05-C-0141

CC Protocol #:
PRMC Protocol #: P6557
Medarex Protocol #: MDX010-24

Abbreviated Title: MDX-010 for patients with pancreatic cancer

Treatment of patients with locally advanced and metastatic pancreatic adenocarcinoma with the single agent MDX-010 (anti-CTLA4)

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Précis: Patients with inoperable, Stage IV pancreatic adenocarcinoma, will be stratified based on locally advanced or metastatic disease and treated with infusional MDX-010, a human monoclonal antibody (mab) to CTLA-4. Patients will be treated with a maximum of 2 courses of therapy (each course: 3 mg/kg every three weeks x 4). This study is a phase II assessment with overall response as the primary endpoint.

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1.0 Introduction

1.1 Study Objective:

Primary Objective:

To assess the clinical response (PR and CR) to MDX-010 as a single agent in patients with locally advanced pancreatic adenocarcinoma.

To assess the clinical response (PR and CR) to MDX-010 as a single agent in patients with metastatic pancreatic adenocarcinoma.

Secondary Objective:

Define the MTD over the range of doses proposed.

[redacted]

[redacted]

2.0 Eligibility Assessment and Enrollment

2.1 Eligibility Criteria:

2.1.1 Inclusion Criteria

A. Any patient ≥ 18 years of age with a histologic diagnosis of stage IV pancreatic adenocarcinoma that is clinically evaluable, with at least one site of measurable disease.

B. Patients must be ≥ 3 weeks beyond their last treatment (radiation, chemotherapy, etc.) for pancreas carcinoma and recovered from any serious toxicity experienced during treatment.

C. Women should be either: post-menopausal for at least one (1) year; surgically incapable of bearing children; or utilizing a reliable form of contraception. Women of childbearing potential must have a negative urine pregnancy test conducted during screening.

D. Because the risk of a negative influence of this therapy on reproductive processes, men who may father a child must agree to the use of male contraception for the duration of their participation in the trial.

E. Life expectancy ≥3 months.

F. ECOG Performance Status ≤ 2.

G. Biliary obstruction must be effectively drained by endoscopic, operative or interventional means.

H. Gastric outlet obstruction must be effectively drained by endoscopic, operative or interventional means.

I. Required values for initial laboratory test:

- WBC ≥2500/ml
- ANC ≥1500/ml
- Platelets ≥100 x 10^3/ml
- Hemoglobin ≥9 g/dl
- Hematocrit ≥27 %
- Creatinine <2.0 mg/dl
- HBsAg negative
- HIV negative
- Anti-HCV non-reactive, or RNA-PCR (-) if reactive.

2.1.2 Exclusion Criteria

A. Pancreatic fistula, biliary fistula, or enteric fistula not controlled with an appropriate drain.

B. Any other prior malignancy, except for the following: adequately treated basal or squamous cell skin cancer, superficial bladder cancer, carcinoma *in situ* of the cervix, or any other cancer from which the patient has been disease-free for five (5) years or more.

C. A diagnosis of pancreatic cancer consistent with acinar cell carcinoma, pancreaticoblastoma, malignant cystic neoplasms, endocrine neoplasms, squamous cell carcinoma, as well as Vater and periampullary duodenal or common bile duct malignancies. Patients with pancreatic adenocarcinomas with associated intraductal papillary mucinous neoplasm identified in the specimen will be included in the study since these adenocarcinomas are ductal in origin, and have a similar natural history to all other pancreatic ductal adenocarcinomas.

D. Active autoimmune disease or history of autoimmune disease (including uveitis and autoimmune inflammatory eye disease).

E. Active uncontrolled infection, this includes positive results from HIV, HBsAg and anti-HCV.

F. Pregnancy or nursing: due to the possibility that MDX-010 could have a detrimental effect on the developing immune system of the fetus or infant, exposure in utero or via breast milk will not be allowed.

G. Any underlying medical condition which, in the opinion of the principal investigator, will make the administration of study drug hazardous or obscure the interpretation of adverse events.

H. Any concurrent medical condition requiring the use of systemic or topical corticosteroids or the use of immunosuppressive agents (e.g. cyclosporin and its analog, or chemotherapy agents). All corticosteroid use must have been discontinued > four (4) weeks prior to trial entry.

I. Prior treatment with any anti-CTLA4 mAb.

2.2 Research Eligibility Evaluation: All screening evaluation studies will be completed within 28 days of initiating therapy.

2.2.1 Physical examination

A history and physical examination will be completed during the screening phase. A physical examination will be completed on the day of admission for the first therapy. Information about the physical and neurological examinations must be present in the source documentation at the study site. Significant findings that are present prior to the start of study medication must be included in the Relevant Medical History CRF/Current Medical Conditions CRF. Significant findings made after the start of study medication that meet the definition of an adverse event must be recorded on the Adverse Event CRF.

2.2.2 Vital Signs

Blood pressure (systolic and diastolic), pulse rate, respiration rate, and temperature will be assessed during screening and at baseline for each dose, then every 30 minutes during administration of MDX-010 infusion, and for one hour after administration, and then routinely unless otherwise indicated. Appropriately sized sphygmomanometer cuffs must be utilized for each patient.

2.2.3 Performance Status

Patient performance status will be graded according to ECOG Performance Status criteria (Appendix 1).

2.2.4 Ophthalmologic examination

Ophthalmologic examination will be performed at baseline and at the end of each course and if any ocular symptoms develop. Visual acuity evaluations will be performed during each such assessment. All reports will be filed with the patient's source documentation. Appropriate CRF's must be completed.

2.2.5 Electrocardiograph

A standard 12-lead electrocardiograph will be performed. Upon receiving the interpretation of the electrocardiograph, the investigator will ensure completion of the electrocardiogram CRF indicating all relevant findings. The electrocardiograph tracing with interpretation will be filed with the patient's source documents. Subsequent ECGs will be obtained if clinically indicated.

2.2.6 Diagnostic imaging

Chest, abdominal and pelvic CT or MRI and chest x-ray will be performed at baseline. The most effective diagnostic modality must be employed consistently throughout the study. The same imaging modality, method of assessment, or technique must be used throughout the study to identify any new lesion. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously.

2.2.7 Pregnancy tests

Women of childbearing potential must have a negative urine pregnancy test conducted during screening and a negative urine pregnancy test within 72 hours prior to Day 0, with results verified prior to dose administration.

2.2.8 Hepatitis panel

- Hepatitis B surface antigen (HBsAg)
- Hepatitis C virus antibody (anti-HCV) (or Hep C RNA-PCR if antibody positive)

Test results must be negative for trial entry.

2.2.9 HIV

Human immunodeficiency virus antibody titer test results must be negative for trial entry.

2.2.10 Autoimmune panel

- Antithyroglobulin antibody
- Antinuclear antibody (ANA) test, if positive test for Extractable nuclear antigen (ENA), if ENA positive, then the following tests will be performed (If negative, then a sample of serum will be stored for subsequent testing in the event that the ANA becomes positive):

    - Anti-phospholipid antibody
    - Anti-neutrophil cytoplasm antibody
    - CH50
    - Anti-DNA antibody
    - Anti-SSA antibody
    - Anti-SSB antibody
    - Rheumatoid factor (RF)

2.2.11 Thyroid function test

Thyroid stimulating hormone (TSH) – if abnormal, run full Thyroid function test (TFT panel, including Free T3 and Total T4).

2.2.12 Hematology

- Hemoglobin
- Hematocrit
- Complete blood cell count with differential and platelet count (direct) and sedimentation rate

2.2.13 Biochemistry

- Albumin
- Alkaline phosphatase
- ALT
- AST
- Bilirubin (total and direct)
- Calcium
- Chloride
- Bicarbonate
- Creatinine
- Glucose
- Lactate dehydrogenase (LDH)
- Potassium
- Sodium
- Total protein
- Urea nitrogen (BUN)
- Uric acid

2.2.14 Urinalysis

A urinalysis will be performed at baseline and after each course of therapy.

2.2.15 HLA Typing

Standard HLA typing will be performed at baseline.

2.3 Patient Registration and Treatment Randomization:

Authorized staff must register an eligible candidate with ORKAND within 24 hours of signing the consent. A registration checklist from the Web site [redacted] must be completed and faxed to ORKAND at [redacted] After confirmation of eligibility at ORKAND, ORKAND staff will call the Pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents.

3.0 Study Implementation

3.1 Study Design

This is an open-label study of repeated doses of a human monoclonal antibody (mAb) to CTLA-4 (MDX-010) administered to patients with advanced pancreatic adenocarcinoma. It is designed to determine if a dose of MDX-010 at 3 mg/kg administered every 3 weeks can cause tumor regression. Patients with measurable unresectable pancreatic carcinoma will be enrolled in two groups. One group of patients will have locally advanced, unresectable disease defined on imaging by the absence of metastatic disease beyond the draining lymph nodes and local invasion of the SMA or celiac arteries, and/or thrombosis of the SMV/portal vein complex, and/or unresectable invasion of neighboring structures. The second group of patients will have metastatic disease that is distant to the draining lymph nodes.

In this study, patients will receive 3 mg/kg MDX-010 antibody intravenously every three weeks. Our experience with MDX-010 in patients with melanoma or renal cell cancer has shown a correlation between severe autoimmunity and tumor response. It has also shown a higher rate of both autoimmune toxicity and tumor response when MDX-010 is administered at repeated doses of 3 mg/kg. Two separate groups of 21-41 patients will be treated with intravenous infusion of MDX-010 at 3mg/kg for all doses. One of the groups will have locally advanced disease, while the other group will have distant metastases. The two groups will be evaluated separately using the same single arm, two-stage phase II design described in Section 5.5.

Four doses will be designated as a course of therapy and evaluations will be conducted at the end of each course, 3 weeks after the 4th infusion. An informal interim evaluation may be performed 3 weeks after the 2nd infusion to rule out rapid disease progression, but the formal evaluation with tumor measurements will be performed approximately 3 weeks after the 4th dose. CT scanning may be performed at any time during protocol implementation in the event that there is clinical evidence of disease progression

Treatment will be limited to 2 courses of therapy. Patients that respond and subsequently relapse will be treated with additional courses of therapy. Patients may come off study at any time if rapid disease progression occurs.

Patients in the locally advanced disease cohort may experience sufficient tumor response that their disease is rendered resectable. If this occurs, these patients will be treated with standard pancreatic resection rendering them NED (no evidence of disease).

3.2 Drug Administration:

MDX-010: All MDX-010 doses will be administered as an intravenous infusion controlled by an infusion pump. For administration, MDX-010 is to be injected into the IV bag and diluted in 0.9% Normal Saline, USP, to a concentration between 0.2 mg/ml and 1 mg/ml as specified in Section 8.1, and should be administered over 90 minutes through an add-on filter set with 1.2 μm air-eliminating filter [redacted]

Do not administer as an i.v. push or bolus. If ≥ Grade 3 bronchospasm or other hypersensitivity reaction occurs, the infusion should be discontinued and no additional MDX-010 should be administered.

Surgical guidelines

Patients in the locally advanced disease cohort may experience sufficient tumor response that their disease is rendered resectable. If this occurs, these patients will be treated with standard pancreatic resection rendering them NED (no evidence of disease).

Resections will generally consist of proximal pancreatectomy (Whipple's pancreaticoduodenectomy) or distal pancreatectomy. Rarely, unusual resections of the pancreas (pylorus preserving proximal pancreatectomy, total pancreatectomy, Appleby's procedure, middle segment pancreatectomy, dorsal pancreatectomy, etc.) will be completed at the discretion of the operating clinician. Proximal pancreatectomies will follow the procedure outlined by [redacted] with variation and vascular reconstruction as indicated by anatomical or tumor characteristics. Distal and other types of resection will follow standard procedures.

Postoperatively, patients will be monitored in the ICU and will be routinely intubated for the initial 12 hours. Patients will receive nasogastric decompression, fluid resuscitation, prophylactic antibiotics, and pancreatic enzyme replacement during the postoperative period. Characteristically, patients will have gastrostomy and feeding tubes placed without intra-abdominal drains. These are expected postoperative events and will not be considered toxicities.

3.3 Treatment Modifications:

3.3.1 MDX-010

There will be no intra-patient dose modifications of MDX-010. Patients will discontinue treatment with MDX-010 if they experience an adverse event felt to be possibly or probably related to MDX-010 antibody that meets the following criteria:

- A patient who requires systemic steroid therapy for any reason will not receive further treatment with MDX-010 but will be followed until off study criteria are met.
- Any infusion related reaction of $\geq$ grade 3. Infusion related reactions are defined as acute reactions that develop and resolve within 48 hours of the start of an infusion. This includes reactions that are responsive to therapy within that time frame except for Grade 3 fever that resolves within 48 hours. Exclusions to discontinuing therapy will be made in the presence of an objective response when the toxicity resolves prior to the next infusion.
- Any autoimmune toxicity of > grade 2 that has the potential to be life threatening with continued antibody administration and is not associated with a potential therapeutic response, except rash, vitiligo or asymptomatic autoantibody detection. An autoimmune reaction is defined as an inflammatory process that compromises the function of any organ and is not attributable to another etiology.
- Any autoimmune toxicity (any grade) that does not resolve by the time that additional dosing with MDX-010 is considered. Patients may delay subsequent doses in a course by up to a maximum of 3 weeks while awaiting resolution of an autoimmune toxicity.
- Uveitis or episcleritis that is symptomatic (causing eye pain, photosensitivity, or blurred vision)
- Exclusions to these criteria include inflammation of < grade 4 that is attributable to a local anti-tumor reaction that could potentially be a therapeutic response. This

includes inflammatory reactions at the site of tumor resection or in draining lymph nodes, or in sites suspicious for metastasis.

If any two patients of the trial develop a $\geq$ Grade III non-skin-related toxicity or grade IV skin-related toxicity attributable to the investigational agent, except for those noted above, that cannot be alleviated or controlled by appropriate care (see Sections 4.0 through 4.5) and/or steroid therapy within 14 days of the initiation of the supportive care and/or steroid therapy, accrual to this study will stop until the principal investigator, in consultation with the sponsors and NCI IRB, review the events to determine the need to revise the protocol and informed consent.

3.3.2 Blinding

This is an open-label study.

3.3.3 Treatment compliance

Records of study medications used, and dosages administered, will be kept during the study. The study monitor will note drug accountability during site visits and at the completion of the study.

3.4 On Study Evaluation

During the treatment phase, patients will be monitored according to the Assessments delineated below:

3.4.1 Assessment prior to each dose of MDX-010

3.4.1.1. Physical examination

3.4.1.2. Assessment of performance status

3.4.1.3. Hematology (Hemoglobin, Hematocrit, Complete blood cell count with differential and platelet count (direct), and biochemistry testing (Albumin, Alkaline phosphatase, ALT, AST, Bilirubin (total and direct), Calcium Chloride, Bicarbonate, Creatinine, Glucose, Lactate dehydrogenase (LDH), Potassium, Sodium, Total protein, Urea nitrogen (BUN), Uric acid). A urine pregnancy test will be performed and confirmed negative prior to each dose.

3.4.1.4. Blood pressure (systolic and diastolic), pulse rate, temperature and respiratory rate at baseline for each dose, then every 30 minutes throughout the MDX-010 infusion, and for one hour after infusion, and then routinely unless otherwise indicated.

3.4.1.5. Assessment of adverse events

3.4.1.6. Assessment of concomitant medications

3.4.2 Assessment prior to each new course

3.4.2.1. Physical examination

3.4.2.2. Assessment of performance status

3.4.2.3. Diagnostic imaging appropriate to tumor evaluation, using the same imaging modality, method of assessment, or technique used for baseline evaluation. Repeat diagnostic imaging will be performed after each course of therapy (approximately day 55).

3.4.2.4. Ophthalmologic examination at the completion of course 1 and again if any ocular symptoms develop, including retinal pigmentation changes. Visual acuity will be performed during each assessment.

3.4.2.5. Autoimmune Panel:

Antithyroglobulin antibody

ANA, if positive perform the ENA, if ENA positive, perform the following tests (If negative, then a sample of serum will be stored for subsequent testing in the event that the ANA becomes positive at a later date):

- Anti-phospholipid antibody
- Anti-neutrophil cytoplasm antibody
- CH50
- Anti-DNA antibody
- Anti-SSA antibody
- Anti-SSB antibody
- Rheumatoid factor (RF)

3.4.2.6. Thyroid function tests, as defined for baseline in Section 2.2.12.

3.4.2.7. Hematology (Hemoglobin, Hematocrit, Complete blood cell count with differential and platelet count (direct) and sedimentation rate, and biochemistry testing (Albumin, Alkaline phosphatase, ALT, AST, Bilirubin (total and direct), Calcium Chloride, Bicarbonate, Creatinine, Glucose, Lactate dehydrogenase (LDH), Potassium, Sodium, Total protein, Urea nitrogen (BUN), Uric acid)

3.4.2.8. Pulmonary function tests will be conducted if patients develop any clinical sign or symptom suggestive of deterioration of pulmonary function.

. 3.4.2.~~10~~ 9a. PBMC (peripheral blood mononuclear cells) sample

Peripheral blood mononuclear cells (PBMC) will be isolated and purified from samples obtained at baseline and after every course, by drawing 75 ml of blood at these times according to the schedule. In addition, 5 ml of serum will be obtained and stored at baseline and at the time of each blood draw.

TABLE 3.4.2

Schedule

	On-Study Evaluation								Follow up
Visit	2	3	4	5	6	7[7]			
Day	0	21 ±2d	42 ±2d	63 ±2d	84 ±2d	105 ±4d			Variable[1]
MDX-010 Dose (mg/kg)	3	3	3	3	3	3			
Adverse events	X	X	X	X	X	X			X
[redacted]	X	X	X	X	X	X			X
Physical examination	X	X	X	X	X	X			X
Assessment for ocular symptoms	X	X	X	X	X	X			X
Vital signs[3]	X	X	X	X	X	X			X
Performance Status	X	X	X	X	X	X			X
Ophthalmologic examination**					X				
Pulmonary Function Testing[2]									
Diagnostic imaging					X	X			X
Hematology		X	X	X	X				X
Biochemistry		X	X	X	X	X			X
Urinalysis					X				
Urine pregnancy test[4]	X	X	X	X		X			
ANA[5]					X				
Antithyroglobulin					X				
Thyroid Function Test[6]					X				
Blood sample					X				
Infusion of MDX-010	X	X	X	X		X			
Disease Response					X				X

- [1] 3-month intervals for 1 year, 6-month intervals for 2 years, and 12-month intervals until recurrence of disease
- [2] [2]PFT's will be performed if patients develop any clinical sign or symptom suggestive of deterioration of pulmonary function.
- [3] Vital signs will be monitored every 30 minutes for the duration of the MDX-010 infusion and for one hour following infusion completion, and then routinely unless otherwise indicated.
- [4] A negative urine pregnancy test will be confirmed prior to each dose of MDX-010 in women of child-bearing potential.
- [5] If ANA positive, perform the ENA. If ENA positive, perform the tests indicated in Section 3.4.2.5.
- [6] If abnormal, run full thyroid panel, including Free T3 and Total T4.
- [7] Subsequent Courses (after the first course) will receive MDX-010 every 3 weeks X 4 if the patient is stable or has a partial or mixed response with toxicities of grade 1 or less after the 1st course. Subsequent courses for patients with stable, partial or mixed response, or for patients with complete or partial responses that have relapsed, may be offered.

** Additional ophthalmologic exams will be performed if the patient experiences ocular symptoms.

[redacted]

3.6 Off Study Criteria:

Patients may be removed from the study in the following situations:

- Protocol violations
- Disease progression
- Subject withdrew consent
- Lost to follow up
- Death

Medarex reserves the right to discontinue any study for administrative reasons at any time. If appropriate, reimbursement for reasonable expenses will be made. Authorized physicians must notify ORKAND when a patient is taken off study.

3.7 Post Study Evaluation (Follow up):

Patients will undergo physical examination, including vital signs, blood sampling for hematological and biochemical evaluation and, as clinically indicated, chest radiography, pulmonary function, diagnostic imaging, three weeks following the last treatment, then at three month intervals for 1 year, at 6 month intervals for two years, and then at 12 month intervals or until disease progresses. Prior to termination of participation in the study, each patient will undergo physical examination, diagnostic imaging, and blood sampling for hematological, biochemical, and immune function assessments.

4.0 Supportive Care

Concomitant medications to control side effects of therapy will be given if patients have documented symptoms. Meperidine (25-50 mg) will be given intravenously if severe chilling develops. Other supportive therapy will be given as required. If patients require systemic steroid therapy they will be taken off treatment.

4.1 Acute hypersensitivity

Acute hypersensitivity reactions to MDX-010 antibody should be managed as outlined below.

- For mild symptoms: (Localized cutaneous reactions such as mild pruritis, flushing, or rash.) Decrease the rate of infusion until recovery from symptoms, remain at bedside and monitor patient; complete MDX-010 antibody infusion at the initial planned rate. Diphenhydramine 50 mg, may be administered at the discretion of the treating physician.
- For moderate symptoms: (Any symptom not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritis, flushing, rash, dyspnea, or hypotension with systolic BP >80 mmHg.) Interrupt MDX-010 antibody infusion, administer diphenhydramine 50 mg i.v., remain at bedside and monitor patient until resolution of symptoms. Corticosteroids may abrogate any immune response, but may be administered at the discretion of the treating physician. If systemic steroid therapy was not needed, then at the discretion of the treating physician, MDX-010 infusion may be resumed after recovery of symptoms. At the discretion of the treating physician, MDX-010 antibody infusion may be resumed at one half the initial infusion rate, then increased incrementally to the initial infusion rate. If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional MDX-010 should be administered. At the discretion of the treating physician, additional oral or i.v. antihistamine may be administered.
- For severe symptoms: (Any reaction such as life threatening bronchospasm, systolic blood pressure <80 mm Hg, or angioedema.) Immediately discontinue infusion of MDX-010 and initiate appropriate therapy (potentially to include epinephrine 1 mg i.v. or subcutaneously and/or diphenhydramine 50 mg i.v. or solumedrol 100 mg i.v.) as needed. Monitor patient until resolution of symptoms. No further MDX-010 will be administered.

4.2 Delayed hypersensitivity reactions

In case of late-occurring hypersensitivity symptoms (e.g., appearance within one week after treatment of a localized or generalized pruritis), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

4.3 Treatment of ≥ Grade III Autoimmune Adverse Events

For **skin-related** ≥ Grade III autoimmune toxicity, including severe generalized pruritis or rash, symptomatic treatment will be given. The types of therapy may include local skin care, antihistamines, or corticosteroids (which can be local/topical or systemic) as clinically indicated. At the discretion of the principal investigator, patients experiencing a skin-related autoimmune toxicity ≥ Grade III who have not required systemic steroids may resume MDX-010 once the skin symptoms improve (see Section **3.3.1**). Patients who require systemic steroid therapy will not receive further treatments with MDX-010.

Treatment for **non-skin-related** autoimmune adverse events ≥ Grade III will be prescribed as clinically indicated depending on the severity of the symptoms and/or physical manifestations. Treatment may include oral, locally-delivered (e.g., per rectum) or i.v. steroids and/or other supportive care. No further doses of MDX-010 will be given once a patient develops a ≥ Grade III non-skin-related autoimmune adverse event attributable to the investigational agents or if the patient requires systemic steroid therapy.

4.4 Treatment of ≥ Grade III Non-autoimmune-mediated Adverse Events

Treatment for any ≥ Grade III adverse event not felt to be due to an autoimmune process may be treated as clinically indicated. No further doses of MDX-010 will be given once a patient experiences a non-skin-related ≥ Grade III adverse event attributable to the investigational agents.

4.5 Treatment of Any Ocular Toxicity

Patients who report any visual symptom will be immediately referred to an ophthalmologist. Upon evaluation by the ophthalmologist, the patient will be treated as deemed appropriate by the ophthalmologist, including peri-ocular steroid injections or steroid eyedrops if necessary. No further doses of MDX-010 will be given once a patient experiences an autoimmune ocular toxicity attributable to the investigational agents.

5.0 Data Collection and Evaluation

5.1 Data Collection

Investigators or designee must enter the information required by the protocol onto the Medarex Case Report Forms (CRFs). Medarex monitors, or their designee, will review the CRFs for completeness and accuracy, and instruct site personnel to make any required corrections and/or additions. Once the CRFs are completed and all queries are resolved they will be placed in a Medarex central database for data management.

Data items from the CRFs will be entered into the study database using electronic data capture. The information entered into the database will be systematically checked using error messages printed from validation programs and database listings. Errors or omissions will be queried and returned to the investigational site for resolution. Quality control audits of the database will be made after entering data from each visit.

Concomitant medications, coexistent diseases and adverse events will be appropriately coded.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time will only be made by joint written agreement between the Medarex Clinical Trial Leader, the Trial Statistician and the Data Manager.

5.2 Data Safety and Monitoring Plan

Careful evaluation to ascertain the toxicity and anti-tumor efficacy of therapy will be performed. The principal investigator will monitor the data and toxicities to identify

trends. The principal investigator will be responsible for revising the protocol as needed to maintain safety. The NCI IRB will review submitted adverse events monthly to also evaluate trends and will require a follow up plan from the principal investigator whenever a trend is identified.

5.3 Response Criteria:

5.3.1 Clinical Response

5.3.1.1 Evaluation of target lesions[1]

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.
Progression (PD):	At least a 20% increase in the sum of 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 references the smallest sum LD.

5.3.1.2 Evaluation of non-target lesions[2]

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level.
Non-Complete Response:	Persistence of one or more non-target lesions
Progression (PD):	Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions.

5.3.1.3 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.

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1 All measurable lesions up to a maximum of 10 lesions 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 repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

5.3.1.4 Confirmatory Measurement/Duration of Response

Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed at least 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6-8 weeks.

5.3.1.5 Duration of overall response

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

5.3.1.6 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.

5.4 Toxicity Criteria:

Information about all adverse events, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Case Report Form and followed, as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study treatment, even if the experience is not considered to be treatment-related.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment. Clinical experiences occurring

before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Case Report Form. Abnormal laboratory values or test results inducing clinical signs or symptoms are recorded on the Adverse Events Case Report Form under the signs, symptoms or diagnoses associated with them.

As far as possible, each adverse event will also be described by: its duration (start and end dates), the severity grade (Cancer Therapy Evaluation Program Common Toxicity Criteria, CTC AE 3.0, located on the internet at http://ctep.cancer.gov/reporting/ctc.html) and its relationship to treatment (unrelated/unlikely/possible/probable/definite), and the action(s) taken.

Serious adverse events

Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report Form. To ensure patient safety, each of such serious adverse events must also be reported to Medarex within 24 hours of learning of its occurrence.

A serious adverse event is defined in general as an untoward (unfavorable) experience which:

- Is fatal or life-threatening,
- Requires or prolongs hospitalization,
- Is significantly or permanently disabling or incapacitating,
- Constitutes a congenital anomaly or a birth defect,
- Jeopardizes the patient and may require medical or surgical intervention to prevent one of the outcomes listed above
- Is ≥ grade 4 severity hematological adverse event
- Is ≥ grade 3 severity non-hematological adverse event
- Is ≥ grade 3 severity infusion adverse event (occurring ≤24 hours after start of infusion)

Events not considered to be serious adverse events are: hospitalizations occurring under the following circumstances--planned before entry into the clinical study, for elective treatment of a condition unrelated to the studied indication or its treatment, or part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition; events occurring on an emergency, outpatient basis that do not result in admission (unless fulfilling the criteria above).

This study will utilize the CTC AE 3.0 for toxicity and adverse event reporting. A copy of the CTC AE 3.0 can be downloaded from the CTEP web site: http://ctep.cancer.gov/reporting/ctc.html. All appropriate treatment areas should have access to a copy of the CTC AE 3.0.

5.5 Statistical Section:

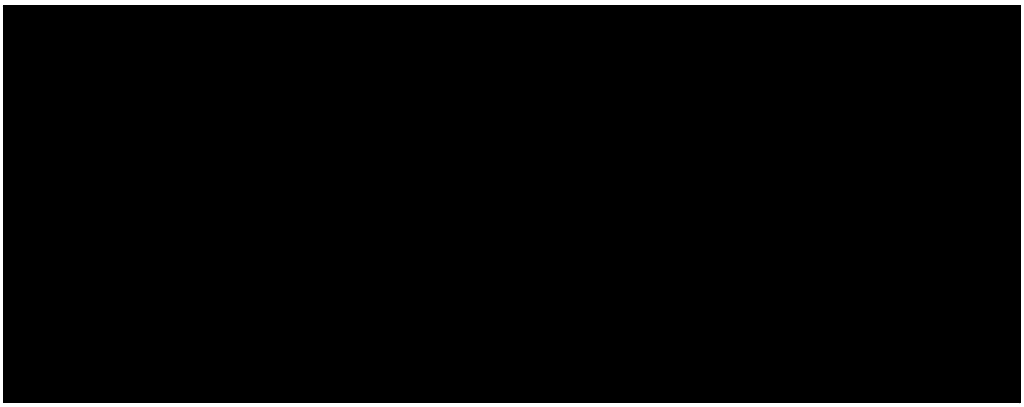
The primary objective of this study is to determine whether single agent MDX-010 antibody is able to result in clinical responses (PR or CR) in patients with stage IV pancreatic cancer. Our experience with MDX-010 in the melanoma and renal cell population has shown a correlation between autoimmune toxicity and tumor response.

For each of the two groups, this trial will be conducted as a Phase II clinical trial using an optimal design [redacted] The trial will seek

to rule out an undesirably low response probability of 5% (p0=0.05) in favor of a level which demonstrates potentially useful activity of 20% (p1=0.20). With an alpha=0.05 (5% probability of accepting a poor combination, and beta=0.10 (10% probability of rejecting a good combination), initially 21 patients will be enrolled. If 0-1 of 21 have a clinical response as defined in section 5.3, then accrual will stop and we will conclude that the combination is not sufficiently active in the disease being studied. If 2+/21 patients respond, then accrual will continue until 41 patients have been enrolled. If 2-4 of 41 respond, this will be insufficient activity to warrant further evaluation. If 5+/41 have documented clinical responses, the agent will be considered active in pancreatic carcinoma. Under this design if the null hypothesis were true (5% true response probability), there is a 72% probability of early termination.

It is expected that it will require 2-4 years to accrue up to 82 evaluable patients.

6.0 Human Subjects Protections



6.2 Participation of children

Minors will not be treated in this study.

6.3 Evaluation of Benefits and Risks/Discomforts

The patients to be entered in this protocol have locally advanced and metastatic cancer and limited life expectancies. The experimental treatment has a chance to provide clinical benefit though this is unknown. All possible benefits and risks will be carefully explained to all patients and informed consent documents will be signed by the patient prior to entrance into the protocol.

6.4 Consent and assent processes and documentation

All patients are thoroughly screened prior to admission onto this study. During this time, the patient, along with family members, will be presented with a detailed description of the protocol treatment. The specific requirements, objectives, advantages and disadvantages will be presented. The Informed Consent document is given to the patient and they are asked to review it and ask questions prior to agreeing to participate in this protocol. The patient is reassured that participation on this trial is entirely voluntary and

that they can withdraw or decide against treatment at any time without adverse consequences. The Principal Investigator, senior physician, research nurse or medical staff fellow under the supervision of the PI is responsible for completing the consent process and a copy of the consent is offered to the patient.

7.0 Data Reporting

7.1 Definition of serious adverse events

A serious adverse event is defined as an untoward (unfavorable) experience, which meets any of the following criteria:

- Is fatal or life-threatening
- Requires or prolongs hospitalization
- Is significantly or permanently disabling or incapacitating
- Constitutes a congenital anomaly or a birth defect
- Jeopardizes the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

7.2 Reporting responsibility

Any serious adverse event occurring in a patient after providing informed consent, while receiving study treatment, and until four (4) weeks after stopping study treatment must be reported. The period after discontinuing study treatment may be extended if there is a strong suspicion that the drug has not yet been eliminated. All serious adverse events must also be reported for the period in which the study interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Each serious adverse event must be reported by the investigator to Medarex within 24 hours of learning of its occurrence, even if it is not treatment-related. Each serious adverse event must also be reported to NCI IRB.): The NCI AE form will be used for submitting adverse events on this study within 24 hours to the NCI IRB e-mail address, with a written report to follow in 10 working days.

Follow-up information about a previously reported serious adverse event must also be reported to Medarex. If the serious adverse event has not been previously documented (new occurrence) and it is thought to be related to study drug, an investigator alert, to inform all investigators involved in any study with the same drug that this serious adverse event has been reported, may be issued.

7.3 Reporting procedures

The investigator must complete the Serious Adverse Event Report Form in English. Serious adverse events are graded using the Cancer Therapy Evaluation Program Common Toxicity Criteria, CTC AE 3.0, located on the Internet at http://ctep.cancer.gov/reporting/ctc.html. Adverse events not included in the Cancer Therapy Evaluation Program Common Toxicity Criteria, CTC AE 3.0 must be reported according to the definitions in Section 7.4.

The investigator must report serious event information to the NCI IRB and Medarex and send a completed SAE form by facsimile transmission within 24 hours to the NCI IRB and Medarex [redacted] or their designee.

Follow-up information is sent to the same person to whom the original Serious Adverse Event Form was sent, re-stating the date of the original report. Either a new Serious Adverse Event Form is sent (stating that this is a follow-up), or the original one resent (with the new information highlighted and a new date provided). The follow-up must describe whether the experience has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The form and facsimile transmission confirmation sheet must be retained.

Contact persons and numbers - The telephone and facsimile transmission numbers of study related personnel are listed in the investigator folder provided for each individual site.

Questions referring to a specific serious adverse event occurring in a study patient should be directed to the local clinical development contact person or as specified in the investigator folder provided for the site. Questions concerning the facsimile transmission of a Serious Adverse Event Form should be directed to Medarex or their designee.

7.4 Instructions for completing adverse event case report form

Adverse event: Any unfavorable symptom, sign, or disease (excluding an abnormal laboratory finding) temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. Syndromes, when diagnosed by a physician, are reported as adverse events.

Each adverse event is to be reported on an Adverse Event Case Report Form. As far as possible, each adverse event must also be described by:

- Its duration (start and end dates)
- Its severity grade its relationship to treatment
- Its relationship to treatment
- The action(s) taken

Adverse events are graded using the Cancer Therapy Evaluation Program Common Toxicity Criteria, CTC AE 3.0 (located on the Internet at http://ctep.cancer.gov/reporting/ctc.html). Adverse events not included in the Cancer Therapy Evaluation Program Common Toxicity Criteria, CTC AE 3.0 must be reported and graded according to the definitions provided below.

General grade definitions for severity of adverse events	
Grade	Quality
0	No adverse event or within normal limits
1	Mild adverse event
2	Moderate adverse event
3	Severe undesirable adverse event
4	Life threatening or disabling adverse event

5	Death related to adverse event

Attribution of adverse event: Assign attribution of each adverse event using the criteria provided in the table below.

General definitions for attribution of adverse events		
Code	Descriptor	Definition
5	Definite	The adverse event is clearly related to the investigational agent(s)
4	Probable	The adverse event is likely related to the investigational agent(s)
3	Possible	The adverse event is possibly related to the investigational agent(s)
2	Unlikely	The adverse event is doubtfully related to the investigational agent(s)
1	Unrelated	The adverse event is clearly not related to the investigational agent(s)

Action(s) taken: Assign actions taken in response to an adverse event using the criteria provided in the table below.

General definitions for actions taken in response to an adverse event	
Code	Action
0	No action taken
1	Study drug dosage adjusted / temporarily interrupted
2	Study drug permanently discontinued due to this adverse event
3	Concomitant medication taken
4	Non-drug therapy given
5	Hospitalization / prolonged hospitalization

7.5 Recording of data and retention of documents

Data on patients collected on CRFs during the trial will be documented in an anonymous fashion and the patient will only be identified by the patient number, and by his/her initials if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the patient, both Medarex and the investigator are bound to keep this information confidential.

All the information required by the protocol must be provided and any omissions require explanation. All CRFs must be completed and available in a timely fashion, preferable no more than five (5) days after the patient's visit, so that the monitor may check the entries for completeness, accuracy and legibility, ensure the CRF is signed by the investigator and transmit the data to Medarex.

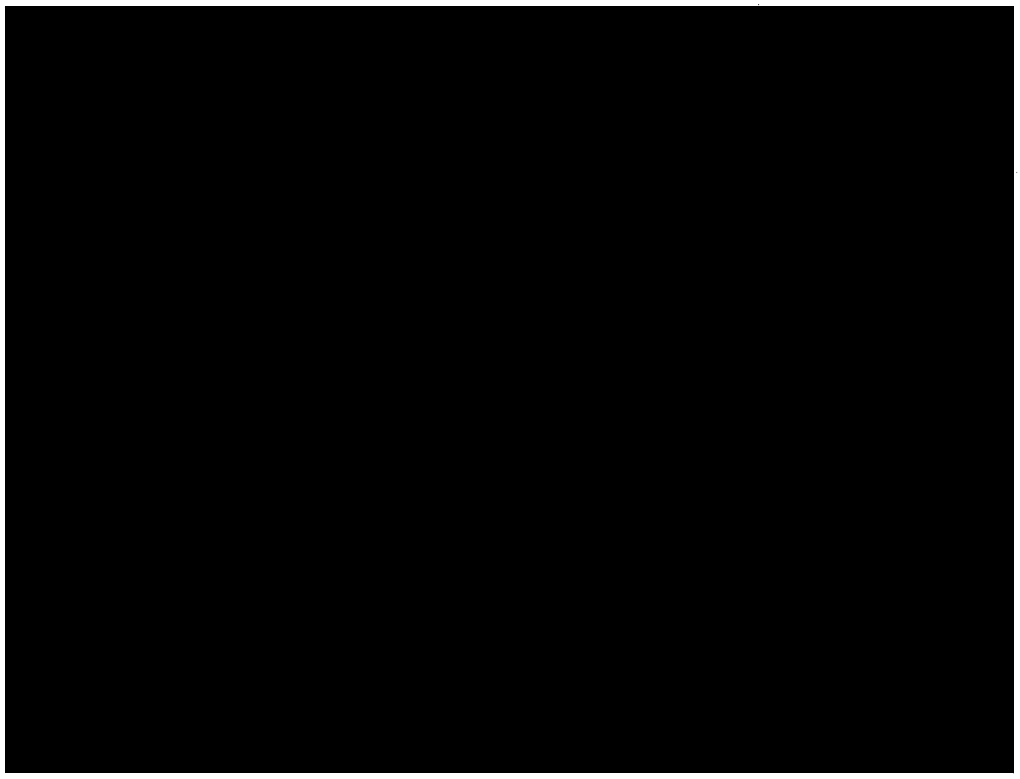
The investigator must maintain source documents for each patient in the study. All information on CRFs must be traceable to these source documents, which are generally maintained in the patient's file. The source documents must contain all demographic and medical information, including laboratory data, electrocardiograms, etc., as well as a copy of the signed informed consent form, which must indicate the study number and title of the trial.

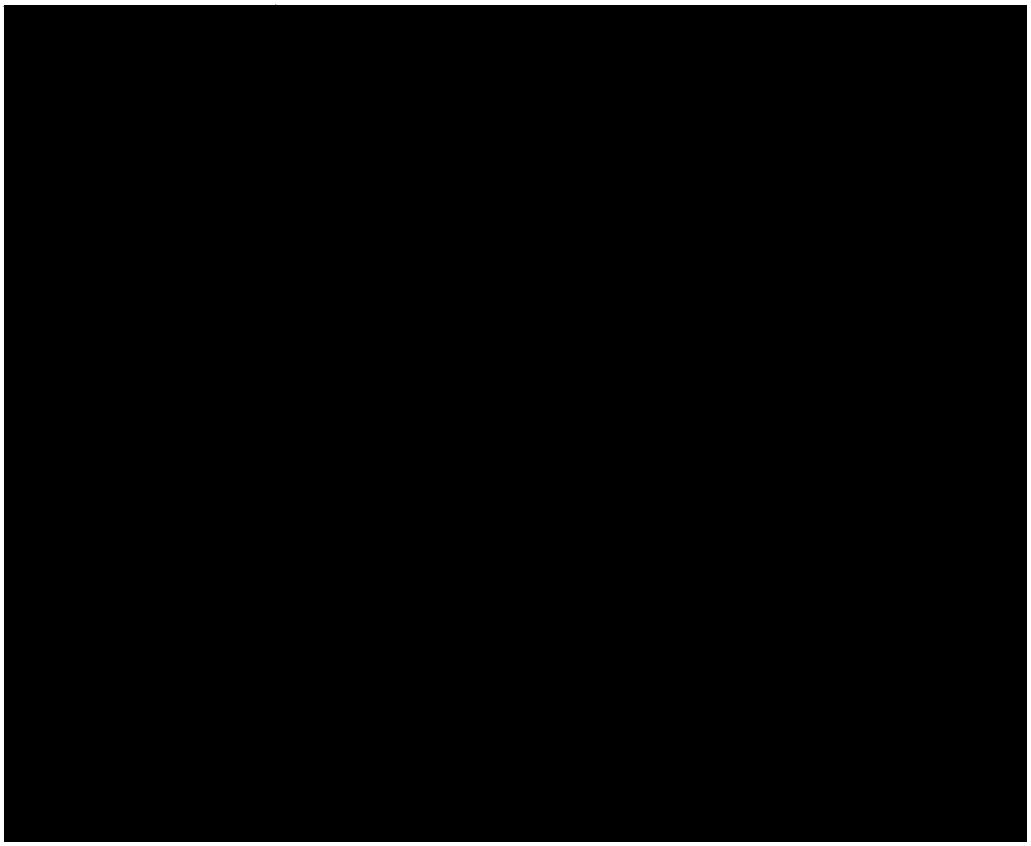
The investigator must retain essential documents, listed below, as long as needed to comply with national and international regulations (generally two years after discontinuing clinical development or after the last marketing approval). Medarex will notify the investigator(s)/institution(s) when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

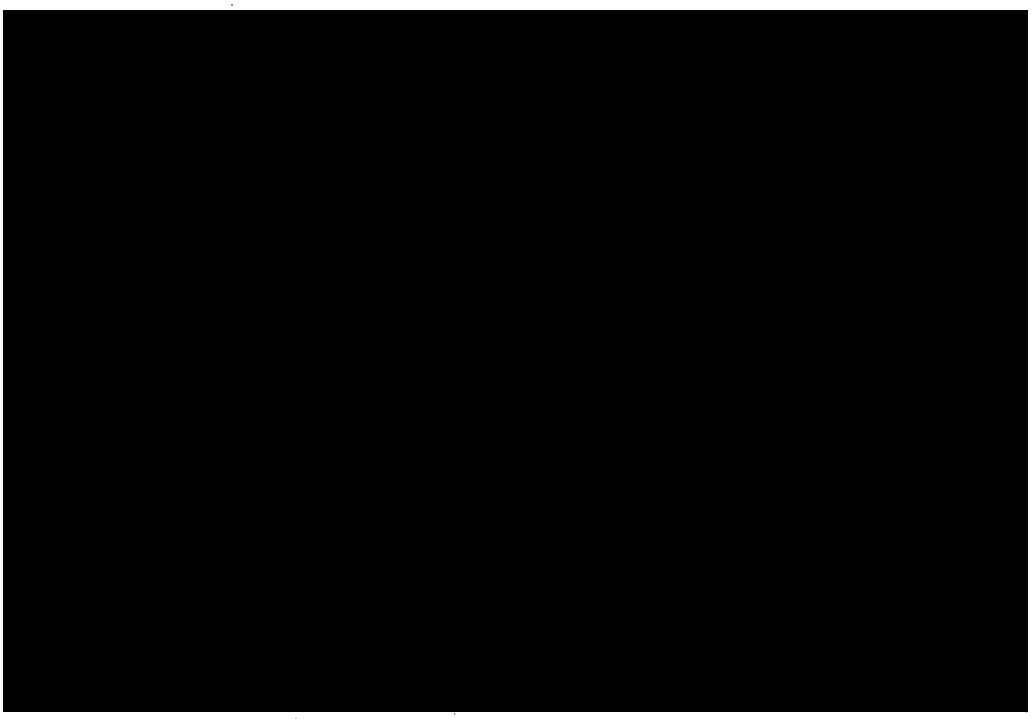
- IRB/IEC approvals for the study and all amendments to protocol
- All source documents and laboratory records
- CRF copies
- Patients' informed consent forms
- FDA form 1572
- Any other pertinent study document

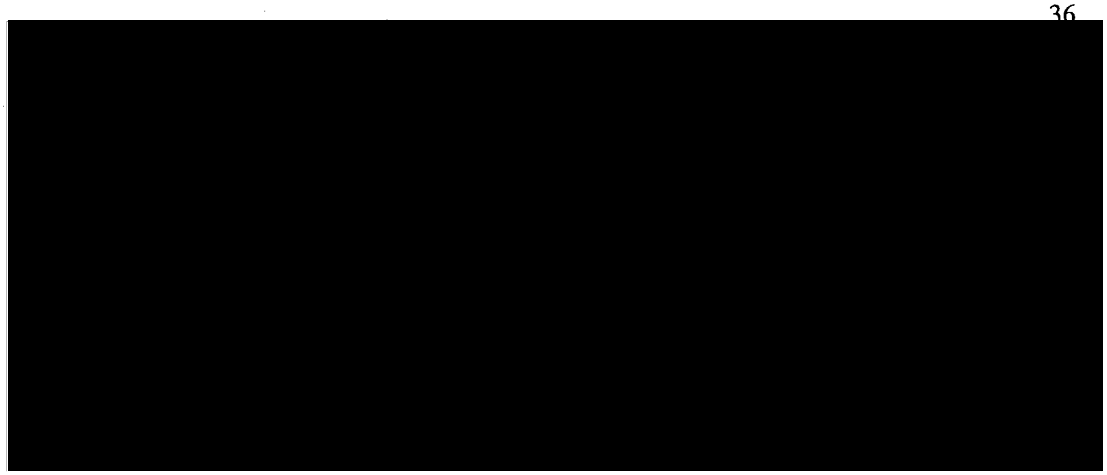
7.6 Auditing procedures

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance audit may be conducted. This audit of clinical research activities is conducted to evaluate compliance with internal SOPs, and with the principles of Good Clinical Practice. A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If a regulatory authority requests an inspection, the investigator must inform Medarex immediately that this request has been made.









9.0 Administrative requirements

9.1 Publication of results

Any formal presentation or publication of data collected from this trial will be considered as a joint publication by the investigator(s) and the appropriate personnel of Medarex. Authorship will be determined by mutual agreement.

Medarex must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 days for a journal submission). Medarex will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), and to provide any relevant supplementary information. Authorship of communications arising from pooled data will include members of each of the contributing centers as well as Medarex personnel.

9.2 Administrative procedures

9.2.1 Changes to the protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by Medarex and the investigator before implementation. Amendments significantly affecting the safety of patients, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB of all centers, and, in some countries, by the regulatory authority. A copy of the written approval of the IRB, which becomes part of the protocol, must be given to the Medarex monitor or their designee. Examples of amendments requiring such approval are:

- Increase in drug dosage or duration of exposure of patients
- Significant change in the study design (e.g. addition or deletion of a control group)
- Increase in the number of invasive procedures to which patients are exposed
- Addition or deletion of a test procedure for safety monitoring.

These requirements for approval must in no way prevent any immediate action from being taken by the investigator or by Medarex in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented by him/her for safety reasons Medarex must be notified and the IRB at the center must be informed within 10 working days.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB of each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval that can be treated as administrative amendments include:

- Changes in the staff used to monitor trials (e.g. Medarex staff versus a CRO)
- Minor changes in the packaging or labeling of study drug.

9.2.2 Monitoring procedures

Before study initiation, at a site initiation visit or at an investigator's meeting, a Medarex representative will review the protocol and case report forms (CRFs) with the investigator(s) and their staff. During the study the Medarex monitor or their designee will visit the site regularly, to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and also to ensure that study medication is being stored, dispensed and accounted for according to specifications. The investigator and key trial personnel must be available to assist the Medarex monitor during these visits.

The investigator must give the monitor access to relevant hospital or clinical records, to confirm their consistency with the CRF entries. No information in these records about the identity of the patients will leave the study center. Medarex monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs and the recording of primary safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

The investigator is responsible for completing the CRFs in a timely fashion, preferably within five (5) days of the patient's visit and the Medarex monitor is responsible for reviewing them and clarifying and resolving any data queries. A copy of the CRFs is retained by the investigator, who must ensure that it is stored with other study documents, such as the protocol, the investigators brochure and any protocol amendments, in a secure place.