VEGF Receptor-2 Antagonist
Ramucirumab, LY3009806, IMC-1121B

Drug Discovery Platform: Cancer Angiogenesis and Tumor Microenvironment

Derived from Adams RH and Alitalo K; Hicklin DJ and Ellis LM.
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.

RAINFALL: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Capecitabine and Cisplatin With or Without Ramucirumab as First-line Therapy in Patients With Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma*

Key Inclusion Criteria
- Metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma
- No prior first-line systemic therapy
- Measurable or nonmeasurable but evaluable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- HER2-negative, metastatic gastric or GEJ adenocarcinoma

Randomization 1:1
- Placebo IV on days 1 and 8† + 80 mg/m² cisplatin IV on day 1‡ + 1000 mg/m² capecitabine PO BID on days 1-14†
- 8 mg/kg ramucirumab IV on days 1 and 8† + 80 mg/m² cisplatin IV on day 1‡ + 1000 mg/m² capecitabine PO BID on days 1-14†

Primary endpoint: Progression-free survival

† Capecitabine and ramucirumab are administered over a 21-day cycle.
‡ Cisplatin is administered over a 21-day cycle for up to six cycles.

Key Exclusion Criteria
- Adenocarcinoma of the esophagus
- HER2-positive status
- Uncontrolled hypertension prior to initiating study treatment
- Documented brain metastases, leptomeningeal disease, or uncontrolled spinal cord compression
- Significant bleeding disorders or vasculitis, or a significant bleeding episode from the gastrointestinal tract within 12 weeks prior to randomization
- Experienced any arterial thromboembolic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to randomization

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02314117].

* This clinical trial is being conducted globally.

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**Key Exclusion Criteria**
- Known T790M EGFR mutation
- Known leptomeningeal carcinomatosis, uncontrolled/unstable spinal cord compression, or brain metastases
- Prior treatment with an EGFR-tyrosine kinase inhibitor or other chemotherapy
- Serious illness or medical condition
- History of gross hemoptysis
- Significant bleeding disorders
- Radiologically documented evidence of major blood vessel invasion or encasement by cancer
- Radiographic evidence of intratumor cavitation
- History of any arterial thrombotic event within 6 months prior to enrollment
- Known significant ophthalmologic abnormalities of the surface of the eye

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02411448].

*This clinical trial is being conducted globally.

**Part A:** 10 mg/kg ramucirumab IV Q2W + 150 mg/day erlotinib PO once daily

**Part B:** Randomization 1:1

**Phase 1b†**

Phase 3

**Primary endpoint:** Safety and tolerability

**Part A:**
- 10 mg/kg ramucirumab IV Q2W + 150 mg/day erlotinib PO once daily

**Part B:**
- Placebo IV Q2W + 150 mg/day erlotinib PO once daily

**Primary endpoint:** Progression-free survival

Participants continue study treatment until development of progressive disease or unacceptable toxicity.

† The phase 1b portion of this study is complete.

**Key Inclusion Criteria**
- Stage IV non-small cell lung cancer (NSCLC)
- Eligible for first-line treatment with erlotinib
- Documented evidence of a tumor harboring an activating epidermal growth factor receptor (EGFR) mutation (defined as exon 19 deletion or exon 21 [L858R] substitution)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- At least one measurable lesion
- Mandatory for part B: Provision of adequate archived stage IV NSCLC tissue sample

**RELAY:** A Multicenter, Randomized, Double-Blind Study of Erlotinib in Combination With Ramucirumab or Placebo in Previously Untreated Patients With EGFR Mutation-Positive Metastatic Non-small Cell Lung Cancer*

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.
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.

**Key Inclusion Criteria**
- Locally advanced or unresectable or metastatic urothelial (transitional cell) carcinoma of the bladder, urethra, ureter, or renal pelvis
- Disease progression during or within 14 months of completing the first-line platinum regimen
- Participants who received treatment with one immune checkpoint inhibitor (eg, PD-1, PD-L1, or CTLA4) may have a longer interval since prior platinum-containing therapy (≤24 months)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Willing to provide blood, urine, and tissue samples for research purposes
- Adequate organ function

**Key Exclusion Criteria**
- Received more than one prior systemic chemotherapy regimen for metastatic disease
- Received more than one prior antiangiogenic agent
- Received radiation therapy within 4 weeks prior to randomization or has not recovered from toxic effects of the treatment that was given >4 weeks prior to randomization
- History of uncontrolled hereditary or acquired bleeding or thrombotic disorders
- Grade ≥3 bleeding event within 3 months prior to randomization
- Uncontrolled intercurrent illness, including, but not limited to, symptomatic anemia, uncontrolled hypertension, symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia, psychiatric illness, or any other serious uncontrolled medical disorders in the opinion of the investigator
- Any arterial, venous thrombotic, or thromboembolic events, including, but not limited to, myocardial infarction, transient ischemic attack, or cerebrovascular accident, within 6 months prior to randomization
- Known untreated brain metastases, uncontrolled spinal cord compression, or leptomeningeal disease

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02426125].

*This clinical trial is being conducted globally.
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*

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
- Adequate hematologic and biochemical parameters

Key Exclusion Criteria
- Uncontrolled hypertension
- Esophageal or gastric varices requiring treatment
- Received prior anti-VEGF pathway therapy other than sorafenib
- Hepatic locoregional treatment after sorafenib
- Ongoing or recent hepatorenal syndrome
- Prior liver transplant
- 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

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

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

Key Inclusion Criteria
- Gastric or gastroesophageal junction (GEJ; Siewert types I-III) adenocarcinoma
- Documented disease progression during or within 6 months after the last dose of first-line chemotherapy for metastatic disease or during or within 6 months after the last dose of neoadjuvant or adjuvant therapy
- Prior chemotherapy regimens must include a platinum and/or a fluoropyrimidine component and must not include an antiangiogenic agent (either approved or experimental treatment). Exposure to antineoplastic therapy in addition to platinums and/or fluoropyrimidines is acceptable if the agents were used in the first-line metastatic or neoadjuvant/adjuvant setting
- Progressed after discontinuing one or more components of first-line chemotherapy because of toxicity but continued to receive the other component(s)
- Metastatic disease or locally advanced disease that is measurable or nonmeasurable but evaluable by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Participants are eligible if they are considered not appropriate, for whatever reason, for treatment with ramucirumab in combination with paclitaxel
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function

Key Exclusion Criteria
- Squamous cell or undifferentiated gastric cancer
- Chronic therapy with nonsteroidal anti-inflammatory agents (e.g., indomethacin, ibuprofen, naproxen, or similar agents) or other antiplatelet agents (e.g., clopidogrel, ticlopidine, dipyridamole, or anagrelide) within 7 days prior to randomization
- Radiotherapy within 14 days prior to randomization
- Received more than one line of prior therapy in this setting
- Prior systemic chemotherapy with a cumulative dose of >900 mg/m² epirubicin or >400 mg/m² doxorubicin
- Prior treatment with agents targeting the VEGF or VEGF receptor-2 signaling pathway, including previous exposure to ramucirumab
- Documented brain metastases, leptomeningeal disease, or uncontrolled spinal cord compression
- Significant bleeding disorder or vasculitis, or had a grade ≥3 bleeding episode within 12 weeks prior to randomization
- Any arterial thromboembolic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to randomization

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02443883].

*A clinical trial is being conducted globally.
A Randomized Phase 2 Trial Evaluating Alternative Ramucirumab Doses in Combination With Paclitaxel in Second-line Metastatic or Locally Advanced, Unresectable Gastric or Gastroesophageal Junction Adenocarcinoma*

Key Inclusion Criteria

- Gastric or gastroesophageal junction (GEJ) adenocarcinoma
- Disease progression during or within 4 months after the last dose of first-line chemotherapy or during or within 6 months after the last dose of neoadjuvant or adjuvant therapy
- Prior combination chemotherapy, which must include a platinum and/or a fluoropyrimidine and must not include a taxane or an antiangiogenic agent
- Evaluable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function, including total bilirubin ≤1.5× the upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3× ULN. If the liver has tumor involvement, AST and ALT <5× ULN
- Minimum estimated life expectancy of 12 weeks
- Resolution of all clinically significant toxic effects from previous therapy to grade 1 or less by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
- Males must be sterile or agree to use a reliable method of birth control. Females must be surgically sterile, postmenopausal, or agree to use a highly effective method of birth control. Females with childbearing potential must have a negative serum pregnancy test

Key Exclusion Criteria

- Therapy with nonsteroidal anti-inflammatory agents or other antiplatelet agents. Aspirin use at doses up to 325 mg/day is permitted
- Radiotherapy within 14 days prior to randomization
- Previous chemotherapy with a cumulative dose of >900 mg/m² epirubicin or >400 mg/m² doxorubicin
- Documented brain metastases or leptomeningeal disease
- Significant bleeding disorder or vasculitis
- Any arterial thromboembolic event within 6 months
- Symptomatic congestive heart failure orsymptomatic cardiac arrhythmia
- Uncontrolled hypertension, despite antihypertensive intervention
- Major surgery within 28 days
- History of gastrointestinal perforation or fistula within 6 months
- History of inflammatory bowel disease or Crohn’s disease requiring medical intervention within 12 months
- Bowel obstruction or history of chronic diarrhea that is considered clinically significant
- Child-Pugh class B or C
- Serious illness or medical condition, including HIV infection
- Concurrent active malignancy other than nonmelanomatous skin cancer, in situ carcinoma of the cervix, or other noninvasive carcinoma or in situ neoplasm
- Serious nonhealing wound, peptic ulcer, or bone fracture
- Experienced any grade 3 or 4 venous thromboembolic event that is not adequately treated

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02514551].

* This clinical trial is being conducted globally.

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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.

A Randomized Phase 2 Trial Evaluating Alternative Ramucirumab Doses in Combination With Paclitaxel in Second-line Metastatic or Locally Advanced, Unresectable Gastric or Gastroesophageal Junction Adenocarcinoma*
A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of S-1 and Oxaliplatin With or Without Ramucirumab as First-line Therapy Followed by Paclitaxel With Ramucirumab as Second-line Therapy in Patients With Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma*

Key Inclusion Criteria
• Metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma. Participants with esophageal cancer are not eligible
• No prior first-line systemic therapy for gastric or GEJ adenocarcinoma (prior adjuvant or neoadjuvant therapy is permitted)
• Participants whose disease has progressed after ≥6 weeks following the last dose of systemic treatment in the adjuvant/ neoadjuvant setting are eligible
• Measurable or nonmeasurable but evaluable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
• Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
• Adequate organ function
• Life expectancy of ≥12 weeks
• Males and females with reproductive potential must agree to use medically approved contraceptive precautions during the study period and at least 6 months after the last dose of study treatment or longer if required by local regulations
• Willing to provide a blood sample for research purposes

Key Exclusion Criteria
• HER2-positive status. Participants with a negative test or having an indeterminate result due to any reason are eligible, provided these participants are not eligible for treatment directed against tumors that overexpress HER2
• Radiation therapy within 14 days prior to randomization. Any lesion requiring palliative radiation or that has been irradiated previously cannot be considered for response assessment
• Documented brain metastases, leptomeningeal disease, or uncontrolled spinal cord compression
• Major surgery within 28 days prior to randomization
• Currently enrolled in, or discontinued study drug within the last 28 days from, a clinical trial involving an investigational product or nonapproved use of a drug or device (other than the study drug used in this trial), or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study. Those participating in surveys or observational studies are eligible for this study
• Pregnant or breast-feeding. Females of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to first dose of study treatment
• Any prior malignancies
• Any condition that does not permit compliance with the study and follow-up procedures or suggests that the participant is, in the investigator’s opinion, not an appropriate candidate for the study

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02539225].

*This clinical trial is being conducted outside the United States.

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.
A Single-Arm, Phase 2 Study of Ramucirumab in Combination With Weekly Docetaxel in Patients With Stage IV Non-small Cell Lung Cancer Following Disease Progression After Prior Platinum-Based Chemotherapy*

Key Inclusion Criteria

- Stage IV non-small cell lung cancer (NSCLC) with disease progression after prior platinum-based chemotherapy regimen for locally advanced or metastatic disease
- Prior immunotherapy for NSCLC is allowed
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Measurable disease at the time of first dose of study treatment, documented by computed tomography (CT) scan or magnetic resonance imaging (MRI)
- Resolution of all clinically significant toxic effects of prior locoregional cancer therapy, surgery, or other anticancer therapy to grade ≤ 1 by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0
- Adequate organ function
- Urinary protein is < 2+ on dipstick or routine urinalysis
- Males must be sterile or agree to use a highly effective method of contraception. Females must be surgically sterile, postmenopausal, or agree to use a highly effective method of contraception. Females with childbearing potential must have a negative serum or urine pregnancy test within 72 hours of the first dose of study treatment

Key Exclusion Criteria

- Prior therapy with docetaxel or ramucirumab
- More than one prior chemotherapy regimen for locally advanced or metastatic NSCLC or any concurrent anticancer treatment
- Major surgery ≤ 28 days or subcutaneous venous access device placement ≤ 7 days prior to first dose of study treatment, or elective or planned major surgery during the course of the trial
- Bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection, Crohn’s disease, ulcerative colitis, or chronic diarrhea
- Peripheral neuropathy grade ≥ 2 (NCI-CTCAE v4.0)
- Symptomatic, active, or untreated central nervous system metastases
- Radiological documented evidence of major blood vessel invasion or encasement by cancer, or radiographic evidence of intratumor cavitation
- History of uncontrolled thrombotic disorder or arterial hypertension
- Chronic therapy with nonsteroidal anti-inflammatory drugs or other antiplatelet agents. Aspirin use at doses up to 325 mg/day is permitted
- History of gross hemoptysis (defined as bright red blood of ≥ ½ tsp) within 2 months of study entry
- Serious cardiac condition, eg, congestive heart failure New York Heart Association class 2-4, symptomatic or poorly controlled cardiac arrhythmia, or arterial thrombotic event within 6 months prior to first dose of study treatment
- Serious or nonhealing wound, ulcer, or bone fracture ≤ 28 days prior to first dose of study treatment
- Significant bleeding disorders, vasculitis, or a significant bleeding episode ≥ 3 months prior to first dose of study treatment
- History of GI perforation and/or fistulae within 6 months prior to first dose of study treatment

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02831491].

* This clinical trial is being conducted globally.

VEGF Receptor-2 Antagonist Ramucirumab, LY3009806, IMC-1121B

Stage IV NSCLC following disease progression after prior platinum-based chemotherapy

Ramucirumab IV Q3W† + docetaxel (IV TIW‡)

Primary endpoint: Safety and tolerability of ramucirumab in combination with docetaxel

† Ramucirumab is administered intravenously (IV) on day 1 of a 28-day cycle.
‡ Docetaxel is administered IV on days 1, 8, and 15 of a 28-day cycle.

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.
An Open-Label, Multicenter, Phase 1 Study of Ramucirumab Plus Pembrolizumab in Patients With Locally Advanced and Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma, Non-small Cell Lung Cancer, or Transitional Cell Carcinoma of the Urothelium*

Key Inclusion Criteria
- Metastatic disease or locally advanced, unresectable disease
- Cohort A and B: Gastric or gastroesophageal junction (GEJ) adenocarcinoma with documented disease progression after one to two prior lines of systemic therapy (second or third line)
- Cohort A1: Biliary tract adenocarcinoma with documented disease progression after at least one to two prior lines of systemic therapy (second or third line)
- Cohort A2: Gastric or GEJ adenocarcinoma with no prior systemic therapy (first line)
- Cohort C: Non-squamous or squamous non-small cell lung cancer (NSCLC) with documented disease progression after one to three prior lines of systemic therapy (second line or later)
- Cohort D: Transitional cell carcinoma of the urothelium (bladder, urethra, or renal pelvis) with documented disease progression after one to three prior lines of systemic therapy (second line or later)
- Cohort E: Non-squamous or squamous NSCLC with no prior systemic therapy (first line)
- Cohort F: Nonsquamous or squamous NSCLC with documented disease progression after one to three prior lines of systemic therapy (second line or later)
- Adequate organ function
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Availability of tumor tissue for biomarker analysis from a newly obtained core or excisional biopsy or willing to undergo a tumor biopsy

Key Exclusion Criteria
- Known brain metastases
- Received more than three lines of prior systemic therapy for gastric or GEJ adenocarcinoma or more than four lines for NSCLC or urothelial cancer
- Active autoimmune disease
- Known HIV infection
- Active hepatitis B or C infection
- Received any previous systemic therapy targeting VEGF or VEGF receptor or PD-1, PD-L1, or PD-L2 signaling pathways
- Received a live vaccine within 30 days prior to enrollment
- Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to enrollment
- Elective or planned major surgery during the course of the trial or has undergone major surgery within 28 days prior to enrollment

Please visit www.clinicaltrials.gov for more information on this clinical trial (NCT02443324).

* This clinical trial is being conducted globally in partnership with Merck Sharp & Dohme Corp.

Phase 1a
- Standard dose of ramucirumab IV on days 1 and 8 + pembrolizumab IV on day 1 (gastric or GEJ adenocarcinoma)

Phase 1b
- Alternative dose of ramucirumab IV on day 1 + pembrolizumab IV on day 1 (NSCLC)

Primary endpoint: Establish safety and pharmacokinetic profile

Primary endpoint: Establish safety and pharmacokinetic profile

Tumor-specific expansion cohorts†
- Cohort A*: Standard dose of ramucirumab IV on days 1 and 8 + pembrolizumab IV on day 1 (gastric or GEJ adenocarcinoma)
- Cohort A1*: Standard dose of ramucirumab IV on days 1 and 8 + pembrolizumab IV on day 1 (biliary tract cancer)
- Cohort A2*: Standard dose of ramucirumab IV on days 1 and 8 + pembrolizumab IV on day 1 (gastric or GEJ adenocarcinoma)
- Cohort B*: Alternative dose of ramucirumab IV on day 1 + pembrolizumab IV on day 1 (NSCLC)
- Cohort C*: Alternative dose of ramucirumab IV on day 1 + pembrolizumab IV on day 1 (NSCLC)
- Cohort D*: Alternative dose of ramucirumab IV on day 1 + pembrolizumab IV on day 1 (urothelial cancer)
- Cohort E*: Alternative dose of ramucirumab IV on day 1 + pembrolizumab IV on day 1 (NSCLC)

† Ramucirumab and pembrolizumab are administered over a 21-day cycle.
‡ Study treatment is at least 24 weeks.

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.

Vegf Receptor-2 Antagonist Ramucirumab, L5293800, JMC-1211B
A Phase 1 Study of Ramucirumab, a Human Monoclonal Antibody Against the Vascular Endothelial Growth Factor-2 (VEGFR2) Receptor, in Children With Refractory Solid Tumors, Including CNS Tumors*

Key Inclusion Criteria
• Pediatric patients (12 months to 21 years) with recurrent or refractory central nervous system (CNS) and non-CNS tumors [except germ-cell tumors, which can be confirmed by appropriate serum tumor markers]
  - Part A: Recurrent or refractory non-CNS solid tumors
  - Part B: Recurrent or refractory CNS tumors
• No known curative therapeutic options available
• Measurable or evaluable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
• Performance status: Karnofsky ≥50% for participants >16 years and Lansky ≥50 for participants ≤16 years

Key Exclusion Criteria
• Active or recent history of serious bleeding events
• Active or recent history of gastrointestinal perforations, ulcers, fistulas, or abscesses
• Active or recent history of hypertensive crisis or hypertensive encephalopathy
• Active nonhealing wound or bone fracture
• History of solid organ transplant

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02564198].

* This clinical trial is being conducted in the United States.

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**Key Inclusion Criteria**
- Diagnosed with one of the following types of cancer:
  - Gastric/gastroesophageal junction (GEJ) adenocarcinoma: Measurable, metastatic disease or locally advanced, unresectable disease with documented disease progression after one to two prior lines of systemic therapy
  - Non-small cell lung cancer (NSCLC): Measurable, metastatic disease or locally advanced, unresectable disease with documented disease progression after one to three prior lines of systemic therapy
  - Hepatocellular carcinoma (HCC): Measurable, metastatic disease or locally advanced, unresectable disease with documented disease progression after discontinuation of sorafenib therapy, or intolerance to sorafenib therapy, and alpha-fetoprotein ≥1.5× upper limit of normal
- Availability of tumor tissue for biomarker analysis
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function

**Key Exclusion Criteria**
- Known brain metastases
- History of prior cancers not included in this study that either were not treated with curative intent or have been active within the past 5 years
- History of allogeneic organ transplant
- Active or prior documented autoimmune disease within the past 24 months
- Current HIV infection or AIDS-related illness, or a history of immunodeficiency
- Active hepatitis B or C infection, or coinfection with both hepatitis B and C virus
- For gastric/GEJ and NSCLC participants, chronic hepatitis B or C infection. For HCC participants, those with chronic hepatitis B virus (HBV) infection with a negative HBV DNA test and who are on antiviral therapy and those with chronic hepatitis C virus infection are eligible
- History of interstitial lung disease, idiopathic pulmonary fibrosis, pneumocystosis, noninfectious pneumonitis, or radiation-induced or drug-induced pneumonitis
- Prior systemic therapy targeting PD-1 or PD-L1/2 signaling pathways, and other immune checkpoint inhibitors
- Prior systemic therapy with ramucirumab

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02572687].

*This clinical trial is being conducted globally in partnership with AstraZeneca.

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An Open-Label, Multicenter, Phase 1 Study of Ramucirumab Plus MEDI4736 in Patients With Locally Advanced and Unresectable or Metastatic Gastrointestinal or Thoracic Malignancies*

**Phase 1a**
- **Ramucirumab + MEDI4736 IV Q3W (NSCLC)**
- **Ramucirumab + MEDI4736 IV Q2W (gastric/GEJ)**
- **Ramucirumab + MEDI4736 IV Q2W (HCC)**

**Primary endpoint:** Safety and tolerability

**Phase 1b**
- **Tumor-specific expansion cohorts**
  - Cohort A: Ramucirumab + MEDI4736 IV Q3W (NSCLC)
  - Cohort B: Ramucirumab + MEDI4736 IV Q2W (gastric/GEJ)
  - Cohort C: Ramucirumab + MEDI4736 IV Q2W (HCC)

**Primary endpoint:** Establish safety, pharmacokinetic profile, and preliminary efficacy

Participants may continue to receive study treatment until discontinuation criteria are met.

1 Ramucirumab and MEDI4736 are administered over a 21-day cycle.
2 Ramucirumab and MEDI4736 are administered over a 28-day cycle.
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.

**VEGF Receptor-2 Antagonist Ramucirumab, LY3009806, IMC-1121B**

An Open-Label, Phase 1a/1b Study of Ramucirumab in Combination With Other Targeted Agents in Advanced Cancers*

**Key Inclusion Criteria**

- **For arm 1:**
  - Advanced or metastatic colorectal cancer (mCRC)
  - At least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECEIST) version 1.1
  - Prior second-line treatment with oxaliplatin and/or irinotecan. If the patient has RAS wild-type CRC, he or she also must have received prior treatment with an epidermal growth factor receptor monoclonal antibody
  - **For arm 2:**
  - Mantle cell lymphoma (MCL) with measurable nodal disease
  - Relapsed after or refractory to first-line combination chemotherapy with or without stem cell transplant and at least one other locally available therapy
  - No prior systemic therapy with agents targeting PD-1, PD-L1, or PD-1/PD-L2 signaling pathways, or other immune checkpoint inhibitors (eg, anti-CD137 or anti-CTLA4 antibodies)
  - Adequate organ function
  - Candidate for experimental therapy after available standard therapies have failed to provide clinical benefit
  - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
  - Males and females with reproductive potential must agree to use medically approved contraceptive precautions during the study period and for at least 3 months after the last dose of study treatment

**Key Exclusion Criteria**

- Prior or concurrent malignancies, including hematologic cancer, primary brain tumor, sarcoma, and other solid tumors, unless in complete remission with no therapy for a minimum of 5 years
- Previously documented brain metastases, leptomeningeal disease, or uncontrolled spinal cord compression
- Active gastrointestinal (GI) disease characterized by inflammatory bowel disease, malabsorption syndrome, or frequent grade ≥2 diarrhea
- Peptic ulcer, bone fracture ≤28 days prior to enrollment, or placement of a subcutaneous venous access device ≤7 days prior to the first dose of study treatment unless the procedure is of low risk of bleeding in the judgment of the investigator
- Uncontrolled hypertension
- Any arterial, venothrombotic, or thromboembolic events, including, but not limited to, myocardial infarction, transient ischemic attack, or cerebrovascular accident, within 6 months prior to enrollment
- History of GI perforation and/or fistulae within 6 months prior to enrollment
- Grade ≥3 bleeding event within 3 months prior to enrollment
- Congestive heart failure or poorly controlled cardiac arrhythmia
- For arm 1: Serious illness or medical condition including, but not limited to, active or uncontrolled clinically serious infection or inadequate biliary drainage with evidence of unresolved biliary obstruction
- For arm 2: Serious illness or medical condition including, but not limited to, prior autologous stem cell transplant within 75 days prior to the initial dose of study drug, prior allogeneic stem cell transplant, or active or uncontrolled clinically serious infection including chronic viral hepatitis

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02745769].

*This clinical trial is being conducted globally.

**Phase 1a**

**Arm 1:** Standard dose of ramucirumab IV on days 1 and 15 + merestinib PO QD (mCRC)

**Arm 2:** Standard dose of ramucirumab IV on days 1 and 15 + abemaciclib PO Q12H (MCL)

**Phase 1b**

**Tumor-specific expansion period**

**Arm 1:** Standard dose of ramucirumab IV on days 1 and 15 + merestinib PO QD (mCRC)

**Arm 2:** Standard dose of ramucirumab IV on days 1 and 15 + abemaciclib PO Q12H (MCL)

Primary endpoint: Safety and tolerability of combination therapy

Primary endpoint: Safety and tolerability

Arm 1†: Standard dose of ramucirumab IV on days 1 and 15 + merestinib PO QD (mCRC)

Arm 2†: Standard dose of ramucirumab IV on days 1 and 15 + abemaciclib PO Q12H (MCL)

† Ramucirumab, merestinib, and abemaciclib are administered over a 28-day cycle.
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.

Key Inclusion Criteria
- Locally advanced or metastatic non-small cell lung cancer (NSCLC) not amenable to curative therapy
- At least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Disease progression immediately following first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment, regardless of prior chemotherapy
- EGFR T790M-positive status using a test validated and performed locally after disease progression on EGFR TKI treatment
- Urinary protein that is ≤ 2+ on dipstick or routine urinalysis
- Adequate organ function
- Resolution of all clinically significant toxic effects of prior systemic cancer therapy, surgery, or radiotherapy to grade ≤ 1 by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

Key Exclusion Criteria
- Previous treatment with an EGFR monoclonal antibody (except for past treatment for squamous cell carcinoma of the head and neck or metastatic colorectal cancer)
- Previous treatment with an EGFR TKI within 8 days or approximately 5x half-life, whichever is longer, of the first dose of study treatment
- Symptomatic or growing brain metastases ≤ 6 weeks prior to enrollment. Patients with asymptomatic and stable brain metastases are eligible
- Serious concomitant illness or medical condition(s) including, but not limited to, active infection including hepatitis B or C, or HIV
- History of another malignancy within the past 3 years
- Significant bleeding disorder or vasculitis, grade ≥ 3 bleeding episode within 12 weeks prior to enrollment, or history of gross hemoptysis within 2 months prior to enrollment
- Arterial thrombotic event or arterial thromboembolic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to enrollment
- History of deep vein thrombosis, pulmonary embolism, or any other significant venous thromboembolism during the 3 months prior to study enrollment. Participants with venous thromboembolism occurring 3 to 6 months prior to study enrollment are allowed if being treated with low molecular weight heparin
- History of GI perforation and/or fistula within 6 months prior to enrollment
- Uncontrolled hypertension prior to initiating study treatment, despite antihypertensive intervention
- Currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of osimertinib) medications or herbal supplements known to be potent inducers of CYP3A4

Please visit www.clinicaltrials.gov for more information on this clinical trial. [NCT02789343].

*This clinical trial is being conducted globally.
**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 designed to bind and block 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 phase I clinical trials, including combination clinical trials in immuno-oncology, and in clinical trials in patients with bladder cancer, gastric cancer, hepatocellular carcinoma, non-small cell lung cancer, and pediatric cancer.

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**Study Schemas Not Available**

[NCT02359058] Gastrointestinal Cancer A Study of Ramucirumab Combination Therapy in Japanese Participants Who Have Advanced Stomach Cancer

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**References:**  