Essai Clinique

Généré le 29 avr. 2024 à partir de

Titre	Essai clinique de phase III à répartition aléatoire et à double insu sur l'emploi d'une chimiothérapie néoadjuvante par l'atézolizumab ou d'un placebo chez des patientes atteintes d'un cancer du sein triple négatif, suivie d'un traitement adjuvant par l'atézolizumab ou d'un placebo.
Protocole ID	NSABP B-59
ClinicalTrials.gov ID	NCT03281954
Type(s) de cancer	Sein
Phase	Phase III
Stade	Néo-adjuvant/induction
Type étude	Traitement
Médicament	Chimiothérapie avec Atezolizumab
Institution	CENTRE HOSPITALIER DE L'UNIVERSITE DE MONTREAL
Ville	Montréal
Investigateur principal	Dre Saima Hassan
Coordonnateur	Ana Lydia Tkalec 514-890-8000 poste 14186
Statut	Fermé
But étude	The main purpose of this study is to learn if the usual chemotherapy given before surgery (neoadjuvant therapy) for breast cancer plus the experimental drug, atezolizumab, is better than the usual chemotherapy plus a placebo. (A placebo is a drug that looks like the study drug but contains no medication.) The usual chemotherapy in this study is paclitaxel (WP) and carboplatin followed by doxorubicin and cyclophosphamide (AC) or epirubicin and cyclophosphamide (EC). Usually, after neoadjuvant therapy and surgery for triple negative breast cancer, no additional treatment is given unless the cancer returns. This study will also look at continuing treatment after surgery with atezolizumab or the placebo. To be better, atezolizumab given with the neoadjuvant therapy should be better at: 1) decreasing the amount of tumor in the breast than the placebo given with the usual chemotherapy and 2) decreasing the chance of the cancer from returning after surgery. Another purpose of this study is to test the good and bad effects of atezolizumab when added to the usual chemotherapy. Atezolizumab may keep your cancer from growing but it can also cause side effects.
Critères d'éligibilité	• 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. • The diagnosis of invasive adenocarcinoma of the breast must have been made by core needle biopsy. • A pretreatment research core biopsy of the primary tumor must be performed with submission of 2 cores for required correlative studies. These specimens will NOT be returned to the site. • 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.) • 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. Material from either the diagnostic core biopsy or the research biopsy can

	be used for central testing depending on local preferences and standards. • The ECOG performance status must be 0-1. • 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. • Ipsilateral axillary lymph nodes must be evaluated by imaging (mammogram, ultrasound, and/or MRI) within 84 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.) • 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. • Blood counts performed within 28 days prior to randomization must meet the following criteria: • ANC must be ≥ 1500/mm3; • platelet count must be ≥ 100,000/mm3; and • hemoglobin must be ≥10 g/dL. • 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. • Patients with AST or ALT or alkaline phosphatase > ULN are eligible for inclusion in the study if liver imaging (CT, MRI, PET-CT, or PET scan) performed within 28 days prior to randomization does not demonstrate metastatic disease and the requirements in criterion (just above) are met. • Patients with alkaline phosphatase that is > ULN but less than or equal to 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) performed within 28 days prior to randomization does not demonstrate metastatic disease. • Patients with N2 or N3 nodal disease or T3 primary disease must undergo liver and bone imaging (as described in 4.1.13 and 4.1.14) within 28 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. • Creatinine clearance ≥ 40 mL/min (see Section 7.2.1 for instructions regarding calculation of creatinine clearance) performed within 28 days prior to randomization. • PT/INR ≤ ULN within 28 days of randomization. Patients receiving therapeutic anti-coagulants are not eligible. • A serum TSH and AM cortisol must be obtained within 28 days prior to randomization to obtain a baseline value. • 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. • For women 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; hormonal contraceptives that inhibit ovulation; hormone-releasing intrauterine devices; copper 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. • Patient must be willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.
Critères d'exclusion	• Excisional biopsy or lumpectomy performed prior to study entry. • FNA alone to diagnose the breast cancer. • 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. • Definitive clinical or radiologic evidence of metastatic disease. • Previous history of contralateral invasive breast cancer. (Patients with synchronous and/or

previous contralateral DCIS or LCIS are eligible.)
- Previous history of ipsilateral invasive breast cancer or ipsilateral DCIS. (Patients with synchronous or previous ipsilateral LCIS are eligible.)
- 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.
- Treatment including radiation therapy, chemotherapy, or targeted therapy, for the currently diagnosed breast cancer 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. 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.
- 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 greater than or equal to 3 BP medications are not eligible.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells.
- Known allergy or hypersensitivity to the components of the atezolizumab formulation.
- Known allergy or hypersensitivity to the components of the doxorubicin, cyclophosphamide, carboplatin, or paclitaxel formulations.
- Known allergy or hypersensitivity to liposomal or pegylated G-CSF formulations.
- 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 for a more comprehensive list of autoimmune diseases and immune deficiencies) 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.
- 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.
- Patients known to be HIV positive.
- 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.
- 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.
- Patients with clinically active tuberculosis.
- Severe infection within 28 days prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.
- Prior allogeneic stem cell or solid organ transplantation.
- 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.
- 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.
- 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.
- 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.
- 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.
- Nervous system disorder (paresthesias, peripheral motor neuropathy, or peripheral sensory neuropathy) ≥ Grade 2, per the CTCAE v4.0.
- Symptomatic peripheral ischemia.
- 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).
- Use of any investigational agent within 28 days prior to randomization.