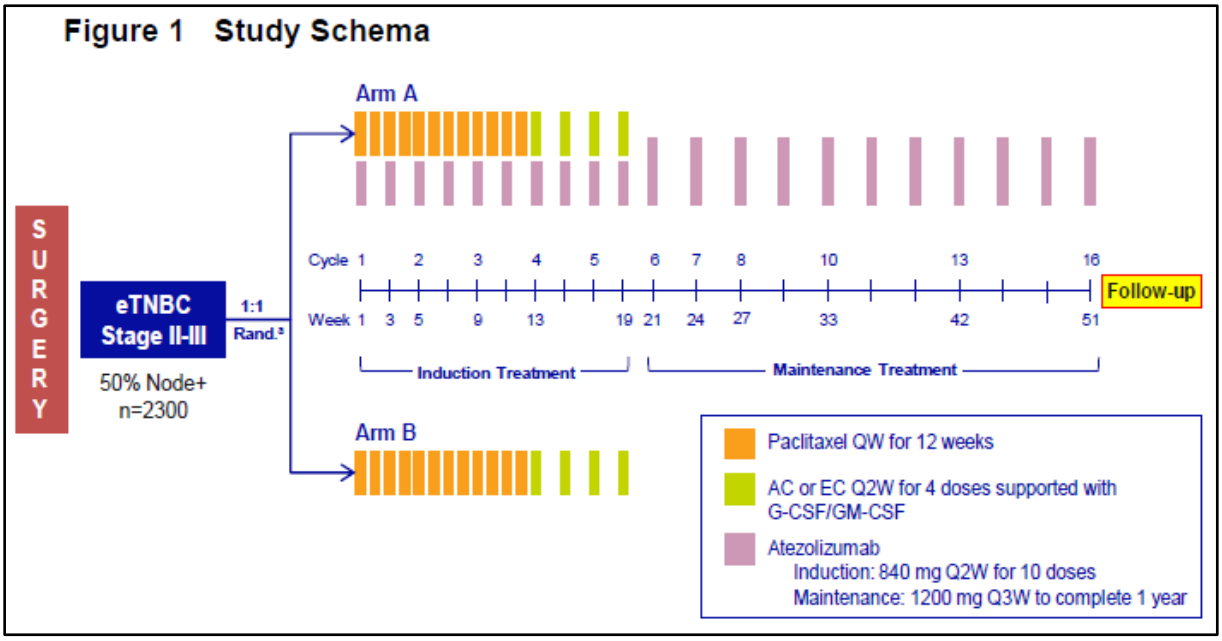
CGFL CENTRE GEORGES FRANÇOIS LECLERC Ensemble, dépassons le cancer	**CRITERES DE SELECTION** **ETUDE IMPASSION030**	Identité patient (coller étiquette patient)
Version 1.0 du 24/10/2021	Investigateur en charge du patient : …… PI : **Pr Sylvain LADOIRE** Mail :sladoire@cgfl.fr *A contacter pour adresser/inclure patient externe au CGFL*	Arc : **Kevin LEBERRE** Poste : 3465

« IMPASSION 030 »

Étude de phase III, multicentrique, randomisée, en ouvert, comparant l'atézolizumab (anticorps anti−PD-L1) en association à la chimiothérapie adjuvante à base d'anthracycline/taxane versus chimiothérapie seule chez des patients atteints d'un cancer du sein triple négatif opérable.



VALIDATION DES CRITERES DE SELECTION

Critères d'inclusion :

Signed Informed Consent Form.	□ oui □ non
Ability to comply with protocol, in the investigator's judgment.	□ oui □ non
Women or men aged > 18 years at time of signing ICF.	□ oui □ non

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Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.	□ oui □ non
Non-metastatic operable Stage II−III breast cancer. Patients with node-negative disease must have a pathological tumor size > 2 cm. Patients with node-negative multifocal, multicentric or bilateral breast cancer are eligible providing that at least one lesion is > 2 cm in size.	□ oui □ non
Histologically documented TNBC (negative HER2, ER, and PgR status) HER2 negativity will be defined by central laboratory assessment using ISH or IHC assays per ASCO/CAP criteria (Wolff et al. 2013) and ER/PgR negativity will be defined by central laboratory assessment using IHC per ASCO/CAP criteria (Hammond et al. 2010). Central laboratory assessment will occur prior to randomization. Patients with multifocal invasive tumors (more than one tumor confined to the same quadrant as the primary tumor) or multicentric invasive tumors (more than one tumor in different quadrants of the same breast) are eligible provided all discrete lesions are sampled and centrally confirmed as TNBC. Patients with non-TNBC invasive components are not eligible to participate in this study.	□ oui □ non
Confirmed tumor PD-L1 evaluation as documented through central testing of representative tumor tissue specimen.	□ oui □ non
Adequately excised: Patients must have undergone either breast-conserving surgery or mastectomy/nipple- or skin-sparing mastectomy. For patients who undergo breast-conserving surgery, the margins of the resected specimen must be histologically free of invasive tumor and ductal carcinoma in situ (DCIS) as determined by the local pathologist. If pathologic examination demonstrates tumor at the line of resection, additional operative procedures may be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo total mastectomy to be	□ oui □ non

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eligible. *In cases in which the patient underwent breast conserving surgery and there was a microscopic positive deep margin (with no other positive margins), if the tumor was resected up to the chest wall muscle and the surgeon considers that a mastectomy will not provide a negative deep margin, the patient does not need to undergo a mastectomy in order to be eligible.* Patients with margins positive for lobular carcinoma in situ (LCIS) are eligible without additional resection. For patients who undergo mastectomy/nipple- or skin-sparing mastectomy, margins must be free of gross residual tumor. It is recommended that patients should have a negative microscopic margin in accordance with local pathology protocol. Patients with a microscopic positive deep margin are eligible (see radiotherapy [RT] guidelines in **Error! Reference source not found.**).	
Pathological tumor-node-metastasis staging (Union for International Cancer Control/American Joint Committee on Cancer [UICC/AJCC], 8th edition): Patient must have had sentinel lymph node biopsy (SLNB) and/or axillary lymph node dissection *(ALND)* for evaluation of pathologic nodal status. Axillary nodal dissection*(s)* should yield a total of at least six nodes *(including the axillary lymph nodes resected at the SLNB plus the lymph nodes collected at the axillary nodal dissection).* Patients with positive SLNB should undergo axillary dissection unless all of the following characteristics apply (Giuliano et al. 2011): - No palpable nodes - No more than 2 pathologically positive lymph nodes - Breast-conserving surgery has been completed *with tangential whole breast irradiation planned OR mastectomy with regional nodal radiotherapy planned.* - Clinical tumor size < T2 (5 cm) In the case that all of the above are applicable, it is not mandatory to have the axillary dissection, but it is left at the discretion of the investigator as per site standard practice. *In the case of subjects with tumors >2cm and regional lymph node found to have micrometastases or isolated tumor cells.* Pathological classification of regional lymph node micro metastases (tumor deposits	□ oui □ non

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> 0.2 mm and < 2 mm) is considered to be pN1, and isolated tumor cells are considered to be pN0. The study population will be enriched for patients with node-positive disease such that the final population will contain at least 50% node-positive patients.	
Patients with synchronous bilateral invasive disease are eligible only if all bilateral invasive lesions are histologically confirmed as triple negative by central lab and have completed adequate pathological tumor-node metastasis staging bilaterally as described above.	□ oui □ non
No more than 8 weeks (56 days) may elapse between definitive breast surgery (or the last surgery with curative intent if additional resection is required for breast cancer) and randomization.	□ oui □ non
Baseline LVEF > 53% measured by ECHO (preferred) or MUGA scans. Baseline LVEF to be conducted within 28 days prior to *randomization*	□ oui □ non
Adequate hematologic and end-organ function, as defined by the following laboratory results obtained within 28 days prior to *randomization*: Absolute neutrophil count (ANC) >1500 cells/µL (without G-CSF support within 2 weeks prior to Cycle 1, Day 1) Lymphocyte count > 500 cells/µL Platelet count >100,000 cells/µL (without transfusion within 2 weeks prior to Cycle 1, Day 1) Hemoglobin > 9.0 g/dL Patients may be transfused or receive erythropoietic treatment to meet this criterion. AST, ALT, and alkaline phosphatase < 2.5 * the upper limit of normal (ULN) Serum total bilirubin < 1.0* ULN Patients with known Gilbert disease who have serum bilirubin level < 3 * ULN may be enrolled. For patients not receiving therapeutic anticoagulation: INR or aPTT < 1.5 * ULN within 28 days prior to *randomization*.	□ oui □ non

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For patients receiving therapeutic anticoagulation: stable anticoagulant regimen and stable INR during the 28 days immediately preceding *randomization*. Creatinine clearance > 30 mL/min (calculated using the Cockcroft-Gault formula) Serum albumin > 2.5 g/dL	
Negative HIV test at screening.	□ oui □ non
Negative hepatitis B surface antigen (HBsAg) test at screening.	□ oui □ non
Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening. The HBV DNA test will be performed only for patients who have a positive total HBcAb test.	□ oui □ non
Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening. The HCV RNA test will be performed only for patients who have a positive HCV antibody test.	□ oui □ non
Representative formalin-fixed, paraffin embedded (FFPE) tumor specimen from surgical resection in paraffin blocks (preferred) or at least 25 unstained slides, with an associated pathology report documenting locally assessed ER, PgR, and HER2 negativity. *Patients with 20 to 25 unstained slides available at baseline may be eligible upon discussion with the Medical Monitor.* Tumor tissue should be of good quality based on total and viable tumor content and must be evaluated centrally for PD-L1 expression prior to enrollment. Fine-needle aspiration, brushing, cell pellet from cytology specimens are not acceptable. Patients whose tumor tissue is not evaluable for PD-L1 expression are not eligible. If multiple tumor specimens are submitted, patients may be eligible if at least one specimen is evaluable for PD-L1. For the purpose of stratification, the PD-L1 score of the patient will be the maximum PD-L1 score among the samples.	□ oui □ non

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For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below: Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab, or 6 months after the last dose of paclitaxel or doxorubicin / *epirubicin*, or 12 months after the last dose of cyclophosphamide, whichever is later. Women must refrain from donating eggs during the same period. A woman is considered to be of childbearing potential if she is postmenarcheal, 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 sterilization, hormone-releasing intrauterine devices, and 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 adequate methods of contraception.	□ oui □ non
For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below: With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 6 months after the last dose of paclitaxel, *or doxorubicin / epirubicin or 12 months after the last dose of* cyclophosphamide, *whichever is later*. Men must refrain from donating sperm during this same period. With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of paclitaxel, *or doxorubicin / epirubicin or 12 months after the last dose of* cyclophosphamide, *whichever is later* to avoid exposing the embryo.	□ oui □ non

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The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.	
Women who are not postmenopausal (< 12 months of non-therapy-induced amenorrhea) *and* have not undergone a sterilization procedure must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.	□ oui □ non
Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of PRO questionnaires	□ oui □ non

Critères de non inclusion :

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Prior history of invasive breast cancer.	□ oui □ non
Any T4 tumor as defined by tumor-node metastasis classification in ICC/AJCC, 8th edition, including inflammatory breast cancer	□ oui □ non
For the currently diagnosed breast cancer, any previous systemic anti-cancer treatment (e.g., neoadjuvant or adjuvant), including, but not limited to, chemotherapy, anti-HER2 therapy (e.g., trastuzumab, trastuzumab emtansine, pertuzumab, lapatinib, neratinib, or other tyrosine kinase inhibitors), hormonal therapy, or anti-cancer RT other than planned in the context of this study and described in Appendix 8.	□ oui □ non
Previous therapy with anthracyclines or taxanes for any malignancy	□ oui □ non
History of DCIS and/or LCIS that was treated with any form of systemic, hormonal therapy, or RT to the ipsilateral breast where invasive cancer subsequently developed. Patients who had their DCIS/LCIS treated only with surgery and/or contralateral DCIS treated with RT are allowed to enter the study.	□ oui □ non

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Contraindication to RT when adjuvant RT is clinically indicated.	□ oui □ non
Cardiopulmonary dysfunction as defined by any of the following prior to randomization: History of NCI CTCAE v5.0 Grade > 3 symptomatic congestive heart failure or New York Heart Association (NYHA) criteria Class □ II Angina pectoris requiring anti-anginal medication, serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality, or clinically significant valvular disease High-risk uncontrolled arrhythmias (i.e., atrial tachycardia with a heart rate > 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block [second degree AV-block Type 2 Mobitz 2, or third-degree AV-block]) Significant symptoms (Grade >2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia Myocardial infarction within 12 months prior to randomization Uncontrolled hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure >100 mmHg) Evidence of transmural infarction on ECG Requirement for oxygen therapy	□ oui □ non
Prior malignancies within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (i.e., adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer).	□ oui □ non
History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.	□ oui □ non
Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells.	□ oui □ non
Known allergy or hypersensitivity to any component of the atezolizumab formulation.	□ oui □ non
Known allergy or hypersensitivity to any component of the paclitaxel (e.g., polyoxyl 35 castor oil), cyclophosphamide, or doxorubicin/epirubicin formulations	□ oui □ non

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Known allergy or hypersensitivity to *G-CSF* or GM-CSF formulations.	□ oui □ non
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's syndrome, Guillain-Barré syndrome, or multiple sclerosis with the following exceptions: Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study. Patients with controlled Type I diabetes mellitus who are on an insulin regimenmay 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 eligible for the study 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. There has been 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.	□ oui □ non
History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.	□ oui □ non
Current treatment with anti-viral therapy for HBV	□ oui □ non
Urinary outflow obstruction	□ oui □ non
Active tuberculosis	□ oui □ non

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Severe infections within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia	□ oui □ non
Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.	□ oui □ non
Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment or anticipation of need for a major surgical procedure during study treatment	□ oui □ non
Prior allogeneic stem cell or solid organ transplant	□ oui □ non
Administration of a live attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the study or within 5 months after the last dose of atezolizumab. Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist□) within 28 days prior to initiation of study treatment, during treatment or within 5 months following the last dose of atezolizumab (for patients randomized to atezolizumab).	□ oui □ non
Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications.	□ oui □ non
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.	□ oui □ non
Treatment with systemic immunostimulatory agents (including, but not limited to, interferons,interleukin-2) within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment.	□ oui □ non
Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine,	□ oui □ non

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methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] alpha agents) within 2 weeks prior to initiation of study treatment or anticipation of need for systemic immunosuppressive medication during the study. Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.	□ oui □ non
Pregnant or lactating, or intending to become pregnant during the study.	□ oui □ non
Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, and inherited liver disease	□ oui □ non
Under any legal protection (tutorship/curatorship).	□ oui □ non

Date : _____

Signature de l'investigateur : _____