CGFL CENTRE GEORGES FRANÇOIS LECLERC Ensemble, dépassons le cancer	**CRITERES DE SELECTION** **FRESCO-2**	Identité patient (coller étiquette patient)
Version 1.0 du 10/03/2015	Investigateur : Pr Ghiringhelli	Arc : Céline S 3427

VALIDATION DES CRITERES DE SELECTION

Critères d'inclusion

1. Provide written informed consent	☐ oui ☐ non
2. Age ≥18 years	☐ oui ☐ non
3. Histologically and/or cytologically documented metastatic colorectal adenocarcinoma. RAS, BRAF, and microsatellite instability microsatellite instability (MSI)/mismatch repair (MMR) status for each patient must be documented, according to country level guidelines;	☐ oui ☐ non
Subjects must have progressed on or been intolerant to treatment with either trifluridine/tipiracil (TAS-102) or regorafenib. Subjects are considered intolerant to TAS-102 or regorafenib if they have received at least 1 dose of either agents and were discontinued from therapy for reasons other than disease progression. Subjects who have been treated with both TAS-102 and regorafenib are permitted. Subjects must also have been previously treated with standard approved therapies: fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wildtype, 4. an anti-EGFR therapy;	☐ oui ☐ non
Subjects with microsatellite-high (MSI-H) or mismatch repair deficient (dMMR) tumors must have been treated with immune checkpoint inhibitors if approved and available in the subject's country unless the patient is ineligible for treatment with a checkpoint 5. inhibitor;	☐ oui ☐ non
Subjects who received oxaliplatin in the adjuvant setting and developed metastatic disease during or within 6 months of completing adjuvant therapy are considered eligible without receiving oxaliplatin in the metastatic setting. Subjects who developed metastatic disease more than 6 months after completion of oxaliplatin-containing adjuvant treatment must be treated with oxaliplatin-based therapy in the metastatic setting 6. to be eligible;	☐ oui ☐ non
7. Body weight ≥40kg;	☐ oui ☐ non
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1;	☐ oui ☐ non
Have measurable disease according to RECIST Version1.1 (RECIST v1.1), assessed locally. Tumors that were treated with radiotherapy are not measurable per RECIST 9. v1.1, unless there has been documented progression of those lesions;	☐ oui ☐ non
10. Expected survival >12 weeks	☐ oui ☐ non

For female subjects of childbearing potential and male subjects with partners of childbearing potential, agreement to use a highly effective form(s) of contraception, that results in a low failure rate (<1% per year) when used consistently and correctly, starting during the screening period, continuing throughout the entire study period, and for 90 days after taking the last dose of study drug. Such methods include: oral hormonal contraception (combined estrogen/ progestogen, or progestogen-only) associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal ligation, vasectomized partner, or true sexual abstinence in line with the preferred and usual lifestyle of the subject. Highly effective contraception should always be combined with an additional barrier method (eg, diaphragm, with a spermicide). The same criteria are applicable to male subjects involved in this clinical trial if they have a partner of childbirth potential, and male subjects must always use a 11. condom;	☐ oui ☐ non
Subjects with BRAF-mutant tumors must have been treated with a BRAF inhibitor if approved and available in the subject's country unless the patient is ineligible for 12. treatment with a BRAF inhibitor;	☐ oui ☐ non

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Critères de non inclusion

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1. Absolute neutrophil count (ANC) <1.5×109/L, platelet count <100 × 109/L, or hemoglobin <9.0 g/dL. Blood transfusion within 1 week prior to enrollment for the purpose of increasing the likelihood of eligibility is not allowed;	□ oui □ non
Serum total bilirubin >1.5 × the upper limit of normal (ULN). Subjects with Gilbert syndrome, bilirubin <2 X ULN, and normal aspartate aminotransferase (AST)/ alanine 2. aminotransferase (ALT) are eligible	□ oui □ non
ALT or AST >2.5 × ULN in subjects without hepatic metastases; ALT or AST >5 × 3. ULN in subjects with hepatic metastases;	□ oui □ non
Serum creatinine >1.5 × ULN or creatinine clearance <60 mL/min. Creatinine clearance can either be measured in a 24-hour urine collection or estimated by the Cockcroft-Gault 4. equation;	□ oui □ non
Urine dipstick protein ≥2+ or 24-hour urine protein ≥1.0 g/24-h. Subjects with greater than 2+ proteinuria by dipstick must undergo a 24-hour urine collection to assess urine **Clinical Study Protocol 2019-013-GLOB1 Fruquintinib** **Amendment 1 Version 1** **Hutchison MediPharma Page 47** **CONFIDENTIAL** protein level. For conversions between quantitative and qualitative results, please see 5. Appendix 9;	□ oui □ non
6. Uncontrolled hypertension, defined as: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mm Hg despite optimal medical management;	□ oui □ non
7. International Normalized Ratio (INR) >1.5 x ULN or activated partial thromboplastin time (aPTT) >1.5 × ULN, unless the subject is currently receiving or intended to receive anticoagulants for prophylactic purposes;	□ oui □ non
History of, or active gastric/duodenal ulcer or ulcerative colitis, active hemorrhage of an unresected gastrointestinal tumor, history of perforation or fistulas; or any other condition that could, in the investigator's judgment, result in gastrointestinal hemorrhage or 8. perforation; within the 6 months prior to screening;	□ oui □ non
History or presence of hemorrhage from any other site (eg, hemoptysis or hematemesis) 9. within 2 months prior to screening;	□ oui □ non
History of a thromboembolic event, including deep vein thrombosis (DVT), pulmonary 10. embolism (PE), or arterial embolism within 6 months prior to screening;	□ oui □ non
11. Stroke and/or transient ischemic attack within 12 months prior to screening;	□ oui □ non
Clinically significant cardiovascular disease, including but not limited to acute myocardial infarction or coronary artery bypass surgery within 6 months prior to enrollment, severe or unstable angina pectoris, New York Heart Association Class III/IV congestive heart failure, ventricular arrhythmias requiring treatment, or left ventricular 12. ejection fraction (LVEF) <50% by echocardiogram;	□ oui □ non

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Mean corrected QT interval using the Fridericia method (QTcF) >480 msec or any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or 13. unexplained sudden death under 40 years of age in a first-degree relative;	□ oui □ non
Concomitant medications with a known risk of causing QT prolongation and/or Torsades de Pointes (See list in Appendix 4; source list is continuously updated online at 14. www.crediblemeds.org);	□ oui □ non
Systemic anti-neoplastic therapies (except for those described in Exclusion Criterion 18) or any investigational therapy within 4 weeks prior to the first dose of study drug, including chemotherapy, radical radiotherapy, hormonotherapy, biotherapy and 15. immunotherapy;	□ oui □ non
Systemic small molecule targeted therapies (eg, tyrosine kinase inhibitors) within 5 halflives 16. or 4 weeks (whichever is shorter) prior to the first dose of study drug;	□ oui □ non
Palliative radiotherapy for bone metastasis/lesion within 2 weeks prior to the initiation of 17. study drug;	□ oui □ non
Brachytherapy (ie, implantation of radioactive seeds) within 60 days prior to the first 18. dose of study drug;	□ oui □ non
Use of strong inducers or inhibitors of CYP3A4 within 2 weeks (or 5 half-lives, whichever is longer) before the first dose of study drug (see Appendix 4 for a list of 19. applicable drugs);	□ oui □ non
Surgery or invasive procedure (ie, a procedure that includes a biopsy; central venous catheter placement is allowed) within 60 days prior to the first dose of study drug or 20. unhealed surgical incision;	□ oui □ non
Any unresolved toxicities from a previous antitumor treatment greater than National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) v5.0 21. grade 1 (except for alopecia or neurotoxicity grade≤2);	□ oui □ non
22. Known human immunodeficiency virus (HIV) infection;	□ oui □ non
23. Known history of active viral hepatitis. For subjects with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Subjects with HCV infection who are currently on treatment are eligible if they have an undetectable HCV viral load;	□ oui □ non
24. Clinically uncontrolled active infection requiring IV antibiotics	□ oui □ non
25. Tumor invasion of a large vascular structure (eg, pulmonary artery, superior or inferior vena cava);	□ oui □ non
26. Women who are pregnant or lactating;	□ oui □ non

27. Brain metastases and/or spinal cord compression untreated with surgery and/or radiotherapy, and without clinical imaging evidence of stable disease for 14 days or longer; subjects requiring steroids within 4 weeks prior to start of study treatment are excluded;	□ oui □ non
28. Other malignancy, except for non-melanoma skin cancer, in situ cervical ca or bladder ca (Tis and T1) that have been adequately treated during the 5 years prior to screening;	□ oui □ non
29. Inability to take medication orally, dysphagia or an active gastric ulcer resulting from previous surgery (eg, gastric bypass) or a severe gastrointestinal disease, or any other condition that investigators believe may affect absorption of the investigational product;	□ oui □ non
30. Other disease, metabolic disorder, physical examination anomaly, abnormal laboratory result, or any other condition (eg, current alcohol or drug abuse) that investigators suspect may prohibit use of the investigational product, affect interpretation of study results, or put the subject at undue risk of harm based on the investigator's assessment;	□ oui □ non
31. Known hypersensitivity to fruquintinib or any of its (or placebo) inactive ingredients including the azo dyes Tartrazine - FD&C Yellow 5 and Sunset yellow FCF - FD&C Yellow 6;	□ oui □ non
32. Subjects who have received prior fruquintinib;	□ oui □ non
33. Live vaccine ≤28 days before the first dose of study drug(s) Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed	□ oui □ non

Date : _____

Signature de l'investigateur : _____