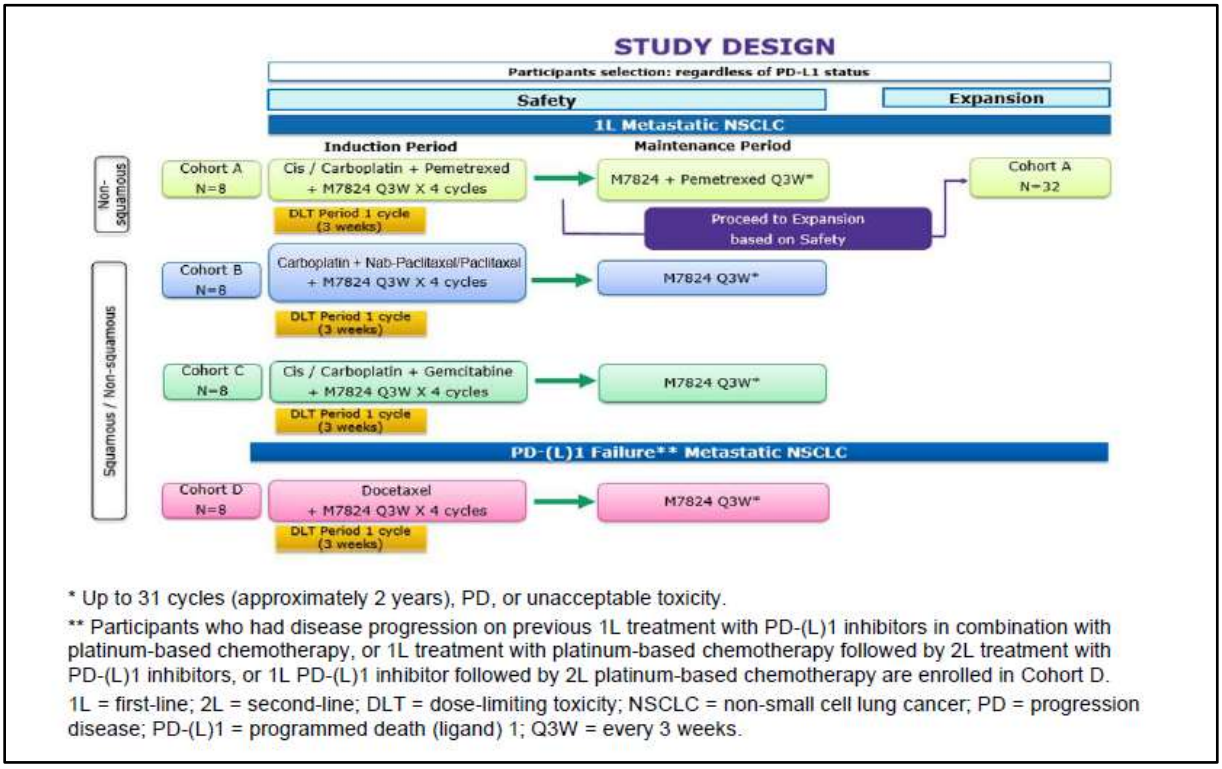
CGFL Centre Georges François Leclerc — Ensemble, dépassons le cancer	**CRITERES DE SELECTION** **ETUDE MS200647_0024** **MERK INTRAPID**	Identité patient (coller étiquette patient)
Version 1.0 du 28/10/2021	Investigateur en charge du patient : …….. PI : **Pr GHIRINGHELLI** Mail **:** fghiringhelli@cgfl.fr *A contacter pour adresser/inclure patient externe au CGFL*	Arc : **Magali ARNAUD** Poste : 3210

« MS200647 »
Étude de phase Ib/II, en ouvert, portant sur le M7824 en association à une chimiothérapie chez des patients atteints d'un cancer bronchique non à petites cellules de stade IV



* Up to 31 cycles (approximately 2 years), PD, or unacceptable toxicity.

** Participants who had disease progression on previous 1L treatment with PD-(L)1 inhibitors in combination with platinum-based chemotherapy, or 1L treatment with platinum-based chemotherapy followed by 2L treatment with PD-(L)1 inhibitors, or 1L PD-(L)1 inhibitor followed by 2L platinum-based chemotherapy are enrolled in Cohort D.

1L = first-line; 2L = second-line; DLT = dose-limiting toxicity; NSCLC = non-small cell lung cancer; PD = progression disease; PD-(L)1 = programmed death (ligand) 1; Q3W = every 3 weeks.

VALIDATION DES CRITERES DE SELECTION

Critères d'inclusion :

1. Age Are ≥ 18 years of age inclusive at the time of signing the informed consent.	□ oui □ non
2. Type of Participant and Disease Characteristics : Are participants who have histologically confirmed diagnosis of Stage IV NSCLC	□ oui □ non

CGFL Centre Georges François Leclerc – Ensemble, dépassons le cancer	**CRITERES DE SELECTION** **ETUDE MS200647_0024** **MERK INTRAPID**	Identité patient (coller étiquette patient)
Version 1.0 du 28/10/2021	Investigateur en charge du patient : …….. PI : **Pr GHIRINGHELLI** Mail **:** fghiringhelli@cgfl.fr *A contacter pour adresser/inclure patient externe au CGFL*	Arc : **Magali ARNAUD** Poste : 3210

International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology (IASLC Staging Manual in Thoracic Oncology, V8) and: **a.** Participants in Cohort A, B, and C must not have received prior systemic therapy treatment for their Stage IV NSCLC. Completion of treatment with cytotoxic chemotherapy, biological therapy, and/or radiation as part of neoadjuvant/adjuvant/unresectable locally advanced therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease. **b.** Resolution of toxic effects of previous chemotherapy therapy to Grade ≤ 1 must be confirmed prior to enrollment. For radiation toxicity or prior major surgeries, participants should have recovered from side effects and/or complications. **c.** Participants who had disease progression on previous 1L treatment with PD-(L)1 inhibitors in combination with platinum-based chemotherapy, or 1L treatment with platinum-based chemotherapy followed by 2L treatment with PD-(L)1 inhibitors, or 1L PD-(L)1 inhibitor followed by 2L platinum-based chemotherapy are enrolled in Cohort D, as long as therapy was completed at least 28 days of the first study intervention. **d.** Have measurable disease based on RECIST 1.1 **e.** Have a life expectancy of at least 3 months **f.** Availability of fresh biopsies or archived tumor material (< 6 months old) (excluding bone biopsies) adequate for biomarker analysis is mandatory at Screening, central laboratory confirmation is required. If participant received systemic therapy after the archival biopsy was taken, a fresh biopsy will be required prior to study entry if clinically feasible. Archived tumor material should be collected only if fresh biopsies material is not available. **g.** See Section 5.2 for exclusion criteria for participants with EGFR mutation, ALK translocation, ROS1 rearrangement, or BRAF V600E mutation.	
3. ECOG PS of 0 to 1 at study entry and date of first dose	□ oui □ non

CGFL CENTRE GEORGES FRANÇOIS LECLERC Ensemble, dépassons le cancer	**CRITERES DE SELECTION** **ETUDE MS200647_0024** **MERK INTRAPID**	Identité patient (coller étiquette patient)
Version 1.0 du 28/10/2021	Investigateur en charge du patient : …….. PI : **Pr GHIRINGHELLI** Mail **:** fghiringhelli@cgfl.fr *A contacter pour adresser/inclure patient externe au CGFL*	Arc : **Magali ARNAUD** Poste : 3210

4. Have adequate organ function as indicated by the following laboratory values **a.** Adequate hematological function defined by absolute neutrophil count (ANC)≥ 1.5 × 109/L, platelet count ≥ 100 × 109/L, and hemoglobin ≥ 9 g/dL **b.** Adequate hepatic function defined by a total bilirubin level ≤ the upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ 1.5 × ULN and alkaline phosphatase (ALP) ≤ 2.5 ULN. For participants with liver involvement in their tumor, AST ≤ 5.0 × ULN, ALT ≤ 5.0 × ULN, and bilirubin ≤ 3.0 × ULN is acceptable **c.** Adequate renal function defined by creatinine ≤ 1.5 × ULN or calculated creatinine clearance (CrCL) ≥ 50 mL/min for participant with Creatinine > 1.5× ULN (glomerular filtration rate [GFR] can also be used) Note: CrCL should be calculated per institutional standard. If no local guideline is available, CrCL should be calculated using the Cockcroft-Gault Method : CrCL = ([140-age] × weight [kg] × [0.85 for females only]) / (72 × creatinine) **d.** Adequate coagulation function defined as international normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 × ULN unless the participant is receiving anticoagulant therapy, and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN unless the participant is receiving anticoagulant therapy	□ oui □ non
5. Sex : Contraceptive use by males or females will be consistent with local regulations on contraception methods for those participating in clinical studies. **a.** Male Participants: Contraceptive measures should be continued as per guidance specified in labeling document for approved chemotherapies. If not specified, continue measures similar to investigational agent i.e. agree to the following during the study intervention period and for at least 4 months	□ oui □ non

after the last dose of study intervention or as per guidance specified in labeling document for approved chemotherapies.

- Refrain from donating sperm PLUS, either :
- Abstain from intercourse with a WOCBP female

OR

- Use a male condom: When having sexual intercourse with a woman of childbearing potential (WOCBP), who is not currently pregnant, and advise her to use a highly effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 3, since a condom may break or leak.

b. Female Participants:

- Are not pregnant or breastfeeding, and at least one of the following conditions applies :

- Not a WOCBP, as defined in Appendix 3

 OR

- If a WOCBP, use a highly effective contraceptive method (i.e., with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 3for the following time periods:
  - Before the first dose of the study intervention(s), if using hormonalcontraception: Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses OR Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay.
  - During the intervention period
- Contraceptive measures should be continued as per guidance specified in labeling document for approved chemotherapies. If not specified, continue measures similar to investigational agent i.e. after the study intervention period (i.e., after the last dose of study intervention is administered or as per guidance specified in labeling document for approved chemotherapies) for at least 2 months after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period.
- Have a negative pregnancy test, as required by local regulations on W1D1 before the first dose of study intervention.

CGFL Centre Georges François Leclerc – Ensemble, dépassons le cancer	**CRITERES DE SELECTION** **ETUDE MS200647_0024** **MERK INTRAPID**	Identité patient (coller étiquette patient)
Version 1.0 du 28/10/2021	Investigateur en charge du patient : …….. PI : **Pr GHIRINGHELLI** Mail **:** fghiringhelli@cgfl.fr *A contacter pour adresser/inclure patient externe au CGFL*	Arc : **Magali ARNAUD** Poste : 3210

• Additional requirements for pregnancy testing during and after study intervention are inSchedule of Activities (Section 1.3). • The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.	
6. Informed Consent Can give signed informed consent, as indicated in Appendix 2 (Study Governance), which includes compliance with the requirements and restrictions listed in the informed consentform (ICF) and this protocol.	□ oui □ non

Critères de non inclusion :

1. Medical Conditions and Diagnostic Assessments The participant's tumor harbors an EGFR sensitizing (activating) mutation, ALK translocation, ROS1 rearrangement, or BRAF V600E mutation, if targeted therapy is locally approved. For participants with non-squamous histology : **a.** EGFR mutation status and/or ALK translocation, ROS1 rearrangement, and/or BRAF V600E mutation (if indicated) status must be available at the site **b.** Investigators must be able to produce the source documentation of the EGFR mutation and ALK translocation status **c.** ROS1 testing is required in participants who have had negative EGFR/ALK testing if targeted therapy is locally approved. **d.** BRAF V600E mutation is required if targeted therapy is locally approved **e.** If unable to provide source documentation nor to test for these molecular changes,formalin fixed paraffin embedded tumor tissue of any age should be submitted to a central laboratory designated by the Sponsor for such testing.	□ oui □ non

f. If an EGFR sensitizing mutation, ALK translocation, or ROS1 rearrangement, or BRAF V600E is not detected, additional information regarding other mutation status is not required. For participants enrolled who are with NSCLC of predominantly squamous histology, molecular testing will not be required as this is not standard of care and is not mandated by the current National Comprehensive Cancer Network (NCCN) guidelines.	
2. Mixed small cell with NSCLC cancer histology	□ oui □ non
3. Has received major surgery within 4 weeks prior to the first dose of study intervention; received thoracic radiation therapy (RT) of > 30 Gy within 6 months prior to the first dose of study intervention.	□ oui □ non
4. Previous malignant disease (other than the target malignancy to be investigated in thisstudy) within the last 3 years. Participants with a history of cervical carcinoma in situ, ductal carcinoma in situ, uperficial or noninvasive bladder cancer, or basal cell or squamous cell carcinoma in situ previously treated with curative intent are NOT excluded. Participants with other localized malignancies treated with curative intent need to be discussed with the Medical Monitor.	□ oui □ non
5. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are clinically stable for at least 2 weeks after the end of the RT and have no evidence of new or enlarging brain metastases evaluated by imaging, preferably brain magnetic resonance imaging (MRI). In addition, any steroids administered as part of this therapy must be completed at least 3 days prior to study intervention. Stable brain metastases by this definition should be established prior to the first dose of study medication and after at least 2 weeks from the last dose of RT. Participants with known untreated, asymptomatic brain metastases (i.e. no neurological symptoms, no requirements for corticosteroids, no or minimal surrounding edema, and no lesion >1.5 cm) may participate after discussion with the Medical Monitor and will	□ oui □ non

	require regular imaging of the brain as a site of disease, preferably by MRI.	
6.	Active autoimmune disease that has required systemic treatment in the past 1 year (e.g., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs), OR is receiving systemic steroid therapy < 3 days prior to the first dose of study intervention or receiving any other form of immunosuppressive medication. Participants requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at low doses (typically ≤ 10 mg of prednisone or equivalent per day). Equivalent hydrocortisone doses are also permitted if administered as a replacement therapy. Participants with diabetes Type I, vitiligo, alopecia, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible. Consult Medical Monitor for other autoimmune diseases.	□ oui □ non
7.	Known severe hypersensitivity (Grade ≥ 3 National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0) to study intervention or any components in their formulations, or uncontrolled asthma (i.e., 3 or more features of partially controlled asthma). Occurrence of irAEs during previous treatment with checkpoint inhibitors could potentially constitute an exclusion criterion in participants candidate for treatment in Cohort D. Investigator must carefully evaluate benefit-risk assessment on a case basis and discuss it with the Medical Monitor and the Sponsor medical responsible prior participant's enrollment.	□ oui □ non
8.	Receipt of any organ transplantation, including allogeneic stem-cell transplantation, but with the exception of transplants that do not require immunosuppression (e.g., corneal transplant, hair transplant).	□ oui □ non

CGFL Centre Georges François Leclerc – Ensemble, dépassons le cancer	**CRITERES DE SELECTION** **ETUDE MS200647_0024** **MERK INTRAPID**	Identité patient (coller étiquette patient)
Version 1.0 du 28/10/2021	Investigateur en charge du patient : …….. PI : **Pr GHIRINGHELLI** Mail **:** fghiringhelli@cgfl.fr *A contacter pour adresser/inclure patient externe au CGFL*	Arc : **Magali ARNAUD** Poste : 3210

9. Has interstitial lung disease (ILD) OR has had a history of pneumonitis that has required oral or intravenous steroids. Participants with a history of radiation pneumonitis which has clinically and radiologically resolved and not requiring treatment with steroids may be eligible. Investigator must carefully evaluate benefit-risk assessment on a case basis and discuss it with the Medical Monitor and the Sponsor's Medical Responsible prior to participant's enrollment.	□ oui □ non
10. Significant acute or chronic infections including, among others : **a.** Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (no testing at Screening required). If an Investigator has a strong suspicion of HIV infection without known history for a participant in Screening, however participant refuses testing, discuss with Medical Monitor to assess eligibility. (Note: HIV testing is not mandated for study inclusion; however, if it is performed at any point in Screening or while on study, a site must consent the participant for HIV testing as per local standard guidance). **b.** Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (HBV surface antigen positive and HBV core antibody positive with reflex to positive HBV DNA, or HBV core antibody positive alone with reflex to positive HBV DNA, or positive HCV antibody with reflex to positive HCV RNA) at Screening. Discuss with the Medical Monitor if history of HBV or HCV infection is known. If medically indicated, participants infected with HBV must be treated and on a stable dose of antivirals (e.g., entecavir, tenofovir, or lamivudine; adefovir or interferon are not allowed) at study entry and with planned monitoring and management according to appropriate labeling guidance. Participants on active HCV therapy at study entry must be on a stable dose without documented clinically significant impaired liver function test or hematologic abnormalities (must meet criteria below) and with planned monitoring and management according to appropriate labeling guidance. HBV and/or HCV viral serology must be monitored according to Schedule of Activities in these participants.	□ oui □ non

c. Participants with active tuberculosis (history of exposure or history of positive tuberculosis test; plus presence of clinical symptoms, physical, or radiographic findings).	
11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with participation for the full duration of the study, or is not in the best interest of the participant, in the opinion of the treating Investigator. Participants with history of bleeding diathesis or recent major bleeding events considered by the Investigator as high risk for investigational drug treatment are also excluded.	□ oui □ non
12. Prior/Concomitant Therapy For participants in Cohorts A, B and C: Has received prior systemic therapy for Stage IV NSCLC, including anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).	□ oui □ non
13. Is expected to require any other form of systemic or localized antineoplastic therapy while on study (including maintenance therapy with another agent for NSCLC, RT, and/or surgical resection).	□ oui □ non
14. Use of a prohibited concomitant drug, as defined in Section 6.5.2	□ oui □ non
15. Has received or will receive a live vaccine within 30 days prior to the first administration of study intervention. Seasonal flu vaccines that do not contain a live virus are permitted. Contact Medical Monitor if screening extension is needed for participant vaccinated within 30 days of planned first dose.	□ oui □ non

CGFL CENTRE GEORGES FRANÇOIS LECLERC Ensemble, dépassons le cancer	**CRITERES DE SELECTION** **ETUDE MS200647_0024** **MERK INTRAPID**	Identité patient (coller étiquette patient)
Version 1.0 du 28/10/2021	Investigateur en charge du patient : …….. PI : **Pr GHIRINGHELLI** Mail **:** fghiringhelli@cgfl.fr *A contacter pour adresser/inclure patient externe au CGFL*	Arc : **Magali ARNAUD** Poste : 3210

16. Has an active infection requiring systemic therapy/antibiotics (except as indicated, discuss alternative scenarios with the Medical Monitor).	□ oui □ non
17. Prior/Concurrent Clinical Study Experience Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 6 months of the first dose of study intervention.	□ oui □ non
18. Diagnostic Assessments Unable to tolerate computed tomography (CT) or MRI in the opinion of the Investigator and/or allergy to contrast material.	□ oui □ non
Other Exclusions : **19.** Known active alcohol or drug abuse. **20.** Any psychiatric condition that would prohibit the understanding or rendering of informed consent or consistent participation in study procedures	□ oui □ non
21. Legal incapacity or limited legal capacity.	□ oui □ non

Date : _____

Signature de l'investigateur : _____