Response to CTEP Approval Letter with Recommendations from Review of Amendment #10 of Protocol #NRG-BR004 (NRG Oncology Amendment #6) dated 8/5/2022

I. Recommendations:

#	Section	Comments
1.	Cover Page Study Data Submission	*Please delete the highlighted language below:* Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions. ~~Do **not** submit study data or forms to the CTSU. Do **not** copy the CTSU on data submissions.~~ **PI Response: The change was made as requested.**
2.	8.2.1 IRB Approval	*Please revise the following, as indicated:* 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). **PI Response: The change was made as requested.**
3.	8.2.1 IRB Approval	*It is indicated that this study is open to international sites. Therefore, please include the following language in this section:* 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. **PI Response: The change was made as requested.**
4.	8.2.4 Downloading Site Registration Documents	*Please revise the following language:* Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download stie registration forms:

#	Section	Comments
		Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password; Click on *Protocols* in the upper left of the screen Enter the protocol number in the search field at the top of the protocol tree, or Click on the By Lead Organization folder to expand, then select *NRG* ~~Oncology~~, and protocol number (*NRG-BR004*); Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.) **PI Response: The change was made as requested.**
5.	8.2.6 Delegation of Tasks Log	*Please revise the following language:* 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. **PI Response: The change was made as requested.**
6.	13.4 Data Quality Portal	Please delete the following highlighted text in this section: 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, and forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms. The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP. To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Forms Status, and DQP Reports modules. ~~Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.~~ **PI Response: The change was made as requested.**

II. Company Comments – Recommendations (no response required):

#	Section	Comments
7.	14.8.3.3	Minor suggestions: Type I error rate of 0.05 "(2-sided)". The last sentence: 43% at the primary analysis. What does it mean? **PI Response: The type 1 error rate of 0.05 was clarified to indicate that it is a two-sided test. Under the original design, we would have 80% power to detect a PFS HR=0.733. Under the amended design, we would have 80% power to detect a PFS HR=0.6. In this statement: "The chance to detect a PFS hazard ratio at 0.733, as originally designed, would be about 43% at the primary analysis," we basically stated that the power to detect a PFS HR=0.733 under the amended design would be about 43%.**

III. Additional Change

#	Section	Comments
8.	ICD	The date has been changed to match the most recent version of the protocol.

NRG ONCOLOGY
NRG-BR004
(ClinicalTrials.gov NCT03199885)

A Randomized, Double-Blind, Phase III Trial of Taxane/Trastuzumab/Pertuzumab with Atezolizumab or Placebo in First-Line HER2-Positive Metastatic Breast Cancer

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: Alliance for Clinical Trials in Oncology, Canadian Cancer Trials Group, ECOG-ACRIN Cancer Research Group, NRG Oncology, and SWOG.

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The following NCTN Group Study Champion have been added to this trial:

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SWOG	[redacted], MD Michigan Medicine Breast Oncology Clinic Rogel Cancer Center Ann Arbor, Michigan 48109 734-647-8902 [redacted]

Protocol Agents

NCI-Supplied Agents: Atezolizumab/Placebo (NSC 783608)
Trastuzumab (NSC 688097) – commercial agent supplied to U.S. sites only

Commercial Agents: Paclitaxel (NSC 673089)
Docetaxel (NSC 628503)
Pertuzumab (NSC 740102)

IND #: [redacted]
IND Sponsor: DCTD, NCI

Participating Sites
☒ U.S.
☒ Canada
☐ Approved International Member Sites

Document History

	Version/Date
Amendment 7	August 15, 2022
Amendment 6	July 14, 2022
Amendment 5	January 14, 2022
Amendment 4	June 28, 2021
Amendment 3	March 30, 2021
Amendment 2	March 9, 2020
Amendment 1	August 5, 2019
Pre-Activation Revision	February 14, 2019
Initial	October 11, 2018

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	For patient enrollments:	For study data submission:
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at 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) 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 Web page of the CTSU Members' website located at https://www.ctsu.org. Access to the CTSU Members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. 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 CTSU Regulatory Support System (RSS).		
For clinical questions (i.e., patient eligibility or treatment-related), contact the Clinical Coordinating Department at NRG Oncology at 1-800-477-7227 or by e-mail at ccdPGH@NRGOncology.org.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission), contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923 or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU website is located at https://www.ctsu.org.		

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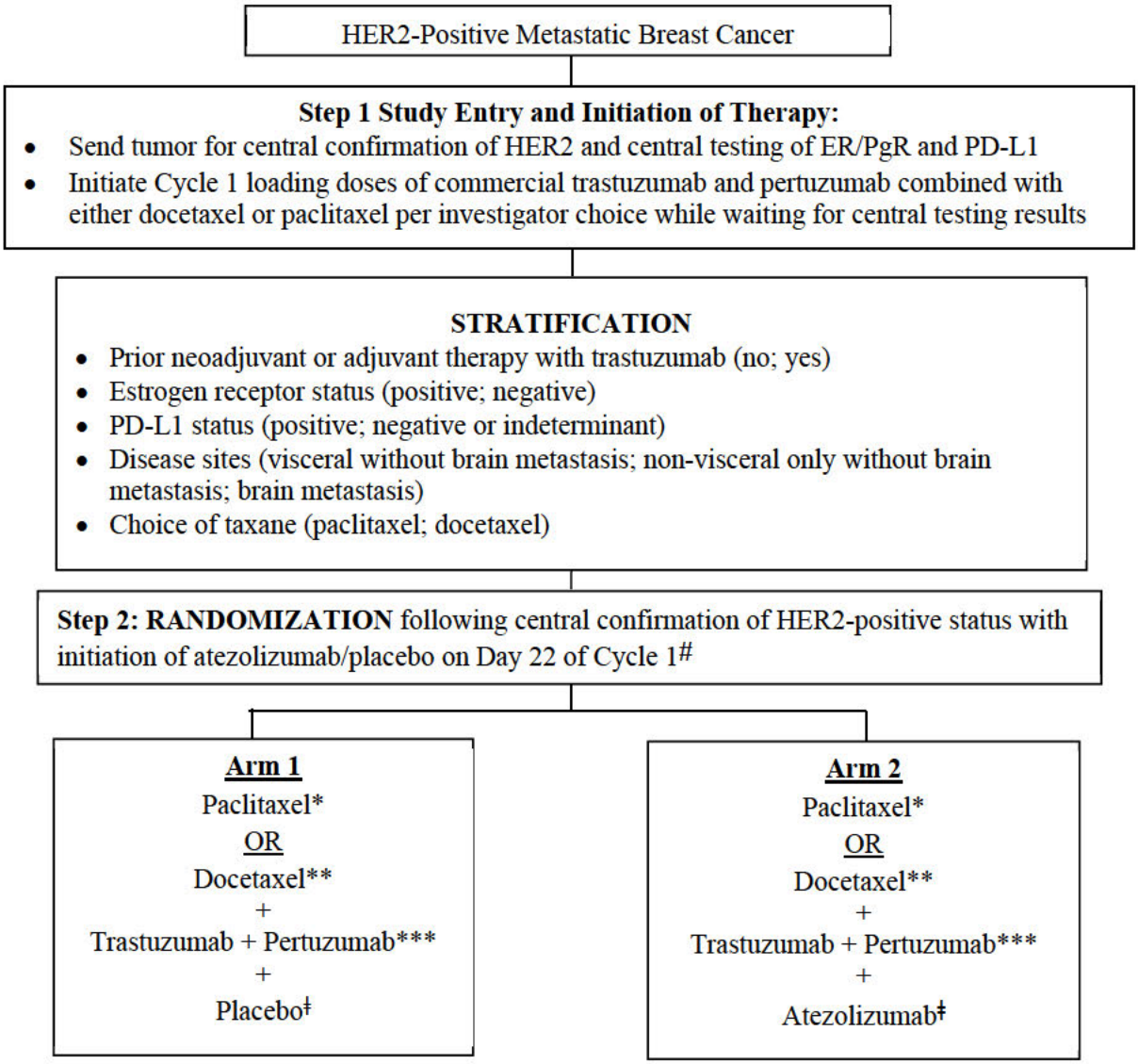
The NRG-BR004 study was permanently closed to accrual on May 20, 2022. Modified scheduled status updates, as outlined on Table 2A, will be completed for patients enrolled prior to study accrual closure.

Figure 1. NRG-BR004 SCHEMA



\# Randomization is 1:1.

* Paclitaxel: 80 mg/m^2 IV weekly on Days 1, 8, 15, 22, 29, and 36 of an every 6-week cycle for a minimum of 3 cycles with additional cycles at the investigator's discretion **OR**

** Docetaxel: 75 mg/m^2 IV on Days 1 and 22 of an every 6-week cycle for a minimum of 3 cycles with additional cycles at the investigator's discretion.

*** Trastuzumab + Pertuzumab: Trastuzumab 6 mg/kg IV with pertuzumab 420 mg IV Days 1 and 22 every 6 weeks until progression.

‡ Atezolizumab 1200 mg IV or placebo IV Days 1 and 22 every 6 weeks until progression or for 2 years.

1.0 OBJECTIVES

1.1 Primary Objective

To determine whether the addition of atezolizumab to a regimen of pertuzumab and trastuzumab combined with a taxane (paclitaxel or docetaxel) will improve the progression-free survival (PFS), assessed by investigator using RECIST 1.1 criteria, relative to the addition of a placebo to a regimen of pertuzumab and trastuzumab combined with a taxane (paclitaxel or docetaxel) in patients with newly documented HER2-positive measurable metastatic breast cancer.

1.2 Secondary Objectives

1.2.1 To determine whether the addition of atezolizumab to a regimen of pertuzumab and trastuzumab combined with a taxane (paclitaxel or docetaxel) will improve the overall survival (OS) relative to the addition of placebo to a regimen of pertuzumab and trastuzumab, combined with a taxane (paclitaxel or docetaxel).

1.2.2 To determine whether the addition of atezolizumab to a regimen of pertuzumab and trastuzumab combined with a taxane (paclitaxel or docetaxel) will improve the overall objective response (OR) in the cohort of patients randomized 6 months or more prior to study accrual closure assessed by investigator using RECIST 1.1 criteria, relative to the addition of placebo to a regimen of pertuzumab and trastuzumab combined with a taxane (paclitaxel or docetaxel).

1.2.3 To determine the immune-related toxicity profile of the two treatment regimens.

1.2.4 To determine the cardiac safety profile of the two treatment regimens.

1.3 Exploratory Objectives

1.3.1 To determine whether the addition of atezolizumab to a regimen of pertuzumab and trastuzumab combined with a taxane (paclitaxel or docetaxel) will decrease the incidence of subsequent brain metastases in patients without known brain metastases at study entry relative to the addition of placebo to a regimen of pertuzumab and trastuzumab combined with a taxane (paclitaxel or docetaxel).

1.3.2 To determine the utility of PD-L1 IHC staining as a predictive and prognostic biomarker associated with clinical response, as assessed by investigator using RECIST 1.1 criteria, to atezolizumab in combination with trastuzumab and pertuzumab combined with a taxane (paclitaxel or docetaxel).

1.3.3 To identify potential biomarkers that can predict benefit from the addition of atezolizumab in patients with newly documented HER2-positive measurable metastatic breast cancer treated with a regimen of pertuzumab and trastuzumab combined with a taxane (paclitaxel or docetaxel).

1.3.4 To explore the toxicity profile of the two treatment regimens using patient-reported symptomatic adverse events in addition to standard adverse event reports.

1.3.5 To determine the feasibility and added value of frequent assessment of toxicity using PRO-CTCAE with ePRO reporting**.**

1.3.6 To explore whether the addition of atezolizumab to a regimen of pertuzumab and trastuzumab combined with a taxane (paclitaxel or docetaxel) will contribute to increased patient-reported fatigue in comparison to the addition of placebo to a regimen of pertuzumab and trastuzumab combined with a taxane (paclitaxel or docetaxel).

2.0 BACKGROUND

2.1 Introduction

The Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study demonstrated substantial improvement in long-term outcomes with the addition of pertuzumab to trastuzumab and docetaxel as first-line treatment for patients with HER2-positive metastatic breast cancer (MBC). While median progression-free survival (PFS) was improved by 6 months and median overall survival (OS) by an impressive 16 months with the addition of pertuzumab, two-thirds of patients receiving the 3-drug combination had disease progression by 3 years, and one third had died by that time (Baselga 2012, Swain 2015). Over half of the patients receiving dual HER-targeted therapy had expired by 5 years with most deaths due to progressive breast cancer. Novel approaches for treatment continue to need to be explored for these patients.

One approach is to continue efforts to understand the multiple mechanisms of resistance to the disruption of oncogenic signaling pathways that evolve while patients are on prolonged therapy with trastuzumab and pertuzumab. Identification and understanding of these mechanisms may help develop additional therapies that can provide benefit for the subsets of patients with specific resistance mechanisms. However, this approach will require development of an array of agents to inhibit a variety of evolving resistance mechanisms and, ultimately, resistance to the additional therapies seems probable. If a promising alternative approach is available for study that offers potential for managing the problem of evolving resistance in an innovative manner, it should be aggressively pursued.

The mechanisms of action for the therapeutic HER2-targeted monoclonal antibodies in combination with chemotherapy are complex, but a rapidly evolving body of literature indicates an important component of the activity is mediated through the adaptive immune system initially by antibody-dependent cell-mediated cytotoxicity (ADCC) (Bianchini 2014). Cross-priming of antigen specific cytotoxic T-cells following ADCC also occurs, but the impact of T-cell activation may be abrogated by upregulation and interaction of normal checkpoint inhibitors of cytotoxic T-cell function such as programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1). Suppression of these inhibitors with monoclonal antibodies co-administered with dual HER2-targeted monoclonal antibodies and chemotherapy could improve the long-term efficacy of the therapy. The safety and activity of the PD-1 and PD-L1 inhibitors have been demonstrated in a wide range of cancers, and justify evaluation in patients with newly documented metastatic HER2-positive breast cancer, many of whom will have developed recurrent disease after receiving HER2-targeted monoclonal antibodies in the neoadjuvant and adjuvant settings. We propose a randomized Phase III clinical trial to evaluate the efficacy and the safety of the addition of the PD-L1 inhibitor, atezolizumab, to a regimen of paclitaxel, trastuzumab, and pertuzumab versus a regimen of paclitaxel, trastuzumab, and pertuzumab in HER2-positive MBC in the first-line setting.

The development of trastuzumab and the incorporation of the monoclonal antibody as the core therapy of HER2-positive MBC have been transformative (Slamon 2001). Binding of the antibody to the overexpressed HER2 receptors that occur as a result of amplification of the HER2 gene, substantially enhances the efficacy of numerous chemotherapeutic agents through inhibition of the aberrantly activated downstream pathways impacted by the HER family of receptors. These activated pathways drive the aggressive phenotype of HER2-positive breast cancer and promote resistance to chemotherapy and endocrine therapy. This landmark advancement in the treatment of this aggressive phenotype of breast cancer has been of even greater clinical relevance because of the remarkable safety profile of trastuzumab.

However, primary resistance to trastuzumab is present in an important minority of the HER2-positive cancers in these patients and the large majority eventually develop resistance to trastuzumab. Efforts to understand mechanisms of resistance to trastuzumab and identify therapies to address those mechanisms have met with some notable success. The co-administration of a second monoclonal antibody, pertuzumab, targeting the dimerization domain of the HER2 protein, with trastuzumab and docetaxel in the CLEOPATRA trial improved median PFS by 6 months and resulted in an unprecedented improvement in median OS of 16 months to almost 5 years (Baselga 2012, Swain 2015). Again, this substantive improvement in outcomes was achieved without the addition of substantial toxicities. However, these patients require prolonged administration of these therapies and, ultimately, the large majority still develop resistant disease and eventually succumb to their cancer. Efforts to understand the mechanism of resistance may identify additional therapies that can further prolong survival, but to date efforts to target key downstream proteins thought to play a role in resistance have not been very effective and have been associated with substantial additional toxicities (André 2015, Hurvitz 2015). Alternative strategies that cannot be overcome by the complex pathway resistance mechanisms need to be identified and aggressively evaluated.

Fortunately, the activity of trastuzumab and pertuzumab is not limited to the ability of the drugs to interrupt oncogenic signaling pathways. The antibodies were developed with functional Fc receptors to provide opportunity for development of adaptive immunity through ADCC. Following cell death through ADCC, presentation of tumor antigens and tumor antigens complexed with the antibodies to antigen processing cells can activate an adaptive immune response generating cytotoxic memory CD8+ T cells. Recognition of the increased activity of trastuzumab in the presence of CD8+ tumor infiltrating lymphocytes (TILs) supports active investigation of therapies that can enhance the adaptive immune response (Bianchini 2014). Preclinical studies have demonstrated the therapeutic effect of trastuzumab depends on both innate and adaptive immunity. An important new group of therapeutic agents are the checkpoint inhibitor monoclonal antibodies, particularly those that can abrogate the inhibitory signals of cancer cells through PD-L1 and PD-1 interactions with cytotoxic T cells in the tumor microenvironment. These new therapeutics have demonstrated remarkable activity and manageable toxicity in patients with melanoma, non-small cell lung, bladder, and head and neck cancer. Pilot studies in triple-negative breast cancer (TNBC) and colon cancer in patients with mismatch repair defects have demonstrated efficacy and a favorable toxicity profile (Nanda 2014, Emens 2015, Powles 2014, Le 2015). While only a minority of patients respond to monotherapy with these agents, responses are often prolonged. This data suggests that efforts to augment the immune-based components of trastuzumab therapy with these agents may be more productive than efforts to address the resistance mechanisms that evolve to overcome the interruption of oncogenic signaling.

Pertuzumab also promotes ADCC and may augment the ADCC of trastuzumab (El-Sahwi 2010). These two well-tolerated monoclonal antibodies initially interrupt oncogenic signaling in a majority of patients and provide for ongoing ADCC with potential development of adaptive immunity. An important minority of patients receiving HER2-targeted monoclonal antibody therapy and chemotherapy for first-line treatment of HER2-positive MBC continue to enjoy freedom from progression even after discontinuing the medications following years of therapy. One explanation could be that the adaptive immune response in some of these patients was sufficient to eradicate their metastatic disease. The failure of the adaptive immunity to eliminate the cancer in the large majority of patients could be explained in part by upregulation of PD-1 in the tumor microenvironment, as well as expression of PD-L1 in the cancer cells surviving the initial therapy. Inhibition of the local immunosuppressive effects of PD-L1 expression by co-administration of an anti-PD-1 monoclonal antibody may overcome a potential major mechanism

of resistance independent of signaling pathway resistant mechanisms. Demonstration of therapeutic synergy between the ADCC inducing monoclonal antibodies trastuzumab and pertuzumab, which target a cancer-specific antigen (HER2), and a PD-1 checkpoint inhibitor could represent another transformative change for patients with HER2-positive breast cancer. It could also have broad potential implications for the field of immuno-oncology.

2.2 HER2-Positive Metastatic Breast Cancer

Pertuzumab and trastuzumab bind to different HER2 epitopes and have complementary mechanisms of action. Combining them has been an effective therapeutic strategy for potent inhibition of HER2 signaling and stimulation of adaptive immunity through ADCC. The anti-tumor effects of the combination are greater than either agent alone in breast cancer cell lines and HER2-positive tumor models (Scheuer 2009, Nahta 2004, Lee-Hoeflich 2008, Arpino 2007).

The combination of pertuzumab and trastuzumab has demonstrated activity in patients with HER2-positive MBC (Baselga 2010, Baselga 2012, Portera 2008). A Phase II study of pertuzumab in combination with trastuzumab demonstrated an objective response rate (ORR) of 24.2% in patients with MBC progressing after prior trastuzumab therapy. The clinical benefit rate (CBR) was 50% and was well-tolerated (Baselga 2010).

The CLEOPATRA study evaluated docetaxel/trastuzumab (control group) compared to docetaxel/trastuzumab plus pertuzumab (pertuzumab group) as first-line treatment for patients with HER2-positive MBC (Baselga 2012). Women received the standard every-3-week dose of trastuzumab (loading dose of 8 mg/kg followed by 6 mg/kg) and pertuzumab (loading dose of 840 mg followed by 420 mg) until progression. Women also received docetaxel 75 mg/m^2 every 3 weeks; at the investigator's discretion, the dose could be increased to 100 mg/m^2. It was recommended that patients receive at least six cycles of chemotherapy. The primary endpoint, median PFS (independently assessed), was improved by 6.1 months from 12.4 months in the control group to 18.5 months in the pertuzumab group (HR 0.62; 95% CI 0.51-0.75; $p<0.001$). The ORR was 69.3% in the control group compared to 80.2% in the pertuzumab group (Baselga 2012).

The median OS was improved by a remarkable 15.7 months from 40.8 months in the control group to 56.5 months in the pertuzumab group (HR 0.68; 95% CI, 0.56-0.84; $p<0.001$). The estimated Kaplan-Meier overall survival rate at 3 years in the pertuzumab group was 68.2% (95% CI, 63.4-72.9) and 57.6% (95% CI, 52.4-62.7) at 4 years (Swain 2015). The incidences of the following adverse events (any grade) were at least 5% higher in the pertuzumab group compared to the control group: diarrhea (68.4% vs. 48.7%), rash (37.5% vs. 24%), mucosal inflammation (27.2% vs. 19.9%), headache (25.7% vs. 19.2%), upper respiratory infection (20.8% vs. 14.4%), febrile neutropenia (13.7% vs. 7.6%), dry skin (11.3% vs. 6.1%), and muscle spasms (10.3% vs. 5.1%). However, the adverse events were mostly grade 1 or 2. The incidences of grade 3 or higher diarrhea and febrile neutropenia were only slightly increased in the pertuzumab group compared to the control group, respectively (9.3% vs. 5.1% and 13.7% vs. 7.6%) (Swain 2015). The pertuzumab regimen did not increase the rate of cardiac dysfunction, and in fact, left ventricular systolic dysfunction (any grade) was reported less frequently in the pertuzumab group compared to the control group (6.6% vs. 8.6%) (Swain 2015).

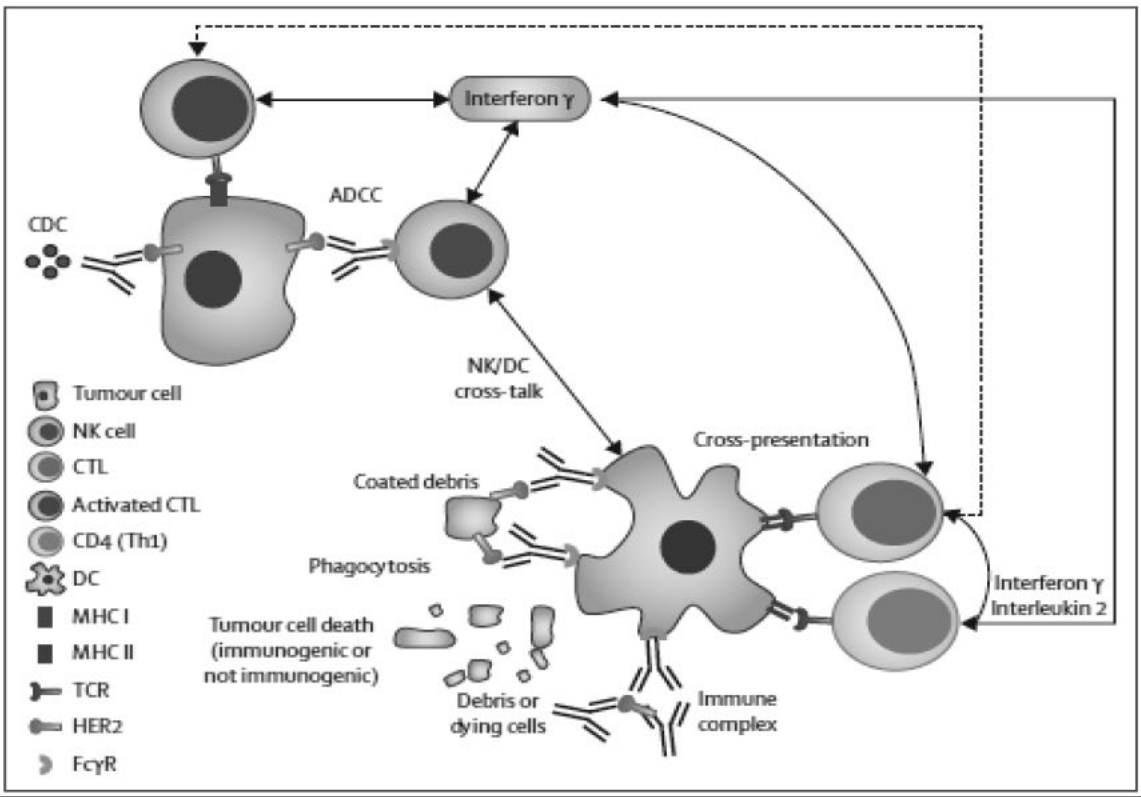
A Phase II study evaluated the efficacy and safety of weekly paclitaxel with trastuzumab and pertuzumab in patients treated in the first- or second-line metastatic setting. The median PFS for the entire study cohort was 19.5 months (95% CI, 14-26 months). The PFS was 24.2 months (95% CI, 14 months-not reached) for those without prior treatment and 16.4 months (95% CI, 8.5 months-not reached) for those with prior treatment. Grade 3/4 adverse events included fatigue (6%), diarrhea (3%), sensory neuropathy (3%), palmar-plantar erythrodysesthesia (3%),

elevation in AST (3%), elevation in ALT (3%), nausea (1.5%), and dry skin (1.5%) (Dang 2015). At least one episode of Grade 2 diarrhea occurred in 22% of patients, and 87% had at least one episode of Grade 1 diarrhea (Dang 2017). Overall, the treatment regimen was effective, well-tolerated, and was associated with substantially lower rates of problematic diarrhea than docetaxel-based therapy. This regimen will thus be utilized in this trial that is evaluating the incorporation of Atezolizumab which is also associated with potential for treatment-related diarrhea. Taxane-based chemotherapy with pertuzumab and trastuzumab is considered to be standard of care in first-line HER2-positive MBC (NCCN 2015).

2.3 Immune System and HER2-Targeted Treatment in Breast Cancer

Preclinical and clinical evidence demonstrate the immune system contributes substantially to the treatment effects of trastuzumab. A recent review of the immune response to HER2-targeted therapy by Bianchini and Gianni provides a schematic overview of the key mechanisms involved (see Figure 2).

Figure 2. Key mechanisms of involvement of the immune system in response to trastuzumab and other HER2-targeted monoclonal antibodies



ADCC=antibody-dependent cell-mediated cytotoxicity. CDC=compliment-dependent cytotoxicity. CTL=cytotoxic T lymphocyte. DC=dendritic cell. FcγR=Fcγ receptor. NK=natural killer. TCR=T-cell receptor. Th1=T helper 1 cell.

Bianchini G and Gianni L. Lancet Oncol 2014;15:e58-68

Trastuzumab and pertuzumab were designed to induce immune-mediated effects through activation of antibody binding Fc receptors (FcR) on dendritic cells and natural killer (NK) cells. Activation of the FcR on NK cells induces ADCC (Barok 2007, Gennari 2004, Varchetta 2007).

Preclinical and clinical studies have demonstrated that ADCC is one of the mechanisms underlying the clinical efficacy of trastuzumab (Barok 2007, Kute 2009, Gennari 2004). The JIMT-1 HER2-positive human breast cancer cell line is intrinsically resistant to trastuzumab in vitro. However, trastuzumab caused significant growth inhibition of JIMT-1 cells in an immunocompetent xenograft model. Trastuzumab-F(ab')$_2$ which does not contain the Fc portion of trastuzumab IgG was not an effective treatment in this model, indicating the activity occurred through FcR activated ADCC (Barok 2007).

A pilot study of neoadjuvant trastuzumab showed a correlation between response to trastuzumab and ADCC activity of peripheral blood leukocytes. Treatment with trastuzumab has also been shown to increase NK cell activity and response correlates with the intensity of ADCC (Gennari 2004, Varchetta 2007).

Trastuzumab treatment appears to require an adaptive immune response to achieve maximal therapeutic effects. Data from Park et al. provide evidence that T cells are necessary for tumor regression with single agent trastuzumab. The effect of the monoclonal antibody was greatly reduced in murine models in which T-cells and B-cells were deficient and in murine models depleted of CD8-positive T cells. In both of these models, there was an initial response followed by a rapid relapse of tumor (Park S 2010).

Augmentation of the immune response produced by ADCC occurs through cross-priming of cytotoxic T cells. Dendritic cells present tumor antigens and immune complexes to the cell surface of T cells of the immune system that become HER2-specific cytotoxic T cells and undergo clonal expansion. Cross talk between NK cells and dendritic cells can be induced by monoclonal antibodies and contributes to tumor antigen specific T-cell immunity (Lee 2011).

The activity of HER2-specific cytotoxic T cells might be inhibited by the expression of PD-L1 on the surface of HER2-positive cells that were not eliminated by inhibition of oncogenic signaling or ADCC. This immune tolerance could provide a survival mechanism that allows cells time to acquire resistance to the oncogenic signaling inhibition. Recently, Bianchini and Gianni et al. demonstrated in the NeoSphere trial that increased PD-L1 expression was associated with reduced pathologic complete response (pCR) (Bianchini 2015).

In a preclinical study, an anti-PD-1 monoclonal antibody significantly improved the activity of anti-ErbB-2 antibody (Stagg 2011). Two multicenter neoadjuvant trials enrolled patients with HER2-positive breast cancer. Core biopsies were obtained at baseline and after a brief exposure to single agent trastuzumab or nab-paclitaxel. Significant increases in a signature of immune cells (Immune Index) was seen following a brief exposure to trastuzumab in HER2-enriched tumors (Trial 03-311[Discovery], p=0.05: Trial 211B [Validation], p=0.02). The increased Immune Index was also predictive of response after exposure to trastuzumab (Trial 03-311, p=0.03; Trial 211B, p=0.04). These results demonstrate immune cell function is upregulated in patients following one dose of trastuzumab and is associated with response to subsequent therapy (Varadan 2016).

In aggregate, these studies suggest that therapies which inhibit PD-1/PD-L1 could augment the immune-mediated effects of trastuzumab and pertuzumab.

2.4 **Atezolizumab**

Binding of PD-L1 to its receptors suppresses T-cell migration, proliferation, secretion of cytotoxic mediators, and restricts tumor cell killing (Park JJ 2010, Yang 2011, Paterson 2011, Butte 2007, Dong 1999). Inhibiting PD-L1/PD-1 interaction restores antitumor T-cell activity (Akbari 2010, Matsumoto 2008).

Atezolizumab is a human immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells (Investigator's Brochure 2016). Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells. Atezolizumab targets human programmed death-ligand 1 (PD-L1) and inhibits the interaction with its PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved in the United States for the treatment of locally advanced or metastatic urothelial carcinoma and as well as metastatic non-small cell lung carcinoma.

2.4.1 Mechanism of Action

PD-L1 expression is prevalent in many human tumors (e.g., lung, bladder, ovarian, melanoma, colon carcinoma), and its overexpression has been associated with poor prognosis in patients with several cancers (Thompson 2006, Hamanashi 2007, Okazaki 2007, Hino 2010). PD-L1 binds to two known inhibitory receptors expressed on activated T cells (PD-1 and B7.1), and receptor expression is sustained in states of chronic stimulation such as chronic infection or cancer (Blank 2005, Keir 2008). Ligation of PD-L1 with PD-1 or B7.1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or inhibition of T cells. Aberrant expression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank 2007). Therefore, interruption of the PD-L1/PD-1 and PD-L1/B7.1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity.

Blockade of PD-L1 or PD-1 with monoclonal antibodies has been reported to result in strong and often rapid antitumor effects in several mouse tumor models (Iwai 2002, Strome 2003). These data suggest that tumor-specific T cells may be present in the tumor microenvironment in an inactive or inhibited state, and blockade of the PD-L1/PD-1 pathway can reinvigorate tumor-specific T-cell responses.

Collectively, these data establish the PD-L1/PD-1 pathway as a promising new therapeutic target in patients with advanced tumors. Immune-related adverse events (AEs) reported from the two recent studies were consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance.

2.4.2 Summary of Nonclinical Experience

The safety, pharmacokinetics (PK), and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, PK, and toxicokinetics of atezolizumab.

Overall, the nonclinical PK and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed phase 1 starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic

activity of down-modulating the PD-L1/PD-1 pathway and supported entry into clinical trials in patients.

Refer to the Atezolizumab Investigator's Brochure for details on the nonclinical studies.

2.4.3 Summary of Clinical Experience

A summary of clinical data from company-sponsored atezolizumab trials is presented below. Details of all ongoing studies can be found in the Atezolizumab Investigator's Brochure.

2.4.4 Clinical PK and Immunogenicity

On the basis of available preliminary PK data (0.03-20 mg/kg), atezolizumab shows linear PK at doses ≥1 mg/kg (Investigator's Brochure 2016). Based on an analysis of exposure, safety, and efficacy data, the following factors had no clinically relevant effect: age (21−89 years), body weight, gender, positive ATA status, albumin levels, tumor burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG status. No formal PK drug-drug interaction studies have been conducted with atezolizumab, and the interaction potential is unknown. Further details can be found in the current Investigator's Brochure.

The development of anti-therapeutic antibodies (ATAs) has been observed in patients in all dose cohorts and was associated with changes in PK for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg) (Investigator's Brochure 2016). Patients dosed at ≥ 10 mg/kg maintained C_{min} values well above the target serum concentration of 6 mcg/mL despite the detection of ATAs. Accordingly, the development of detectable ATAs does not appear to have a clinically significant impact on PK for doses above 10 mg/kg. To date, no relationship between the development of measurable ATAs and safety or efficacy has been observed.

2.4.5 Clinical Safety Summary

As of May 10, 2016, atezolizumab has been administered (alone or in combination with other agents) to approximately 6053 patients with solid tumors and hematologic malignancies (Investigator's Brochure 2016). The first-in-human monotherapy study PCD4989g (in patients with locally advanced or metastatic solid tumors or hematologic malignancies) provides the majority of monotherapy safety data, with 629 safety-evaluable patients as of the data extraction date. Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of AEs have been determined.

Fatigue, decreased appetite, nausea, diarrhea, constipation, and cough were commonly reported AEs in single and combination therapy (Investigator's Brochure 2016). AE profiles are similar across tumor types studied, including non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), triple-negative breast cancer (TNBC), and urothelial carcinoma (UC), and are consistent with the mechanism of action of atezolizumab. The overall immune-mediated AEs reported were considered moderate in severity, and the majority of patients were able to continue on atezolizumab therapy.

As of the data extraction date of December 15, 2015, there were 629 safety-evaluable patients from the first-in-human phase 1a study PCD4989g (Investigator's Brochure 2016). The median age was 61 years. Of the 629 patients, 619 patients (98.4%) reported at least one AE of any grade or attribution to atezolizumab, and 316 patients (50.2%) experienced at least one grade 3 or 4 AE of any attribution. A total of 444 patients (70.6%) reported at least one treatment-related AE, and 86 patients (13.7%) experienced at least one treatment-related grade 3 or 4 AE. The most frequently observed AEs of any grade and attribution (occurring in ≥ 10% of treated patients)

include fatigue, decreased appetite, nausea, pyrexia, constipation, cough, dyspnea, diarrhea, anemia, vomiting, asthenia, back pain, headache, arthralgia, pruritus, rash, abdominal pain, insomnia, peripheral edema, and dizziness.

Serious AEs (SAEs) have been reported in 261 patients (41.5%) in study PCD4989g (Investigator's Brochure 2016). Reported SAEs were consistent with the underlying disease. Treatment-related SAEs (57 patients [9.1%]) included pyrexia, dyspnea, pneumonitis, malaise, fatigue, hypoxia, colitis, and bone pain. Pooled single-agent safety data from 1978 patients with UC, NSCLC, and other indications (including trial PCD4989g) indicate that the most frequent (>1% of patients) serious adverse drug reactions (regardless of grade) include dyspnea (3.0%), back pain (1.2%), and abdominal pain (1.1%). A list of AEs considered "expected" for atezolizumab is presented in Section 7.3.2.

2.4.6 Immune-Related Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated AEs have been closely monitored during the atezolizumab clinical program (Investigator's Brochure 2016). To date, immune-related adverse events associated with atezolizumab include hepatitis, pneumonitis, colitis, pancreatitis, nephritis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, and meningoencephalitis.

Cases of myocarditis have been reported in patients receiving atezolizumab treatment in clinical trials. As of 17 May 2018, approximately 16,815 clinical trial patients and 20,783 post-marketing patients have been exposed to atezolizumab. A cumulative analysis of the Genentech safety database (data cut-off date 17 May 2017) identified two cases of myocarditis (Genentech 2018). Immune-mediated myocarditis has been reported in patients treated with other immune checkpoint inhibitor therapy.

For further details, see the most recent Atezolizumab Investigator's Brochure.

2.4.7 Clinical Efficacy Summary

Patients with multiple tumor types were included in study PCD4989g, with the largest cohorts consisting of patients with NSCLC, RCC, and UC (Investigator's Brochure 2016). Objective responses with atezolizumab monotherapy were observed in a broad range of malignancies, including NSCLC, RCC, melanoma, UC, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma. Both the preliminary and more mature efficacy data available suggest that treatment with atezolizumab as a single agent or in combination with other therapeutic agents results in anti-tumor activity across a range of tumor types and hematologic malignancies (UC, NSCLC, RCC, TNBC, melanoma, CRC, and NHL) and across lines of therapy. Clinical benefit was observed in terms of objective responses, durability of responses, and overall survival (OS). Improved efficacy of atezolizumab was observed in the unselected patient population, as well as in patients with higher PD-L1 expression on TCs or ICs (e.g., NSCLC) or on ICs only (e.g., mUC, RCC).

2.5 **Atezolizumab in Breast Cancer**

Atezolizumab (MPDL3280A) is a monoclonal anti-PD-L1 antibody that was evaluated in a cohort of 115 women with metastatic TNBC (Emens 2015, Schmid 2017). This included 63% of women initially selected for high PD-L1 expression levels (at least 5% of tumor-infiltrating immune cells were PD-L1 positive) and 33% of patients with TNBC regardless of PD-L1 expression. Four percent of patients had unknown PD-L1 expression levels. Efficacy was evaluated in 112 patients and safety was evaluated in 115 patients. PD-L1 expression was

centrally evaluated on tumor-infiltrating immune cells based on an IHC assay. Atezolizumab was administered at 15 mg/kg, 20 mg/kg, or 1200 mg IV every 3 weeks. The objective response rate (ORR) was 10% (95% CI, 5-17) among the 112 evaluable patients. The one and two year overall survival rates for these responders were 100% and for non-responders, the overall survival rates were 33% and 11%, respectively. The median duration of response was 21 months (2.8 to 26.5+). Atezolizumab was generally well-tolerated. Treatment-related Grade 3 or 4 adverse events were reported in 11% of patients and adverse events leading to treatment discontinuation occurred in 3% of the cases. Two treatment related Grade 5 adverse events, pulmonary hypertension and death (unspecified) were reported in a hospitalized patient.

Preliminary results of a Phase 1b study evaluating the combination of atezolizumab in combination with nab-paclitaxel at 125 mg/m^2 demonstrated activity in patients with metastatic TNBC. A total of 32 patients were evaluable for efficacy. The confirmed ORR for patients receiving any line of therapy was 38% (95% CI 21,56) [46% (19,75) in first line, 22% (3,60) in second line, and 40% (12,74) in third line]. The stable disease rate was 44%. Safety information was available for all 32 patients with a median follow-up of 6.1 months. Treatment-related Grade 3/4 AEs occurred in 69% of patients which included neutropenia (47%), thrombocytopenia (9%), anemia (6%), decreased WBC (6%), and diarrhea (6%). Six patients discontinued nab-paclitaxel due to an adverse event. Treatment discontinuations were related to fatigue (n=1; grade 2), asthenia (n=1; Grade 2), peripheral neuropathy (n=3; Grade 1, 2, and 3), and pneumonia (n=1; Grade 3). The combination of nab-paclitaxel and atezolizumab showed high response rates and was well-tolerated (Adams 2016).

2.6 Rationale for Dose Selection/Regimen/Modification

Atezolizumab/placebo will be administered at a fixed dose of 1200 mg Q3W by IV infusion with taxane (paclitaxel or docetaxel)/trastuzumab/pertuzumab until the taxane has been completed. Atezolizumab/placebo will then be administered at a fixed dose of 1200 mg Q3W by IV infusion with trastuzumab and pertuzumab every 3 weeks until progression or for 2 years.

Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight−based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng 2016). A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians, reduces potential for dosing errors, reduces complexity in the logistical chain at treatment facilities, and reduces wastage.

The NRG-BR004 clinical trial will evaluate a standard of care regimen of either weekly paclitaxel or every 3-week docetaxel, in combination with trastuzumab and pertuzumab administered with atezolizumab or placebo, in HER2-positive MBC in the first-line setting. A minimum of 18 weeks of taxane chemotherapy will be administered, with trastuzumab and pertuzumab continuing until progression. Atezolizumab/placebo will be administered for 24 months or until progression to provide exposure to atezolizumab/placebo combined with the HER2-targeted monoclonal antibodies for 6 months beyond the median PFS in the CLEOPATRA trial.

The definitive analysis for PFS will occur at about 41 months after the study has initiated. Following first progression, patients will be assessed for survival, late immune toxicities, and subsequent immuno-oncology therapy. Since the median OS was almost 5 years in patients receiving docetaxel/trastuzumab/pertuzumab, we propose that patients will be followed for up to 8.5 years to determine the possible impact of the therapy on OS. There are no trials currently being conducted in this setting to evaluate the addition of atezolizumab or other checkpoint inhibitors to standard first-line therapy of metastatic HER2-positive breast cancer.

2.7 Rationale for Amendment #3 to Allow Investigator Discretion on Choice of Taxane

Since accrual remained below projections one year after activation, an investigator survey was released to identify barriers to accrual and trial participation among NCTN sites. The information supplemented information we had received from investigators during the activation and the first year of accrual. Three major barriers were identified. First, central testing can take 5-7 days to confirm eligibility and drug shipment following randomization can also take up to 7 days; therefore, patients entering BR004 may have a delay of 2-3 weeks before therapy can be initiated. In some instances, an extensive burden of disease at presentation has precluded participation in the trial because of the need to begin therapy on an urgent basis. Second, the weekly paclitaxel regimen is problematic for patients living at a distance from their cancer center, particularly in areas with large rural populations, and this issue has been magnified by the COVID-19 pandemic. Investigators have indicated the option of every-3-week docetaxel would be helpful in addressing this barrier. Finally, the exclusion of biosimilar trastuzumab was beginning to be problematic as some insurance policies began to require use of biosimilars and an increasing number of cancer centers began to preferentially use biosimilars to reduce costs.

The biosimilar issue will be addressed by provision of trastuzumab by Genentech distributed by the Pharmaceutical Management Branch (PMB) for randomized patients throughout their treatment period while on the medication. The other two issues related to the delay in initiating therapy due to the requirement for central testing and the frequency of administration required for the paclitaxel administration will be addressed by amending the protocol to enroll patients and administer Cycle 1 based on local testing results, while tissue is sent for central testing for confirmation of HER2-positive status and determination of PD-L1 status required for stratification prior to randomization. Upon receipt of confirmation of HER2-positive status and determination of PD-L1 status, patients will be randomized in time for atezolizumab/placebo and trastuzumab to be shipped from the PMB to be available for initiation of atezolizumab/placebo on Day 22 of Cycle 1 along with the continuation of trastuzumab provided by the PMB and pertuzumab and chemotherapy that will continue to be provided as part of routine care. With this process, patients will not have to delay starting therapy while central testing and post-randomization drug shipment occurs. This approach will also allow for assessment of tolerance to the standard components of the treatment regimen prior to initiation of atezolizumab/placebo, which will be important in evaluating and managing treatment-related diarrhea.

Finally, results of two double blind, placebo-controlled Phase III studies evaluating atezolizumab in patients with untreated metastatic TNBC have been reported since BR004 was developed. The first of the studies to report was the IMpassion-130 study, which randomized patients 1:1 to receive atezolizumab/placebo Days 1 and 15 in combination with nab-paclitaxel 100 mg/m^2 Days 1, 8, and 15 in 28-day cycles (Schmid 2018). Median PFS was 7.2 months with atezolizumab plus nab-paclitaxel, as compared with 5.5 months with placebo plus nab-paclitaxel (HR 0.80; 95% confidence interval [CI], 0.69-0.92; P = 0.002). Among the cohort of patients with PD-L1-positive tumors, median PFS was 7.5 months and 5.0 months, respectively (HR, 0.62; 95% CI, 0.49 to 0.78; P<0.001). Among patients with PD-L1-positive tumors, median OS was improved from 15.5 months to 25.0 months, respectively (hazard ratio, 0.62; 95% CI, 0.45 to 0.86). No new adverse effects were identified. Based on these results and an acceptable safety profile the combination was approved by the FDA on March 11, 2019, in patients with PD-L1-positive untreated metastatic TNBC.

More recently, results from the IMpassion-131 study were presented at the European Society of Medical Oncology. IMpassion-131 randomized patients with untreated metastatic TNBC to receive atezolizumab/placebo 2:1 in combination with paclitaxel 80 mg/m^2 Days 1, 8, and 15 in 21-day cycles. Atezolizumab + paclitaxel did not improve PFS compared with placebo +

paclitaxel in the PD-L1-positive population with a stratified HR of 0.82, (95% CI 0.60 - 1.12, p = 0.20, stratified log-rank test). Median PFS was 6.0 months in the atezolizumab arm and 5.7 months in the placebo arm. In the intent-to-treat (ITT) population, the median PFS was 5.7 months in the atezolizumab arm and 5.6 months in the placebo arm (stratified HR: 0.86 [0.70 - 1.05], p= 0.1343 stratified log-rank test [not formally tested due to the hierarchy]). An interim analysis of OS was also planned at the time of the formal analysis of PFS. At that time with deaths in only 27% of the ITT population, OS showed a negative trend for atezolizumab in the PD-L1-positive population (stratified HR: 1.55, 95% CI [0.86, 2.80]). A similar trend was observed in the ITT population (stratified HR: 1.31, 95% CI [0.94 - 1.82]). An update of OS with 9 months of additional follow-up with deaths in 47% of the ITT population, was included in the ESMO presentation and demonstrated a HR of 1.12 (95% CI [0.76, 1.65]) for OS in the PD-L1 positive cohort with a 2-year OS rate of 51% in the placebo arm and 49% in the atezolizumab arm. A similar trend was observed in the ITT population (stratified HR: 1.11, 95% CI [0.87, 1.42]), with 2-year OS rates of 45% vs 42%, respectively (Miles 2020).

The safety of atezolizumab in combination with paclitaxel appeared consistent with the known safety profiles of the individual medicines, and no new safety signal was identified. The rates of AEs with fatal outcomes were balanced (1.8% vs 2.1%, respectively, in the placebo arm vs atezolizumab arm) with no discernable pattern. Infection-related events were the most common cause of fatal AEs for both arms and were balanced between arms. SAEs were higher in the atezolizumab arm (16.1% vs 22.7%), with pneumonia being the only event occurring in > 2% of patients. Grade 3-4 events were also higher in the atezolizumab arm (43.1% vs 49.4%) with neutropenia, neutrophil count increase, and peripheral neuropathy occurring in ≥ 5% of patients.

BR004 is evaluating atezolizumab as an additional component to the highly effective regimen of trastuzumab and pertuzumab in combination with a taxane in HER2-positive metastatic breast cancer with an expected median PFS of 18-19 months. This represents a very different patient population from the first-line TNBC population evaluated in IMpassion-130 and IMpassion-131, which reported a median PFS of 5.5 months and 5.6 months in the control arms of those trials when treated with single agent nab-paclitaxel and paclitaxel, respectively. Thus, the results of the IMpassion-131 and IMpassion-130 studies do not warrant removal of paclitaxel from the BR004 study. Therefore, BR004 will retain use of weekly paclitaxel as an option for the choice of standard chemotherapy but as noted will be amended to allow the option of docetaxel.

2.8 Early Closure to Accrual of NRG-BR004

On 05/20/2022, the NRG BR004 study was permanently closed to further accrual, and patients receiving atezolizumab/placebo discontinued experimental treatment. Patients were to continue to receive trastuzumab in combination with pertuzumab and taxane where appropriate. This decision was made in consultation between NRG Oncology leadership, the study team, the Data Monitoring Committee (DMC), and NCI CTEP when an imbalance in deaths between the study arms while on-treatment became evident on April 27, 2022, following report of a 6th on-treatment death in one of the study arms compared with no on-treatment deaths reported in the other arm.

A potential imbalance was noted during the DMC review of the BR004 safety data in February 2022, when it was seen that the 4 reported deaths on treatment had all on occurred on one arm of the study. However, there was no consistent pattern of toxicities among the four Grade 5 events and there were no imbalances in Grade 3 or Grade 4 toxicities or drug delivery between the two arms. Therefore, the NRG BR004 team remained blinded to the treatment, and the study was continued without modification. Subsequently, 2 additional on-treatment deaths were reported, the first on [redacted] and the second on [redacted]. Since the deaths were again on the same study

arm, accrual was halted until the DMC could review unblinded safety data, narratives of the deaths, and the overall context of the trial.

The DMC met on May 10, 2022, and reviewed the unblinded safety data in detail, including the narratives from the six deaths which had occurred on the atezolizumab arm. The analysis and interpretation of the narratives by the DMC follows:

Case Number	Event Analysis	Interpretation by DMC
1	Rapid progression of hepatic metastases in days after starting protocol-based therapy	Unrelated to treatment
2	Diarrhea attributed to pertuzumab, with malnutrition, admitted for non-neutropenic sepsis, then with progressive pneumonic infiltrates and liver failure, also complicated by tumor progression.	Probably related to treatment
3	Evidence for immune-related side effects (elevated TSH, low cortisol), with subsequent admission for nausea, vomiting, diarrhea, hypotension, and later pneumonia.	Related to treatment
4	Non-neutropenic fever with diarrhea, and tissue evidence for immune mediated colitis, with subsequent re-admission for fever, colitis, and diarrhea, found unexpectedly deceased at home two days after hospital discharge.	Related to treatment
5	Non-neutropenic sepsis complicated by pulmonary edema and cardiac injury	Related to treatment
6	Elderly patient with history of atrial fibrillation, admitted to hospital with atrial fibrillation and rapid ventricular response/dyspnea, developed progressive multi-system organ failure in setting of worsening congestive heart failure and mitral valve regurgitation.	Not directly related to treatment though possibly aggravated by treatment

The DMC also evaluated the persistent low accrual since activation and the lack of meaningful increase in accrual following an extensive protocol revision in the summer of 2021 designed to address identified barriers to accrual, the context of a similar pattern of imbalance in on-treatment deaths seen in the IMpassion050 study in HER2-positive early breast cancer which evaluated the addition of atezolizumab/placebo added to trastuzumab and pertuzumab in combination with sequential anthracycline/taxane neoadjuvant chemotherapy reported in June of 2021 in an ESMO Virtual Plenary session (Huober 2021, Huober 2022), and the current landscape of metastatic therapies for HER2-positive disease. The DMC recommended that based on 1) the presence of an uncertain but material signal regarding the adverse event risk, 2) the continuing accrual challenges, and 3) a determination that the clinical question being addressed in BR004, while potentially important, is no longer sufficiently compelling to incur the risk of either severe adverse events or an uninformative result due to low accrual, the trial should be permanently closed to further enrollment. Since only 190 of the planned 600 patients (32%) had been accrued, the ability to detect a clinically relevant improvement in outcomes effectively precluded closure to further accrual, continued exposure of first line HER2-positive patients to potential risks of atezolizumab was difficult to justify as these patients generally derive substantial benefit from

dual HER2 targeted therapy in combination with a taxane. Based on these considerations, a decision was made to also discontinue atezolizumab/placebo in patients who were receiving the investigational component of the trial therapy and unblind investigators and patients so that investigators know which patients should be monitored for possible immune-related adverse events that can occur after stopping atezolizumab.

With Amendment #6, the BR004 protocol is being amended to provide for continued follow-up for the primary endpoint of PFS and the secondary endpoint of OS through April 2024. While it is unlikely that statistically significant improvement in PFS can be demonstrated with the reduced sample size, it is important to assess the primary endpoint in the two arms with reasonable follow-up, and to assess the numerical differences in survival as a predefined endpoint. The follow-up period will also provide opportunity to continue to monitor for post therapy immune-related adverse events. Secondary endpoints requiring central review, the original larger sample size or extended follow-up are being removed with this amendment, as are requirements for submission of scans for independent review of response, which had been a secondary endpoint of the trial. The secondary endpoint of overall response is being modified to be evaluated in the cohort of patients randomized 6 months or more prior to study accrual closure. Follow-up requirements will also be limited to investigator determined assessment of disease status to encourage patients to allow continued submission of follow-up information until closure to follow-up in 2024.

3.0 PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

The NRG-BR004 study was permanently closed to accrual on May 20, 2022. Modified scheduled status updates, as outlined on Table 2A, will be completed for patients enrolled prior to study accrual closure.

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Clinical Coordinating Department (CCD).

3.1 Patient Selection Guidelines

Investigators should consider all relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if an individual patient is an appropriate candidate for this trial.

Submission of tumor tissue obtained at the time of diagnosis of de novo metastatic disease or locally recurrent or metastatic disease is required for all patients. (see Section 3.3.5 and Section 10.0). Investigators should check with their site Pathology department regarding release of tumor tissue before approaching patients about participation in the trial.

3.2 Patient Entry and Randomization

The following sections outline procedures for Study Entry, Randomization, and ordering Study Drug at randomization.

3.2.1 Step 1 Study Entry and Initiation of Study Therapy: Begin Cycle 1 and provide tissue for central confirmation of HER2-positive status

- The authorized site staff must obtain signed informed consent from the potential patient before any study specific procedures are performed.
- The authorized site staff must determine patient eligibility. See Sections 3.3 and 3.4.
- Entry in OPEN: Patients will be assigned a unique patient identifier which will be used to identify the samples used for central confirmation of HER2 and ER/PgR and for PD-L1 testing, the eCRFs in Medidata RAVE, and any other trial-related communications.
- Preferentially send tissue that is HER2-positive per ***local*** testing for central confirmation of HER2 and ER/PgR and PD-L1 testing. See Section 10.0 if insufficient material available.
- Once potential eligibility has been confirmed and consent signed, initiate Cycle 1 treatment with standard loading doses of trastuzumab and pertuzumab obtained by the investigator from commercial supply and paclitaxel or docetaxel per institutional standards while waiting on results of central testing. When HER2-positive is confirmed on central testing, patient should be randomized. Patients who are **not** confirmed to be HER2-positive by central confirmation testing will not be randomized, will be taken off study, treated per investigator discretion, and will not be followed on BR004.

3.2.2 Step 2 Randomization

- Following central confirmation of a positive HER2 status and central testing of ER/PgR and PD-L1, the authorized site staff will randomize the patient using OPEN. For the purposes of stratification, the PD-L1 results will be provided to the NRG Oncology SDMC. Results will not be provided to the investigator or the patient. **Randomization within 14 days from study entry will ensure that the PMB-supplied agents will be received at the site for treatment on Day 22 of Cycle 1.**

- OPEN will randomly assign treatment (atezolizumab or placebo). The treatment allocation will be blinded for the Investigator and the patient.
- Randomization will automatically trigger study drug shipment to the site in time to begin atezolizumab/placebo on Day 22 of Cycle 1. Details of drug ordering procedures can be found in Section 9.1.2.

3.3 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.3.1 The patient must have signed and dated an IRB-approved consent form that conforms to federal and institutional guidelines.

3.3.2 The trial is open to female and male patients.

3.3.3 Patients must be ≥ 18 years old.

3.3.4 Patient must have an ECOG Performance Status of 0 or 1 (see Appendix A).

3.3.5 Histologically confirmed adenocarcinoma of the breast with locally recurrent, unresectable disease or metastatic disease outside the CNS ***confirmed as described below***. Eligible patients include those with either:

- De novo metastatic disease presenting without prior history of HER2-positive breast cancer:
  - Diagnosis should have been made from a biopsy of a metastatic disease site, but biopsy from the breast primary or involved regional lymph nodes is acceptable if biopsy of the metastatic sites was thought to carry excessive risk for the patient.
- Locally recurrent or metastatic disease following prior therapy for early breast cancer:
  - Diagnosis must have been made from the biopsy of the locally recurrent or metastatic disease.
  - There must be an interval of ≥ 6 months between completion of neoadjuvant/adjuvant HER2-targeted therapy and documentation of locally recurrent or metastatic HER2-positive disease by biopsy.

3.3.6 Patients must have measurable disease based on RECIST 1.1, as determined by the site, which has not been irradiated to be eligible.

3.3.7 Patients with brain metastases are eligible if they meet ALL the following criteria:

- Four or fewer metastatic sites to CNS
- Largest unexcised tumor does not exceed 3 cm
- No metastases to brain stem, midbrain, pons, medulla or the optic nerves and chiasm
- Must have measurable disease outside the CNS, based on RECIST 1.1, as determined by the site, which has not been irradiated.
- If patient presented with symptoms from CNS metastases, the symptoms must have resolved with initiation of steroids and initial local therapy (surgery, radiation therapy, or both).
- Must have been evaluated by Medical Oncologist and plan is to administer trastuzumab, pertuzumab, and a taxane as first-line systemic therapy.
- May have received administration of trastuzumab OR lapatinib concurrently with radiation therapy for brain metastases. Toxicities related to lapatinib if administered, should be ≤ grade 1 per the CTCAE v5.0, and the lapatinib must have been completed at least 2 weeks prior to study entry.
- No history of intracranial hemorrhage or spinal cord hemorrhage.
- No neurosurgical resection or brain biopsy within 10 days prior to study entry.

3.3.8 After study entry and before randomization, send tissue for central HER2 confirmation. A tumor specimen obtained at the time of diagnosis of locally recurrent or metastatic disease must have been determined to be HER2-positive based on ***local testing*** according to ASCO/CAP guidelines (Wolff 2018). HER2 status should initially be assessed using a FDA-cleared IHC assay. Positive is defined as IHC 3+ staining intensity. If HER2 IHC results are equivocal (2+), then HER2 status will be determined using an FDA-cleared HER2 ISH test according to ASCO/CAP guidelines. ***Note: Once HER2-positive is confirmed on central testing, patients will be randomized to atezolizumab/placebo. Randomization within 14 days from study entry will ensure that the PMB-supplied agents will be received at the site for treatment on Day 22 of Cycle 1.***

3.3.9 The tumor specimen obtained at the time of diagnosis used for HER2 testing must also have ***central testing*** for PD-L1 status. Patients will be eligible irrespective of PD-L1 testing result including PD-L1 indeterminant.

3.3.10 The tumor specimen obtained at the time of diagnosis used for HER2 and PD-L1 testing should also have ***central testing*** for ER and PgR according to current ASCO/CAP Guideline Recommendations for hormone receptor testing (http://www.asco.org). Patients with < 1% ER and PgR staining by IHC will be classified as negative. If enough material for central confirmation of ER and PgR is unavailable, local testing results for ER and PgR may be used for eligibility.

3.3.11 Localized palliative radiation therapy to sites of non-measurable disease is allowed for symptom management and may begin prior to study entry and continue following study entry while receiving study therapy.

3.3.12 Patients must have imaging of the chest/abdomen/pelvis, preferably with a CT scan, and a bone scan within 5 weeks prior to study entry. (Note: If a patient is unable to receive CT contrast, a MRI of the abdomen/pelvis and non-contrast chest CT should be performed. PET/CT ***is not*** an acceptable alternative.)

3.3.13 MRI of the brain (or contrast CT scan of the brain if patients are unable to undergo MRI) must be obtained in patients with symptoms suggesting possible central nervous system (CNS) metastatic disease. Neuroimaging is recommended but not required in asymptomatic patients.

3.3.14 Adequate hematologic function within 14 days prior to study entry defined as follows:

- ANC must be ≥ 1200/mm^3;
- Platelet count must be ≥ 100,000/mm^3;
- Hemoglobin must be ≥ 8 g/dL.

3.3.15 Adequate hepatic function within 14 days prior to study entry:

- total bilirubin must be ≤ 1.5 x ULN for the lab ***or*** direct bilirubin ≤ ULN for patients with bilirubin levels > 1.5 x ULN;
- AST and ALT must be ≤ 2.5 x ULN for the lab ***or*** ≤ 5 x ULN for patients with liver metastases.

3.3.16 Adequate renal function determined within 14 days prior to study entry defined as the most recent serum creatinine ≤ 1.5 x ULN ***or*** measured or calculated creatinine clearance ≥ 50 mL/min using the Cockroft-Gault formula for patients with creatinine levels > 1.5 x ULN for the lab.

For Women

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

For Men

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

3.3.17 Patients not receiving anti-coagulant therapy must have PT and INR ≤ 1.5 x ULN within 14 days prior to study entry. For laboratories that do not report an ULN for the INR assay, use ≤ 1.5 as the value for the ULN. Patients receiving anti-coagulants should have a baseline INR assessed, but the value does not affect eligibility.

3.3.18 A serum TSH and AM (preferably in morning) cortisol must be obtained within 14 days prior to study entry to obtain a baseline value. Patients with abnormal TSH or AM cortisol baseline levels should be further evaluated and managed per institutional standards. Asymptomatic patients who require initiation or adjustment of medication or are followed without initiating treatment based on endocrinologist's recommendations are eligible.

3.3.19 LVEF assessment must be performed within 6 weeks prior to study entry. (LVEF assessment performed by echocardiogram is preferred; however, MUGA scan may be substituted based on institutional preferences.) The LVEF must be ≥ 50% regardless of the cardiac imaging facility's lower limit of normal.

3.3.20 Administration of atezolizumab may have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality. Women of child-bearing potential and men must agree to use adequate contraception (non-hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 5 months (150 days) after the last dose of atezolizumab/placebo and 7 months after the last dose of trastuzumab and pertuzumab. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.3.21 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of study entry are eligible for this trial.

3.4 Ineligibility Criteria

Patients with one or more of the following conditions are NOT eligible for this study.

3.4.1 Patients with brain metastases are excluded if they meet ANY of the following criteria:

- Symptoms from brain metastases have not resolved prior to study entry
- Five or more clearly identified foci of metastases to the brain
- Largest unexcised tumor exceeds 3 cm
- Spinal cord metastases
- Medical Oncologist plans to employ HER2-directed tyrosine kinase inhibitor as component of systemic therapy
- Metastatic disease limited to CNS

3.4.2 Leptomeningeal carcinomatosis.

3.4.3 History of systemic anti-cancer therapy (e.g., chemotherapy, targeted therapy) for MBC except as described in Eligibility Criterion 3.3.7.

3.4.4 History of exposure to cumulative doses of doxorubicin greater than 360 mg per square meter of body-surface area or its equivalent.

3.4.5 Prior treatment with mTOR inhibitors or CDK 4/6 inhibitors in combination with endocrine therapy for treatment of metastatic disease.

3.4.6 Prior treatment with CD137 agonists or immune checkpoint-blockade therapies, including anti-CD40, anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies.

3.4.7 History of *non-breast* malignancies (except for in situ cancers treated only by local excision and basal cell and squamous cell carcinomas of the skin) within 5 years prior to study entry.

3.4.8 Uncontrolled hypertension defined as sustained systolic BP > 150 mmHg or diastolic BP > 90 mmHg. (Patients with initial BP elevations are eligible if initiation or adjustment of BP medication lowers pressure to meet entry criteria.)

3.4.9 History of asymptomatic LVEF decline to < 40% during or after prior HER2-targeted therapy even if the current LVEF is ≥50%.

3.4.10 Cardiac disease (history of and/or active disease) that would preclude the use of the drugs included in the treatment regimens. This includes but is not confined to:

Active cardiac disease

- angina pectoris that requires the current use of anti-anginal medication;
- ventricular arrhythmias except for benign premature ventricular contractions;
- supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication;
- conduction abnormality requiring a pacemaker;
  valvular disease with documented compromise in cardiac function; or
- symptomatic pericarditis.

History of cardiac disease

- prior myocardial infarction documented by elevated cardiac enzymes or persistent regional wall abnormalities on assessment of LV function;
- history of documented CHF defined as symptomatic heart failure with an LVEF < 40%; or
- documented cardiomyopathy.

3.4.11 Nervous system disorder (paresthesia, peripheral motor neuropathy, or peripheral sensory neuropathy) ≥ grade 2, per the CTCAE v5.0.

3.4.12 History of severe allergic, anaphylactic, or other hypersensitivity reactions to pertuzumab or trastuzumab or to any of its excipients, as well as any chimeric or humanized antibodies or fusion proteins.

3.4.13 Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or other recombinant antibodies.

3.4.14 Known allergy or hypersensitivity to the components of the atezolizumab formulation or to any of the study drugs or excipients, (e.g., Cremophor® EL, polysorbate 80).

3.4.15 History or risk of autoimmune disease, including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis.

- Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.
- Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.
- Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:

- Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
- Rash must cover less than 10% of body surface area (BSA)
- Disease is well controlled at baseline and only requiring low-potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)
- No acute exacerbations of underlying conditions within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

3.4.16 Treatment with systemic immunomodulatory medications (including but not limited to interferons, IL-2) within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to study entry.

3.4.17 Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and ***anti-tumor*** necrosis [anti-TNF] factor agents) within 14 days prior to study entry or anticipation of need for systemic immunosuppressive medications during the study. Note: Intranasal and inhaled corticosteroids or systemic corticosteroids at doses that do not exceed 10 mg/day of prednisone or an equivalent corticosteroid are allowed.

3.4.18 Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 2 weeks prior to study entry.

3.4.19 Active hepatitis B virus (HBV) infection, defined as having a positive hepatitis B surface antigen (HBsAg) test at screening.

Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, are eligible for the study if active HBV infection is ruled out on the basis of HBV DNA viral load per local guidelines.

3.4.20 Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test at screening confirmed by a polymerase chain reaction (PCR) positive for HCV RNA.

3.4.21 Patients with clinically active tuberculosis.

3.4.22 Severe infection within 4 weeks prior to study entry, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.

3.4.23 Prior allogeneic stem cell or solid organ transplantation.

3.4.24 Symptomatic peripheral ischemia.

3.4.25 History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis ***or*** ≥ grade 1 pulmonary fibrosis, per the CTCAE v5.0, on screening chest CT scan.

3.4.26 Administration of a live, attenuated vaccine within 4 weeks prior to study entry or anticipation that such vaccine will be required during the study.

Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to study entry, during treatment or within 5 months following the last dose of atezolizumab/placebo.

3.4.27 Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications.

3.4.28 Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements or interfere with interpretation of study results.

3.4.29 Pregnancy or lactation at the time of study entry or intention to become pregnant during the study. ***(Note: Pregnancy testing according to institutional standards for women of childbearing potential must be performed within 3 days prior to study entry.)***

3.4.30 Use of any investigational product within 4 weeks prior to study entry.

4.0 REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

The NRG-BR004 study was permanently closed to accrual on May 20, 2022. Modified scheduled status updates, as outlined on Table 2A, will be completed for patients enrolled prior to study accrual closure.

With Amendment #3, accrual to the PRO-CTCAE substudy is closed. Patients enrolled on the PRO-CTCAE substudy prior to Amendment #3 will continue to complete the scheduled assessments as outlined on Table 2. Accrual to the QOL substudy will continue.

Tests, exams, and other studies required prior to study entry and randomization are listed on Table 1. Requirements following randomization are outlined on Table 2.

Table 1. Tests, exams, and other requirements prior to study entry and randomization

Required Assessments	Prior to study entry		Prior to randomization
Consent form signed by the patient	X		
Local determination of HER2 status (see Section 3.3.8)	X		
Central determination of HER2 and hormone receptor status and PD-L1 status (see Sections 3.3.8, 3.3.9, 3.3.10, 10.0)			X[a]
History & physical exam	X[b]	Within 4 weeks	
Performance status (see Appendix A)	X		
Height & weight	X		
Assessment of BP and BP meds	X		
Assessment of concomitant medications	X[c]		
CBC/differential/platelet count	X	Within 14 days	
Total bilirubin/AST/ALT/Alkaline phosphatase	X		
Calcium, fasting blood glucose, albumin, sodium, potassium	X		
Creatinine or creatinine clearance (calculated or measured)	X		
TSH and AM (preferably drawn in morning) Cortisol	X		
PT/INR	X		
Hepatitis B Surface Antigen, Hepatitis B Core Antibody, Hepatitis C Antibody	X[d]		
Pregnancy test	X[e]	Within 3 days	
Echocardiogram (or MUGA scan)	X[f]	Within 6 weeks	
12-Lead ECG	X		
Imaging of chest/abdomen/pelvis	X[g]	Within 5 weeks	
Bone scan	X[h]		
Neuroimaging	X[i]		

Table continued on next page.

Table 1. Tests, exams, and other requirements prior to study entry and randomization *(continued)*

Required Assessments	Prior to study entry	Prior to randomization
Optional submission of unstained slides (see Section 10.0)	X[j]	
Optional submission of blood sample for ctDNA	X[k] (before atezolizumab/placebo therapy begins)	
Quality of Life (QOL) questionnaire	X[l]	
If patient not randomized, an adverse event assessment is to be performed 30 days after last treatment received after study entry and prior to randomization		X[m]

a ***Submission of unstained slides for central confirmation of HER2 and ER/PgR and PD-L1 testing after study entry but prior to randomization is mandatory.*** For patients presenting with ***de novo metastatic disease***, unstained slides from metastatic disease are preferred, but unstained slides from breast primary or involved regional lymph nodes may be submitted as an alternative. For patients presenting with ***locally recurrent or metastatic disease following prior therapy for early breast cancer***, unstained slides from the metastatic disease or locally recurrent disease must be submitted. A "Notice of HER2 Eligibility" must appear in Medidata Rave to confirm testing for HER2, ER/PgR, and PD-L1 has been completed before a patient can be randomized. See Section 10.0 and the NRG-BR004 Pathology, Correlative Science, and Imaging Submission Instructions.

b History and physical by a physician or other healthcare professional.

c Include all prescribed and over-the-counter medications, supplements, herbal therapies (see Section 5.4.3)

d Hepatitis B virus DNA must be collected in patients who have negative serology for Hepatitis B surface antigen and positive serology for antibody to hepatitis B core antigen.

e For women of childbearing potential: Pregnancy testing should be performed according to institutional standards within 3 days prior to study entry.

f ***Echocardiogram is the preferred method for assessment of LVEF.*** However, LVEF assessment by MUGA scan is permitted. All subsequent LVEF assessments should be performed by the same method (echocardiogram or MUGA scan) that was performed at baseline.

g The same method (CT or MRI) used for baseline tumor measurements should be used at all other tumor measurement time points. If patient is unable to receive CT contrast, a MRI of the abdomen/pelvis and non-contrast chest CT should be performed. PET/CT ***is not*** an acceptable alternative contrast enhanced imaging method. ***Note:*** Copies of all disease imaging scans are to be submitted to Bioclinica for retrospective central independent review (see the NRG-BR004 Pathology, Correlative Science, and Imaging Submission Instructions and the BR004 Bioclinica site manual). See Section 13.1 for submission of disease imaging scan reports.

h If PET/CT was previously performed within the 5 weeks prior to study entry and demonstrated no evidence of bone metastases, baseline bone scan is recommended but not required.

i MRI of the brain (or contrast CT scan of the brain if patients are unable to undergo MRI) is required if symptoms suggest possible CNS metastatic disease. However, neuroimaging is also recommended in asymptomatic patients.

j Submission of unstained slides within 45 days following study entry is ***required for all patients who agreed to optional tissue submission*** in the consent form. See Section 10.0 and the NRG-BR004 Pathology, Correlative Science, and Imaging Submission Instructions.

Table continued on next page.

Table 1. Tests, exams, and other requirements prior to study entry and randomization *(continued)*

k	***Requirement for all patients who agreed to optional blood collection and submission*** in the consent form. See Section 10.0 and the NRG-BR004 Pathology, Correlative Science, and Imaging Submission Instructions for ctDNA kit ordering instructions.
l	The QOL questionnaire must be administered after the informed consent is signed (see Section 11.0). For QOL reporting, this study uses Medidata Patient Cloud ePRO. Remember to register the patient to the Patient Cloud. For instructions on registering the patient, please refer to Section 8.5 and Appendix B. The study-specific QOL items for this protocol can be found on the CIRB Documents>Amendment Reviews section of the CTSU protocol webpage (https://www.ctsu.org).
m	Patients who are not confirmed to be HER2-positive by central confirmation testing will not be randomized and will be taken off study and treated per investigator discretion. Patients will not be followed on BR004.

Table 2. Tests, exams, and other requirements during therapy and through Year 10 for Arm 1 and Arm 2

The NRG-BR004 study was permanently closed to accrual on May 20, 2022. Modified scheduled status updates, as outlined on Table 2A, will be completed for patients enrolled prior to study accrual closure.

With Amendment #3, accrual to the PRO-CTCAE substudy is closed. Patients enrolled on the PRO-CTCAE substudy prior to Amendment #3 will continue to complete the scheduled assessments as outlined on Table 2. Accrual to the QOL substudy will continue.

Required assessments *(See footnotes **a, b, and c**)*	**During Paclitaxel or Docetaxel Therapy (Within 3 days of Days 1 and 22 of each 6-week cycle)**	**During Trastuzumab, Pertuzumab, Atezolizumab/Placebo (Within 3 days of Day 1 of each 6-week cycle through Year 2)**	**30 to 45 days after the last dose of atezolizumab/placebo**	**Years 3 through 5** *(from study entry)*	**Years 6 through 10** *(from study entry)*
History & physical exam**d**	X (every 3 weeks)	X (every 6 weeks)		X (every 3 months)	X (every 6 months)
Vital signs	X (every 3 weeks)	X (every 6 weeks)		X (every 3 months)	X (every 6 months)
Adverse event assessment**e**	X (every 3 weeks)	X (every 6 weeks)	X	X (every 3 months)	X (every 6 months)
Concomitant medication assessment**f**	X	X	X		
CBC/differential/platelet count**g**	X (every 3 weeks)	X (every 6 weeks)	X	X (every 6 months)	X (every 6 months)
Total bilirubin/AST/ALT/Alk phos	X (every 3 weeks)	X (every 6 weeks)	X	X (every 6 months)	X (every 6 months)
Creatinine, calcium, glucose, albumin, sodium, potassium	X (every 3 weeks)	X (every 6 weeks)	X	X (every 6 months)	X (every 6 months)
TSH and Cortisol**h**	X (every 6 weeks while on atezolizumab/placebo)		X		
Imaging of chest/abdomen/pelvis for disease assessment**i,j**	X (prior to Weeks 10, 19, and 28 and then at 9, 12, 15, 18, 21, and 24 months from study entry)			X (every 3 months through Year 3 and every 6 months for Years 4 and 5)	X (every 6 months)
MRI of brain**k** (only if metastatic brain disease present at study entry)	X (prior to Weeks 10, 19, and 28 and then at 9, 12, 15, 18, 21, and 24 months from study entry)			X (every 3 months through Year 3 and every 6 months for Years 4 and 5)	X (every 6 months)

Table continued next page.

Table 2. Tests, exams, and other requirements during therapy and through Year 10 for Arm 1 and Arm 2 *(continued)*

Required assessments *(See footnotes **a, b, and c**)*	**During Paclitaxel or Docetaxel Therapy (Within 3 days of Days 1 and 22 of each 6-week cycle)**	**During Trastuzumab, Pertuzumab, Atezolizumab/Placebo (Within 3 days of Day 1 of each 6-week cycle through Year 2)**	**30 to 45 days after the last dose of atezolizumab/placebo**	**Years 3 through 5** *(from study entry)*	**Years 6 through 10** *(from study entry)*
MRI of brain**k** (only if metastatic brain disease present at study entry)	X (prior to Weeks 10, 19, and 28 and then at 9, 12, 15, 18, 21, and 24 months from study entry)			X (every 3 months through Year 3 and every 6 months for Years 4 and 5)	X (every 6 months)
Echocardiogram (or MUGA scan)l	X (every 12 weeks from study entry)			X (every 6 months)	X (every 12 months)
Bone scan	X (every 6 months from study entry)			X (every 6 months through Year 3 and every 12 months for Years 4 and 5)	
Quality of Life (QOL) questionnaire**m**	X (at 12 and 24 weeks from study entry)	X (12, 18, and 24 months from study entry)		X (at 30 months only)	
PRO-CTCAE assessment**m**	X (weekly Cycles 1-2; every 3 weeks Cycles 3-4)	X (every 6 weeks)		X (at 30 months only)	
Submission of blood sample for ctDNA**n**	X (prior to Weeks 10, 19, and 28 and then at 9, 12, 18, and 24 months from study entry)			X (every 6 months)	
Submission of unstained slides at time of progression**o**	X				

a History and physical, blood tests, x-rays, scans, and other testing may be performed more frequently at the discretion of the investigator.

b Patients who discontinue all protocol therapy for reasons other than disease progression must follow the exams, assessments, and tissue sample submissions outlined on Table 2. ***Further therapy will be at the investigator's discretion and treatments administered prior to progression must be reported in eCRF.***

c *While tests, exams, and assessments, **are not required** following disease progression, follow-up for subsequent cancer events and immune-related events, post progression therapies with immune therapy, and for survival continues to be required every 6 months through Year 10. (See Section 7.0 for adverse event reporting requirements.)*

Table continued on next page.

Table 2. Tests, exams, and other requirements during therapy and through Year 10 for Arm 1 and Arm 2 *(continued)*

d History and physical with exams (by physician or other healthcare professional) appropriate for therapy-related assessments and follow-up evaluations.

e See Section 7.6 for instructions regarding adverse event reporting.

f Include all prescribed and over-the-counter medications, supplements, herbal therapies (see Section 5.4.3).

g CBC/differential/platelet count may be checked more frequently per institutional policy. If obtained, the results must be reviewed prior to administration of paclitaxel or docetaxel. The trastuzumab and pertuzumab may be started prior to obtaining results.

h Cortisol should be collected preferably in the morning. After atezolizumab/placebo is discontinued, patients should be monitored for signs and symptoms of endocrinopathies (e.g., fatigue) and testing considered for TSH and cortisol as clinically indicated.

i The same method (CT or MRI) used for ***baseline tumor measurements*** should be used at all other tumor measurement time points. Scans may be performed within 14 days of the scheduled scan assessment through Year 2. Scans may be performed +/- 3 weeks for scans done in Years 3 through 10. Follow the scan schedule until documented progression. If therapy with atezolizumab/placebo is continued in the setting of possible pseudoprogression, repeat scans are required in 4 to 6 weeks (see Section 12.2.8). If patients discontinue protocol therapy in the absence of disease progression, tumor assessments should continue unless they have started alternative (non-protocol) anti-cancer therapy, withdraw consent, or the study is terminated by the sponsor, whichever occurs first. ***Note:*** Copies of all disease imaging scans are to be submitted to Bioclinica for retrospective central independent review (see the NRG-BR004 Pathology, Correlative Science, and Imaging Submission Instructions and the BR004 Bioclinica site manual). See Section 13.1 for submission of disease imaging scan reports.

j **Beginning in Year 2 the following substitutions for** disease assessment scans of regions of the body not previously involved with malignancy on imaging may be made at investigator discretion to reduce radiation or gadolinium exposure:

- No disease in the chest at entry – A chest x-ray may be substituted for a CT scan of the chest.
- No disease in the abdomen at entry – An ultrasound of the abdomen may be substituted for a CT scan of the abdomen.
- No disease in the pelvis at entry – An ultrasound of the pelvis may be substituted for a CT scan of the pelvis.

At the time of progression, patients should have imaging of the chest/abdomen/pelvis, preferably with a CT scan, and a bone scan performed to document extent of disease.

Note: In the event of declining renal function or dye allergy, chest CT may be performed without contrast and MRI of abdomen and pelvis may be substituted for CT scan.

k Any patient with worsening and/or new neurological symptoms will be evaluated per institutional standards.

l ***Echocardiogram is the preferred method for assessment of LVEF.*** However, LVEF assessment by MUGA scan is permitted. All LVEF assessments should be performed by the same method (echocardiogram or MUGA scan) that was performed at baseline.

m PRO-CTCAE assessments are expected from only those patients who completed the baseline PRO-CTCAE prior to Amendment #3. This study uses Medidata Patient Cloud ePRO for QOL and PRO-CTCAE reporting. Remember to register the patient to the Patient Cloud. For instructions on registering the patient, please refer to Section 8.5 and Appendix B. The study-specific QOL and PRO-CTCAE items for this protocol can be found on the CIRB Documents>Amendment Reviews section of the CTSU protocol webpage (https://www.ctsu.org).

Table continued on next page.

Table 2. Tests, exams, and other requirements during therapy and through Year 10 for Arm 1 and Arm 2 *(continued)*

n ***Requirement for all patients who agreed to optional blood collection and submission*** in the consent form. See Section 10.0 and the NRG-BR004 Pathology, Correlative Science, and Imaging Submission Instructions for ctDNA kit ordering instructions. A blood sample must also be collected at the time of tumor recurrence (see Section 10.0).
o Submission of unstained slides at the time of tumor progression (if biopsy was performed) is only required for patients who have agreed to the ***optional tumor sample submission*** when signing the consent form (see Section 10.0 and the NRG-BR004 Pathology, Correlative Science, and Imaging Submission Instructions).

Table 2A. Required status updates after study closure through April 2024 for Arm 1 and Arm 2

The NRG-BR004 study was permanently closed to accrual on May 20, 2022. Modified scheduled status updates, as outlined on Table 2A, will be completed for patients enrolled prior to study accrual closure.

Required status updates	First follow-up visit post-activation of Amendment #6[a]	Subsequent follow-up visits (every 6 months)[b]
Vital status	X	X
Adverse events of special interest assessment[c]	X	X
Monitoring for initial disease progression and survival status[c]	X	X

a **A**fter activation of Amendment #6, the first follow-up visit will occur 3 months from the last scheduled follow-up visit.

b After the first follow-up visit post-activation of Amendment #6, patient follow-up visits will change to an every-6-month schedule through April 2024.

c Follow-up for breast cancer progression, second malignancies, adverse events of special interest, and survival continues to be required every 6 months through April 2024. (See Section 7.5.4 and Section 7.7 for reporting requirements.)

5.0 TREATMENT REGIMENS

5.1 Treatment Regimen for Arm 1 and Arm 2

This is a double-blind trial; neither the patient nor the investigator/healthcare providers will know the treatment assigned.

- Once potential eligibility has been confirmed and consent signed, initiate Cycle 1 treatment with standard loading doses of trastuzumab and pertuzumab obtained by the investigator from commercial supply and paclitaxel or docetaxel per institutional standards while waiting on results of central testing. Once eligibility has been confirmed by central testing and the patient has been randomized, the first dose of atezolizumab/placebo should be administered on Day 22 of Cycle 1.
- After study entry, a tumor specimen must be submitted for central testing so that results are received in time for patient randomization within 14 days from study entry. This will ensure that the PMB-supplied agents will be received at the site for treatment on Day 22 of Cycle 1.
- Patients who are not confirmed to be HER2-positive by central testing will not be randomized and will be taken off study and treated per investigator discretion. A final adverse event assessment should be performed at 30 days after the last treatment received after study entry and prior to randomization. Patients will not continue to be followed on BR004.
- Atezolizumab/placebo should begin within 7 days following randomization.
- ***Adverse events and results of laboratory safety assessments are to be reviewed prior to administration of components of study therapy pertinent to that parameter.***
- ***Central venous access is strongly recommended.***

Table 3. Treatment regimen for Arm 1 and Arm 2

Drug	Dose	Dosing Interval	Planned Duration
Pertuzumab (P)[a] *(Use of premeds is at the investigator's discretion or institutional policy.)*	*First dose (loading dose):* 840 mg IV over 60 minutes (±10 minutes)**[b,c]** *Subsequent doses:* 420 mg IV over 30-60 minutes**[c,d]**	Days 1 and 22 every 6 weeks	Until progression
Trastuzumab (T)[a] *(Use of premeds is at the investigator's discretion or institutional policy.)*	*First dose (loading dose):* 8 mg/kg IV over 90 minutes (±10 minutes)**[b,c]** *Subsequent doses:* 6 mg/kg IV over 30-60 minutes**[c,d]**	Days 1 and 22 every 6 weeks	Until progression
Paclitaxel (WP)[b,e] **OR** **Docetaxel (D)[b,f]** *(Premeds may be modified at the investigator's discretion or institutional policy.)*	**Paclitaxel (WP)[b,e]** 80 mg/m2 IV over 60 minutes (-5 or +10 minutes) *See footnote **f** for premedications*	Days 1, 8, 15, 22, 29, and 36 every 6 weeks	Minimum of 3 cycles with additional cycles allowed in absence of progression or toxicity at the investigator's discretion
	Docetaxel (D)[b,f] 75 mg/m2 IV over 60 minutes (-5 or +10 minutes) *See footnote **f** for premedications*	Days 1 and 22 every 6 weeks	

Table continued on next page.

Table 3. Treatment regimen for Arm 1 and Arm 2 *(continued)*

Drug	Dose	Dosing Interval	Planned Duration
Atezolizumab/ Placebo	**1200 mg IV** diluted in 250 mL polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO) infusion bag containing 0.9% NaCl solution (NSS) or **placebo IV**. Administer through an intravenous line with a sterile, non-pyrogenic, low-protein binding in-line filter (pore size of 0.2 – 0.22 micron)**g,h**	Day 22 of Cycle 1 and then Days 1 and 22 every 6 weeks	Two years in absence of progression
	First Infusion	**Subsequent Infusions**	
	• No premedication for atezolizumab/placebo is permitted prior to the atezolizumab/placebo infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • Atezolizumab/placebo should be infused over 60 (± 15) minutes. • If clinically indicated, vital signs should be measured every 15 (± 5) minutes during the infusion and at 30 (± 10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab/placebo should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (± 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (± 10) minutes after the infusion.	

Table continued on next page.

Table 3. Treatment regimen for Arm 1 and Arm 2 *(continued)*

Atezolizumab/ Placebo	Because of the risk of an anaphylactic reaction, it is important to have the following equipment available: **Equipment Needed** • Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer • Oxygen • Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice • Antihistamines • Corticosteroids • IV infusion solutions, tubing, catheters, and tape

Note: During paclitaxel or docetaxel therapy, patients are to be assessed every 3 weeks during the 6-week cycle. While on antibody therapies alone, patients are to be assessed every 6 weeks. In order to keep the AE reporting cycles consistent for the first 2 years of study therapy, a treatment cycle will be 6 weeks (see Table 2).

a Initiate Cycle 1 treatment with standard loading doses of trastuzumab and pertuzumab obtained by the investigator from commercial supply.

b Pertuzumab, trastuzumab, paclitaxel or docetaxel should be administered sequentially. Paclitaxel or docetaxel should be administered after pertuzumab and trastuzumab. An observation period of 30 to 60 minutes is recommended after each pertuzumab infusion and before starting any subsequent infusion of trastuzumab or paclitaxel but may be adjusted by institutional standards.

c See Table 10 for LVEF requirements for continuation of trastuzumab and pertuzumab, and atezolizumab/placebo.

d See Table 11 for instructions regarding trastuzumab and pertuzumab infusion-related and allergic reactions.

e Patients should receive premedications as follows for initial paclitaxel dose.

- Dexamethasone 8-12 mg IV, completed 30 minutes before paclitaxel administration.
- Diphenhydramine hydrochloride 25-50 mg IV or PO and an H-2 blocker IV or PO (cimetidine 300 mg, ranitidine 50 mg, or famotidine 20 mg) before paclitaxel administration.
- Dexamethasone should be tapered and discontinued for subsequent paclitaxel cycles if tolerated and may be discontinued per investigator discretion.
- Diphenhydramine hydrochloride 25-50 mg and the H-2 blocker may also be tapered and discontinue per investigator discretion.

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Table 3. Treatment regimen for Arm 1 and Arm 2 *(continued)*

f	Patients should receive premedications as follows before initial docetaxel dose. • Dexamethasone 8 mg BID the day before and the day of chemotherapy. At investigator discretion, dexamethasone may be continued on the day after chemotherapy. An equivalent dose of other corticosteroids may be substituted (dexamethasone 8 mg = methylprednisolone 40 mg = prednisone 50 mg = prednisolone 50 mg). • Administration of IV dexamethasone as a substitute for oral dexamethasone prior to chemotherapy is at the investigator's discretion. • Dexamethasone dose and duration may be tapered for subsequent docetaxel cycles per investigator discretion. At the investigator's discretion, other non-steroidal premedications, e.g., diphenhydramine hydrochloride 50 mg IV and H-2 blocker IV (cimetidine 300 mg, ranitidine 50 mg, or famotidine 20 mg) may be given in addition to dexamethasone.
g	If an infusion-related reaction, cytokine-release syndrome, or anaphylactic reaction occurs, see Section 6.12 for additional treatment management information.
h	Refer to Section 9.1.1 for compatible infusion set materials including inline filter.

5.2 Endocrine Therapy Following Paclitaxel and Docetaxel

Initiation of endocrine therapy for patients who are ER-positive or PgR-positive is not recommended until progression but may be initiated per investigator discretion following completion of paclitaxel or docetaxel. The endocrine therapies that may be administered after completing paclitaxel or docetaxel include tamoxifen, aromatase inhibitors, fulvestrant, and luteinizing hormone-releasing hormone agonists. Co-administration of everolimus or CDK 4/6 inhibitors ***is not*** permitted. Patients should continue to follow the study calendar (see Table 2).

5.3 Dose Determinations

5.3.1 Calculations of BSA and Chemotherapy Doses

- Recommended chemotherapy doses will be provided at the time of study entry.
- Recalculations of BSA and chemotherapy doses are required if the patient has a 10% or greater weight change (+/-) from baseline or from the last weight used to calculate BSA and drug doses. At investigator discretion and institutional practice, the BSA and chemotherapy doses may be recalculated prior to each treatment.

5.3.2 Rounding Doses

Follow institutional practice for standard drug rounding.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Bone-directed therapy

Bisphosphonates and denosumab are allowed.

5.4.2 Antiemetic Therapy

Antiemetic therapy should be administered according to National Comprehensive Cancer Network (NCCN) (https://www.nccn.org) or American Society of Clinical Oncology (ASCO) (http://www.asco.org) clinical practice guidelines.

5.4.3 Concomitant Therapy Precautions

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 14 days prior to initiation of study entry to the treatment discontinuation visit. Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown.

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, H1-receptor antagonists (e.g., diphenhydramine) and/or H2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists).

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific immune-related adverse events when associated with atezolizumab or placebo therapy (refer to the Atezolizumab Investigator's Brochure for details).

5.4.4 Prohibited Therapies

The following types of treatment, in addition to any cancer therapy other than the therapy specified in this protocol, are prohibited until the time of disease progression or discontinuation of protocol therapy.

- ***Chemotherapy***

  Administration of chemotherapy other than the chemotherapy specified in this protocol is prohibited.

- ***Targeted therapy or immunotherapy***

  Administration of targeted therapy or immunotherapy other than the targeted therapy and immunotherapy specified in the protocol is prohibited.

- ***Live virus vaccines***

  Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to study entry, during study treatment, and for 5 months after the last dose of atezolizumab/placebo.

- ***Systemic immunomodulatory or immunosuppressive medications***
  - Systemic immunomodulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to study entry and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
  - Systemic immunosuppressive medications (including, but not limited to, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.

5.4.5 Participation in Other Trials

Patients are not permitted to participate in other therapeutic trials until after progression. If a BR004 patient is considering participation in a supportive therapy trial, contact the NRG Oncology Clinical Coordinating Department.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment should continue as specified in the above treatment modality sections until one of the following criteria applies:

- Disease progression
- 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
  - 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 female patient or the partner of a male patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

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

6.0 TREATMENT MODIFICATIONS/MANAGEMENT

6.1 General Instructions

- The CTCAE v5.0 must be used to grade the severity of AEs. Refer to http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol-directed action.
- Dose reductions for paclitaxel and docetaxel must be based on the AE requiring the greatest modification.
- Paclitaxel and docetaxel doses that have been reduced may not be escalated.
- There are no dose reductions for trastuzumab, pertuzumab, and atezolizumab/placebo.
- If necessary, the timing of a treatment may be adjusted to 2 days earlier or 2 days later than the scheduled date of treatment, though paclitaxel doses should not be administered within 5 days of each other.
- Atezolizumab/placebo must not be administered beyond 2 years after the first dose (Day 22) of the first treatment cycle regardless of any missed doses or treatment delays.
- Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 21 days of the scheduled interruption. The reason for interruption should be documented in the patient's study record.
- When rescheduling study therapy for non-medical adjustments, refer to the memo "Scheduling Protocol Therapy during the Holidays." This memo provides information regarding treatment over holidays/vacations and other non-medical delays (e.g., physician or patient schedules). This memo is updated annually and is posted on the CTSU Web site under the specific protocol supplemental documents.

6.2 Tumor Progression

Progression of disease is defined in Section 12.0, and study therapy should generally be discontinued at the time of initial documentation of RECIST 1.1 criteria for progression. However, in cases in which the investigator believes pseudoprogression may have occurred, protocol therapy may be continued, but repeat scans must be obtained in 4 to 6 weeks to determine if true progression has occurred. If follow-up scans determine true progression has occurred, the date of progression will be considered the date of the initial scan meeting RECIST 1.1 criteria for analysis purposes. If pseudoprogression is confirmed, the patient will continue therapy and follow-up per protocol until true progression is documented.

6.3 Treatment Decisions When Components of Therapy Must Be Held or Discontinued

- If Cycle 1, Day 22 trastuzumab is held due to toxicity, delay initiation of atezolizumab/placebo until trastuzumab is resumed.
- Trastuzumab, pertuzumab, and atezolizumab/placebo therapy should continue in the absence of progression if chemotherapy is discontinued before completion of all planned cycles.
- If trastuzumab, pertuzumab, or atezolizumab/placebo is discontinued in the absence of progression, chemotherapy doses may be continued if the patient is benefitting from the therapy.

- If trastuzumab and pertuzumab have been discontinued, atezolizumab/placebo must also be discontinued.
- If trastuzumab, pertuzumab, and atezolizumab/placebo must be omitted for a cycle due to cardiac toxicities, maintain the chemotherapy schedule if clinically appropriate.
- If trastuzumab must be omitted for a cycle for toxicities related to trastuzumab other than hypersensitivity, the pertuzumab and atezolizumab/placebo must also be held. Maintain the chemotherapy schedule if clinically appropriate.
- If criteria for administration of either pertuzumab or atezolizumab/placebo are not met when criteria for trastuzumab administration are met, the agent not meeting criteria should be omitted for that cycle and resumed once criteria for resumption are met with subsequent doses of trastuzumab.
- A loading dose of trastuzumab or pertuzumab may be given at the investigator's discretion, if ≥ 6 weeks have elapsed since the prior dose of trastuzumab or pertuzumab. The maintenance dose will be administered for subsequent doses.
- If atezolizumab/placebo must be held for > 16 weeks for toxicities related to atezolizumab/placebo, atezolizumab/placebo must be discontinued.
- If alternative (non-protocol) anti-cancer therapy is given at any time, protocol therapy must be discontinued.
- **If all protocol therapy is discontinued, further therapy is at the investigator's discretion. If protocol therapy has been discontinued for ANY reason other than disease progression, the study calendar for assessing response status should continue to be followed until first progression is documented. This should occur even if non-protocol therapy has been initiated.**

6.4 Management of Atezolizumab/Placebo Immune-Mediated Toxicities and Potential Unblinding

6.4.1 Supportive Care Guidelines

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab/placebo may not have an immediate therapeutic effect, and more severe immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents. Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined in the following sections. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids.

Toxicities associated or possibly associated with atezolizumab/placebo treatment should be managed according to standard medical practice. Investigators are encouraged to review and refer to the American Society for Clinical Oncology Clinical Practice Guidelines for management of immune-mediated adverse events in patients treated with immune checkpoint inhibitors (Brahmer 2018), along with the dose modification guidelines provided in this protocol for evaluation and management of potential immune adverse events. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Additional tests, such as autoimmune serologies or biopsies, should be used to evaluate for a possible immunogenic etiology.

For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to atezolizumab/placebo.

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined in the following sections).

6.4.2 Overall Management for Immune-Mediated Adverse Events

The following guidelines should be followed for management of immune-mediated reactions/immune-mediated adverse events (irAEs):

- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.).
- In the absence of a clear alternative etiology, events should be considered potentially immune-mediated.
- Symptomatic or topical therapy should be considered for **Grade 1 and mild or transient (≤ 3 days) Grade 2 irAEs**, **unless otherwise specified in each immune-mediated toxicity section**.
- For **persistent (≥ 3 days) Grade 2 or Grade 3 irAEs**, hold atezolizumab/placebo and promptly begin prednisone orally 1-2 mg/kg/day **unless otherwise specified in each immune-mediated toxicity section**.
  - If toxicity does not improve within 5 days, hospitalize and treat as severe Grade 3 irAE.
  - Begin steroid taper over no less than 4 weeks when toxicity improves to ≤ Grade 1.
  - If symptoms recur or worsen during corticosteroid tapering, contact the Protocol Officer.
- For **severe Grade 3 and Grade 4 irAEs, hospitalize** and begin IV methylprednisolone 2-4 mg/kg/day or equivalent.
  - If no response within 3 days, consider additional immunosuppression (infliximab, cyclophosphamide). Contact the Protocol Officer.
  - If symptoms recur or worsen during corticosteroid tapering, contact the Protocol Officer. Consider increasing the corticosteroid dose (prednisone dose [e.g., up to 2-4 mg/kg/day or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate.
- Discontinuation of study drug is not mandated for grade 3 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.). Continuation of atezolizumab/placebo in this situation should be based upon a benefit/risk analysis for the patient.

6.4.3 Management of Atezolizumab/Placebo Immune-Mediated Toxicities and Potential Unblinding

Management of certain AEs of concern, including immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies, pancreatitis, neuropathies, meningoencephalitis, and potential ocular toxicities are presented in the Atezolizumab Investigator's Brochure. See the atezolizumab/placebo management guidelines in this document, administration of First and Subsequent Atezolizumab Infusions in Table 3, and guidelines for the management of infusion-related reactions, cytokine-release syndrome, and anaphylaxis in Table 16.

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism,

adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome.

In general, for Grade 3 or 4 toxicities which have the potential for being immune-mediated, unblinding should be requested to determine if a patient had been receiving atezolizumab or placebo. Management of patients with Grade 3 or 4 immune-mediated toxicities will require aggressive immunosuppressive therapies if a patient has been receiving atezolizumab. If a patient had been receiving placebo, alternative therapies and additional diagnostic testing may be indicated. Patients with Grade 2 toxicities may have atezolizumab/placebo held and observed without initiation of immunosuppressive therapy, with consideration of rechallenge without unblinding if medically appropriate. However, if a decision is made to initiate immunosuppressive therapy, unblinding should be considered to determine if the patient was receiving atezolizumab or placebo to determine if the immunosuppressive therapy is appropriate.

Unblinding is permitted for medical management of toxicity and to guide initiation of steroids and other immunosuppressives. When the unblinding is requested, the date and reason for unblinding must be fully documented in source documents and recorded in the case report forms. If unblinding occurs, the site staff should make every effort to ensure that the treatment arm in which the unblinded patient was assigned is not communicated to any sponsor personnel or designee involved in the study. ***If unblinding occurs, the atezolizumab/placebo must be permanently discontinued.*** When this occurs, provision of trastuzumab is also discontinued. Patients will transition to trastuzumab and pertuzumab obtained by the investigator from commercial supply. The institution is responsible for providing continued follow-up (for patients whose treatment assignment has been unblinded) on the same schedule as indicated in the study protocol for patients who have not been unblinded, unless otherwise specified (see Table 2). See Section 9.6 for instructions on unblinding patient treatment.

6.5 Management of Diarrhea Potentially Related to Study Therapy

6.5.1 Evaluation and Management of Diarrhea

Diarrhea is an expected potential toxicity with the use of trastuzumab, pertuzumab, and docetaxel in BR004, generally occurring shortly after initiation of the therapy. Diarrhea may also occur at any time due to immune-colitis from atezolizumab/placebo at any time following initiation of therapy, though the incidence of early diarrhea is low. Therefore, the timing of onset of the diarrhea should be taken into consideration when evaluating and managing diarrhea, particularly Grade 1 and Grade 2 diarrhea. Evaluation and management of diarrhea will also be impacted by whether or not patients are receiving chemotherapy with trastuzumab and pertuzumab as well as co-administration of atezolizumab/placebo. Investigators should also remember immune-colitis may occur subsequent to discontinuation of atezolizumab/placebo, so patients developing diarrhea following completion or discontinuation of atezolizumab/placebo should be evaluated for possible immune-mediated diarrhea/colitis.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

If immune-mediated diarrhea has not been documented and an alternative specific etiology for diarrhea is found that suggests it is not treatment-related, dose modifications for treatment-related

diarrhea do not have to be followed, and investigators may continue portions or all of therapy without modifications per investigator discretion. These decisions must be documented in the source documents.

Patient education should include instructions regarding the importance of prompt reporting of diarrhea, early intervention with antidiarrheal medication such as loperamide, and non-pharmacologic interventions (e.g., increasing fluid intake, eating frequent small meals, avoiding foods that are high in lactose, etc.). Refer to ASCO Recommended Guidelines for Treatment of Cancer Treatment-Induced Diarrhea for additional recommendations regarding diarrhea (Benson 2004).

Patients should be carefully monitored for signs and symptoms of associated enterocolitis (such as abdominal pain, blood or mucus in stool, with or without fever in addition to the diarrhea) as well as bowel perforation (i.e., peritoneal signs and ileus). This is essential in patients receiving docetaxel, particularly if associated with neutropenia. Patients with diarrhea accompanied by abdominal pain or febrile neutropenia should be admitted to the hospital.

- All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be administered via IV infusion.
- Always evaluate for potential infectious causes of diarrhea.
- At onset of diarrhea, promptly initiate loperamide.
- **Acceptable Grade 2 diarrhea** will be determined by the investigator and patient but must **also be characterized by ALL of the following:**
    - Maintenance of fluid and electrolyte balance with oral hydration.
    - Absence of abdominal pain or no worsening of abdominal pain in patients with pre-existing abdominal pain due to metastatic disease.
    - Absence of fever ≥ 38° C.
    - Absence of visible blood in the stool.
- For **Unacceptable Grade 2 diarrhea/colitis,** consult GI for lower endoscopy or flexible sigmoidoscopy with biopsy to confirm or rule out immune-mediated colitis. If a patient is experiencing abdominal pain or fever, particularly if associated with neutropenia, the patient should be admitted to the hospital.
- For **Grade 3 diarrhea/colitis**, hospitalize and evaluate for both immune and non-immune etiologies of diarrhea/colitis. Promptly consult GI for consideration of lower endoscopy. If biopsy can be performed, initiate corticosteroids without unblinding, pending results of lower endoscopy biopsy. If patient is too ill for lower endoscopic biopsy, promptly initiate steroids and request unblinding to help guide management. For patients with Grade 3 diarrhea of ≤ 3 days duration based solely on an increase in the number of stools to ≥ 7 over baseline, who are maintaining fluid and electrolyte balance with oral hydration, are free of abdominal pain, are free of fever ≥ 38°C and are free of blood in the stool may be evaluated as an outpatient per investigator discretion.
- For **Grade 4 diarrhea/colitis**, hospitalize and evaluate for both immune and non-immune etiologies of diarrhea/colitis. Promptly consult GI for consideration of lower endoscopy. Promptly initiate steroids and request unblinding to help guide further management.

6.5.2 Treatment Management and Dose Modifications for Treatment-Related Diarrhea or Colitis

The following tables provide dose modifications for patients in Arm 1 and Arm 2 for the time patients are receiving study therapy.

- Refer to Table 4 for management of atezolizumab/placebo for patients experiencing treatment-related diarrhea or colitis while on therapy. If diarrhea occurs early following initiation of atezolizumab/placebo with trastuzumab and pertuzumab, atezolizumab/placebo should be held and not resumed until tolerance to trastuzumab and pertuzumab has been established.
- Refer to Table 5 for management of trastuzumab, pertuzumab, and paclitaxel for patients experiencing **treatment-related diarrhea or colitis while receiving paclitaxel**.
- Refer to Table 6 for management of trastuzumab, pertuzumab, and docetaxel for patients experiencing **treatment-related diarrhea or colitis while receiving docetaxel**.
- Refer to Table 7 for management of trastuzumab and pertuzumab for patients experiencing **treatment-related diarrhea or colitis following completion of chemotherapy**.

Table 4. Dose modifications and instructions for atezolizumab/placebo for treatment-related diarrhea or colitis

See Section 6.5.1 for management of diarrhea or colitis.

CTCAE v5.0 Adverse Event	CTCAE Grade	Management of atezolizumab/placebo
Diarrhea, Colitis	Grade 1 Diarrhea	• Initiate symptomatic treatment. • Continue atezolizumab/placebo. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
	Acceptable Grade 2 Diarrhea	• Initiate symptomatic treatment. • Continue atezolizumab/placebo.
	Unacceptable Grade 2 Diarrhea or Grade 2 Colitis	• Initiate symptomatic treatment. • Hold atezolizumab/placebo. • Refer to GI specialist for evaluation and sigmoidoscopy. • Endoscopic evaluation should include random biopsy to look for lymphocytic infiltrate even if no clear visual evidence of colitis is seen by endoscopist. - If immune colitis documented, discontinue atezolizumab/placebo and request unblinding. - If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. • If immune colitis not documented, resume atezolizumab/placebo when tolerance to trastuzumab, pertuzumab, and chemotherapy has been established.

Table continued on next page.

Table 4. Dose modifications and instructions for atezolizumab/placebo for treatment-related diarrhea or colitis *(continued)*

CTCAE v5.0 Adverse Event	CTCAE Grade	Management of atezolizumab/placebo
Diarrhea, Colitis	Grade 3 Diarrhea and Colitis	• Hospitalize for evaluation and management (patients with Grade 3 diarrhea of ≤ 3 days duration based solely on an increase in the number of stools to ≥ 7 over baseline with no evidence of colitis may be evaluated as an outpatient per investigator discretion). • Hold atezolizumab/placebo. • Consult GI specialist for urgent evaluation and consideration of endoscopy with possible biopsy. • If immune colitis documented or if patient too ill for lower endoscopy and biopsy, discontinue atezolizumab/placebo and request unblinding to guide further management. - Initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. - For patients with documented or presumed immune colitis who had received atezolizumab with progressive symptoms despite corticosteroid therapy, or who relapse following corticosteroid taper and do not improve with re-escalation of corticosteroids, administer infliximab 5 mg/kg. Repeat dose in 2 weeks if symptoms not improved. Maintain corticosteroid dosing during infliximab dosing period, taper once symptoms are improving. • If immune colitis not documented and patient was not unblinded, resume or discontinue atezolizumab/placebo per investigator discretion when tolerance to trastuzumab, pertuzumab, and chemotherapy has been established.

Table continued on next page.

Table 4. Dose modifications and instructions for atezolizumab/placebo for treatment-related diarrhea or colitis *(continued)*

CTCAE v5.0 Adverse Event	CTCAE Grade	Management of atezolizumab/placebo
Diarrhea, Colitis	Grade 4 Diarrhea and Colitis	• Hospitalize for evaluation and management. • Consult GI specialist for urgent evaluation and consideration of lower endoscopy and biopsy. • Discontinue atezolizumab/placebo and request unblinding to guide further medical management. - Promptly initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. • For patients with documented or presumed immune colitis who had received atezolizumab, with progressive symptoms despite corticosteroid therapy and do not improve with re-escalation of corticosteroids, administer infliximab 5 mg/kg, repeat dose in 2 weeks if symptoms not improved. Maintain corticosteroid dosing during infliximab dosing period, taper once symptoms are improving.

Table 5. Dose modifications and instructions for trastuzumab, pertuzumab, and paclitaxel for treatment-related diarrhea or colitis **during paclitaxel administration**

See Section 6.5.1 for management of diarrhea.

CTCAE v5.0 Adverse Event	CTCAE Grade	Management of Trastuzumab, Pertuzumab, and Paclitaxel
Diarrhea, Colitis	Grade 1 Diarrhea	• Initiate symptomatic treatment. • Continue trastuzumab, pertuzumab, and paclitaxel.
	Acceptable Grade 2 Diarrhea	• Initiate symptomatic treatment. • Continue trastuzumab and paclitaxel. • Continue or hold pertuzumab per investigator discretion.

Table continued on next page.

Table 5. Dose modifications and instructions for trastuzumab, pertuzumab, and paclitaxel for treatment-related diarrhea or colitis **during paclitaxel administration** *(continued)*

CTCAE v5.0 Adverse Event	CTCAE Grade	Management of Trastuzumab, Pertuzumab, and Paclitaxel
Diarrhea, Colitis	Unacceptable Grade 2 Diarrhea, Grade 2 Colitis	• Initiate symptomatic treatment. • Hold trastuzumab, pertuzumab, and paclitaxel pending results of endoscopic biopsy. - If immune colitis documented, resume paclitaxel at same dose level when ≤ Grade 1. Resume pertuzumab when tolerance to trastuzumab and paclitaxel established. - If immune colitis NOT documented, resume paclitaxel with one dose level reduction when ≤ Grade 1. Resume pertuzumab when tolerance to trastuzumab and paclitaxel established. • If Unacceptable Grade 2 diarrhea occurs a **2nd or 3rd time <u>with co-administration of atezolizumab/placebo</u>**, hold trastuzumab, pertuzumab, and paclitaxel pending results of lower endoscopic biopsy. - If immune colitis documented, resume trastuzumab and paclitaxel at same dose level when ≤ Grade 1. Resume pertuzumab when tolerance to trastuzumab and paclitaxel established. - If immune colitis NOT documented, resume paclitaxel with one dose level reduction and trastuzumab when ≤ Grade 1. Resume or discontinue pertuzumab when tolerance to trastuzumab and paclitaxel established.
	Unacceptable Grade 2 Diarrhea, Grade 2 Colitis	• If Unacceptable Grade 2 diarrhea occurs a **2nd or 3rd time <u>without co-administration of atezolizumab/placebo</u>**, hold trastuzumab, pertuzumab, and paclitaxel. - If diarrhea resolves to ≤ Grade 1 within 1 week, resume paclitaxel with one dose level reduction and trastuzumab. Resume pertuzumab when tolerance to trastuzumab and paclitaxel established. - If diarrhea does not improve within 3 days refer for endoscopic biopsy. o If immune colitis documented, resume trastuzumab and paclitaxel at same dose level when ≤ Grade 1. Resume pertuzumab when tolerance to trastuzumab and paclitaxel established. o If immune colitis NOT documented, resume trastuzumab and paclitaxel with one dose level reduction when ≤ Grade 1. Discontinue or resume pertuzumab when tolerance to trastuzumab and paclitaxel established. • If Unacceptable Grade 2 diarrhea occurs a **4th time**, continue trastuzumab but discontinue paclitaxel and pertuzumab.

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Table 5. Dose modifications and instructions for trastuzumab, pertuzumab, and paclitaxel for treatment-related diarrhea or colitis **during paclitaxel administration** *(continued)*

CTCAE v5.0 Adverse Event	CTCAE Grade	Management of Trastuzumab, Pertuzumab, and Paclitaxel
Diarrhea, Colitis	Grade 3 Diarrhea, Colitis	• Initiate symptomatic treatment. • Hold trastuzumab, pertuzumab and paclitaxel pending results of lower endoscopic biopsy. - If immune colitis documented, resume paclitaxel at same dose level and trastuzumab when ≤ Grade 1. Resume pertuzumab when tolerance to trastuzumab and paclitaxel established. - If immune colitis NOT documented, resume paclitaxel with one dose level reduction and trastuzumab when ≤ Grade 1. Discontinue or resume pertuzumab when tolerance to trastuzumab and paclitaxel established. • If Grade 3 diarrhea occurs a **2nd time**, hold trastuzumab, pertuzumab, and paclitaxel pending results of lower endoscopic biopsy. - If immune colitis documented, resume paclitaxel at same dose level and trastuzumab when ≤ Grade 1. Resume pertuzumab when tolerance to trastuzumab and paclitaxel established. - If immune colitis NOT documented, resume paclitaxel with one dose level reduction and trastuzumab when ≤ Grade 1. Discontinue or resume pertuzumab when tolerance to trastuzumab and paclitaxel established. • If Grade 3 diarrhea occurs a **3rd time**, hold trastuzumab, pertuzumab, and paclitaxel pending results of lower endoscopic biopsy. - If immune colitis documented, resume trastuzumab and discontinue or resume paclitaxel with one dose level reduction when ≤ Grade 1. Discontinue or resume pertuzumab when tolerance to trastuzumab and paclitaxel established. - If immune colitis NOT documented, resume trastuzumab when ≤ Grade 1. Discontinue or resume paclitaxel with one dose level reduction and resume or discontinue pertuzumab when tolerance to trastuzumab has been established.
	Grade 4 Diarrhea, Colitis	• Hold trastuzumab, pertuzumab, and paclitaxel pending results of lower endoscopic biopsy. - If immune colitis documented, resume paclitaxel at reduced dose level and trastuzumab when ≤ Grade 1. Resume or discontinue pertuzumab when tolerance to trastuzumab and paclitaxel established. - If immune colitis NOT documented, resume trastuzumab and discontinue or resume paclitaxel with one dose level reduction when ≤ Grade 1. Discontinue pertuzumab.

Table 6. Dose modifications and instructions for trastuzumab, pertuzumab, and docetaxel for treatment-related diarrhea or colitis **during docetaxel administration**

Note: If diarrhea management becomes persistently problematic, an alternative to dose reductions of docetaxel per investigator discretion would be conversion to paclitaxel for subsequent cycles. See Section 6.5.1 for management of diarrhea.

CTCAE v5.0 Adverse Event	CTCAE Grade	Management of Trastuzumab, Pertuzumab, and Docetaxel
Diarrhea, Colitis	Grade 1 Diarrhea	• Initiate symptomatic treatment. • Continue trastuzumab, pertuzumab, and docetaxel.
	Acceptable Grade 2 Diarrhea	• Initiate symptomatic treatment. • Continue trastuzumab and docetaxel at same dose level or reduce one dose level per investigator discretion. • Continue or hold pertuzumab per investigator discretion.
	Unacceptable Grade 2 Diarrhea, Grade 2 Colitis	• Initiate symptomatic treatment. • Hold trastuzumab, pertuzumab, and docetaxel pending results of endoscopic biopsy. - If immune colitis documented, resume docetaxel at same dose level and trastuzumab when ≤ Grade 1. Resume pertuzumab when tolerance to trastuzumab and docetaxel established. - If immune colitis NOT documented, resume docetaxel with one dose level reduction and trastuzumab when ≤ Grade 1. Resume pertuzumab when tolerance to trastuzumab and docetaxel established. • If Unacceptable Grade 2 diarrhea occurs a **2nd or 3rd time with co-administration of atezolizumab/placebo**, hold trastuzumab, pertuzumab, and docetaxel pending results of lower endoscopic biopsy. - If immune colitis documented, resume docetaxel at same dose level and trastuzumab when ≤ Grade 1. Resume pertuzumab when tolerance to trastuzumab and docetaxel established. - If immune colitis NOT documented, resume docetaxel with one dose level reduction and trastuzumab when ≤ Grade 1. Resume or discontinue pertuzumab when tolerance to trastuzumab and docetaxel established.

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Table 6. Dose modifications and instructions for trastuzumab, pertuzumab, and docetaxel for treatment-related diarrhea or colitis **during docetaxel administration** *(continued)*

CTCAE v5.0 Adverse Event	CTCAE Grade	Management of Trastuzumab, Pertuzumab, and Docetaxel
Diarrhea, Colitis	Unacceptable Grade 2 Diarrhea, Grade 2 Colitis	• If Unacceptable Grade 2 diarrhea occurs a **2nd or 3rd time <u>without co-administration of atezolizumab/placebo</u>**, hold trastuzumab, pertuzumab, and docetaxel. - If diarrhea resolves to ≤ Grade 1 within 1 week, resume docetaxel with one dose level reduction and trastuzumab. Resume or discontinue pertuzumab when tolerance to trastuzumab and docetaxel established. - If diarrhea does not improve within 3 days refer for endoscopic biopsy. o If immune colitis documented, resume docetaxel at same dose level and trastuzumab when ≤ Grade 1. Resume or discontinue pertuzumab when tolerance to trastuzumab and docetaxel established. o If immune colitis NOT documented, resume docetaxel with one dose level reduction and trastuzumab when ≤ Grade 1 following 2nd episode. Resume trastuzumab and discontinue docetaxel following 3rd episode. Resume or discontinue pertuzumab when tolerance to trastuzumab and docetaxel established. • If Unacceptable Grade 2 diarrhea occurs a **4th time**, hold trastuzumab and resume when ≤ Grade 1. Discontinue pertuzumab.
	Grade 3 Diarrhea, Colitis	• Initiate symptomatic treatment. • Hold trastuzumab, pertuzumab, and docetaxel pending results of lower endoscopic biopsy. - If immune colitis documented, resume docetaxel at same dose level and trastuzumab when ≤ Grade 1. Resume pertuzumab when tolerance to trastuzumab and docetaxel established. - If immune colitis NOT documented, resume docetaxel with one dose level reduction and trastuzumab when ≤ Grade 1. Resume pertuzumab when tolerance to trastuzumab and docetaxel established.

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Table 6. Dose modifications and instructions for combination of trastuzumab, pertuzumab, and docetaxel for treatment-related diarrhea or colitis **during docetaxel administration** *(continued)*

CTCAE v5.0 Adverse Event	CTCAE Grade	Management of Trastuzumab, Pertuzumab, and Docetaxel
Diarrhea, Colitis	Grade 3 Diarrhea, Colitis	• If Grade 3 diarrhea occurs a **2nd time**, hold trastuzumab, pertuzumab, and docetaxel pending results of lower endoscopic biopsy. - If immune colitis documented, resume docetaxel at same dose level or with one dose level reduction per investigator discretion and trastuzumab when ≤ Grade 1. Resume or discontinue pertuzumab when tolerance to trastuzumab and docetaxel established. - If immune colitis NOT documented, resume docetaxel with one dose level reduction and trastuzumab when ≤ Grade 1. Resume or discontinue pertuzumab when tolerance to trastuzumab and docetaxel established. • If Grade 3 diarrhea occurs a **3rd time**, hold trastuzumab, pertuzumab, and docetaxel pending results of lower endoscopic biopsy. - If immune colitis documented, resume trastuzumab and discontinue docetaxel or resume with one dose level reduction when ≤ Grade 1. Discontinue or resume pertuzumab when tolerance to trastuzumab and docetaxel established. - If immune colitis NOT documented, resume trastuzumab when ≤ Grade 1. Discontinue docetaxel and resume or discontinue pertuzumab when tolerance to trastuzumab established.
	Grade 4 Diarrhea, Colitis	• Hold trastuzumab, pertuzumab, and docetaxel pending results of lower endoscopic biopsy. - If immune colitis documented, resume docetaxel at reduced dose level and trastuzumab when ≤ Grade 1. Resume pertuzumab when tolerance to trastuzumab and docetaxel established. - If immune colitis NOT documented, resume trastuzumab and discontinue or reduce docetaxel one or two dose levels when ≤ Grade 1. Discontinue or resume pertuzumab when tolerance to trastuzumab and docetaxel established.

Table 7. Dose modifications and instructions for trastuzumab and pertuzumab for treatment-related diarrhea or colitis **following completion of chemotherapy administration**

See Section 6.5.1 for management of diarrhea or colitis.

CTCAE v5.0 Adverse Event	CTCAE Grade	Management of Trastuzumab and Pertuzumab
Diarrhea, Colitis	Grade 1 Diarrhea	• Initiate symptomatic treatment. • Continue trastuzumab and pertuzumab.
	Acceptable Grade 2 Diarrhea	• Initiate symptomatic treatment. • Continue trastuzumab and pertuzumab.
	Unacceptable Grade 2 Diarrhea, Grade 2 Colitis	• Initiate symptomatic treatment. • Refer to GI specialist for evaluation and sigmoidoscopy. • Hold trastuzumab and pertuzumab until ≤ Grade 1 then resume trastuzumab and pertuzumab. • If Unacceptable Grade 2 diarrhea occurs a **2nd time <u>with co-administration of atezolizumab/placebo</u>**, hold trastuzumab and pertuzumab pending results of lower endoscopic biopsy. - If immune colitis documented, resume trastuzumab and pertuzumab when ≤ Grade 1. - If immune colitis NOT documented, resume trastuzumab when ≤ Grade 1. Resume or discontinue pertuzumab when tolerance to trastuzumab established. • If Unacceptable Grade 2 diarrhea occurs a **2nd time <u>without co-administration of atezolizumab/placebo</u>**, hold trastuzumab and pertuzumab. - If diarrhea resolves to ≤ Grade 1 within 1 week, resume trastuzumab. Resume pertuzumab when tolerance to trastuzumab established. - If diarrhea does not improve within 3 days refer for endoscopic biopsy. o If immune colitis documented, resume trastuzumab and pertuzumab when ≤ Grade 1. Resume pertuzumab when tolerance to trastuzumab established. o If immune colitis NOT documented, resume trastuzumab when ≤ Grade 1 following 2nd episode. Resume or discontinue pertuzumab when tolerance to trastuzumab established.

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Table 7. Dose modifications and instructions for trastuzumab and pertuzumab for treatment-related diarrhea or colitis **following completion of chemotherapy administration** *(continued)*

CTCAE v5.0 Adverse Event	CTCAE Grade	Management of Trastuzumab and Pertuzumab
Diarrhea, Colitis	Unacceptable Grade 2 Diarrhea, Grade 2 Colitis	• If Unacceptable Grade 2 diarrhea occurs a **3rd time <u>with co-administration of atezolizumab/placebo</u>**, hold trastuzumab and pertuzumab pending results of lower endoscopic biopsy. - If immune colitis documented, resume trastuzumab when ≤ Grade 1. Resume or discontinue pertuzumab when tolerance to trastuzumab established. - If immune colitis NOT documented, resume trastuzumab when ≤ Grade 1. Discontinue pertuzumab. • If Unacceptable Grade 2 diarrhea occurs a **3rd time <u>without co-administration of atezolizumab/placebo</u>**, hold trastuzumab and pertuzumab pending results of lower endoscopic biopsy. - If diarrhea resolves to ≤ Grade 1 within 1 week, resume trastuzumab. Resume pertuzumab when tolerance to trastuzumab established. - If diarrhea does not improve within 3 days refer for endoscopic biopsy. o If immune colitis documented, resume trastuzumab when ≤ Grade 1. Resume pertuzumab when tolerance to trastuzumab established. o If immune colitis NOT documented, resume trastuzumab when ≤ Grade 1. Discontinue pertuzumab. • If Unacceptable Grade 2 diarrhea occurs a **4th time**, discontinue trastuzumab.
	Grade 3 Diarrhea, Colitis	• Initiate symptomatic treatment. • Hold trastuzumab and pertuzumab pending results of endoscopic biopsy. - If immune colitis documented, resume trastuzumab when ≤ Grade 1. Resume pertuzumab when tolerance to trastuzumab established. - If immune colitis NOT documented, resume trastuzumab when ≤ Grade 1 and discontinue pertuzumab. • If Grade 3 diarrhea occurs a **2nd time**, hold trastuzumab and pertuzumab. - If immune colitis documented, resume trastuzumab when ≤ Grade 1. Resume or discontinue pertuzumab when tolerance to trastuzumab established. - If immune colitis NOT documented, resume trastuzumab when ≤ Grade 1. Discontinue pertuzumab if still on medication. • If Grade 3 diarrhea occurs a **3rd time**, discontinue trastuzumab.

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Table 7. Dose modifications and instructions for trastuzumab and pertuzumab for treatment-related diarrhea or colitis **following completion of chemotherapy administration** *(continued)*

CTCAE v5.0 Adverse Event	CTCAE Grade	Management of Trastuzumab and Pertuzumab
Diarrhea, Colitis	Grade 4 Diarrhea, Colitis	• Admit to hospital and consider endoscopic biopsy of colon. - If immune colitis documented, resume trastuzumab when ≤ Grade 1. Resume or discontinue pertuzumab when tolerance to trastuzumab established. - If immune colitis NOT documented, resume trastuzumab when ≤ Grade 1. Discontinue pertuzumab.

6.6 Management of Cardiac Toxicity Related to Study Therapy

6.6.1 Evaluation and Management of Cardiac Toxicity

- Cardiac toxicity, particularly left ventricular dysfunction is an expected potential toxicity with the use of trastuzumab and pertuzumab in BR004. Because the potential exists for additive or synergistic toxicity, patients should be monitored for signs and symptoms of cardiotoxicity, including left ventricular dysfunction and cardiac arrhythmias.
- For Grade 1 and 2 cardiac toxicities refer to cardiologist for evaluation.
- For Grade 3 or Grade 4 cardiac toxicities, hospitalize on telemetry and obtain an urgent cardiology consult. Promptly initiate high dose IV corticosteroid therapy.

6.6.2 Evaluation and Management of Immune-mediated Myocarditis

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (*e.g.*, B-NP [B-Natriuretic Peptide]) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope.

Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, *e.g.*, in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy. All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an electrocardiogram (ECG), a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 8.

6.6.3 Management of Trastuzumab, Pertuzumab, and Atezolizumab/Placebo during Episodes of Cardiac Toxicity

Note: If both trastuzumab and pertuzumab are discontinued for **non-immune** cardiac toxicity, atezolizumab/placebo should also be discontinued.

Table 8. Treatment modifications and instructions for cardiac toxicities related to trastuzumab, pertuzumab, or atezolizumab/placebo

CTCAE v5.0 Adverse Event	CTCAE Grade	Instructions for Each Agent Patient is Receiving
Heart Failure	1	• Hold atezolizumab/placebo. Consult Table 10 for management of trastuzumab and pertuzumab. • Consult cardiologist to conduct cardiac evaluation including LVEF assessment, troponin, BNP, and ECG. • If ventricular dysfunction confirmed, request unblinding for medical management. – If receiving atezolizumab, treat with 1-2 mg/kg/day oral prednisone or equivalent. – If steroids initiated, taper corticosteroids over 4-6 weeks. • If receiving atezolizumab, resume trastuzumab and pertuzumab if held when steroid taper completed and LVEF ≥ 40%. • If receiving placebo, resume trastuzumab and pertuzumab if held when LVEF ≥ 40%.
Heart Failure, Ejection Fraction Decreased to LVEF of 40-50%, or Myocarditis	2	• Hold atezolizumab/placebo. • Hold trastuzumab and pertuzumab. • Consult cardiologist to conduct cardiac evaluation including LVEF assessment, troponin, and EKG. • If ventricular dysfunction confirmed, admit to the hospital on telemetry and request unblinding for medical management. • If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent. – When improved to ≤ Grade 1, taper corticosteroids over 4-6 weeks. • If myocarditis confirmed, request unblinding for medical management. – If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent. – When improved to ≤ Grade 1, taper corticosteroids over 4-6 weeks. • If receiving atezolizumab, resume trastuzumab and pertuzumab when steroid taper completed, symptoms have resolved, and LVEF ≥ 40%. • If receiving placebo, resume trastuzumab and pertuzumab when symptoms have resolved and LVEF ≥ 40%.
Ejection Fraction Decreased **when LVEF > 50%** associated with a 10-19% absolute drop from baseline	2	• Manage as per Table 10 based on LVEF value irrespective of value decline.

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Table 8. Treatment modifications and instructions for cardiac toxicities related to trastuzumab, pertuzumab, or atezolizumab/placebo *(continued)*

CTCAE v5.0 Adverse Event	CTCAE Grade	Instructions for Each Agent Patient is Receiving
Heart Failure, Ejection Fraction Decreased, Left Ventricular Dysfunction, or Myocarditis	3,4	• Discontinue atezolizumab/placebo. • Hold trastuzumab and pertuzumab. • Admit to the hospital on telemetry. • Consult cardiologist to conduct cardiac evaluation including LVEF assessment, troponin, and EKG. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • Request urgent unblinding to guide subsequent medical management. • If receiving atezolizumab, resume trastuzumab and pertuzumab per investigator discretion when steroid taper completed and LVEF ≥ 40%. • If receiving placebo, discontinue trastuzumab and pertuzumab.
Other Cardiac Toxicities	1	• Continue trastuzumab and pertuzumab. • Continue atezolizumab/placebo at the discretion of the investigator. • Consult cardiologist to conduct cardiac evaluation including LVEF assessment, troponin, and EKG. • If intervention not indicated, continue trastuzumab and pertuzumab and resume atezolizumab/placebo if held by investigator. • If intervention indicated, manage per the appropriate toxicity grade.
	Grade 2 requiring discontinuation of atezolizumab/ placebo (see list in Table 9)	• Hold atezolizumab/placebo. • Hold trastuzumab and pertuzumab. • Consult cardiologist to conduct cardiac evaluation including LVEF assessment, troponin, and EKG. • If cardiac toxicity confirmed, request unblinding for medical management and consider hospitalization. - If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent if hospitalized. If not hospitalized initiate 1-2 mg/kg/day oral prednisone with close outpatient follow-up. - When improved to ≤ Grade 1, taper corticosteroids over 4-6 weeks. • If receiving atezolizumab, resume trastuzumab and pertuzumab when steroid taper completed and toxicity has resolved to ≤ Grade 1. • If receiving placebo, resume trastuzumab and pertuzumab when toxicity has resolved to ≤ Grade 1.

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Table 8. Treatment modifications and instructions for cardiac toxicities related to trastuzumab, pertuzumab, or atezolizumab/placebo *(continued)*

CTCAE v5.0 Adverse Event	CTCAE Grade	Instructions for Each Agent Patient is Receiving
Other Cardiac Toxicities Other Cardiac Toxicities	Grade 2 NOT requiring discontinuation of atezolizumab/ placebo	• Hold atezolizumab/placebo. • Hold trastuzumab and pertuzumab. • Consult cardiologist to conduct cardiac evaluation including LVEF assessment, troponin, and EKG. • Resume trastuzumab and pertuzumab when improved to ≤ Grade 1. • Resume atezolizumab/placebo per investigator discretion when improved to ≤ Grade 1.
	3,4	• Discontinue atezolizumab/placebo. • Hold trastuzumab and pertuzumab. • Admit to the hospital on telemetry. • Consult cardiologist to conduct cardiac evaluation including LVEF assessment, troponin, and EKG. • **Request urgent unblinding for medical management.** - If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent. - When event resolves to Grade 1 or better, taper corticosteroids over 4-6 weeks. • If receiving atezolizumab, resume trastuzumab and pertuzumab per investigator discretion when steroid taper completed and improved to ≤ Grade 1. • If receiving placebo, permanently discontinue trastuzumab and pertuzumab.

Table 9. CTCAE Grade 2 Other Cardiac Disorders

CTCAE Grade 2 Other Cardiac Disorders AEs That Require Referral to Cardiologist and Discontinuation of Atezolizumab/Placebo Therapy if Toxicity Confirmed	
CARDIAC DISORDERS – CTCAE v5.0	
Adverse Event	Grade 2 Criteria
Atrioventricular block complete	Non-urgent intervention indicated
Chest pain-cardiac	Moderate pain; pain on exertion; limiting instrumental ADL; hemodynamically stable
Mobitz (type) I atrioventricular block	Symptomatic; medical intervention indicated
Mobitz (type) II atrioventricular block	Symptomatic; medical intervention indicated
Pericarditis	Symptomatic pericarditis (e.g., chest pain)
Pericardial effusion	Asymptomatic effusion size small to moderate
Restrictive cardiomyopathy	Symptomatic without signs of heart failure
Right ventricular dysfunction	Symptoms with moderate activity or exertion
Sick sinus syndrome	Symptomatic, intervention not indicated; change in medication initiated
Ventricular arrhythmia	Non-urgent medical intervention indicated
Ventricular tachycardia	Non-urgent medical intervention indicated

6.6.4 Management of Trastuzumab, Pertuzumab, and Atezolizumab/Placebo During an **Asymptomatic** Decrease in LVEF

The results of the LVEF assessments during trastuzumab, pertuzumab, and atezolizumab/placebo therapy will be used to determine if the antibodies can be continued (refer to Table 10).

- If both trastuzumab and pertuzumab are discontinued for **non-immune** cardiac toxicity, atezolizumab/placebo should also be discontinued.
- If atezolizumab/placebo must be discontinued due to **immune-mediated** cardiac toxicity, trastuzumab and pertuzumab may be resumed per investigator discretion when steroid taper is completed and cardiac toxicity has resolved to ≤ Grade 1.
- Echocardiogram is the preferred method for assessment of LVEF. However, LVEF assessment by MUGA scan is permitted.
- ***All LVEF assessments should be performed by the same method*** (either echocardiogram or MUGA scan) that was performed at baseline.
- Investigators are strongly urged to schedule the LVEF assessment at the same cardiac imaging facility that performed the patient's baseline LVEF assessment.

6.6.5 Management of Trastuzumab, Pertuzumab, and Atezolizumab/Placebo Based on LVEF Assessments in Asymptomatic Patients

Table 10. Trastuzumab, pertuzumab, and atezolizumab/placebo management based on LVEF assessments

The following are instructions for patients who have an **asymptomatic decrease in LVEF** from baseline at the scheduled assessment time points during therapy. **Note: A cardiology consultation is mandatory for any patient with an LVEF < 50%.**		
LVEF	**Asymptomatic decrease in LVEF percentage points (absolute drop) from baseline**	
	Decrease of < 10 percentage points	**Decrease of ≥ 10 percentage points**
≥ 50%	Continue trastuzumab, pertuzumab, and atezolizumab/placebo	
40-49%	Hold atezolizumab/placebo, continue trastuzumab and pertuzumab. Repeat ECHO/MUGA in 3 weeks*	Hold atezolizumab/placebo, trastuzumab, and pertuzumab. Repeat ECHO/MUGA in 3 weeks*
< 40%	Manage as Grade 3 ejection fraction decreased in Table 8.	
**** Treatment rules based on "repeat" LVEF results:*** • If the repeat LVEF is ≥ 50%, continue/resume trastuzumab and pertuzumab, and resume atezolizumab/placebo. • If the repeat LVEF is 40-49%, manage as Grade 2 ejection fraction decreased in Table 8. • If the repeat LVEF is < 40%, manage as Grade 3 ejection fraction decreased in Table 8.		

6.7 **Treatment Modifications for Other Toxicities Related to Trastuzumab and Pertuzumab**

Table 11. Treatment modifications and instructions for other toxicities related to trastuzumab and pertuzumab

CTCAE v5.0 Adverse Event	CTCAE Grade	Management
Injury, Poisoning and Procedural Complications		
Infusion-related reaction	1, 2, 3, 4	See instructions for allergic reaction
Immune System Disorders **Note:** Follow instructions in Section 6.12 for management of atezolizumab/placebo.		

Table continued on next page.

Table 11. Treatment modifications and instructions for other toxicities related to trastuzumab and pertuzumab *(continued)*

CTCAE v5.0 Adverse Event	CTCAE Grade	Management
Allergic reaction	1	Slow the infusion of and assess the patient; management is at the investigator's discretion.
	2	Stop infusion and administer support medications per investigator's discretion. When symptoms resolve to ≤ Grade 1, infusion may be resumed later that day at a slower rate or on the next day at a slower rate with pre-meds. Pre-meds should be used for all subsequent treatments.
	3	Administer IV interventions as indicated per investigator discretion. Antibody causing the reaction may be discontinued at the investigator's discretion. If continued, follow instructions for Grade 2.
	4	Discontinue agent causing reaction.
Anaphylaxis	3	At investigator's discretion, discontinue agent causing reaction. If continued, follow instructions for Grade 3 allergic reactions.
	4	Discontinue agent causing reaction.
Respiratory, Thoracic, and Mediastinal Disorders **Note:** Follow instructions in Section 6.8 for management of atezolizumab/placebo.		
Adult Respiratory Distress Syndrome	3,4	Discontinue trastuzumab and pertuzumab.
Cough	2,3	Follow instructions in footnote **a**.
Dyspnea	1, 2, 3	Hold trastuzumab and pertuzumab; rule out heart failure and non-infectious lung disease; follow instructions in footnote **a**.
	4	Discontinue trastuzumab and pertuzumab.
Hypoxia	2,3	Follow instructions in footnote **a**.
	4	Discontinue trastuzumab and pertuzumab.
Pneumonitis	2	Follow instructions in footnote **a**.
	3,4	Discontinue trastuzumab and pertuzumab.

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Table 11. Treatment modifications and instructions for other toxicities related to trastuzumab and pertuzumab *(continued)*

CTCAE v5.0 Adverse Event	CTCAE Grade	Management
Respiratory, Thoracic, and Mediastinal Disorders **Note:** Follow instructions in Section 6.8 for management of atezolizumab/placebo.		
Pulmonary edema	2,3	Follow instructions in footnote **a**.
	4	Discontinue trastuzumab and pertuzumab.
Pulmonary fibrosis	1, 2, 3, 4	Discontinue trastuzumab and pertuzumab.
Pulmonary hypertension	1, 2, 3, 4	Discontinue trastuzumab and pertuzumab.
Other		
Other clinically significant AEs**b**	2	Hold trastuzumab and/or pertuzumab until ≤ Grade 1.
	3	Hold trastuzumab until ≤ Grade 1. Hold pertuzumab until ≤ Grade 1 or discontinue.
	4	Hold trastuzumab until ≤ Grade 1 or discontinue. Discontinue pertuzumab.

a Hold trastuzumab and/or pertuzumab and determine etiology. Unless prohibited based on instructions for other clinical diagnoses (i.e., other AEs), resume trastuzumab and/or pertuzumab when ≤ Grade 1 (if the AE requiring trastuzumab and/or pertuzumab to be held was ≥ Grade 2). Resume trastuzumab and pertuzumab when Grade 0 if the AE requiring trastuzumab and pertuzumab to be held was dyspnea.

b Determination of "clinically significant" is at the investigator's discretion and applies to those adverse events that *can be attributed to trastuzumab and/or pertuzumab and are not related to chemotherapy or atezolizumab/placebo.*

6.8 Pulmonary Events

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients should be assessed for pulmonary signs and symptoms throughout the study.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Patients with documented pneumonitis should be monitored with serial chest CTs until resolution or stable. Management guidelines for pulmonary events are provided in Table 12.

Table 12. Management guidelines for pulmonary events, including pneumonitis, related to atezolizumab/placebo

CTCAE v5.0 Adverse Event/Grade	Management
Pulmonary event, Grade 1	• Continue atezolizumab/placebo and monitor closely. • Consider diagnostic imaging. If pneumonitis documented, monitor on serial imaging until resolution or stable. • Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	• Hold atezolizumab/placebo. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or bronchoscopic alveolar lavage. • If evaluation fails to define non-immune etiology OR defines an immune etiology, discontinue atezolizumab/placebo and request unblinding if required for medical management. - If receiving atezolizumab, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Pulmonary event, Grade 3 or 4	• Refer patient to pulmonary and infectious disease specialists for bronchoscopy or bronchoscopic alveolar lavage. • Discontinue atezolizumab/placebo and request unblinding. - If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

6.9 Hepatic Events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 13.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 13. Management guidelines for hepatic events related to atezolizumab/placebo

CTCAE v5.0 Adverse Event/Grade	Management *(Refer to Section 6.21.3 for management of paclitaxel)*
Hepatic event, Grade 1	• Continue atezolizumab/placebo. • If LFT values are above normal limits, monitor LFTs weekly until resolved to within normal limits or to baseline values.
Hepatic event, Grade 2	• Hold atezolizumab/placebo and recheck LFTs in 3-7 days. - If LFTs are improving or have increased by < 25 IU and remain Grade 2, monitor LFTs weekly until LFTs return to ≤ Grade 1. - If LFTs increase further by a minimum of 25 IU but remain Grade 2, discontinue atezolizumab/placebo and request unblinding if required for medical management. • If patient was unblinded and was receiving atezolizumab, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Hepatic event, Grade 3 or 4	• Refer to hepatic specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Discontinue atezolizumab/placebo and request unblinding. - If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

6.10 Endocrine Events

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 14.

Patients experiencing one or more unexplained AEs possibly indicative of endocrine dysfunction (including headache, fatigue, myalgias, impotence, mental status changes, and constipation) should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (*e.g.,* TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and MRI of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency. Table 14 describes dose management guidelines for hyperthyroidism, hypothyroidism, symptomatic adrenal insufficiency, and hyperglycemia.

Table 14. Management guidelines for endocrine events related to atezolizumab/placebo

CTCAE v5.0 Adverse Event/Grade	Management
Asymptomatic Hypothyroidism	• Continue atezolizumab/placebo. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly until improvement documented.
Symptomatic Hypothyroidism	• Hold atezolizumab/placebo. • Initiate treatment with thyroid replacement hormone. • Monitor TSH every 3-4 weeks. • Consider patient referral to endocrinologist. • Resume atezolizumab/placebo when symptoms are controlled and thyroid function is improving.
Asymptomatic Hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab/placebo. • Monitor TSH every 3-4 weeks. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic Hyperthyroidism	• Hold atezolizumab/placebo. • Refer to endocrinologist. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Resume atezolizumab/placebo when symptoms are controlled and thyroid function is improving. • For life-threatening hyperthyroidism, discontinue atezolizumab/placebo and request unblinding. - If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Hypopituitarism Grade 1	• Hold atezolizumab/placebo until evaluated by endocrinologist. • If diagnosis confirmed, follow guidelines for Grades 2, 3, 4 hypopituitarism.
Hypopituitarism Grades 2, 3, 4	• Refer patient to endocrinologist. • Discontinue atezolizumab/placebo and request unblinding if required for medical management. - If receiving atezolizumab initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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Table 14. Management guidelines for endocrine events related to atezolizumab/placebo *(continued)*

CTCAE v5.0 Adverse Event/Grade	Management
Hypophysitis (panhypopituitarism), Grades 2, 3, 4	• Perform brain MRI (pituitary protocol). • Refer patient to endocrinologist. • Discontinue atezolizumab/placebo and request unblinding if required for medical management. - If receiving atezolizumab initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Adrenal insufficiency (primary) Grade 1	• Hold atezolizumab/placebo until evaluated by endocrinologist. • If primary adrenal insufficiency confirmed treat as symptomatic adrenal insufficiency.
Symptomatic adrenal insufficiency *A disorder characterized by the adrenal cortex not producing enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency.*	• Refer patient to endocrinologist. • Perform appropriate imaging. • Hold atezolizumab/placebo and request unblinding if diagnosis confirmed. - If receiving atezolizumab initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Hyperglycemia, Grades 1, 2	• Continue atezolizumab/placebo. • Investigate for diabetes. If patient has developed Type 1 diabetes, treat as a Grade 4 event. If patient has not developed Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia Grade 3	• Withhold atezolizumab/placebo. • Initiate treatment with insulin. • If patient has developed Type 1 diabetes, treat as a Grade 4 event. If patient has not developed Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab/placebo when glucose levels are stable.

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Table 14. Management guidelines for endocrine events related to atezolizumab/placebo *(continued)*

CTCAE v5.0 Adverse Event/Grade	Management
Hyperglycemia, Grade 4	• Hold atezolizumab/placebo. • Initiate treatment with insulin. • Monitor for glucose control. • Resume or discontinue atezolizumab/placebo at investigator discretion when symptoms resolve, and glucose levels are stable.

6.11 Ocular Events

An ophthalmologist should evaluate visual complaints (*e.g.,* uveitis, retinal events). Management guidelines for ocular events are provided in Table 15.

Table 15. Management guidelines for ocular events related to atezolizumab/placebo

CTCAE v5.0 Adverse Event/Grade	Management
Ocular event, Grade 1	• Continue atezolizumab/placebo. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, manage as a Grade 2 event.
Ocular event, Grade 2	• Hold atezolizumab/placebo. • Refer to ophthalmologist. • If immune-mediated toxicity is suspected, permanently discontinue atezolizumab/placebo and request unblinding if required for medical management. - If receiving atezolizumab, initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.
Ocular event, Grade 3 or 4	• Refer patient to ophthalmologist. • Permanently discontinue atezolizumab/placebo and request unblinding if required for medical management. - If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

6.12 Infusion-Related Reaction and Cytokine-Release Syndrome

No premedication is indicated for the administration of the first dose of atezolizumab/placebo. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with the first dose of atezolizumab/placebo may receive premedication with antihistamines, antipyretics and/or analgesics (*e.g.,* acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines

and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

Severe IRRs may result in anaphylaxis, which requires discontinue of atezolizumab/placebo. See Table 16 for management of grade 3 or 4 anaphylaxis.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz 2017, Adashek 2019) including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table 16.

Table 16. Management guidelines for infusion-related reactions and cytokine-release syndrome related to atezolizumab/placebo

Event	Management *(Refer to Table 26 for management of paclitaxel, Table 27 for management of docetaxel, and Table 11 for trastuzumab and pertuzumab)*
Grade 1[a] Fever[b] with or without constitutional symptoms	• Immediately interrupt atezolizumab/placebo infusion and administer symptomatic treatment per institutional practice. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue atezolizumab/placebo. • Administer symptomatic treatment,[c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.

Table continued on next page.

Table 16. Management guidelines for infusion-related reactions and cytokine-release syndrome related to atezolizumab/placebo *(continued)*

Event	Management *(Refer to Table 26 for management of paclitaxel, Table 27 for management of docetaxel, and Table 11 for trastuzumab and pertuzumab)*
Grade 2[a] Fever[b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen[d] by nasal cannula or blow-by	• Immediately interrupt atezolizumab/placebo infusion if infusion not completed. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. If symptoms do not resolve within 30 minutes, discontinue atezolizumab/placebo and unblind. • If symptoms recur after restart of the infusion discontinue atezolizumab/placebo. • Administer symptomatic treatment per institutional practice).[c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Clinical Coordinating Department. • If evaluation fails to define etiology, consider unblinding if required for medical management.

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Table 16. Management guidelines for infusion-related reactions and cytokine-release syndrome related to atezolizumab/placebo *(continued)*

Event	Management *(Refer to Table 26 for management of paclitaxel, Table 27 for management of docetaxel, and Table 11 for trastuzumab and pertuzumab)*
Grade 3[a] Fever[b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, non-rebreather mask, or venturi mask	• Immediately stop atezolizumab/placebo infusion.[f] • Request unblinding to guide further management. • Administer aggressive symptomatic treatment as per institutional guidelines[c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours) if receiving atezolizumab. • Consider anti-cytokine therapy.[e] • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments[f] may be considered at the discretion of the investigator. • Permanently discontinue atezolizumab/placebo.
Grade 3 or 4 anaphylactic reaction	In the event of a suspected anaphylactic reaction during atezolizumab infusion, the following procedures should be performed: 1. Stop the study drug infusion. 2. Permanently discontinue atezolizumab/placebo. 3. Call for additional medical assistance. 4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible. 5. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge. 6. Continue to observe the patient and document observation.

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Table 16. Management guidelines for infusion-related reactions and cytokine-release syndrome related to atezolizumab/placebo *(continued)*

Event	Management *(Refer to Table 26 for management of paclitaxel, Table 27 for management of docetaxel, and Table 11 for trastuzumab and pertuzumab)*
Grade 4[a] Fever[b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently stop atezolizumab/placebo. • Administer symptomatic treatment.[c] • Request unblinding to guide further management. • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids if receiving atezolizumab (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] For patients who are refractory to anti-cytokine therapy, experimental treatments[f] may be considered at the discretion of the investigator. • Hospitalize patient until complete resolution of symptoms.

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; HLH = hemophagocytic lymphohistiocytosis; IRR = infusion-related reaction; MAS = macrophage activation syndrome.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

a. Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.
b. Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.
c. Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.
d. Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.
e. There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz 2017, Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.
f. Refer to Riegler 2019 for information on experimental treatments for CRS.

6.13 Management of Pancreatic Events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 17.

Table 17. Management guidelines for pancreatic events, including pancreatitis, related to atezolizumab/placebo

CTCAE v5.0 Adverse Event/Grade	Management
Amylase and/or lipase elevation, Grade 1	• Continue atezolizumab/placebo. • Monitor amylase and lipase prior to dosing.
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5-2.0 x ULN:** • Continue atezolizumab/placebo. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), hold atezolizumab/placebo. • If non-immune etiology not identified, discontinue atezolizumab/placebo and request unblinding if required for medical management. - If receiving atezolizumab, begin treatment with 1-2 mg/kg/day oral prednisone or equivalent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. **Asymptomatic with amylase and/or lipase > 2.0-5.0 x ULN:** • Treat as a Grade 3 or 4 event.

Table continued on next page.

Table 17. Management guidelines for pancreatic events, including pancreatitis, related to atezolizumab/placebo *(continued)*

CTCAE v5.0 Adverse Event/Grade	Management
Amylase and/or lipase elevation, Grade 3 or 4	• Hold atezolizumab/placebo. • Refer patient to gastrointestinal specialist. • Monitor amylase and lipase every 2 to 3 days until improved. • May resume atezolizumab/placebo with next cycle if amylase and lipase are ≤ Grade 1. • For prolonged elevation (e.g., > 3 weeks), continue to hold atezolizumab/placebo. • If non-immune etiology not identified, discontinue atezolizumab/placebo and request unblinding if required for medical management. - If receiving atezolizumab, begin treatment with 1-2 mg/kg/day oral prednisone or equivalent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Immune-mediated pancreatitis, Grade 2 or 3	• Hold atezolizumab/placebo. • Monitor amylase and lipase every 2 to 3 days until improved. • For prolonged elevation (e.g., > 3 weeks), hold atezolizumab/placebo. • Refer patient to gastrointestinal specialist. • May resume atezolizumab/placebo with next cycle if amylase and lipase are ≤ Grade 1. • If non-immune etiology not identified, discontinue atezolizumab/placebo and request unblinding if required for medical management. - If receiving atezolizumab, begin treatment with 1-2 mg/kg/day oral prednisone or equivalent. - When amylase and lipase levels resolve to Grade 1, taper corticosteroids over ≥ 1 month.
Immune-mediated pancreatitis, Grade 4	• Refer patient to gastrointestinal specialist. • Discontinue atezolizumab/placebo and request unblinding. - If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

6.14 Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 18.

Table 18. Management for dermatologic events related to atezolizumab/placebo

CTCAE v5.0 Adverse Event/Grade	Management
Dermatologic event, Grade 1	• Continue atezolizumab/placebo. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (*e.g.*, antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab/placebo. • Refer to dermatologist and consider skin biopsy. • Initiate treatment with topical corticosteroids. • If rash does not improve, discontinue atezolizumab/placebo and consider unblinding if required for medical management. - If receiving atezolizumab, initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Bullous dermatitis, Grade 2	Treat as Grade 3 or 4 Dermatologic event.
Dermatologic event, Grade 3 or 4	• Refer patient to dermatologist. • Discontinue atezolizumab/placebo and request unblinding. - If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day of methylprednisolone or equivalent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold atezolizumab/placebo for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines as above for dermatologic event Grade 3 or 4. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab/placebo.

6.15 Neurological Disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor

neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 19.

Table 19. Treatment management guidelines for neurological disorders related to atezolizumab/placebo

CTCAE v5.0 Adverse Event/Grade	Management	
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab/placebo. • Investigate etiology.	
Immune-mediated sensory neuropathy Grade 2	**Grade 2 while receiving paclitaxel*:** • Withhold atezolizumab/placebo. • Oral steroids should **not** be initiated for first or second episodes. • Resume atezolizumab/placebo if event resolves to Grade 1 or better within 3 weeks. • If event does not resolve to Grade 1 or better within 3 weeks: – Refer patient to neurologist – Consider unblinding if required for medical management. – If receiving atezolizumab, begin treatment with 1-2 mg/kg/day oral prednisone or equivalent. – When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.	**Grade 2 if not receiving paclitaxel*:** • Refer patient to neurologist. • Discontinue atezolizumab/placebo. • Request unblinding if required for medical management. - If receiving atezolizumab, begin treatment with 1-2 mg/kg/day oral prednisone or equivalent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Immune-mediated motor neuropathy Grade 2	• Refer patient to neurologist. • Discontinue atezolizumab/placebo and request unblinding. - If receiving atezolizumab, begin treatment with 1-2 mg/kg/day oral prednisone or equivalent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.	

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Table 19. Treatment management guidelines for neurological disorders related to atezolizumab/placebo *(continued)*

CTCAE v5.0 Adverse Event/Grade	Management
Immune-mediated neuropathy, Grade 3 or 4	• Refer patient to neurologist. • Discontinue atezolizumab/placebo and consider unblinding if required for medical management. - If receiving atezolizumab, begin treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Refer patient to neurologist and initiate treatment as per institutional guidelines. • Discontinue atezolizumab/placebo and request unblinding. - If receiving atezolizumab, begin treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
* Refer to Section 6.21.3 for concurrent dose modifications for chemotherapy.	

6.16 Immune-mediated meningoencephalitis

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 20.

Table 20. Management guidelines for immune-mediated meningoencephalitis related to atezolizumab/placebo

CTCAE v5.0 Adverse Event/Grade	Management
Immune-mediated meningoencephalitis, all grades	• Refer patient to neurologist. • Permanently discontinue atezolizumab/placebo and request unblinding. - If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

6.17 **Immune-Mediated Renal Events**

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 21.

Table 21. Management and evaluation of immune-mediated renal events (potential immune-mediated nephritis)

CTCAE v5.0 Adverse Event/Grade	**Management**
Renal event, Grade 1	• Continue atezolizumab/placebo. • If creatinine value is above normal limits, monitor weekly.
Renal event, Grade 2	• Hold atezolizumab/placebo and recheck creatinine in 3-7 days. - If creatinine is improving but remains Grade 2, continue to hold atezolizumab/placebo and monitoring creatinine weekly until ≤ Grade 1. - If repeat creatinine value does not improve but remains Grade 2, refer to nephrologist for evaluation and continue to hold atezolizumab/placebo. – If evaluation fails to define non-immune etiology OR defines an immune etiology, discontinue atezolizumab/placebo and request unblinding for medical management. • If patient was unblinded and was receiving atezolizumab, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Renal event, Grade 3 or 4	• Refer to nephrologist for evaluation and consideration of renal biopsy to establish etiology of renal injury. • Discontinue atezolizumab/placebo and request unblinding. - If receiving atezolizumab, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

6.18 **Immune-mediated myositis**

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are amongst the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in

dermatomyositis), biochemical (serum creatine-kinase increase), and imaging (electromyography/MRI) features and is confirmed with a muscle-biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 22.

Table 22. Management and evaluation of immune-mediated myositis

CTCAE v5.0 Adverse Event/Grade	**Management**
Myositis, Grade 1 (mild pain with elevated CK)	• Hold atezolizumab/placebo. • Refer patient to rheumatologist or neurologist. • If evaluation fails to define non-immune etiology OR defines an immune etiology, discontinue atezolizumab/placebo and request unblinding if required for medical management. - If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - When CK elevation resolves and pain improved, taper corticosteroids over ≥ 1 month. • If non-immune etiology identified, may resume or discontinue atezolizumab/placebo per investigator discretion.
Myositis, Grade 2 (moderate pain with weakness)	• Hold atezolizumab/placebo. • Refer patient to rheumatologist or neurologist. • If evaluation fails to define non-immune etiology OR defines an immune etiology, discontinue atezolizumab/placebo and request unblinding if required for medical management. - If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. • If non-immune etiology identified, may resume or discontinue atezolizumab/placebo per investigator discretion.

Table continued on next page.

Table 22. Management and evaluation of immune-mediated myositis *(continued)*

CTCAE v5.0 Adverse Event/Grade	Management
Myositis, Grade 3 or 4 (pain with severe weakness)	• Hold atezolizumab/placebo. • Refer patient to neurologist or rheumatologist. • Evaluate for associated myocarditis and consider consulting cardiologist. • Respiratory support may be required in more severe cases. • Discontinue atezolizumab/placebo and request unblinding. - If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility) and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

6.19 Hemophagocytic lymphohistiocytosis and macrophage activation syndrome

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2017). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count < 100×10^9/L (100,000/mcL)
  - ANC < 1.0×10^9/L (1000/mcL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count ≤ 181×10^9/L (181,000/mcL)
  - AST ≥ 48 U/L

- Triglycerides >1.761 mmol/L (156 mg/dL)
- Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 23.

Table 23. Management and evaluation of hemophagocytic lymphohistiocytosis and macrophage activation syndrome

Event	Management
Suspected HLH or MAS	● Permanently discontinue atezolizumab/placebo and contact Protocol Officer. ● Consider patient referral to hematologist. ● Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. ● Consider initiation of IV corticosteroids and/or an immunosuppressive agent. ● If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ● If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH=hemophagocytic lymphohistiocytosis; MAS=macrophage activation syndrome.

6.20 Management Guidelines for Other Immune-Mediated Toxicities Potentially Related to Atezolizumab/Placebo

Table 24. Management guidelines for **other immune-mediated toxicities** potentially related to atezolizumab/placebo not covered on other tables

CTCAE v5.0 Grade	Management
Grade 2	• Hold atezolizumab/placebo. • Refer to appropriate specialists for evaluation and consideration of biopsy to evaluate for immune infiltrate if appropriate. • If immune-mediated toxicity is confirmed, permanently discontinue atezolizumab/placebo and request unblinding if required for medical management. - If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent.
Grade 3 or 4	• Hold atezolizumab/placebo. • Refer to appropriate specialist and consideration of biopsy to evaluate for immune infiltrate if appropriate. • Consider hospitalization. • Contact Protocol Officer. • If immune–mediated toxicity is confirmed or suspected request unblinding to guide medical management. - If receiving atezolizumab, initiate treatment with 1-2 mg/kg/day oral prednisone or 1 mg/kg/day intravenous methylprednisolone per investigator discretion. - Convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - When event resolves to Grade 1 or better, taper corticosteroids over 4-6 weeks.

6.21 Liver dysfunction (Hy's Law)

Hy's Law is based on the observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. A diagnosis of potential drug-induced liver injury caused by a study drug can only be determined/inferred by excluding other potential causes of liver injury (e.g., other drugs or viral hepatitis) and by ruling out an obstructive cause for the elevated bilirubin (e.g., alkaline phosphatase should not be substantially elevated) (FDA-Guidance 2009, Temple 2006).

6.21.1 Definition of Cases Potentially Meeting Hy's Law Criteria

Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- *Patients with AST or ALT baseline values within the normal range* who subsequently present with AST or ALT > 3 times the ULN concurrent with a total bilirubin > 2 times the ULN with no evidence of hemolysis and an alkaline phosphatase < 2 times the ULN or not available.
- *Patients with pre-existing AST or ALT baseline values above the normal range* who subsequently present with AST or ALT > 2 times the baseline values and > 3 times the ULN, or ≥ 8 times the ULN (whichever is smaller) concurrent with a total bilirubin of > 2 times the ULN and increased by one ULN over baseline or > 3 times the ULN (whichever is smaller) with no evidence of hemolysis and an alkaline phosphatase < 2 times the ULN or not available.

6.21.2 Evaluation of Potential Hy's Law Cases

The patient should return to the investigational site to be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results and **managed as Grade 3/4 hepatotoxicity per Table 13**. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. The possibility of recurrent disease should be considered.

Potential Hy's Law cases should be reported as serious adverse events (see Section 7.5.4).

6.22 Treatment Management for Paclitaxel and Docetaxel for Arms 1 and 2

If necessary, the timing of a treatment may be adjusted to 2 days earlier or 2 days later than the scheduled date of treatment. For general chemotherapy instructions, see Section 6.1 and Section 6.3.

- Dose modifications for paclitaxel are based on the dose level changes outlined in Table 25.
- See Table 28 for management of taxane-related neuropathy and Table 29 for taxane-related musculoskeletal pain. Instructions for management of all other toxicities related to paclitaxel are listed on Table 26 and related to docetaxel are on Table 27. See Section 6.5.1 for management of diarrhea.

Table 25. Dose levels for paclitaxel and docetaxel (Arm 1 and Arm 2)

	Dose Level 0 ***Starting Dose*** **(mg/m^2)**	**Dose Level -1 (mg/m^2)**	**Dose Level -2 (mg/m^2)**	**Dose Level -3**
Paclitaxel	80	60	45	Discontinue
Docetaxel	75	60	50	Discontinue

6.22.1 Management of Anemia

Chemotherapy should not proceed with ≥ grade 3 anemia. Transfusion is acceptable for improving the hemoglobin value to allow therapy to continue without delay. The patient should be assessed to rule out other causes of anemia. *Use of erythropoiesis-stimulating agents is prohibited.*

6.22.2 Management of Infusion-Related Reaction

If a hypersensitivity and/or infusion reaction occurs during paclitaxel or docetaxel administration, nab-paclitaxel may be substituted per investigator and local guidelines for subsequent nab-paclitaxel doses with starting dose and dose modifications if necessary per investigator discretion. Alternatively, patients may convert to the alternative taxane per investigator discretion. Patients continue on study and continue to follow protocol requirements outlined on Table 2.

6.22.3 Dose Modifications for Taxane Chemotherapy (Paclitaxel or Docetaxel)

Table 26. Dose modifications and instructions for paclitaxel (Arm 1 and Arm 2)

Important table instructions: • Dose modifications must be based on AEs that occurred between treatments (column 2) ***and*** AEs present on the scheduled treatment day (column 3). ***Refer to other applicable instructions in Section 6.1 and Section 6.3.*** Dose modifications must be based on the AE requiring the greatest modification. • Refer to Section 6. 22.1 for management of **anemia**.		
CTCAE v5.0 Adverse Event/Grade	Modifications for AEs that occurred between treatments but DID NOT REQUIRE A DELAY OR AN OMISSION OF A TREATMENT (See footnote **a**)	Modifications for AEs that REQUIRE A DELAY OR AN OMISSION OF A TREATMENT (See footnote **b**)
Neutrophil count decreased: Grade 2	Maintain dose	Maintain dose
Grades 3, 4	Maintain dose	**ANC**: *Hold until ≥ 1000/mm^3;* *First occurrence:* ↓ one dose level. *Second occurrence:* add G-CSF**c** prophylaxis for subsequent doses. *Third occurrence:* ↓ one dose level.
Platelet count decreased: Grades 2, 3	Maintain dose	*Hold until ≥ 75,000/mm^3. If recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Grade 4	↓ one dose level	*Hold until ≥ 75,000/mm^3* ↓ one dose level
Diarrhea (if related to chemotherapy): Refer to Section 6.5		
Immune System Disorders **Allergic reaction/Anaphylaxis (*despite premedication)*** Grades 1, 2, 3 ***(Refer to Section 6.22.2)***	Treat as per institutional policy; may re-challenge (maintain dose) or convert to alternative taxane.	Treat as per institutional policy; may re-challenge (maintain dose) or convert to alternative taxane.
Grade 4	Discontinue	Discontinue
Infection or febrile neutropenia: Grade 2 (N/A for febrile neutropenia)	**If infection was present but not neutropenic:** Maintain dose **If infection and neutropenia were present:** Maintain dose ***or*** modify dose per grade 3.	
Grade 3	*For initial episode*, ↓ one dose level for ***subsequent doses***. *For second episode*, ↓ one dose level for subsequent doses, or maintain dose and add G-CSF**c** prophylaxis for ***subsequent doses*** per investigator discretion. *For third episode*, ↓ one dose level for ***subsequent doses*** or discontinue. *For fourth episode*, discontinue.	
Grade 4	For *initial episode*, ↓ one dose level for ***subsequent doses***. For *second episode*, discontinue.	

Table continued on next page.

Table 26. Dose modifications and instructions for paclitaxel (Arm 1 and Arm 2) *(continued)*

CTCAE v5.0 Adverse Event/Grade	Modifications for AEs that occurred between treatments but DID NOT REQUIRE A DELAY OR AN OMISSION OF A TREATMENT (See footnote **a**)	Modifications for AEs that REQUIRE A DELAY OR AN OMISSION OF A TREATMENT (See footnote **b**)
Other clinically significant AEs probably related to paclitaxel:[d]		
Grade 2	Maintain dose or ↓ one dose level	Maintain dose or ↓ one dose level
Grade 3	Maintain dose or ↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or discontinue	↓ one dose level or discontinue

a ***Treatment may not proceed until clinically significant AEs are ≤ Grade 1*** (except neutrophils, which must be ≥ 1000/mm^3.

b Hold and check weekly. ***With exception of neutrophils, resume treatment when toxicity is ≤ Grade 1.*** If toxicity has not resolved to ≤ Grade 1 after 3 weeks of delay, discontinue paclitaxel.

c Only ***filgrastim*** is to be given after each dose of paclitaxel. At the investigator's discretion, filgrastim may be given for 3-5 days after each dose of paclitaxel. Pegfilgrastim is prohibited during paclitaxel.

- Do not administer G-CSF within 24 hours of chemotherapy.
- Use of (prophylactic) filgrastim is required for all remaining doses in regimen.
- If required by institutional standards, GM-CSF may be administered as an alternative.

d Determination of "clinically significant" of paclitaxel AEs is at the discretion of the investigator.

Table 27. Dose modifications and instructions for docetaxel (Arm 1 and Arm 2)

Important table instructions: • Dose modifications must be based on AEs that occurred between treatments (column 2) ***and*** AEs present on the scheduled treatment day (column 3). ***Refer to other applicable instructions in Section 6.1 and Section 6.3.*** Dose modifications must be based on the AE requiring the greatest modification. • Refer to Section 6. 22.1 for management of **anemia**.		
CTCAE v5.0 Adverse Event/Grade	Modifications for AEs that occurred between treatments but DID NOT REQUIRE A DELAY OR AN OMISSION OF A TREATMENT (See footnote **a**)	Modifications for AEs that REQUIRE A DELAY OR AN OMISSION OF A TREATMENT (See footnote **b**)
Neutrophil count decreased: Grade 2	Maintain dose	Maintain dose
Grades 3, 4	Maintain dose	**ANC**: *Hold until ≥ 1000/mm^3;* *First occurrence:* add G-CSF**c** prophylaxis for subsequent doses. *Second occurrence:* ↓ one dose level. *Third occurrence:* ↓ one dose level.
Platelet count decreased: Grades 2, 3	Maintain dose	*Hold until ≥ 75,000/mm^3. If recovery takes:* 1 wk – maintain dose; 2-3 wks – ↓ one dose level
Grade 4	↓ one dose level	*Hold until ≥ 75,000/mm^3* ↓ one dose level
Diarrhea (if related to chemotherapy): Refer to Section 6.5		
Immune System Disorders **Allergic reaction/Anaphylaxis (*despite premedication)*** Grades 1, 2, 3 ***(Refer to Section 6.22.2)***	Treat as per institutional policy; may re-challenge (maintain dose) or convert to alternative taxane	Treat as per institutional policy; may re-challenge (maintain dose) or convert to alternative taxane
Grade 4	Discontinue	Discontinue
Infection or febrile neutropenia: Grade 2 (N/A for febrile neutropenia)	**If infection was present but not neutropenic:** Maintain dose **If infection and neutropenia were present:** Add G-CSF**c** prophylaxis for subsequent doses.	
Grade 3	*For initial episode*, add G-CSF**c** prophylaxis for ***subsequent doses***. *For second episode*, ↓ one dose level for subsequent doses. *For third episode*, ↓ one dose level for ***subsequent doses*** or discontinue. *For fourth episode*, discontinue.	
Grade 4	For *initial episode*, add G-CSF prophylaxis and ↓ one dose level for ***subsequent doses***. For *second episode*, discontinue.	

Table continued on next page.

Table 27. Dose modifications and instructions for docetaxel (Arm 1 and Arm 2) *(continued)*

CTCAE v5.0 Adverse Event/Grade	Modifications for AEs that occurred between treatments but DID NOT REQUIRE A DELAY OR AN OMISSION OF A TREATMENT (See footnote **a**)	Modifications for AEs that REQUIRE A DELAY OR AN OMISSION OF A TREATMENT (See footnote **b**)
Other clinically significant AEs probably related to docetaxel:[d] Grade 2	Maintain dose or ↓ one dose level	Maintain dose or ↓ one dose level
Grade 3	Maintain dose or ↓ one dose level	↓ one dose level
Grade 4	↓ one dose level or discontinue	↓ one dose level or discontinue

a ***Treatment may not proceed until clinically significant AEs are ≤ Grade 1*** (except neutrophils, which must be ≥ 1000/mm^3.

b Hold and check weekly. ***With exception of neutrophils, resume treatment when toxicity is ≤ Grade 1.*** If toxicity has not resolved to ≤ Grade 1 after 3 weeks of delay, discontinue docetaxel.

c Pegfilgrastim or similar long-acting formulation is preferred to G-CSF but investigators should follow institutional standards.

- Do not administer G-CSF within 24 hours of chemotherapy.
- Use of (prophylactic) filgrastim is required for all remaining doses in regimen.
- If required by institutional standards, GM-CSF may be administered as an alternative.

d Determination of "clinically significant" of docetaxel AEs is at the discretion of the investigator.

Table 28. Treatment management for taxane-related neuropathy (Arm 1 and Arm 2)

Nervous System Disorders • Paresthesias • Peripheral sensory neuropathy	**1–6 Days Duration Between Doses of Taxane**	**Persistent for ≥ 7 Days *or* Caused Treatment to be Delayed or Omitted**
Grade 1	Maintain dose	
Grade 2	Maintain taxane dose[a]	Decrease taxane one dose level[b]
Grade 3	**First episode:** Decrease taxane one dose level[a] **Second episode:** Discontinue taxane	Discontinue taxane
Grade 4	Discontinue taxane	

a Hold until improved to ***less than moderate symptom intensity*** on the next treatment day.

b Hold taxane (Arm 1 and Arm 2) for ***persistent moderate intensity*** Grade 2 neuropathy. When improved to ***less than moderate symptom intensity***, resume treatment with dose modification for taxane. If ***moderate intensity*** Grade 2 toxicity persists after 3 weeks of delay, discontinue taxane.

Table 29. Treatment management for taxane-related musculoskeletal pain (Arm 1 and Arm 2)

Note: The treatment management instructions in Table 29 apply to patients with **musculoskeletal pain not controlled by analgesics**. Use of narcotics and NSAIDs is encouraged to maintain the taxane dose if possible.

Musculoskeletal and Connective Tissue Disorders • Arthralgia • Myalgia	**1–6 Days Duration Between Doses of Taxane**	**Persistent for ≥ 7 Days *or* Caused Treatment to be Delayed or Omitted**
Grade 1 *(despite analgesics)*	Maintain taxane dose	
Grade 2 *(despite analgesics)*	Maintain taxane dose	Maintain taxane dose or Decrease taxane one dose level*
Grade 3 *(despite analgesics)*	**First episode:** Decrease taxane one dose level **Second episode:** Discontinue taxane	**First episode:** Decrease taxane one dose level* or Discontinue taxane **Second episode**: Discontinue taxane
* Hold taxane (Arm 1 and Arm 2) for ***persistent*** Grade 2 or 3 musculoskeletal pain. When ≤ Grade 1, resume treatment with dose modification for taxane. If Grade 2 or Grade 3 toxicity persists after 3 weeks of delay, discontinue taxane.		

7.0 ADVERSE EVENTS REPORTING REQUIREMENTS

The NRG-BR004 study was permanently closed to accrual on May 20, 2022. Please see Table 2A for immune-related adverse event reporting requirements for patients enrolled prior to study accrual closure.

7.1 Study Agents

7.1.1 U.S. and Canadian Institutions

- ***Investigational Agent***

  The investigational agent is atezolizumab/placebo.

- ***Commercial Agents***

  The commercial agents are paclitaxel, docetaxel, pertuzumab, and trastuzumab.

7.2 Adverse Events and Serious Adverse Events

7.2.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting.

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

7.2.3 Definition of a Serious Adverse Event

Any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours)
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient 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).

7.3 Adverse Events for Study Agents

7.3.1 Commercial Agents

Refer to the current FDA-approved package insert or current Health Canada-approved product monograph for detailed pharmacologic and safety information for paclitaxel.

Paclitaxel

Common adverse events (> 20%) include: anemia, neutropenia; infection; diarrhea; nausea; vomiting; mucositis; allergic reaction; thrombocytopenia; pain; myalgia/arthralgia; peripheral motor and sensory neuropathies; and alopecia.

Less common events (≤20%) include: sinus bradycardia; pneumonitis; pleural effusion; pulmonary fibrosis; and thromboembolic event.

Rare but serious events (< 3%) include: myocardial infarction; heart failure; and colonic perforation.

Docetaxel

Common adverse events (> 20%) include: thrombocytopenia; neutropenia; infection; anemia; diarrhea; nausea; vomiting; constipation; mucositis; irregular menstruation or amenorrhea; fatigue; fever; erythema multiforme; edema; pain; peripheral motor and sensory neuropathies; watering eyes; nail changes; rash; pruritus; and alopecia.

Less common events (≤20%) include: irregular heart rate; chest pain; dyspnea; wheezing; thromboembolic event; acute kidney injury; abdominal pain; Stevens-Johnson syndrome.

Rare but serious events (< 3%) include: Leukemia secondary to oncology chemotherapy; allergic reaction.

Pertuzumab

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted in Table 30). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 9575 patients.* Below is the CAEPR for Pertuzumab.

> **NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.
>
> **NOTE**: Frequencies of AEs on this CAEPR are based on pooled clinical data from treatment arms, pivotal clinical trials using pertuzumab in combination with trastuzumab and docetaxel in patients with MBC (metastatic breast cancer), and pertuzumab in combination with trastuzumab and chemotherapy in patients with EBC (early stage breast cancer).

Table 30. Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pertuzumab (NSC 740102)

Version 2.4, July 6, 2019[1]

Adverse Events with Possible Relationship to Pertuzumab (CTCAE 5.0 Term) [n= 9575]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 2)***
CARDIAC DISORDERS			
		Heart failure	
EYE DISORDERS			
	Watering eyes		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	General disorders and administration site conditions - Other (mucosal inflammation)		
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[2]		***Allergic reaction[2] (Gr 2)***
		Anaphylaxis[2]	
INFECTIONS AND INFESTATIONS			
Infection[3]			***Infection[3] (Gr 3)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Dermatitis radiation		
	Infusion related reaction[4]		***Infusion related reaction[4] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Ejection fraction decreased	
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***

Table 30. Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pertuzumab (NSC 740102) *(continued)*

Version 2.4, July 6, 2019[1]

Adverse Events with Possible Relationship to Pertuzumab (CTCAE 5.0 Term) [n= 9575]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dsygeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
	Paresthesia		
	Peripheral motor neuropathy		
	Peripheral sensory neuropathy		
PSYCHIATRIC DISORDERS			
	Insomnia		***Insomnia (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***
	Dry skin		
	Nail changes		***Nail changes (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		
	Pruritus		***Pruritus (Gr 2)***
	Rash[5]		***Rash[5] (Gr 2)***
VASCULAR DISORDERS			
	Hot flashes		

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

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

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Chest pain - cardiac; Left ventricular systolic dysfunction; Pericardial effusion
EYE DISORDERS - Blurred vision; Dry eye; Eye disorders – Other (diplopia)
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Dry mouth; Esophagitis; Gastroesophageal reflux disease; Hemorrhoids
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Flu like symptoms; Generalized edema; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatobiliary disorders - Other (hepatitis fulminant); Hepatobiliary disorders - Other (hepatocellular injury)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture; Injury, poisoning and procedural complications - Other (post-procedural inflammation); Injury, poisoning and procedural complications - Other (procedural pain); Injury, poisoning and procedural complications - Other (skin toxicity); Wound complication; Wound dehiscence
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Creatinine increased; GGT increased; Investigations - Other (granulocytopenia); Lymphocyte count decreased; Platelet count decreased; Weight gain; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hypoglycemia; Hypokalemia; Hypomagnesemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (dermatomyositis syndrome); Musculoskeletal and connective tissue disorder - Other (spinal pain)
NERVOUS SYSTEM DISORDERS - Amnesia; Dysarthria; Lethargy; Nervous system disorders - Other (osmotic demyelination syndrome); Somnolence; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Depression
RENAL AND URINARY DISORDERS - Acute kidney injury; Dysuria; Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Amenorrhea; Breast pain; Irregular menstruation; Reproductive system and breast disorders - Other (metrorrhagia); Vaginal dryness
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS – Bronchospasm[4]; Nasal congestion; Oropharyngeal pain; Pleural effusion; Pneumonitis; Postnasal drip; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (painful respiration); Rhinorrhea
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Erythroderma; Hyperhidrosis; Nail discoloration; Pain of skin; Rash acneiform; Skin and subcutaneous tissue disorders - Other (onycholysis); Skin and subcutaneous tissue disorders - Other (onychomadesis); Skin hyperpigmentation; Urticaria
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Lymphedema; Thromboembolic event; Vascular disorders - Other (hyperemia)

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

Trastuzumab

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are

protocol specific exceptions to expedited reporting to NCI (except as noted on Table 31). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 4407 patients.* Below is the CAEPR for Trastuzumab (Herceptin) and Herceptin Hylecta™ (SQ trastuzumab).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Table 31. Comprehensive Adverse Events and Potential Risks list (CAEPR) for Trastuzumab (Herceptin, NSC 688097) and Herceptin Hylecta™ (SQ trastuzumab, NSC 827797)

Version 2.6, December 14, 2021[1]

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

Table continued on next page.

Table 31. Comprehensive Adverse Events and Potential Risks list (CAEPR) for Trastuzumab (Herceptin, NSC 688097) and Herceptin Hylecta™ (SQ trastuzumab, NSC 827797) *(continued)*

Version 2.6, December 14, 2021[1]

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

Table continued on next page.

Table 31. Comprehensive Adverse Events and Potential Risks list (CAEPR) for Trastuzumab (Herceptin, NSC 688097) and Herceptin Hylecta™ (SQ trastuzumab, NSC 827797) *(continued)*

Version 2.6, December 14, 2021[1]

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

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

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

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

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

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

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

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

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

CARDIAC DISORDERS - Asystole; Atrial fibrillation; Atrial flutter; Chest pain - cardiac; Myocardial infarction; Myocarditis; Sinus bradycardia; Ventricular arrhythmia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo
EYE DISORDERS - Dry eye; Extraocular muscle paresis
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Constipation; Duodenal ulcer; Dyspepsia; Enterocolitis; Esophagitis; Gastric hemorrhage; Gastritis; Gastrointestinal pain; Small intestinal perforation; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Generalized edema; Sudden death NOS
HEPATOBILIARY DISORDERS: - Cholecystitis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Dermatitis radiation; Fracture; Injury, poisoning and procedural complications – Other (incision site pain); Injury, poisoning and procedural complications – Other (procedural pain)
INVESTIGATIONS - Alanine aminotransferase increased; Creatinine increased; Weight gain; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperkalemia; Hypoalbuminemia; Hypokalemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Chest wall pain; Flank pain; Generalized muscle weakness; Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) – Leukemia secondary to oncology chemotherapy; Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Amnesia; Depressed level of consciousness; Encephalopathy; Leukoencephalopathy; Muscle weakness left-sided; Paresthesia; Seizure; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Amenorrhea
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Epistaxis; Nasal congestion; Oropharyngeal pain; Pharyngolaryngeal pain; Pleural effusion[5]; Pulmonary hypertension; Respiratory failure; Wheezing[5]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Eczema; Erythema multiforme; Hyperhidrosis; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Skin hyperpigmentation; Stevens-Johnson syndrome
VASCULAR DISORDERS - Hematoma; Thromboembolic event

Note: Trastuzumab (Herceptin) and/or Herceptin Hylecta™ (SQ trastuzumab) 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.

7.3.2 Investigational Agent

Atezolizumab

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted in Table 32). 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 3097 patients.* Below is the CAEPR for Atezolizumab (MPDL3280A).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Table 32. Comprehensive Adverse Events and Potential Risks list (CAEPR) for Atezolizumab (MPDL 3280A, NSC 783608)

Version 2.3, March 11, 2021[1]

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
		Heart failure[2]	
		Myocarditis[2]	
		Pericardial effusion[2]	
		Pericardial tamponade[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
		Adrenal insufficiency[2]	
		Endocrine disorders - Other (diabetes)[2]	
	Hyperthyroidism[2]		
		Hypophysitis[2]	
	Hypothyroidism[2]		
EYE DISORDERS			
		Eye disorders – Other (ocular inflammatory toxicity)[2]	
		Uveitis[2]	

Table continued on next page.

Table 32. Comprehensive Adverse Events and Potential Risks list (CAEPR) for Atezolizumab (MPDL 3280A, NSC 783608) *(continued)*

Version 2.3, March 11, 2021[1]

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis[2]	
	Diarrhea		***Diarrhea (Gr 2)***
	Dysphagia		
	Nausea		***Nausea (Gr 2)***
		Pancreatitis[2]	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever[3]		
	Flu like symptoms[3]		
HEPATOBILIARY DISORDERS			
		Hepatic failure[2]	
		Hepatobiliary disorders - Other (hepatitis)[2]	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[3]		
		Anaphylaxis[3]	
		Cytokine release syndrome[3]	
		Immune system disorders - Other (systemic immune activation)[2]	
INFECTIONS AND INFESTATIONS			
Infection[4]			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[3]		
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased[2]		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased[2]		
		Creatinine increased	
	GGT increased[2]		
	Lipase increased*		
		Platelet count decreased	
	Serum amylase increased*		

Table continued on next page.

Table 32. Comprehensive Adverse Events and Potential Risks list (CAEPR) for Atezolizumab (MPDL 3280A, NSC 783608) *(continued)*

Version 2.3, March 11, 2021[1]

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
		Hyperglycemia[2]	
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		
	Back pain		
		Generalized muscle weakness	
	Myalgia		
		Myositis[2]	
NERVOUS SYSTEM DISORDERS			
		Ataxia[2]	
		Encephalopathy[2]	
		Nervous system disorders - Other (encephalitis non-infective)[2]	
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (meningitis non-infective)[2]	
		Myasthenia gravis[2]	
		Paresthesia[2]	
		Peripheral motor neuropathy[2]	
		Peripheral sensory neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		Renal and urinary disorders - Other (nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
	Hypoxia		
	Nasal Congestion		***Nasal congestion (Gr 2)***
		Pleural effusion[2]	
		Pneumonitis[2]	

Table continued on next page.

Table 32. Comprehensive Adverse Events and Potential Risks list (CAEPR) for Atezolizumab (MPDL 3280A, NSC 783608) *(continued)*

Version 2.3, March 11, 2021[1]

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Bullous dermatitis[2]	
		Erythema multiforme[2]	
	Pruritus		
	Rash acneiform		
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])[2]	
	Skin and subcutaneous tissue disorders - Other (lichen planus)[2]		
		Skin and subcutaneous tissue disorders - Other (exanthematous pustulosis)[2]	
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis[2]	

*Denotes adverse events that are <3%.

[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]Atezolizumab, being a member of a class of agents involved in the inhibition of "immune checkpoints," may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. Immune-mediated adverse reactions have been reported in patients receiving atezolizumab. Adverse events potentially related to atezolizumab may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of atezolizumab, administration of corticosteroids and supportive care.

[3]Infusion reactions, including high-grade hypersensitivity reactions, anaphylaxis, and cytokine release syndrome, which have been observed following administration of atezolizumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of atezolizumab.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on atezolizumab (MPDL3280A) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that atezolizumab (MPDL3280A) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders – Other (pancytopenia); Febrile neutropenia

CARDIAC DISORDERS - Cardiac arrest; Ventricular tachycardia
GASTROINTESTINAL DISORDERS - Constipation; Dry mouth; Ileus
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS – Portal vein thrombosis
INVESTIGATIONS – Lymphocyte count decreased; Neutrophil count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Muscle cramp: Pain in extremity
NERVOUS SYSTEM DISORDERS - Headache
PSYCHIATRIC DISORDERS - Confusion; Insomnia; Suicide attempt
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Pulmonary hypertension; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin[2]; Hyperhidrosis
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event

Note: Atezolizumab (MPDL3280A) 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.

7.4 PRO-CTCAE Assessment Items

The NRG-BR004 study was permanently closed to accrual on May 20, 2022. Modified scheduled status updates, as outlined on Table 2A, will be completed for patients enrolled prior to study accrual closure. Patients will not be required to complete the PRO-CTCAE assessments.

With Amendment #3, accrual to the PRO-CTCAE substudy is closed. Patients enrolled on the PRO-CTCAE substudy prior to Amendment #3 will continue to complete the scheduled assessments as outlined on Table 2. Accrual to the QOL substudy will continue.

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.

PRO-CTCAE is intended to enhance the quality of adverse event data reporting in clinical trials, provide data that complements and extends the information provided by clinician reporting using CTCAE, represent the patient perspective of the experience of symptomatic adverse events, and improve detection of potentially serious adverse events. The selection of PRO-CTCAE should be complimentary to the clinician-identified AEs for ongoing monitoring. To enhance the toxicity monitoring in this study, and in line with the goals of the FDA and NCI in examining the added value of patient reported outcomes to standard toxicity evaluations (Kleutz 2016), we are planning to monitor toxicity with PRO-CTCAE items along with their standard assessments as described in the AE reporting section of this protocol (see Section 7.0). This has been found acceptable in clinical trials as recently reported by Basch (Basch 2017). We have selected key symptoms for monitoring that reflect the standard drug exposures in the trial, including those associated with atezolizumab. A key question is whether or not atezolizumab will exacerbate any of the common symptoms associated with the standard treatments that are being given to both treatment arms. As has been recommended by the NCI (Basch 2016), symptoms will be assessed prior to initiation of treatment (baseline), and then weekly during the first 12 weeks (Cycles 1-2) after the initiation of therapy. Subsequent assessments will occur at less frequent intervals and coincide with the timing of the investigator-evaluated AEs (i.e., on the same schedule). The

frequent monitoring, especially during the first 12 weeks, is designed to evaluate whether or not interim monitoring of symptoms (more frequent than at the time of usual visits), captures toxicity more accurately than when done intermittently. While missing data is a threat with such frequent assessments, use of an electronic monitoring approach (ePRO), where patients are sent an electronic link that allows them to easily respond to the survey items, should facilitate regular reporting. We list below the particular symptoms that will be assessed. In addition, patients will be offered a free text space to report on additional symptoms they may be having.

The PRO-CTCAE items used for the BR004 listed study are listed below. Refer to Section 11.6 for additional information.

CTCAE Term	PRO-CTCAE Terms with Attributes
Anorexia	Decreased appetite (Severity and Interference)
Nausea	Nausea (Frequency and Severity)
Dyspnea	Shortness of breath (Severity and Interference)
Peripheral sensory neuropathy	Numbness and tingling in hands or feet (Severity and Interference)
Abdominal pain	Pain in the abdomen (Frequency, Severity, and Interference)
Arthralgia	Joint pain (Frequency, Severity, and Interference)
Fatigue	Fatigue (Severity and Interference)
Diarrhea	Loose or watery stools (Frequency)
Rash maculo-papular	Rash (Present/Absent)
Pruritus	Itchy skin (Severity)
Cough	Cough (Severity and Interference)
Mucositis oral	Mouth or throat sores (Severity and Interference)

7.5 Expedited Reporting of Adverse Events

NRG Oncology will follow procedures for the centralized reporting of adverse events for BR004, which requires that adverse events/serious adverse events be reported to the NRG Oncology SDMC. NRG Oncology forwards reports to CTEP and, when necessary, the appropriate regulatory agencies. All serious adverse events that meet expedited reporting criteria defined in Table 33 will be reported via the **CTEP Adverse Event Reporting System, CTEP-AERS, accessed via Rave-CTEP-AERS Integration**.

Refer to Section 13.5 for important operational details/information about Rave-CTEP-AERS Integration and how to obtain the Expedited Safety Reporting Rules Evaluation User Guide.

NRG Oncology is identified in CTEP-AERS as the Lead Group for CTEP-AERS reporting.

Submitting a report via CTEP-AERS serves as notification to the NRG Oncology Statistics and Data Management Center (SDMC) and satisfies NRG Oncology requirements for expedited adverse event reporting.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to CTEP as the IND sponsor for this study by telephone at 301-897-7497 and to the NRG Oncology SDMC by phone at 412-624-2666. An electronic report must be submitted into CTEP-AERS upon re-establishment of the Internet connection.

7.5.1 Expedited Reporting Methods

- **Per CTEP NCI Guidelines for Adverse Events Reporting Requirements, a CTEP-AERS 24-Hour Notification** must be submitted to the NCI **within 24 hours** of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS **3 Calendar Day Report** (see Table 33).
- **CTEP-AERS 3 Calendar Day Report** requires that a complete report is electronically submitted to the NRG Oncology Lead Group **within 3 calendar days** of submission of the CTEP-AERS 24-hour notification (see Table 33).
- **CTEP-AERS 5 Calendar Day Report** requires that a complete report is electronically submitted to the NRG Oncology Lead Group **within 5 calendar days** of learning of the AE (see Table 33).
- Reports submitted via CTEP-AERS 24-hour notification are available for review by both the NCI and NRG Oncology after submission. **All other CTEP-AERS reports are first sent to the NRG Oncology Lead Group and then are forwarded to the NCI.** The timelines in Table 33 have been set so that the information can be forwarded to the NCI in a timely manner per the NCI's/CTEP's guidelines.
- **Supporting documentation** is requested by the IND sponsor for this study (CTEP/DCTD) and NRG Oncology as needed to complete adverse event review. All CTEP-AERS documentation is faxed to CTEP at 301-897-7404. When submitting supporting source documentation, remove all identifiers and include the protocol number, patient ID number, and CTEP-AERS ticket number on each page.
- A serious adverse event that meets expedited reporting criteria as outlined in the AE Reporting Table but is assessed by the CTEP-AERS as "An action is NOT recommended", must still be reported to fulfill NRG Oncology safety reporting obligations. Therefore, sites must override the "NOT recommended" assessment. CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.5.2 Expedited Reporting Requirements

Expedited reporting requirements begin with the administration of the first study therapy dose. Expedited reporting requirements for all patients are provided in Table 33.

7.5.3 Expedited Reporting Requirements for Adverse Events

Table 33. Expedited reporting requirements for adverse events that occur on studies under an IND within 30 days of the last administration of the investigational agent atezolizumab/placebo and/or commercial agents (trastuzumab/pertuzumab/paclitaxel/docetaxel)[1]

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

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the study therapy (21 CFR 312.64)

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

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

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI and/or NRG Oncology via CTEP-AERS within the timeframes detailed in the table below and Protocol Section 7.5.1.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	5 Calendar Days			24-Hour, 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		5 Calendar Days	

NOTE: ***Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR for atezolizumab/placebo.*** See Section 7.5.4 for adverse events of special interest.

Expedited AE reporting timelines are defined as:

- "24-Hour, 3 Calendar Days" – The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report to the NRG Oncology Lead Group within 3 calendar days of the initial 24-hour report.
- "5 Calendar Days" – A complete expedited report on the AE must be submitted to the NRG Oncology Lead Group within 5 calendar days of learning of the AE.

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

Expedited 24-hour notification followed by complete report with 3 calendar days for:

- All Grade 4 and Grade 5 AEs

Expedited 5 calendar days reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

Effective Date: May 5, 2011

7.5.4 Adverse Events of Special Interest

Adverse Events of Special Interest: Adverse events of special interest (AESI) require expedited reporting via CTEP-AERS regardless of attribution from the first dose of study therapy through April 2024. Adverse events of special interest for this study include the following:

Atezolizumab AESIs

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 6.21) and based on the following observations:
  - Treatment-emergent ALT or AST > 3 x ULN (or > 3 x baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin > 2 x ULN (of which ≥ 35% is direct bilirubin). Report as Hepatobiliary disorders - Other, potential drug-induced liver injury.
  - Treatment-emergent ALT or AST > 3 x ULN (or 3 x baseline value in disease states where LFTs may be elevated at baseline) combination with clinical jaundice. Report as Hepatobiliary disorders - Other, potential drug-induced liver injury.
- Suspected transmission of an infectious agent by the study treatment (STIAMP), defined as – Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected. Report as ≥ Grade 2 Infections and infestations – Other and specify the infectious agent identified.
- Pneumonitis
- Colitis
- Pancreatitis
- Hypophysitis
- Adrenal insufficiency
- Hyperthyroidism
- Diabetes mellitus (≥ Grade 2 Hyperglycemia)
- Hepatitis including AST or ALT > 5 x ULN (≥ Grade 3)
- Systemic lupus erythematosus. Report as Immune system disorders – Other, systemic lupus erythematosus.
- Guillain-Barré syndrome
- Myasthenic syndrome. Report as Nervous system disorders-Other, myasthenic syndrome.
- Myasthenia gravis. Report as Myasthenia gravis.
- Meningoencephalitis. Report as Encephalitis infection.
- Hypersensitivity. Report as allergic reaction.
- Infusion-related reactions. Report as Infusion related reaction.
- Cytokine release syndrome
- Influenza-like illness. Report as Flu like symptoms.
- Systemic inflammatory response syndrome. Report as Immune system disorders – Other, systemic inflammatory response syndrome.
- Systemic immune activation. Report as Immune system disorders – Other, systemic immune activation.
- Nephritis. Report as Renal and urinary disorders – Other, nephritis.
- Optic neuritis. Report as Eye disorders – Other, optic neuritis.
- Retinitis. Report as Eye disorders – Other, retinitis.
- Uveitis

- Myositis. Report as myositis.
- Myopathy. Report as Musculoskeletal and connective tissue disorder – Other, myopathy.
- Rhabdomyolysis
- Serious Adverse Cutaneous Reactions (SCARs) – erythema multiforme, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS)
- Vasculitis
- Autoimmune hemolytic anemia. Report as Blood and lymphatic system disorders – Other, autoimmune hemolytic anemia.
- Cardiac disorders > Grade 2 (e.g., atrial fibrillation, myocarditis, pericarditis)

Trastuzumab AESI

- Congestive heart failure. Report as Cardiac disorders – Other, congestive heart failure.

Pertuzumab AESI

- Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of monoclonal antibodies. Report as Ejection fraction decreased.

7.5.5 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.5.6 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.

All secondary malignancies that occur during or subsequent to treatment must be reported via CTEP-AERS within 10 days of learning of the secondary malignancy. Three options are available to describe the event:

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

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the BR004 Follow-up Folder in Medidata Rave. Supporting documentation should be uploaded into the relevant form in the Follow-up folder in Medidata Rave using available upload fields within those forms. Please upload each document into a different upload field, as any later uploads into a given field erases the document that exists there.

7.5.7 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 within the BR004 Follow-up Folder in Medidata Rave (see Section 7.7).

7.5.8 Expedited Reporting of Pregnancy, Pregnancy Loss, and Death Neonatal

Any pregnancy, pregnancy loss, or death neonatal occurring in a female patient or a male patient's partner from the time of consent to 5 months (150 days) after the last dose of atezolizumab/placebo or 7 months after the last dose of trastuzumab and pertuzumab must be reported via CTEP-AERS as a medically significant event. Definitions and reporting instruction for these events are provided in the Cancer Therapy Evaluation Program's (CTEP) revised NCI guidelines for Investigators: Adverse Event Reporting Requirements (Section 5.5.6) located at the following CTEP website: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf). ***Upon learning of a pregnancy, pregnancy loss, or death neonatal that occurs during study or within 5 months (150 days) after the last dose of atezolizumab/placebo or 7 months after the last dose of trastuzumab and pertuzumab the investigator is required to:***

- ***Immediately discontinue study therapy.***
- Call the NRG Oncology Clinical Coordinating Department.
- Within 5 working days of learning of the event, and as required by the NCI Guidelines for Investigators: Adverse Event Reporting Requirements (Section 5.5.6.):
  - Create and submit a CTEP-AERS report;
  - Complete the Pregnancy Information Form (located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm); and
  - Fax the completed Pregnancy Information Form with all available supporting documentation to CTEP at 301-897-7404.
- The pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same **Pregnancy Information Form** used for the initial report.
- Additional information on any pertuzumab and trastuzumab exposed pregnancy and infant will be requested by Genentech/Roche Drug Safety at specific time points (i.e., after having received the initial report, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life).
- Pregnancy loss is defined in CTCAE v5.0 as "Death in utero." Report pregnancy loss expeditiously as Grade 4 "pregnancy loss" under the Pregnancy, puerperium and perinatal conditions system organ class (SOC). A pregnancy loss is not reported as a Grade 5 event.
- For questions concerning pregnancy, contact the AE Reporting Nurse.

7.6 Routine Reporting of Adverse Events

7.6.1 Reporting Routine Adverse Events Through Medidata Rave

- Reporting of routine adverse events is done through Medidata Rave (see Section 13.2).
- **All ≥ grade 1 adverse events not reported via CTEP-AERS** that occurred during study therapy must be reported on the BR004 Adverse Event forms through Medidata Rave.
- Reporting of AEs is not required following documented disease progression or diagnosis of a second primary malignancy.
- Supporting documentation for each AE reported on the BR004 Adverse Event forms through Medidata Rave must be maintained in the patient's research record. When submission of supporting documentation to the NRG Oncology Statistics and Data Management Center is required, remove patient names and identifiers such as social security number, address, telephone number, etc., from reports and supporting documentation.

7.6.2 Schedule for Reporting Routine Adverse Events

Adverse event reports are to be submitted through Medidata Rave, **even if no AEs were experienced by the patient**.

- Submit the BR004 Adverse Event Report Form every 6 weeks after the start of study therapy through 2 years and 30 to 45 days after last dose of atezolizumab/placebo.
- Submit the BR004 Adverse Event Report Form every 3 months in Years 3 through 5 and every 6 months in Years 6 through 10.

7.6.3 Reporting PRO-CTCAE

Symptomatic Adverse Events reported by patients through PRO-CTCAE are not safety reporting and may be presented with other routine AE data.

7.7 Reporting Breast Cancer Progression and Second Primary Cancer

Report disease progression and second primary cancer (a malignancy which is unrelated to the treatment of a prior malignancy and which is not a metastasis from the initial malignancy) within the BR004 Follow-up folder in Medidata Rave. Supporting documentation should be uploaded into the relevant form in the Follow-up folder in Medidata Rave using available upload fields within those forms. Please upload each document into a different upload field, as any later uploads into a given field erases the document that exists here. (See Section 7.5.6 for reporting instructions for ***secondary*** malignancies.)

8.0 REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES

8.1 CTEP Registration Procedures

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

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management 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 types.

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

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. 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:

- An addition to a site roster
- Assignment of the treating, crediting, 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 act as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

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

8.2 Cancer Trials Support Unit Registration Procedures

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

8.2.1 IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. 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 in order for the processing of the IRB/REB approval record to be completed:

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

8.2.2 Additional Requirements

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

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

8.2.3 Protocol Specific Requirements for NRG-BR004 Site Registration

- Site Initiation Visit

8.2.4 Downloading Site Registration Documents

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

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *NRG*, and protocol number (*NRG-BR004*);
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

8.2.5 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 in order to receive further instruction and support.

8.2.6 Delegation of Tasks 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 include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

In addition, the following task assignment restrictions apply to this protocol:

The individual initiating the DTL for the site should upload the above listed training documentation when making the task assignment. The designated reviewer will accept or reject the documentation. A note regarding rejection of any training documents will display on the Site DTL Browser next to the task assignment. The DTL cannot be submitted for CI sign-off until the minimum number of persons are assigned to the task and have met the training requirements.

Canadian sites participating under Canadian Cancer Trials Group (CCTG), should complete the DTL in CCTG's Ripple application when CCTG holds the Clinical Trials Agreement with Health Canada. Ripple is integrated with the CTSU DTL application for this trial.

8.2.7 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.

8.3 Patient Enrollment

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.4 Oncology Patient Enrollment Network (OPEN)

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 Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or to 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 (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.

8.5 ePRO Registration Process

8.5.1 Medidata Patient Cloud ePRO

This study includes the use of Medidata Patient Cloud ePRO (electronic patient-reported outcomes). The ePRO application allows patients to report clinical trial information (patient reported outcomes (PROs)) directly from their mobile devices into the Medidata Clinical Cloud. In this document *ePRO application* refers to the application accessed by the site via iMedidata and Rave, and *ePRO mobile app* refers to the app accessed by the patient on a mobile device. After the patient is registered to the trial via OPEN, and the patient is willing to participate in electronic data collection, the site staff will complete a registration for the patient to the ePRO application through iMedidata. Sites are not permitted to delete the ePRO component from the protocol or from the informed consent form. Site staff must complete the required eLearning (assigned in iMedidata) for the ePRO application before registering a patient. Information about the training is in Appendix B. The registration to the ePRO application will create a unique patient registration code that the site staff will provide to the patient. The patient (with assistance from the site staff) should be instructed to download the appropriate ePRO mobile app onto his/her own device (IOS, Android, phone, or tablet) and use the unique patient registration code to create an account. Once the patient's account is set up, the patient will be able to complete the submission of patient-reported outcomes electronically for the trial.

There are multiple versions of the ePRO mobile app available. Ensure that the correct version of the ePRO mobile app is downloaded by the patient by verifying the correct version per the protocol requirements. Note only one version of the app is active per protocol and this protocol is using *Patient Cloud*.

For sites providing a shared institutional device for use by multiple patients on site:

- The site staff should assist the patient with access and registration to the ePRO application and access to the ePRO mobile app, and the patient can then complete the

electronic data submission independently. Site staff may need to assist patients with logging on to the device at each visit.

8.5.2 CRA Patient Registration Instructions for ePRO

Site staff must complete the required ePRO online training (assigned in iMedidata) for studies using the ePRO application before registering a patient. Reference materials for the Patient Cloud (current) app can be found at the links below; the landing page contains patient registration information as well as links to additional resources on the left side of the screen: Patient Cloud Patient Registration Instructions.

The subject registration process starts in iMedidata. To register a patient:

i. Select the **Patient Cloud Registration** link for your study.

ii. From the patient management app, select your **STUDY** and **SITE** from the drop down menus and click **Launch**.

iii. Register your first patient. Create a **subject ID** and select a **Country / Language** from the drop down (required data fields). The subject initials are optional but are helpful in identifying which subject ID maps with which activation code. When finished, click **Add**.

iv. The subject will be added and will include the date the patient was added, the subject ID, subject 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 indicates if the patient has registered. When the patient has registered, the status will change from "invited" to "registered".

8.6 Reimbursement

To receive site reimbursement for biospecimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the NRG-BR004 specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement. The collection of specimens for exploratory endpoints is not funded by CTEP and will be reimbursed by the sponsor with non-CTEP funding.

8.7 Investigator-Initiated Discontinuation of Study Therapy

In addition to the conditions outlined in the protocol, the investigator may require a patient to discontinue study therapy if one of the following occurs:

- the patient develops a serious side effect that cannot be tolerated or that cannot be controlled with other medications,
- the patient's health gets worse,
- the patient is unable to meet the study requirements, or
- new information about the study therapy or other treatments for breast cancer becomes available.

If study therapy is stopped, study data, other materials, and the tumor samples (at the time of disease progression) should be submitted according to the study schedule unless the patient withdraws from the study (see Section 8.9).

8.8 Patient-Initiated Discontinuation of Study Therapy

Even after a patient agrees to take part in this study, the patient may stop study therapy or withdraw from the study at any time. If study therapy is stopped but the patient still allows the investigator to submit information, study data, other materials, and the tumor samples (at the time of disease progression) should be submitted according to the study schedule.

8.9 Patient-Initiated Consent Withdrawal from the Study

If a patient chooses to have no further interaction regarding the study (i.e., allow no future follow-up data to be submitted to NRG Oncology), the consent withdrawal form is to be completed via the Add-Event function in Medidata Rave.

9.0 DRUG INFORMATION

9.1 Atezolizumab (IND #[redacted] NSC #783608)

The current version of the Investigator Brochure (IB) will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB Coordinator.

9.1.1 Atezolizumab/Placebo

Atezolizumab/placebo used for this study is considered investigational in the U.S. and by Health Canada to be investigational/used outside the authorized indication in Canada.

- ***Other Names:*** Tecentriq™, MPDL3280A
- ***Classification:*** monoclonal antibody
- ***Molecular Weight:*** 150 KD
- ***Mode of Action:*** anti-PD-L1
- ***Description:*** Atezolizumab is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids). Atezolizumab targets human PD-L1 and inhibits its interaction with its receptor PD-1. Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells (Butte 2007). ***(Note: The placebo will be identical in appearance to atezolizumab and comprise the same excipients but without atezolizumab drug product.)***
- ***How Supplied:*** Atezolizumab/placebo is provided by Genentech/F.Hoffmann-La Roche LTD and distributed by the Pharmaceutical Management Branch, CTEP, NCI. The agent is supplied in a single-use, 20-mL glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. Atezolizumab is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, at a pH of 5.8. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume.
- ***Preparation:*** The prescribed dose of atezolizumab/placebo should be diluted in 250 mL 0.9% NaCl and infused through a 0.2 micrometer in-line filter. The IV bag may be constructed of PVC or PO; the IV infusion line may be constructed of PVC or PE; and the 0.2 micrometer in-line filter may be constructed of PES. The prepared solution may be stored at 2°C-25°C for up to 8 hours.
- ***Storage:*** 2°C-8°C (36°F-46°F) Vial contents should not be frozen or shaken and should be protected from direct sunlight.

  If a storage temperature excursion is identified, promptly return atezolizumab/placebo to 2°C-8°C (36°F-46°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

- ***Stability:*** Stability studies are ongoing.

  CAUTION: No preservative is used in atezolizumab/placebo; therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial.

- ***Route of Administration:*** IV infusion

- ***Method of Administration:*** Atezolizumab/placebo is administered as an intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not administer atezolizumab/placebo as an intravenous push or bolus. No premedication is indicated for administration of Cycle 1 of atezolizumab/placebo. Patients who experience an infusion related reaction with Cycle 1 of atezolizumab/placebo may receive premedication with antihistamines or antipyretics/analgesics (e.g. acetaminophen) for subsequent infusions.

- ***Potential Drug Interactions:*** Cytochrome P450 enzymes as well as conjugation/glucuronidation reactions are not involved in the metabolism of atezolizumab. No drug interaction studies for atezolizumab have been conducted or are planned. There are no known interactions with other medicinal products or other form of interactions.

- ***Patient Care Implications:*** Male patients and female patients of childbearing potential should utilize contraception and take active measures to avoid pregnancy while undergoing atezolizumab/placebo treatment and for at least 5 months (150 days) after the last dose of atezolizumab/placebo.

  Refer to Section 6.4 for information on evaluation and management of potential immune-mediated adverse events.

9.1.2 Procurement of Atezolizumab/Placebo and Trastuzumab

- Atezolizumab/placebo and open-label trastuzumab will be supplied free of charge by Genentech, a Member of the Roche Group/F.Hoffmann-La Roche LTD, and will be distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI). **(NOTE: Canadian supplies of trastuzumab will be obtained from commercial sources.)**

- The placebo will be centrally supplied and distributed by Genentech, a Member of the Roche Group/F.Hoffmann-La Roche LTD and will be identical in appearance to atezolizumab and comprise the same excipients but without atezolizumab drug product.

- NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

- No starter supplies will be available for this study. Patient-specific clinical supplies will be sent to the registering investigator at the time of randomization and should arrive within approximately 5 to 7 days. This randomization will be performed by the NRG Statistics and Data Management Center (SDMC). The assigned NRG patient ID number must be recorded by the registering institution for proper agent dispersion. Once a patient has been registered,

the NRG SDMC will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the NRG SDMC the day the patient is registered and will be processed by the PMB the next business day and shipped the following business day. Shipments within the United States will be sent by FedEx and shipments to Canada will be sent by FedEx International (generally one to two-day delivery). Thus, if a patient is registered on Monday, NRG would enter a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. Sites could expect to receive their order approximately Thursday or Friday. Shipments to United States sites can be expedited (i.e., receipt on Thursday in example above) by the provision of an express courier account name and number to the NRG SDMC at the time the patient is randomized.

The initial request will be for 3 vials (a 9 week supply at a dose of 1200 mg or placebo) of atezolizumab 1200 mg or matching Placebo and 13 vials of trastuzumab (sufficient for the loading dose and two additional doses). After 6 weeks (three weeks before needed), sites may reorder an additional 3 vials (a 9 week supply at a dose of 1200 mg or placebo) of atezolizumab 1200 mg or matching Placebo and 12 vials of trastuzumab (a 9 week supply) using the PMB Online Agent Order Processing (OAOP) application (https://ctepcore.nci.nih.gov/OAOP/). Active CTEP -registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam/index.jsp) and the maintenance of an “active” account status and a “current” password. The assigned patient ID number (e.g., "999999") and the patient initials (e.g., "L, FM") must be entered in the "Patient or Special Code" field. A separate order is required for each patient ID number (e.g., "999999") being ordered. All drug orders will be shipped directly to the physician responsible for treating the patient.

Each blinded or open-label, patient-specific box will be labeled with:

- The protocol number (i.e., NRG-BR004)
- The box number (i.e., “Box 1 of 2”, “Box 2 of 2”, etc.)
- The number of vials (i.e., ”4 vials”)
- The patient ID number (e.g., "999999")
- The patient initials (i.e., Last initial, First initial, Middle initial [e.g., “L, FM”])
- The agent identification (i.e., “Atezolizumab 1200 mg or Placebo” or "Trastuzumab 150 mg")
- A blank line for the pharmacist to enter the patient’s name
- Storage instructions (i.e., “Store in refrigerator [2 – 8°C]. Do not freeze. Do not shake.”)
- Emergency contact instructions
- A Julian date

The Julian date indicates the day the vials were labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2017 = 17, 2018 = 18) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a box labeled and shipped on January 1, 2018 would have a Julian date of ‘18001’ and a box labeled and shipped on December 31, 2018 would have a Julian date of ‘18365’. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all vials (i.e., both atezolizumab and Placebo) shipped on or before that date thus eliminating any

chance of breaking the blind. The Julian Date – Order number (e.g., 2017352-0003) from the patient-specific label must be used as the Lot number on the NCI DARF.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (240) 276-6575 Monday through Friday between 8:30am and 4:30pm Eastern Time. You may also contact the PMB via e-mail at PMBAfterHours@mail.nih.gov.

9.1.3 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Registration (RCR): RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
  - Refer to the Policy and Guidelines for Investigational Agent Ordering for order processing time and conditions. Normal order processing time is two business days. An express courier account number must be provided for next-day delivery. International orders require additional processing and shipment transit time and are not available for next day delivery.
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP/
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov

  PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET).

9.1.4 Transfer of Atezolizumab/Placebo or Trastuzumab

Patient-specific agent supplies MAY NOT be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to PMBAfterhours@mail.nih.gov a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov). The patient ID number (e.g., "99999"') and the patient initials (e.g., "L, FM") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "NRG-BR004").

9.1.5 Return of Atezolizumab/Placebo or Trastuzumab

When it is necessary to return unused study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov). The patient ID number (e.g., "99999") and the patient initials (e.g., "L, FM") should be entered in the "Lot Number" field.

9.1.6 Drug Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov). A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "99999") on this protocol. NOTE: The Julian Date – Order number combination found in the upper right-hand portion of the patient-specific label must be used as the Lot Number. This number will be used in the event of a stock recovery or recall of the investigational agent. **(NOTE: U.S. sites must maintain a Drug Accountability Form (DARF) for the patient specific atezolizumab/placebo and trastuzumab. Canadian sites must maintain a DARF for the patient specific atezolizumab/placebo but are not required to maintain a DARF for trastuzumab, which is obtained from commercial sources.)**

9.2 Paclitaxel (NSC #673089)

9.2.1 Availability/Supply

Paclitaxel is obtained by the investigator from commercial supply.

9.2.2 Product Description

Refer to the paclitaxel package insert or monograph.

9.2.3 Preparation

Refer to the current FDA-approved package inserts or current Health Canada-approved product monographs provided with paclitaxel and the site-specific pharmacy for standard drug preparation instructions, handling, and storage. Canadian-specific instructions for labeling, storage, and documentation of receipt, disposition, and return or destruction will be provided separately to Canadian investigators.

9.2.4 Route of Administration

Please see Section 5.1 (Table 3) for administration instructions.

9.2.5 Adverse Events

Please refer to the current FDA-approved package inserts and current Health Canada-approved product monographs provided with paclitaxel and the site-specific pharmacy for toxicity information and Section 7.3.

9.3 Docetaxel (NSC #628503)

9.3.1 Availability/Supply

Docetaxel is obtained by the investigator from commercial supply.

9.3.2 Product Description

Refer to the docetaxel package insert or monograph.

9.3.3 Preparation

Refer to the current FDA-approved package inserts or current Health Canada-approved product monographs provided with docetaxel and the site-specific pharmacy for standard drug preparation instructions, handling, and storage. Canadian-specific instructions for labeling, storage, and documentation of receipt, disposition, and return or destruction will be provided separately to Canadian investigators.

9.3.4 Route of Administration

Please see Section 5.1 (Table 3) for administration instructions.

9.3.5 Adverse Events

Please refer to the current FDA-approved package inserts and current Health Canada-approved product monographs provided with docetaxel and the site-specific pharmacy for toxicity information and Section 7.3.

9.4 Pertuzumab (NSC #740102)

9.4.1 Availability/Supply

Pertuzumab is obtained by the investigator from commercial supply.

9.4.2 Product Description

Refer to the pertuzumab package insert or monograph.

9.4.3 Preparation

Refer to the current FDA-approved package inserts or current Health Canada-approved product monographs provided with pertuzumab and the site-specific pharmacy for standard drug preparation instructions, handling, and storage. Canadian-specific instructions for labeling, storage, and documentation of receipt, disposition, and return or destruction will be provided separately to Canadian investigators.

9.4.4 Route of Administration

Please see Section 5.1 (Table 3) for administration instructions.

9.4.5 Adverse Events

Please refer to the current FDA-approved package inserts and current Health Canada-approved product monographs provided with pertuzumab and the site-specific pharmacy for toxicity information and Section 7.3.

9.5 Trastuzumab (NSC #688097)

9.5.1 Availability/Supply

US supply (Please see Section 9.1.2 for procurement information.):

Genentech supplies and the Pharmaceutical Management Branch, CTEP, NCI, distributes trastuzumab as a lyophilized sterile powder, under vacuum. Each carton contains one vial of 150 mg trastuzumab as a lyophilized preparation for parenteral administration. The commercially-

labeled 150 mg vials are formulated in histidine/histidine-HCl monohydrate, α,α-trehalose dihydrate, and polysorbate 20. **NOTE: The 150 mg vials are not multi-use vials.**

Canadian Supply:

Canadian institutions will obtain trastuzumab from commercial sources. Commercial labeling, preparation and administration guidelines should be followed.

9.5.2 Product Description

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

9.5.3 Preparation

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

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

Dilution

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

9.5.4 Route of Administration

Trastuzumab is given by slow intravenous infusion only. The initial dose is 8 mg/kg as a loading dose, followed by every three-week doses at 6 mg/kg. The loading dose is infused over 90 minutes (+/- 10 minutes). If this is well tolerated, subsequent infusions may be given over 30-60 minutes. Please see Section 5.1 (Table 3) for detailed administration instructions.

9.5.5 Storage

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

9.5.6 Stability

Do not use beyond the expiration date stamped on the product label.

9.5.7 Adverse Events

Please refer to the current FDA-approved package inserts and current Health Canada-approved product monographs provided with trastuzumab and the site-specific pharmacy for toxicity information and Section 7.3.

9.6 **Unblinding**

When unblinding is required, local investigators must contact the NRG Oncology SDMC at 412-624-2666 and state that they wish to unblind a patient's study drug assignment. The same procedure applies to 24-hour emergency unblinding. A data file is maintained for the study and can be accessed by a limited number of designees within the NRG Oncology SDMC who serve the study in an administrative, nonclinical capacity. The NRG Oncology SDMC personnel will require the protocol number, the patient ID number, the patient's initials (e.g., "LFM"), and the reason for the unblinding request in order to unblind the study drug assignment. After the confirmation of the indication for unblinding is obtained, the investigator will be notified immediately of the patient's treatment assignment. A computer record will be created to identify the patient as having been unblinded. The institution is responsible for providing continued follow-up (for patients whose treatment assignment has been unblinded) on the same schedule as indicated in the study protocol for patients who have not been unblinded, unless otherwise specified (see Table 2).

10.0 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

The NRG-BR004 study was permanently closed to accrual on May 20, 2022. Modified scheduled status updates, as outlined on Table 2A, will be completed for patients enrolled prior to study accrual closure. Biospecimen submissions are no longer required.

10.1 Overview of Tumor Specimen Submissions

Tumor sample submission at study entry is a protocol requirement and, therefore, mandatory for participation in the study (see Table 34 for specific requirements). NOTE: A "Notice of HER2 Eligibility" must appear in Medidata Rave to confirm testing for HER2, ER/PgR, and PD-L1 has been completed before a patient can be randomized.

By signing the BR004 consent form, the patient agrees to a tumor sample submission. Submission of optional tumor tissue and blood specimens is only required for patients who agree to submission of optional tumor tissue and blood in the BR004 consent form.

Table 34. Mandatory and optional sample requirements

Specimen Type	Collection Time Points	Submission Information	Shipping
Mandatory • De novo (newly diagnosed)**a,b,c** – **3-5 unstained positively charged slides (4 microns)** from the metastatic disease, breast primary, or involved regional lymph nodes submitted for central PD-L1 testing – **8 unstained positively charged slides (3-5 microns)** from the metastatic disease, breast primary, or involved regional lymph nodes for central confirmation of HER2 and ER/PgR status • Recurrent**b,c** – **3-5 unstained positively charged slides (4 microns)** from biopsy done to confirm recurrent/metastatic cancer submitted for central PD-L1 testing – **8 unstained positively charged slides (3-5 microns)** from biopsy done to confirm recurrent/metastatic cancer submitted for central confirmation of HER2 and ER/PgR status	Baseline (at study entry)	***Refer to the CTSU Member website (www.ctsu.org) for the BR004 Pathology, Correlative Science, and Imaging Submission Instructions for detailed submission instructions.***	**Shipment of 3-5 unstained positively charged slides:** HistoGeneX Attn. Sample Reception Team - P1064 1331 W 75th Street Suite 401 Naperville, IL 60540 USA **Shipment of 8 unstained positively charged slides for central confirmation of HER2 and ER/PgR status:** Magee-Womens Hospital of UPMC, Department of Pathology 300 Halket Street 4th Floor, Room 4139 Pittsburgh, PA 15213 Attn: NRG-BR004

Table continued on next page.

Table 34. Mandatory and optional sample requirements *(continued)*

Specimen Type	Collection Time Points	Submission Information	Shipping
Optional • De novo (newly diagnosed)[a] – **10-15 unstained positively charged slides (3-5 microns)** from the metastatic disease, breast primary, or involved regional lymph nodes • Recurrent – **10-15 unstained positively charged slides (3-5 microns)** from biopsy done to confirm recurrent/metastatic cancer	Baseline (Submission of unstained slides within 45 days following randomization)	***Refer to the CTSU Member website (www.ctsu.org) for the BR004 Pathology, Correlative Science, and Imaging Submission Instructions for detailed submission instructions.***	NSABP Division of Pathology NRG Oncology Biospecimen Bank-Pittsburgh 1307 Federal Street Suite 303 Pittsburgh, PA 15212
10-15 unstained positively charged slides (3-5 microns)[d]	Tumor Progression		
Optional Plasma collected in Streck Cell-Free DNA BCT® tube (2 tubes)	• Baseline • Prior to Weeks 10, 19, and 28 • At 9, 12, 18, and 24 months • Every 6 months Year 3 through Year 5 (in absence of progression) • Tumor progression		Baylor College of Medicine NRG Oncology Serum Bank Room 330C One Baylor Plaza Houston, TX 77030

a Slides from the diagnostic biopsy performed to determine metastatic disease must be submitted; however, if a biopsy of the metastatic disease may have excessive risk to the patient as determined by the investigator, slides from the breast primary or involved regional lymph nodes may be submitted.

b If there is insufficient material for central confirmation of HER2 and for PD-L1 testing, a research biopsy may be done to obtain tumor tissue. It is strongly recommended that the research biopsy be done before therapy is started at study entry.

c The priority for testing if there is limited tumor tissue available:
1.) Four unstained positively charged slides for central confirmation of HER2. **Note:** Central confirmation of HER2 is mandatory for eligibility.
2.) Three to five unstained positively charged slides for central testing of PD-L1
3.) Two unstained positively charged slides for central confirmation of ER and PgR.

d If a biopsy was done at the time of tumor progression, submission of slides is required for patients who have agreed to the optional tumor sample submission in the BR004 consent form.

10.2 Specimen Submission Information

Refer to the BR004 Pathology, Correlative Science, and Imaging Submission Instructions in the Members' Area of the CTSU website for details regarding submission of specimens.

- If there is insufficient material available for the mandatory specimen submissions as outlined on Table 34, the prioritization for specimen submissions is:
  - Four unstained positively charged slides (3-5 microns) from the locally recurrent or metastatic disease are to be submitted to Magee-Womens Hospital of UPMC, Department of Pathology for central confirmation of HER2.
  - Three to five unstained positively charged slides (4 microns) from the locally recurrent or metastatic disease are to be submitted to HistoGeneX for central PD-L1 testing.
  - Two unstained positively charged slides (3-5 microns) from the locally recurrent or metastatic disease are to be submitted to Magee-Womens Hospital of UPMC, Department of Pathology for central confirmation of ER/PgR. If sufficient material for central confirmation of ER and PgR is unavailable, local testing results for ER and PgR may be used for eligibility.
- For patients who agree to the optional submissions of tissue and blood:
  - Unused slides that were sent for central confirmation of HER2 and ER/PgR at Magee-Womens Hospital of UPMC, Department of Pathology will be sent to the NRG Oncology Biospecimen Bank – Pittsburgh upon notification from the NRG Oncology SDMC that a patient has agreed to the optional submission of tumor tissue. For patients who did not agree to the optional submission of tissue, the unused slides will be retained and stored by the Magee-Womens Hospital of UPMC, Department of Pathology.
  - Two Streck Cell-Free DNA BCT tubes drawn at the time points listed on Table 34.
  - Ten to fifteen unstained positively charged slides (3-5 microns) from the locally recurrent or metastatic disease and from tumor progression (if biopsy was performed) are to be submitted to the NRG Oncology Biospecimen Bank – Pittsburgh.

10.3 Integral Marker Testing

10.3.1 HER2 Testing

The HER2 IHC testing will be performed using the FDA cleared assay Ventana anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody according to the package insert without modification.

The reflex HER2 FISH testing, when required, will be performed using the FDA cleared DAKO assay according to the package insert without modification.

10.3.2 ER/PgR Testing

Estrogen receptor antibody SP1 is performed using the FDA cleared /VIEW detection on the Benchmark ULTRA (Ventana, Tucson, AZ) according to the package insert without modification. Progesterone receptor antibody 1E2 is performed using the FDA cleared /VIEW detection on the Benchmark ULTRA (Ventana, Tucson, AZ) according to the package insert without modification.

10.3.3 Reporting and Location of Testing

Results will be provided to the investigator.

Magee-Womens Hospital of UPMC, Department of Pathology
300 Halket Street, 4th Floor, Room 4139
Pittsburgh, PA 15213
Atten: NRG-BR004

10.3.4 PD-L1 Testing

PD-L1 expression within biopsied tumor will be assessed as an integral marker. The association between PD-L1 expression and prognosis has been extensively investigated for a range of solid tumors, suggesting that its expression is a negative prognostic indicator. For study entry, tumor PD-L1 status determination must be documented through central testing of a representative tumor tissue specimen.

10.3.5 Method of Testing

Central testing of PD-L1 will be performed at Histogenex, a CAP-accredited, CLIA-certified reference laboratory. PD-L1 testing will be performed with the FDA cleared assay Ventana PD-L1 (SP142) assay kit which uses the OptiView DAB IHC detection kit and OptiView Amplification kit on a Ventana BenchMark Ultra Instrument along with the specified antibody.

10.3.6 Reporting and Location of Testing

For the purposes of stratification, the results will be provided to the NRG Oncology SDMC. Results will not be provided to the investigator or the patient.

HistoGeneX
Attn. Sample Reception Team – P1064
1331 W 75th Street
Suite 401
Naperville, IL 60540
USA

10.4 **Exploratory Analyses**

We will further explore the prognostic and predictive utility (of the efficacy of atezolizumab) of potential immune biomarkers such as the immune-mediated gene expression signatures, antibodies status from multiplex immunofluorescence, stromal tumor infiltrating lymphocytes (sTIL), intrinsic subtype of the tumor, and cell-free circulating tumor DNA (ctDNA). An amendment or proposal for any correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of biological samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

11.0 SPECIAL STUDIES (NON-TISSUE)

The NRG-BR004 study was permanently closed to accrual on May 20, 2022. Modified scheduled status updates, as outlined on Table 2A, will be completed for patients enrolled prior to study accrual closure. Patients will not be required to complete the QOL and PRO-CTCAE assessments.

With Amendment #3, accrual to the PRO-CTCAE substudy is closed. Patients enrolled on the PRO-CTCAE substudy prior to Amendment #3 will continue to complete the scheduled assessments as outlined on Table 2. Accrual to the QOL substudy will continue.

11.1 Quality of Life (QOL) Background

11.1.1 General Considerations

The therapeutic goal of this study is to prolong survival among patients with newly diagnosed metastatic breast cancer through the focused use of agents that target HER2-neu overexpression in their tumors. A taxane of investigator choice (paclitaxel or docetaxel) will be the chemotherapy backbone for the trial and will be received by patients in both arms of the study, along with trastuzumab and pertuzumab. The primary QOL question for this trial is whether or not the addition of an immune modulatory agent contributes to the established toxicity of chemotherapy with the two HER2-targeted therapies that all patients will be receiving. In the CLEOPATRA Trial (Baselga 2012), the most frequent toxicities recorded by standard CTCAE were diarrhea in 66.8%, fatigue in 37.6% and mucositis in 27.8% of patients. These toxicity reports are likely an underestimate of what patients might report.

However, the CLEOPATRA trial also included a companion QOL study that used the FACT-B as its study questionnaire with a primary analysis that focused on the FACT-B-Trial Outcome Index (TOI) (Cortes 2013), and a post-hoc analysis that looked at the symptom scale of the FACT-B. The CLEOPATRA QOL study did not detect a significant contribution to deterioration in functioning with the addition of pertuzumab to the treatment regimen, although both treatment groups had a decline in the TOI during the first 18 weeks on therapy that improved back to baseline by 12 months (Cortes 2013). An exploratory post-hoc symptom deterioration analysis suggested that the pertuzumab arm might have been better with symptoms worsening earlier in the control group, possible due to greater efficacy in the pertuzumab arm. However, the symptom items in FACT-B symptom scale are broad and were not targeted to the key items identified by the CTCAE toxicity noted earlier. Specific toxicities of paclitaxel and the antibody therapies are described earlier in the CAEPR tables, and specific toxicities of concern are neuropathy, diarrhea, musculoskeletal pain, mucositis, and fatigue. To a large extent, these overlap with the independent toxicities of atezolizumab, so measurement of these symptoms will be essential as they could be exacerbated by the anti-PD-L1 therapy.

In considering the addition of an anti-PD-L1 monoclonal antibody to the proposed standard therapy, we must take into consideration what is known about this class of agents, and the symptom profile expected. As described earlier in Sections 2.4 and 2.5, the most common adverse events reported in ≥10% of treated patients were fatigue, decreased appetite, nausea, pyrexia, constipation, cough, dyspnea, diarrhea, anemia, vomiting, asthenia, back pain, headache, arthralgia, pruritus, rash, abdominal pain, insomnia, peripheral edema and dizziness. Only a limited amount of data is available specifically in breast cancer patients, as noted in Section 2.5. Thus, we need to ensure that the QOL study for this trial addresses the symptoms that are prominent in association with this class of agents, in particular fatigue.

11.1.2 Fatigue as the Primary QOL Endpoint

For more than two decades, fatigue in cancer patients has been recognized as one of the most prevalent and troublesome side effects of cancer and its treatment, having adverse effects on quality of life (Jacobsen 2004, Bower 2014). Fatigue is often a direct consequence of the cancer, especially when associated with uncontrolled metastatic disease. However, fatigue may also be a specific consequence of cancer-directed treatments (e.g., radiation, chemotherapy, immunotherapy) (Bower 2014). It is generally agreed that fatigue is subjective, and must be assessed by self-report, rather than by an observer, and there are currently many reliable and valid questionnaires to assess fatigue (Jacobsen 2004, Lai 2014). Fatigue impacts the physical, emotional, social and cognitive functioning of cancer patients (Donovan 2015), and as such serves as an effective composite measure of well-being during and after cancer therapy. In this trial, we expect that fatigue will be an important side effect of both treatments and that some patients will have fatigue even before treatment starts. Fatigue was not specifically assessed in the CLEOPATRA QOL study, nor do we have any self-reported data on fatigue from recent immunotherapy trials. However, given the hypothesized efficacy of the experimental treatment arm, with increased disease response and prolonged progression-free survival, we expect that any additional fatigue associated with the immunotherapy will be balanced by reduced fatigue from better disease control, and propose to examine the trajectory of fatigue during the first 12 months on treatment. We believe that this will be the most important QOL outcome for future patients once the trial results are available.

11.1.3 Assessment Approach, Considerations, and Questionnaires

In addition to the assessment of fatigue as the primary QOL outcome, we will also assess the impact of the study treatments on physical functioning and symptoms (Kluetz 2016). To this end, examination of the longitudinal pattern of physical functioning, disease and treatment associated symptoms among the secondary outcomes assessed in the QOL study. The CLEOPATRA QOL study gives some suggestion that there is a decline in functioning during the first 18 weeks of treatment; however, the FACT-B-TOI items are a mixture of diverse symptoms and functions, and thus it is difficult to predict how physical functioning and symptoms will be affected by the planned treatments in this trial.

Specifically, this trial will have a heterogeneous sample of patients with metastatic disease who are likely to have more limited metastatic burden (i.e., scan detected only metastases without clinical symptoms; de novo stage IV disease), although some patients may have had extensive prior neoadjuvant and adjuvant therapies.

This heterogeneity will likely affect the baseline physical functioning and symptoms of the enrolled patients. Thus, we will take this into account in the QOL analysis. For example, newly-diagnosed stage IV disease patients may be a special subgroup who may have better baseline physical functioning and symptoms and may better tolerate the study therapy. In addition, these patients may represent a potential group of long-term survivors. We will also examine patients who did and did not have previous HER2-directed therapy.

Other considerations in a trial of patients with metastatic disease include potential for QOL study attrition as disease progression is expected to be significantly greater in the standard arm. Thus, we plan to do more frequent assessments early in the study where less asymmetry is likely in comparison of the two arms based on progression. However, we plan to continue assessment through the 24 months of planned immunotherapy, with a final assessment at 30 months to determine whether or not there are any residual effects once this treatment has been discontinued,

allowing us to descriptively capture the patient experience during the full course of experimental treatment. Of note, the CLEOPATRA QOL study had relatively high compliance with data collection (>75%) out to 99 weeks, especially in the treatment arm with pertuzumab (Cortes 2013).

We plan to use the following questionnaires for this QOL study: The Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue scale, which is a 7-item self-report measure, will be used to assess severity, frequency, and daily pattern of fatigue as the primary outcome. The impact of treatment on physical functioning will be assessed with the PROMIS Physical Function (PF) domain using the 6-item short form scale (Jensen 2015). Using PRO-CTCAE, we will assess the following treatment related symptoms, which have been commonly reported in therapeutic trials of PD-L1 inhibitors: fatigue, diarrhea, mucositis, neuropathy, rash, itching, cough, and musculoskeletal pain. Finally, core disease-related symptoms that are common across cancers will be measured as suggested by Reeve et al. (Reeve 2014) and will supplement those already being measured as part of treatment-related symptoms (i.e., insomnia, pain, anorexia, dyspnea, cognitive problems, anxiety, nausea, depression, constipation) and will also be taken from the PRO-CTCAE. We will also include the FACT-B-TOI as an overall measure of QOL, and as means of comparing this study population to the patients included in the CLEOPATRA trial (Baselga 2012, Cortes 2013).

11.2 Aims and Hypotheses

11.2.1 Primary QOL Aim

To compare the severity of fatigue experienced by patients receiving atezolizumab to patients without this therapy during the first year after randomization, as measured by the PROMIS Fatigue questionnaire.

11.2.2 Secondary QOL Aims

- To compare the physical functioning of patients receiving atezolizumab to patients receiving placebo over all of the data collection time points.
- To compare the severity and frequency of treatment- and disease-related symptoms over all of the data collection time points experienced by patients receiving atezolizumab to patients receiving placebo.
- To compare the severity of fatigue experienced by patients receiving atezolizumab to patients receiving placebo over all of the data collection time points.
- To examine the impact of treatment and treatment-related symptoms on physical functioning at 12 months in patients receiving atezolizumab compared to patients receiving placebo.
- To examine overall QOL experienced at 12 and 24 months by patients assigned to atezolizumab compared to patients assigned to placebo.

11.2.3 Primary QOL Hypothesis

During the first year after randomization, the average level of fatigue experienced by patients assigned to atezolizumab will not be worse than that experienced by patients assigned to placebo as it is defined in Section 14.6.2.

11.2.4 Secondary QOL Hypotheses

- There will be no difference in physical functioning between patients assigned to atezolizumab and patients receiving placebo at 12 weeks after randomization. Patients assigned to atezolizumab will experience better physical functioning at 24 and 30 months than patients who receive placebo.
- Patients assigned to atezolizumab will experience greater severity and frequency of treatment-related symptoms during the 12 months on therapy, but these will resolve by 30 months. In contrast, patients on atezolizumab will have improved disease-related symptoms during treatment and at the first follow-up assessment after the end of this treatment (30 months after randomization) than patients assigned to receive placebo.
- Patients assigned to atezolizumab will experience greater level of fatigue at 12 weeks after randomization than patients assigned to placebo but there will be no difference in fatigue between the two treatment groups at 30 months after randomization.
- Patients who have greater treatment-related symptoms will have poorer physical functioning at 12 months.
- There will be no difference in QOL between patients assigned to atezolizumab and patients assigned to placebo at the 12- and 24-month time points.

11.3 Administration of BR004 Patient-Completed Questionnaires

11.3.1 Time points for Administration

The BR004 QOL questionnaire (Form QOL) will be administered via the Medidata Patient Cloud app at the following time points:

- Prior to study entry after the BR004 consent form has been signed.
- Following study entry:
  - 12 weeks
  - 24 weeks
  - 12 months
  - 18 months
  - 24 months
  - 30 months

11.4 Administration Instructions

Questionnaires are to be administered per Section 11.3.1. For patients who complete the questionnaires on-site using devices supplied by the institution or for patients opting out of Medidata Patient Cloud (ePRO), after the baseline assessment, questionnaires should be administered during an office visit if at all possible, preferably while the patient is waiting to be seen. When a follow-up visit is delayed, completion of the QOL questionnaire may also be delayed. The QOL questionnaire may be completed via paper. Once the questionnaire is completed by the patient, the site staff should review it to ensure that no items were unintentionally left blank. When absolutely necessary, the questionnaire may be administered by mail or phone. The completed questionnaire will be data that is manually entered in Rave by site staff. The paper forms should not be submitted to NRG Oncology but should be retained in the patient's chart for audit purposes.

If a patient who opted out of Medidata Patient Cloud does not come into clinic, the questionnaire will either be mailed to the patient or the site staff will call the patient to complete the questionnaire. If the patient does not return the questionnaire within two weeks, the patient will be called and either another questionnaire will be sent, or the patient will complete the questionnaire over the phone with the site staff.

Patients who never initiate BR004 study therapy or who experience disease progression should not continue participating in the QOL study.

The relevant QOL Coversheet should also be completed when the patient completes the matching form, whether via Medidata Patient Cloud, paper, phone, or mail. This notifies NRG Oncology that the assessment was completed and provides information about how the assessment was completed. If a patient declines to complete a scheduled QOL assessment or if the assessment is not completed for any other reason (and cannot be completed by phone or mail), the reason the assessment was missed must be reported on the QOL Coversheet in Medidata Rave. For patients who agree to use ePRO for OQL collection, please refer to Appendix B.

11.5 QOL Patient Population

All patients enrolled in BR004 who read or understand English, Spanish, or French must be offered participation in the QOL study. QOL will be evaluated in 526 consecutively enrolled BR004 patients who have completed the baseline questionnaire. If a patient chooses to not complete the baseline QOL questionnaire or if completion of the baseline questionnaire is missed, the patient will not be included in the QOL patient sample but will still be eligible for BR004. Please complete the QOL Coversheet in Rave to report patient refusal or missed assessments.

11.6 Additional Toxicity Monitoring with PRO-CTCAE

With Amendment #3, accrual to the PRO-CTCAE substudy is closed. Patients enrolled on the PRO-CTCAE substudy prior to Amendment #3 will continue to complete the scheduled assessments as outlined on Table 2. Accrual to the QOL substudy will continue.

Additional toxicity monitoring with PRO-CTCAE will be conducted. The following 23 items, covering 12 symptoms, will be assessed: fatigue (2), mucositis (2), diarrhea (1), numbness and tingling (2), rash (1), itching (1), cough (2), shortness of breath (2), abdominal pain (3), joint pain (3), nausea (2), and decreased appetite (2). Also, a free-text item will be included. Refer to Section 7.4 for additional information regarding toxicity monitoring with PRO-CTCAE.

11.6.1 Primary Objective (Feasibility Stage)

To assess the feasibility of frequent assessment of toxicity with ePRO reporting and to assess the degree of data missingness in the first 100 patients who read or understand English, Spanish, or French accrued to the study.

11.6.2 Secondary Objectives

- To monitor the patient experience of common expected toxicities from the agents being evaluated in this study.
- To monitor toxicities more frequently than standard AE reporting to determine if there are interval toxicities not captured by the every 3- to 6 week assessments.
- To capture baseline toxicities (pre-treatment) that may influence the subsequent treatment toxicity experience.
- To compare the PRO–CTCAE data with the Investigator report of AE for the same items.

- To examine the pattern of treatment toxicity over time during the first 12 weeks of PRO-CTCAE monitoring.

11.7 Administration of PRO-CTCAE

11.7.1 Time Points for Administration

The BR004 PRO-CTCAE assessment will be administered via Medidata Patient Cloud at the following time points:

- Prior to study entry after the BR004 consent form has been signed.
- Following study entry:
  - Weekly during the first 12 weeks (Cycles 1-2)
  - Every three weeks (Cycles 3-4)
  - Every six weeks (through 2 years)
  - At 30 months

11.7.2 Recall Period

A 1-week recall period will be used for the PRO-CTCAE data collected during Cycles 1-2, and a 3-week recall period will be used for all other assessments.

11.8 Administration Instructions

For patients who complete the assessments on-site using devices supplied by the institution, please use the following guidelines:

- For the weekly assessments (Cycles 1-2), a patient should complete the assessment during the weekly treatment visit. An assessment that is not obtained at a weekly visit will be considered a missed assessment. Assessments should resume with the next visit.
- After the first 12 weeks, assessments are to be administered at the subsequent time points, so that when a visit is delayed, the PRO-CTCAE assessment may also be delayed.
- PRO-CTCAE assessments should be discontinued at the time of progression.

Questionnaires are to be administered per Section 11.7.1. For patients who complete the questionnaires on-site using devices supplied by the institution or for patients opting out of Medidata Patient Cloud (ePRO), after the baseline assessment, questionnaires should be administered during an office visit if at all possible, preferably while the patient is waiting to be seen. When a follow-up visit is delayed, completion of the PRO-CTCAE assessment may also be delayed. If unable to complete the PRO-CTCAE assessment via Medidata Patient Cloud, the PRO-CTCAE assessment may be completed via paper. Once the assessment is completed by the patient, the site staff should review it to ensure that no items were unintentionally left blank. When absolutely necessary, the assessment may be administered by mail or phone. The completed assessment will be data that is manually entered in Rave by site staff. The paper forms should not be submitted to NRG Oncology but should be retained in the patient's chart for audit purposes.

If a patient who opted out of Medidata Patient Cloud does not come into clinic, the assessment will either be mailed to the patient or the site staff will call the patient to complete the assessment. If the patient does not return the assessment within two weeks, the patient will be called and

either another assessment will be sent, or the patient will complete the assessment over the phone with the site staff.

Patients who never initiate BR004 study therapy or who experience disease progression should not continue participating in the PRO-CTCAE study.

The relevant PRO-CTCAE Coversheet should also be completed when the patient completes the matching form, whether via Medidata Patient Cloud, paper, phone, or mail. This notifies NRG Oncology that the assessment was completed and provides information about how the assessment was completed. If a patient declines to complete a scheduled PRO-CTCAE assessment or if the assessment is not completed for any other reason (and cannot be completed by phone or mail), the reason the assessment was missed must be reported on the PRO-CTCAE Coversheet in Medidata Rave. For patients who agree to use ePRO for PRO-CTCAE collection, please refer to Appendix B.

11.9 PRO-CTCAE Patient Population

With Amendment #3, accrual to the PRO-CTCAE substudy is closed. Patients enrolled on the PRO-CTCAE substudy prior to Amendment #3 will continue to complete the scheduled assessments as outlined on Table 2. Accrual to the QOL substudy will continue.

The first 100 patients enrolled in NRG-BR004 who read or understand English, Spanish, or French, have the ability to use Medidata Patient Cloud reporting, and who have completed the baseline PRO-CTCAE assessment will be required to participate in the PRO-CTCAE feasibility study. If a patient chooses to not complete the baseline PRO-CTCAE assessment or if completion of the baseline assessment is missed, the patient will not be included in the PRO-CTCAE patient sample but will still be eligible for BR004. Please complete the PRO-CTCAE Coversheet in Rave to report patient refusal or missed assessments.

12.0 MEASUREMENT OF EFFECT

Tumor response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Eisenhauer 2009) except in the documentation of progressive disease (PD).

12.1 Definitions

12.1.1 Evaluable Toxicity

All patients will be evaluable for toxicity from the time of their first administration of protocol therapy.

12.1.2 Evaluable for Objective Response

Patients who have measurable disease present at baseline and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of the first 3 weeks of treatment will also be considered evaluable.)

12.2 Disease Parameters

12.2.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) ≥ 10 mm by CT scan with slice thickness no greater than 5 mm, MRI, or calipers in clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). The same method (CT or MRI) used at baseline should be used at all other tumor measurement time points.

In rare instances in which none of the metastatic sites can be used as a measurable lesion, the breast primary, if intact, can be used as a measurable lesion. If it meets the criterion of ≥ 10 mm, it can be monitored on serial chest CT or on breast imaging techniques (e.g., mammography, ultrasound). The breast primary should not be used as a site of measurable disease if other sites of measurable disease have been identified. This should only be done when resection of the breast primary is not anticipated.

12.2.2 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

12.2.3 Non-Measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

12.2.4 Special Considerations Regarding Tumor Measurability

- **Bone lesion measurability**

  When evaluating bone lesions, the following should be considered:

  - Bone scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
  - Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
  - Blastic bone lesions are non-measurable.

- **Cystic lesions**
  - Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are presented in the same patient, these are preferred for selection as target lesions.
- **Tumors with prior local treatment**
  - Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

12.2.5 Target Lesions

Up to a maximum of five measurable lesions (maximum 2 lesions per organ), should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and lend themselves reproducible repeated measurements by CT scan or MRI. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference by to further characterize any objective tumor regression in the measurable dimension of the disease.

12.2.6 Non-Target Lesions

All other lesions (or sites of disease) including pathological lymph nodes which are not used as target lesions should be identified as **non-target lesions** and should also be recorded at baseline. All sites of non-target lesions must be assessed along with the target lesions. Measurements of

these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.2.7 Lesions

If new lesions appear and there is clinical doubt as to whether a lesion is new or an inflammatory change, follow-up scans are required in no less than 6 weeks. If the new lesion is confirmed as unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to be something other than the tumor by a scan obtained at least 6 weeks after the initial scan), the date of progression is taken to be the date on which the new lesion was first detected. If a lesion reappears after disappearing in a patient previously declared to have a CR, PD is declared. However, if such a lesion behaves in this manner in a patient with SD or PR, confirmation as stated above defines the response or progression.

12.2.8 Pseudoprogression

Delayed responses after a tumor flare have been reported in patients who have received immune-based therapy. Caution must be exercised not to confuse a possible tumor flare with PD. In scenarios where pseudoprogression of previously targeted or not-targeted lesions is suspected, follow-up scans are required in 4 to 6 weeks. Based on that repeating imaging, if there is confirmatory evidence of tumor progression, the date of PD will be documented as the initial evaluation. However, if subsequent response is confirmed, no progression is documented and the imaging schedule reverts to that otherwise stated in the protocol.

12.3 Response Criteria

12.3.1 Evaluation of Target Lesions

- *Complete response (CR)*

  Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm).

- *Partial response (PR)*

  At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

- *Progressive disease (PD)*

  At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression.)

- *Stable disease (SD)*

  Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.3.2 Evaluation of Non-Measurable/Non-Target Lesions

- *Complete response (CR):* Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

- *Non-CR/Non-PD:* Persistence of one or more non-target lesion(s).
- *Progressive disease (PD):* Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

12.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

In BR004, the next regularly scheduled scan will be used for confirmation. Extra scans are not required.

Refer to Table 35 and Table 36 for a summary of the criteria that contribute to the determination of response.

Table 35. Time point response: patients with target (± non-target) disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-CR/Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD**	Yes or No	PD
Any	Any	Yes	PD

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion (Eisenhauer 2009).

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Table 36. Time point response: patients with non-target disease only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD*
Not all evaluated	No	Inevaluable
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.5 **Symptomatic Deterioration**

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping protocol therapy.

12.6 **Duration of Response**

12.6.1 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

12.6.2 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

12.7 **Progression-Free Survival**

Progression-free survival is defined as the time from randomization to the first documented progressive disease, as determined using the current RECIST 1.1 criteria, or death from any causes, whichever occurs first.

13.0 DATA AND RECORDS

The NRG-BR004 study was permanently closed to accrual on May 20, 2022. Modified scheduled status updates, as outlined on Table 2A, will be completed for patients enrolled prior to study accrual closure.

13.1 Data Management/Collection

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

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site: 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 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 Regulatory Support System (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 staff must either click on the link in the email or log into 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 Medidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required 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 display under the study name.

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

QOL and PRO-CTCAE items will be collected using ePRO. The patient will use personal hand-held devices or tablets. Once a patient submits the responses, the data goes directly from the

device into the Rave database. There are no documents to audit. The electronic responses are the source documentation.

All imaging tests performed during this study must be submitted to Bioclinica. Refer to the NRG-BR004 Pathology, Correlative Science, and Imaging Instructions and the BR004 Bioclinica site manual for imaging submission procedures. ***Submission of images to Bioclinica is not required following the discontinuation of study therapy and study closure to accrual on May 20, 2022.***

13.2 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7.5 and Section 7.6 for information about expedited and routine reporting. 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.

Summary of Data Submission: Refer to the CTSU Member website for the table of Required Forms and Materials.

13.3 Enhanced Centralized Data Monitoring

13.3.1 Central Monitoring

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). This application is 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 the CRA or Investigator roles in Rave 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 members' website under Auditing & Monitoring > Source Document Portal in the Help Topics button or by contacting the CTSU Help Desk (1-888-823-5923 or ctsucontact@westat.com).

13.3.2 Quality Assurance Enhancements

Site Initiation Visit

The study initiation will be conducted via video posted on a secure website and available for all NCTN Member Institutions. It is mandatory that the Principal Investigator (PI) (the PI on the

IRB documentation) and at least one research associate (RA) view the initiation video. During the site initiation video, at a minimum, the following activities will be performed by NRG Oncology:

- An in-depth review of the protocol using a lecture format.
- Presentation of study requirements and procedures including, but not limited to: study objectives, study design, eligibility criteria, enrollment procedures, schedule of evaluations, criteria for patient discontinuation, adverse event reporting (definitions, SAE reporting procedures), study drug administration, study time frame, drug ordering, blood and tumor sample submission requirements (if applicable), and laboratory procedures;
- Discussion of the structure of the auditing/monitoring process for the Study;
- Discussion of the patient enrollment procedures;
- Discussion of the importance of maintaining adequate source and regulatory documents;
- Review of Electronic Case Report Forms and completion guidelines including visit-specific pages, correction procedure, patient identification numbers, and the data query resolution process;
- Review of the NRG Oncology contact list;
- Discussion of the Drug Accountability Log requirements;
- Documentation of all attendees by obtaining a signed confirmation of completion from the attendees

13.3.3 Eligibility

The source records which document the eligibility for the first one to three individuals enrolled from each site (as identified by a unique NCI identifier) will be reviewed for completeness and consistency with the eligibility criteria, the data reported during the enrollment process and the data reported on the case report forms (CRFs). (Sites enrolling rapidly to the trial will undergo monitoring for up to three patients.) Documents are to be submitted within two weeks of patient enrollment.

In the event that this monitoring identifies unacceptable enrollment procedures or significant deviations from eligibility criteria, then the site will need to submit a corrective action plan within two weeks of being notified of the findings of the centralized monitoring. The source records for the eligibility of treatment for the next individual enrolled to the study from the site are again to be submitted and reviewed. In the event of significant repeated deviations from the protocol, accrual at the site may be suspended per discretion of the overall Study Chair.

The pretreatment documents to be reviewed include:

- Pathology Report to document the diagnosis of locally recurrent or metastatic disease.
- Medical history and physical examinations records and laboratory results, including all blood tests.
- LVEF assessments
- Consent forms will be submitted to the SDMC and reviewed upon receipt for signatures, date of consent, and patient consent to optional sample collection/use.

13.3.4 Enhanced Consent Form Review

Central review of the consent form for the essential elements of informed consent (as defined by the Department of Health and Human Services Office for Human Research Protection) for the first signed consent form and signed amended consent forms (when required by protocol amendment) submitted from each site (as identified by a unique NCI identifier) will be performed in real time after first patient entry.

13.3.5 Drug Accountability, Drug-Dose Compliance, and Adverse Events

The source records and adverse events (AEs) during the first cycle of treatment for the first one to three individuals enrolled from each site will be reviewed for compliance with the protocol, completeness and consistency with the data reported on the case report forms, and drug accountability records. The documents listed below should be submitted at two time-points: (1) within two weeks of Cycle 1, Day 22 of treatment (for records and AEs during the first 3 weeks of treatment), and (2) within two weeks of Day 1, Cycle 2 of treatment (for records and AEs during the second 3 weeks of treatment).

In the event that this monitoring identifies unacceptable procedures or significant deviations from protocol procedures, then the site will need to submit a corrective action plan within two weeks. The source records for the first cycle of treatment for the next individual enrolled to the study from the site should then again be submitted and reviewed. In the event of significant repeated deviations from the protocol, accrual at the site may be suspended per discretion of the overall Study Chair.

The documents to be reviewed include:

- Study drug orders treatment dose calculations and administration records.
- Reports from protocol-directed laboratory studies.
- Reports from any additional tests performed to document an adverse event.
- All progress notes relating to pre-therapy history and physical and AE assessments
- Pharmacy drug accountability records.
- Summaries of hospital admissions and discharge for hospitalizations.
- Summaries of surgical procedures performed.

13.3.6 Endpoint Review

Medical Review Nurse will perform ongoing centralized medical review of copies of source documents related to all endpoints as they are reported to verify the event.

De-identified copies of disease imaging scan reports must be submitted at the following time points:

- Baseline
- Progression
- At the time of PR or CR
- At the time of confirmation of PR or CR

13.3.7 Enhanced Record Review

The enhanced record review will be conducted by the NRG SDMC at any NCTN institution which enrolled a patient on the Study.

- *Time of Site Visit Audits*

  During the audit visits that occur under the CTEP audit procedures, additional cases will be reviewed to ensure that all sites that enrolled patients to the Study will be selected for review.

13.4 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, and forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

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

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

Complications or unexpected outcomes reporting is required as part of this clinical trial, to ensure the safety of participants enrolled in the studies as well as those who will enroll in future studies. See Section 7.0 for information about reporting complications or unexpected outcomes.

13.5 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of post-baseline 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.**

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period and used to collect AEs that start during the period or persist from the previous reporting period. CRA will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

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. 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.

13.6 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis. Reports are due January 31, April 30, July 31, and October 31.

14.0 STATISTICAL CONSIDERATIONS

The NRG-BR004 study was permanently closed to accrual on May 20, 2022. Refer to Section 14.8 for the amended statistical considerations. Due to the timing of the unblinding of study therapy and the termination of patient accrual to NRG-BR004, it will not be possible to achieve the study aims initially proposed for the study. For historical reference, the text in this section remains as stated before the unblinding occurred. Effective with Amendment #6 to this protocol, follow-up data collected through April 2024, will be used to monitor for late-immune adverse events and to assess PFS and OS outcomes.

14.1 Study Design

NRG-BR004 is a Phase III, randomized, double-blind, clinical trial. Patients will be randomized in a 1:1 ratio to receive a regimen of pertuzumab and trastuzumab with a taxane (paclitaxel or docetaxel) and either atezolizumab or placebo.

Patients will be stratified by 1) prior neoadjuvant or adjuvant therapy with trastuzumab (no; yes), 2) estrogen receptor status (positive; negative), 3) PD-L1 status (positive; negative or indeterminant), 4) disease sites (visceral without brain metastasis; non-visceral only without brain metastasis; brain metastasis), and 5) choice of taxane (paclitaxel; docetaxel). A stratified random permuted blocks scheme will be followed for the treatment assignment.

14.2 Study Endpoints

14.2.1 Primary Endpoint

The primary endpoint is PFS, defined as the time from randomization to the first documented progressive disease, as determined by investigator using the current RECIST 1.1 criteria, or death from any causes, whichever occurs first.

14.2.2 Secondary Endpoints

Secondary endpoints of this study are:

- Overall survival (OS), defined as time from randomization to death from any cause.
- Overall objective response (OR), defined as complete response or partial response according to the current RECIST 1.1 criteria, on two consecutive occasions ≥ 4 weeks apart.
- Duration of objective response, defined as the period from the date of initial confirmed partial response (PR) or complete response (CR) until the date of progressive disease or death from any cause. Tumor responses will be based on the current RECIST 1.1 criteria.
- Progression-free survival, overall objective response, and the duration of objective response, as assessed by a blinded central review using the RECIST 1.1 criteria.
- Cumulative incidence of brain metastases, with event time defined as time from randomization to documentation of brain metastases in patients who do not have brain metastases at entry.
- Frequencies of adverse events, including cardiac events and late immune-mediated toxicities, categorized using the NCI Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0).

14.3 **Primary Objective and Primary Hypothesis**

14.3.1 Primary Objective

The primary objective is to determine whether the addition of atezolizumab to a regimen of taxane chemotherapy (paclitaxel or docetaxel), administered with pertuzumab and trastuzumab will improve PFS, assessed by investigator using RECIST 1.1 criteria, relative to the addition of a placebo to a regimen of taxane chemotherapy (paclitaxel or docetaxel) administered with pertuzumab and trastuzumab, and placebo in patients with newly documented HER2-positive measurable metastatic breast cancer.

14.3.2 Primary Hypothesis

The addition of atezolizumab to a regimen of taxane chemotherapy (paclitaxel or docetaxel), administered with pertuzumab and trastuzumab is superior to the addition of placebo to a regimen of taxane chemotherapy (paclitaxel or docetaxel) administered with pertuzumab and trastuzumab in patients with newly documented HER2-positive measurable metastatic breast cancer, as measured by PFS per RECIST 1.1 as assessed by investigators from the participating institutions.

14.3.3 Power Justification

In this trial, patients will be randomized to receive atezolizumab added to a regimen of taxane chemotherapy (paclitaxel or docetaxel) administered with pertuzumab and trastuzumab or a placebo added to a regimen of taxane chemotherapy (paclitaxel or docetaxel) administered with pertuzumab and trastuzumab. In the CLEOPATRA study, the median PFS time was 16.5 months for patients with HER2-positive measurable MBC who were randomized to docetaxel, pertuzumab, and trastuzumab. We assume that patients on the arm treated with a placebo added to a regimen of taxane chemotherapy (paclitaxel or docetaxel) administered with pertuzumab and trastuzumab will have a similar PFS. In this trial, it is hypothesized that the addition of atezolizumab will improve the median PFS time by 6 months from 16.5 months to 22.5 months, which corresponds to a hazard ratio at 0.733. With a type I error rate of 0.05, we would have 80% power to detect such an improvement in median PFS from the addition of atezolizumab when 326 PFS events are observed at the definitive analysis in this study (Schoenfeld 1983).

14.3.4 Expected Sample Size and Accrual Estimates

Based on accrual data from the CLEOPATRA study and accrual pattern before protocol Amendment #3, it is expected that 20 patients with newly documented HER2-positive measurable MBC will be enrolled each month. By March 22, 2021, a total of 99 patients were enrolled. After Amendment #3, we expect the monthly accrual rates will increase at about 5, 7, 10, 12, 15, and 20 during the first 6 months and reach 20 per month afterwards. We expect to complete the target accrual of 600 patients after another 29 months. Considering the event rates, a 5% annual loss-to-follow-up rate and time needed for clinical assessment and data collection, the definitive analyses will be carried out at about 59 months after the initiation of this study or 40 months after Amendment #3.

14.4 **Statistical Analyses**

14.4.1 Analysis Populations

The intent-to-treat population is defined as all patients who are randomized in the study. Analyses of PFS, OS, brain metastasis, overall objective response, and duration of objective

response will be based on the ITT population. For analysis on brain metastasis, patients with brain metastasis at study entry will be excluded. For duration of response, only patients who have developed PR or CR during the study will be included in the analysis.

The safety population includes all patients who have received study medication (atezolizumab or placebo) along with a taxane (paclitaxel or docetaxel) pertuzumab and trastuzumab have at least one safety assessment on treatment.

14.4.2 Analyses of Data on the Primary Endpoint

The intention-to-treat principle will be used for primary analyses of the endpoints. Therefore, the analyses will be performed on all randomized patients.

The event time for PFS is defined as time from randomization to the first occurrence of documented disease progression, as determined using the current RECIST 1.1 criteria, or death from any causes. PFS is censored at the last adequate tumor assessment using the RECIST 1.1 criteria for patients who have not had disease progression and are still alive by the data closure date. For patients who never have any tumor assessment or survival follow-up, their PFS is censored at time of randomization. As the primary analysis, the stratified log-rank test will be used to compare the PFS between the two treatment arms with the following stratification factors: prior neoadjuvant or adjuvant therapy with trastuzumab (no; yes), estrogen receptor status (positive; negative), PD-L1 status (positive; negative or indeterminant), disease sites (any visceral without brain metastasis; non-visceral only without brain metastasis; brain metastasis), and choice of taxane (paclitaxel; docetaxel). In case sparse strata pose a problem for the stratified log-rank test, we plan to collapse on disease sites before performing the test because we do not expect many patients with brain metastasis. However, if the enrollment data show a different pattern, we will consider alternative proposals to collapse the sparse strata and amend the protocol before the definitive analysis. The Kaplan-Meier estimates will be calculated by treatment arms (Kaplan 1958). We will use stratified Cox proportional hazards models to estimate the hazard ratio associated with the addition of atezolizumab vs placebo after adjusting for the stratification factors, and the following potential confounders: nature of the distant metastasis (de novo vs. recurrent), age, and number of metastatic sites (<3, ≥3) (Cox 1975). The Efron's method will be used to handle the ties in event times. The underlying assumption of proportional hazards will be evaluated using Schoenfeld residuals and martingale residuals (Lin 1993). If there is indication of assumption violation, time-dependent Cox models or Cox models with penalized smoothing spline will be explored (Kalbfleisch 2000). Cox proportional hazards models will be further used to study the interactions between treatment and patient characteristics such as estrogen receptor status, disease site, nature of the distant metastasis (de novo vs. recurrent), age, number of metastatic sites (<3, ≥3), and potential biomarkers for predicting the magnitude of superiority of atezolizumab to placebo in this study population.

Disease progression will be formally assessed every three months during the first three years and every six months during Years 4 through 10. However, some patients may miss follow-up visits and do not have adequate tumor assessment for a prolonged time period. For patients who developed disease progression or died without an adequate tumor assessment within a lengthy period (five months during the first three years after study entry and eight months after three years) prior to the event, we will censor their PFS at their last radiological assessment determining a lack of progression and perform sensitivity analyses on the PFS data accordingly. Anticipating that some patients may take non-protocol anti-cancer therapies, in the sensitivity analyses we will also consider censoring their PFS at the last radiological assessment prior to the off-protocol therapies either only for those who do not develop a PFS event later on or for all

these patients regardless whether or not they develop disease progression or die after the non-protocol anti-cancer therapies. Patients who discontinue all protocol therapy in the absence of progression should continue to be followed per study calendar until they have first progression event. Non-protocol therapy must be reported in eCRF.

14.4.3 Analyses of Data on Overall Survival

Overall survival (OS) is defined as time from randomization to death due to any cause. Following the determination of the first disease progression, patients will be assessed every 6 months for survival. For patients who are alive at the last tumor assessment or survival follow-up, their OS is censored at the corresponding occasion. For patients who never have any tumor assessment or survival follow-up, their OS is censored at time of randomization. The intent-to-treat analyses will be performed for OS. The stratified log-rank test will be used as the primary analysis to compare the OS between the two treatment arms, and a two-sided alpha level at 0.05 will be used for claiming statistical significance. The stratification factors are the same as what are used in the stratified log-rank test for the primary analysis on PFS. The Kaplan-Meier estimates will be calculated by treatment arms. We will use stratified Cox proportional hazards models to estimate the hazard ratio associated with the addition of atezolizumab vs placebo after adjusting for the stratification factors and other potential confounders such as nature of the distant metastasis (de novo vs. recurrent), age, and number of metastatic sites (< 3, ≥ 3). The Efron's method will be used to handle the ties in event times. The underlying assumption of proportional hazards will be evaluated using Schoenfeld residuals and martingale residuals (Lin 1993). Cox proportional hazards models will be further used to study the interactions between treatment and patient characteristics such as estrogen receptor status, disease site, nature of the distant metastasis (de novo vs. recurrent), age, number of metastatic sites (< 3, ≥ 3), and potential biomarkers for predicting the magnitude of superiority of atezolizumab to placebo in OS in this study population.

To control the type I error, the hypothesis testing in comparing PFS and OS between the two treatment arms will follow a hierarchical fixed sequence testing procedure with PFS as the primary endpoint and OS as the secondary endpoint. If there is no statistical significant difference in PFS between the two treatment arms, analysis of OS data will be performed without a formal test or claim for statistical significance. If the atezolizumab arm is shown to be statistically significantly superior to the placebo arm with a 2-sided alpha level at 0.05, a formal comparison in OS between the atezolizumab arm and the placebo arm will be performed with a 2-sided alpha level at 0.05.

The final analysis of OS will be performed when 326 deaths are observed. If OS were the sole endpoint under consideration other than a secondary endpoint of the hierarchical fixed sequence testing procedure, we would have 80% power to detect a hazard ratio of 0.733 in OS as well as between the atezolizumab arm and the placebo arm with a two-sided alpha level at 0.05. Anticipating that the median OS of the placebo arm is about 56.5 months according to the CLEOPATRA study, the final analysis of OS is expected at about ten years after study initiation.

14.4.4 Analyses of Data on Other Secondary Efficacy Endpoints

Following the determination of the first disease progression, patients will be assessed every 6 months for survival, late immune toxicities, and use of subsequent immuno-oncology (IO) therapy. Late IO toxicities will be collected up to final analysis of OS, death, or receipt of alternative IO therapy. If the study is shown negative at the definitive analysis of the PFS data, further follow-up will be limited to survival and late IO toxicities. Similar to PFS, intent-to-treat analyses will be performed for brain metastases. Patients with brain metastasis at study entry will

be excluded from the analysis on brain metastasis. The event time is time from randomization to the occurrence of brain metastasis. Patients who are alive or die without brain metastasis at their last follow-up are censored at their last follow-up. Patients who never have any tumor assessment or survival follow-up are censored at time of randomization. The stratified log-rank test will be used to compare the risk of brain metastasis between the two treatment arms. The stratification factors are the same as what are adopted for the analysis on PFS. The Kaplan-Meier estimates will be calculated by treatment arms. We will use stratified Cox proportional hazards models to estimate the hazard ratio associated with the addition of atezolizumab vs placebo after adjusting for the stratification factors and other potential confounders such as nature of the distant metastasis (de novo vs. recurrent), age, and number of metastatic sites (< 3, ≥ 3).

The duration of objective response is defined as the duration from the initial confirmed PR or CR until the date of disease progression or death from any cause. Because patients who never developed PR or CR during the study will not be included in the analysis, the comparison in the duration of objective response between the two treatment arms will be performed similar to the analysis of quality-adjusted lifetime (Zhao 2001).

The overall objective response is defined as CR or PR according to the current RECIST 1.1 criteria, on two consecutive occasions, ≥ 4 weeks apart. Patients with disease localized only to the bone will not be included in the analysis of objective response. Patients who never have subsequent tumor assessment during the study will be regarded as non-responders. The stratified Cochran-Mantel-Haenszel test will be used to compare the object response between the treatment arms.

The PFS, overall objective response, and duration of objective response, as assessed by a blinded central review using the RECIST 1.1 criteria, will be compared as secondary endpoints between the two treatment arms via similar aforementioned analytical methods as their counterparts as determined by investigators. The blinded central review uses CT/MRI images to assess PFS. Patients with a breast primary as the only measurable lesion, which is being followed by mammogram or ultrasound rather than CT scan, will not be included in the secondary analyses of PFS, overall objective response, and duration of objective response based on blinded central review. Submission of images for blinded review are no longer required for these patients.

Exploratory analyses will be performed with PFS assessed under the iRECIST criteria to tease out pseudoprogression due to temporary tumor flare from progressive disease in patients under immunotherapy. The statistical analysis of this exploratory endpoint will follow the same approach as that for the primary endpoint except that the iRECIST criteria will be used for assessing disease progression instead of the RECIST 1.1 criteria. If pseudoprogression is very rare in this study, we will not pursue the analysis of this secondary endpoint.

Analysis of objective response, duration of objective response, toxicity profiles, and PFS as assessed via iRECIST criteria will occur at the definitive analysis of PFS. The analysis of brain metastasis will be performed at the same time as the final analysis of OS.

14.4.5 Early Safety Run-in Analysis of Adverse Events

In order to provide an early safety look, a formal analysis of the toxicity data will be performed at sixteen weeks after the hundredth patient is randomized and reviewed by the DMC. All toxicity data collected from the first 100 patients up to that time point are included in this analysis.

14.4.6 Monitoring and Analyses of Adverse Events Data and Drug Delivery

All adverse events, including late immune-mediated events and cardiac toxicity, will be graded according to the CTCAE v5.0, and the endpoint for the safety analyses is the proportions of the highest grades in various adverse events categories. Comparisons of the adverse events between the two treatment arms will be done by the Fisher's exact test. Immune-mediated adverse events will be tabulated. The DMC will review safety data every 6 months after the study is activated.

In addition to reporting the cumulative toxicity data for all study patients to the DMC, we will also report toxicity data by timing of occurrence during specific periods of treatment after study entry: first 6 months, between 6 months and 12 months, 12-24 months and after 24 months. During the first 6 months after study entry, most of the patients on study treatments would have paclitaxel or docetaxel and HER2-targeted therapies with or without atezolizumab. Between 6 months and 24 months after study entry, most of patients on study treatments would have HER2-targeted therapies with or without atezolizumab. From 24 months on, most of patients on study treatments would only have HER2-targeted therapies. Analysis of the adverse events data will be performed at the definitive analysis of PFS. Final analysis of long term safety data, especially the late-immune mediated events data, will also be performed when the final analysis of OS occurs.

We will monitor drug delivery and share with the DMC. For paclitaxel or docetaxel, we will monitor the distribution of number of doses (mean, median, and standard deviation) for each 6-week cycle overall and by treatment arm. For trastuzumab and pertuzumab, we will monitor the distribution of administered doses every three months overall and by treatment arm during the first year of protocol therapy.

In order to assess the potential cardiac side effects due to trastuzumab, pertuzumab, and atezolizumab, we will perform LVEF assessments every 3 months during the first 2 years and report to DMC the overall distribution of LVEF assessments and by treatment arm.

PRO-CTCAE data will not be included in the formal analysis of the toxicity data and will not be shared with the DMC as it is being collected as part of a feasibility study. See Section 14.6.2 for details.

14.4.7 Evaluation of Potential Prognostic and Predictive Markers Retrieved from Tissue Samples

14.4.7.1 PD-L1 Expression

The PD-L1 expression is determined by the VENTANA anti-PD-L1 (SP142) Rabbit Monoclonal Primary Antibody assay and scored in two categories: IC0 and IC1/2/3. Tissue samples that are scored IC1/2/3 are called PD-L1 positive. Clinical response to therapies targeting the PD1/PD-L1 axis has been shown to be associated with expression of PD-L1 in a number of cancers (Topalian 2012, Herbst 2014, Borghaei 2015, Fehrenbacher 2016, Herbst 2016, Rosenberg 2016), including HER2-positive breast cancer (Loi 2017). The expression of PD-L1 in at least one percent of tumoral immune cells using the SP142 PDL1 IHC assay has been associated with clinical response to atezolizumab in the OAK and POPLAR studies in metastatic NSCLC (Rittmeyer 2017, Fehrenbacher 2016), the IMvigor210 study in metastatic urethral carcinoma (Rosenberg 2016) and the IMmotion151 in metastatic renal cell carcinoma (Motzer 2018). A retrospective analysis of the Phase 1 PDC4989g atezolizumab monotherapy clinical study suggests that PD-L1 expression in at least one percent of tumoral immune cells may be associated with improved overall response rate and overall survival in TNBC patients (Li 2018). Based on these data, additional studies

are testing the association of PD-L1 status (using this ≥ 1 percent immune cell cutoff for the SP142 PDL1 IHC assay) with benefit of atezolizumab treatment in breast cancer (Mittendorf 2018, Miles 2018).

The PD-L1 status (positive vs. negative will be the primary predictive marker under investigation in this correlative science sub-study. Patients with indeterminant PD-L1 status will be excluded in the following analysis. At first, contingency table analyses will be used to explore the association between PD-L1 expression (positive vs negative, or in ordinal scale) and clinicopathological characteristics such as ER, tumor grade, disease sites. Two-sample t-test or the nonparametric Wilcoxon rank-sum test will be used to study the association between PD-L1 status (positive vs negative) and continuous clinicopathological characteristics such as age. The stratified Cox proportional hazard model that includes treatment, the PD-L1 status and their interaction will be used to test whether the PD-L1 status is a predictor for the benefit in PFS from atezolizumab (vs placebo), in patients with newly documented HER2-positive measurable metastatic breast cancer treated with a regimen of paclitaxel or docetaxel, pertuzumab, and trastuzumab. Potential confounders such as the nature of the distant metastasis (de novo vs. recurrent), age, and number of metastatic sites (< 3, ≥ 3) will be adjusted. The likelihood ratio test will be used for testing the interaction term in the model and the alpha level for claiming statistical significance is 0.05. Subsequently, interaction between treatment and PD-L1 expression in the ordinal scale or nominal scale will be explored in such Cox models to look for potential trend or cut-off in PD-L1 expression. In case there is no enough evidence to support PD-L1 as a predictive marker for benefit from atezolizumab, stratified Cox models will be used to determine whether PD-L1 status is a prognostic marker for PFS, after adjusting for other potential confounders and treatment, in the study population. Similar analyses will be performed with OS as the endpoint. Contingency table analyses and logistic regression models will be used to study the prognostic and predictive utility of PD-L1 status on the overall objective response.

We expect that 40% of the study patients will be PD-L1 positive. With 326 PFS events at the definitive analysis, we will have about 86% power to detect a ratio of 0.5 between the efficacy of atezolizumab (vs placebo), in terms of hazard ratio, among PD-L1 positive patients and the efficacy of atezolizumab among PD-L1 negative patients under a 2-sided type I error at 0.05.

14.4.7.2 Other Potential Immune Markers

We will further explore the prognostic and predictive utility (of the efficacy of atezolizumab) of potential immune biomarkers such as the immune-mediated gene expression signatures, antibodies status from multiplex immunofluorescence, cell-free circulating tumor DNA (ctDNA), stromal tumor infiltrating lymphocytes (sTIL), and intrinsic subtype of the tumor. Formal proposals with detailed statistical analysis plan will be submitted to CTEP for approval according to NCTN guidelines.

14.5 **Study Monitoring**

14.5.1 Interim Futility Monitoring of the Primary Objective

One interim futility analysis will be performed when the number of PFS events reaches 218. The protocol statistician will prepare necessary data with treatment blinded. Another NRG Oncology statistician will have access to the treatment assignment and perform the comparison in PFS

between the atezolizumab arm and the placebo arm via the stratified log-rank test with the following stratification factors: prior neoadjuvant or adjuvant therapy with trastuzumab (no; yes), estrogen receptor status (positive; negative), PD-L1 status (positive; negative or indeterminant), disease sites (any visceral without brain metastasis; non-visceral only without brain metastasis; brain metastasis), and choice of taxane (paclitaxel; docetaxel). The futility bound is a one-sided p-value at 0.05 in favor of the placebo arm under this stratified log-rank test. To cross this futility bound, the estimated hazard ratio between the atezolizumab arm and the placebo arm is at least 1.25. This NRG Oncology statistician will only present whether or not the futility bound has been crossed to the NRG Oncology Data Monitoring Committee (DMC). The result from this interim futility analysis will be used by the DMC to decide together with all other information relevant to the trial if it is appropriate to make a recommendation regarding the continuation of the trial as planned. The interim futility analysis is expected to occur at about 47 months after the initiation of the study.

14.5.2 Interim Analyses of the Overall Survival

If the atezolizumab arm is shown to be statistically significantly superior to the placebo arm in the primary analysis on PFS, two superiority interim analyses of OS will be performed. The first interim analysis of OS will be performed at the time of the definitive analysis of PFS. Anticipating that the median OS of the control arm is about 56.5 months according to the CLEOPATRA study and assuming that the hazard ratio in OS between the two treatment arms remains at 0.733, about 133 deaths are expected at that occasion. The second interim analysis of OS will be performed when 229 deaths occur in this study. The decision boundaries of the two interim analyses will be two-sided with alpha levels fixed at 0.005 and 0.01, respectively. Alpha spending will be used to determine the significance level of the final analysis (Fleming 1984). Anticipating that 133 and 229 deaths will occur at the first two interim analyses and 326 deaths occur at the final analysis of OS, we expect the two-sided significance level of the final analysis will be approximately 0.047 in order to control the type I error rate at 0.05. Depending on the actual number of deaths observed at the first interim analysis, the two-sided alpha level for the final analysis may need to be adjusted slightly according to the alpha spending function approach for type I error control at 0.05. The protocol will be amended after the first interim analysis of OS to reflect that change if the number of deaths then differ from 133, although the adjustment is expected to be minimal. The second interim analysis of OS is anticipated at about six years and 9 months after study initiation.

If this trial fails to demonstrate the superiority of the atezolizumab arm in PFS, two analyses of OS will be performed without a formal test or claim for statistical significance. The first analysis of OS will be performed at the time of the definitive analysis of PFS and the second analysis of OS will be performed when 326 deaths are observed or 10 years after the study initiation, whichever occurs first.

14.5.3 Monitoring of Patient Accrual

The NRG Oncology DMC will review the study twice a year with respect to patient accrual, including accrual rate and disease sites.

14.5.4 Monitoring of Protocol Treatment

Treatment adherence data will be summarized every 6 months and shared with the DMC.

14.5.5 Further Monitoring

The NRG Oncology DMC will review morbidity, serious adverse events, and loss to follow-up. We expect that the annual loss to follow-up is at most 5%. If the annual follow-up is more than 5% at 2 years after the initiation of this study, we will study the loss to follow-up data, identify possible causes, and take actions to reduce loss to follow-up.

The NRG Oncology DMC also will review the study on an "as needed" basis.

14.6 Statistical Consideration for QOL Study

14.6.1 QOL sample size

A sample of 420 patients is sufficient to provide a statistical power of 86% to detect non-inferiority of atezolizumab, compared to placebo, in terms of average level of fatigue during the first year after randomization. The two-sided probability of type I error is 0.05 and the margin of non-inferiority is 30% of the standard deviation of the average fatigue score during the first year after randomization. Adjusting upward dropout rate of 20%, we will require 526 patients to participate in the QOL study.

14.6.2 QOL Analyses

The timing of patient's baseline assessment will be different beginning with Amendment #3 (at randomization prior Amendment #3 vs. at study entry after Amendment #3). In addition, starting with Amendment #3, docetaxel will also be allowed as an option for the choice of standard chemotherapy. To account for these differences, all analyses will be adjusted for the choice of a taxane and the timing of patient's randomization to the study (prior Amendment #3, paclitaxel after Amendment #3, docetaxel after Amendment #3).

For our primary hypothesis, the average PROMIS Fatigue score over three time points during the first year after study entry (12 weeks, 24 weeks, and 12 months) will be computed for each patient. To address the primary hypothesis on QOL, we will compare the means of those scores between the two treatment groups. The non-inferiority of atezolizumab in terms of fatigue will be claimed if the upper bound of the two-sided 95% confidence interval for the difference of these two means is below the defined margin of non-inferiority. A linear mixed model for repeated measures with adjustment for the corresponding baseline score, time, and nature of distant metastasis (de novo vs. recurrent) will be used to impute the PROMIS Fatigue score for patients with missing assessments. Presence of treatment-by-time interaction will be investigated in this linear mixed model.

To assess the effect of atezolizumab on physical functioning, the PROMIS PF scale scores will be compared between the two treatment groups using a linear mixed model for repeated measures with adjustment for the baseline score, time, and nature of distant metastasis (de novo vs. recurrent). Presence of treatment-by-time interaction will be investigated. Similar analysis will be performed to evaluate the effect of atezolizumab on fatigue as measured by the PROMIS Fatigue scale over all of the data collection time points and on QOL as measured by FACT-B-TOI over 12 and 24 months.

To assess the effect of atezolizumab on treatment- and disease-related symptoms over time, the distributions of the corresponding PRO-CTCAE items will be compared between the two treatment groups using a mixed ordinal logistic regression model. The model will also include the corresponding baseline measurement, time, and nature of distant metastasis (de novo vs. recurrent). Presence of treatment-by-time interaction will be tested for each of these endpoints.

The descriptive and graphical methods suggested in Basch et al. (Basch 2016) will be used to summarize the distributions of different symptoms by treatment group over time.

To examine the impact of treatment and treatment-related symptoms on physical function at 12 months after study entry, a multiple linear regression model will be performed with the PROMIS PF scale score as an outcome and treatment and treatment-related symptoms as covariates. Presence of treatment by each individual symptom item interactions will be investigated.

The clinical meaningfulness of all comparisons will be considered (Yost 2011).

14.6.3 Missing QOL Data

A certain amount of missing data is expected; however, we have extensive experience in the collection of patient-reported outcome data with excellent adherence to data collection across multiple studies as such data are considered as part of institutional performance metrics. Prospective calendars and reminder systems are in place to ensure collection of these data. The information from patients with missing data will be reviewed in order to determine whether data analytic procedures are likely to be biased. Patients with missing data will be reviewed for imbalances in factors such as trial arm, treatment adherence, institution, and reason for non-adherence. When QOL data are missing at a particular time point, data from prior time points will be reviewed in order to investigate whether missing status was preceded by a significant change in QOL scores. In addition, we will investigate whether missing item status is related to other scores on the same questionnaire. If no missing data mechanism can be detected following this review, the data will be analyzed assuming that the data are missing at random. If, on the other hand, a non-random missing data mechanism appears to be present, we will undertake to develop an appropriate analytic strategy to control for the potential bias. We will also present sensitivity analyses based on varying assumptions about the missing-data mechanism.

14.6.4 Statistical Consideration for PRO-CTCAE Monitoring

With Amendment #3, accrual to the PRO-CTCAE substudy is closed. Patients enrolled on the PRO-CTCAE substudy prior to Amendment #3 will continue to complete the scheduled assessments as outlined on Table 2. Accrual to the QOL substudy will continue.

14.6.4.1 Primary Analysis (Feasibility Stage)

The frequent PRO-CTCAE data collection will be conducted in the first 100 patients who read or understand English, Spanish, or French accrued to the study.

An early feasibility look will be performed after 50 patients are randomized. The descriptive and graphical methods will be used to summarize the available data (combined across treatment groups) and assess the amount of data missing. If it appears that a substantial amount of data is missing, the appropriate activities will be initiated to boost the data collection.

Twelve weeks after the hundredth patient is randomized (when the toxicity data on the first 2 cycles is available from the first 100 patients), the feasibility of weekly assessment (Cycles 1-2) of toxicity with ePRO reporting will be assessed. A cutoff of 25% of expected data missing will be used to determine feasibility. A patient will be defined as compliant if he/she has submitted 75% or more of the scheduled assessments (at least 9 out of 12 weekly assessments), otherwise the patient will be considered to be non-compliant. A formal test of $H_0: p \leq 0.25$ vs. $H_a: p > 0.25$, where p is the

proportion of compliant patients, will be conducted using an α-level of 0.05. After reviewing the compliance data, the study team will reassess the feasibility of the PRO-CTCAE data collection from all patients in the trial.

At the end of the study, a thorough analysis of the available PRO-CTCAE data (Cycles 1-2) will be performed. Univariate and multivariate logistic regression will be used to assess the factors that are associated with patients' compliance with the weekly assessments. All tests will be based on an alpha level of 0.05.

14.6.4.2 Secondary Analyses

The descriptive and graphical methods suggested in Basch et al. (Basch 2016) will be used to summarize the distributions of different symptoms by treatment group over time. The patterns of differences between the toxicities reported on a weekly or cycle basis will be investigated. The agreement between patients and clinicians assessment of the toxicity will be assessed using weighted κ statistic.

Since PRO-CTCAE is a novel assessment strategy of the patient-reported outcomes, a preferred statistical methodology for the analyses of these data is still under investigation. Therefore, additional analyses of the data will be considered if the new approaches emerge.

The analyses dealing with the missing PRO-CTCAE data will be similar to the ones described in Section 14.6.3. The use of the clinician-reported AE data as an approach to missing patient-reported data will also be considered (Basch 2016).

14.7 **Gender/Ethnicity/Race Distribution**

Possible racial and ethnic variation in response to the treatment under consideration is of great concern to African-Americans. Researchers have noted poorer survival rates for African-American breast cancer patients as compared to Caucasians (Baquet 1986, Youn 1984). This difference has been attributed to many factors, including more advanced disease at the time of diagnosis (Satariano 1986), social and economic factors (Bassett 1986), or specific tumor characteristics such as ER status (Crowe 1986, Mohla 1982). Although outcomes tend to be less favorable for African-Americans, significant race-by-treatment interactions have not been previously reported suggesting that, where treatment efficacy exists, both groups appear to benefit. Previous NSABP investigations of the relationship between race and prognosis support these conclusions (Dignam 1997, Costantino 1987).

Potential for the enrollment of minority patients in this protocol is enhanced by NRG Oncology's recognition of the importance of increasing minority accrual. To this end, we provide educational opportunities for NRG Oncology investigators and coordinators to increase their awareness and skills related to recruitment of racial and ethnic minority populations. The distributions of ethnicity and race for BR004 are projected from the North American participants of the CLEOPATRA study (Roche 2016). The ethnicity distribution of the US participants of the CLEOPATRA study consists of 9.6% Hispanic and 90.4% non-Hispanic. The racial distribution in the US CLEOPATRA population is 83% white; 11% black, not of Hispanic origin; 3% Asian; 0% American Indian or Alaskan Native, and 3% others. Note that the majority of non-US North American CLEOPATRA participants were from countries other than Canada from where most of international participants of this study come, the expected distributions of race and ethnicity for international participants of BR004 are estimated based on those distributions of both US and non-US CLEOPATRA populations.

Both male and female breast cancer patients will be accrued. Based on the statistical report (http://seer.cancer.gov/csr/1975_2011/results_merged/sect_04_breast.pdf) on the Seer database, the incidence rate of male breast cancer is about 1% of that for female breast cancer (Howlader 2014).

The prognostic effect of race/ethnicity will be evaluated using statistical models. Unfortunately, because of power limitations, we will not be able to compare effects separately for the different cultural or racial groups.

Table 37. Expected racial and ethnic composition of NRG-BR004

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	5	0	0	0	5
Asian	14	0	0	0	14
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	49	0	0	0	49
White	373	4	40	0	417
Other	14	0	17	0	31
Total	455	4	57	0	516

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	4	0	5	0	9
Asian	2	0	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	0	0	0	2
White	50	0	13	0	63
More Than One Race	4	0	4	0	8
Total	62	0	22	0	84

14.8 **Amended Statistical Considerations**

Patient accrual was permanently closed, and atezolizumab/placebo was discontinued on May 20, 2022, due to an imbalance of Grade 5 toxicities coupled with continued slow accrual rates that had not improved following protocol modifications to address identified barriers. Patients were also unblinded on June 21, 2022, and notified of treatment assignment. We plan to follow enrolled patients for an additional 2 years to assess progression-free survival and overall survival in the control and intervention arms. The following statistical considerations reflect this change.

14.8.1 Study Design

NRG-BR004 was designed as a Phase III randomized, placebo-controlled, and double-blinded clinical trial. One hundred and ninety patients were randomized in a 1:1 ratio to receive a regimen of pertuzumab and trastuzumab with a taxane (paclitaxel or docetaxel) and either atezolizumab or placebo. By May 20, 2022, 93 patients were randomized to receive placebo and the other 97 patients were randomized to receive atezolizumab.

Patients were stratified by 1) prior neoadjuvant or adjuvant therapy with trastuzumab (no; yes), 2) estrogen receptor status (positive; negative), 3) PD-L1 status (positive; negative or indeterminant), 4) disease sites (visceral without brain metastasis; non-visceral only without brain metastasis; brain metastasis), and 5) choice of taxane (paclitaxel; docetaxel). A stratified random permuted blocks scheme was followed for the treatment assignment.

14.8.2 Study Endpoints

14.8.2.1 Primary Endpoint

The primary endpoint is PFS, defined as the time from randomization to the first documented progressive disease, as determined by investigator using the current RECIST 1.1 criteria, or death from any causes, whichever occurs first.

14.8.2.2 Secondary Endpoints

- Overall survival (OS), defined as time from randomization to death from any cause.
- Overall objective response (OR), defined as complete response or partial response according to the current RECIST 1.1 criteria, on two consecutive occasions ≥ 4 weeks apart.
- Frequencies of adverse events, including cardiac events and late immune-mediated toxicities, categorized using the NCI Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0).

14.8.3 Primary Objective and Primary Hypothesis

14.8.3.1 Primary Objective

The primary objective is to determine whether the addition of atezolizumab to a regimen of taxane chemotherapy (paclitaxel or docetaxel), administered with pertuzumab and trastuzumab will improve PFS in patients with newly documented HER2-positive measurable metastatic breast cancer.

14.8.3.2 Primary Hypothesis

The addition of atezolizumab to a regimen of taxane chemotherapy (paclitaxel or docetaxel), administered with pertuzumab and trastuzumab is superior to a regimen of taxane chemotherapy (paclitaxel or docetaxel) administered with pertuzumab and trastuzumab in patients with newly documented HER2-positive measurable metastatic breast cancer, as measured by PFS per RECIST 1.1 as assessed by investigators from the participating institutions.

14.8.3.3 Power Justification

In this trial, by May 20, 2022, 190 patients were randomized to receive a regimen of taxane chemotherapy (paclitaxel or docetaxel) administered with pertuzumab and trastuzumab with atezolizumab or a placebo. In the CLEOPATRA study, the median PFS time was 16.5 months for patients with HER2-positive measurable MBC who were randomized to docetaxel, pertuzumab, and trastuzumab. We assume that patients on the arm without atezolizumab have a similar PFS. We plan to perform the definitive analysis with data closure on April 30, 2024. With a type I error rate of 0.05 (for a two-sided test), we would have 80% power to detect a PFS hazard ratio at 0.6 between the atezolizumab arm and the control arm at the primary analysis when about 121 PFS events are to be observed (Schoenfeld 1983). The chance to detect a PFS hazard ratio at 0.733, as originally designed, would be about 43% at the primary analysis.

14.8.4 Statistical Analyses

14.8.4.1 Analysis Populations

The intent-to-treat (ITT) population is defined as all patients who are randomized in the study. Analyses of PFS and OS will be based on the ITT population. Analyses of the overall objective response will be the sub-cohort of patients who were randomized six months or more prior to the study accrual closure to allow time for response assessment and confirmation as well as a reasonable exposure to study medication.

The safety population includes all patients who have received study medication (atezolizumab or placebo) along with a taxane (paclitaxel or docetaxel), pertuzumab and trastuzumab and have at least one safety assessment on treatment.

14.8.4.2 Analyses of Data on the Primary Endpoint

The intention-to-treat principle will be used for primary analyses of the endpoints. Therefore, the analyses will be performed on all randomized patients.

The event time for PFS is defined as time from randomization to the first occurrence of documented disease progression, as determined using the current RECIST 1.1 criteria, or death from any causes. PFS is censored at the last adequate tumor assessment using the RECIST 1.1 criteria for patients who have not had disease progression and are still alive by the data closure date. For patients who never have any tumor assessment or survival follow-up, their PFS is censored at time of randomization. As the primary analysis, the stratified log-rank test will be used to compare the PFS between the two treatment arms with the following stratification factors: prior neoadjuvant or adjuvant therapy with trastuzumab (no; yes), estrogen receptor status (positive; negative), PD-L1 status (positive; negative or indeterminant), disease sites (any visceral without brain metastasis; non-visceral only without brain metastasis; brain metastasis),

and choice of taxane (paclitaxel; docetaxel). Because sparsity may pose a problem for the stratified log-rank test, we plan to collapse on choice of taxane and disease sites before performing the test because only seven patients had brain metastasis at study entry. The Kaplan-Meier estimates will be calculated by treatment arms (Kaplan 1958). We will use stratified Cox proportional hazards models to estimate the hazard ratio associated with the addition of atezolizumab vs placebo after adjusting for the stratification factors, and the following potential confounders: nature of the distant metastasis (de novo vs. recurrent), age, and number of metastatic sites (< 3, ≥ 3) (Cox 1975). The Efron's method will be used to handle the ties in event times. The underlying assumption of proportional hazards will be evaluated using Schoenfeld residuals and martingale residuals (Lin 1993). If there is indication of assumption violation, time-dependent Cox models or Cox models with penalized smoothing spline will be explored (Kalbfleisch 2000). Cox proportional hazards models will be further used to study the interactions between treatment and patient characteristics such as estrogen receptor status, disease site, nature of the distant metastasis (de novo vs. recurrent), age, number of metastatic sites (< 3, ≥ 3), and potential biomarkers for predicting the magnitude of superiority of atezolizumab to placebo in this study population.

After this protocol amendment, disease progression status will be updated every six months until April 30, 2024. Patients who discontinue all protocol therapy in the absence of progression should continue to be followed per study calendar.

14.8.4.3 Analyses of Data on Overall Survival

Overall survival (OS) is defined as time from randomization to death due to any cause. After this protocol amendment, patients will be assessed every 6 months for survival. For patients who are alive at the last follow-up, their OS is censored at the corresponding occasion. For patients who never have any tumor assessment or survival follow-up, their OS is censored at time of randomization. The intent-to-treat analyses will be performed for OS. The stratified log-rank test will be used as the primary analysis to compare the OS between the two treatment arms, and a two-sided alpha level at 0.05 will be used for claiming statistical significance. The stratification factors are the same as what are used in the stratified log-rank test for the primary analysis on PFS. The Kaplan-Meier estimates will be calculated by treatment arms. We will use stratified Cox proportional hazards models to estimate the hazard ratio associated with the addition of atezolizumab vs placebo after adjusting for the stratification factors and other potential confounders such as nature of the distant metastasis (de novo vs. recurrent), age, and number of metastatic sites (< 3, ≥ 3). The Efron's method will be used to handle the ties in event times. The underlying assumption of proportional hazards will be evaluated using Schoenfeld residuals and martingale residuals (Lin 1993). Cox proportional hazards models will be further used to study the interactions between treatment and patient characteristics such as estrogen receptor status, disease site, nature of the distant metastasis (de novo vs. recurrent), age, number of metastatic sites (< 3, ≥ 3), and potential biomarkers for predicting the magnitude of superiority of atezolizumab to placebo in OS in this study population. The analyses of OS will be performed at the same time as that for the primary analysis of PFS data.

14.8.4.4 Analyses of Data on Other Secondary Efficacy Endpoints

Following this protocol amendment, patients will be assessed every 6 months for survival, late immune toxicities, and use of subsequent immuno-oncology (IO) therapy. Late IO toxicities will be collected up to final analysis of OS, death, or receipt of alternative IO therapy.

The overall objective response is defined as CR or PR according to the current RECIST 1.1 criteria, on two consecutive occasions, ≥ 4 weeks apart. Patients with disease localized only to

the bone will not be included in the analysis of objective response. This analysis will be restricted to the sub-cohort of patients randomized six months or more prior to May 20, 2022. Only response data collected up to May 20, 2022, will be included in this analysis. Patients who never have subsequent tumor assessment during the study will be regarded as non-responders. The stratified Cochran-Mantel-Haenszel test will be used to compare the object response between the treatment arms.

All adverse events, including late immune-mediated events and cardiac toxicity, will be graded according to the CTCAE v5.0, and the endpoint for the safety analyses is the proportions of the highest grades in various adverse events categories. Comparisons of the adverse events between the two treatment arms will be done by the Fisher's exact test. Immune-mediated adverse events will be tabulated. Up to this protocol amendment, the DMC has reviewed safety data every 6 months after the study was activated.

To assess the potential cardiac side effects due to trastuzumab, pertuzumab, and atezolizumab, we will perform LVEF assessments every 3 months during the first 2 years and monitor the overall distribution of LVEF assessments and by treatment arm.

Analysis of the overall objective response, the adverse events data, including the late-immune mediated events data, will be performed at the definitive analysis of PFS.

14.8.4.5 Evaluation of Potential Prognostic and Predictive Markers Retrieved from Tissue Samples

The PD-L1 expression is determined by the VENTANA anti-PD-L1 (SP142) Rabbit Monoclonal Primary Antibody assay and scored in two categories: IC0 and IC1/2/3. Tissue samples that are scored IC1/2/3 are called PD-L1 positive. Clinical response to therapies targeting the PD1/PD-L1 axis has been shown to be associated with expression of PD-L1 in a number of cancers (Topalian 2012, Herbst 2014, Borghaei 2015, Fehrenbacher 2016, Herbst 2016, Rosenberg 2016), including HER2-positive breast cancer (Loi 2017). The expression of PD-L1 in at least one percent of tumoral immune cells using the SP142 PDL1 IHC assay has been associated with clinical response to atezolizumab in the OAK and POPLAR studies in metastatic NSCLC (Rittmeyer 2017, Fehrenbacher 2016), the IMvigor210 study in metastatic urethral carcinoma (Rosenberg 2016) and the IMmotion151 in metastatic renal cell carcinoma (Motzer 2018). A retrospective analysis of the Phase 1 PDC4989g atezolizumab monotherapy clinical study suggests that PD-L1 expression in at least one percent of tumoral immune cells may be associated with improved overall response rate and overall survival in TNBC patients (Li 2018). Based on these data, additional studies are testing the association of PD-L1 status (using this ≥ 1 percent immune cell cutoff for the SP142 PDL1 IHC assay) with benefit of atezolizumab treatment in breast cancer (Mittendorf 2018, Miles 2018).

The PD-L1 status (positive vs. negative will be the primary predictive marker under investigation in this correlative science sub-study. Patients with indeterminant PD-L1 status will be excluded in the following analysis. At first, contingency table analyses will be used to explore the association between PD-L1 expression (positive vs negative, or in ordinal scale) and clinicopathological characteristics such as ER, tumor grade, disease sites. Two-sample t-test or the nonparametric Wilcoxon rank-sum test will be used to study the association between PD-L1 status (positive vs negative) and continuous clinicopathological characteristics such as age. The stratified Cox proportional hazard model that includes treatment, the PD-L1 status and their interaction will be used to test whether the PD-L1 status is a predictor for the benefit in PFS from atezolizumab (vs control), in patients with newly documented HER2-positive measurable metastatic breast cancer treated with a regimen of paclitaxel or docetaxel, pertuzumab, and trastuzumab. Potential confounders such as the nature of the distant metastasis (de novo vs. recurrent), age, and number of metastatic sites (< 3, ≥ 3) will be

adjusted. The likelihood ratio test will be used for testing the interaction term in the model and the alpha level for claiming statistical significance is 0.05. Subsequently, interaction between treatment and PD-L1 expression in the ordinal scale or nominal scale will be explored in such Cox models to look for potential trend or cut-off in PD-L1 expression. In case there is not enough evidence to support PD-L1 as a predictive marker for benefit from atezolizumab, stratified Cox models will be used to determine whether PD-L1 status is a prognostic marker for PFS, after adjusting for other potential confounders and treatment, in the study population. Similar analyses will be performed with OS as the endpoint. Contingency table analyses and logistic regression models will be used to study the prognostic and predictive utility of PD-L1 status on the overall objective response.

We will further explore the prognostic and predictive utility (of the efficacy of atezolizumab) of potential immune biomarkers such as the immune-mediated gene expression signatures, antibodies status from multiplex immunofluorescence, cell-free circulating tumor DNA (ctDNA), stromal tumor infiltrating lymphocytes (sTIL), and intrinsic subtype of the tumor. Formal proposals with detailed statistical analysis plan will be submitted to CTEP for approval according to NCTN guidelines.

14.8.4.6 Comparison in the incidence of subsequent brain metastasis

Intent-to-treat analyses will be performed to compare the incidence of brain metastases between the two treatment arms. Patients with brain metastasis at study entry will be excluded from the analysis on brain metastasis. The event time is time from randomization to the occurrence of brain metastasis. Patients who are alive or die without brain metastasis at their last follow-up are censored at their last follow-up. Patients who never have any tumor assessment or survival follow-up are censored at time of randomization. The stratified log-rank test will be used to compare the risk of brain metastasis between the two treatment arms. The stratification factors are the same as what are adopted for the analysis on PFS. The Kaplan-Meier estimates will be calculated by treatment arms. We will use stratified Cox proportional hazards models to estimate the hazard ratio associated with the addition of atezolizumab after adjusting for the stratification factors and other potential confounders such as nature of the distant metastasis (de novo vs. recurrent), age, and number of metastatic sites ($< 3, \geq 3$).

14.8.5 Study Monitoring

There will not be any interim analysis. The study team will continue monitoring for late adverse immune mediated adverse events, progression events, and deaths and will provide a report every six months.

14.8.6 Statistical consideration for the QOL and PRO-CTCAE substudy

No formal statistical analyses of the collected QOL data will be performed. The descriptive statistics for PROMIS Fatigue score, PROMIS PF scale scores, and FACT-B-TOI will be presented.

Statistical Consideration for PRO-CTCAE substudy

The feasibility of weekly assessment (Cycles 1-2) of toxicity with ePRO reporting will be assessed. A cutoff of 25% of expected data missing will be used to determine feasibility. A patient will be defined as compliant if he/she has submitted 75% or more of the scheduled assessments (at least 9 out of 12 weekly assessments), otherwise the patient will be considered to

be non-compliant. A formal test of $H_0: p \leq 0.25$ vs. $H_a: p > 0.25$, where p is the proportion of compliant patients, will be conducted using an α-level of 0.05.

Univariate and multivariate logistic regression will be used to assess the factors that are associated with patients' compliance with the weekly assessments (Cycles 1-2). All tests will be based on an alpha level of 0.05.

The descriptive and graphical methods (Basch 2016) will be used to summarize the distributions of different symptoms by treatment group over time. The patterns of differences between the toxicities reported on a weekly or cycle basis will be investigated. The agreement between patients and clinicians' assessment of the toxicity will be assessed using weighted κ statistic.

Since PRO-CTCAE is a novel assessment strategy of the patient-reported outcomes, a preferred statistical methodology for the analyses of these data is still under investigation. Therefore, additional analyses of the data will be considered if the new approaches emerge.

14.8.7 Gender/Ethnicity/Race Distribution

Among 190 enrolled participants, ethnic information was not available from seven domestic patients. The racial and ethnic composition of the rest of the 183 patients are displayed in the following table.

Table 38. Racial and ethnic composition of NRG-BR004

DOMESTIC ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	0	2	0	3
Asian	9	1	0	0	10
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	17	1	1	0	19
White	126	2	13	0	141
Other	2	0	5	0	7
Total	156	4	21	0	181

Table continued on next page.

Table 38. Racial and ethnic composition of NRG-BR004 *(continued)*

INTERNATIONAL (including Canadian participants) 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	1	0	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	1	0	0	0	1
More Than One Race	0	0	0	0	0
Total	2	0	0	0	2

15.0 PUBLICATION INFORMATION AND ADMINISTRATIVE AGREEMENTS

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

- Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agent(s) contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

- For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    - NCI will provide all Collaborator(s) with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    - Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
    - Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

- Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

- When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

- Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

- Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

  E-mail: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

16.0 REFERENCES

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APPENDIX A
ASSESSMENT OF PERFORMANCE STATUS AND ACTIVITIES OF DAILY LIVING

1.0 PERFORMANCE STATUS

ECOG or Zubrod Scale		Karnofsky Score
0	Fully active; able to carry on all pre-disease performance without restriction	90-100%
1	Restricted in physically strenuous activity but ambulatory	70-80%
2	Ambulatory and capable of self-care; but unable to carry out any work activities	50-60%
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	30-40%
4	Completely disabled	10-20%

2.0 ACTIVITIES OF DAILY LIVING

The following definitions for activities of daily living (ADL) should be used when the CTCAE v5.0 grading criteria are based on ADL:

- *Instrumental ADL* refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- *Self-care ADL* refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

APPENDIX B
MEDIDATA PATIENT CLOUD ePRO OPERATIONAL PROCEDURES

In this document ePRO application refers to the application accessed by the site via iMedidata and Rave, and ePRO mobile app refers to the app accessed by the patient on a mobile device.

1.0 Introduction

Electronic collection of patient-reported outcomes (ePRO) through Medidata's ePRO application is preferred for collection of PRO-CTCAE in patients who read or understand English, Spanish, or French and were enrolled in the PRO-CTCAE substudy prior to Amendment #3 and for collection of QOL for all patients who read or understand English, Spanish, or French. Sites are not permitted to delete the ePRO component from the protocol or from the informed consent form. Traditional paper submission is the other option. Patients who will be submitting PRO data via the ePRO mobile app must be registered to the ePRO application by an authorized site staff after the patient has been registered to the study. Patients may use their own mobile device or one provisioned by the site.

Sites can use a site-specific tablet for multiple study participants. If a site-specific tablet is used, CRAs need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log in to the ePRO mobile app with their passwords or their PIN codes on the same device.

2.0 ePRO Mobile Application Download

Note that there are multiple versions of the ePRO mobile app. Patients should be instructed to download the version chosen by the study team for the protocol. The patient will receive an error upon logging into the ePRO mobile app if the wrong version is downloaded. The version being used on this trial is:

Patient Cloud

3.0 CRA Site Users

Site staff require access to the ePRO application. This access is granted through iMedidata and is similar to the process of obtaining access to Rave studies. Site staff will receive an invitation to the ePRO application which they must accept in order to begin registering patients. Staff who have not previously activated their iMedidata/Rave account at the time of initial approval of site registration will also receive a separate invitation from iMedidata to activate their account. Medidata Account Activation and Study Invitation Acceptance instructions are located on the CTSU members' website under Data Management > Rave Home > Learn More About Rave > Medidata Account Activation and Study Invitation Acceptance. Site staff will not be able to access the study in the ePRO application until all required Rave and study specific trainings (eLearnings assigned in iMedidata) are completed.

Additional information on iMedidata/Rave is available on the CTSU members' website under the Data Management tab and further under the Rave subtab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4.0 **CRA Instructions for Setting the Patient Cloud Mobile App to Multi-User Mode**

Sites conducting studies entirely on-premise, where participants travel to the sites to fill out questionnaires, can use multi-user mode. Multi-user mode lets multiple study participants log in to the ePRO mobile app with their passwords or their PIN codes on the same device. If patients will be using devices supplied by the institution, site staff will need to help the patient to access the device if the device is locked.

The study provider will download the ePRO mobile app to the device and set the ePRO mobile app to multi-user mode if applicable. **Verify the correct ePRO mobile app (Patient Cloud OR Patient Cloud ePRO) is downloaded per the protocol requirements. Note only 1 version of the app is active per protocol. On this protocol the app is named Patient Cloud and its icon is:

Patient Cloud

To switch from personal mode (default setting) to multi-user mode:

1. Tap **About** at the bottom of the log in screen.
2. Scroll to the bottom and tap **Advanced User**.
3. Tap **Mode**, then select **Multi-User**.
4. Tap **Yes** to confirm.
5. Tap the back arrows to return to the log in screen.

Note: If enabling multi-user mode on a device, it is highly recommended that completion reminders are turned off on that device.

5.0 **Patient Users**

To use the ePRO mobile app, patients will need to use their own device (IOS, Android phone, or tablet) or one provided at the site. For instructions for patients using their own device refer to section #6 below. 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.

Sites can provide a site-specific tablet for multiple study participant use on site. If a site-specific tablet is used, study staff need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log into the ePRO mobile app with their passwords or their PIN codes on the same device. **Refer to Section 4.0 above on Setting the Patient Cloud App to Multi-User Mode.**

6.0 **Patient Instructions for Accessing the Patient Cloud Using Your Personal Device**

Downloading the Patient Cloud ePRO Mobile App

If you are using your personal device, and you do not have the ePRO mobile app with the icon shown below, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. If the ePRO mobile app is already on the device, or if you are using a provider's device, you can skip this section. There are multiple versions of the ePRO mobile app available. Ensure that the correct version of the ePRO mobile app is downloaded. For this study the app is named Patient Cloud and its icon looks like this:

Patient Cloud

You will need an email address that you agree to use for this purpose. The email address is needed to uniquely identify you on the ePRO Application, and to reset your password if needed. Your email 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 email 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 (when using an Apple device):

1. An Apple ID is required for downloading the ePRO mobile app.
2. Tap the **App Store** icon on your device.
3. Search for the appropriate ePRO mobile app ("**Patient Cloud"** see the icon above) and follow the installation instructions.

For Android:

1. A Google account is required for downloading the ePRO mobile app.
2. Tap the **Play Store** icon.
3. Search for the appropriate ePRO mobile app **("Patient Cloud"**, see the icon above) and follow the installation instructions.

Registering

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 ePRO mobile 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 ePRO mobile app.

1. If registering from the ePRO mobile app, open the Patient Cloud app, tap **Register** on the bottom of the log in page. If registering on the web, open the URL https://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 response to the security questions.

9. Tap **Create my account** to complete your registration.

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

Logging in to the ePRO Mobile App

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 ePRO mobile 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 ePRO mobile app (Patient Cloud). 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 right 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 (3 vertical dots) on the top right of most pages and selecting **Set PIN**.

Resetting Your Password

You can reset your password by using the options menu at the top right of most pages.

1. Tap the **Options** menu icon (3 vertical dots).
2. Tap **Reset Password**.
3. Follow the instructions to reset your password.

Completing and Submitting Forms

Once logged into the ePRO mobile app, forms related to your study are displayed on the Tasks List page. Select a form, and complete and submit the form. New forms can appear on the Tasks Lists page at any time, depending on how the study is designed.

There are two types of forms displayed on the Tasks 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.

To complete and submit form(s):

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you may be given the opportunity to review and change your responses prior to submitting.
3. If given the opportunity to review and update, review your responses by scrolling down the list: if you need to change an answer, tap the question to go back and change the answer.
4. 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.

7.0 Patient Compliance

The patient data imports directly from a device into the Rave database. There are no documents to audit. The patient-submitted electronic responses are the source documentation.

8.0 Security

All data is encrypted on the device (256 bit encryption and Hyper Text Transfer Protocol Secure [https]) and the app requires each user to have a unique username and password for access. 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 to the Rave database. Except for the patient's email address, no identifying information is stored in iMedidata. The patient's email links the device (used) and (ePRO) account to where the data is stored. The patient's email is not visible to anyone in the system.

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

The ePRO application is 21 CFR Part 11 compliant and acts as a gateway between the 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.

9.0 Site checklist for activities prior to consenting a patient

Accept study invitation at iMedidata.com.

- Site staff must be rostered in RSS and have received an invitation to the ePRO application.

Site staff must have already completed required eLearning assigned in iMedidata for the ePRO application before gaining access to the study in Rave. Contact the LPO to request appropriate Rave access to register patients in the ePRO application.

Verify the IOS or Android operating system is using the most current version.

Verify that the correct ePRO mobile app is being used. Note only 1 version of the ePRO mobile app is active per protocol.

If using institutional shared devices, first patient only: Verify the ePRO mobile app is in Multi-User mode.

See the following webpage for more information about Patient Cloud iOS and Android ePRO apps. The landing page contains general information as well as links to additional resources on the left side of the screen https://learn.mdsol.com/patient-cloud/ecoa/en/get-started-with-patient-cloud-ios-and-android-apps-125282823.html.

Note: Sites should consider copying this site checklist and placing it in the clinic or area where site is consenting patients to ePRO and also copy the correct image and name of the ePRO mobile app version with it to help remind staff and patients of the correct version being used in the protocol. The correct version for this protocol is named "Patient Cloud" and has an icon with a cloud and a sun.

Patient Cloud