Herbert Irving Comprehensive Cancer Center

Columbia University Irving Medical Center
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COLUMBIA

TITLE: A SINGLE ARM, MULTICENTER, PHASE II, OPEN-LABEL TRIAL TO EVALUATE EFFICACY OF ISATUXIMAB IN PATIENTS WITH MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE

ClinicalTrials.gov ID: NCT04614558

Protocol version date: 09/28/2022

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Protocol Synopsis

Title	A Single Arm, Multicenter Phase II, open label trial to evaluate efficacy of Isatuximab in patients with monoclonal gammopathy of renal significance
Short Title	Isatuximab for therapy of MGRS
Phase	Phase 2
Methodology	Open label single arm
Study Duration	Patient will get therapy for a total of 6 months duration on the protocol. Overall given the time requirement for enrollment we anticipate the study to take about 2 years from the start of enrollment to the last patient finishing the treatment.
Study Center(s)	Two
Objectives	The primary objective is to evaluate the efficacy of Isatuximab in patients with MGRS 1. Primary Objective is to evaluate the efficacy of Isatuximab to improve renal dysfunction in patients with MGRS. 2. Secondary Objectives a) Establish safety of Isatuximab in patients with MGRS b) Determine molecular basis of MGRS by performing next generation sequencing of immunoglobulin heavy and light chain genes in plasma cells of patients with MGRS
Number of Subjects	27

Study Product, Dose, Route, Regimen	Isatuximab IVPB 10 mg/kg qweekly for 4 doses and then every 2 weeks thereafter for a total of 6 months
Duration of administration	3 hours
Statistical Methodology	We will use Bayesian toxicity and Bayesian Futility rules to conduct the study. The study will be a single arm, prospective, multi-center, phase II, open- label study including 27 subjects in total. The study will consist of a screening phase, treatment phase, post-treatment observation phase and follow-up phase. The subjects will receive Isatuximab in IV form (10mg/kg q weekly x 4 doses followed by 10mg/kg q2weeks) for a total of 6 month duration. Overall we expect to complete the accrual in and therapy in 2 years in all the subjects. Patients will be followed for an additional one year post therapy for outcome follow-up. Our primary objective is to evaluate the efficacy of Isatuximab in patients with MGRS. We will measure this by patient response by once a month during the treatment phase and every 2 months for 12 months after treatment completion. Response is defined in two ways: a "Complete renal response" (Decrease in 24 hour urine proteinuria to <500mg/24 hours), and a "Partial renal response" (Decrease in 24 hour urine proteinuria >50% from baseline) (see 13.2 Determination of organ response). From our historical data, the historical response rate for therapies used for MGRS like disorders is around 30%, and we hypothesize that we will see a response of 55%, and a sample size of 27 subjects gives us 80% power to detect this difference, based on a one-sided one proportion Z-test at 0.05 significance.

1. STUDY OBJECTIVES

1.1 Primary Objective

a) The primary objective is to evaluate the efficacy of Isatuximab in patients with MGRS.

1.2 Secondary Objective

c) Establish safety of Isatuximab in patients with MGRS

d) Determine molecular basis of MGRS by performing next generation sequencing of immunoglobulin heavy and light chain genes in plasma cells of patients with MGRS

2. BACKGROUND

Renal disease is frequently seen in plasma cell disorders and is typically mediated by either a tubular crystallization of light chain (cast nephropathy) which is typically seen as part of the diagnosis of multiple myeloma characterized by a relatively high tumor mass leading to production of a high burden of light chains which cause the renal pathology. The second group is the renal diseases associated with low grade lymphoproliferative disorders which can include indolent B-cell lymphoid disorder, including the so-called 'smoldering' asymptomatic MM and low-grade lymphoplasmacytic lymphoma with Waldenstrom's macroglobulinemia, or a monoclonal gammopathy of undetermined significance (MGUS). In this setting, structural peculiarities of the monoclonal protein, particularly the variable domain, and not the rate of production, are the main determinants of renal lesions. The disorder is characterized by deposition of immunoglobulin light or heavy chain in the kidneys leading to renal dysfunction and in many cases associated proteinuria. A kidney biopsy is typically required to make the diagnosis of these disorders. The mechanism of renal injury in these disorders are related to either direct toxicity by the deposition of the immunoglobulin in renal parenchyma or complement activation in C3 glomerulopathy.

Monoclonal gammopathy is a common disorder but only a small fraction of patients with MGUS develop renal disease and the reason for abnormal deposition of immunoglobulin in renal parenchyma remains unclear in these disorders. The proposed research will be conducted as a part of clinical trial which intends to prospectively evaluate the effect of anti-plasma cell therapy on renal outcomes in patients with monoclonal gammopathy of renal significance (MGRS). We specifically intend to sequence the immunoglobulin heavy and light chain genes to determine any abnormalities that could lead to production of a misfolded immunoglobulin thus leading to deposition in renal parenchyma.

3. INVESTIGATIONAL AGENT

Isatuximab (SAR) is an IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38 (12). CD38 is expressed on lymphoid and myeloid cells as well as in a several non-hematopoetic tissues Purkinje cells and neurofibrillary tangles in the brain, epithelial cells in the prostate, β-cells in the pancreas, osteoclasts in the bone, retinal cells in the eye, and sarcolemma of smooth and striated muscle (21). Expression of CD38 in hematopoietic cells

depends on the differentiation and activation status of the cell. Lineage-committed hematopoietic cells express the protein, while it is lost by mature cells and expressed again on activated lymphocytes. For example, the majority of medullary thymocytes show expression of CD38, circulating T cells do not express CD38, while expression is induced in activated T cells. CD38 is also expressed on B cells, whereby plasma cells express particularly high levels of CD38. Approximately 80% of resting NK cells and monocytes express CD38 at lower levels, as do various other hematological cell types, including lymph node germinal center lymphoblasts, intrafollicular cells, dendritic cells, erythrocytes, and platelets (22). In addition CD38 is universally expressed on plasma cells and present on all malignant plasma cells in multiple myeloma (23) making it an attractive target in this disease.

4. STUDY DESIGN

4.1 General Design

The study will be a single arm, prospective, multi-center, phase II, open- label study including 27 subjects in total. The study will consist of a screening phase, treatment phase, post-treatment observation phase and follow-up phase. The subjects will receive Isatuximab in IV form (10mg/kg q weekly x 4 doses followed by 10mg/kg q2weeks) for a total of 6 month duration. Overall we expect to complete the accrual in 2 years and complete therapy on all the subjects at 33 months on all patients. Patients will be followed for an additional one year post therapy for outcome follow-up.

4.2 Number of Participants

A total of 27 subjects will be enrolled in the study.

5. SUBJECT SELECTION AND WITHDRAWAL

Each of the criteria in the following section must be met in order for a patient to be considered eligible for participation. Create a numbered list of criteria participants must be to be eligible for study enrollment at the time of registration.

5.1 Inclusion Criteria

1. Renal biopsy proven diagnosis of an MGRS disorder including one of the following:

    a) Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID)
    b) C3 glomerulopathy associated with monoclonal gammopathy

    A concurrent diagnosis of Monoclonal gammopathy (with +ve Serum and/or Urine protein electrophoresis or Bone marrow biopsy) is required in patients with C3 glomerulopathy but not for other disorders. Patients with concurrent MGUS, non-high risk smoldering myeloma are eligible for enrollment.

2. Measurable Proteinuria ≥1gram over 24 hours.

3. Prior Therapy: Newly diagnosed as well as patients with previous therapy but persistent renal dysfunction and persistent proteinuria ≥1gram over 24 hours are eligible for enrollment. Patients who received a prior CD38 antibody therapy are not eligible for study. In patients who have received prior therapy a wash out period of 12 weeks for chemotherapy based therapies and 24 weeks for Rituximab based therapies is required between completion of prior therapy and cycle 1 Day1 of study therapy.

4. Age ≥18 years.

5. ECOG performance status ≤2.

6. Life expectancy of greater than 6 months

7. Participants must have normal organ and marrow function as defined below:
   Leukocytes ≥3,000/mcL
   absolute neutrophil count ≥1,500/mcL
   platelets ≥100,000/mcL
   total bilirubin within normal institutional limits
   AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal
   eGFR ≥30 mL/min/1.73 m^2.

6.2 Exclusion Criteria

1. Participants who have had chemotherapy based therapy within 12 weeks or Rituximab based therapy within prior 24 weeks prior to starting the cycle 1 Day 1 of trial theapy

2. Participants who are receiving any other investigational agents concurently.

3. History of severe allergic reactions or anaphylaxis attributed to compounds of similar chemical or biologic composition to Isatuximab.

4. Diagnosis of Multiple Myeloma or High risk smoldering Multiple Myeloma* or a B cell lymphoma meeting criteria for therapy.

5. Renal Biopsy showing the coexistence of other significant diagnosis e.g. advanced diabetic nephropathy. If the concurrent diagnosis such as diabetic or hypertensive nephropathy are mild on renal biopsy and MGRS lesions is the predominant pathology, patient can be enrolled on the study after discussion with the PI.

6. 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.

7. Pregnant and Lactating women are excluded from this study because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Isatuximab. Females of childbearing potential (FCBP) must have a negative baseline pregnancy test within 14 days prior to registration. This may be either a serum or urine pregnancy test, with a sensitivity of at least 50 mIU/mL. FCBP must also agree to have a pregnancy test prior to the start of each treatment cycle. FCBP or male subjects with female partners of childbearing potential shall be required to use highly effective contraceptive methods (a failure of <1% per year whenused consistently and correctly) starting 2 weeks before first isatuximab administration, while on therapy and for 5 months following the last dose of isatuximab. A woman is considered of childbearing potential, ie fertile, following menarche and until becoming post- menopausal unless permanently sterile. The following highly effective methods of contraception are accepted:

   a) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation
   b) Placement of an intrauterine device or intrauterine hormone-releasing system
   c) Bilateral tubal ligation, Hysterectomy or bilateral oophorectomy
   d) Sexual abstinence during the entire period of risk associated with study treatments

   Men must agree to use a condom with either cap, diaphragm or sponge with spermicide (double barrier method) during sexual contact with a FCBP, even if they have had a successful vasectomy starting 2 weeks before first isatuximab administration, while on therapy and for 5 months following the last dose of isatuximab.

8. HIV-positive Participants are ineligible because of increased risk of lethal infections when treated with immunosuppressive therapy.

*Multiple Myeloma and Smoldering multiple myeloma criteria in appendix 1 and 2.

6.3 Inclusion of Women and Minorities

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

6.4 Subject Recruitment

Rectuitment of subjects with be done primarily from the investigators clinical practice as well as referral from nephrology departments.

6.5 Early Withdrawal of Subjects

6.5.1 When and How to Withdraw Subjects

- Unacceptable toxicity from therapy including severe allergic reactions such as anaphylaxis from the therapy.
- Evidence of disease progression with increase in proteinuria or worsening renal function that in the opinion of treating physician require change in treatment. We recommend giving at least 2 months of therapy prior to making such decision.
- If the patient fails to comply with the defined treatment plan and follow-up evaluations, the patient will be removed from the study as per the determination of treating physician
- If the patient withdraws consent for continued participation, he/she will be removed from study.

6.5.2 Data Collection and Follow-up for Withdrawn Subjects

Subjects who are taken off the study prematurely will continue to be followed for overall survival, renal progression free survival for one year after being taken off the study. Subjects withdrawn because of unacceptable adverse events will be followed-until resolution or stabilization of the adverse event as well as for efficacy and survival as above.

7. STATISTICAL CONSIDERATIONS

The study will be a single arm, prospective, multi-center, phase II, open- label study including 27 subjects in total. Considering that we are likely to see about 10% screen failure and drop out rate we intend to enrol 27 patients in the study. The study will consist of a screening phase, treatment phase, post-treatment observation phase and follow-up phase. The subjects will receive Isatuximab in IV form (10mg/kg q weekly x 4 doses followed by 10mg/kg q2weeks) for a total of 6 month duration. Overall we expect to complete the accrual in and therapy in 2 years in all the subjects. Patients will be followed for an additional one year post therapy for outcome follow-up.

Our primary objective is to evaluate the efficacy of Isatuximab in patients with MGRS. We will measure this by patient response by once a month during the treatment phase and every 2 months for 12 months after treatment completion. Response is defined in two ways: a “Complete renal response” (Decrease in 24 hour urine proteinuria to <500mg/24 hours), and a “Partial renal response” (Decrease in 24 hour urine proteinuria >50% from baseline). From the historical data, the historical response rate for therapies used for MGRS like disorders is around 30%, and we hypothesize that we will see a response of 55%, and a sample size of 27 subjects gives us 80% power to detect this difference, based on a one-sided one proportion Z-test at 0.05 significance.

We will also apply a Bayesian futility rule that suspends enrolment if the posterior probability of futility being equal to or lower than 0.35 is 70% or higher. This monitoring rule uses Beta (0.5,0.5) as its prior distribution. The evaluation will take place after the first 10 patients have each completed six cycles of therapy, and every 2 patients thereafter. The decision rule for early futility stopping is:

Early stopping if only X responses	In first N subjects
0-2	10
0-3	12
0-3	14
0-4	16
0-5	18
0-5	20
0-6	22

The operating characteristics of the stopping rule for futility is:

True response rate	0.1	0.33	0.55
% of early stops to futility	99.8	48	10.4
Expected sample size	10	18	23

Throughout the trial, if 13 patients or more have a response, the predictive probability of having a successful and effective result (i.e., 55% response rate) at the end of the trial is over 80%.

Our secondary objective is to characterize safety, tolerability, and feasibility of treatment of the subjects, by monitoring toxicity and safety, as well as surgery related adverse events. Evaluable patients are defined as the patients that receive at least one dose are included in safety and efficacy analyses. Only grade 4 toxicities or severe adverse events (SAE) which in the opinion of the treating physician and PI necessitate stopping of further therapy will be considered relevant to stopping rules described below.

To evaluate this objective we will apply a Bayesian toxicity rule that suspends the enrolment if the posterior probability of risk being larger than 0.30 is 65% or higher. The monitoring rule uses Beta (0.6, 1.4) as its prior distribution. The decision rule for toxicity stopping when treating up to 27 patients (if no dropouts occur due to non-toxicity related factors) is as follows:
We will use a cohort size of 2 patients for toxicity monitoring. The decision rule for toxicity stopping is:

Study Termination if:	3 AEs	4 AEs	5 AEs	6 AEs	7 AEs	8 AEs	9 AEs	10 AEs
And number of patients between	4-6	4-10	6-12	6-16	8-20	8-22	10-27	10-27

The operating characteristics of the stopping rule for toxicity is:

Risk of AE	0.25	0.3	0.33	0.4	0.45	0.5
% of Time study stops	44	62	78	89	95	98
Expected sample size	19	15	12	10	8	7

For this secondary objective, we specifically intend to sequence the immunoglobulin heavy and light chain genes to determine any abnormalities that could lead to production of a misfolded immunoglobulin thus leading to deposition in renal parenchyma. Samples will be obtained from the patients' bone marrow aspirate and sequencing will be done on site in collaboration with the Columbia University Separtment of Systems Biology and Biostatistics Core.

In the study we expect that we will be able to isolate CD138+ve cells in about 80% (N=21) of the 27 patients enrolled With our clonality assay we intend to assess the percentage of patients with kappa and lambda gene restriction. Typically in patients with MGUS we expect to find a 2:1 ratio of kappa:lambda restriction. We will assess this group for clonality to see if we can detect significant differences in this ratio. We will set the confidence level at 90% in statistical tests (2-sided where appropriate), to assess any possible differences in our sequenced data and previous data. We have set this level because we believe a 10% type 1 error is within our tolerance so that we would not overlook anything of potential interest. FDR adjustment will be used for the sequenced data comparisons.

Analytical plan for outcomes. We will use the following analytical plan for our outcomes.

Primary end point of our study is as follows

1. Evaluate the overall renal response rate in patients with MGRS treated with Isatuximab: The primary objective of our trial is to esudy the efficacy of Isatuximab in this patient population. Renal response will be defined as decrease in 24-hour proteinuria by >50% at any point post therapy. This overall response will be evaluated in a one proportion Z-test against the historical response rate (also described in 15.1). In addition, we will further classify the overall response rate as complete response defined at decrease in 24-hour proteinuria to less than 500mg/day, partial response defined as >50% decrease and stable disease defined as <50% decrease in proteinuria. Each response rate value will be reported as percentage of patients achieving that outcome out of the total evaluable patients. In addition we will also calculate the median, standard deviation, 95% confidence intervals and range of values for change in 24-hour proteinuria seen in all the patients. As part of the efficacy analysis we will also evaluate median progression-free survival which will be defined as the median duration of time from start of treatment to time of progression or death, whichever occurs first. Progression will be defined as increase in 24-hour proteinuria at any point by >50% from the lowest value or 25% worsening in creatinine clearance. This outcome will be expressed as a median (95% CI) and will be determined using the Kaplan-Meier method.

Secondary endpoints are described below

1. Safety of Isatuximab in patients with MGRS: We will determine the safety of Isatuximab in this patient population as a secondary end-point in this study. Each patient wll be followed for potential adverse events which will be graded by severity according to CTCAE criteria. Monitoring rules for Toxicity and Futility will be

employed to determine if early stopping is needed (15.2). The adverse events will be reported as percentage of patients experiencing any particular adverse events. In addition we will also determine if any of the adverse events lead to delay in therapy or discontinuation of therapy. This will also be reported as a percentage. In addition we will report the median time to development of particular adverse events and time to resolution.

2. Next generation sequencing of Immunoglobulin heavy and light chain gene: This will be an exploratory analysis to evaluate the isolated clonal plasma cells for presence of any particular imuunoglobulin gene mutations in patients with MGRS. The results will be reported as the percentage of patients in whom a particular mutation is detected.

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