Amendment

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Protocol Title: Phase II Study of IMC-A12 in Patients with Mesothelioma who have been Previously Treated with Chemotherapy

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* Signature signifies that investigators on this protocol have been informed that the collection and use of personally identifiable information at the NIH are maintained in a system of record governed under provisions of the Privacy Act of 1974. The information provided is mandatory for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural research protocols and used solely for those purposes. Questions may be addressed to the Protrak System Owner.

** I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

IRB Meeting Date: Expedited

DEC Clearance Date: NA

Protocol Version Date: 07/29/2015

Phase II Study of IMC-A12 in Patients with Mesothelioma who have been Previously Treated with Chemotherapy

Abbreviated title: Ph II IMC-A12 in Mesothelioma

NCI Protocol number: 8792

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Drug Sponsor: CTEP (Completed with sponsor as of 07/28/15)

NCI Supplied Agent: IMC-A12

IND # 100947

PRÉCIS/SCHEMA

Background:

Platinum-based chemotherapy is the standard of care for advanced unresectable malignant mesothelioma. New options for treatment are necessary in patients with advanced disease that have progressed on platinum-based therapy. The insulin-like growth factor (IGF) pathway is being studies in various malignancies including mesothelioma. IMC-A12 is an anti-IGF-1R monoclonal antibody that has shown activity in patients with various malignancies.

Objectives:

Primary Objective:

- To determine the clinical response rate (PR+CR) to IMC-A12 monotherapy in patients with advanced mesothelioma.

Secondary Objectives:

- To determine response duration, progression free survival (PFS) and overall survival (OS).
- To assess safety of IMC-A12 in patients with mesothelioma

Exploratory Objectives:

- To evaluate tumor IGF-1R expression and correlation with response
- To correlate response to therapy with changes in FDG-PET imaging.
- To monitor serum mesothelin and CA-125 levels prior to and during therapy.

Eligibility:

- Patients with histologically confirmed malignant pleural or peritoneal mesothelioma who have previously been treated on at least one platinum-containing chemotherapy regimen with progressive disease documented prior to study entry, or have refused cytotoxic chemotherapy
- Measurable disease by modified RECIST criteria for pleural mesothelioma or by RECIST criteria for peritoneal mesothelioma
- Adequate renal, hepatic and hematopoietic function
- No major surgery, radiotherapy, chemotherapy or biologic therapy within 28 days of IMC-A12 therapy

Design:

- Patients will receive IMC-A12 at a dose of 20 mg/kg intravenously once every three weeks
- Treatment with IMC-A12 alone will continue until disease progression
- Toxicity will be assessed every cycle by the CTEP Version 4.0 of CTCAE
- Tumor response assessments will be performed every 2 cycles

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1.1 PRIMARY PROTOCOL OBJECTIVES

- To determine the clinical response rate (PR+CR) to IMC-A12 monotherapy in patients with advanced mesothelioma.

1.2 SECONDARY PROTOCOL OBJECTIVES

- To determine response duration, progression free survival (PFS) and overall survival (OS).
- To assess safety of IMC-A12

1.3 EXPLORATORY ANALYSIS

- To evaluate tumor IGF-1R expression and correlation with response
- To correlate response to therapy with changes in FDG-PET imaging.
- To monitor serum mesothelin and CA-125 levels prior to and during therapy.

2 BACKGROUND

2.1 PERITONEAL AND PLEURAL MESOTHELIOMA

Malignant mesothelioma is a rare and lethal disease, which is known to arise in the serosal surfaces of the pleural and peritoneal cavities, and rarely, in the pericardial cavity or the tunica vaginalis. Mesothelioma accounts for 0.10% of deaths annually in the United States.[1] Malignant pleural mesothelioma is the most common of these, comprising of 80% of the cases and an annual incidence of about 2,500 in the United States. The median survival from diagnosis of pleural mesothelioma is approximately 12 months, whereas peritoneal mesothelioma can be considerably longer.[2-3] The most important risk factor for the development of pleural mesothelioma is asbestos exposure. As it was first noted among workers with occupational asbestos exposure three or four decades prior to disease occurrence, mesothelioma is known as a sentinel disease for asbestos exposure. However, mesothelioma can occur as the result of other mineral exposures (such as erudite), therapeutic radiation, and, possibly inflammation. According to an analysis of SEER data in 2008, about 58% of cases are estimated to have asbestos as a cause.[1]

In pleural mesothelioma, the majority of patients present with stage III or IV disease, and 85-90% of patients are considered unresectable at diagnosis. Males and patients with sarcomatoid histologic findings have worse prognoses, along with those presenting with extensive disease, poor performance status, elevated leukocyte counts, anemia, thrombocytosis, [4-5]. Treatment options for pleural mesothelioma include palliative surgery or radiotherapy, and chemotherapy. While such trimodality therapy has shown some long-term survival of selected patients, a recent case series examining trimodality therapy in Australia failed to show a benefit for patients receiving extrapleural pneumonectomy.[6] The approved first-line combination chemotherapy regimen in the US is pemetrexed and cisplatin, a regimen that has been shown to increase

survival time compared to cisplatin alone.[3] In this randomized phase III study, 226 patients received pemetrexed and cisplatin while as 222 patients received cisplatin alone. The response rates were 41.3% in the pemetrexed/cisplatin arm versus 16.7% in the control arm (p<.0001). The median overall survival time in patients treated with pemetrexed and cisplatin was 12.1 months versus 9.3 months in patients treated with cisplatin alone (P=.020, two-sided log-rank test). Treatment with other chemotherapeutic agents, alone or in combination, also plays a significant role worldwide. However, to date, no additional regimen has shown a significant effect on survival.[7-8] There remains a need for second-line regimens to assist in improving outcomes for patients with this deadly disease.

As noted, peritoneal mesothelioma is a much rarer diagnosis, with perhaps 250 patients diagnosed in the United States every year.[9] Similar to ovarian cancer, patients can present with non-specific symptoms of abdominal distension, pain, bloating, changes in bowel habits, weight loss, ascites, and fever.[10] The non-specific nature of symptoms helps explain why patients can have signs and symptoms for months before a proper diagnosis is made.[11] Case series at a variety of centers have shown improved survival and symptom reduction with operative cytoreduction and continuous hyperthermic peritoneal perfusion (CHPP).[12-15] Patients who relapse or are not considered candidates for surgical debulking are often treated with agents found to be useful in pleural mesothelioma, most significantly, pemetrexed and cisplatin.[11, 16] Prognosis has been found to vary widely in peritoneal mesothelioma with a retrospective analysis of 25 patients exhibiting the differences. Amongst 25 patients analyzed, patients surviving less than four years had a median survival of around 12 months. However, patients surviving greater than four years had a median survival of 7 years.[17] Patients with resectable disease who undergo extensive cytoreductive surgery and CHPP have also been shown to have prolonged survival of greater than 5 years.[12, 15] Despite this improved prognosis relative to pleural disease, patients undergoing therapy for peritoneal mesothelioma have few well-studied treatment options due in large part to the rare incidence of the disease. Nonetheless, an improved prognosis overall, coupled with treatment options, has led to an overall mesothelioma population enriched with peritoneal patients. The peritoneal mesothelioma population would thus benefit from research into agents with potential therapeutic benefits for this rare disease.

2.2 IMC-A12

IMC-A12 (cixutumumab) is a recombinant human IgG1/λ monoclonal antibody directed at the Type I Insulin-Like Growth Factor Receptor (IGF-1R) (ImClone Systems, Inc). IMC-A12 binds IGF-1R with high affinity (K_d=0.04 nM) and blocks the interaction between IGF-1R and its ligands, insulin-like growth factors I (IGF-1) and II (IGF-2), and induces internalization and degradation of IGF-1R. IMC-A12 has demonstrated tumor growth inhibition in a wide range of *in vitro* and *in vivo* human cancer models. Enhancement in antitumor activity has also been shown when IMC-A12 is combined with chemotherapy, radiotherapy, inhibitors of the epidermal growth factor receptor (EGFR) or HER-2, and other molecularly targeted agents.

Comprehensive background information regarding IMC-A12's physical, chemical, and pharmaceutical properties, formulation, non-clinical studies and effects in humans can be found in the Investigator's Brochure for IMC-A12. During the course of the study, additional background information regarding IMC-A12 will be made known via revisions to the Investigator's Brochure and Safety Update letters rather than amendments to this section of the protocol. The Investigators Brochure will be reviewed at least annually to determine whether an

update is necessary. Please refer to these documents for an updated presentation of experience with IMC-A12.

2.2.1 IGF-1R and IGF system

IGF-1R is expressed on the cell surface as a dimer composed of two extracellular α-chains and two membrane-spanning β-chains in a disulfide-linked β-α-α-β configuration. Surface IGF-1R is a preformed dimmer and requires domain rearrangements rather than oligomerization for activation. Upon binding to the ligand (IGF-1 or IGF-2), IGF-1R undergoes autophosphorylation and conformational changes. Downstream signaling is mediated through subsequent phosphorylation of intracellular substrates, mainly insulin receptor substrates 1-4 (IRS 1-4) and Shc, which lead to activation of the mitogen-activated protein kinase (MAPK) and PI3K/Akt pathways.[18-20]

IGF-1R belongs to the insulin receptor family that includes Insulin Receptor (IR), IGF-1R (homodimer), IGF-1R/IR (hybrid receptor), and IGF-2R (mannose 6-phosphate receptor). IGF-1R/IR hybrids act like homodimers, preferentially binding and signaling with IGFs. IR exists in two isoforms: IR-B (traditional insulin receptors) and IR-A (a fetal form which is re-expressed in selected tumors and preferentially binds IGF-2). IGF-2R is a non-signaling receptor that acts as a "sink" for IGF-2.[18]

The ligands, IGF-1 and IGF-2, are abundant in the serum of adults.[21] IGF-1 is secreted primarily by the liver upon stimulation by human growth hormone (GH), but can also be produced locally in tissues including muscle and bone. IGF-2 is not dependent upon GH and is expressed in a variety of tissues. Six well-characterized insulin-like growth factor binding proteins (IGF-BP-1 through -6) associate with IGF ligands in serum to stabilize the IGFs and modulate their ability to bind with IGF-1R. As a result of their association with the IGF-BPs, only about 2% of IGF ligands exist in free form in serum. Local bioavailability of IGF-1/2 for IGF-1R signaling is also subject to regulation by IGF-BP protease and presence of the non-signaling, IGF-2-binding IGF-2R.

2.2.2 Physiological function of IGF-1R and IGF

The IGF-1R is ubiquitously expressed in normal tissues at low levels. Functional aspects of IGF-1R signaling include the regulation of cellular metabolism, cell proliferation, cell size, and cellular differentiation.[20-22] Specific ablation of IGF-1R results in perinatal death. IGF-1 or IGF-2 knockout mice are also growth retarded (approximately 60% of normal). Overexpression of either IGF-1 or IGF-2 in transgenic mice has demonstrated a growth-promoting effect on most tissues, including increased weights of the brain, heart, kidney, spleen, thymus, and uterus.[23-24] Conversely, targeted disruption of the IGF-signaling pathway using IGF-1 or IGF-1R knockout mice generated adverse effects on the development of selected tissues from neonates including muscle (hypoplasia), spinal cord (increased cell density), skin (translucent, thin, decreased follicles), and bone (delayed ossification).

IGF-1 has low affinity to the insulin receptor and its effect on insulin sensitivity is mostly mediated through suppression of the GH. Direct effect of IGF-1 on glucose homeostasis may be limited to skeletal muscles and kidney via IGF-1R. Deletion of IGF-1R in muscles could result in insulin resistance in mice. In humans, infusion of recombinant IGF-1 has been shown to improve insulin sensitivity and glucose control in patients with type 2 diabetes or insulin resistance.[25-26]

2.2.3 Role of IGF-1R/IGF in Cancer Growth and Progression

In vitro and *in vivo* studies have implicated IGF-1R and IGF-1/2 signaling in the development, maintenance, and progression of cancer. Expression of IGF-1R is critical for anchorage-independent growth, a well recognized property of malignant cells. Studies have shown that anchorage independence can be acquired when the number of IGF-1R is increased to a certain threshold.[18-19] IGF-1 and IGF-2 are strong mitogens for a wide variety of cancer cell lines including prostate,[27] breast,[28-31] colon,[32-34] myeloma,[35] and melanoma.[36] High circulating levels of IGF-1 in serum have been associated with an increased risk of breast, prostate, and colon cancer.[37] IGF-1R signaling regulates a number of cellular processes including proliferation, anti-apoptosis, motility and angiogenesis.

Expression of IGF-1R is observed in most solid tumors and hematologic malignancies examined to date.[19, 38-39] Transcription of the IGF-1R gene is up-regulated by growth factors (*e.g.* PDGF and EGF), hormones (*e.g.,* growth hormone [GH] and estrogen), and oncogenes (*e.g.,* c-myb, Wilm's Tumour 1 gene), and downregulated by tumor suppressor genes (*e.g.,* Wt1 and p53). Overexpression of IGF-2, modification of IGF-BPs and downregulation of IGF-2R has also been demonstrated in cancer cells. However, while presence of IGF-1R is important, there is no clear correlation between the level of IGF-1R expression and its functional or activation status. Furthermore, unlike other growth factor receptors such as EGFR and Her2, activation mutation of the IGF-1R gene has not been reported and gene amplification is extremely rare in the tumors that have been tested.[40]

Several genetic abnormalities related to IGF-1R signaling have been described. For example, in Ewing's sarcoma (EWS), the EWS/FLI1 translocation product was found to directly interact with IGF-BP3 promoter and repress its expression,[41] and IGF-1R is required for transformation by the EWS/FLI-1 fusion protein.[41-42] Deletion or loss of heterozygosity (LOH) of the IGF-2R gene has been described in some tumor types, including hepatocellular cancer (HCC) and breast cancer.[43] Loss of imprinting of the IGF-2, first described in Wilm's tumor, has later been identified in adult tumors and associated with an increased risk of colon cancer.[44-45] These genetic changes may increase the production of IGF-2 or the bioavailability of IGF-2 for IGF-1R signaling.

2.2.4 Targeting IGF-1R in anti-cancer therapy

Several approaches to inhibit the IGF-1R signaling have been investigated, including antagonistic monoclonal antibodies and small molecule tyrosine kinase inhibitors.[46] A number of humanized or fully human anti-IGF-1R monoclonal antibodies are under development, including CP-751,871 (Pfizer), IMC-A12 (ImClone), AMG479 (Amgen), RO 1705 (Roche) and 19D12 (Schering-Plough).

Agents inhibiting the IGF-1R pathway have shown anti-tumor events in multiple human cancer models both in vitro and in vivo, particularly the pediatric tumor models for EWS and rhabdomyosarcoma.[47] In early clinical trials with AMG479, durable objective response was observed in a patient with EWS.[48]

The IGF-1R/IGF pathway has also been shown to have extensive crosstalk with the estrogen receptor (ER), EGFR and HER2 signaling, and may play an important role in the resistance/escape mechanisms of cytotoxic drugs and EGFR/HER2-targeted agents. In multiple preclinical studies, combination regimens with IGF-1R targeting agents enhanced the anti-tumor

activity of chemotherapy, radiotherapy, hormonal therapy (anti-estrogen or anti-androgen),[49] EGFR/HER2 inhibitors and agents targeting downstream molecules such as mTOR.[50-51]

2.2.5 IMC-A12

ImClone Systems has developed a fully human IgG_1 monoclonal antibody, IMC-A12, which specifically targets the human IGF-1R. IMC-A12 possesses high affinity for IGF-1R and acts as an antagonist of IGF-1 and IGF-2 ligand binding and signaling. IMC-A12 does not bind to or recognize the human insulin receptor. In addition to blockade of ligand binding, this antibody inhibits the IGF-1R pathway by effecting the internalization and degradation of IGF-1R, leading to a reduction in surface receptor density on treated cells. IMC-A12 inhibits the proliferation and growth of a variety of human tumor cell lines, both in vitro and in vivo.

2.2.5.1 Nonclinical studies with IMC-A12 in human tumor models

Single agent antitumor activity of IMC-A12: *In vitro,* IMC-A12 treatment inhibited ligand-induced growth of various tumor cell lines, including breast, prostate (androgen-dependent and -independent), pancreatic, lung, colon, and myeloma.[52-55] Growth inhibition was also demonstrated in tamoxifen- or trastuzumab-resistant breast cancer cell lines.[55] Treatment with IMC-A12 also significantly inhibited anchorage-independent growth of breast, pancreatic, lung, colon, and myeloma cell lines in soft agar.[55]

In vivo tumor growth inhibition has also been demonstrated against various subcutaneous xenograft models, including human colon, breast, lung, pancreatic, prostate, and renal carcinoma, and an orthotopic anaplastic thyroid cancer model.[53, 55-56] However, tumor regressions were infrequent.

IMC-A12 in combination regimens: The combination of IMC-A12 with chemotherapy has been tested in xenograft models. Enhanced tumor control was observed in combination with a number of agents, including paclitaxel, 5-FU/LV, cisplatin, and docetaxel.[54-56] Near complete tumor growth inhibition was demonstrated in a HT-29 colon carcinoma xenograft with IMC-A12 in combination with CPT-11.[55] In some models, the combination of IMC-A12 with chemotherapy led to sustained tumor control and improvement in survival.[56] IMC-A12 treatment blocks the antiapoptotic effects of IGF-1 in response to chemotherapy in MCF-7 breast cancer cells and enhances the antitumor effect of chemotherapy in cell culture.[55] IMC-A12 has also shown benefit when administered in combination with radiation in models of human lung cancer.[55]

IMC-A12 also shows enhanced antitumor effect in combination with targeted agents, including cetuximab, mTOR inhibitors, HER2 inhibitors, among others.

IMC-A12 Pharmacokinetic (PK) and Pharmacodynamic (PD) studies in tumor models: Results from human xenograft tumor models suggested that optimal tumor growth inhibition can be achieved at an IMC-A12 steady state level of 60 to 158 μg/mL.[55] PD changes demonstrated in xenograft models included downregulation of the IGF-1R levels and phosphorylation, inhibition of the downstream signals (MAPK and AKT phosphorylation) as well as induction of cellular events such as apoptosis, G1 or G2-M arrest, and decrease in the proliferation index.[53-55] Downregulation of IGF-1R phosphorylation in endothelial cells was also observed with *in vivo* treatment of IMC-A12.[56]

2.2.5.2 IMC-A12 Nonclinical toxicology and PK studies

IMC-A12 binds to murine, primate, and human IGF-1R with similar affinity. The toxicity of IMC-A12 has been evaluated in three studies in cynomolgus monkeys that received 1, 4, or 13 weekly doses of IMC-A12. In addition, mice have been treated in numerous xenograft studies, in which body weight and general health status are available. A tissue cross-reactivity study has been conducted with a full panel of monkey and human tissues to support the overall safety assessment. Detailed descriptions of all studies are provided in the IMC-A12 Investigator's Brochure; results are also briefly summarized below.

Table 1: Repeated-Dose Toxicology/Pharmacokinetic Studies

Species/Group size	Route and schedule	Doses (mg/kg)	Major Findings
4-dose study in Cynomolgus monkey 3/sex in main study, 3 males per recovery groups; examined 7 weeks after last dose	IV slow bolus **Once per week with 2 week gap after the first dose**	**0, 6, 22, and 80**	• No treatment-related effects on survival, clinical signs, food consumption, clinical chemistry, hematology (other than procedure-related anemia and reticulocytosis), urinalysis, ophthalmology, or blood pressure • Dose-dependent slight body weight losses • Decreasing trends in absolute and relative thymus and spleen weights. • Dose-dependent thymic atrophy. After 7-week recovery period thymic atrophy was reversible at low-dose, partly recovered at mid-dose, and not recovered at high-dose. • Anti-IMC-A12 incidence as 0 of 6, 0 of 8, 1 of 8, and 0 of 8 evaluable for the 0-, 6-, 22-, and 80-mg/kg groups, respectively. • Mean Values: C_{max}=153, 528, and 2182 µg/mL; AUC_{inf}= 14032, 60620, and 253726 h●µg/mL; half-life = 5.0, 7.0, and 7.7 days; clearance=0.434, 0.370, and 0.329 mL/h/kg
13-dose study in Cynomolgus monkey **3/sex in main study; 4 to 6 per sex distributed in recovery groups; examined 8 and 12 weeks after last dose**	10 min IV infusion, once per week	**0, 6, 22, and 80**	• No treatment-related effects on survival, clinical signs, urinalysis, immunophenotyping, ophthalmology, or cardiovascular endpoints • Body weight losses were 0-14%, 4-16%, and 4-21% for the 6-, 22-, and 80-mg/kg groups, respectively. Weight was regained in recovery. • Decreasing trends in RBCs, HCT, and hemoglobin in both sexes (statistically significant in high-dose females) on day 86; decreased RBCs and HCT in high-dose females on day 28 • Decreased mean platelet volume in all female groups • Decreased absolute and relative thymus weights associated with minimal to marked atrophy, depletion of cortical thymocytes, loss of corticomedullary junction, and fat replacement (no change in peripheral lymphocyte

			counts) • Decreased absolute and relative uterine weights associated with diffuse hypoplasia • Ovarian immaturity consisting of a relative increase in the ovarian cortex with a less developed medulla and decreased follicles in different stages of development • Increasing trend in relative heart:body weights in males and mid-dose females, but not relative heart:brain weights (in change in EKG, or histopathology) • Anti-IMC-A12 incidence was 1 of 12, 4 of 8, 0 of 8, and 1 of 12 evaluable for the 0-, 6-, 22-, and 80-mg/kg groups, respectively. • Mean Values: Cmax=186, 748, and 2434 μg/mL; AUCinf=16276, 67659, and 267733 h•μg/mL; half-life = 3.6, 4.6, and 4.4 days; clearance=0.413, 0.377, and 0.332 mL/h/kg

2.2.5.3 Clinical experience with IMC-A12 – ImClone-sponsored clinical trials

There have been two concurrent ImClone-sponsored phase 1, single-agent studies in solid tumors. In the first trial (CP13-0501), IMC-A12 was administered IV weekly, with planned dose escalation from 3, 6, 10, 15 to 27 mg/kg. In the second trial (CP-0502), IMC-A12 was given on biweekly schedule with escalation from 6 mg/kg to 27 mg/kg. In addition, six disease-specific phase 2 trials have been initiated and are ongoing (CP13-0603, CP13-0604, CP13-0605, CP13-0706, CP13-0707, and CP18-0601).

Results from CP13-0501 (Phase I for weekly schedule) are summarized below:[55, 57]

A total of 24 patients have been enrolled and treated on this trial (7 at 3 mg/kg, 9 at 6 mg/kg, 6 at 10 mg/kg, and 2 at 15 mg/kg).

Adverse event (AE) data for all 24 patients demonstrated that IMC-A12 was well tolerated at doses up to 15 mg/kg. All patients have experienced at least one AE regardless of relationship to IMC-A12, including fatigue (n=10), nausea (n=9), and vomiting (n=8). Seventeen patients had IMC-A12-related AEs. The most significant AE to date has been **hyperglycemia**, observed in 4 patients and considered a dose-limiting toxicity (DLT) (grade 3) in 2 patients. Oral diabetic agents (glipizide and/or metformin) were used in three patients: two patients were able to resume IMC-A12 with stable control of the glucose; one patient with pancreatic cancer and pancreatic radiation had persistent hyperglycemia and was taken off study. One case of Grade 3 fatigue was also reported at the 6 mg/kg dose level.

Mild weight loss was noted in seven of nine patients over this initial study period (median decrease 1kg; 1% of body weight). The contribution of IMC-A12 to these modest changes in body fat/weight is uncertain.

Efficacy was the secondary endpoint of the trial. There were no objective responses among the 16 patients. Eleven patients experienced stable disease (SD, > 6 weeks): two patients at the 3 mg/kg dose, five patients at the 6 mg/kg dose, and two patients at the 10 mg/kg dose, and two

patients at the 15 mg/kg dose. Four patients had SD >8 months (male breast cancer and HCC at 3 mg/kg, pheochromocytoma at 10 mg/kg, and lymphangiomatosis at 15 mg/kg).

Non-compartmental PK analysis reveals a mean $T_{1/2}$ of 148 and 209 hrs, mean C_{max} of 333 and 415 μg/mL, and mean $AUC_{0\text{-}Inf}$ of 51317 and 80727 hr*μg/mL at the 3 and 6 mg/kg dose levels, respectively. At the steady states of the 6 and 10 mg/kg doses, the trough levels reached 145 μg/mL and 259 μg/mL, respectively. The recommended phase 2 dose from this trial is 6 mg/kg when given on a weekly schedule.

Monitoring of circulating markers revealed a marked elevation of GH and IGF-1 after treatment with IMC-A12. There was also an increase in the levels of insulin and C-peptide post treatment.

Results for CP13-0502 (phase I for every-two-week schedule):[55]

Sixteen patients were enrolled on this study: five patients at 6 mg/kg, 9 patients at 10 mg/kg, and 2 patients at 15 mg/kg.

The most frequently reported AE, regardless of relationship to IMC-A12, was fatigue (n=7) and nausea (n=6); nine patients experienced grade ≥3 AEs, including dyspnea (n=3), disease progression, fatigue, pain, cellulitis, dehydration, mental status changes, nausea, vomiting, QTC prolongation, back pain, and muscle spasms. The grade ≥3 fatigue and QTC prolongation (both in the 10 mg/kg cohort) were considered at least possibly related to IMC-A12.

Four patients have experienced SD, with two patients experiencing SD ≥7 months.

The recommended phase 2 dose of IMC-A12 when given on an every-other-week dosing schedule is 10 mg/kg.

Interim Results for Phase 2 studies:[55, 58]

Six disease-specific phase 2 trials have been sponsored by ImClone and are ongoing, including IMC-A12 monotherapy treatment in patients with prostate cancer (CP13-0603), in patients with Ewing's sarcoma, rhabdomyosarcoma, leiomyosarcoma, adipocytic sarcoma, and synovial sarcoma (CP13-0707), and combination with anti-estrogen therapy in breast cancer (CP13-0604), cetuximab in colorectal cancer (CRC) (CP13-0605) and head and neck cancer (CP13-0706), and mitoxantrone in prostate cancer (CP18-0601).

CP13-0603: Interim results have been presented for the phase 2 trial of IMC-A12 monotherapy in patients with chemotherapy-naïve, androgen-independent metastatic prostate cancer.[55, 58] In that study of 31 patients, the most common AEs related to IMC-A12 were fatigue (n=12, 40%; 7% ≥ grade 3), hyperglycemia/diabetes mellitus (n=7, 23%; 16% ≥ grade 3), visual disturbances/flash (n=5) which did not persist or worsen with continued treatment, dry mouth (n=3), and infusion-related reaction (n=3). None of the patients experiencing grade 3 hyperglycemia equired discontinuation of the agent; however, one patient required insulin. Other AEs ≥ grade 3 include one case each of thrombocytopenia, non-insulin dependent diabetes, pneumonia (with fatal outcome), hyperkalemia, and reversible posterior leukoencephalopathy syndrome (RPLS). No objective responses have been observed; 14 patients had a best response of SD (>6 weeks) with 9 patients progression free at 6 months. Overall TTP was 4.8 months. Five of 15 patients with measureable disease experienced a reduction in sum lesion diameter, and 4 patients experienced a decrease in prostate-specific antigen (PSA) from baseline, one of whom decrease of ≥50% from baseline.

8109 (CTEP-sponsored): Preliminary results from a phase 1 trial with IMC-A12 in combination with temsirolimus indicate that the combination is well tolerated,[59] but the maximum tolerated dose has not yet been determined and full assessment of the safety profile is ongoing. Among the 11 patients treated, the most common grade 1-2 toxicities include hyperglycemia (n=6), hypertriglyceridemia (n=6), dysgeusia (n=5), fatigue (n=5), leucopenia (n=4), mucositis (n=4), and ocular flashes of light (n=3). Grade 3-4 toxicities included one case each of nausea, vomiting, and thrombocytopenia.

ADVL-0721 (CTEP-sponsored): Twenty-four patients were enrolled in a pediatric phase 1 trial examining IMC-A12 monotherapy.[60] Two dose levels of IMC-A12 were examined (6 and 9 mg/kg weekly); after an initial safety cohort, an expanded cohort was opened for Ewing sarcoma (ES) patients to be treated at each dose level. One DLT was observed at the 6 mg/kg IMC-A12 dose level (grade 4 thrombocytopenia); no DLTs were observed at 9 mg/kg or in the ES cohort. One patient with ES had a partial response, and a majority of patients at both dose levels exhibited a greater than 50% reduction in PMBC IGF-1R protein levels. AEs ≥grade 2 in the first course of treatment considered related to IMC-A12 included anemia (n=4), lymphopenia (n=2), neutropenia (n=2), leucopenia (n=1), increased transaminases (n=2), opportunistic infection (n=1), and hyperglycemia (n=1). Pharmacokinetics demonstrated mean trough concentrations (C_{min}) were 59.8±31.1 and 117±70.8 µg/mL at the 6 and 9 mg/kg dose levels, respectively. The recommended phase 2 dose of IMC-A12 in children is 9 mg/kg when given on a weekly schedule.

Pharmacokinetic data for IMC-A12 and recommended phase 2 dose

The phase 2 doses of IMC-A12 are based on the dose levels tested in the ImClone-sponsored trials with different schedules: 6 mg/kg weekly,10 mg/kg q2w, or 20 mg/kg q3w. The MTD has not been determined in these trials, and the dose selection is based on feasibility and the "effective plasma levels" extrapolated from xenograft models at therapeutic doses of the agent.

Summarized below is the preliminary PK data from selected trials. In general, the plasma level is proportional to dose; the clearance decreases and the C_{min} increases with repeated dosing, with the steady state level being reached after 3-4 courses of therapy. It should be noted that for certain doses and schedules, available data are limited to very few patients and additional PK studies are ongoing.

Schedule	Dose	Trial	C_{min}	T1/2	Clearance
Weekly	6 mg/kg	CP13-0501 CP13-0502	• 95 ug/mL (1st dose) • 154 ug/mL (4th dose) (n=2)	• 4.7 d (1st dose) • 8.7 d (4th dose)	•0.15 mL/h/kg (1st dose) •0.07 mL/h/jg(4th dose)
Q2w	10 mg/kg	CP13-0501; CP13-0502	• 43 ug/mL (1st dose) (n=1) [Mean Conc. On D7: 168 ug/mL] C_{min} after repeated doses not available	• 3.4 d (1st dose) (n=7)	•0.143 mL/h/kg (1st dose) •0.055 mL/h/kg(2nd dose)

Q2w	10 mg/kg	CP13-0603	• 68 ±17 ug/mL (1st dose) • 174 ±115 ug/mL (prior to5th cycle)	•	•0.143 mL/h/kg (1st dose) •0.055 mL/h/kg(2nd dose)
Q3w	20 mg/kg	CP13-0501	• 140 ug/mL (1-2 cycle) • 198-313 ug/mL (3-4 cycles)	• 8.6-9.3 d (3-4th cycle)	

Adverse events in patients

As of 30 April 2009, adverse events have been reported for a total of 243 patients treated in eight Phase 1 and Phase 2 clinical studies of IMC-A12 (24 in CP13-0501, 14 in CP13-0502, 29 in CP13-0603, 15 in CP13-0604, 61 in CP13-0605, eight in CP13-0706, 51 in CP13-0707, and 41 in CP18-0601).

Main AEs associated with IMC-A12 are described below. For a comprehensive list of AEs, refer to the CAEPR table and the investigator's brochure and the description of individual trials above.

Hyperglycemia: hyperglycemia is a class adverse effect of all IGF-1R targeting agents. Hyperglycemia of all grades has been observed in 20-30% patients receiving IMC-A12 and grade 3 hyperglycemia is uncommon (10-20%). The rate of hyperglycemia may be increased in patients with history of diabetes or in presence of corticosteroids use. Grade 4 hyperglycemia is extremely rare but has been reported in patients on IMC-A12 studies. In most cases hyperglycemia can be well controlled with oral medications while IMC-A12 is continued or resumed.

Influsional reactions: infusional reactions associated with IMC-A12 is usually very mild. Rarely however, grade 4 hypersensitivity reactions have been reported.

2.3 RATIONALE FOR THE STUDY

Mesothelioma is an aggressive disease with poor prognosis. Combination treatment with cisplatin and pemetrexed is the only FDA approved regimen for this disease. Since almost all patients progress after initial treatment with this regimen they are candidates for second-line therapy. There is no clearly defined standard for treating these patients and therefore an urgent need to develop more efficacious treatments for patients with peritoneal and pleural mesothelioma who have already received chemotherapy.

Insulin-like growth factor-1 receptor (IGF-1R) is a receptor tyrosine kinase that has proliferative and anti-apoptotic effects.[61-62] It has been shown that altered expression of the IGF-1 signaling cascade and increased activity of IGF-1R results in proliferation of several tumor types and may also contribute to resistance to anticancer therapies including cytotoxic chemotherapy and biologic therapies.[63-66]

The insulin-like growth factor 1 receptor (IGF-1R) pathway is activated in malignant mesothelioma cell lines and tissues. Treatment with AG1024, an inhibitor of the IGF-1R pathway, significantly decreased cell proliferation and attenuated the phosphorylation of Akt and p44/42. In addition, it significantly enhanced the cytotoxic effects of cisplatin in human

malignant mesothelioma cell lines. A study by Kai et al suggests that IGF-1R inhibition could reduce toxicity and chemoresistance to traditional anticancer drugs in malignant mesothelioma patients.[67] Another preclinical trial by Jacobson et al suggests that IGF-1 signaling in mesothelioma cells drives cell proliferation, motility, and tumourigenesis through its ability to activate cap-mediated protein translation complex through PI3K/Akt/mTOR signaling.[68] In earlier studies by Pass et al, the inhibitory effect of IGF-1R antisense transcripts on hamster mesothelioma demonstrated by decreased growth and tumorigenicity in vitro and in vivo may have implications for the therapy of human mesothelioma.[69-70]

IMC-A12 is a fully human monoclonal antibody that to IGF-1R and blocks its interaction with its ligands IGF-1 and IGF-2. This leads to internalization and degradation of IGF-1R. IMC-A12 has demonstrated single-agent activity against many tumor cell lines including breast, colon, prostate, lung, pancreatic cancer and myeloma.[53]

2.4 CORRELATIVE STUDIES BACKGROUND

Mesothelin is a 40-kDa cell surface glycoprotein that is highly expressed in mesothelioma, ovarian, pancreatic and some other cancers.[71-73] Within malignant pleural mesothelioma, the expression of mesothelin is closely related to the histological subtype of the tumor, being expressed on the epithelial but not sarcomatous tumor tissues. On biphasic tumors, mesothelin is expressed on the epithelial component. Small amounts of mesothelin shed into the circulation may be detected by sandwich ELISA. It has been suggested that elevated soluble mesothelin levels may correlate with advanced disease stage and total tumor burden. The biological function of mesothelin is unknown. A trans-intracellular binding activity with CA-125, a tumor antigen routinely used in the diagnosis and monitoring of ovarian cancer has been noted.[74] Among normal human tissues mesothelin is expressed on mesothelial cells of the pleura, pericardium, and peritoneum, but is absent from vital organs including heart, liver, lung, kidney and nervous tissue.

Subjects' sera will be collected for retrospective determination of circulating mesothelin concentrations prior to each cycle and at the end of study. Soluble mesothelin levels, as measured by ELISA, may be a correlate of total tumor burden and may predict PK or therapeutic/toxic response. For details on sample collection procedure and storage instructions, please see Section **9**. CA-125 is a routine clinical laboratory service, and CA-125 levels will be assessed by the Department of Laboratory Medicine at the NIH Clinical Center.

In addition, subjects' tumor cells (archival paraffin block biopsy used to establish diagnosis) will be tested for expression of both IGF-1R and mesothelin by immunohistochemistry. As noted above, there is published literature on IGF-1R expression in mesothelioma cell lines, but immunohistochemical results of archival tumor specimens in mesothelioma have not been reported. Tests will be performed in a central laboratory. Mesothelin expression has been performed extensively for clinical trials in mesothelioma at the National Cancer Institute, and these will be patients' tumor cells will be tested for expression by immunohistochemistry as well. For sample collection procedure and shipping instructions, please see Section **9**.

It is assumed that the outcome of the secondary exploratory evaluations may assist in designing further studies of IMC-A12 in advanced mesothelioma, if the primary objective of the study were be reached.

3 PATIENT SELECTION

3.1 INCLUSION CRITERIA

3.1.1 Subjects must have histologically confirmed pleural or peritoneal mesothelioma not amenable to potentially curative surgical resection. The diagnosis will be confirmed by the pathology department / CCR / NCI.

3.1.2 Patients must have had at least one prior platinum-containing chemotherapy regimen. There is no limit to the number of prior chemotherapy regimens received.

3.1.3 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques or as >10 mm with spiral CT scan. See section **11** for the evaluation of measurable disease.

3.1.4 Patients must not have had major surgery, radiation therapy, chemotherapy, biologic therapy (including any investigational agents), or hormonal therapy (other than replacement), within 4 weeks prior to entering the study and must have evidence of stable or progressive disease to be eligible.

3.1.5 Age ≥18 years. Since mesothelioma is extremely rare in children they are excluded from this study.

3.1.6 Life expectancy of greater than 3 months.

3.1.7 Performance status (ECOG) ≤ 2 (**Appendix A**).

3.1.8 Patients must have adequate organ and marrow function (as defined below).

-	leukocytes	≥3,000/mm^3
-	absolute neutrophil count	≥1,500/mm^3
-	hemoglobin	≥ 9 g/dL
-	platelets	≥100,000/ mm^3
-	total bilirubin	≤1.5 X institutional upper limit of normal (ULN)
-	AST(SGOT)/ALT(SGPT)	≤3 X institutional ULN (5x if LFT elevations due to liver metastases)
-	creatinine	≤1.5 X institutional ULN
	OR	
-	creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

Patients may be transfused to obtain a hemoglobin of ≥9 g/Dl.

3.1.9 The patient must have fasting serum glucose < 160 mg/dL

3.1.10 The effects of IMC-A12 on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (barrier method of birth control; abstinence) for the duration of study therapy and for 3 months after the last dose of IMC-A12. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. While hormonal methods of birth control are effective, we ask that female patients who are participating in the study cease hormonal forms of birth control, as these methods of birth control (birth control pills, injections, or implants) may affect the study drug. Patients must be off hormonal forms of birth control for at least 4 weeks prior to initiating the study.

3.1.11 Ability to comply with intravenous administration schedule, and the ability to understand and the willingness to sign a written informed consent document.

3.2 EXCLUSION CRITERIA

3.2.1 Patients with symptomatic brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. However, patients who have had treatment for their brain metastases and whose brain metastatic disease status has remained stable for at least 3 months without steroids may be enrolled at the discretion of the principal investigator.

3.2.2 Patients with poorly controlled diabetes mellitus. Patients with a history of diabetes mellitus are allowed to participate, provided their blood glucose is below 160 mg/dL when fasting and if they are on a stable dietary or therapeutic regimen for this condition with their HbA1C of less than 7%.

3.2.3 Uncontrolled medical illness including, but not limited to, ongoing or uncontrolled, symptomatic congestive heart failure (AHA Class II or worse), uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.4 HIV positive patients with poorly controlled viral loads (viral load > 50 copies HIV/ml), and/or AIDS-defining illnesses will be excluded due to the possibility that IMC-A12 may worsen their condition and the likelihood that the underlying condition may obscure the attribution of adverse events with respect to IMC-A12. HIV positive patients with mesothelioma not meeting the above criteria can be considered for inclusion in the study.

3.2.5 Patients may not be receiving any other investigational agents.

3.2.6 History of another invasive malignancy in the last five years. Adequately treated non-invasive, non-melanoma skin cancers as well as in situ carcinoma of the cervix will be allowed.

3.2.7 Prior treatment with drugs of the IGF-1R inhibitor class.

3.2.8 Patients with tumor amenable to potentially curative therapy as assessed by the investigator. In patients with peritoneal mesothelioma who have had no prior surgery, a surgical consultation will be obtained to see if the patient is a candidate for debulking surgery.

3.2.9 Pregnant women are excluded from this study because IMC-A12 is a monoclonal antibody to IGF-1R with the potential for teratogenic or abortifacient effects. IgG antibody may also potentially be secreted in milk and therefore breastfeeding women should be excluded. Because of the potential of teratogenic or abortifacient effects women of childbearing potential and men must agree to use adequate contraception (barrier methods) before, during the study and for a period of 3 months after the last dose of the investigational agent.

3.2.10 Patients must not be on hormonal forms of birth control or hormone replacement therapy, as this may affect the study drug. Patients must be off hormonal forms of birth control or hormone replacement therapy for at least 4 weeks prior to initiating the study.

3.2.11 History of allergic reactions attributed to compounds of similar chemical or biologic composition to IMC-A12.

3.3 INCLUSION OF WOMEN AND MINORITIES

Both men and women and members of all races and ethnic groups are eligible for this trial. Every effort will be made to recruit women and minorities in this study.

Accrual Targets						
Ethnic Category	**Sex/Gender**					
	Females		**Males**		**Total**	
Hispanic or Latino	3	+	7	=	10	
Not Hispanic or Latino	15	+	30	=	45	
Ethnic Category: Total of all subjects	18 (A1)	+	37 (B1)	=	55 (C1)	
Racial Category						
American Indian or Alaskan Native	1	+	1	=	2	
Asian	1	+	3	=	4	
Black or African American	3	+	6	=	9	
Native Hawaiian or other Pacific Islander	1	+	1	=	2	
White	12	+	26	=	38	
Racial Category: Total of all subjects	18 (A2)	+	37 (B2)	=	55 (C2)	
	(A1 = A2)		(B1 = B2)		(C1 = C2)	

3.4 ON-STUDY RESEARCH EVALUATION

3.4.1 Complete history and physical examination (including height, weight, vital signs and ECOG performance score) with documentation of (i) measurable disease, (ii) narcotic use and pain assessment and (iii) prior therapies (surgical, radio therapeutic and cytotoxic) will be conducted within 2 weeks prior to starting therapy. A complete medication history will be obtained prior to starting, including medications at baseline, over the counter medications, homeopathic remedies, vitamins, and alternative therapies, history of opportunistic infections (mucocutaneous candidiasis (oropharyngeal thrush, onychomycosis, disseminated varicella zoster as defined as >2 dermatomes or 2 noncontiguous dermatomes or other infections. If infections were present did they occur in the presence of immunosuppressive therapy.

3.4.2 Imaging Studies (Baseline) - Every patient should have a baseline clinical evaluation with CT scans of chest, abdomen and/or pelvis areas of known or suspected disease involvement prior to receiving treatment. In some patients an MRI may be more appropriate. Patients will also have FDG-PET scans to better define the extent of their disease and response to therapy. This must be completed within 28 days prior to the commencement of therapy (i.e. day 1 dose).

3.4.3 Laboratory Evaluation [baseline labs are to be obtained within one week prior to enrollment].

- Hematological Profile: CBC with differential and platelet count, prothrombin time, activated partial thromboplastin time.
- Biochemical Profile: electrolytes, BUN, creatinine, glucose, AST, ALT, alkaline phosphatase, bilirubin, albumin, total protein, LDH, calcium, phosphorous, magnesium, amylase and lipase, triglycerides, cholesterol, LDL, HDL, HbA1C and urinalysis.
- EKG (baseline)
- Pregnancy test for female patients of childbearing age and anatomic ability.

3.4.4 Tissue for correlative studies: A block of primary tissue (or 10 unstained sections on charged slides) from the time of diagnosis will be required from each patient. Tissue blocks from a known recurrence will be accepted if original tumor samples are unavailable. Referring institutions will send the tumor block or 10 unstained sections on charged slides to CCR/NCI for correlative studies and confirmation of diagnosis.

4 PATIENT REGISTRATION

4.1 REGISTRATION PROCESS

- Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://intranet.cancer.gov/ccr/welcome.htm) must be completed and faxed to 301-480-0757. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail. Please note, it is very important for all registrars to acquire encrypted e-mail from NIH Help

Desk, since the verification of registration includes patient's information. A recorder is available during non-working hours.

- Questions about eligibility should be directed to the Study Coordinator and Research Nurse:

Barbara Schuler, RN
10 Center Drive
Bldg 10, Rm 12N214
Bethesda, MD 20892
Telephone: 301-435-5398
Fax: 301-402-8801
Email: schulerb@mail.nih.gov

Technical questions about the form should be directed to the Central Registration Office (301-402-1732)

4.2 OFF STUDY CRITERIA:

Authorized physicians or their designee must notify the NCI CRO when a patient is taken off study. An off-study form from the web site (http://intranet.cancer.gov/ccr/welcome.htm) main page must be completed and faxed to 301-480-0757.

Patients will be removed from study for:

- Withdrawal of consent
- Death

5 TREATMENT PLAN

5.1 IMC-A12 ADMINISTRATION

IMC-A12 will generally be administered on an outpatient basis except when admission is required for logistical reasons since most patients seen at NCI come from all over the country. Reported adverse events and potential risks for IMC-A12 are described in Section **7**. Appropriate dose modifications for IMC-A12 are described in Section **6**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

- IMC-A12 will be administered at 20 mg/kg intravenously over 60 minutes or not to exceed 25mg/minute once every 3 weeks (+ or – 1 day cycle 3 and beyond). The calculated dose will be based on the actual body weight. The dose will be recalculated if there is ≥ 10 % chance in body weight from baseline.

5.1.1 Special Precautions/Safety Issues:

- Patients who have an ongoing study agent-related serious adverse event upon study completion or at discontinuation from the study will be contacted by the investigator or his/her designee periodically until the event is resolved or determined to be irreversible.
- Infusional reactions: Routine premedication is not required for the first dose of IMC-A12. If infusional reactions occur, acetaminophen, diphenhydramine, steroids or other medications may be given for symptom control and for premedication as needed. Anaphylactic precautions should be observed during IMC-A12 administration.
- Hyperglycemia/diabetes: Patients who develop hyperglycemia should be monitored and managed according the dose modification guidelines below.

  In order to adequately document the severity and clinical impact of hyperglycemia, **the Case Report Form** should be specifically designed to collect the requirement of diabetic medications (including the drug name, dose, start/terminating dates

- Prolonged use of systemic corticosteroids is discouraged because of their potential to cause and exacerbate hyperglycemia. Intermittent use of corticosteroids (dose, name, start/off dates) should also be documented in Case Report Forms.

5.2 SUPPORTIVE CARE GUIDELINES

5.2.1 Patients will be allowed to use erythropoietin or analogs prior to entry and during the course of the study.

5.2.2 No concomitant use of alternative, complementary therapies or over-the-counter agents will be allowed without approval of the PI.

5.2.3 Nausea/vomiting: Patients will not be given antiemetics prophylactically. If a patient develops nausea/vomiting, antiemetics will be instituted for treatment of this side effect according to clinical center antiemetic guidelines.

5.2.4 Diarrhea: If severe diarrhea develops, and does not have an identifiable cause other than IMC-A12 administration, loperamide 2 mg p.o. q2h while awake and Loperamide 4 mg p.o q4h during bed time may be administered until the patient is free of diarrhea for 12 hours, at which time loperamide will be discontinued. This regimen can be repeated for each diarrheal episode. The occurrence of liquid stools after a 12h diarrhea-free period will be considered a new episode. If patient develops blood or mucus in the stool, dehydration or hemodynamic instability, Loperamide will be discontinued and the patient will be treated with IV fluids as needed. Other potentially helpful treatments may also be administered, such as somatostatin analogues, probanthine, etc.

"Note: this dosage regimen may exceed the usual dosage recommendations (16 mg/day) for loperamide, but is the dosing regimen specified for diarrhea associated with irinotecan administration."

5.2.5 Hyperglycemia: If persistent hyperglycemia develops during treatment it will managed initially with oral hypoglycemics. If this therapy is found to be inadequate, insulin analogues may be used.

5.3 DURATION OF THERAPY (OFF TREATMENT CRITERIA)

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression as defined by section **11**.
- Intercurrent illness that prevents further administration of treatment.
- Delay of treatment of ≥ 3 weeks.
- Unacceptable adverse event(s) (section **7**).
- Non compliance to therapy regimen as determined by the principal investigator or associate investigator.
- Patient decides to withdraw, stops therapy, or starts a new treatment.
- Deterioration of the patient's condition that render further treatment unacceptable in the judgment of the investigator.
- Death.

5.4 POST-TREATMENT FOLLOW UP

If a patient goes off treatment due to a drug related adverse event, the patient will be followed until the event resolves, returns to baseline or stabilizes. In addition, if the patient goes off treatment for other than disease progression, the patient will undergo tumor restaging every 9 weeks +/- 1 week until PD. Subsequently, patients will be followed every 4 months either in the clinic or interviewed over the telephone to assess current condition, new treatment modalities (surgery/ radiation therapy/ chemotherapy) and for overall survival.

6 DOSING DELAYS/DOSE MODIFICATIONS

- Grading of AEs for dose modification is based on CTEP Version 4.0 of CTCAE
- The maximum delay of IMC-A12 for any reason, including toxicities, is 3 weeks
- The maximum number of dose reduction is 2
- If a patient is discontinued from IMC-A12 due to IMC-A12 related toxicities, the patient should be followed for assessment of the toxicities until the AEs resolve or are deemed irreversible.

Levels of Dose reduction (EVERY THREE WEEKS)

Dose Level	IMC-A12 Dose
1	20 mg/kg every 3 weeks
(-1)	15 mg/kg every 3 weeks
(-2)	10 mg/kg every 3 weeks

Treatment Modification for IMC-A12-Related Adverse Events	CTCAE. Grade	Action to be taken
• The maximum delay of IMC-A12 for any reason, including toxicities, is 3 weeks • The maximum number of dose reduction is *2*		
Allergic reactions **or** **anaphylaxis** or **Infusion-related reactions**	G1 Allergic or infusional reactions Transient flushing or rash, drug fever ≤38	• Slow infusion rate by 50% and monitor patient for worsening of condition
	G2 Allergic or infusional reactions Rash, flushing, urticaria, dyspnea, drug fever >38	• Stop infusion; symptom control (diphenhydramine hydrochloride 50 mg IV, acetaminophen 650 mg for fever, and oxygen if needed) • Resume infusion at 50% of the prior rate once the reaction has decreased to ≤ grade 1. Monitor patient for worsening condition • For subsequent dose, premedicate with diphenhydramine hydrochloride 50 mg IV • If grade 1-2 infusion reactions reoccur with subsequent dose, add dexamethasone 10 mg IV or equivalent to premedications above (Only dose interruption/discontinuation, but not dose reduction, is required for allergic/infusional reactions)
	G3 Allergic or infusional reactions or anaphylaxis Bronchospasm; angioedema, hypotension	• Stop infusion immediately and remove the infusion tube • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV (or equivalent), bronchodilators for bronchospasms, and other medications as medically indicated. Hospital admission should be considered

Treatment Modification for IMC-A12-Related Adverse Events	CTCAE. Grade	Action to be taken
• The maximum delay of IMC-A12 for any reason, including toxicities, is 3 weeks • The maximum number of dose reduction is 2		
		• Discontinue IMC-A12 treatment
	G4 Allergic or infusional reactions or anaphylaxis	• Stop infusion and remove the infusion tube • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV (or equivalent), and other anaphylaxis medications as indicated. Epinephrine or bronchodilators should be administered as indicated. Hospital admission for observation may be indicated • Discontinue IMC-A12 treatment
Hyperglycemia; glucose intolerance	G1-2	• Continue IMC-A12 • Initiate or increase oral diabetic agents as clinically indicated
	NO symptoms AND glucose <300 mg/mL	• Initiate/increase insulin and /or oral diabetic agents • May continue IMC-A12
	Symptomatic OR glucose ≥300 mg/mL	• Hold IMC-A12 • Initiate/increase insulin and/or oral diabetic agents • Resume IMC-A12 with one dose reduction IF patient is asymptomatic, AND glucose is consistently <220 mg/mL on stable dose of insulin and /or oral diabetic agents
	G4	• Hold IMC-A12 • Initiate/increase insulin and/or oral diabetic agents • Resume IMC-A12 with one dose reduction IF patient is asymptomatic, AND glucose is consistently <220 mg/mL on stable dose of insulin and /or oral diabetic agents
Blood/bone marrow (Neutropenia, or thrombocytopenia)	G1-2	• Continue IMC-A12
	G3-4	• Hold IMC-A12 until grade decreases to <grade 2 • Resume with one dose reduction (if cytopenia is judged to be related to IMC-A12)

Treatment Modification for IMC-A12-Related Adverse Events	CTCAE. Grade	Action to be taken
• The maximum delay of IMC-A12 for any reason, including toxicities, is 3 weeks • The maximum number of dose reduction is 2		
Other unspecified IMC-A12-related AEs (except controlled nausea/vomiting)	G2	• IMC-A12 may continue or be held at physician's discretion depending on the nature of the AE • If held, may resume at initial or one dose reduction depending on nature of the AE
	G3	• Hold IMC-A12 until symptoms resolve to ≤grade 1 • Resume with one dose reduction
	G4	• Discontinue IMC-A12 • Upon consultation with the study chair, resumption of IMC-A12 may be considered if a patient is benefiting from therapy (and the grade 4 toxicity is transient), has recovered to ≤grade 1 and unlikely to recur with retreatment

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 DEFINITIONS

7.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per section **7.7.**

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon

appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LIST (CAEPR) FOR CIXUTUMUMAB (IMC-A12, NCS 742460)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further

clarification. *Frequency is provided based on 470 patients.* Below is the CAEPR for cixutumumab (IMC-A12).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, December 19, 2011[1]

Adverse Events with Possible Relationship to Cixutumumab (IMC-A12) (CTCAE 4.0 Term) [n= 470]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
EAR AND LABYRINTH DISORDERS			
	Hearing impaired[2]		
EYE DISORDERS			
	Blurred vision		
	Flashing lights		
	Floaters		
GASTROINTESTINAL DISORDERS			
	Diarrhea		***Diarrhea (Gr 3)***
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Infusion related reaction		***Infusion related reaction (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 2)***
		Anaphylaxis	
INVESTIGATIONS			
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 3)***

	Platelet count decreased		
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
Hyperglycemia			***Hyperglycemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)		
	Myalgia		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (renal failure)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		***Pruritus (Gr 2)***
	Rash acneiform		***Rash acneiform (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Middle to high range sensorineural hearing loss has been reported in patients treated with monoclonal antibodies to Insulin-like Growth Factor-1 Receptor (IGF-1R).

[3]Infection may include all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Also reported on Cixutumumab (IMC-A12) trials but with the relationship to Cixutumumab (IMC-A12) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pure red cell aplasia); Febrile neutropenia;

CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Atrial flutter; Cardiac arrest; Cardiac disorders - Other (right atrial thrombus); Left ventricular systolic dysfunction (when used in combination with doxorubicin); Myocardial infarction; Palpitations; Sinus bradycardia; Sinus tachycardia

EAR AND LABYRINTH DISORDERS - Tinnitus; Vertigo

EYE DISORDERS - Dry eye; Eye disorders - Other (blindness); Eye disorders - Other (central chorioretinopathy); Eye disorders - Other (visual acuity reduced); Eye disorders - Other (visual disturbance, visual field defect, visual impairment)

GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Colitis; Colonic perforation; Constipation; Dry mouth; Dyspepsia; Esophageal pain; Esophageal stenosis; Esophageal ulcer; Gastrointestinal disorders - Other (eructation); Gastrointestinal disorders - Other (feces discolored); Gastrointestinal disorders - Other (lip ulceration); Gastrointestinal disorders - Other (pneumoperitoneum); Mucositis oral; Pancreatitis; Typhlitis; Upper gastrointestinal hemorrhage

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema limbs; Non-cardiac chest pain; Pain; Sudden death NOS

HEPATOBILIARY DISORDERS - Hepatic failure

INFECTIONS AND INFESTATIONS - Infection[3]

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Vascular access complication; Wound complication

INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CPK increased; Cardiac troponin I increased; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; Lipase increased; Neutrophil count decreased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (polydipsia)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Bone pain; Chest wall pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Musculoskeletal and connective tissue disorder - Other (pain in jaw); Neck pain; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage)

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Headache; Intracranial hemorrhage; Ischemia cerebrovascular; Leukoencephalopathy; Paresthesia; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Seizure; Somnolence; Syncope; Tremor

PSYCHIATRIC DISORDERS - Agitation; Confusion; Depression; Psychosis

RENAL AND URINARY DISORDERS - Proteinuria; Renal and urinary disorders - Other (chromaturia); Renal and urinary disorders - Other (nocturia); Renal and urinary disorders - Other (polyuria); Urinary incontinence

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal obstruction

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Hypoxia; Laryngeal hemorrhage; Laryngeal mucositis; Pleural effusion; Pneumonitis; Pneumothorax; Postnasal drip; Respiratory failure; Sore throat

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Palmar-plantar erythrodysesthesia syndrome; Purpura; Skin ulceration

VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: Cixutumumab (IMC-A12) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.3 ADVERSE EVENT CHARACTERISTICS

- **CTCAE term (adverse event description) and grade:** The descriptions and grading scales found in the revised CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTEP Version 4.0 of CTCAE. A copy of the CTEP Version 4.0 of CTCAE can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **'Expectedness'**: Adverse events can be 'Unexpected' or 'Expected' (see Section **7.2** above) for expedited reporting purposes only. 'Expected' adverse events (the ASAEL) are ***bold and italicized*** in the CAEPR (Section **7.2**).

- **Attribution** of the adverse event:
  - Definite – The adverse event *is clearly related* to the study treatment.
  - Probable – The adverse event *is likely related* to the study treatment.
  - Possible – The adverse event *may be related* to the study treatment.
  - Unlikely – The adverse event *is doubtfully related* to the study treatment.
  - Unrelated – The adverse event *is clearly NOT related* to the study treatment

7.4 EXPEDITED ADVERSE EVENT REPORTING

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients. The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section **7.4.1**).

- In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.
- All AEs reported via CTEP-AERS must also be reported via the routine AE reporting defined by the protocol.

7.4.1 CTEP-AERS Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

Phase 2 and 3 Trials									
	Grade 1	**Grade 2**	**Grade 2**	**Grade 3**		**Grade 3**		**Grades 4 & 5[2]**	**Grades 4 & 5[2]**
				Unexpected		**Expected**			
	Unexpected and Expected	**Unex-pected**	**Expected**	**with Hospitali-zation**	**without Hospitali-zation**	**with Hospitali-zation**	**without Hospitali-zation**	**Unex-pected**	**Expected**
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**

CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

December 15, 2004

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within <u>24 hours</u> of learning of the event followed by a complete CTEP-AERS report within <u>5 calendar days</u> of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within <u>10 calendar days</u> of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the

exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

7.4.2 Expedited Adverse Event Reporting Exclusions

For this protocol, there are no AE reporting exclusions.

Note: All deaths on study must be reported using expedited reporting regardless of causality. Attribution to treatment or other cause should be provided. The NCI IRB will receive a copy of all expedited AE reports.

7.5 ROUTINE ADVERSE EVENT REPORTING

All Adverse Events must be reported in routine study data submissions. AEs reported through CTEP-AERS must also be reported in routine study data submissions.

7.6 SECONDARY AML/MDS

AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy. Second malignancies and non-AML/MDS secondary malignancies (e.g., endometrial cancer in a breast cancer patient receiving tamoxifen) should NOT be reported via CTEP-AERS but should be submitted as part of the study results via routine CDUS reporting.

7.7 NCI-IRB REPORTING

7.7.1 NCI-IRB Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report to the NCI-IRB:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All serious non-compliance

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

7.7.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance.

3. A tabular summary of the following adverse events:
    - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
    - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
    - All Grade 5 events regardless of attribution;
    - All Serious Events regardless of attribution.

    NOTE: Grade 1 events are not required to be reported.

7.7.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

8 PHARMACEUTICAL INFORMATION

8.1 IMC-A12 (NSC 742460)

Other Names: A12 "Cixutumumab."

Molecular Weight:

Lot No.	Whole Antibody (kDa)	Light Chain (kDa)	Heavy Chain (kDa)
1644-7*	149.1	22.8	52.0
Theoretical**	146.4	22.7	50.5

* IMC-A12 reference standard **Molecular Weight

Classification: Human monoclonal antibody (mAb)) of IgG1

8.1.1 Product Description: A fully human monoclonal antibody of IgG1 selectively inhibiting human insulin like growth factor-I receptor (IGF-1R).

How supplied: ImClone Systems and Lilly supply cixutumumab and DCTD/NCI distributes it. Cixutumumab is available as a 10 mg/mL (500 mg/50 mL) or 15 mg/mL (750 mg/50 mL) aqueous solution. Each single-use vial contains a sterile solution in citrate-based saline (10 mM sodium citrate, 100 mM sodium chloride, 100 mM glycine, and 0.01% Tween® -80) at pH 6.5. The vials are Type I glass, stoppered with a Flurtec coated **latex-free** plug style stopper and sealed with an aluminum flip-off seal cap. The solution is clear to slightly opalescent, colorless to pale yellow liquid, without visible particulates.

Storage: Store the intact vials refrigerated at (2^0 – 8^0 C) protected from light. Do Not Freeze.

Preparation: Do not mix lot numbers or drug concentration when preparing the solution.

Withdraw the calculated amount of IMC-A12 from the vial(s) and transfer it into ethylene vinyl acetate (EVA), AVIVA (non-PVC), polyolefin, or polyvinyl chloride (PVC) IV bag, or an evacuated glass bottle. IMC-A12 solution can be given undiluted if volume ≥ 250 mL. For doses with volumes less than 250 mL, dilute the IMC-A12 solution further to 250 mL of 0.9% NaCl, USP. Mix by gently inverting the solution bag. Do not shake.

Method of administration: Administer IMC-A12 solution intravenously over one hour or not to exceed 25 mg/minute via an infusion set that has an in-line, 0.22 micron, protein-sparing filter (e.g., paclitaxel IV set). Following the infusion, flush the IV-line with normal saline.

If the dose is 10 mg/kg every two weeks, administer IMC-A12 solution intravenously over one hour, or not to exceed 25 mg/minute. If the dose is 20 mg/kg every three weeks, administer IMC-A12 solution intravenously over ninety minutes for patients >75 kg, and over one hour for ≤ 75 kg. The infusion rate should not to exceed 25 mg/minute

Stability: Shelf life surveillance of the intact vials is ongoing. Although stability data show that IMC-A12 IV solution is stable up to 24 hours at 2^0- 25^0C, IMC-A12 IV solution has no antibacterial preservative. Use the prepared solution immediately after preparation, or refrigerate it and use it within 24 hours. Do not freeze or shake the prepared solution.

Route of administration: Intravenous infusion

Patient Implication: Monitor patients for hypersensitivity reactions during and following the IMC-A12 administration. If patients experience hypersensitivity reactions, slow the infusion by 50%. Refer to the protocol for specific administration rate, premedication, and supportive of care guidelines.

8.1.2 Availability

IMC-A12 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

8.1.3 Agent Ordering

NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied

investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Agent may be requested by completing a Clinical Drug Request (NIH-986) and faxing it to the Pharmaceutical Management Branch at (301) 480-4612. For questions about drug orders, transfers, returns, or accountability call (301) 496-5725 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.1.4 Agent Accountability

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and to obtain a copy of the DARF and Clinical Drug Request form.)

9 CORRELATIVE/SPECIAL STUDIES

Recognizing the difficulties in obtaining new and repeat tumor samples in mesothelioma, two main principles for assessments of laboratory correlates will be followed:

- utilization of already existing tumor biopsies (mainly from the initial diagnosis, and/or surgery), and in rare instances use of newly obtained pre-treatment biopsies
- evaluation of surrogate markers which can be assessed via peripheral blood samples

9.1 SERUM MESOTHELIN AND CA-125 LEVELS

Blood samples will be taken at baseline and prior to each cycle. CA-125 levels analyzed by the NIH Clinical Center Laboratory, at baseline and prior to each cycle. Soluble mesothelin samples will be analyzed according to the instructions below.

9.1.1 Instructions For Soluble MESOTHELIN Samples

Mesothelin Serum Samples: Collection

All blood samples will be taken by either direct venipuncture or an indwelling venous access. At each sample collection time, blood (2mL) will be drawn into a 3.5-mL serum separator tube (tiger top tube) labeled as follows:

- Subject ID Number
- Study Number
- Time and date of collection

9.1.2 Mesothelin Serum Samples: Processing

Each sample should be processed in the following manner:

Allow blood to clot for 10 minutes and centrifuge to separate the serum within 30 minutes of collection. If unable to process within 30 minutes, then whole blood tubes may be stored upright in refrigerator (4-8°C) for up to 48 hours prior to processing. Processing of samples within 30 minutes is strongly preferred. Stability studies will establish if degradation of soluble mesothelin in whole blood during 0.5 to 48 hours is significant and therefore if the data from these samples should be included in the analysis. If whole blood is refrigerated, a comment should be entered in the CRF comments field. Pre-labeled tubes will be provided, see study manual for details.

Transfer the serum into two pre-labeled cryotubes and immediately freeze by placing on dry ice. Transfer frozen serum samples into a – 70°C freezer for storage.

9.1.3 Mesothelin Serum Samples Storing

All serum samples will be stored in Dr. Raffit Hassan's Lab at NCI, Bldg 37, Bethesda, MD.

9.2 IMMUNOHISTOCHEMISTRY ANALYSIS OF IGF-1R AND MESOTHELIN FOR CORRELATIVE STUDIES

9.2.1 Collection of Specimen:

Archival material: A block of archival tumor material will be requested from each patient. A recent resection sample or blocks of tissue from the original resection are requested. Where a block cannot be released by the governing pathology department, 5 x 8µm re-cuts on charged slides will be requested.

9.2.2 Methods:

Immunohistochemistry for IGF-1R (#3027; Cell Signal, Danvers, MA) is performed. After deparaffinization and rehydration, the slides are blocked for hydrogen peroxidase and with BSA. After incubation with the primary anti-IGF-1R antibody at 1:100 dilution, secondary anti-rabbit antibody was added. Detection was made with streptavidin-HRP, followed by counter-staining with hematoxylin. For relative quantification, controls slides were made with xenografts with tumor cell lines containing known levels of IGF-1R (+++, ++, +). Slides were scanned with Scanscope at 20X (Aperio, Vista, CA) and scored.

Immunohistochemistry will be performed in collaboration with Dr. Maria Merino, Pathology Branch, Bldg 10/2N212.

9.2.3 Mesothelin IHC will be performed by the NIH Clinical Center Department of Pathology as part of routine staining in their initial review of patient's tumor specimens.

10 STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ☐4 weeks pri
condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study/Baseline[g]	C1 Wk 1	Wk 2	Wk 3	C2 Wk 1	Wk 2	Wk 3	C3 Wk 1	Wk 2	Wk 3	C4 Wk 1	Wk 2	Wk 3	Continue until off study or off therapy	Off Treatment Visit[e]	Every 4 month survival follow up[f]
Informed consent	X													X		
Demographics	X													X		
Medical history	X													X		X
Concurrent meds	X	X----------												X		
					----------X											
Physical exam	X	X			X			X			X			X	X	
Vital signs	X	X			X			X			X			X	X	
Height	X															
Weight[h]	X	X			X			X			X			X	X	
Performance Status	X	X			X			X			X			X	X	
CBC w/differential	X				X			X			X			X	X	
IGF-1, IGF-2, and IGF-BP's	X				X											
Electrolyte [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Other serum chemistry[b]	X				X			X			X			X Q3W		
Lipid profile; Amylase, Lipase, HbA1C (fasting sample)[c]	X				X			X			X			X Q6W	X	
PT/PTT	X															
Urine analysis	X															

EKG	X															
Adverse event evaluation	X	X---------- ----------X													X	
Tumor measurements	X	Tumor measurements are repeated every *6* weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.													X	
Serum mesothelin and CA-125 levels	X	Serum mesothelin and CA-125 levels will be obtained at baseline and at the start of every cycle.												X Q3W		
PET scan	X							X								
B-HCG	X[d]															
Archival Tissue for correlative studies	X															

a. Glucose, Na+, K+, bicarbonate, BUN, Cl, creatinine, LDH, Ca++, Mg++, phosphorus

b. Albumin, total protein, alkaline phosphatase, SGOT(AST), SGPT(ALT), total bilirubin, uric acid

c. Lipid profile (Triglyceride, cholesterol, LDL, HDL); Amylase, lipase; HbA1C (fasting sample)

d. Serum or urine pregnancy test (women of childbearing potential).

e. Off-treatment evaluation. **If a patient goes off treatment due to a drug related adverse event, the patient will be followed until the event resolves, returns to baseline or stabilizes. In addition, if the patient goes off treatment for other than disease progression, the patient will undergo tumor restaging every 9 weeks +/- 1 week until PD.**

f. Patients will be followed every 4 months either in the clinic or by telephone interview to assess current condition, new treatment modalities (surgery/ radiation therapy/ chemotherapy) and for overall survival.

g. Pre-treatment history and physical should be completed not more than 14 days prior to day 1 of therapy. Pre-treatment laboratory data should be checked not more than 7 days prior to day 1 of therapy.

h. IMC-A12 dose would need to be re-calculated only if there is a >10% change since the last cycle.

11 MEASUREMENT OF EFFECT

11.1 ANTITUMOR EFFECT – PERITONEAL AND PLEURAL MESOTHELIOMA

For the purposes of this study, patients should be re-evaluated for response every 2 cycles (*6 weeks)*. Responses should be confirmed at least *4* weeks following initial documentation of objective response.

For peritoneal mesothelioma, response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Committee. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

For pleural mesothelioma, response and progression will be evaluated using the modified RECIST criteria for mesothelioma, which will be described below.

11.2 DEFINITIONS – PERITONEAL AND PLEURAL MESOTHELIOMA

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with IMC- A12.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Progression Free Survival (PFS) is defined as the time interval from the start of treatment to documented evidence of disease progression.

Overall Survival (OS) is defined as the time interval from the start of treatment to the date of death.

11.3 PERITONEAL MESOTHELIOMA MEASUREMENTS

11.3.1 Peritoneal Mesothelioma Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial

effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target 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 recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated 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.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

*11.3.2 **Peritoneal Mesothelioma Methods for Evaluation of Measurable Disease***

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

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

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US) When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

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 in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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.

11.3.3 Peritoneal Mesothelioma Response Criteria

11.3.3.1 Peritoneal Mesothelioma Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum on study LD (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

11.3.3.2 Peritoneal Mesothelioma Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Incomplete Response/
Stable Disease (SD): *Persistence* of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.3.3.3 Peritoneal Mesothelioma Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

11.3.4 Peritoneal Mesothelioma Confirmation

11.3.4.1 The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

11.3.4.2 To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

11.3.4.3 In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

11.3.5 Peritoneal Mesothelioma Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

11.4 PLEURAL MESOTHELIOMA

The assessment tool selected for use in this protocol to determine success in meeting the primary and major secondary endpoints is the EORTC modified RECIST criteria. The RECIST criteria were initially considered for this purpose; however, the application of RECIST criteria could be variably interpreted by different investigators in mesothelioma, leading to unsatisfactory results.[75] According to the authors, the modified RECIST criteria were designed to address the unique growth pattern of pleural mesothelioma.

Below is an excerpt from an article written by Byrne and Nowak[75] that describes the recommended modifications to the RECIST Criteria developed by the EORTC. For the purpose of assessing efficacy for this clinical trial, these modified criteria will be used in conjunction with the RECIST Quick Reference tool, a copy of which has also been provided on the following pages, and is available on the NCI web site: http://ctep.cancer.gov/guidelines/recist.html.

"The Modified RECIST criteria we have developed were as follows:

Tumour thickness perpendicular to the chest wall or mediastinum was measured in 2 positions at 3 separate levels on transverse cuts of CT scan. The sum of the 6 measurements defined a pleural unidimensional measure. Transverse cuts at least 1 cm apart and related to anatomical landmarks in the thorax were chosen to allow reproducible assessment at later time points. If measurable tumour was present, transverse cuts in the upper thorax, above the level of division of the main bronchi were preferred. At reassessment, pleural thickness was measured at the same position at the same level and by the same observer. This was not necessarily the greatest tumour thickness at that level.

Nodal, subcutaneous and other bidimensionally measurable lesions were measured unidimensionally as per the RECIST criteria. Unidimensional measurements were added to obtain the total tumour measurement. CR was defined as the disappearance of all target lesions with no evidence of tumour elsewhere, and PR was defined as at least a 30% reduction in the total tumour measurement. A confirmed response required a repeat observation on 2 occasions 4 weeks apart. Progressive disease (PD) was defined as an increase of at least 20% in the total

tumour measurement over the nadir measurement, or the appearance of 1 or more new lesions. Subjects with stable disease (SD) were those who fulfilled the criteria for neither PR nor PD."

11.4.1 Pleural Mesothelioma Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this Category Also Requires:**
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

11.4.2 Pleural Mesothelioma Confirmation

11.4.2.1 The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

11.4.2.2 To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

11.4.2.3 In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

11.4.3 Pleural Mesothelioma Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

11.5 REPORTING OF RESULTS

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients.

Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment etc.). However, these subanalyses may not serve as the basis

for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

The 95% confidence intervals should be provided.

11.6 OTHER IMAGING STUDIES - PET SCANS

FDG-PET scanning is of interest as part of this study for the following reasons: -

i) it may help evaluate a pharmacodynamic change due to the potential impact of IGF-1R on glucose metabolism or transport

ii) FDG-PET changes may correlate with clinical activity

FDG-PET scans will be performed as part of this study, primarily for clinical reasons to assess disease activity. Patients enrolled on the study will undergo FDG-PET scan at baseline and at the time of restaging every 6 weeks after start of therapy.

12 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7(Adverse Events: List and Reporting Requirements).

12.1 DATA REPORTING

12.1.1 Monitoring Method

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Data will be collected in the Center for Cancer Research C3D database and will be transmitted to CDUS electronically.

Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP web site (http://ctep.cancer.gov). **Note**: **All** adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via CDUS.

12.1.2 Responsibility for Submissions

Participating sites will enter data into C3D. The coordinating center is responsible for quarterly CDUS submissions for all sites.

12.1.3 Site Audits

The sponsor will be responsible for all site audits.

12.1.4 Additional Data Reporting

Due to the unique toxicity concerns with hyperglycemia associated with IMC-A12 and the currently limited experience with this toxicity/management**, the AE CRFs (baseline and post-treatment) should include check boxes to specifically query for the following AE information**:

The following Items (Check boxes) should be included in the on study and AE CRFs:

1. **Hyperglycemia** (per CTEP Version 4.0 of CTCAE under METABOLISM - hyperglycemia): presence or absence; grade; Onset date; or resolution date; whether or not requiring A12 dose reduction; whether or not require A12 discontinuation
2. **Diabetes** (per CTEP Version 4.0 of CTCAE under ENDOCRINE – diabetes): presence or absence; grade; Onset date; or resolution date; whether or not requiring A12 dose reduction; whether or not requiring A12 discontinuation
3. If any of the above is Yes, query the use of **diabetic medications**:

- Oral diabetic drugs: Yes or No. If yes, name, start date, off date, dose
- Insulin: Yes or no. If yes, start date, off date.

4. ***Concomitant use of corticosteroids***

12.2 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)/CLINICAL TRIALS AGREEMENT (CTA)

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as Collaborator(s)) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborators" (http:// ctep.cancer.gov/industry) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements ,

the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):

a) NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b) Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

c) Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected, used, and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborators' confidential/ proprietary information.

13 STATISTICAL CONSIDERATIONS

13.1 STUDY DESIGN/ENDPOINTS

The primary objective of this phase II clinical trial is to determine clinical response rate (PR+CR) to IMC-A12 monotherapy in patients with advanced mesothelioma. The secondary objectives are to determine progression free survival (PFS) and overall survival (OS). Exploratory objectives include the study of tumor expression of IGF-1R, change in serum mesothelin levels following treatment, and to determine the relationship between response to therapy and changes in FDG-PET imaging according to modified RECIST criteria for mesothelioma.

Patients with pleural mesothelioma and peritoneal mesothelioma will be eligible for the study, and will be evaluated in separate strata.

For patients with pleural mesothelioma, the study will be conducted as an optimal two-stage phase II trial in order to rule out an unacceptably low 5% clinical response rate (PR+CR: p0=0.05) in favor of a targeted rate consistent with 20% (p1=0.20).[76] With alpha=0.10 (probability of accepting a poor regimen=0.10) and beta = 0.10 (probability of rejecting a good regimen=0.10), the study will initially enroll 12 evaluable patients with pleural mesothelioma, and if 0 of the 12 are able to have a response then no further patients will be accrued. If 1 or more of the first 12 patients have a response, then accrual would continue until a total of 37 patients have been treated in this stratum. A temporary pause in the accrual to the trial may be necessary to ensure that enrollment to the second stage is warranted. If there are 1 to 3 patients with a response in the total of 37 patients with pleural mesothelioma, then this would be an uninterestingly low rate, while if there were 4 or more patients of the 37 who have a response, this would be sufficiently interesting to warrant further study of this agent in later trials. Under the null hypothesis (5% response rate), the probability of early termination is 54%.

Patients with peritoneal mesothelioma are more rarely diagnosed; thus the evaluation in those patients will be performed using a smaller study design. Since the patients are rarer, a single stage design with the following characteristics will be used. A total of 15 evaluable patients with peritoneal mesothelioma will be enrolled and their clinical responses determined. If there are 2 or more clinical responses (PR+CR) in these 15 patients, then the probability of having this occur will be 83.3% if the true probability of a response was 20%, while it will only be 17.1% if the true probability of a response would be 5%. Thus, observing 2 or more responses in 15 patients will provide reasonable evidence that the true response rate is likely to be consistent with 20% and greater than 5%, given the rare nature of the disease. In addition to determining the actual response rates, 80% and 95% confidence intervals will also be formed about the observed response rate and presented.

As secondary evaluations, in each of the two strata, time to response, duration of response, PFS and OS will be reported separately using Kaplan-Meier curves and appropriate 95% confidence intervals. These findings will be compared informally to other similar published results in

patients with the same disease. In addition, separately for the two types of mesothelioma, the expression of IGF-1R, differences in serum mesothelin levels, and FDG-PET imaging parameters will be determined for all patients. The absolute levels before and after treatment as well as changes from baseline will be compared between patients who are responders (PR+CR) and non-responders (PD+SD) using an exact Wilcoxon rank sum test. The results obtained will be considered exploratory and will be presented without adjustment for multiple comparisons, but in the context of a hypothesis generating analysis. In addition, if results for the two strata are similar, with $p>0.50$ for comparisons between the parameter values for any given parameter, the findings of these exploratory parameters may be pooled between the two strata and reported as well.

In order to enroll up to 37 patients with pleural mesothelioma and 15 with peritoneal mesothelioma, it is expected that 2-3 years may be required. The accrual ceiling will be set at 55 in order to allow for a small number of inevaluable patients.

13.2 SAMPLE SIZE/ACCRUAL RATE

It is anticipated that 1-2 patients per month with pleural mesothelioma and 1-2 patients with peritoneal mesothelioma may be enrolled onto this trial. With a total ceiling of 37 for pleural mesothelioma and 15 for peritoneal mesothelioma, a total of 52 patients may be required. To allow for a very small number of inevaluable patients, the accrual ceiling will be set at 55. With a total of 3-4 patients enrolled per month, accrual should be completed within approximately 1-2 years.

13.3 ANALYSIS OF SECONDARY ENDPOINTS

Durations of response, progression free survival, and overall survival will be determined actuarially using the Kaplan-Meier method.

A variety of immunohistochemistry evaluations, plasma studies, and other correlative studies will be undertaken as exploratoryobjectives during the conduct of this trial.

Immunohistochemistry results after treatment will be compared to baseline using McNemar's test for paired categorical data (or a marginal homogeneity test if appropriate). Continuously distributed data will be compared between responders and non-responders using a Wilcoxon rank sum test because of the potentially limited number of responders which may be identified.

Other descriptive, exploratory methods will be used as appropriate, and any p-values determined for analyses performed as secondary objectives will be presented without any formal adjustment for multiple comparisons, but will be described in the context of the secondary nature of the analysis and the number of such analyses performed.

13.4 REPORTING AND EXCLUSIONS

13.4.1 Evaluation of toxicity.

All patients will be evaluable for toxicity from the time of their first treatment with *IMC- A12.*

13.4.2 Evaluation of response.

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4)

progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

14 HUMAN SUBJECTS PROTECTIONS

14.1 RATIONALE FOR SUBJECT SELECTION

This study will be open to all individuals with relapsed or refractory pleural or peritoneal mesothelioma regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. For safety reasons, only pregnant women and children are excluded from this study. This study will be recruited through internal referral, our local physician referral base, and through various cancer information hotlines (i.e., Clinical Studies Support Center, 1-800-4Cancer). All individuals with relapsed or refractory pleural or peritoneal mesothelioma that have progressed after one cycle of standard care chemotherapy are eligible according to the eligibility criteria within section **3**. This is a Phase II trial designed to evaluate the efficacy of IMC-A12 in patients with advanced pleural and peritoneal mesothelioma, the side effect profile of IMC-A12, and the assessment of several biological endpoints. Patients must have failed first-line platinum-based therapy for advanced pleural or peritoneal mesothelioma. Subjects from both genders and all racial /ethnic groups are eligible for this study if they meet the eligibility criteria outlined in section **3**. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but in this preliminary study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, accrual may be expanded or a follow-up study may be written to investigate those differences more fully.

14.2 JUSTIFICATION FOR EXCLUSIONS

Due to lack of knowledge of the effects of IMC-A12 on the fetus or on infants, as well as the possibility of teratogenic effects, pregnant and nursing women will be excluded from this trial. Patients with HIV on protease inhibitors are excluded because information on drug interactions

of anti-HIV agents with IMC-A12 are lacking. Patients with unstable or serious medical conditions (ongoing or active infection, symptomatic congestive heart failure (AHA Class II or worse), unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements) are excluded due to the possibility that IMC-A12 may worsen their condition and the likelihood that the underlying condition may obscure the attribution of adverse events with respect to IMC- A12.

14.3 PARTICIPATION OF CHILDREN

Patients under the age of 18 years will be excluded from study. Since mesothelioma is extremely rare in children they are excluded from the study.

14.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The potential benefit to a patient who enters study is a reduction in the bulk of his/her tumor, which may or may not have a favorable impact on symptoms and/or survival. Potential risks include the possible occurrence of any of a range of side effects that are listed in the pharmaceutical section and the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis as described earlier.

14.5 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, treatment plan, research objectives and follow-up of this trial. The patient will be provided an IRB-approved consent for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient at a subsequent visit. The original of the signed informed consent will be placed in the patient's medical record and a copy will be held in the research record.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on study.

15 DATA AND SAFETY MONITORING PLAN

Any new significant finding that may affect the patient’s willingness to continue in the study will be shared with patients. Data will be monitored regularly by the coordinating center in order to identify significant toxicity trends. Confidentiality will be maintained as much as possible, consistent with applicable regulations. Names of participants or identifying material will not be released without patient permission, except when such release is required by law. No patient’s name or identifying information will be released in any publication or presentation. Records are maintained according to current legal requirements, and are made available for review according to the requirements of the Food and Drug Administration (FDA) or other authorized user, only under guidelines established by the Federal Privacy Act.

16 REFERENCES:

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17

APPENDICES

17.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

17.2 APPENDIX B: STAGING SYSTEM FOR PLEURAL MESOTHELIOMA

International Mesothelioma Interest Group (IMIG) Staging system for Pleural Mesothelioma (1995)

Primary tumor (T)

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

T1: Tumor involves same side pleura of the chest wall, with or without focal involvement of the pleura on the outer side of lung

T1a: Tumor involves same side pleura of the chest wall, no involvement of pleura on the outer surface of lung

T1b: Tumor involves same side pleura of the chest wall with focal involvement of pleura on the outer surface of lung

T2: Tumor involves same side pleura of the chest wall with at least one of the following features:

- Confluent tumor on the outer surface of the lung
- Involvement of the muscles of the diaphragm
- Involvement of the lung tissue deeper to the mesothelium covering the lung

T3: Tumor involves same side pleura of the chest wall with at least one of the following features:

- Involvement of the endothoracic fascia
- Involvement of the mediastinal fat
- Single focus of tumor involving the soft tissue of the chest wall
- Involvement of pericardium just on the out aspect (without penetration of pericardium)

T4: Tumor involves same side pleura of the chest wall with at least one of the following features:

- Diffuse or multi-focal involvement of the soft tissue of the chest wall
- Involvement of the rib
- Invasion through the diaphragm to the peritoneal cavity
- Invasion of any mediastinal organ
- Direct extension to the pleura on the other side
- Invasion into spine
- Penetration of the pericardium
- Pericardial effusion which is positive for cancer cells

- Involvement of heart muscle
- Involvement of the nerves of brachial plexus

Lymph node involvement (N)

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node involvement

N1: Involvement of same side broncho-pulmonary and or hilar lymph nodes only

N2: Involvement of subcarinal lymph node(s), and or same side or opposite side internal mammary or mediastinal lymph node(s)

N3: Involvement of opposite side mediastinal, internal mammary, or hilar lymph node(s) and or same side or opposite side supraclavicular or scalene lymph node(s)

Distant metastasis (M)

Mx: Distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis present

Staging

Stage 1

- T1 N0 M0

Stage IA

- T1a N0 M0

Stage IB

- T1b N0 M0

Stage II

- T2 N0 M0

Stage III

- T1, T2 N1 M0
- T1, T2, N2, M0
- T3, N0, N1, M0

Stage IV

- T4 Any N M0
- Any T N3 M0
- Any T, Any N, M1

INSTITUTE: National Cancer Institute

STUDY NUMBER: 10-C-0146 PRINCIPAL INVESTIGATOR: Raffit Hassan, M.D.

STUDY TITLE: Phase II Study of IMC-A12 in Patients with Mesothelioma who have been Previously Treated with Chemotherapy

Continuing Review Approved by the IRB on 08/12/15

Amendment Approved by the IRB on 08/12/15 (F) Date Posted to Web: 08/15/15

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

The purpose of this study is to determine what effects the drug IMC-A12 has on you and your cancer. IMC-A12 is a new (experimental) agent that has not yet been approved by the Food and Drug Administration (FDA). IMC-A12 is a monoclonal antibody that was designed to inhibit a

protein called Type I Insulin-Like Growth Factor (IGF-1R). An antibody is a natural protein product of the body used by the body's immune system to fight foreign or diseased cells. IMC-A12 blocks the Insulin-like Growth Factor 1 receptor (IGF-1R). IGF-1R is found on many types of cancer cells including mesothelioma and is thought to play an important role in helping these cells to grow and divide. IMC-A12 is a manufactured antibody specifically designed to inhibit the IGF-1R. We hope that IMC-A12 may stop or slow growth and spread of your mesothelioma.

IMC-A12 is an investigational or experimental anti-cancer agent that has not yet been approved by the Food and Drug Administration for use in mesothelioma.

Why are you being asked to take part in this study?

You are being asked to take part in this study because you have mesothelioma that has progressed despite prior chemotherapy.

How many people will take part in this study?

About 55 people will take part in this study. Fifteen patients with peritoneal mesothelioma will be treated with IMC-A12. Twelve patients with pleural mesothelioma will be treated with IMC-A12. If 1 or more patients in the pleural mesothelioma group respond to treatment, then an additional 25 patients will be treated in that group. Thus, a total of 37 pleural mesothelioma patients are the most that would be able to enter the study. Therefore, a maximum of 55 patients will be enrolled, to allow for a certain number of inevaluable patients.

Description of Research Study

What will happen if you take part in this research study?

After you are accepted for this study and you choose to take part, you will receive IMC-A12 at a dose of 20 mg/kg through a vein once every three weeks until disease progression or until significant adverse effects develop. Dose reductions and dose interruptions will be allowed per the protocol.

In the absence of any complications that might need admission to the hospital, this study, and all associated blood tests and imaging studies would be performed in an outpatient setting.

Before you begin the study

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Routine physical examination, including measurement of vital signs, height, and weight
- Blood tests to check blood counts, blood chemistry, coagulation parameters, and blood cholesterol
- Urine analysis
- Serum or Urine pregnancy test (for women of childbearing potential)
- EKG
- CT scans (or MRI of the appropriate anatomic location whenever appropriate) to measure cancer lesions and a PET scan to evaluate activity
- Biopsy to obtain cancer tissue (unless this procedure has been performed in the past and tissue is available for review and further analysis)

During the study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Blood tests and radiological studies as described above

You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- Blood test to check blood chemistry (including blood glucose)

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- Blood test to study different biological markers that we anticipate will be affected after treatment with the study drug

Before taking any over-the-counter medicines, herbal supplements, or other types of alternative therapies, such as nutritional supplements, vitamin or mineral supplements, please check with your study doctor.

When you have finished taking the study drug (IMC-A12)

You will undergo all tests as you did before entering the study, with the exception of an EKG and tests for checking coagulation parameters. If you are taken off study due to the development of severe side effects we will contact you periodically until the side effect has resolved or is determined to be irreversible. In addition, we will follow up with you 30 days after you are taken off study to interview you about your medical history, and get details on any medications that you might be on at that time. Subsequently we will contact you annually to interview you about your medical history and discuss any new developments relevant to your disease.

Study Chart

You will receive the study drug (IMC-A12) every 3 weeks in this study. This 3 week period of time is called a cycle. The cycle will be repeated as long as there is no progression of disease and you are tolerating the treatment well. Each cycle is numbered in order. The chart below shows what will happen to you during Cycle 1 and future treatment cycles as explained previously. The left-hand column shows the day in the cycle and the right-hand column tells you what to do on that day.

Cycle 1

Day	What you do
Up to 4 weeks before starting study	• Get radiological studies (e.g. CT scans)
Up to 7 days before starting study	• Get routine blood tests.
Day of starting study	• Arrive in out-patient clinic and after clinic visit go to the Day-Hospital to begin treatment.
Day 1	• Get study-specific blood tests including collection of research blood.
Day 22	• Return to the outpatient clinic for the next office visit and to begin the next cycle.

Future cycles

Day	What you do
Days 1-21	• Keep taking the study drug on the first day of each cycle if you have no bad

	side effects and the cancer is not getting worse. Call the doctor at 301-435-5609 if you do not know what to do. • Study-specific blood tests will only be performed on Day 1. • Routine blood tests (to check serum electrolytes, blood glucose, liver and kidney function) will be performed once every week. These tests can also be performed at a laboratory close to your home and the results faxed to us at 301-480-2590. • Get radiological studies every other cycle (more if clinically indicated).
Day 22	• Return to the outpatient clinic for the next office visit and to begin the next cycle.

How long will I be in the study?

You will be asked to take the study drug (IMC-A12) until disease progression or until significant adverse effects develop. While receiving the study drug, you will be seen in the clinic every 3 weeks. After disease progression or if significant adverse events develop, you will be considered in the off-therapy portion of the study. If you go off therapy due to significant adverse events, the study doctor may ask you to visit the office for follow-up exams as often as needed until the event stabilizes. If you go off therapy for any reason other than disease progression, the study doctor will ask you to visit the clinic every 9 weeks (plus or minus 1 week), until disease progression does occur. After that, you will be followed either in the clinic or by telephone interview every 4 months to assess your condition. We would like to keep track of your medical condition for the rest of your life. Keeping in touch with you and checking on your condition helps us look at the long-term effects of the study.

What does this study involve?

Treatment with the study drug IMC-A12, study-specific blood tests and radiological studies according to the plan described above.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options:

- Getting treatment or care for your cancer without being in a study

- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study drug. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the study drug include those which are:

Likely:

- Fatigue or tiredness
- Increased blood sugar level

Less Likely:

- Lack of enough red blood cells (anemia)
- Hearing loss
- Blurred vision
- Seeing flashing lights
- Seeing spots before the eyes (floaters)

- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Decreased number of a type of white blood cell (lymphocyte)
- Decreased number of a type of blood cell that help to clot blood (platelet)
- Weight loss
- Loss of appetite
- Dehydration (when your body does not have as much water and fluid as it should)
- Muscle spasms
- Muscle pain
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Stuffy or runny nose, sneezing
- Itching
- Acne
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Hives

Rare but Serious:

- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Kidney failure

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 3 months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

While hormonal methods of birth control are effective, we ask that female patients who are participating in the study cease hormonal forms of birth control, as these methods of birth control (birth control pills, injections, or implants) may affect the study drug. Patients must be off hormonal forms of birth control for at least 4 weeks prior to initiating the study.

Effective forms of birth control include:

- Abstinence
- intrauterine device (IUD)
- tubal ligation
- vasectomy

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Also since the investigational drug persists for some time in the body (determined by the half life of the drug) reproductive precautions mentioned above should persist for 3 months after the last dose of the drug. Check with your study doctor about what kind of birth control methods to use and how long to use them (please see further details in the section on 'Birth Control' above). Some methods might not be approved for use in this study. Pregnancy testing is required for women with childbearing potential prior to enrollment on the study.

For more information about risks and side effects, ask your study doctor.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if the experimental drug IMC-A12 will cause your tumors to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in

this study, although the knowledge gained from this study may help others in the future who have cancer.

Research Subject's Rights

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.
In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.
- The study agent (IMC-A12), will be provided free of charge while you are participating in this study. However, if you should need to take the study agent much longer than is usual, it is possible that the supply of free study agent that has been supplied to the NCI could run out. If this

happens, your study doctor will discuss with you how to obtain additional drug from the manufacturer and you may be asked to pay for it.

- You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Pharmaceutical Collaborator (The pharmaceutical collaborator is the drug company that provides the investigational drug (IMC-A12) through the Cancer Therapy Evaluation Program (CTEP).

Stopping Therapy

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drug can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest

- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- if you do not follow the study rules
- if the study is stopped

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to ImClone or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using the experimental drug IMC-A12 developed by ImClone Inc. through a joint study with your researchers and the company. The company also provides financial support for this study.

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part

in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

Blood and tissue samples collected from you may be stored and used in the future to study scientific questions related to this protocol. If there are any risks to you or your family associated with these scientific studies which are not covered in this consent form, your consent will be obtained before such studies are performed.

Things to Think About

The choice to let us keep the left over tissue for future research is up to you. No matter what you decide to do, it will not affect your care. If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any tissue that remains will no longer be used for research. In the future, people who do research may need to know more about your health. While we may give them reports about your health, we will not give them your name, address, phone number, or any other information that will let the researchers know who you are. Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records. Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

Benefits

The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Optional Studies

We would like to keep some of the tissue and blood that are collected for future research. These specimens will be identified by a number and not your name. The use of your specimens will be for research purposes only and will not benefit you. It is also possible that the stored specimens may never be used. Results of research done on your specimens will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you decide now that your tissue and blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue and blood. Then any tissue and blood that remain will be destroyed.

Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. No matter what you decide to do, it will not affect your care.

1. My tissue and blood specimens may be kept for use in research to learn about, prevent, or treat cancer or other health problems.

Yes No Initials_____

2. Someone may contact me in the future to ask permission to use my specimen(s) in new research not included in this consent.

Yes No Initials_____

Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

OTHER PERTINENT INFORMATION

1. **Confidentiality.** When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

   The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. **Policy Regarding Research-Related Injuries.** The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. **Payments.** The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. **Problems or Questions.** If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Raffit Hassan, M.D., NIH Building 10, Room 4-5330, Bethesda, Maryland 20892. Another researcher you may call is Arun Rajan, M.D. You may reach them through the NIH page operator at 301-496-1211. If you have any questions about the use of your tissue for future research studies, you may also contact the Office of the Clinical Director, Telephone: 301-496-4251.

   You may also call the Clinical Center Patient Representative at 301-496-2626.

5. **Consent Document.** Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative — Date

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian — Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian — Date — Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM AUGUST 12, 2015 THROUGH AUGUST 11, 2016.

Signature of Investigator — Date

Print Name

Signature of Witness — Date

Print Name