

TYPE OF CANCER: Advanced Solid Tumors
TYPE OF TRIAL: Phase I
TRIAL SPONSOR: Amgen

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STUDY SUMMARY

An Open-Label, Dose Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of AMG 386 with AMG 706, AMG 386 with Bevacizumab, AMG 386 with Sorafenib, and AMG 386 with Sunitinib in Adult Patients with Advanced Solid Tumors

TREATMENT OVERVIEW

Each subject will be on study for approximately two weeks of screening, eight weeks of study treatment and thirty days of follow-up.

PRETREATMENT ASSESMENT

- Signed informed consent
- Collection of concomitant medication
- Physical Examination
- Vital signs
- ECG (1 tracing only)
- For subjects on cohorts 10-11: baseline assessment of left ventricular ejection fraction (LVEF) using either echocardiography (ECHO) or multigated radionuclide angiography (MUGA). For each patient once a modality (either ECHO or MUGA) has been selected, the same modality should be used in later periodic assessments.
- Hematology (including reticulocyte count)
- Serum chemistry panel
- Coagulation panel
- Urinalysis with microscopic examination
- Urine or serum pregnancy test in women of child bearing potential (72 hrs before enrollment)
- Clinical Staging: Imaging for measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) will be performed within 4 weeks before enrollment. Contrast enhanced CT or MRI imaging of a brain tumor must be performed within 8 weeks before enrollment.
- Collection of archival paraffin-embedded tumor tissues (required for all subjects).

ENTRANCE CRITERIA FOR PARTICIPATION IN TRIAL

Inclusion Criteria

- Men or women ≥ 18 years old.
- Subjects must have a pathologically documented, and definitively diagnosed, advanced solid tumor that is refractory to standard treatment, for which no standard therapy is available, or for subjects who refuse standard therapy
- Subjects enrolling in cohorts 6 - 7 and 10 - 11 must have pathologically documented and definitively diagnosed advanced renal cell carcinoma
- Measurable disease or evaluable (non-measurable) disease per Response Evaluation Criteria in Solid Tumors (RECIST) guidelines
- Eastern Cooperative Oncology Group (ECOG) performance status of < 2
- Life expectancy of > 3 months as documented by the investigator
- Hematological function, as follows:
 - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$
(Without granulocyte-colony stimulating factor support within 2 weeks of study Day1)
 - Platelet count $\geq 100 \times 10^9/L$ (without transfusion within 4 weeks of study Day 1)
 - Hemoglobin > 9 g/dL (without transfusion within 4 weeks of study Day 1)
- Renal function, as follows:
 - Creatinine < 2.0 mg/dL for cohorts 1 – 4
 - Creatinine $< 2 \times$ ULN for cohorts 6 – 7 and 10 -11
 - Urinary protein quantitative value of < 30 mg in urinalysis or $< 1+$ on dipstick, unless quantitative protein is < 500 mg in a 24 hour urine sample
- Hepatic function, as follows:
 - Aspartate aminotransferase (AST) $< 2.5 \times$ upper limit of normal (ULN) (if liver metastases are present, $\leq 5 \times$ ULN)
 - Alanine aminotransferase (ALT) $< 2.5 \times$ ULN (if liver metastases are present, $\leq 5 \times$ ULN)
 - Alkaline phosphatase $< 2.0 \times$ ULN (if bone or liver metastases are present, $\leq 5 \times$ ULN)
 - Bilirubin $< 2.0 \times$ ULN
 - Prothrombin time (PT) or partial thrombolastin time (PTT) $< 1.5 \times$ ULN
- Able to tolerate oral medications and infusions
- Subjects enrolling in cohorts 2, 4, 6 and 7 must be able to self-administer AMG 706 or sorafenib on an empty stomach (fasting for 1 hour before and 1 hour postdose) once daily for AMG 706 or twice daily for sorafenib. Subjects enrolling in cohorts 10 and 11 must be able to self-administer sunitinib once daily. All subjects receiving AMG 706, sorafenib, or sunitinib must be able to maintain a record of drug accountability
- Willing to provide existing and/or future paraffinembedded tumor samples
- Female subject is post-menopausal (no menstrual period for a minimum of 12 months), surgically sterilized, using an oral or implanted contraceptive, using a double-barrier birth control or an intrauterine device and is willing to use

contraception for 6 months following the last study drug administration and has a negative serum pregnancy test upon entry into this study

- Male subject is willing to use contraception upon enrollment, during the course of the study, and for 3 months following the last study drug administration
- Competent to comprehend, sign, and date an institutional review board (IRB) - approved informed consent form

Exclusion Criteria

- History of lymphoma or leukemia
- Symptomatic or untreated central nervous system metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation, and corticosteroids
- Subjects with head and neck cancer
- For the bevacizumab/ AMG 386 cohorts: Subjects with lung squamous cell tumors
- For the bevacizumab/ AMG 386 cohorts: Subjects with ovarian cancer
- For the bevacizumab / AMG 386 cohorts: Subjects with large central (located adjacent to or within the hilum or mediastinum) tumor lesions ≥ 3 centimeters, regardless of histology
- History of arterial or venous thrombosis or pulmonary embolism within 1 year before enrollment; history of bleeding diathesis
- Cardiovascular events within 1 year before enrollment, such as myocardial infarction, unstable/severe angina, coronary/peripheral artery bypass graft, unstable cardiac arrhythmia requiring medication, symptomatic congestive heart failure (New York Heart Association $>$ class II), cerebrovascular accident or transient ischemic attack
- LVEF $\leq 45\%$ (for cohorts 10 and 11)
- Heart rate < 50 / min (for cohorts 10 and 11)
- Chronic uncontrolled hypertension [diastolic > 85 mmHg; systolic > 145 mmHg]
- History of pulmonary hemorrhage or gross hemoptysis within 6 months before enrollment
- History of significant GI surgery or disease, which would impair absorption
- Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Events (CTCAE) grade 0 or 1, or to levels dictated in the inclusion/exclusion criteria with the exception of alopecia
- Any co-morbid medical condition that would increase the risk of toxicity
- Active infection within 2 weeks before enrollment
- Subject known to have tested positive for HIV
- Subject known to have chronic hepatitis (e.g., hepatitis B or hepatitis C)
- For subjects in cohorts involving AMG 706, sorafenib, or sunitinib (2, 4, 6, 7, 10 and 11) the following therapies and treatments are excluded:
 - Concurrent or prior rifampin phenobarbital (within 2 weeks before enrollment),

- Strong CYP 3A inhibitors such as ketoconazole, itraconazole, clarithromycin, erythromycin, nefazodone, grapefruit (i.e. whole fruit or fruit juice), or any HIV protease inhibitors (within 1 week prior to enrollment)
- Immune modulators such as cyclosporine and tacrolimus (within 1 week prior to enrollment)
- St. John's Wort or any herbal therapy containing St. John's Wort (within 1 week prior to enrollment)
- Coumarin anticoagulants including warfarin, at doses greater than 2 mg/day. The concurrent use of low molecular weight heparin or low dose warfarin (i.e., \leq 2 mg daily for prophylaxis against central venous catheter thrombosis is acceptable.
- Prior anti-tumor therapies, defined as:
 - Treatment with anti-cancer therapy within 30 days before study day 1 [including chemotherapy, retinoid therapy, (e.g., all-trans retinoic acid, isotretinoin), vaccine therapy, or tumor directed antibody therapy], except for treatment with bevacizumab within 42 days before study day 1, unless prior written approval is received from the sponsor
 - Hormonal anti-tumor therapy within 30 days before enrollment. Does not include hormones for non-cancer related conditions (eg, insulin for diabetes, HRT) or the use of gonadotropinreleasing hormone (GnRH) agonists for prostate cancer
 - Therapeutic or palliative radiation therapy within 2 weeks before enrollment (subjects must have resolution of any significant adverse effects from radiation therapy received prior to 2 weeks before enrollment)
- Prior treatment with AMG 386
- Prior radiation therapy to the abdomen
- For cohorts 1-4, prior treatment with bevacizumab, sorafenib, sunitinib, or investigational agents known to directly inhibit the functions of vascular endothelial growth factor, vascular endothelial growth factor receptors, angiopoietins, or angiopoietin receptors, unless prior written approval is received from the sponsor
- For cohorts 6-7, prior treatment with sorafenib unless prior written approval is received from the sponsor
- For cohorts 10-11, prior treatment with sunitinib, unless prior written approval is received from the sponsor
- For cohorts 7, 10 and 11, treatment with bevacizumab within 42 days before study day 1, unless prior written approval is received from the sponsor
- Known allergy to the excipients, or study drugs
- History of allergic reactions to bacterially produced proteins
- Subject has previously entered this study
- Major surgery within 30 days before enrollment or recovering from prior surgery
- Subject who is pregnant or nursing
- Any disorder that compromises the ability of the subject to give written informed consent and/or comply with the study procedures