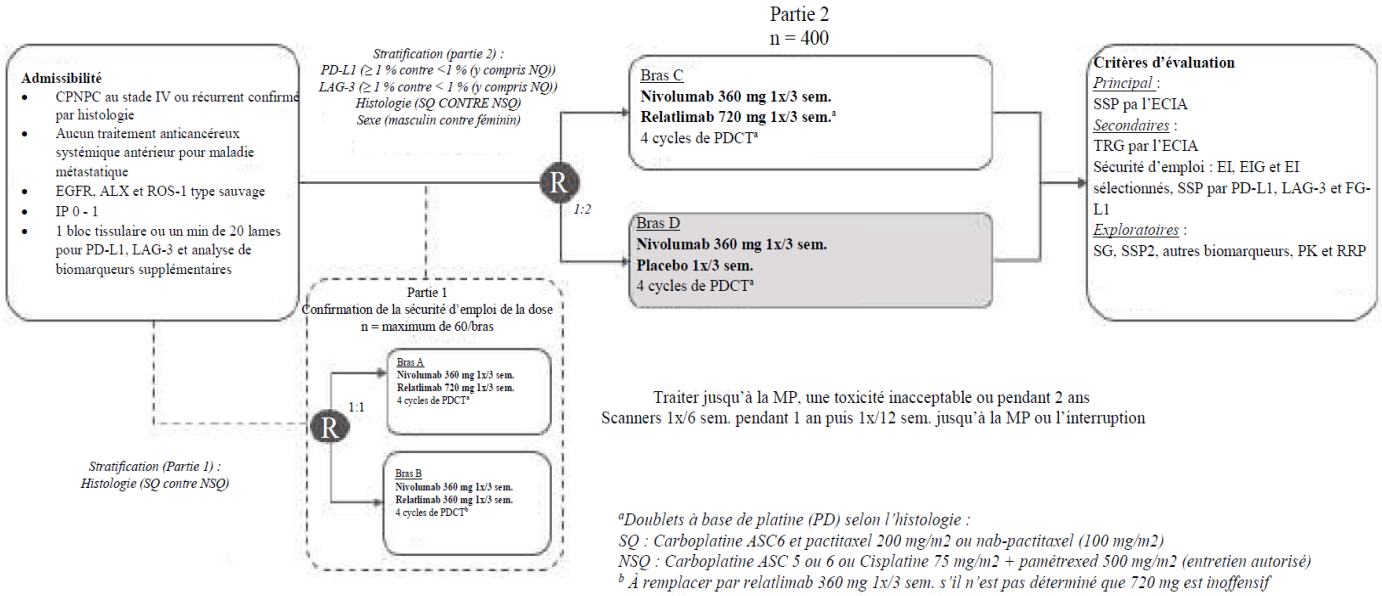
CGFL CENTRE GEORGES FRANÇOIS LECLERC Ensemble, dépassons le cancer	**CRITERES DE SELECTION** **ETUDE BMS CA224 104 / RELATIVITY**	Identité patient (coller étiquette patient)
Version 2.0 du 27/04/2021	Investigateur en charge du patient : PI : cfraisse@cgfl.fr *A contacter pour adresser/inclure patient externe au CGFL*	Arc : Suzy Poste : 3434

Étude randomisée en double aveugle de phase 2 portant sur le relatlimab plus le nivolumab en association avec une chimiothérapie contre le nivolumab en association avec une chimiothérapie en tant que traitement de première ligne chez des participants atteints d'un cancer du poumon non à petites cellules (CPNPC) au stade IV ou récurrent (BMS CA224 104 / RELATIVITY).



VALIDATION DES CRITERES DE SELECTION

Critères d'inclusion

1. Signed Written Informed Consent a) Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written ICF in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal participant care. b) Participants must be willing and able to comply with scheduled visits, treatment schedule, and laboratory testing.	□ oui □ non
2. Type of Participant and Target Disease Characteristics a) Eastern Cooperative Oncology Group (ECOG) PS of ≤1 at screening and confirmed prior to randomization. b) Participants must have a life expectancy of at least 3 months at the time of first dose.	□ oui □ non

c) Histologically confirmed metastatic NSCLC of SQ or NSQ histology with Stage IV A/B (as defined by the 8th International Association for the Study of Lung Cancer Classification) or recurrent disease following multi-modal therapy for locally advanced disease.

i) An FFPE tissue block containing enough tissue to cut 20 sections (preferred) or a minimum of 20 unstained slides of tumor tissue from core biopsy, punch biopsy,excisional biopsy, or surgical specimen obtained during screening or prior to enrollment (within 3 months of enrollment if stored at 2-8oC or within 2 months of enrollment if stored at ambient temperature and with no intervening systemic anti-cancer treatment between time of acquisition and enrollment) must be sent to the central laboratory. Fine needle aspirates or other cytology samples are not acceptable. Biopsies of bone lesions that do not have a soft tissue component are also unacceptable for submission.

ii) Central lab must provide IRT with confirmation of results of tumor tissue prior to participant randomization in Part 2 of the study only. In Part 1 results can be recieved after randomziation begins.

iii) Participants must have PD-L1 and LAG-3 immunohistochemistry (IHC) results from central laboratory during the screening period prior to randomization in Part 2.

Note: Please refer to Section 9.8.2 for additional details on tumor tissue requirements.

d) Participants should not have received any systemic anti-cancer therapy after the date that the submitted tumor tissue was obtained.

e) No prior systemic anti-cancer treatment (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease.

f) Prior definitive chemoradiation for locally advanced disease is permitted as long as the last administration of chemotherapy or radiotherapy (whichever was given last) occurred at least 6 months prior to enrollment.

g) Prior adjuvant or neoadjuvant chemotherapy for early-stage lung cancer is permitted if completed at least 6 months prior to initiating study treatment.

h) Prior palliative radiotherapy to non-central nervous system (CNS) lesions must have been completed at least 2 weeks prior to treatment. Participants with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of first treatment are strongly encouraged to receive palliative radiotherapy prior to treatment.

i) Measurable disease by CT or MRI per RECIST v1.1 criteria (Appendix 5); radiographic tumor assessment performed within 28 days prior to randomization.

j) Target lesions may be located in a previously irradiated field if there is documented radiographic disease progression in that site after the completion of radiation therapy.	
3. Age and Reproductive Status Investigators shall counsel women of child bearing potential (WOCBP), and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of stud drug, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant. • The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention. • Local laws and regulations may require the use of alternative and/or additional contraception methods. a) Female Participants i) Females, ages 18 or local age of majority. ii) Women who are not of childbearing potential are exempt from contraceptive requirements. iii) Women participants must have documented proof that they are not of childbearing potential. iv) WOCBP must have a negative highly sensitive urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study treatment. (1) If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. v) Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Assessments. vi) The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy. vii) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below and included in the ICF. viii) WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4) ix) A female participant is eligible to participate if she is not pregnant or breastfeeding,and at least one of the following conditions applies : (1) Is not a WOCBP OR (2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described in Appendix 4 during the intervention period and for at least 33 weeks after the last dose of any study drugs or	□ oui □ non

intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period. b) Male Participants i) Males, ages 18 or local age of majority. ii) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below. iii) Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg vaginal, anal, oral) with WOCBP even if the participant has undergone a successful vasectomy or if the partner is pregnant. iv) Male participants are required to use a condom during the intervention period and for at least 33 weeks after the last dose of study intervention. v) Female partners of males participating in the study should be advised to use highly effective methods of contraception during the study intervention period and for at least 33 weeks after the last dose of the male participant's study intervention. vi) Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the intervention period and for at least 33 weeks after the last dose of study intervention. vii) Male participants must refrain from donating sperm during the intervention period and for at least 33 weeks after the last dose of study intervention. viii) Breastfeeding partners should be advised to consult their health care providers about using appropriate highly effective contraception during the time the participant is required to use condoms.	

<u>Critères de non inclusion</u>

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1. Medical Conditions a) Women who are breastfeeding b) Mutation status : i) EGFR mutations which are sensitive to available targeted inhibitor therapy (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution mutations) are excluded. All participants with NSQ histology must have been tested for EGFR mutation status; use of an FDA-approved or local Health Authority test (tissue or blood) is strongly encouraged. Participants with NSQ histology and unknown EGFR status are excluded. ii) ALK translocations which are sensitive to available targeted inhibitor therapy are excluded. All participants with NSQ histology must have been tested for ALK mutation status; use of an FDA-approved or local Health Authority test is strongly encouraged. Participants with NSQ histology and unknown ALK status are excluded.	□ oui □ non

iii) ROS-1 translocations which are sensitive to available targeted inhibitor therapy are excluded. All participants with NSQ histology must have been tested for ROS-1 translocation status. Participants with NSQ histology and unknown ROS-1 status are excluded
iv) Known BRAFV600E mutations which are sensitive to available targeted inhibitor therapy are excluded. If BRAF mutation status is unknown or indeterminate, participant may enroll.

c) Participants with untreated CNS metastases. Participants are eligible if CNS metastases are asymptomatic and do not require immediate treatment or have been treated and participants have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). In addition, participants must have been either off corticosteroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to enrollment. Brain imaging performed within 28 days prior to randomization must document radiographic stability of CNS lesions and should be performed after completion of any CNS-directed therapy.

d) Participants with leptomeningeal metastases (carcinomatous meningitis).

e) Concurrent malignancy requiring treatment or history of prior malignancy active within 2 years prior to enrollment (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before registration and the participant has no evidence of disease). Participants with history of prior early-stage basal/SQ cell skin cancer or noninvasive or in situ cancers that have undergone definitive treatment at any time are also eligible.

f) Participants with an active, known, or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

g) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization or other immunosuppressive medications within 30 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

h) Known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome-defining opportunistic infection within the last year, or a current CD4 count <350 cells/µL. NOTE: Testing for HIV must be performed at sites where mandated locally (participants enrolled with known HIV need monitoring of CD4 counts and viral load during the study and antiretroviral therapy administered as clinically indicated).

i) Participants with serious or uncontrolled medical disorders.

j) Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before first treatment.

k) Participants with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.

l) Participants with history of myocarditis, regardless of etiology.

m) Known medical condition that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results. n) Severe acute respiratory coronavirus 2 (SARS-CoV-2) infection (either suspected or confirmed) within 12 weeks of screening. Note: Certain participants with resolving mild or asymptomatic SARS-CoV-2 infection > 4 weeks prior to screening may be included; for these participants, the Sponsor's Medical Monitor must be consulted to confirm eligibility. Note: COVID PCR viral testing may be required prior to randomization based on specific country/regional guidelines, and the result of this testing may impact study participation. Testing results should be discussed with the Medical Monitor to confirm eligibility.	
2. Prior/Concomitant Therapy a) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. b) Prior treatment with LAG-3-targeted agents. c) Concurrent use of immunosuppressive agents. d) Concurrent use of immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.3). e) Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC). f) Participants who have received a live/attenuated vaccine within 30 days before first treatment. g) Treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. Refer to Section 7.7.1 for prohibited therapies.	□ oui □ non
3. Physical and Laboratory Test Findings a) Participants with ≥ Grade 2 peripheral neuropathy b) Troponin T (TnT) or I (TnI) i) > 2 x institutional upper limit of normal (ULN).	□ oui □ non

ii) TnT or TnI levels between > 1 to 2× ULN will be permitted if a repeat assessment remains ≤ 2 x ULN and participant undergoes a cardiac evaluation. When repeat levels within 24 hours are not available, a repeat test should be conducted as soon as possible. c) Left ventricular ejection fraction (LVEF) assessment with documented LVEF < 50% by either transthoracic echocardiogram (TTE) or multiple gated acquisition scan (TTE preferred test) within 6 months prior to start of study treatment. d) White blood cells < 2000/µL (SI units: < 2× 10^9/L) e) Neutrophils < 1500/µL (SI units: < 1.5× 10^9/L) f) Platelets < 100× 10^3/µL (SI units: < 0.1× 10^9/L) g) Hemoglobin < 9.0 g/dL (SI units: < 9 g/L) h) Serum creatinine > 1.5 × ULN, unless creatinine clearance (CrCl) ≥ 50 mL/min (measured or calculated using the Cockcroft-Gault formula) i) Aspartate aminotransferase (AST) / alanine aminotransferase (ALT): > 3.0 x ULN (> 5 x ULN if liver metastases are present) j) Total bilirubin (TB) > 1.5 x ULN (except participants with Gilbert syndrome who must have a TB level of < 3.0 x ULN) k) Any positive test result for hepatitis B virus or hepatitis C virus (HCV) indicating presence of virus (eg, hepatitis B surface antigen [Australia antigen] positive, or hepatitis C antibody [anti-HCV] positive [except if HCV-ribonucleic acid (RNA) negative]).	
4. Allergies and Adverse Drug Reaction a) History of allergy or hypersensitivity to study drug components. b) Any contraindication to any of the study drugs. Investigators should refer to local package insert or Summary of Product Characteristics.	□ oui □ non
5. Other Exclusion Criteria a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and BMS approval is required.) b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.	□ oui □ non

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c) Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a participant's ability to comply with the study requirements, substantially increase risk to the participant, or impact the interpretability of study results. d) Participants with a history of screen failure to any anti-PD-1 or anti-PD-L1 antibody clinical trial due to PD-L1-negative status.	

Date : _____

Signature de l'investigateur : _____