of Cycles 2-4, following the US Package Insert for Phesgo®.

5.2.1.4 Additional Pre-Surgical Systemic Therapy (for patients who progress during THP)

In patients with evidence of disease progression during neoadjuvant THP, additional pre-surgical therapy should be given at the discretion of the treating oncologist. The selected treatment regimen will be at the discretion of the treating oncologist, however the recommended regimen is four cycles of doxorubicin and cyclophosphamide. A biopsy performed at the time of treatment change, prior to initiation of new anti-cancer therapy, is strongly recommended to confirm residual cancer, but is not required.

Patients who receive additional pre-surgery therapy will be considered as not achieving pCR to THP, will be considered as receiving off study treatment and these patients will continue to be followed per protocol (Arm B).

The treating oncologist must indicate the reason for administering additional pre-operative chemotherapy, or any other non-protocol assigned systemic therapy in the medical record.

Rev. Add7

5.3 Post-neoadjuvant treatment tumor evaluation prior to surgery

Rev. Add3

5.3.1 Breast and Axillary Imaging

All patients are required to have breast imaging prior to surgery. Imaging may be performed from up to one week before Cycle 4 day 1 to a maximum of up to 4 weeks after the last dose of any neoadjuvant therapy. The same imaging modality that was used at baseline is encouraged prior to surgery to assess tumor response. If a pre-treatment MRI was obtained, it is encouraged to obtain a post-treatment MRI as well, especially in cases where breast conservation is being considered.

Axillary imaging with ultrasound or MRI is required as part of pre-surgery evaluation for all patients who initially had biopsy proven nodal involvement or had suspicious axillary nodes that prompted axillary sampling.

5.3.2 Physical Exam Evidence of Residual Disease

If residual tumor is suspected after neoadjuvant THP, confirmation of this disease by FNA or core is encouraged. If tumor is confirmed, it is up to the treating oncologist to decide whether additional chemotherapy is given prior to surgery or whether to proceed to surgery at that time. The choice of chemotherapy is at the discretion of the treating oncologist. The treating oncologist must indicate in the medical report why the patient is receiving additional chemotherapy prior to surgery.

Any patient who receives additional chemotherapy prior to surgery will NOT be considered as attaining pCR (regardless of results at surgery); patients who receive additional (non-protocol assigned) pre-operative chemotherapy will be analyzed in Arm B (no pCR). It is recommended but not mandated that a biopsy confirm suspected residual disease before additional preoperative (non-protocol-assigned) chemotherapy is administered. Patients with documented residual disease will be analyzed in Arm B.

5.4 Surgery

Rev. Add2

5.4.1 Definitive Breast Surgery

Lumpectomy and/or mastectomy must be performed no later than 126 days (i.e., 18 weeks) from administration of the first dose of neoadjuvant taxane therapy. Exception to this requirement are patients with proven residual disease who receive additional chemotherapy prior to surgery; such patients will be analyzed with Arm B regardless of pathologic response at surgery. The treating oncologist must indicate in the medical report why the patient is receiving more chemotherapy.

5.4.2 Axillary Surgery

General Standards

For patients with a clip in their biopsy-proven metastatic lymph node, efforts must be made to ensure the clipped node has been removed, by either SLNB if performed (the clipped node and additional SLN(s) must be removed), and/or ALND. Methods to ensure clipped node removal can include pre-operative localization, or specimen radiograph after node removal. Examples of acceptable pre-operative localization techniques include but are not limited to needle/wire, radioactive seed, carbon tattooing, RFA chip, magnetic seed, SAVI scout. Any technique to localize the biopsied node after neoadjuvant chemotherapy is acceptable.

Rev. Add7
Rev. Add8

For patients undergoing SLNB, an ALND must be performed in the following situations:

Rev. Add2

- **Any patient: if sentinel node mapping fails**
- **A patient with biopsy proven nodal involvement at baseline: if either a previously placed clipped node is not removed or fewer than 2 SLN are identified at SLNB.**

If ALND is not performed within 12 weeks of the initial surgery, the patient cannot be considered to have pCR and will NOT be included in Arm A; patients who do not have an ALND will be analyzed in Arm B.

Performance of lympho-venous procedures, such as axillary reverse mapping, are up to the discretion of the surgeon.

Rev. Add3

If the SLN(s) are positive on intraoperative frozen section evaluation or on final pathologic evaluation by hematoxylin & eosin (H&E) staining then a completion ALND should be performed.

For patients with ITCs identified by H&E or IHC staining after SLNB (ypN0i+), the treating surgeon will decide whether to perform a completion axillary dissection. These patients will be considered as NOT having obtained pCR and must be treated per Arm B of the protocol (no pCR).

5.4.2.1 **Patients with cN0 at baseline**

For patients with clinically node negative disease at baseline, SLNB or ALND must be performed after neoadjuvant systemic therapy. Mapping technique (i.e., single versus dual tracer) will be at the discretion of the treating surgeon.

5.4.2.2 **Patients with cN1 at baseline**

For patients with clinically node positive disease [cN1, mobile axillary node(s)] **and < 4 suspicious axillary nodes on pre-treatment axillary ultrasound** who become clinically node negative by physical examination following completion of their neoadjuvant systemic therapy, SLNB or ALND must be performed after preoperative therapy. If SLNB is performed, dual tracer with both radioisotope and blue dye must be employed.

For patients with clinically node positive (cN1) disease and ≥4 suspicious lymph nodes on pre-treatment ultrasound, an **ALND* is strongly encouraged** regardless of the response to THP but is not mandated.

5.4.2.3 **Patients with cN2 at baseline (matted/fixed nodes)**

For patients with cN2 disease, an ALND* must be performed after preoperative therapy.

5.4.2.4 **Patients with clinically involved nodes after THP neoadjuvant therapy**

If residual tumor is suspected in the axillary nodes after THP, confirmation of this disease by FNA or core is encouraged. In this situation, it is up to the treating oncologists to decide whether additional chemotherapy is given prior to surgery or whether to proceed to surgery at that time. These patients will be considered as NOT having obtained pCR and must be treated per Arm B of the

protocol (no pCR). For patients with residual axillary disease after THP, an ALND should be performed.

Patients with documented residual disease will be considered non-pCR. Patients with documented residual disease will be analyzed in Arm B.

*For patients undergoing planned ALND for ≥4 lymph nodes on pre-treatment ultrasound or cN2 disease, it is encouraged to perform a SLNB and removal of the clipped node as a separate specimen prior to performance of ALND, to address a study objective to determine the false negative rate of SLNB/clipped node retrieval in these patients.

Rev. Add2

5.4.2.5 Pathology Assessment and Reporting of Resected Specimen. Pathology worksheet to collect the factors that allow subsequent determination of RCB score must be provided to the pathologist evaluating the definitive breast surgery specimen for patients with residual disease. The pathology worksheet can be found on the CTSU website.

Primary Tumor

It is highly recommended that the pathology report of the primary tumor in the breast include identification of the original tumor through either notation of treatment response in the tumor bed or identification of the biopsy clip.

If more than one invasive cancer was identified before neoadjuvant therapy, then pathologic response must be reported for each invasive lesion.

If contralateral mastectomy is performed concurrently, the pathology report from the contralateral breast must be reported if invasive disease or in-situ breast cancer is identified.

If residual cancer is found in the primary tumor bed the pathology report must include the following information:

1) Primary Tumor Bed Area (2 dimensions)

2) Overall Cancer Cellularity (as percentage of area)

3) Percentage of Cancer That Is in situ Disease

Axillary Lymph Nodes

Immunohistochemical (IHC) staining by treating institution is not mandated for evaluation of sentinel nodes found to be negative by H&E. If the histopathologic evaluation of the H&E section is indeterminate, then IHC for cytokeratins of a section from each of the lymph node slices is strongly encouraged.

Pathologic reporting of axillary nodes must include the following information:

1) Number of Lymph nodes involved with cancer
2) Diameter of largest metastasis in the node

Pathologic reporting of sentinel lymph node samples must include the following additional information (mandated):

1) Number of sentinel nodes examined
2) Number of positive sentinel lymph nodes
3) If the sentinel nodes were negative, whether immunohistochemistry for cytokeratins was performed and interpreted

5.5 Post-Operative/Adjuvant Therapy – Arms A (pCR) and B (Residual Invasive Disease)

5.5.1 **Arm A:** pCR (no invasive disease in breast or nodes; ypT0/Tis ypN0)

5.5.1.1 Systemic Therapy

One cycle is 3 weeks (21 days)

Rev. Add4 Rev. Add5 Rev. Add7

Post-Operative Cycle 1 of HP should preferably begin 21 days after the last pre-operative HP cycle. Physicians may continue HP awaiting final pathology to determine if patient will be on Arm A or Arm B, but may also wait until pathology report is finalized. For patients on Arm A (pCR), HP should be initiated **as soon as possible** after surgery (and not later than 4-5 weeks after surgery). If a patient has a pCR (Arm A), and > 4 week time period has elapsed between the pre and post-surgery dose, a loading dose should be given for trastuzumab. If a patient has a pCR (Arm A), and > 6 weeks have elapsed between the pre and post-surgery dose, a loading dose should be given for pertuzumab.

Rev. Add3

Trastuzumab (or FDA approved biosimilar) 6mg/kg IV on day 1 of each cycle for 13 cycles* **

Pertuzumab 420 mg IV on day 1 of each cycle for 13 cycles* **

Radiation Therapy and Endocrine Therapy if appropriate

Rev. Add4

Patients with hormone receptor-positive disease must be prescribed endocrine therapy with the goal of at least 5 years of therapy. For patients with tumors that are ER low-positive (1-9% as defined by ASCO/CAP) endocrine therapy should be prescribed.

Timing of endocrine therapy initiation: endocrine therapy may be prescribed concurrently with radiation or after completion of radiation. Endocrine therapy should be started no later than 2 months after radiation therapy is completed. For patients not receiving radiation, endocrine

therapy should be started no later than 2 months after breast surgery (excision or mastectomy).

*Most patients will have received 4 doses pre-operatively and will receive 13 doses post-operatively. However, if more than 4 doses were administered before definitive breast surgery, then a total of 17 (pre-and post-surgery doses) will be administered (e.g., 5 doses pre-operatively and 12 doses post-operatively).

Rev. Add3

NOTE:

- If substituting trastuzumab-hyaluronidase SC for IV trastuzumab, administer a fixed dose of 600mg/10,000units/5mL SC over 2-5 minutes on Day 1 of each cycle, following the US Package Insert for Herceptin Hylecta®.
- If substituting pertuzumab-trastuzumab-hyaluronidase SC for both IV pertuzumab and IV trastuzumab, administer a fixed maintenance dose of 600mg/600mg/20,000units/10mL SC over 5 minutes on Day 1 of each cycle, following the US Package Insert for Phesgo®.

5.5.1.2 Radiation Therapy

Patients who undergo lumpectomy (breast conserving surgery) must receive breast radiation therapy; the addition of a boost is up to the treating oncologist. For breast conservation and post-mastectomy radiation therapy (PMRT), the decision for hypofractionation versus conventional radiation therapy will be up to the treating oncologist.

Patients in Arm A (pCR) must receive adjuvant trastuzumab (or FDA approved biosimilar) and pertuzumab as per protocol during radiotherapy.

For patients in Arm A (pCR) radiotherapy must be initiated within 9 weeks of surgery.

Rev. Add8

For patients who are clinically node negative prior to systemic therapy and remain node negative, regional nodal irradiation (RNI)/PMRT should not be administered. (For patients with residual cancer in breast, including those with initial T3N0 disease, decisions about radiation will be left to the treating team). Patients who are clinically node negative prior to systemic therapy but pathologically node positive after chemotherapy must receive RNI/PMRT.

For patients with biopsy-proven axillary node involvement before chemotherapy who have negative axillary nodes after chemotherapy, the treating oncologist will decide whether to give RNI in addition to breast irradiation or to use PMRT or not. Patients may

enroll in the NRG 9353 (NSABP B-51/RTOG 1304) trial if available.

Patients with biopsy-proven axillary node involvement before chemotherapy who have positive axillary nodes after chemotherapy must receive RNI/PMRT.

5.5.1.3 Endocrine Therapy

Adjuvant endocrine therapy must be given according to established guidelines (NCCN guidelines V5.2020 for invasive breast cancer). All patients with ER-positive breast cancer (ER >10%) who attain pCR **must** be prescribed endocrine therapy with the goal of at least 5 years of therapy. For patients with tumors that are ER low-positive (1-9% as defined by ASCO/CAP) endocrine therapy should be prescribed.

Rev. Add4

Timing of endocrine therapy initiation: endocrine therapy may be prescribed concurrently with radiation or after completion of radiation. Endocrine therapy should be started no later than 2 months after radiation therapy is completed. For patients not receiving radiation, endocrine therapy should be started no later than 2 months after breast surgery (excision or mastectomy).

5.5.1.4 Bone Modifying Agents

Receipt of adjuvant bone modifying agents (e.g., bisphosphonates, denosumab) is allowed and will not be considered in the assessment of escalated or de-escalated adjuvant therapy.

5.5.2 **Arm B:** Standard of Care for patients who do NOT achieve pCR with THP

For patients who do not achieve pCR (i.e., invasive disease is found in breast or nodes at surgery), decisions about additional chemotherapy and HER2-targeted therapy will be made by the treating oncologist. This includes patients with ITCs isolated tumor cells (ITCs) found in axillary nodes by H&E or IHC (ypN0i+).

All patients are recommended to receive therapy with trastuzumab emtansine (T-DM1) for 14 doses in the post-operative setting. Patients may also receive additional adjuvant chemotherapy. Decisions about systemic therapy will be at the investigator's discretion. For patients with hormone receptor-positive disease, any regimen of adjuvant hormonal therapy may be given at the investigator's discretion.

5.6 Adverse Event Reporting Requirements

All toxicity grades described in this protocol and all reportable adverse events on this protocol will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

5.6.1 Purpose

Adverse event (AE) data collection and reporting, which are a required part of every clinical trial, are done so investigators and regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

5.6.2 **Routine reporting:** Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave clinical data management system. Please refer to Section 4 of the protocol for more information on how to access the Medidata Rave system and the EA1181 forms packet for instructions on where and when adverse events are to be reported routinely.

5.6.3 **Expedited reporting:** In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The remainder of this section provide information and instructions regarding expedited adverse event reporting.

5.6.4 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of an agent in humans, whether or not considered agent related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to treatment.
Unlikely	The AE is *doubtfully related* to treatment.
Possible	The AE *may be related* to treatment.
Probable	The AE is *likely related* to treatment.
Definite	The AE is *clearly related* to treatment.

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.

- **Expectedness:** Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol or drug package insert.

5.6.5 Expedited Adverse Event Reporting Procedure

Adverse events requiring expedited reporting will use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov.

For this study, A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov, so that ECOG-ACRIN, the NCI, and all appropriate regulatory agencies will be notified of the event in an expeditious manner.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2900)
- the FDA (1-800-FDA-1088)

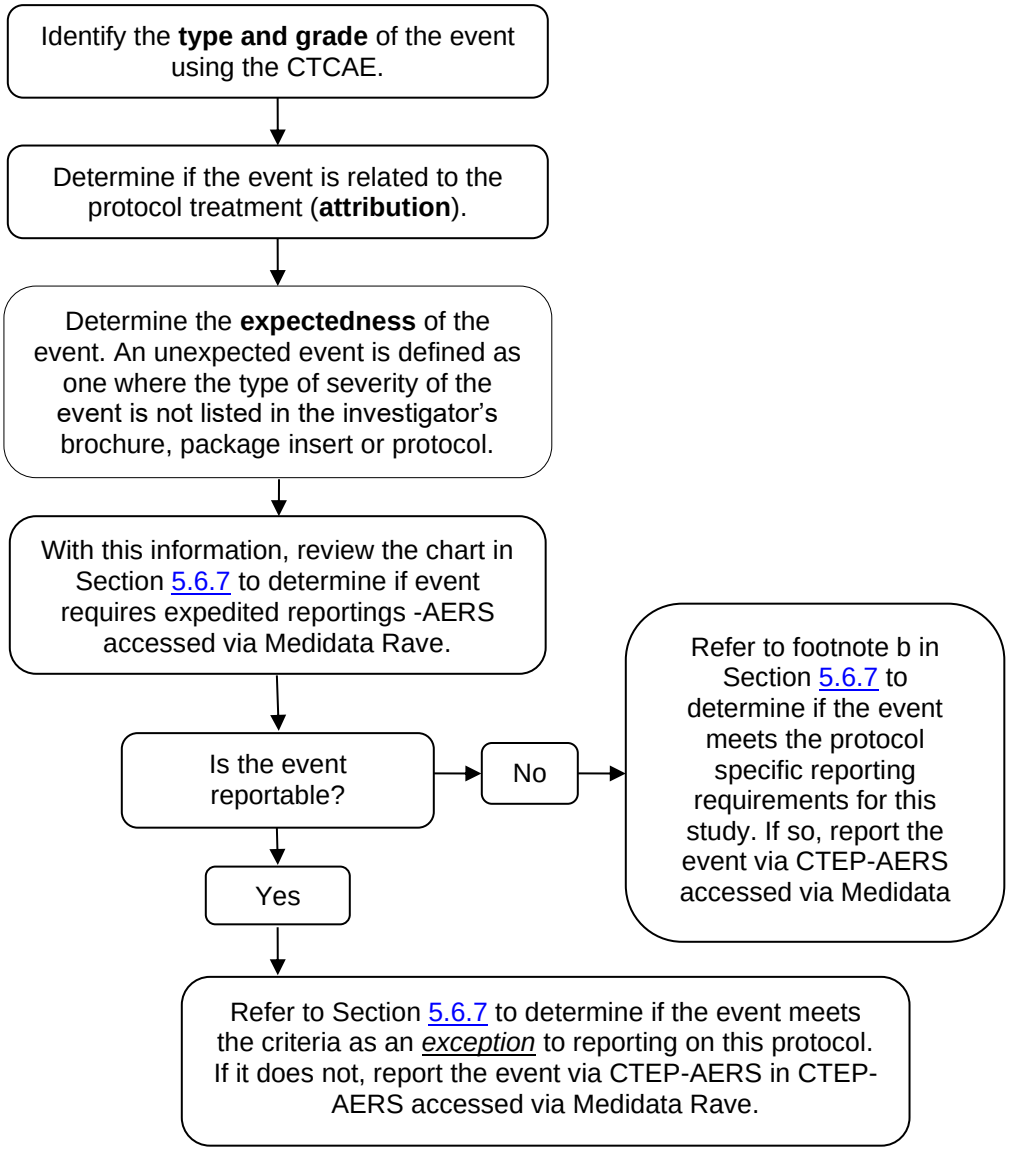
For this study, an electronic report MUST be submitted via CTEP-AERS immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) in the same timeframe.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.6.6 Many factors determine the requirements for expedited reporting of adverse events on each individual protocol. The instructions and tables in the following sections have been customized for protocol EA1181 and outline the specific expedited adverse event reporting requirements for study EA1181.

5.6.7 Steps to determine if an event is to be reported in an expedited manner



5.6.8 Expedited Reporting Requirements for all patients during pre-operative THP and for patients on Arm A (pCR) during protocol-defined therapy on protocol EA1181

Commercial Agents: Paclitaxel, Trastuzumab (or FDA approved biosimilar), Pertuzumab, Docetaxel, Trastuzumab-Hyaluronidase SC, Pertuzumab-Trastuzumab-Hyaluronidase SC

Rev. Add3

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only

Attribution	**Grade 4**		**Grade 5[a]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	See footnote (b) for special requirements.
Unrelated or Unlikely			7 calendar days	7 calendar days	
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

5.6.9 Other recipients of adverse event reports and supplemental data

Adverse events determined to require expedited reporting must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.6.10 Second Primary Cancer Reporting Requirements

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

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this**

protocol). Second malignancies require ONLY routine reporting as follows:

1. Complete a Second Primary Form in Medidata Rave within 14 days.
2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.

- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

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

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

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

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

Rev. Add6

5.7 Comprehensive Adverse Events and Potential Risks List (CAEPR)

5.7.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Trastuzumab (Herceptin, NSC 688097) and Trastuzumab-Hyaluronidase (Herceptin Hylecta, NSC 827797)

Rev. Add3

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		

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**
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)***
	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)***

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**
	Bone pain		***Bone pain (Gr 2)***
	Muscle cramp		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Tumor Pain		***Tumor pain (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		
	Headache		***Headache (Gr 2)***
	Peripheral sensory neuropathy		
PSYCHIATRIC DISORDERS			
	Depression		
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Adult respiratory distress syndrome[3,5]	
	Allergic rhinitis		***Allergic rhinitis (Gr 2)***
		Bronchospasm	
	Cough		***Cough (Gr 2)***
	Dyspnea[3,5]		***Dyspnea (Gr 3)***
	Hypoxia[5]		***Hypoxia (Gr 2)***
		Pneumonitis[5]	
		Pulmonary edema[5]	
		Pulmonary fibrosis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Nail changes		
	Nail loss		
	Rash acneiform		***Rash acneiform (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria[3]		***Urticaria[3] (Gr 2)***
VASCULAR DISORDERS			
	Hot flashes		
	Hypertension[3]		
	Hypotension[3]		
	Lymphedema		
	Vascular disorders - Other (vasodilation)		

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

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

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

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

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

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

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

Adverse events reported on trastuzumab (Herceptin) and/or Herceptin HylectaTM (SQ trastuzumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that trastuzumab (Herceptin) and/or Herceptin HylectaTM (SQ trastuzumab) caused the adverse event:

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

EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo

EYE DISORDERS - Dry eye; Extraocular muscle paresis

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

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

HEPATOBILIARY DISORDERs - Cholecystitis

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

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

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

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

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

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

PSYCHIATRIC DISORDERS - Anxiety; Confusion

RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Amenorrhea

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

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

VASCULAR DISORDERS - Hematoma; Thromboembolic event

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

5.7.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pertuzumab (NSC 740102); or for Pertuzumab-Trastuzumab-Hyaluronidase (Phesgo, NSC 827796) in addition to those listed above for Trastuzumab

Rev. Add3

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 neutropenia		***Febrile neutropenia (Gr 2)***
CARDIAC DISORDERS			
		Heart failure	
EYE DISORDERS			
	Watering eyes		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (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%)**	
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)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		

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%)**	
	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 popular, rash maculo-papular.

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Leukocytosis

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

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

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

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

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

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

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

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

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

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

PSYCHIATRIC DISORDERS - Anxiety; Depression

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

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

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

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

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

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

Rev. Add2

5.8 Dose Modifications

Clinicians may modify doses and delay therapy as deemed necessary due to toxicity, and must do everything possible to resume treatment as early and safely as possible.

If dose reduction is required, it is recommended that reduction is permanent and that doses must not be re-escalated.

For delayed or missed doses of trastuzumab (or FDA approved biosimilar), if a dose is missed by >1 week, then a re-loading dose (4 mg/kg if patient receives trastuzumab weekly; 8 mg/kg if on an every-3-week schedule) must be administered as soon as possible, followed by the usual maintenance dose administered 7 or 21 days later (based on patient's maintenance dose/schedule).

Rev. Add8

For pertuzumab, if the time between 2 sequential infusions is > 6 weeks, the initial loading dose must be re-administered followed every 3 weeks thereafter by standard dose. If pertuzumab must be held or discontinued due to toxicity, trastuzumab (or FDA approved biosimilar) must be administered on schedule without delay.

Rev. Add5
Rev. Add7

NOTE: If a patient has a pCR (Arm A), and > 4 week time period has elapsed between the pre and post-surgery dose, a loading dose should be given for trastuzumab. For a patient on Arm A, if > 6 weeks has elapsed between the pre- and post-surgery dose, a loading dose should be given for pertuzumab.

5.8.1 Dose Modification for Obese Patients

Dose calculations will be based on actual body weight.

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. All dosing is to be determined solely by the patient's BSA as calculated from actual weight.

Rev. Add2

5.8.2 Paclitaxel (Guidance for Dose Modifications)

If paclitaxel dose is held, trastuzumab (or FDA approved biosimilar) and pertuzumab must still be administered on schedule.

Event	Weekly Paclitaxel Dose Modification
Neutropenia	
≥ 1000/mm^3	No change
< 1000 mm^3	Hold paclitaxel until ANC ≥1000, resume based on timing of recovery (continue trastuzumab and pertuzumab): ≤ 1 week – no change >1 but ≤ 3 weeks - reduce dose 20% for subsequent cycles > 3 weeks – stop paclitaxel
Neutropenic Fever	
ANC < 1000 mm^3, fever ≥ 38.5	Interrupt paclitaxel until resolved (ANC >1000, fever <38.5) but continue trastuzumab and

Event	Weekly Paclitaxel Dose Modification
	pertuzumab, resume according to number of episodes: 1st = no change 2nd = 20% dose reduction 3rd = stop paclitaxel
Thrombocytopenia	
≥ 100,000/mm^3	No change
75-99,999/mm^3	Hold paclitaxel until ≥ 100,000 but continue trastuzumab and pertuzumab; resume based on timing of recovery: ≤ 1 week – no change >1 but ≤ 3 weeks - reduce dose 20% for subsequent cycles > 3 weeks – stop paclitaxel
<75,000	Hold paclitaxel until ≥ 100,000 but continue trastuzumab and pertuzumab. Resume with 20% dose reduction for subsequent cycles. If > 3 weeks delay is required, stop paclitaxel
Anemia	
All grades	No change – management is at the investigator's discretion. Transfusions are preferred to dose delays or dose reductions.
Hepatic Dysfunction	
Transaminases < 10 times ULN and bilirubin level ≤ 1.25 times ULN	• No dose modifications
Transaminases < 10 times ULN and bilirubin level 1.26 to 2 times ULN	• Reduce paclitaxel to 60 mg/m^2
Transaminases <10 times ULN and bilirubin level 2.01 to 5 times ULN	• Reduce paclitaxel to 40 mg/m^2
Transaminases ≥10 times ULN or bilirubin level >5 times ULN	• Patient must be permanently discontinued from paclitaxel therapy.
Nausea or Vomiting	
Grade 1 or 2	• No dose modifications
≥ Grade 3	• Hold paclitaxel until resolved to ≤ Grade 1, then restart with 20% dose reduction in subsequent cycles. (If paclitaxel is held, continue trastuzumab and pertuzumab).

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Event	Weekly Paclitaxel Dose Modification
Mucositis (any type)	
Grade 0-2	• No change
Grade 3 or 4	Hold paclitaxel until resolved to ≤ Grade 1, reduce dose 20% in subsequent cycles. (Continue trastuzumab and pertuzumab).
Diarrhea	
Grade 2	• If grade 2 diarrhea is present on the day of any treatment, paclitaxel must be delayed until the diarrhea has resolved to grade 1 or 0, and then resume paclitaxel at 80 mg/m^2. Treat prophylactically in subsequent cycles with loperamide or diphenoxylate. (Continue trastuzumab and pertuzumab). • If diarrhea causes a delay of >21 days, the patient must be permanently discontinued from paclitaxel therapy. • If patient experiences ≥ grade 2 despite prophylaxis, causing a delay in paclitaxel administration, then paclitaxel must be dose reduced by 20%. • If clinically significant diarrhea continues despite prophylaxis AND dose reduction, stop paclitaxel.
Grade 3 or 4	• If grade 3 or 4 diarrhea occurs, delay paclitaxel until the diarrhea has resolved to grade 1 or 0, then the dose of paclitaxel must be reduced by 20%. Continue trastuzumab and pertuzumab on schedule. • If diarrhea causes a delay of >21 days, the patient must be permanently discontinued from paclitaxel therapy. • Once the paclitaxel dose has been decreased, it must not be re-escalated. • Optimal use of anti-diarrheal agents is encouraged.
Neurologic Toxicity: Neuropathy (motor and sensory) **Encourage limb cooling for all patients either as prevention or treatment of neuropathy in conjunction with any dose modifications required.**	
Grade 0-2	• No change • If patient or physician is uncomfortable treating with grade 2 neuropathy, paclitaxel may be dose reduced by 20% but this is not required.
Grade 3	• Hold paclitaxel until resolved to ≤ Grade 2, reduce paclitaxel dose 20% in all subsequent cycles. If > 3 weeks delay is required, stop paclitaxel. • Consider switch to docetaxel

Event	Weekly Paclitaxel Dose Modification
	If paclitaxel is held, trastuzumab and pertuzumab must be continued on schedule.
Grade 4	• Discontinue paclitaxel.

Hypersensitivity or Anaphylaxis **Institutions may manage hypersensitivity reactions per institutional practice. Below is one recommended schema.**	
Grade 1 Mild Symptoms: mild flushing, rash, pruritis	• No treatment needed. • Complete infusion and observe in treatment area.
Grade 2 Moderate Symptoms: moderate flushing, rash, mild dyspnea, chest discomfort	• Stop paclitaxel. • Administer diphenhydramine 25 mg and dexamethasone 10 mg IV. Methylprednisolone (60mg IV) may be used instead of dexamethasone. • After recovery, resume infusion at a slower rate 10 ml/hour for 15 minutes, then 25 ml/hour for 15 minutes, then, if no further symptoms, at full dose rate until infusion is complete. • If moderate or severe symptoms recur after re-challenge, stop paclitaxel infusion. • Patient may be rechallenged after premedication with dexamethasone 8 mg po or IV q6hrs x 4 doses (moderate symptoms) or 20 mg po or IV q6hrs x 4 doses (severe symptoms) and diphenhydramine 25 mg po or IV q6hrs x 4 doses (moderate or severe symptoms).Methylprednisolone (60mg IV) may be used instead of dexamethasone. • The paclitaxel must be administered at a slower rate. 10 ml/hour for 15 minutes, then 25 ml/hour for 15 minutes, then, if no further symptoms, at full dose rate until infusion is complete.
Grade 3 Severe/life threatening Symptoms: hypotension requiring pressors, angioedema, respiratory distress requiring bronchodilators, generalized urticaria	• Stop paclitaxel. • Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Methylprednisolone (60mg IV) may be used instead of dexamethasone. • Add epinephrine or bronchodilators if indicated. • Patient may be rechallenged after premedication with dexamethasone 20 mg po or IV q6hrs x 4 doses and diphenhydramine 25 mg po or IV q6hrs x4 doses. Methylprednisolone (60mg IV) may be used instead of dexamethasone.

	• The paclitaxel must be administered at a slower rate, 10 ml/hour for 15 minutes, then 25 ml/hr for 15 minutes, then, if no further symptoms, at full dose rate until infusion is complete.
Cardiac Arrhythmias	
Asymptomatic, EKG-documented arrhythmias	• Stop paclitaxel and manage arrhythmia according to standard practice.
Asymptomatic sinus bradycardia or tachycardia	• No intervention necessary.
Sinus bradycardia or tachycardia associated with hypersensitivity reaction	• Please see hypersensitivity guidance above.
Other clinically significant toxicities excluding fatigue, alopecia and leukopenia	
Grade 0 or 1	• No dose modifications
Grade 2	• Hold until resolved to ≤ Grade 1, resume at previous dose. Increase supportive care measures if possible.
≥ Grade 3	• Hold until resolved to ≤ Grade 1, resume with 20% dose reduction for subsequent cycles. If Grade 3 or greater toxicity recurs, stop paclitaxel.

Rev. Add2

5.8.3 Docetaxel (Guidance for Dose Modifications)

If docetaxel dose is held, trastuzumab (or FDA approved biosimilar) and pertuzumab must still be administered on schedule.

Event	Docetaxel Dose Modification
Platelet Count Decrease/Thrombocytopenia	
≥ 100,000/mm^3	No dose modification
Grade 1 75-99,999/mm^3	Hold until ≥ 100,000, resume based on timing of recovery: If ≤ 1 week – no dose modification. If >1 but ≤ 3 weeks - reduce dose by 20% dose for subsequent cycles. If > 3 weeks delay is required, stop docetaxel.
≥ Grade 2 < 75,000/mm^3	Hold until ≥ 100,000/mm^3, resume with 20% dose reduction for subsequent cycles. If > 3 weeks delay is required, stop docetaxel.
Neutropenia	
Grade 0 or 1	No dose modification
Grade 2	Hold until resolved to ≤ Grade 1 (ANC ≥ 1500/mm^3), resume at previous dose. Increase supportive care measures if possible.
≥ Grade 3	Hold until resolved to ≤ Grade 1, resume dose

Event	Docetaxel Dose Modification
	by 20% for subsequent cycles. If Grade 3 or greater toxicity recurs, stop docetaxel.
Febrile Neutropenia	
≥ Grade 3 ANC < 1000/mm^3 With temperature of >38.3^o C	Interrupt until resolved (ANC ≥1000mm^3, fever ≤ 38.3^o C), resume according to number of episodes: 1st = no dose modification required 2nd = dose reduction by 20% 3rd = stop docetaxel.
Hepatic Dysfunction (Blood Bilirubin or Alanine aminotransferase increase)	
Transaminases < 10 times ULN and bilirubin level ≤ 1.25 times ULN	No dose modifications
Transaminases < 10 times ULN and bilirubin level 1.26 to 2 times ULN	Reduce docetaxel to 60 mg/m^2
Transaminases <10 times ULN and bilirubin level 2.01 to 5 times ULN	Reduce docetaxel to 37.5 mg/m^2
Transaminases ≥10 times ULN or bilirubin level >5 times ULN	Patient must be permanently discontinued from docetaxel therapy.
Diarrhea*	
Grade 0 or 1	No dose modification
≥ Grade 2	Treat prophylactically in subsequent cycles with loperamide or diphenoxylate. If patient experiences ≥ grade 2 despite prophylaxis, docetaxel must be dose reduced by 20%. If clinically significant diarrhea continues despite prophylaxis AND dose reduction, stop docetaxel.
*If patients experience > grade 2 diarrhea and concurrent grade 3 or 4 neutropenia, hold Docetaxel until ANC ≥ 1000/mm^3 and diarrhea ≤ grade 2.	
Peripheral (Motor or Sensory) Neuropathy **Encourage limb cooling for all patients either as prevention or treatment of neuropathy in conjunction with any dose modifications required.**	
Grade 0-2	No dose modification If patient or physician is uncomfortable treating with grade 2 neuropathy, docetaxel may be dose reduced by 20% but this is not required.
≥ Grade 3	Hold until resolved to ≤ Grade 2, reduce dose by 20% in subsequent cycles. If > 3 weeks delay is required, stop docetaxel.
Mucositis (any)	
Grade 0-2	No dose modification
≥ Grade 3	Hold until resolved to ≤ Grade 1, reduce dose

Event	Docetaxel Dose Modification
	by 20% in subsequent cycles.

Hypersensitivity or Anaphylaxis **Institutions may manage hypersensitivity reactions per institutional practice. Below is one recommended schema.**	
Mild symptoms: mild flushing, rash, pruritis	Consider decreasing the rate of infusion until recovery from symptoms, stay at bedside or monitor patient Then, complete docetaxel infusion at initial planned rate.
Moderate symptoms: moderate flushing, rash, mild dyspnea, chest discomfort	Stop docetaxel. Administer diphenhydramine 50 mg and dexamethasone 10 mg IV. After recovery, resume infusion at half the previous rate for 15 minutes. If no further symptoms occur, complete the infusion at the full dose rate. Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine must be given for the next cycle of treatment, and the rate of infusion must be decreased initially ante increased back to initial planned rate.
Severe symptoms: hypotension requiring pressors, angioedema, respiratory distress requiring bronchdilators	Stop docetaxel. Administer diphenhydramine 50 mg and dexamethasone 10 mg IV. Add epinephrine or bronchodilators as needed. Do not restart.
Life threatening symptoms: Anaphylaxis, urgent intervention indicated	Stop Docetaxel. Do not restart.
Other clinically significant toxicities excluding fatigue, alopecia and leukopenia	
Grade 0 or 1	No dose modifications
Grade 2	Hold until resolved to ≤ Grade 1, resume at previous dose. Increase supportive care measures if possible.
≥ Grade 3	Hold until resolved to ≤ Grade 1, resume with 20% dose reduction for subsequent cycles. If Grade 3 or greater toxicity recurs, stop docetaxel.
Life threatening symptoms: Anaphylaxis, urgent intervention indicated	Stop docetaxel. Do not restart.

Rev. Add2

5.8.4 Nab-Paclitaxel (Guidance for Dose Modifications)

If nab-paclitaxel dose is held, trastuzumab (or FDA approved biosimilar) and pertuzumab must still be administered on schedule.

Event	Nab-paclitaxel Dose Modification
Hematologic Toxicity	
Requirements to initiate any cycle of nab- paclitaxel	ANC ≥ 1000/mm^3
Neutropenia	
≥ 1000/mm^3	No change
ANC < 1,000 mm^3	Hold until ANC ≥1000, resume based on timing of recovery: ≤ 1 week – no change >1 but ≤ 3 weeks - reduce dose 20% for subsequent cycles > 3 weeks – stop nab-paclitaxel
Neutropenic Fever	
ANC ≤ 1000, fever ≥ 38.5	Interrupt until resolved (ANC >1000, fever <38.5), resume according to number of episodes: 1st = no change 2nd = 20% dose reduction 3rd = stop nab-paclitaxel
Thrombocytopenia	
≥ 100,000/mm^3	No change
75-99,999/mm^3	Hold until ANC ≥1000, resume based on timing of recovery: ≤ 1 week – no change >1 but ≤ 3 weeks - reduce dose 20% for subsequent cycles > 3 weeks – stop nab-paclitaxel
< 75,000	Hold until ≥ 100,000, Resume with 20% dose reduction for subsequent cycles. If > 3 weeks delay is required, stop nab-paclitaxel.
Anemia	
All grades	No change – management is at the investigator's discretion. Transfusions are preferred to dose delays or dose reductions.
Hepatic Dysfunction	
Transaminases <10 times ULN and bilirubin level ≤1.25 times ULN	No dose modification

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Event	Nab-paclitaxel Dose Modification
Transaminases <10 times ULN and bilirubin level 1.26 to 2 times ULN	Reduce nab-paclitaxel to 100 mg/m^2
Transaminases <10 times ULN and bilirubin level 2.01 to 5 times ULN	Reduce nab-paclitaxel to 62.5 mg/m^2
Transaminases≥10 times ULN or bilirubin level >5 times ULN	Patient must be permanently discontinued from nab-paclitaxel therapy.
Nausea or Vomiting	
Grade 1-2	• No dose modifications
≥ Grade 3	• Interrupt until ≤ Grade 1, then resume with 20% dose reduction in subsequent cycles. (If nab- paclitaxel is held, continue trastuzumab and pertuzumab).
Mucositis (any type)	
Grade 0-2	• No change
Grade ≥ 3	• Hold until resolved to ≤ Grade 1, reduce dose 20% in subsequent cycles.
Diarrhea	
Grade 2	• If grade 2 diarrhea is present on the day of any treatment, the treatment must be delayed until the diarrhea has resolved to grade 1 or 0, and then resume nab-paclitaxel at 125 mg/m^2 • If diarrhea causes a delay of >21 days, the patient must be permanently discontinued from nab-paclitaxel therapy. • Optimal use of anti-diarrheal agents is encouraged. • If patient experiences ≥ grade 2 despite prophylaxis, causing a delay in nab-paclitaxel administration, then nab-paclitaxel must be dose reduced by 20%. • If clinically significant diarrhea continues despite prophylaxis AND dose reduction, stop paclitaxel.
Grade 3 or 4	• If grade 3 or 4 diarrhea occurs, delay treatment until the diarrhea has resolved to grade 1 or 0, then the dose of nab-paclitaxel must be reduced by 20%. • If diarrhea causes a delay of >21 days, the patient must be permanently discontinued from nab-paclitaxel therapy. • Once the nab-paclitaxel dose has been decreased, it must not be re-escalated. • Optimal use of anti-diarrheal agents is encouraged.

Event	Nab-paclitaxel Dose Modification
Neurologic Toxicity: Neuropathy (motor and sensory) **Encourage limb cooling for all patients either as prevention or treatment of neuropathy in conjunction with any dose modifications required.**	
Grade 0-2	• No dose modifications • If patient or physician is uncomfortable treating with grade 2 neuropathy, nab-paclitaxel may be dose reduced by 20%. • Patients who develop worsening neurotoxicity with each infusion, even if it remains grade 2, must be carefully evaluated to determine if a dose reduction would be appropriate.
Grade 3	• Patient must not receive additional treatment until the toxicity has resolved to ≤ grade 2. • The next infusion may be delayed up to 3 weeks to allow for neurologic toxicity to improve. • If it does not resolve to ≤ grade 2 after 3 weeks, the patient will be permanently discontinued from nab-paclitaxel. • Re-treatment must be initiated with a 20% dose reduction of nab-paclitaxel when the toxicity resolves to grade 2 or less. All subsequent infusions will be administered using the reduced dose. • If grade 3 toxicity develops with additional infusions, further dose reductions may be made to a minimum dose of 75 mg/m^2. • Patients whose toxicity does not improve after dose reduction to 75 mg/m^2 must discontinue therapy.
Grade 4	• Discontinue nab-paclitaxel.
Other clinically significant toxicities excluding fatigue, alopecia and leukopenia	
Grade 0 or 1	• No dose modifications
Grade 2	• Hold until resolved to ≤ Grade 1, resume at previous dose. Increase supportive care measures if possible.
≥ Grade 3	• Hold until resolved to ≤ Grade 1, resume with 20% dose reduction for subsequent cycles. If Grade 3 or greater toxicity recurs, stop nab-paclitaxel
Life threatening symptoms: Anaphylaxis, urgent intervention indicated	• Stop nab-paclitaxel • Do not restart.

Rev. Add2

5.8.5 Trastuzumab (or FDA approved biosimilar) and Pertuzumab (Guidance for Dose Modifications; not mandatory

It is advised that there be no dose reduction/modification for trastuzumab (or FDA approved biosimilar) or pertuzumab.

5.8.5.1 Infusion Associated Symptoms

During the first infusion, a symptom complex of fever and/or chills may occur. These are usually mild-to-moderate and may be accompanied by nausea, vomiting, headache, dizziness, rigors, pain, hypotension, rash, and asthenia. These symptoms occur infrequently during subsequent infusions.

Permanently discontinue trastuzumab (or FDA approved biosimilar) and/or pertuzumab for anaphylaxis reaction

5.8.5.2 Fever During Infusion

Grade 1 (Grade: 38°C - 39°C [100.4°- 102.2°F] OR Grade 2: 39.1°C - 40°C [102.3°- 104°F] - Stop infusion and give antipyretics. Once temperature is <38°C, resume infusion at a slower rate.

Grade 3 (>40°C [104°]) or Grade 4: (40°C [104°F] for 24 hours) - Stop infusion immediately and give antipyretics. If temperature drops to <38°C within 3 hours, resume infusion at a slower rate. If fever does not resolve within 3 hours, inpatient monitoring is strongly recommended. If temperature drops to <38°C within 3 days, re-challenge at a slower rate. If temperature remains >38°C after 3 days, abandon this administration and subsequent administration is at the discretion of the investigator.

5.8.5.3 Diarrhea

Any Grade: use of optimal anti-diarrheal medications is strongly recommended.

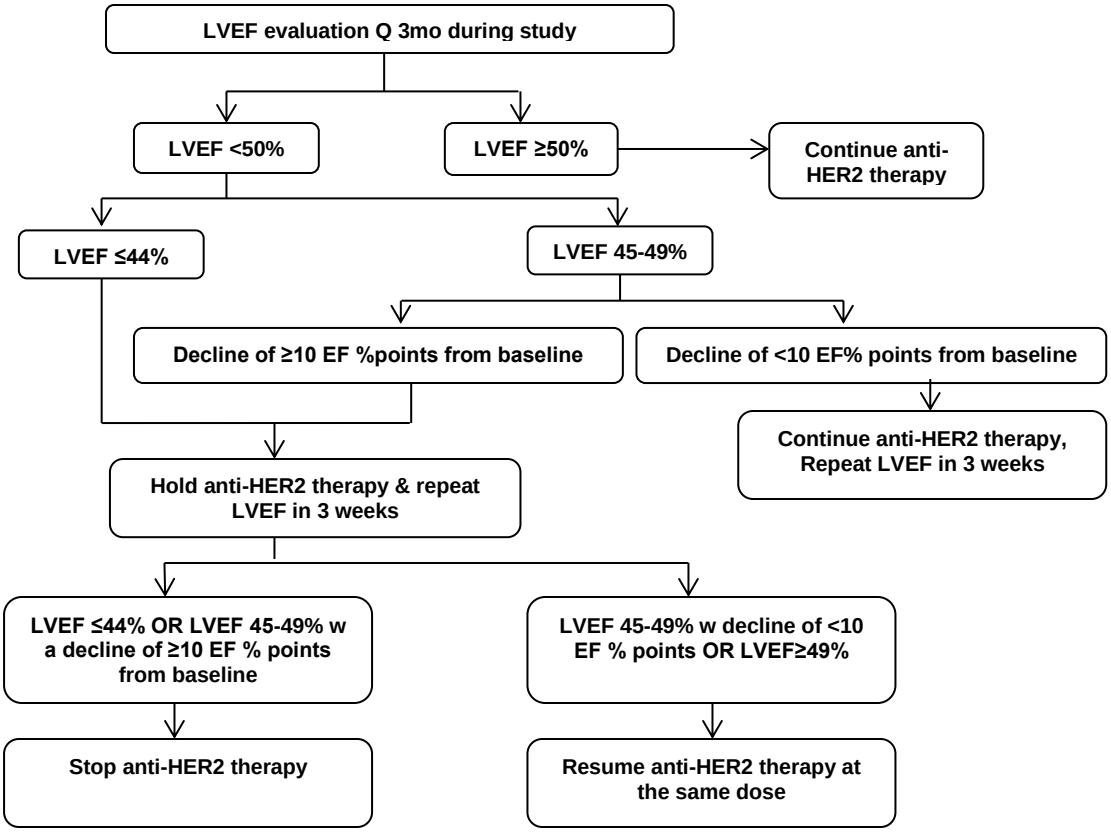
5.8.5.4 Pulmonary

Any (e.g., Adult Respiratory Distress Syndrome [ARDS], pneumonitis/pulmonary infiltrates, etc.) – delay trastuzumab (or FDA approved biosimilar) and pertuzumab until diagnosis is clear. If pneumonitis/fibrosis, or pulmonary infiltrate is confirmed, and the relationship to trastuzumab (or FDA approved biosimilar) cannot be excluded, trastuzumab (or FDA approved biosimilar) must be permanently discontinued.

5.8.5.5 Cardiac

Left Ventricular Ejection Fraction

Please see figure below regarding frequency of LVEF assessments and parameters to hold or continue trastuzumab therapy based on EF assessments:



Treatment with trastuzumab (or FDA approved biosimilar) and pertuzumab is recommended if:

- The LVEF continues to remain ≥ 50

  OR

- The LVEF decreases to < 50 but there is a < 10 percentage point drop from baseline in an asymptomatic patient

Treatment with trastuzumab (or FDA approved biosimilar) or pertuzumab is prohibited in an asymptomatic patient if:

- The LVEF is ≤ 44%

  OR

- The LVEF is 45-49% with a ≥ 10 percentage point decrease from baseline

Grade 3 CHF

Monitor for signs and symptoms of CHF (i.e., dyspnea, tachycardia, cough, neck vein distention, cardiomegaly,

hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, etc.).

If patient develop these signs and symptoms, it is recommended to hold trastuzumab (or FDA approved biosimilar) and pertuzumab, If CHF occurs while also on paclitaxel, continuation of paclitaxel is at the discretion of the investigator.

Confirm diagnosis of CHF with either a MUGA scan/echocardiogram. Once a diagnosis of CHF is confirmed, trastuzumab (or FDA approved biosimilar) and pertuzumab must be permanently discontinued.

Follow-up at 3, 6, and 12 months from time of CHF diagnosis with MUGA scan/echocardiogram.

Grade 4 CHF (severe refractory CHF or requiring intubation)

Trastuzumab (or FDA approved biosimilar) and pertuzumab must be permanently discontinued.

Rev. Add8

Follow up at 3, 6, and 12 months (+/- 2 weeks) with MUGA scan or echocardiogram.

5.9 Supportive Care and Concomitant Medication

All supportive measures consistent with optimal patient care will be given throughout the study (e.g., placement of venous access devices). Antiemetic therapy must be administered based on institutional guidelines.

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to registration to the end of treatment visit. All concomitant medications must be reported to the investigator and recorded. All concomitant medications are to be reported until the end of treatment visit. The following treatments are permitted throughout the duration of the study treatment phase and during follow-up:

- Standard therapies for pre-existing medical conditions unless listed as prohibited therapy in section below. Any medication intended solely for supportive care (e.g., analgesics, anti-diarrheal, anti-depressants) may be used at the investigator's discretion.
- Hematopoietic growth factors (e.g., G-CSF, granulocyte macrophage colony stimulating factor) may be used at investigator's discretion for management of treatment-emergent neutropenia and/or for secondary prophylaxis as per NCCN guidelines or local standard practice. **However, prophylactic growth factor is mandatory with docetaxel.**
- Bisphosphonate or denosumab therapy to be used in accordance with the approved labeled indication and/or nationally recognized treatment guidelines.

Explicitly prohibited therapies prior to the end of treatment visit include:

- Anti-cancer therapies other than those administered in this study, including cytotoxic chemotherapy, radiotherapy (except for adjuvant radiotherapy for

breast cancer after completion of chemotherapy), immunotherapy, biological, hormonal or targeted (e.g., lapatinib, neratinib) anti-cancer therapy. Ovarian suppression (e.g., Lupron) is allowed during the neoadjuvant treatment for fertility preservation.

Rev. Add7

- Any systemically active oral, injected, or implanted hormonal method of contraception except for progesterone coated intrauterine devices (IUDs) that had been previously implanted (prohibited for patients with ER-positive breast cancer). Patients with ER-negative breast cancer who received any of these therapies may be analyzed for all protocol objectives/endpoints.

Rev. Add3

- Estrogen-replacement therapy (prohibited for patients with ER-positive breast cancer). Patients with ER-negative breast cancer who received any of these therapies may be analyzed for all protocol objectives/endpoints.
- Any investigational agent, except those used for this study.

5.10 Duration of Therapy

Rev. Add2

All patients will receive 12 weeks of pre-operative THP therapy (4 cycles). This must be completed by week 16 (allowing for any needed dose delays) Sections 5.2 and 5.4.1. Definitive tumor surgery must occur no later than 126 days (18 weeks) from initiation of neoadjuvant THP. If surgery occurs more than 21 days from the 4th dose of trastuzumab (or FDA approved biosimilar) (HP) then a 5th (or 6th) dose of HP must be administered before surgery. For patients who attain pCR, there will be no interruption of HP therapy; it will be administered every 3 weeks before surgery, after surgery and during radiation (if indicated). A total of 17 doses of HP will be administered for patients who attain pCR (Arm A) including doses administered before surgery and after surgery. When HP therapy is finished, this marks the end of protocol-defined therapy for patients in Arm A (pCR). Patients with hormone receptor positive disease must receive endocrine therapy for at least 5 years; however the specific type of endocrine therapy and duration of endocrine therapy is not mandated in this study as is not considered protocol-defined therapy.

Rev. Add4

NOTE: If ER is 10% or higher, anti-estrogen therapy must be prescribed. If ER is 1-9%, anti-estrogen should be prescribed.

For patients who do not attain pCR, subsequent therapy (chemotherapy, T-DM1 etc.) will be decided by the treating oncologist. For patients who do NOT attain pCR (Arm B), any treatment other than THP x 4 cycles will not be considered as protocol-defined therapy.

Patients will receive protocol therapy unless:

- Treatment is completed per protocol
- Patient experiences unacceptable toxicity or disease progression.
- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the EA1181 Forms Packet.
- Patient withdraws consent.
- Non-protocol therapies are administered.

Rev. Add7

5.11 Duration of Follow-up

Rev. Add9

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for recurrence/progression and survival for 15 years from the date of surgery. Patients will be followed through completion of all protocol therapy. Patients will be followed every 3 months (+/- 1 week) for first 12 months after surgery, then every 6 months (+/- 2 week) if the patient is 2-5 years from surgery, and then every 12 months (+/- 30 days) if the patient is 5-15 years from date of surgery.

6. Measurement of Effect

6.1 Neoadjuvant Breast Response Criteria – pCR (Pathologic Complete Response)

6.1.1 **pCR will be defined as the absence of invasive cancer in breast and axillary nodes (ypT0/Tis, ypN0). DCIS is allowed for pCR designation to be made.**

6.1.2 If more than one (including bilateral) HER2-positive breast cancer was present prior to pre-operative THP, absence of invasive disease in breast and axillary nodes is required for all prior invasive cancers. DCIS is allowed for pCR designation to be made.

Rev. Add1

6.2 Neoadjuvant Breast Response- Residual Disease (Pathology Worksheet reference)

See Section 5.4.2.5 for important elements of pathology report. Pathology worksheet to collect the factors that allow subsequent determination of RCB score must be provided to the pathologist evaluating the definitive breast surgery specimen ahead of time. The pathology worksheet can be found on the CTSU website.

Rev. Add1

6.3 Progression during Neoadjuvant Therapy

Disease progression (either clinical or radiographic) during the pre-operative phase (THP) must be documented. It is strongly recommended, though not mandated, that suspected progression be confirmed with a biopsy. Patients who receive additional chemotherapy (or any therapy that is not protocol-defined) before surgery will not be analyzed with pCR arm (Arm A) **regardless of the pathologic response status**; these patients will be analyzed in Arm B.

6.4 Recurrence and Survival

6.4.1 Recurrence

Recurrence must be documented by biopsy and/or evidence of disease on radiologic studies. Abnormal blood studies alone (e.g., elevated transaminases or alkaline phosphatase) are not sufficient evidence of relapse. Whenever possible, histologic proof of recurrence must be obtained.

6.4.2 Ipsilateral Breast Tumor Recurrence (IBTR)

Recurrence occurring within the ipsilateral breast in a patient who has had prior breast conserving therapy (i.e., lumpectomy). Patients who develop an IBTR must continue to be followed for other sites of recurrence, which must be reported if they occur. Development of invasive disease in the ipsilateral breast must be reported as IBTR, not as a new primary cancer. New sites of ductal carcinoma in situ (DCIS) must be reported, but will not be considered an IBTR and follow-up for IBTR must continue.

6.4.3 Local, Regional Recurrence (LRR)

One or both of the following: (a) nodal relapse: recurrence in regional lymph nodes (e.g., ipsilateral axillary, supraclavicular, or internal mammary lymph nodes), and/or (b) recurrence in the skin and/or

chest wall in a patient who has had a prior mastectomy or breast conserving surgery. Patients who develop an LRR must continue to be followed for other sites of recurrence, which must be reported if they occur.

6.4.4 Distant Recurrence

The development of a distant recurrence of breast cancer, including distant organs (e.g., brain, liver, lungs, bone, etc.) and/or non-regional lymph nodes (e.g., mediastinal, cervical, contralateral axilla, etc.). Patients who develop a distant recurrence must continue to be followed for survival; other sites of recurrence/progression do not need to be reported.

6.4.5 Second Primary Breast Cancer

Evidence of invasive breast cancer in the contralateral breast. Histologic confirmation of second primary breast cancers is required. New sites of DCIS must be reported, but do not be considered an event for purposes of analysis, and patients with DCIS must continue to be followed for development of invasive disease. Patients who develop a second primary breast cancer must continue to be followed for other sites of breast cancer recurrence, which must be reported if it occurs.

6.4.6 Second Primary Cancer (Non-Breast)

Any non-breast invasive cancer except squamous or basal cell carcinoma of the skin. New in situ cancers at any site (except breast) must not be reported. Patients who develop a second primary cancer must continue to be followed for breast cancer recurrence, which must be reported if it occurs.

6.4.7 Recurrence-Free Survival

The time from date of surgery until the date of the first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, local/regional recurrence, distant recurrence, or death from any cause.

6.4.8 Disease-Free Survival (DFS)

The time from the date of surgery until the date of ipsilateral breast tumor recurrence, local/regional recurrence, distant recurrence, second primary cancer (breast or non-breast), or death from any cause.

6.4.9 Event-Free Survival

The time from the date of registration until the date of progressive disease (during neoadjuvant therapy), ipsilateral breast tumor recurrence, local/regional recurrence, distant recurrence, second primary cancer (breast or non-breast), or death from any cause.

6.4.10 Distant Recurrence-Free Interval (DRFI)

Date of surgery to the date of distant recurrence of breast cancer, as defined in Section 6 or of death with distant recurrence, if death is the first manifestation of distant recurrence.

6.4.11 Recurrence-Free Interval (RFI)

Date of surgery to the date of first recurrence of breast cancer (IBTR, LRR, or DR) or to the date of death with recurrence, if death is the first manifestation of recurrence.

6.4.12 Overall Survival

Date of surgery to date of death from any cause.

6.4.13 Breast Cancer-Specific Survival

Date of surgery to date of death from breast cancer.

7. Study Parameters

Rev. Add2

7.1 Therapeutic Parameters

1. NOTE: A window of +/- 3 working days is allowed for all below procedures unless otherwise specified, to account for holidays, vacation, scheduling issues.
2. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done within 4 weeks prior to registration.

Rev. Add7

3. All required prestudy chemistries, as outlined in Section 3, should be done ≤ 4 weeks (28 days) before Step 1 registration – unless specifically required on Day 1 as per protocol.

Rev. Add1
Rev. Add4

	Prior to Registration (≤ 28 days)	Cycles 1-4		Pre-Surgery Visit[14, 17]	Post-Surgery Visit[15, 18]	Adjuvant dual HER2 targeted tx (Complete 17 cycles total)	Post Treatment to 15 years from surgery[12]
		Day 1	Days 8 and 15				
Demographics	X						
Rev. Add5 History and Physical[1]	X	X				X[12]	X
ECOG PS	X	X					X
Rev. Add5 Weight, Vital Signs	X	X	X[16]			X[19]	X
Height	X	X					
Rev. Add3 CBC with Differentials[2]	X	X[2]	X[2]				
Serum Chemistry	X[3]	X[4]					
Serum Pregnancy Test[5]	X						
Cardiac Assessment[6]	X			X[6]		X[6]	
Breast Imaging[7]	X			X[7]			X
Whole-Body Staging[8]	X						
Surgical Assessment[9]	X			X			
Axillary Assessment[10]	X			X			
Rev. Add1 Adverse Event Evaluation[11]	X	X		X	X	X[11]	

		Prior to Registration (≤ 28 days)	Cycles 1-4		Pre-Surgery Visit[14, 17]	Post-Surgery Visit[15, 18]	Adjuvant dual HER2 targeted tx (Complete 17 cycles total)	Post Treatment to 15 years from surgery[12]
			Day 1	Days 8 and 15				
Rev. Add8	MRI Image Submission[20]	X			X			
Rev. Add1	Research Blood[13]	See Sections 7.2 and 10						
	Biological Sample Submissions	See Sections 7.2 and 10						

1. Physical examination must include examination of breast and local-regional lymphatics. Clinical T and N staging according to AJCC cancer staging manual anatomic staging table 8th edition must be documented. At subsequent visits with medical or surgical providers (or more frequently, if clinically indicated), breast examination and evaluation of local-regional lymphatics must be performed, with breast tumor measurements performed and documented. Physical examination may be done up to 72 hours prior to day 1. Additional physical examinations must be focused on organ systems related to adverse events. (Rev. Add9)

2. Hemoglobin, hematocrit, platelet count, WBC count, and differential including absolute neutrophil count prior to registration. For treatment cycles, complete blood count with either differential or ANC is acceptable and must be drawn on day 1, 8 and 15 for weekly paclitaxel (or nab-paclitaxel) and on day 1 for docetaxel. Labs may be drawn up to 72 hours prior to treatment day. (Rev. Add3, Rev. Add9)

3. Sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, total bilirubin (and direct bilirubin when total bilirubin >ULN), ALT, AST, and ALP are required at baseline.

4. On day 1 of each THP cycle, only CBC/ANC (see footnote 2) and LFTs (ALT, AST, ALP, and total bilirubin) are required. Other chemistries are not required. Day 1 required labs may be drawn up to 72 hours prior to day 1. (Rev. Add3, Rev. Add9)

5. All patients of childbearing potential (including those who have had a tubal ligation) must have a negative [blood test or urine test] within 14 days prior to registration to rule out pregnancy. If the pregnancy test (e.g., HCG level) is abnormal but is felt to represent a false positive test for pregnancy (e.g., due to treatments being administered for egg harvesting, or because of recent miscarriage), a note by the treating gynecologist explaining why the team is confident the woman is not pregnant is required. (Rev. Add8)

6. LVEF assessment (by either echocardiogram or MUGA scan) must be done prior to Cycle 1 Day1 (can be done up to 8 weeks before registration) and then every 3 months +/- 2 weeks (either starting from the baseline ECHO or from C1D1) during the pre-operative therapy phase and continuing on through post-operative phase while the patient is on trastuzumab (or FDA approved biosimilar) and pertuzumab therapy. For patients on Arm B, the treating clinicians can determine the frequency of LVEF assessment; this is not mandated by the protocol for patients on Arm B. The same mode of LVEF assessment (either echocardiogram or MUGA scan) is preferred each time. It is up to the treating clinicians whether to begin counting 3 months from the screening LVEF assessment or from Cycle 1 day 1 of THP. (Rev. Add3, Rev. Add8)

7. All subjects are required to have a bilateral mammogram and a diagnostic breast ultrasound [on the side of the cancer(s)] (with or without breast MRI) performed at screening. An axillary ultrasound on the side of the cancer(s) is also required. Either mammogram/ultrasound (including imaging of the ipsilateral axilla) or breast MRI must be performed within 60 days of registration. (Rev. Add2, Rev. Add3, Rev. Add7)

Rev. Add3 Prior to surgery: pre-surgery imaging is required to assess response of the tumor (including any suspicious lymph nodes at baseline) Imaging may be performed from up to one week before Cycle 4 day 1 to a maximum of up to 4 weeks after the last dose of any neoadjuvant therapy. The same imaging modality that was used at screening is encouraged prior to surgery to assess tumor response.

*Breast MRI is strongly recommended in patients in whom breast conserving therapy is being considered, although not required if practical or financial considerations preclude it, as long as the target lesion can be adequately measured by mammogram and/or ultrasound.

Rev. Add3 Axillary imaging with ultrasound or breast MRI is required as part of pre-surgery evaluation for all patients who initially had biopsy proven nodal involvement or had suspicious axillary nodes that prompted axillary sampling.

Rev. Add5 Annual breast mammogram +/- 60 days is mandated x 15 years for any patient who does not undergo bilateral mastectomies.

8. Subjects with AJCC 8th Edition Anatomic Stage III disease according to AJCC staging manual edition 8 or with abnormal liver function tests, symptoms or abnormal physical exam must have CT scans of chest, abdomen and pelvis as well as a bone scan or PET-CT performed during screening to rule out metastatic disease. Staging scans for all other patients are at the discretion of the treating oncologists.

Rev. Add7 9. All subjects will be seen and examined by the treating surgeon at screening (within 42 days of registration) and at the Pre-Operative Visit. Each visit will include a clinical breast and lymph node examination and review of the imaging studies to determine whether the subject is a candidate for potentially curative surgery. Eligibility for breast-conserving therapy must also be documented along with any contraindications if present. The pre-op visit with surgeon may occur anytime between cycle 4 day 1 and date of surgery.

Rev. Add7 10. An axillary assessment will be performed within 60 days prior to registration. Ipsilateral axillary lymph nodes will be assessed as clinically normal or clinically suspicious by physical examination and will be assessed as clinically normal or clinically suspicious independently by imaging which

Rev. Add3 must include ultrasound and may include breast MRI. Axillary imaging and/or biopsy do not need to be repeated if performed prior to the screening period.

The number of suspicious axillary nodes on baseline axillary ultrasound must be recorded. Subjects with suspicious nodes documented by physical exam OR by imaging will have a biopsy of the nodes (fine needle aspirate or core needle biopsy). If clinical evaluation and biopsy results are discordant, the biopsy may be repeated at the discretion of the Investigator. **Clip placement in the involved positive node is required (only one node requires clipping, in the case of multiple suspicious nodes)**.

11. Adverse event evaluation must occur at D1 of each cycle during Cycle 1-4 of pre-operative therapy.

For patients who attain pCR and do not receive adjuvant chemotherapy after surgery (Arm A) AEs will be collected at the first post-surgery treatment (i.e., C1 post-operative trastuzumab (or FDA approved biosimilar) and pertuzumab) and every 3 months (+/- 1 week) at the clinician

Rev. Add7 visit during post-operative trastuzumab (or FDA approved biosimilar) and pertuzumab.

For patients with residual disease or any patients who receive post-operative adjuvant chemotherapy (Arm B), AEs will not be collected unless required in Section 5. All therapies administered after surgery will be collected on CRFs. Patients in Arm B will be followed for recurrence and survival.

Rev. Add1 All patients will be followed for recurrence and survival according to follow-up visit schedule outlined in #12 below.

Rev. Add9 12. Follow-up: every 3 months (+/- 1 week) for 12 months after surgery, every 6 months (+/- 2 week) if patient is 1-5 years from surgery, every 12

Rev. Add5 months (+/- 30 days) if patient is 5-15 years from date of surgery. No specific requirements if patient is more than 15 years from surgery. Annual mammogram +/- 60 days required during annual follow-up.

Rev. Add3 13. Streck tubes will be collected on all patients at the following time points: 1) Cycle 1 Day 1 (or any time before the start of chemotherapy or other systemic therapy if residual disease) - two streck tubes for CTCs mandatory; two additional streck tubes for cfDNA for patients who consent; 2) Cycle 2 Day 1- two streck tubes for CTCs mandatory; two additional streck tubes for cfDNA for patients who consent; 3) Pre-Surgery (can be collected at the surgical visit or any time at least 1 week after Cycle 4 and before surgery; this does not require an extra visit with the medical
Rev. Add5 oncologist) - two mandatory streck tubes for CTCs; 4) Post-Surgery [any time after surgery before the first post-surgery systemic therapy is administered or at the first post-surgery visit for trastuzumab (or FDA approved biosimilar) and pertuzumab (or other systemic therapy if residual disease)] - two streck tubes for CTCs mandatory; two additional streck tubes for cfDNA for patients who consent and who have pCR. On the day of the first post-surgery systemic therapy, ideally blood is collected before treatment, but it is acceptable to collect the blood after treatment on that day if that is preferred and; 5) After completion of all HER2-targeted therapy - two streck tubes for CTCs mandatory; two additional streck tubes for cfDNA for patients who consent **and who have pCR**. See Section 7.2

14. AEs for Cycle 4 may be obtained by phone any time before surgery, at least 1 week after Cycle 4.

15. First visit for trastuzumab (or FDA approved biosimilar) and pertuzumab after surgery (or other therapy such as chemotherapy or T-DM1 if patient had residual disease).

Rev. Add3 16. Vital signs must be taken at each visit. Weight is only required day 1 of each cycle during pre-operative treatment. Dose recalculation must occur only if weight changes ≥ 10% (i.e., greater than CTCAE Grade 1 weight gain or loss) from baseline weight. Day 8 and 15 visits are NOT required for patients receiving docetaxel.

Rev. Add4 17. HP must be continued every 3 weeks until surgery, unless toxicity prohibits. Thus, within the window required for surgery, up to 2 cycles of HP
Rev. Add8 might be administered after completion of THP. No exam or labs are needed at those visits.
Rev. Add4

Rev. Add5 18. Post-Operative Cycle 1 of HP should preferably begin 21 days after the last pre-operative HP cycle was administered. Physicians may continue
Rev. Add7 HP awaiting final pathology to determine if patient will be on Arm A or Arm B but may also wait until pathology report is finalized. For patients on Arm A (pCR), HP should be initiated **as soon as possible** after surgery (and not later than 4-5 weeks after surgery). If a patient has a pCR (Arm A), and > 4 week time period has elapsed between the pre- and post-surgery dose, a loading dose should be given for trastuzumab. If a patient has a pCR (Arm A), and > 6 weeks has elapsed between the pre- and post-surgery dose, a loading dose should be given for pertuzumab.

Rev. Add5 19. After surgery, vital signs are only required (and must be recorded) at clinician visits (e.g., every 12 weeks during post-surgery trastuzumab and pertuzumab infusions when patient is seeing clinician).

Rev. Add8 20. Standard of care MRIs acquired at baseline and prior to surgery are to be submitted through TRIAD per study aims in Sections 2.2.2 and 2.3.2. Submission via TRIAD can take place up to 6 months after the MRI is acquired. Please see Section 12 for further details.

Rev. Add2

7.2 Biological Sample Submissions

Specimens are to be submitted as outlined in Section 10.

Specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).

Biological Materials	Prior to Start of Treatment	Cycle Two, Day One [After One Cycle of THP]	Pre-Surgery[8]	Definitive Surgery	Post-Surgery	After Completion of HER2-Directed Adjuvant Therapy	Submit to:
MANDATORY for Defined Laboratory Research Studies							
Blood (two 10mL Streck Cell-Free DNA tubes)[5]	X[3]	X	X		X[4]	X	Epic Sciences
From patients who answer "Yes" to "I agree to provide additional blood and tissue samples for future health research."							
Tumor Tissue (FFPE block and H&E slide)[1,9]	X			X[7]			CBPF
Blood (two 10mL Streck Cell-Free DNA tubes)[2]	X[3]	X			X[6]	X[6]	CBPF

Rev. Add8 1. Tumor tissue (FFPE block and H&E slide) and related pathology reports from the archived clinical (diagnostic) biopsy and from the residual disease on the definitive surgical specimen (from patients with no pCR) are to be submitted within one month for future undefined research studies (per patient consent) as outlined in Section 10.

Rev. Add3 2. Kits are being provided for the collection and shipment of the blood specimens being submitted to CBPF. See Appendix IV for instructions. Kit orders will on average be delivered within three (3) business days from the time the order is placed

3. Cycle one, day one, or any time before start of chemotherapy (or other systemic therapy if residual disease).

Rev. Add3 Rev. Add5 4. Any time after surgery before the first post-surgery systemic therapy is administered or at the first post-surgery visit for trastuzumab (or FDA approved biosimilar) and pertuzumab (or other systemic therapy if residual disease). On the day of the first post-surgery systemic therapy, ideally blood is collected before treatment, but it is acceptable to collect the blood after treatment on that day if that is preferred.

Rev. Add3 Rev. Add1 5. Kits are being provided for the collection and shipment of the blood specimens being submitted to Epic Sciences. See Section 10.2 for instructions. Kits will on average be delivered within five (5) days from the time the order is placed.

6. From patients with pCR (treatment Arm A).

7. From patients with no pCR (treatment Arm B).

Rev. Add3

8. Can be collected at the surgical visit or any time at least one (1) week after Cycle 4 and before surgery, this does not require an extra visit with the medical oncologist.

Rev. Add8 9 An H&E slide of the baseline tumor (from the diagnostic tumor biopsy already performed as part of clinical care) must be submitted from all patients who consent even if block cannot be sent; an H&E slide of residual cancer at surgery must be submitted from all patients on Arm B who consent even if block cannot be sent.

8. Drug Formulation and Procurement

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

8.1 Paclitaxel (NSC 673089)

NOTE: Please refer to the commercial package insert for more information.

8.1.1 Other Names

Taxol

8.1.2 Classification

Anti-microtubule agent

8.1.3 Mode of Action

Promotes microtubule assembly and stabilizes tubulin polymers by preventing their depolarization, resulting in the formation of extremely stable and nonfunctional microtubules, and consequently inhibition of many cell functions.

Rev. Add2

8.1.4 Storage and Stability

Unopened vials of Taxol (paclitaxel) Injection are stable until the date indicated on the package when stored between 20°–25° C (68°–77° F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Freezing does not adversely affect the product. Solutions diluted to a concentration of 0.3 to 1.2 mg/mL in normal saline, 5% dextrose, 5% dextrose and normal saline, or 5% dextrose in Ringer's solution are stable for up to 27 hours when stored at room temperature and normal room light.

8.1.5 Dose Specifics

80mg/m^2 on days 1, 8, and 15 of each cycle

8.1.6 Preparation

The concentrated solution must be diluted prior to use in normal saline, 5% dextrose, 5% dextrose and normal saline, or 5% dextrose in Ringer's solution to a concentration of 0.3 -1.2 mg/mL. Solutions exhibit a slight haze, common to all products containing non-ionic surfactants. Glass, polypropylene, or polyolefin containers and non-PVC-containing (nitroglycerin) infusion sets should be used. A small number of fibers (within acceptable limits established by the USP) have been observed after dilution. Therefore, a hydrophilic 0.22 micron in-line filter should be used. Analyses of solutions filtered through IVEX-2 and IVEX-HP (Abbott) 0.2 micron filters showed no appreciable loss of potency.

Solutions exhibiting excessive particulate formation should not be used.

8.1.7 Route of Administration

Intravenous infusion

8.1.8 Incompatibilities

Avoid the use of PVC bags and infusion sets due to leaching of DEHP (plasticizer). Ketoconazole may inhibit paclitaxel metabolism, based on in vitro data.

8.1.9 Availability

Commercially available

8.1.10 Side Effects

Refer to Package Insert for Adverse Events.

8.1.11 Nursing/Patient Implications

1. Monitor CBC and platelet count prior to drug administration.
2. Symptom management of expected nausea, vomiting, and stomatitis.
3. Monitor for and evaluate abdominal pain occurring after paclitaxel administration (especially in severely neutropenic patients and in those receiving G-CSF) due to the risk of ischemic and neutropenic enterocolitis.
4. Advise patients of possible hair loss.
5. Cardiac monitoring for assessment of arrhythmias in patients with serious conduction abnormalities.
6. Monitor liver function tests.
7. Advise patient of possible arthralgias and myalgias which may occur several days after treatment. Monitor for symptoms of peripheral neuropathy.
8. Monitor for signs and symptoms of hypersensitivity reactions. Insure that the recommended premedications have been given. Premedications (diphenhydramine, steroids, and H2 blocker) appear to reduce the incidence and severity of hypersensitivity reactions but do not provide complete protection. Emergency agents (diphenhydramine and epinephrine) should be available.
9. Evaluate IV site regularly for signs of infiltration. It is not known if paclitaxel is a vesicant; however, the CremophorEL vehicle for this drug can cause tissue damage.
10. In-line filtration with a 0.22 micron filter should be used.

8.1.12 References

Rowinsky EK, Casenave LA, Donehower RC. Taxol: A novel investigational microtubule agent. J Natl Cancer Inst 1990; 82:1247-1259.

Gregory RE, DeLisa AF. Paclitaxel: A new antineoplastic agent for refractory ovarian cancer. Clin Pharm 1993; 12: 401-415.

Rowinsky EK, Eisenhauer EA, Chaudry V, et al. Clinical toxicities encountered with paclitaxel. Semin Oncology 1993; 20:1-15.

Walker FE. Paclitaxel: Side effects and patient education issues. Semin Oncology Nurs 1993; 9(suppl 2):6-10.

8.2 Docetaxel (NSC 628503)

NOTE: Please refer to the commercial package insert for more information.

8.2.1 Other Names

Taxotere, RP 56976

8.2.2 Classification

Antimicrotubule agent

8.2.3 Mode of Action

Docetaxel, a semisynthetic analog of taxol, promotes the assembly of tubulin and inhibits microtubule depolymerization. Bundles of microtubules accumulate and interfere with cell division.

8.2.4 Storage and Stability

Store intact vials between 2^{o} and 25^{o}C (36^{o} and 77^{o}F). Retain in the original package to protect from bright light. The final dilution (in either 0.9% sodium chloride or 5% Dextrose solution) is stable for 4 hours if stored between 2^{o} and 25^{o}C (36^{o} and 77^{o}F).

8.2.5 Dose Specifics

75 mg/m^2 IV day 1 of each cycle.

8.2.6 Preparation

Just prior to use, allow the docetaxel vial to reach room temperature for 5 minutes. Add the entire contents of the ethanol diluent vial and mix by gently rotating the vial for 45 seconds. Allow to stand for 5 minutes at room temperature, and check that the solution is homogeneous and clear (persistent foam is normal). The resulting solution contains 10 mg/mL of docetaxel. Please note that the solution contains 15% overfill. Dosing amounts should be based in the concentration per extractable volume, not the total volume of the vial. The desired dose is diluted in D5W or NS. The volume of the infusion should be adjusted in order to have a final docetaxel concentration of between 0.3 mg/mL and 0.74 mg/mL. Non-PVC-containing intravenous infusion bags and administration sets should be used to avoid patient exposure to the plasticizer DEHP.

8.2.7 Route of Administration

Intravenous infusion

8.2.8 Incompatibilities

Intravenous bags and administration sets containing DEHP (di-[2-ethylexyl] phthalate). No further information available.

8.2.9 Availability

Commercially available

8.2.10 Side Effects

Refer to Package Insert for Adverse Events.

8.2.11 Nursing/Patient Implications

1. Monitor CBC and platelet count prior to drug administration.
2. Symptom management of expected nausea, vomiting, and stomatitis.
3. Advise patients of possible hair loss.
4. Monitor for signs and symptoms of hypersensitivity reactions. Insure that recommended pre-medications are given.
5. Monitor liver function tests.
6. Evaluate site regularly for signs of infiltration.
7. Monitor for symptoms of peripheral neuropathy.
8. Monitor for signs of fluid retention and cutaneous reactions.

8.2.12 Prophylactic growth factor

The recommended dose for prophylactic growth factor, Neulasta (pegfilgrastim; Granulocyte Colony-Stimulating Factor (G-Csf)), is 6 mg/0.6 mL. This may be given either subcutaneously or Onpro (On Body Injector).

8.2.13 References

Investigator's Brochure: Docetaxel. Rhone-Poulenc Rorer, June 14, 1995.

Pazdur R, *et al.* Phase I trial of Taxotere; Five-day schedule. J Natl Cancer Inst 84:1781-8, 1992.

Pazdur R, *et al.* Phase I trial of Taxotere (RP56976). Proc Am Soc Clin Oncol 11:111, 1992.

Burris H, *et al.* A phase I clinical trial of Taxotere as a 6-hour infusion repeated every 21 days in patients with refractory solid tumors. Proc Am Soc Clin Oncol 11:137, 1992.

Bissett D, *et al.* Phase I study of Taxotere (RP56976) given as a 24-hour infusion. Proc Am Assoc Cancer Res 33:526, 1992.

Bruno R, *et al.* Clinical pharmacology of Taxotere (RP56976) given as a 1-2 hour infusion every 2-3 weeks. Proc Am Assoc Cancer Res 33:261, 1992.

DeValeriola D, *et al.* Phase I pharmacokinetic study of Taxotere (RP56976) administered as a weekly infusion. Proc Am Assoc Cancer Res 33:1563, 1992.

8.3 Nab-Paclitaxel

NOTE: Please refer to the commercial package insert for more information.

8.3.1 Other Names

ABI-007, nab-paclitaxel, paclitaxel protein-bound particles for injectable suspension

8.3.2 Classification

Antimicrotubular, Taxane Derivative

8.3.3 Mode of Action

Nab-Paclitaxel is a biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. This composition provides a novel approach of increasing intra-tumoral concentrations of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell. This albumin-specific receptor mediated process involves the binding of albumin to a specific receptor (gp60) on the intralumminal endothelial cell membrane, resulting in activation of a protein (caveolin-1), which initiates an internalization process in the endothelial cell through the formation of caveolae, with transport of the intact albumin-bound chemotherapeutic complex via these caveolae to the underlying tumor interstitium (Desai et al, 2004). A protein specifically secreted by the tumor (SPARC) binds albumin, allowing release of the hydrophobic drug to the tumor cell membrane (Desai et al, 2004). Nab-Paclitaxel is the first biologically interactive nanoparticle product leveraging this gp-60/caveolin-1/caveolae/SPARC pathway to increase intra-tumoral concentration of the drug and reducing toxic effects in normal tissue.

8.3.4 Storage and Stability

Storage: Store the vials in original cartons at 20º C to 25º C (68º F to 77ºF). Retain in the original package to protect from bright light.

Stability: Unopened vials of Nab-Paclitaxel are stable until the date indicated on the package when stored between 20ºC to 25ºC (68ºF to 77ºF), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial

Reconstituted Nab-Paclitaxel should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag

The suspension for infusion prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 25º C) and lighting conditions for up to 8 hours

8.3.5 Dose Specifics

125 mg/m^2 IV on days 1, 8, and 15 of each cycle.

The use of an in-line filter is not recommended.

8.3.6 Reconstitution and use of Nab-Paclitaxel

Rev. Add2

1. Calculate the patient's body surface area on day 1 of cycle 1. Dose modification is only required if weight changes ≥ 10% from baseline weight.

Rev. Add3

2. Calculate the total dose (in mg) to be administered by:
   - **Total Dose (mg) = BSA x (study dose mg/m^2)**
3. Calculate the total number of vials required by:

$$\textbf{Total Number of Vials} = \frac{\textbf{Total Dose (mg)}}{\textbf{100 (mg/vial)}}$$

Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (e.g., if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).

4. Using sterile technique, prepare the vials for reconstitution.
5. Swab the rubber stoppers with alcohol.
6. Aseptically, reconstitute each Nab-Paclitaxel vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
   - **Slowly** inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of **1 minute**, using the sterile syringe directing the solution flow onto the **inside wall** of the vial.
   - **DO NOT INJECT** the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.
   - Once the injection is complete, allow the vial to sit for a **minimum of 5 (five) minutes** to ensure proper wetting of the lyophilized cake/powder.
   - **Gently** swirl and/or invert the vial **slowly** for at least **2 minutes** until complete dissolution of any cake/powder occurs. Avoid generation of foam. Rapid agitation or shaking will result in foaming.
   - If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.
   - Each ml of reconstituted product will contain 5 mg of paclitaxel.
7. Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient:
   - **Dosing volume (ml) = Total dose (mg) / 5 (mg/ml)**
8. The reconstituted suspension should be milky and homogeneous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed.
9. Once the exact volume of reconstituted Nab-Paclitaxel has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures.
10. Further dilution is not necessary. Inject the calculated dosing volume of reconstituted Nab-Paclitaxel suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag.

11. Administer the calculated dosing volume of reconstituted Nab-Paclitaxel suspension by IV infusion over 30 minutes. The use of in-line filters is not recommended because the reconstituted solution may clog the filter.

8.3.7 Route of Administration

IV infusion

8.3.8 Incompatibilities

Intravenous bags and administration sets containing DEHP (di-[2-ethylexyl] phthalate). No further information available.

8.3.9 Availability

Nab-Paclitaxel is available commercially.

8.3.10 Side Effects

Refer to Package Insert for Adverse Events.

8.3.11 Nursing/Patient Implications

Nab-Paclitaxel is injected into a vein [intravenous (I.V.) infusion] over 30 minutes. The use of an in-line liter is not recommended.

8.3.12 References

FDA approved package insert.

8.4 Trastuzumab (NSC 688097)

NOTE: Please refer to the commercial package insert for more information.

8.4.1 Other Names

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

8.4.2 Classification

Monoclonal antibody

8.4.3 Mode of Action

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

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

8.4.4 Description

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.

8.4.5 Storage

Store at 2−8°C (36−46°F) prior to reconstitution.

8.4.6 Dose Specifics

Initial loading dose of 8mg/kg IV on cycle 1 day 1; Subsequent doses will be administered at 6mg/kg IV on day 1 of each cycle

If preferred, trastuzumab may be administered weekly with an initial loading dose of 4mg/kg IV on cycle 1 day 1; Subsequent doses will be administered at 2 mg/kg IV weekly thereafter.

8.4.7 Route of Administration

Intravenous infusion

8.4.8 Incompatibilities

Formal drug-drug interaction studies have not been performed, but clinical treatment with other chemotherapy agents (anthracyclines, cyclophosphamide, taxanes, fluoropyrimidines, cisplatin, gemcitabine, capecitabine, anastrozole) did not appear to influence trastuzumab kinetics.

8.4.9 Availability

Commercially available

8.4.10 Side Effects

See Section 5.7.1 for side effects.

8.5 Pertuzumab (NSC 740102)

NOTE: Please refer to the commercial package insert for more information.

8.5.1 Other Names

Perjeta®, RO4368451

8.5.2 Classification

HER2/neu receptor antagonist

8.5.3 Mode of Action

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

8.5.4 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.

8.5.5 Storage

Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use.

Keep vial in the outer carton in order to protect from light. **DO NOT FREEZE. DO NOT SHAKE.**

8.5.6 Dose Specifics

Initial loading dose of 840mg IV on cycle 1 day 1; Subsequent doses will be administered at 420 mg IV day 1 of each cycle.

8.5.7 Route of Administration

Intravenous infusion

8.5.8 Incompatibilities

Do not use dextrose (5%) solution.

8.5.9 Availability

Commercially available

8.5.10 Side Effects

See Section 5.7.2 for side effects.

8.6 Biosimilar drugs

Refer to the drug packet inserts for drug information and adverse events.

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8.7 Pertuzumab-Trastuzumab-Hyaluronidase (NSC 827796)

NOTE: Please refer to the commercial package insert for more information.

8.7.1 Other Names

PHESGO®

8.7.2 Classification

Monoclonal antibody and HER2/neu receptor antagonist

8.7.3 Mode of Action

Pertuzumab-Trastuzumab-Hyaluronidase is a combination product containing pertuzumab and trastuzumab at fixed doses, along with hyaluronidase.

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

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

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

8.7.4 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.

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.

8.7.5 Storage and Stability

Store at 2−8°C (36−46°F) prior to use. Product is available in a single-dose vial, ready to use.

In syringe, product may be stored up to 24 hours refrigerated (2−8°C) or 4 hours at ambient temperature, protected from light. Do not shake.

8.7.6 Dose Specifics

This product is available in two fixed doses:

A fixed dose of 1200mg pertuzumab, 600mg trastuzumab and 30,000units hyaluronidase in a 15mL vial. This strength is meant for initial dose (Cycle 1) only, not maintenance dose.

A fixed dose of 600mg pertuzumab, 600mg trastuzumab and 20,000units hyaluronidase in a 10mL vial. This strength is meant for maintenance dosing.

If substituting this product in place of IV trastuzumab and IV pertuzumab, it may only be administered on Day 1 per cycle, the weekly schedule does not apply. This agent replaces both individual medications and should never be given in combination with either individual medication in the same cycle.

8.7.7 Route of Administration

Subcutaneous injection, as 1200mg/600mg/30,000units in 15mL over 8 minutes (initial dose, Cycle 1 only), or 600mg/600mg/20,000units in 10mL over 5 minutes (maintenance dose, subsequent cycles).

8.7.8 Incompatibilities

Formal drug-drug interaction studies have not been performed, but clinical treatment with other chemotherapy agents (anthracyclines, cyclophosphamide, taxanes, fluoropyrimidines, cisplatin, gemcitabine, capecitabine, anastrozole) did not appear to influence trastuzumab kinetics.

8.7.9 Availability

Commercially available

8.7.10 Side Effects

See Section 5.7.1 for side effects.

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8.8 Trastuzumab-Hyaluronidase (NSC 827797)

NOTE: Please refer to the commercial package insert for more information.

8.8.1 Other Names

HERCEPTIN HYLECTA®

8.8.2 Classification

Monoclonal antibody

8.8.3 Mode of Action

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

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

8.8.4 Description

Trastuzumab-Hyaluronidase 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-Hyaluronidase 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.

8.8.5 Storage and Stability

Store at 2−8°C (36−46°F) prior to use. Product is available in a single-dose vial, ready to use.

In syringe, product may be stored up to 24 hours refrigerated (2−8°C) or 4 hours at ambient temperature, protected from light. Do not shake.

8.8.6 Dose Specifics

Fixed dose of 600mg/10,000units in 5mL for subcutaneous administration. **If substituting this product in place of IV trastuzumab, it may only be administered on Day 1 per cycle, the weekly schedule does not apply.**

8.8.7 Route of Administration

Subcutaneous injection

8.8.8 Incompatibilities

Formal drug-drug interaction studies have not been performed, but clinical treatment with other chemotherapy agents (anthracyclines, cyclophosphamide, taxanes, fluoropyrimidines, cisplatin, gemcitabine, capecitabine, anastrozole) did not appear to influence trastuzumab kinetics.

8.8.9 Availability

Commercially available

8.8.10 Side Effects

See Section 5.7.1 for side effects.

9. Statistical Considerations

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One major change is made to the study design in the Amendment #5: RFS in HER2-positive/ER-positive patients and RFS in HER2-positive/ER-negative patients are now two primary endpoints (vs. RFS in all HER2-positive patients as the primary endpoint). The two cohorts will be designed and analyzed separately with the same hypotheses (i.e., null: 3-year RFS<=92%, alternative: 3-year RFS=95%). The sample size is increased accordingly (n=2156 vs. n=1250). ER status will be defined according to established criteria (*Allison, etal. J Clin Oncol 2020 Apr 20;38(12):1346-1366*) and reported by local sites in case report form. As of July 17, 2021, 554 patients have enrolled to the trial. Given the observed proportion of ER status so far and the expected pCR rate in each cohort, the two cohorts would be expected to reach the target accrual goal (i.e., 388 patients with pCR after neoadjuvant THP therapy) at similar time. If the ER status distribution and/or pCR rate changes with time and one cohort reaches its accrual goal first, accrual will terminate for this cohort, and accrual for the other cohort will continue until accrual goal is reached for that cohort.

Another change in the study design is the expected accrual rate. Previously we expected an average of 35 patients would be enrolled each month over the whole accrual period. The actual accrual has kept increasing quickly since the first patient enrollment in March 2020, the average accrual rate in the past six months was 58 patients per month (range: 49-70), and it was 65 patients per month in the past 3 months (June-August 2021). There are still sites that are activating this trial, it is expected the accrual rate will stabilize at about 65 patients per month from now on. The expected average accrual rate is now about 52 patients per month since study activation and is used in the Amendment #5.

The combination of the significant increase in the total sample size (n=2156 vs. n=1250 patients) and much higher than previously expected accrual rate (52 vs. 35 patients per month) results in a slightly longer accrual period (3.5 years vs 3 years) and study duration (final analysis is expected at 7.5 years vs. 6.5 years) compared to the previous design.

Sample size for the CTC correlative objective has no change in the Amendment #5. Expansion of the sample size for it will be discussed with Epic Sciences and will be included in future amendment if approved.

9.1 Study Objectives

The primary objective of this single arm trial is to evaluate a de-escalation of standard therapy for patients with clinical stages II or IIIa (according to AJCC cancer staging manual anatomic staging table, 8th edition) HER2-positive breast

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cancer. Specifically, the study has independent primary objectives to determine if 3-year recurrence-free survival (RFS) is greater than 92% among clinical stages II or IIIa patients with HER2-positive breast cancer (including ER-positive patients and ER-negative patients) who achieve pCR (ypT0/is ypN0) after preoperative therapy with 12 weeks of a taxane, trastuzumab (or FDA approved biosimilar) and pertuzumab (THP x 12). RFS is defined as the time from date of surgery until the date of the first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of locoregional invasive breast tumor, distant recurrence, and death from any cause. Post-operatively, patients

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will receive standard of care adjuvant locoregional therapy, plus completion of 12 months of HER2-targeted therapy (and standard endocrine therapy for patients

with hormone receptor-positive disease). In the study, HER2-positive status will be based on the local HER2 test result according to the 2018 ASCO/CAP HER2 Testing Guideline Focused Update. Patients with the following HER2 test results (dual ISH ratio < 2.0 and HER2 copy number ≥6.0, but IHC 2+ and not 3+) were allowed to enroll to the trial prior to Amendment #3, and such patients will be deemed ineligible after Amendment #3. Six patients with the above HER2 test results have already been enrolled to the trial prior to Amendment #3; they are unlikely to attain pCR and will be excluded from the primary analysis even if a pCR is attained in view of the unclear HER2 biology of these tumors (see Section 1.4). ER status will be based on the local ER test result according to established criteria (Allison, etal. J Clin Oncol 2020 Apr 20;38(12):1346-1366), and ≥1% of cells staining will be defined as ER-positive for the primary endpoint analysis.

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9.2 Statistical Consideration for the Primary Objective

Given the de-escalation nature of the trial, it will test a non-inferiority hypothesis. A typical non-inferiority randomized phase III trial would require a very large sample size and long duration of follow up, which is not feasible. Thus, EA1181 will have a single arm design for each cohort separately (i.e., HER2-positive/ER-positive cohort, HER2-positive/ER-negative cohort) and apply the precedent established by the single arm APT study in patients with a lower anatomic risk. In EA1181, the null hypothesis is a 3-year RFS rate for patients who achieve pCR with preoperative THP that would be considered unacceptably low given the non-inferiority hypothesis of the study. The alternative hypothesis is a 3-year RFS that would be considered good enough to forgo further chemotherapy. Rejecting the null hypothesis would provide evidence that patients who achieve a pCR with preoperative THP have a clinically acceptable prognosis with continuation of HP therapy and no further postoperative chemotherapy.

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Based on data from previous trials in similar patient populations (6, 20) and extensive discussions among the study investigators, we concluded that, for the study patients who have stage II or IIIa HER2-positive breast cancer and have achieved pCR after treatment with neoadjuvant THP x 12 weeks, the 3-year RFS will be considered unacceptable if it is 92% or less (null hypothesis), and it will be considered worthwhile if the 3-year RFS is at least 95% (alternative hypothesis). and the lowest confidence margin excludes 92%. For the alternative hypothesis of 95% 3-year RFS rate, we are referencing the 3-year invasive disease-free survival (IDFS) in the node positive cohort of the APHINITY Trial for the arm that received both trastuzumab and pertuzumab and had a 3-year IDFS of 92%. For EA1181, we feel we will be selecting the best of these patients with a higher initial anatomic stage and who achieve pCR after THP x 12 weeks. In addition, the IDFS endpoint includes both contralateral breast cancer and new primary non-breast cancers that are not included in RFS (the endpoint in the COMPASS trial), and these additional “events” occur in 1-2% of patients in many studies. The same null and alternative hypotheses will apply to both patient cohorts (ie, HER2-positive/ER-positive cohort, HER2-positive/ER-negative cohort), hence the same number of patients with pCR will be required in each cohort (see Section 9.2.2).

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A single arm trial evaluating a de-escalation of a standard of care would usually be considered a phase II study. A one-sided type I error of 0.025 will be used in this trial since the trial is aimed to provide a definitive answer given that its results could potentially change clinical practice if the primary objective is met.

9.2.1 Projected Accrual Rate

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At the time of the study design, it was expected that about 35 patients would be enrolled to the trial each month based upon several factors listed below. The actual accrual so far, however, has been doing much better than that. The average accrual rate was 58 patients per month in the past six months, and 65 patients per month in the past 3 months. Based on the observed accrual rate, we expected the overall average accrual rate for this trial will be about 52 patients per month.

1) Over the last 10 years, neoadjuvant therapy has become a standard approach in HER2-positive disease, due to the valuable prognostic information obtained from the response to therapy and the availability of new drugs, such as pertuzumab, in this space. This is particularly true for those with clinical stage II-IIIa disease, the population that is eligible for this trial.
2) Data from the recent publication of the KATHERINE trial showed a 50% reduction in the risk of recurrence of invasive breast cancer or death among patients with HER2-positive early breast cancer who had residual invasive disease after completion of neoadjuvant therapy and who were then treated with post-neoaduvant T-DM1 compared to trastuzumab. These results further increase the likelihood that clinicians will opt to treat patients with HER2-positive clinical stage II-IIIa disease with neoadjuvant therapy, in order to identify patients with a higher residual risk of future recurrence who could benefit from a change in HER2-targeted therapy to T-DM1.
3) Our proposed design expands on lessons learned from the APT trial, a study that enrolled 410 patients with low risk, node-negative, HER2-positive disease (mostly stage 1 and some with tumors up to 3.0 cm) in just 3 years in a small number of institutions. Taken together, these factors strongly support the notion that the breast cancer community is receptive to a study like EA1181 that will test the hypothesis that surgery as a functional biomarker can be used to identify patients with HER2-positive breast cancer and a higher baseline anatomic risk who have disease that is particularly responsive to HER2-targeted therapy and could be effectively treated with chemotherapy de-escalation and have an excellent clinical outcome.

The focus on de-escalation of chemotherapy in EA1181 is of key interest to the breast cancer research community, for providers and for patients, and is one of the research priorities established by the NCI Breast Cancer Steering Committee. ECOG-ACRIN sites were polled and enthusiastically support this concept. The Alliance also has a track record of successful preoperative trials from their legacy groups. Achieving the target accrual in a timely fashion will be further supported by a collaborative approach across NCTN groups. While EA1181 will be led by ECOG-ACRIN, trial activation throughout the NCTN and a shared trial steering committee comprised of EA and Alliance breast committee leaders will enable the study to accrue at the projected rate.

9.2.2 Sample Size Consideration and Accrual

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With 388 eligible patients with pCR after neoadjuvant therapy and 33 RFS events, the trial would have about 80% power to detect the difference in the failure hazard of 0.0171 vs. 0.0278 (i.e., 3-year RFS 95% vs 92%), assuming exponential distribution of RFS, in each patient cohort separately. This corresponds to a hazard ratio of 1.63 for null to alternative with a one-sided type I error rate of 0.025. As the two primary endpoints are independent, there is no split in type I error rate. The sample size/power calculation is based on Wald test for the log failure rate parameter for this design.

Assuming 60% of pCR rate among HER2-positive/ER-negative patients and 30% pCR rate among HER2-positive/ER-positive patients and about 10% drop-out rate after registration due to some reason (e.g., early discontinuation of THP therapy due to adverse events, rare events of progression of disease that precludes surgery, patients who achieve pCR but do not continue on de-escalation arm), the trial will enroll 718 HER2-positive/ER-negative patients and 1438 HER2-positive/ER-positive patients in about 3.5 years, based on an average accrual rate of 52 patients per month after study activation (see Section 9.2.1). Data about pCR rate and drop-out status will be collected in real time, and the two assumptions will be monitored twice a year via ECOG-ACRIN DSMC for each patient cohort. If the observed proportions for pCR and drop-out are not consistent with the assumptions used in the design, the sample size for EA1181 will be adjusted accordingly and analysis will be conducted to explore the reasons. Based on the observed rate of ER status as of July 17, 2021, it is expected that the two patient cohorts will reach its accrual goal at similar time (i.e., 3.5 years after study activation). In case that the ER status distribution changes with time and one cohort reaches its accrual goal first, accrual will terminate for this cohort, and the other cohort will continue open to accrual until reaching its target accrual.

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It will take 3.5 years of follow up to achieve the required number of RFS events for the final analysis for the primary objective in each patient cohort. There will be two interim analyses planned at about 3.8 and 4.3 years after the enrollment of the first patient to the study, respectively (see Section 9.2.3).

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Patients with 2-3 cm, ER+ and node negative disease have “borderline” risk of recurrence, and there is concern that inclusion of these patients could lead to escalation of treatment in this subset of patients for whom a full year of adjuvant pertuzumab might not otherwise be recommended. In EA1181, these patients will be included in the HER2-positive/ER-positive cohort but the study will cap them at 20%, i.e., no more than 78 HER2-positive/ER-positive patients with pCR will fall into this subset in the primary analysis population for the HER2-positive/ER-positive cohort. This number is chosen based on the observed 23% of patients with 2-3 cm, ER+ and node negative disease in the KRISTINE study and will be monitored twice a year via ECOG-ACRIN DSMC. At the DSMC meeting when it is the first time to see 70 or more patients in this subset have been

enrolled before the accrual completion of the cohort, enrollment of this subset will be closed in four weeks from the date of the data pull for the DSMC meeting, and the study protocol will be amended accordingly to clarify that. As of July 20, 2022, when the data were pulled for the fall 2022 DSMC meeting, 73 patients with ≤3 cm, ER+ and node negative disease had been observed in the primary analysis population in the HER2-positive/ER-positive cohort. Announcement of EA1181 closure of the patients with 2-3 cm, ER+ and node negative HER2-positive/ER-positive disease was sent to all sites on July 27, 2022 to close the accrual for this subset.

9.2.3 Interim Analysis Plan

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EA1181 is investigating a de-escalation of standard therapy, and a harm analysis for RFS is planned for the trial in each patient cohort in case patients do noticeably worse than expected when forgoing adjuvant chemotherapy. The harm analysis will be conducted when about 25% of the patients are evaluable for the primary endpoint of 3-year RFS (i.e., patients either experience a recurrence/death or have been followed for 3 years without one) in each patient cohort. In this harm analysis, termination of one or both cohort will be considered by ECOG-ACRIN and CTEP if the 3-year RFS is significantly less than the null of 92% based on a one-sided significance level of 5%. The harm analysis will take place at about 3.8 years after the enrollment of the first patient to the study based on the assumed accrual rate and hazard rate. In addition, an interim futility analysis will be conducted at about 4.3 years after the enrollment of the first patient when about 40% of the patients are evaluable for the primary endpoint. One or both cohorts will terminate early if the observed 3-year RFS rate is below the null of 92% in the interim futility analysis. Accrual to the trial will continue while interim analysis is being conducted.

9.2.4 Analysis Plan for Primary and Secondary Objectives

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The HER2-positive/ER-positive cohort and HER2-positive/ER-negative cohort will be analyzed separately. Efficacy endpoints are defined in accordance to the STEEP system, the start point is date of surgery for EA1181 since it is a single arm trial. RFS is the primary endpoint, defined as the time from date of surgery until the date of the first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of locoregional invasive breast tumor, distant recurrence, and death from any cause. Secondary endpoints include invasive disease-free survival (IDFS), distant disease-free survival (DDFS), distant relapse-free survival (DRFS), recurrence-free interval (RFI), and overall survival (OS). IDFS is defined as the time from date of surgery until the date of the first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of locoregional invasive breast tumor, distant recurrence, contralateral invasive breast cancer, second primary non-breast invasive cancer (other than squamous or basal cell skin cancer) and death from any cause. DDFS is defined as the time from date of surgery until the date of the first occurrence of one of the following events: distant recurrence, second primary non-breast invasive cancer (other than squamous or basal cell skin

cancer) and death from any cause. DRFS is defined as the time from date of surgery until the date of the first occurrence of one of the following events: distant recurrence and death from any cause. RFI is defined as the time from date of surgery until the date of the first occurrence of recurrence of ipsilateral invasive breast tumor, recurrence of locoregional invasive breast tumor, distant recurrence, and death from breast cancer. OS is defined as the time from date of surgery until the date of death from any cause. Another secondary endpoint is event-free survival (EFS), defined as the time from study registration to any of the following events: progression of disease that precludes surgery, local or distant recurrence, or death from any cause.

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The final analysis will take place at about 7.5 years (3.5 years of accrual plus 3.5 years of follow-up plus 6 months of data cleaning) after trial activation unless the full information is reached at an earlier time point (i.e., the final analysis will be conducted no later than 7.5 years after trial activation as if fewer than 33 RFS events occurred by then it would indicate a lower hazard rate than hypothesized). For the above primary (RFS) and secondary clinical endpoints (IDFS, DDFS, DRFS, RFI, and OS), all HER2-positive patients who have a pCR after neoadjuvant THP therapy and do not receive any adjuvant chemotherapy will be included in the final analysis in each cohort, regardless of its eligibility status and whether patient completes the full 17 doses of HER2-targeted therapy or not after surgery. EFS will be assessed in all patients who register to the trial, regardless of its eligibility status. Kaplan-Meier method will be used to estimate the survival curve for all time-to-event endpoints in the overall analysis population and by pretreatment clinical stage and ER status. Greenwood method will be used to estimate the 95% confidence interval for 3-year rate. Wald test will be conducted to test whether the observed 3-year RFS is better than the null hypothesis. For all secondary clinical endpoints, the analysis will be descriptive and there will be no statistical test. Analyses pertaining to adverse events will be based on all treated cases and will be conducted separately for neoadjuvant therapy in all patients and adjuvant therapy in pCR patients. Adverse events will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All treatment-emergent and baseline adverse events and hematological/biochemical toxicities based on laboratory measurements, as well as drug related AEs, will be summarized by NCI CTCAE v5.0 worst grade. The incidence of deaths and treatment-emergent serious adverse events (defined as number of patients experiencing the AE divided by all treated patients) will be summarized using binominal proportions and binomial exact 95% confidence intervals. The incidence of adverse events leading to discontinuation of protocol therapy will be summarized and listed as well.

9.3 Statistical Consideration for Circulating Tumor Cells Objectives

In EA1181, detection of circulating tumor cells (CTC) will be determined using the Epic Sciences CTC detection and characterization platform both before

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neoadjuvant THP therapy and after completion of neoadjuvant THP therapy. We hypothesize that the detection of CTC at baseline will predict lower pCR rate, and the detection of CTC at baseline, after 3 weeks of THP, after 12 weeks of THP (before surgery), after surgery before any additional therapy, and after completion of HER2-targeted therapy will predict worse RFS for the patients who achieve pCR after neoadjuvant THP therapy. CTC detection will be coded as a binary variable (positive versus negative), and positive CTC will be defined as ≥1 cell/7.5 mL in the blood. In order to test the hypothesis about CTC and RFS, research blood is mandatory for all patients enrolled in the trial, and all patients with research blood and successful assay results about CTC will be included in the analysis. For this objective, HER2-positive/ER-positive and HER2-positive/ER-negative patients will be combined in the primary analysis, and each cohort will be analyzed separately as exploratory analysis. The CTC analysis will be conducted in the first 1250 patients only. The study will be over-powered for the analysis about baseline CTC and pCR, both the statistical significance and clinical significance will be considered when the results are being interpreted in terms of the prognostic value of CTC for pCR.

9.3.1 Power calculation for pCR rates by baseline CTC

It is assumed that among the 1250 patients enrolled to the trial, 80% of them (n=1000) will have a successful assay results about CTC status at baseline (i.e., 20% of patients either have no blood sample or have assay failure on the blood sample), and about 20% are expected to be CTC positive at baseline. Hence, about 200 patients will be CTC positive and 800 patients will be CTC negative before neoadjuvant THP therapy in this trial.

With 200 evaluable patients in CTC positive group and 800 patients in CTC negative group at baseline, the trial has at least 80% power to detect a 12% difference in pCR rates between the two subsets using Fisher exact test with two-sided type I error of 0.05 e.g., there will be about 84% power to compare pCR rates of 52% vs 40%.

9.3.2 Power calculation for 3y RFS by CTC

It is assumed that among the 450 patients with pCR after neoadjuvant therapy, 80% of them (n=360) will have a successful assay results about CTC status at both baseline and after neoadjuvant therapy. The CTC analysis will be conducted at the final analysis time for the primary objective (i.e., 6 years after study activation), a total of 33 RFS events are expected to have occurred to the 450 pCR patients by then. Assuming the same distribution of the 80% patients with successful assay results with the 20% with assay failure, about 26 RFS events will occur to the 360 patients with pCR and having known CTC status.

At baseline, we expect about 72 patients will be CTC positive and 288 patients will be CTC negative assuming 20% CTC detection rate before neoadjuvant THP therapy. With 360 patients with pCR and 26 RFS events at the analysis time, the minimal HR for positive CTC versus negative CTC that could be detected with at least 80% power at two-sided type I error of 0.05 will be 3.1, assuming the 3-year RFS is 95% for the overall sample (i.e., under the alternative hypothesis of the primary objective of the trial) and the proportion of positive CTC is

20%. The minimal HR that can be detected with 80% power will be 3.5, 3.0 and 3.5 if the proportion of positive CTC is 10%, 30% and 40% at baseline, respectively.

Regarding the association between CTC detection after the neoadjuvant THP therapy and RFS, we assume about 5% patients will be CTC positive after neoadjuvant therapy, the minimal HR for positive CTC versus negative CTC that could be detected with at least 80% power at two-sided type I error of 0.05 will be 4.5, assuming the 3-year RFS is 95% for the overall sample.

9.3.3 Analysis Plan

The proportion of CTC detection at each assessment time point and the proportions of patients whose CTC disappear or persist after neoadjuvant THP therapy will be estimated with 95% exact binomial CI. Factors associated with CTC detection at baseline and persistence of CTC after neoadjuvant therapy (i.e., positive CTC at both baseline and after neoadjuvant THP therapy) will be analyzed using Chi square test and logistic regression models.

For pCR rate by CTC detection at baseline, all patients with a known CTC status (positive vs negative) who receive at least one dose of protocol therapy will be included in the analysis regardless whether they receive surgery or not, and whether they are eligible or not. The pCR rate will be compared between CTC positive and CTC negative groups using Fisher exact test. The association of detection of CTC at baseline and after neoadjuvant THP therapy with RFS will be analyzed using Cox proportional hazard models. Available potential confounding variables will be adjusted in the Cox models. Association of change of CTC after neoadjuvant THP therapy (negative at both assessments vs. positive at baseline and negative after neoadjuvant therapy vs. positive at both assessments) with RFS will be also explored using Cox proportional hazard model. Kaplan-Meier method will be used to estimate the survival curve for RFS in each group. The significance level is two-sided 0.05 for all the tests without adjustment for multiple comparisons.

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9.4 Statistical Consideration for MRI Radiomics Objectives

If we allow ~2.5 months for substudy approval and that the trial continues to enroll around 70 participants per month, we estimate approximately 860 future patients will be consented and eligible for the radiomics substudy. Based on breast MRI rates for the patients enrolled to date, we estimate approximately 70% of eligible subjects will have baseline MRIs. Radiomic feature extraction is described in Section 11.2.3. The study expects approximately 40% pCR rate and at least 92% 3-year EFS.

9.4.1 Power calculation for pCR rates by baseline MRI Radiomics

It is assumed that among the final ~860 patients to be enrolled to the trial, 70% of them (n=602) will have baseline breast MRI examinations (i.e., 30% of patients have assessments only by mammography or ultrasound) and be eligible for the MRI study, and about 70% of sites will provide acceptable imaging data (some may not participate in

imaging transmission and some imaging protocols may deviate substantially from standard breast MRI guidelines). Hence, we estimate about 420 patients will have baseline MRIs available for the secondary MRI radiomics study objective, of whom we expect 168 will achieve pCR and 386 will remain event-free within 3 years of follow-up.

Previous models, based on substantially smaller datasets, suggest an AUC of around 0.8 (95% CI [0.61-0.98]) using baseline radiomics features (Braman et al, 2019) and an AUC of around 0.76 (95% CI [0.66, 0.86]) using radiologist assessment of post-treatment/presurgery MRI (Scheel et al, 2018). The substantially larger sample size allows us to build more complex models, which is expected to increase the marker AUC. With an expected AUC of 0.88, we have >80% power to test the hypothesis that the new marker has an AUC that is greater than 0.8 (LeDell, Petersen, van der Laan, 2015). Furthermore, a sample size of 420 results in an expected width of 0.12 for a 95% confidence interval for the AUC (compared to a width of 0.37 (Braman et al, 2019) and 0.2 (Scheel et al, 2018). Previous markers have reported sensitivity of 0.94 and specificity of 0.58 (Braman et al, 2019) resulting in an nPV of 0.895.

9.4.2 Analysis Plan

The features to be used are described in Section 11.2.3. The prediction model for the probability of achieving pCR will be built using a LASSO model with a logit link function where the associated penalization term is calculated using five-fold cross-validation.

Prior breast MRI radiomics studies have typically had much smaller sample sizes (e.g., ranging between 56-132; Li, et al 2016, Ashraf, et al 2014, Wu, et al 2018, Braman et al, 2019, Jahani, et al 2019) and therefore this larger study has strong potential to support more detailed analysis and modeling. To take advantage of the larger sample size, we will explore if more complex machine learning algorithms such as random forests (Breiman, 2001) have additional predictive value compared to the simpler LASSO model (where the comparisons will be based on the cross-validated evaluation measures discussed in the next paragraph). The machine learning algorithms rely on several tuning parameters (e.g., number of trees for random forests) and five-fold nested cross-validation will be used to select the most important tuning parameters.

The primary evaluation measure will be the area under the curve (AUC). We will also consider positive predictive value, and negative predictive value with all confidence intervals estimated non-parametrically. Positive and negative predictive values rely on selecting a cut-off for classification. To select a cut-off for classification, the Youden index will be used to find the optimal cut-off point on the receiver operating characteristic curve. We will use nested five-fold cross-validation to calculate all evaluation measures. Nested cross-validation avoids over-optimism due to potential overfitting and it also ensures that the tuning parameter selection is accurately reflected in the prediction error. The goal of this aim is to

develop markers and perform early-internal evaluation of the markers and we will not perform external validation. To be considered for inclusion in a therapeutic trial a more formal validation on an external data source is needed.

As a secondary end-point, we will also explore EFS risk prediction models such as the proportional hazards-based LASSO model (Tibshirani, 1997; Steingrimsson, 2019). Due to few expected events, any analysis based on EFS is expected to have low power and will be interpreted in that context.

Rev. Add9

9.5 Statistical considerations for TILs objectives

Histopathologic analysis of percentage of tumor-infiltrating lymphocytes (TILs) will be performed in the study one or more a single full-face HE-stained tumor section slides in the baseline tumor and in the residual tumor. Assessment will be performed using criteria described by the International TILS Working Group (https://www.tilsinbreastcancer.org) (Salgado et al, 2015). Stromal TILs will be defined as the percentage of tumor stroma containing infiltrating lymphocytes. Scoring will be performed as previously described (Adams et al, 2014).

9.5.1 Sample size/Power calculation

We hypothesize that the 3-yr RFS will be significantly longer in patients with high sTILs (sTILs > 60%) vs low sTILs (sTILs < 10%) in the baseline tumor in all patients enrolled to the trial. Based on the meta-analysis by Denkert et al, we expect about 40% of the patients will have low sTILs (<10%), 40% will have intermediate sTILs (10%-60%) and 20% will have high sTILs (>60%) (Denkert et al, 2018).

Assuming 3-year RFS of 95% for pCR patients (i.e., the primary objective for EA1181) and 89% for non-pCR patients (including those had no surgery and those had residual disease after surgery) based on the T-DM1 arm in KATHERINE trial, we will have about 320 RFS events among all the 2156 patients at the final analysis time (vonMincwitz, 2018). So far, about 80% patients enrolled have consented to the biomarker study and about 90% of them either submitted blocks or H&E slides. Assuming the 80% of patients with consent and the 90% of them who actually submitted tumor tissue (either block or H&E slide) is a representative sample of all patients **and the** above **proportion**s **will remain the same until the completion of accrual**, then we will have about 230 RFS events in the 1552 consented patients who submitted blocks/H&E slides at the final analysis time, about 930 patients (20% + 40%) will have either high or low sTILs.

With a total of 930 patients and about 138 RFS events (assuming 60% of the events), the minimal hazard ratio (HR) that can be detected with two-sided type I error of 0.05 and 80% power using log rank test is 0.565 for high vs. low sTILs. The number of events available and included in the analysis will affect the detectable minimal HR (e.g., minimal HR would be 0.498 if 100 RFS event, 0.537 if 120 RFS events, and it would be 0.592 if 160 RFS events and 0.614 if 180 RFS events). Overall, the study has adequate power to detect a moderate and large HR.

With 930 patients (310 with high sTILs and 620 with low sTILs), the study will have 82% power to detect a pCR rate of 45% vs 35% with one-sided type I error rate of 0.025, using two-sample Fisher Exact test. Overall, the study has adequate power to detect a small difference in pCR. Both the statistical significance and clinical significance need to be considered when interpreting the pCR results.

9.5.2 Analysis Plan

The sTILs data will be analyzed at the final analysis time (ie, no specific further follow up for this objective). The distribution of sTILs level at baseline will be described using mean and standard deviation or median and range, whichever is appropriate. Factors associated with sTILs level at baseline will be explored using multivariable linear regression model. Fisher exact test will be used to examine the association between high vs low sTILs and pCR. Univariate and multivariable logistic regression models will also be constructed to examine the association of pCR with baseline sTILs level as continuous variable and categorical variable (low vs intermediate vs high). Kaplan-Meir method, log rank test, and Univariate and multivariable Cox proportional hazard models will be used to evaluate the association between baseline sTILs and RFS endpoint, with sTILs being included as a categorical variable (low vs intermediate vs high). Cox models with TILs being included as a continuous variable will be fit as well. These analyses will be conducted first in all patients and subsequently in patients with HER2-positive/ER-positive breast cancer and in patients with HER2-positive/ER-negative breast cancer, separately. Different cutoff points for sTILs will be explored in the above analyses using sensitivity, specificity, positive predictive value, area under the ROC curves, and the STEPP and MFPI analyses.

9.6 Statistical Consideration for To-Be-Defined Exploratory Correlative Objectives

EA1181 has three exploratory correlative objective, the analysis of TILs, immune activation gene signatures, change in intrinsic subtype from baseline to surgery and plasma tumor cell-free DNA tumor-specific mutations. The association of these biomarkers with pCR and/or long-term outcomes will be explored.

An amendment or proposal for these and any additional correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of biological samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

9.7 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data and Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or

blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Center.

Rev. Add5

9.8 Gender and Ethnicity

Male breast cancer accounts for approximately 1% of all breast cancers, and about 15% of breast cancer patients are HER2-positive. Meanwhile, patients with T1N0 or metastatic disease are not eligible for the study. We could anticipate that all patients who participate in the study will be female patients with HER2-positive disease. For the 2156 HER2-positive patients, based on previous data from E1100, E1104, E1105, and E2103 studies, the anticipated accrual in subgroups defined by gender and race/ethnicity is:

Racial Categories	**Ethnic Categories**				Total
	Hispanic or Latino		Not Hispanic or Latino		
	Females	Males	Females	Males	
American Indian or Alaskan Native	0	0	0	0	0
Asian	0	0	17	0	17
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Black or African American	17	0	276	0	293
White	103	0	1743	0	1846
Racial Category: Total of all subjects	120	0	2036	0	2156

Rev. Add7

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

10. Specimen Submissions

Rev. Add8 Tumor tissue (FFPE block and H&E slide) from the archived diagnostic clinical biopsy specimen and from the tumor excision for patients with no pCR from the residual
Rev. Add3 disease on the definitive surgical specimen are to be submitted for future undefined research studies (per patient consent).

Rev. Add3 Blood is to be submitted for defined laboratory research studies (mandatory) or undefined future research studies (per patient consent).

Rev. Add2 **NOTE:** There are two separate kits that need to be ordered for shipment of blood specimens to both EA CBPF (per patient consent) and Epic Sciences (mandatory). Ordering instructions are outlined below.

All specimens must be clearly labeled with the ECOG-ACRIN protocol number [EA1181], the patient's initials and ECOG-ACRIN patient sequence number, the collection date, and specimen type. For pathology materials, it is strongly recommended that full patient names be provided.

It is required that all specimens submitted on this trial be entered and tracked via the ECOG-ACRIN Sample Tracking System (STS) (Section 10.4). An STS shipping manifest form is to be included with every submission.

10.1 Submissions of Tissue and Blood to ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)

Rev. Add3 Submit from patients who answer 'Yes' to 'I agree to provide additional blood and tissue samples for future health research.'

Rev. Add3 If you have any questions concerning tumor tissue and blood submissions please contact the ECOG-ACRIN CBPF at (844) 744-2420 or eacbpf@mdanderson.org

Rev. Add3 Kits for the collection and shipment of the blood specimens are ordered online from Cenetron Central Laboratories. Instructions are provided in Appendix IV. Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000. Kits must be ordered after the patient has been registered to the trial and will generally arrive within three (3) business days from when the order was placed.

10.1.1 Pathology Material Submissions to EA CBPF

Submitting pathologist and clinical research associate may refer to Appendix I, which outlines the Pathology Submission Guidelines.

Rev. Add8 The tumor tissue specimens and pathology reports are to be labeled with the institution's assigned pathology accession ID# as well as the information above.

10.1.1.1 **Required Materials**

Forms: Must be submitted with all pathology submissions.

- STS generated shipping manifest form
- Copy of the institutional diagnostic and surgical pathology reports (for archived clinical biopsy and residual tumor specimens)

10.1.1.2 Archived Tumor Tissue from Clinical Biopsy

Rev. Add2
Rev. Add2
Rev. Add8
Rev. Add3
Rev. Add9

- Formalin-fixed paraffin-embedded (FFPE) tumor tissue block from the clinical biopsy containing representative tumor tissue. At least two (2) complete tissue cores (these are the actual cores collected by the needle during the actual biopsy) must be included and both cores must contain at least 5mm of invasive cancer. If one core has < 5 mm of invasive cancer, then at least 1cm (in total) of invasive cancer must be submitted. **A representative H&E slide must be included for all patients, even if a block cannot be submitted.** If a site is unable to provide a tumor block, submit twenty (20) 5 µm unstained, uncharged, air-dried plus slides from the thickest part of the tumor from the diagnostic biopsy core.
- Quality assurance procedures will be performed on all tissues received by the CBPF. In patients for whom the FFPE tissue block was found not to be adequate, sites are requested to send a replacement specimen to ensure that adequate tissue is available.
- If there is an urgent medical need, a site, on behalf of a study patient, may request in writing to CBPF (use 'Specimen Return Request Form' from CBPF or access from http://www.ecog.org/ecoginst/trans/) that a block be returned to the site for reasons of clinical management of the patient.

10.1.1.3 Residual Disease Surgical Tumor Tissue Specimen

Rev. Add2
Rev. Add8
Rev. Add7

Formalin-fixed paraffin-embedded (FFPE) tumor tissue block containing a representative portion of the patient's invasive primary breast cancer (portion containing at least 5 mm in largest dimension, if possible, and at least 20% invasive breast cancer tissue) obtained from the residual disease must be submitted on the definitive surgical specimen from patients with no pCR. **A representative H&E slide must be included for all Arm B patients, even if a block cannot be submitted.**

- Quality assurance procedures will be performed on all tissues received by the CBPF. In patients for whom the FFPE tissue block was found not to be adequate, sites are requested to send a replacement specimen to ensure that adequate tissue is available.
- If there is an urgent medical need, a site, on behalf of a study patient, may request in writing to CBPF (use 'Specimen Return Request Form' from CBPF or access from http://www.ecog.org/ecoginst/trans/) that a block be returned to the site for reasons of clinical management of the patient.
- **If a site is unable to provide a tumor block,** submit a core punch biopsy from the tissue block or unstained

slides from the tissue block from the definitive surgical resection specimen. The CBPF (844-744-2420) can provide a punch core biopsy kit to the site for this purpose. For slides, submit twenty (20) 5 µm unstained, uncharged, air-dried plus slides from the thickest part of the tumor.

Rev. Add3

If possible, at least two (2) complete tissue cores must be included and both cores must contain at least 5 mm of

Rev. Add8

invasive cancer. If a block or core punches cannot be submitted, an H&E slide must still be submitted.

Rev. Add3

10.1.1.4 Blood Submissions to EA CBPF (for cfDNA)

Blood specimens are to be collected at the following four time points:

- Baseline before THP (Cycle 1, Day 1, any time before start of chemotherapy or other systemic therapy if residual disease)
- After One Cycle of THP (Cycle 2, Day 1)

Rev. Add3
Rev. Add5

- After Surgery, any time after surgery before the first post-surgery systemic therapy is administered or at the first post-surgery visit for trastuzumab (or FDA approved biosimilar) and pertuzumab (or other systemic therapy if residual disease)] **(from patients with pCR)**
- After Completion of HER2-Directed Adjuvant Therapy **(from patients with pCR)**

10.1.2 Specimen Preparation Guidelines

Streck Cell-Free DNA Tubes (four [4] times points)

- Draw two (2) 10mL Streck Cell-Free DNA BCT tubes of whole blood at each time point. Fill each tube completely.
- Ensure at least 10mL of blood is drawn in each tube. Avoid low volume to minimize agitation during shipping.
- Immediately after collection, gently invert tubes 180 degrees and back 10 times to ensure adequate mixing.
- Maintain blood at room temperature (6ºC to 37ºC) until shipping. **Do Not** place Streck tubes in refrigerator. Ship to EA CBPF day of collection.
- **NOTE:** The two Streck tubes for CTC (see Section 10.2.1) must be collected **after** the first two Streck tubes for future cfDNA studies.

10.1.3 Shipping Procedures

Tumor tissue specimens from the archived clinical biopsy and from the residual disease are to be shipped at ambient temperature (cool packs in warmer months) within one (1) month following registration or collection.

Rev. Add3

Blood specimens are to be shipped at ambient temperature on the day of collection Monday through Friday via overnight courier.

Ship using the CBPF's FedEx account using the FedEx on-line ship manager.

Ship to:

Rev. Add3

MD Anderson Cancer Center CBPF
Mike Balco
Life Science Plaza - Suite 910
2130 West Holcombe Boulevard, LSP9.4227
Houston, TX 77030

Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

Access to the FedEx shipping account for shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can only be obtained by logging onto fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your institution needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org

An STS shipping manifest form must be generated and shipped with all specimen submissions.

Rev. Add3

10.2 Mandatory Submission of Blood (CTCs) to Epic Sciences (five [5] time points)

If you have any questions concerning specimen collection and shipment, please contact Epic Sciences at (858) 356-6610 or partners@epicsciences.com.

Blood specimens are to be collected at the following time points:

- Baseline before THP (Cycle 1, Day 1, or any time before start of chemotherapy or other systemic therapy if residual disease)
- After One Cycle of THP (Cycle 2, Day 1)

Rev. Add3

- After Four Cycles of Neoadjuvant HP (Pre-Surgery - can be collected at the surgical visit or any time at least one week after Cycle 4 and before surgery, this does not require an extra visit with the medical oncologist))

Rev. Add5

- After Surgery, any time after surgery before the first post-surgery systemic therapy is administered or at the first post-surgery visit for trastuzumab (or FDA approved biosimilar) and pertuzumab (or other systemic therapy if residual disease)
- After Completion of HER2-Directed Adjuvant Therapy

Rev. Add8

Epic Sciences will be providing collection and shipping kits to include Streck Cell-Free DNA BCT tubes and shipping containers. Please complete online form provided in link below to order blood collection kits:

Rev. Add1

https://forms.office.com/r/iXNRpX2NNx

Indicate Epic Project ID as 'EP-002' and for type of collection kit indicate '2-tube blood collection kit – TR'. Kits will generally arrive within seven (7) business days from when the order was placed.

Please use FedEx account number: 680817251 when shipping specimens to Epic Sciences for this trial only.

10.2.1 Specimen Preparation Guidelines

The first 5mL of blood collected from the fresh venipuncture cannot be used for the collection into the Streck tubes due to possibility of contaminating epithelial cells during venipuncture. Please ensure that at least one (1) blood tube of 5mL or more is collected prior to collection of the CTC specimen to avoid adversely affecting the test results.

Rev. Add2

NOTE: The two Streck tubes for CTCs must be collected after the first two Streck tubes for future cfDNA in patients who consented to cfDNA blood collection (see Section 10.1.2).

Prevention of Backflow:

Since Streck Cell-Free DNA tubes contain chemical additives, it is important to avoid possible backflow from the tube. To guard against backflow, observe the following precautions:

- Keep patient's arm in the downward position during the collection procedure
- Hold the tube with the stopper uppermost
- Release tourniquet once the blood starts to flow into the tube, or within two minutes of application
- Tube contents should not touch stopper or the end of the needle during the collection procedure

Blood Collection Instructions:

- Confirm blood tube is not expired. Expired tubes should not be used for blood collection.
- Draw whole blood specimen into two (2) 10mL Streck Cell-Free DNA tubes. Fill tube until blood flow stops.

  NOTE: Epic requires minimum of 4mL of blood per time point, but a full 10mL tube of blood should be provided when possible.
- **Remove tube from adapter and immediately mix by gentle inversion 8 to 10 times. Tube inversion prevents clotting. Inadequate or delayed mixing may result in inaccurate tests results.**
- Label the tube with ECOG-ACRIN protocol number (EA1181), ECOG-ACRIN five-digit patient sequence number and date and time of blood draw. Unlabeled blood tubes may not be processed.
- Keep specimen at room temperature and ship on day of collection in shipper provided at ambient temperature. **Do not** place Streck tubes in refrigerator.

10.2.2 Specimen Shipment Procedures (to Epic Sciences)

Rev. Add2 **Please use FedEx account number: 680817251 when shipping specimens to Epic Sciences for this trial only.**

Specimens should be shipped overnight day of collection.

Rev. Add3 **Epic Sciences is open for specimen receipt and processing Monday – Saturday. Please mark courier slip with 'Saturday Delivery' if shipping on Thursday and Fridays.**

Rev. Add1 Clinical sites should provide email notification of specimen shipment to Epic Sciences on the day of collection, send notification to: partners@epicsciences.com

The email should contain:

- Trial Code (EA1181/EP-002)
- ECOG-ACRIN 5-Digit Patient Sequence Number
- Collection Date and Time
- Time Point/Visit
- Tracking Information

Do not place 'Infectious Substance' sticker on shipper, as this can result in a delay of shipment.

Rev. Add2 Ship specimens day of collection via FedEx overnight to:

Epic Sciences
Attn: EA1181 / EP-002
9381 Judicial Drive, Suite 200
San Diego, CA 92121
Phone: (858) 356-6610
Fax: (858) 356-5852

An STS shipping manifest form must be generated and shipped with all specimen submissions.

10.3 Use of Specimens in Research

Rev. Add9 H&E slides will be digitally scanned by the ECOG-ACRIN Central Biorepository and Pathology Facility and forwarded to Dr. Sunil Badve at Emory University for TILs analysis.

Specimens submitted will be processed to maximize their utility for current and future research projects and may include, but not limited to, extraction of plasma, serum, DNA and RNA.

NOTE: EA1181 has several exploratory correlative objectives, including tumor intrinsic subtyping, immune activation gene signatures, DNA copy number changes and mutations, and plasma tumor cell-free DNA tumor-specific mutations. The association of these biomarkers with pCR and/or long-term survival outcomes will be explored.

An amendment or proposal for these and any additional correlative science studies to be performed on biological specimens will be submitted to CTEP/NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of biological specimens will include the

appropriate background, experimental plans with assay details, and a detailed statistical section. Specimens for testing will not be released until the appropriate NCI approvals have been obtained.

Specimens from patients who consented to allow their specimens to be used for future approved research studies will be retained in an ECOG-ACRIN designated central repository. For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility. Specimens will be de – identified prior to distribution for any approved research studies.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future study. Pathology materials may be retained for documentation purposes or returned to the site. All other specimens will be destroyed per guidelines of the respective repository.

10.4 ECOG-ACRIN Sample Tracking System

It is **required** (barring special circumstances) that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). As of June 2007, the software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the specimen required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest must be generated and shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu .

Study Specific Notes:

Generic Specimen Submission Form (#2981v3) will be required only if STS is unavailable at time of specimen submission. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory.

Retroactively enter all specimen collection and shipping information when STS is available.

10.5 Sample Inventory Submission Guidelines

Inventories of all specimens submitted will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized will be submitted by the laboratories to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

11. Biomarker Studies

11.1 Blood-Based Biomarkers

We hypothesize that circulating tumor cells (CTCs) detected in blood will predict response (pCR) and/or recurrence (RFS) after neoadjuvant therapy in the COMPASS trial. These circulating markers have demonstrated prognostic significance in several cohort studies. However, the clinical utility of these markers has not been established in the neoadjuvant setting. The COMPASS trial will potentially provide the necessary data to establish clinical utility of circulating biomarkers when measured before, during and after neoadjuvant and adjuvant therapy in HER2-positive patients. We hypothesize that these markers will complement pCR in predicting long term outcomes and be useful in identifying patients in whom escalation and de-escalation strategies are appropriate. Moreover, these markers may be useful in identifying targets for intervention in patients who have not had a complete pathologic response to neoadjuvant therapy.

Rev. Add3

11.1.1 CTC Detention (Enumeration and Special Studies) in Blood

In 2004, the seminal work by Cristofanilli et al. demonstrated that CTC count was an independent prognostic factor for progression-free survival (PFS) and OS in metastatic BC (Cristofanili et al, 2004). In a large study involving 2,026 primary BC patients, CTCs have been detected in the blood of approximately 22% of patients after surgery and before adjuvant therapy (Rack et al, 2012). In the adjuvant setting, CTC detection (≥ 1 CTC in 7.5 mL of blood) before chemotherapy has shown to be an independent predictor of disease-free survival (DFS) and OS and, not only the presence but also the quantity of CTCs has proven to be associated with worse outcome. Moreover, the persistence of CTCs after adjuvant treatment significantly correlates with a decreased DFS (Rack et al, 2012; Lucci et al, 2012). CTC evaluation in patients with early-stage BC could provide useful information for adjuvant treatment decision-making. However, in this particular context, CTCs are observed with low frequency. Thus, CTC detection methods with higher sensitivity could be necessary for their clinical use. Moreover, further studies are needed to better define its efficacy in both the prediction of outcome in the neoadjuvant setting and monitoring the effect of HER2-directed therapy.

The Epic Sciences CTC detection and characterization platform enables enumeration of CTCs as well as evaluation of protein biomarker expression and subcellular localization when used with their 1) 4 or 5-color immunofluorescence assays, 2) gene amplifications, deletions or rearrangements by DNA FISH and 3) genomic aberrations via mutation or copy number variation (CNV) analysis via next-generation sequencing (NGS).

Analytical validation in terms of assay performance, accuracy, linearity, specificity and precision of CTC enumeration was published in by Werner et al (Werner et al, 2015). An excerpt of data that highlights the performance of key parameters is shown below.

Performance Characteristics	Assessment Parameter	Spike-In CLCs	Measured Parameter
Accuracy	Recovery of nucleated cells	0 to 300 CLSs/slide (7 serial dilutions)	% Recovery of Nucleated Cells
Linearity (Reportable Range)	Assay Linearity	0 to 300 CLCs/Slide (7 serial dilutions)	Linear Regression of CLC Count
Specificity	False Positive CLC Detection	Unspiked healthy donor slides	CLC Count
Precision/Repeatability	Intra-Assay (n=3 replicate tests / run) Inter-Assay (n=5 runs / 3 operators) Intra-Operator (n=3 runs / operator) Inter-Operator (n=3 runs / 3 operators)	(i) 25 CLCs/slide (ii) 300 CLCs/slide	% CV CLC Count

These are the analytical characteristics assessed to benchmark the performance of the Epic Sciences CTC detection and characterization platform. Varying concentrations of COLO-205 cell line cells (CLCs) were spiked into healthy donor blood, red blood cells were lysed, and 3 x 106 nucleated cells were deposited onto slides, ranging from 0-300 CLCs/slide. Slides were stained with a cocktail of CK, CD45 and DAPI antibodies. Assay accuracy, linearity, specificity and precision were determined as described in the methods. For each analysis, a "run" is comprised of three tests, with each test consisting of two replicate slides.

11.1.1.1 Specimen Processing and Assessment for CTCs

CTC enumeration on the Epic Sciences platform consists of:

1. **Slide Prep:** Upon receipt of patient blood specimen, whole blood is lysed and nucleated cells are deposited on up to 12 microscope slides that are frozen at -80 ºC until analysis.
2. **Cell Staining and Scanning:** Slides are immunofluorescently stained and scanned by Epic's rapid fluorescent scanning method, which images each nucleated cell.

3. **CTC Identification and Biomarker Analysis:** A digital pathology algorithm, which includes protein expression and morphology, differentiates candidate CTCs from surrounding white blood cells (WBCs). CTCs are confirmed and classified into one of the following categories (1) Traditional CTCs, (2) CTC clusters, (3) CK(-) CTCs and (4) Apoptotic CTCs (see CTC basics to review these different classes of CTCs).

The Epic Sciences' platform analyzes all nucleated cells within a blood specimen at single cell resolution. Cells from a patient's blood specimen are deposited on replicate glass slides and compared for morphological features, expression of biomarkers and nuclear integrity, using immunofluorescent staining. Guided by cell phenotype and marker expression, CTCs are individually recovered from the slide surface. Their genomes are amplified (WGA) and analyzed by next-generation sequencing (NGS) for the presence of point mutations, copy number alterations, genome wide chromosomal instability, ploidy or genome wide scarring.

Rev. Add8

11.2 Radiomics Biomarkers

In this sub study, standard of care breast MR imaging for patients enrolled in the EA1181 trial will be collected for baseline and post-treatment/pre-surgery time points, which will be submitted and archived through TRIAD. Anonymized MR images will be accessed and analyzed by ECOG-ACRIN Radiomics working group investigators, with an aim to develop predictive radiomic signatures of therapy response in breast cancer patients receiving anti-HER2 therapy.

11.2.1 Breast MRI Requirements:

Breast MRI examinations may be performed per standard of care at the site. In line with standard guidelines, a dedicated bilateral breast MRI scan is expected, including a dynamic contrast-enhanced (DCE) MRI sequence with pre and post-contrast T1-weighted imaging and injection of gadolinium-based contrast agent (0.1 mmol/kg via intravenous catheter) followed by saline flush (ACR, 2020).

11.2.2 American College of Radiology (ACR) Core Laboratory Quality Assurance Review

All MRI imaging should be submitted to the ACR Core Laboratory via TRIAD for Image Quality Assurance (IQA) review.

Upon image receipt, an Imaging Technologist will perform an IQA review to ensure that all imaging has been submitted in its entirety. In the event that an exam is deemed incomplete, a Core Lab Imaging Technologist will issue a query within the Medidata Rave data management system.

Please note: Please refrain from anonymizing the DICOM header of any exam prior to uploading into the TRIAD application. Custom DICOM editing can exclude an exam from the final analysis, due to the omission of technical data elements. These elements include, but

are not limited to, the study date, scanner station name, scanner serial number, and any scan acquisition parameter. TRIAD has been uniquely configured to locate and scrub all PHI from the exam's DICOM header, during the image transfer to ensure the anonymity of our trial patients.

11.2.3 Breast MR Image Interpretation and Analysis:

Lesions will be segmented and analyzed using semi-automated software tools. Established DCE-MRI kinetics-based markers of functional tumor volume (FTV) and signal enhancement ratio (SER) will be measured as previously described (Partridge et al, 2016; Hylton, 2016). Additionally, a large panel of radiomics features will be extracted from the DCE MRI scans using an established algorithm such as the PyRadiomics package in Python (3.6.4) (van Griethuysen et al, 2017). Image preprocessing techniques such as intensity normalization, gray-level standardization, cubic interpolation etc. will be implemented to help alleviate the effects of differences in scan acquisition across the multisite data. A range of imaging features will be extracted (approximately 100), examples of which include: 1) First-order statistics (intensity histogram metrics), 2) Shape-based descriptors, 3) Gray level co-occurrence matrix (GLCM) features related to heterogeneity of intensities, 4) Gray level size zone matrix features, 5) Gray level run length matrix (GLRLM) features, and a variety of other higher order features. Preprocessing steps and radiomic feature extraction will be performed Dimensionality reduction approaches, such as principal component analysis and independent component analysis, and feature selection approaches may be used as appropriate to alleviate feature correlations and multiple comparisons.

11.3 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secure data transfer to the ECOG-ACRIN Operations Office - Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the Investigator.

Rev. Add8 **12. Imaging Sub-study**

12.1 Submission of Routine Breast MRIs to ECOG-ACRIN (baseline and pre-surgery)

All trial sites will be expected to contribute MRIs for the radiomics substudy. We expect most participants will undergo as standard of care (SOC), a baseline breast MRI for pretreatment assessment, and that many will also undergo post-treatment MRI prior to surgery, depending on institutional standard of care and physician preference.

TRIAD:

12.1.1 MRI Imaging Timepoints for Submission

- Baseline SOC Breast MRI, if completed
- Post-treatment SOC Breast MRI, prior to surgery, if completed

MRI submission via TRIAD should occur up to 6 months post MRI acquisition date. The ECOG-ACRIN Imaging Core Lab will work with research sites to support TRIAD setup and submission of Breast MRI images. Exemptions to the image submission requirement will be granted to sites on a case-by-case basis if deemed not feasible by the ECOG-ACRIN imaging team, including if this requirement is substantially affecting accrual.

12.1.2 Digital Imaging Data Submission Using TRIAD

TRIAD is the American College of Radiology (ACR)'s proprietary image exchange application that will be used as the sole method of data transfer to the ACR Clinical Research Center Core Laboratory for this trial. TRIAD can be installed on one or several computers of choice within the institutional "firewall" and on the institutional network; internet access is required. The TRIAD application can then be configured as a DICOM destination on either scanner(s) and/or PACS system for direct network transfer of study related images into the TRIAD directory. When properly configured, the TRIAD software de-identifies, encrypts, and performs a lossless compression of the images before they are transferred to the ACR Imaging Core Laboratory image archive in Philadelphia.

12.1.3 DICOM Requirements

Please refrain from anonymizing the DICOM header of any exam prior to uploading into the TRIAD application. Custom DICOM editing can exclude an exam from the final analysis, due to the omission of technical data elements. These elements include, but are not limited to, the study date, scanner station name, scanner serial number, and any scan acquisition parameter. TRIAD has been uniquely configured to locate and scrub all PHI from the exam's DICOM header, during the image transfer to ensure the anonymity of our study participants. All anonymization occurs locally at the site, so no PHI is transmitted through the Internet.

Images that are provided to ACR must comply with the DICOM Part 10 standard and must be in a file format compatible with that standard. The DICOM image files must be stored in DICOM part 10 format directly from the DICOM equipment which generated them (no intermediate image processing tools to generate "DICOM compatible" files are supported). The DICOM images may be created in one of the lossless compressed formats supported by the DICOM standard. These requirements need to be followed for every image submission to ACR CRI, including Screening and Baseline images.

12.1.4 TRIAD Access Requirements

Site staff who will submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to CTEP Registration Procedures of the protocol for instructions on how to request a CTEP-IAM account. To submit images, the site user must be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users

should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

12.1.5 TRIAD Installations

When a user applies for a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/ This process can be done in parallel to obtaining your CTEP-IAM account username and password. If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org or call 703-390-9858.

13. Electronic Data Capture

Please refer to the **EA1181** Forms Completion Guidelines for the forms submission schedule. Data collection will be performed in Medidata Rave.

Rev. Add1 Required submission of patient demographic data for this study will be submitted automatically via OPEN.

NOTE: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

14. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

15. References

1. Hudis CA, Barlow WE, Costantino JP, Gray RJ, Pritchard KI, Chapman JA, Sparano JA, Hunsberger S, Enos RA, Gelber RD, Zujewski JA. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol. 2007;25(15):2127-32. doi: 10.1200/JCO.2006.10.3523. PubMed PMID: 17513820.
2. Figueroa-Magalhaes MC, Jelovac D, Connolly R, Wolff AC. Treatment of HER2-positive breast cancer. Breast (Edinburgh, Scotland). 2014;23(2):128-36. Epub 2013/12/24. doi: 10.1016/j.breast.2013.11.011. PubMed PMID: 24360619; PMCID: PMC4466908.
3. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Jr., Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673-84. Epub 2005/10/21. doi: 353/16/1673 [pii] 10.1056/NEJMoa052122. PubMed PMID: 16236738.
4. Perez EA, Romond EH, Suman VJ, Jeong JH, Sledge G, Geyer CE, Jr., Martino S, Rastogi P, Gralow J, Swain SM, Winer EP, Colon-Otero G, Davidson NE, Mamounas E, Zujewski JA, Wolmark N. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014;32(33):3744-52. doi: 10.1200/JCO.2014.55.5730. PubMed PMID: 25332249; PMCID: PMC4226805.
5. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, Mackey J, Glaspy J, Chan A, Pawlicki M, Pinter T, Valero V, Liu MC, Sauter G, von Minckwitz G, Visco F, Bee V, Buyse M, Bendahmane B, Tabah-Fisch I, Lindsay MA, Riva A, Crown J, Breast Cancer International Research G. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273-83. doi: 10.1056/NEJMoa0910383. PubMed PMID: 21991949; PMCID: 3268553.
6. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, Suter T, Arahmani A, Rouchet N, Clark E, Knott A, Lang I, Levy C, Yardley DA, Bines J, Gelber RD, Piccart M, Baselga J, Committee AS, Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J

Med. 2017;377(2):122-31. doi: 10.1056/NEJMoa1703643. PubMed PMID: 28581356; PMCID: PMC5538020.

7. Prowell TM, Pazdur R. Pathological complete response and accelerated drug approval in early breast cancer. N Engl J Med. 2012;366(26):2438-41. doi: 10.1056/NEJMp1205737. PubMed PMID: 22646508.
8. Miller KD. Questioning Our APHINITY for More. N Engl J Med. 2017;377(2):186-7. doi: 10.1056/NEJMe1706150. PubMed PMID: 28581347.
9. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnefoi H, Cameron D, Gianni L, Valagussa P, Swain SM, Prowell T, Loibl S, Wickerham DL, Bogaerts J, Baselga J, Perou C, Blumenthal G, Blohmer J, Mamounas EP, Bergh J, Semiglazov V, Justice R, Eidtmann H, Paik S, Piccart M, Sridhara R, Fasching PA, Slaets L, Tang S, Gerber B, Geyer CE, Jr., Pazdur R, Ditsch N, Rastogi P, Eiermann W, von Minckwitz G. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384(9938):164-72. doi: 10.1016/S0140-6736(13)62422-8. PubMed PMID: 24529560.
10. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, Wolmark N, Rastogi P, Schneeweiss A, Redondo A, Fischer HH, Jacot W, Conlin AK, Arce-Salinas C, Wapnir IL, Jackisch C, DiGiovanna MP, Fasching PA, Crown JP, Wulfing P, Shao Z, Rota Caremoli E, Wu H, Lam LH, Tesarowski D, Smitt M, Douthwaite H, Singel SM, Geyer CE, Jr., Investigators K. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019;380(7):617-28. doi: 10.1056/NEJMoa1814017. PubMed PMID: 30516102.
11. Prowell TM, Beaver JA, Pazdur R. Residual Disease after Neoadjuvant Therapy - Developing Drugs for High-Risk Early Breast Cancer. N Engl J Med. 2019;380(7):612-5. doi: 10.1056/NEJMp1900079. PubMed PMID: 30763188.
12. Prat A, Carey LA, Adamo B, Vidal M, Tabernero J, Cortes J, Parker JS, Perou CM, Baselga J. Molecular features and survival outcomes of the intrinsic subtypes within HER2-positive breast cancer. J Natl Cancer Inst. 2014;106(8). doi: 10.1093/jnci/dju152. PubMed PMID: 25139534; PMCID: PMC4151853.
13. Llombart-Cussac A, Cortes J, Pare L, Galvan P, Bermejo B, Martinez N, Vidal M, Pernas S, Lopez R, Munoz M, Nuciforo P, Morales S, Oliveira M, de la Pena L, Pelaez A, Prat A. HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial. Lancet Oncol. 2017;18(4):545-54. doi: 10.1016/S1470-2045(17)30021-9. PubMed PMID: 28238593.
14. Prat A, Bianchini G, Thomas M, Belousov A, Cheang MC, Koehler A, Gomez P, Semiglazov V, Eiermann W, Tjulandin S, Byakhow M, Bermejo B, Zambetti M, Vazquez F, Gianni L, Baselga J. Research-based PAM50 subtype predictor identifies higher responses and improved survival outcomes in HER2-positive breast cancer in the NOAH study. Clin Cancer Res. 2014;20(2):511-21. doi: 10.1158/1078-0432.CCR-13-0239. PubMed PMID: 24443618.
15. Carey LA, Berry DA, Cirrincione CT, Barry WT, Pitcher BN, Harris LN, Ollila DW, Krop IE, Henry NL, Weckstein DJ, Anders CK, Singh B, Hoadley KA, Iglesia M, Cheang MC, Perou CM, Winer EP, Hudis CA. Molecular Heterogeneity and Response to Neoadjuvant Human Epidermal Growth Factor Receptor 2 Targeting in CALGB 40601, a Randomized Phase III Trial of Paclitaxel Plus Trastuzumab With or Without Lapatinib. J Clin Oncol. 2016;34(6):542-9. doi:

10.1200/JCO.2015.62.1268. PubMed PMID: 26527775; PMCID: PMC4980567 online at www.jco.org. Author contributions are found at the end of this article.

16. Tolaney SM, Barry WT, Dang CT, Yardley DA, Moy B, Marcom PK, Albain KS, Rugo HS, Ellis M, Shapira I, Wolff AC, Carey LA, Overmoyer BA, Partridge AH, Guo H, Hudis CA, Krop IE, Burstein HJ, Winer EP. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med. 2015;372(2):134-41. doi: 10.1056/NEJMoa1406281. PubMed PMID: 25564897; PMCID: PMC4313867.
17. Tolaney SM, Barry WT, Guo H, Dillon D, Dang CT, Yardley DA, et al. Seven-year (yr) follow-up of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC). DOI: 10.1200/JCO.19.00066 Journal of Clinical Oncology 37, no. 22 (August 1 2019) 1868-1875.
18. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, Lluch A, Staroslawska E, de la Haba-Rodriguez J, Im SA, Pedrini JL, Poirier B, Morandi P, Semiglazov V, Srimuninnimit V, Bianchi G, Szado T, Ratnayake J, Ross G, Valagussa P. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(1):25-32. doi: 10.1016/S1470-2045(11)70336-9. PubMed PMID: 22153890.
19. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, Tausch C, Seo JH, Tsai YF, Ratnayake J, McNally V, Ross G, Cortes J. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2013;24(9):2278-84. Epub 2013/05/25. doi: 10.1093/annonc/mdt182. PubMed PMID: 23704196.
20. Gianni, Lancet 2016; 17(6):791-800
21. Cassidy JT, Petty RE. Acute renal failure. In: Brunswald E; Kurt J; Petersdorf RG, et al., editors. Harrison's principles of internal medicine. New York: McGraw-Hill; 1987. p. 1149-5 Symmans WF, Wei C, Gould R, Yu X, Zhang Y, Liu M, Walls A, Bousamra A, Ramineni M, Sinn B, Hunt K, Buchholz TA, Valero V, Buzdar AU, Yang W, Brewster AM, Moulder S, Pusztai L, Hatzis C, Hortobagyi GN. Long-Term Prognostic Risk After Neoadjuvant Chemotherapy Associated With Residual Cancer Burden and Breast Cancer Subtype. J Clin Oncol. 2017;35(10):1049-60. doi: 10.1200/JCO.2015.63.1010. PubMed PMID: 28135148; PMCID: PMC54553525.
22. Untch M, Fasching PA, Konecny GE, Hasmuller S, Lebeau A, Kreienberg R, Camara O, Muller V, du Bois A, Kuhn T, Stickeler E, Harbeck N, Hoss C, Kahlert S, Beck T, Fett W, Mehta KM, von Minckwitz G, Loibl S. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. J Clin Oncol. 2011;29(25):3351-7. doi: 10.1200/JCO.2010.31.4930. PubMed PMID: 21788566.
23. van Ramshorst MS, van Werkhoven E, Mandjes IAM, Schot M, Wesseling J, Vrancken Peeters M, Meerum Terwogt JM, Bos MEM, Oosterkamp HM, Rodenhuis S, Linn SC, Sonke GS. Trastuzumab in combination with weekly

paclitaxel and carboplatin as neo-adjuvant treatment for HER2-positive breast cancer: The TRAIN-study. Eur J Cancer. 2017;74:47-54. doi: 10.1016/j.ejca.2016.12.023. PubMed PMID: 28335887.

24. Gianni L, Eiermann W, Semiglazov V, Lluch A, Tjulandin S, Zambetti M, Moliterni A, Vazquez F, Byakhov MJ, Lichinitser M, Climent MA, Ciruelos E, Ojeda B, Mansutti M, Bozhok A, Magazzu D, Heinzmann D, Steinseifer J, Valagussa P, Baselga J. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet Oncol. 2014;15(6):640-7. doi: 10.1016/S1470-2045(14)70080-4. PubMed PMID: 24657003.
25. de Azambuja E, Holmes AP, Piccart-Gebhart M, Holmes E, Di Cosimo S, Swaby RF, Untch M, Jackisch C, Lang I, Smith I, Boyle F, Xu B, Barrios CH, Perez EA, Azim HA, Jr., Kim SB, Kuemmel S, Huang CS, Vuylsteke P, Hsieh RK, Gorbunova V, Eniu A, Dreosti L, Tavartkiladze N, Gelber RD, Eidtmann H, Baselga J. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. Lancet Oncol. 2014;15(10):1137-46. doi: 10.1016/S1470-2045(14)70320-1. PubMed PMID: 25130998.
26. Gianni L, Pienkowski T, Im YH, Tseng LM, Liu MC, Lluch A, Staroslawska E, de la Haba-Rodriguez J, Im SA, Pedrini JL, Poirier B, Morandi P, Semiglazov V, Srimuninnimit V, Bianchi GV, Magazzu D, McNally V, Douthwaite H, Ross G, Valagussa P. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016;17(6):791-800. doi: 10.1016/S1470-2045(16)00163-7. PubMed PMID: 27179402.
27. Krop IE, Hillman D, Polley M-Y, Tanioka M, Parker J, Huebner L, et al. Invasive disease-free survival and gene expression signatures in CALGB (Alliance) 40601, a randomized phase III neoadjuvant trial of dual HER2-targeting with lapatinib added to chemotherapy plus trastuzumab. Presented at the 40th annual San Antonio Breast Cancer Symposium (SABCS), December 5-9 2017, General Session 3.
28. Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, Bilous M, Ellis IO, Fitzgibbons P, Hanna W, Jenkins RB, Press MF, Spears PA, Vance GH, Viale G, McShane LM, Dowsett M. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol. 2018:JCO2018778738. doi: 10.1200/JCO.2018.77.8738. PubMed PMID: 29846122.
29. Guarneri V, Frassoldati A, Bottini A, Cagossi K, Bisagni G, Sarti S, Ravaioli A, Cavanna L, Giardina G, Musolino A, Untch M, Orlando L, Artioli F, Boni C, Generali DG, Serra P, Bagnalasta M, Marini L, Piacentini F, D'Amico R, Conte P. Preoperative chemotherapy plus trastuzumab, lapatinib, or both in human epidermal growth factor receptor 2-positive operable breast cancer: results of the randomized phase II CHER-LOB study. J Clin Oncol. 2012;30(16):1989-95. doi: 10.1200/JCO.2011.39.0823. PubMed PMID: 22493419.
30. Robidoux A, Tang G, Rastogi P, Geyer CE, Jr., Azar CA, Atkins JN, Fehrenbacher L, Bear HD, Baez-Diaz L, Sarwar S, Margolese RG, Farrar WB, Brufsky AM,

Shibata HR, Bandos H, Paik S, Costantino JP, Swain SM, Mamounas EP, Wolmark N. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. Lancet Oncol. 2013;14(12):1183-92. Epub 2013/10/08. doi: 10.1016/s1470-2045(13)70411-x. PubMed PMID: 24095300.

31. Symmans WF, Peintinger F, Hatzis C, Rajan R, Kuerer H, Valero V, Assad L, Poniecka A, Hennessy B, Green M, Buzdar AU, Singletary SE, Hortobagyi GN, Pusztai L. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol. 2007;25(28):4414-22. Epub 2007/09/06. doi: JCO.2007.10.6823 [pii]10.1200/JCO.2007.10.6823. PubMed PMID: 17785706.
32. Lipscomb J, Reeve BB, Clauser SB, et al: Patient-reported outcomes assessment in cancer trials: taking stock, moving forward. J Clin Oncol 25:5133-40, 2007.
33. S. Department of Health and Human Services, U.S. Food and Drug Administration: Guidance for Industry: Patient-Reported Outcome Measures—Use in Medical Product Development to Support Labeling Claims. 2009. http://www.fda.gov/downloads/Drugs/ GuidanceComplianceRegulatoryInformation/Guidances/ UCM193282.pdf.
34. Basch E, Abernethy AP, Mullins CD, et al: Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness research in adult oncology. J Clin Oncol 30:4249-55, 2012.
35. Bruner DW, Bryan CJ, Aaronson N, et al: Issues and challenges with integrating patient-reported outcomes in clinical trials supported by the National Cancer Institute-sponsored clinical trials networks. J Clin Oncol 25:5051-7, 2007.
36. Norton WE, Chambers DA, Kramer BS: Conceptualizing De-Implementation in Cancer Care Delivery. J Clin Oncol 37:93-96, 2019.
37. von Minckwitz G, Procter M, de Azambuja E, et al: Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med 377:122-131, 2017.
38. Vickberg SM: The Concerns About Recurrence Scale (CARS): a systematic measure of women's fears about the possibility of breast cancer recurrence. Ann Behav Med 25:16-24, 2003.
39. Mast ME: Survivors of breast cancer: illness uncertainty, positive reappraisal, and emotional distress. Oncol Nurs Forum 25:555-62, 1998.
40. Mehnert A, Berg P, Henrich G, et al: Fear of cancer progression and cancer-related intrusive cognitions in breast cancer survivors. Psychooncology 18:1273-80, 2009.
41. Koch L, Bertram H, Eberle A, et al: Fear of recurrence in long-term breast cancer survivors-still an issue. Results on prevalence, determinants, and the association with quality of life and depression from the cancer survivorship--a multi-regional population-based study. Psychooncology 23:547-54, 2014.
42. Custers JA, van den Berg SW, van Laarhoven HW, et al: The Cancer Worry Scale: detecting fear of recurrence in breast cancer survivors. Cancer Nurs 37:E44-50, 2014.
43. Elwyn G, Laitner S, Coulter A, et al: Implementing shared decision making in the NHS. BMJ 341:c5146, 2010.
44. Katz SJ, Belkora J, Elwyn G: Shared decision making for treatment of cancer: challenges and opportunities. J Oncol Pract 10:206-8, 2014.

45. Oshima Lee E, Emanuel EJ: Shared decision making to improve care and reduce costs. N Engl J Med 368:6-8, 2013.
46. Janz NK, Wren PA, Copeland LA, et al: Patient-physician concordance: preferences, perceptions, and factors influencing the breast cancer surgical decision. J Clin Oncol 22:3091-8, 2004.
47. Singh JA, Sloan JA, Atherton PJ, et al: Preferred roles in treatment decision making among patients with cancer: a pooled analysis of studies using the Control Preferences Scale. Am J Manag Care 16:688-96, 2010.
48. Tariman JD, Berry DL, Cochrane B, et al: Preferred and actual participation roles during health care decision making in persons with cancer: a systematic review. Ann Oncol 21:1145-51, 2010.
49. Nicolai J, Buchholz A, Seefried N, et al: When do cancer patients regret their treatment decision? A path analysis of the influence of clinicians' communication styles and the match of decision-making styles on decision regret. Patient Educ Couns 99:739-46, 2016.
50. Creswell J CP: Designing and Conducting Mixed Methods Research, 2nd Edition. Washington DC, Sage Publications, Inc., 2011.
51. Simard S, Thewes B, Humphris G, et al: Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. J Cancer Surviv 7:300-22, 2013.
52. Moser A, Stuck AE, Silliman RA, et al: The eight-item modified Medical Outcomes Study Social Support Survey: psychometric evaluation showed excellent performance. J Clin Epidemiol 65:1107-16, 2012.
53. Kind AJH, Buckingham WR: Making Neighborhood-Disadvantage Metrics Accessible-The Neighborhood Atlas. N Engl J Med 378:2456-2458, 2018.
54. Avis NE, Smith KW, McGraw S, et al: Assessing quality of life in adult cancer survivors (QLACS). Qual Life Res 14:1007-23, 2005.
55. Ashley L, Smith AB, Jones H, et al: Traditional and Rasch psychometric analyses of the Quality of Life in Adult Cancer Survivors (QLACS) questionnaire in shorter-term cancer survivors 15 months post-diagnosis. J Psychosom Res 77:322-9, 2014.
56. Sohl SJ, Levine B, Avis NE: Evaluation of the Quality of Life in Adult Cancer Survivors (QLACS) scale for early post-treatment breast cancer survivors. Qual Life Res 24:205-12, 2015.
57. Avis NE, Ip E, Foley KL: Evaluation of the Quality of Life in Adult Cancer Survivors (QLACS) scale for long-term cancer survivors in a sample of breast cancer survivors. Health Qual Life Outcomes 4:92, 2006.
58. Devins GM: Using the illness intrusiveness ratings scale to understand health-related quality of life in chronic disease. J Psychosom Res 68:591-602, 2010.
59. Hays RD, Bjorner JB, Revicki DA, et al: Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. Qual Life Res 18:873-80, 2009.
60. Degner LF, Sloan JA, Venkatesh P: The Control Preferences Scale. Can J Nurs Res 29:21-43, 1997.
61. Brehaut JC, O'Connor AM, Wood TJ, et al: Validation of a decision regret scale. Med Decis Making 23:281-92, 2003.

62. Lerman C, Croyle R: Psychological issues in genetic testing for breast cancer susceptibility. Arch Intern Med 154:609-16, 1994.
63. Partridge A, Adloff K, Blood E, et al: Risk perceptions and psychosocial outcomes of women with ductal carcinoma in situ: longitudinal results from a cohort study. J Natl Cancer Inst 100:243-51, 2008.
64. de Souza JA, Yap BJ, Wroblewski K, et al: Measuring financial toxicity as a clinically relevant patient-reported outcome: The validation of the COmprehensive Score for financial Toxicity (COST). Cancer 123:476-484, 2017.
65. de Souza JA, Yap BJ, Hlubocky FJ, et al: The development of a financial toxicity patient-reported outcome in cancer: The COST measure. Cancer 120:3245-53, 2014.
66. Simard S, Thewes B, Humphris G, et al: Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. J Cancer Surviv 7:300-22, 2013.
67. Moser A, Stuck AE, Silliman RA, et al: The eight-item modified Medical Outcomes Study Social Support Survey: psychometric evaluation showed excellent performance. J Clin Epidemiol 65:1107-16, 2012.
68. Avis NE, Smith KW, McGraw S, et al: Assessing quality of life in adult cancer survivors (QLACS). Qual Life Res 14:1007-23, 2005.
69. Ashley L, Smith AB, Jones H, et al: Traditional and Rasch psychometric analyses of the Quality of Life in Adult Cancer Survivors (QLACS) questionnaire in shorter-term cancer survivors 15 months post-diagnosis. J Psychosom Res 77:322-9, 2014.
70. Sohl SJ, Levine B, Avis NE: Evaluation of the Quality of Life in Adult Cancer Survivors (QLACS) scale for early post-treatment breast cancer survivors. Qual Life Res 24:205-12, 2015.
71. Avis NE, Ip E, Foley KL: Evaluation of the Quality of Life in Adult Cancer Survivors (QLACS) scale for long-term cancer survivors in a sample of breast cancer survivors. Health Qual Life Outcomes 4:92, 2006.
72. Hays RD, Bjorner JB, Revicki DA, et al: Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. Qual Life Res 18:873-80, 2009.
73. Devins GM: Using the illness intrusiveness ratings scale to understand health-related quality of life in chronic disease. J Psychosom Res 68:591-602, 2010.
74. Brehaut JC, O'Connor AM, Wood TJ, et al: Validation of a decision regret scale. Med Decis Making 23:281-92, 2003.
75. Lerman C, Croyle R: Psychological issues in genetic testing for breast cancer susceptibility. Arch Intern Med 154:609-16, 1994.
76. Ringash, J., et al., *Interpreting clinically significant changes in patient-reported outcomes.* Cancer, 2007. **110**(1): p. 196-202.
77. Cristofanilli, M., et al., *Circulating tumor cells, disease progression, and survival in metastatic breast cancer.* N Engl J Med, 2004. **351**(8): p. 781-91.
78. Rack, B., et al., *CTCs in primary breast cancer (I).* Recent Results Cancer Res, 2012. **195**: p. 179-85.
79. Lucci, A., et al., *Circulating tumour cells in non-metastatic breast cancer: a prospective study.* Lancet Oncol, 2012. **13**(7): p. 688-95.

80. Werner, S.L., et al., *Analytical Validation and Capabilities of the Epic CTC Platform: Enrichment-Free Circulating Tumour Cell Detection and Characterization.* J Circ Biomark, 2015. **4**: p. 3.
81. Carey LA, et al Clin Cancer Res. 2014;20(2):511-21. doi: 10.1158/1078-0432.CCR-13-0239. PubMed PMID: 24443618.
82. Prat A, et al. J Natl Cancer Inst. 2014;106(8). doi: 10.1093/jnci/dju152. PubMed PMID: 25139534; PMCID: PMC4151853.
83. Prat A, et al. Mol Oncol. 2011;5(1):5-23. doi: 10.1016/j.molonc.2010.11.003. PubMed PMID: 21147047; PMCID: PMC5528267.
84. Prat A, et al. Breast. 2015;24 Suppl 2:S26-35. doi: 10.1016/j.breast.2015.07.008. PubMed PMID: 26253814.
85. Cancer Genome Atlas N. Comprehensive molecular portraits of human breast tumours. Nature. 2012;490(7418):61-70. doi: 10.1038/nature11412. PubMed PMID: 23000897; PMCID: PMC3465532.
86. Fumagalli . JAMA Oncol 2016.
87. Llombart-Cussac Lancet Oncol 2017.
88. Prat et al. SABCS 2017 poster.
89. Swain et al Journal of Clinical Oncology 36, no. 15_suppl (May 20 2018) 580.
90. Carey et al, 40601 revised analysis , personal communication.
91. Llombart-Cussac A et al. Lancet Oncol. 2017;18(4):545-54. doi: 10.1016/S1470-2045(17)30021-9. PubMed PMID: 28238593.
92. https://www.accessdata.fda.gov/cdrh_docs/reviews/k130010.pdf.
93. http://prosigna.com/docs/Prosigna_Packet_Insert_US.pdf.
94. https://www.nanostring.com/application/files/8215/2840/5449/LBL-C0191-09.pdf.
95. Denkert C, Loibl S, Noske A, et al: Tumor associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol 28:105-113, 2010.
96. Denkert, von Minckwitz, Brase, Sinn, Gade et al. Tumor infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human eidemal growth factor receptor 2-positive and triple-negative primary breast cancers. Journal of Clinical Oncology, 33: 983-991, 2015.
97. Salgado, Denkert, Demaria, Sirtaine, Klauschen, Pruneri, Wienert, et al. The evaluation of tumor infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILS Working Group 2014. Annals of Oncology 26: 259-271, 2015.
98. Adams S, Gray RJ, Demaria S, Goldstein L, et al. Prognostic Value of Tumor-Infiltrating Lymphocytes in Triple Negative Breast Cacners from Two Phase III Randomized Adjuvant breast Cancer Trials: ECOG 2197 and ECOG 1199. Journal of Clinical Oncology 32: 2959-2966, 2014.
99. Stroun M, et al. The origin and mechanism of circulating DNA. Ann N Y Acad Sci 2000;906:161-8.
100. Diehl, Frank, et al. "Circulating mutant DNA to assess tumor dynamics." Nature medicine 14.9 (2008): 985-990.
101. Higgins, Michaela J., et al. "Detection of tumor PIK3CA status in metastatic breast cancer using peripheral blood." Clinical cancer research 18.12 (2012): 3462-3469.

102. Beaver, Julia A., et al. "Detection of cancer DNA in plasma of patients with early-stage breast cancer." Clinical cancer research 20.10 (2014): 2643-2650.

103. Dawson, Sarah-Jane, et al. "Analysis of circulating tumor DNA to monitor metastatic breast cancer." New England Journal of Medicine 368.13 (2013): 1199-1209.

104. Forshew, Tim, et al. "Noninvasive identification and monitoring of cancer mutations by targeted deep sequencing of plasma DNA." Science translational medicine 4.136 (2012): 136ra68-136ra68.

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105. Chan, KC Allen, et al. "Cancer genome scanning in plasma: detection of tumor-associated copy number aberrations, single-nucleotide variants, and tumoral heterogeneity by massively parallel sequencing." Clinical chemistry 59.1 (2013): 211-224.

106. Wolff, Antonio C et al. “Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update.” Journal of clinical oncology : official journal of the American Society of Clinical Oncology vol. 36,20 (2018): 2105-2122. doi:10.1200/JCO.2018.77.8738.

107. Hanna, Wedad M., et al. "HER2 in situ hybridization in breast cancer: clinical implications of polysomy 17 and genetic heterogeneity." Modern Pathology 27.1 (2014): 4-18.

108. Tse, Chun Hing, et al. "Determining true HER2 gene status in breast cancers with polysomy by using alternative chromosome 17 reference genes: implications for anti-HER2 targeted therapy." Journal of clinical oncology 29.31 (2011): 4168-4174.

109. Troxell, Megan L., et al. "Evaluation of Her-2/neu status in carcinomas with amplified chromosome 17 centromere locus." American journal of clinical pathology 126.5 (2006): 709-716.

110. Moelans, Cathy B., et al. "Molecular profiling of invasive breast cancer by multiplex ligation-dependent probe amplification-based copy number analysis of tumor suppressor and oncogenes." Modern pathology 23.7 (2010): 1029-1039.

111. Marchio, Caterina, et al. "Mixed micropapillary–ductal carcinomas of the breast: a genomic and immunohistochemical analysis of morphologically distinct components." The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland 218.3 (2009): 301-315.

112. Yeh, I-Tien, et al. "Clinical validation of an array CGH test for HER2 status in breast cancer reveals that polysomy 17 is a rare event." Modern pathology 22.9 (2009): 1169-1175.

113. Vranic, Semir, et al. "Assessment of HER2 gene status in breast carcinomas with polysomy of chromosome 17." Cancer 117.1 (2011): 48-53.

114. Stoss, Oliver C., et al. "Impact of updated HER2 testing guidelines in breast cancer—re-evaluation of HERA trial fluorescence in situ hybridization data." Modern Pathology 28.12 (2015): 1528-1534.

115. Ballard, Morgan, et al. "'Non-classical'HER2 FISH results in breast cancer: a multi-institutional study." Modern Pathology 30.2 (2017): 227-235.

116. Press, Michael F., et al. "Assessing the new American Society of Clinical Oncology/College of American Pathologists guidelines for HER2 testing by fluorescence in situ hybridization: Experience of an academic consultation practice." Archives of pathology & laboratory medicine 140.11 (2016): 1250-1258.

117. Press, Michael F., et al. "HER2 gene amplification testing by fluorescent in situ hybridization (FISH): Comparison of the ASCO-College of American Pathologists guidelines with FISH scores used for enrollment in breast cancer international research group clinical trials." Journal of Clinical Oncology 34.29 (2016): 3518.

118. Gillies RJ, Kinahan PE, Hricak H. Radiomics: Images Are More than Pictures, They Are Data. Radiology. 2016;278(2):563-77. Epub 2015/11/19. doi: 10.1148/radiol.2015151169. PubMed PMID: 26579733; PMCID: PMC4734157.

119. Saltz J, Almeida J, Gao Y, Sharma A, Bremer E, DiPrima T, Saltz M, Kalpathy-Cramer J, Kurc T. Towards Generation, Management, and Exploration of Combined Radiomics and Pathomics Datasets for Cancer Research. AMIA Jt Summits Transl Sci Proc. 2017;2017:85-94. Epub 2017/08/18. PubMed PMID: 28815113; PMCID: PMC5543366.

120. Kuhl CK, Mielcareck P, Klaschik S, Leutner C, Wardelmann E, Gieseke J, Schild HH. Dynamic breast MR imaging: are signal intensity time course data useful for differential diagnosis of enhancing lesions? Radiology. 1999;211(1):101-10. Epub 1999/04/06. doi: 10.1148/radiology.211.1.r99ap38101. PubMed PMID: 10189459.

121. Li KL, Partridge SC, Joe BN, Gibbs JE, Lu Y, Hylton NM. Invasive Breast Cancer: Predicting Disease Recurrence Using High Spatial Resolution Signal Enhancement Ratio (SER) Imaging. Radiology. 2008;248(1):79-87.

122. Esserman L, Kaplan E, Partridge S, Tripathy D, Rugo H, Park J, Hwang S, Kuerer H, Sudilovsky D, Lu Y, Hylton N. MRI phenotype is associated with response to doxorubicin and cyclophosphamide neoadjuvant chemotherapy in stage III breast cancer. Ann Surg Oncol. 2001;8(6):549-59. Epub 2001/07/18. doi: 10.1007/s10434-001-0549-8. PubMed PMID: 11456056.

123. Hylton NM, Gatsonis CA, Rosen MA, Lehman CD, Newitt DC, Partridge SC, Bernreuter WK, Pisano ED, Morris EA, Weatherall PT, Polin SM, Newstead GM, Marques HS, Esserman LJ, Schnall MD, Team AT, Investigators IST. Neoadjuvant Chemotherapy for Breast Cancer: Functional Tumor Volume by MR Imaging Predicts Recurrence-free Survival-Results from the ACRIN 6657/CALGB 150007 I-SPY 1 TRIAL. Radiology. 2016;279(1):44-55. Epub 2015/12/02. doi: 10.1148/radiol.2015150013. PubMed PMID: 26624971; PMCID: PMC4819899.

124. Li H, Zhu Y, Burnside ES, Drukker K, Hoadley KA, Fan C, Conzen SD, Whitman GJ, Sutton EJ, Net JM, Ganott M, Huang E, Morris EA, Perou CM, Ji Y, Giger ML. MR Imaging Radiomics Signatures for Predicting the Risk of Breast Cancer Recurrence as Given by Research Versions of MammaPrint, Oncotype DX, and PAM50 Gene Assays. Radiology. 2016;281(2):382-91. Epub 2016/10/19. doi: 10.1148/radiol.2016152110. PubMed PMID: 27144536; PMCID: PMC5069147.

125. Reig B, Heacock L, Geras KJ, Moy L. Machine learning in breast MRI. J Magn Reson Imaging. 2019. Epub 2019/07/06. doi: 10.1002/jmri.26852. PubMed PMID: 31276247.

126. Ashraf AB, Daye D, Gavenonis S, Mies C, Feldman M, Rosen M, Kontos D. Identification of intrinsic imaging phenotypes for breast cancer tumors: preliminary associations with gene expression profiles. Radiology. 2014;272(2):374-84. Epub 2014/04/08. doi: 10.1148/radiol.14131375. PubMed PMID: 24702725; PMCID: PMC4564060.

127. Wu J, Li X, Teng X, Rubin DL, Napel S, Daniel BL, Li R. Magnetic resonance imaging and molecular features associated with tumor-infiltrating lymphocytes in

breast cancer. Breast Cancer Res. 2018;20(1):101. Epub 2018/09/05. doi: 10.1186/s13058-018-1039-2. PubMed PMID: 30176944; PMCID: PMC6122724.

128. Braman N, Prasanna P, Whitney J, Singh S, Beig N, Etesami M, Bates DDB, Gallagher K, Bloch BN, Vulchi M, Turk P, Bera K, Abraham J, Sikov WM, Somlo G, Harris LN, Gilmore H, Plecha D, Varadan V, Madabhushi A. Association of Peritumoral Radiomics With Tumor Biology and Pathologic Response to Preoperative Targeted Therapy for HER2 (ERBB2)-Positive Breast Cancer. JAMA Netw Open. 2019;2(4):e192561. Epub 2019/04/20. doi: 10.1001/jamanetworkopen.2019.2561. PubMed PMID: 31002322; PMCID: PMC6481453.
129. Jahani N, Cohen E, Hsieh MK, Weinstein SP, Pantalone L, Hylton N, Newitt D, Davatzikos C, Kontos D. Prediction of Treatment Response to Neoadjuvant Chemotherapy for Breast Cancer via Early Changes in Tumor Heterogeneity Captured by DCE-MRI Registration. Sci Rep. 2019;9(1):12114. Epub 2019/08/23. doi: 10.1038/s41598-019-48465-x. PubMed PMID: 31431633; PMCID: PMC6702160.
130. Scheel JR, Kim E, Partridge SC, Lehman CD, Rosen MA, Bernreuter W, Pisano ED, Marques HS, Morris EA, Weatherall PT, Polin SM, Newstead GM, Esserman LJ, Schnall MD, Hylton NM. Performance of Preoperative MRI, Clinical Examination and Mammography for Assessing Residual Disease and Predicting pCR in Breast Cancer Patients Post-Neoadjuvant Chemotherapy: Findings of the American College of Radiology Imaging Network (ACRIN) Trial 6657. Am J Roentgenol. 2018;210(6):1376-85. Doi: 10.2214/AJR.17.18323.
131. LeDell E, Petersen M, van der Laan M. Computationally efficient confidence intervals for cross-validated area under the ROC curve estimates. Electronic Journal of Statistics. 2015;9(1):1583.
132. Breiman L. Random forests. Machine Learning. 2001;45(1):5-32. doi: 10.1023/A:1010933404324.
133. Tibshirani R. The lasso method for variable selection in the Cox model. Stat Med. 1997;16(4):385-95. Epub 1997/02/28. doi: 10.1002/(sici)1097-0258(19970228)16:4<385::aid-sim380>3.0.co;2-3. PubMed PMID: 9044528.
134. Steingrimsson JA. Deep Learning for Survival Outcomes (preprint). arXiv 2019;1904:10345.
135. ACR. American College Radiology. American college of radiology breast MRI accreditation program: modalities. Available from: http://www.acraccreditation.org/Modalities/Breast-MRI. 2020
136. Partridge SC, Vanantwerp RK, Doot RK, Chai X, Kurland BF, Eby PR, Specht JM, Dunnwald LK, Schubert EK, Lehman CD, Mankoff DA. Association Between Serial Dynamic Contrast-Enhanced MRI and Dynamic 18F-FDG PET Measures in Patients undergoing Neoadjuvant Chemotherapy for Locally Advanced Breast Cancer. J Magn Reson Imaging. 2010;32(5):1124-31.
137. van Griethuysen JJM, Fedorov A, Parmar C, Hosny A, Aucoin N, Narayan V, Beets-Tan RGH, Fillion-Robin JC, Pieper S, Aerts H. Computational Radiomics System to Decode the Radiographic Phenotype. Cancer Res. 2017;77(21):e104-e7. Epub 2017/11/03. doi: 10.1158/0008-5472.CAN-17-0339. PubMed PMID: 29092951; PMCID: PMC5672828.
138. Ignatiadis, M., Van den Eynden, G., Roberto, S., Fornili, M., Bareche, Y., Desmedt, C., ... & Sotiriou, C. (2019). Tumor-infiltrating lymphocytes in patients

receiving trastuzumab/pertuzumab-based chemotherapy: a TRYPHAENA substudy. *JNCI: Journal of the National Cancer Institute*, *111*(1), 69-77.

139. Kim, R. S., Song, N., Gavin, P. G., Salgado, R., Bandos, H., Kos, Z., ... & Pogue-Geile, K. L. (2019). Stromal tumor-infiltrating lymphocytes in NRG oncology/NSABP B-31 adjuvant trial for early-stage HER2-positive breast cancer. *JNCI: Journal of the National Cancer Institute*, *111*(8), 867-871.

140. Salgado, R., Denkert, C., Campbell, C., Savas, P., Nuciforo, P., Aura, C., ... & Loi, S. (2015). Tumor-infiltrating lymphocytes and associations with pathological complete response and event-free survival in HER2-positive early-stage breast cancer treated with lapatinib and trastuzumab: a secondary analysis of the NeoALTTO trial. *JAMA oncology*, *1*(4), 448-455.

141. Perez EA, Ballman KV, Tenner KS, Thompson EA, Badve SS, Bailey S, et al. Association of stromal tumor-infiltrating lymphocytes with recurrence-free survival in the N9831 adjuvant trial in patients with early-stage Her2-positive breast cancer. JAMA Oncol. 2016;2(1):56-64. https://doi.org/10.1001/jamaoncol.2015.3239 PMid:26469139

142. Loi S, Michiels S, Salgado R, Sirtaine N, Jose V, Fumagalli D, et al. Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial. Ann Oncol. 2014;25(8):1544–50. pmid:24608200

143. Denkert, C., von Minckwitz, G., Darb-Esfahani, S., Lederer, B., Heppner, B. I., Weber, K. E., ... & Loibl, S. (2018). Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. *The lancet oncology*, *19*(1), 40-50.

144. Salgado et al. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2015;26(2):259-71. doi: 10.1093/annonc/mdu450. PubMed PMID: 25214542.

145. Solinas, C., Ceppi, M., Lambertini, M., Scartozzi, M., Buisseret, L., Garaud, S., ... & Ignatiadis, M. (2017). Tumor-infiltrating lymphocytes in patients with HER2-positive breast cancer treated with neoadjuvant chemotherapy plus trastuzumab, lapatinib or their combination: A meta-analysis of randomized controlled trials. *Cancer treatment reviews*, *57*, 8-15.

146. Bianchini, G., Pusztai, L., Pienkowski, T., Im, Y. H., Bianchi, G. V., Tseng, L. M., ... & Gianni, L. (2015). Immune modulation of pathologic complete response after neoadjuvant HER2-directed therapies in the NeoSphere trial. *Annals of Oncology*, *26*(12), 2429-2436.

147. Angelis et al. De Angelis, C., Nagi, C., Hoyt, C. C., Liu, L., Roman, K., Wang, C., ... & Schiff, R. (2020). Evaluation of the Predictive Role of Tumor Immune Infiltrate in Patients with HER2-Positive Breast Cancer Treated with Neoadjuvant Anti-HER2 Therapy without ChemotherapyTILs as a Predictive Biomarker in HER2+ Breast Cancer. *Clinical Cancer Research*, *26*(3), 738-745

148. Asano, Y., Kashiwagi, S., Goto, W., Takada, K., Takahashi, K., Hatano, T., ... & Ohira, M. (2017). Prediction of survival after neoadjuvant chemotherapy for breast cancer by evaluation of tumor-infiltrating lymphocytes and residual cancer burden. *BMC cancer*, *17*(1), 1-10.

149. Kurozumi, S., Inoue, K., Matsumoto, H., Fujii, T., Horiguchi, J., Oyama, T., ... & Shirabe, K. (2019). Prognostic utility of tumor-infiltrating lymphocytes in residual

tumor after neoadjuvant chemotherapy with trastuzumab for HER2-positive breast cancer. *Scientific reports*, *9*(1), 1-8.

150. Ladoire, S., Mignot, G., Dabakuyo, S., Arnould, L., Apetoh, L., Rébé, C., ... & Ghiringhelli, F. (2011). In situ immune response after neoadjuvant chemotherapy for breast cancer predicts survival. *The Journal of pathology*, *224*(3), 389-400.

Rev. Add3

EA1181 (CompassHER2 Part 1 or CompassHER2 pCR): Preoperative THP and postoperative de-escalation in patients who achieve a pathologic complete response

The CompassHER2 Trials (COMprehensive use of Pathologic response ASSessment to escalate or de-escalate therapy in HER2-positive breast cancer)

Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. Guidelines for Submission of Pathology Materials
2. Instructional memo to submitting pathologists
3. ECOG-ACRIN Generic Specimen Submission Form (#2981v3)

Rev. Add2

Guidelines for Submission of Pathology Materials

Pathology Submissions:

1. Archived Tumor Tissue from Diagnostic Clinical Biopsy

Rev. Add3

- Formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks from the clinical biopsy containing representative tumor tissue. At least two (2) complete tissue cores (these are the actual cores collected by the needle during the actual biopsy) should be included and both cores should contain at least 5mm of invasive cancer. If one

Rev. Add8

core has <5mm of invasive cancer, then at least 1cm (in total) of invasive cancer should be submitted. **A representative H&E slide must be included for all**

Rev. Add9

patients, even if a block cannot be submitted.

  If a site is unable to provide a tumor block, please submit twenty (20) 5 µm unstained, uncharged, air-dried plus slides from the thickest part of the tumor from the diagnostic biopsy core.

- Quality assurance procedures will be performed on all tissues received by the CBPF. In patients for whom the FFPE tissue block was found not to be adequate, sites are requested to send a replacement specimen to ensure that adequate tissue is available.
- If there is an urgent medical need, a site, on behalf of a study patient, may request in writing to CBPF (use 'Specimen Return Request Form' from CBPF or access from http://www.ecog.org/ecoginst/trans/) that a block be returned to the site for reasons of clinical management of the patient.

2. Residual Disease Surgical Tumor Tissue Specimen

- Formalin-fixed paraffin-embedded (FFPE) tumor tissue block containing a representative portion of the patient's invasive primary breast cancer (portion

Rev. Add3

containing at least 5mm in largest dimension, if possible, and at least 20% invasive breast cancer tissue) obtained from the residual disease must be submitted on the definitive surgical specimen from patients with no pCR. **A representative H&E slide**

Rev. Add9

must be included for all Arm B patients, even if a block cannot be submitted.

  If a site is unable to provide a tumor block, submit a core punch biopsy from the tissue block or unstained slides from the tissue block from the definitive surgical resection specimen. The CBPF (844-744-2420) can provide a punch core biopsy kit to the site for this purpose. For slides, submit twenty (20) 5 µm unstained, uncharged, air-dried plus slides from the thickest part of the tumor.

- Quality assurance procedures will be performed on all tissues received by the CBPF. In patients for whom the FFPE tissue block was found not to be adequate, sites are requested to send a replacement specimen to ensure that adequate tissue is available.
- If there is an urgent medical need, a site, on behalf of a study patient, may request in writing to CBPF (use 'Specimen Return Request Form' from CBPF or access from http://www.ecog.org/ecoginst/trans/) that a block be returned to the site for reasons of clinical management of the patient.
- If a site is unable to provide a tumor block, a core punch biopsy from the tissue block

Rev. Add3

is requested. The CBPF (844-744-2420) can provide a core punch biopsy kit to the site for this purpose. If possible, at least two (2) complete tissue cores should be

Rev. Add8

included and both cores should contain at least 5mm of invasive cancer. . If a block or core punches cannot be submitted, an H&E slide must still be submitted.

Forms and Reports:

NOTE: Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials and will expedite any required communications with the institution (including pathologists).

The following items are to be included with the pathology materials:

- Institutional Diagnostic and Surgical Pathology Report (for archived clinical biopsy and residual tumor specimens)
- ECOG-ACRIN Generic Specimen Submission Form (#2981v3) [if STS is unavailable]
- Sample Tracking System (STS) Shipping Manifest Form

3. Mail pathology materials to:

Rev. Add3

MD Anderson Cancer Center CBPF
Mike Balco
Life Science Plaza - Suite 910
2130 West Holcombe Boulevard, LSP9.4227
Houston, TX 77030
Phone: Toll Free (844) 744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility.

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

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Edmund Lattime, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: Submission of Pathology Materials for EA1181: The CompassHER2 Trials (COMprehensive use of Pathologic response ASSessment to escalate or de-escalate therapy in HER2-positive breast cancer)

Rev. Add3 EA1181 (CompassHER2 Part 1 or CompassHER2 pCR): Preoperative THP and postoperative de-escalation in patients who achieve a pathologic complete response

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol request the submission of pathology materials for future undefined research studies.

Please return the diagnostic and surgical pathology reports, the blocks and any other required pathology materials to the Clinical Research Associate (CRA). The CRA will forward all required pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF).

Pathology materials submitted for this study will be retained at the ECOG-ACRIN Central Repository for future research studies per patient consent. Paraffin blocks will be returned upon request for purposes of patient management.

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at (1-844-744-2420 (713-745-4440 Local or International Sites) or email: eacbpf@mdanderson.org

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address: _____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

9/12/14

Rev. Add3

EA1181 (CompassHER2 Part 1 or CompassHER2 pCR): Preoperative THP and postoperative de-escalation in patients who achieve a pathologic complete response

The CompassHER2 Trials (COMprehensive use of Pathologic response ASSessment to escalate or de-escalate therapy in HER2-positive breast cancer)

Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

Rev. Add3

EA1181 (CompassHER2 Part 1 or CompassHER2 pCR): Preoperative THP and postoperative de-escalation in patients who achieve a pathologic complete response

The CompassHER2 Trials (COMprehensive use of Pathologic response ASSessment to escalate or de-escalate therapy in HER2-positive breast cancer)

Appendix III

ECOG Performance Status

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

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Appendix IV

EA1181 Collection and Shipping Kit Order Instructions

Rev. Add8

Specimen Collection/Shipping Kits are being provided by CENETRON CENTRAL LABORATORIES for blood specimens being submitted to the ECOG-ACRIN Central Biorepository and Pathology Facility and are to be ordered ONLINE.

Starter kits are not available. Kit requests are to be made after patient registration (preferred) but can be ordered after patient consent.

Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000.

Ordering Process:

- Following registration of the patient to the trial, go to the website www.cenetron.com/ and click on the 'Order Kits' button at the top right. It is recommended that kits be ordered same day as patient registration.
- The order form is not study specific and can be used for any study. Complete the online form as follows:
  - Sponsor (REQUIRED): ECOG-ACRIN
  - Contact Name (REQUIRED): Name of the institution kit contact.
  - Protocol Number (REQUIRED): EA1181
  - Phone Number (REQUIRED): Phone number of the kit contact. Please ensure that this is a number that can be reached from an external caller
  - FAX Number: Fax number of the kit contact
  - Investigator: Last name of the kit contact is adequate
  - Email (REQUIRED): Email of the institution kit contact. Must be entered twice to confirm
  - Date Supplies Needed (REQUIRED): Add three (3) business days or more to order date. (Reminder that weekends and holidays must also be considered in this timeline)
    - KIT NAME (REQUIRED): EA1181 Collection Kit
  - Quantity: 1
  - Comments: Provide EA1181 Patient Case ID# and full shipping address
    - Patient Case ID =' #####
    - 'Ship Kit to' name of the individual to whom the kit is being shipped. (May be different than the kit contact provided above)
    - Full street address, town, state and zip code
  - Answer the security question

Please complete this form correctly, including the valid ECOG-ACRIN patient case number and complete shipping address. If information is missing the kit processing will be delayed.

Rev. Add3

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Appendix V

Patient Clinical Trial Wallet Card

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: EA1181

Study Drug(S): Paclitaxel, Docetaxel, Nab-Paclitaxel, Trastuzumab, and Pertuzumab

Version *July 2019*

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov