A Randomized, Double-Blind, Phase III Trial of Neoadjuvant Chemotherapy with Atezolizumab/Placebo in Patients with Triple-Negative Breast Cancer Followed by Adjuvant Continuation of Atezolizumab/Placebo (NSABP B-59/GeparDouze)

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Background

- Triple-negative breast cancer (TNBC) is a heterogeneous group of cancers characterized by:
  - <1% of cells positive for estrogen receptor (ER) and progesterone receptor (PgR)
  - Negative for HER2 amplification or overexpression
- TNBC is associated with higher percentages of pathological complete response (pCR) to neoadjuvant chemotherapy (NACT), and women with a pCR have a favorable prognosis.
- Patients with TNBC and residual disease following NACT have higher risk for recurrence than patients with other subtypes of breast cancer with residual disease.[1,2]
- Once metastatic disease develops, patients have poor survival.
- Primary results have demonstrated clinically relevant efficacy and an acceptable safety profile of therapeutic blockade of PD-L1 binding by atezolizumab in patients with metastatic TNBC. [3,4,5]

Study Overview

- GeparDouze (NSABP B-59/GBG96; NCT 03281954) is a phase III, randomized, double-blind, placebo-controlled study of neoadjuvant administration of atezolizumab/placebo in combination with anthracycline-/taxane-/carboplatin-based NACT in patients with early TNBC. After surgery patients will reinitiate atezolizumab/placebo as adjuvant therapy to complete 1 year of treatment (Figure 1). Radiotherapy based on local standards is co-administered with atezolizumab/placebo.
- GeparDouze will randomize (1:1) 1520 patients with primary cT1c-cT3 TNBC and centrally assessed HR-status, HER2-status, and PD-L1-status on core biopsy (Table 1).

Objectives and Endpoints

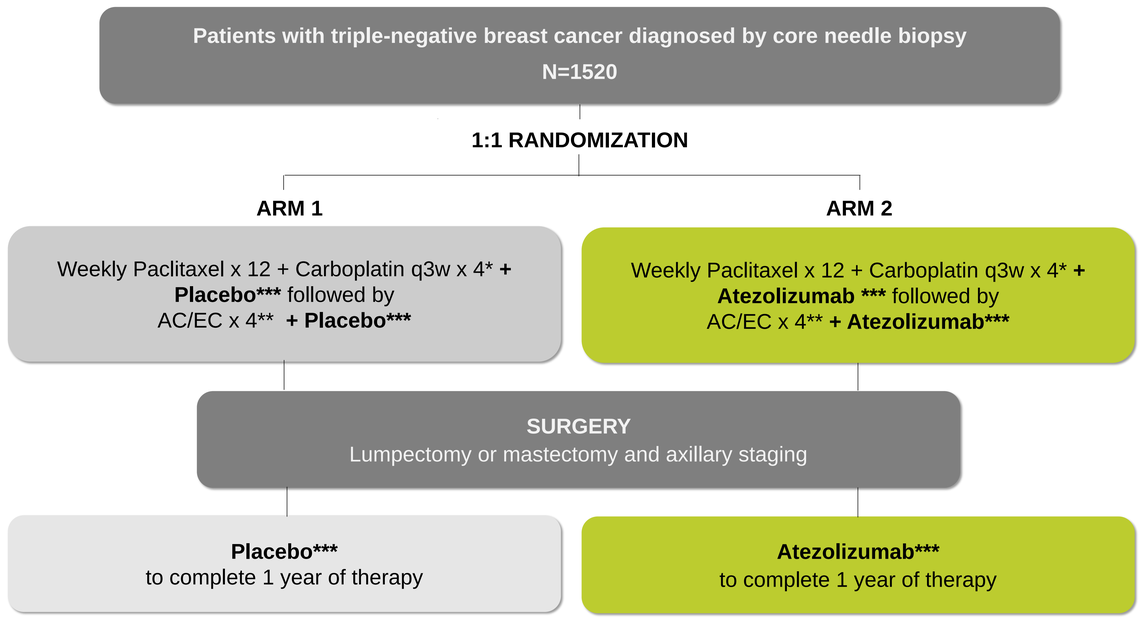
- **Co-primary objectives:**
  To determine whether the addition of atezolizumab to chemotherapy improves pCR (ypT0/Tis ypN0) **and** event-free survival (EFS).
- **Secondary objectives (selection):**
  - To assess other pCR definitions, survival endpoints, toxicity and cardiac safety.
- **Correlative objectives (selection, Table 1):**
  - To evaluate PD-L1 expression and tumor-infiltrating lymphocytes (TILs) as predictors for pCR and EFS.
  - To evaluate TILs in patients with residual breast cancer after surgery as predictor for EFS.
  - Use baseline and on-therapy specimens to explore potential new biomarkers of response and resistance.
  - To evaluate the microbiome of breast cancer patients.
  - To evaluate the rate of chemotherapy induced ovarian failure at specific timepoints and its effect on the outcome.

Table 1. GeparDouze Biomaterial Collection

Study requirements	Screening	Prior to 2nd atezolizumab/ placebo	Prior to surgery	Surgery	3-6 weeks after surgery	12 and 24 months after randomization	Relapse
FFPE tissue breast tumor (biopsy)	X	X (500 pts)					
FFPE tissue from residual tumor				X			
Plasma collection ctDNA	X		X		X	X	X
Serum collection ovarian function study (optional) Only pts ≤45 years without history of hysterectomy and/or ovarectomy	X		X			X (6, 12, 18 and 24 months after last dose of chemotherapy)	
Stool sample collection microbiome testing (optional)	X						

Abbreviations: ctDNA: circulating tumor DNA FFPE: formalin-fixed, paraffin-embedded; pts: patients

Figure 1. GeparDouze Study Design



Stratification variables are:

- Group (NSABP Foundation, Inc.; GBG)
- Tumor size (1.1-3.0cm; >3.0cm)
- Schedule of epirubicin (E) or doxorubicin (A) in combination with cyclophosphamide (C) (q2w; q3w)
- Clinical nodal status (positive; negative)
- PD-L1 status (positive; negative or indeterminate)

Study Treatment:

* Carboplatin AUC 5 IV q3w x 4 doses in combination with paclitaxel 80mg/m^2 IV weekly x 12 doses

** Doxorubicin (A) 60mg/m^2 IV or epirubicin (E) 90mg/m^2 IV in combination with cyclophosphamide (C) 600mg/m^2 IV x 4 doses; q2w vs q3w per investigator's decision

*** Atezolizumab 1200mg or placebo IV q3w administered for 1 year with break for surgery

Key Inclusion Criteria

- Age ≥ 18 years
- Females or males
- Diagnosis of invasive adenocarcinoma of the breast by core needle biopsy
- Primary tumor must be:
  - T_2 or T_3 if node negative
  - T_{1c}, T_2 , or T_3 if node positive
- Central testing must confirm HER2 negativity aw well as ER and PgR negativity by ASCO/CAP guidelines
- 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
- LVEF ≥55%

Key Exclusion Criteria

- Excisional biopsy or lumpectomy performed prior to study entry
- Surgical axillary staging procedure prior to randomization.
- Previous therapy with anthracyclines or taxanes for any malignancy
- Cardiac disease (history of and/or active disease) that would preclude the use of the drugs included in the treatment regimens
- Active or history of autoimmune disease or immune deficiency with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone
  - Patients with controlled type 1 diabetes mellitus on a stable dose of insulin regimen
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only […]

Amendment #2: Important changes

- Allowance of postneoadjuvant capecitabine for patients with non-pCR after NACT
- Addition of disease-free survival as secondary endpoint
- Adjustment of inclusion and exclusion criteria
- Update of the toxicity guidelines according to new Investigator´s Brochure
- Addition of a guidance concerning the ongoing global pandemic of coronavirus disease (COVID-19)
- Implementation of ovarian function substudy (Table 1) for GBG sites for Patients ≤45 years without history of hysterectomy and/or bilateral ovarectomy

Conclusion

- GeparDouze (NSABP B-59/GBG96) is an academic collaboration between NSABP and GBG. The aim of this phase III, double-blind, placebo-controlled study is to determine whether the addition of atezolizumab to NACT and adjuvant therapy improves efficacy and to provide further data on safety of atezolizumab in patients with early TNBC.
- Recruitment has started in 12/2017 and is expected to take place across North America and Europe.
- First results from the phase III IMpassion031 study of neoadjuvant atezolizumab in combination with NACT in early TNBC will be presented during this meeting in the Proffered Paper Session Early Breast Cancer on September 20, 2020.

Conflict of Interest

First Author: Grants and other from Abbvie, Amgen, Astra Zeneca, Celgene, Novartis, Pfizer, Roche and Daiichi-Sankyo; Other from Seattle Genetics, PriME/ Medscape, Lilly, Samsung, Eirgenix, BMS, Puma and MSD; grants from Teva, Vifor and Immunomedics; personal fees from Chugai; pending patent EP14153692.0.

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