MEDAREX

Statistical Analysis Plan

Product Name (No.): MDX-010

Protocol No.: MDX010-24

A phase II trial of single agent ipilimumab (MDX-010 anti CTLA-4) for subjects with locally advanced or metastatic pancreatic adenocarcinoma

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1. Introduction

This statistical analysis plan (SAP) reflects the analysis of protocol MDX010-24 as amended up to Amendment D. This SAP is being written with consideration of the recommendations outlined in the International Conference on Harmonization (ICH) Guidelines E3 (Structure and Content of Clinical Study Report) and E9 (Statistical Principles for Clinical trials).

The primary objective of this study is to assess the efficacy of ipilimumab. However, the study was terminated. So the efficacy data from this study will not be analyzed. This analysis plan will focus on analysis of subject safety information.

2. Study Description

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is to assess the clinical response (partial response (PR) and complete response (CR)) to ipilimumab as a single agent in subjects with locally advanced pancreatic adenocarcinoma.

2.2 Study Design

2.2.1 Overview

This is an open-label study of repeated doses of a human monoclonal antibody (mAb) to CTLA-4 (ipilimumab) administered to subjects with advanced pancreatic adenocarcinoma. It is designed to determine if a dose of ipilimumab at 3 mg/kg administered every 3 weeks can cause tumor regression. Subjects with measurable unresectable pancreatic carcinoma will be enrolled in two groups: locally advanced, unresectable disease group and metastatic disease group.

The study consists of three phases: Screening, Treatment, and Follow-up as shown in Table 1.

Table 1: Study Design

Phase	Screening	Treatment					Eval & follow-up
Visit	1	2	3	4	5	6[3]	variable[1,2]
Day(s)	-28 to 0	0	21 ±2d	Eval & 42 ±2d	63 ±2d	Eval & 84 ±2d	variable[1]
MDX-010		X	X	X	X	X	

1: 3-month intervals for 1 year, 6-month intervals for 2 years, and 12-month intervals until recurrence of disease.
2: Up to 2 subsequent courses of 4 infusions each ipilimumab (every 3 weeks x 4) may be given to subjects with complete or partial responses that have relapsed (PD).
3: A second course of 4 additional infusion ipilimumab (every 3 weeks x 4) may be given if the subject shows toxicities of grade 1 or less after the first course.

Four doses will be designated as a course of therapy and evaluations will be conducted at the end of each course. 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. A second course of treatment may be offered to subjects with progressive disease who tolerate the first course of treatment and are willing to undergo a second course of treatment with ipilimumab rather than pursue an alternate therapy at that time.

Treatment will be limited to 2 courses of therapy. Subjects that respond (PR or CR) and subsequently relapse will be treated with up to 2 additional courses of therapy. Subjects may come off study at any time if rapid disease progression occurs.

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

2.3 Study Procedures and Schedule

2.3.1 Overview

Subjects with measurable unresectable pancreatic carcinoma will be enrolled in two groups. One group of subjects will have locally advanced, unresectable disease. The second group of subjects will have metastatic disease that is distant to the draining lymph nodes.

In this study, subjects will receive 3 mg/kg ipilimumab antibody intravenously every three weeks. Four doses will be designated as a course of therapy and evaluations will be conducted at the end of each course.

2.3.2 Screening Phase and Baseline

The Screening Phase was defined as the period prior to administration of study drug.

Baseline is defined as the last measurement before the first dose of study drug unless otherwise indicated.

2.3.3 Treatment Phase /Retreatment Cycle

Four doses will be designated as a course of therapy and evaluations will be conducted at the end of each course, three weeks after the 4th infusion. An informal interim evaluation may be performed three weeks after the 2nd infusion to rule out rapid disease progression, but the formal evaluation with tumor measurements will be performed approximately three 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. A second course of treatment may be offered to subjects with progressive disease who tolerate the first course of treatment and are willing to undergo a second course of treatment with ipilimumab rather than pursue an alternate therapy at that time. Treatment will be limited to 2 courses of therapy. Subjects that respond (PR or CR) and subsequently relapse will be treated with up to 2 additional courses of therapy. Subjects may come off study at any time if rapid disease progression occurs. Subjects in the locally advanced disease group may experience sufficient

tumor response that their disease is rendered resectable. If this occurs, these subjects will be treated with standard pancreatic resection rendering them NED (no evidence of disease).

2.3.4 Follow-up Phase

Subjects will undergo physical examination, including vital signs, blood sampling for hematological, biochemical and HAHA 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.

2.3.5 Study Completion/Early Withdrawal Visit

Prior to termination of participation in the study, each subject will undergo physical examination, diagnostic imaging, and blood sampling for hematological, biochemical, and immune function assessments.

2.3.6 Study Flow Chart

Table 2: Schedule of Assessments, Day 0 through Termination of Participation

Schedule						
	On-Study Evaluations					Follow-up
Visit	2	3	4	5	6[7]	Variable[1,8]
Day	0	21 ±2d	42 ±2d	63 ±2d	84 ±2d	
MDX-010 Dose (mg/kg)	3	3	3	3	3	
Adverse events	X	X	X	X	X	X
[redacted]	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X
Assessment for ocular symptoms	X	X	X	X	X	X
Vital signs[3]	X	X	X	X	X	X
Performance Status	X	X	X	X	X	X
Ophthalmologic examination**					X	
Pulmonary Function Testing[2]					X	X
Diagnostic imaging					X	X
Hematology		X	X	X	X	X
Biochemistry (including amylase and lipase)		X	X	X	X	X
Urinalysis					X	X
Pregnancy test[4]	X	X	X	X	X	
ANA[5]					X	
Antithyroglobulin					X	
Thyroid Function Test[6]					X	
Blood (PBMC) sample					X	
PK sample[9]	X			X		
HAHA sample[10]	X				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 ecurrence of disease.
2: PFT's will be performed if subjects develop any clinical sign or symptom suggestive of eterioration of pulmonary function..
3: Vital signs will be monitored every 30 minutes for the duration of the ipilimumab infusion and for one hour following infusion completion, and then routinelyunless otherwise indicated.
4: A negative pregnancy test will be confirmed prior to each dose of ipilimumab in women of childbearing potential; refer to section 2.2.7 C of the protocol.
5: If ANA positive, perform the EBA. If ENA positive, perform the tests indicated in Section 3.4.2.5 of the protocol.
6: If abnormal, run full thyroid panel, including Free T3 and Total T4.
7: A second course of 4 additional infusion ipilimumab (every 3 weeks x 4) may be given if the subject shows toxicities of grade 1 or less after the first course.
8: Up to 2 Subsequent courses of 4 infusions each ipilimumab (every 3 weeks x 4) may be given to subjects with complete or partial responses that have relapsed (PD).
9: For 5 subjects in each group, blood samples (5 mL) for the analysis of plasma concentrations of ipilimumab will be drawn prior to the 1st and 4th doses of ipilimumab and again at 1 hour post-infusion.
10: For 5 subjects in each group, blood samples (1 mL) for the analysis of HAHA will be drawn at baseline and 3 weeks after the last infusion of the subject's last course of treatment.
**: Additional ophthalmologic exams will be performed if the subject experiences ocular symptoms

3. Study Populations

3.1 Safety Population

Safety population includes all subjects in the study who received at least 1 dose or any partial dose of study medication.

4. Analysis Parameters

4.1 Safety Parameters

The safety parameters include treatment emergent adverse events (TEAE), immune related adverse events (irAE), clinical laboratory tests (hematology, biochemistry, urinalysis, pregnancy test, antinuclear antibody (ANA), autoimmune panel, antithyroglobulin, thyroid function tests, HAHA (5 subjects in each group), etc.), ophthalmologic examination, pulmonary function test, vital sign measurements, ECOG, and physical examinations, etc.

[redacted]

4.3 Other Parameters

Other parameters include ECG and chest X-ray.

5. Statistical Method

All data collected in this study will be analyzed by the Biostatistics group in Medarex, Inc. or its designees.

All data will be listed individually. For quantitative parameters, descriptive statistics will include the mean, standard deviation, minimum, median, and maximum. For qualitative parameters, descriptive statistics will include the frequency and percentage.

5.1 General Statistical Considerations

Unless otherwise indicated, the statistical significance will be declared if the two-sided p-value is ≤ 0.05.

5.2 Protocol Violations

Any protocol violations that impact clinical activity were determined by the investigator and Medarex medical monitor.

5.3 Sample Size Determination

The primary objective of this study is to assess the clinical response of partial response (PR) or complete response (CR) to ipilimumab as a single agent in subjects with locally advanced pancreatic adenocarcinoma. This trial was 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% (p_0=0.05) in favor of a level which demonstrates potentially useful activity of 20% (p_1=0.20). With α=0.05 and β=0.10. Initially 21 subjects will be enrolled. If $\leq$1 out of 21 subjects has an objective response (confirmed CR or PR), then accrual will stop and it will conclude that the treatment is not sufficiently active. If $\geq$2 out of 21 subjects demonstrate objective responses, then accrual will continue until 41 subjects have been enrolled. In the second stage, if 2-4 of 41 subjects respond, this will be insufficient activity to warrant further evaluation. If $\geq$5 of 41 subjects have documented objective responses, the treatment will be considered active in pancreatic carcinoma.

5.4 Disposition of Subjects

The frequency (number and percentage) of subjects in safety population will be presented. The frequency of reasons for discontinuation will also be presented.

5.5 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics including age, sex, race, height, weight, time since diagnosis, cancer stages, medical history, prior therapies, prior surgeries, etc. will be summarized by group.

5.6 Study Drug Exposure

The MDX-010 total dosage (mg) and number of doses will be summarized by group using descriptive statistics.

[redacted]

5.8 Efficacy Analysis

Efficacy analysis will not be performed.

5.9 Safety Analysis

5.9.1 Adverse Events

All adverse events (AEs) and serious adverse events (SAEs) as documented by the investigator will be coded using the version 10.1 of Medical Dictionary for Regulatory Activities (MedDRA™).

Treatment-emergent adverse event (TEAE) is defined as an adverse event that emerges during treatment or within 70 days of the last dose of the study drug including the retreatment cycles, having been absent pre-treatment or worsens relative to the pre-treatment state. Any study drug related AEs will also be treated as TEAEs regardless of the start date. All adverse events regardless of being treatment emergent or not will be displayed in the AE listings. The treatment emergent AEs will be summarized using descriptive statistics. The non treatment emergent AEs will be listed separately.

An overview summary of subjects with any AE, any severe AE, any study drug related AE, any serious AE will be presented in a table. AEs will also be summarized in other tables as sorted by 1) system organ class and preferred term; 2) Grade 3 or above AEs by system organ class and preferred term; 3) Serious AEs by system organ class and preferred term; 4) system organ class, preferred term, and severity; 5) Serious AEs by system organ class, preferred term, and severity; 6) system organ class, preferred term, and relationship to study drugs; 7) system organ class, preferred term, severity and relationship to study drugs; and 8) Serious AE by system organ class, preferred term, severity and relationship to study drugs. In addition, the immune related AEs will be summarized by system organ class and preferred term.

5.9.2 Vital Signs

The observed vital signs (temperature, systolic and diastolic blood pressures, pulse rate, and respiration rate) at each visit and change from baseline to each post-baseline visit will be summarized by group using descriptive statistics.

5.9.3 Clinical Laboratory Tests

Clinical laboratory test values outside the normal range will be flagged in the data listing.

Laboratory data (hematology, biochemistry, urinalysis, pregnancy test, antinuclear antibody (ANA), autoimmune panel, antithyroglobulin, thyroid function tests, etc.) will be

summarized by group for scheduled visits based on individual visit values as well as change from baseline. Shift tables from baseline to post-baseline visits will also be presented.

5.9.4 Physical Examination

The abnormal findings in physical examination will be summarized by group using descriptive statistics.

5.9.5 Diagnostic Tests

Diagnostic test results (including ophthalmologic examination, ECG, chest radiograph, autoimmune panel, and thyroid function test, etc.) will be summarized by group using descriptive statistics.

5.10 Deviation from Protocol

The trial used the Simon two-stage optimal design [redacted] If at most one of 21 subjects enrolled in the first stage have a clinical response, then accrual will stop and we will conclude that the treatment is not sufficiently active in the disease being studied. If two or more of the 21 subjects respond, then accrual will continue until 41 subjects have been enrolled.

There was no clinical response in the first stage, so the trial was terminated.

The primary objective of this study is to assess the efficacy of ipilimumab. The planned efficacy analysis in protocol include: evaluation of target lesions and non-target lesions, evaluation of best overall response, duration of overall response and duration of stable disease. However, the study was terminated. So the efficacy data from this study will not be analyzed. The statistical analysis will be focused on subject safety information.

6. Data Imputation Rules

6.1 Missing and Partial Missing Adverse Event Data

Under certain circumstances, partially missing data of AE onset date may be imputed in order to avoid eliminating information from summary tables of treatment emergent adverse event. If the day of one adverse event onset date is missing but the month and year are available, the adverse event could be flagged as treatment emergent as long as the date being estimated within 70 days after the last dose of MDX-010 administration. There will be no attempt to impute missing or partially missing date for the listing of adverse events.

7. Interim Analysis

There is no interim analysis.

8. Statistical Software

All statistical analyses will be performed using SAS® Version 9.1.3 or higher.

9. Appendices

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