IGM-8444-001

Titre de l'essai

AN OPEN-LABEL, MULTICENTER, PHASE 1a/1b STUDY OF IGM-8444 AS A SINGLE AGENT AND IN COMBINATION IN SUBJECTS WITH RELAPSED, REFRACTORY, OR NEWLY DIAGNOSED CANCERS

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https://clinicaltrials.gov/study/NCT04553692

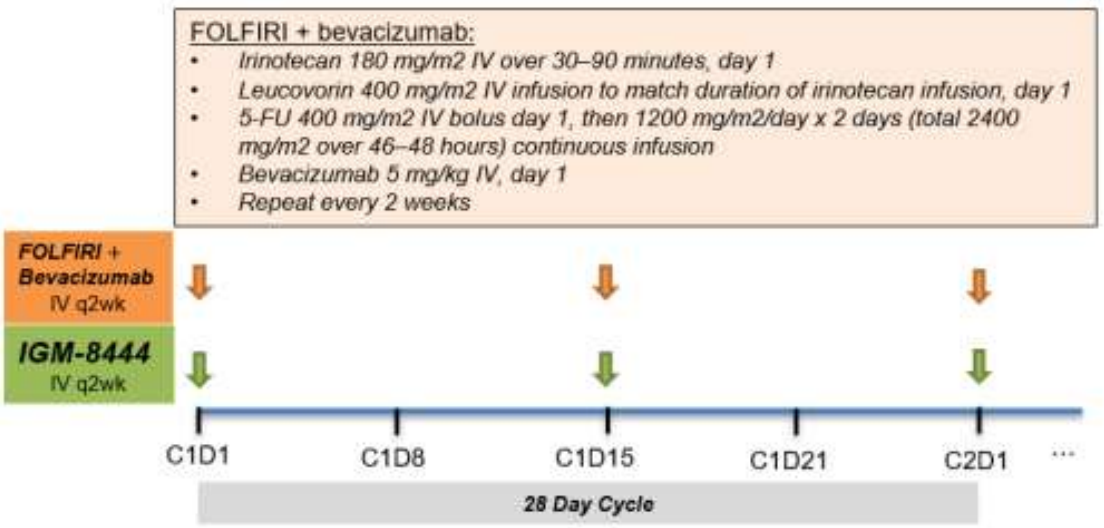
Population cible de Phase 1b : Subjects with colorectal cancer

Traitement à l'étude (phase Ib):

IGM-8444
FOLFIRI (5-Fluorouracil + Leucovorin+irnotecan)+Bevacizumab

Schéma de traitement (phase Ib): :

Figure 4 Dosing in the Randomized CRC Cohort



Rythme des visites (phase 1b) :

APPENDIX 10 PHASE 1B: RANDOMIZED COHORT SCHEDULE OF ACTIVITIES

	Screening [a]	Cycle 1 [b]								Cycles 2-13 [b]						EOT [c]	SFU [d]	LTFU
Day (Window)	–28 to –1	1 (± 1)	2	3	8 (±1)	15 (±1)	16 (±1)	17 (±1)	22 (±1)	1	2 (±2)	3 (±2)	15 (±2)	16 (±2)	17 (±2)			

LES CRITERES D'INCLUSIONS ET DE NON INCLUSIONS :

LES CRITERES D'INCLUSIONS : Les patient(e)s répondant à l'ensemble des critères suivants seront éligibles pour participer à l'étude :

	OUI	NON	NA
1- Signed Informed Consent Form (ICF)			
2- Age ≥ 18 years at time of signing ICF			
3- Ability to comply with the study protocol, in the investigator's judgement			
4- ECOG Performance Status of 0 or 1 with the exception noted for AML patients below			
5- Archival or fresh tumor tissue available for biomarker evaluation unless discussed with Medical Monitor			
6- For women of childbearing potential or men, agreement to use one highly effective form of non-hormonal contraception or one highly effective form and one effective form of non-hormonal contraception through the course of study treatment and for 3 months after the last dose of IGM-8444 single agent treatment, for 6 months after 5-fluorouracil-based chemotherapy treatment, 30 days after venetoclax treatment, 3 months after birinapant treatment, 6 months after docetaxel treatment, 6 months after gemcitabine treatment, 6 months after azacitidine treatment, 6 months after bevacizumab treatment, and 6 months after the last dose of irinotecan treatment. o A woman is considered not to be of childbearing potential if she is postmenopausal, defined by amenorrhea for ≥ 12 months and age ≥ 45 years, and FSH and estradiol are within postmenopausal range, or age ≥ 60, or has undergone hysterectomy and/or bilateral oophorectomy o Highly effective forms of contraception are defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly o Effective forms of contraception are defined as acceptable birth control methods that result in a failure rate of more than 1% per year when used consistently and correctly			
7- For women of childbearing potential, a negative serum pregnancy test within 7 days prior to commencement of dosing; women who are considered not to be of childbearing potential are not required to have a pregnancy test.			
8- Male subjects must agree to abstain from sperm donation for 3 months after the last dose of IGM-8444, for 6 months after 5-fluorouracil-based chemotherapy treatment, 30 days after			

venetoclax treatment, 3 months after birinapant treatment, 6 months after docetaxel treatment, 6 months after gemcitabine treatment, 6 months after azacitidine treatment, 6 months after bevacizumab treatment, and 6 months after the last dose of irinotecan treatment.			
Subjects enrolled in the CRC (or FOLFIRI-eligible) containing combination cohorts must also meet the following criteria for study entry: a. Histologic documentation of incurable, locally advanced or metastatic colon or rectal adenocarcinoma or carcinoma with the noted exception for dose escalation below b. Subjects who are either refractory to or intolerant of existing standard therapy or for whom no effective further standard of care therapy option exists c. **For Phase 1b CRC cohort:** Must be FOLFIRI-naïve and must have received only 1 prior therapeutic regimen ("therapeutic" is defined as any cytotoxic, biologic, or targeted therapy [approved or investigational] with intent to treat the cancer) administered for the treatment of cancer in the advanced/metastatic setting. d. INR ≤ 1.5 x ULN unless subject is receiving anticoagulant therapy and PT or PTT is within therapeutic range of intended use of anticoagulants and no clinically significant bleeding event within 6 months. e. Adequate organ function as evidenced by (hematologic parameters must be assessed at least 14 days from the last growth factor support or prior transfusion, if any): o ANC ≥ 1000/µL o Total hemoglobin ≥ 9 g/dL o Platelet count ≥ 100,000/µL o Serum creatinine ≤ 1.5 x ULN, or estimated creatinine clearance ≥ 50 mL/min or estimate of glomerular filtration rate ≥ 50 mL/min/1.73 m2 (Cockcroft-Gault or other institutional methods) o Serum AST and serum ALT ≤ 2 x ULN ▪ AST and ALT ≤ 3 x ULN is allowed if liver function abnormalities are due to underlying malignancy. o Total serum bilirubin ≤ 1.5 x ULN regardless of liver involvement secondary to tumor. ▪ Inclusion of subjects with increased serum indirect bilirubin (≤ 3 x ULN) due to Gilbert's syndrome is permitted. o Alkaline phosphatase ≤ 2.5 x the ULN o Albumin ≥ 3.0 g/dL			

o No clinically significant pleural or peritoneal effusion requiring drainage **f. <u>For dose-escalation cohorts only:</u>** o Subjects with incurable, locally advanced or metastatic colon or rectal adenocarcinoma or carcinoma for whom FOLFIRI is considered an appropriate therapy. ▪ Other incurable, locally advanced, or metastatic tumor types, investigators deem appropriate for FOLFIRI therapy may be enrolled after consultation with Medical Monitor. **g. <u>For dose expansion cohorts only:</u>** o Subjects with incurable, locally advanced or metastatic colon or rectal adenocarcinoma or carcinoma for whom FOLFIRI ± bevacizumab (and approve biosimilars) is considered an appropriate therapy. o At least one target lesion that can be accurately measured per RECIST v.1.1.			

<u>LES CRITERES D'EXCLUSIONS :</u> Les patient(e)s répondant à un de l'ensemble des critères suivants seront non-éligibles pour participer à l'étude :

	<u>OUI</u>	**<u>NON</u>**	**<u>NA</u>**
1. Pregnancy or breastfeeding			
2. Prior DR5 agonist therapy			
3. Concomitant use of agents well known to cause liver toxicity o Combination partners proposed in protocol and essential supportive medications used for ensuring patient safety during study treatment are permitted			
4. Current treatment with medications that are well known to prolong the QT interval			

o Subjects deemed to be clinically stable per the judgement of the investigator based on length of time on medications and baseline QTcF results being within normal limits are eligible.			
5. History of severe allergic or anaphylactic reactions to antibody therapy (or recombinant antibody-related fusion proteins)			
6. Prior use of any chemotherapeutic agent or small molecule inhibitors (SMI) within 2 weeks or 5 half-lives, whichever is shorter, prior to first dose of study treatment			
7. Treatment with a monoclonal antibody, or any other anticancer agent (including biologic, experimental, or hormonal therapy) investigational or otherwise, that is not chemotherapy or a SMI, within 4 weeks or five half-lives of the drug, whichever is shorter, prior to first dose of study treatment, with the following exceptions: o Hormonal therapy with gonadotropin-releasing hormone (GnRH) agonists or antagonists for prostate cancer o Hormone-replacement therapy or oral contraceptives			
8. Palliative radiation to bone metastases within 2 weeks prior to Day 1.			
9. Major surgical procedure within 4 weeks prior to Day 1			
10. Known active or uncontrolled bacterial, viral (including COVID-19), fungal, mycobacterial, parasitic, or other infection (including HIV and atypical mycobacterial disease but excluding fungal infections of the nail beds) at study enrollment or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1 o Patients with AML who have infections controlled with IV or oral antibiotics may be eligible to start treatment after discussion with Medical Monitor			
11. Subjects with active Hepatitis B virus (HBV) infection, defined as having a positive hepatitis B surface antigen (HBsAg) test at screening o Subjects with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible. o HBV DNA should be obtained in these subjects prior to study treatment administration.			

12. Subjects with active Hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV RNA testing at screening o Subjects who are positive for HCV antibody are eligible only if PCR is negative for HCV RNA.			
13. Evidence of significant uncontrolled concomitant diseases, such as cardiovascular disease (including stroke, New York Heart Association Class III or IV cardiac disease or myocardial infarction within 6 months prior to screening, unstable arrhythmias, and unstable angina); pulmonary, nervous system, renal, hepatic, endocrine, or gastrointestinal disorders; autoimmune disease, or a serious non-healing wound or fracture.			
14. History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree atrioventricular heart block, or evidence of prior myocardial infarction within previous 6 months			
15. History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, left ventricular hypertrophy), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome.			
16. Diagnosis of any secondary malignancy within 3 years prior to enrollment, except for those patients treated with curative intent and no evidence of active disease.			
17. Untreated or active central nervous system (CNS) metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control). Subjects with a history of treated CNS metastases are eligible, provided that they meet all of the following criteria: o Evaluable or measurable disease outside the CNS o Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study o The screening CNS radiographic study is 8 weeks since completion of radiotherapy and 4 weeks since the discontinuation of corticosteroids and anticonvulsants			
18. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving			

reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications.			
19. Current Grade > 1 toxicity (except alopecia and anorexia) from prior therapy or underlying disease. Subjects with current Grade 2 chronic toxicities that are well-controlled by medications may be enrolled after discussion with Medical Monitor.			
20. **<u>For bevacizumab-containing chemotherapy cohorts only:</u>** o Recent history of hemoptysis of ≥ 1/2 teaspoon of red blood o History of gastrointestinal (GI) perforations and fistulae o Patients with uncontrolled hypertension			
21. **<u>For randomized FOLFIRI Phase 1b combination dose cohort only:</u>** o Subjects who have previously received FOLFIRI treatment for advanced or metastatic disease o Subjects with a complete deficit of dipyrimidine dehydrogenase (DPD)			
22. Inability to comply with study and follow-up procedures			