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A Phase I/ Randomized Phase II Study of Gemcitabine plus Erlotinib plus MK-0646, Gemcitabine plus MK-0646, and Gemcitabine plus Erlotinib for Patients with Advanced Pancreatic Cancer

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1. OBJECTIVES

1.1 Primary Objectives:

- **Phase I**: Determine the maximal tolerated dose (MTD) of MK-0646 in combination with gemcitabine or gemcitabine plus erlotinib and recommended phase II dose.
- **Phase II**:
  - Assess progression-free survival (PFS) with a) gemcitabine plus MK-0646 b) gemcitabine plus erlotinib plus MK-0646 and c) gemcitabine plus erlotinib
  - Explore IGF1 tissue level as a predictive biomarker for MK-0646 therapy in phase II expansion cohort.

1.2 Secondary Objectives:

- Assess overall response rate (ORR), treatment toxicity, and overall survival (OS) with the addition of MK-0646 to gemcitabine or gemcitabine plus erlotinib.
- Correlate PFS and OS with IGF-1, IGFBP-3 levels and the expression of p-IRS, IGF-1R, EMT biomarkers, Akt, Erk, mTOR, and PI13k in tumor cells.
- To assess the incidence of single nucleotide polymorphisms of the IgF1R pathway related genes (IGF1, IGF1R, IRS1 and IRS2). These genotypes will be correlated with the clinical endpoints of this study, including OS, ORR and PFS.

2. BACKGROUND

2.1 Pancreatic Cancer

The five-year survival rate of patients with pancreatic cancer has not improved over time and remains below 5%. Gemcitabine, the most widely used chemotherapeutic agent in pancreatic cancer has a palliative role and provides a survival advantage as compared with 5-fluorouracil for advanced, unresectable disease.[1] No significant improvement in survival was observed in phase III trials when doublets of gemcitabine plus a cytotoxic drug were compared with single-agent gemcitabine. These doublets have included cytotoxic agents, such as cisplatin, 5-fluorouracil, capecitabine, exatecan, oxaliplatin and irinotecan.[2-5] The addition of targeted agents, including cetuximab, bevacizumab, farnesyl transferase inhibitors and matrix metalloproteinase inhibitors to gemcitabine have also led to disappointing results.[6-8] Gemcitabine plus erlotinib may result in a modest survival improvement when compared with single-agent gemcitabine.[9] However, whether this modest survival advantage is accompanied by an improved quality of life is unknown at the current time. Pharmacological studies have shown that fixed-dose rate gemcitabine, administered at 10 mg/m^2/minute, results in a pharmacodynamic and clinical advantage due to saturable kinetics noted after the rapid, 30-minute infusional schedule.[10] However, the course of this chemotherapy-refractory disease is unlikely to be altered by cytotoxic drugs alone and the addition of molecularly-targeted agents, based on the knowledge of pancreatic carcinogenesis, is likely to lead to therapeutic gains.

2.2 IgF-1R and Pancreatic Cancer

IGF-1R initiates signals that activate the phosphoinositide 3-kinase (PI3-kinase)/Akt and MEK/ Erk pathways and is thought to play a crucial role in the pathology underlying pancreatic and other cancers.

The signaling cascades that are activated by the IGF-1R and IGF-2R transmembrane receptor tyrosine kinases are regulated by the IGF family of-ligands (IGF-1 and -2), their binding proteins (IGFBP 1-10), specific proteases and IGFBP-interacting molecules. IGF-1R signaling inhibition enhances gemcitabine and cisplatin-induced apoptosis in pancreatic cancer xenografts and ovarian cancer cell lines, respectively.[11, 12] IGFBPs transport IGFs to the peripheral circulation and are the major determinants of IGF bioavailability. IGFBP-3, one of the most important members of the IGFBP family, binds to 75% of the circulating IGF. Decreased IGFBP-3 levels are associated with an increased risk of endometrial, head and neck and hepatocellular cancer progression[13-15], while inconsistent findings were reported with pancreatic cancer.[16, 17] Upon ligand binding, IGF-1R is activated and results in autophosphorylation of tyrosine 950 in the juxtamembrane which can serve as the docking site for the insulin receptor substrates (IRS)1-4 and shc. In parallel to the PI-3 kinase signaling pathway, recruitment of Grb2/SOS by p-IRS-1 and shc leads to recruitment of Ras and activation of the Raf/ MEK/Erk pathway, eventually leading to cellular proliferation. We recently showed that IRS-specific small interfering RNA potently inhibited activation of PI3-kinase and Akt in transfected pancreatic cancer cells.[18] Activated IRS and IGF-1R expression in the tumor may be important predictors for response to IGF-1R-directed therapy, while changes in activated Erk and Akt expression resulting from IGF-1R inhibition may be important for the assessment of a pharmacodynamic effect.

We postulate that the IgF1R inhibitor plus gemcitabine combination is worthy of investigation in pancreatic cancer. In summary, IGF-1R is an attractive target in pancreatic cancer, due to the important role of the Erk and PI3-kinase/ Akt signaling in this disease. IGF-1R inhibition enhances the anti-tumor effect of gemcitabine in preclinical studies.

2.3 IgF1R and EGFR inhibition

EGFR expression is common in pancreatic cancer and represents an important target in this disease. EGFR overexpression, mutation, and gene amplification are associated with increased sensitivity and improved outcome with the EGFR tyrosine kinase inhibitor erlotinib.[19] As discussed above, the EGFR tyrosine-kinase inhibitor erlotinib is FDA-approved for the treatment of pancreatic cancer, based on the superior survival of the gemcitabine plus erlotinib combination vs. gemcitabine monotherapy. Response to erlotinib is influenced by mutations in EGFR and K-ras gene. Patients with mutant EGFR but no K-ras mutations are most responsive to erlotinib treatment. Those who respond to EGFR inhibition will ultimately develop resistance which can be attributed to multiple mechanisms including development of secondary EGFR mutations, c-met amplification, and potentially cross talk between EGFR and IGF-1R pathways.

Cross talk between the EGFR and IGF1R pathways has been shown to contribute to transformation, growth, and tumor responsiveness to EGFR inhibitors. Combination therapy with EGFR monoclonal antibody C225 and recombinant humanized anti-IGF-1R antibody h7C10 in A549 NSCLC xenografts models of wild-type EGFR and activated ras mutation led to 95% growth inhibition as opposed to 72% with C225 alone.[20] Ueda et al, demonstrated that the expression of IgF1R and EGFR was commoner in metastatic disease sites than in the primary, surgically-resected pancreatic cancer.[21] Suppression of IGF1R signaling not only augmented erlotinib activity in wild-type EGFR NSCLC tumor cells, but also abolished resistance to erlotinib and induced apoptosis in erlotinib-resistant NSCLC cells.[22] Dual inhibition of EGFR and IGF1R pathways therefore may improve responsiveness in patients with wild-type (WT) EGFR and/or activating K-ras mutation tumors who are otherwise less responsive to erlotinib single agent treatment; may delay the development of acquired resistance to erlotinib, or overcome acquired resistance to erlotinib after initial response; and may further improve response to erlotinib in patients with mutant EGFR.

2.4 **MK-0646**

MK-0646 is a humanized IgG1 monoclonal antibody that binds to the insulin-like growth factor receptor type 1 (IGF-1R) and is being developed for the treatment of cancer based on the hypothesis that monoclonal antibodies to growth factor receptor tyrosine kinases are effective cancer treatments. IGF-1R is a receptor tyrosine kinase and activation and overexpression of IGF-1R induces mitosis, is required to establish and maintain a transformed phenotype, and protects cells against apoptosis. Multiple cancer types are potential indications for treatment with an IGF-1R antibody.

2.4.1 **Pharmacology of MK-0646**

MK-0646 is a humanized antibody against the human insulin-like growth factor receptor I (IGF-1R). It binds to IGF-1R from non-human primates (cynomolgus and rhesus macaques), but does not recognize mouse, rat, or dog receptor. MK-0646 binds human IGF-1R with a K_d of 0.9 nM and specifically recognizes IGF-1R over the closely related insulin receptor (InsR). MK-0646 is of IgG1 isotype and has the potential to elicit antibody-dependent cellular cytotoxicity (ADCC).

MK-0646 inhibits IGF-1 and IGF-2 -dependent proliferation of MCF7 breast cancer cells *in vitro* with similar potency. Binding of MK-0646 results in receptor down-regulation and pathway inhibition, with reduced levels of phospho-IGF-1R and of the downstream effectors phospho-Akt and phospho-MapK (range >50% to >90%). Receptor down-regulation on various human tumor cell lines ranged from 8 to 80% and correlated significantly with receptor density and with the ratio of IGF-1R to InsR. Receptor internalization from 75% to 100% was also demonstrated by flow cytometry on human $CD8^-$ T cells and granulocytes exposed to MK-0646 ex vivo. Receptor internalization in vivo was demonstrated in granulocytes and $CD8^-CD3^+$ T cells isolated from cynomolgus macaques treated with a single dose of MK-0646. IGF-1R was completely internalized starting approximately 4 hours

following infusion and remained internalized through Day 6 and Day 10 after a 0.5 mg/kg and 2 mg/kg dose, respectively.

MK-0646 shows anti-tumor activity in mouse xenograft models with multiple human tumor cell lines derived from lung, breast, colon and pancreatic carcinomas. When administered weekly for five weeks to mice bearing A549 NSCLC xenografts, MK-0646 resulted in dose-dependent tumor growth inhibition, reaching a maximum of ~60% inhibition at 50 μg antibody per dose, and concomitant downregulation of IGF-1R and phospho-IGF-1R levels by > 80%.

The therapeutic efficacy of MK-0646 was also evaluated using [^{18}F]FDG PET/CT imaging in geriatric rhesus macaques with naturally-occurring ileocecocolic adenocarcinomas that overexpress IGF-1R. In two animals in which the once-weekly 10 mg/kg IV dosing regimen achieved the targeted trough serum levels of 3 μg/mL, MK-0646 monotherapy caused regression of the adenocarcinomas. By Day 9 post-first dose a decrease in the [^{18}F] FDG PET-defined volume of hypermetabolic activity was apparent in both animals (57% and 85% reduction, respectively), corresponding with a 33% and 34% decrease in CT-defined tumor volume. Following 6 weeks of treatment, the final imaging studies demonstrated CT-defined tumor regression of 58% and 19%, respectively. In a third geriatric rhesus similarly dosed with MK-646 there was no response but MK-0646 was non-detectable at all time points. Serum analysis suggested that this was due to development of a robust anti-human antibody response.

Studies have been conducted in propofol anesthetized rhesus and cynomolgus macaque monkeys to discover a radiotracer for IGF1R that could be used to identify tumors and patients for therapy that have the highest likelihood of response. A total of 46 scans have been conducted using either ^{64}Cu labeled Fab2 MK-0646, ^{64}Cu MK-0646 or ^{123}I-MK-0646 in the absence and presence of MK-0646. An adverse reaction to MK-0646 infusion was observed in one anesthetized cynomolgus monkey that had been previously exposed to ^{123}I MK-0646 one week earlier. In plasma from this animal ^{123}I MK-0646 was unstable and converted rapidly to high and low molecular weight products suggesting an immune response. The adverse event observed was consistent with an apparent anaphylactic reaction. Two other cynomolgus monkeys similarly exposed had no reaction.

2.4.2 P**harmacokinetics and Metabolism of MK-0646**

The pharmacokinetics of MK-0646 were evaluated following intravenous (iv) administration of MK-0646 at 10 mg/kg to CD-1 mice, Sprague-Dawley rats, and Cynomolgus monkeys, and at 3 mg/kg to Beagle dogs. In all species studied, MK-0646 exhibited a very low clearance (ranging from 0.005 mL/min/kg in dogs and monkeys to 0.02 mL/min/kg in rats), low volume of distribution (0.05 - 0.27 L/kg) and long half-life (ranging from 5 days in monkeys to 14 days in mice). In rats and monkeys, the pharmacokinetics of MK-0646 was linear over an iv dose range of 10 to 100 mg/kg. However, apparent non-linearity in the pharmacokinetics was noted over a low dose range in monkeys; after 0.5 and 2 mg/kg doses, values for clearance and half-life were 0.02 and 0.01 mL/min/kg, and approximately 1 and 2 days, respectively. This apparent non-linearity is not unexpected and consistent with a

specific receptor-mediated elimination mechanism commonly observed with other monoclonal antibodies. Based on an allometric scaling method, it is anticipated that in humans MK-0646 would also exhibit a very low clearance and low volume of distribution, with a relatively long half-life. However, as was the case in monkeys, there is also a possibility for non-linear pharmacokinetics (increased clearance and shorter half-life than predicted values) following administration of a low dose range (≤10 mg/kg) of MK-0646 in humans.

2.4.3 **Toxicity of MK-0646**

MK-0646, a humanized monoclonal antibody (IgG1) against the insulin-like growth factor receptor type 1 (IGF-1R) was tested in a series of preclinical toxicity studies in order to support the initiation of studies in humans. The preclinical toxicity studies included in vitro hemolytic assays, an ex vivo tissue cross-reactivity study with human and cynomolgus monkey tissues, and a 4-week repeated-dose toxicity study followed by a 6-week recovery period in cynomolgus monkeys and a 12-week repeated-dose toxicity study in cynomolgus monkeys. A 39-week repeated-dose toxicity study followed by an 8-week treatment-free period in cynomolgus monkeys is currently on-going.

There was no hemolysis with up to 18.18 mg/mL of MK-0646 (MK-0646 20 mg/mL) in cynomolgus or human washed red blood cells or with the vehicle.

The cross-reactivity of MK-0646 with cryosections of human and cynomolgus monkeys' tissues was studied by immunohistochemistry using biotin-conjugated MK-0646 (biotin-MK-0646). The tissue distribution of staining with biotin-MK-0646 was similar in cynomolgus monkey tissues and in human tissues, with the exception of the staining of the spinal cord, observed in human tissues only, although inconsistently. This difference is not likely of significance, since MK-0646 is unlikely to penetrate the blood/central nervous system barrier.

In a 4-week intravenous repeated-dose toxicity study followed by a 6-week recovery period in cynomolgus monkeys, MK-0646 was administered via 1-hour intravenous infusion once weekly at dose levels of 3, 10, and 40 mg/kg/week. The mean systemic exposures (expressed as area under the curve, $AUC_{0\text{-}168\ hr}$, sexes combined) to MK-0646 after 4 weekly infusions at dose levels of 3, 10, and 40 mg/kg/week were 2.98 ± 1.12, 17.8 ± 1.41 and 70.4 ± 6.70 mg/hr/mL, respectively. For some animals in the 3 mg/kg/week dose group, substantial reductions in serum MK-0646 concentrations and/or individual toxicokinetic parameters were observed after 4 weekly infusions, when compared with values following the first administration and were likely due to the presence of anti-MK-0646 antibodies. There were no observable differences in serum MK-0646 concentrations or toxicokinetic parameters in the 10 mg/kg/week and 40 mg/kg/week dose groups. MK-0646 was generally well tolerated. There was no treatment-related mortality. There were no treatment-related effects on physical signs, food consumption, ophthalmic examinations, neurological examinations, blood pressure or heart rate measurements, electrocardiographic assessments, and urinalyses. There was a treatment-related decrease in body weight occurring by the end of the 4-week treatment period in some animals in the 3-, 10- and 40 mg/kg/week dose groups. The effect

was slight to moderate (generally less than 10% decrease compared to individual prestudy values), and partially reversible. There was a reversible treatment-related decrease in serum alkaline phosphatase levels in all treated-groups that did not correlate with any other alterations and that was not considered of any toxicologic significance. There were no treatment-related changes in any of the other hematological, (including the distribution of peripheral blood T and B lymphocyte subsets), coagulation and serum biochemical parameters examined. There was a treatment-related histomorphological thymic atrophy in both sexes, at all dose levels, at the end of the 4-week treatment period. This effect was fully reversible after the recovery period, in females at all dose-levels and in males in the 3 mg/kg/week and 10 mg/kg/week dose groups. The thymic effects were partially reversible in males in the 40 mg/kg/week dose group. MK-0646 did not cause a treatment-related increase in local irritation at the injection site. Anti-MK-0646 antibodies were detected in the recovery animals across all MK-0646-treated groups, at a higher incidence and mean titer in the 3 mg/kg/week and 10 mg/kg/week dose groups (compared to the 40 mg/kg/week dose group). In all cases, anti- MK-0646 antibodies were able to neutralize MK-0646 in a cell-based receptor internalization assay.

Based on histomorphological thymic atrophy, consistent with a pharmacologically-mediated effect, body weight loss, and a decrease in serum alkaline phosphatase levels (considered of no toxicological significance), the no-effect level of MK-0646 for this study was <3 mg/kg/week. The no-adverse effect level of MK-0646 for this study was >40 mg/kg/week.

Mean trough (168-hour) concentrations were 8.69 ± 1.04, 45.2 ± 6.33 and 129 ± 15.2 µg/mL in the 3-, 10-, and 40-mg/kg/week dose groups, respectively, on Drug Day 7; and 5.02 ± 3.55, 53.4 ± 15.0 and 234 ± 43.5 µg/mL in the respective dose groups on Drug Day 28.

In a 12-week intravenous repeated-dose toxicity study in cynomolgus monkeys, MK-0646 was administered via 1-hour intravenous infusion once weekly at a dose level of 40 mg/kg/week. The mean systemic exposure (expressed as area under the curve, $AUC_{0\text{-}168\ hr}$, sexes combined) to MK-0646 at 40 mg/kg/week was 62.3 ± 3.03 mg/hr/mL on Drug Day 1 and was 97.1 ± 10.7 mg/hr/mL on Drug Day 71. MK-0646 was generally well tolerated. There was no treatment-related mortality. There were no treatment-related effects on physical signs, food consumption, ophthalmic examinations, blood pressure or heart rate measurements, electrocardiographic assessments, and urinalyses.

There was a treatment-related decrease in body weight in treated males (incidence: 2/3). This effect was slight (less than 9% decrease compared to individual prestudy values, by the end of the dosing period) and was not considered adverse. There were treatment-related decreases in serum alkaline phosphatase and gamma glutamyltransferase levels in both sexes, that were not associated with any other alterations and that were not considered of any toxicologic significance. There were no treatment-related changes in any of the other hematological (including the distribution of peripheral blood T and B lymphocyte subsets), coagulation and serum biochemical parameters examined. There was a treatment-related decrease in thymus weights in all treated females and males, that corresponded histomorphologically to thymic

atrophy. There was no evidence of treatment-related local irritation at the injection site, associated with the intravenous infusion of MK-0646.

Based on histomorphological thymic atrophy, consistent with a pharmacologically-mediated effect, body weight loss (considered not adverse), and decreases in serum alkaline phosphatase and gamma glutamyltransferase levels (considered of no toxicological significance), the no-effect level of MK-0646 for this study was <40 mg/kg/week**.** The no adverse effect level of MK-0646 for this study was >40 mg/kg/week

In an on-going 39-week repeated-dose toxicity study followed by an 8-week treatment-free period, cynomolgus monkeys are administered MK-0646 (MK-0646 20 mg/mL) via 1-hour intravenous infusion once weekly at dose levels of 3, 10, or 40 mg/kg/week. Preliminary data collected and analyzed up to week 25 show that the administration of MK-0646 was well tolerated and not associated with any treatment-related clinical signs, ophthalmological findings, food consumption changes, changes in cardiovascular or urinary parameters. One female administered 40 mg/kg/week was sacrificed early on day 62, due to a moribund state caused by acute inflammatory and necrotic changes in the gastrointestinal tract. Any relationship to treatment is currently considered unlikely, pending histopathological assessment of all animals at study termination. There was a transient reduction in mean body weight during the first 7 weeks in the mid- and high-dose groups, a slight decrease in red blood cell parameters in the high-dose groups and in the mid-dose females, a slight decrease in alkaline phosphatase in the high-dose and mid-dose groups and in the low-dose females and a slight transient increase in total bilirubin in the mid- and high-dose females.

2.4.4 **Clinical Studies of MK-0646**

The activity of MK-0646 in vitro as well as in vivo cancer models, along with the toxicity profile for this compound, position the drug for first-in-human studies to be conducted in cancer patients.

MK 0646 is currently being tested in two Phase I studies: 1) An Open-Label, Dose Escalation Phase I Trial of MK-0646 Given as a Once Weekly Infusion in Patients With Advanced Solid Tumors and Multiple Myeloma (PN001) and 2) An Open-Label, Dose Escalation Phase I Trial of MK-0646 Given as a One to Two Hour Every Other Week Infusion in Patients With Relapsed or Refractory Locally Advanced or Metastatic Cancers (PN002). The preliminary analysis of safety parameters in the ongoing Phase I studies demonstrates that MK-0646 has been generally well-tolerated in advanced cancer patients. There have been a total of 44 patients treated with MK-0646. These patients have been treated with doses as high as 15 mg/kg weekly (PN001) or 20 mg/kg loading followed by 5 mg/kg maintenance (PN002). No maximum tolerated dose has been identified.

Preliminary pharmacokinetic analysis from PN001 suggests that mean MK-0646 serum concentrations after the first IV dose appear to decline at least biexponentially after peak through 168 hrs. The mean terminal half-life for the 15 mg/kg cohort averaged 95 hours, with a trend toward increasing values with dose. In general, the clearance and volume of

distribution were in very good agreement with the values obtained in cynomolgus monkeys. The mean serum clearance for the 15.0 mg/kg cohort averaged 0.007 mL/min/kg, which was relatively unchanged from the values for 5.0 and 10 mg/kg. Mean trough concentrations exceeded the target of 25 mg/mL for doses greater than 5.0 mg/kg. Efficacy is not a primary objective of Phase I studies, and no objective responses have been observed to date.

2.5 **Erlotinib**

2.5.1 **Clinical Pharmacology of Erlotinib**

Bioavailability of erlotinib following a 150-mg oral dose is about 60% and peak plasma levels occur 4 hours after dosing. Food increases bioavailability substantially, to almost 100%. [23] The pharmacokinetics of erlotinib is dose dependent, and repetitive daily treatment does not result in drug accumulation when administered at an average dose of 150 mg/day. The maximum concentration of drug was achieved 3 hours after a single dose. [24] A pharmacokinetic analysis in patients receiving single-agent erlotinib, showed a median half-life of 36.2 hours. Time to reach steady-state plasma concentration would therefore be 7 to 8 days.

2.5.2 **Drug Interactions of Erlotinib**

In vitro assays of cytochrome *P*450 metabolism showed that erlotinib is metabolized primarily by CYP3A4 and to a lesser extent by CYP1A2 and the extrahepatic isoform CYP1A1. *In vitro* and *in vivo* studies suggest that erlotinib is cleared primarily by the liver; caution should be used when giving erlotinib to patients with hepatic impairment.

2.6 **Gemcitabine**

2.6.1 **Clinical Pharmacology of Gemcitabine**

Gemcitabine is a pyrimidine antimetabolite that inhibits DNA synthesis by inhibition of DNA polymerase and ribonucleotide reductase, specific for the S-phase of the cycle. Gemcitabine is phosphorylated intracellularly by deoxycytidine kinase to gemcitabine monophosphate, which is further phosphorylated to active metabolites gemcitabine diphosphate and gemcitabine triphosphate. Gemcitabine diphosphate inhibits DNA synthesis by inhibiting ribonucleotide reductase; gemcitabine triphosphate incorporates into DNA and inhibits DNA polymerase.

Pharmacodynamics/Kinetics of gemcitabine are as follows: Distribution: V_d: Male: 15.6 mL mL/m^2; Female: 11.3 L/m^2. The protein binding of gemcitabine is low. Metabolism: Hepatic, metabolites: di- and triphosphates (active); uridine derivative (inactive). Half-life elimination: Infusion time: ≤1 hour: 32-94 minutes; Infusion time: 3-4 hours: 4-10.5 hours. Time to peak: 30 minutes. Excretion: Urine (99%, 92% to 98% as intact drug or inactive uridine metabolite); feces (<1%).

2.6.2 **Drug Interactions of Gemcitabine**

Bleomycin: Concurrent use with gemcitabine may lead to severe pulmonary toxicity.
Fluorouracil: Gemcitabine may increase the levels/effects of fluorouracil; Ethanol use with gemcitabine therapy may lead to GI irritation.

2.7 **Study Rationale**

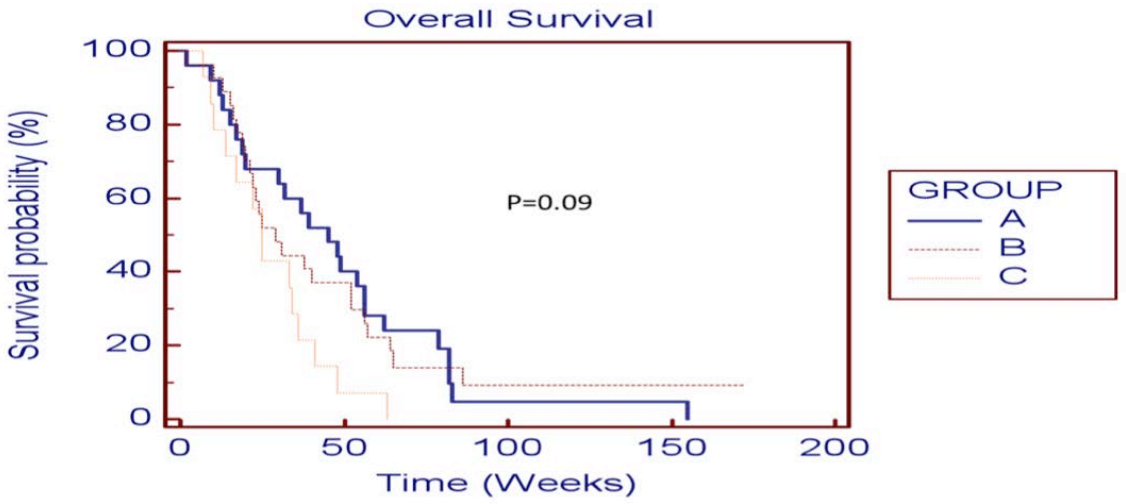
The MEK/ Erk and the PI3-kinase/ Akt signaling pathways play an important role in cellular proliferation, survival (anti-apoptosis) and drug resistance in pancreatic cancer. Our recent study demonstrated the prognostic importance of activated (p-)Erk and Akt in surgically resected specimens of pancreatic cancer.[25] There was a significant association between p-Erk expression and epithelial-mesenchymal transition (EMT) in these cases.[26] We also demonstrated that the PI3-kinase/ Akt pathway was constitutively activated in pancreatic cancer, which in turn activated two important transcription factors, NF-kappaB and c-myc.[27] Antagonists of PI3-kinase and MEK were also shown in this study to inhibit pancreatic cancer cell proliferation. Therefore, the inhibition of signals that trigger p-Erk and Akt activation in pancreatic cancer is likely to have a therapeutic impact. The insulin-like growth factor receptor-1 (IGF-1R) initiates signals that activate the PI3-kinase/Akt and MEK/ Erk pathways and is thought to play a crucial role in the pathology underlying pancreatic and other cancers.

MK-0646, a humanized antibody against IGF-1R, blocks the interaction of the IGF-I and II ligands with the IGF-1R and induces the internalization and degradation of this receptor. IGF-1R signaling inhibition enhances gemcitabine and cisplatin-induced apoptosis in pancreatic cancer xenografts and ovarian cancer cell lines, respectively.[28, 29] It is believed that there is crosstalk or pathway switching between the EGFR and the IGF-1R, which can ultimately influence the effectiveness of anti-EGFR agents, such as the small molecule inhibitors gefitinib or erlotinib. IGF-1R activation may be associated with acquired resistance to gefitinib and other EGFR-targeted therapies.[30, 31] It was demonstrated that cytoplasmic expression of EGFR and membrane expression of IGF1R were more frequent in higher-grade pancreatic cancers and correlated with poor prognosis.[32] Therefore simultaneous targeting of EGFR plus IgF1R has a sound scientific basis. The hypotheses to be tested are: a. MK-0646 can be combined safely with gemcitabine or with gemcitabine plus erlotinib in the phase I or II setting, b. Gemcitabine plus erlotinib plus MK-0646 and gemcitabine plus MK-0646 result in an improved PFS as compared with gemcitabine plus erlotinib, c. Improved RR, OS and QOL will result in the MK-0646 containing arms as compared with gemcitabine plus erlotinib, and d.IGF1/ IGFBP-3 ratio, pretreatment tissue levels of p-Erk, Akt, IRS-p, IGF-1R, mTOR, and PI3K correlate with response and e. SNPs related to IgF1R pathway may correlate with clinical response to MK-0646.

Phase I portion of this study has been completed. The next, randomized phase II portion has been completed with 45 patients enrolled in the 3 arms (15 in arm A, B and C).

Updated analysis of the present study on 8/7/2012 indicates that the median overall survival in arm A

(Gemcitabine + MK-0646), arm B (Gemcitabine + MK-0646 + Erlotinib) and arm C (Gemcitabine + Erlotinib) was 45 weeks, 29 weeks and 25 weeks, respectively (p=0.09). There was no significant progression-free survival difference between the three arms, however (Fig.1). Based on these data, we hypothesize that a subset of patients treated with MK-0646 experience therapeutic benefit and our goal is to explore hypothesis-based predictive biomarkers in a phase II expansion cohort of patients treated as per Arm A.



A: Gem + MK0646: 45 wks; B: Gem + MK0646 + Erlotinib: 29 wks; C: Gem + Erlotinib (control): 25 wks

Fig.1 Updated survival of patients treated on current study (Aug 2012)

2.8 **Correlative Studies Background**

2.8.1 **IGF-1 and IGFBP-3 circulating levels**

More than 80% of circulating IGF-1 is bound to IGFBP-3, in a protein complex that is confined to the vascular compartment. Tissue IGF bioactivity is thought to be determined by free IGF, the component of IGF not bound to IGF binding proteins, which binds to the IGF-1R on the target cell surface.[33] High plasma levels of IGF-1 and low levels of IGFBP-3 are associated with the development of prostate, colorectal, and premenopausal breast cancer. In a nested case-control study within four large, prospective cohorts, no association was observed between prediagnostic plasma levels of IGF-I, or IGFBP-3 and incident diagnosis of pancreatic cancer.[34] However, these levels have not been correlated with response to IGF-1R directed therapy. We hypothesize that elevated levels of IGF-1 and/or depressed levels of IGFBP-3 would predict responsiveness to MK-0646 IGF-1R inhibition.

2.8.2 **IGF-1R Signaling Pathway Proteins Tissue Levels**

IGF-1R is composed of two covalently linked polypeptide chains, each with an extracellular -subunit and a transmembrane ß-subunit, which possesses tyrosine kinase activity. Ligand binding of IGF-1 to IGF-1R results in a conformational change leading to transphosphorylation of one ß-subunit by the other. Activated IGF-1R recruits and

phosphorylates adaptor proteins belonging to the IRS family. The phosphorylated adaptor proteins then serve as docking sites for other signaling molecules, resulting in the activation of the downstream pathways such as PI3K/AKT and ERK1/2. We hypothesize that elevated phosphorylated/ total IGF-1R, IRS, AKT, mTOR, PI3K, and ERK 1/2 ratios would predict responsiveness to MK-0646 IGF-1R inhibition. Based on recent data, tissue IGF1 mRNA expression may be a promising predictive biomarker for MK-0646 therapy. In the current study, 21 core biopsy samples were analyzed for IGF1 expression using RT-PCR. In 8 patients, where in the expression was above the median value, overall survival was >11 months in 4 cases. While these data are very limited, they are supported by study PN004 results. In the recent colorectal cancer trial of MK-0646 (PN004), patients with advanced colorectal cancer received irinotecan + cetuximab (control arm) or irinotecan + cetuximab + MK-0646 (at 7.5 mg/kg or 10 mg/kg dose levels). IGF1 expression was an adverse prognostic factor in the control arm. However, in the treatment arms, an improved PFS was noted with MK-0646 in those with high IGF-1 expression (Fig.2).

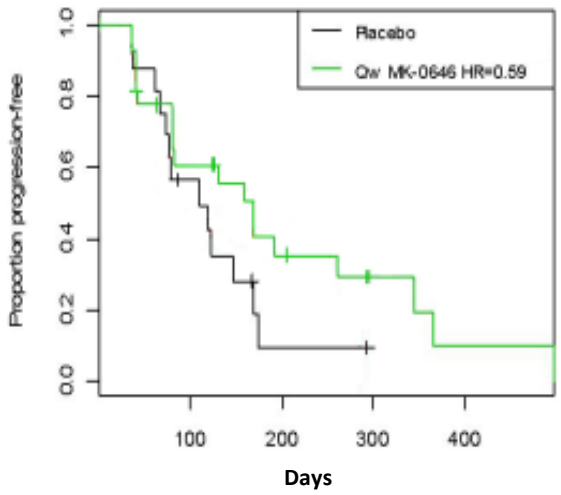


Figure 2. Kaplan-Meier estimates for PFS by treatment arm in patients with high tissue IGF-1 in colorectal study PN004

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Pathologically or cytologically confirmed diagnosis of pancreatic adenocarcinoma, AJCC stage IV (See Appendix H).

3.1.2 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. Measurable disease must be present outside a previous radiation field or if inside, it must be a new lesion.

3.1.3 At least 6 months must have elapsed after completion of adjuvant therapy (if applicable).

3.1.4 Age ≥18 years.

3.1.5 ECOG Performance Status 0-1 (Karnofsky ≥60%; see Appendix I).

3.1.6 Patients must have adequate organ and marrow function as defined below:

- leukocytes	≥3,000 cells/mm^3
- absolute neutrophil count	≥1,500 cells/mm^3
- platelets	≥100,000 cells/mm^3
- total bilirubin	<1.5mg/dl
- AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal without liver metastasis ≤5 X institutional upper limit of normal for patients with liver metastasis
- creatinine	within normal institutional limits
OR	
- creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

3.1.7 Fasting blood glucose ≤160 mg/dl, prior to study enrollment. (For higher values, blood glucose may be controlled by dietary intervention, oral hypoglycemics and/ or insulin prior to enrollment).

3.1.8 Women of child-bearing potential: (defined as not post-menopausal for 12 months or no previous surgical sterilization) and fertile men must agree to use adequate contraception for the duration of study participation. Acceptable contraception is defined as double-barrier methods (any double combination of: IUD, male or female condom with spermicidal gel, diaphragm, sponge, cervical cap). Acceptable contraception must be used for 90 days after last dose of study drugs. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.9 Ability to understand and the willingness to sign a written informed consent document. Signed informed consent form must be obtained prior to initiation of study evaluations and/or activities.

3.1.10 INR <1.5 (or ≤3 if on anticoagulation therapy).

3.1.11 In phase II expansion cohort, which is primarily for predictive biomarker correlation, patients enrolled will be those with pre-existing core biopsies of primary tumor or metastatic site or must be willing to undergo a biopsy for correlative studies.

3.2 Exclusion Criteria

3.2.1 Prior systemic chemotherapy or biological therapy for metastatic disease.

3.2.2 Prior exposure to IGF-1R inhibitors.

3.2.3 Patients with known 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.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to the agents used in the study.

3.2.5 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.6 Pregnant or nursing women are excluded from this study because there is an unknown but potential risk for adverse events in infants secondary to treatment of the mother the study agents. If a pregnancy test (serum or urine) is positive, patient will be excluded.

3.2.7 Patients who are known to be HIV-positive are ineligible because these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.8 No other prior malignancy is allowed except for the following: adequately treated basal or squamous cell skin cancer, in situ cervical cancer, or any other cancer from which the patient has been disease-free for two years.

3.2.9 Patients must not be currently enrolled in a therapeutic study for pancreatic cancer.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

All patients must be registered on the M. D. Anderson Cancer Center Clinical Oncology Research (CORe) system prior to initiation of treatment.

Once the Phase II portion of the study begins, participants will be assigned to treatment arms by adaptive randomization performed through the Department of Biostatistics at M.D.

Anderson Cancer Institute. No randomization is planned in the phase II expansion cohort. Please refer to Section 13 for additional details.

5. TREATMENT PLAN

This is an open label single center two-part study in which the combination of gemcitabine, erlotinib and MK-0646 will be evaluated for the first time in a clinical setting to patients with advanced, untreated pancreatic cancer.

Clinical endpoints to be evaluated are evaluation of MTD, progression-free survival, response rate, adverse experiences, and overall survival.

5.1 **Study Agents**

Reported adverse events and potential risks for MK-0646, gemcitabine and erlotinib are described in Section 7. Appropriate dose modifications for these agents are described in Section 6. No other investigational or commercial agents or therapies may be administered concurrently with the intent to treat the patient's malignancy.

Treatment will be administered on an outpatient basis. A cycle is defined as 4 weeks in duration. MK-0646 and gemcitabine must be administered at M. D. Anderson Cancer Center.

Treatment schedules shall have a standing window of allowance of +/- 1 day. In addition, any treatment day that falls on a weekend or holiday may be scheduled on the next business day.

5.2 **Phase I**

The Phase I portion of the study will be an open label safety assessment of:

a. Gemcitabine (G) + MK-0646 (MK)
b. Gemcitabine (G) + MK-0646 (MK) + erlotinib (E)

Two dose levels of MK-0646 (5 mg/kg and 10 mg/kg) will be evaluated in each arm, using a standard "3+ 3" phase I design

	Arm A	Arm B
Level 1	G 1000 mg/m^2 Days 1, 8, 15 MK **5** mg/kg Days 1, 8, 15, 22	G 1000 mg/m^2 Days 1, 8, 15 MK 5 mg/kg Days 1, 8, 15, 22 E 100 mg Days 1-28
Level 2	G 1000 mg/m^2 Days 1, 8, 15, MK **10** mg/kg Days 1, 8, 15, 22	G 1000 mg/m^2 Days 1, 8, 15 MK 10 mg/kg Days 1, 8, 15, 22

		E 100 mg Days 1-28

Sequential Enrollment of Patients

Arm A, Level 1	G 1000 mg/m^2 MK **5** mg/kg	Enroll 3-6 patients (as per "3 + 3" method) and evaluate for DLT. Once all patients have completed cycle 1, if criteria are met to continue escalation, accrual may proceed in Arm B, Level 1. 🡻
Arm B, Level 1	G 1000 mg/m^2 Erlotinib 100 mg MK **5** mg/kg	Enroll 3 patients.* Once 3 patients are enrolled, accrual may begin in Arm A, Level 2. 🡻
Arm A, Level 2	G 1000 mg/m^2 MK **10**mg/kg	Enroll 3 patients.* 🡻
Arm B, Level 2	G 1000 mg/m^2 Erlotinib 100 mg MK **10** mg/kg	Do not enroll any patients in Arm B, Level 2 until all patients enrolled in Arm A, Level 2 **and** Arm B, Level 1 have completed 1 cycle of therapy and are evaluable for DLT. If criteria for dose escalation are met **in both levels**, enroll 3-6 patients in Arm B, Level 2.

* If cohort requires expansion, up to 3 additional patients will be enrolled. If criteria for cohort expansion are met both in Arm B, Level 1 and Arm A, Level 2, expansion of the cohort will be completed first in the Arm/Level where DLT first occurred.

- Patients will not be randomized to a treatment arm in the Phase I portion of the study. Enrollment will begin on arm (a). Arm (b) will begin enrollment at a particular dose level only when enrollment at that dose level is complete in Arm (a). Thus, enrollment at dose level 1 in Arm (b) will begin only after dosing at level 1 is completed safely in Arm (a).

- A minimum of 3 patients will be treated at each dose level. Once 3 patients are enrolled in Arm A, Level 1, additional accrual will be held until all 3 patients have completed their first cycle. If there is one DLT, up to 3 additional patients will be entered at the same dose level and evaluated for DLT. If the criteria for dose escalation are met, 3 new patients will be enrolled in Arm B, Level 1. Once 3 patients have been enrolled in Arm B, Level 1, 3 patients may be accrued to Arm A, Level 2. Patients in both of these Arms/Levels will be evaluated for DLT during cycle 1. If DLT is observed, up to 3

additional patients will be enrolled in the Arm/Level that DLT occurred, as described above. Once accrual and cycle 1 evaluation have been completed in Arm B, Level 1 and Arm A, Level 2, if the criteria for dose escalation are met in both arms, accrual may proceed in Arm B, Level 2.

- If at any time 2 patients develop DLTs at a level, this level will be considered above the MTD. In each arm, six patients will be treated at the dose identified as the MTD. The MTD is defined as the highest dose level that can be administered with ≤ 1 DLT observed in 6 patients.

Definition of Dose-Limiting Toxicity
All toxic effects will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

An adverse event must be considered by the Investigator to be at least possibly related to study treatment to qualify as a DLT. Infusion reactions are to be treated as indicated in section 5.4.1 and will not be regarded as DLTs, unless they recur and are serious and life-threatening, despite these measures.

All enrolled patients who complete one cycle of therapy or fail to complete one cycle of therapy due to toxicity will be included in the determination of the MTD. If a patient fails to complete one cycle of therapy at any dose level, for reasons other than toxicity, that patient is deemed not evaluable for determining the MTD and is to be replaced.

The evaluation for DLT will be during cycle 1 (first 4 weeks of treatment). DLT will be defined as:

- **Hematologic:** grade 4 thrombocytopenia; grade 4 neutropenia of $\geq$7 days duration or $\geq$grade 3 neutropenia of any duration with fever $\geq$ 38.5° C.
- **Nonhematologic:** grade 3 or 4 events, excluding hyperglycemia, rash, nausea, vomiting, and/or diarrhea, unless these occur despite maximal prophylaxis and/or treatment.
- **Delayed dosing** for >14 days due to toxic effects.

In Arm A, the order of drug administration is gemcitabine followed by MK-0646.
In Arm B, the order of drug administration is erlotinib followed by gemcitabine followed by MK-0646.

Table 1. Arm A (Phase I)

Level	Agent	Dose	Route	Schedule	Cycle Length
1	Gemcitabine *followed by* MK-0646	1000 mg/m^2 in 500 cc NS **5** mg/kg	IV over 100 minutes IV over 60 minutes	Days 1,8,15 Days 1,8,15,22	4 weeks (28 days)
2	Gemcitabine *followed by* MK-0646	1000 mg/m^2 in 500 cc NS **10** mg/kg	IV over 100 minutes IV over 60 minutes	Days 1,8,15 Days 1,8,15,22	

Table 2 Arm B (Phase I)

Level	Agent	Dose	Route	Schedule	Cycle Length
1	Erlotinib *followed by* Gemcitabine *followed by* MK-0646	100 mg 1000 mg/m^2 in 500 cc NS **5** mg/kg	Oral IV over 100 minutes IV over 60 minutes	Days 1-28 Days 1,8,15 Days 1,8,15,22	4 weeks (28 days)
2	Erlotinib Gemcitabine *followed by* MK-0646	100 mg 1000 mg/m^2 in 500 cc NS **10** mg/kg	Oral IV over 100 minutes IV over 60 minutes	Days 1-28 Days 1,8,15 Days 1,8,15,22	

MK-0646 will be administered intravenously at 5 mg/kg once a week for 4 weeks and then dose escalated in a new cohort to 10 mg/kg weekly. Gemcitabine will be administered at 1000 mg/m^2 over 100 min as a fixed-dose rate infusion once a week for 3 weeks. Since there is no evidence suggesting overlapping toxicities of erlotinib and MK-0646, in Arm B erlotinib will be administrated orally at 100 mg daily.

5.3 **Phase II**

Assuming safety and tolerability of the combination, the MTD determined in Part I will be used in the Phase II portion of the trial. Patients participating in Phase II will be randomly assigned to one of the three treatment arms:

a. Gemcitabine + MK-0646
b. Gemcitabine + erlotinib + MK-0646
c. Gemcitabine + erlotinib

Participants will be assigned to treatment arms by adaptive randomization performed through the Department of Biostatistics at M.D. Anderson Cancer Center. Please refer to Section 13 for additional details. In the phase II expansion cohort, arm A (Gemcitabine + MK-0646) will be expanded by adding 30 subjects, who have a prior core biopsy of tumor or are agreeable for a trial-specific biopsy for correlative studies.

As previously indicated, one of the hypotheses of this study is that the combination of erlotinib and MK-0646 may delay the development of acquired resistance to erlotinib, or overcome acquired resistance to erlotinib after initial response. Therefore, upon disease progression, patients in the gemcitabine + erlotinib will be permitted to cross over to the combination treatment arm of gemcitabine + erlotinib + MK-0646. The dose of MK-0646 will be the recommended phase II dose. Note: in the phase II expansion cohort, all patients will receive MK-0646, therefore no cross-over is planned.

In Arm A, the order of drug administration is gemcitabine followed by MK-0646. In Arm B, the order of drug administration is erlotinib followed by gemcitabine followed by MK-0646. In Arm C, the order of drug administration is erlotinib followed by gemcitabine

Table 3 – Phase II – Arm A (Gemcitabine + MK-0646)

Agent	Dose	Route	Schedule	Cycle Length
Gemcitabine *followed by*	1000 mg/m^2 in 500 cc NS	IV over 100 minutes	Days 1,8,15	4 weeks (28 days)
MK-0646	Ph I MTD mg/kg	IV over 60 minutes	Days 1,8,15,22	

Table 4 - Phase II – Arm B (Gemcitabine + erlotinib + MK-0646)

Agent	Dose	Route	Schedule	Cycle Length
Erlotinib *followed by*	100 mg	Oral	Days 1-28	
Gemcitabine *followed by*	1000 mg/m^2 in 500 cc NS	IV over 100 minutes	Days 1,8,15	4 weeks (28 days)
MK-0646	Ph I MTD mg/kg	IV over 60 minutes	Days 1,8,15,22	

Table 5 – Phase II – Arm C (Gemcitabine + erlotinib)

Agent	Dose	Route	Schedule	Cycle Length
Erlotinib *followed by*	100 mg	Oral	Days 1-28	
Gemcitabine	1000 mg/m^2 in 500 cc NS	IV over 100 minutes	Days 1,8,15	4 weeks (28 days)

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Premedications

No specific premedications are recommended for MK-0646.

Although serious allergic reactions have not been described with this antibody, which is fully humanized, routine medications and procedures for allergic reactions will be available in the treatment center. These reactions will be treated with IV fluids, antihistamines, NSAIDS, acetaminophen, narcotics, oxygen, pressors, and corticosteroids.

Patients will be monitored for infusion reactions and hypersensitivity (during infusion and at least two hours afterward until such toxicities (if any) resolve.

Ondansetron 8 mg IV $\pm$ dexamethasone 10 mg IV is recommended prior to gemcitabine administration. Other 5HT3 antagonists may be used if clinically indicated.

No additional premedications are generally recommended with erlotinib. Oral antiemetics may be used if clinically indicated.

5.4.2 **Management of Stomatitis/Oral Mucositis/Mouth Ulcers**:

Stomatitis/oral mucositis/mouth ulcers should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with erlotinib as mouth ulcers, rather than mucositis or stomatitis. If the examination reveals mouth ulcers rather than a more general inflammation of the mouth, the event should be classified as such. Follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

A. For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouthwash or salt water (0.9%) mouthwash several times a day until resolution.

B. For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®). Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents. Antifungal agents must be avoided unless a fungal infection is diagnosed. Topical antifungal agents are preferred if an infection is diagnosed to avoid possibility of drug interactions. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

5.4.3 **Management of Hyperglycemia**

Hyperglycemia may be observed in patients receiving anti IGF-1R therapy. Optimal glucose control should be achieved before starting a patient on this therapy and should be monitored closely. Endocrinology consult is encouraged.

5.4.4 **Management of Skin Rash**

Patients should be informed that skin toxicity is to be expected during treatment with erlotinib. Skin toxicity may take the form of dry skin, rash, acneiform eruption, or hair or nail changes. Prophylactic treatment of the skin may prevent or reduce skin toxicity. The patient should be encouraged to use an alcohol-free, emollient cream applied twice a day to the entire body as soon as the patient starts therapy with erlotinib. Creams and ointments are recommended because they have a greater ability to retain moisture than lotions. Examples of suitable

emollient creams include: Neutrogena® Norwegian formula, SARNA® Ultra, Vanicream™, Aveeno® (fragrance-free formulation), and Eucerin® cream. Other over-the-counter aqueous creams or emulsifying ointments may also provide symptomatic benefit. Lotions should be avoided because they often contain alcohol, which will dry the skin. Patients should also be encouraged to use a titanium dioxide or zinc oxide-based sunscreen product applied to sun-exposed areas twice per day.

Patients who develop skin toxicity and are symptomatic should be treated with topical therapy such as clindamycin lotion or gel. If needed, oral minocycline or oral doxycycline may be combined with the topical therapy. For more severe rash, oral corticosteroids may be beneficial. Patients who fail to respond to these measures may have the dose of erlotinib interrupted or reduced. Minocycline is known to interfere with anticoagulants and oral contraceptives. Patients treated with minocycline who are taking anticoagulants and/or oral contraceptives should be monitored accordingly.

5.4.5 **Management of Non-Infectious Diarrhea**

Antidiarrheal medications may be introduced if clinically indicated. Previous Phase I and II studies of erlotinib have demonstrated the frequency and severity of diarrhea can be managed with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea resolves for 12 hours. Alternatives include diphenoxylate and sandostatin. In the event of severe or persistent diarrhea, nausea, anorexia, or vomiting associated with dehydration, erlotinib therapy should be interrupted and appropriate measures should be taken to intensively treat the dehydration. Since there have been rare reports of hypokalemia and/or acute renal failure (including fatalities), secondary to severe dehydration, renal function and serum electrolytes (including potassium) should be monitored in this setting. All interruptions or changes to study drug administration must be recorded.

5.4.6 **Management of Non-infectious Pneumonitis**

Both asymptomatic radiological changes (grade 1) and symptomatic non-infectious pneumonitis (grade 2 = not interfering with activities of daily living or grade 3 = interfering with activities of daily living and oxygen indicated) have been noted in patients receiving erlotinib therapy. Non-infectious pneumonitis has been associated with EGFR inhibitors. In order to monitor for asymptomatic (grade 1) pulmonary infiltrates, a chest X-ray is required if a CT scan of chest is not used for bi-monthly disease evaluations. Additional chest X-rays/CT scans may be done, when clinically necessary. If non-infectious pneumonitis develops, consultation with a pulmonologist should be considered. For any pneumonitis suspected to be secondary to erlotinib, this medication will be discontinued permanently.

5.5 **Duration of Therapy/Criteria for Removal from Study**

Treatment may continue until one of the following criteria applies:

- Disease progression or symptomatic deterioration
- Intercurrent illness that prevents further administration of treatment
- Any clinical adverse event or laboratory abnormality which in the opinion of the treating investigator indicates that continued treatment is not in the best interest of the patient
- Treatment delay > 21 days for any reason
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

6. DOSING DELAYS/DOSE MODIFICATIONS

This study will utilize the CTCAE Version 3.0 for toxicity and adverse event reporting.

Doses of gemcitabine and MK-0646 will be calculated based on the patient's current weight recorded at the beginning of each cycle. If there is a dose adjustment during a cycle of therapy the patient's current weight will be used. **Once a study drug dose is reduced, it may not be re-escalated.** The only exception to this is for patients currently being treated at a dose of gemcitabine below 250 mg/m^2 (see section 6.2 for clarification).

If in the opinion of the treating investigator, a toxicity requiring a dose reduction or omission is clearly related to one of the study drugs but not the others, the other drugs are not required to be omitted and/or reduced.

If any single drug must be discontinued permanently, study treatment may be continued if in the opinion of the treating investigator the patient is deriving benefit from the other drug(s).

6.1 **Dose Modification of Erlotinib**

Dosage adjustments are based on grade of toxicity experienced by the patient. Reduction of erlotinib is in a 50 mg decrement. The lowest dose on the study allowed is 50 mg.

Table 6 - Erlotinib Dose Levels

Starting Level	100 mg
-1	50 mg

Criteria for dose-modification in case of suspected Erlotinib toxicity and re-initiation of Erlotinib treatment.

Table 7 - Dose Modification Criteria for Erlotinib-related Toxicities

Toxicity (NCI CTCAE v3.0)	Dose Modification
Diarrhea	
Grade 1 or 2	None. Initiate therapy with loperamide.
Grade 3 or 4	Interrupt Erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower.
Rash	
Grade 1	None
Grade 2	None. Initiate treatment as in section 5.4.4 if rash persists and is intolerable to patient or worsens over 10 – 14 days.
Grade 3	Reduce by 1 dose level. If rash persists or worsens over 10 - 14 days, then interrupt Erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower.
Grade 4	Permanently discontinue Erlotinib
Interstitial Lung Disease	
Any Grade	If ILD is suspected, Erlotinib should be interrupted immediately pending diagnostic evaluation. If ILD is diagnosed, Erlotinib should be discontinued permanently and appropriate treatment instituted as necessary.
Other Toxicities	
Grade 1 or 2	None
Grade 3	Interrupt Erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower.
Grade 4	Permanently discontinue Erlotinib

6.2 **Dose Modification of Gemcitabine**

Dosage adjustments are based on grade of toxicity experienced by the patient.

Hematologic: Patients receiving gemcitabine should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. If

marrow suppression is detected, therapy should be modified or suspended according to the guidelines below in Table 8.

Table 8: Dose Modification Criteria for Gemcitabine-Related Hematologic Toxicities (Also see 6.2.2)

Absolute granulocyte count (AGC) (cells/mm^3)		Platelet count (cells/mm^3)	% of current dose
≥1000	And	≥75,000	100
500-999	Or	50,000-74,999	75
<500	Or	<50,000	Hold until resolution to ≥ 1,000 cells/mm^3 AGC and ≥ 75,000 cells/mm^3 platelets, then give at 75% of current dose.
Febrile neutropenia			Hold until resolution to ≥ 1,000 cells/mm^3 AGC, then give at 75% of current dose.

Laboratory evaluation of renal and hepatic function, including transaminases and serum creatinine, should be performed prior to initiation of therapy as outlined in the study calendar. Gemcitabine should be administered with caution in patients with evidence of significant renal or hepatic impairment as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations.

Table 9 - Dose Modification Criteria for Gemcitabine-Related Non-Hematologic Toxicities (Also see 6.2.2)

Toxicity	Dose Modification
Grade	% of Current Dose
0-1	100
2	75
3	Hold until resolution to ≤Grade 1 or baseline, then give at 75% of current dose.
4	Hold until resolution to ≤Grade 1 or baseline, then give at 50% of current dose.

6.2.2 Additional Gemcitabine Dose Modification Information

If a patient is at a dose of 330 mg/m^2 or less of gemcitabine and requires a 25% dose reduction, the minimum dose will be initially capped at 250 mg/m^2.

If further dose reduction is required for toxicity, the first step would be to administer gemcitabine at a dose of 250 mg/m^2 on Days 1 and 15 (skipping Day 8) instead of every week (Days 1, 8, 15). Further dose reductions below 250 mg/m2 will be permitted as per Tables 8 and 9, if deemed to be in the patient's best interest by the Investigator.

Any patient who is currently receiving weekly (Days 1, 8, 15) gemcitabine at a dose below 250 mg/m^2 may have this dose increased to 250 mg/m^2 every 2 weeks, at the discretion of the Investigator. Future dose reductions will be made as indicated in the paragraph above.

Growth factors, including Neupogen and Neulasta, can be used at the Investigators discretion as per the American Society of Clinical Oncology (ASCO) guidelines.

6.3 **Dose Modification for MK-0646**

Guidelines for MK-0646

The following toxicities, if thought to be due to MK-0646, would cause modifications in MK-0646 dosing:

- Grade 3 or Grade 4 non-hematologic toxicity, except alopecia and inadequately controlled diarrhea, nausea and vomiting, and hyperglycemia
- Anemia will not be considered dose limiting; patients are allowed erythropoietin and blood transfusions are needed
- Infusion reactions and hypersensitivity reactions will not require dose reduction

Dosage adjustments are based on grade of toxicity experienced by the patient. Up to 2 dose reductions are allowed for MK-0646.

Toxicity (NCI CTCAE Grade) † *	**MK-0646**		
	Dose	Occurrence	Dose Reduction
1	5 mg/kg	1	No change
		2	No change
	10 mg/kg	1	No change
		2	No change
2	5 mg/kg	1	No change
		2	No change
	10 mg/kg	1	No change
		2	No change
3	5 mg/kg	1	Discontinue MK-0646
	10 mg/kg	1	Omit dose until resolved to less than or equal to Grade 2 and then continue at 7.5 mg/kg every 2 weeks
		2	Omit dose until resolved to less than or equal to Grade 2 and then continue at 6.0 mg/kg every 2 weeks
		3	Discontinue MK-0646
4	5 mg/kg	1	Discontinue MK-0646
	10 mg/kg	1	Omit dose until resolved to less than or equal to Grade 2 and then continue dosing at 6.0 mg/kg every 2 weeks if toxicity is not considered life-threatening
		2	Discontinue MK-0646

† For non-hematologic toxicities exclude alopecia, anorexia, asthenia, inadequately treated hyperglycemia.
*** See table below for auditory toxicity.**

Auditory Toxicity (New Onset or Change in Baseline Grade) Grade	MK-0646 Action
1 or 2	No Change.
3	Permanently discontinue MK-0646
4	Permanently discontinue MK-0646

6.4 New Cycle of Therapy

A new cycle of therapy will be delayed until:

- Absolute neutrophil count ≥1000 cells/mm^3 and platelet count ≥100,000 cells/mm^3
- Recovery from any treatment-related non-hematological toxicity to baseline or ≤ grade 1. In case of ongoing grade 2 hearing loss, MK-0646 may continue if in the opinion of the Investigator, continued treatment is beneficial to the patient.

6.5 Adverse Event Follow-Up

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value suspected to be related to the study agent(s) must be followed at least weekly until the adverse event or abnormal laboratory resolves or returns to grade 1. If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study.

7. ADVERSE EVENTS LIST AND REPORTING REQUIREMENTS

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug(s) even if the event is not considered to be related to study drug(s). Medical conditions/diseases present before starting study drug(s) are only considered adverse events if they worsen after starting study drug(s). Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The Recommended Adverse Event Recording Guidelines in Section 7.4 will be used.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- the severity grade (Grade 1 to Grade 5)
- its relationship to the study drug(s) (unrelated, unlikely, possible, probable, or definite)
- its duration (start and end dates or if continuing at final exam)
- action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
- whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the [Investigators' Brochure] or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.1 **Adverse Effects of MK-0646**

MK-0646 has been administered at high doses, up to 20 mg/kg, without any dose-limiting toxicities. Some of the expected toxicities, based on clinical and preclinical studies are listed below.

Hepatic: transient hyperbilirubinemia, altered alkaline phosphatase, liver enzymes changes (decrease in alkaline phosphatase and GGT was noted in animal studies).

Although there were a total of 58 unique preferred clinical adverse experience terms reported to have occurred in ≥2% of the patient population, only 18 of these unique terms were observed in >5% of the patient population. Greater than 10% of the patient population experienced abdominal pain, nausea, asthenia, fatigue, hyperglycemia, vomiting, anemia, back pain, constipation, cough, diarrhea, anorexia, dyspnea, and weight decreased (note: listed in order of decreasing frequency). Between 5% and 10% of the patient population experienced peripheral edema, urinary tract infection, hypotension, and pyrexia (note: listed in order of decreasing frequency).

Other adverse effects noted are: thrombocytopenia, skin rash, headaches, dizziness, tumor pain, chills, and vasculitis.

The Food and Drug Administration recently provided new safety information regarding monoclonal antibodies to IGF-1R. Adverse reactions of middle to high range sensorineural hearing loss were reported in both healthy volunteer subjects and patients with malignancies

who received as little as one dose of antibody. The FDA deemed this information applicable to all antibodies targeting the IGF-1 receptor.

7.2 **Adverse Effects of Erlotinib**

Common: - diarrhea (54%), nausea (33%), vomiting (23%), anorexia (52%), dyspnea (41%), cough (33%), fatigue (52%), rash (75%), visual changes, keratitis, and conjunctivitis (12%).

Serious: - bleeding (including GI when administered with anticoagulants) and elevated liver enzymes.

7.3 **Adverse Effects of Gemcitabine**

Occurring in >10%:

Cardiovascular: Peripheral edema (20%), edema (13%)

Central nervous system: Pain (10% to 48%), fever (30% to 41%), somnolence (5% to 11%)

Dermatologic: Rash (24% to 30%), alopecia (15% to 18%), pruritus (13%)

Gastrointestinal: Nausea/vomiting (64% to 71%; grades 3/4: 1% to 13%), constipation (10% to 31%), diarrhea (19% to 30%), stomatitis (10% to 14%)

Hematologic: Anemia (65% to 73%; grade 4: 1% to 3%), leukopenia (62% to 71%; grade 4: ≤1%), neutropenia (61% to 63%; grade 4: 6% to 7%), thrombocytopenia (24% to 47%; grade 4: ≤1%), hemorrhage (4% to 17%; grades 3/4: <1% to 2%); myelosuppression is the dose-limiting toxicity

Hepatic: Transaminases increased (67% to 78%; grades 3/4: 1% to 12%), alkaline phosphatase increased (55% to 77%; grades 3/4: 2% to 16%), bilirubin increased (13% to 26%; grades 3/4: <1% to 6%)

Renal: Proteinuria (10% to 45%; grades 3/4: <1%), hematuria (13% to 35%; grades 3/4: <1%), BUN increased (8% to 16%; grades 3/4: 0%)

Respiratory: Dyspnea (6% to 23%)

Miscellaneous: Flu-like syndrome (19%), infection (8% to 16%; grades 3/4: <1% to 2%)

Occurring in 1% to 10%:

Local: Injection site reactions (4%)

Neuromuscular & skeletal: Paresthesia (2% to 10%)

Renal: Creatinine increased (2% to 8%)

Respiratory: Bronchospasm (<2%)

7.4 **Adverse Event Attribution**

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

Recommended Adverse Event Recording Guidelines					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

7.5 **Serious Adverse Events**

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

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

7.6 Serious Adverse Events Reporting

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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

7.7 Investigator Communications with Study Supporter

A SAE must be reported by the Principal Investigator to Merck & Co., Inc. Attention: Worldwide Product Safety, by FAX (215-993-1220) within two working days of learning of its occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 2 working days.

7.8 Pregnancies

Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported to Merck & Co., Inc. Attention: Worldwide Product Safety, by FAX (215-993-1220) within 2 working days of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications. Patients who become pregnant will be taken off the study agents.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational and commercial agents administered in this study can be found in Section 7.

8.1 MK-0646: Physical, Chemical, and Pharmaceutical Properties and Formulation

General Information

MK-0646 is a humanized IgG1 monoclonal antibody (mAb) against IGF-1R (insulin-like growth factor receptor type 1). This IGF-1R mAb blocks IGF-1- and IGF-2–mediated proliferation of cells and auto-phosphorylation of the receptor without acting as an agonist. In addition to its effect on signaling pathways, MK-0646 may also have the potential for antibody-directed cellular cytotoxicity. Drug Product

The final drug product is formulated at Merck & Co., Inc. (Merck, West Point, PA, U.S.) as a sterile, clear liquid at a target concentration of 20 mg/mL The drug product contains the excipients listed in the Investigators Brochure. These components are controlled and tested to the standards appropriate for their intended use and function.

Stability **:** Drug product stability studies are ongoing.

Storage: Vials are stored at 2–8 °C.

Supplier: MK-0646 will be provided free of charge by Merck, Inc. for this study.

8.2 **Gemcitabine**

Product description: Gemcitabine is manufactured by Eli Lilly, Incorporated. Two vials are available: 200 mg lyophilized powder in 10 ml size, sterile single use vial and 1000 mg lyophilized powder in 50 ml size, sterile single use vial.

Solution preparation: The recommended diluent for reconstitution of gemcitabine is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for gemcitabine upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided. To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200 mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1 g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL, which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200 mg vial or 1.3 mL for the 1 g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL.

Reconstituted gemcitabine is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and

discoloration, prior to administration, whenever solution or container permit. If particulate matter or discoloration is found, do not administer.

Storage and Stability: When prepared as directed, gemcitabine solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F). Discard unused portion. Solutions of reconstituted Gemcitabine should not be refrigerated, as crystallization may occur.

Route of administration: Gemcitabine will be administered intravenously at a rate of 10 mg/m^2/minute. Thus 1000 mg/m^2 will be administered over 100 minutes.

Supplier: Commercial product will be used.

8.3 **Erlotinib**

Product description: The 25 mg, 100 mg and 150 mg strengths are supplied as white film-coated tablets for daily oral administration.

Storage: Store at 25°C (77°F); excursions permitted to 15° — 30°C (59° — 86°F).

Route of administration: Erlotinib is administered orally. Tablets should be taken once daily preferably in the morning with up to 200 mL of water at least one hour before or two hours after the ingestion of food.

Supplier: Commercial product will be used.

9. CORRELATIVE/SPECIAL STUDIES

9.1 **A. IGF-1 and IGFBP-3 Circulating Levels**

Serum IGF-1and IGFBP-3 will be measured at screening and cycle 1, day 22, 1 hour post dose (+/-30 min) using Enzyme-Linked Immunosorbent Assay (ELISA). These tests will be performed in the biochemistry laboratory at M. D. Anderson Cancer Center.

9.1 B. Free IGF1 levels.

Blood samples (archival) obtained from subjects in the trial will also be analyzed for free IGF1 level. One sample per patient (obtained per patient) will be sent. One frozen vial of minimum 400 ul is required. If the volume is larger than needed, residual sample will be shipped back by vendor after testing is completed. De-identified samples will be sent on dry ice to the following vendor:

Attention: Deanna Stevens
Aushon BioSystems, Inc.
43 Manning Road, 1st floor
Billerica, MA 01821-3925
Ph: 978-436-6424
Fax: 978-667-3970
Each sample will be labelled with: protocol #, patient trial ID #.

9.2 **IGF-1R Signaling Pathway Proteins Tissue Levels**

For the Phase II expansion cohort, core biopsies from metastatic site or from primary tumor will be utilized for the following tests. Archival core biopsies, or study-specific biopsies that are formalin-fixed and paraffin-embedded will be used.

a. Pretreatment core biopsies (archived or study-specific) will be analyzed for expression of p- IRS, IGF-1R, Akt, Erk, mTOR, and PI3k by immunohistochemistry . In addition we will also examine IGF-1 mRNA expression using RT-PCR. The sample requirements for this test are as follows:
    - Unstained slides for molecular marker analysis (4 μm of formalin-fixed, paraffin-embedded tissue sections; minimum 5 slides, maximum: 20). Alternatively, paraffin-embedded tissue blocks can also be shipped.

- Tissue sample shipping instructions are as follows:
    - Shipments should be sent Monday through Thursday by priority overnight delivery.
    - **Do not ship on Fridays or on days prior to holidays.**

  Label the sample with the following information
    - Protocol Number
    - Patient Trial ID # and initials
    - Date of tumor tissue collection
    - Specimen – Origin of Tumor Tissue

- Samples will be sent in batched shipments to the following address:

Almac Diagnostics, 19 Seagoe Industrial Estate, Craigavon, BT63 5QD. United Kingdom; Tel: +44(0)28 3833 7575.

9.3 Single nucleotide polymorphisms of IgF1R and related genes

The following analysis will not be performed in the Phase II expansion cohort.
If the patient agrees, a 5 ml blood sample will be collected on day 1 prior to treatment in a green top tube (Heparinized tube). Samples will be delivered to Dr. Donghui Li's laboratory at 2SCRB2.3207 and processed for isolation of peripheral lymphocytes. DNA will be extracted from the cells using a Promega Maxiwell automated system. Single nucleotide polymorphisms of the IGF1, IGF1R, IRS1, and IRS2 genes will be analyzed using the Sequenom method. (See Appendix E).

10. STUDY CALENDAR (Table 11)

Procedure	Screening Phase (within 14 days of treatment start except MRI/CT scans and audiometry testing may be obtained within 28 days)	Treatment Phase								End of Treatment[J]
		Cycle 1				Cycle 2 onward[I]				
		Day 1[A]	Day 8[B]	Day 15[B]	Day 22[B]	Day 1[A]	Day 8[B]	Day 15[B]	Day 22[B]	
Informed consent	X									
Hematology[C]	X	X	X	X	X[P]	X	X	X		X
Serum chemistry[D]	X	X	X	X	X[P]	X	X	X		X
PT/INR[E]	X									
CA19-9 estimation	X					X				X
Complete urinalysis with microscopic examination	X									
Medical history	X	X								
Physical examination (PE)	X	X		X		X				X
Height	X									
Vital signs[F], weight	X	X	X	X	X[P]	X	X	X	X[P]	X
ECOG performance status	X	X		X		X				X
Review concomitant medications[G]	X	X		X		X				X
Archival Tumor Tissue (Core biopsy) if available or trial-specific tumor biopsy in the phase II expansion cohort	X									
CT Scans or MRI of chest, abdomen, pelvis	X								X[N]	X
12-lead ECG	X									
Serum or urine pregnancy test (if applicable)	X									
Comprehensive audiometry testing[R]	X									
Adverse event evaluation[H]	X	X	X[0]	X	X[0]	X	X[0]	X[0]	X[0]	X
IGF-1 and IGFBP-3 correlative (diagnostic center)	X[S]				X[S]					
Tissue expression and EMT biomarkers in the phase II expansion cohort	X									
IgF1R correlative (optional) (Dr. Donghui Li's Lab). NOTE: This will NOT be performed in the Phase II expansion cohort.		X[M]								
Collect Serum for HAHA-shipped to Merck's designated lab, PPD[L, P, Q,] NOTE: This will NOT be performed in the Phase II expansion cohort.		X[L,]			X[L]				X[L]	X[L]
Survival Status										X[K]

A. For Cycle 1, any evaluations performed for screening assessments that were performed within 3 days prior to Day 1 do not need to be repeated on Day 1. Except as previously noted, Day 1 evaluations of each cycle may be performed up to 2 days prior to Day 1.
B. Days 8, 15, and 22 evaluations may be performed up to 1 day prior.
C. Hematology includes hemoglobin, hematocrit, platelets, total white blood cell count (WBC) and differential.
D. Serum chemistry includes sodium, potassium, chloride, CO_2, calcium, phosphorus, fasting glucose, creatinine, blood urea nitrogen, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase and uric acid.
E. PT (INR) evaluation will be included for baseline evaluations. If warfarin anticoagulation is required, patients should have their PT/INR monitored at least weekly until stabilized and then on a periodic basis.
F. Pulse, blood pressure, respiration rate, and temperature
G. Patients will be instructed to notify study personnel if there are any changes to their concomitant medications.
H. In addition to scheduled adverse event evaluations, research nurse will review adverse events weekly with patients as clinically indicated. Patients will also be instructed to inform the study research nurse any time they experience new adverse events or previously reported events increase in severity.
I For subsequent cycles, assessments will continue as previously described for Cycle 2. Imaging studies will be performed after every 2 cycles (within 7 days of the end of Cycle 2, Cycle 4, Cycle 6, etc.). Treatment may continue until one of the criteria for treatment discontinuation outlined in Section 5.5 applies.
J. Evaluations will be performed within 30 days (+ 7 days allowed) of last dose of study drug(s). CA19-9 and imaging studies are not required if disease progression was previously documented. In patients who discontinue study treatment for reasons other than progression, imaging studies will continue to be performed every 8 weeks until disease progression is documented. Any adverse event assessed to be related to study therapy that has not returned to Grade 1 or baseline will continue to be followed after this evaluation until recovery or the treating investigator determines the event is irreversible.
K. Each patient who discontinues study treatment will be followed for survival every 3 months ($\pm$ 1 week). Follow-up may be done either by phone contact or a clinic visit.
L. HAHA will NOT be performed in the Phase II expansion cohort. Serum HAHA should be measured at baseline (Screening Phase or pretreatment C1D1), at Week 4 (Cycle 1 – Day 22), at Week 8 (Cycle 2 – Day 22), and every eight weeks thereafter; and at Week 4 and Week 8 and Week 12 Post-study (End of Treatment). (See Appendix F). After baseline assessment +/- 7 day window is allowed.
M. This will NOT be performed in the Phase II expansion cohort. This test will be drawn pre-treatment on cycle 1 day 1 after it is determined that patient qualifies for the study.
N. CT/MRI evaluations will be performed at the end of every 2 cycles (weeks 8, 16, etc.).
O. The research nurse may call the patients weekly as clinically indicated if they are not scheduled for treatment. This call would be to determine if the patient is having a major toxicity that would require holding treatment. If the call occurs, this information will be documented in a telephone note, formal AE reporting will be done at the end of each cycle.
P. Not required for patients on Phase II part of the study who are randomized to Gemcitabine and Erlotinib.
Q. Not required for patients who are crossed-over to Gemcitabine + Erlotinib + MK-0646. (As described in Section 5.3).
R. Comprehensive audiometry testing will be performed at baseline on all patients enrolled in the phase II portion of the study. Audiometry testing will be repeated in any patient treated with MK-0646 who has suspected change in hearing. Follow-up testing will be performed as clinically indicated.
S. IGF1 and IGFBP3 level will be drawn at screening and on Cycle 1, Day 22; one hour (+/-30 min) post dose # 4 of MK-0646

Please refer to table 11 and accompanying footnotes for any time allowances (windows) for performing study evaluations.

10.1 **Pre-treatment Evaluations**

Except for MRI/CT scans and audiometry testing which may be performed within 28 days, the following baseline evaluations shall be performed within 14 days to treatment initiation:

- **Hematology**: must include hemoglobin, hematocrit, platelets, total white blood cell count (WBC) and differential. PT (INR) evaluation will be included for baseline evaluations. If warfarin anticoagulation is required, patients should have their PT/INR monitored at least weekly until stabilized and then on a periodic basis.
- **Serum chemistry**: must include sodium, potassium, chloride, CO_2, calcium, phosphorus, fasting glucose, creatinine, blood urea nitrogen, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase and uric acid.
- **CA 19-9 estimation**
- **Complete urinalysis with microscopic examination**
- **Medical History and Physical Exam**
- **ECOG Performance Status**
- **Vital signs:** height (first visit), pulse, blood pressure, respiration rate, temperature and weight.
- **Assessment of concurrent medications**
- **Assessment of baseline AEs.**
- **12-Lead ECG**
- **Serum or urine pregnancy test** for women of childbearing potential
- **Comprehensive audiometry testing**
- **Radiological evaluation**: Chest, abdomen and pelvis by either CT scan or MRI. Same imaging technique should be used on a patient throughout the study.
- **Determination if archival tumor tissue (Core biopsy) is available** for correlative studies. If inadequate, patient will undergo core biopsy of tumor with informed consent in the expansion cohort.

10.2 **During Treatment Evaluations**

Prior to Treatment on Day 1 of Cycle 1

- **When it has been determined the patient qualifies for the study, blood samples for determination of circulating levels of IGF-1, IGFBP-3 (section 9.1) will be collected. HAHA samples must be collected in all patients except those assigned to treatment with Gemcitabine + Erlotinib. HAHA will NOT be performed in the Phase II expansion cohort.**

During cycle 1:

- **Hematology and serum chemistry:** obtained on Days 1, 8, 15, and 22.*
- **Physical Exam:** obtained on Days 1 and 15
- **ECOG Performance Status:** obtained on Days 1 and 15
- **Vital signs and weight:** obtained on Days 1, 8, 15, and 22*
- **Determination of erlotinib dose compliance (**if applicable)
- **Blood sample for circulating level of IGF-1 and IGFBP-3 will be collected on Cycle**

1, Day 22, 1 hour post dose of MK-0646.

- **Assessment of concurrent medications:** obtained on Days 1, and 15 Patients also will be instructed to notify study personnel at any time there are changes to their concomitant medications.
- **Adverse event evaluation:** obtained on Days 1 and 15. In addition to scheduled adverse event evaluations, research nurse will review adverse events weekly with patient as clinically indicated. Patients will also be instructed to inform the study research nurse any time they experience new adverse events or previously reported events increase in severity.
- **Collect Serum for HAHA:** collected on Day 22 of Cycle 1. (Not required for patients assigned to Gemcitabine + Erlotinib). This will NOT be performed in the Phase II expansion cohort.

***** Day 22 assessment not required for patients assigned to treatment with Gemcitabine + Erlotinib.

During cycles 2 and beyond:

- **Hematology and serum chemistry:** obtained on Days 1, 8, 15 of every cycle
- **CA 19-9 estimation:** Day 1 of every cycle.
- **Physical Exam:** Day 1 of each cycle
- **ECOG Performance Status:** Day 1 of each cycle
- **Vital signs and weight:** obtained on Days 1, 8, 15, and 22*****
- **Determination of erlotinib dose compliance** (if applicable)
- **Assessment of concurrent medications:** Day 1 of each cycle. Patients also will be instructed to notify study personnel at any time there are changes to their concomitant medications.
- **Adverse event evaluation:** obtained Day 1 of each new cycle. In addition to scheduled adverse event evaluations, research nurse will review adverse events weekly with patient as clinically indicated. Patients will also be instructed to inform the study research nurse any time they experience new adverse events or previously reported events increase in severity.
- **Radiological evaluation (CT scan or MRI):** evaluation shall be performed at the end of every 2 cycles (weeks 8, 16, etc.).
- **Collect Serum for HAHA:** collected on Day 22 of Cycle 2 and every 8 weeks thereafter. (Not required for patients assigned to treatment with Gemcitabine + Erlotinib). This will NOT be performed in the Phase II expansion cohort.

***** Day 22 assessment not required for patients assigned to treatment with Gemcitabine + Erlotinib.

Follow-up audiometry testing will be performed for any MK-0646 treated patient who has suspected change in hearing from baseline evaluation. Frequency of any subsequent testing will be as clinically indicated.

10.3 **End of Treatment Evaluations**

When a patient discontinues study treatment, the following evaluations will be completed 30 days (+ 7 days) from last dose of study drug

- **Physical exam**
- **ECOG Performance Status**
- **Vital Signs and weight**
- **Hematology and serum chemistry**
- **Assessment of concurrent medications**
- **Determination of erlotinib dose compliance** (if applicable)
- **Adverse event evaluation**: Any adverse event assessed to be related to study therapy that has not returned to Grade 1 or baseline will continue to be followed after this evaluation until recovery or the treating investigator determines the event is irreversible.
- **Collect Serum for HAHA:** collect at Week 4, Week 8 and Week 12 Poststudy (End of Treatment) (+/- 7 day window allowed. Not required for patients assigned to treatment with Gemcitabine + Erlotinib). This will NOT be performed in the Phase II expansion cohort.
- **CA 19-9**
- **Imaging studies** are not required if disease progression was previously documented or if performed within the last 5 weeks. In patients who discontinue study treatment for reasons other than progression, imaging studies will continue to be performed every 8 weeks until disease progression is documented.

Survival Status

Each patient who discontinues study treatment will be followed for survival at least every 3 months. This may be done either by phone contact or a clinic visit.

11. MEASUREMENT OF EFFECT

11.1 **Antitumor Effect – Solid Tumors**

For the purposes of this study, patients should be reevaluated for response every eight weeks.

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (one-dimensional measurement) of the tumor lesions are used in the RECIST criteria.

11.1.1 **Definitions**

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with the study agents.

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.)

11.1.2 **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).

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.

11.1.3 **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.
The Research Nurse will complete a Tumor Measurement worksheet for each patient, which will be signed by the doctor and sent to medical records to be scanned into the Research Folder.
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 marker such as CA 19-9 level 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.

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.

11.1.4 **Response Criteria**

11.1.4.1 **Evaluation of Target Lesions**

Complete Response (CR):Disappearance of all target lesions

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 LD recorded since the treatment started or the appearance of one or more new lesions.

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

11.1.4.2 **Evaluation of Non-Target Lesions**

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

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

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 Principal Investigator.

11.1.4.3 **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.

Table 12 Evaluation of Best Overall Response

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.

11.1.5 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.

11.1.6 **Progression-Free Survival**

PFS is defined as the time from date of first dose of study drug until date of disease progression (clinical or radiological) or death, if progression not previously documented. .

11.1.7 **Overall Survival**

Overall survival is defined as the time from the date of the first dose of study drug to the date of death. In the absence of death confirmation, survival time will be censored at the date of the last study follow-up.

12. DATA COLLECTION

Designated research personnel must enter the information required by the protocol onto electronic Case Report Forms (CRFs). The University of Texas M. D. Anderson Cancer Center's Protocol Data Management System©(PDMS) CRF system will be used for this study. PDMS is a clinical research information management system. The PDMS CRF is an electronic document designed to record all the protocol-required information to be reported on each trial subject.

PDMS provides data entry templates as defined in the protocol. Laboratory results are automatically transferred from M. D. Anderson Cancer Center Laboratory Medicine's server to PDMS each morning. Users must have clearance through the M. D. Anderson Cancer Center Information

Services Security Department in order to access PDMS. PDMS login is password protected.

13. STATISTICAL CONSIDERATIONS

Overview of Statistical Considerations

Part One:

Phase I study of (a) gemcitabine + MK-0646 and (b) gemcitabine + erlotinib + MK-0646. We are only considering two dose levels, so we will carry out a 3+ 3 phase I design.

- Enrollment will begin on arm (a). Arm (b) will begin enrollment at a particular dose level only when enrollment at that dose level is complete in Arm (a). Thus, enrollment at dose level 1 in arm (b) will begin only after dosing at level 1 is completed safely in arm (a).
- A minimum of 3 patients will be treated at each dose level. Once 3 patients are enrolled in Arm A, Level 1, additional accrual will be held until all 3 patients have completed their first cycle. If there is one DLT, up to 3 additional patients will be entered at the same dose level and evaluated for DLT. If the criteria for dose escalation are met, 3 new patients will be enrolled in Arm B, Level 1. Once 3 patients have been enrolled in Arm B, Level 1, 3 patients may be accrued to Arm A, Level 2. Patients in both of these Arms/Levels will be evaluated for DLT during cycle 1. If DLT is observed, up to 3 additional patients will be enrolled in the Arm/Level that DLT occurred, as described above. Once accrual and cycle 1 evaluation have been completed in Arm B, Level 1 and Arm A, Level 2, if the criteria for dose escalation are met in both arms, accrual may proceed in Arm B, Level 2.
- If at any time 2 patients develop DLTs at a level, this level will be considered above the MTD. In each arm, six patients will be treated at the dose identified as the MTD. The MTD is defined as the highest dose level that can be administered with ≤ 1 DLT observed in 6 patients.

Part two:

The phase II part of the study will utilize an adaptive randomization design with 3 arms: Arm A: gemcitabine + MK-0646 (G+I), Arm B: gemcitabine + erlotinib + MK-0646 (G+E+I), and Arm C: gemcitabine +erlotinib (G+E). The primary endpoint is progression-free survival (PFS). Technical details of the adaptive randomization algorithm are given in the Appendix. Briefly, the first 45 patients will be equally randomized among the three arms. Thereafter, as the trial progresses and data accrue, the randomization will become unbalanced and in favor of the treatment arm that, on average, has better results in terms of PFS. A minimum of 45 and a maximum of 78 patients will be accrued in the phase II part of this study. Based on an anticipated accrual rate of 4 patients per month, it will take about 20 months to enroll all 78 patients.

Additionally, a safety monitoring rule will be in place, allowing us to stop accruing patients to

treatments that appear to be unsafe. Each arm will be monitored separately using the following stopping rule: Pr(Toxicity rate >.30|data) > 0.95 and starting from the 5th patient. A beta(0.6, 1.4) prior is assumed for the toxicity rate and the corresponding stopping boundaries are to stop the trial if, at any given time, (number of patients with toxicities/number of evaluable patients) >/= 4/5, 5/6, 6/9, 7/11, 8/13, 9/16, 10/19, 11/21, 12/24, 13/26, 14/29, 15/32, 16/35, 17/37, 18/40, 19/43, 20/46.

Part Three (expansion phase):

We will expand Arm A: gemcitabine + MK-0646 (G+I) by adding an additional 30 patients. The estimated accrual rate is 2-3 patients per month. The primary objective for this expansion cohort is to further explore IGF1 tissue level as a predictive biomarker for MK-0646 therapy. To meet this goal, we will combine the data already collected up- to-date from 21 patients treated in arm A (6 from phase I MTD cohort and 15 from phase II) with these 30 patients' data in order to further assess the potential differential effect of MK-0646 treatment on PFS among patients with high vs. low IGF-1 groups. Our hypothesis is that patients with relatively higher IGF1 level may benefit more from the therapeutic effect of MK-0646. Our preliminary data showed that the median PFS was 8.0 months (95% CI: 1.8 – Not estimable) and 2.0 months (95% CI: 1.2 – not estimable), respectively, among patients with high versus low IGF1 level (using median as the cutoff).

In this expansion phase of the trial, we will continue to monitor those patients treated with G+M for futility (based on PFS) and safety.

Futility Monitoring

The Bayes factor single-arm time-to-event model (Johnson & Cook, 2009) will be used to monitor the PFS. Based on the preliminary data on 15 patients treated with gemcitabine+erlotinib (G+E, control arm) in the randomized portion of this study (part 2), the median PFS for this control arm was 2.1 month (mean PFS= 3.0 months), and we expect that the treatment of G+M would prolong the median PFS to be 3.6 months (mean PFS = 5.2 months). Therefore, under this Bayesian hypothesis testing based design framework, the null hypothesis is a median PFS of 2.1 months, while the alternative hypothesis is a median PFS of 3.6 months. We assume that the sample distribution of PFS follows an exponential distribution, and use an inverse moment prior for the mean PFS under the alternative hypothesis. We will stop the trial for futility if the posterior probability of the alternative hypothesis is less than 0.10, i.e. Pr(H1|Data) < 0.10.

The operating characteristics of the design were produced using a design software, **BayesFactorTTE**, version 1.0.0, developed by the Department of Biostatistics at M. D. Anderson Cancer Center.

Scenario	**True median (mean) PFS**	**Pr(Stopping for the null)**	**Average # patients treated (10%, 25%, 50%, 75%, 90%)**

1	2.1 (3.03)	0.919	23.27 (10, 14, 20, 30, 47)
2	3 (4.33)	0.373	40.87 (15, 29, 51, 51, 51)
3	3.6 (5.19)	0.116	47.51 (34, 51, 51, 51, 51)
4	4.6 (6.64)	0.016	50.43 (51, 51, 51, 51, 51)

Stopping Boundaries

The entire design output from running the BayesFactorTTE is attached as an Appendix, which includes the input parameters, simulation results, as well as the stopping boundaries for declaring futility.

Trial Conduct

Patient enrollment and futility stopping rule assessment will be conducted through a website developed and maintained by the Department of Biostatistics (https://biostatistics.mdanderson.org/ClinicalTrialConduct/). The Clinical Trial Conduct (CTC) website resides on a secure server, and access is gained through usernames and passwords provided to personnel responsible for enrolling patients and updating patient data. The website is accessed through a browser using secure socket layer technology. Personnel responsible for enrolling patients on trials will be trained in the use of the trial website, with emphasis on the importance of timely updating of follow-up times and recording of events. The futility monitoring rules described above will be automatically evaluated each time patient data are updated on the trial website. If the stopping rule is met, the study statistician, research nurse, and principal investigator will each receive an automatic email notification.

Toxicity Monitoring

In addition, we will expand the toxicity monitoring for the G+M arm to account for a maximum of 51 patients (i.e., 21 already enrolled plus 30 more in the expansion). Again, the Bayesian design of Thall, Simon, Estey (1995) will be applied in all patients treated with G+M. Specifically, the trial will be stopped if Prob(π_T>0.30 | data)>0.95. That is, if at any given time, there is more than 95% probability that the toxicity rate of the G+M is greater than 30%, the trial will be stopped. We will apply this toxicity stopping rule starting from the 5th patient. A beta(0.6, 1.4) prior is assumed for the toxicity rate and the corresponding stopping boundaries are to stop the trial if, at any given time, (number of patients with toxicities/number of evaluable patients) >/= 4/5, 5/6, 6/9, 7/11, 8/13, 9/16, 10/19, 11/21, 12/24, 13/26, 14/29, 15/32, 16/35, 17/37, 18/40, 19/43, 20/46, 21/49. The operating characteristics for the toxicity monitoring rule are shown below.

True Toxicity Rate	Pr (Stop the trial early)	Median # patients (25th, 75th percentile)
0.2	0.025	51 (51,51)
0.25	0.065	51 (51,51)
0.3	0.174	51 (51,51)

0.35	0.376	51 (25,51)
0.4	0.627	34 (12, 51)

Analysis Plan:

The probability of PFS and OS will be estimated using the method of Kaplan and Meier. For PFS, we will also compute the posterior probability of the null and alternative hypothesis being true. To explore the association between patients' tissue IGF-1 level and their PFS outcome, we will first dichotomize the IGF-1 level as "high" vs. "low", using the sample median as cutoff. The median PFS and the corresponding 95% confidence interval will be estimated for each subgroup separately. Log-rank test will also be performed to assess whether there is any significant difference in PFS between these two groups of patients. Patients' AE data will be summarized by AE term, grade and relationship to the study drug using descriptive statistics.

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Appendix 1: Statistical Output

Simulation output from the Bayes factor one-arm time-to-event design.

Output Report

BayesFactorTTE (version 1.0.0)

Bayes Factor One-arm Time-to-event Outcome

8/22/2012 9:51:27 AM

Random seed for simulation: 12345

Input file name: InputFile_BayesFactorTTE.txt

Output file name: output.html

Design input parameters:

Parameter	Value
Maximum number of patients	51
Null hypothesis of median (mean) TTE in month	2.1 (3.03)
Alternative hypothesis of median (mean) TTE in month	3.6 (5.19)
Cutoff to stop for inferiority if Pr(H1|Data) <	0.1
Cutoff to stop for superiority if Pr(H1|Data) >	1
Accrual rate per month	3
Number of repetitions for the simulation	1000
Do you need to print out the stopping boundaries	Yes

Note: H1 = alternative hypothesis

Simulation Results

Scenario	True median (mean) TTE	Pr(Stopping for H0)	Average # patients treated (10%, 25%, 50%, 75%, 90%)
1	2.1 (3.03)	0.919	23.27 (10, 14, 20, 30, 47)
2	3 (4.33)	0.373	40.87 (15, 29, 51, 51, 51)
3	3.6 (5.19)	0.116	47.51 (34, 51, 51, 51, 51)
4	4.6 (6.64)	0.016	50.43 (51, 51, 51, 51, 51)

Note:H0 = null hypothesis;

Stopping Boundaries

Number Events	Max total time-on-test in days (months) to claim inferiority
0	0 (0)
1	0 (0)
2	0 (0)
3	0 (0)
4	94 (3.1)
5	218 (7.2)
6	341 (11.2)
7	463 (15.2)
8	585 (19.2)
9	706 (23.2)
10	827 (27.2)
11	948 (31.1)
12	1068 (35.1)
13	1188 (39)
14	1308 (43)
15	1427 (46.9)
16	1546 (50.8)
17	1665 (54.7)
18	1783 (58.6)
19	1902 (62.5)
20	2020 (66.4)
21	2138 (70.2)
22	2256 (74.1)
23	2373 (78)
24	2490 (81.8)
25	2608 (85.7)
26	2725 (89.5)
27	2841 (93.3)

28	2958 (97.2)
29	3075 (101)
30	3191 (104.8)
31	3307 (108.6)
32	3423 (112.5)
33	3539 (116.3)
34	3655 (120.1)
35	3771 (123.9)
36	3887 (127.7)
37	4002 (131.5)
38	4117 (135.3)
39	4233 (139.1)
40	4348 (142.9)
41	4463 (146.6)
42	4578 (150.4)
43	4693 (154.2)
44	4808 (158)
45	4922 (161.7)
46	5037 (165.5)
47	5151 (169.2)
48	5266 (173)
49	5380 (176.8)
50	5494 (180.5)