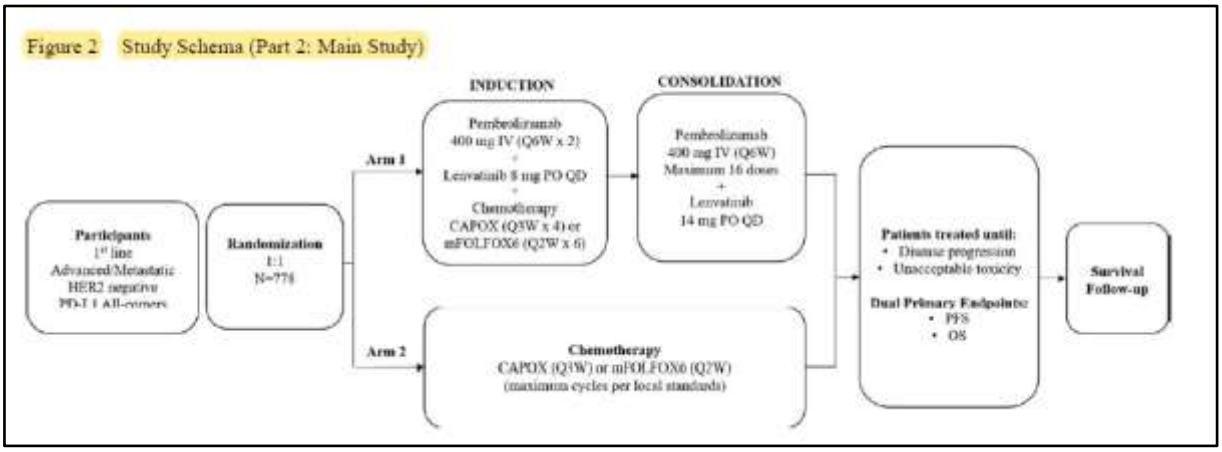
CGFL Centre Georges François Leclerc – Ensemble, dépassons le cancer	**CRITERES DE SELECTION** **ETUDE MERCK MK7902-015**	Identité patient (coller étiquette patient)
Version 1.0 du 25/10/2021	Investigateur en charge du patient : …….. PI : **Pr GHIRINGHELLI** Mail : fghiringhelli@cgfl.fr *A contacter pour adresser/inclure patient externe au CGFL*	Arc : **Kevin LE BERRE** Poste : 3465

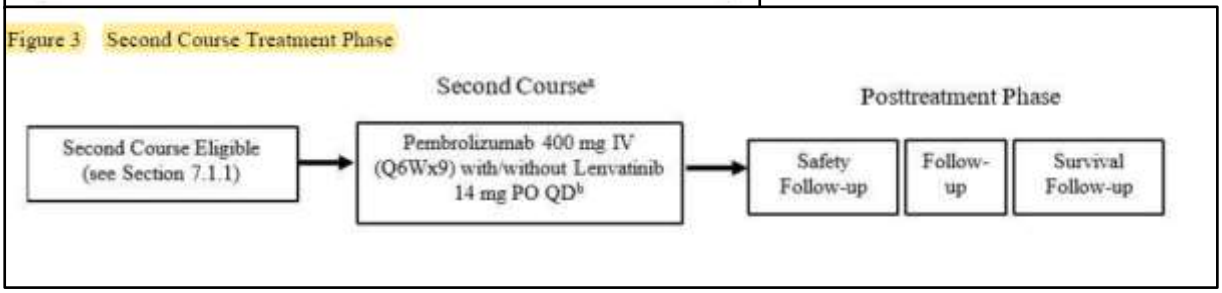
« MK7902-015 »

Etude randomisée de phase III évaluant l'efficacité et la sécurité du Pembrolizumab (MK-3475) plus Lenvatinib (E7080/MK-7902) plus chimiothérapie en comparaison avec le traitement standard comme traitement de première intention chez des participants atteints d'adénocarcinome gastrique ou de la jonction gastro-oesophagienne avancé ou métastatique HER2 négatif



Stratification Factors:
- PD-L1 (CPS ≥1 or CPS <1)
- Region (East Asia, North America + Western Europe versus Rest of World)
- ECOG (0 or 1)
- Chemotherapy (CAPOX or mFOLFOX6)

Dual Primary Endpoints: PFS and OS
Secondary Endpoint: ORR, DOR and Safety



Critères d'inclusion :

1. Has histologically and/or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic gastroesophageal adenocarcinoma.	□ oui □ non

2. Is not expected to require tumor resection during the treatment course.	□ oui □ non
3. Has gastroesophageal adenocarcinoma that is not HER-2/neu positive. Note: Participants with gastroesophageal adenocarcinoma that is known to be HER-2/neu positive are not eligible. If HER-2/neu status is unknown, site should follow local standards if HER-2/neu testing is required as SOC.	□ oui □ non
4. Has measurable disease as defined by RECIST 1.1 by scan with IV contrast as determined by the local site investigator/radiology assessment. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions since the completion of radiation (by scans with contrast).	□ oui □ non
5. Is male or female at least 18 years of age inclusive, at the time of signing the informed consent.	□ oui □ non
6. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 7 days after last dose of lenvatinib or 90 days after last dose of chemotherapy, whichever comes last: - Refrain from donating sperm PLUS either: - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent OR - Must agree to use contraception as detailed below unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]): - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men 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-vaginal penetration. Please note that 7 days after lenvatinib is stopped, if the participant is on pembrolizumab only, no male contraception measures are needed. Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.	□ oui □ non
7. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies: - Is not a WOCBP OR - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period through 120 days after last dose of pembrolizumab, 30 days after last dose of lenvatinib, or	□ oui □ non

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180 days after last dose of chemotherapy whichever occurs last, or not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The Investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. - A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within 24 hours before the first dose of study intervention. Note: 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. Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2. 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. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.	
8. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study.	□ oui □ non
9. Has a performance status of 0 or 1 on the ECOG Performance Scale within 3 days prior to the first dose of study treatment.	□ oui □ non
10. Has provided a tumor tissue sample for PD-L1 and MSI biomarker analysis. If the initial tissue is inadequate for the analysis, an additional specimen will need to be provided.	□ oui □ non
11. Has adequately controlled BP with or without antihypertensive medications, defined as BP ≤150/90 mm Hg and no change in antihypertensive medications within 1 week prior to randomization.	□ oui □ non
12. Has adequate organ function as defined in the following table (Table 3). Specimens must be collected within 10 days prior to the start of study intervention : - Neutrophiles ≥ 1500 /mcL - Plaquettes ≥ 100,000 /mcL - Hemoglobine ≥ 9 g/dL or ≥ 5.6 mmol/L - Clairance créatinine ≥ 50 mL/min - Total bilirubine ≤ 1.5 X ULN OR Direct bilirubin ≤ ULN for participants with total bilirubin levels > 1.5 ULN - ASAT et ALAT ≤ 2.5 X ULN OR ≤ 5 X ULN for participants with liver metastases - Albumine ≥ 3.0 g/dL - INR ou PT, aPTT ≤ 1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants	□ oui □ non

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Critères de non inclusion :

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1. Has had previous therapy for locally advanced unresectable or metastatic gastric/GEJ/esophageal adenocarcinoma. Note: Participants may have received prior neoadjuvant or adjuvant therapy as long as it was completed at least 6 months prior to randomization and progression occurred at least 6 months following completion of therapy.	□ oui □ non
2. Has had major surgery within 28 days prior to first dose of study interventions. Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study intervention.	□ oui □ non
3. Has had radiotherapy within 14 days of randomization. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.	□ oui □ non
4. Has a known additional malignancy that is progressing or has required active treatment within the past 5 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.	□ oui □ non
5. Has known CNS metastases and/or carcinomatous meningitis.	□ oui □ non
6. Has severe hypersensitivity (≥ Grade 3) to treatment with an mAb or known sensitivity or intolerance to any component of lenvatinib, pembrolizumab, study chemotherapy agents and/or to any excipients, murine proteins, or platinum containing products.	□ oui □ non
7. Has had an allogeneic tissue/solid organ transplant.	□ oui □ non
8. Has perforation risks or significant GI bleeding, such as: o Has had a serious nonhealing wound, peptic ulcer, or bone fracture within 28 days prior to randomization o Has preexisting ≥ Grade 3 GI or non-GI fistula o Has significant bleeding disorders, vasculitis, or has had a significant bleeding episode from the GI tract within 12 weeks prior to randomization	□ oui □ non
9. Has GI obstruction, poor oral intake (CAPOX patients), or difficulty in taking oral medication (CAPOX patients). G-tubes, J-tubes and nasogastric tubes will not be permitted for treatment administration of capecitabine. Participants with existing esophageal stent are not eligible. Also, participants with known gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that may affect the absorption of lenvatinib.	□ oui □ non
10. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory TCR (eg, CTLA-4, OX40, CD137).	□ oui □ non

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11. Has received prior therapy with anti-VEGF TKI or anti-VEGF mAb.	□ oui □ non
12. Has received a live or live-attenuated vaccine within 30 days before the first dose of study drug. Note: Killed vaccines are allowed (see Section 6.5 for more information and Section 10.7.2 for country-specific [UK and Germany] requirements).	□ oui □ non
13. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention. Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.	□ oui □ non
14. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed.	□ oui □ non
15. Has radiographic evidence of encasement or invasion of a major blood vessel, or of intratumoral cavitation. NOTE: The degree of proximity to major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy	□ oui □ non
16. Has inadequate cardiac function assessed as: * Left ventricular ejection fraction (LVEF) below the institutional normal range as determined by a MUGA or ECHO. • QTcF value >470 msec for males and > 480 msec for females (mean of 3 measurements corrected for HR using Fridericia's formula). • Cardiac function will be assessed using 12-lead ECG scan and ECHO performed by the investigator or other qualified person prior to enrollment in the study. For country-specific requirements, see Appendix 7.	□ oui □ non
17. Has urine protein ≥1 g/24 hours. Note: Participants with proteinuria ≥2+ (≥100 mg/dL) on urine dipstick testing (urinalysis) will undergo 24-hour urine collection for quantitative assessment of proteinuria. Participants may be eligible if 24-hour urine protein ≤1 g.	□ oui □ non
18. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study intervention.	□ oui □ non
19. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.	□ oui □ non
20. Has a known history of active TB (Mycobacterium tuberculosis). No testing for TB is required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.	□ oui □ non
21. Has an active infection requiring systemic therapy.	□ oui □ non

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22. Has poorly controlled diarrhea (eg, watery stool, uncontrollable bowel movement with supportive medication, Grade ≥2 and number of defecations, ≥5/day).	□ oui □ non
23. Has accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs within 2 weeks prior to enrollment. If the participant is receiving diuretic drugs for other reasons, it is acceptable. Consult with the Sponsor if the participant has more than trivial/trace fluid accumulation.	□ oui □ non
24. Has a history or current evidence of any condition (eg, but not limited to, known deficiency of the enzyme DPD, etc.), therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the investigator (refer to Appendix 7 for country-specific requirements). Participants with a contraindication to SOC therapy should be excluded based on the following: • Has a history of a GI condition or procedure that in the opinion of the investigator may affect oral study drug absorption. • Has a history of a severe and unexpected reaction to a fluoropyrimidine-containing treatment. • Has severe dyspnea at rest related to advanced disease stage or oxygen-dependent complications. • Has hypokalemia, hypomagnesemia, or hypocalcemia. • Participant had clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study intervention.	□ oui □ non
25. Has peripheral neuropathy ≥ Grade 2.	□ oui □ non
26. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study.	□ oui □ non
27. Has clinically significant cardiovascular disease within 12 months from first dose of study intervention, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability. Note: Medically controlled arrhythmia would be permitted.	□ oui □ non
28. Has a known history of HIV (HIV 1/2 antibodies). No testing for HIV is required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.	□ oui □ non
29. Has a known history of hepatitis B (defined as HBsAg reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. No testing for hepatitis B/C is required unless mandated by local health authority. Refer to Appendix 7 for country-specific requirements.	□ oui □ non
30. Has weight loss of >20% within the last 3 months.	□ oui □ non

Date : _____ Signature de l'investigateur : _____