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December 3, 2024

Margaret Mooney, MD
Clinical Investigations Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute

Dear Dr. Mooney,

Please see the attached responses and protocol resubmission for Alliance A011801, "*The CompassHER2 Trials (COMprehensive use of Pathologic Response ASSessment to optimize Therapy in HER2-positive Breast Cancer): CompassHER2 Residual Disease (RD), A Double-Blinded, Phase III Randomized Trial of T-DM1 and Placebo Compared with T-DM1 and Tucatinib.*" The study team's responses to each review item are included in bold text.

Please let us know what further information we may provide.

Sincerely,

Anna Weiss, MD
Executive Officer
Alliance for Clinical Trials in Oncology

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

#	Section	Comments
1.	General	As the secondary objective related to CTCs has been omitted, there is no need for mandatory blood collections. The protocol already contains optional blood collections for biobanking/future research. Please remove all references to mandatory blood collection from the protocol and ICD, and the funding for the mandatory blood collection should also be removed from the funding sheet. **PI Response: We have replaced the previous objectives related to CTCs with ct-DNA objectives. The collection for ct-DNA is a mandatory blood collection, and it is required for all patients.**
2.	General	Please confirm that specimens that have previously been shipped directly to EPIC Sciences will be returned to the EA Biobank. **PI Response: Samples have been returned to the Alliance biobank from EPIC Science**
3.	14.2	The first paragraph of this section states "A011801 has two secondary correlative objectives, involving the studies of TILS and circulating tumor cells outlined below. In addition, the protocol seeks to address several to-be-determined correlative objectives involving tumor intrinsic subtyping and ctDNA." This should be edited to remove the reference to CTC analyses, as they will no longer be performed. **PI Response: Section 14.2 has been revised to include the language about ctDNA.**
4.	ICD	The revisions to the Optional Studies Section of the Informed Consent regarding "Unknown Future Studies" and "What is involved in this optional sample collection" is inconsistent with other sections of the informed consent. For example, in the first sentence under "Unknown future studies," the phrase "blood samples and" has been removed, as the optional biobanking component will now only consist of tissue submission. Please review and reconcile language regarding biobanking of blood samples in the main part of the Informed Consent and Optional Studies section of the Informed Consent. Blood samples You will need to have blood samples taken for the study. ~~These samples~~Up to 4 teaspoons of blood will be collected at the beginning of the study, at cycles 2 and 3 of treatment, at completion of study treatment, one year after completion of study treatment, and if your cancer comes back. ~~These~~ Some of these blood samples will be used to ~~test for certain cells~~study the changes of drug level in your ~~blood that could help determine who may be at increased risk of their cancer coming back. You~~body, and ~~your study doctor~~some of these samples will ~~not get the results of~~ be stored in a biobank for unknown future use. Please see the section later in this ~~testing.~~ form for more information about biobanking. **PI Response: The current submitted version of consent reflects the mandatory blood collection in Streck tubes for the ct-DNA objectives using Signatera assay; the mandatory tissue collection for TILs; the mandatory blood submission for pharmacokinetics and the removal of the biobanking of blood in Streck tubes.**

Recommendations:

<table>
<tr><th>#</th><th>Section</th><th>Comments</th></tr>
<tr><td>5.</td><td>4.1 Investigator and Research Associate registration with CTEP</td><td>
Please revise the following language:

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain ~~a~~ Cancer Therapy Evaluation Program (CTEP~~) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam~~ credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

Investigator (IVR)—MD, DO, or international equivalent;
Non-Physician Investigator (NPIVR)—advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
Associate Plus (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.

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>
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#	Section	Comments
		CV (optional) ✓ ✓ ✓ In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following: **PI Response: This section has been updated as requested.**

6.	4.2.2 Downloading Site Registration Documents	*Please revise the following language:*
		loading 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 their 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 or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users)~~;
		• 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 *Alliance,* and protocol number *A011801.*
		• 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: The section has been revised as requested.

7.	6.0 Data Collection and Submission	*Please revise the following language:* Medidata Rave is the 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. Requirements to access Rave via iMedidata: • Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems 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;

#	Section	Comments
		• Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and • Rave Read Only or RAVE SLA 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. This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL. ~~Upon initial site registration approval for the study in the Regulatory application, 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.~~ Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. 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 who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application 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 or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.~~ No action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Pending study invitations (previously sent but not accepted or declined by a site user) will be automatically accepted and study access in Rave will be automatically granted for the site user. Account activation instructions are located on the CTSU website in the *Data Management* section under the Data Management Help Topics > Rave resource materials (*Medidata Account Activation and Study Invitation*).

#	Section	Comments
		Additional information on iMedidata/Rave is available on the CTSU members' website in the *Data Management > Rave section* or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com. **PI Response: The section has been revised as requested.**

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A011801

THE COMPASSHER2 TRIALS (COMPREHENSIVE USE OF PATHOLOGIC RESPONSE ASSESSMENT TO OPTIMIZE THERAPY IN HER2-POSITIVE BREAST CANCER): COMPASSHER2 RESIDUAL DISEASE (RD), A DOUBLE-BLINDED, PHASE III RANDOMIZED TRIAL OF T-DM1 AND PLACEBO COMPARED WITH T-DM1 AND TUCATINIB

[X]	**Update:**	[ ]	**Status Change:**
[X]	Eligibility changes	[ ]	Activation
[X]	Therapy / Dose Modifications / Study Calendar changes	[ ]	Closure
[X]	Informed Consent changes	[ ]	Suspension / temporary closure
[X]	Scientific / Statistical Considerations changes	[ ]	Reactivation
[ ]	Data Submission / Forms changes		
[X]	Editorial / Administrative changes		
[X]	Other: CTSU language updates		

No recommended IRB level of review is provided by the Alliance since the CIRB is the IRB of record for this trial. The site has 30 days after the posting of this amendment to implement it at their site. Please refer to the amendment application and CIRB guidelines for further instructions.

UPDATES TO THE PROTOCOL:

Cover Page

- Dr. Sailaja Kamaraju has been added as the Health Disparities Co-chair.
- Karla Ballman's email address and phone number have been updated.
- Claire Yee has replaced Tyler Zemla as Health Outcomes Statistician. All contact information has been updated.
- Jack Beranek has replaced Laura Hoffman as Protocol Coordinator. All contact information has been updated.
- The IVR numbers have been removed from the ECOG-ACRIN and SWOG Champions' contact information.
- Dr. Phillip Blanchette has been added as the CCTG Champion.

Study Resources

- The bolded and italicized note regarding the A011801 study mailbox has been moved to the top of the page to increase visibility and awareness for sites.
- Nikki Moxon's phone number has been removed.
- Zoe Ngo has replaced Myounghee Lee as the A011801 Pharmacy Contact.
- The address for the Alliance Biorepository at Washington University (WUSTL) has been updated.

Schema

The abbreviated eligibility criteria and the Note under the schema have been updated to align with the changes made in Section 3.0.

CTSU Contact Information

The CTSU Contact Information table has been updated in its entirety to align with the current boilerplate language.

Section 1.2.4 (Blood-based studies)

The reference to circulating tumor cells(CTCs) has been removed from this paragraph as we will not be performing CTC analyses.

Section 2.3 (Secondary correlative objectives)

Objectives 2.3.3 and 2.3.4 have been edited to remove CTC analysis and replace with ctDNA, as Epic Sciences has withdrawn from the study and thus will not be performing the CTC analyses.

Section 3.2.1.2 (Patients with clinical stage T1-4…)

A new second sentence has been added to indicate that patients with clinical stage TX disease at presentation are eligible if their pathologic staging meets eligibility criteria.

Section 3.2.1.4 (Patients with weakly ER-positive…)

This criterion has been updated to include "-positive and/or PR-positive" for clarity.

Section 3.2.2.2 (Prior receipt of T-DM1…)

A new second sentence has been added to the second paragraph to clarify that patients receiving TCHP who did not receive planned carboplatin doses due to the nationwide carboplatin shortage are eligible.

Section 3.2.2.5 (All systemic therapy should have been completed…)

In the last sentence of the first paragraph, the parenthetical phrase "(while awaiting a surgical date or an official pathology report)" has been removed.

Section 3.2.2.6 (Toxicities related to prior systemic…)

This criterion has been revised in its entirety for clarity and to include nail changes from prior taxane-based chemotherapy as an example of a non-clinically significant AE.

Section 3.2.8.5 (Patients for whom radiotherapy…)

A new second sentence has been added to indicate that patients who refuse a recommended course of radiotherapy are also excluded.

Section 3.2.10 (Other)
Two new footnotes * and ** have been added to the first sentence to clarify the definitions of the "screening" and "pre-chemotherapy" echo/MUGA assessments.

Section 4.1 (Investigator and Research Associate Registration with CTEP)
Changes have been made to this section to comply with the new CTSU template language.

Section 4.2 (Cancer Trials Support Unit Registration Procedures)
Changes have been made to this section to comply with the new CTSU template language.

Section 4.3 (Patient Registration Requirements)
Changes have been made to this section to comply with the new CTSU template language.

Section 4.3.2 (Patient-reported outcomes)
The text under "Patient questionnaire booklets" has been revised in its entirety to reflect the new process for downloading PRO booklets from the CTSU website.

Section 4.4 (Patient registration/randomization procedures)
Changes have been made to this section to comply with the new CTSU template language.

Section 4.5 (Registration to substudies and companion studies)
A new sentence was added to state that QOL HO-1 sub-study has met accrual and has been closed. The date of closure was added in the first bullet point in this section.

Section 4.6.1 (Stratification Factors)
- The "note" in the first bullet has been updated to "Note 1" to account for the new Notes 2 and 3 added below.
- A new Note 2 has been added to clarify which treatments do and do not count as receipt of post-operative chemotherapy for eligibility purposes.
- A new Note 3 has been added to clarify that continuation of trastuzumab + pertuzumab (HP) pre- or post-operatively as maintenance therapy is allowed.

Section 5.0 (Study Calendar)
- A new footnote B has been added to the "after every 4 cycles (+/- 7 days)" time point of the Echo/MUGA row to clarify the schedule for echo/MUGA assessments in the event of a treatment hold or delay. Subsequent footnotes have been renumbered.
- In the row for "Tissue submission for TIL analysis (if available)", the parenthetical footnote 5 has been removed from the X in the "Prior to Registration" column, as footnote 5 is not relevant to tissue submission.
- The heading for the "Blood submission for CTC and PK analysis" row has been revised to remove "CTC" and replace with ctDNA due to the withdrawal of Epic Sciences. Additionally, the "X(5)" has been removed from the "Prior to Registration" column and moved to the "Day 1 of each 21-day cycle (+/- 3 days)" column, as the PK samples are collected only at cycles 2 and 3.
- The first sentence of footnote ** has been moved to its own new footnote C, and the word "within" has also been added to clarify the timing for the post-treatment echocardiogram or MUGA. Subsequent footnotes have been renumbered.
- Footnote ** has been revised in its entirety to clarify the timing of the 6-month follow-up visits.

- In the first sentence of footnote 3, the phrase "in the medical record by any member of the care team" has been replaced with "by a count of the returned pills in the pharmacy-issued bottle." Two new sentences have also been added to describe how to proceed if a patient does not complete the pill diary or return the bottle.
- Footnote E has been re-formatted for readability.

Section 6.1 (Data Collection and Submission)

This section has been revised in its entirety to align with the current CTSU boilerplate language.

Section 6.2 (Specimen collection and submission)

- The second paragraph has been revised to remove all references to CTC analysis and to clarify the uses for the Streck and EDTA tubes (biobanking for future research for Streck tubes, and PK studies for EDTA tubes).
- The third paragraph has been revised in its entirety to reflect that the optional biobanking now only includes tissue submission at recurrence.
- A new footnote ** has been added to the column for "1 year after completion of study therapy (+/- 1 month)" in Table 1 to clarify sample collection requirements when patients discontinue study drugs early. The subsequent footnote has been renumbered as footnote ***.
- Footnotes *, **, *** have been edited for clarity and easier readability.
- In the row for "Whole blood (Streck tubes)" in Table 1, the row has been edited removing reference to Epic Sciences.
- In the row for "Plasma for PK analysis (lavender top EDTA tube, kits provided)" in Table 1, the "1 x 5 mL" entries for Cycles 2 and 3 Day 1 have been updated to "2 x 5 mL" for clarity to account for the pre- and post- dosing PK draws.
- The last row heading of Table 1, "Whole blood (Streck tubes, kits provided." has been deleted as these will not be collected.
- Footnote 2 has been removed due to the withdrawal of Epic Sciences, and replaced with the text from footnote 5. Subsequent footnotes have been renumbered, and the previous footnote 5 has been removed accordingly.
- Table 2 (PK Collection Schedule) has been revised in its entirety for further clarification.

Section 6.3 (Submission of Patient Completed Measures)

- A sentence was added stating the HO-1 substudy has met accrual goals and has closed.
- The third sentence of the second paragraph has been removed for accuracy.
- The fourth paragraph has been revised in its entirety to reflect the new process for downloading PRO booklets from the CTSU website.
- In the last column, the "+/- 45-day" window has been added to the ePRO section of the column heading.
- The last row heading, "Time per survey," has been updated to "Time estimated per survey" to clarify that this is an estimate rather than a time limit for patients.

Section 7.0 (Treatment Plan/Intervention)

- The phrase "After Cycle 1" has been added to the first sentence of the third paragraph for clarity.
- The first paragraph under "Ado-trastuzumab emtansine (T-DM1)" has been reworded in its entirety to match the wording in Section 5.0 regarding calculated dose changes and weight changes.

Section 8.1.3 (Treatment with hormones…)

- The first sentence has been updated to include several more indications for allowable use of steroids.
- A new sentence has been added to the end of this section to clarify that topical or intravaginal hormonal therapies are allowed.

Section 8.1.6 (Alliance Policy Concerning the Use of Growth Factors)

The last paragraph has been updated to say "Filgrastim (G-CSF) and biosimilar products" instead of "Filgrastim (G-CSF) tbo-filgrastim".

Section 8.2 (Dose Modifications)

- A new fifth paragraph has been added to clarify how to handle doses held for non-toxicity reasons.
- The phrase "and patient re-initiates trastuzumab per standard of care, and" has been added to the second sentence of the sixth (previously fifth) paragraph for clarity.
- A new sentence has been added to the end of the sixth (previously fifth) paragraph to describe how to proceed if only the tucatinib/placebo is discontinued.
- Table 2 (Recommended Tucatinib/Placebo Dose Reduction Schedule) has been revised to clarify the specific numbers of each tablet that would correspond with each dose.
- An asterisk has been added to the Table 4 heading, with a corresponding note at the bottom of the table including instructions for patients with documented gallbladder pathology.
- Under "Tucatinib Adverse Events of Special Interest: Hepatotoxicity (see Section 9.3.3 for reporting requirements)," the second and third bullets have been updated to align with the current protocol template provided by the pharmaceutical partner for tucatinib.

Section 9.1.1 (Rave-CTEP-AERS integration)

Minor revisions have been made to the second and fifth paragraphs to align with the current CTSU boilerplate language.

Section 9.3.1 (Late Phase 2 and Phase 3 Studies…)

This table has been replaced with the current version Effective date: August 30, 2024.

Section 9.3.2 (Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements)

The table of Adverse Events of Special Interest has been updated in its entirety to align with the current protocol template provided by the pharmaceutical partner for tucatinib.

Section 9.4 (CAEPRs)

All references to the SPEER column have been removed, as Alliance is the IND holder for this study.

Section 10.2 (Tucatinib [ONT-380, NSC# 803413] or Placebo)

- Under "Storage," a new third sentence has been added to clarify that individual bottles dispensed to the patient may be stored under ambient temperatures for transport to the patient's home, per updated pharmacy instructions.
- Under "Administration," the first sentence has been updated to indicate that tucatinib or placebo should be taken approximately 8 to 12 hours apart between doses.
- The "Pharmacokinetics (Clinical)" section has been revised in its entirety to align with the updated Investigator's Brochure.

Section 10.3 (Ado-trastuzumab emtansine [T-DM1, KADCYLA®, Trastuzumab-MCC-DM1, PRO132365, RO5304020; NSC# 780263])

- Under "Formulation," the phrase "16- mg per vial" has been corrected to "160 mg per vial."
- The first sentence under "Administration" has been revised to add the phrase "non-protein absorptive" for clarity.
- A note has been added at the end of the "Administration" section to clarify the infusion length for patients who had one dose of T-DM1 prior to enrolling on the study.

Section 11.1 (Evaluation of Breast Cancer Outcomes)

A note has been added to the end of this section to align with the most recent Data Completion Guidelines for disease response assessment.

Section 12.3.1 (Duration of Follow-up)

This section has been updated in its entirety to match the revised wording in Section 5.0.

Section 12.3.3 (Follow-up for Specimen and QOL Submission)

An additional sentence was added specifying patients who discontinue treatment early should still complete the PRO's.

Section 13.14 (Other Pre-Specified Outcomes: NIH-Required Analyses)

This section has been added to align with the Alliance and NCI model protocol template.

Section 14.2 (Correlative Science)

This section has been updated to replace the CTC analyses with ct-DNA.

Section 14.2.2 (formerly Section 14.2.3) (Biobanking for Future Correlative Science Studies [mandatory and optional])

- The previous text in Section 14.2.2 (Circulating Tumor Cells [CTC] – mandatory for all patients) regarding circulating tumor cells (CTC) has been completely removed due to the withdrawal of Epic Sciences and replaced with this section now focused on Circulating Tumor DNA (ctDNA), which will now being collected.

Section 15.1 (Request for early site study closure)

This new section has been added per the Alliance model protocol template to include instructions for closing the study with the site's IRB of record.

Section 16.2 (On-site Monitoring)

The second sentence was edited so that the monitoring language mirrors that of the actual monitoring plan

Section 17.0 (References)
Additional references have been added to support edits in section 14.2.2.

Appendix I (Electronic Patient-Reported Outcomes [ePRO] Instructions)
In Section 4.0 (Checklist for activities prior to consenting a patient) of the appendix, the first bullet has been removed, as the eLearnings are not required to access Patient Cloud.

Appendix II (Patient Medication Diary – Tucatinib/Placebo)

- The version number has been updated to Version 2.
- Item #2 in the patient instructions has been revised to include the dosage taken for each dose level, as well as the corresponding number of each tablet. The second sentence of item #2 has been updated to reflect that the tucatinib/placebo pills can be stored at ambient temperature during transport to and from the patient's home.
- A new third sentence has been added to item #5 in the patient instructions to refer to the new Example #2 in the table.
- A second example has been added to the table to show how a patient would record a missed dose.
- The Spanish version of the Patient Medication Diary has been removed from this appendix and will be posted as a separate document on CTSU once updated and approved.

Appendix IV (CYP3A4 Inducers)
Apalutamide has been added to the list of Strong Inducers.

Appendix V (CYP2C8 Inhibitors/Inducers)
A list of Moderate Inhibitors has been added.

Appendices IX (Patient Information Sheets [Version 2]), X (Domains Of Subjective Extent of Nonadherence [DOSE-Nonadherence]), XI (Functional Assessment Of Cancer Therapy-Breast [Fact-B] – Version 4), XII (PRO-CTCAE* -NCI-PRO-CTCAE™ Items)
These appendices have been removed and compiled into a separate PRO booklet to be posted on CTSU as a standalone document. Subsequent appendices have been renumbered.

Appendix IX (A011801 Supportive Care)
This new appendix has been added as a resource to provide guidance for sites on supportive care and management of treatment-related toxicities. The subsequent appendix has been renumbered.

UPDATES TO THE MODEL CONSENT FORM:

What are the risks and benefits of taking part in this study?
The last sentence of the second-to-last paragraph under "Risks" regarding a "boxed warning" in the package insert has been removed.

What exams, tests, and procedures are involved in this study?
Under the "Blood samples" heading:

- The second sentence has been revised to explain when samples will be collected and what they will be used for as a result of the change in analysis from CTC ct-DNA.

What risks can I expect from taking part in this study?

- The "Genetic Testing Risks" section has been removed due to the withdrawal of Epic Sciences and CTC analyses.
- Under "Drug Risks," the last sentence of the note under the side effect tables for both T-DM1 and tucatinib (regarding a "boxed warning" in the package insert) have been removed.
- Under "Drug Risks," the tucatinib risk tables have been updated to align with the current risk profile from the pharmaceutical partner for tucatinib.

Who will see my medical information?

- The sixth bullet concerning Epic Sciences has been deleted as they won't be processing samples and has been replaced with information on Natera, a global company specializing in cell-free DNA testing in oncology, women's health, and organ health that will now be processing the samples.
- In the seventh bullet under the list of organizations who may see patient data, the phrase "Only at selected sites participating in ICAREdata®" has been added for clarity.

Optional quality of life study

This section has been deleted as the accrual goal has been met and we have closed the QOL to enrollment.

Optional sample collections for known laboratory studies and/or storage for possible future studies

- In the first sentence of the first paragraph, the phrase "blood and" has been removed, as the optional biobanking component will now only consist of tissue submission.
- In the first sentence under "Unknown future studies," the phrase "blood samples and" has been removed, as the optional biobanking component will now only consist of tissue submission.
- In the first sentence of the third paragraph under "Unknown future studies," the phrase "blood and" has been removed, as the optional biobanking component will now only consist of tissue submission.
- In item #1 under "What is involved in this optional sample collection?", the first sentence has been removed as blood samples are now mandatory and no longer part of the optional biobanking component. The phrase "and an additional 4 teaspoons of blood" has also been removed from the last sentence of item #1.
- The first bullet under "What are the risks in this optional sample collection?" has been removed, as blood collection is no longer part of optional biobanking.

UPDATES TO THE PRO BOOKLETS:

Participant Information Sheet

In all booklets, the Participant Information Sheet has been replaced with a cover page and a generic Participant Information Sheet used across Alliance trials.

Domains of Subjective Extent of Nonadherence (DOSE-Nonadherence)

In Booklets B and C, the instructions under Part 1 and Part 2 of this measure have been revised to specify "tucatinib or placebo" instead of the general "insert medication name or class" direction in parentheses. The parenthetical "insert medication name or class" instruction had been retained in error.

A replacement protocol and model consent form have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A011801

THE COMPASSHER2 TRIALS (COMPREHENSIVE USE OF PATHOLOGIC RESPONSE ASSESSMENT TO OPTIMIZE THERAPY IN HER2-POSITIVE BREAST CANCER): COMPASSHER2 RESIDUAL DISEASE (RD), A DOUBLE-BLINDED, PHASE III RANDOMIZED TRIAL OF T-DM1 AND PLACEBO COMPARED WITH T-DM1 AND TUCATINIB

This is an FDA registration trial.

Industry-supplied agent(s): tucatinib (Seattle Genetics) NSC #803413 or placebo; Commercial agent(s): ado-trastuzumab emtansine (T-DM1) (NSC #780263)
IND Holder: Alliance; IND #147035
ClinicalTrials.gov Identifier: NCT04457596

Study Chair
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Study Resources:

Please copy the A011801 study mailbox, A011801@alliancenctn.org, on all study communications.

Expedited Adverse Event Reporting https://ctepcore.nci.nih.gov/ctepaers	**Medidata Rave® iMedidata portal** https://login.imedidata.com
OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org	**Biospecimen Management System** http://bioms.allianceforclinicaltrialsinoncology.org

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CRS_intake@mckesson.com

Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox regulatory@allianceNCTN.org
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox pharmacovigilance@alliancenctn.org
Questions regarding specimens/specimen submissions:	Alliance Biorepository at Washington University (WUSTL)
Questions regarding drug supply	McKesson Specialty Pharmacy CRS_intake@mckesson.com
Questions regarding drug administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 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), or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is 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. Refer to 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 page located on the CTSU members' website (https://www.ctsu.org). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
Supplies can be ordered by downloading and completing the CTSU Supply Request Form (available on the protocol-specific page on the CTSU website) and submitting it as instructed on the form.		
For clinical questions (i.e., patient eligibility or treatment-related) see the Protocol Contacts, Page 2.		
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 CompassHER2 Trials (COMprehensive Use of Pathologic Response ASSessment to Optimize Therapy in HER2-Positive Breast Cancer): CompassHER2 Residual Disease (RD), A Double-Blinded, Phase III Randomized Trial of T-DM1 and Placebo Compared with T-DM1 and Tucatinib

Eligibility Criteria (see Section 3.2)

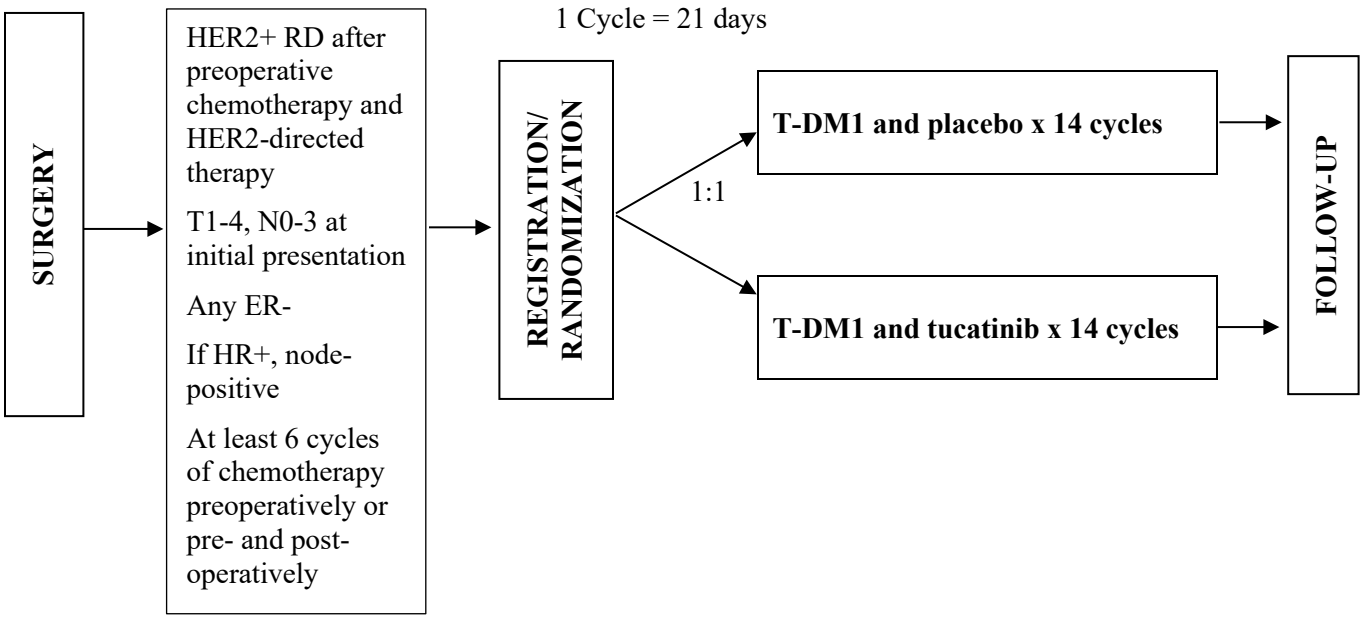
- HER2-positive breast cancer per Section 3.2.1
- Patients must have received neoadjuvant chemotherapy with one of the following regimens: THP, TMP, AC-TH(P); TCH(P); FAC-TH(P), or FEC-TH(P). See Section 3.2.2.
- Prior receipt of T-DM1 in the neoadjuvant setting is not allowed.
- Prior treatment must have consisted of ≥ 6 cycles of chemotherapy and HER2-directed therapy, with a total duration of ≥ 12 weeks, including at least 9 weeks of preoperative taxane and trastuzumab with or without pertuzumab (or FDA-approved biosimilars). Patients who have received at least 9 weeks of preoperative taxane, pertuzumab and margetuximab are also eligible if they received ≥ 6 cycles of chemotherapy prior to registration. See Section 3.2.2.
- Patients who received neoadjuvant systemic therapy which included experimental HER2-directed therapy are potentially eligible, as long as the investigational agent was not a HER2-targeted antibody-drug conjugate (e.g. T-DM1 or trastuzumab deruxtecan) or a HER2 targeted tyrosine kinase inhibitor (TKI) (e.g. tucatinib, lapatinib, neratinib).
- No adjuvant treatment with any anti-cancer investigational drug within 28 days prior to registration
- Patients may have received ≤ 1 cycle of T-DM1 in the adjuvant setting. See Section 3.2.2.
- Both of the following points must be true:
  -An interval of no more than 12 weeks between the completion date of the last definitive treatment and the date of registration AND
  -Patients must be registered on study within ≤ 180 days of the date of the most recent definitive breast cancer surgery (not including reconstructive surgery).
- All systemic chemotherapy should have been completed preoperatively unless participating in EA1181 (CompassHER2 pCR) or the BIG DECRESCENDO Trial (which is very similar to EA1181 in terms of the study design, drugs, and eligibility criteria). See Section 3.2.2.5.
- Patients who participated in EA1181 or MA41 and proceeded to surgery immediately after the de-escalated trial regimen must receive postoperative chemotherapy to complete a total of ≥ 6 cycles of systemic treatment prior to registration on A011801, as outlined above (e.g. 4 cycles pre-operatively, and 2 cycles post-operatively). See Section 3.2.2.5.
- Toxicities related to prior systemic treatment should have resolved or be at baseline, apart from alopecia, peripheral neuropathy ≤ grade 1, and other AEs not felt to be of clinical significance by the treating physician (e.g. nail changes from prior taxane-based chemotherapy).
- Adequate excision: surgical removal of all clinically evident disease in the breast and lymph nodes (see Section 3.2.2)
- Not pregnant and not nursing
- Age ≥ 18 years (male or female)
- ECOG Performance Status 0-1
- Patients with known active and/or untreated Hepatitis B or Hepatitis C or chronic liver disease are ineligible. Patients with a diagnosis of Hepatitis B or C that has been treated and cleared and normal liver function are eligible to participate in the study if the other eligibility parameters are met.
- No stage IV (metastatic) breast cancer
- No history of any prior (ipsi- or contralateral) invasive breast cancer within 3 years of registration
- No patients with ER+ HER2+ residual invasive disease that is lymph node-negative per the surgical pathology report
- No evidence of recurrent disease following preoperative therapy and surgery
- No patients for whom radiotherapy would be recommended for breast cancer treatment but for whom it is contraindicated because of medical reasons (e.g., connective tissue disorder or prior ipsilateral breast radiation). Patients who refuse a recommended course of radiotherapy are also excluded.

Required Initial Laboratory Values

Absolute neutrophil count (ANC): ≥ 1000/mm^3
Hemoglobin: ≥ 8 g/dL
Platelet count: ≥ 100,000/mm3
Total bilirubin: ≤ 1.0 x ULN (or direct bilirubin within the institutional normal range for patients with Gilbert's syndrome)
AST and ALT: ≤ 2.5 x ULN
Creatinine: ≤ 1.5 x upper limit of normal (ULN)

- No history of exposure to the following cumulative doses of anthracyclines: Doxorubicin > 240 mg/m2; Epirubicin or Liposomal Doxorubicin-Hydrochloride (Myocet®) > 480 mg/m2. For other anthracyclines, exposure equivalent to doxorubicin > 240 mg/m2.
- No cardiopulmonary dysfunction as defined in Section 3.2.8.
- No current severe uncontrolled systemic disease
- No major surgical procedure unrelated to breast cancer or significant traumatic injury within 28 days prior to registration or anticipation of the need for major surgery during the course of study treatment. See Section 3.2.8.
- No history of intolerance, including Grade 3 to 4 infusion reaction or hypersensitivity to trastuzumab or murine proteins or any components of the product
- No peripheral neuropathy of any etiology that exceeds grade 1 (mild symptoms)
- No assessment by the investigator as being unable or unwilling to comply with the requirements of the protocol.
- See Section 3.2.9 for concomitant medication restrictions.
- Screening left ventricular ejection fraction (LVEF) ≥ 50% on echocardiogram (ECHO) or multiple-gated acquisition (MUGA) after receiving neoadjuvant chemotherapy and no decrease in LVEF by more than 15 absolute percentage points from the pre-chemotherapy LVEF. Or, if pre-chemotherapy LVEF was not assessed, the screening LVEF must be ≥ 55% after completion of neoadjuvant chemotherapy. Note: LVEF assessment may be repeated once up to 3 weeks following the initial screening assessment to assess eligibility.

Schema



Note: HR stands for "hormone-receptor." Patients with weakly ER-positive (1-10%) and/or PR-positive (1-10%) and node-negative disease per the surgical pathology report are eligible.

Treatment is to continue until breast cancer recurrence, completion of 14 cycles, or unacceptable adverse event. Patients will be followed for 10 years after registration or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Chemotherapy will be conducted at the registering institution. Radiation and surgery may be conducted at a non-registering institution. The non-registering institution does not need to be an NCTN site.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

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1.0 BACKGROUND

1.1 Rationale for Selected Approach and Trial Design

In the CompassHER2 trials (COMprehensive use of PAthologic response ASSessment to Escalate and De-Escalate Therapy in human epidermal growth factor receptor 2 [HER2]-positive Breast Cancer), we hypothesize that the use of preoperative single-agent taxane plus combination HER2-targeted therapy (trastuzumab and pertuzumab) will allow the use of pathologic response as a functional biomarker to assess subsequent recurrence risk and tailor additional therapy in patients with clinical stage II-III HER2-positive breast cancer. In CompassHER2 pCR (led by ECOG-ACRIN, EA1181), the focus is on therapy de-escalation if there is a pathologic complete response (pCR) after preoperative HER2-directed therapy with THP. Of note, although CompassHER2 pCR and CompassHER2 RD are scientifically related, they are separate studies. This protocol describes the second trial, CompassHER RD (led by the ALLIANCE, A011801), where RD stands for residual disease. In CompassHER2 RD, eligible patients with high-risk residual HER2-positive disease (e.g. all patients with ER-negative disease and node-positive ER+ disease) are randomized to standard therapy with adjuvant T-DM1 (based on practice changing data from the KATHERINE trial) and placebo, vs. adjuvant T-DM1 and the potent HER2 selective tyrosine kinase inhibitor (TKI) tucatinib (ONT-380). The primary goal of the study is to further improve iDFS outcomes in this patient population.

1.1.1 De-escalating therapy in HER2-positive breast cancer

HER2-positive breast cancer represents 10-15% of invasive breast cancers[1]. Pivotal NSABP-31, N9831 and BCIRG 006 trials established the addition of trastuzumab to cytotoxic chemotherapy (either anthracycline and cyclophosphamide, followed by taxane or docetaxel and carboplatin) as standard treatment by demonstrating significant improvement in outcomes (~50% reduction in recurrence and ~30% improvement in survival)[2-4]. Modern systemic regimens used to treat HER2-positive breast cancer typically involve 2-3 cytotoxic agents, 1-3 HER2-directed agents, and take 1-2 years to complete.

A logical next step is an attempt to de-escalate treatment and spare selected patients the significant treatment-associated toxicities without compromising their long-term outcomes. Anthracycline-based treatment can lead to the rare (~1%) but potentially lethal risk of secondary acute leukemia and myelodysplastic syndrome (MDS), as well as severe cardiomyopathy (~ 2%)[5, 6]. Carboplatin's dose-limiting toxicity is myelosuppression [7]; often necessitating the use of granulocyte-colony stimulating growth factors (G-CSF) which carries additional side effects and financial burden. Platinum compounds also increase the risk of peripheral neuropathy, ototoxicity and renal failure [8, 9].

In the Adjuvant Paclitaxel and Trastuzumab (APT) trial, patients with early stage HER2-positive breast cancer were administered 12 doses of weekly paclitaxel with trastuzumab for 1 year in the adjuvant setting [10]. Updated follow up showed that the 7-year DFS was 93.3% and overall survival (OS) was 95%[11]. Almost all patients enrolled in this trial had stage I disease, suggesting that clinical stage can identify subsets of patients with HER2-positive disease who are at low risk for recurrence when treated with less aggressive and toxic regimens; however few patients fall in this clinically low risk category.

Therefore, given that many patients with early stage HER2-positive breast cancer have an excellent prognosis with modern treatments, the concept of treatment de-escalation is becoming increasingly important as we attempt to balance the benefits versus the risks of systemic therapy[12]. One strategy for identifying patients with HER2-positive breast

cancer for whom de-escalation or more intensive therapy is appropriate is to use the neoadjuvant platform to identify those who achieve a pathologic complete response (pCR)[13]. To this end, the ECOG-ACRIN study CompassHER2 pCR will test the ability to de-escalate therapy among patients who have an excellent response to neoadjuvant HER2-targeted therapy and provide robust data that could impact clinical practice as described further below.

In CompassHER2 pCR (EA1181), a de-escalated strategy for single agent chemotherapy plus dual HER2-targeting, no additional chemotherapy will be given to patients who achieve a pCR. CompassHER2 pCR will test the hypothesis that pCR after de-escalated therapy will result in 3-year RFS no worse than 92%. The De-Escalation of adjuvant ChemotheRapy in HER-2 positive, EStrogen reCEptor-negative, Node-negative, early breast cancer patients who achieved pathological complete response after neoadjuvant chemotherapy and Dual HER-2 blOckade (DECRESCENDO) trial (BIG DECRESCENDO, or MA41) is similar in design and patient eligibility to the CompassHER2 pCR trial. This trial will test chemotherapy plus dual-HER2 blockade, using a similar regimen as CompassHER2 pCR.

This trial, CompassHER2 RD (A011801) is based on the knowledge of poor outcomes in patients with residual disease after chemotherapy plus HER2-directed therapy, and aims to build upon existing strategies to augment care in the residual disease setting. CompassHER2 RD will include eligible patients drawn from CompassHER2 pCR but will not be limited to this population; many if not most of the enrolled patients will come to the RD trial without participating in CompassHER2 pCR.

1.1.2 Escalation strategies in HER2-positive breast cancer with residual disease after neoadjuvant therapy

Although many patients do very well with combination HER2-directed therapy and chemotherapy, others remain at substantial risk for a local and/or distant breast cancer recurrence[14]. Therefore, accurate identification of patients with high-risk features is important in order to individualize treatment decisions. In prior research noted above, patients with HER2-positive breast cancer and residual disease after polychemotherapy plus either single or dual HER2-directed therapy had poor outcomes, with 6-year relapse rates of approximately 35% in NeoALTTO [15] and 5-year rates over 20% in CALGB 40601. Therefore, patients with residual disease after the completion of preoperative HER2-directed therapy and chemotherapy have an inferior prognosis, and investigation of additional treatment strategies is warranted. Postneoadjuvant trials, whereby patients who have residual invasive breast cancer after preoperative systemic therapy are randomized to standard of care treatment +/- additional systemic therapy, are an attractive treatment option for this patient subgroup.

Ado trastuzumab emtansine (T-DM1) is an antibody-drug conjugate (ADC) of trastuzumab and a cytotoxic compound, emtansine (DM1), a microtubule inhibitor and maytansine derivative [16]. T-DM1 facilitates intracellular delivery of DM1 to HER2-amplified cells while retaining trastuzumab activity. In patients with advanced HER2-positive breast cancer previously treated with chemotherapy and trastuzumab, T-DM1 resulted in superior overall survival (OS) and a favorable risk-benefit profile compared with lapatinib and capecitabine and other late-line therapies, resulting in FDA approval for use in patients with HER2-positive metastatic breast cancer (MBC)[17]. Studies evaluating the use of T-DM1 in the neoadjuvant and adjuvant setting have been conducted, or are underway [18-21]. Notably, results of a phase II study showed that patients with early HER2-positive breast cancer could tolerate 17 cycles of adjuvant T-DM1 following anthracycline based

therapy[22], which led the way for further evaluation of T-DM1 in patients with high risk early stage HER2-positive breast cancer who did not achieve a pCR after standard chemotherapy and HER2-directed therapy.

In the phase III, open-label KATHERINE trial, patients with HER2-positive early breast cancer who had residual disease in the breast and/or axilla at surgery after receiving preoperative systemic therapy containing trastuzumab and a taxane (+/- an anthracycline), were randomized 1:1 to 14 cycles of trastuzumab or T-DM1[23]. The primary endpoint was invasive disease-free survival (iDFS). At the interim analysis, it was noted that, of 1486 randomly assigned patients, invasive disease or death had occurred in 91 patients in the T-DM1 arm (12.2%) and 165 patients in the trastuzumab arm (22.2%). The approximate percentage of patients who were free of invasive disease at 3 years was 88.3% in the T-DM1 arm and 77.0% in the trastuzumab arm; these findings were statistically significant (hazard ratio for invasive disease or death, 0.50; 95% confidence interval, 0.39 to 0.64; P <0.001). Of note, 80% of patients received an anthracycline-based regimen, and 19% received dual HER2-targeted therapy with trastuzumab and pertuzumab. These findings have changed practice, with T-DM1 approved as adjuvant HER2-directed therapy for patients with HER2-positive early breast cancer who have residual disease after preoperative chemotherapy and HER2-directed therapy. Unfortunately, the incidence of CNS relapses was similar in the T-DM1 and control arms of KATHERINE and comprised 40% of the relapses; therefore, the prevention of breast cancer brain metastases remains an unmet clinical need. CompassHER2 RD will aim to further improve iDFS outcomes in patients with residual HER2-positive invasive breast cancer after preoperative chemotherapy and HER2-directed therapy. In KATHERINE, several subsets continued to do particularly poorly; the 3-year iDFS in patients with ER-/HER2+ disease was 82% in the T-DM1 arm, and patients with node-positive disease had a 3-year iDFS of 83 % in spite of T-DM1 [23]. Therefore, novel treatment strategies are still needed to improve outcomes both overall and in these patient subgroups.

The oral potent HER2-specific TKI tucatinib is in clinical development in HER2-positive MBC. Tucatinib differs from the other small molecule HER2-specific TKIs (which are dual inhibitors of both EGFR and HER2) in that it selectively inhibits HER2. Tucatinib demonstrated activity as monotherapy or in combination with chemotherapy or trastuzumab in HER2-positive murine xenograft models, including intracranial tumor xenograft models[24]. A phase I first-in-human study was initially conducted to evaluate tucatinib monotherapy in HER2-positive advanced solid tumors (n=50), including patients with HER2-positive MBC (n=43). There was a lower incidence and severity of diarrhea and rash with tucatinib than that typically associated with dual HER2/EGFR inhibitors, and notable antitumor activity in patients with heavily pretreated HER2-positive MBC was observed. Specifically, in patients with HER2-positive MBC (n = 22) treated at doses ≥ the maximum tolerated dose (MTD), the objective response rate (ORR) was 14% [all partial responses (PR)] and the clinical benefit rate (CBR)(PR + stable disease ≥ 24 weeks) was 27%.

Based on the above findings, further clinical development of tucatinib ensued. A phase Ib study of tucatinib with capecitabine and trastuzumab in advanced HER2-positive MBC with and without brain metastases was conducted[25]. Eligible patients had received prior treatment with trastuzumab, pertuzumab and T-DM1. Sixty patients were enrolled and treated. Tucatinib was administered twice a day combined with capecitabine 1000 mg/m2 orally BID for 14 days of a 21-day cycle, trastuzumab 6 mg/kg IV once every 21 days, or both. A modified 3 + 3 dose-escalation design was used to determine the recommended phase 2 dose (RP2D), starting with tucatinib combined with capecitabine or trastuzumab

(n=33), and subsequently evaluating the triplet combination (n=27). Common adverse events (AEs) noted in patients at the RP2D irrespective of causality, grade, and treatment arm included diarrhea (67%), nausea (60%), palmar-plantar erythrodysesthesia syndrome (44%), fatigue (38%), and vomiting (38%). In all patients, treatment-related AEs ≥ grade 3 included fatigue (8%), diarrhea (7%), and palmar-plantar erythrodysesthesia (7%). The proportion of patients with measurable disease who had an objective response was 83% in the tucatinib and capecitabine group, 40% in the tucatinib and trastuzumab group, and 61% among the 23 patient treated in the tucatinib, capecitabine and trastuzumab group. The median PFS in the triplet arm was 7.8 months and the CBR was 74%. Therefore, the triplet combination was associated with an acceptable toxicity profile and preliminary antitumor activity. Of note, a 42% response rate in patients with brain metastases was noted, likely because small molecule TKIs such as tucatinib are more likely to have greater CNS penetration compared with monoclonal antibodies such as trastuzumab and pertuzumab. Based on these results, the double-blinded randomized pivotal HER2CLIMB trial (ONT-380-206; NCT02614794) was designed to further evaluate the efficacy and safety of the tucatinib triplet combination.

Results of the HER2CLIMB trial were reported in late 2019 and formed the primary basis for breakthrough therapy designation and April 2020 marketing approval of tucatinib under the trade name TUKYSA, in combination with trastuzumab and capecitabine, in the United States [26]. In this study, patients with metastatic or advanced HER2-positive breast cancer who had previously received trastuzumab, pertuzumab and T-DM1 were randomized to receive trastuzumab, capecitabine and tucatinib vs. trastuzumab and capecitabine alone. Forty-seven percent of study participants had brain metastases at the time of enrollment. HER2CLIMB met its primary endpoint of PFS, demonstrating that the triplet therapy arm was superior to doublet therapy. Specifically, PFS at 1 year was 33.1% in the tucatinib-containing arm and 12.3% in the placebo-containing arm (hazard ratio for disease progression or death, 0.54; 95% confidence interval [CI], 0.42 to 0.71; P<0.001), and the median duration of PFS was 7.8 months and 5.6 months, respectively. Overall survival (OS) at 2 years was 44.9% in the tucatinib-containing arm and 26.6% in the placebo-containing arm (hazard ratio for death, 0.66; 95% CI, 0.50 to 0.88; P = 0.005), and the median OS was 21.9 months and 17.4 months, respectively. Among the patients with brain metastases, progression-free survival at 1 year was 24.9% in the tucatinib-containing arm and 0% in the placebo-containing (hazard ratio, 0.48; 95% CI, 0.34 to 0.69; P<0.001), and the median PFS was 7.6 months and 5.4 months, respectively. In terms of toxicities, tucatinib combined with trastuzumab and capecitabine was well tolerated with an acceptable safety profile. The most commonly noted AEs in the tucatinib arm included diarrhea, palmar-plantar erythrodysaesthesia syndrome (PPE), nausea, fatigue, and vomiting. Grade 3 or greater AEs in the tucatinib arm vs. the control arm included diarrhea (12.9 vs. 8.6 %), PPE (13.1 vs. 9.1%), elevated aspartate aminotransferase (AST) levels (4.5 vs. 0.5 percent), and elevated alanine aminotransferase (ALT) (5.4 vs. 0.5 %). Prophylactic antidiarrheal agents were not mandated. Adverse events resulting in treatment discontinuations were infrequent in both the tucatinib and control arms (5.7 and 3.0 %).

Another phase Ib trial evaluated the combination of T-DM1 and tucatinib in advanced HER2-positive breast cancer with and without brain metastases[27]. Fifty-seven T-DM1-naive patients who had received a median of two prior HER2-directed therapies were treated. The MTD of tucatinib was 300 mg BID with dose-limiting toxicities (DLT) seen at 350 mg BID. Pharmacokinetic analysis did not show a drug-drug interaction with T-DM1. AEs observed among the 50 patients treated at the MTD regardless of causality included nausea (72%), diarrhea (60%), fatigue (56%), epistaxis (44%), headache (44%), vomiting (42%), constipation (42%), and decreased appetite (40%); the majority of adverse

events were grade 1 or 2. Tucatinib-related toxicities that were ≥ grade 3 included thrombocytopenia (14%) and transaminitis (12%). Overall, the objective response rate was 48%, and the median progression-free survival (PFS) was 8.2 months. Given these encouraging results, various studies evaluating tucatinib combinations in different clinical settings are ongoing or planned[28].

The CompassHER2 RD study aims to further improve iDFS outcomes in patients with HER2-positive breast cancer who have residual disease after preoperative systemic therapy, and are at particularly high risk of disease recurrence (e.g. all patients with ER-HER2+ disease and patients with high-risk ER+HER2+ disease, e.g. node-positive disease after neoadjuvant systemic therapy.) Eligible patients in this randomized phase III trial will be randomized to complete 14 cycles of standard of care therapy with T-DM1 and placebo or T-DM1 combined with tucatinib (a total of 14 cycles of adjuvant therapy will be administered in both study arms).

1.2 Correlative Research

In addition to pathologic response, there are biologic variables important in response to and prognosis after HER2-directed therapy. HER2-positive breast cancer is comprised of several intrinsic molecular subtypes - luminal A, luminal B, HER2-enriched (HER2-E), basal-like and normal-like. In the neoadjuvant CALGB 40601 and NeoALTTO trials, embedded correlative analyses revealed a high level of intertumoral heterogeneity with regard to both tumor genomics and tumor microenvironment, both of which significantly impacted pCR rates[29]. In NeoALTTO, CALGB 40601, and the phase II neoadjuvant PAMELA study (that used only HER2-directed therapy without chemotherapy), the HER2-E subtype was associated with superior pCR rates [29-31]. This consistent finding suggests that patients with HER2-E disease who do very well with dual HER2-directed therapy may not require chemotherapy or require limited chemotherapy.

Multiple studies have found that individual genes or pathway level DNA alterations were predictive of responses to HER2-directed therapy, including NeoALTTO [32], and the German Breast Group (GBG) trials [33]. In CALGB 40601, integrated DNA and RNA analyses suggested that copy number alterations were independently associated with pCR when RNA subtype was taken into account[34]. This supports the plan to examine DNA alterations in addition to RNA expression in the correlative studies proposed for this trial. More recent studies suggest that tumor-specific DNA aberrations can be detected early using circulating tumor DNA (ctDNA)[14] which may provide a valuable intermediate biomarker for relapse and long-term outcome. The importance of the immune microenvironment in response to therapy and outcome is also clearly emerging. Several trials have illustrated the prognostic impact of activated immune cells in the tumor microenvironment of HER2-positive breast cancer; both TILS and activated immune signatures are associated with improved pCR and EFS [29, 31, 35-38] and function independently of tumor-associated features. Studies examining de-escalation strategies should examine these potential mechanisms to identify highly responsive disease.

1.2.1 Tumor gene signatures and differential treatment benefit in HER2-positive breast cancer

As discussed above, other biologic factors distinct from pCR rates can influence response to and prognosis after HER2-directed therapy. HER2-positive breast cancer is comprised of several intrinsic molecular subtypes - luminal A, luminal B, HER2-E, basal-like and normal-like[39]. In several neoadjuvant trials, the HER2-E subtype has been associated with a superior response to neoadjuvant HER2-targeted therapy; chemotherapy de-escalation may be appropriate for selected patients in this subgroup [30, 40]. However, data

is lacking regarding long-term outcomes in the setting of HER2-positive residual disease. In the neoadjuvant CALGB (ALLIANCE) 40601 trial evaluating trastuzumab and lapatinib based regimens, the presence of residual disease after neoadjuvant therapy appeared to be a stronger negative prognostic factor in patients with HER2E tumors than in those patients with luminal cancers, but the sample size of these subgroups was small and they were not formally compared in that study[41]. Pernas et al. performed a single-institution retrospective analysis (n=150) of intrinsic subtypes in baseline and residual HER2-positive breast cancer following completion of neoadjuvant chemotherapy and HER2-directed therapy[42].They evaluated the association of the HER2-E subtype with pCR and gene expression changes in paired samples (pre- and post-treatment). Analyses of paired samples from 26 patients who had residual disease showed that a lower proportion of HER2-E and twice the number of luminal tumors were noted at baseline, and luminal A was the most common subtype in residual tumors. The majority (81.8%) of HER2-E tumors changed to non-HER2-E, whereas most luminal A samples maintained the same subtype in the residual disease setting. Although the HER2-E subtype was predictive of pCR beyond HR status following trastuzumab-based chemotherapy in this study, further research is needed as regards the clinical relevance of intrinsic molecular subtype in residual HER2-positive breast cancer.

Tumor intrinsic subtype and other gene signatures have also been evaluated as predictors of benefit of dual HER2 blockade approaches in HER2-positive early stage breast cancer. In the neoadjuvant setting, intrinsic subtype did not predict EFS benefit of lapatinib when added to trastuzumab, although this study was not powered to address this question definitively[41]. Similarly, in the APHINITY adjuvant study, intrinsic subtype was not associated with benefit of pertuzumab added to trastuzumab[43]. However, in both those studies, gene signatures of immune activation were associated with greater benefit of dual blockade. These findings suggest that immune related gene signatures may identify patients most likely to benefit from combination HER2-targeted therapy generally. In CompassHER2 RD, we will test the hypotheses that gene signatures of immune activation and/or intrinsic subtype may be associated with treatment benefit of T-DM1 and tucatinib vs. T-DM1 and placebo. We also will explore new gene signatures that combine tumor subtype genes and immune related genes as potential predictors of tucatinib benefit.

1.2.2 Residual cancer burden (RCB) and Long- Term Outcomes in HER2-Positive Breast Cancer

Residual cancer burden (RCB) after preoperative chemotherapy +/-HER2-directed therapy has long-term prognostic implications in breast cancer patients treated with curative intent. Symmans et al. studied five prospective breast cancer cohorts to determine the long-term prognosis of each phenotypic subset of breast cancer by measuring the RCB index score and class after preoperative chemotherapy [44]. The index score was calculated from the largest area and cellularity of residual invasive primary carcinoma and the number of positive lymph nodes and size of largest metastasis. pCR (stage yp-T0/is, ypN0) has RCB = 0; and RCB class is minimal (RCB-I), moderate (RCB-II), or extensive (RCB-III), on the basis of predefined cut points of 1.36 and 3.28 index scores[45]. RCB accurately predicted long-term survival outcomes after preoperative chemotherapy in all three breast cancer phenotypic subsets. Specifically, in patients with HER2-positive breast cancer who received preoperative chemotherapy and HER2-directed therapy (TH-FEC), estimates of 10-year relapse-free survival rates in the four RCB classes (pCR, RCB-I, RCB-II, and RCB-III) were 95%, 77%, 47%, and 21%. In CompassHER2 RD, we will prospectively determine whether RCB has a greater association with long-term outcomes in HER2-

positive breast cancer patients undergoing post-neoadjuvant treatment compared with American Joint Committee on Cancer (AJCC) stage.

1.2.3 TILS and Immune Biomarkers in Residual HER2-Positive Breast Cancer

An association between the presence of tumor-infiltrating lymphocytes (TILs) in biopsy specimens and improved prognostic outcomes in several malignancies, including breast cancer, has been described[46-48]. Higher TIL levels have also been shown to predict benefit of HER2-targeted therapy[43]. During preoperative systemic therapy, significant fluctuations in TILs levels may be observed[49]. It is hypothesized that chemotherapy exerts its cytotoxic effects by triggering an immune response against the tumor via activation of cytotoxic lymphocytes and dendritic cells, which results from exposure of these cells to antigens resulting from apoptosis and cell death[50, 51]. There is therefore considerable interest in studying the role of TILs in residual disease.

For example, Hamy et al. conducted a study to evaluate TIL levels before and after neoadjuvant therapy with chemotherapy and trastuzumab, in 175 patients with HER2-positive breast cancer [49]. They noted that TIL levels decreased in 78% of the patients during the course of preoperative treatment, and that the TIL level decrease was predictive of a pCR ($p < 0.001$). There was no correlation between baseline TIL levels and prognosis, however in those patients who had residual disease at surgery ($n = 107$), TIL levels greater than 25% were associated with inferior survival outcomes (HR 7.89; 95% CI 1.68–37.77, $p = 0.009$). This study demonstrates that the role of TILs in residual disease warrants further study, and the interpretation of TIL levels may vary according to the subtype of breast cancer and prior use of targeted therapies (e.g. trastuzumab).

The prognostic implications of TILs in residual disease in breast cancer has been demonstrated in various studies, however the majority of these trials were small and retrospective and used different methodologies to quantify TILs. Given the need for standardization in this regard, the International TILs Working Group on Breast Cancer recently published recommendations for the use of TILs in BC, including parameters for evaluation in the residual disease setting[52]. In CompassHER2 RD, we will evaluate the association of TIL levels in both the primary tumor and the residual disease specimen with iDFS. We will also examine whether TIL levels are associated with treatment benefit of T-DM1 and tucatinib vs. T-DM1 and placebo.

1.2.4 Blood-based studies

The detection of circulating tumoral DNA (ctDNA) from blood offers a relatively noninvasive approach to identify patients with clinically-occult tumor burden or minimal residual disease (MRD), who may be at increased risk of recurrence. Garcia-Murillas et al. screened 55 breast cancer patients who had completed neoadjuvant systemic therapy and surgery for breast cancer for the presence of plasma ctDNA at subsequent follow-up visits[53]. Twenty-one patients analyzed in this prospectively accrued study had HER2-positive disease. There was a significant association between disease recurrence and the presence of ctDNA (HR 25.1; 95% CI 4.08–130.5, $p < 0.0001$). Notably, the median lead time between detection of ctDNA and clinical recurrence was 7.9 months, demonstrating the potential of ctDNA as an early predictor of recurrence in the surveillance of breast cancer patients. It was observed that the sensitivity of the ctDNA technique was increased when multiple and consecutive samples were analyzed. Further, the authors were able provide insight on the genetic events underpinning metastases formation by massive parallel sequencing of the ctDNA, which could inform novel therapy selection based on the patients' individual mutations. In CompassHER2 RD, we plan to evaluate the

association of ctDNA (obtained at baseline, immediately after completion of study therapy, and at one year after completion of study therapy with iDFS in our patient population.

Evaluation of ctDNA in this study is described in Section 14.2.

1.2.5 Prevention of Breast Cancer Brain Metastases (BCBM)

As outlined above, patients with residual invasive HER2-positive breast cancer after receipt of chemotherapy and HER2-directed therapy are at increased risk of distant disease recurrence. CNS relapses comprised 40% of the relapses in the KATHERINE trial; this devastating diagnosis is associated with considerable morbidity and mortality [54]. Treatment of patients with BCBM is very challenging and remains a major unmet clinical need. Novel treatments are urgently needed to both prevent and treat BCBM more effectively [55]. Studying clinical and biologic predictors of relapse is an important first step. In CompassHER2 RD we will study baseline clinical and biologic variables associated with CNS tropism, and we will potentially evaluate whether a specific plasma-derived tumor DNA (ptDNA) signature is able to accurately identify patients who will subsequently develop brain metastases. Yu and colleagues have demonstrated that there is an association between SEMA4D, MYC and the development of BCBM based on analyses of circulating tumor cells (CTCS) derived from patients with ER-positive breast cancer[56]. However, given that SEMA4D may work with HER2 in promoting the migration of malignant cells to the CNS, this finding may also be relevant in the genesis of HER2-positive CNS metastases (Yu et al., unpublished data). In KATHERINE, the incidence of brain metastases was similar in the T-DM1 arm and the standard of care therapy arm (trastuzumab)[23]. In CompassHER2 RD, we will determine whether the combination of T-DM1 and tucatinib is superior to T-DM1 and placebo in the prevention of BCBM. Brain metastases-free survival (BMFS) will be assessed as a secondary objective.

1.2.6 Local Regional Considerations

With regards to local treatment of the breast, patients on the CompassHER2 RD trial can be treated with either breast conservation or mastectomy. In the setting of breast conservation, margin status following neoadjuvant chemotherapy is an understudied topic. Margin consensus guidelines from Society of Surgical Oncology, American Society of Clinical Oncology, and American Society for Radiation Oncology included invasive[57] and pre-invasive[58] disease but excluded pre-treated patients. In a single institution study of 382 patients, margin status did not impact 5-year locoregional free survival, disease free survival, or overall survival, suggesting that “no-ink-on-tumor” may be an acceptable margin width for patients who undergo neoadjuvant systemic therapy. This study unfortunately includes a small sample size and only 117 HER2+ patients[59]. Because the appropriate margin width is unknown, CompassHER2 RD provides a valuable opportunity to examine optimal margin width following neoadjuvant systemic therapy.

Hypofractionated, or short course, radiation has become the standard of care following lumpectomy when regional nodal treatment is not required[60]. Hypofractionation in this setting has been shown to result in equivalent local control and a similar or improved toxicity profile. Short course radiation in the setting of post-mastectomy radiation (PMRT) or regional nodal radiation (RNI) is more controversial[61]. Recently several clinical trials have been published suggesting equivalent efficacy and safety in this population[62-64]. Given this data, there has been an increasing acceptance of hypofractionation in patients requiring PMRT or RNI such as NCIC MA.39, looking at the role of breast-only radiation versus RNI. The one remaining setting in which traditional 2Gy/day fractionation remains a standard of care, is in women with breast reconstruction post mastectomy. This

population has a high risk of reconstruction complications, made worse with PMRT22-24 so it is being studied in a randomized trial Alliance A221505. Given the data in support of hypofractionation and the current trials investigating its use, CompassHER2 RD allows hypofractionation as an acceptable radiation schedule for both breast conservation and mastectomy patients.

For patients treated with breast conservation, an optional lumpectomy boost will be allowed. Randomized studies have established a small but significant reduction in local risk recurrence with the addition of a post-lumpectomy tumor bed "boost"[65, 66]. The Lyon trial[66] enrolled 1034 patients between 1986 to 1992 who were < 70 years of age with tumors ≤ 3cm and surgical margins ≥ 1cm to a boost vs. no boost of radiation after 50Gy delivered to the whole breast. The 5-year risk of relapse was significant reduced from 4.5% to 3.6% with the addition of the lumpectomy boost (p=0.044). The EORTC boost trial[65] was a larger study, enrolling 5569 patients from 1989 to 1996 < age 70 with tumors ≤ 5cm to boost vs. no boost of radiation after 50Gy delivered to the whole breast. If margins were negative, defined as no tumor on ink, patients received 16Gy in 8 fractions. The initial publication from that trial confirmed a benefit in the overall population with a 5-year local recurrence rate decreasing from 7.3% to 4.3% with the addition of the lumpectomy boost (p < 0.001). A 20-year follow-up was recently published showing a persistent benefit to a boost, 17% vs. 12% local recurrence overall (p < 0.001)[67]. These studies were conducted before widespread use of ER, PR and HER2 markers; there is little data to inform the impact of tumor biology on the benefit of a boost. ASTRO's whole breast irradiation guideline provides some guidance on patient selection for boost radiation[68], but notably does not address patients who have received pre-operative systemic therapy. Thus, the role of the boost remains understudied in both HER2 positive patients, and patients receiving pre-operative systemic therapy, thus the CompassHER2 trials provide an opportunity to evaluate the impact of the boost on locoregional outcomes.

1.2.7 Patient reported outcomes

A patient-reported outcome (PRO) is "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."[69] PRO measures (PROMs) have been developed and validated to elicit information about treatment toxicities, quality of life, and other aspects of the patient experience during and after cancer therapy. Previous research has shown that, compared to PRO data, clinician reporting of symptomatic outcomes is incomplete and sometimes inaccurate[70-72]. PROs are, therefore, a critical source of data to subsequently inform medical decision making between patients and their doctors.

In CompassHER2 RD, we will assess several PROs for patients who consent to participate, including quality of life (QOL), self-reported patient adherence to oral therapy (and reasons for nonadherence), and patient-reported symptoms. Given the increased emphasis in providing high-quality care for cancer patients, the widespread incorporation of pertinent PROs stratified by treatments received and other parameters is imperative to ensure the highest level of care for breast cancer patients. Additional information about the rationale for specific PRO assessments is included in Section 14.0 (Correlative and Companion Studies).

1.3 Study design rationale

CompassHER2 RD is directed towards those patients with HER2+ disease who do not achieve a pCR either on CompassHER2 pCR or who did not participate in CompassHER2 pCR but received an off-trial neoadjuvant regimen and are otherwise eligible. Postoperatively such patients will be offered the opportunity to enroll on CompassHER2 RD. Adjuvant chemotherapy

must be completed prior to enrollment on the post-neoadjuvant randomized trial. Based on the adjuvant APHINITY trial[73], which demonstrated only a modest (1-2%) absolute benefit of pertuzumab added to trastuzumab and chemotherapy, we are allowing, but not mandating, pertuzumab to have been given preoperatively. Radiotherapy, if recommended, can be given in conjunction with adjuvant T-DM1 and tucatinib/placebo. However, selected patients who have commenced/completed radiotherapy and/or who have already commenced adjuvant T-DM1 may also be candidates for this study. Patients will also receive adjuvant endocrine therapy as appropriate.

1.4 Trial Importance

As noted above, HER2-positive disease is an example of a breast cancer subtype whose outcomes have been transformed by virtue of the multiple effective drugs that have markedly improved the cure rate for this disease. However, this improvement comes at the cost of the toxic and highly expensive (neo)adjuvant regimens given to any breast cancer cohort. This trial, along with CompassHER2 pCR, aims to examine rational approaches to de-escalating and escalating therapy in HER2-positive early breast cancer.

CompassHER2 RD will answer several important questions:

1. For patients with HR- HER2+, or high-risk HR+ HER2+ breast cancer who do not achieve a pCR after neoadjuvant chemotherapy and HER2-directed therapy, can treatment with T-DM1 and tucatinib (with endocrine therapy if appropriate) improve outcomes compared to standard adjuvant T-DM1 therapy and placebo (with endocrine therapy, if appropriate)?

2. Do tumor, blood, or microenvironmental features of the tumor contribute to our ability to prognosticate after HER2-directed therapy, or identify those who benefit from adjuvant treatment with T-DM1 and tucatinib vs. T-DM1 and placebo?

3. From the patient's perspective, does the addition of tucatinib result in added symptomatic toxicity and impaired quality of life?

1.5 Protocol Summary

CompassHER2 RD (A011801) is a randomized trial in patients with residual disease after a predefined course of neoadjuvant HER2-directed treatment. While CompassHER2 RD allows entry for eligible patients who did not participate in CompassHER2 pCR, there is high interest in maximizing participation from CompassHER2 pCR in whom substantial data regarding preoperative clinical and biologic characteristics will already have been obtained. We estimate that 30-50% of patients who will participate in CompassHER2 RD will also have participated in CompassHER2 pCR or a similar trial; the other 50-70% of patients will be recruited separately. Patients treated with de-escalated therapy on CompassHER2 pCR or a similar trial will be required to receive further standard of care chemotherapy (e.g. AC X 4 or Carboplatin-H(P) x 4) or additional TH(P) prior to randomization on CompassHER2 RD, totaling at least 6 cycles of chemotherapy (including treatment administered pre and postoperatively) to be eligible for CompassHER2 RD. Enrollees who did not participate in CompassHER2 pCR or a similar trial must have already completed a standard HER2-directed neoadjuvant regimen (e.g. TCH(P) x 6, or AC-TH(P)), so will receive no additional systemic therapy prior to randomization. However, patients who received 4 cycles of neoadjuvant THP off study may be eligible if they receive an additional 2-4 cycles of chemotherapy postoperatively, prior to enrollment. In CompassHER2 RD, eligible participants with HER2-positive residual disease will be randomized 1:1 to complete a total of 14 cycles of T-DM1 and placebo vs. T-DM1 and tucatinib, with concurrent standard endocrine therapy, if applicable. Adjuvant radiotherapy +/- endocrine therapy, as applicable, can be administered in conjunction with T-DM1 and

tucatinib/placebo. Selected patients who have already begun or completed adjuvant radiotherapy, and/or who have recently commenced adjuvant T-DM1 as standard of care, may also be eligible.

2.0 OBJECTIVES

2.1 Primary objective

To determine if the iDFS with T-DM1 and tucatinib is superior to the iDFS in the control arm (T-DM1 + placebo) when administered to high risk patients with HER2-positive breast cancer and residual disease after neoadjuvant HER2-directed therapy.

2.2 Secondary objectives

2.2.1 To evaluate whether treatment with tucatinib plus T-DM1 compared to treatment with T-DM1 alone (T-DM1 plus placebo) improves the following:

- overall survival (OS)
- breast cancer free survival (BCFS)
- distant recurrence-free survival (DRFS)
- disease-free survival (DFS)
- brain metastases-free survival (BMFS).

2.2.2 To evaluate whether treatment with tucatinib plus T-DM1 compared to treatment with T-DM1 alone (T-DM1 plus placebo) reduces the incidence of brain metastases.

2.3 Secondary correlative objectives

2.3.1 To evaluate the association of TIL levels in both the primary tumor and the residual disease specimen with iDFS

2.3.2 To determine whether there is evidence of differential treatment benefit of T-DM1 and tucatinib compared to T-DM1 and placebo in high TIL cancers compared to low TIL cancers (assessed in both the pre-neoadjuvant tumor tissue and the residual cancer tissue)

2.3.3 To evaluate the association between iDFS and the presence of detectable ctDNA at baseline, at completion of study therapy and/or 1 year after completion of study therapy

2.3.4 To determine the difference in absolute magnitude of benefit of tucatinib (in terms of iDFS) in the subgroup of patients with detectable ctDNA at baseline and the subgroup of patients without detectable ctDNA at baseline

Local regional exploratory objectives

2.3.5 To determine local regional recurrence following breast conservation based on margin width (no ink on tumor, close, >2mm).

2.3.6 To determine local regional recurrence following breast conservation with or without boost.

2.3.7 To compare regional recurrence based on axillary surgery – SLNB vs. ALND – among patients with residual nodal disease.

Patient-Reported Outcomes

2.3.8 Primary Objective

To compare QOL after approximately 8 cycles of the study as assessed by the FACT-B Trial Outcome Index between patients randomized to T-DM1 + tucatinib or T-DM1 + placebo. Hypothesis: QOL will be non-inferior in the T-DM1 + tucatinib arm compared to the T-DM1 + placebo arm at cycle 9, day 1.

2.3.9 Secondary Objective

To compare QOL after approximately 13 cycles of the study as assessed by the FACT-B Trial Outcome Index between patients randomized to T-DM1 + tucatinib or T-DM1 + placebo. Hypothesis: QOL will be non-inferior in the T-DM1 + tucatinib arm compared to the T-DM1 + placebo arm at cycle 14, day 1.

2.3.10 Exploratory Objectives

- To compare various QOL domains after approximately 8 and 13 cycles of the study as assessed by the 5 subscales of the FACT-B questionnaire between patients randomized to T-DM1 + tucatinib or T-DM1 + placebo. This analysis is exploratory, though we anticipate the direction of the comparisons to be consistent with Primary and Secondary Hypotheses.
- To compare self-reported patient adherence and reasons for nonadherence after 1, 4, 8, and 13 cycles of the study as assessed by the Voils instrument (Domains of Subjective Extent of Nonadherence [DOSE-Nonadherence]) between patients randomized to T-DM1 + tucatinib or T-DM1 + placebo. This analysis is exploratory, though we anticipate that patients in the T-DM1 + tucatinib arm will experience more frequent and severe symptoms leading to greater nonadherence.
- To compare self-reported symptomatic adverse events as outlined in section 14.1.1 after 1, 4, 8, and 13 cycles of the study assessed by the PRO-CTCAE between patients randomized to T-DM1 + tucatinib or T-DM1 + placebo. This analysis is exploratory in nature.

2.4 To-be-determined correlative objectives

2.4.1 To evaluate the association of ctDNA tumor-specific mutations (at baseline and after completion of adjuvant HER2-directed therapy) with iDFS

2.4.2 To evaluate the association of breast cancer intrinsic subtype and other transcriptional signatures in both the primary tumor and the residual disease specimen with iDFS

2.5 Pharmacokinetics objectives

The pharmacokinetics (PK) objectives for this study are as follows:

2.5.1 To characterize the PK of T-DM1 in all patients

2.5.2 To characterize the PK of tucatinib in tucatinib-treated patients

2.5.3 To investigate exposure–effect (efficacy and safety) relationships in tucatinib-treated patients

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.
- Patients who cannot swallow or absorb oral formulations of the agent(s).

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study and 7 months after last dose of study drug due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ 3.2.1 HER2-positive breast cancer

___3.2.1.1 HER2-positive status will be based on <u>pretreatment biopsy material</u> and defined as an immunohistochemistry (IHC) score of 3+ and/or positive by in situ hybridization (ISH) according to current ASCO/CAP guidelines. Central testing is not required.

- Known hormone receptor (HR) status as defined by ASCO/CAP guidelines (based on pretreatment biopsy material). Hormone receptor positive status can be determined by either known positive ER or known positive PR status; hormone receptor negative status must be determined by both known negative ER and known negative PR.

___**3.2.1.2** Patients with clinical stage T1-4, N0-3 disease at presentation and residual invasive disease postoperatively as defined above are eligible. Patients with clinical stage TX disease at presentation are also eligible if their pathologic staging meets eligibility criteria. (Note: Patients with T1a/bN0 tumors at initial breast cancer diagnosis are not eligible).

___**3.2.1.3** Patients with residual HR-negative, HER2+ disease in the breast and/or lymph nodes per the surgical pathology report are eligible. Patients with HR-positive, HER2+ disease must have disease in their lymph node(s) per the surgical pathology report in order to qualify for the study. The presence of residual invasive disease in the breast is not mandatory for node-positive patients.

___**3.2.1.4** Patients with weakly ER-positive and/or PR-positive (1-10%) breast cancer (based on the pretreatment core biopsy) are eligible even if they have node-negative disease per the surgical pathology report.

___**3.2.1.5** The residual disease tissue (breast and/or lymph nodes) is not required to be HER2-positive, as eligibility for A011801 is based on a positive HER2 status at the time of the initial breast cancer diagnosis.

Note: The presence of micrometastases in lymph nodes after preoperative therapy counts as residual disease, whereas the presence of isolated tumor cells does not.

___**3.2.1.6** Patients with synchronous bilateral invasive disease are eligible provided both lesions were confirmed to be HER2-positive, and at least one of the lesions meets the criteria outlined above. Multifocal disease is allowed, as long as the largest biopsied breast tumor was HER2-positive.

___ **3.2.2 Prior Treatment**

___**3.2.2.1** Patients must have received neoadjuvant chemotherapy with one of the following regimens: THP, TMP, AC-TH(P); TCH(P); FAC-TH(P), or FEC-TH(P).

Note: apart from TCHP, where T is docetaxel, treatment with docetaxel or paclitaxel is acceptable.

___**3.2.2.2** Prior receipt of T-DM1 in the neoadjuvant setting is not allowed.

___ Prior treatment must have consisted of ≥ 6 cycles of chemotherapy and HER2-directed therapy, with a total duration of ≥ 12 weeks, including at least 9 weeks of preoperative taxane and trastuzumab with or without pertuzumab (or FDA-approved biosimilars). Patients who have received at least 9 weeks of preoperative taxane, pertuzumab and margetuximab are also eligible if they received ≥ 6 cycles of systemic therapy prior to registration.

Note: Patients who complete at least nine of a planned twelve doses of weekly paclitaxel, or three of a planned four doses of docetaxel, or four of a planned six cycles of docetaxel, but discontinue prematurely due to toxicity are eligible. This also applies to patients receiving TCHP who did not receive planned carboplatin doses due to the nationwide carboplatin shortage. Patients receiving dose-dense chemotherapy regimens are also eligible. Prior use of nab-paclitaxel (Abraxane) instead of paclitaxel or docetaxel is permitted. Prior use of subcutaneous trastuzumab (Hylecta) and subcutaneous trastuzumab and pertuzumab (Phesgo) is also allowed.

___ Patients who received neoadjuvant systemic therapy which included experimental HER2-targeted therapy/therapies are potentially eligible, as long as

the investigational agent was not a HER2-targeted antibody-drug conjugate (e.g. T-DM1 or trastuzumab deruxtecan) or a HER2 targeted tyrosine kinase inhibitor (TKI) (e.g. tucatinib, lapatinib, neratinib).

___**3.2.2.3** No adjuvant treatment with any anti-cancer investigational drug within 28 days prior to registration.

___**3.2.2.4** Patients may have received ≤ 1 cycle of T-DM1 in the adjuvant setting. Note: These patients will be randomized to receive a further 14 cycles of T-DM1 and tucatinib/placebo as tolerated. The most recent cycle of T-DM1 should have been administered ≤ 5 weeks prior to registration.

- **Note: Both** of the following two criteria need to be met for the patient to be eligible for this study:

  ___ An interval of no more than 12 weeks between the completion date of the last definitive treatment (e.g. postoperative chemotherapy or radiation, or if neither given, breast surgical date) and the date of registration. Concurrent radiation therapy is permitted while receiving study treatment.

  ___ Patients must be registered on study within ≤ 180 days of the date of the most recent definitive breast cancer surgery (not including reconstructive surgery).

___**3.2.2.5** All systemic chemotherapy should have been completed preoperatively unless participating in EA1181 (CompassHER2 pCR) or the BIG DECRESCENDO Trial (which is very similar to CompassHER2 pCR in terms of study design, drugs, and eligibility). However, patients who received 4 cycles of neoadjuvant THP off study can receive a further 2-4 cycles of chemotherapy postoperatively to meet eligibility for A011801. Patients who participated in EA1181 or MA41 and proceeded to surgery immediately after the de-escalated trial regimen must receive postoperative chemotherapy to complete a total of ≥ 6 cycles of systemic treatment prior to registration on A011801, as outlined above (e.g. 4 cycles pre-operatively, and 2 cycles post-operatively). The postoperative chemotherapy regimen prescribed is at the discretion of the treating oncologist (i.e. 2-4 cycles AC or THP, other). Continuation of trastuzumab + pertuzumab (HP) pre- or post-operatively as maintenance therapy is allowed for all study participants.

Note: Treatment received as part of EA1181 (i.e., the number of cycles of pre-operative chemotherapy and HER2-directed therapy) counts towards A011801 eligibility only, and does not count toward the total number of treatment cycles to be administered on A011801.

___**3.2.2.6** Toxicities related to prior systemic treatment should have resolved or be at baseline, apart from alopecia, peripheral neuropathy ≤ grade 1 and other AEs not felt to be of clinical significance by the treating physician (e.g. nail changes from prior taxane-based chemotherapy).

___**3.2.2.7** Adequate excision: surgical removal of all clinically evident disease in the breast and lymph nodes as follows:

___ Breast surgery: total mastectomy with no gross residual disease at the margin of resection, or breast-conserving surgery with histologically negative margins of excision with the following exception: if the margins of resection include the pectoralis

fascia or subcutaneous tissue, and no further surgery can be done to clear that margin, the patient may be enrolled.

___ For patients who undergo breast-conserving surgery, the margins of the resected specimen must be histologically free of invasive tumor and ductal carcinoma in situ (DCIS) as determined by the local pathologist. If pathologic examination demonstrates tumor at the line of resection, additional operative procedures may be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo total mastectomy to be eligible. Patients with margins positive for classic lobular carcinoma in situ (LCIS) are eligible without additional resection.

Lymph node surgery:

___ The axilla needs to be evaluated with either sentinel node biopsy or axillary lymph node dissection. If patients have a sentinel lymph node biopsy and sentinel nodes are negative for residual disease, no further axillary treatment is necessary. If patients have a sentinel lymph node biopsy and sentinel nodes are positive for residual nodal disease, then ALND is strongly encouraged. If ALND is not performed, then nodal irradiation to the level I/II axilla is required. If patients have micro- or macro-metastatic nodal disease, regional nodal irradiation is required.

___ **3.2.3 Not pregnant and not nursing, because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.**

Therefore, for women of childbearing potential only, a negative serum pregnancy test done ≤ 7 days prior to registration is required.

___ **3.2.4 Age ≥ 18 years (male or female)**

___ **3.2.5 ECOG Performance Status 0-1**

___ **3.2.6 Adequate hepatic, renal, and bone marrow function.**

Required Initial Laboratory Values:

Absolute Neutrophil Count (ANC) ≥ 1,000/mm3

Hemoglobin ≥ 8 g/dL (Note: PRBC transfusion is **not** permitted to achieve eligibility)

Platelet Count ≥ 100,000/mm3

Creatinine ≤ 1.5 x upper limit of normal (ULN)

Total Bilirubin ≤ 1.0 x upper limit of normal (ULN) or direct bilirubin within the institutional normal range for patients with Gilbert's syndrome

AST / ALT ≤ 2.5 x upper limit of normal (ULN)

___ **3.2.7** Patients with known active and/or untreated Hepatitis B or Hepatitis C or chronic liver disease are ineligible. Patients with a diagnosis of Hepatitis B or C that has been

treated and cleared and normal liver function are eligible to participate in the study if the other eligibility parameters are met.

___ 3.2.8 Comorbid conditions

The following are excluded:

___3.2.8.1 Stage IV (metastatic) breast cancer

___3.2.8.2 History of any prior (ipsi- or contralateral) invasive breast cancer within 3 years of registration

___3.2.8.3 Patients with ER+HER2+ residual invasive disease that is lymph node-negative per the surgical pathology report

___3.2.8.4 Evidence of recurrent disease following preoperative therapy and surgery.

___3.2.8.5 Patients for whom radiotherapy would be recommended for breast cancer treatment but for whom it is contraindicated because of medical reasons (e.g., connective tissue disorder or prior ipsilateral breast radiation). Patients who refuse a recommended course of radiotherapy are also excluded.

___**3.2.8.6** History of exposure to the following cumulative doses of anthracyclines: Doxorubicin > 240 mg/m^2; Epirubicin or Liposomal Doxorubicin-Hydrochloride (Myocet®) > 480 mg/m^2. For other anthracyclines, exposure equivalent to doxorubicin > 240 mg/m^2.

___**3.2.8.7** Cardiopulmonary dysfunction as defined by any of the following:

- History of NCI CTCAE v 5.0 Grade ≥ 3 symptomatic congestive heart failure (CHF) or New York Heart Association (NYHA) criteria Class ≥ II
- Angina pectoris requiring anti-anginal medication, serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality, or clinically significant valvular disease
- High-risk uncontrolled arrhythmias: i.e., atrial tachycardia with a heart rate > 100/min at rest, significant ventricular arrhythmia (ventricular tachycardia) or higher-grade AV-block (second degree AV-block Type 2 [Mobitz 2] or third degree AV-block)
- Significant symptoms (Grade ≥ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia while on or since receiving preoperative therapy.
- History of a decrease in LVEF to < 40% with prior trastuzumab treatment (e.g., during preoperative therapy)
- Uncontrolled hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 100 mmHg)

___**3.2.8.8** Current severe, uncontrolled systemic disease

___**3.2.8.9** Major surgical procedure unrelated to breast cancer or significant traumatic injury within 28 days prior to registration or anticipation of the need for major surgery during the course of study treatment. Laparoscopic or vaginal hysterectomies and reconstructive surgery are not considered major surgeries for the purposes of study eligibility.

___**3.2.8.10** History of intolerance, including Grade 3 to 4 infusion reaction or hypersensitivity to trastuzumab or murine proteins or any components of the product

___**3.2.8.11** Peripheral neuropathy of any etiology that exceeds grade 1 (mild symptoms)
___**3.2.8.12** Assessment by the investigator as being unable or unwilling to comply with the requirements of the protocol.

___ **3.2.9 Concomitant medications**

- Use of a strong CYP3A4 or CYP2C8 inhibitor within 2 weeks, or use of a strong CYP3A4 or CYP2C8 inducer within 5 days prior to registration (see Appendix IV and V) is prohibited.

  Please note that use of sensitive CYP3A substrates (Appendix VI) should be avoided two weeks before registration and during study treatment. Additionally, CYP3A4 or CYP2C8 inducers are prohibited as concomitant medications within 5 days following discontinuation of tucatinib treatment. Patients who require medications that are known to be sensitive substrates of CYP3A4 with a narrow therapeutic window should be excluded. See Section 8.1 for more information regarding the use of CYP3A4 or CYP2C8 inhibitors, inducers, and substrates during protocol treatment.

___ **3.2.10 Other**

Screening* left ventricular ejection fraction (LVEF) ≥ 50% on echocardiogram (ECHO) or multiple-gated acquisition (MUGA) after receiving neoadjuvant chemotherapy and no decrease in LVEF by more than 15 absolute percentage points from the pre-chemotherapy** LVEF. Or, if pre-chemotherapy LVEF was not assessed, the screening LVEF must be ≥ 55% after completion of neoadjuvant chemotherapy. Note: LVEF assessment may be repeated once up to 3 weeks following the initial screening assessment to assess eligibility.

*Screening assessment refers to the assessment done after the completion of neoadjuvant treatment but before the date of A011801 registration

**Pre-chemotherapy assessment refers to the assessment done before the start of neoadjuvant treatment

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);

- Associate Plus (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.

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)	✓	✓	✓		

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

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.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

4.2 Cancer Trials Support Unit Registration Procedures

This study is supported by the NCI CTSU.

IRB Approval:

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (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. 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 email 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 for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an 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, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

4.2.1 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 applicable protocol-specific requirements (PSRs).

4.2.2 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 their 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)

- 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 *Alliance,* and protocol number *A011801.*
- 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.)

4.2.3 Submitting regulatory documents

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 to receive further instruction and support.

4.2.4 Checking site's registration status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 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.

4.2.5 Delegation of Task Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and to activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

Canadian sites participating under the Canadian Cancer Trials Group (CCTG), should complete the DTL in CCTG's Roster Interface Program & Participants List Environment (RIPPLE) application when CCTG holds the Clinical Trials Agreement with Health Canada. RIPPLE is integrated with the CTSU DTL application for this trial.

4.3 Patient Registration Requirements

4.3.1 Informed consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patients with impaired decision-making capacity may be enrolled on this study, where institutional policy and IRB of record allow.

4.3.2 Patient-reported outcomes

Electronic patient reported outcomes (ePRO): This study includes the use of ePRO, (electronic patient-reported outcomes). After the patient is registered to the trial, the CRP will complete a second registration to the Patient Cloud. The CRP will create a unique patient registration code by accessing the Patient Cloud through iMedidata Rave. Patients (with assistance from CRPs) will need to download the Patient Cloud app on their own device and use the unique registration code given by the CRP to create an account. Once completed, the patient will be able to complete the submission of patient reported outcomes electronically.

Prior to registration, the patient should be asked about the availability of an electronic device and willingness to complete the patient-reported questionnaires on the device. The patient should be informed that the same method of completion must be used by the patient throughout the duration of the study for all time points. See Appendix I for further instructions on setting up ePRO.

Patient questionnaire booklets

The current version of the patient-completed booklet can be downloaded from the CIRB Approved Documents tab of the A011801 page of the CTSU website at the time of patient registration. Patient questionnaire booklets will only be available in English and Spanish.

4.3.3 Protected health information

In order to conduct the exploratory analyses for this study, it will be necessary to collect the following information from all participants:

1) Birth Date
2) Ethnicity and race
3) Zip code + 4

This information will be collected in OPEN and stored with the study data in Medidata Rave to be used for the analysis.

4.4 Patient registration/randomization procedures

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 LPOs'

registration/randomization systems or the 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:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the 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:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may 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 in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol-specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

4.5 Registration to substudies and companion studies

4.5.1 Registration to substudies described in Section 14.0

The accrual goal for the HO-1 sub-study has been met, therefore, it was closed on 7/22/2024.

There is one substudy within Alliance A011801.This correlative science study must be offered to all patients enrolled on Alliance A011801 (although patients may opt to not participate). This substudy is only open to patients who can read and comprehend English or Spanish. This substudy does not require separate IRB approval. The substudy included within Alliance A011801 is:

- **Closed as of 7/22/2024**: Quality of life substudy, Alliance A011801-HO1 (Section 14.1).

If a patient answers "yes" to "I choose to take part in the quality of life study and will fill out these forms," they have consented to participate in the substudy described in Section 14.1. The patient should be registered to Alliance A011801-HO1 at the same time they are registered to the treatment trial (A011801). Questionnaires should be submitted per Section 14.1.

CCTG sites: Please see Section 6.3.1 for information regarding French-translated questionnaires.

4.6 Stratification Factors and Treatment Assignments

The randomization routine is found in Section 13.0 (Statistical Considerations).

4.6.1 Stratification Factors

1) Receipt of post-operative chemotherapy: yes vs. no
    - Note 1: One cycle of post-neoadjuvant T-DM1 prior to enrollment on A011801 does **not** count as a cycle of post-operative chemotherapy.
    - Note 2: Cycles of adjuvant trastuzumab + pertuzumab do NOT count as cycles of post-operative chemotherapy. Cycles of any other adjuvant treatment, as allowed in Section 3.2.2.5, DO count as receipt of post-operative chemotherapy.
    - Note 3: Continuation of trastuzumab + pertuzumab (HP) pre- or post-operatively as maintenance therapy is allowed for all study participants.
2) HR status: positive (ER and/or PR positive) vs. negative (ER negative and PR negative)
3) Pathologic lymph node status: positive vs. negative

4.6.2 Treatment Assignments

The factors defined in Section 4.6.1 will be used as stratification factors.

After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups.

1) T-DM1 and placebo
2) T-DM1 and tucatinib

5.0 STUDY CALENDAR

Pre-study Testing Intervals

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

To be completed ≤ 28 DAYS before registration: All laboratory studies, history and physical.

	Prior to Registration*	Day 1 of each 21-day cycle (+/- 3 days)	Day 12 of Cycles 1 and 2 (+/- 3 days)	After every 4 cycles (+/- 7 days)	Post-treatment follow up**	At recurrence, withdrawal, or removal**
Tests & Observations						
History and physical, weight, PS***	X	X			X	X
Height	X					
Pulse, Blood Pressure	X	X				
Echo/MUGA	A(1)			B(1)	C(1)	
Adverse Event Assessment	X(2)	X(2)			D	
Patient Medication Diary		X(3)				
Laboratory Studies						
Complete Blood Count, Differential, Platelets	X	X				
Serum Creatinine	X	X				
Albumin, glucose	X	X				
AST, ALT, Alk. Phos., Bili	X	X	E			
Serum HCG	X(4)					
Tissue submission for TIL analysis (if available)	X					
Blood submission for ctDNA and PK analysis		X(5)				
Correlative studies: For patients who consent to participate						
QOL assessment	See Section 6.3 for a schedule of QOL assessments. To be completed using ePRO. See Section 4.3.2 and Appendix I for further instructions.					
Tissue samples for biobanking	See Section 6.2 for a schedule of tissue sample submission.					

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 21 days prior to treatment. For subsequent cycles, labs, scans, tests and observations may be obtained no more than 3 days prior to day 1 of treatment.

** The first follow-up visit is at 6 months (+/- 45 days) after the discontinuation of protocol treatment.. Thereafter, post-treatment follow-up visits are required every 6 months (+/- 45 days) from the date of last contact from the previous follow-up cycle. Patients will reach the maximum follow-up period once they reach 10 years after registration or until they experience a CNS disease event. If a CNS event occurs, the patient is followed for survival every 12 months until 10 years following registration. See also Section 12.0.

*** Drug dosages need not be changed unless the calculated dose changes by ≥ 10% or weight changes by > 10%.

1 The same test (ECHO or MUGA) should be used to monitor cardiac function for an individual patient during the trial.

2 Please refer to Appendix XII and Section 9.1 for PRO-CTCAE items (for patients who consent to A011801-HO1).

3 The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented by a count of the returned pills in the pharmacy-issued bottle. If a patient does not complete the pill diary or return the bottle, sites should enter UNK (unknown) for that cycle and log as a protocol deviation in Rave. Sites should utilize the comment field to indicate any additional info on the UNK event.

4 For women of childbearing potential (see Section 3.2). Must be done ≤ 7 days prior to registration.

5 Blood for PK analysis is only to be collected on Cycle 2 Day 1 and Cycle 3 Day 1. See Sections 6.2 and 14.2.

A Obtain any time between completion of neoadjuvant chemotherapy and registration to A011801.

B If study treatment is held or delayed, ECHO/MUGA timing should continue once every 12 weeks (+/- 7 days) from the previous ECHO/MUGA.

C ECHO or MUGA is required within 30 days after the last dose of study treatment, unless already done within 12 weeks prior.

D Grade 3+ adverse events that occur more than 30 days after the last study treatment date that are attributed as possibly, probably, or definitely related to study treatment are to be reported. See Sections 9.2 and 9.3.

E Day 12 (+/- 3 days) liver enzymes during **Cycle 1** are **optional.**

Day 12 (+/- 3 days) liver enzymes during **Cycle 2** are **mandatory.**

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule

A Data Submission Schedule (DSS) is available on the Alliance study webpage, within the Case Report Forms section. The Data Submission Schedule is also available on the CTSU site within the study-specific Case Report Forms folder.

6.1.2 Medidata Rave

Medidata Rave is the 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.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; 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 a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associate (A) registration type.

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

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. 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.

No action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Pending study invitations (previously sent but not accepted or declined by a site user) will be

automatically accepted and study access in Rave will be automatically granted for the site user. Account activation instructions are located on the CTSU website in the *Data Management* section under the Data Management Help Topics > Rave resource materials (*Medidata Account Activation and Study Invitation*). Additional information on iMedidata/Rave is available on the CTSU members' website in the *Data Management > Rave section* or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

Please see ICAREdata® Section 6.1.9 for additional information about data storage for select sites participating in this special project.

6.1.3 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 Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

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

6.1.4 Supporting documentation to be submitted to the Alliance

This study requires supporting documentation for diagnosis of HER2-positive residual invasive breast cancer after preoperative systemic therapy. Supporting documentation will include:

- Original (pretreatment) biopsy report confirming breast cancer diagnosis, including information as regards ER, PR and HER2-status.
- Surgical pathology report confirming residual invasive carcinoma in the breast and/or lymph nodes after preoperative therapy.
- Surgical pathology report confirming disease recurrence (when applicable)
- Simulation plan and treatment details for those patients who received/ are receiving/ will receive adjuvant radiotherapy as part of their breast cancer treatment.

Supporting documentation is to be submitted via the CTSU Source Document Portal (see Section 6.1.6).

Submission of additional source documents will be required for this study for the purpose of on-site and central monitoring. See Section 16.0.

6.1.5 Rave-CTEP-AERS integration

See Section 9.1.1 for information regarding submission of adverse event information utilizing the Rave-CTEP-AERS integration.

6.1.6 Central Monitoring (CM) using the CTSU Source Document Portal (SDP)

Central Monitoring (CM) Review is required for this protocol. CM allows Lead Protocol Organizations (LPOs) to remotely compare data entered in Rave to source documentation to ensure that sites are adhering to the protocol and central monitoring plan as well as accurately transcribing data from patients' charts (i.e., source data verification).

Sites can upload source documents required for CM Review as documented in the central monitoring plan using the Source Document Portal (SDP) application. This application is also available on the CTSU members' website under Auditing & Monitoring and may also be accessed using a direct link within Rave on the CM Alert form. Site staff with any of the Rave roles on a relevant site roster can view and upload source documents. Prior to saving source documents on the SDP, each site is responsible for removing or redacting any Personally Identifiable Information (PII) (note that functionality to do this redaction exists within the SDP itself). Designated LPO staff will review each document after it has been loaded on the SDP to ensure the appropriate documents have been uploaded and to ensure PII is redacted.

Additional information on the SDP is available on the CTSU SDP application under Browser > Document Repository in the Help Topics button or by contacting the CTSU Help Desk (1-888-823-5923 or ctsucontact@westat.com).

6.1.7 DMU Monitoring

This study has been assigned Demography monitoring.

Required submission of patient demographic data will be submitted automatically via OPEN.

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

6.1.8. Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s).

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

Please see Section 16.0 for a description of Central Data Monitoring and On-Site Monitoring for this trial.

6.1.9 ICAREdata®

Selected sites will be participating in the ICAREdata® project. The Integrating Clinical Trials and Real-world Endpoints data (ICAREdata) initiative is a program led by the Alliance Data Innovation Lab, which is a component of the Alliance for Clinical Trials in Oncology.

The ICAREdata® project aims to expand the ability to achieve clinical research goals by providing new ways to collect data required for clinical trials. Today, virtually all clinical trials data are collected using special forms and computer applications, such as a software known as Medidata Rave. Instead of using these "add on" data collection systems, the ICAREdata project will gather study data directly from the Electronic Health Record (EHR). As with all research data collections, data collected by the ICAREdata project are stored in a secured repository.

Select institutions will be invited to participate and will receive training on the specific ICAREdata® requirements. As with all clinical trials data management, the nature of data collected using the ICAREdata methods will be specific to a particular research protocol, and might include demographic information, diagnosis, laboratory values, physician assessments, and other results, such as adverse event reports. The Data Innovation Lab will manage data collection, working with the IT department at these sites to configure the EHR to deliver mCODE (minimal common oncology data elements) data and other required outcome data in the form of structured ICAREdata questions. Clinicians will provide the study-required data by answering standardized questions or data fields as part of their encounter visit with the subjects. The IT departments will also work to implement the data transfer capability from the site EHR to the Alliance Data Innovation Lab via a secure/tested extraction method.

Investigators and research staff at limited select sites that utilize the EHR research adverse events data collection tool will be asked to complete a brief voluntary survey. The research staff and investigator's email addresses at these predetermined sites will be submitted at the time of Adverse Events data collection tool training. The survey will take approximately 5 minutes to complete. It will solicit feedback on the investigators and study staff experiences including overall staff acceptance, usability, preferences for using the tool to document any adverse events. The plan survey administration timeline is at baseline and then a select period thereafter. Ultimately, the survey will be used to gather general feedback of the usability of the tool across multiple site-level stakeholders.

Data will be encrypted at-rest and in-transit using a secure interface with an established authorization protocol handled by the ICAREdata infrastructure. Alliance Data Lab staff will issue a client ID and credentials to participating ICAREdata sites that will be used to authenticate those sites for access to the ICAREdata infrastructure service/extraction method to submit data. The clinical site will be responsible for securely storing these credentials (e.g., installed on a server that an IT administrator manages) such that those staff responsible for submitting data will have the proper access. Data will be stored and maintained in HIPAA compliant data repositories (such as AWS) and access controlled by an identity server with strict management to ensure confidentiality, integrity, and availability of PHI. Strict access controls will be maintained. Only authorized Alliance Data Lab personnel will have access to the data and scope of access will be further controlled based on role and level of need to know.

Participating institutions may email the Alliance Data Innovation Lab at ICAREdata@alliancefoundationtrials.org with any questions.

6.2 Specimen collection and submission

The Alliance A011801 Correlative Science Manual (CSM) contains instructions for specimen collection, processing and shipping. The manual can be found on the BioMS and CTSU websites. Questions regarding the CSM should be addressed to the contacts specified in the manual.

For all patients registered to Alliance A011801: BC360 analysis and other tissue-based studies will be conducted using the paraffin breast tissue from the diagnostic breast biopsies and the definitive breast surgery specimens . In addition, ct-DNA analysis will be conducted using Whole blood in Streck tubes. Rationale and methods for the scientific components of these studies are described in Section 14.0**For patients consented to biobanking:** All participating institutions must ask patients for their consent to participate in biobanking for future research, although patient participation is optional. For patients who consent to participate, tissue will be collected at recurrence.

Table 1: Specimen Collection Schedule

	≤ 28 days after registration	**Cycle 2 Day 1**	**Cycle 3 Day 1**	**At completion of study therapy (+/- 1 month)***	**1 year after completion of study therapy (+/- 1 month)****	**Recurrence *****
Mandatory for <u>all</u> patients registered to A011801:						
Paraffin block/slides	X[1]					
Whole blood (Streck tubes), kits provided)[2]	2 x 10 mL			2 x 10 mL	2 x 10 mL	2 x 10 mL
Plasma for PK analysis (lavender top EDTA tube, kits provided)[2]		2 x 5 mL	2 x 5 mL			
For patients who consent to biobanking, submit the following:						
Paraffin block/slides						X[3]

*Completion of study therapy is defined as the last dose of T-DM1 OR Tucatinib/placebo.,

**Patients who discontinue T-DM1 or tucatinib/placebo early for any reason will have the one-year sample collected.

***Obtain if patient has disease recurrence before completion of the last planned dose of study therapy, or within the follow-up period (10 years post-registration)

1. Tumor tissue and related pathology reports from BOTH:
   a. the archived initial diagnostic biopsy specimen (prior to starting neoadjuvant therapy) and

b. the residual disease on the definitive surgical specimen should be submitted.

If patient consents to biobanking, any remaining tissue will be stored at the Alliance Biobank for unknown future use.

For patients who previously participated in EA1181: The EA1181 patient ID numbers will be collected in the BioMS, OPEN and Medidata Rave databases. If the tissue specimen was previously submitted for EA1181 and is therefore not available to submit for A011801, this will not be a protocol deviation. This should be recorded in the specimen submission CRF in Rave.

2. See Table 2 below for a detailed PK collection schedule.

3. Tumor tissue from a site of tumor recurrence (when applicable), only if tissue was collected per standard of care. No new research biopsy is required.

4. For ctDNA and buffy coat. Kits are being provided for the collection and shipment of the peripheral blood specimens being submitted to the biobank.

Table 2 – PK Collection Schedule

Cycle	Day	Time Point
2	1	**Pre-T-DM1 Draw** Draw sample 12 hours (+/- 4 hours) post last dose of tucatinib/placebo • Note: If > 16 hours post the last dose of tucatinib/placebo, still draw the pre-T-DM1 sample. • Note: If tucatinib/placebo was taken < 8 hours prior to the draw, still draw the pre-T-DM1 sample. • Note: If the patient held the first daily dose of tucatinib/placebo for the pre-T-DM1 draw, the dose can be taken at any point within 1 hour after the pre-T-DM1. (2nd daily dose should be taken no earlier than ~10 hours post 1st daily dose) **Post-T-DM1 Draw** Draw sample within 1 hour after the end of the T-DM1 infusion.
3	1	**Pre-T-DM1 Draw** Draw sample 12 hours (+/- 4 hours) post last dose of tucatinib/placebo • Note: If > 16 hours post the last dose of tucatinib/placebo, still draw the pre-T-DM1 sample. • Note: If tucatinib/placebo was taken < 8 hours prior to the draw, still draw the pre-T-DM1 sample. • Note: If the patient held the first daily dose of tucatinib/placebo for the pre-T-DM1 draw, the dose can be taken at any point within 1 hour after the pre-T-DM1. (2nd daily dose should be taken no earlier than ~10 hours post 1st daily dose) **Post-T-DM1 Draw** Draw sample within 1 hour after the end of the T-DM1 infusion.

If a subject is scheduled for a morning appointment, their morning dose of tucatinib or placebo should be held until after PK sample collection prior to the start of T-DM1 infusion. If they are

scheduled for an afternoon appointment, their morning dose should be taken as scheduled, and PK sample collection should be done at the time of their appointment prior to T-DM1 infusion, ahead of the evening dose. A total of 5 mL of blood in an EDTA tube will be collected at each time point for both tucatinib and T-DM1 PK. Both time of dosing (for both drugs) and time of sample collection must be accurately recorded in the patient records and in Medidata Rave.

6.3 Submission of Patient Completed Measures

The HO-1 substudy has met its accrual goals and has closed to patient accrual as of **7/22/2024**.

It is strongly recommended that patients complete the measures using ePRO. Paper booklets should be offered only to those patients who are not willing and/or are unable to use an electronic device for completion of questionnaires.

For patients using ePRO: The data from the patients' responses are submitted directly from the device into the Rave database. There are no documents to audit. The electronic responses are the source documentation.

For patients who are not willing and/or unable to use ePRO: The current version of the patient-completed booklets can be downloaded from the CIRB Approved Documents tab of the A011801 page of the CTSU website. Booklets must be given to patients to complete and patients should be instructed to return the booklets/responses to site staff (either in person, by mail, by email, or by phone), and site staff will enter patient responses into Rave. The method of administration (in person, by mail, etc.) should be documented in the source documents. At visits in which booklets are to be completed, the booklet should be given to the patient before any discussion of the patient's health status or test results. The method of collection should be documented in Rave. Booklet administration schedule is provided below.

The schedule below only pertains to patients who consent to participate in the Quality of Life study. Verbal administration of the measures for visually impaired patients is permitted if the measure and verbal administration of the measure is conducted in a language understandable to the patient. For patients registered to A011801-HO1, submit patient-completed questionnaires at the following time points:

Domain	Instrument	Booklet: At Registration* ePRO: Within 14 days after registration	Booklet: Cycle 2 Day 1 ePRO: 22 days (+/- 7 days) after registration	Booklet: Cycle 5 Day 1 ePRO: 98 days (+/- 7 days) after registration	Booklet: Cycle 9 Day 1 ePRO 182 days (+/- 7 days) after registration	Booklet: Cycle 14 Day 1 ePRO: 287 days (+/- 7 days) after registration	Booklet: 18 and 24 months (+/- 45 days) post-registration ePRO: 540 and 720 days (+/- 45 days) post-registration
Quality of Life	Functional Assessment of Cancer Therapy-Breast (FACT-B)**	X			X	X	X
Symptoms	Patient-Reported Outcomes Common Terminology Criteria for Adverse Events***	X	X	X	X	X	X
Adherence to oral therapy	DOSE-Nonadherence		X	X	X	X	
Time estimated per survey		15 min	12 min	12 min	15 min	15 min	13 min

* After registration but prior to start of study treatment

** Male patients should skip any questions on the FACT-B that specifically refer to females (e.g., "I am able to feel like a woman").

*** PRO-CTCAE includes 10 symptoms: anxiety, numbness and tingling, nausea, vomiting, diarrhea, constipation, shortness of breath, fatigue, hand-foot syndrome (palmar-planter erythrodysesthesia), and headaches. Branching/skip logic permits for further assessment of symptom attributes (e.g. severity or symptom interference) if a particular symptom is present.

6.3.1 Patient Language Considerations

All instruments are available in English and Spanish. Ad-hoc translation of the measures in other languages is not permitted.

CCTG institutions are to provide patient completed booklets translated into French to French speakers. The site is responsible for transcribing the patient responses from the French version into the English version within Medidata Rave to submit to the Alliance Statistics and Data Center. The institution should retain the completed French version as source documentation.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 14 days after randomization.

For questions regarding treatment, please see the study contacts page.

After Cycle 1, it is acceptable for individual chemotherapy doses to be delivered within a +/- 3-day window before and after the protocol-defined date for Day 1 of a new cycle. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

Protocol therapy will consist of 14 cycles of either T-DM1 and placebo or T-DM1 and tucatinib administered every 3 weeks (1 cycle = 21 days). This also applies to patients who received extra cycles of trastuzumab and pertuzumab perioperatively, and to patients who received one dose of T-DM1 postoperatively before enrolling on A011801. Treatment may be prematurely discontinued if the patient develops unacceptable side-effects, or is diagnosed with relapsed breast cancer.

Recommended pretreatment (both arms [i.e. T-DM1 pre-medications]):

The instructions in this table are recommendations only, and not requirements. Pre-medications for T-DM1 can be administered per institutional guidelines.

Agent	DOSE	ROUTE	DAYS
Acetaminophen	650mg	oral as needed	Day 1, prior to T-DM1 administration
Diphenhydramine*	50mg	In 100 ml 0.9% NaCL IV infusion over 15 minutes	
Meperidine	25mg	IV push every 15 minutes as needed for rigors May repeat once (maximum total dose 50 mg)	

* If the first cycle of T-DM1 is well tolerated, the dose of diphenhydramine can be decreased to 25 mg and/or switched to oral administration going forward.

T-DM1 + tucatinib arm:

Agent	Dose	Route	Schedule
T-DM1	3.6 mg/kg	IV	Day 1 Q3W
Tucatinib	300 mg	PO	BID daily

T-DM1 + placebo arm:

Agent	Dose	Route	Schedule
T-DM1	3.6 mg/kg	IV	Day 1 Q3W
Placebo	N/A	PO	BID daily

Ado-trastuzumab emtansine (T-DM1)

Ado-trastuzumab emtansine (T-DM1) will be administered on Day 1 (+/- 3 days) of a 3-week cycle at a dose of 3.6 mg/kg IV. The total dose will calculated based on the patient's weight on Day 1 of (or up to 3 days before) each cycle with no upper limit. Drug dosages need not be changed unless the calculated dose changes by ≥ 10% or weight changes by > 10%.

Ado-trastuzumab emtansine doses may be reduced to as low as 2.4 mg/kg, according to the dose modification guidelines in Section 8.2 (Table 3). The start of a cycle may be delayed up to 14 days to allow toxicities to resolve. If the timing of a protocol-mandated procedure, such as administration of ado-trastuzumab emtansine, coincides with a holiday that precludes the procedure, the procedure should be performed within 3 days of the scheduled date (unless otherwise specified in the protocol) and, when possible, on the earliest following date, with subsequent protocol-specified procedures rescheduled accordingly.

The first infusion of ado-trastuzumab emtansine will be administered over 90 minutes (±10 minutes). Infusions maybe slowed or interrupted for patients experiencing infusion associated symptoms. Vital signs must be assessed before and after the first dose administration. Following the initial dose, patients will be observed for at least 90 minutes for fever, chills, or other infusion associated symptoms. If prior infusions were well-tolerated (without any signs or symptoms of infusion reactions), subsequent doses of ado-trastuzumab emtansine may be administered over 30 minutes (±10 minutes), with a minimum 30-minute observation period after infusion. Further, the dose of diphenhydramine can be decreased to 25 mg and/or switched to oral administration going forward. Local health authority guidelines must be followed with regard to further observation and monitoring, if applicable.

Premedication for nausea and infusion reactions are not commonly required but may be given at the investigator's discretion.

Ado-trastuzumab emtansine will be continued until disease recurrence, completion of 14 cycles, participant discontinuation, study closure, or intolerable toxicity.

Concomitant use of strong CYP3A4 inhibitors (Appendix IV) (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) with T-DM1 should be avoided due to the potential for an increase in DM1 exposure and toxicity.

Tucatinib/placebo

TUCATINIB SAFETY PLAN

Clinical Laboratory Evaluation:

All safety labs will be analyzed by the site's local laboratory(ies). The chemistry panel is to include the following tests: calcium, total protein, albumin, blood urea nitrogen (BUN), creatinine, bicarbonate, glucose, potassium, chloride, and sodium. Liver function tests (LFT) are to include the following: AST/SGOT, ALT/SGPT, total bilirubin, and alkaline phosphatase. The hematology panel is to include the following tests: complete blood count (CBC) with differential, hemoglobin, hematocrit (Hct), and platelets.

Safety Plan for Cardiotoxicity

Trastuzumab and other HER2-targeted therapies are known to increase the risk of the development of declines in LVEF. Cardiac function should be monitored closely. Assessment of cardiac ejection fraction will be performed by MUGA or ECHO at screening and at least once every 12 weeks thereafter until study discontinuation, and 30 days after the last treatment dose (unless done within 12 weeks prior to 30-day follow-up visit).

Tucatinib/placebo will be taken orally Q12H (±2 hours) on Days 1 through 21 of a 21-day cycle and should be taken at the same time of the initial start of the T-DM1 infusion.

For Cycle 2 and beyond, a delay of ≤7 days in the start of a cycle (Day 1) for justifiable reasons (for example, inclement weather, holidays, or weekends) other than adverse events will be permitted and does not constitute a protocol violation.

For Cycle 2 and beyond, a delay of ≤14 days in the start of a cycle (Day 1) to allow for recovery from adverse events will be permitted and does not constitute a protocol violation.

Of note, adjuvant radiotherapy (if applicable) and/or adjuvant endocrine therapy (including ovarian function suppression injections) should be commenced in conjunction with T-DM1 and placebo/tucatinib. However, some patients on this study will have commenced/completed adjuvant radiotherapy before registration. Please refer to the sections on adjuvant radiotherapy and endocrine therapy below for further details.

Adjuvant Radiotherapy

Concomitant adjuvant radiotherapy includes the following:

- For patients undergoing breast-conserving surgery, whole breast irradiation is required. Primary tumor bed boost may be administered according to the treating physician. Regional nodal irradiation, to include the supraclavicular and internal mammary nodes, is strongly encouraged if the patient presented with clinical T3N1, T4N0-1, or N2-3 disease, or if there is any residual disease in lymph nodes. Given the increased risk of pneumonitis with concomitant T-DM1 noted in KATHERINE (2.6% vs. 0.8%), we recommend limiting the ipsilateral V20 to ≤ 35%.
- For post-mastectomy patients, chest wall and regional nodal irradiation, to include the supraclavicular and internal mammary nodes, is strongly encouraged if the patient presented with clinical T3N1, T4N0-1, or N2-3 disease, or if there is residual disease in lymph nodes; it is recommended for T3N0. Given the increased risk of pneumonitis with concomitant T-DM1, we recommend limiting the ipsilateral V20 to ≤ 35%. Scar boost is optional.
- For post-mastectomy patients who do not meet these criteria, radiotherapy is at the discretion of the treating physician based on institutional standards. Radiotherapy does not need to be performed at the institution where the patient is enrolled on CompassHER2 RD.

- Radiotherapy should be initiated within 60 days of surgery in the absence of complications requiring delay. When indicated, it is recommended that radiotherapy is given concurrently with study therapy. Plans for reconstructive surgery should take the protocol therapy into consideration. Hypofractionation of adjuvant whole breast, chest wall and regional node radiotherapy may be done according to local institutional guidelines.

Concomitant Hormonal Therapy

- Concomitant hormonal therapy may be administered according to standard of care recommendations. Please refer to the most current version of the appropriate guidelines for further information. Female patients must be classified according to one of the following menopausal status definitions on the basis of their pre-chemotherapy status:
- Premenopausal < 12 months since last menstrual period AND no prior bilateral ovariectomy AND not receiving estrogen replacement OR biochemical evidence of premenopausal status, according to local policies.
- Postmenopausal > 12 months since last menstrual period with no prior hysterectomy OR prior bilateral ovariectomy OR biochemical evidence of postmenopausal status, according to local policies Female patients should be treated according to local guidelines. A minimum of 5 years of hormonal therapy should be planned. Adjuvant endocrine therapy can be given in conjunction with the study treatment.

NOTE: Endocrine therapy in male patients is to be given according to local guidelines

7.1 Patient Unblinding

If a patient meets the primary study endpoint (i.e., experiences an invasive breast cancer recurrence), they may be unblinded upon request. Once a patient is unblinded they will be removed from current therapy. For emergency unblinding procedures, please see Section 8.3.

8.0 DOSE AND TREATMENT MODIFICATIONS, UNBLINDING

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

Supportive treatments will be given according to label instructions as medically indicated for patients in each cohort. Concomitant medications can be administered at the Investigator's discretion to conform to standard practice during the treatment period.

8.1.1 Patients should not receive any other treatment which would be considered treatment for the primary neoplasm or impact the primary endpoint.

8.1.2 **Patients should receive full supportive care while on this study.** This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 **Treatment with hormones or other chemotherapeutic agents may not be administered** except for steroids given for adrenal failure, asthma, chronic obstructive pulmonary disease (COPD), hay fever, severe hives, eczema, painful joints or muscles (arthritis, tennis elbow and frozen shoulder), pain caused by an irritated or trapped nerve (e.g. severe sciatica), inflammatory bowel disease (Crohn's) or lupus; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic in solid tumor protocols. Importantly, the use of standard adjuvant endocrine therapy for ER-positive HER2-positive breast

cancer is permitted and recommended. Topical or intravaginal hormonal therapies are allowed.

8.1.4 Antiemetics may be used at the discretion of the attending physician, with the exception of steroids above.

8.1.5 Diarrhea management is per the discretion of the treating physician. Diarrhea could be managed conservatively with medications such as loperamide.

Patients with severe diarrhea should be assessed for intravenous hydration and correction of electrolyte imbalances.

8.1.6 Alliance Policy Concerning the Use of Growth Factors

Blood products should be utilized as clinically warranted and following institutional policies and recommendations.

Epoetin (EPO): Use of epoetin in this protocol is prohibited.

Filgrastim (G-CSF) and biosimilar products, and sargramostim (GM-CSF) are prohibited.

8.1.7 Hypersensitivity/infusion reactions

Treat hypersensitivity and infusion reactions to T-DM1 per institutional standards.

8.1.8 CYP3A4 Inhibitors

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed during this trial, or within 2 weeks prior to registration. The following drugs are EXAMPLES of strong inhibitors of CYP3A4 and are not allowed during treatment with T-DM1 or tucatinib/placebo.

- Indinavir
- Clarithromycin
- Ketoconazole

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A4. Please see Appendix IV. Other examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.1.9 CYP3A4 Inducers

Chronic concomitant treatment with strong inducers of CYP3A4 is not allowed during this trial, or within 5 days prior to registration. The following drugs are EXAMPLES of strong inducers of CYP3A4 and are not allowed during treatment with T-DM1 or tucatinib/placebo.

- Voriconazole
- Telithromycin

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4. Please see Appendix IV. Other examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.1.10 CYP2C8 Inhibitors

Chronic concomitant treatment with strong inhibitors of CYP2C8 is not allowed during on this trial, or within 2 weeks prior to registration. The following drug is an EXAMPLE of a strong inhibitor of CYP2C8 and is not allowed during treatment with T-DM1 or tucatinib/placebo.

- Gemfibrozil

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP2C8. Please see Appendix V. Other examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.1.11 CYP2C8 Inducers

Chronic concomitant treatment with strong inducers of CYP2C8 is not allowed during this trial or within 5 days prior to registration. The following drug is an EXAMPLE of a strong inducer of CYP2C8 and is not allowed during treatment with T-DM1 or tucatinib/placebo.

- Rifampin

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP2C8. Please see Appendix V. Other examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.1.12 CYP3A Substrates (sensitive)

Chronic concomitant treatment with sensitive CYP3A substrates during this trial or within 2 weeks prior to starting treatment on this trial should be avoided. The following drugs are EXAMPLES of sensitive CYP3A substrates and should be avoided during treatment with T-DM1 or tucatinib/placebo.

- Buspirone
- Darunavir

If the use of sensitive CYP3A substrates is unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information. Because lists of these agents are constantly changing, please consult and review any drugs that may be sensitive CYP3A4 substrates. Please see Appendix VI. Other examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.1.13 Cytochrome P-450 CYP3A4 Substrates with a Narrow Therapeutic Index

Chronic concomitant treatment with cytochrome P-450 CYP3A4 substrates with a narrow therapeutic index during this trial or within 2 weeks prior to starting treatment on this trial is prohibited. The following drugs are EXAMPLES of cytochrome P-450 CYP3A4 substrates with a narrow therapeutic index and are not allowed during treatment with T-DM1 or tucatinib/placebo.

- Cyclosporine

- Everolimus

Because lists of these agents are constantly changing, please consult and review any drugs that may be cytochrome P-450 CYP3A4 substrates with a narrow therapeutic index. Please see Appendix VII. Other examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.2 Dose Modifications

Investigational study drug (tucatinib or placebo) and T-DM1 dose-reduction recommendations are described in the tables later in this section. These tables include guidelines for dose modification recommendations (including dose holds, dose reductions, or discontinuation of drug) in response to potential AEs.

Dose reductions or treatment interruption/discontinuation for reasons other than those listed in the tables below may be made by the investigator if it is deemed in the best interest of subject safety. Whenever possible, these decisions should first be discussed with the Study Chair.

All AEs and clinically significant laboratory abnormalities should be assessed by the investigator for relationship to tucatinib and T-DM1. An AE may be considered related to tucatinib alone, T-DM1 alone, to both drugs, or to neither. In the event that the relationship is unclear, discussion should be held with the Study Chair, to discuss which study drug(s) should be held and/or modified.

Doses held for toxicity will not be replaced. Investigational study drug or T-DM1 should be discontinued if a delay greater than 14 days is required due to treatment-related toxicity.

Doses held for reasons other than treatment-related toxicity (e.g., surgery) should be per the treating physician's discretion as it relates to the indication for and the duration of same. Doses can be held longer than 14 days as long as it is not related to any treatment toxicity.

Protocol-defined visits and cycle numbering will be determined by T-DM1 dosing, allowing for dose holds or delays with T-DM1. In the event T-DM1 is discontinued, and patient re-initiates trastuzumab per standard of care, and study treatment with tucatinib continues, protocol-defined visits and cycle numbering will proceed using a 21-day cycle regardless of dose holds or delays for tucatinib. If T-DM1 is discontinued and the patient does **not** re-initiate trastuzumab, the patient should enter clinical follow-up and be followed per standard of care per treating physician's discretion. If tucatinib/placebo is discontinued, the patient should enter clinical follow-up and be followed per standard of care per the treating physician's discretion.

Dose Modifications for ado-trastuzumab emtansine (T-DM1)

If significant ado-trastuzumab emtansine –related adverse events have not recovered to Grade ≤1 or baseline grade by day 1 of each cycle of T-DM1, the next scheduled dose may be delayed for up to 14 days. "Significant" and "related" will be based on the judgement of the investigator in consultation with the Study Chair, when appropriate. For example, alopecia, even if considered related, would most likely not be considered significant. Fatigue may or may not be considered either related or significant.

In general, when the significant and related adverse event (or any other adverse event for which the investigator chooses to delay dosing) resolves to Grade ≤1 or baseline, the patient may resume ado-trastuzumab emtansine if the delay has not exceeded 14 days from when the last dose of T-DM1 was due to have been administered. Patients should be re-evaluated weekly during the delay whenever possible. If dosing resumes, the patient may receive ado-trastuzumab emtansine either at the previous dose level or at one dose level lower (see Table 1) based on the

specific instructions in the sections below. If possible, future cycle intervals should remain every 21 days.

If a patient requires a dose reduction for specific adverse events as described in the following sections, dosing will be reduced by one dose level per Table 1. No re-escalation of the ado-trastuzumab emtansine dose will be allowed.

If T-DM1 is discontinued, patients can continue on tucatinib/placebo; however, adjuvant trastuzumab per standard of care **must** be re-initiated to complete a total of 14 cycles of treatment per study protocol. Initiation of adjuvant pertuzumab in addition to trastuzumab may be considered appropriate for some patients, and is at the discretion of the treating physician. If a patient is unable and/or unwilling to recommence adjuvant trastuzumab as outlined above, s/he will not be able to receive further treatment on study.

Table 1: Recommended T-DM1 Dose Reduction Schedule for Adverse Events

If the event is considered unrelated to T-DM1, no dose reduction is required. Dosing may be held based on the judgement of the investigator but is not required.

Up to two dose reductions of T-DM1 will be allowed. In the case of recurrent toxicity after two dose reductions, treatment with T-DM1 should be discontinued.

The T-DM1 dose should not be re-escalated after a dose reduction is made.

Dose Reduction Schedule	Dose Level
Starting dose	3.6 mg/kg
First dose reduction	3 mg/kg
Second dose reduction	2.4mg/kg
Requirement for further dose reduction	Discontinue treatment

If T-DM1 is discontinued, patients can continue on tucatinib/placebo; however, adjuvant trastuzumab+/- pertuzumab **must** be re-initiated as outlined above.

Table 2: Dose modifications for tucatinib/placebo

If the event is considered unrelated to tucatinib, no dose reduction is required; dosing may be held based on the judgement of the investigator but is not required. Up to three dose reductions for tucatinib are allowed. The tucatinib/placebo dose should not be re-escalated after a dose reduction is made.

Table 2 Recommended Tucatinib/Placebo Dose Reduction Schedule

Starting Dose[a]	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction	Requirement for further dose reduction
300 mg PO BID *2 of the 150 mg tablets	250 mg PO BID *1 of the 150 mg tablets + *2 of the 50 mg tablets	200 mg PO BID *1 of the 150 mg tablets + *1 of the 50 mg tablets	150 mg PO BID *1 of the 150 mg tablets	Discontinue treatment

a. Dose reductions of greater increments than those listed in this table (i.e. more than 50 mg per dose reduction) may be made if considered clinically appropriate by the treating physician. However, tucatinib may not be dose reduced below 150 mg BID.

Table 3: Clinical Adverse Events <u>Other Than</u> Hepatic Dysfunction, Left Ventricular Dysfunction, Thrombocytopenia, Nodular Regenerative Hyperplasia or Pulmonary Fibrosis (Interstitial Lung Disease) Related to Either Tucatinib/Placebo and T-DM1

Note: it is appropriate to follow the guidelines as listed below in situations if it is unclear whether the clinical adverse event is related to tucatinib/placebo or T-DM1. In that situation, both drugs should be modified per the guidelines in the tables below, if applicable. The Study Chair should be contacted if there are additional questions.

	Tucatinib/Placebo	**T-DM1**
Clinical adverse event	Related to tucatinib/placebo	Related to T-DM1
Grade 1 or 2	Dose omission or dose reduction not required	Dose omission or dose reduction not required
Grade 3 AEs	Hold until severity ≤ Grade 1 or pre-treatment level. Restart at next lowest dose level	Do not administer until severity ≤ Grade 1 or pre-treatment level. Reduce to next lowest dose level
Grade 4 AEs (with the exception of alopecia)[a]	Permanently discontinue tucatinib	Do not administer until severity ≤ Grade 1 Reduce to next lowest dose level
Peripheral Neuropathy (Grade 3-4)	Grade 3: Hold tucatinib until recovery to ≤ Grade 1, then resume tucatinib at the next lower dose level. Grade 4: discontinue tucatinib.	Do not administer until severity ≤ grade 2

a. No dose modifications are required for alopecia

Table 4: Hepatotoxicity*

Dose modifications may be required in the case of liver function abnormalities, regardless of relationship to study drug. If the patient experiences any of the below hepatotoxicities, follow the below dose reduction instructions for BOTH T-DM1 and tucatinib/placebo.

Liver enzymes will be obtained on day 1 of every cycle. In addition, liver enzymes will be obtained on day 12 (+/- 3 days) of cycle 2. Mid-cycle liver enzymes during cycle 1 are optional. Values obtained on day 1 will be used to modify doses of T-DM1 and tucatinib; values obtained on day 12 (+/- 3 days) may be used to modify dose of tucatinib.

The grading of ALT, AST and TBili below is based on CTCAE 4.03.

Tucatinib day 1 of every cycle, and tucatinib day 12 (+/- 3 days) of cycle 2:

Grade 1 or 2 elevation of AST or ALT will not require dose modification or omission of tucatinib. If Grade 2 elevation of TBili is seen, tucatinib dose will be held until severity ≤ Grade 1; then resume drug at the same dose level. If Grade 3 elevation of AST or ALT is seen, tucatinib dose will be held until severity ≤ Grade 1; then resume drug at the next lower dose level. If Grade 4 elevation of AST or ALT is seen, tucatinib dose will be permanently discontinued. If Grade 3 or 4 elevation of TBili is seen, tucatinib dose will be permanently discontinued. If ALT/AST > 3 x ULN and TBili > 2 x ULN is seen, tucatinib dose will be permanently discontinued.

T-DM1 day 1 of every cycle:

T-DM1 dose will be modified according to the label recommendation in the adjuvant setting. For Grade 2 and 3 elevations of ALT, T-DM1 should be held until they recover to Grade ≤1, and then reduce one dose level. For Grade 2 elevations of AST, T-DM1 should be held until it recovers to Grade ≤1, and then treat at the same dose level. If Grade 3 elevation of AST is seen, T-DM1 dose will be held until severity ≤ Grade 1; then resume drug at the next lower dose level. If Grade 4 elevation of AST or ALT is seen, T-DM1 dose will be permanently discontinued. If TBili > 1.0 to ≤ 2.0 x the ULN is seen, T-DM1 dose will be held until TBili is ≤ 1.0 x ULN; then resume drug at the next lower dose level. If TBili > 2 x ULN at any time, T-DM1 dose will be permanently discontinued.

Severity Grade	Lab	Tucatinib/Placebo	T-DM1 (scheduled dosing day)
Increased Alanine Transaminase (ALT)			
Grade 2 (> 3.0 to ≤ 5 x ULN on day of scheduled treatment)	ALT	Dose omission or modification not required	Hold T-DM1 until severity ≤ Grade 1. Then resume drug at the next lowest dose level
Grade 3 (> 5 to ≤ 20 x ULN on day of scheduled treatment)	ALT	Hold tucatinib/placebo until recovery to ≤ Grade 1. Then resume drug at the next lower dose level.	Hold T-DM1 until severity ≤ Grade 1. Then resume drug at the next lowest dose level
Grade 4 (> 20 x ULN at any time)	ALT	Permanently discontinue drug	Permanently discontinue drug
Increased Aspartate Transaminase (AST)			
Grade 2 (> 3.0 to ≤ 5 x ULN on day of scheduled treatment)	AST	Dose omission or modification not required	Hold T-DM1 until severity ≤ Grade 1. Then resume at the same dose level
Grade 3 (> 5 to ≤ 20 x ULN on day of scheduled treatment)	AST	Hold tucatinib/placebo until recovery to ≤ Grade 1. Then resume drug at the next lower dose level.	Hold T-DM1 until severity ≤ Grade 1. Then resume drug at the next lowest dose level
Grade 4 (> 20 x ULN at any time)	AST	Permanently discontinue drug	Permanently discontinue drug
Hyperbilirubinemia			
(> 1.0 to ≤ 2.0 x the ULN on day of scheduled treatment)	TBili	See tucatinib Tbili elevation dose modification requirements below	Hold drug until total bilirubin ≤ 1.0 x ULN, then resume drug at the next lowest dose level
(> 2 x ULN at any time)	TBili	See tucatinib Tbili elevation dose modification requirements below	Permanently discontinue drug
Grade 2 bilirubin (>1.5 to 3 × ULN)	TBili	Hold tucatinib/placebo until recovery to ≤ Grade 1, then resume drug at the same dose level.	See T-DM1 Tbili elevation dose modification requirements above

Grade 3 bilirubin (> 3 to 10 × ULN) or Grade 4 bilirubin (> 10 × ULN)	TBili	Permanently discontinue drug.	See T-DM1 Tbili elevation dose modification requirements above
ALT/AST > 3 x ULN and TBili > 2 x ULN at any time		Permanently discontinue drug	Permanently discontinue drug

***Note:** If patient has documented gall bladder pathology, hold both study drugs until gall bladder pathology is treated and labs return to severity ≤ Grade 1. However, restart at last administered dose. No dose modification required.

Abbreviations: alanine aminotransferase (ALT); aspartate aminotransferase (AST); upper limit of normal (ULN).

Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

Tucatinib Adverse Events of Special Interest: Hepatotoxicity (see Section 9.3.3 for reporting requirements)

- AST or ALT elevations that are > 3 X ULN with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin > 2 X the ULN, except in patients with documented Gilbert's syndrome. Measurement of conjugated and unconjugated bilirubin should be performed in cases of hyperbilirubinemia, including actual or suspected Gilbert's syndrome, to assist in determination of its etiology.
- AST or ALT elevations > 5 x ULN at any time
- Total bilirubin elevations > 3 x ULN at any time

Nodular regenerative hyperplasia

Tucatinib/placebo and T-DM1 should both be discontinued permanently in patients diagnosed with nodular regenerative hyperplasia.

Thrombocytopenia

T-DM1 dose modification guidelines for thrombocytopenia are provided in Table 5. Dose modifications of tucatinib/placebo are not required for thrombocytopenia.

Table 5: Dose Modification Guidelines for Thrombocytopenia

	Tucatinib/Placebo	**T-DM1**
Grade 1 or Grade 2 thrombocytopenia	Dose modification not required	Dose modification not required
Grade 3 thrombocytopenia Platelet count 25,000/mm3 to < 50,000/mm	Dose modification not required	Hold until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm3), and then restart at same dose level If patient requires ≥ 2 treatment delays due to thrombocytopenia, consider reducing by one dose level.

Grade 4 thrombocytopenia Platelet count < 25,000/mm3	Dose modification not required	Hold until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm3), and then reduce one dose level

Table 6: Left Ventricular Dysfunction

LVEF ≥ 50%	**LVEF 45% to < 50% and decrease is < 10% points from baseline**	**LVEF 45% to < 50% and decrease is ≥ 10% points from baseline**	**LVEF < 45%**	**Symptomatic CHF, Grade 3-4 LVSD, or Grade 3-4 heart failure or Grade 2 heart failure accompanied by LVEF < 45%**
Continue treatment with T-DM1	Continue treatment with T-DM1. Repeat LVEF assessment within 3 weeks.	Do not administer T-DM1. Repeat LVEF assessment within 3 weeks. If the LVEF remains < 50% and has not recovered to within 10% points from baseline, discontinue T-DM1.	Do not administer T-DM1. Repeat LVEF assessment within 3 weeks. If LVEF < 45% is confirmed, discontinue T-DM1.	Discontinue T-DM1 and tucatinib/placebo
Abbreviations: Congestive Heart Failure (CHF); Left Ventricular Systolic Dysfunction (LVSD); Left Ventricular Ejection Fraction (LVEF).				

Note*: Per tucatinib USPI, no special dose modification for tucatinib (or placebo) is needed for LVEF decrease, except if LVEF is < 45% and patient is symptomatic. Dose modifications for tucatinib should therefore follow the standard dose modifications schedule outlined in **Table 3.**

Table 7: Pulmonary Toxicity

Pneumonitis	**Tucatinib/Placebo**	**T-DM1**
Grade 1	Dose omission or reduction not required	Permanently discontinue drug unless related to radiotherapy
Grade 2	Dose omission or reduction not required	Permanently discontinue drug

Grade 3	Hold tucatinib until severity ≤ grade 1 or pretreatment grade level. Then resume at the next lower dose level.	Permanently discontinue drug
Grade 4	Permanently discontinue drug	Permanently discontinue drug

N.B. As above, T-DM1 should be permanently discontinued in patients diagnosed with interstitial lung disease (ILD) or pneumonitis (any grade), unless grade 1 pneumonitis which can be attributed to recent radiotherapy.

Dose modifications for tucatinib are recommended for related events only, whereas dose modifications for T-DM1 are recommended regardless of causality, apart from grade 1 pneumonitis.

PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol-directed action.

8.2.1 Hypersensitivity and/or Infusion Reactions

Treat hypersensitivity and infusion reactions to T-DM1 per institutional standards.

8.2.2 Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation. Physicians may consult the published guidelines of the American Society of Clinical Oncology Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 30(13): 1553-1561, 2012. No dose modifications for obese patients taking tucatinib are recommended.

8.3 Unblinding Procedures

Unblinding can be done only in cases of an emergency or if the patient develops a breast cancer recurrence. Follow the directions below to unblind patient treatment. Please note that if a treatment assignment is unblinded, the patient must discontinue protocol therapy.

8.3.1 Emergency Unblinding Procedures

Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Contact the Alliance Executive Officer on call by calling 773-702-6800, pressing 1 to speak with an operator, and then asking for pager ID 8625 to return the call.

The institution must provide the following information to the Alliance Executive Officer:

- Alliance study ID (i.e., “A011801”)
- Alliance patient ID number (e.g., “999999”)
- Patient initials (e.g., “L,FM”)
- Institution name
- Name and telephone number of treating physician
- Name and contact information of person requesting the unblinding procedure
- Name and contact information of person to inform of treatment assignment
- Reason for emergency unblinding

Please remember that emergency unblinding request may be authorized only by an Alliance Executive Officer, and emergency unblinding applies only if unblinding would influence management of the medical situation. After the Executive Officer deems unblinding is warranted, the treatment assignment will be provided to the contact person at the treating site.

8.3.2 Protocol-specified unblinding

Trial participants may be unblinded upon request upon invasive breast cancer recurrence. Contact the Alliance Registration Office at 507-284-4130 during regular business hours. Upon confirmation by the Primary Statistician (or designee) that the recurrence criteria have been met, the treatment assignment may be unblinded. No Alliance Executive Officer (or designee) approval is required.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

Clinician graded CTCAE is the AE safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken. The specific PRO-CTCAE items for this protocol can be found in Appendix XII. PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0.

9.1.1 Rave-CTEP-AERS integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave.**

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational study agent/intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the box Send All AEs for Evaluation and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: *Protocols > Documents> Protocol Related Documents> Adverse Event Reporting;* and
- Additional resources: *Resources > CTSU Operations Information> User Guides & Help Topics.*

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

9.1.2 Solicited adverse events

The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v5.0 Term	CTCAE v5.0 System Organ Class (SOC)	PRO-CTCAE Term (for patients participating in A011801-HO1)
Neutrophil count decreased	Investigations	
Platelet count decreased	Investigations	
Rash maculo-papular	Skin and subcutaneous tissue disorders	
Epistaxis	Respiratory, thoracic and mediastinal disorders	
Diarrhea[1]	Gastrointestinal disorders	Diarrhea
Nausea	Gastrointestinal disorders	Nausea
Vomiting	Gastrointestinal disorders	Vomiting
Blood bilirubin increased	Investigations	
Aspartate aminotransferase increased	Investigations	
Alanine aminotransferase increased	Investigations	
Anemia	Blood and lymphatic system disorders	
Mucositis oral	Gastrointestinal disorders	
Palmar-plantar erythrodysesthesia syndrome	Skin and subcutaneous tissue disorders	Hand-foot syndrome

Peripheral motor neuropathy	Nervous system disorders	
Peripheral sensory neuropathy	Nervous system disorders	Numbness and tingling

[1]Number of stools per day should also be collected for all patients at baseline.

Symptomatic adverse events reported by patients through PRO-CTCAE are not safety reporting and may be presented with other routine Adverse Event data. Symptoms reported using the PRO-CTCAE will include anxiety, numbness and tingling, nausea, vomiting, diarrhea, constipation, shortness of breath, fatigue, hand-foot syndrome (palmar-planter erythrodysesthesia), and headaches.

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible	a	a	a, b	a, b	a, b
Probable	a	a	a, b	a, b	a, b
Definite	a	a	a, b	a, b	a, b

a) **Adverse Events CRF** - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date.

b) **Late Adverse Events CRF** - Applies to AEs occurring greater than 30 days after the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 **Late Phase 2 and Phase 3 Studies:** Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators MUST immediately report to the sponsor (NCI) ANY SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An AE is considered serious if it results in ANY of the following outcomes:

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

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

Grade 1-3 Timeframes	Grade 4-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

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

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-Hour notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 4-5 SAEs
- Within 10 calendar days for Grade 1-3 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: August 30, 2024

9.3.2 Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

Exclusions

≤ Grade 4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.

Grade 1-3 nausea or vomiting and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting

Grade 3 nausea or vomiting does not require AERS reporting, but should be reported via routine AE reporting.

Death

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders 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.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

Pregnancy loss and neonatal death

Pregnancy loss is defined in CTCAE as "Death in utero." Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

New Malignancies

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization

or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Secondary Malignancy

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

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

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

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via Rave.

Second Malignancy

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

Adverse Events of Special Interest

The Adverse Events of Special Interest for this study include:

AE Term	**CTCAE v5.0 term**	**CTCAE v5.0 System Organ Class (SOC)**
Diarrhea, Grade 3 or greater	Diarrhea	Gastrointestinal disorders
AST or ALT elevations that are > 3 X ULN with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin > 2 X the ULN, except in patients with documented Gilbert's syndrome [1]	Hepatic failure	Hepatobiliary disorders
AST or ALT elevations > 5 x ULN at any time	Aspartate aminotransferase increased	Investigations
	Alanine aminotransferase increased	Investigations
Total bilirubin elevations > 3 x ULN at any time	Blood bilirubin increased	Investigations

Overdose, even if it is not associated with clinical symptoms or abnormal laboratory values	Injury, poisoning and procedural complications - Other, specify	Injury, poisoning and procedural complications

1. Measurement of conjugated and unconjugated bilirubin should be performed in cases of hyperbilirubinemia, including actual or suspected Gilbert's syndrome, to assist in determination of its etiology.

The Adverse Events of Special Interest listed above should be reported via CTEP-AERS (24 hour; 5 calendar days) and the Adverse Events form in Medidata Rave®.

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

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. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2009 patients.* Below is the CAEPR for ado-trastuzumab emtansine.

Version 2.1, July 23, 2018[1]

Adverse Events with Possible Relationship to Ado-Trastuzumab Emtansine (CTCAE 5.0 Term) [n= 2009]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
CARDIAC DISORDERS		
		Atrial fibrillation
		Left ventricular systolic dysfunction
EYE DISORDERS		
		Blurred vision
	Dry eye	
	Watering eyes	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	

Adverse Events with Possible Relationship to Ado-Trastuzumab Emtansine (CTCAE 5.0 Term) [n= 2009]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Constipation	
	Diarrhea	
	Dry mouth	
	Dyspepsia	
		Gastrointestinal hemorrhage[2]
	Mucositis oral	
Nausea		
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema limbs	
Fatigue[3]		
	Fever[4]	
		Infusion site extravasation
		Multi-organ failure
HEPATOBILIARY DISORDERS		
		Gallbladder pain
		Hepatic failure[5,6]
		Hepatobiliary disorders - Other (nodular regenerative hyperplasia)[6]
IMMUNE SYSTEM DISORDERS		
		Allergic reaction[7]
INFECTIONS AND INFESTATIONS		
	Conjunctivitis	
	Infection[8]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Bruising	
		Infusion related reaction[4]
INVESTIGATIONS		
	Alanine aminotransferase increased	

Adverse Events with Possible Relationship to Ado-Trastuzumab Emtansine (CTCAE 5.0 Term) [n= 2009]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased	
		Blood bilirubin increased
		Creatinine increased
		Ejection fraction decreased
	Neutrophil count decreased	
	Platelet count decreased	
		White blood cell decreased
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Hypokalemia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
Myalgia		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
		Leukemia secondary to oncology chemotherapy
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Dysgeusia	
		Encephalopathy[5]
Headache		
		Intracranial hemorrhage
	Nervous system disorders - Other (peripheral neuropathy)[9]	
		Seizure
PSYCHIATRIC DISORDERS		
		Confusion
	Insomnia	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
		Vaginal hemorrhage

Adverse Events with Possible Relationship to Ado-Trastuzumab Emtansine (CTCAE 5.0 Term) [n= 2009]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough[3]	
	Dyspnea[3,4]	
	Epistaxis	
		Pleural effusion
		Pneumonitis[3]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
		Bullous dermatitis
		Palmar-plantar erythrodysesthesia syndrome
	Rash maculo-papular	
		Stevens-Johnson syndrome
VASCULAR DISORDERS		
	Hypertension	
		Thromboembolic event

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

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

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

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

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

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

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

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

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

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

10.0 DRUG INFORMATION

10.1 General Considerations:

The total administered dose of chemotherapy may be rounded up or down within a range of 10% of the actual calculated dose.

It is not necessary to change the doses of ado-trastuzumab emtansine due to changes in weight unless the calculated dose changes by ≥10%.

All study agents are to be administered at the registering institution. However, standard of care endocrine therapy, if applicable, may be administered at a non-registering institution.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

10.2 Tucatinib (ONT-380, NSC# 803413) or Placebo

Tucatinib is a potent, selective, adenosine triphosphate (ATP)-competitive small molecule inhibitor of the receptor tyrosine kinase HER2.

Chemical Name: (N4-(4-([1,2,4]triazole[1,5-a]pyridine-7-yloxy0-3-methylphenyl)-N6-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine hemiethanolate

Molecular Formula: C26H24N8O2•1/2C2H5OH

Molecular Weight (unsolvated free base): 480.5

Agent ordering and agent accountability

Tucatinib or placebo is patient specific, and may NOT be dispensed to another patient. Patient-specific supply may be confirmed by checking to see if a patient ID number is included on the drug invoice and the bottle.

The initial shipment (4 months of patient-specific supply) will be ordered upon registration by site pharmacy. The initial supply will include 150 mg strength tablets. If a dose adjustment is

required, the site should request 50 mg strength tablets. Use the McKesson tucatinib/placebo order form on the A011801 study page on the Alliance and CTSU websites.

Investigator Brochure Availability

The investigator brochure for tucatinib may be obtained by contacting the Alliance Central Protocol Operations Program office at protocols@alliancenctn.org.

Availability

Tucatinib or matching placebo will be supplied by McKesson as patient specific. Sites should order through McKesson as soon as patient is registered.

Tucatinib is supplied as a film-coated yellow oval-shaped tablet in 150 mg dosage strength and a film-coated yellow round tablet in 50 mg dosage strength for oral administration. The tucatinib tablets are packaged in high-density polyethylene bottles containing a desiccant. The bottles are closed with a polypropylene child-resistant screw cap and are induction sealed. Each tucatinib tablet contains tucatinib (supplied as amorphous solid dispersion with copovidone), microcrystalline cellulose, sodium chloride, potassium chloride, sodium bicarbonate, silicon dioxide, crospovidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, talc, and yellow iron oxide.

Matching placebo 150 mg and 50 mg tablets are formulated with pharmaceutically common excipients, coated and supplied in the same format as the active tablets. Each bottle contains 50 tablets. Each placebo tablet contains lactose monohydrate, microcrystalline cellulose, crospovidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, talc, and yellow iron oxide.

Storage

Tucatinib and placebo products are stored under refrigeration (2 - 8°C) and should be handled with care. The sponsor will not be providing cooler bags for transporting tucatinib or placebo. Individual bottles dispensed to the patient may be stored under ambient temperatures for transport to and from the patient's home.

Stability

Sites are responsible for monitoring the expiration dates of their own study drug products and ensuring patients will not receive expired medications. The expiration dates are printed on the bottle labels and on the shipment packing slip.

Preparation

Tucatinib or placebo are required to be dispensed in the original manufacturer's product container with sufficient quantity to cover next visit.

When agents are required to be dispensed in the original manufacturer's drug product container and a site's policy dictates provision of exact quantities for dispensing purposes, removal of the extra agent from the manufacturer's container is the only way this can be satisfied and destroying the extra is allowed. Sites may dispense entire unopened bottles and reconcile or dispose of the remaining drug prior to the next cycle.

Administration

Tucatinib or placebo should take orally twice daily with or without food, approximately 8 to 12 hours apart between doses. If a dose is missed but within 6 hours from the dosing time, the missed dose may be taken as soon as possible. If the time has been passed more than 6 hours from the dosing time, the dose should be skipped and the next dose should be taken at the next

dosing time. If a patient misses or vomits a dose, the next dose should be taken at its scheduled time. Tablets must be swallowed whole and may not be crushed, chewed or dissolved in liquid.

Drug Accountability

Institutional pharmacists should refer to the CTMB Guidelines section 5.3 and the PMB website training videos. Drug accountability record form should be documented per patient specific. Within 90 days after off treatment of the patient and/or the last patient is treated at the institutions, drug may be destroyed at site per institutional policies.

Drug Interactions

Findings from a completed drug-drug interaction (DDI) study indicate tucatinib is predominantly eliminated by CYP2C8, and to a lesser extent, CYP3A. Strong CYP2C8 inhibitors and strong CYP2C8 or CYP3A inducers are prohibited as concomitant medication during study.

Findings from an completed drug-drug interaction (DDI) study indicate that co-administration of multiple doses of tucatinib (300 mg BID) with midazolam (a sensitive CYP3A substrate) increased the geometric mean midazolam exposure (AUC) approximately 5.85-fold (90%CI 5.14 to 6.66) in healthy subjects, compared with administration of midazolam alone. The findings indicate a potential safety risk to humans exposed to tucatinib who are taking concomitant medications that are sensitive CYP3A substrates, as administration of tucatinib may potentially increase exposure to the concomitant medication. Therefore, concomitant use of tucatinib with sensitive CYP3A substrates should be avoided. Consider using an alternate medication which is not a sensitive CYP3A substrate. If the use of sensitive CYP3A substrates is unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information.

Strong inducers of CYP3A4 are prohibited as concomitant medications during study treatment and within two weeks of discontinuation of study treatment – Partial and more complete lists of strong inhibitors and inducers may be found in other reference material.

Pharmacokinetics (Clinical)

Absorption: Plasma tucatinib exposure demonstrated dose proportional increases at oral doses from 50 to 300mg. Following a single oral dose of 300mg tucatinib, the median time to peak plasma concentration was approximately 2 hours (range: 1 to 4 hours). Time to steady state concentration was approximately 4 days.

Effect of Food: Food increased exposure of tucatinib from the tablet by approximately 50% after administration of the tablet in the fed state compared to the fasted state. Absorption of tucatinib from the tablet was delayed when administered with food, but Cmax was not significantly changed. Omeprazole (increased gastric pH) had no effect on tucatinib absorption following tablet administration. The effect of food was not clinically meaningful, thus tucatinib may be administered without regard to food.

Distribution: The plasma protein binding was 97.1% at clinically relevant concentrations.

Elimination: the geometric mean (CV%) CL/F of tucatinib was determined to be 53 (43) L/h with a corresponding effective elimination half-life of 11.9 hours in the typical subject with metastatic breast cancer.

Metabolism: Tucatinib is metabolized primarily by CYP2C8 and to a lesser extent via CYP3A.

Excretion: Tucatinib is predominantly eliminated by the hepatobiliary route, while elimination through the renal route is minimal.

Adverse Events

The most commonly reported TEAEs, regardless of assessment of relatedness to tucatinib are as follows:

Tucatinib single agent treatment

Most common AEs (>25%): nausea, fatigue, diarrhea, and vomiting

Common AEs (>10%): constipation, cough, headache, pain in extremity, urinary tract infection, musculoskeletal chest pain, back pain, myalgia, abdominal pain, anorexia, dyspnea, dizziness, AST increased, ALT increased, hypomagnesemia, and combined rash (including terms of rash, erythema, dermatitis acneiform, rash maculopapular, rash erythematous, rash pruritic, and skin exfoliation)

Tucatinib in combination with ado-trastuzumab emtansine

Most common AEs (>25%): nausea, diarrhea, fatigue, headache, vomiting, epistaxis, thrombocytopenia, constipation, hypokalemia, AST increased, decreased appetite, ALT increased, cough, dyspepsia, and dizziness

Common AEs (>10%): dry mouth, urinary tract infection, arthralgia, anemia, blood alkaline phosphatase increased, hyperbilirubinemia, insomnia, oropharyngeal pain, pyrexia, vision blurred, weight decreased, muscular weakness, abdominal pain, dyspnea, edema peripheral, rash, asthenia, dyspepsia, hyponatremia, hypophosphatemia, pain in extremity, blood creatinine increased, confusional state, hypomagnesaemia, lymphedema, muscle spasms, musculoskeletal chest pain, myalgia, neuropathy peripheral, and stomatitis

Tucatinib must not be administered to pregnant or nursing women.

Nursing Guidelines

1. Tucatinib can be taken regardless of food intake (i.e. with or without food)
2. Gastrointestinal side effects are common, including diarrhea, nausea, and vomiting. Treat symptomatically and monitor for effectiveness of intervention.
3. Rash is common and can present in different forms (i.e. dermatitis, maculopapular, etc.) Instruct patient to report any rash to the study team.
4. Patients may experience myalgias and other musculoskeletal pain. Treat symptomatically and monitor for effectiveness.
5. Instruct patients to report cough, dyspnea or other difficulty with breathing to the study team.
6. Monitor LFT's as these can be elevated and serious.

10.3 Ado-trastuzumab emtansine (T-DM1, KADCYLA®, Trastuzumab-MCC-DM1, PRO132365, RO5304020; NSC# 780263)

Ado-trastuzumab emtansine is HER2 targeted antibody-drug conjugate (ADC) which contains the humanized anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitory drug DM1 (maytansine derivative) via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate).

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

Agent ordering and agent accountability

Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Investigator Brochure Availability

Consult the package insert for the most current and complete information.

Availability

Ado-trastuzumab emtansine (T-DM1) is commercially available and site will treat enrolled patients through site's central pharmacy supply.

Formulation

Ado-trastuzumab emtansine is provided as a lyophilized powder in single-use vials; 100 mg per vial or 160 mg per vial of ado-trastuzumab emtansine.

Storage

Store vials in a refrigerator at 2 - 8°C until time of reconstitution. Do not freeze or shake.

Stability

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

The diluted solution should be used immediately. If not used immediately, the diluted solution may be stored at 2 - 8°C for up to 24 hours. Diluted solutions stored past 24 hours should be discarded. Do not freeze or shake.

Preparation

Use aseptic technique for reconstitution and preparation of dosing solution. Appropriate procedures for the preparation of chemotherapeutic drugs should be used.

Reconstitution: Using a sterile syringe, slowly inject 5 mL of sterile water for injection into the 100 mg ado-trastuzumab emtansine vial, or 8 mL of sterile water for injection into the 160 mg ado-trastuzumab emtansine vial to yield a solution containing 20 mg/mL. Swirl the vial gently until completely dissolved. Do Not Shake. Inspect the reconstituted solution for particulates and discoloration. The reconstituted solution should be colorless to pale brown. Do not use if the reconstituted solution contains visible particulates or is cloudy or discolored.

Dilution: Determine the volume of 20 mg/mL reconstituted ado-trastuzumab emtansine solution needed based on patient weight, withdraw the amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride injection. Do not use Dextrose (5%) solution. Gently invert the bag to mix the solution. Do Not Shake vigorously. Ado-trastuzumab emtansine is compatible with polyvinyl chloride (PVC), latex-free PVC-free polyolefin (PO) bags, polyethylene (PE) bags.

Administration

Ado-trastuzumab emtansine is administered as intravenous infusion using a 0.22 micron non-protein absorptive polyethersulfone (PES) filter. Do not administer as an IV push or bolus.

Do not mix, or administer with other medications.

First infusion: administer infusion over 90 minutes. Patients should be observed during the infusion and for at least 90 minutes following the initial dose for fever, chills, or other infusion related reactions.

Subsequent infusions: administer over 30 minutes if prior infusions were well tolerated. Patients should be observed during the infusion and for at least 30 minutes after infusion.

Note: If a patient had one dose of T-DM1 prior to enrolling on A011801 and the infusion was well-tolerated, the first infusion of T-DM1 on A011801 (second infusion overall) may be administered over 30 minutes.

Drug Interactions

No formal drug-drug interaction studies with ado-trastuzumab emtansine have been conducted. *In vitro* studies indicate that DM1, the cytotoxic component of ado-trastuzumab emtansine, is metabolized mainly by CYP3A4 and to a less extent by CYP3A5. Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) with ado-trastuzumab emtansine should be avoided due to the potential for an increase in DM1 exposure and toxicity. Consider an alternative medication with no or minimal potential to inhibit CYP3A4. If concomitant use of strong CYP3A4 inhibitors is unavoidable, consider delaying ado-trastuzumab emtansine treatment until the strong CYP3A4 inhibitors have cleared from the circulation (approximately 10 days after the last dose of the medication) when possible. If a strong CYP3A4 inhibitor is coadministered and ado-trastuzumab emtansine treatment cannot be delayed, patients should be closely monitored for adverse reactions.

Pharmacokinetics

Distribution: Maximum concentrations (Cmax) of ado-trastuzumab emtansine conjugate and DM1 were observed close to the end of infusion. In vitro, the mean binding of MD1 to human plasma proteins was 93%. In vitro, DM1 was a substrate of Pgp.

Metabolism: In vitro studies indicate that DM1 undergoes metabolism by CYP3A4/5. Dm1 did not inhibit or induce major CYP450 enzymes in vitro. In human plasma, ado-trastuzumab emtansine catabolized MCC-DM1, Lys-MCC-Dm1, and Dm1 were detected at low levels.

Elimination: Following IV infusion of ado-trastuzumab emtansine the clearance was 0.68 L/day and the elimination half-life (t1/2) was approximately 4 days. No accumulation of ado-trastuzumab emtansine was observed after repeated dosing of IV infusion every 3 weeks.

Effect of renal impairment: Pharmacokinetics of the ado-trastuzumab emtansine is not affected by mild (CLcr: 30 – 59 mL/min) to moderate (CLcr: 60 – 89 mL/min) renal impairment as compared to normal renal function (CLcr ≥ 90 mL/min)

Adverse Events

Consult the package insert for the most current and complete information.

Nursing Guidelines

1. Initial infusion should be given over 90 minutes using a 0.22micron in non-PES filter. Do not administer with D5W, as an IV push or bolus. Subsequent doses can be administered over 30 minutes if initial infusion well tolerated.
2. Monitor LFT's closely as liver failure and death have been reported in patients who have received T-DM1.
3. Patients may experience reduced LVEF, and all patients should have LVEF function evaluated prior to starting therapy and at designated time points throughout therapy with

T-DM1. Instruct patient to report any cardiac symptoms (sudden onset fatigue, SOB, chest pain, palpitations, lower extremity edema, etc.) to study team immediately.

4. Cytopenias are common most notably thrombocytopenia. Monitor CBC w/diff and instruct patient to report signs and symptoms of infection, and/or unusual bruising or bleeding to the study team.
5. Anaphylactic reactions can be seen with infusion. Monitor patients closely during first infusion and immediately stop infusion and administer emergency medications per institutional protocol if patient displays signs of allergic reaction. Patients should be observed for a period after completion of infusion for infusion related side effects (i.e. fever chills, other infusion related symptoms)
6. Gastrointestinal side effects can include- nausea, vomiting, constipation, diarrhea, abdominal pain, xerostomia, and stomatitis. Treat symptomatically and monitor for effectiveness of intervention.
7. Instruct patients to report any shortness of breath, cough or worsening of cough to study team immediately as ILD and pneumonitis are known side effects of agent.
8. Peripheral neuropathy is a known side effect. Monitor for this prior to each infusion and report any increase from baseline to treating physician/provider. Patients who have grade 3 or 4 PN should have their infusion held per protocol.
9. Agent is known to cause significant birth defects and/or fetal death. Discuss with patients the need for effective contraception.
10. Assess patient medication list, including OTC medications and herbal products. Patients should avoid concomitant use with agents that are strong CYP3A4 inhibitors, as there is potential for increased T-DM1 toxicity.
11. Myalgias are common. Treat symptomatically and monitor for effectiveness of intervention.

11.0 MEASUREMENT OF EFFECT

11.1 Evaluation of Breast Cancer Outcomes

Disease will be monitored according to ASCO-guidelines. The diagnosis of a first breast cancer recurrence or second primary can be made only when both the clinical and laboratory findings confirm the presence of disease. Suspicious findings do not constitute criteria for breast cancer recurrence. PET scans may be performed at the discretion of the investigator. However PET scans, in the absence of objective findings on CT, MRI, or other imaging studies do not meet the criteria of an acceptable method of determining breast cancer recurrence for this study. Any recurrence of malignant disease should be proven by biopsy whenever possible. Treatment of a breast cancer recurrence or second primary cancer will be at the discretion of the enrolling physician.

For all confirmed breast cancer recurrence or second primary cancers, the time to event will be based on the earliest date of diagnostic evidence. Initial diagnosis of the event should not be a first occurrence of symptoms, but must be based on a clinical assessment with objective findings, whether by physical exam or radiological determination that is subsequently confirmed (if applicable) as defined below.

Note: Disease Response Assessment is considered an imaging assessment (breast and/or other systemic staging) +/- biopsy that either rules out or confirms local or distant breast cancer recurrence.

11.1.1 Invasive Ipsilateral Breast Cancer Recurrence

Ipsilateral breast after previous lumpectomy

Defined as evidence of invasive tumor (not including DCIS and LCIS) in the ipsilateral breast after lumpectomy. Patients who develop clinical evidence of tumor recurrence in the remainder of the ipsilateral breast should have a biopsy of the suspicious lesion to confirm the diagnosis. Confirmed by positive histology or cytology.

Ipsilateral after previous mastectomy

Defined as evidence of invasive tumor in any soft tissue or skin of the ipsilateral chest wall. This includes the area bounded by the midline of the sternum, extending superiorly to the clavicle, and inferiorly to the costal margin. Soft tissue recurrences in this area extending into the bony chest wall or across the midline will be considered as evidence of local recurrence. Confirmed by positive histology or cytology.

11.1.2 Invasive Regional Recurrence

Defined as the development of tumor in the ipsilateral internal mammary lymph nodes, ipsilateral axillary lymph nodes or supraclavicular lymph nodes as well as extranodal soft tissue of the ipsilateral axilla. Regional recurrence does not include tumor in the opposite breast. Confirmed by positive histology or cytology, or radiologic evidence (especially in case of PET activity or visible internal mammary lymph nodes on CT or MRI if no biopsy was performed).

11.1.3 Distant Recurrence

Defined as evidence of tumor in all areas, with the exception of those described in a) and b) above

Confirmed by the following criteria:

– Skin, subcutaneous tissue, and lymph nodes (other than local or regional)

Positive cytology, aspirate or biopsy, OR

Radiological (CT scan, MRI, PET, or ultrasound) evidence of metastatic disease

– Bone

X-ray, CT scan, or MRI evidence of lytic or blastic lesions consistent with bone metastasis, OR

Bone scan (requires additional radiological investigation, alone not acceptable in case of diagnostic doubt), OR

Biopsy proof of bone metastases or cytology

– Bone marrow

Positive cytology or histology or MRI scan

– Lung

Radiologic evidence of multiple pulmonary nodules consistent with pulmonary metastases

Positive cytology or histology (practically rarely performed with the exception of solitary nodules)

NOTE: For solitary lung lesions, cytological or histological confirmation should be obtained in case of diagnostic doubt. Proof of neoplastic pleural effusions should be established by cytology or pleural biopsy.

– Liver

Radiologic evidence consistent with liver metastases, OR

Liver biopsy or fine needle aspiration

NOTE: If radiological findings are not definitive (especially with solitary liver nodules), a liver biopsy is recommended; however, if a biopsy is not performed, serial scans should be obtained if possible to document stability or progression.

– Central nervous system

Positive MRI or CT scan, usually in a patient with neurologic symptoms, OR

Biopsy or cytology (e.g., for a diagnosis of meningeal involvement). However, meningeal involvement may also be diagnosed by CT scan or MRI and depending from the general status of the patient additional investigations (including cytology of the cerebrospinal fluid).

11.1.4 Invasive Contralateral Breast Cancer

Defined as evidence of invasive breast cancer in the contralateral breast or chest wall. The diagnosis of a second primary breast cancer must be confirmed histologically.

11.1.5 Second Primary Invasive Cancer (non-breast)

Any positive diagnosis of a second (non-breast) primary cancer other than basal or squamous cell carcinoma of the skin, or CIS of the cervix will be considered an event in the analysis of the IDFS including second primary non-breast cancer endpoint; however, they will not be included in the IDFS primary endpoint.

LCIS and DCIS of the breast and myelodysplastic syndrome are not considered progression events. The diagnosis of a second primary cancer must be confirmed histologically.

All second primary malignancies are to be reported whenever they occur during the study. See Section 9.3.

NOTE: Patients diagnosed with a second primary malignancy not requiring systemic therapy (i.e., chemotherapy, hormonal therapy, targeted therapy, etc.) and with no evidence of breast cancer recurrence will remain on study and should continue with study drug treatment according to the protocol and schedule of assessment, if considered by the investigator to be in the patient's best interest, whenever possible.

11.1.6 Other noteworthy events

The following events should be recorded on the "Notice of New DCIS or LCIS" eCRF:

-Ipsilateral and contralateral LCIS

-Ipsilateral and contralateral DCIS

NOTE: These events are not considered recurrent disease, but must be recorded.

11.2 Definitions of Analysis Variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol (Section 13.0).

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Protocol Treatment

Protocol treatment is to continue for 42 weeks (14 cycles). Please see the study calendar (Section 5.0) and the treatment section (Section 7.0) for treatment and follow-up time periods.

12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

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

- Disease recurrence* and/or clinical progression (if applicable)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
- Pregnancy (if applicable)
- All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
- The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent (if applicable)

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

*Follow-up and Confirmation of Disease Recurrence

The diagnosis of a breast cancer recurrence or second primary tumor should be confirmed histologically whenever possible. Some patients may have a suspicious recurrence that leads to death quite quickly without the possibility of confirming relapse of disease. Efforts should be made to obtain an autopsy report in such cases. The earliest date of diagnosis of recurrent disease should be used and recorded. This date should be based on objective clinical, radiological, histological or cytological evidence. Recurrent disease includes local, regional, or distant recurrence and contralateral breast cancer. Patients who have a diagnosis of in situ breast disease or second (non-breast) malignancies should be maintained on a regular follow-up schedule wherever possible in order to fully capture any subsequent recurrent disease events. The definitions of and procedures for confirming disease recurrence, death, and other. Noteworthy events on follow-up are given below:

a) Local invasive recurrence

b) Regional recurrence

c) Distant recurrence

d) Contralateral invasive breast cancer

e) Second primary invasive cancer

12.3 Follow-up

12.3.1 Duration of Follow-up

The first follow-up visit is at 6 months (+/- 45 days) after the date the patient discontinue protocol treatment. Thereafter, post-treatment follow-up visits are required every 6 months (+/- 45 days) from the date of last contact from the previous follow-up cycle. Patients will reach the maximum follow-up period once they reach 10 years after registration or until they experience a CNS disease event. If a CNS event occurs, patient moves to survival follow-up and survival information is required every 12 months until 10 years following registration. See Section 5.0.

12.3.2 Follow-up for Patients who Stop Study Treatment Early

All patients will be followed regardless of the reason for discontinuing study treatment. Patients will be followed for disease status (including distant recurrence and brain metastases, even after loco-regional recurrence, as well as for brain metastases after distant recurrence at another site), and overall survival. Follow-up will be the same for patients who stopped treatment due to toxicity and those who receive non-protocol therapy.

12.3.3 Follow-up for Specimen and QOL Submission

Blood samples will be collected at completion of study therapy, and one year after completion of study therapy. See Section 6.2.

For patients who consent to A011801-HO1, some patient-reported outcomes will be completed at 18 and 24 months after registration. Patients who discontinue treatment early for any reason should still complete the patient-reported outcomes. Patients in survival follow-up should not complete the patient-reported outcomes. See Section 6.3.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

12.5 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Randomized phase II and phase III: Baseline, off treatment, and post-treatment follow up (i.e., relapse, progression, and survival) data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

13.0 STATISTICAL CONSIDERATIONS

PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting. PRO-CTCAE data are exploratory and not currently intended for use in data safety monitoring or adverse event stopping rules.

13.1 Study Design

This trial is a two-arm, multicenter, randomized, double-blinded, placebo-controlled, phase III superiority trial to compare the efficacy and safety of standard adjuvant therapy with T-DM1 and placebo (total of 14 cycles) compared with T-DM1 and tucatinib (total of 14 cycles) in patients with HER2-positive breast cancer who have residual tumor present in the breast and/ or axillary lymph nodes following preoperative therapy. Eligible patients will be randomized in a 1:1 fashion to receive either T-DM1 and placebo or T-DM1 and tucatinib. Patients on both arms will receive endocrine therapy, if applicable, and will receive radiation (or not) determined by the treating physician. The primary endpoint is iDFS.

13.2 Sample Size, Accrual Time, and Study Duration

The total sample size will be 981 evaluable patients. Evaluable patients are those who are randomized and eligible. The determination of this sample size was performed using EAST (version 6.4.1) based on a two-tailed test of hypothesis at an alpha level of 0.05 and with 80% power. The following assumptions were used in the sample size determination:

- average monthly accrual rate of 25 patients
- two-sided level of significance of 0.05
- 80% power
- interim analysis for futility after 50% of the iDFS events
- 3-year iDFS rate for the control arm of 82%
- minimum detectable HR = 0.70 (corresponding to a 3-year iDFS of 87% on experimental arm)

The final analysis will be performed when there are 248 iDFS events observed. We will allow up to a 5% over-accrual to account for patients who cancel or withdraw prior to treatment or are lost to follow-up. The maximum accrual to the trial will be 1031 patients with a goal of having 981 evaluable patients.

The projected accrual rate of 25 patients per month is based on the following rationale. Specifically, the ACOSOG Z1041 (Buzdar et al., Jama Oncol 2019), CALGB 40601(Carey et al, JCO 2016), and NSABP B41(Robidoux et al., Lancet Oncol 2013) studies enrolled 11, 8-9, and 11 patients per month, respectively, in an era before neoadjuvant treatment of HER2-positive breast cancers was standard of care. Further, research biopsies were required in CALGB

40601 limiting eligibility. All three of those groups are now either in the Alliance, or have endorsed the concept of A011801. The NRG has already contributed to concept development. Given that ECOG-ACRIN, which is running the aligned CompassHER2 pCR trial (EA1181) has also contributed to concept development, it is realistic to assume similar accrual to come from that group. We are hopeful that SWOG and CCTG will similarly participate. For these reasons, we hope and anticipate that we will have broad exposure across NCTN sites. In addition, although our eligibility criteria are more restrictive than the aforementioned studies, the overall number of potentially eligible patients in 2019 and beyond is greater. At the time that the prior neoadjuvant trials were conducted, the standard of care was to treat most HER2+ patients adjuvantly, now the reverse is true in that only small, node-negative patients are treated with surgery first. Further, in the wake of the KATHERINE data, the concept of additional systemic therapy improving outcomes in patients with residual HER2-positive invasive disease after preoperative systemic therapy is widely accepted. Given these advances (and the fact that selected high-risk patients treated with T-DM1 still have suboptimal iDFS outcomes), it is likely that oncologists and eligible patients will be motivated to participate in this study when clinically appropriate.

We are therefore of the opinion that an accrual rate of approximately 25 patients per month is a reasonable estimate, in spite of the fact that only the subset of neoadjuvant patients with residual disease will be eligible for this study.

The anticipated accrual period under the assumptions above is approximately 40 months from when the first patient is accrued. It is anticipated that the data will be mature approximately 83 months from when the first patient is accrued.

13.3 Statement and Definition for Primary Endpoint

The primary endpoint is a modified invasive disease-free survival (iDFS), which is defined as the time from randomization to one of the following events: invasive local, regional or distant recurrence, invasive contralateral breast cancer or death from any cause[74]. Patients who are alive at the time of analysis without documentation of any of these events will be censored at the time of last follow-up for disease status.

A secondary endpoint will be done that uses the unmodified iDFS definition that will include a secondary primary invasive cancer (other than basal or squamous cell carcinoma of the skin, or CIS of the cervix) as an event in addition to the ones listed above for the primary endpoint.

13.4 Definitions for Secondary Endpoints

- *Overall survival* (OS): This is defined as the time from randomization until death from any cause. Patients who are alive at the time of analysis will be censored at the time of last follow-up.
- *Breast cancer-free survival* (BCFS): This is defined as the time from randomization to invasive local, regional, or distant recurrence, or invasive contralateral breast cancer[97]. Patients who are alive at the time of analysis without documentation of any of these events will be censored at the time of last follow-up for disease status. Patients who died prior to any of these events will be censored at date of death.
- *Distant recurrence-free survival* (DRFS): This is defined as the time from randomization to the first incidence of distant recurrence. Patients who are alive at the time of analysis without documentation of distant recurrence will be censored at the time of last follow-up for disease status. Patients who died prior to any distant recurrence will be censored at date of death.

- *Disease-free survival* (DFS): This is defined as the time from randomization to the first incidence of an invasive local, regional, or distant recurrence, second primary non-breast cancer event, or contralateral or ipsilateral DCIS.
- *Brain metastases-free survival* (BMFS): This is defined as the time from randomization to documentation of involvement of the CNS by metastatic cancer including parenchymal brain and spinal cord metastases as well as leptomeningeal carcinomatosis. Patients who are alive at the time of analysis without documentation of a brain metastasis as defined above will be censored at the time of last follow-up for disease status. Patients who died prior to any brain-metastases recurrence will be censored at date of death.
- *Incidence of brain metastases*: An incident of brain metastases is documentation of involvement of the CNS by metastatic cancer including parenchymal brain and spinal cord metastases as well as leptomeningeal carcinomatosis.

13.5 Randomization Procedure

Randomization will be 1:1 and will use a dynamic balancing algorithm. There will be three stratification factors used in the randomization. The factors that will be used are:

- Receipt of post-operative chemotherapy: yes vs. no
- HR-status: positive (ER and/or PR positive) vs. negative (ER negative and PR negative)
- Pathologic lymph node status: positive vs. negative

13.6 Analysis Plan for Primary Endpoint

All randomized patients will be included in the final analysis according to an intent-to-treat analysis. The final analysis will be performed when there are 248 iDFS events. A Kaplan-Meier method will be used to estimate the survival curves and a stratified log-rank test will be used to compare the iDFS of the two arms. A stratified Cox model will be used to estimate the hazard ratio (HR). The other time to event variables (BCFS, DRFS, BMFS, and OS) will also be summarized with Kaplan-Meier curves and compared between the arms using a stratified log-rank test and stratified Cox model.

There will be one interim analysis performed for futility after half of the iDFS events have been observed. If the HR is greater than 1.0, it will be recommended that trial accrual be halted. The accrual will not be suspended for the interim analysis. It may be the case that accrual is completed before the interim analysis is complete. In this case, the study team will make a decision in conjunction with the DSMB and CTEP whether to report the results prior to obtaining the necessary number of events.

13.7 DSMB Reporting

Interim monitoring will be conducted by the Alliance Data and Safety Monitoring Board (DSMB) and will be scheduled to coincide with the semi-annual calendar of the board's meetings. Under standard monitoring procedures, the DSMB will consider evidence regarding safety (adverse events, adherence) and the feasibility of completing the trial (accrual rate).

Adherence will be reported to the DSMB using descriptive statistics to summarize by arm compliance to study treatment. For compliance, the proportion that completed 80% of the total doses over the past period (6 months) and a 95% confidence interval will be reported for the number of patients on treatment at each study visit.

The iDFS (primary endpoint definition) event rate will also be reported to the DSMB for the control arm to ensure that it is consistent with the projected rate based on historical data.

Specifically, the study team will report the observed iDFS rate at 3 years with the corresponding 95% confidence interval once there is sufficient follow-up to estimate this quantity. Specifically, we will start reporting this value to the DSMB once there have been 200 patients with 3 years or more of follow-up and continue reporting for each subsequent DSMB report.

13.8 Secondary Analysis Plans

If there appears to be clinically significant imbalances of baseline variables between the treatment arms, a secondary analysis of the primary endpoint will use stratified Cox model to compare the treatment effects that include the variables that are deemed imbalanced between the arms as adjusting variables. The randomization stratification variables will be the stratified variables in the model.

The time-to-event secondary endpoints will be analyzed using a stratified logrank test as well as a stratified Cox proportional hazards model. If there are clinically significant imbalances in baseline characteristics between the treatment arms, a second analysis will be done using a stratified Cox model with the variables that are imbalance added as adjusting variables. The cumulative incidence of brain metastases will be determined as the crude cumulative incidence as well as with incidence with competing risks where the competing event is death. The key secondary endpoint of OS will be tested if the primary endpoint iDFS is statistically significant at two sided 0.05 level.

13.9 Adverse Event Stopping Rule

If after a total of 50 patients have been enrolled to the trial 25% or more patients experience a grade 4+ AE, the study team will recommend accrual be suspended. While accrual is suspended, the study team will carefully review and document the grade 4+ adverse events. On the basis of this, a recommendation will be made to the DSMB to terminate the study due to unacceptably high adverse event rate, to modify the treatment regimen(s) in an attempt to reduce future grade 4+ events, or to continue the trial as planned. The trial can only re-open to accrual after DSMB approval is obtained.

13.10 Accrual Monitoring Stopping Rule

Accrual to the trial will be monitored closely. The study team will evaluate accrual within the 5th to 6th quarters from study activation. If accrual during these quarters is less than 50% of what was projected for these quarters, we will plan modifications including the potential for closure

13.11 Primary Endpoint Completion Time Estimation

It is anticipated that the primary endpoint will be mature about 83 months after the first patient is randomized. The final analysis can occur after 248 iDFS events have been observed.

13.12 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	10	0	0	0	10
Asian	34	1	1	0	36
Native Hawaiian or Other Pacific Islander	4	0	0	0	4
Black or African American	85	1	13	0	99
White	650	7	137	1	795
More Than One Race	11	0	9	0	20
Total	794	9	160	1	964

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	3	0	0	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	0	1	0	3
White	59	0	1	0	60
More Than One Race	1	0	0	0	1
Total	65	0	2	0	67

13.13 Descriptive Factors

The descriptive factors will include the stratification variables (Section 4.6), type of breast cancer surgery (mastectomy versus breast conserving), and ECOG performance status (0 versus 1).

13.14 Other Pre-Specified Outcomes: NIH-Required Analyses

Estimates of treatment effect and the corresponding 95% confidence intervals (CIs) will be provided as follows (with an understanding that sometimes the CI or estimate will not be computable because of scant data).

- Estimates of iDFS and the corresponding 95% confidence intervals (CIs) by sex.
- Estimates of iDFS and the corresponding 95% confidence intervals (CIs) by race.

- Estimates of iDFS and the corresponding 95% confidence intervals (CIs) by ethnicity.

14.0 CORRELATIVE AND COMPANION STUDIES

There will be one optional substudy (A011801-HO1) in which all patients are encouraged to participate (see Section 14.1). There will also be two mandatory correlative studies and optional biobanking (see Section 14.2).

14.1 Patient-Reported Outcomes (Alliance A011801-HO1) – Optional ("mandatory ask")

14.1.1 Background

A patient-reported outcome (PRO) is "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."[69] PROs provide information regarding how patients perceive health and treatment effects, and how treatments influence outcomes, and they are useful in evaluating how disease and therapeutic interventions impact many aspects of a patients' life [75]. Compared to PRO data, clinician reporting of symptomatic outcomes has been shown to be incomplete and sometimes inaccurate[70-72]. The incorporation of PROs into therapeutic clinical trials is, therefore, critical to inform medical decision making between patients and their doctors.

The CompassHER2 RD study is powered to identify an absolute iDFS difference of 5% between the investigational and placebo arms. However, polling of advocates when the study was designed showed that a 3% difference in iDFS would be considered clinically meaningful. Finding such a small difference is not feasible in the timeframe and with the likely recruitment numbers anticipated. Therefore, there is a preplanned joint analysis with the Breast International Group (BIG), to determine whether a smaller benefit of the investigational therapy is demonstrated. This preplanned joint analysis with BIG will allow for identification of smaller differences deemed meaningful by patient advocates. If a smaller benefit is identified, the results of our proposed quality-of-life (QoL) analysis could inform clinical decision making.

In CompassHER2 RD, we will assess QoL, self-reported patient adherence to their assigned treatment arm and reasons for nonadherence[76], and patient-reported symptoms. The rationale for inclusion of each PRO and information about the instruments to be used are briefly described below.

QoL: FACT-B

The Functional Assessment of Cancer Therapy-Breast (FACT-B) includes a measure of overall QoL in cancer patients (FACT-G), as well as a breast cancer concerns subscale (BCS) about breast cancer specific issues, including body image, sexual issues, and additional physical symptoms[77, 78]. The FACT-G has four subscales: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB). In cancer therapy trial such as CompassHER2 RD, the domains of the FACT family of tools that are most likely to change are PWB, FWB, and the BCS. The other scales are less likely to change in a cancer treatment trial (their focus in on psychosocial well-being, and they are generally more likely to change when the investigational intervention is psychosocial or behavioral in nature). The Treatment Outcome Index (TOI) combines the PWB, FWB, and BCS scales. The total FACT-B includes all scale scores, including the two that are less likely to change in a treatment trial. Including the two subscales that are unlikely to change may obscure a difference between treatment arms.

For this study, we will focus the primary analysis on the TOI in order to investigate whether QoL among patients treated with combination T-DM1 and tucatinib is non-inferior to QoL among patients treated with T-DM1 alone. The minimally important difference in scores for the TOI is 5-6 points [79, 80]. The FACT-B takes approximately 10 minutes to complete.

Adherence to oral therapy and reasons for nonadherence

In recent years, there has been an increase in the development and use of oral anti-cancer medications for breast cancer patients. However, adherence rates are often suboptimal, leading to lower survival rate, a higher risk of recurrence, and increased healthcare costs[81]. In CompassHER2 RD, we will study self-reported patient adherence to their assigned treatment arm and reasons for nonadherence using an instrument developed by Voils et al (Domains of Subjective Extent of Nonadherence [DOSE-Nonadherence]). We will analyze adherence relative to study outcomes, including an exploratory analysis of whether tucatinib is associated with less or more adherence to endocrine therapy among participants with hormone receptor positive breast cancer. We will explore adherence relative to study outcomes. The DOSE-Nonadherence scale is administered in two parts: a brief assessment of self-reported adherence to oral therapy and, among patients who report nonadherence, an assessment of reasons for nonadherence using 5-point scales ("not at all" to "very much")[76]. This measure takes approximately 1 minute to complete.

Patient-reported symptoms: PRO-CTCAE

Clinician reporting of adverse events misses up to 50% of symptomatic adverse events, compared to PRO assessment[82]. In this study, we will assess symptomatic adverse events using PRO-CTCAE measures for anxiety, numbness and tingling, nausea, vomiting, diarrhea, constipation, shortness of breath, fatigue, palmar-plantar erythrodysesthesia (hand-foot syndrome), and headaches. These symptoms were selected based on the known toxicity profiles of T-DM1 and tucatinib. In addition, we will measure patient-reported anxiety and compare anxiety in patients treated on CompassHER2 RD to those treated on CompassHER2 pCR (EA1181). The PRO-CTCAE includes branching logic for skip patterns, which minimizes participant burden while allowing for the full capture of data attributes (e.g. presence/absence, frequency, severity, symptom interference).

The Patient-Reported Outcomes version of Common Terminology Criteria for Adverse Events (PRO-CTCAE) was developed by the National Cancer Institute to capture patient self-reports of symptomatic toxicities during cancer treatment[75]. The PRO-CTCAE is a standardized self-report measure that allows patients to report the frequency, severity, and interference of symptoms that may be experienced. The PRO-CTCAE has demonstrated favorable validity, reliability, and responsiveness in a large heterogeneous United States sample of cancer patients undergoing treatment[83]. Furthermore, the use of the PRO-CTCAE to collect information about participant symptoms in a multicenter trial is feasible, with high participant compliance with self-reporting (92.0%) in a recent Alliance study of patients undergoing treatment for rectal cancer[84]. This measure takes approximately 5 minutes to complete.

14.1.2 Objectives

Primary:

To compare QOL after approximately 8 cycles of the study as assessed by the FACT-B Trial Outcome Index between patients randomized to T-DM1 + tucatinib or T-DM1 + placebo. Hypothesis: QOL will be non-inferior in the T-DM1 + tucatinib arm compared to the T-DM1 + placebo arm at cycle 9, day 1.

Secondary:

To compare QOL after approximately 13 cycles of the study as assessed by the FACT-B Trial Outcome Index between patients randomized to T-DM1 + tucatinib or T-DM1 + placebo. Hypothesis: QOL will be non-inferior in the T-DM1 + tucatinib arm compared to the T-DM1 + placebo arm at cycle 14, day 1.

Exploratory:

To compare various QOL domains after approximately 8 and 13 cycles of the study as assessed by the 5 subscales of the FACT-B questionnaire between patients randomized to T-DM1 + tucatinib or T-DM1 + placebo. This analysis is exploratory, though we anticipate the direction of the comparisons to be consistent with Primary and Secondary Hypotheses.

To compare self-reported patient adherence and reasons for nonadherence after 1, 4, 8, and 13 cycles of the study as assessed by the DOSE-Nonadherence instrument between patients randomized to T-DM1 + tucatinib or T-DM1 + placebo. This analysis is exploratory, though we anticipate that patients in the T-DM1 + tucatinib arm will experience more frequent and severe symptoms leading to greater nonadherence.

To compare self-reported symptomatic adverse events as outlined in section 14.1.1 after 1, 4, 8, and 13 cycles of the study assessed by the PRO-CTCAE between patients randomized to T-DM1 + tucatinib or T-DM1 + placebo. This analysis is exploratory in nature.

14.1.3 Methods

The instruments to be used and analytic plans are briefly described below. Timing of survey domains is described in the table in Section 6.3.

QoL: FACT-B

The Functional Assessment of Cancer Therapy-Breast (FACT-B) includes a measure of overall QoL in cancer patients (FACT-G), as well as a breast cancer specific subscale concerning breast cancer specific issues, including body image, sexual issues, and additional physical symptoms [77, 78]. The FACT-G has four subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being, with minimally important differences in scores ranging from 7-8 points (overall score) and 1-3 points (individual domains)[79, 85]. The addition of tucatinib is likely to result in diminished QoL during treatment, with a subsequent resolution in this effect once treatment has been completed. Therefore, we will compare QoL by treatment arm by survey time-point. The primary analysis will focus on the Treatment Outcome Index (TOI), a combination of the physical and functional subscales as well as the breast cancer specific subscale. As described in section 14.1.1, the TOI is more sensitive to treatment-related QoL changes than is the FACT-B total score. However, we will also analyze the individual subscales and the total FACT-B score in separate, secondary analyses.

Domains of Subjective Extent of Nonadherence (DOSE-Nonadherence)

This instrument developed by Voils et al. is administered in two parts: a brief assessment of self-reported adherence to oral therapy and, among patients who report nonadherence, an assessment of reasons for nonadherence using 5-point scales ("not at all" to "very much").[76] Patients treated in the investigational arm (T-DM1 + tucatinib) are likely to experience more frequent and severe symptoms compared to those in the standard arm (T-DM1 + placebo). Treatment-related symptoms is a common reason for nonadherence to

oncologic treatment and may diminish the clinical benefit derived from treatment escalation. In this study, adherence to oral therapy and reasons for nonadherence will be compared by treatment arm. We will analyze adherence relative to study outcomes, including an exploratory analysis of whether tucatinib is associated with less or more adherence to endocrine therapy among participants with hormone receptor positive breast cancer. We will also explore adherence relative to study outcomes.

Patient-reported symptoms: PRO-CTCAE

The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a standardized self-report measure that allows patients to report the frequency, severity, and interference of up to 78 symptoms that may be experienced [75]. The PRO-CTCAE has demonstrated favorable validity, reliability, and responsiveness in a large heterogeneous United States sample of cancer patients undergoing treatment [83]. In this study, we will assess symptomatic adverse events using PRO-CTCAE measures for: anxiety, numbness and tingling, nausea, vomiting, diarrhea, constipation, shortness of breath, fatigue, palmar-plantar erythrodysesthesia (hand-foot syndrome), and headaches. Patients treated in the investigational arm are likely to experience more frequent and severe symptoms compared to those in the standard arm (T-DM1 + placebo). The incidence and severity of symptoms as well as, where relevant, symptom interference, will be compared by treatment arm.

14.1.4 Statistical Analyses

Primary Endpoint:

For the primary analysis, a single mixed model of the change in FACT-B Trial Outcome Index will be analyzed. The mixed model will compare the C9D1 and C14D1 time points between randomized arms. In addition to a randomized arm covariate, the model will include a randomized arm-by-time interaction term and will use the planned cycle of assessment as the categorical time value. Unstructured covariance will initially be used, though alternative covariance structures will be investigated with the final covariance structure selected based on minimization of the Akaike information criterion. A contrast will be used to compare mean change from baseline at C9D1 between arms. If the two-sided 95% confidence interval excludes a difference of 5 favoring the T-DM1 + placebo arm, then non-inferiority will be concluded. The difference of 5 points represents a clinically meaningful effect based on the work of Eton at al[79], using the pooled standard deviation (computed as 14.6 points) of the TOI scale as reported in Eton at al[79].

A total sample size of 362 patients (181 per arm) achieves 90% power to detect non-inferiority using a one-sided two-sample equal variance t-test with a margin of non-inferiority of -5 at a significance level of 0.025. The power for this substudy was calculated using PASS[86].

Secondary Endpoint:

For the secondary analysis, the same mixed model as described above will be analyzed. A contrast will be used to compare mean change from baseline at C14D1 between arms. Similarly, if the two-sided 95% confidence interval excludes a difference of 5 favoring the T-DM1 + placebo arm, then non-inferiority will be concluded at this time point.

Exploratory Endpoints:

For the exploratory analyses, mixed models will be constructed and analyzed using the subscale scores for the 5 main subscales associated with the FACT-B. Similar contrasts and tests will be analyzed according to the plan mentioned above.

For the Voils DOSE-Nonadherence instrument, non-adherence (yes/no) will be derived based on the patient's answers. At each time point the percentage of non-adherent patients will be compared between arms. For patients that are non-adherent, the reasons for non-adherence will be analyzed descriptively.

For each of the PRO-CTCAE items mentioned in section 14.1.1, the maximum grade for each patient will be recorded and analyzed. Frequency tables will be reviewed to determine the patterns for each of the adverse events across between arms.

14.2 Correlative Science

A011801 has two secondary correlative objectives, involving the studies of TILS and ctDNA outlined below. In addition, the protocol seeks to address a to-be-determined correlative objective involving tumor intrinsic subtyping..

An amendment or proposal for this to-be-determined objective 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.

14.2.1 Tumor Tissue for Tumor Infiltrating Lymphocyte (TILs) Analysis (mandatory for all patients)

An association between the presence of tumor-infiltrating lymphocytes (TILs) in tumor tissue and improved prognostic outcomes in several malignancies, including breast cancer, has been described[46-48, 87]. However, data on the prognostic significance of TILs in HER2-positive early stage breast cancer treated with HER2-targeted therapy regimens has been somewhat mixed. A large meta-analysis demonstrated a strong independent association between higher levels of TILs in the primary tumor and improved outcomes, but some individual studies have failed to show a significant association between TIL levels and prognosis. The situation is further complicated in patients who are treated in the neoadjuvant setting, since during preoperative systemic therapy, significant fluctuations in TILs levels may be observed[49]. It is postulated that chemotherapy exerts its cytotoxic effects by triggering an immune response against the tumor via activation of cytotoxic lymphocytes and dendritic cells, which results from exposure of these cells to antigens resulting from apoptosis and cell death[50, 51]. There is therefore considerable interest in studying the role of TILs in patients treated with neoadjuvant therapy, in both the pretreatment tumor tissue and in residual disease after therapy. For example, Hamy et al. conducted a study to evaluate TIL levels before and after neoadjuvant therapy with chemotherapy and trastuzumab, in 175 patients with HER2-positive breast cancer [49]. They noted that TIL levels decreased in 78% of the patients during the course of preoperative treatment, and that the TIL level decrease was predictive of a pCR ($p < 0.001$). This study demonstrates that the role of TILs in residual disease warrants further study, and the interpretation of TIL levels may vary according to the subtype of breast cancer and prior use of targeted therapies (e.g. trastuzumab).

Assessment of TIL levels may also identify patients most likely to benefit from HER2-targeted therapy. Recent data from the APHINITY trial, a large phase 3 study evaluating the addition of pertuzumab to adjuvant chemotherapy and trastuzumab, demonstrate that patients with the highest quartile of TILs in the primary cancer derived more benefit from the addition of pertuzumab than those patients with lower levels of TILs (interaction p value 0.003) [43]. In contrast, in the NeoALTTO trial, baseline TIL levels did not predict

benefit of lapatinib when added to trastuzumab and chemotherapy, but this was a smaller study that was not powered to address this question. Data on the predictive value of TILs in residual cancer samples is largely unknown. One limitation of the current data on TILs in breast cancer is that several different methodologies have been used to quantify TILs in previous studies. Given the need for standardization in this regard, the International Immuno-Oncology Biomarker Working Group on Breast Cancer recently published recommendations for the use of TILs in BC, including parameters for evaluation of both pretreatment tumor tissue and residual post-treatment tissue [88].

In CompassHER2 RD, we will evaluate the association of TIL levels in both the primary tumor and the residual disease specimen with iDFS. We will also examine whether TIL levels are associated with treatment benefit of T-DM1 and tucatinib vs. T-DM1 and placebo.

We hypothesize that:

a) Patients with higher TILs in baseline (pre-neoadjuvant therapy) tumor tissue will have superior iDFS compared to patients with lower TILs

b) The benefit of tucatinib compared to placebo will be greater in patients with increased TIL levels in baseline (pre-neoadjuvant therapy) tumor tissue

c) Patients with higher TILs in residual cancer tissue (post-neoadjuvant therapy) will have superior iDFS compared to patients with lower TILs

d) The benefit of tucatinib compared to placebo will be greater in patients with increased TIL levels in residual cancer tissue (post-neoadjuvant therapy)

14.2.1.1 Objectives

- To evaluate the association of TIL levels in both the primary tumor and the residual disease specimen with iDFS
- To determine whether there is evidence of differential treatment benefit of T-DM1 and tucatinib compared to T-DM1 and placebo in high TIL cancers compared to low TIL cancers (assessed in both the pre-neoadjuvant tumor tissue and the residual cancer tissue)

14.2.1.2 Methods

It is mandatory for tumor tissue from the archived clinical biopsy specimen (pre-neoadjuvant therapy) and from the residual disease at time of definitive surgery specimen be submitted. See the Correlative Science Manual for processing and shipping instructions.

TILs will be centrally assessed on hematoxylin and eosin (H&E) stained sections using standard guidelines from the International TILS Working Group[52]. This methodological approach has demonstrated good reproducibility and inter-observer concordance. For example, in a ring study of 100 samples from the NSABP B31 study of HER2+ cancers, the mean concordance amongst 7 pathologists was 90.8%[89]. Detailed methods for the TIL assessment procedure, including a training slide set, are included in Appendix VIII. Briefly,

1) 4–5 µm H&E stained sections of formalin fixed and paraffin embedded (FFPE) tissue from the patients initial (pre-neoadjuvant therapy) core biopsy and the residual (post-neoadjuvant) tumor surgical specimen will be collected. Evaluation of one section per patient is considered sufficient.

2) The area for evaluation is defined as only within the borders of the invasive cancer – DCIS and adjacent normal tissue is excluded as are areas of necrosis or crush artifact
3) The section is scanned at low magnification to identify areas of stroma – only stromal TILs are evaluated
4) All mononuclear cells are counted – polymorphonuclear leukocytes are excluded
5) The percentage of stromal TILs is calculated as area occupied by mononuclear inflammatory cells over the total intratumoral stromal area

14.2.1.3 Statistical Considerations

The association of TIL levels with the modified iDFS outcome (the trial primary endpoint) will be determined with a Cox model. Specifically, two Cox models will be generated to obtain a point estimate and 95% confidence interval (CI) for the HR that summarizes the association of TIL level and iDFS. The first model will have the modified iDFS as the outcome variable and the baseline TIL level as the variable of interest. The model will also contain treatment arm (tucatinib versus placebo) as an adjusting variable. A second model will include all known prognostic variables as additional adjusting variables. To determine whether the benefit of tucatinib compared to placebo is greater in patients with higher level of baseline TILs, two Cox models will again be used. Both will use the modified iDFS (primary endpoint) as the outcome variable. The first model will include the baseline TIL level and treatment arm (tucatinib versus placebo) as main effects and the TIL level by treatment arm interaction term. If the interaction term is statistically significant (p-value < 0.05), this will be evidence of differential tucatinib benefit based on the level of TILs. The second Cox model will include the main effects as interaction term as well as known prognostic factors as adjusting variables.

The analysis will be the same for determining the association of TIL levels in samples obtained after the breast surgery. Specifically, Cox models will be used to determine the association of the post-surgery TIL levels with iDFS. The first model will contain the TIL level (variable of interest) and treatment arm (adjusting variable). The second model will contain these two variables as well as other known prognostic factors (additional adjusting variables). Likewise, a similar analysis as done for baseline TIL levels will be done to determine whether there is differential tucatinib benefit for different TIL levels. Two Cox models will be generated with the first having the post-surgery TIL level and treatment arm as main effects and their interaction term. The second model will have the main effects, the interaction term and known prognostic factors as adjusting variables. If the TIL level by treatment arm interaction term is statistically significant (p-value < 0.05), this will be evidence that there is differential benefit of tucatinib based on the post-surgery TIL level.

Power: It is assumed that among the 981 patients enrolled in the trial, 80% of them (n = 785) will have usable TIL values at baseline (i.e. 20% of patients are expected to either have no available sample or the assay failed). There will be approximately 80% power (with a two-sided 0.05 level of significance) to detect a hazard ratio of 1.5 for a half standard deviation change in the TIL level based on a sample size of 785 patients and 198 (= 80% × 248) iDFS events.

14.2.2 Circulating Tumor DNA (ctDNA) – mandatory for all patients

Although the presence of residual disease after neoadjuvant therapy is a negative prognostic factor in patients with HER2+ breast cancer, only a minority of such patients develop disease recurrence. Having additional biomarkers to identify patients with residual

disease most likely to recur would be clinically useful and could help guide adjuvant therapy selection. We hypothesize that circulating tumor DNA (ctDNA) detected in blood will predict iDFS in A011801.

The presence of ctDNA has demonstrated prognostic significance in multiple cohort studies in early breast cancer. In a meta-analysis of 16 studies involving 1122 primary BC patients, detection of ctDNA after neoadjuvant therapy was associated with markedly inferior PFS (HR 9.55, 95% CI 2.13-42.8) compared with patients who did not have detectable ctDNA[91]. Studies that have evaluated ctDNA in serial timepoints in the adjuvant setting have shown even stronger prognostic value of ctDNA detection[92]. Despite these data, the clinical utility of ctDNA assessment has not been established in the early disease setting. Further studies are needed to better understand the usefulness of ctDNA in both the prediction of outcome in the early disease setting and assessing the benefit of HER2-directed therapy. A011801 will potentially provide the necessary data to establish clinical utility of circulating biomarkers when measured after surgery and/or after adjuvant therapy.

In A011801, we will collect peripheral blood for ctDNA analysis at (1) baseline (prior to study therapy); 2) after completion of study therapy, 3) 1 year after completion of study therapy, and 4) at recurrence (when applicable). These blood draws will be mandatory for all patients enrolled in A011801. ctDNA results will not be provided to the clinician or patient for clinical decision making.

We hypothesize that:

a) Patients with detectable ctDNA at baseline will have inferior iDFS compared to patients without detectable ctDNA at baseline

b) The magnitude of benefit of the addition of tucatinib will be greater in patients with detectable ctDNA at baseline than in patients without detectable ctDNA at baseline

c) Patients with detectable ctDNA after completing study therapy and/or 1 year after completing study therapy will have inferior iDFS compared to patients without detectable ctDNA at both of those timepoints

14.2.2.1 Objectives

- To evaluate the association between iDFS and the presence of detectable ctDNA at baseline, at completion of study therapy and/or 1 year after completion of study therapy
- To determine the difference in absolute magnitude of benefit of tucatinib (in terms of iDFS) in the subgroup of patients with detectable ctDNA at baseline and the subgroup of patients without detectable ctDNA at baseline

14.2.2.2 Methods

The Signatera(™) assay is a commercially available ctDNA-based molecular residual disease test. Signatera involves whole-exome sequencing (WES) of tumor and matched normal blood samples to design up to a 16plex patient-specific multiplex PCR assay. This assay is run on the associated patients' plasma cell-free DNA to detect ctDNA. More detailed information regarding assay methodology and performance characteristics is included below.

WES of tumor tissue and matched normal DNA from blood. WES is performed using tumor and normal genomic DNA isolated from tumor tissue and matched normal biospecimens, respectively. Targeted exome capture is performed using a custom capture

probe set. The resulting libraries are sequenced on the NovaSeq platform (Illumina, Inc.) to achieve the deduplicated on-target average coverage of 200× for tumor tissue and 50× average on-target coverage for the associated matched normal sample.

Somatic variant calling and Signatera ctDNA assay design. Using the WES data, somatic variant calling is performed using a proprietary consensus variant calling method developed by Natera, Inc. WES data are analyzed for quality metrics and sample concordance, and then processed through a proprietary bioinformatics pipeline that allows the identification of somatic single-nucleotide variants ("SNVs"). A prioritized list of variants is used to design PCR amplicons.

Following plasma circulating free DNA (cfDNA) extraction and library preparation, multiplexed targeted PCR is conducted on an aliquot of the cfDNA library, followed by amplicon-based sequencing. A sample is considered ctDNA positive if 2 or more targeted SNVs are found to be above the calling confidence threshold. The sample MTM/ml, which is the sample mean tumor molecules per mL of plasma, is also reported for samples that are ctDNA-positive.

Analytical studies of the Natera Signatera assay, as previously published, have demonstrated a more than 95% sensitivity at 0.01% variant allele frequency with high specificity[93].

Mandatory Submission of Peripheral Blood (ctDNA) (four timepoints)

Peripheral blood specimens (two Streck tubes) for ctDNA analysis will be collected at the following time points:

- Baseline (prior to study therapy)
- After completion of study therapy (± 1 month), i.e. day of completion of last planned dose of T-DM1 and study drug without disease recurrence
- 1 year after completion of study therapy (± 1 month)
- At recurrence (when applicable), i.e. disease recurrence before completion of last planned dose of study therapy, or within the follow-up period (10 years post-registration)

See the Correlative Science Manual for processing and shipping instructions.

14.2.2.3 Statistical Considerations

In A011801, detection of ctDNA will be determined using the Natera Signatera assay both at study baseline and after completion of study therapy. We hypothesize that the detection of ctDNA at baseline, at completion of study therapy and/or 1 year after completion of study therapy will predict lower iDFS. ctDNA detection will be coded as a binary variable (positive versus negative), and positive ctDNA will be defined as 2 or more targeted SNVs above the calling confidence threshold. There are limited studies that have examined the postoperative ctDNA detection rate in patients with HER2+ breast cancer who have completed neoadjuvant therapy, but have not started adjuvant therapy. The largest such study included 55 patients and found that 13% had detectable ctDNA using a digital PCR assay[94]. Given that this rate included both patients who had a pCR as well as those that had residual disease, in A011801, which only includes patients with residual disease, the baseline ctDNA detection rate is assumed to be higher (20%). Of note, there are currently no data on the detection rate in this specific population using the Natera Signatera assay . However, the observation that the Natera platform has higher sensitivity than digital PCR in other settings further supports that the ctDNA detection rate will be at least 20% in A011801.

The association between ctDNA status (positive versus negative) and modified iDFS (trial primary endpoint) will first be evaluated using a log rank test for the iDFS curves generated by the Kaplan-Meier estimator. In addition, two Cox models will be used to estimate the strength of the association of ctDNA status and iDFS using a point estimate and 95% confidence interval for the HR. The first model will have iDFS as the outcome variable, ctDNA status (positive versus negative) as the variable of interest, and treatment arm (tucatinib versus placebo) as an adjusting variable. The second model will be the same with the addition of other known prognostic factors as adjusting variables. To determine whether the tucatinib benefit differs by ctDNA status (positive versus negative), two Cox models will be used. The first will include ctDNA status and treatment arm as main effects as well as their interaction term. The second model will include the same variables as the first model with the addition of established prognostic variables. If the ctDNA status by treatment arm interaction term is statistically significant (p-value < 0.05), this will be evidence of differential tucatinib benefit based on ctDNA status. In this case, a stratified analysis will be done to determine the treatment HR value within the ctDNA positive group and the HR value within the ctDNA negative group.

The calculation of iDFS will be changed for each of the later timepoint evaluations of ctDNA status: completion of treatment and one-year after the completion of treatment. Specifically, the iDFS will be measured from the completion of therapy to an iDFS event and from one-year after the completion of therapy to an iDFS event, respectively. Patients who had an iDFS event prior to the start of the iDFS calculation will be omitted from the analysis. The analysis plan is similar to that for the evaluation of baseline ctDNA status. A log rank test will be used to compare the iDFS between patients who are ctDNA positive at the completion of treatment (or 1 year after the completion of treatment) to those who are ctDNA negative at that time point. Two Cox models will be used to estimate the strength of the association using a HR. The first will include ctDNA status at the timepoint of interest and treatment arm (adjusting variable). The second will have the same variables with the addition of known prognostic variables. Power: It is assumed that among the 981 patients enrolled in the trial, 80% of them (n = 785) will have usable ctDNA values at baseline (i.e. 20% of patients are expected to either have no available sample or the assay failed). There will be approximately 80% power (with a two-sided 0.05 level of significance) to detect a hazard ratio of 1.5 (ctDNA positive versus ctDNA negative at baseline) with a sample size of 157 ctDNA positive patients and 628 ctDNA negative patients and 198 iDFS events.

14.2.2 Biobanking for Future Correlative Science Studies (optional)

The blood collected in Streck tubes for biobanking for future use may be used for circulating tumor DNA analysis in the future. The tissue will be used for potential genomics and proteomics studies, etc. Testing of banked samples will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

14.2.3 Pharmacokinetic Analysis

Individual (subject) tucatinib and T-DM1 concentrations at each sampling time will be listed; corresponding summary statistics at each sampling time will also be calculated. Additional exploratory population pharmacokinetic and exposure-response analyses will be conducted by Seattle Genetics and specified separately in a pharmacometric analysis plan.

15.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING

There are no credentialing requirements for this trial.

15.1 Request for early site study closure

Institutions cannot close this trial without discussion with the Alliance regulatory team unless express permission has been granted by Alliance regulatory. Please contact regulatory@alliancenctn.org with any questions.

16.0 MONITORING PLAN

This trial will utilize both central and on-site monitoring in order to ensure complete and consistent data collection.

16.1 Central Data Monitoring and Source Data Verification

Centralized data monitoring activities will be performed for the first three treatment cycles for all patient cases enrolled at each site (as identified by a unique CTEP Institution Code). The cases selected for central data monitoring will be reviewed for completeness and consistency via source data verification (SDV) with source documents compared to the data reported via the electronic Case Report Forms in Rave. Central data monitoring with SDV will be performed for all patients for key eligibility and response/disease outcomes. The first three treatment cycles will be reviewed for all patients.

A source document is a document in which data collected for a clinical trial is first recorded. This data is usually later entered in the Case Report Forms. The ICH-GCP guidelines define source documents as original documents, data, and records.

The following data and documents will be reviewed via centralized data monitoring and source documents should be uploaded within the two weeks after registration:

1) **Informed Consent:** De-identified last page of the signed and dated informed consent document including any pages with responses indicated by patient for optional studies (patient's full signature should be redacted, but date should be retained).
2) **Key Eligibility Criteria:**
    a. Documentation of Residual Disease: Surgical pathology report
    b. Disease Status: Diagnostic (core biopsy) pathology report, operative report, imaging reports, and additional relevant source documents
    c. Prior Treatment: Clinic notes and other relevant source documents.
    d. Comorbid Conditions: Laboratory reports, ECHO report, clinic notes, and other relevant source documents

See the Data Submission Schedule, available on the Alliance and CTSU websites, for additional details regarding source data verification of key eligibility criteria.

3) **Treatment Verification/IP Administration:** Applicable drug administration and dosing records to document the first three cycles of treatment.
4) **Disease Outcome/Response:** Applicable radiology and imaging assessment reports to document primary endpoint/claimed response.

Sites should ensure that patient identifiers have been removed from all pages that will be uploaded and add study-specific identifying information (i.e. Alliance Patient ID) and then scan and upload all documents to Rave. Please ensure that all pages are legible and correct.

In the event central monitoring or review of performance indicators (KPIs) identify deficiencies, then additional central monitoring, an unscheduled on-site monitoring visit, or an audit visit may be triggered. Deficiencies or KPIs that may elicit one of these responses include, but are not limited to:

- Accrual rate
- Eligibility
- Early termination
- Data submission timeliness
- Outstanding forms
- Outstanding queries
- Query responsiveness
- Protocol deviations

16.2 On-site Monitoring

On-site monitoring will be conducted according to Alliance procedures. Member networks that accrue 3-9 patients will be monitored approximately every 12 months during the treatment phase of the study. Member networks that accrue 10 or more patients will be monitored approximately every 6 months during the treatment phase of the study. Member networks that accrue less than three patients will not be monitored on site, unless other deficiencies have been identified, and thus indicate the need for a monitoring visit.

The first on-site monitoring visit will occur after the third patient has been enrolled and within 6 months of the third enrollment.

At the end of each on-site monitoring visit, the monitor will debrief the site study team and highlight areas that need improvement (if applicable). Any actions or findings will be documented in a visit follow-up letter, and on-site monitoring visit follow-up letters will be distributed to the Network Principal Investigator and Lead Clinical Research Professional 10 business days but no later than 15 business days of the last day of the on-site monitoring visit.

All affiliate/component sites will be monitored at the main member site during scheduled onsite visits, unless a separate on-site visit is deemed necessary. All records from affiliate/component sites must be accessible to monitors. Institutions that utilize electronic medical records must provide monitors access to electronic records. Institutions that utilize paper records must ensure that the records are certified copies.

Routine monitoring visits will be scheduled at approximately 6-12-month intervals, depending on accrual and other KPIs to ensure proper oversight of trial execution. Frequency of monitoring visits may be adjusted and will be determined based upon factors such as enrollment rate, data quality, protocol compliance, site performance, and the available amount of data to be monitored. Interim remote monitoring visits may also be scheduled.

Deficiencies impacting the protection of rights and safety of human patients, unreported or underreported safety information, or other non-compliance may result in an increase in the percentage of patient data monitored or monitoring visit frequency.

At minimum, 25% of patients enrolled to the trial will have on-site SDV of the following:

- Primary endpoint
- Secondary endpoint, per protocol Section 2.2.2

At selected sites, a minimum of 25% of patients will be selected for on-site SDV of the following:

- Eligibility

At selected sites, 100% of patients will be selected for on-site SDV of the following:

- Informed consent
- Expedited adverse events/serious adverse events
- Treatment administration
- Patient termination

On-site audits will be conducted according to the NCI Clinical Trials Monitoring Branch guidelines.

17.0 REFERENCES

1. Figueroa-Magalhaes, M.C., et al., *Treatment of HER2-positive breast cancer.* Breast, 2014. **23**(2): p. 128-136.
2. Romond, E.H., et al., *Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.* N Engl J Med, 2005. **353**(16): p. 1673-84.
3. Perez, E.A., et al., *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): p. 3744-52.
4. Slamon, D., et al., *Adjuvant trastuzumab in HER2-positive breast cancer.* N Engl J Med, 2011. **365**(14): p. 1273-83.
5. Smith, R.E., et al., *Acute myeloid leukemia and myelodysplastic syndrome after doxorubicin-cyclophosphamide adjuvant therapy for operable breast cancer: the National Surgical Adjuvant Breast and Bowel Project Experience.* J Clin Oncol, 2003. **21**(7): p. 1195-204.
6. Perez, E.A., et al., *Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31.* J Clin Oncol, 2011. **29**(25): p. 3366-73.
7. Duffull, S.B. and B.A. Robinson, *Clinical pharmacokinetics and dose optimisation of carboplatin.* Clin Pharmacokinet, 1997. **33**(3): p. 161-83.
8. Travis, L.B., et al., *Chemotherapy-induced peripheral neurotoxicity and ototoxicity: new paradigms for translational genomics.* J Natl Cancer Inst, 2014. **106**(5).
9. Liu, H.E., et al., *Multiple analytical approaches demonstrate a complex relationship of genetic and nongenetic factors with cisplatin- and carboplatin-induced nephrotoxicity in lung cancer patients.* Biomed Res Int, 2014. **2014**: p. 937429.
10. Tolaney, S.M., et al., *Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer.* N Engl J Med, 2015. **372**(2): p. 134-41.
11. Tolaney, S.M., et al., *Seven-year (yr) follow-up of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC).* Journal of Clinical Oncology, 2017. **35**.
12. Joensuu, H., *Escalating and de-escalating treatment in HER2-positive early breast cancer.* Cancer Treat Rev, 2017. **52**: p. 1-11.
13. Gingras, I., et al., *HER2-positive breast cancer is lost in translation: time for patient-centered research.* Nat Rev Clin Oncol, 2017.
14. Loibl, S. and L. Gianni, *HER2-positive breast cancer.* Lancet, 2017. **389**(10087): p. 2415-2429.
15. *Huober JB, Holmes EC, Baselga J, De Azambuja E, Untch M, Fumagalli D, et al. Survival outcomes of the NeoALTTO study: Updated results of a randomized multicenter phase III neoadjuvant trial.Journal of Clinical Oncology 2017 35:15_suppl, 512-512*
16. Krop, I.E., et al., *Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA.* Ann Oncol, 2015. **26**(1): p. 113-9.
17. CancerNetwork, *FDA Approves T-DM1 (Kadcyla) for HER2-Positive Breast Cancer.*
18. Okines, A.F., *T-DM1 in the Neo-Adjuvant Treatment of HER2-Positive Breast Cancer: Impact of the KRISTINE (TRIO-021) Trial.* Rev Recent Clin Trials, 2017. **12**(3): p. 216-222.
19. Harbeck, N., et al., *De-Escalation Strategies in Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Early Breast Cancer (BC): Final Analysis of the West German Study Group Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial Optimizing Risk Assessment and Therapy Response Prediction in Early BC HER2- and Hormone Receptor-Positive Phase II Randomized Trial-Efficacy, Safety, and Predictive Markers for 12 Weeks of Neoadjuvant Trastuzumab Emtansine With or Without Endocrine Therapy (ET) Versus Trastuzumab Plus ET.* J Clin Oncol, 2017. **35**(26): p. 3046-3054.

20. Wuerstlein, R. and N. Harbeck, *Neoadjuvant Therapy for HER2-positive Breast Cancer.* Rev Recent Clin Trials, 2017. **12**(2): p. 81-92.
21. Doroshow, D.B. and P.M. LoRusso, *Trastuzumab emtansine: determining its role in management of HER2+ breast cancer.* Future Oncol, 2018. **14**(7): p. 589-602.
22. Krop, I.E., et al., *Feasibility and cardiac safety of trastuzumab emtansine after anthracycline-based chemotherapy as (neo)adjuvant therapy for human epidermal growth factor receptor 2-positive early-stage breast cancer.* J Clin Oncol, 2015. **33**(10): p. 1136-42.
23. von Minckwitz, G., et al., *Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer.* N Engl J Med, 2018.
24. Moulder, S.L., et al., *Phase I Study of ONT-380, a HER2 Inhibitor, in Patients with HER2(+)-Advanced Solid Tumors, with an Expansion Cohort in HER2(+) Metastatic Breast Cancer (MBC).* Clin Cancer Res, 2017. **23**(14): p. 3529-3536.
25. Murthy, R., et al., *Tucatinib with capecitabine and trastuzumab in advanced HER2-positive metastatic breast cancer with and without brain metastases: a non-randomised, open-label, phase 1b study.* Lancet Oncol, 2018. **19**(7): p. 880-888.
26. Murthy, R.K., et al., *Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer.* N Engl J Med, 2019.
27. Borges, V.F., et al., *Tucatinib Combined With Ado-Trastuzumab Emtansine in Advanced ERBB2/HER2-Positive Metastatic Breast Cancer: A Phase 1b Clinical Trial.* JAMA Oncol, 2018. **4**(9): p. 1214-1220.
28. Commission, U.S.S.a.E., *Exhibit 99.3: Clinical Development of Tucatinib.*
29. Carey, L.A., et al., *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): p. 542-9.
30. Llombart-Cussac, A., et al., *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): p. 545-554.
31. Fumagalli, D., et al., *RNA Sequencing to Predict Response to Neoadjuvant Anti-HER2 Therapy: A Secondary Analysis of the NeoALTTO Randomized Clinical Trial.* JAMA Oncol, 2016.
32. Shi, W., et al., *Pathway level alterations rather than mutations in single genes predict response to HER2-targeted therapies in the neo-ALTTO trial.* Ann Oncol, 2017. **28**(1): p. 128-135.
33. Loibl, S., et al., *PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab.* Ann Oncol, 2016. **27**(8): p. 1519-25.
34. Tanioka M, F.C., Carey LA, Hyslop T, Pitcher BN, Parker JA, et al., *Integrated Analysis of Multidimensional Genomic Data on CALGB 40601 (Alliance), a Randomized Neoadjuvant Phase III Trial of Weekly Paclitaxel (T) and Trastuzumab (H) with or without Lapatinib (L) for HER2-positive Breast Cancer. Presented at the San Antonio Breast Cancer Symposium (SABCS) Meeting.* December 6-10, 2016.
35. Salgado, R., et al., *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 Oncol, 2015. **1**(4): p. 448-54.
36. Denkert, C., et al., *Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers.* J Clin Oncol, 2015. **33**(9): p. 983-91.
37. Loi, S., *Immune targeting in breast cancer: in whom and with what?* Oncology (Williston Park), 2015. **29**(5): p. 386-7.
38. Krop IE, H.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), General Session 3. 2017.
39. Prat, A., T. Pascual, and B. Adamo, *Intrinsic molecular subtypes of HER2+ breast cancer.* Oncotarget, 2017. **8**(43): p. 73362-73363.
40. Prat, A., et al., *HER2-enriched subtype and ERBB2 expression in HER2-positive breast cancer treated with dual HER2 blockade.* J Natl Cancer Inst, 2019.
41. Krop, I.e.a. *Event-Free Survival and Gene Expression Signatures in CALGB (ALLIANCE) 40601*. in *San Antonio Breast Cancer Symposium (SABCS)*. 2017. San Antonio, TX.
42. Pernas, S., et al., *PAM50 Subtypes in Baseline and Residual Tumors Following Neoadjuvant Trastuzumab-Based Chemotherapy in HER2-Positive Breast Cancer: A Consecutive-Series From a Single Institution.* Front Oncol, 2019. **9**: p. 707.
43. Krop, I.e.a. *Genomic Correlates of Response to Adjuvant Trastuzumab and Pertuzumab in HER2+ Breast Cancer: Biomarker Analysis of the APHINITY Trial.* . in *American Society of Clinical Oncology (ASCO)*. 2019. Chicago, IL.
44. Symmans, W.F., et al., *Long-Term Prognostic Risk After Neoadjuvant Chemotherapy Associated With Residual Cancer Burden and Breast Cancer Subtype.* J Clin Oncol, 2017. **35**(10): p. 1049-1060.
45. Symmans, W.F., et al., *Measurement of Residual Breast Cancer Burden to Predict Survival After Neoadjuvant Chemotherapy.* Journal of Clinical Oncology, 2007. **25**(28): p. 4414-4422.
46. Caparica, R., et al., *Post-neoadjuvant treatment and the management of residual disease in breast cancer: state of the art and perspectives.* Ther Adv Med Oncol, 2019. **11**: p. 1758835919827714.
47. Solinas, C., et al., *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 Treat Rev, 2017. **57**: p. 8-15.
48. Mao, Y., et al., *The value of tumor infiltrating lymphocytes (TILs) for predicting response to neoadjuvant chemotherapy in breast cancer: a systematic review and meta-analysis.* PLoS One, 2014. **9**(12): p. e115103.
49. Hamy, A.S., et al., *Stromal lymphocyte infiltration after neoadjuvant chemotherapy is associated with aggressive residual disease and lower disease-free survival in HER2-positive breast cancer.* Ann Oncol, 2017. **28**(9): p. 2233-2240.
50. Akbulut, H., et al., *Chemotherapy targeted to cancer tissue potentiates antigen-specific immune response induced by vaccine for in vivo antigen loading and activation of dendritic cells.* Mol Ther, 2008. **16**(10): p. 1753-60.
51. Bracci, L., et al., *Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer.* Cell Death Differ, 2014. **21**(1): p. 15-25.
52. Salgado, R., et al., *The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014.* Ann Oncol, 2015. **26**(2): p. 259-71.
53. Garcia-Murillas, I., et al., *Mutation tracking in circulating tumor DNA predicts relapse in early breast cancer.* Sci Transl Med, 2015. **7**(302): p. 302ra133.
54. Lin, N.U., et al., *CNS metastases in breast cancer: old challenge, new frontiers.* Clin Cancer Res, 2013. **19**(23): p. 6404-18.
55. Lin, N.U. and E.P. Winer, *Brain metastases: the HER2 paradigm.* Clin Cancer Res, 2007. **13**(6): p. 1648-55.
56. Klotz, R., et al., *Abstract 3023: Dissecting mechanisms of breast cancer metastasis through patient-derived circulating tumor cells.* Cancer Research, 2018. **78**(13 Supplement): p. 3023-3023.
57. Moran, M.S., et al., *Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer.* J Clin Oncol, 2014. **32**(14): p. 1507-15.

58. Morrow, M., et al., *Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Ductal Carcinoma In Situ.* Ann Surg Oncol, 2016. **23**(12): p. 3801-3810.
59. Choi, J., et al., *Margins in Breast-Conserving Surgery After Neoadjuvant Therapy.* Ann Surg Oncol, 2018. **25**(12): p. 3541-3547.
60. Whelan, T.J., et al., *Regional Nodal Irradiation in Early-Stage Breast Cancer.* N Engl J Med, 2015. **373**(4): p. 307-16.
61. Badiyan, S.N., et al., *Hypofractionated regional nodal irradiation for breast cancer: examining the data and potential for future studies.* Radiother Oncol, 2014. **110**(1): p. 39-44.
62. Khan, A.J., et al., *Hypofractionated Postmastectomy Radiation Therapy Is Safe and Effective: First Results From a Prospective Phase II Trial.* J Clin Oncol, 2017. **35**(18): p. 2037-2043.
63. Wang, S.L., et al., *Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial.* Lancet Oncol, 2019. **20**(3): p. 352-360.
64. Koukourakis, M.I., et al., *Postmastectomy hypofractionated and accelerated radiation therapy with (and without) subcutaneous amifostine cytoprotection.* Int J Radiat Oncol Biol Phys, 2013. **85**(1): p. e7-13.
65. Bartelink, H., et al., *Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation.* N Engl J Med, 2001. **345**(19): p. 1378-87.
66. Romestaing, P., et al., *Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France.* J Clin Oncol, 1997. **15**(3): p. 963-8.
67. Bartelink, H., et al., *Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial.* Lancet Oncol, 2015. **16**(1): p. 47-56.
68. Smith, B.D., et al., *Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline.* Pract Radiat Oncol, 2018. **8**(3): p. 145-152.
69. Administration, U.F.a.D. *Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* 2009 December 2009 December 27, 2019]; Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.
70. Basch, E., *The missing voice of patients in drug-safety reporting.* N Engl J Med, 2010. **362**(10): p. 865-9.
71. Fromme, E.K., et al., *How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30.* J Clin Oncol, 2004. **22**(17): p. 3485-90.
72. Pakhomov, S.V., et al., *Agreement between patient-reported symptoms and their documentation in the medical record.* Am J Manag Care, 2008. **14**(8): p. 530-9.
73. von Minckwitz, G., et al., *Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer.* N Engl J Med, 2017. **377**(2): p. 122-131.
74. Hudis, C.A., et al., *Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system.* J Clin Oncol, 2007. **25**(15): p. 2127-32.
75. Basch, E., et al., *Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE).* J Natl Cancer Inst, 2014. **106**(9).
76. Voils, C.I., et al., *Improving the measurement of self-reported medication nonadherence.* J Clin Epidemiol, 2011. **64**(3): p. 250-4.
77. Cella, D.F., et al., *The Functional Assessment of Cancer Therapy scale: development and validation of the general measure.* J Clin Oncol, 1993. **11**(3): p. 570-9.

78. Brady, M.J., et al., *Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument.* J Clin Oncol, 1997. **15**(3): p. 974-86.
79. Eton, D.T., et al., *A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale.* J Clin Epidemiol, 2004. **57**(9): p. 898-910.
80. Osoba, D., *Rationale for the timing of health-related quality-of-life (HQL) assessments in oncological palliative therapy.* Cancer Treat Rev, 1996. **22 Suppl A**: p. 69-73.
81. Lin, C., et al., *Breast cancer oral anti-cancer medication adherence: a systematic review of psychosocial motivators and barriers.* Breast Cancer Res Treat, 2017. **165**(2): p. 247-260.
82. Basch, E., L.J. Rogak, and A.C. Dueck, *Methods for Implementing and Reporting Patient-reported Outcome (PRO) Measures of Symptomatic Adverse Events in Cancer Clinical Trials.* Clin Ther, 2016. **38**(4): p. 821-30.
83. Dueck, A.C., et al., *Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).* JAMA Oncol, 2015. **1**(8): p. 1051-9.
84. Basch, E., et al., *Feasibility of Implementing the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events in a Multicenter Trial: NCCTG N1048.* Journal of Clinical Oncology, 2018. **36**(31): p. 3120-+.
85. King, M.T., et al., *Meta-analysis provides evidence-based interpretation guidelines for the clinical significance of mean differences for the FACT-G, a cancer-specific quality of life questionnaire.* Patient Relat Outcome Meas, 2010. **1**: p. 119-26.
86. NCSS, L., *PASS 2020 Power Analysis and Sample Size Software* 2020: Kaysville, UT, USA.
87. Denkert, C., et al., *Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy.* Lancet Oncol, 2018. **19**(1): p. 40-50.
88. Dieci, M.V., et al., *Update on tumor-infiltrating lymphocytes (TILs) in breast cancer, including recommendations to assess TILs in residual disease after neoadjuvant therapy and in carcinoma in situ: A report of the International Immuno-Oncology Biomarker Working Group on Breast Cancer.* Semin Cancer Biol, 2018. **52**(Pt 2): p. 16-25.
89. Kim, R.S., et al., *Stromal Tumor-infiltrating Lymphocytes in NRG Oncology/NSABP B-31 Adjuvant Trial for Early-Stage HER2-Positive Breast Cancer.* J Natl Cancer Inst, 2019. **111**(8): p. 867-871.
90. Hachad, H., I. Ragueneau-Majlessi, and R.H. Levy, *A useful tool for drug interaction evaluation: the University of Washington Metabolism and Transport Drug Interaction Database.* Hum Genomics, 2010. **5**(1): p. 61-72.
91. PMID: 38460249
92. PMID: 31369045
93. PMID: 30992300
94. PMID: 31369045

APPENDIX I: ELECTRONIC PATIENT-REPORTED OUTCOMES (EPRO) INSTRUCTIONS

1.0 Introduction

Electronic collection of patient-reported outcomes is preferred but not mandatory. Patients will need to use their own device (IOS or Android phone or tablet). Short term data will only appear on the patient's device until responses are completed. The patient data will import directly into the database once the patient clicks the submit button and will no longer be on the patient's device.

Site staff access

Site users of ePRO and the Patient Cloud require the same access as those using Rave. Access to the trial in the Patient Cloud is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access the Patient Cloud via iMedidata, the site user must have an active CTEP-IAM account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in the Patient Cloud until all required Medidata and study specific trainings are completed.

Users who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance).

Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

2.0 Security

All data are encrypted on the device (128 bit on file +https transfer) and the app requires a user to have a username and password. If the user is idle for too long (5 minutes inactivity time), the app will time out and the user will need to log in again.

The data will only reside on the device for a short period of time. Once the user clicks "submit," the data is securely transferred over https between the device and internal relay. No identifying information is stored in iMedidata (only email address is stored).

The Patient information (email/password) does not reside in Medidata Rave EDC and the patient accounts are hidden in iMedidata from sites and sponsors in the Patient Cloud Relay.

The ePRO application is Part 11 compliant and acts as a gateway between device and Medidata Clinical Cloud (MCC).

Messages and information communicated to and from the Patient Cloud are encrypted and therefore this information cannot be read if intercepted while in transit.

3.0 CRP Training for ePRO

Please visit the Medidata Learning Tool for reference information on Patient Cloud for CRAs.

4.0 Checklist for activities prior to consenting a patient

- Accept study invitation at iMedidata.com

Note: you must be rostered in RSS and have received an invitation to Patient Cloud

- Verify the IOS or Android operating system is using the most current version
- Verify Patient Cloud app is using the most current version
- Refer to https://learn.mdsol.com/patient-cloud/en/video-library-for-providers-102101952.html to review Quick reference guides

5.0 Instructions for ePRO patient registration

Please visit the Medidata Learning Tool for additional screen shots and video tutorials on how to register participants to the study.

i. The patient registration process starts in iMedidata. Begin by clicking on the Patient Cloud Registration link for this study

ii. The patient management app will display, select your STUDY and SITE from the drop downs and click Launch.

iii. Now the first patient can be registered. Create a subject ID and select a Country / Language from the drop down, (these are the only required data fields). The patient initials are optional, but may help in identifying which subject ID maps with which activation code. When finished, click Add.

iv. The patient added will appear at the top of the table and will include the date the patient was added, the subject ID, initials, (if included) and a unique auto-generated activation code. The activation code is unique for each patient and linked to the subject ID, it is not interchangeable. In addition, there is a status section, which determines if the patient has registered. When the patient has registered the status will change from invited to registered.

6.0 Patient Users

To use the Patient Cloud, patients will need to use their own device (IOS, Android phone or tablet). Short term data will only appear on the patient's device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and will no longer be visible on the patient's device.

Patient compliance: The patient data imports directly from her/his device into the Rave database. There are no documents to audit. The electronic responses are the source documentation.

Patient Instructions for Accessing the Patient Cloud App using their personal device

Downloading the Patient Cloud App:

Please ensure that the patient downloads the following app from the app store, and not Patient Cloud ePRO (which is the legacy app).

If you are using your personal device, and you do not have the Patient Cloud app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. **If the Patient Cloud app is already on the device, or if you are using a provider's device, you can skip this section.**

You will need an email address that you agree to use for this purpose. The e-mail address is needed to identify you on the Patient Cloud Application and for you to receive notifications to let you know when forms are due. Your e-mail address will only be used for this survey study, and will not be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an e- mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS:

1. An Apple ID is required for downloading the Patient Cloud app.
2. Tap the App Store icon.
3. Search for Medidata Patient Cloud and follow the installation instructions.

Note: Patient Cloud is listed as an iPhone App in the App store. When using an iPad, please view the search results under iPhone apps.

For Android:

1. A Google account is required for downloading the Patient Cloud app
2. Tap the Play Store icon.
3. Search for Medidata Patient Cloud and follow the installation instructions.

Registering on the App:

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the Patient Cloud app.

Note: You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud app.

1. If registering from the Patient Cloud app, tap Register on the bottom of the log in page. If registering on the web, open the URL shield.imedidata.com on a web browser.
2. Enter your activation code and tap Activate.
3. On the next page, read the instructions and tap Next.
4. Read the privacy notice and tap I agree. Then tap OK to confirm.
5. Enter and confirm your email address. Tap Next.
6. Enter and confirm your password. Tap Next.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap Create my account to complete your registration.

If you registered on the Patient Cloud app, it automatically logs you out. If you registered on the web, you are presented with the option to download the Patient Cloud app. You can then proceed to log in with the credentials you created.

Logging in to the App after registration:

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

Note: If you do not remember your password, tap Forgot Password, and follow the instructions provided.

Setting a PIN Code:

The first time you log in to the Patient Cloud app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the Patient Cloud app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap Forgot PIN and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

Resetting Your Password:

You can reset your password by using the options menu at the top left of most pages.

1. Tap the options menu icon.
2. Tap Reset Password.
3. Follow the instructions to reset your password.

Completing and Submitting Forms:

Once logged in, forms related to your study display on the Tasks page. If you are enrolled in multiple studies, select the appropriate study first, and then select a form. New forms can appear on the Tasks page at any time, depending on how the study is designed.

There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a  icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you are given the opportunity to review and change your responses prior to submitting.
3. Review your responses by scrolling down the list.
4. If you need to change an answer, tap the question to go back and change the answer.
5. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

Electronic Patient-Reported Outcomes (ePRO) Instructions for Patients

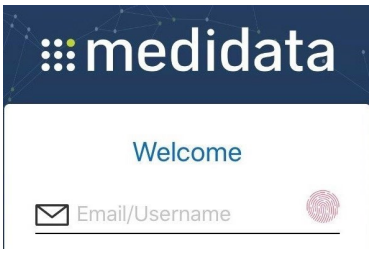
Download the Patient Cloud app

Create a username and password for the Patient Cloud app by selecting the 'Have an Activation Code?' option on the login screen. Use the activation code from your clinic.

Log in to the Patient Cloud app

See your forms on the main screen

Complete, review, and submit your forms



Tip: Your username must be in email format (for example, jodiesmith20@email.com).

Tip: When a form is due, you will see the alarm clock with the date and time the form will close.

For help with the Patient Cloud app, please ask your study team.

APPENDIX II: PATIENT MEDICATION DIARY – TUCATINIB/PLACEBO

(VERSION 2)

Today's date _____ **Dose** _____

Patient Name_____ (initials acceptable) **Patient Study ID** _____

	INSTRUCTIONS FOR THE PATIENT: 1. Complete this form while you take **tucatinib/placebo**. This form is a 21-day diary. You may need to complete more than one form between clinic visits. 2. You will take your dose of **tucatinib/placebo** twice daily approximately 12 hours apart between doses. The tucatinib/placebo pills must be refrigerated at all times, except during transport to and from your home. • Full dose: 300 mg per dose (2 of the 150 mg tablets – see Example #1 below) • First reduced dose: 250 mg per dose (1 of the 150 mg tablets + 2 of the 50 mg tablets) • Second reduced dose: 200 mg per dose (1 of the 150 mg tablets + 1 of the 50 mg tablets) • Third reduced dose: 150 mg per dose (1 of the 150 mg tablets) 3 Take the **tucatinib/placebo** pills with or without food. 4. Record the date, the number of tablets you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time. 5. If a dose is missed, do not make up that dose if it has been over six hours since that dose was due. Instead, resume dosing with the next scheduled dose. See Example #2 below for how to record this on the form. 6. Swallow tablets whole, do not crush or chew. 7. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am 8. Please return this form to your doctor at your next appointment. You may need to return more than one form per clinic visit. You will also be asked to return your pill bottles at each visit.

CYCLE #: _____

Day	Date	Time of daily dose #1	# of tablets taken		Time of daily dose #2	# of tablets taken		Comments
			150 mg (oval)	50 mg (round)		150 mg (oval)	50 mg (round)	
Example #1	*01/01/2020*	*9:00 AM*	*2*	*N/A*	*9:00 PM*	*2*	*N/A*	*None*
Example #2	*01/01/2020*	*9:00 AM*	*2*	*N/A*	*9:00 PM*	*0*	*N/A*	*Missed the evening dose*
1								
2								
3								
4								
5								
6								
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21								

	Patient's Signature	Date
	Physician's Office will complete this section: 1. Date patient started protocol treatment _____ 2. Date patient was removed from study _____ 3. Total number of tablets taken this month (each size) _____ 4. Physician/Nurse/Data Manager's Signature _____	

APPENDIX III: PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARDS

(VERSION 1)

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

Patient Name:	**Diagnosis:**	**Trial #:**	A011801
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**	Ado-trastuzumab emtansine (T-DM1)

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by the National Cancer Institute.

These are the things that your healthcare providers need to know:

Ado-trastuzumab emtansine (T-DM1) interacts with CYP3A4, certain specific enzymes in your liver or other tissues like the gut.

	Explanation
CYP isoenzymes	The enzyme(s) in question is CYP3A4. Ado-trastuzumab emtansine is broken down by this enzyme and may be affected by other drugs that inhibit or induce this enzyme.

These are the things that you need to know:

The study drug, ado-trastuzumab emtansine (T-DM1), may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (*e.g.* St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inhibitors of CYP3A4.

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

NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI
EMERGENCY INFORMATION		**DRUG INTERACTIONS**	
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** Ado-trastuzumab emtansine (T-DM1) interacts with CYP3A4 enzyme in your liver or other tissue like your gut and must be used very carefully with other medicines.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** A011801 **Study Drug(S):** Ado-trastuzumab emtansine (T-DM1)	**Use caution and avoid the following drugs if possible:** Examples include but are not limited to: Ketoconazole, Itraconazole, Clarithromycin, Atazanavir, Indinavir, Nefazodone, Nelfinavir, Ritonavir, Saquinavir, Telithromycin, Voriconazole	Your healthcare providers should be aware of any medicines that are strong inhibitors of CYP3A4. **Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor.	Version mmm/yyyy
For more information: 1-800-4-CANCER	**For more information:** 1-800-4-CANCER	**For more information:** 1-800-4-CANCER	**For more information:** 1-800-4-CANCER
cancer.gov | clinicaltrials.gov	cancer.gov | clinicaltrials.gov	cancer.gov | clinicaltrials.gov	cancer.gov | clinicaltrials.gov

Fold at dotted lines:

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

Patient Name:	**Diagnosis:**	**Trial #:**	A011801
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**	Tucatinib/placebo

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by the National Cancer Institute.

These are the things that your healthcare providers need to know:

Tucatinib/placebo interacts with CYP2C8 and CYP3A4, certain specific enzymes in your liver or other tissue like the gut.

	Explanation
CYP isoenzymes	The enzyme(s) in question is/are CYP2C8 and CYP3A4. Tucatinib interacts with strong CYP2C8 inhibitors, strong CYP2C8 inducers, and strong CYP3A4 inducers. Tucatinib/placebo may be affected by other drugs that inhibit and induce these enzymes.

These are the things that you need to know:

The study drug, tucatinib/placebo, may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (*e.g.* St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers of CYP3A4 or CYP2C8 and strong inhibitors of CYP2C8.

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

NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI
EMERGENCY INFORMATION		**DRUG INTERACTIONS**	
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** Tucatinib/placebo interacts with CYP2C8 and CYP3A4, enzymes in your liver or other tissues like the gut, and must be used very carefully with other medicines.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** A011801 **Study Drug(S):** Tucatinib/placebo	**Use caution and avoid the following drugs if possible:** Examples include but are not limited to: CYP3A4 inducers: Carbamazepine, Enzalutamide, Mitotane, Phenytoin, Rifampin, St. John's Wort CYP2C8 inducers: Rifampin CYP2C8 inhibitors: Clopidogrel, Gemfibrozil	Your healthcare providers should be aware of any medicines that are strong inducers of CYP2C8 or CYP3A4, and strong inhibitor of CYP2C8. **Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor.	Version mmm/yyyy
For more information: 1-800-4-CANCER	**For more information:** 1-800-4-CANCER	**For more information:** 1-800-4-CANCER	**For more information:** 1-800-4-CANCER
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APPENDIX III: SPANISH

APÉNDICE III: VOLANTE Y TARJETAS PARA LA BILLETERA SOBRE LAS INTERACCIONES DE LOS FÁRMACOS PARA LA PACIENTE

(VERSIÓN 1)

Información para las pacientes, sus cuidadores y el equipo de atención médica ajeno al estudio sobre posibles interacciones con otros fármacos y suplementos herbales

Nombre de la paciente:	**Diagnóstico:**	**Ensayo n.º:**	A011801
Médico del estudio:	**N.º de teléfono del médico del estudio:**	**Fármaco(s) del estudio:**	Ado-trastuzumab emtansina (T-DM1)

Muestre este documento a todos sus proveedores de atención médica (médicos, asistentes médicos, enfermeras, farmacéuticos) y dígales que está participando en un ensayo clínico patrocinado por el Instituto Nacional del Cáncer.

Esto es lo que sus proveedores de atención médica deben saber:

El ado-trastuzumab emtansina (T-DM1) interactúa con CYP3A4, ciertas enzimas específicas en el hígado u otros tejidos como el intestino.

	Explicación
Isoenzimas CYP	La enzima en cuestión es CYP3A4. El ado-trastuzumab emtansina es descompuesto por esta enzima y puede verse afectado por otros fármacos que inhiben o inducen esta enzima.

Esto es lo que usted debe saber:

El fármaco del estudio, ado-trastuzumab emtansina (T-DM1), puede interactuar con otros fármacos, lo que puede causar efectos secundarios. Por este motivo, es muy importante informar a sus médicos sobre todos los medicamentos, incluidos: (a) medicamentos que estaba tomando antes de este ensayo clínico, (b) medicamentos que empezó o dejó de tomar durante este estudio, (c) medicamentos que compra sin receta (medicamento de venta libre), (d) hierbas o suplementos (p. ej., hierba de San Juan). Es útil llevar con usted los envases de los medicamentos o una lista actualizada de los medicamentos.

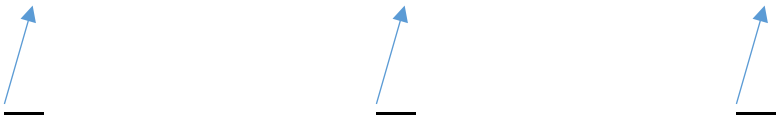
Antes de que usted se inscriba en el ensayo clínico, su médico del estudio trabajará con sus proveedores de atención médica habituales para revisar cualquier medicamento y suplemento herbal que se considere un fuerte inhibidor de CYP3A4.

- ¡Tenga mucho cuidado! Los medicamentos de venta libre (incluidos los suplementos herbales) pueden contener ingredientes que podrían interactuar con el fármaco del estudio. Hable con sus médicos o farmacéuticos para determinar si podría haber algún efecto secundario.
- Asegúrese de que su médico sepa que debe evitar ciertos medicamentos recetados.

- Su proveedor de atención médica habitual debe consultar una fuente de consulta médica actualizada con frecuencia o llamar a su médico del estudio antes de recetar cualquier medicamento nuevo o de suspender algún medicamento que esté tomando.

NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI
INFORMACIÓN DE EMERGENCIA		**INTERACCIONES DE LOS FÁRMACOS**	
Muestre esta tarjeta a todos sus proveedores de atención médica. Llévela con usted en caso de que vaya a la sala de emergencias.	Informe a sus médicos **antes** de **empezar** o **dejar** cualquier medicamento. **¡Consulte a su médico o farmacéutico si necesita un medicamento de venta libre o suplemento herbal!**	**Lleve esta tarjeta con usted en todo momento** El ado-trastuzumab emtansina (T-DM1) interactúa con la enzima CYP3A4 en el hígado u otros tejidos como el intestino y debe utilizarse con mucho cuidado con otros medicamentos.	
Nombre de la paciente: **Diagnóstico:** **Médico del estudio:** **N.º de teléfono del médico del estudio:** **N.º de ensayo del NCI:** A011801 **Fármaco(s) del estudio:** Ado-trastuzumab emtansina (T-DM1)	**Tenga cuidado y evite los siguientes fármacos si es posible:** Los ejemplos incluyen, entre otros: Ketoconazol, itraconazol, claritromicina, atazanavir, indinavir, nefazodona, nelfinavir, ritonavir, saquinavir, telitromicina, voriconazol	Sus proveedores de atención médica deben estar al tanto de cualquier medicamento que sea un fuerte inhibidor de CYP3A4. **Antes de recetarle cualquier medicamento nuevo**, su proveedor de atención médica debe consultar una **fuente de consulta médica actualizada con frecuencia** para obtener una **lista de los fármacos que debe evitar**, o comunicarse con su médico del estudio.	Versión mmm/aaaa
Para obtener más información: 1-800-4-CANCER	**Para obtener más información:** 1-800-4-CANCER	**Para obtener más información:** 1-800-4-CANCER	**Para obtener más información:** 1-800-4-CANCER
cancer.gov | clinicaltrials.gov	cancer.gov | clinicaltrials.gov	cancer.gov | clinicaltrials.gov	cancer.gov | clinicaltrials.gov

Doblar en las líneas de puntos:



Información para los pacientes, sus cuidadores y el equipo de atención médica ajeno al estudio sobre posibles interacciones con otros fármacos y suplementos herbales

Nombre de la paciente:	**Diagnóstico:**	**Ensayo n.º:**	A011801
Médico del estudio:	**N.º de teléfono del médico del estudio:**	**Fármaco(s) del estudio:**	Tucatinib/placebo

Muestre este documento a todos sus proveedores de atención médica (médicos, asistentes médicos, enfermeras, farmacéuticos) y dígales que está participando en un ensayo clínico patrocinado por el Instituto Nacional del Cáncer.

Esto es lo que sus proveedores de atención médica deben saber:

El tucatinib/placebo interactúa con CYP2C8 y CYP3A4, ciertas enzimas específicas en el hígado u otros tejidos como el intestino.

	Explicación
Isoenzimas CYP	La(s) enzima(s) en cuestión es(son) CYP2C8 y CYP3A4. El tucatinib interactúa con inhibidores fuertes de CYP2C8, con inductores fuertes de CYP2C8, y con inductores fuertes de CYP3A4. El tucatinib/placebo puede verse afectado por otros fármacos que inhiben e inducen estas enzimas.

Esto es lo que usted debe saber:

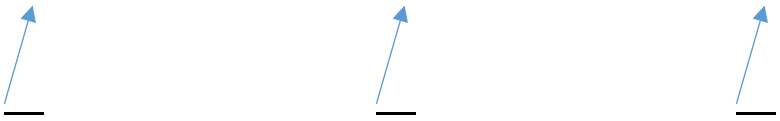
El fármaco del estudio, tucatinib/placebo, puede interactuar con otros fármacos, lo que puede causar efectos secundarios. Por este motivo, es muy importante informar a sus médicos sobre todos los medicamentos, incluidos: (a) medicamentos que estaba tomando antes de este ensayo clínico, (b) medicamentos que empezó o dejó de tomar durante este estudio, (c) medicamentos que compra sin receta (medicamento de venta libre), (d) hierbas o suplementos (p. ej., hierba de San Juan). Es útil llevar con usted los envases de los medicamentos o una lista actualizada de los medicamentos.

Antes de que usted se inscriba en el ensayo clínico, su médico del estudio trabajará con sus proveedores de atención médica habituales para revisar cualquier medicamento y suplemento herbal que se considere un fuerte inductor de CYP3A4 o CYP2C8 y un fuerte inhibidor de CYP2C8.

- ¡Tenga mucho cuidado! Los medicamentos de venta libre (incluidos los suplementos herbales) pueden contener ingredientes que podrían interactuar con el fármaco del estudio. Hable con sus médicos o farmacéuticos para determinar si podría haber algún efecto secundario.
- Asegúrese de que su médico sepa que debe evitar ciertos medicamentos recetados.
- Su proveedor de atención médica habitual debe consultar una fuente de consulta médica actualizada con frecuencia o llamar al médico del estudio antes de recetar cualquier medicamento nuevo o de suspender algún medicamento que esté tomando.

NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI
INFORMACIÓN DE EMERGENCIA		**INTERACCIONES DE LOS FÁRMACOS**	
Muestre esta tarjeta a todos sus proveedores de atención médica. Llévela con usted en caso de que vaya a la sala de emergencias.	Informe a sus médicos **antes** de **empezar** o **dejar** cualquier medicamento. **¡Consulte a su médico o farmacéutico si necesita un medicamento de venta libre o suplemento herbal!**	**Lleve esta tarjeta con usted en todo momento** El tucatinib/placebo interactúa con CYP2C8 y CYP3A4, enzimas en el hígado u otros tejidos como el intestino y debe utilizarse con mucho cuidado con otros medicamentos.	
Nombre de la paciente: **Diagnóstico:** **Médico del estudio:** **N.º de teléfono del médico del estudio:** **N.º de ensayo del NCI:** A011801 **Fármaco(s) del estudio:** Tucatinib/placebo	**Tenga cuidado y evite los siguientes fármacos si es posible:** Los ejemplos incluyen, entre otros: Inductores de CYP3A4: Carbamazepina, enzalutamida, mitotano, fenitoína, rifampicina, hierba de San Juan Inductores de CYP2C8: Rifampicina Inhibidores de CYP2C8: Clopidogrel, gemfibrozil	Sus proveedores de atención médica deben estar al tanto de cualquier medicamento que sea un fuerte inductor de CYP2C8 o CYP3A4 y un fuerte inhibidor de CYP2C8. **Antes de recetarle cualquier medicamento nuevo**, su proveedor de atención médica debe consultar una **fuente de consulta médica actualizada con frecuencia** para obtener una **lista de los fármacos que debe evitar**, o comunicarse con su médico del estudio.	Versión mmm/aaaa
Para obtener más información: 1-800-4-CANCER	**Para obtener más información:** 1-800-4-CANCER	**Para obtener más información:** 1-800-4-CANCER	**Para obtener más información:** 1-800-4-CANCER
cancer.gov | clinicaltrials.gov	cancer.gov | clinicaltrials.gov	cancer.gov | clinicaltrials.gov	cancer.gov | clinicaltrials.gov

Doblar en las líneas de puntos:



APPENDIX IV: CYP3A4 INDUCERS

CYP3A4 inhibitors and inducers include but are not limited to the following. There could also be additional new drugs and marketed drugs that could be identified as inhibitors/inducers with continued research.

Drug[a]

Strong Inducers

Apalutamide

Carbamazepine

Enzalutamide

Mitotane

Phenytoin

Rifampin

St. John's Wort

Moderate Inducers

Phenobarbital

Note: Any additional strong CYP3A4 inducers that are identified or become commercially available while the clinical trial is ongoing are also prohibited.

[a.] FDA. "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers" (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency)

APPENDIX V: CYP2C8 INHIBITORS/INDUCERS

CYP2C8 inhibitors and inducers include but are not limited to the following. There could also be additional new drugs and marketed drugs that could be identified as inhibitors/inducers with continued research.

Drug[a]
Strong Inhibitors
Gemfibrozil
Moderate Inhibitors
Clopidogrel
Deferasirox
Teriflunomide
Moderate Inducers
Rifampin

Note: Any additional strong CYP2C8 inhibitors/inducers that are identified or become commercially available while the clinical trial is ongoing are also prohibited.

a FDA. "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers" (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency)

APPENDIX VI: CLINICAL SUBSTRATES FOR CYP3A-MEDIATED METABOLISM

The following table provides examples of clinical substrates for CYP3A-mediated metabolism and is not intended to be an exhaustive list.

Sensitive (AUC increase ≥5-fold with strong index inhibitor)	**Moderate Sensitive** (AUC increase 2 to 5-fold with strong index inhibitor)
alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir[a], ebastine, everolimus, ibrutinib, lomitapide, lovastatin[b], midazolam, naloxegol, nisoldipine, saquinavir[a], simvastatin[b], sirolimus, tacrolimus, tipranavir[a], triazolam, vardenafil	alprazolam, aprepitant, atorvastatin[c], colchicine, eliglustat[d], pimozide, rilpivirine, rivaroxaban, tadalafil
budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir[a], lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	

Note: Sensitive substrates are drugs that demonstrate an increase in area under the concentration-time curve (AUC) of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction (DDI) studies. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to < 5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Sensitive substrates of CYP3A with ≥ 10-fold increase in AUC by co-administration of strong index inhibitors are shown above the dashed line. Other elimination pathways may also contribute to the elimination of the substrates listed in the table above and should be considered when assessing the drug interaction potential.

a Usually administered to patients in combination with ritonavir, a strong CYP3A inhibitor.

b Acid form is an organic anion transporting polypeptide 1B1 (OATP1B1) substrate.

c Listed based on pharmacogenetic studies.

d Sensitive substrate of CYP2D6 and moderate sensitive substrate of CYP3A.

DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [90].

Source: (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1)

APPENDIX VII: CYTOCHROME P-450 CYP3A4 SUBSTRATES WITH A NARROW THERAPEUTIC INDEX

The table below contains EXAMPLES of CYP3A4 substrates with a narrow therapeutic index, but it is not an exhaustive list. Because lists of these agents are constantly changing, please consult and review any drugs that may be cytochrome P-450 CYP3A4 substrates with a narrow therapeutic index. Please see Appendix VII. Other examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

Aminophylline	Pimozide	Paclitaxel	Venetoclax	Rucaparib	Bosutinib	
Amiodarone	Quinidine		Vemurafenib	Belinostat	Olaparib	Romidepsin
Argatroban	Sirolimus	Acenocoumarol	Vandetanib	Etoposide	Brentuximab vedotin	Sonedegib
Busulfan	Tacrolimus	Methotrexate	Alpelisib	Teniposide	Brigatinib	Rucaparib
Carbamazepine	Temsirolimus	Clozapine	Daunorubicin	Ixabepilone	Neratinib	Ribociclib
	Theophylline	Zanubrutinib		Idelalisib	Sunitinib	Dabrafenib
Cyclosporine	Tianeptine	Abiraterone	Docetaxel	Ifosfamide	Palbociclib	Copanlisib
Digitoxin	Warfarin	Vinorelbine	Doxorubicin	Imatinib	Nilotinib	Dacomitinib
Dofetilide		Acalabrutinib	Trabectedin	Ixazomib	Panobinostat	Encorafenib
Everolimus	Cisapride	Vinflunine	Thiotepa	Midostaurin	Cabergoline	Erdafitinib
		Cytarabine	Enasidenib	Ceritinib	Pazopanib	Ivosidenib
Fosphenytoin	Dronedarone	Vincristine	Entrectinib	Cobimetinib	Cabozantinib	Crizotinib
	Ibrutinib	Vinblastine	Erlotinib	Bortezomib	Pexidartinib	Ponatinib
Phenprocoumon	Dasatinib	Alectinib	Axitinib	Ruxolitinib	Sorafenib	

APPENDIX VIII: TIL COUNTING TIPS[52]

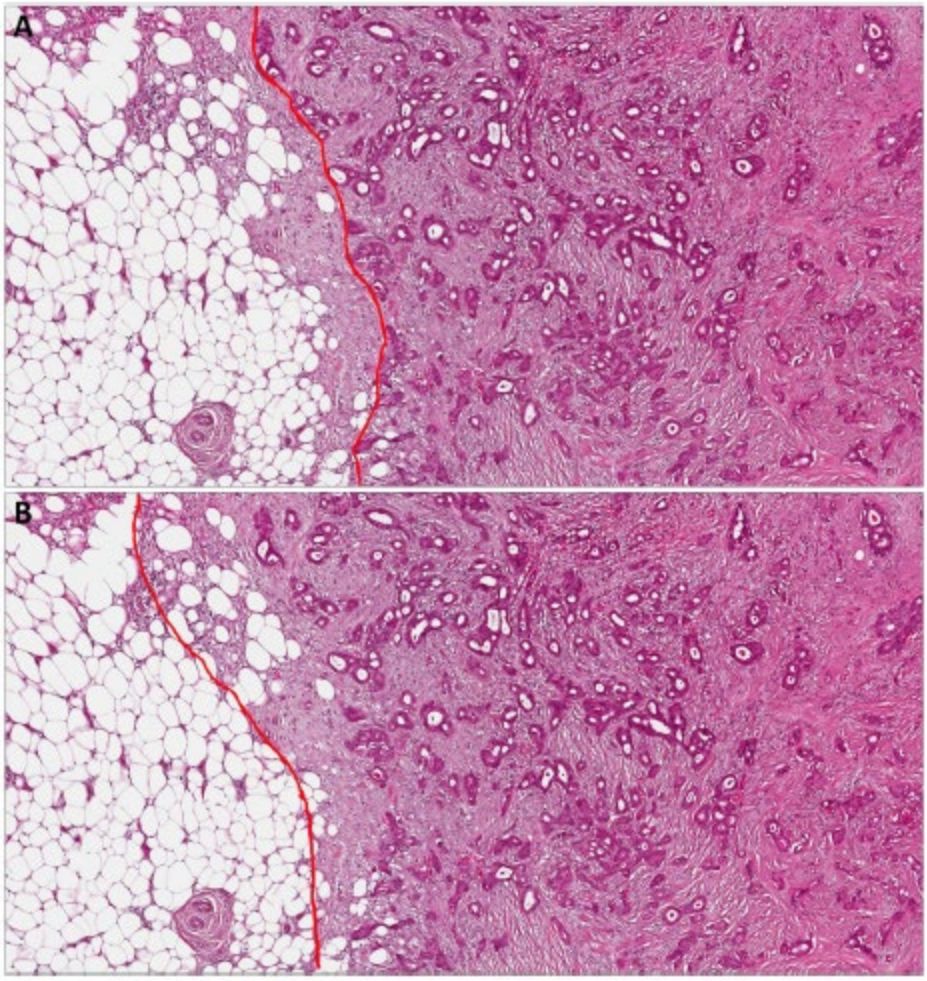
Supplementary Figure 1

Uncertain precise location of the tumour border as an example of an open question when assessing TILs. The tumour border can be the lateral edge of invasive carcinoma cells (A) or as including the peripheral desmoplastic/fibroinflammatory reaction (B).

Supplementary information 1: list of questions given to experts pertinent for TILs assessment in breast cancer

Supplementary information 2: Tutorial on standardized evaluation of TILs in breast cancer for daily clinical and research practice of clinical trial setting

Supplementary information 3: Open questions in the assessments of TILs


A
B

S1 Supplementary Table 1

QUESTIONS
Could you detail the methodology you have used in your study?
At what microscope magnification did you score the slides?
Is slide thickness important?
Did you assess the TIL's in zones with crush-artefacts?
Were the slides scored individually or by two pathologists together or independently?
In the case of full sections, how many slides did you asses per patient?
Did you assess interslide heterogeneity of TIL's in order to define the number of slides to read per patient?
Did you assess tertiary lymphoid structures (TLS)?
If yes, what were the criteria you used to define these TLS?
Did you assess the number of the TLS?
Did you asses the location within a tumor of these TLS?
How did you cope with heterogeneity of TIL-infiltration within a slide?
Did you limit yourself to lymphocytes and plasma cells or did you take other cells also into account, for example neutrophils?
Did you consider the stromal and the intra-tumoral (=within tumor nests) compartment as separate or together?
Did you take all TIL's into account or were the TIL's around 1. DCIS-, 2. normal ducts or 3. areas of necrosis not taken into account?
Could you detail the total number of patients analyzed, the BC subtype in which the TIL's were analyzed and whether treatment was received or not?
Could you detail whether the scoring was performed on core biopsies or full sections?
Could you detail whether and how reproducibility was assessed between the pathologists who scored the slides?
Did you perform a pilot-study in order to assess concordance between the pathologists on the to be used methodology before starting to read the slides for your study?
Could you detail what level of concordance between the pathologists was considered as being acceptable?
Which error margin between 2 pathologists was considered as acceptable? Please include the reasons hereof.
Could you detail how you determined the cut-off for a lymphocyte predominant subtype?
Was this predefined? If yes, explain how.

Was this lymphocyte predominant cut-off different according to subtype?
Do you use the same lymphocyte predominant cut-off for both cores and full sections?
Did you use alternative methods for assessing TIL's, like digital imaging purposes or immunohistochemistry? If IHC was used, please state the epitopes you have stained.
Any idea whether pre-analytical variables, for example fixation time affects the TIL-evaluation? Is this important to know?
How would you suggest validating a morphological biomarker?
Is performing a RING-study useful to assess interlaboratory-concordance?
If yes, how would you suggest organizing this?
What are your thoughts on performing a meta-analysis of all studies done so far, both in the neoadjuvant as in the adjuvant setting?

S2 Supplementary table 2 Open questions in the assessment of Tumor Infiltrating Lymphocytes (TILs)

- Which is the exact margin of the tumor border, the desmoplastic reaction or the tumor cell infiltrates? (Supplementary Figure 1)
- Should the lymphocytes in normal lobules and around DCIS-foci located in between invasive tumor nests be taken into account?
- Can tertiary lymphoid structures (TLS) be characterized merely based on morphology?
- Should TLS be taken into account outside the defined tumor border? Do they reflect a specific type of tumor-immune interaction?
- When there is a gradient between regions with high TILs trailing off into a region of lower TILs, how can this regional heterogeneity best be assessed?
- Can the methodology used for TIL-assessment in primary tumors also be used for metastatic lesions?

Standardized evaluation of Tumor-Infiltating Lymphocytes (TILs) in Breast Cancer for daily clinical and research practice or clinical trial setting

A tutorial prepared by the International Working Group for TILs in Breast Cancer - 2014

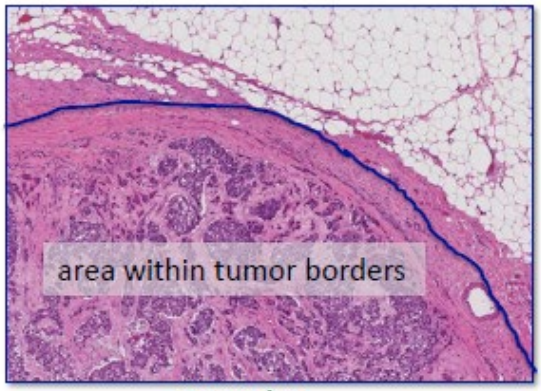
Carsten Denkert
Roberto Salgado
Sandra Demaria

Aim of this tutorial

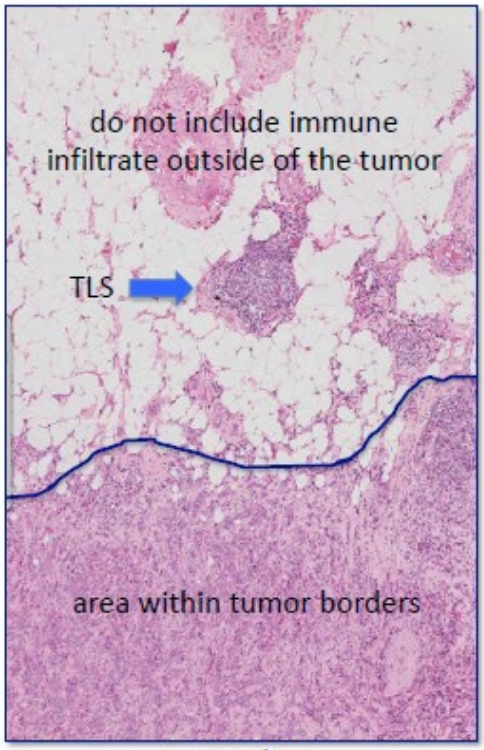
- To provide a guideline to pathologists for the standardized evaluation of tumor-infiltrating lymphocytes based on H&E slides of core biopsies or tumor resections.
- Please consult the manuscript for more specific details.

Step 1: Define area for TILs evaluation

- Only TILs within the borders of the invasive tumors are evaluated
- The invasive edge is included in the evaluation, but not reported separately
- Immune infiltrates outside of the tumor borders, e.g. in adjacent normal tissue or DCIS are not included



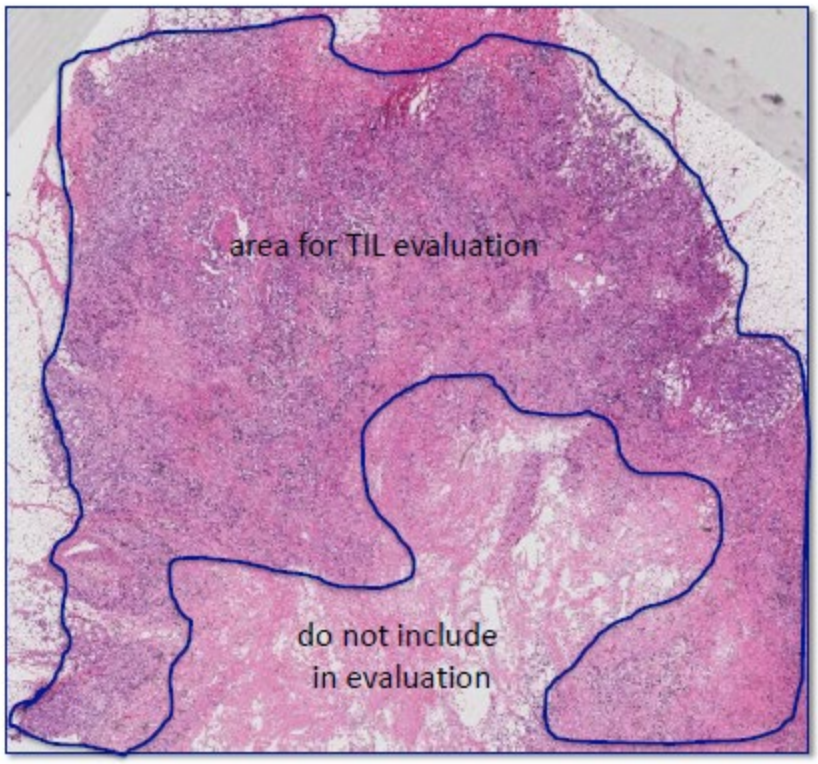
Example 1



Example 2

Step 1: Define area for TILs evaluation

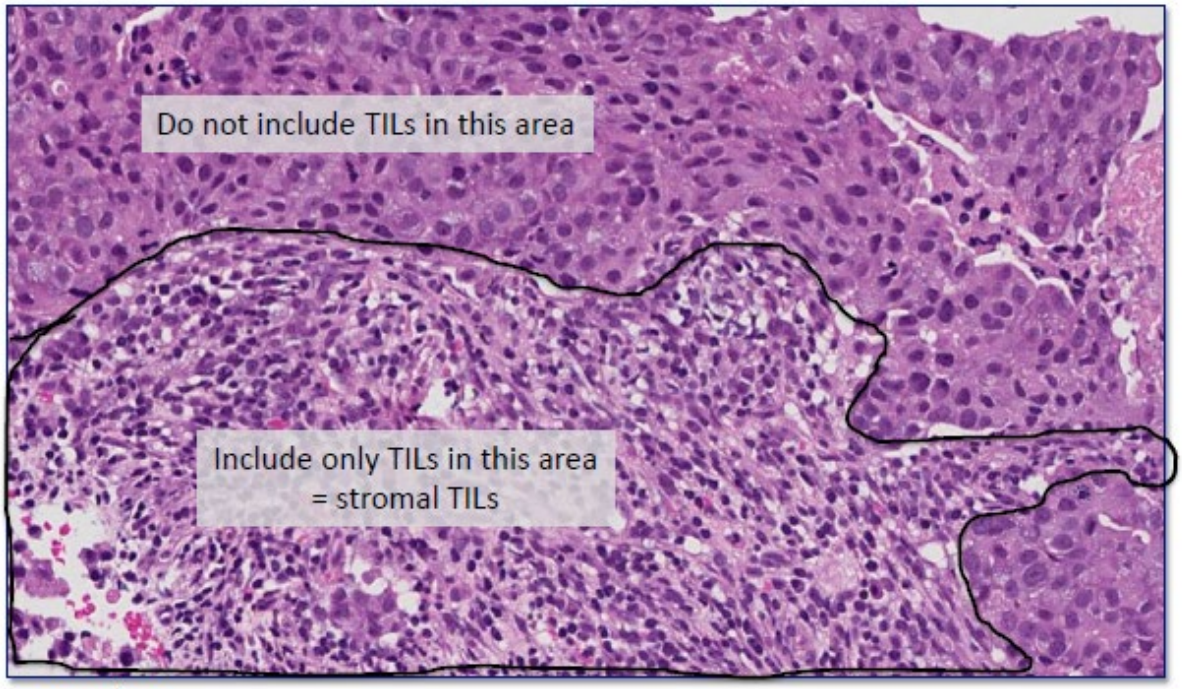
- Large areas of central necrosis or fibrosis are not included in the evaluation



Example 3

Step 2: Focus on stromal TILs

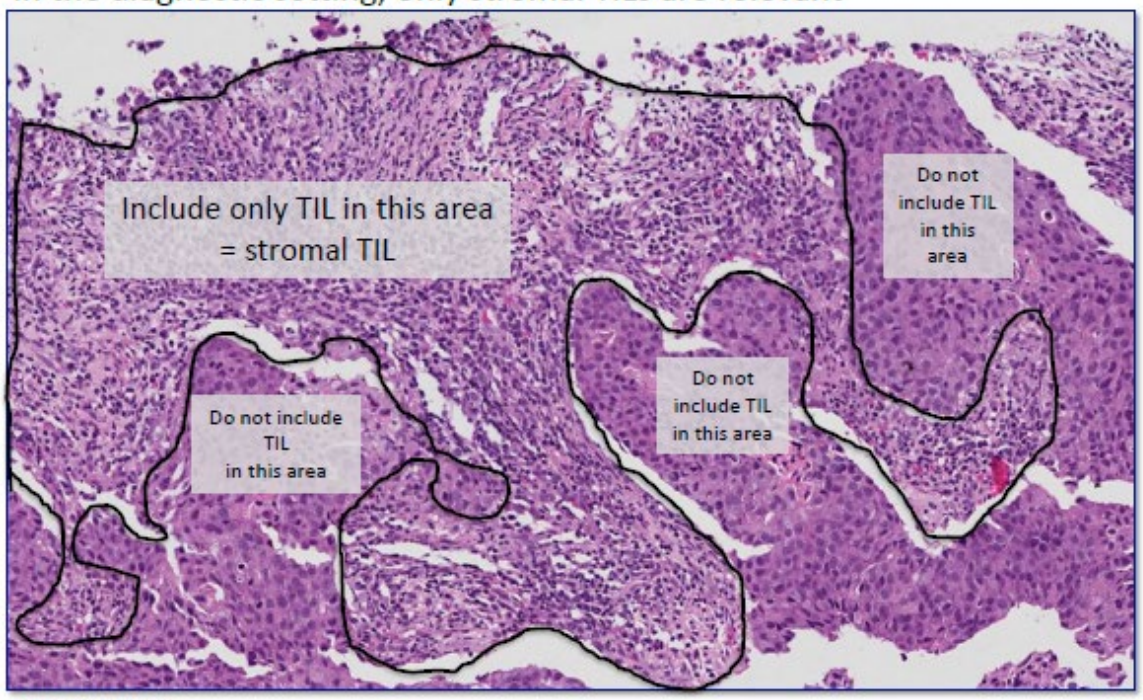
- In the diagnostic setting, only stromal TILs are relevant



Example 4

Step 2: Focus on stromal TILs

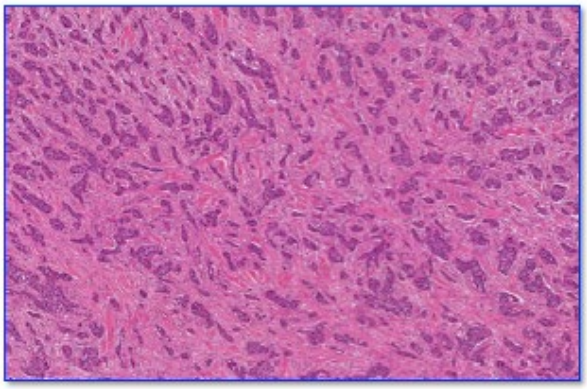
- in the diagnostic setting, only stromal TILs are relevant



Example 5

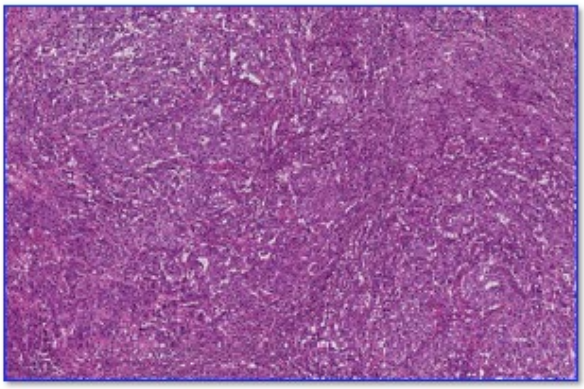
Step 2: Scan tumor at low magnification – focus on the tumor stroma

- Stroma contains predominantly collagenous tissue, few round cells



Example 6

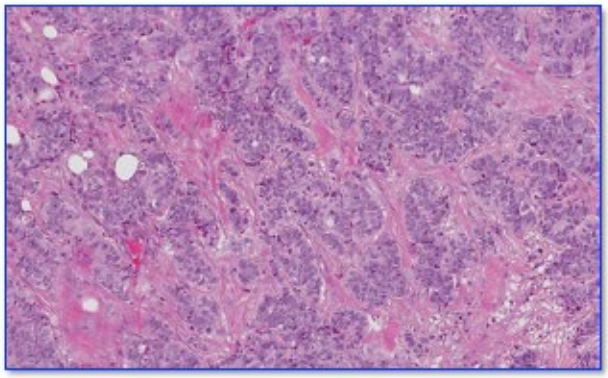
- Stroma contains predominantly round cell infiltrate, collagenous tissue difficult to recognize



Example 6

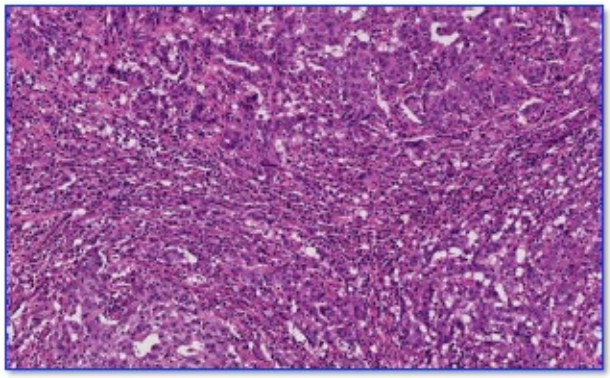
Step 2: Scan tumor at low magnification – focus on the tumor stroma

- Stroma contains predominantly collagenous tissue, few round cells



Example 8

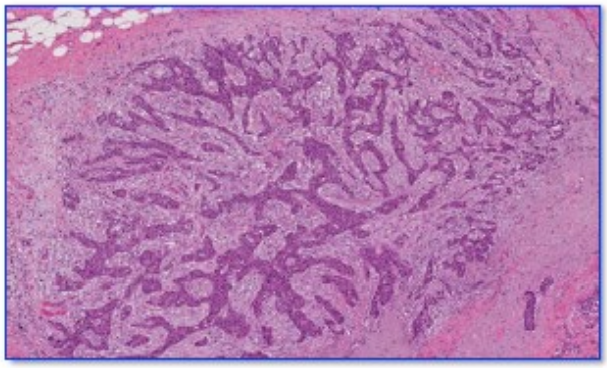
- Stroma contains predominantly round cell infiltrate, collagenous tissue difficult to recognize



Example 9

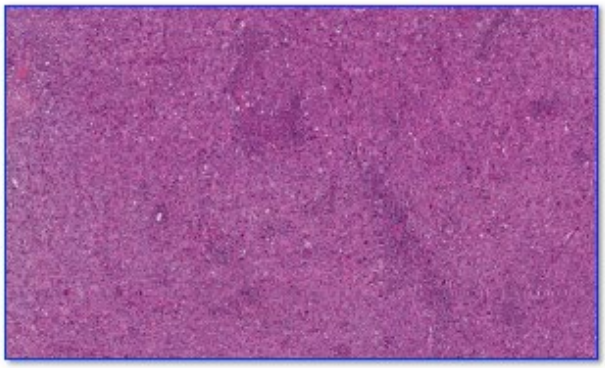
Step 2: Scan tumor at low magnification – focus on the tumor stroma

- Stroma contains predominantly collagenous tissue, few round cells



Example 10

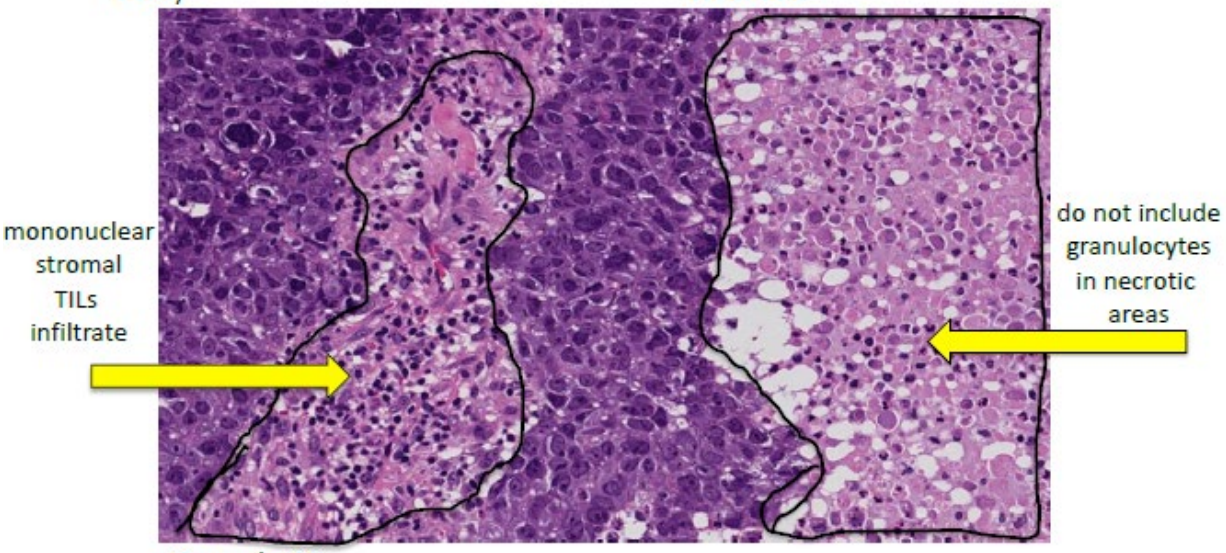
- Stroma contains predominantly round cell infiltrate, collagenous tissue difficult to recognize



Example 11

Step 3: Determine type of inflammatory infiltrate

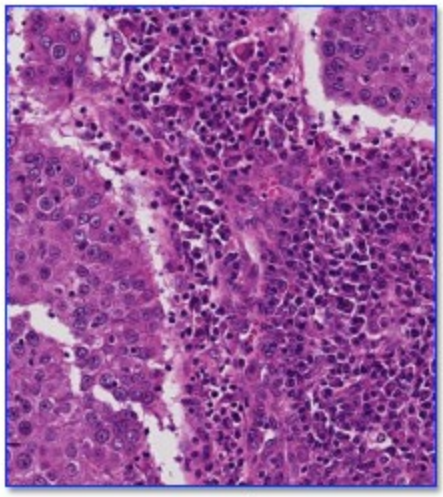
- Include only mononuclear infiltrate (lymphocytes & plasma cells)
- Do not include granulocytic infiltrate in areas of tumor necrosis



Example 12

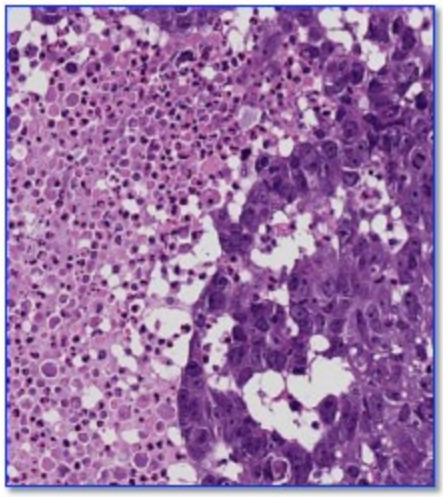
Step 3: Determine type of inflammatory infiltrate

- Include only mononuclear infiltrate (lymphocytes & plasma cells)



Example 13

- do not include granulocytic infiltrate in areas of tumor necrosis



Example 14

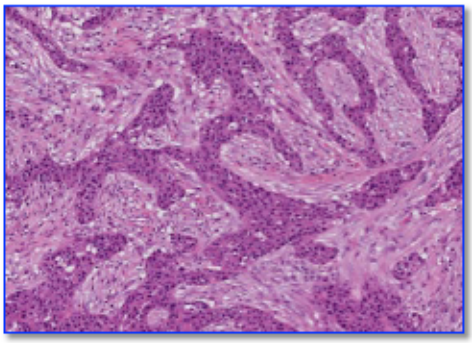
Step 4: As a first approach, include tumor in one of three groups based on low magnification and assess % stromal TILs (continue with Step 5 for percentage)

Group A: tumor with no/minimal immune cells

Group B: tumor with intermediate / heterogeneous infiltrate

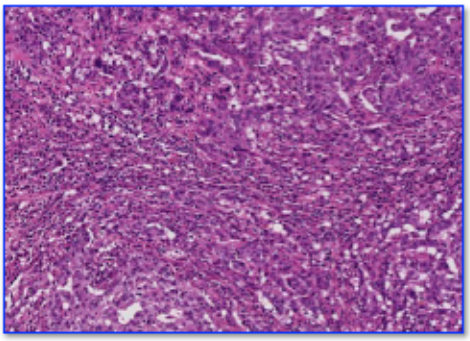
Group C: tumor with high immune infiltrate

0-10% stromal TILs | 10-40% stromal TILs | 40-90% stromal TILs



Example 15

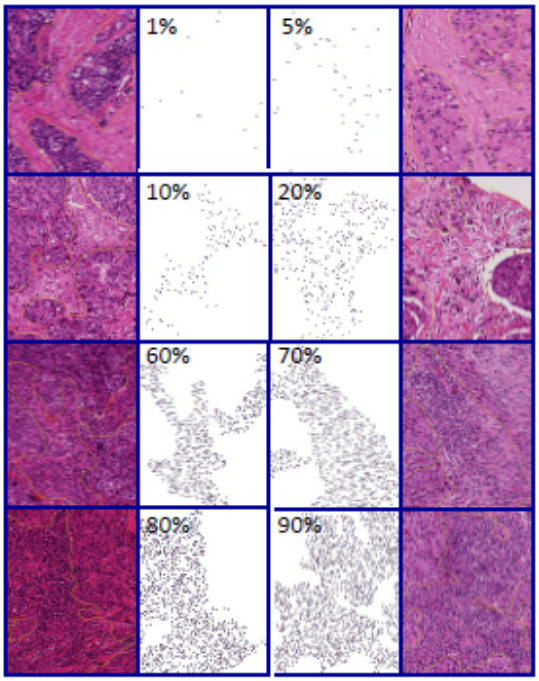
For this intermediate group evaluate different areas at higher magnification.



Example 16

The denominator used to determine the % stromal TILs is the area of stromal tissue (i.e. area occupied by mononuclear inflammatory cells over total intratumoral stromal area), not the number of stromal cells (i.e. fraction of total stromal nuclei that represent mononuclear inflammatory cell nuclei)

Step 5: Report percentage of stromal lymphocytes



- Report the average of the stromal area, do not focus on hot spots.
- For intermediate group evaluate different areas at higher magnification.
- Please note that lymphocytes to not form solid aggregates, therefore even with 90-100% stromal TILs there will still be some space between the individual lymphocytes.

Please send any questions or comments to:

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APPENDIX IX: A011801 SUPPORTIVE CARE

A011801 Supportive Care: Management of Treatment-Related Toxicities (Including G1 and G2)

Introduction:
The purpose of this document is to summarize potential strategies which can be used to mitigate treatment-related toxicities on A011801, including low-grade toxicities. This document is a guide only, as ultimately recommendations for supportive care will be per protocol guidelines and based on clinical evaluation and decision making as per the treating team. Importantly, these guidelines do not supersede the recommendations provided in the dose modification section of the protocol and the clinical judgment of the treating provider.

NCI CTCAE Version 5.0:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

1. Diarrhea

(See link at top of document for NCI CTCAE grading)

Uncomplicated Diarrhea: Patients with mild to moderate (grade 1 or 2) diarrhea and no moderate to severe abdominal cramping, grade 2 or worse nausea/vomiting, decreased performance status, fever, frank bleeding, or suspected dehydration. These patients can initially be managed conservatively at home.

Complicated Diarrhea: Patients who present with grade 3 or 4 diarrhea, and those with grade 1 or 2 diarrhea associated with moderate to severe abdominal cramping, grade 2 or worse nausea/vomiting, declining performance status, fever, sepsis, neutropenia, frank bleeding, or dehydration are classified. These patients often require hospitalization for supportive care.

Uncomplicated (G1 and G2) Diarrhea Management:

- Eat regular small meals (bananas, plain pasta, rice, applesauce, toast)
- Avoid lactose based products, alcohol, caffeine and high osmolar supplements
- Drink 8-10 large glasses of clear fluids daily (broths, Gatorade)
- Stop laxatives, stool softeners, medications and supplements which may cause diarrhea
- Commence oral loperamide (initial dose of 4 mg, followed by 2 mg every 4 hours after each loose bowel motion)
- Ensure patient records output from stool/stoma and monitor for symptoms of complicated diarrhea

Diarrhea resolving/resolved

- Deescalate loperamide dose to 4 mg every 4 hours until diarrhea free for 12 hours

- Gradually add solid foods to diet
- Consider chemotherapy dose reduction

Risk factors for complicated diarrhea:

- Abdominal cramping
- Nausea/vomiting grade 2 or worse
- Deteriorating performance status
- Fever
- Sepsis
- Neutropenia
- Grossly bloody stool
- Dehydration
- Chest pain
- Prior admission for chemotherapy-related diarrhea

If grade 1 or grade 2 diarrhea persist after 12-24 hours, and no risk factors for complicated diarrhea:

- Evaluate patient in person, check vital signs, perform abdominal examination, assess hydration status
- Stool workup to out rule infection
- CBC and electrolytes
- Fluid and electrolyte repletion as needed
- Commence second-line antidiarrheal agent (octreotide 100-150 mcg 3 times daily subcutaneously, or diphenoxylate atropine or deodorized tincture of opium)

If progression to severe diarrhea (NCI CTCAE grade 3 or 4 or persistent grade 1 or 2 diarrhea with added risk factors for complicated diarrhea), proceed as follows:

UpToDate Link: https://www.uptodate.com/contents/management-of-acute-chemotherapy-related-diarrhea#:~:text=Loperamide%20is%20the%20preferred%20approach,stool%2C%20maximum%2016%20mg%20daily

Patient Information Link: https://www.cancer.gov/about-cancer/treatment/side-effects/diarrhea

Note: If low-grade symptoms persist and/or worsen, consider dose reduction(s) as per protocol Section 8.2. Also consider further medical evaluations and interventions based on patient's medical history and clinical presentation.

2. Fatigue

(See link at top of document for NCI CTCAE grading)

Fatigue Management

- Rule out and address other medical causes of fatigue (anemia, hypothyroidism, sleep disorder, etc.)
- Manage contributing symptoms (nausea, disordered sleep, pain, depression, anxiety and anorexia)
- Structured support groups, individual counseling for stress management, anxiety and depression
- Regular exercise: 150 minutes of moderate aerobic exercise (cycling, swimming, fast walking) with additional 2-3 strength training (weight lifting) sessions weekly
- Use local resources to enable patients to increase exercise
- Refer to physical therapy or an exercise specialist for patients at increased risk of injury (e.g., patients who have neuropathy, cardiomyopathy, or lymphedema).
- Behavioral interventions, i.e. cognitive behavioral therapy, psychoeducational therapy, and nutritional consultation.
- Sleep hygiene (insomnia)
- Mindfulness based approaches and meditation, gentle yoga, Tai Chi/qigong, acupuncture
- Bio field therapies (touch therapy, reiki)
- Mind body practices (massage therapy, music therapy, relaxation)
- Consider psychostimulants only after excluding other causes of fatigue and if other interventions have been unsuccessful
- Encourage short planned rest breaks and prioritization of activities that are most important to the patient.

UpToDate Link: https://www.uptodate.com/contents/cancer-related-fatigue-treatment?search=management%20of%20cancer%20related%20fatigue&sectionRank=2&usage_type=default&anchor=H19&source=machineLearning&selectedTitle=1~34&display_rank=1#H74068150

Patient Information Link: cancer.net/navigating-cancer-care/videos/side-effects/coping-with-cancer-related-fatigue

Note: If low grade symptoms persist and/or worsen, consider dose reduction(s) as per protocol Section 8.2. Also consider further medical evaluations and interventions based on patient's medical history and clinical presentation.

3. Peripheral Neuropathy

(See link at top of document for NCI CTCAE grading)

Neuropathy Management

Strongest Evidence

- Physical therapy and rehabilitation
- Pharmacotherapy: duloxetine (30 mg daily for one week, then 60 mg daily)
- Adjustments to drug dose, administration, or regimen (more severe symptoms)

Strategies with weaker evidence, possibly helpful and have limited harms

- Exercise (muscle-strengthening and balancing exercise program)
- Acupuncture
- Acupressure and reflexology
- Scrambler therapy (device that delivers patient-specific electrocutaneous stimulation to the skin)

Other (Investigational Only, *not recommended per current guidelines*)

- Tricyclic antidepressants (nortriptyline and amitriptyline)
- Oral mucosal cannabinoid extract
- Gabapentinoids (gabapentin or pregabalin)
- Glutamine
- Topical treatments containing amitriptyline and ketamine with and without baclofen
- Topical menthol
- Topical capsaicin
- Neurofeedback

UpToDate Link: https://www.uptodate.com/contents/prevention-and-treatment-of-chemotherapy-induced-peripheral-neuropathy

Patient Information Link: https://www.mdanderson.org/patients-family/diagnosis-treatment/emotional-physical-effects/peripheral-neuropathy.html#:~:text=Chemotherapy%3A%20Chemotherapy%20can%20also%20cause,cause%20damage%20to%20nearby%20nerves

Note: If low grade symptoms persist and/or worsen, consider dose reduction(s) as per protocol Section 8.2. Also consider further medical evaluations and interventions based on patient's medical history and clinical presentation.

4. Nausea and Vomiting

(See link at top of document for NCI CTCAE grading)

Nausea Management

- Encourage adequate hydration and prophylactic antinausea medications (even if asymptomatic)

- Eat 5 or 6 small meals a day instead of 3 larger ones, especially if nauseated.
- Some patients benefit from eating or drinking a small amount before treatment. Others feel better if they do not have any food or drink before treatment.
- When nauseated, avoid foods that are spicy, greasy, or "heavy." Good alternatives are bland foods (crackers, rice, toast, soup broths, clear soda, tea, bananas, chicken (broiled or baked), oatmeal, yogurt, plain pasta, and ice pops.
- Eat and drink slowly
- Avoid triggers (cooking)
- Ginger ale or over-the-counter ginger supplements
- Consider acupuncture

Pharmacotherapy

- Per Beacon plan for T-DM1+ tucatinib/placebo: premedications (standard: ativan 0.5 mg, Aloxi0.25mg IV and Pepcid 20mg IV all once pretreatment). Consider adjusting as needed.
- PRN medications (depending on individual patient factors, such as long QTc): compazine 10mg every 6 hours as needed (1st line); ondansetron 8mg every 8 hours as needed (2nd line)

Management of Anticipatory Nausea and Vomiting

- Muscle relaxation with guided imagery
- Hypnosis
- Behavior changing methods
- Biofeedback
- Distraction (such as watching a TV show)

UpToDate Link: https://www.uptodate.com/contents/prevention-of-chemotherapy-induced-nausea-and-vomiting-in-adults
Patient Information Link: https://www.cancer.gov/about-cancer/treatment/side-effects/nausea/nausea-pdq

Note: If low grade symptoms persist and/or worsen, consider dose reduction(s) as per protocol Section 8.2. Also consider further medical evaluations and interventions based on patient's medical history and clinical presentation.

5. Headache

(See link at top of document for NCI CTCAE grading)

Headache Management

General: Treat any underlying or potential causes based on medical history and physical examination.

Supportive Care:

- Ensure adequate rest
- Stress reducing activities
- Hydration
- Eating well
- Avoiding/reducing caffeine intake

Complementary Therapy

- Massage
- Visual imagery
- Relaxation
- Acupuncture

Medications (Prevention, treatment and alleviation of symptoms)

- Over the counter pain relievers such as ibuprofen (Advil, Motrin) and acetaminophen (Tylenol)
- Prescription analgesia (codeine-based)
- Tricyclic antidepressants
- Triptan medications such as sumatriptan (Alsuma, Imitrex, Zecurity)

Patient Information Links:

- https://www.cancercenter.com/integrative-care/headaches
- https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/headaches

Note: If low grade symptoms persist and/or worsen, consider dose reduction(s) as per protocol Section 8.2. Also consider further medical evaluations and interventions based on patient's medical history and clinical presentation.

6. Epistaxis

(See link at top of document for NCI CTCAE grading)

Patient information (Includes guidelines for patients experiencing active bleeds and when to seek medical assistance):
https://chemocare.com/chemotherapy/side-effects/nosebleeds.aspx

Epistaxis (mild)

- Nasal sprays (Normal saline spray, ocean spray)
- Antiseptic and barrier ointments

- Advise patients to avoid digital trauma
- Tylenol per label (if pain at site)
- Review patient medication list (aspirin or aspirin containing products, herbal remedies, OTC remedies, vitamins)

Note: If low grade symptoms persist and/or worsen, consider dose reduction(s) as per protocol Section 8.2. Also consider further medical evaluations and interventions based on patient's medical history and clinical presentation.

7. Radiation Dermatitis (Breast and regional lymph nodes)
(See link at top of document for NCI CTCAE grading)

Radiation Dermatitis: General Principles of Care

- Protect skin in the treatment field from irradiation and friction during radiotherapy, and for two to four weeks after the conclusion of same
- Keep the irradiated area clean and dry
- Wash the area with tepid water and mild soap (liquid, fragrance-free, body washes with a near-physiologic pH of 4 to 6 optimal. Examples: Neutrogena®, Dove®, baby soap, Basis®, or Cetaphil®)
- Apply unscented, lanolin-free, water-based moisturizers two to three times every day
- Avoid perfumes and alcohol-based lotions
- Wear loose-fitting clothes to avoid friction
- Avoid applying corn starch or baby powder in skin folds
- Avoid exposure to sunlight
- Avoid wet shaving within the treatment area; an electric razor may be used
- Remind patients to gently clean and dry the skin in the radiation field prior to each therapy session

Radiation Dermatitis Management (Preventative and Grade 1 Dermatitis)

- Prophylactic topical corticosteroids
- Skin care (cleansing and moisturizing with hydrophilic [oil-in-water] moisturizers)
- Low- to medium-potency topical corticosteroids: apply to radiation field once to twice daily during treatment (Low potency examples: Dexamethasone sodium phosphate cream (0.1%); Hydrocortisone acetate cream [1%], Methylprednisolone acetate cream [0.25%]; Moderate potency examples: Triamcinolone acetonide cream [0.1%], Hydrocortisone butyrate cream [0.1%])

Radiation Dermatitis Management (Grade 2 and 3 Dermatitis)

- Soft, absorbent, silicone foam bandages
- Topical and/or systemic antibiotics if associated bacterial superinfection

UpToDate Link: https://www.uptodate.com/contents/radiation-dermatitis#H1388050

Patient Information Link: https://www.mskcc.org/cancer-care/patient-education/skin-care-guidelines-patients-receiving-radiation-therapy

Note: If low grade symptoms persist and/or worsen, consider dose reduction(s) as per protocol Section 8.2. Also consider further medical evaluations and interventions based on patient's medical history and clinical presentation.

8. Non-radiation-induced skin toxicities

General Skin Care

- Use a thick, alcohol-free emollient lotion or cream at least twice a day, including immediately after bathing.
- Avoid sun exposure. Use a sunscreen with an SPF of 30 or higher and also wear a hat and sunglasses.
- Bathe/shower in cool or tepid water and pat skin dry.
- Avoid soaps, lotions, and laundry detergents with alcohol, perfumes, or dyes.
- Wear gloves to do housework or gardening.
- Keep hydrated and try not to scratch or rub skin.

Papulopustular eruption:

- Preventative: low-potency topical steroids (class VII) and sunscreen; consider prophylactic systemic antibiotics (tetracyclines)
- Treatment: low-potency topical steroids (class VI/VII); clindamycin 1% topical; systemic antibiotics (tetracyclines); Isotretinoin (20-30 mg/day)

Xerosis/Fissures: Bland emollient creams and keratolytics: urea, salicylic acid, lactic acid, and zinc oxide; Medium- to high-potency topical steroids (class II-IV); liquid glues or cyanoacrylate

Photosensitivity: Sun precautions, i.e. photoprotective clothing and the use of broad-spectrum sunscreens

Edema: Low sodium diet (2 g/day); consider diuretics if severe

Morbilliform eruption: Topical steroids (class III/IV) or brief course of oral steroids; hold treatment if grade III/IV

Pigmentary changes: Usually reversible with dose reduction/treatment cessation

Note: If low grade symptoms persist and/or worsen, consider dose reduction(s) as per protocol Section 8.2. Also consider dermatology evaluation and further medical evaluations and interventions based on patient's medical history and clinical presentation.

APPENDIX X: TRIAL PARTICIPANT THANK YOU LETTER

Trial Participant Thank You Letter

We ask that the physician use the template to prepare a letter thanking the participant for enrolling in this Alliance trial. The template is intended as a guide and can be downloaded from the study page on the Alliance website at www.AllianceNCTN.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 Alliance 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.

Sample Template

[PARTICIPANT NAME] [DATE] [PARTICIPANT ADDRESS]

Dear [PARTICIPANT SALUTATION],

Thank you for agreeing to take part in this important research study. With the help of people like you who participate in clinical trials, we will achieve our goal of effectively treating and ultimately curing cancer.

There are many reasons why individuals choose to participate in a clinical trial. Sometimes it is because they want access to a specific medication or because they want to do whatever they can to help someone else with cancer. Whatever your reason for participating, you are making a contribution towards finding better treatments and ultimately eliminating this disease for future patients.

You will receive high quality care while participating in this clinical trial. My research staff and I 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 participants.

On behalf of [INSTITUTION] and the Alliance for Clinical Trials in Oncology, we thank you again for your participation in this clinical trial and look forward to partnering with you.

Sincerely, [PHYSICIAN NAME]