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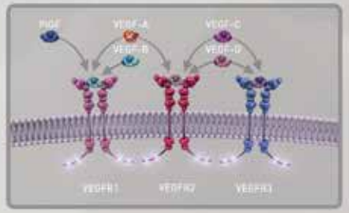
Ramucirumab
LY3009806
IMC-1121B

VEGF RECEPTOR-2 ANTAGONIST



Adams RH and Alitalo K[1]; Hicklin DJ and Ellis LM[2]

Target

Angiogenesis is a tightly regulated, multiple-step process, which results in the formation of new blood vessels from preexisting vasculature and is an important component in the development and progression of malignant disease. Signaling by vascular endothelial growth factor (VEGF) receptor-2 in endothelial cells plays a role in inducing normal and pathologic angiogenesis and is activated by binding of ligands VEGF-A, VEGF-C, and VEGF-D.[1-3]

Molecule

Ramucirumab (LY3009806, IMC-1121B) is a human IgG1 monoclonal antibody receptor antagonist that has been shown in vitro to bind to and block the activation of VEGF receptor-2 by blocking the binding of VEGF receptor ligands VEGF-A, VEGF-C, and VEGF-D.[4,5]

Clinical Development

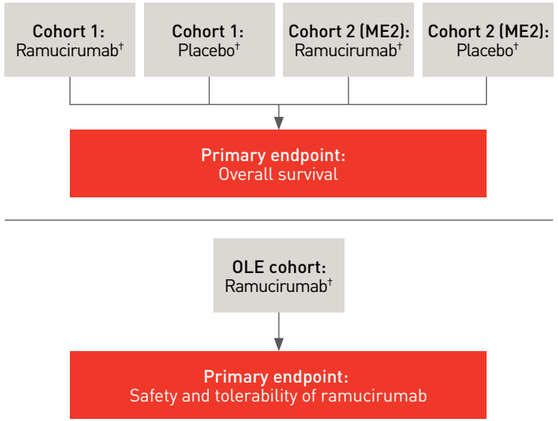
Ramucirumab is being investigated in clinical trials in patients with gastric cancer, hepatocellular carcinoma, non-small cell lung cancer, pediatric cancer, sarcoma, or other advanced solid tumors, and in a clinical trial studying experimental dosing in healthy participants.

References: 1. Adams RH, Alitalo K. *Nat Rev Mol Cell Biol.* 2007;8(6):464-478. **2.** Hicklin DJ, Ellis LM. *J Clin Oncol.* 2005;23(5):1011-1027. **3.** Olsson AK, et al. *Nat Rev Mol Cell Biol.* 2006;7(5):359-371. **4.** Lu D, et al. *J Biol Chem.* 2003;278(44):43496-43507. **5.** Zhu Z, et al. *Leukemia.* 2003;17(3):604-611.

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

REACH-2

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ramucirumab and Best Supportive Care (BSC) Versus Placebo and BSC as Second-line Treatment in Patients With Hepatocellular Carcinoma and Elevated Baseline Alpha-Fetoprotein (AFP) Following First-line Therapy With Sorafenib*



Participants may continue treatment until discontinuation criteria are met.

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

* This clinical trial is being conducted globally. ME2 cohort is being conducted in China only. REACH-2 eligibility criteria, including baseline serum AFP criterion, are based on the efficacy and safety results of REACH.

† Ramucirumab or placebo equivalent is administered 8 mg/kg intravenously on day 1 of a 14-day cycle.

Key Inclusion Criteria

- Hepatocellular carcinoma (HCC)
- Barcelona Clinic Liver Cancer stage C or B that is refractory or not amenable to locoregional therapy
- At least one target lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Child-Pugh class A
- Baseline serum AFP ≥400 ng/mL
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Received prior sorafenib as the only systemic therapeutic intervention and experienced radiographically confirmed disease progression during or after discontinuation or discontinued sorafenib because of intolerance (main and maximum extended enrollment [ME2] cohorts only)
- Received ≤2 prior systemic therapy regimens, excluding prior sorafenib or chemotherapy for the treatment of HCC (open-label expansion [OLE] cohort only)
- Adequate hematologic and biochemical parameters

Key Exclusion Criteria

- Uncontrolled hypertension
- Esophageal or gastric varices requiring treatment
- Ongoing or recent hepatorenal syndrome
- Liver transplant (main and ME2 cohorts only; participants with prior liver transplant may be eligible for OLE cohort)
- Major surgery within 28 days
- Arterial thrombotic event within 6 months
- Received prior therapeutic anticoagulation or chronic antiplatelet agents, including nonsteroidal anti-inflammatory drugs
- History of or current hepatic encephalopathy (any grade) or ascites grade ≥2

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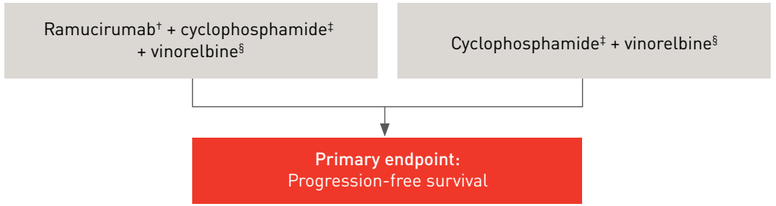
Please visit **www.clinicaltrials.gov** for more information on this clinical trial [NCT02435433].

CAMPFIRE

A Randomized, Open-Label Phase 1/2 Study Evaluating Ramucirumab in Pediatric Patients and Young Adults With Relapsed, Recurrent, or Refractory Desmoplastic Small Round Cell Tumor*



The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

* This clinical trial is being conducted globally.
† Ramucirumab is administered intravenously (IV).
‡ Cyclophosphamide is administered PO.
§ Vinorelbine is administered IV.
|| Additional criteria apply.

Key Inclusion Criteria

- If in the US, aged 12 months to 29 years. If in the EU, aged 36 months to 29 years and >11 kg at study entry
- Relapsed, recurrent, or refractory desmoplastic small round cell tumors
- Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Received at least one prior line of systemic treatment (including neoadjuvant/adjuvant chemotherapy), including approved therapies for which the patient is eligible
- Discontinued all previous treatments for cancer or investigational agents ≥7 days prior to study entry and recovered from select acute effects to grade ≤2 for alopecia and decreased tendon reflex, and to grade ≤1 for all other effects at the time of enrollment||
- Adequate organ function for at least 7 days prior to first dose of study drug||
- Female participants of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to randomization. Male and female participants must agree to use highly effective contraception for the duration of the study and up to 3 months following the last dose of ramucirumab and vinorelbine, and 12 months following the last dose of cyclophosphamide

Key Exclusion Criteria

- Eligible for surgical resection at time of enrollment
- Active infections requiring therapy, including HIV or hepatitis A, B, or C
- Prior allogeneic bone marrow or solid organ transplant
- Major surgical, laparoscopic, or significant traumatic injury within 28 days prior to enrollment. Surgical or other wounds must be adequately healed prior to enrollment
- Evidence of active bleeding, a bleeding diathesis or vasculitis, or a history of significant (grade ≥3) bleeding event, hemoptysis or pulmonary hemorrhage, a DVT or PE requiring medical intervention, or esophageal varices within 3 months prior to enrollment
- History of central nervous system arterial/venous thromboembolic events, including transient ischemic attack or cerebrovascular accident within 6 months prior to study enrollment, myocardial infarction or unstable angina within the prior 6 months, New York Heart Association (NYHA) grade ≥2 congestive heart failure, serious and inadequately controlled cardiac arrhythmia, significant vascular disease, or clinically significant peripheral vascular disease
- History of fistula, gastrointestinal ulcer or perforation, or intra-abdominal abscess within 3 months of study enrollment
- History of hypertensive crisis or hypertensive encephalopathy within 6 months of study enrollment
- Known hypersensitivity to ramucirumab, cyclophosphamide, vinorelbine, or any of the excipients of the medicinal product
- Severe liver cirrhosis (Child-Pugh class B or worse), cirrhosis with a history of hepatic encephalopathy, clinically meaningful ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis, or history of hepatorenal syndrome
- Bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection, Crohn's disease, ulcerative colitis, or chronic diarrhea
- Urinary outflow obstruction, grade 2 hematuria, or noninfectious cystitis at the time of screening
- Severe and/or uncontrolled concurrent medical disease or psychiatric illness/social situation that, in the opinion of the investigator, could cause unacceptable safety risks or compromise protocol compliance
- Prior treatment with/progression on combination cyclophosphamide and vinorelbine regimen; prior treatment with ramucirumab

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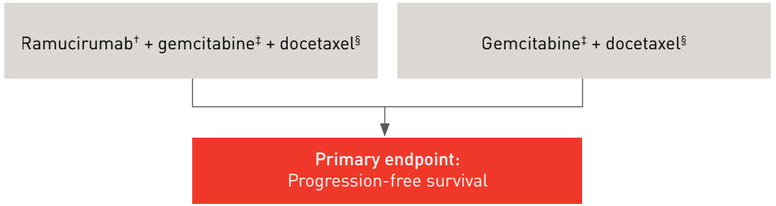
Please visit **www.clinicaltrials.gov** for more information on this clinical trial [NCT04145349].

CAMPFIRE

A Randomized, Open-Label Phase 1/2 Study Evaluating Ramucirumab in Pediatric Patients and Young Adults With Relapsed, Recurrent, or Refractory Synovial Sarcoma*



The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

* This clinical trial is being conducted globally.
† Ramucirumab is administered intravenously (IV).
‡ Gemcitabine is administered IV.
§ Docetaxel is administered IV.
|| Additional criteria apply.

Key Inclusion Criteria

- If in the US, aged 12 months to 29 years. If in the EU, aged 36 months to 29 years and >11 kg at study entry
- Relapsed, recurrent, or refractory synovial sarcoma
- Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Received at least one prior line of systemic treatment (including neoadjuvant/adjuvant chemotherapy) that contains ifosfamide and/or doxorubicin, or any approved therapies for which they are eligible
- Discontinued all previous treatments for cancer or investigational agents ≥7 days prior to study entry and recovered from the acute effects to grade ≤2 for alopecia and decreased tendon reflex and to grade ≤1 for all other effects at the time of enrollment||
- Adequate hematologic and organ function for at least 7 days prior to first dose of study drug||
- Female participants of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to randomization. Male and female participants must agree to use highly effective contraception for the duration of the study and up to 3 months following the last dose of ramucirumab and 6 months following the last dose of docetaxel and gemcitabine

Key Exclusion Criteria

- Eligible for surgical resection at time of enrollment
- Active infections requiring therapy, including HIV or hepatitis A, B, or C
- Prior allogeneic bone marrow or solid organ transplant
- Major surgical, laparoscopic, or significant traumatic injury within 28 days prior to enrollment. Surgical or other wounds must be adequately healed prior to enrollment
- Evidence of active bleeding, a bleeding diathesis or vasculitis, or a history of significant (grade ≥3) bleeding event, hemoptysis or pulmonary hemorrhage, a DVT or PE requiring medical intervention, or esophageal varices within 3 months prior to enrollment
- History of central nervous system arterial/venous thromboembolic events, including transient ischemic attack or cerebrovascular accident within 6 months prior to study enrollment, myocardial infarction or unstable angina within the prior 6 months, New York Heart Association (NYHA) grade ≥2 congestive heart failure, serious and inadequately controlled cardiac arrhythmia, significant vascular disease, or clinically significant peripheral vascular disease
- History of fistula, gastrointestinal ulcer or perforation, or intra-abdominal abscess within 3 months of study enrollment
- History of hypertensive crisis or hypertensive encephalopathy within 6 months of study enrollment
- Nonhealing wound, unhealed or incompletely healed fracture, or a compound bone fracture at the time of enrollment
- Known hypersensitivity to ramucirumab, gemcitabine, docetaxel, or agents formulated with polysorbate 80
- Severe liver cirrhosis (Child-Pugh class B or worse), cirrhosis with a history of hepatic encephalopathy, clinically meaningful ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis, or history of hepatorenal syndrome
- Bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection, Crohn's disease, ulcerative colitis, or chronic diarrhea
- Urinary outflow obstruction, grade 2 hematuria, or noninfectious cystitis at the time of screening
- Severe and/or uncontrolled concurrent medical disease or psychiatric illness/social situation that, in the opinion of the investigator, could cause unacceptable safety risks or compromise protocol compliance
- Prior treatment with/progression on combination gemcitabine and docetaxel; prior treatment with ramucirumab

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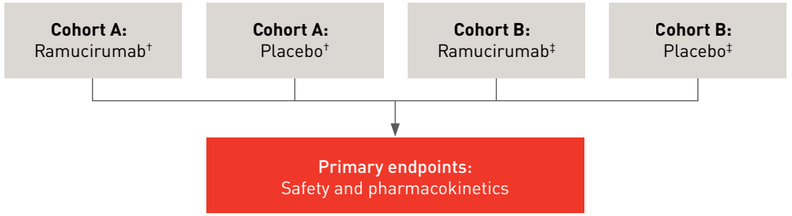
Please visit **www.clinicaltrials.gov** for more information on this clinical trial [NCT04145700].

NCT04495478

A Single-Dose Study in Healthy Participants to Characterize Ramucirumab Pharmacokinetics and Investigate Injection-Site Reactions Following an Intravenous Infusion or Subcutaneous Administration of Ramucirumab*



The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

* This clinical trial is being conducted in the United States.
† Ramucirumab or placebo equivalent is administered intravenously.
‡ Ramucirumab or placebo equivalent is administered subcutaneously.

Key Inclusion Criteria

- Overtly healthy male or a female (not pregnant and agrees to take birth control measures until study completion)
- Body weight ≥70 kg and body mass index of 18-32 kg/m^2
- Normal blood pressure, pulse rate, electrocardiogram (ECG), and blood and urine laboratory test results

Key Exclusion Criteria

- Currently participating in or completed a clinical trial within the last 30 days or any other type of medical research judged to be incompatiblewith this study
- Previously participated or withdrawn from this study
- Current or previous health problems, laboratory test results, or ECG readings that, in the opinion of the doctor, could make it unsafe to participate, or could interfere with understanding the results of the study
- Blood loss of more than 500 mL within the previous 30 days of study screening

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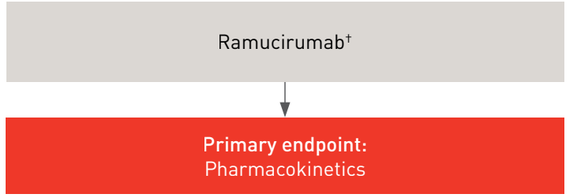
Please visit **www.clinicaltrials.gov** for more information on this clinical trial [NCT04495478].

NCT04557384

A Phase 1, Nonrandomized, Open-Label Investigation of Subcutaneous Ramucirumab Administration in Participants With Advanced Solid Tumors*



The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

* This clinical trial is being conducted globally.
† Ramucirumab is administered subcutaneously.

Key Inclusion Criteria

- Evaluable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Appropriate candidate for experimental therapy and exhausted all anticancer treatments with proven clinical benefit; have hepatocellular carcinoma or gastric cancer and have received prior treatment, and intravenous (IV) ramucirumab monotherapy is clinically acceptable treatment after progression; or have a diagnosis for which IV ramucirumab in combination with additional anticancer therapy is clinically acceptable treatment (cohorts B and C only)
- Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1
- Discontinued all previous treatments for cancer with adequate wash-out period and recovered from the acute effects of therapy
- Adequate hematologic, hepatic, and renal functions and electrolytes
- Males and females of child-bearing potential must agree to use highly effective contraceptive methods during study treatment and for 5 months following the last dose of study drug

Key Exclusion Criteria

- Uncontrolled hypertension defined as systolic blood pressure (BP) >150 mmHg or diastolic BP >90 mmHg despite standard medical management
- Significant bleeding disorders or experienced grade 3/4 gastrointestinal (GI) bleeding within 3 months prior to enrollment
- Hepatic impairment (such as severe liver cirrhosis Child-Pugh B [or worse], cirrhosis with a history of hepatic encephalopathy, clinically meaningful ascites requiring ongoing treatment with diuretics and/or paracentesis, or history of hepatorenal syndrome)
- Experienced any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, ≤6 months prior to randomization
- Clinically relevant congestive heart failure (New York Heart Association [NYHA] grade ≥2) or symptomatic or poorly controlled cardiac arrhythmia
- Symptomatic central nervous system metastases
- History of GI perforation and/or fistula within 6 months prior to enrollment
- Active, uncontrolled systemic bacterial, viral, or fungal infection, or serious ongoing uncontrolled intercurrent illness
- Serious or nonhealing wound, ulcer, or bone fracture within 4 weeks prior to enrollment
- Prior IV ramucirumab treatment

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Please visit **www.clinicaltrials.gov** for more information on this clinical trial [NCT04557384].

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

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Active Trials Currently Not Enrolling

[NCT02539225] Gastrointestinal Cancer
A Study of Ramucirumab in Participants With Gastric or Gastroesophageal Junction Adenocarcinoma

[NCT02898077] Gastrointestinal Cancer
A Study of Paclitaxel With or Without Ramucirumab (LY3009806) in Participants With Gastric or Gastroesophageal Cancer

[NCT02411448] Lung Cancer
RELAY: A Study of Ramucirumab (LY3009806) in Combination With Erlotinib in Participants With EGFR Mutation-Positive Metastatic NSCLC

[NCT02789345] Lung Cancer
A Study of Ramucirumab (LY3009806) or Necitumumab (LY3012211) Plus Osimertinib in Participants With Lung Cancer

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Pipeline information is current through April 27, 2021.

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