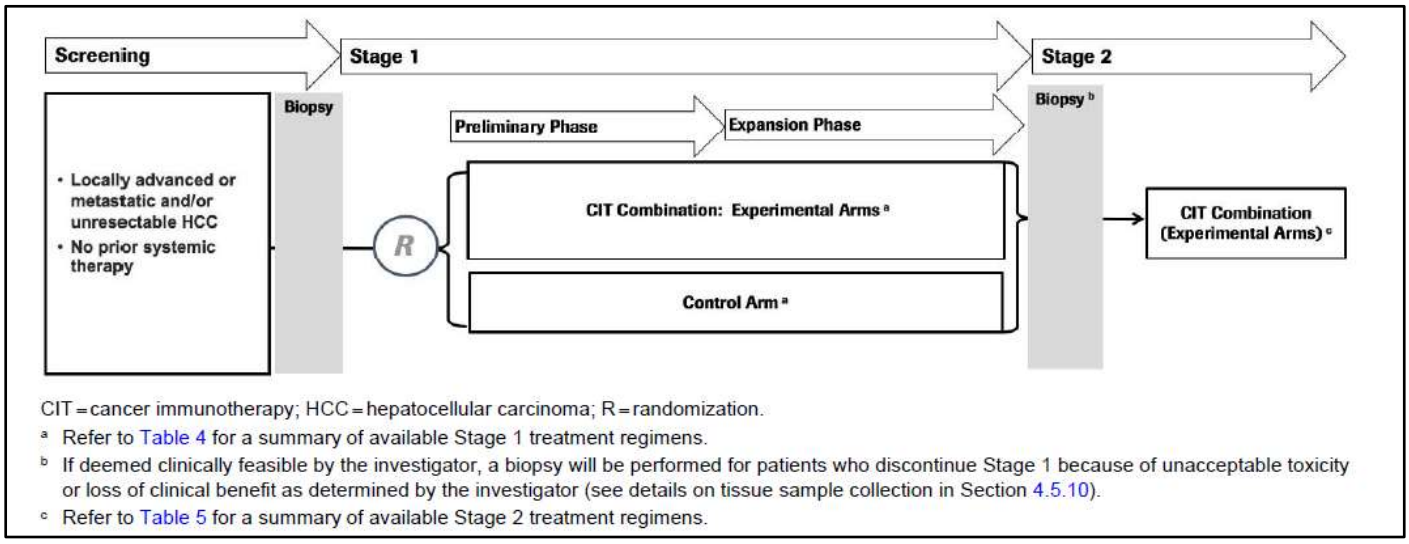
CGFL Centre Georges François Leclerc Ensemble, dépassons le cancer	**CRITERES DE SELECTION** **ETUDE GO 42216**	Identité patient (coller étiquette patient)
Version 1.0 du 04/11/2021	Investigateur en charge du patient : …….. PI : **Pr GHIRINGHELLI** Mail : fghiringhelli@cgfl.fr *A contacter pour adresser/inclure patient externe au CGFL*	Arc : **Magali ARNAUD** Poste : 3210

« GO 42216 : MORPHEUS LIVER »

ÉTUDE PARAPLUIE DE PHASE Ib/II, EN OUVERT, MULTICENTRIQUE, RANDOMISÉE ÉVALUANT L'EFFICACITÉ ET LA SÉCURITÉ D'EMPLOI DE MULTIPLES IMMUNOTHÉRAPIES EN TRAITEMENT COMBINÉ CHEZ DES PATIENTS ATTEINTS DE CANCERS DU FOIE AVANCÉS (MORPHEUS−FOIE)



CIT = cancer immunotherapy; HCC = hepatocellular carcinoma; R = randomization.

[a] Refer to Table 4 for a summary of available Stage 1 treatment regimens.

[b] If deemed clinically feasible by the investigator, a biopsy will be performed for patients who discontinue Stage 1 because of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see details on tissue sample collection in Section 4.5.10).

[c] Refer to Table 5 for a summary of available Stage 2 treatment regimens.

VALIDATION DES CRITERES DE SELECTION

Critères d'inclusion

Patients must meet all of the following criteria to qualify for Stage 1. In case of a screen fail, the corresponding Inclusion Criteria number is specified below in parenthesis for use in Almac:

1. Age ≥18 years at the time of signing Informed Consent Form	□ oui □ non
2. ECOG Performance Status of 0 or 1 (see Appendix 4) within 7 days prior to randomization	□ oui □ non
3. Locally advanced or metastatic and/or unresectable HCC with diagnosis confirmed by histology/cytology or clinically by AASLD criteria in cirrhotic patients For cirrhotic patients with no histological confirmation of diagnosis, clinical confirmation is required per AASLD criteria (see Appendix 5).	□ oui □ non
4. Child-Pugh class A (see Appendix 6) within 7 days prior to randomization	□ oui □ non

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5. Disease that is not amenable to curative surgical and/or locoregional therapies Patients with progressive disease after surgical and/or locoregional therapies are eligible..	□ oui □ non
6. No prior systemic treatment (including systemic investigational agents) for HCC Prior treatment with herbal therapies, including traditional Chinese medicines, with anti-cancer activity noted in the label are allowed, provided that these medications are discontinued prior to randomization.	□ oui □ non
7. Life expectancy ≥ 3 months, as determined by the investigator	□ oui □ non
8. Availability of a representative tumor specimen that is suitable for determination of PD-L1 and/or additional biomarker status via central testing Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted after Medical Monitor approval has been obtained, provided the patient has not received any anti-cancer therapy, *including locoregional liver-directed therapy,* since the time of the biopsy. A formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 16 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report. If only 10-15 slides are available, the patient may still be eligible for the study, after Medical Monitor approval has been obtained. Refer to Section 4.5.10 for additional information on tumor specimens collected at screening..	□oui □ non

Patients must meet all of the following criteria to qualify for Stage 1 and to qualify for Stage 2::

9. Signed Informed Consent Form	□ oui □ non
10. Ability to comply with the study protocol, in the investigator's judgment	□ oui □ non
11. Measurable disease (at least one target lesion) according to RECIST v1.1 Patients who received prior locoregional therapy (e.g., radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolization, transarterial embolization, etc.) are eligible provided the target lesion(s) have not been previously treated with locoregional therapy or the target lesion(s) within the field of local therapy have subsequently progressed in accordance with RECIST v1.1..	□ oui □ non
12. Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 7 days prior to initiation of study treatment: - ANC ≥ 1.5 □ 109/L (1500/µL) without granulocyte colony-stimulating factor support - Lymphocyte count ≥ 0.5 □ 109/L (500/µL)	□ oui □ non

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- Platelet count ≥ 75 □ 109/L (75,000/□L) without transfusion - Hemoglobin ≥ 90 g/L (9.0 g/dL) *without transfusion* Patients *must not have required transfusion during screening or within 2 weeks prior to screening* to meet this criterion - AST, ALT, and ALP ≤ 5 □ upper limit of normal (ULN) - Bilirubin ≤ 3 X ULN - Creatinine 1.5 ≤ ULN or creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft-Gault formula) - Albumin ≥ 28 g/L (2.8 g/dL) without transfusion - For patients not receiving anticoagulation: INR or aPTT ≤ 1.5 □ ULN	
13. Documented virology status of hepatitis, as confirmed by screening tests for HBV and HCV – For patients with active HBV: HBV DNA <500 IU/mL during screening, initiation of anti-HBV treatment at least 14 days prior to randomization and willingness to continue anti-HBV treatment during the study (per local standard of care; e.g., entecavir) – Patients with HCV, either with resolved infection (as evidenced by detectable antibody) or chronic infection (as evidenced by detectable HCV RNA), are eligible	□ oui □ non
14. Negative HIV test at screening	□ oui □ non
15. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as outlined for each specific treatment arm in Appendices 10□*Appendix 15*	□ oui □ non
16. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating sperm, as outlined for each specific treatment arm in Appendices 10□*Appendix 15*.	□ oui □ non

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Critères de non inclusion

Patients who meet any of the following criteria will be excluded from Stage 1. In case of a screen fail, the corresponding Exclusion Criteria number is specified below in parenthesis for use in Almac:

.

1. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti□CTLA-4, anti PD-1, and anti PD-L1 therapeutic antibodies	□ oui □ non
2. Treatment with investigational therapy within 28 days prior to initiation of study treatment	□ oui □ non
3. Treatment with locoregional therapy to liver (e.g., radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial hemoembolization, transarterial embolization, etc.) within 28 days prior to initiation of study treatment, or non-recovery from side effects of any such procedure	□ oui □ non
4. Untreated or incompletely treated esophageal and/or gastric varices with bleeding or that are at high risk for bleeding Patients must undergo an esophagogastroduodenoscopy (EGD), and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment. Patients who have undergone an EGD within 6 months of prior to initiation of study treatment do not need to repeat the procedure	□ oui □ non
5. A prior bleeding event due to esophageal and/or gastric varices within 6 months prior to initiation of study treatment	□ oui □ non
6. Adverse events from prior anti-cancer therapy that have not resolved to Grade ≤ 1 or better, with the exception of alopecia of any grade.	□ oui □ non
7. Inadequately controlled hypertension, defined as systolic blood pressure (BP) > 150 mmHg and/or diastolic BP >100 mmHg (average of at least three readings at two or more sessions) Anti-hypertensive therapy to achieve these parameters is allowed.	□ oui □ non

8. History of hypertensive crisis or hypertensive encephalopathy	□ oui □ non
9. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of study treatment	□ oui □ non

10. History of hemoptysis (≥2.5 mL of bright red blood per episode) within 1 month prior to initiation of study treatment	□ oui □ non
11. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)	□ oui □ non
12. Current or recent (≤10 days prior to initiation of study treatment) use of aspirin (>325 mg/day) or treatment with clopidogrel, dipyramidole, ticlopidine, or cilostazol	□ oui □ non
13. Current or recent (≤10 days prior to initiation of study treatment) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose Prophylactic anticoagulation for the patency of venous access devices is allowed provided the activity of the agent results in an INR <1.5 x ULN and aPTT is within normal limits within 14 days prior to initiation of study treatment. For prophylactic use of anticoagulants or thrombolytic therapies, the approved dose as described local label may be used.	□ oui □ non
14. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to initiation of study treatment	□ oui □ non
15. History of abdominal or tracheoesophageal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess within 6 months prior to initiation of study treatment.	□ oui □ non
16. History of intestinal obstruction and/or clinical signs or symptoms of GI obstruction, including subocclusive or occlusive syndrome related to the underlying disease, or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding prior to initiation of study treatment Patients with signs or symptoms of subocclusive or occlusive syndrome or with intestinal obstruction at the time of initial diagnosis may be enrolled if they had received definitive (surgical) treatment for symptom resolution.	□ oui □ non
17. Evidence of abdominal free air that is not explained by paracentesis or recent surgical Procedure	□ oui □ non
18. Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture	□ oui □ non
19. Grade ≥2 proteinuria, as demonstrated by ≥2+ protein on dipstick urinalysis and ≥1.0 g of protein in a 24-hour urine collection) All patients with ≥2+protein on dipstick urinalysis at screening must undergo a 24-hour urine collection for protein. Patients with <2+ protein on dipstick urinalysis are eligible for the study.	□ oui □ non

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20. Metastatic disease that involves major airways or blood vessels, or centrally located mediastinal tumor masses (<30 mm from the carina) of large volume Patients with vascular invasion of the portal *or hepatic* veins may be enrolled.	□ oui □ non
21. History of intra-abdominal inflammatory process within 6 months prior to initiation of study treatment, including, but not limited to, peptic ulcer disease, diverticulitis, or colitis	□ oui □ non
22.. Radiotherapy within 28 days or abdominal/pelvic radiotherapy within 60 days prior to initiation of study treatment with the exception of palliative radiotherapy to bone lesions within 7 days prior to initiation of study treatment	□ oui □ non
23. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to initiation of study treatment; or abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 60 days prior to initiation of study treatment; or anticipation of need for major surgical procedure during the course of the study or non-recovery from side effects of any such procedure	□ oui □ non
24. Chronic daily treatment with a nonsteroidal anti-inflammatory drug (NSAID) The occasional use of NSAIDs for the symptomatic relief of medical conditions such as headache or fever is allowed.	□ oui □ non
25. Eligible only for the control arm	□ oui □ non

Exclusion Criteria for <u>Stage 1</u> and <u>Stage 2</u>
Patients who meet any of the following criteria will be excluded from Stage 1 and from Stage 2.
:

26. Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC	□ oui □ non
27. History of hepatic encephalopathy	□ oui □ non
28. Moderate or severe ascites	□ oui □ non

29. Co-infection with HBV and HCV Patients with a history of HCV infection but who are negative for HCV RNA by PCR will be considered non-infected with HCV.	□ oui □ non
30. Symptomatic, untreated, or actively progressing central nervous system (CNS) Metastases Asymptomatic patients with treated CNS lesions are eligible, provided that **all** of the following criteria are met: - Measurable disease, per RECIST v1.1, must be present outside the CNS. - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage. - The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment. - The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anti-convulsant therapy at a stable dose is permitted. - Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord). - There is no evidence of interim progression between completion of CNS-directed therapy and initiation of study treatment. Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan	□ oui □ non
31. History of leptomeningeal disease	□ oui □ non
32. Uncontrolled tumor-related pain Patients requiring pain medication must be on a stable regimen at study entry. Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period. Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for locoregional therapy if appropriate prior to enrollment.	□ oui □ non

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33. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently) Patients with indwelling catheters (e.g., PleurX®) are allowed.	□ oui □ non
34. Uncontrolled or symptomatic hypercalcemia (ionized calcium >1.5 mmol/L, calcium >12 mg/dL, or corrected calcium >ULN)	□ oui □ non
35. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 8 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:. Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study. Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study. Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met: - Rash must cover □ 10% of body surface area. - Disease is well controlled at baseline and requires only low-potency topical corticosteroids. - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months s	□ oui □ non
36 . History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan – History of radiation pneumonitis in the radiation field (fibrosis) is permitted.	□ oui □ non
37. Active tuberculosis (TB) as documented by a positive purified protein derivative (PPD) skin test or TB blood test and confirmed by a positive chest X-ray within 3 months prior to initiation of study treatment	□ oui □ non

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Patients with a positive PPD skin test or TB blood test followed by a negative chest X-ray may be eligible for the study.	
38 . Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina	□ oui □ non
39. Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study	□ oui □ non
40. History of malignancy other than HCC within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.	□ oui □ non
41. Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia*, or any active infection that, in the opinion of the investigator, could impact patient safety*	□ oui □ non
42. Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment – Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.	□ oui □ non
43. Prior allogeneic stem cell or solid organ transplantation	□ oui □ non
44. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications	□ oui □ non
45. Pregnancy or breastfeeding, or intending to become pregnant during the study women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment	□ oui □ non
46. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of Atezolizumab	□ oui □ non

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47. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins	□ oui □ non
48. Known hypersensitivity to Chinese hamster ovary cell products or recombinant human antibodies	□ oui □ non
49. Known allergy or hypersensitivity to any of the study drugs or any of their excipients	□ oui □ non
50. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment	□ oui □ non
51. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti□TNF-□ agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions: - Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor confirmation has been obtained. - Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.	□ oui □ non
52. Grade □ 3 hemorrhage or bleeding event within 8 weeks prior to initiation of study treatment	

Exclusion Criteria for Tiragolumab-Containing Arm

Patients who meet any of the following criteria will be excluded from the tiragolumab-containing arm during Stage 1**:**

.

1. Prior treatment with an anti-TIGIT agent	□ oui □ non
2. Active Epstein-Barr virus (EBV) infection or known or suspected chronic active EBV infection at screening Patients with a positive EBV viral capsid antigen (VCA) IgM test at screening are	□ oui □ non

excluded from this arm. An EBV polymerase chain reaction (PCR) test should be performed as clinically indicated to screen for active infection or suspected chronic active infection. Patients with a positive EBV PCR test are excluded from this arm	

Exclusion Criteria for Tocilizumab-Containing Arm

Patients who meet any of the following criteria will be excluded from the tocilizumab-containing arm during Stage 1 :

1. Preexisting CNS demyelinating or seizure disorders	□ oui □ non
2. History of diverticulitis, chronic ulcerative lower GI disease (e.g., Crohn disease, ulcerative colitis), or other symptomatic lower GI conditions that might predispose a patient to GI perforation	□ oui □ non
3. Active current infection or history of recurrent bacterial, viral, fungal, mycobacterial, or other infection, including, but not limited to, TB, atypical mycobacterial disease, and herpes zoster, but excluding fungal infections of the nail bed Patients with active or chronic HBV or HCV infection are eligible (see Section 4.1.1.2). *For patients who are positive for HCV RNA: anti-HCV treatment should be provided prior to study enrollment per local standard of care and institutional guidance, based on the investigator's clinical assessment*	□ oui □ non
4. Untreated latent TB Patients who have initiated therapy for latent TB at least 4 weeks prior to initiation of study treatment, with the remaining course of therapy continuing during the study, are eligible.	□ oui □ non
5. History of, or currently active, primary or secondary immunodeficiency	□ oui □ non
6. Platelet count □ 150 x 109/L (150,000/µ L)	□ oui □ non

Exclusion Criteria for SAR439459-Containing Arm

Patients who meet any of the following criteria will be excluded from the SAR439459-containing arm during Stage 1::

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1. Prior treatment with an anti-TGFβ inhibitor	□ oui □ non
2. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to initiation of study treatment	□ oui □ non
3. Use of therapeutic doses of anticoagulants or antiplatelet agents (enoxaparin 1 mg/kg, aspirin 300 mg, or clopidogrel 300 mg daily, or equivalent) within 7 days prior to initiation of study treatment Prophylactic dosing of anticoagulants is allowed	□ oui □ non
4. Underlying cancer predisposition syndromes including, but not limited to, history of hereditary breast and ovarian cancer syndrome, Ferguson-Smith syndrome, multiple self-healing epithelioma, familial adenomatous polyposis, hereditary non-polyposis colorectal cancer, multiple endocrine neoplasia or Li-Fraumeni syndrome	□ oui □ non
5. History of clinically significant valvular heart disease (including valve replacement)	□ oui □ non
6. History of vascular malformation or aneurysm	□ oui □ non
7. History of newly diagnosed pulmonary embolism or deep vein thrombosis within 6 months prior to initiation of study treatment	□ oui □ non

Exclusion Criteria for TPST-1120□ □Containing Arm

Patients who meet any of the following criteria will be excluded from the TPST-1120□ containing arm during Stage 1:

1. Treatment with fibrates (e.g., gemfibrozil, fenofibrate) within 28 days prior to initiation of study treatment	□ oui □ non
2. Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) or strong CYP3A4 inducers (e.g., efavirenz, nevirapine, ritonavir, barbiturates, and topiramate)	□ oui □ non

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3. QTc interval □ 470 msec at screening	□ oui □ non
4. Inability to swallow oral medications as a whole without having to chew, crush, or open and empty the powder out of capsules	□ oui □ non
5. Serum cholesterol □ 400 mg/dL (or 10.34 mmol/L)	□ oui □ non
6. Triglycerides □ 400 mg/dL (or 4.52 mmol/L)	□ oui □ non

Exclusion Criteria for RO7247669-Containing Arm

Patients who meet any of the following criteria will be excluded from theRO7247669-containing arm during Stage 1:

1. Prior treatment with an anti□ lymphocyte activation gene-3 (LAG-3) agent	□ oui □ non
2. Left ventricular ejection fraction (LVEF) □ 50% assessed by either transthoracic echocardiogram (TTE) or multiple-gated acquisition (MUGA) scan (TTE preferred test) within 6 months from first study drug administration	□ oui □ non
3. Troponin T (TnT) or troponin I (TnI) □ institutional ULN Patients with TnT or TnI levels between □ 1 and □□2 x ULN are eligible if repeat levels within 24 hours are □ 1 x ULN. If repeat levels within 24 hours are between □ 1 and □ 2 x ULN, patients may undergo a cardiac evaluation and be considered for treatment, following a discussion with the Medical Monitor	□ oui □ non

<u>Bras Stade 1</u> :

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Atézolizumab + Bévacizumab (bras contrôle)	□ Oui □ Non, pourquoi :
Atézolizumab + Bévacizumab + Tiragolumab	□ Oui □ Non, pourquoi :
Atézolizumab + Bévacizumab + Tocilizumab	□ Oui □ Non, pourquoi :
Atézolizumab + Bévacizumab + SAR439459	□ Oui □ Non, pourquoi :
Atézolizumab + Bévacizumab + TPST-1120	□ Oui □ Non, pourquoi :
RO7247669 + Bévacizumab	□ Oui □ Non, pourquoi :

Date : _____

Signature de l'investigateur : _____