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Phase 2 Study of the Anti-Angiogenesis Agent Axitinib (AG-013736) in Patients with Stage III Malignant Melanoma

Protocol Synopsis

Title:

Phase 2 Study of the Anti-Angiogenesis Agent Axitinib (AG-013736) in Patients with Stage III Malignant Melanoma

Rationale:

Stage III malignant melanoma is defined by lymph node involvement in a local basin (TNM staging: Any T; N1,2 or 3; M0) and has a 5 year survival rate of from 27 to 68%, indicating that is can often be an incurable and fatal disease for a significant proportion of patients. Surgical resection of the primary lesion and affected lymph nodes is the current standard of care. Although it would be of value to have an effective adjuvant therapy for this stage of disease, to date no treatment has led to significantly improved overall survival. While interferon has been applied with some benefit and can result in a significant prolongation in disease free survival, no overall survival benefit has been substantiated. IFN and its pegylated version are both approved by the FDA for this indication, but enthusiasm for their use is tempered by their significant toxicity. Like IFN, chemotherapy has not been demonstrated to prolong survival for stage III melanoma. New agents are required in order to improve the survival of patients with stage III melanoma. However, because large-scale clinical trials are often necessary to demonstrate the safety and effectiveness of a drug, it is desirable determine if new agents provide some measure of effectiveness of these new agents prior to investing in such studies. Because of the poor prognosis of patients with stage III melanoma and indications that anti-angiogenesis compounds might have clinically meaningful activity in this disease, a Phase 2 trial of the vascular endothelial growth factor receptor tyrosine kinase (VEGFR TK) inhibitor AG-013736 is warranted to determine its activity and tolerability for Stage III melanoma.

Indication:

Stage III melanoma

Objectives:

The primary objective of this study is:

- determine the response rate of axitinib in patients with Stage III melanoma as measured by the overall response rate by RECIST during the lead in phase. A response will also be considered to have occurred if there is a >/= 25% reduction in the involved nodal basin specific uptake value (SUV) on PET/CT (see Appendix C).

Secondary objectives with are to:

- determine progression-free survival (PFS)
- determine the safety profile of axitinib
- determine duration of response
- determine overall survival
- obtain blood samples for population pharmacokinetic analyses
- explore relationships between clinical response and plasma soluble proteins
- explore relationships between clinical response with tumor and host genomics

Number of Subjects/Sites:

Eighteen patients will be entered into the first stage of a 2-stage Simon Minimax design. If there is ≥1 response, 14 additional patients will be entered. For a total of up to 32 may be treated in order to gain additional safety and activity information should the initial 2-stage trial be positive at the end of Stage 2.

Study Country Location:

United States

Study Population:

In order to be eligible for this study, patients must meet all eligibility criteria and have no exclusion criteria. Major eligibility criteria include:

- Histologically documented stage III melanoma with measurable lymph node involvement.
- No more than prior systemic therapy for Stage III melanoma. (Prior adjuvant therapy with interferon for Stage II does not count as a prior therapy)
- At least 1 target lesion, as defined by RECIST, that has not been irradiated.
- Adequate bone marrow, hepatic, and renal function documented within 14 days prior to treatment.
- Age ≥18 years.

- ECOG performance status of 0 or 1.
- Females must be either not of childbearing potential or of childbearing potential using adequate contraception or practicing abstinence.
- Written informed consent.

Patients must not have any exclusion criteria. Generally, the exclusion criteria are designed to assure patient compliance with the protocol, prevent enrolment of patients with conditions that might confound the evaluation of safety or efficacy, and increase safety by minimizing conditions that might pose a risk to patients treated with the test agent.

Study Design:

This Phase 2, open-label study of the investigational anti-angiogenesis agent axitinib, AG-013736. A 2-stage Simon Minimax design will be used with 18 treated patients in the first stage and 14 treated patients in the second stage. At least 1 patient must have a confirmed response (CR or PR) in the first stage in order to proceed to the second stage. At the end of the study, at least 4 confirmed responses in 32 treated patients must be observed in order to recommend further studies in this patient population.

For a total of up to 32 may be treated in order to gain additional safety and activity information should the trial be positive at the end of Stage 2.

Treatments:

Axitinib will be administered 5 mg orally twice each day (BID) continuously. Dose adjustments will be based on adverse events.

Endpoints:

Primary Endpoint(s):	Response rate according to RECIST criteria A response will also be considered to have occurred if there is a >/= 25% reduction in the involved nodal basin specific uptake value (SUV) on PET/CT (see Appendix C)
Secondary Endpoints:	1) Progression-free survival (PFS) 2) Safety profile of AG-013736 3) Duration of response 4) Overall survival

Safety Measurement/Parameters:

Safety will be assessed by collecting adverse event information on each patient including results of physical examinations and laboratory testing.

Statistical Methods:

Demographic data will be displayed and summary statistics will be provided. The results of safety and efficacy evaluations will be tabulated and displayed.

The estimated response rate and its 95% confidence interval will be provided. The duration of response, progression-free survival, and survival will be summarized.

Study Schedule/Flowchart:

Study tests and procedures will include multiple examinations, laboratory tests, and radiographic procedures according to schedule of tests and procedures in the table below:

TABLE – SCHEDULE OF TESTS AND PROCEDURES

Protocol Activities	**Screening**	**Study Treatment**						
	≤ 18 Days Prior to Enrollment	Day 1 to Day 56 (-3/+3)	Day 57 to Day 91 (-3/+3) Treatment Rest/ Pre-Op[v]	Surgery 14-21 Days Post Last Dose	Recovery 28 Days Post-Sugery[w]	Every 4 Weeks* Progression/Early Termination	Every 16 Weeks	Follow-up Day 28 After Last Dose[x]
Informed consent[a]	X							
Medical history[b]	X							
Concomitant treatment[c]	X	X				X		X
Physical exam[d]	X	X**	X		X	X		X
Weight, height, temperature[e]	X	X	X		X	X		X
Blood pressure, pulse[f]	X	X	X		X	X		X
Home blood pressure monitoring[g]	**Participant Instructed to Monitor throughout study.**							
ECOG performance status[h]	X	X	X		X	X		X
Hematology[j]	X	X**	X		X	X		X
Chemistry[j]	X	X**	X		X	X		X
Urinalysis[k]	X	X**	X		X	X		X
12-Lead electrocardiogram[l]	X		X		X			
Fecal Immuchemical Test [m]	X							
Tumor measurements[n] PET/CT	X		X		X (post surgery baseline		X	
Soluble protein samples[o] Marker of drug activity		X	X			X[y]	X	
Tumor genomics[p]		X		X From node dissection				
Blood genomic sample[q]		X						
Safety assessment (adverse events)[s]		X	X		X			
Survival[t]		**Throughout the study period**						
Serum or urine pregnancy test[u] Until at least one year after the initial dose for the last treated patient	X	X			X		X	X
Axitinib Treatment		X				X		
Treatment held preoperatively			X					
Lymph node dissection				X				

Notes to Table

Tests and procedures should be done on schedule, but occasional changes by +/- 4 days are allowable for holidays, vacations, and other administrative reasons.

* Cycle length is 4 weeks [two cycles prior to surgery].

** Unnecessary to repeat before first dose if screening assessment was performed within 7 days prior to first dose.

[a] Any time prior to any procedures performed solely for this study.

[b] Including use of nicotine products.

[c] Should be collected from screening to the follow-up period.

[d] After the initial complete examination, targeted examinations based on signs and symptoms may be performed.

[e] Height need not be collected after the first measurement.

[f] Blood pressure and pulse to be measured with the patient in the seated position after the patient has been sitting quietly for 5 minutes.

[g] Patients receiving AG-013736 will receive blood pressure monitoring devices. Patients should take blood pressure at least once each day and should be recorded in a patient diary.

[h] See Appendix D for performance status scale.

[i] Hgb, Hct, WBC with differential, and platelets. Prothrombin time and partial thromboplastin time should be done prior to the first dose and then as clinically indicated.

[j] Blood urea nitrogen (BUN), creatinine, sodium (Na^+), potassium (K^+), chloride (Cl^-), bicarbonate (HCO_3^-) or CO_2, alkaline phosphatase, lactate dehydrogenase (LDH), alanine aminotransferase (ALT, or SGPT), aspartate aminotransferase (AST, or SGOT), total protein, albumin, total bilirubin, and glucose.

[k] Protein, glucose, and blood. If protein ≥2+ by semiquantitative method (eg, dipstick) then quantitate by 24-hour urine collection. Dose adjustment may be required. Screening urinalysis should include microscopic examination of the sediment.

[l] Additional ECGs as clinically indicated.

[m] Subjects with a positive fecal immunochemical test (FIT) from blood test result should be evaluated for active gastrointestinal bleeding. Additional tests as clinically indicated.

[n] Tumors assessments by PET/CT will be performed every 8 weeks using RECIST criteria (see Appendix C). Response (CR/PR) requires confirmation at least 4 weeks after the response is noted. For patients who have not progressed after discontinuing study drug, additional tumor assessments should be performed approximately every 8 weeks until patient meets criteria for progression or alternate therapy started.

[o] See Appendix F for collection, processing and shipping instructions. 10 ml of blood will be drawn for this sample.

[p] Optional for patients on Stage 1, required for patients entered on Stage 2 of the study. Second biopsy should be on Day 29 +/-4 days. A punch, core, or excisional biopsy should be used to obtain approximately 4 mm cube of tumor tissue. See Appendix G for processing and shipping instructions.

[q] Genomic analysis will be performed for each subject from a blood sample taken prior to dosing on Day 1. A 5 mL blood sample will be collected in a purple cap EDTA tube. Blood samples will be stored at -20°C until shipment on dry ice to the address given in the Study Manual. Appendix G has further details.

[s] Adverse events should be collected from the time of consent and throughout the study period until at least 28 days after the last dose of study drug and followed until resolution or stabilization.

[t] All patients should be followed for survival at least every 3 months after discontinuing study treatment until at least one year after the initial dose for the last treated patient.

[u] Patient of childbearing potential must have a negative pregnancy test within 7 days prior to treatment and must be using appropriate birth control or practicing abstinence.

[v] Minimum rest period is 14 days prior to surgery.

[w] Minimum rest period is 28 days post surgery; maximum rest period 56 days post surgery.

[x] Patients go off treatment after one year if they have not progressed.

[y] Done at first 4 week mark only.

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1. INTRODUCTION

The American Cancer Society estimates that there will be about 68,720 new cases of melanoma (29,900 in men and 25,200 in women) annually in the United States, and about 8,650 people will die from this cancer.[1] Depending upon type and stage, melanoma may be treated with surgery, cytokines, chemotherapy, immunotherapy, or the newer molecular targeted compounds. Radiation therapy may provide symptomatic relief for metastases to brain, bones, and viscera.

The systemic therapy of advanced disease remains palliative until new agents are found that might afford a better prognosis. Melanomas are often vascular, and a decrease in the number of blood vessels that supply the tumor may starve it of needed nutrients. An approach to blocking the growth of blood vessels that supply the tumor is to inhibit the VEGF receptor tyrosine kinase (VEGFR TK) signaling pathway. Axitinib (AG-013736) is a VEGFR TK inhibitor. Besides having potential anti-angiogenesis properties through VEGFR TK inhibition, it also has additional potential antitumor through platelet derived growth factor receptor (PDGFR) TK inhibition.

Prior to development of a VEGFR TK inhibitor as a systemic treatment for melanoma, it is necessary to determine if this compound has sufficient antitumor activity to warrant large clinical trials to demonstrate clinical safety and efficacy. This study is designed to provide clinical information on the VEGFR TK inhibitor AG-013736 in patients with melanoma and determine if larger trials are warranted.

1.1. Background on Melanoma

Melanoma is a malignant tumor of melanocytes, cells derived from the neural crest. Most arise in the skin. The American Joint Committee on Cancer (AJCC) has designated staging by tumor-lymph node-metastasis (TNM) classification.[3] Metastases may occur to lymph nodes and are designated N1-N3, depending upon extent of disease. Stage III disease is defined by the presence of lymph node involvement that falls into a basin that drains the site of the primary tumor. Stage III has A,B and C subsets. **Stage IIIA** is defined as **T1a-4a, N1a or N2a, M0:** The melanoma is not ulcerated. It has spread to 1-3 lymph nodes near the affected skin area, but the nodes are not enlarged and the melanoma is found in lymph nodes only when they are viewed under the microscope. There is no distant spread. The thickness of the melanoma is not a factor, although it is usually thick in people with stage III melanoma. **Stage IIIB** is defined by three categories: 1. **T1b-4b, N1a or N2a, M0:** The melanoma is ulcerated. It has spread to 1-3 lymph nodes near the affected skin area, but the nodes are not enlarged and the melanoma is found only when they are viewed under the microscope. There is no distant spread. 2. **T1a-4a, N1b or N2b, M0:** The melanoma is not ulcerated. It has spread to 1-3 lymph nodes near the affected skin area. The nodes are enlarged because of the melanoma. There is no distant spread. 3. **T1a/b-4a/b, N2c, M0:** The melanoma can be ulcerated or not. It has spread to small areas of nearby skin or lymphatic channels around the original tumor, but the nodes do not contain melanoma. There is no distant spread.

Stage IIIC is defined in two categories: 1. **T1b-4b, N1b or N2b, M0:** The melanoma is ulcerated. It has spread to 1 to 3 lymph nodes near the affected skin area. The nodes are enlarged

because of the melanoma. There is no distant spread. 2. **Any T, N3, M0:** The melanoma can be ulcerated or not. It has spread to 4 or more nearby lymph nodes, OR to nearby lymph nodes that are clumped together, OR it has spread to nearby skin or lymphatic channels around the original tumor and to nearby lymph nodes. The nodes are enlarged because of the melanoma. There is no distant spread.

Stage IV disease is defined by distant metastases (M1) including to skin, subcutaneous tissues or distant lymph nodes (M1a); to the lung (M1b); or to other visceral sites or distant metastases to any site associated with an elevated serum lactic dehydrogenase (LDH) (M1c).

1.2. Background on Axitinib, AG-013736

AG-013736 is a substituted indazole derivative that was discovered using structure-based drug design. The mechanism of action of AG-013736 is a direct anti-angiogenic effect mediated by the potent inhibition of vascular endothelial growth factor receptor 2 (VEGFR-2; KDR) kinase activity. AG-013736 is also a potent inhibitor of platelet-derived growth factor receptor beta (PDGFRβ), VEGFR-1 (flt-1), VEGFR-3, and c-kit.

The AG-013736 dose for Phase 2 studies in solid tumors has been determined to be 5 mg twice daily (BID) given orally on an empty stomach based on results of the Phase 1 study.

For single-agent axitinib the most common adverse events reported are hypertension, fatigue, and gastrointestinal toxicity. These side-effects are considered manageable and are an expected class effect. (Kelly RJ, Rixe O. Axitinib-a selective inhibitor of the vascular endothelial growth factor (VEGF) receptor. Target Oncol. 2009 Oct 30. [Epub ahead of print]).

In phase I studies, the dose-limiting toxicity (DLT) was hypertension, which was responsive to medications and was reversible with drug cessation. None of the patients receiving 5 mg bid had hypertension that could not be managed with standard antihypertensive medications. In ongoing clinical programs, subjects receive a starting dose of 5 mg bid with home monitoring of blood pressure (before each dose) and in-clinic monitoring at the time of scheduled visits. Patients who tolerate AG-013736 with no adverse events related to AG-013736 above CTC Grade 1 for any consectutive 8-week period should have their dose increased by 20% unless the patient is responding to therapy. Bleeding events that have occurred among the phase I studies have included 1 fatal case of hemoptysis in a subject with lung adenocarcinoma, epistaxis, breast hemorrhage, hematochezia, rectal hemorrhage, and vaginal hemorrhage. Asymptomatic proteinuria was seen in early studies and consequently, the phase I protocol was amended to exclude subjects with proteinuria at baseline (>500 mg/24 h) and to require dose modifications of axitinib on the basis of proteinuria. The maximum tolerated dose was defined as a 5 mg bid starting dose.

In the phase II study conducted in metastatic renal cell carcinoma (Rixe O, Bukowski RM, Michaelson MD et al (2007) Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: a phase II study. Lancet Oncol 8:975–984), axitinib was given as a single agent and toxicities are reported in Table 1.

	All grades (number of patients)	Grades 3–4, (number of patients)
Diarrhea	31	5
Hypertension	30	8
Fatigue	27	4
Nausea	23	0
Hoarseness	19	0
Anorexia	18	1
Dry skin	17	0
Weight loss	14	0
Dyspepsia	12	0
Vomiting NOS	11	0
Limb pain	10	2
Stomatitis	9	1
Headache	8	0
Dry mouth	8	0
Nail disorder	7	0
Arthralgia	7	1
Constipation	7	0
Abdominal pain NOS	6	0
Rash	6	0
Dysgeusia	6	0
Myalgia	6	1

The most commonly reported treatment related adverse events of severity grade 3 or higher were hypertension (14%), fatigue (10%), diarrhea (4%), palmar plantar erythrodysaesthesia syndrome (3%), hypertension aggravated (2%), and stomatitis (2%). Laboratory abnormalities for subjects with solid tumors who received single-agent axitinib were grade 3/4 hyperglycemia in 5.5%, hyponatremia or elevation in creatinine in 4.6%, elevations in AST in 4.0%, and proteinuria in 0.8%. Hematological abnormalities were grade 3 or 4 neutropenia in 0.8% and thrombocytopenia in 1.0%. Grade 3/4 lymphopenia was reported in 19%. Preliminary evidence suggests that axitinib is safe and has a side-effect profile that gives an advantage over other antiangiogenic drugs. The continuous administration and the constant dose appear to be safe, and compatible with long-term administration. In the phase II RCC study, patients have received axitinib for more than 3 years, with the absence of cumulative toxicity [Rixe O, Bukowski RM, Michaelson MD et al (2007) Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: a phase II study. Lancet Oncol 8:975–984].

Further information on AG-013736 can be found in the Investigator's Brochure (IB).

1.3. Rationale

New agents are required in order to improve the survival of patients with Stage III malignant melanoma. However, because large-scale clinical trials are often necessary to demonstrate the safety and effectiveness of these new agents, it is desirable to provide some measure of effectiveness of these new agents. Because of the poor prognosis of patients with advanced melanoma and indications that anti-angiogenesis compounds might have clinically meaningful activity[11-13], a Phase 2 trial of the VEGFR TK inhibitor AG-013736 (axitinib) is warranted.

Part of this study is to explore the relationship between tumor biomarkers before and after therapy as a predictor of tumor response. Patients will be required to have undergone a diagnostic biopsy of a melanoma lesion before receiving AG-013736 and at the time of enrolment be amenable to providing pathologic material obtained after initial therapy at the time of lymph node resection.

2. STUDY OBJECTIVES

The primary objective of this study is to determine the activity of AG-013736 in metastatic melanoma as measured by the complete response (CR) and partial response (PR) by RECIST. A response will also be considered to have occurred if there is a >/= 25% reduction in the involved nodal basin specific uptake value (SUV) on PET/CT (see Appendix C). Secondary objectives are to:

- Progression free survival
- determine the safety profile of AG-013736
- determine duration of response
- determine overall survival
- obtain blood samples for population pharmacokinetic analyses
- explore relationships between clinical response and plasma soluble proteins
- explore relationships between clinical response with host and tumor genomics

3. METHODs

3.1. Study Design

This will be a 2-stage Minimax, Phase 2, open-label study of the investigational anti-angiogenesis agent AG-013736 in patients with locally metastatic stage III melanoma.

Patients will be consented at the time of diagnosis of stage III disease based on clinical or biopsy results. After obtaining a baseline PET/CT, patients will undergo 2 months of therapy with axitinib. Response will be determined by restaging PET/CT after two months of initial therapy. (Mohr P, Eggermont AM, Hauschild A, Buzaid A. Staging of cutaneous melanoma. Ann Oncol. 2009 20 Suppl 6:vi14-21.; Kumar R, Mavi A, Bural G, Alavi A. Fluorodeoxyglucose-PET in the

management of malignant melanoma. Radiol Clin North Am. 2005 43(1):23-33. Strobel K, Skalsky J, Steinert HC, et al. S-100B and FDG-PET/CT in Therapy Response Assessment of Melanoma Patients. Dermatology 2007, 215:192–201) (Vercellino L, Bousquet G, Baillet G, Barré E, Mathieu O, Just PA, Desgrandchamps F, Misset JL, Hindié E, Moretti JL. 18F-FDG PET/CT imaging for an early assessment of response to sunitinib in metastatic renal carcinoma: preliminary study. Cancer Biother Radiopharm. 2009 Feb;24(1):137-44) Response rates will be determined either by RECIST criteria or by the change in SUV maximum values after two months of therapy according to the method of Stroobants (Stroobants S, Goeminne J, Seegers M, Dimitrijevic S, Dupont P, Nuyts J, Martens M, van den Borne B, Cole P, Sciot R, Dumez H, Silberman S, Mortelmans L, van Oosterom A. 18FDG-Positron emission tomography for the early prediction of response in advanced soft tissue sarcoma treated with imatinib mesylate (Glivec). Eur J Cancer. 2003, 39:2012-20). The following PET criteria will be used: SUV max changes of >25% in the target lesion is considered progression, an SUV change less than 25% higher or less than 25% lower will be considered stable disease, while a decrease in the SUV max in the target of >25% will be considered a partial response. Complete response will be defined as an SUV max similar to the liver background SUV max reading. Patients will then undergo definitive surgical resection of their involved nodal basins. One month after surgical intervention patients will restart axitinib and be followed for disease progression with PET/CT scan performed every 4 months. Patients will have periodic safety evaluations, and dose modifications will be made as appropriate for their treatment. Clinical response evaluations will be performed every 8 weeks. Treatment will continue until tumor progression, unmanageable toxicity, or the patient withdraws consent. Subsequent therapy will be at the discretion of the investigator.

3.2. Study Population

In order to be eligible for this study, patients must meet all eligibility criteria and have no exclusion criteria.

3.2.1. Inclusion Criteria

To be eligible for the study, subjects must satisfy all the following criteria:

1. Histologically documented melanoma with local lymph node stage III metastases.
2. No prior systemic therapy. Prior adjuvant therapy with interferon does not count.
3. No expectation of further effects of prior anticancer therapy.
4. At least 1 target lesion, as defined by RECIST (Appendix C), that has not been irradiated. New lesions that have developed in a previously irradiated field may be used as sites of measurable disease assuming all other criteria are met. All target lesions must have a unidimensional diameter of at least 1 cm for spiral CT scans if the reconstruction algorithm is 0.5 cm), or an SUV value >/= 2.5. Baseline measurements/evaluations must be completed within 4 weeks prior to treatment.
5. Adequate bone marrow, hepatic, and renal function documented within 14 days prior to treatment as documented by:

- absolute neutrophil count (ANC, calculated as the absolute number of neutrophils and bands) ≥1.5 x 10^9 cells/L
- platelets ≥100 x 10^9 cells /L
- AST and ALT ≤2.5 x upper limit of normal (ULN), unless there are liver metastases in which case AST and ALT ≤5.0 x ULN
- total bilirubin ≤1.5 x ULN
- serum creatinine ≤1.5 x ULN or calculated creatinine clearance ≥60 mL/min
- urinary protein <2+ by urine dipstick. If dipstick is ≥2+ then a 24-hour urine collection can be done and the patient may enter only if urinary protein is <2 g per 24 hours

6. Age ≥18 years.
7. ECOG performance status of 0 or 1 (see Appendix D)
8. No evidence of preexisting uncontrolled hypertension as documented by 2 baseline blood pressure readings taken at least 1 hour apart. The baseline systolic blood pressure readings must be ≤140, and the baseline diastolic blood pressure readings must be ≤90. Patients whose hypertension is controlled by antihypertensive therapies are eligible.
9. Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to treatment.
10. Written and voluntary informed consent.

3.2.2. Exclusion Criteria

Subjects with one or more of the following criteria are ineligible for this study:

1. Stage IV disease
2. History of hemoptysis
3. Gastrointestinal abnormalities including:
   - inability to take oral medication
   - requirement for intravenous alimentation
   - prior surgical procedures affecting absorption including gastric resection
   - treatment for active peptic ulcer disease in the past 6 months
   - active gastrointestinal bleeding, unrelated to cancer, as evidenced by hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy.
   - malabsorption syndromes.
4. Previous treatment with anti-angiogenesis agents including thalidomide, or inhibitors of epidermoid growth factor (EGF), platelet derived growth factor (PDGF), or fibroblast growth factors (FGF) receptors.

5. Current use or anticipated inability to avoid use of drugs that are known potent CYP3A4 inhibitors (ie, grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, erythromycin, clarithromycin, ergot derivatives, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, and delavirdine).
6. Current use or anticipated inability to avoid use of drugs that are known CYP3A4 or CYP1A2 inducers (ie, carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, primidone, rifabutin, rifampin, and St. John's wort).
7. Active seizure disorder or evidence of brain metastases. (Appropriate imaging should be done to rule out brain metastases.)
8. A serious uncontrolled medical disorder or active infection that would impair their ability to receive study treatment.
9. History of a malignancy (other than melanoma) except those treated with curative intent for skin cancer (other than melanoma) or in situ breast or cervical cancer or those treated with curative intent for any other cancer with no evidence of disease for 5 years.
10. Major surgical procedure or any radiation therapy within 4 weeks of treatment, minimum rest period is 28 days post surgery; maximum rest period 56 days post surgery.
11. Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent and compliance with the requirements of this protocol.
12. Patients (male and female) having procreative potential who are not using adequate contraception or practicing abstinence.
13. Women who are pregnant or breast-feeding.

3.3. Withdrawal Criteria

When patients are permanently withdrawn from treatment, the primary reason for discontinuation must be provided. Reasons for discontinuation include:

- death
- non-fatal Adverse Event (AE)
- lack of efficacy (insufficient or worsening clinical response)
- protocol deviation (post study start; includes subject noncompliance)
- pregnancy
- did not meet inclusion/exclusion criteria (prestudy start)
- refusal to participate further
- lost to follow-up
- study terminated by sponsor
- other

The reason for a patient's discontinuation from treatment will be documented in the CRF.

Patients who do not receive drug after registration or who have the incorrect histological cancer type will be replaced. Patients who discontinue the study prematurely will not be replaced. All efforts should be made to continue to follow a patient to document disease progression and survival if he/she withdrew from study treatment for reasons other than progressive disease or death.

3.4. Life Style Guidelines

During the study female patients of childbearing potential must take precautions to prevent pregnancy since the effects on the fetus are unknown. Male patients with partners of childbearing potential must take precautions to prevent pregnancy of the partner since the effects of these drugs on sperm are unknown. These restrictions should remain in force for 3 months from the last dose of investigational agent.

3.5. Study Procedures

Study-specific procedures are outlined in the following sections. Administrative and regulatory procedures are provided in Appendix B. Contact information for study personnel is provided in Appendix E.

3.5.1. Physical Examination

A complete physical examination including the assessment of all body systems, the measurement of body weight, height, pulse, temperature, and assessment of ECOG performance status (see Appendix D) will be performed prior to the first dose. After the initial complete examination, targeted examinations based on signs and symptoms may be performed. All examinations must be performed by qualified health care professionals. Findings of all physical examinations should be recorded in the source documents, and any change from baseline considered by the investigator to be clinically significant should be recorded as an adverse event in the case report form.

3.5.2. Blood Pressure Assessments

Blood pressure readings should be taken in the seated position after the patient has been sitting quietly for 5 minutes and are required at each clinic visit.

All patients receiving AG-013736 will be issued a blood pressure monitor and blood pressure measurement diary. Patients will be asked to record their blood pressure measurements at least once each day. Blood pressure readings should be taken in the seated position after the patient has been sitting quietly for 5 minutes. Patients will be instructed to call their physician if they record a systolic blood pressure reading greater than 150 or a diastolic blood pressure reading greater than 90 mm Hg. Parameters may be set up to 15 mm Hg higher for patients whose hypertension is in control with occasional blood pressure spikes.

3.5.3. Hematology

The following hematology tests will be performed at the intervals described in the Schedule of Tests and Procedures Table: hemoglobin (Hgb), hematocrit (Hct), white blood cell count with differential (WBC w/diff), and platelets. Prothrombin time (PT) and partial thromboplastin time (PTT) will be done at baseline and then as clinically indicated.

3.5.4. Clinical Chemistry

The following clinical chemistry tests will be performed at the intervals described in the Schedule of Tests and Procedure Table: blood urea nitrogen (BUN), creatinine, sodium (Na^+), potassium (K^+), chloride (Cl^-), bicarbonate (HCO_3^-) or CO_2, alkaline phosphatase, lactate dehydrogenase (LDH), alanine aminotransferase (ALT, or SGPT), aspartate aminotransferase (AST, or SGOT), total protein, albumin, total bilirubin, glucose, thyroid stimulating hormone (TSH), T3 and T4, spot urine protein and spot urine creatinine.

3.5.5. Urinalysis

The following urinalysis will be performed by routine laboratory test at the intervals described in the Schedule of Tests and Procedures Table: protein, glucose, and blood. Patients with ≥2+ proteinuria will have protein quantitated by 24-hour urine protein determination. As clinically indicated, microscopic examination of the urinary sediment should be performed.

3.5.6. Blood Sample for Soluble Proteins

Plasma samples will be collected according to the schedule in the Table of Tests and Procedures to assess levels of soluble proteins in order to explore correlations with efficacy and biologic activity. Instructions for collection, processing, and shipping are found in Appendix F.

3.5.7. Tumor Biopsies and Blood Sample for Gene Profiling

Lymph node biopsies are requested for pharmacogenomic analysis as it may relate to the clinical response. Expression of genes in the tumor may change as a result of the treatment and these changes may reflect the characteristics of tumors that respond to treatment with AG-013736.

Lymph node resection will be performed following the completion of neoadjuvant therapy. The whole blood sample is used to explore the relationship between clinical response (tumor regression and/or toxicity) and individual genetics. This sample is requested of all patients, but not required as part of patient eligibility. These samples will be anonymized and will be disposed of after study analyses are completed. The tumor and peripheral blood samples will be used to analyze expression of RNA as they may relate to clinical response (tumor regression and/or toxicity) to AG-013736. No other studies will be performed with these samples.

The samples will not be made available to anyone not associated with this study or external investigators. All materials will be destroyed immediately after analysis. No genetic material will be stored. The samples will be identified by patient study identifier only and patient name, date of birth or other information will not be used on sample tube.

3.5.8. Efficacy Assessments

All baseline lesion assessments should be performed as close as possible to but not more than 4 weeks before treatment. At baseline, tumor lesions will be categorized as target or nontarget. All patients will be evaluated for response according to RECIST (see Appendix C) and/or by PET/CT. Because resection of the involved nodal basin will occur within 3 to 4 weeks of initial therapy, no confirmatory scans will be done. All scans for tumor assessment must be performed at the same imaging site for consistency. Transfer of tumor assessment images will be done electronically whenever possible. The tumor assessments will be formally evaluated within 2 weeks of receipt by the vendor. As part of tumor assessments, exploratory studies of volumetric determinations of individual lesions and other methods of measuring tumor size may be performed.

3.5.9. Timing of Procedures

The minimum required prestudy, on study, and follow up evaluations are summarized in the Schedule of Tests and Procedures Table. Other parameters and/or increased frequency of examinations or clinical follow up may be needed depending on the findings during the study. Assessments should be performed on schedule, but a window of +/-4 days is permitted for holidays, vacations, and other administrative reasons.

3.5.9.1. Screening Procedures

All patients being considered for the study and eligible for screening must sign an informed consent for the study prior to any study-specific procedures. Subjects should be screened to determine if they are healthy enough to go back on the investigational agent. Following completion of the pretreatment assessments and confirmation of eligibility by the Lead Investigator, patients may be treated.

3.5.9.2. On-study Procedures

Patients will receive dosing of AG-013736 as outpatients. Clinic visits will be performed, and hematology, clinical chemistry and other safety laboratory tests will be done as shown in the Schedule of Tests and Procedures Table. If significant toxicity (CTC Grade $\geq$3) is encountered, subsequent assessments may be performed as necessary to evaluate the specific toxicity until it resolves to baseline or CTC Grade $\leq$1. Additional clinic visits may be required at the discretion of the investigator.

3.5.9.3. End of Study Procedures

The primary reason for a patient's discontinuation of the test drug will be clearly documented on the CRF. Assessments should be performed as outlined in the Schedule of Tests and Procedures Table.

End of study procedures will be performed at least 28 days after the last date of dosing or until alternative therapy is begun, whichever is sooner. A final safety assessment will be done no sooner than Day 28.

Adverse events that are serious, suspected to be related to study drug, or considered significant by the Lead Investigator must be followed after the time of therapy discontinuation until the event or its sequelae resolve or stabilize at a level acceptable to the investigator and the Pfizer medical monitor or his/her designated representative. Each serious adverse event (SAE) must be reported to Pfizer using the contact information provided in Appendix A.

3.5.9.4. Pregnancy Follow-Up

If the participant, or their partner, become pregnant during the study or within 90 days (180 days for males) after they have stopped taking the study drug, they will be asked to inform the Lead Researcher immediately. They will also be requested to inform the doctor who will be taking care of them or their partner during the pregnancy that they or their partner took part in this study. The study doctor will ask if they, or their partner or their pregnancy doctor would be willing to provide updates on the progress of the pregnancy and its outcome. If they/their partner/their pregnancy doctor agree, this information will be provided to the study sponsor for safety monitoring follow-up.

3.6. Study Completion

The study will be complete when all patients have discontinued study medication and have been followed to progression, death, withdrawal, or have been lost to follow-up or 1 year after the last patient receives their first dose of study treatment, whichever is first. All patients should be followed for progression and survival until the study is complete. Patients who are still being treated at the completion of the study and are deriving benefit may continue treatment under a separate continuation protocol.

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of AG-013736 at any time.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the investigators will ensure that adequate consideration is given to the protection of the patient's interest.

4. STUDY TREATMENTS

4.1. Allocation to Study Treatment

All patients will receive AG-013736.

4.2. Drug Supplies

4.2.1. AG-013736 Dose

The initial dose of AG-013736 will be 5 mg BID administered orally. Doses should be taken as close to 12 hours apart as possible and at approximately the same times each day. Instructions for modifying doses in individual patients can be found in Section 4.2.6.

Patients must be instructed that if they vomit anytime after taking a dose, that they must not "make it up" with an extra dose, but instead resume subsequent doses as prescribed. Any missed dose may be taken up to 3 hours prior to the next scheduled dose, otherwise it should be skipped. All missed or vomited doses should be recorded in the source documents and CRFs.

4.2.2. AG-013736 Formulation and Packaging

AG-013736 will be supplied as 1-mg and 5-mg tablets for oral administration. The tablets are film coated.

4.2.3. AG-013736 Preparation and Dispensing

AG-013736 will be dispensed in opaque plastic bottles to protect the compounds from light.

4.2.4. Compliance

Patients will maintain diaries to include missed or changed doses. Pill counts on returned AG-013736 bottles of drug should be performed.

4.2.5. AG-013736 Drug Storage and Accountability

AG-013736 will be supplied for the study by the Pharmacy Operations Office, Pfizer Global Research and Development. Clinical Trial Material (CTM) will be shipped to the study site with an Investigational Drug Receipt Confirmation form. This form will be completed with protocol number, drug name, lot number, quantity received and condition upon receipt. A copy of the form must be returned via fax to the Pharmacy Operations Office within 24 hours of receipt. A copy will also be returned via mail.

The investigator, or an approved representative (eg, pharmacist), will ensure that all study drug is stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. Drug should be stored at controlled room temperature (15-30°C), avoiding exposure to light.

To ensure adequate records, all study drug will be accounted for in the case report form and drug accountability inventory forms as instructed by Pfizer. Unless otherwise authorized by Pfizer, at the end of the clinical trial all drug supplies unallocated or unused by the subjects must be returned to Pfizer or its appointed agent (eg, a contract research organization).

AG-013736 is considered a hazardous drug (due to possible reproductive toxicity), and should be handled according to the recommended procedures described in the current edition of the American Society of Hospital Pharmacists (ASHP), Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs, American Hospital Formulary Service (AHFS) Drug Information (1999) and its references. Procedures described in each institution's pharmacy or hospital standard operating procedure manual should be followed when handling hazardous drugs.

4.2.6. Dose Interruptions and Modification

4.2.6.1. Dose Interruption and Reduction

Adverse events and other symptoms will be graded according to the current Common Terminology for Adverse Events version 4.0 (CTCAEv4) (see URL: http://ctep.cancer.gov/reporting/ctc.html). This section contains management of adverse events except hypertension, hemoptysis and proteinuria that are discussed in subsequent sections.

Patients developing a treatment-related CTC Grade 2 adverse event that is subjectively intolerable (except alopecia) and cannot be controlled by supportive treatment will have their dosing interrupted and then re-started at the same dose after resolution to CTC Grade ≤1 or baseline. If resolution does not occur within 4 weeks, the patient should be removed from the study.

Patients developing a treatment-related Grade 3 or 4 nonhematologic adverse event (except for alopecia) that cannot be controlled by supportive treatment will have their treatment interrupted. Patients with a treatment-related Grade 4 hematologic adverse event that cannot be controlled by supportive treatment drug will have treatment interrupted. Appropriate follow-up assessments will be done until recovery to less than or equal to CTC Grade 1 or baseline occurs. Upon adequate recovery, treatment can be resumed at a 20% lower dose, rounded down to accommodate dosage form availability. If resolution does not occur within 4 weeks, the patient should be removed from the study.

Any patients with recurring subjectively intolerable toxicity, ie, at least 1-week interruption of treatment for the same adverse event on at least 2 separate occasions, despite optimal supportive care, will resume dosing at a 20% lower dose once adequate recovery is achieved.

If any patient requires more than 2 dose reductions, contact the sponsor for discussion prior to removing the patient from the study. Patients removed from treatment for intolerable toxicity should still be followed for disease progression and survival.

The criteria for dose modification for study drug related adverse events is summarized in the table below:

CRITERIA FOR DOSE MODIFICATION FOR STUDY DRUG RELATED ADVERSE EVENTS	
RELATED ADVERSE EVENTS	**INTERVENTION**
CTC Grade 2 toxicity that is subjectively intolerable (except alopecia) and not controlled by optimal supportive medication	Interrupt dosing; re-start at same dose after resolution to CTC Grade ≤1 or baseline
CTC Grade ≥3 nonhematologic toxicity that is not controlled by optimal supportive medication Grade 4 hematologic toxicity that is not controlled by optimal supportive medication	Interrupt dosing; re-start at 20% lower dose after resolution to CTC Grade ≤1 or baseline
Recurrent subjectively intolerable toxicity (at least a week interruption on 2 occasions) that is not controlled by optimal supportive medication	Interrupt dosing; re-start at 20% lower dose after resolution to CTC Grade ≤1 or baseline

Guidelines for dose reductions for specific adverse events are provided in the following sections.

4.2.6.2. AG-013736 Dose Reduction for Hypertension

Patients treated with AG-013736 will be followed every two weeks in the clinic to monitor blood pressure. Patients will also be instructed to measure their blood pressure (BP) at home when feasible. All blood pressure measurements will be recorded in a diary and brought to the nurse or study coordinator at each clinic visit. Patients will be counseled by the study staff to inform their doctor immediately when their blood pressure parameters meet any of the limits outlined below or if they develop symptoms perceived to be related to elevated BP (eg, headache, visual disturbance).

New or additional antihypertensive therapy (see Section 4.3, Concomitant Medication(s) for guidance) should be started if 2 blood pressure readings, separated by at least 1 hour, show the following: 2 systolic blood pressure readings greater than 150 or 2 diastolic blood pressure readings greater than 100 mm Hg. Alternately, the dose of existing antihypertensive medication(s) may be increased. Furthermore, the early initiation of antihypertensive agents for Grade 1 and Grade 2 hypertension in order to minimize the occurrence of more severe or persistent hypertension while undergoing treatment with AG-013736 will not constitute a Grade 3 toxicity.

Patients on maximal antihypertensive treatment (eg, 4 antihypertensive medications given for 2 weeks) who have 2 systolic blood pressure readings, separated by at least 1 hour, greater than 160, or 2 diastolic blood pressure readings, separated by at least 1 hour, greater than 105, will have treatment with AG-013736 held. (Note: if study drug is held, patients receiving antihypertensive medications should be monitored closely for hypotension.) Blood pressure

measurements used for AG-013736-discontinuation decision-making should be done in the clinic. Treatment with AG-013736 may be restarted at approximately 20% lower dose, rounded down to accommodate dosage form availability, after the systolic blood pressure reduces to less than 150 and the diastolic blood pressure reduces to less than 100.

Patients not on maximal antihypertensive treatment who in a 1-week period have 2 systolic blood pressure readings greater than 200 or 2 diastolic blood pressure readings greater than 110, will have treatment with AG-013736 held. (Note: if study drug is held, patients receiving antihypertensive medications should be monitored closely for hypotension.) Blood pressure measurements used for AG-013736-interruption decision-making should be done in the clinic. Treatment with AG-013736 may be restarted at the previous dose after the systolic blood pressure reduces to less than 150 and the diastolic blood pressure reduces to less than 100.

Guidance on dose interruption and reduction for hypertension is summarized in the table below.

HYPERTENSION MANAGEMENT PLAN			
Degree of Blood Pressure Elevation			**Management**
Systolic Pressure		**Diastolic Pressure**	
2 BP readings separated by at least 1 hour show systolic pressure >150 mm Hg	OR	2 BP readings separated by at least 1 hour show diastolic pressure >100 mm Hg	Maintain dose of study drug; patient to self monitor blood pressure. Institute new or additional antihypertensive medication or increase dose of current medication
2 BP readings separated by at least 1 hour show systolic pressure >160 mm Hg in patients on maximal antihypertensive treatment	OR	2 BP readings separated by at least 1 hour show diastolic pressure >105 mm Hg in patients on maximal antihypertensive treatment	Interrupt dosing; once BP is less than 150/100 restart drug at 20% lower dose
2 BP readings within 1 week show systolic pressure >200 mm Hg in patients who are not on maximal antihypertensive treatment	OR	2 BP readings within 1 week show diastolic pressure >110 mm Hg in patients who are not on maximal antihypertensive treatment	Interrupt dosing; adjust anti-hypertensive medication; once BP less than 150/100 restart drug at previous dose

4.2.6.3. AG-013736 Dose Reduction for Hemoptysis

Bleeding from the lungs will be graded according to the Hemorrhage category of CTC.

Treatment with AG-013736 will be discontinued for hemoptysis of Grade 1 or greater. If Grade 1 hemoptysis resolves within 1 week, treatment with AG-013736 may continue at the current dose level. Patients who experience Grade 1 hemoptysis that does not resolve within

1 week or who experience Grade 2 or greater hemoptysis at any time should be taken off study and not receive further AG-013736.

4.2.6.4. AG-013736 Dose Reduction for Proteinuria

At documentation of ≥2+ proteinuria by dipstick, patients should have a 24-hour urine collection for total protein. Alternatively, the urine protein:creatinine ratio (UPCR) will be evaluated to determine if it is >2. AG-013736 dosing may continue while waiting for the test results.

If <2 g proteinuria/24 hours is reported, or the UPCR is </= 2, patients may continue AG-013736 treatment without dose reduction.

If proteinuria > 2g/24 hours but ≤3.5 g/24 hours or a UPC between 2 and 3.5 is reported, treatment with AG-013736 may continue at a 20% lower dose, rounded down to accommodate dosage form availability. A 24-hour urine collection for total protein and creatinine clearance must be performed every 4 weeks to monitor the degree of proteinuria until it has decreased to <2 g/24 hours. Once the urinary protein is below 2 g/24 hours, urine dipstick determinations may be used.

If UPC is >3.5 or the 24 hour urine shows >3.5 g proteinuria/24 hours is reported, treatment with AG-013736 should be suspended. Twenty-four hour urine collection for total protein and creatinine clearance should be done weekly until results show <2 g proteinuria/24 hours, or a UPC <2, at which time treatment with AG-013736 may be restarted at a 20% lower dose, rounded down to accommodate dosage form availability. Patients, once restarted on AG-013736, will have weekly monitoring for proteinuria by semiquantitative testing (eg, dipstick) as long as the proteinuria reading is 2+ or higher, or, alternatively, by quantitative methods as long as proteinuria is ≥1 g/24 hours. The 24-hour urine collection to monitor the degree of proteinuria should be repeated every 4 weeks until it has decreased to <500 mg/24 hours.

4.2.6.5. Dose Escalation

Patients who tolerate AG-013736 with no adverse events related to AG-013736 above CTC Grade 1 for any consecutive 8-week period should have their dose increased by 20% unless the patient is responding to therapy.

Once a patient has a dose reduction for study drug related toxicity, the dose normally will not be re-escalated. However, patients who tolerate the lower dose without toxicities above Grade 1 for at least 8 weeks may be considered for re-escalation. The investigator and sponsor's medical monitor will discuss the case and decide if re-escalation is appropriate.

Dose escalation to a maximum of 10 mg BID will be considered for patients without an elevation of diastolic blood pressure above 90 mm Hg in Cycle 1 or other significant drug-related toxicities.

4.3. Concomitant Medication(s)

Palliative and supportive care for disease-related symptoms will be offered to all patients on this trial. Low-dose oral steroids (defined as ≤5 mg per day prednisone or equivalent) or topical or inhaled steroids at any dose may be taken during the study. No other chemotherapy, hormonal therapy, radiotherapy, or experimental anticancer medications will be permitted while the patient is on study. Any disease progression requiring other forms of specific anticancer therapy will be cause for discontinuation from study treatment.

In vitro studies with human liver microenzymes and recombinant CYP450 enzymes indicated that AG-013736 metabolism was primarily mediated by the drug-metabolizing enzyme CYP3A, and to a lesser extent by CYP1A2. Additionally, the drug also undergoes N-glucuronidation in liver microsomes of some species. Clinically, there is likelihood that AG-013736 plasma concentrations may be increased in the presence of co-administered potent inhibitors of the CYP3A and glucuronosyltransferase enzymes. The potential exists for drug-drug interactions with CYP3A inhibitors such as grapefruit juice, ketoconazole, miconazole, itraconazole, erythromycin, clarithromycin, verapamil, ergot derivatives, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, and delavirdine. Caution should be exercised in patients receiving AG-013736 in combination with these and other potent CYP3A inhibitors until appropriate clinical drug interaction studies are performed.

AG-013736 metabolism may be induced in patients taking CYP3A4 or CYP1A2 inducers (carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, primidone, rifabutin, rifampin, and St John's wort) and this may reduce AG-013736 plasma concentrations. Patients who require concomitant treatment with CYP3A4 or CYP1A2 inducers are not eligible for the study. Since CYP1A2 is also known to be induced in chronic smokers, there is likelihood that AG-013736 plasma concentrations may be reduced in these individuals.

The ability of AG-013736 to increase concentrations of coadministered drugs was also investigated in studies with human liver microsomes. At expected therapeutic plasma concentrations (0.01 to 1.0 μg/mL), AG-013736 appears most likely to inhibit the drug metabolizing enzymes CYP1A2 and CYP2C8, 2 enzymes not frequently observed as predominant drug metabolizing enzymes. Paclitaxel, theophylline, and tacrine are among the few drugs whose plasma concentrations are likely to be increased by AG-013736.

AG-013736 is highly bound to proteins in human plasma (99.5% bound at concentrations of 0.2 to 20 μg/mL). Therefore, drug interactions with other agents that are also highly bound to plasma proteins are a possibility.

Patients who need to be on chronic antacid therapy with histamine H_2 antagonists (eg, cimetidine [Tagamet®], famotidine [Pepcid®], nizatidine [Axid®], ranitidine [Zantac®]), proton-pump inhibitors (eg, lansoprazole [Prevacid®], rabeprazole [Aciphex®], pantoprazole [Protonix®], and esomeprazole [Nexium®]), or locally acting antacids (eg, Maalox®, Milk of Magnesia®, Amphojel®) should stagger the timing of their AG-013736 and antacid dosing. Patients should avoid use of antacids for 2 hours before through 2 hours after taking AG-013736 tablets. Note, however, that patients taking the proton-pump inhibitor omeprazole (Prilosec®) are not eligible

for this study and that patients should not use omeprazole while taking AG-013736 tablets because omeprazole is a CYP1A2 inducer.

AG-013736 is not likely to have drug-drug interactions with commonly used antihypertensive agents belonging to the class of ACE inhibitors including angiotensin II receptor antagonists (enalapril, captopril, losartan, vasartan), beta-blockers (atenolol, metoprolol, labetalol), or diuretics (hydrochlorothiazide, furosemide). Within the class of calcium channel blockers, verapamil, and to a lesser extent nifedipine, nicardipine, and diltiazem have a potential for increasing plasma AG-013736 plasma concentrations, due to CYP3A inhibition and should not be used as first choice in antihypertensive treatment. Other calcium channel blockers (amlodipine, bepridil, felodipine) are less likely to raise AG-013736 plasma levels.

The information on drug interactions is based on preclinical data from studies using human and animal metabolizing enzyme systems. No formal human drug interaction studies have been performed.

All concomitant medications and blood products, as well as interventions (eg, analgesic use or paracentesis) received by patients from the first dose of study drug until the end of study visit will be recorded on the CRF.

4.4. Salvage Therapy

Patients who progress or who cannot tolerate therapy should be considered for other therapy as appropriate.

5. Safety reporting

All subjects who receive at least one dose of study drug will be evaluable for safety. Investigators and all appropriate staff should review and have access to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0, published May 28, 2009 by the US National Cancer Institute (NCI), which can be downloaded from the NCI website <http://ctep.cancer.gov/reporting/ctc.html>. The reported AE term and CTC severity grade should correspond to the term and severity grade included in the relevant source document/clinic chart. The investigator must endeavor to obtain sufficient information to determine the causality of the adverse event (i.e., study drug, other illness, progressive malignancy, etc.) and must provide his/her opinion of the causal relationship between each AE and each study drug.

5.1. Adverse Events

All observed or volunteered adverse events regardless of suspected causal relationship to the investigational product(s) will be recorded on the adverse event page(s) of the case report form (CRF).

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its

designated representative (see Section 5.4). For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality and indicate that assessment on the CRF. Follow-up of the adverse event, after the date of therapy discontinuation, is required if the adverse event or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator and the Pfizer medical monitor.

5.2. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of effect.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug abuse;
- Drug misuse;
- Drug interactions;
- Drug dependency;
- Exposure *in utero*.

Lack of or insufficient clinical response, benefit, efficacy, or therapeutic effect should not be recorded as an adverse event. Progression of the malignancy under study should not be reported as an adverse event. However, if the malignancy has a fatal outcome during the trial or within the safety reporting period, then disease progression must be recorded as an adverse event (and an SAE with CTC grade 5 (see Section 5.6, Severity Assessment).

5.3. Abnormal Laboratory Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in trial dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

5.4. Serious Adverse Events

A serious adverse event or serious adverse drug reaction is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject and may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

5.5. Hospitalization

Adverse events reported from clinical trials associated with hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets this criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;

- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a Serious Adverse Event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a clinical trial (eg, for a procedure required by the trial protocol);
- Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery);
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

5.6. Severity Assessment

As required on the adverse event case report forms, the investigator will use the following definitions of Severity in accordance with Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (Version 3.0, December 12, 2003) to describe the maximum intensity of the adverse event. If the event is serious, the CTC grade reported in the adverse event CRF must be consistent with the description of CTC grade included in the narrative section of the serious adverse event report.

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 3.0 document but may be used in certain circumstances.)
1	MILD AE
2	MODERATE AE
3	SEVERE AE
4	LIFE-THREATENING OR DISABLING AE
5	DEATH RELATED TO AE

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

5.7. Exposure In Utero

An *exposure in-utero* (EIU) occurs if a female becomes, or is found to be, pregnant either while receiving or having been exposed to (eg, environmental) an investigational medication or product, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to the investigational medication or product.

If any trial subject becomes or is found to be pregnant while receiving an investigational medication/product, the investigator must submit this information to Pfizer medical monitor on an Exposure in Utero Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

The investigator will follow the subject until completion of the pregnancy or until pregnancy termination (ie, induced abortion) and then notify Pfizer medical monitor of the outcome. The investigator will provide this information as a follow up to the initial Exposure in Utero Form. The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, an SAE case is created with the event of ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth or neonatal death]), the investigator should follow the procedures for reporting serious adverse events.

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (ie, no minimum follow-up period of a presumably normal infant is required before an Exposure in Utero Form can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as serious adverse events follows:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month that the investigator assesses as possibly related to the in utero exposure to the investigational medication should be reported.
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5.8. Discontinuations (See also Subject Withdrawal, Section 3.3)

The reason for a subject discontinuing from the trial will be recorded in the CRF. A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol. The investigator must determine the primary reason for discontinuation. Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page.

When a discontinuation is due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

5.9. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial subject. In addition, each trial subject will be questioned about adverse events at each clinic visit following initiation of treatment. The question asked will be "Since your last clinic visit you began taking the investigational medication have you had any health problems?"

5.10. Reporting Requirements (Serious and Nonserious)

Each adverse event is to be classified by the investigator as serious or nonserious. This classification determines the reporting procedures to be followed. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

SAEs are reportable from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the clinical trial, ie, prior to undergoing any trial-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Any serious adverse event occurring at any

other time after completion of the study must be promptly reported if a causal relationship to study drug is suspected.

If a serious adverse event occurs, the Pfizer centralized SAE reporting system (see Appendix A) is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to the Pfizer centralized SAE reporting system must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient trial subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to the Pfizer centralized SAE reporting system in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by the Pfizer centralized SAE reporting system to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

The investigator's assessment of causality must be provided. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. If the investigator's final determination of causality is unknown and the investigator does not know whether or not study drug caused the event, then the event will be handled as "related to study drug" for reporting purposes. If the investigator's causality assessment is "unknown but not related to study drug", this should be clearly documented on study records. In addition, if the investigator determines the adverse event is associated with trial procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

Nonserious adverse events are to be reported on the adverse event CRFs, which are to be submitted to Pfizer as specified in the adverse event report submission procedure for this protocol.

If a subject begins a new anticancer therapy, the adverse event reporting period will end at the time the new treatment is started. Death must be reported if it occurs during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.

5.11. Abnormal Physical Examination Findings

Clinically significant changes, in the judgment of the investigator, in physical examination findings (abnormalities) will be recorded as adverse events.

6. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in an Analysis Plan, which will be dated and maintained by the sponsor. This documentation may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

6.1. Statistical Power and Sample Size Considerations

6.1.1. Sample Size

The primary purpose of this study is to determine the response rate in patients with advanced melanoma. This information would then be used to recommend further study of AG-013736 in this indication if favorable results occur. Implicit in this objective is the need to minimize the number of patients exposed to AG-013736 when unfavorable results occur.

These objectives are met through the use of a 2-stage Minimax design for Phase 2 protocols as discussed by Simon.[11] The 2-stage design is used for testing hypotheses about the true response rate P. For each indication, we define p_0, a response rate at which or below we consider AG-013736 to be ineffective or clinically unimportant, and p_1, a minimum response rate that would merit further clinical development. The null hypothesis, H_o, is $P \leq p_o$. The alternate hypothesis, H_1, is $P \geq p_1$.

The indication being studied in this protocol responds poorly to conventional chemotherapy. Therefore, p_0 and p_1 are set at low response rates of 5% and 20%, respectively. The α and β error rates are set at 0.10 and 0.10, respectively. These criteria result in a sample size for each stage of 18 and 14 patients (based on PASS 2002 software).

If enrolment to this study is stopped and AG-013736 is rejected at any stage because of lack of efficacy, the probability of falsely rejecting it is <0.10 when the true response rate is ≥20%. At the end of Stage 2, if AG-013736 is recommended for further study, the probability of failing to reject the agent is <0.10 when the true response rate is ≤5%. If the true response probability is ≤5%, there is approximately a 40% probability of terminating patient enrolment during Stage 1. However, if the true response probability is ≥20%, then there is only a 1.8% probability that a drug will be discarded erroneously in Stage 1.

Up to 28 additional patients (for a total of up to 32) may be treated in order **to gain additional safety and activity information** should the trial be positive at the end of Stage 2. Their safety and efficacy data will be summarized with all other patients at the end of the study.

6.1.1.1. Stage 1

Initially, 18 patients with the indication and treated with AG-013736 will be evaluated for response (CR or PR). Once 1 or more confirmed responses are documented, the study will proceed to Stage 2. If 1 confirmed response has not been documented by the time 18 patients have been started on treatment, enrolment will be temporarily suspended to allow for treatment and evaluation of these patients.

6.1.1.2. Stage 2

In Stage 2, 14 additional patients will be enrolled and treated, to a total sample size of 32 treated patients. If 4 or more responses (CR or PR) are documented among these 32 patients, the indication will be recommended for further study.

6.2. Methods of Analysis

The emphasis of the statistical analyses in this study will be on estimation. Due to the exploratory nature of this study, no imputation of missing data will be done.

An initial assessment will be done after 18 patients with eligible diagnoses have been treated. If there is at least 1 patient with a confirmed response, the trial will be expanded to a total of 32 treated patients with eligible diagnoses. The final analysis will be conducted when at least 1 of the following conditions is met:

- If 4 or more confirmed responses (CR or PR) are documented among the first 32 treated patients enrolled with eligible disease by the end of Stage 2 and the study is not expanded to add additional patients, the final analysis will take place once data have been compiled on all 32 treated patients through at least 1 year from the date of the first dose for the last patient enrolled. The final analysis will occur sooner if the study is discontinued due to lack of clinical response;
- If the study is expanded to derive further information on safety and activity to be used to aid in the design of additional studies with AG-013736 in this indication, then final analysis will take place once data have been compiled on all treated patients through at least 1 year from the date of the first dose for the last patient enrolled.
- The study is complete as defined in Section 3.6.

6.2.1. Primary Efficacy Parameter

The primary efficacy parameter is the overall response rate. All patients who receive at least 1 dose of AG-013736 and have a baseline assessment of disease will be included in the analysis. Patients who were inadvertently enrolled (eg, patients who are determined to have the incorrect histological cancer type after receiving a dose of medication, based on their screening disease

assessment) will be excluded from analyses and will be replaced. The overall response rate is defined to be the percentage of patients with a confirmed CR or PR. Patients who die, progress, or drop out for any reason after receiving a dose of AG-013736 prior to reaching a CR or PR will be included in the analysis as non-responders.

For response rate, duration of response, and progression-free survival, assessments from the independent third party will be considered the primary data. Additionally, the primary analyses for these endpoints will be based on the data collected from the disease assessment method(s) used starting at baseline to follow a patient's lesions. If PET scans or ultrasound is used on some patients during study who are believed to have central tumor necrosis or intratumor bleeding, these data and any subsequently collected lesion assessment data will not be used in the primary analyses but may be used in exploratory analyses of response rate, duration of response and progression-free survival.

6.2.1.1. Primary Analyses

The response rate (CR or PR) will be provided with an exact 95% 2-sided confidence interval calculated using a method based on the *F* distribution. For the definition of the response categories, see Appendix C.

6.2.2. Secondary Efficacy Parameters

The secondary efficacy parameters are:

The progression free survival.

After discontinuing the study medication, patients may be treated with additional therapy. Data collected after patients have been treated with additional therapy will not be used for efficacy analyses except for survival.

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6.2.2.1. Secondary Analyses

6.2.2.1.1. Response Rate

The response rate (CR or PR) will be provided with an exact 95% 2-sided confidence interval calculated using a method based on the *F* distribution. For the definition of the response categories, see Appendix C.

6.2.2.1.2. Progression-free survival (PFS)

All patients who receive at least 1 dose of AG-013736 and have a baseline assessment of disease will be included in the analysis. Patients who were inadvertently enrolled (eg, patients who are

determined to have the incorrect histological cancer type after receiving a dose of medication, based on their screening disease assessment) will be excluded from analyses.

PFS is defined as the difference in days between the first date that criteria for progression were met or the patient died and the date of first dose of AG-013736. Since the day of first dose and the day criteria for progression were met (or the patient died) are each counted as a full day, 1 day will be added to each calculation. Patients lacking an evaluation of tumor response after their first dose will have their event time censored at 1 day. Patients not experiencing disease progression during the treatment and follow-up periods and who do not die during the treatment period will have their event time censored on the last study date that objective tumor assessments verified lack of disease progression.

An estimate of the PFS curve from the Kaplan-Meier[12] method will be presented. Median event time and a 2-sided 95% confidence interval for the median will be provided.[13]

Duration of Overall Response

Analyses on duration of overall objective response will be done for all patients achieving a PR or CR. Duration of overall objective response is defined as the difference in days between the first date criteria for progression occurred and the first date that criteria for a PR or CR were met. Since the day the criteria for PR or CR were met and the first day criteria for progression occurred are each counted as a full day, 1 day will be added to each calculation. Patients who achieve a PR or CR and who do not experience disease progression during the treatment and follow-up periods and who do not die during the treatment period will have their event time censored on the last study date that objective tumor assessments verified lack of disease progression. Patients who die during the treatment period with no disease progression observed, and still in response, will have their duration calculated using the date of death as a non-censored value. Patients who achieve a PR and then a CR will have times calculated using the date of the PR as the first day.

Estimates of duration of overall response from the Kaplan-Meier[12] method will be presented. Median event time (if appropriate) and a 2-sided 95% confidence interval for the median will be provided. [13] The number of CR and PR patients may be small and thereby limit use of the Kaplan-Meier method to provide reliable information. In this case, descriptive statistics or listings will be provided.

6.2.2.1.3. Survival

All patients who receive at least 1 dose of AG-013736 are eligible for this analysis. Survival time is the difference in days between the date of death and the date of first dose of AG-013736. Since the day of first dose and the day of death are each counted as a full day, 1 day will be added to each calculation. Patients not expiring will have their survival times censored on the last date of known contact that the patient was documented to be alive. Patients lacking data beyond the day of first dose will have their survival times censored at 1 day.

An estimate of the survival time curve from the Kaplan-Meier method will be presented. Median event time and a 2-sided 95% confidence interval for the median will be provided.

6.2.3. Analysis of Dropouts

Patients discontinuing the study over time will be summarized.

6.2.4. Safety Parameters

All patients who receive any study treatment will be included in the final summaries and listings of safety data. Summaries of AEs and other safety parameters will be provided as appropriate

Frequencies of patients experiencing at least one AE will be displayed by body system and preferred term according to MedDRA terminology. Detailed information collected for each AE will include: description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Intensity (severity) of the AEs will be graded according to the CTCAEv4.0. Emphasis in the analysis will be placed on AEs classified as treatment emergent.

Summary tables will present the number of patients observed with AEs and corresponding percentages. The denominator used to calculate incidence percentages consists of patients receiving at least 1 dose of study medication. Within each table, the AEs will be categorized by MedDRA body system and preferred term. Additional subcategories will be based on event intensity and relationship to study drug.

Individual patient listings will be prepared for all AE data. Summary tables for extent of exposure to study medication will also be provided.

6.2.5. Clinical Laboratory Analysis

Listing tables will be prepared for each laboratory measure, and will be structured to permit review of the data by patient as they progress on treatment.

Summary tables will be prepared to examine the distribution of laboratory measures over time. Shift tables may be provided to examine the distribution of laboratory toxicities.

6.2.6. Analysis of Soluble Proteins

Plasma soluble protein will be assessed using 1 or more methods available at the time of the analyses. Possible technologies that are currently being explored include proprietary antibody coated analysis chips and laser excited mass spectroscopy. Plasma levels of soluble proteins (including but not limited to VEGF, placental growth factor [PlGF], and soluble VEGFR2 [sVEGFR2], and Thrombospondin-1) may be associated with angiogenesis or tumor physiology and may correlate with efficacy or biological activity. However, other unidentified proteins may also correlate. While samples will be taken on all patients, assays may only be performed if stage 2 is opened, otherwise, there will be insufficient clinical response to provide clinical correlates. Listing and summary tables will be prepared. Exploratory analyses will be done looking for changes in protein expression that predict for clinical response.

6.2.7. Gene Profiling

6.2.7.1. Tumor Samples

Tumor biopsy samples will be obtained when possible in order to develop primary tumor cell lines for studies directed at the identification of sensitive and resistant biomarkers. Gene profiles will be generated on cell lines using microarrays that have about 25,000 known genes. Exploratory analyses will be performed to detect changes to gene expression caused by treatment with AG-013736. Additional exploratory analyses will be performed to detect potential changes in gene expression that distinguish tumors that respond, or at least regress, from those that are stable or progressing.

Data from the chip analysis will be processed by gene chip expression software. The intensity of each probe set of the array will be captured and expression values calculated using a scanner. Data analysis will be analyzed to identify genes that are differentially expressed between the baseline and treated tumor samples. Data analysis will be performed to identify genes that are differentially expressed on tumors that have responded (or at least regressed) and those that remained stable or progressed. The set of genes that may be associated with the clinical response will be further confirmed by RT-PCR method. In vitro cell cultures will also be tested for response to antiangiogenesis agents in vitro.

7. OVERSIGHT COMMITTEES

A UC Irvine data safety monitoring board will review safety data consisting of the reported adverse events, discontinuations and mortality that occur during the course of the protocol. The DSMB will evaluate the safety of the program using available data from the clinical and SAE databases on a 6 month basis, or more frequently if a safety issue arises. Based on the data review, the committee will make recommendations as to whether any modifications of the trial are warranted.

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APPENDIX A Serious Adverse Event Reporting

All serious adverse events regardless of suspected relationship to study drug must be reported immediately by telephone to the number listed below:

TOLL FREE NUMBER: (877) 433-2619

File SAE report to Pfizer

1. Cover letter (optional)
2. Filled the Form FDA 3500A (MedWatch, download from FDA website)

Fax to 1-866-997-8322

The FAX confirmation will serve as they received the document. Then Pfizer will send out SUSAR to all sites,

APPENDIX B Other Administrative and Regulatory Procedures

1. INTRODUCTION

This appendix provides information necessary to administer this study in compliance with global Good Clinical Practices (GCPs), government regulations, and the policy and procedures of Pfizer Inc.

2. ADMINISTRATIVE PROCEDURES

2.1. Compliance With Good Clinical Practice and Ethical Considerations

This study must be conducted in compliance with Institutional Review Board/ Independent Ethics Committee (IRB/IEC), informed consent regulations, and International Committee on Harmonization (ICH) GCP Guidelines. In addition, all local regulatory requirements will be adhered to, in particular those which afford greater protection to the safety of the trial participants.

This study will be conducted in general according to the Declaration of Helsinki and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

Before initiating a trial, the investigator/institution will have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, subject recruitment procedures (eg, advertisements), and data collection instruments which will be completed by subjects. Protocol amendments, consent form updates, and any amendments to the documents described before must be approved by the IRB/IEC prior to implementation unless such changes are necessary to address immediate safety concerns.

2.2. Informed Consent

The investigator, or a person designated by the investigator, will explain the benefits and risks of participation in the study to each subject, subject's legally acceptable representative (not permitted for Phase 1 normal volunteer studies) or impartial witness and obtain written informed consent prior to the subject entering the study (before initiation of protocol-specified procedures).

The informed consent form must be agreed to by Pfizer and the IRB/IEC and must be in compliance with ICH GCP and in accordance with local regulatory and legal requirements, in language readily understood by the subject. Each subject's original consent form, signed and dated by the subject or by the subject's legally acceptable representative, and a witness to the informed consent discussion, will be retained by the investigator.

2.3. Confidentiality of Subject Information

All subjects will be assigned a study subject number. Subsequently, subjects will be identified in the CRFs only by their initials and that number. Any information published as a result of the

study will be such that it will not permit identification of any subject. The information from this study will be available within Pfizer Inc and may be shared with the regulatory authorities. It may also be the subject of an audit by a regulatory agency (eg, FDA) within the local government. The subject's identity will remain protected except as required for legal or regulatory inquiries.

2.4. Institutional Review Board (IRB) or Ethics Committee (EC) Review and Approval of the Study

An IRB/EC, that is organized and operates according to GCP and applicable laws and regulations, should safeguard the rights, safety, and well-being of all trial subjects. No subject should be admitted to a trial before the IRB/EC issues its written approval/favorable opinion of the trial.

The investigator is responsible for:

- Promptly reporting to the IRB/EC all changes in the research activity and all unanticipated problems involving risks to human subjects or others;
- Submitting a progress report describing the status of the clinical investigation to the IRB/EC at appropriate intervals not exceeding 1 year. Copies of these reports will also be provided to Pfizer Inc;
- Submitting a final progress report to the IRB/EC (if requested) following completion, termination, or discontinuation of the study. Copies of these reports will also be provided to Pfizer Inc;
- Handling all communications with the IRB/EC regarding the study of a Pfizer Inc drug;
- Providing a copy of all communications from the IRB/EC to the investigator regarding its review of and initial approval of the study and its reapprovals to the Pfizer Inc Site Monitor; and
- Documenting and retaining in the institution the identification codes, names, and randomization numbers (where applicable) for all trial participants.

2.5. Clinical Evaluations Not Specified in the Protocol

Procedures not specified in the protocol can be conducted only if required for the successful management of a subject. Additional procedures not related to management of safety parameters must be approved by the Pfizer Inc Clinical/Medical Colleague.

2.6. Monitoring, Verification of Data, Audit, and Inspection

The Lead Investigator is to ensure that the trial participants are aware of and consent that personal information may be reviewed during the data verification process as part of monitoring/auditing by properly authorized agents of Pfizer or subject to inspection by regulatory authorities. In addition, participation and personal information is treated as confidential to the extent the applicable law permits and not publicly available. The audit or

inspection may include, for example, a review of all source documents, drug records, original clinic medical notes, some or all of the facilities used in the trial.

Recruitment at a center may be stopped for reasons of particularly low recruitment, protocol violation, or inadequate data recording.

2.7. Study Summarization and Publication of Study Results

Data analysis, statistical reporting, and research report preparation will be the responsibility of the Lead Investigator or a duly authorized designee. Publication of study results is governed by the requirements specified in the written research agreement between the Investigator and Pfizer Inc.

Information regarding the operations and procedures of Pfizer Inc obtained as a result of or in association with the conduct of this study must be kept confidential. At no time may information on the operations of Pfizer Inc be disclosed directly or indirectly to representatives or agents of other pharmaceutical companies or commercial entities.

3. DOCUMENTATION PROCEDURES

3.1. Retention of Study Records

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor.

The investigator must contact Pfizer Inc for approval prior to discarding any study-related documents, even if retention requirements have been met.

If the lead investigator leaves the institution at which the study has been conducted, he/she or current representative must contact Pfizer Inc to make suitable arrangements to ensure that the study records, including a copy of the master subject log, are retained as specified above and to provide for the continuing access to the records by Pfizer Inc personnel and regulatory authorities.

3.2. Guidelines for Recording Data in the Case Report Forms (CRFs)

The completed CRF is a legal document as it is intended for submission to a regulatory agency as part of a regulatory submission.

In compliance with Good Clinical Practice; the medical records/medical notes, etc, should be clearly marked and permit easy identification of participation by an individual in the specified clinical trial. In some cases, data may be recorded directly onto a CRF instead of medical

records/medical notes and will be considered source documentation. The sponsor will communicate to the investigator any CRFs that will serve as source documentation for the study.

The investigator is to record all data with respect to protocol procedures, drug administration, laboratory data, safety data, and efficacy ratings using CRFs or other data collection methods designed by Pfizer. The investigator's signature is required to attest to the accuracy and completeness of the data. All electronic records and electronic signatures must comply with applicable laws and regulations governing electronic data systems (eg, FDA 21CFR11).

All corrections on a CRF and on source documents must be made in a way that does not obscure the original entry. The correct data must be inserted, dated, and initialed/authorized by study site personnel.

4. PROTOCOL AMENDMENTS

All amendments to the protocol must be approved by the lead investigator, Pfizer Inc, and the IRB/EC of the investigator's institution. The investigator is responsible for submitting any proposed change in the approved protocol in writing to the IRB/EC for review and approval and for sending a copy of the approval to Pfizer Inc.

With the exception of amendments immediately implemented for safety reasons, the amendment will apply to all subjects entered into the study (or all subjects in affected sites for a country or site amendment) after it has gone through the applicable procedure described above and been approved by the IRB/EC.

If the amendment eliminates an apparent immediate safety hazard to the subject (urgent protocol amendment), it may be implemented immediately. The lead investigator will notify his/her IRB/EC of the change in writing within 5 working days of its implementation.

APPENDIX C RECIST Criteria

At baseline, tumor lesions will be categorized as measurable or nonmeasurable (defined below).

All baseline evaluations should be performed as close as possible to the first day of study treatment and never more than 4 weeks before starting therapy.

Measurable Lesions

- Lesions that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥2.0 cm with conventional techniques or ≥1.0 cm with spiral CT scan.
- A tumor lesion that is situated in a previously irradiated area is eligible for measurable disease provided: 1) there has been documented disease progression in this site; 2) the criteria for measurability as outlined above are met; 3) this is not the only site of measurable disease.
- All measurements should be determined using a ruler, calipers or digital technology, and recorded on the CRF in metric notation.

Nonmeasurable Lesions

All other lesions, including small lesions (longest diameter <2.0 cm with conventional techniques or <1.0 cm with spiral CT) and truly nonmeasurable lesions. Truly nonmeasurable lesions include bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis cutis or pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Documentation of Target and Nontarget Lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and measured and recorded at baseline. Target lesions (measurable) should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically. A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as present or absent.

Techniques for Assessing Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at screening and during follow-up. Imaging-based evaluation is

preferred to evaluation by clinical (physical) examination when both methods have been used to assess the antitumor effect of a treatment.

Accepted methods of tumor assessment include:

Clinical examination: clinically detected lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

CT and MRI: CT and MRI are the best currently available and most reproducible methods of measuring target lesions selected for response assessment. Spiral CT should be performed using a </= 5 mm contiguous reconstruction algorithm.

PET/CT Scan: A PET scan will be done to assess the FDG uptake of the nodes involved by melanoma to determine their metabolic activity. Specific uptake values will be recorded for each nodal area of interest. A registration CT will be done to confirm anatomic location. SUV values >2.5 will be considered positive and assessable for response, which will be defined as a 30% reduction in SUV values.

Tumor markers: tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered a complete clinical response.

Cytology and histology: the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Response Criteria

The following RECIST criteria will be the primary method utilized in addition to PET scan results for the assessment and reporting of tumor response data.

Complete Response (CR): Disappearance of all target and nontarget lesions, normalization of tumor marker levels, and no appearance of new lesions indicates complete response

Partial Response (PR): At least a 30% decrease in the sum of the LDs of target lesions (taking as reference the baseline sum), without progression of nontarget lesions and no appearance of new lesions indicates partial response.

Stable Disease (SD): Neither PR or PD criteria are met. Patients who have stable disease (SD) as their only response will be categorized as stable disease if stable disease is documented after the initial 2 month treatment lead in.

Progressive Disease (PD): ≥20% increase in the sum of the LD of target lesions taking as references the smallest sum LD recorded since the treatment started, unequivocal progression of existing nontarget lesions, or the appearance of 1 or more new lesions.

Determination of Best Overall Response:

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference the for PD the smallest measurements recorded since treatment started). For CR and PR the best response assignment will depend on the achievement measurement criteria. Stable disease rate will be defined as the percentage of patients with stable disease based on the total number of patients evaluable for response.

Determination of best overall response is summarized in the following table:

Determination of Best Overall Response			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Overall Response**
CR[a]	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR[b]	Non-PD	No	PR
SD[c]	Non-PD	No	SD
PD[d]	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[a] Complete response.
[b] Partial response.
[c] Stable disease.
[d] Progressive disease.

Reference: Therasse P, Arbuck, SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205-216.

APPENDIX D ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in Am J Clin Onc 5:649-655, 1982.

APPENDIX E Sponsor's Representatives

Sponsor: Pfizer Inc – La Jolla Laboratories
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APPENDIX F BLOOD SAMPLES for Soluble protein assessments: Procedures for Sampling, Handling, Storage, and Shipment

Plasma samples for analysis of soluble proteins will be obtained at the time points designated in the protocol Schedule of Tests and Procedures Table.

1. An indelible marker should be used to record the patient initials, ID number, collection date, and cycle day on the collection tube prior to collection.
2. Collect 10.0 mL of blood into a sodium heparin tube (green top) at the designated times.
3. After collection, gently invert the tube (15 times) to completely mix blood and anticoagulant.
4. Once the sample has been mixed, it should be placed immediately into an ice bath ensuring that the tube is immersed so that the temperature is kept at 2° C to 8°C during all processing steps.
5. Centrifuge at 3500 rpm at 4°C for 10 minutes.
6. Transfer upper layer using a pipette into 4 Nalgene (2 brown capped, and 2 orange capped) cryovials; split approximately a quarter of the sample into each of the vials.
7. Store tubes at –70°C to –80°C.
8. One brown and one orange capped cryovial (primary sample, larger 3.6 mL tubes) should be shipped on the day of collection and one tube each (back-up sample, smaller 1.8 mL tubes) should be retained at the site in a –70°C or –80°C freezer.

APPENDIX G PROCESSING OF SAMPLES FOR GENOMICS ANALYSIS

Pharmacogenomic analysis of tumor samples:

After the patient grants informed consent for the biopsy, at least a 4 mm cube of tumor tissue from a superficial lesion should be obtained by a punch, core, or excisional biopsy. The first portion of the tissue will be placed in lactated Ringer's solution and refrigerated at 4°C for up to 3 days. The remainder of the 4 mm cube should be snap frozen in liquid nitrogen within one hour and stored at -70°C to -80°C. After the patient signs informed consent for peripheral blood sample collection, a blood sample (5 mL) will be collected in purple cap EDTA tubes and stored at -20^{o}C. At the request of Pfizer, samples should be shipped to the analysis laboratory in dry ice according to shipping instructions provided by the gene laboratory identified in the Study Manual. The samples will be stored in a secure environment until the analysis has been completed.

The tumor and peripheral blood samples will be used to analyze expression of RNA as they may relate to clinical response (tumor regression and/or toxicity) to AG-013736. No other studies will be performed with these samples.

Tumor RNA will be extracted and prepared by standard protocols used by the laboratory. From total RNA, cDNA will be generated by reverse transcription. The cDNA will be then fluorescently labeled and hybridized on Affymetrix Gene chips (microarrays) according to instructions provided by the manufacturer. These microarrays contain oligonucleotides representing about 25,000 known genes that represent most of the genes present in the human genome.

Data from the chip analysis will be processed by gene chip expression software. The intensity of each probe set of the array will be captured and expression values calculated using a scanner. Data analysis will be analyzed to identify genes that are differentially expressed between the baseline and treated tumor samples. Data analysis will be performed to identify genes that are differentially expressed on tumors that have responded (or at least regressed) and those that remained stable or progressed. The set of genes that may be associated with the clinical response will be further confirmed by RT-PCR method.

The sample analysis will be anonymized and will be carried out specifically for the purposes of evaluating correlation of RNA patterns with clinical response. The samples will not be made available to anyone not associated with this study or external investigators. All materials (RNA) will be destroyed immediately after analysis. No genetic material will be stored. The samples will be identified by patient study identifier only and patient name, date of birth or other information will not be used on sample tube.