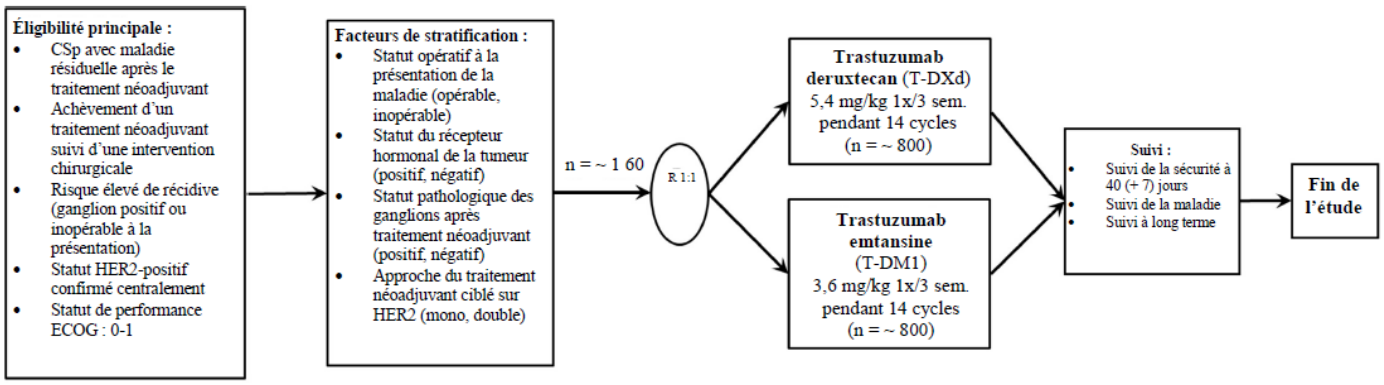
CGFL CENTRE GEORGES FRANÇOIS LECLERC Ensemble, dépassons le cancer	**CRITERES DE SELECTION** **ETUDE DESTINY05**	Identité patient (coller étiquette patient)
Version 1.0 du 10/03/2015	Investigateur en charge du patient : …… PI : Pr LADOIRE Mail : sladoire@cgfl.fr	Arc : Kevin L. Poste : 3465

« Étude de phase 3, multicentrique, randomisée, en ouvert, contrôlée contre traitement actif, portant sur le trastuzumab deruxtecan (T-DXD) comparé au trastuzumab emtansine (T-DM1) chez des patients atteints d'un cancer du sein primaire her2-positif à haut risque présentant une maladie invasive résiduelle au niveau du sein ou des ganglions lymphatiques axillaires après un traitement néoadjuvant »

Figure 1.1: Organigramme des niveaux de l'étude



VALIDATION DES CRITERES DE SELECTION

Critères d'inclusion

1. Sign and date the tissue screening and main ICFs, prior to the start of any study-specific qualification procedures.	☐ oui ☐ non
2. Adults ≥18 y old. (Please follow local regulatory requirements if the legal age of consent for study participation is >18 y old).	☐ oui ☐ non
3. HER2-positive breast cancer, meeting all of the following criteria: ● HER2-positive status will be based on pretreatment biopsy material and defined as an immunohistochemistry (IHC) score of 3+ and/or positive by in situ hybridization (ISH) (as defined in 2018 American Society of Clinical Oncology – College of American Pathologists [ASCO-CAP] guidelines) confirmed by a central laboratory prior to randomization. If sufficient material from the pretreatment biopsy is not available for submission, central HER2 determination for eligibility may be performed on residual tumor tissue from the time of definitive surgery. ● Formalin-fixed paraffin-embedded tumor tissue block or a partial block must be available for central evaluation of HER2 expression. If sites are unable to send a tissue block due to local regulations, at least 7 unstained slides should be sent for central testing, and in addition up to 5 slides for exploratory biomarker research. A central laboratory will perform both IHC and ISH assays for HER2. ● Patients with synchronous bilateral invasive disease are eligible if both primary tumors were confirmed to be HER2-positive.	☐ oui ☐ non

4. Histologically confirmed invasive breast carcinoma at time of disease presentation. Subjects with inflammatory breast cancer are allowed providing all eligibility criteria are met.	☐ oui ☐ non
5. Clinical stage at disease presentation of T1-4, N0-3, M0 prior to neoadjuvant therapy (Note: Patients presenting with T1N0 tumors will not be eligible).	☐ oui ☐ non
6. Pathologic evidence of residual invasive carcinoma in the breast and/or axillary lymph nodes following completion of neoadjuvant therapy meeting one of the following high-risk criteria. ● Inoperable breast cancer at presentation (prior to neoadjuvant therapy), defined as clinical stages T4,N0-3,M0 or T1-3,N2-3,M0. (See Section 10.6.1) ● Operable disease at presentation, defined as clinical stages T1-3,N0-1,M0, with axillary node positive disease (ypN1-3) following neoadjuvant therapy. (See Section 10.6.2).	☐ oui ☐ non
7. Completion of neoadjuvant systemic chemotherapy and HER2-directed treatment: ● Systemic therapy must consist of at least 6 cycles of chemotherapy with a total duration of at least 16 weeks, including at least 9 weeks of trastuzumab (± pertuzumab) and at least 9 weeks of taxane based chemotherapy. Patients may have received an anthracycline as part of neoadjuvant therapy in addition to taxane chemotherapy. ● Patients may have received more than one HER2-directed therapy. ● All planned chemotherapy must be completed prior to surgery as a component of neoadjuvant therapy.	☐ oui ☐ non
8. Adequate excision as confirmed per medical records: surgical removal of all clinically evident disease in the breast and lymph nodes (see Section 8.1.2).	☐ oui ☐ non
9. An interval of no more than 12 weeks between the date of last surgery and the date of randomization.	☐ oui ☐ non
10. Known hormone receptor (HR) status, per local laboratory assessment, as defined by ASCO-CAP guidelines (≥1%): HR-positive status defined by either positive estrogen receptor (ER) or positive progesterone receptor (PR) status. HR-negative status defined by both known negative ER and known negative PR.	☐ oui ☐ non
11. Left ventricular ejection fraction (LVEF) ≥ 50% within 28 days prior to randomization.	☐ oui ☐ non
12. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.	☐ oui ☐ non
13. Has adequate organ function within 14 days before randomization, defined as : ● Platelet count ≥ 100 x 10^9/L (Platelet transfusion is not allowed within 1 week prior to screening assessment)	☐ oui ☐ non

● Hemoglobin ≥ 9.0 g/dL (Red blood cell transfusion is not allowed within 1 week prior to screening assessment) ● Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (G-CSF administration is not allowed within 1 week prior to screening assessment) ● Creatinine Clearance (CrCl) Creatinine clearance ≥ 30 mL/min as calculated using the Cockcroft-Gault equation (Section 10.3.1). ● Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) ≤ 1.5 x upper limit of normal (ULN) ● Total bilirubin ≤ 1.0 x ULN (within normal range) except for patients with Gilbert's syndrome, for whom direct bilirubin should be within the normal range (< 3 x ULN) ● Serum Albumin ≥ 2.5 g/dL ● International normalized ratio (INR) / Prothrombin time (PT) ≤ 1.5 × ULN ● Activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) ≤ 1.5 × ULN	
14. Male and female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 4 months for males and 7 months for females after the last dose of study drug. ● If the subject is a female of childbearing potential, she must have a negative serum pregnancy test at Screening before the first dose of study drug and must be willing to use highly effective birth control, as detailed in Section 10.3.4, upon randomization, during the Treatment Period, and for 7 months, following the last dose of study drug. A female is considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months) unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy). ● If male, the subject must be surgically sterile or willing to use highly effective birth control (Section 10.3.4) upon enrollment, during the treatment period, and for 4 months following the last dose of study drug.	□ oui □ non
15. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4 months after the final study drug administration. Preservation of sperm should be considered prior to enrolment in this study.	□ oui □ non
16. Female subjects must not donate, or retrieve for their own use, ova from the time of Screening and throughout the study treatment period, and for at least 7 months after the final study drug administration.	□ oui □ non

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Critères de non inclusion

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1. Stage IV (metastatic) breast cancer.	□ oui □ non
2. History of any prior (ipsi- or contralateral) breast cancer except lobular carcinoma in situ (LCIS).	□ oui □ non
3. Evidence of clinically evident gross residual or recurrent disease following neoadjuvant therapy and surgery (see Section 8.1.2.1).	□ oui □ non
4. An overall response of progressive disease according to the investigator at the conclusion of preoperative systemic therapy.	□ oui □ non
5. Prior treatment with T-DXd, T-DM1 or other anti-HER2 ADC.	□ oui □ non
6. History of exposure to the following cumulative doses of anthracyclines: ● Doxorubicin > 240 mg/m2 ● Epirubicin or Liposomal Doxorubicin-Hydrochloride > 480 mg/m2 ● For other anthracyclines, exposure equivalent to doxorubicin > 240 mg/m2	□ oui □ non
7. History of other malignancy within the last 5 years except for appropriately treated carcinoma in situ (CIS) of the cervix, non-melanoma skin carcinoma, Stage I melanoma skin carcinoma, Stage I uterine cancer, or other appropriately treated non-breast malignancies.	□ oui □ non
8. History of (noninfectious) ILD/pneumonitis that required steroids or has ILD/pneumonitis noted on computed tomography (CT) scan of the chest at Screening (asymptomatic interstitial changes confined to recent radiation therapy fields are not excluded).	□ oui □ non
9. Known pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (eg, pulmonary emboli within three months prior to randomization, severe asthma, severe chronic obstructive pulmonary disease (COPD), restrictive lung disease, etc.).	□ oui □ non
10. Any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (eg, Rheumatoid arthritis, Sjogren's, sarcoidosis, etc.), or prior lobectomy or pneumonectomy.	□ oui □ non
11. Uncontrolled or significant cardiovascular disease, including: Medical history of myocardial infarction within 6 months before randomization, symptomatic congestive heart failure (CHF) (New York Heart Association Class II to IV), troponin levels consistent with myocardial infarction as defined according to the manufacturer 28 days prior to randomization.	□ oui □ non
12. Has a corrected QT interval per Fridericia's formula (QTcF) prolongation to > 470 msec (females) or > 450 msec (males) based on screening 12-lead electrocardiogram (ECG).	□ oui □ non
13. History of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.	□ oui □ non
14. History of severe hypersensitivity reactions to other monoclonal antibodies (MAb).	□ oui □ non
15. Inadequate washout period before Randomization/Cycle 1 Day 1, defined as:	□ oui □ non

a. Major surgery: < 4 weeks prior to Randomization b. Systemic anticancer chemotherapy: ● Immunotherapy (non-antibody based therapy), retinoid therapy: < 3 weeks prior to Randomization ● Small-molecule targeted agents (eg, 5-fluorouracil-based agents, folinate agents, weekly paclitaxel): < 2 weeks or < 5 half-lives prior to Randomization, whichever is longer c. Antibody-based anticancer therapy: < 4 weeks prior to Randomization d. Chloroquine/Hydroxychloroquine: ≤ 14 days prior to Cycle 1 Day 1	
16. Substance abuse or medical conditions such as clinically significant cardiac or psychological conditions, that may, in the opinion of the investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results.	□ oui □ non
17. Social, familial, or geographical factors that would interfere with study participation or follow-up.	□ oui □ non
18. Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.	□ oui □ non
19. Known human immunodeficiency virus (HIV) infection or active hepatitis B or C infection. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Subjects should be tested for HIV prior to randomization if required by local regulations or institutional review board (IRB)/independent ethics committee (IEC).	□ oui □ non
20. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤ 1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible per the discretion of the investigator after consultation with the Sponsor Medical Monitor or designee.	□ oui □ non
21. Is pregnant or breastfeeding or planning to become pregnant.	□ oui □ non

Date : _____

Signature de l'investigateur : _____