1.0 PROTOCOL SYNOPSIS

Study Title	**A Randomized, Double-Blind, Phase III Clinical Trial of Neoadjuvant Chemotherapy with Atezolizumab or Placebo in Patients with Triple-Negative Breast Cancer Followed by Adjuvant Continuation of Atezolizumab or Placebo**
Study Code	**NSABP B-59/GBG 96**
EudraCT Number **FDA IND Number**	**2017-002771-25** **136073**
Study delivery model and sponsor	This is a collaborative study being conducted by NSABP Foundation, Inc. in partnership with the German Breast Group (GBG), and supported by funding by Genentech, a Member of the Roche Group, and F. Hoffmann-La Roche, Ltd. Two versions of a single protocol have been written to cover this collaborative neoadjuvant breast cancer study. One protocol version covers all patients recruited by GBG and the other protocol version covers patients recruited by NSABP Foundation, Inc. The two versions of the protocol are identical in terms of study objectives and scientific content and only differ in logistical content appropriate for the country(ies) they cover and exploratory studies of the microbiome and ovarian function.
Development phase	NSABP B-59/GBG 96-GeparDouze is a prospective, randomized, double-blind, Phase III clinical trial.
Study overview	In this clinical trial of neoadjuvant and adjuvant administration of atezolizumab/placebo in patients with high risk triple-negative breast cancer, the potential incremental efficacy and safety of neoadjuvant administration of atezolizumab/placebo with a sequential regimen of weekly paclitaxel with every-3-week carboplatin followed immediately by neoadjuvant administration of atezolizumab/placebo with AC/EC will be evaluated. Patients will then undergo surgery (should be performed within 6 weeks after last chemotherapy application). Following recovery from surgery, patients will initiate approximately 6 months of adjuvant therapy with atezolizumab/placebo and receive the same investigational agent they received pre-operatively. Administration of radiation therapy will be based on local standards at the discretion of patients and investigators, but if administered, atezolizumab/placebo will be administered concurrently. Adjuvant atezolizumab/placebo may be delayed until after completion of radiation therapy per investigator discretion. Patients with residual invasive cancer at the time of surgery may receive capecitabine concurrently with atezolizumab/placebo in the adjuvant setting per investigator discretion and local guidelines. Patients with germline *BRCA1* or *BRCA2* mutations with residual invasive cancer at the time of surgery may receive olaparib in the adjuvant setting per investigator discretion and local guidelines. Patients receiving olaparib must discontinue atezolizumab/placebo. In order to proactively identify and further assess any cardiac toxicity that may occur with the combination of anthracyclines and atezolizumab, this study includes a cardiac safety lead-in for the first 60 patients who initiate AC/EC. Research core biopsy of breast primary at baseline is a study requirement for all patients. A research biopsy at 1-4 days prior to the second dose of atezolizumab/placebo is a study requirement for the first 500 patients. One to three representative blocks of residual primary tumor containing the maximum

	amount of tumor and node with the largest focus of metastasis is required from the definitive breast surgery if gross residual disease is ≥ 1.0 cm. If gross residual disease is < 1.0 cm, tissue should be submitted, if possible. Plasma samples for ctDNA analysis will be collected at multiple times during the study. Additional stool and serum samples will be collected from patients who agree to an optional research sample collection.. Accrual for this study was planned to be 1,520 randomized patients. A total of 1550 patients were accrued in 42 months. Follow-up of an additional 22 months after completion of accrual (total time from first patient in to EFS analysis of 64 months) would be sufficient to obtain 252 EFS events.
Study regimen	• 12 weeks Paclitaxel 80 mg/m2 IV weekly + Carboplatin (AUC 5) IV every 3 weeks + Atezolizumab 1200 mg or placebo IV Day 1 every 3 weeks for 4 doses followed by • 4 x Doxorubicin 60 mg/m2 IV + Cyclophosphamide 600 mg/m2 IV OR 4 x Epirubicin 90 mg/m2 IV + Cyclophosphamide 600 mg/m2 IV Day 1 every 2 or 3 weeks + Atezolizumab 1200 mg /placebo IV every 3 weeks • After Surgery: Atezolizumab 1200 mg or placebo IV Day 1 every 3 weeks until 52 weeks after the first dose
Primary aim and endpoint	Event-free survival (EFS) *Aim:* To determine whether the addition of atezolizumab to chemotherapy (weekly paclitaxel plus carboplatin followed by AC or EC) followed by adjuvant atezolizumab improves event-free survival (EFS) in patients with triple-negative breast cancer. *Endpoint:* EFS is defined as time from randomization until event: EFS events are progression on protocol therapy resulting in administration of non-protocol cancer therapy or inoperability, local invasive recurrence following mastectomy, local invasive recurrence in the ipsilateral breast following lumpectomy, regional recurrence, distant recurrence, contralateral invasive breast cancer, second non-breast primary cancer (excluding squamous or basal cell carcinoma of the skin), or death from any cause prior to recurrence or second primary cancer.
Secondary aims and endpoints	• Overall survival (OS) *Aim:* To determine whether the addition of atezolizumab to chemotherapy (weekly paclitaxel plus carboplatin followed by AC or EC) followed by adjuvant atezolizumab improves overall survival (OS) in patients with triple-negative breast cancer. *Endpoint:* Defined as time from randomization until death from any cause. • Pathologic complete response in the breast and lymph nodes (ypT0/Tis ypN0) *Aim:* To determine whether the addition of atezolizumab to chemotherapy (weekly paclitaxel plus carboplatin followed by AC or EC) improves pathologic complete response in the breast and post-therapy lymph nodes evaluated histologically (pCR breast and nodes) in patients with triple-negative breast cancer.

	Endpoint: Defined as the absence of any invasive component in the resected breast specimen and all resected lymph nodes following completion of neoadjuvant therapy (ypT0/Tis ypN0). • Disease-free survival (DFS) *Aim:* To determine whether the addition of atezolizumab to chemotherapy (weekly paclitaxel plus carboplatin followed by AC or EC) followed by adjuvant atezolizumab improves disease-free survival (DFS) in patients with triple-negative breast cancer. *Endpoint:* Defined as time from the first breast surgical procedure (operation) to the first occurrence of disease recurrence or death from any cause. Events defining DFS are ipsilateral invasive breast tumor recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, ipsilateral or contralateral DCIS, second primary non-breast invasive cancer (with the exception of non-melanoma skin cancers and non-breast in situ carcinoma of any site) and death attributable to any cause including breast cancer, non-breast cancer, or unknown cause. • Distant disease-free survival (DDFS) *Aim:* To determine whether the addition of atezolizumab to chemotherapy (weekly paclitaxel plus carboplatin followed by AC or EC) followed by adjuvant atezolizumab improves distant disease-free survival (DDFS) in patients with triple-negative breast cancer. *Endpoint:* Defined as time from randomization until distant recurrence, death from breast cancer, death from other causes, and second primary invasive cancer (non-breast). • Toxicity *Aim:* To evaluate toxicity associated with study therapy added to chemotherapy and radiation therapy. *Aim:* To evaluate immune-adverse events of special interest *Endpoint:* Frequency and severity of adverse events graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0). • Cardiac safety lead-in study *Aim:* To assess for potential augmentation of anthracycline-related cardiac toxicity with co-administration of study therapy. *Endpoints:* Troponin-T levels 1) prior to initial dose of AC/EC following completion of carboplatin/paclitaxel co-administered with atezolizumab/placebo and after administration of the 1st and 3rd cycles of AC/EC prior to administration of atezolizumab/placebo. LVEF levels at 1) baseline prior to initiation of carboplatin/paclitaxel and atezolizumab/placebo, 2) before 3rd cycle of AC/EC, and 3) after surgery.
Exploratory aims and endpoints	• Pathologic complete response in the breast (ypT0/Tis) *Aim:* To determine whether the addition of atezolizumab to chemotherapy

	(weekly paclitaxel plus carboplatin followed by AC or EC) improves pathologic complete response in the breast (pCR breast) in patients with triple-negative breast cancer. *Endpoint:* Defined as the absence of any invasive component in the resected breast specimen (nodal material not considered). • Pathologic complete response in the breast and lymph nodes (ypT0 ypN0) *Aim:* To determine whether the addition of atezolizumab to chemotherapy (weekly paclitaxel plus carboplatin followed by AC or EC) improves pathologic complete response in the breast and post-therapy lymph nodes evaluated histologically (pCR breast and nodes) in patients with triple-negative breast cancer. *Endpoint:* Defined as the absence of any invasive component or DCIS in the resected breast specimen and all resected lymph nodes following completion of neoadjuvant therapy. • Positive nodal status conversion rate *Aim:* To determine whether the addition of atezolizumab to chemotherapy (weekly paclitaxel plus carboplatin followed by AC or EC) improves conversion rate from clinically node-positive to pathologically node-negative. *Endpoint:* Percentage of patients clinically node-positive that convert to pathologically node-negative following completion of neoadjuvant chemotherapy. • Recurrence-free interval (RFI) *Aim:* To determine whether the addition of atezolizumab to chemotherapy (weekly paclitaxel plus carboplatin followed by AC or EC) followed by adjuvant atezolizumab improves recurrence-free interval (RFI) in patients with triple-negative breast cancer. *Endpoint:* Defined as time from randomization until invasive local, regional, or distant recurrence, or death from breast cancer (censored for death from other causes). • Brain metastases free survival *Aim:* To determine whether the addition of atezolizumab to chemotherapy (weekly paclitaxel plus carboplatin followed by AC or EC) followed by adjuvant atezolizumab improves brain metastases free survival in patients with triple-negative breast cancer. *Endpoint:* Defined as time from randomization until documentation of first event brain metastasis or death from any cause. Patients who develop locoregional or distant recurrence outside of the central nervous system as first event will continue to be followed for subsequent development of brain metastases. • Pathologic complete response in the breast and lymph nodes (ypT0/Tis ypN0) in patients with deleterious germline BRCA mutation status *Aim:* To determine whether the addition of atezolizumab to chemotherapy (weekly paclitaxel plus carboplatin followed by AC or EC) improves pathologic complete response in the breast and post-therapy lymph nodes evaluated histologically (pCR breast and nodes [ypT0/Tis ypN0]) in

	patients with deleterious germline BRCA mutation status. • Event-free survival (EFS) in patients with deleterious germline BRCA mutation status *Aim:* To determine whether the addition of atezolizumab to chemotherapy (weekly paclitaxel plus carboplatin followed by AC or EC) followed by adjuvant atezolizumab improves event-free survival (EFS) in patients with deleterious germline BRCA mutation status.
Correlative science aims and endpoints	• *Aim:* To evaluate baseline expression of PD-L1 and expression of PD-L1 following initial dose of atezolizumab with paclitaxel plus carboplatin as predictor for pCR of breast and nodes (ypT0/Tis ypN0) following neoadjuvant administration of atezolizumab with chemotherapy. *Endpoint:* pCR of breast and nodes (ypT0/Tis ypN0) • *Aim:* To evaluate baseline expression of PD-L1 and expression of PD-L1 following initial dose of atezolizumab with paclitaxel plus carboplatin as predictor for EFS following neoadjuvant administration of atezolizumab with chemotherapy followed by adjuvant administration of atezolizumab *Endpoint:* EFS • *Aim:* To evaluate baseline percentages of TILs and percentage of TILs following initial dose of atezolizumab with paclitaxel plus carboplatin as predictor for pCR of breast and nodes following neoadjuvant administration of atezolizumab with chemotherapy *Endpoint:* pCR of breast and nodes (ypT0/Tis ypN0) • *Aim:* To evaluate baseline percentages of TILs and percentage of TILs following initial dose of atezolizumab with paclitaxel plus carboplatin as predictor for EFS following neoadjuvant administration of atezolizumab with chemotherapy followed by adjuvant administration of atezolizumab *Endpoint:* EFS • *Aim:* To evaluate percentages of TILs in patients with residual breast cancer at time of surgery following neoadjuvant administration of atezolizumab with chemotherapy followed by adjuvant administration of atezolizumab as predictor for EFS. *Endpoint:* EFS • *Aim:* To use baseline and on therapy specimens such as plasma ctDNA to explore potential new biomarkers of responses and resistance to neoadjuvant administration of atezolizumab with chemotherapy followed by adjuvant administration of atezolizumab. • *Aim:* To evaluate the microbiome of breast cancer patients and to explore potential new biomarkers, toxicity, immune markers, tumor antigens. • *Aim*: To evaluate the rate of chemotherapy induced ovarian failure in each treatment arm at specific timepoints and its effect on the outcome.
Patient eligibility	Investigators should consider each of these factors when selecting patients for this trial. Investigators should also consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when

	deciding if a patient is an appropriate candidate for this trial. • Study therapy should begin within 2 weeks after randomization and will continue for 1 year total of study therapy (inclusive of neoadjuvant and adjuvant therapy). Discussion should include patient availability and the timing of study therapy. • ***Submission of samples from the breast surgery if there is residual tumor measuring ≥1 cm is required for all patients*** (see Section 6.1). The local country and pathology department policies regarding release of blocks must be considered when screening patients. • *BRCA* mutation testing ***is not required*** for entry in the NSABP B-59/GBG 96-GeparDouze study; however, *BRCA* mutation status (positive; negative, unknown) will be collected at entry. If *BRCA* mutation testing has not been performed, record the *BRCA* mutation status as "Unknown." If *BRCA* mutation status becomes available subsequent to entry, the *BRCA* mutation status should be updated. **Conditions for patient eligibility** 1. The patient must have consented to participate and, prior to beginning specific study procedures, must have signed and dated an appropriate IRB-approved consent form that conforms to federal and institutional guidelines for study treatment and for submission of tumor samples as required by NSABP B-59/GBG 96-GeparDouze for baseline correlative science studies (see Section 6.0). 2. The diagnosis of invasive adenocarcinoma of the breast must have been made by core needle biopsy. 3. Local testing on the diagnostic core must have determined the tumor to be ER-negative, PgR-negative, and HER2-negative by current ASCO/CAP guidelines. (If local testing has determined a tumor to be HER2 equivocal or to have a borderline ER/PgR status (% IHC staining < 10% for both) and other eligibility criteria are met, material may be submitted for central testing to determine eligibility.) 4. Central testing for ER, PgR, and HER2 will be performed, and the tumor must be determined to be ER-negative, PgR-negative, and HER2-negative by current ASCO/CAP Guidelines Recommendations. Formalin-fixed, paraffin-embedded (FFPE) breast tissue from core biopsy has therefore to be sent to the GBG central pathology laboratory prior to randomization for central confirmation of TNBC status and for correlative science studies. 5. The tumor specimen used for central ER, PgR, and HER2 testing must also be used for central testing of PD-L1 status using the Ventana PD-L1 (SP142) assay kit. Patients will be eligible irrespective of PD-L1 testing result including PD-L1 indeterminate. Patients will be classified as positive, negative, or indeterminate for stratification purposes. 6. Patients must be ≥ 18 years old. 7. Patient may be female or male. 8. The ECOG performance status must be 0-1 (see Appendix A). 9. The primary tumor can be clinical stage T2 or T3, if clinically node negative according to AJCC 7th Edition. If the regional lymph nodes are

	cN1 and cytologically or histologically positive or cN2–N3 with or without a biopsy, the primary breast tumor can be clinically T1c, T2, or T3. 10. Ipsilateral axillary lymph nodes must be evaluated by imaging (ultrasound, and/or MRI) within 42 days prior to study entry. If suspicious or abnormal, FNA or core biopsy is recommended. Findings of these evaluations will be used to define the nodal status prior to study entry according to the following criteria: *Nodal status – negative* – Imaging of the axilla is negative; – Imaging is suspicious or abnormal but the FNA or core biopsy of the questionable node(s) on imaging is negative; *Nodal status – positive* – FNA or core biopsy of the node(s) is cytologically or histologically suspicious or positive. – Imaging is suspicious or abnormal but FNA or core biopsy was not performed. 11. Patients with synchronous bilateral or multicentric HER2-negative breast cancer are eligible as long as the highest risk tumor is ER-negative and PgR-negative and meets stage eligibility criteria. All of the other invasive tumors must also be HER2-negative by ASCO/CAP Guidelines based on local testing. Central testing to confirm TNBC status is only required for the highest risk tumor. 12. Blood counts performed within 28 days prior to randomization must meet the following criteria: • ANC must be ≥ 1500/mm^3; • platelet count must be ≥ 100,000/mm^3; and • hemoglobin must be ≥ 10 g/dL. 13. The following criteria for evidence of adequate hepatic function performed within 28 days prior to randomization must be met: • total bilirubin must be ≤ ULN for the lab unless the patient has a bilirubin elevation > ULN to 1.5 x ULN due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin; *and* • alkaline phosphatase must be ≤ 2.5 x ULN for the lab; *and* • AST and ALT must be ≤ 1.5 x ULN for the lab. 14. Patients with AST or ALT or alkaline phosphatase > ULN are eligible for inclusion in the study if liver imaging (CT, MRI, abdominal ultrasound, PET-CT, or PET scan) performed within 28 days prior to randomization does not demonstrate metastatic disease and the requirements in criterion 13 are met. 15. Patients with alkaline phosphatase that is > ULN but ≤ 2.5 x ULN or with unexplained bone pain are eligible for inclusion in the study if bone imaging (bone scan, PET-CT scan, or PET scan) supported by additional studies when indicated (CT, x-ray, MRI) performed within 42 days prior to randomization does not demonstrate metastatic disease.

	16. Patients with N2 or N3 nodal disease or T3 primary disease must undergo liver imaging within 28 days prior to randomization and bone imaging (as described in criteria 14 and 15) within 42 days prior to randomization, irrespective of baseline lab results, and studies must not demonstrate metastatic disease. Chest imaging with chest x-ray PA and Lateral, CT of the chest, or PET-CT must also be performed. 17. Creatinine clearance ≥ 50 mL/min (see Section 7.2.1 for instructions regarding calculation of creatinine clearance) performed within 28 days prior to randomization. 18. PT/INR ≤ ULN within 28 days prior to randomization. For laboratories that do not report an ULN for the INR assay, use ≤ 1.2 as the value for the ULN. Patients receiving therapeutic anti-coagulants are not eligible. 19. A serum TSH and AM (morning) cortisol performed within 28 days prior to randomization 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. 20. LVEF assessment must be performed within 42 days prior to randomization. (LVEF assessment performed by echocardiogram is preferred; however, MUGA scan may be substituted based on institutional preferences.) ***The LVEF must be ≥ 55% regardless of the cardiac imaging facility's lower limit of normal.*** 21. For women of childbearing potential and male patients with female partners of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab/placebo or 12 months after the last dose of chemotherapy. A woman is considered to be of childbearing potential if she is not postmenopausal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). Examples of contraceptive methods with a failure rate of < 1% per year include: bilateral tubal ligation; male partner sterilization; intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. 22. Patient must be willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.
Patient ineligibility	1. Excisional biopsy or lumpectomy performed prior to study entry.

	2. FNA alone to diagnose the breast cancer. 3. Surgical axillary staging procedure prior to randomization. Exception: FNA or core biopsy of an axillary node is permitted for any patient. A pre-neoadjuvant therapy sentinel lymph node biopsy for patients with clinically negative axillary nodes is prohibited. 4. Definitive clinical or radiologic evidence of metastatic disease. 5. Previous history of contralateral invasive breast cancer. (Patients with synchronous and/or previous contralateral DCIS or LCIS are eligible.) 6. Previous history of ipsilateral invasive breast cancer or ipsilateral DCIS. (Patients with synchronous or previous ipsilateral LCIS are eligible.) 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. 8. Treatment including radiation therapy, chemotherapy, or targeted therapy, for the currently diagnosed breast cancer prior to randomization. 9. Previous therapy with anthracyclines or taxanes for any malignancy. 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 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:* – myocardial infarction documented by elevated cardiac enzymes or persistent regional wall abnormalities on assessment of left ventricular function within 6 months prior to randomization; – history of documented CHF; or – documented cardiomyopathy. 11. 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.) Patients requiring ≥ 3 BP medications are not eligible. 12. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins. 13. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells. 14. Known allergy or hypersensitivity to the components of the atezolizumab

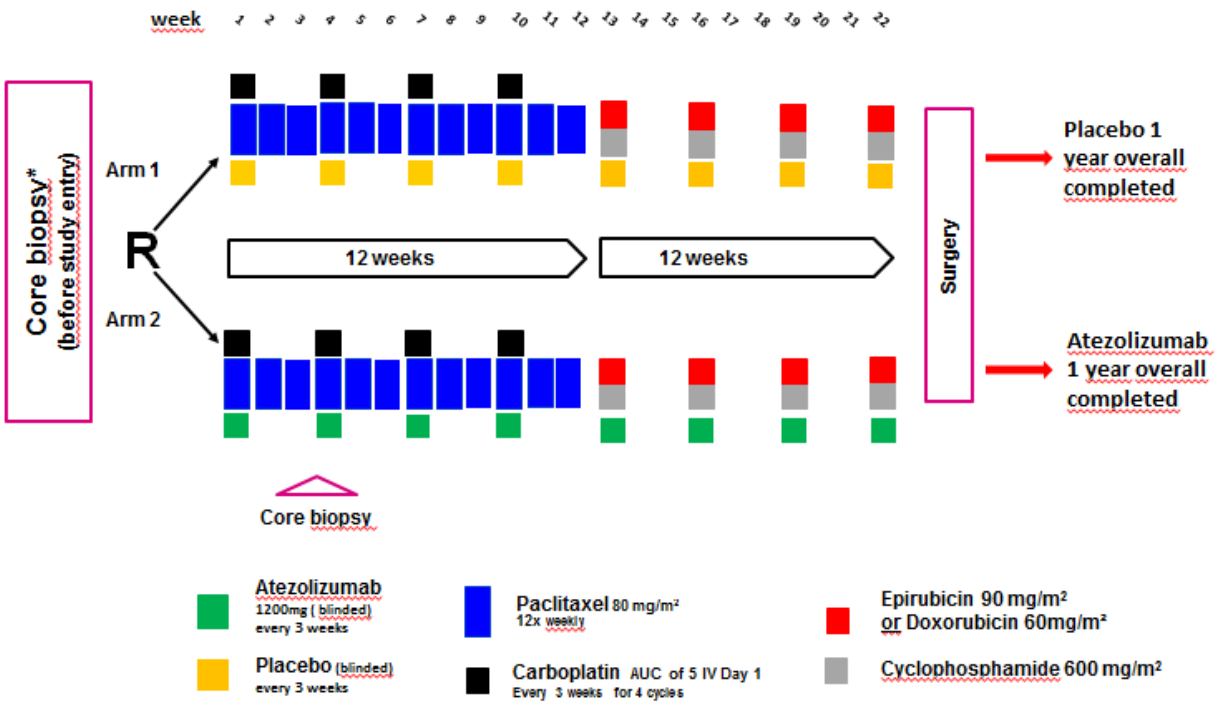
	formulation. 15. Known allergy or hypersensitivity to the components of the doxorubicin, epirubicin, cyclophosphamide, carboplatin, or paclitaxel formulations. 16. Known allergy or hypersensitivity to liposomal or pegylated G-CSF formulations. 17. Active or history of autoimmune disease or immune deficiency, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix B) with the following exceptions: – Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. – Patients with controlled Type 1 diabetes mellitus on a stable dose of insulin regimen may be eligible for this study. – Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are permitted provided all of following conditions are met: • Rash must cover < 10% of body surface area. • Disease is well controlled at baseline and requires only low-potency topical corticosteroids. • No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months. 18. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. 19. Positive test for HIV. 20. 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. 21. 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. 22. Patients with clinically active tuberculosis. 23. Severe infection within 28 days prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.

	24. Prior allogeneic stem cell or solid organ transplantation. 25. Administration of a live, attenuated vaccine within 28 days prior to randomization 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 28 days prior to randomization, during treatment or within 5 months following the last dose of atezolizumab/placebo. 26. 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. 27. 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. 28. Treatment with systemic immunosuppressive medications (including but not limited to interferons, IL-2) within 28 days or 5 half-lives of the drug, whichever is longer, prior to randomization. 29. 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 randomization or anticipation of need for systemic immunosuppressive medications during the study. 30. Nervous system disorder (paresthesias, peripheral motor neuropathy, or peripheral sensory neuropathy) ≥ Grade 2, per the CTCAE v4.0. 31. Symptomatic peripheral ischemia. 32. Pregnancy or lactation at the time of randomization or intention to become pregnant during the study. ***(Note: Negative serum pregnancy test must be obtained within 14 days prior to randomization)***. 33. Use of any investigational agent within 28 days prior to randomization.
Statistical considerations	**Stratification and randomization** Randomization will be accomplished using stratified permuted blocks. Eligible triple-negative breast cancer patients will be randomized to receive either paclitaxel/carboplatin/placebo followed by doxorubicin/cyclophosphamide/placebo or epirubicin/cyclophosphamide/placebo or paclitaxel/carboplatin/atezolizumab followed by doxorubicin/cyclophosphamide/atezolizumab or epirubicin/cyclophosphamide/atezolizumab. The stratification factors for the study are:

	1) Group (NSABP Foundation, Inc.; GBG) 2) Nodal status as determined by protocol-specified criteria (negative, positive) 3) AC/EC (every 2 weeks; every 3 weeks) 4) Clinical size of the primary tumor (1.1-3.0 cm; > 3.0 cm) 5) PD-L1 status (positive; negative, indeterminate, or not available*) * PD-L1 status of patients were not available at randomization for patients enrolled prior to amendments in July 2019. **Patient cohorts used for analysis** • The intent-to-treat (ITT) population (defined as all randomized patients) will be used for analysis of the primary and secondary endpoints except toxicity. Patients will be analyzed according to their randomly assigned treatment regardless of treatment actually received. • The safety population includes all patients who receive at least one dose of study therapy and will be used for the toxicity endpoint. Patients will be analyzed according to treatment actually received, thus any patient receiving at least one dose of atezolizumab/placebo will comprise the experimental group. **Sample size determination and protocol duration for the primary endpoint of EFS** The sample size for this trial is based on the requirements for testing of the EFS endpoint. The hazard rates used for determination were taken from our experience in NSABP B-40 trial. In NSABP B-40, the annual hazard rates were not constant and varied substantially over the first 4 to 5 years. Thus, instead of using a constant hazard rate across time, yearly-specific hazards rates were used. These rates were then reduced by 20% to account for an anticipated effect of adding carboplatin to the treatment regimen based on CALGB 40603 (Sikov SABCS 2015). To achieve monthly precision in estimates of accrual and study duration, the calculation of sample size was based on monthly hazard rates converted from each of the yearly hazard rates described above. The resulting monthly hazard rates are 0.00460 during year 1, 0.01020 during year 2, 0.00440 during year 3, 0.00186 during year 4 and 0.00200 for year 5 and all subsequent years. The original sample size was based on having sufficient statistical power to detect a hazard ratio of 0.70 at α=0.045 assuming a lost-to-follow-up rate of 0.00083 per month. A sample size of 760 patients per arm for a total sample size of 1,520 patients followed to obtain 269 EFS events would provide a test of hypothesis with 80% statistical power at an overall alpha level of 0.045. After allowing for a ramp-up of accrual in the first eighteen months to 40 patients per month and a further ramp-up to 90 per month by accrual month 28, it is anticipated that the accrual rate would peak at 105 patients per month by accrual month 32. With this accrual pattern, it would take about 34 months to accrue 1,520 patients. Follow-up of an additional 30 months after completion of accrual (total study time of 64 months) would be sufficient to obtain 269 EFS events.

	Accrual to NSABP B-59/GBG 96-GeparDouze began in December 2017 and was completed in May 2021 with a total of 1550 patients randomized. Based on actual accrual and the decision to eliminate pCR as a co-primary endpoint, we recalculated the power to detect a hazard ratio of 0.70 attributed to the addition of atezolizumab, assuming a lost-to-follow-up rate of 0.00083 per month, using the actual accrual pattern for the power calculation. With 1550 patients accrued in 42 months, an additional 22 months follow up will allow us to obtain 252 events under the assumptions stated above, which will provide 80% power to detect a HR of 0.7 between the atezolizumab and the placebo arm at an overall 2-sided alpha level of 0.05.
Enrollment period	It was anticipated that it would take about 34 months to accrue 1,520 patients. (Q-IV 2017 – Q-III 2020). The final enrollment period took 42 months to accrue 1,550 patients.
Follow-up	It was anticipated at the start of the study that follow-up of an additional 30 months after completion of accrual would be sufficient to obtain 269 EFS events (total study time of 64 months). With the final enrollment period and accrual information, follow-up of an additional 22 months after completion of accrual should be sufficient to obtain 252 EFS events (total time from first patient in to EFS analysis of 64 months).

Study design AC/EC q3 weekly



Study design AC/EC q2 weekly