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SWOG

A PHASE II STUDY OF ISATUXIMAB (SAR650984) (NSC-795145) FOR PATIENTS WITH PREVIOUSLY TREATED AL AMYLOIDOSIS

NCT#03499808

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NRG/NRG Oncology
SWOG/SWOG

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at: ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM userid and password at the following url: https://crab.crab.org/TXWB/ctsulogon.aspx
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For patient eligibility or data submission questions contact the SWOG Data Operations Center by phone or email: 206/652-2267 myelomaquestion@crab.org **For treatment or toxicity related questions** contact the Study Chair by phone or email: Dr. Terri Parker at 203/737-7059 or terri.parker@yale.edu or Dr. Vaishali Sanchorawala at 617/638-8265 or vaishali.sanchorawala@bmc.org		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

1.0 OBJECTIVES

1.1 Primary Objective

To assess the efficacy as measured by the confirmed overall hematologic response rate (partial response or better) of isatuximab in relapsed/ refractory systemic light chain (AL) amyloidosis.

1.2 Secondary Objectives

a. To evaluate toxicities in the treatment of relapsed/ refractory AL amyloidosis with isatuximab.

b. To evaluate time to hematologic response.

c. To evaluate duration of response.

d. To evaluate progression-free survival (PFS).

e. To evaluate overall survival (OS).

1.3 Other Objectives

a. To evaluate efficacy of isatuximab in relapsed/ refractory immunoglobulin amyloid light chain (AL) amyloidosis as measured by organ specific response rates (cardiac, renal, GI, liver, soft tissue, nerve), in the subset of patients that can be evaluated for organ response.

b. To evaluate time to organ response in the subset of patients that can be evaluated for organ response.

2.0 BACKGROUND

2.1 Study Population

Systemic light chain (AL) amyloidosis is a monoclonal plasma cell disease in which misfolded light chains spontaneously aggregate into soluble oligomers and insoluble fibrils. Extracellular fibril deposition in different organs leads to organ dysfunction and symptoms. Historically, survival after a diagnosis of AL amyloidosis has been short, particularly in patients with advanced cardiac involvement (with a median survival of 3-6 months). *(1)* Current therapy for AL amyloidosis generally targets the small light chain-producing monoclonal plasma cell population in the bone marrow. Therapeutic regimens have been adapted from myeloma therapy.

Approximately 1/3 of AL patients are eligible for high-dose melphalan and autologous stem cell transplantation (ASCT), with the remaining patients generally being treated with alkylator and/or bortezomib-based regimens. The outcomes of 421 subjects treated with HDM-SCT from July 1994 to December 2008 revealed the median event-free survival (EFS) and overall survival (OS) were 2.6 and 6.3 years, respectively. Of 340 subjects, who were evaluable at 1 year beyond HDM-SCT, 43% achieved a complete response (CR) and 78% of them experienced an organ response. For CR subjects, median EFS and OS were 8.3 and 13.2 years, respectively. Among the 195 subjects who did not obtain CR, 52% reached an organ response, and the median EFS and OS were 2 and 5.9 years, respectively. *(2)* Cardiac involvement at diagnosis and response to therapy are the two main determinants of survival in both ASCT and non-ASCT patients.

2.2 Current Standard of Care

The optimal treatment for relapsed or refractory patients remains unclear. In general, treatment strategies that have been successful in the context of myeloma have proven to be beneficial in AL amyloidosis as well. To this end, both the immunomodulatory drugs (IMiDs; thalidomide and lenalidomide) and the proteasome inhibitor bortezomib have been studied as treatments for AL amyloidosis with variable degrees of efficacy and toxicity often requiring dose reduction. There are no currently FDA-approved pharmacologic agents for relapsed AL amyloidosis.

The immunomodulatory drugs (IMiDs), thalidomide and lenalidomide, in combination with dexamethasone are associated with overall hematologic response rates of 40-50% for relapsed AL, with some organ responses seen, though toxicities are significant and dose reductions are often needed. *(3)* Outcomes of AL patients with relapsed and refractory disease previously treated with bortezomib, lenalidomide and autologous stem cell transplant (40-80%) with pomalidomide and dexamethasone resulted in overall hematologic response rates of 48- 51% in two studies. Median time to hematologic response was 1.9 months (range, 0.9-11.3) and median duration of response 19 months. Organ improvement was documented in 18% overall (15% cardiac, 25% renal). Median and 3 year PFS were 14 months and 17% respectively. Median and 3-year OS were 28 months and 41%. *(4,5)* Bortezomib also has significant activity in the newly diagnosed and relapsed setting. *(6,7)* Median time to response with combination cyclophosphamide; bortezomib and dexamethasone (CyBorD) is 2 months. *(8)*

Despite the availability of multiple IMiDs and bortezomib, there remains a desperate need for other treatment options that will be available to patients when they relapse or are intolerant to standard medications. The development of newer classes of drugs with less toxicity at standard doses and novel mechanisms of action for AL are certainly warranted, however, they should be tested cautiously and as single agents to establish preliminary data on efficacy and safety before considered in combination with other agents. Setting an estimated benchmark response rate for this novel drug for relapsed AL cannot be based on responses to other active agents such as the IMiDs or bortezomib as described above, as the class of drug (monoclonal antibody) has never been given to AL patients. Thus, the goal of this single arm open label study is to establish if there is a preliminary efficacy signal without serious toxicity as this is the first study using a CD38 monoclonal antibody in AL. A reasonable expectation for hematologic response may be based on the efficacy seen as a single agent in relapsed multiple myeloma (ORR 27%).

2.3 Isatuximab

Isatuximab (SAR) is an IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38. It is a targeted immunotherapy that attacks tumor cells that overexpress CD38, a transmembrane glycoprotein, in a variety of hematological malignancies including plasma cell malignancies. Isatuximb induces lysis of CD38-expressing tumor cells, including malignant plasma cells by a wide spectrum of mechanisms including complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC). The most common adverse reactions seen are infusion reactions that can be mitigated and managed with corticosteroids and antihistamines, both as prophylaxis and treatment.

Isatuximab has been shown to be efficacious and well tolerated in relapsed and refractory multiple myeloma patients when used as a single agent as well as in various combinations with other agents.

2.4 TED 10893 Phase I Study

Final results are available for the Phase I study TED10893. Preliminary clinical activity results as of the cutoff dates are provided for Phase 2, Stage 1 of Study TED10893.

In the Phase I study (TED10893), 89 patients with CD38-positive hematological malignancies have been treated with isatuximab at doses up to 10 mg/kg QW or 20 mg/kg QW. Six patients (5 with MM, 1 with NHL) were treated in the accelerated escalation cohort. Thirty-nine patients (35 with MM, 2 with NHL, and 2 with chronic lymphocytic leukemia [CLL]) were treated in the basic escalation cohorts. Nineteen and 18 patients with MM (standard or high risk) and high risk MM were treated in dose expansion cohorts 1 and 2, respectively. In an additional cohort, 7 patients with MM were treated with isatuximab, 20 mg/kg QW.

For all 89 treated patients, the median number of cycles administered was 5 (range, 1:56), the median duration of exposure was 10.1 weeks (range, 2:116), and the median relative dose intensity was 98.48%.
Eighty-one patients discontinued treatment (69, due to disease progression (PD), 4 due to adverse events (AEs), 8 for reason recorded as “other,” Consent withdrawal [8 patients]) and 8 remain on treatment. The median time on treatment was 10.1 weeks (range, 2 to 16 weeks).

In 84 patients with MM, the median age was 64 years (range, 40 to 81 years). The median time from diagnosis to first isatuximab dosing was 5.8 years (range, 1.2 to 22.8 years). The median number of prior lines of therapies was 5.0 (range, 1 to 13). Prior therapy included lenalidomide (94.0%), pomalidomide (40.5%), bortezomib (98.8%), and carfilzomib (42.9%).

Among the 89 patients enrolled, and across all the treatment cohorts, Grade ≥3 treatment-emergent AEs (TEAEs) were reported in 53.9% of patients, serious TEAEs in 39.3%, TEAEs with fatal outcome in 2.2%, TEAEs leading to treatment discontinuation in 5.6%, and dose limiting toxicities (DLTs) in 2.2%.

The most common were infusion-associated reaction (IARs) (in 49.4% of the patients, overall, including 2 patients with IARs to pre medication treatment and not related to isatuximab; Grade 3-4 in 2.2%), fatigue (in 37.1% of the patients, overall; Grade 3-4 in 3.4%), nausea (in 32.6% of the patients, overall; Grade 3-4, none), anemia (in 28.1% of the patients, overall; Grade 3-4 in 16.9%), upper respiratory tract infection (in 22.5% of the patients, overall; Grade 3-4, none), cough (in 22.5% of the patients, overall; Grade 3-4, none), back pain (in 20.2% of the patients, overall; Grade 3-4 in 3.4%), and diarrhea (in 20.2% of the patients, overall; Grade 3-4, none).

Overall response rate (≥partial response (PR)) using the European Society for Blood and Marrow Transplantation criteria among the 84 treated MM patients was 20.2% (1 CR, 15 PRs), all responses PR or better are confirmed with 2nd assessment. Clinical benefit rate (≥ minimal response (MR)) was 26.2% and best response was stable disease in 42.9% of the treated MM patients. The MR or better occurred at all dose levels ≥1 mg/kg. In patients treated at doses ≥10 mg/kg in the dose escalation and expansion cohorts (n=63), ORR was 23.8% (15 of 63 patients), and the CBR was 30.2% (19 of 63 patients). In patients treated at 10 mg/kg Q2W in the high-risk cohort (n=18), ORR was 16.7% (3 of 18 patients) and CBR was 27.8% (5 of 18 patients).

In the Phase II, Stage 1 study TED10893, 97 patients were treated in Phase 2, Stage 1 of Study TED10893: 23 patients at 3 mg/kg Q2W, 24 patients at 10 mg/kg Q2W, 25 patients at 10 mg/kg Q2W/Q4W, and 25 patients at 20 mg/kg QW/Q2W. As of the cut-off date (29

February 2016), 85 patients discontinued treatment, 73 due to PD, 7 due to AEs, and 5 due to reason recorded as “other” (non-IMWG confirmed PD [2 patients], Consent withdrawal [2 patients], lack of response [1 patient]). Twelve patients remain on treatment.

Patients received 1 of 4 different doses or schedules of administration. The median age was 62.0 years (range, 38 to 85 years). The median time from diagnosis to first isatuximab dosing was 5.85 years (range, 1.2 to 24.1 years). Patients were generally heavily pretreated and were exposed to most of the available anti-MM treatment. All patients received at least 1 immunomodulatory drug (IMiD) (ie, lenalidomide, pomalidomide) or proteasome inhibitors (ie, bortezomib, carfilzomib, ixazomib).

For all 97 treated patients, the median number of cycles administered was 3 (range, 1:17), the median duration of exposure was 13.1 weeks (range, 4:69), and the median relative dose intensity was 98.85%.

The ORR showed a dose response effect between the 3 mg/kg Q2W (ORR<10%) and doses of 10 mg/kg or higher (ORR ≥20% in all arms). At doses of 10 mg/kg or higher, the response rate ranged from 20% to 29% without a meaningful dose response between the 10 mg/kg and the 20 mg/kg arms.

The median duration of responses were: 12.9 months (3.7–14.8) at 10 mg/kg Q2W; 9.2 months (3.7–13.8) at 10 mg/kg Q2W/Q4W; and 8.75 months (4.6–9.9) at 20 mg/kg QW/Q2W.

The response rates are consistent cross all sub-groups. In patients treated at doses ≥10 mg/kg, ORR was ≥20% in all sub-groups, including patients with high-risk cytogenetics (38% [8/21]).

The median PFS was: 3.7 months (1.84–10.15) across all dose levels. The median OS for 10 mg/kg Q2W group was 18.628 (9.9220 to NC) months, and has not been reached in the 10 mg/kg Q2W/Q4W and 20 mg/kg QW/Q2W arms.

Among the 97 patients enrolled, and across all the treatment cohorts, Grade ≥3 TEAEs were reported in 63.9% of patients, serious TEAEs in 43.3%, TEAEs with fatal outcome in 10.3% (and 5 because of disease progression), and TEAEs leading to treatment discontinuation in 8.2% of the patients (2 due to infusion-related reactions, 1 due to Grade 3 thrombocytopenia, and 5 patients unrelated to toxicity). The most common TEAEs were nausea (35.1%; Grade 3-4, none), fatigue (30.9%; Grade 3-4, none), cough (28.9%; Grade 3-4 in 1%), and dyspnea (26.8%; Grade 3-4 in 3.1%).

Infusion-associated reactions were reported in 49 of 97 patients (50.5%) patients across all dose levels. The severity of the IARs was Grade 3 or higher in 3 (3.1%) patients. The symptoms of IARs with a severity of Grade 3-4 consisted of anaphylactic reaction, hypertension, dyspnea, bronchospasm (in 1 patient each).

2.5 Hypothesis

Although isatuximab has never been used in AL amyloidosis patient, we expect that the efficacy and tolerability will be similar to that of daratumumab as seen in AL amyloidosis. *(9,10,11)*

2.6 Response Criteria

The criteria for hematologic and organ responses have historically been based on the consensus opinion from the Xth International Symposium on Amyloidosis (ISA,2005);

cardiac and hematologic response was subsequently updated at the XIIth ISA (2012) and more recently the renal response criteria have been revised by Palladini et al (2014) which are now widely accepted. We will use these criteria for evaluating hematologic and organ response on this trial (See Section 10.0). *(12,13,14)*

2.7 Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	1
Asian	1	0	0	0	1
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	3	3	0	0	6
White	10	13	2	2	27
More Than One Race	1	2	0	0	3
Total	15	20	2	2	39

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study, isatuximab is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

Diphenhydramine, methylprednisolone, ranitidine and acetaminophen are commercially available and should therefore be purchased by a third party. These drugs will not be supplied by the NCI or industry sponsor.

3.1 Isatuximab (SAR650984) (NSC #795145, IND-138083)

a. PHARMACOLOGY

Mechanism of Action:
Isatuximab is an immunoglobulin G1 monoclonal antibody that selectively binds to the human cell surface antigen molecule CD38 expressed in a number of hematological malignancies from B-lymphocyte, T-lymphocyte, and myeloid origin. The agent works through antibody-dependent cellular-mediated cytotoxicity,

complement-dependent cytotoxicity, antibody dependent cellular phagocytosis, and induction of apoptosis.

b. PHARMACOKINETICS

1. Absorption: Exposure increased more than proportionally with the dose from 0.03 to 20 mg/kg. Some accumulation was observed following 10 or 20 mg/kg administered with qw or q2w schedule. Achievement of steady state has not been formally evaluated yet. Additionally, four doses of 20 mg/kg QW showed that total clearance (sum of nonlinear and linear clearances) approached linear clearance (indicating target saturation) after which the 20 mg Q2W schedule appeared to maintain the total clearance close to the linear clearance.

   Isatuximab has a low clearance to those of non-specific endogenous IgG associated with a half-life of 18 days and the volume of distribution of central compartment (Vp) approached the blood volume. Because isatuximab is an antibody, it is expected to be eliminated by proteolytic catabolism.

2. Distribution: The PK of isatuximab appeared to be nonlinear in the dose range investigated in studies. More precisely, after the first administration, the exposure (AUC1week, AUC2weeks, or AUClast) appeared to increase more than proportionally with the dose up to 10 mg/kg, while no major deviation to the dose proportionality could be observed between 10 mg/kg and 20 mg/kg. This nonlinearity suggests the presence of target-mediated drug disposition with isatuximab.

3. Metabolism: No available data; being evaluated.

4. Elimination: Some accumulation was observed following 10 or 20 mg/kg administered with every-week or every-2-week schedule. Achievement of steady state has not been formally evaluated yet.

c. ADVERSE EFFECTS

1. Adverse Effects:

Adverse Events with Possible Relationship to *"Isatuximab"*		
Likely (> 20%)	**Less Likely (4 – ≤ 20%)**	**Rare but Serious (≤ 3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia	Febrile neutropenia	
Leukopenia	Hyperviscosity syndrome	
Thrombocytopenia		
Lymphopenia		
Neutropenia		
CARDIAC DISORDERS		
	Atrial fibrillation	Cardiopulmonary failure
	Acute coronary syndrome	Stress cardiomyopathy

Adverse Events with Possible Relationship to *"Isatuximab"*		
Likely (> 20%)	**Less Likely (4 – ≤ 20%)**	**Rare but Serious (≤ 3%)**
EYE DISORDERS		
	Eye pain	
	Photophobia	
	Visual impairment	
GASTROINTESTINAL DISORDERS		
Nausea	Constipation	Small intestinal obstruction
Diarrhea	Abdominal pain	Gastrointestinal amyloidosis
Vomiting		Gastrointestinal hemorrhage
		Ileus
		Intussusception
		Obstruction gastric
		Tongue edema
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	Performance decreased	Device malfunction
Pyrexia	Non-Cardiac Chest Pain	Disease progression
Chills	Asthenia	Gait disturbance
	Pain	
	Face edema	
HEPATOBILIARY DISORDERS		
AST increased	Hyperbilirubinemia	
ALT increased		
Alkaline phosphatase increased		
IMMUNE SYSTEM DISORDERS		
		Anaphylactic reaction
INFECTIONS AND INFESTATIONS		
Upper respiratory tract infection	Sepsis	Pneumocystis jirovecii pneumonia
Pneumonia	Lung infection	Bacterial sepsis
	Gastroenteritis	Clostridium difficile colitis
	Herpes zoster	Gastroenteritis rotavirus
	Otitis media	Infectious colitis
	Bronchitis	Abdominal sepsis
	Bronchitis viral	Atypical pneumonia
	Influenza	Infective aortitis
	Varicella	Meningitis bacterial
	Upper respiratory tract infection	Mengingococcal sepsis
	Urinary tract infection	Parainfluenzae virus infection

Adverse Events with Possible Relationship to *"Isatuximab"*		
Likely (> 20%)	**Less Likely (4 – ≤ 20%)**	**Rare but Serious (≤ 3%)**
		Pneumococcal bacteremia
		Pneumonia respiratory syncytial viral
		Pneumonia streptococcal
		Pneumonia mycoplasmal
		Pneumonia viral
		Septic shock
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Infusion related reaction	Fall	
	Hip fracture	
	Humerus fracture	
	Joint injury	
	Procedural hemorrhage	
	Traumatic fracture	
INVESTIGATIONS		
Blood bilirubin increased		
Blood creatinine increased		
METABOLISM AND NUTRITION DISORDERS		
Hypercalcemia	Decreased appetite	Pathological fracture
	Hypercalcemia	
	Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		
Back pain	Bone pain	
	Fracture pain	
	Musculoskeletal chest pain	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (include cysts and polyps)		
		Basal cell carcinoma
		Malignant melanoma
		Myelodysplastic syndrome
		Squamous cell carcinoma of the oral cavity
NERVOUS SYSTEM DISORDERS		
Headache	Dizziness	Cerebral hemorrhage

Adverse Events with Possible Relationship to *"Isatuximab"*		
Likely (> 20%)	**Less Likely (4 – ≤ 20%)**	**Rare but Serious (≤ 3%)**
	Seizure	Transient ischemic attack
		Spinal cord compression
RENAL AND URINARY DISORDERS		
		Acute kidney injury
		Renal failure
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
	Pelvic pain	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Cough	Respiratory alkalosis	Pleural effusion
	Bronchospasm	Pulmonary embolism
	Apnoea	Acute respiratory failure
	Atelectasis	Hemoptysis
	Laryngeal oedema	Pneumoia aspiration
	Laryngospasm	Pulmonary edema
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Rash	Angioedema
VASCULAR DISORDERS		
	Hypotension	Aortic aneurysm
		Extrinsic iliac vein compression
		Hypertensive crisis

2. Pregnancy and Lactation: Reproductive toxicology studies have not yet been performed.

   Drug Interactions: No drug-interactions has been observed between isatuximab and lenalidomide.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

Isatuximab should be administered via a peristaltic pump using an administration set that is polyethylene (PE) or polyvinyl chloride (PVC) DEHP free or polyvinyl chloride (PVC) with DEHP with 0.2 micron in-line filter that is polyether sulfone (PES) or Nylon. Isatuximab initial infusion rate should not exceed 175 mg of isatuximab per hour. In the absence of infusion related reactions (IAR), after 1 hour of infusion, the infusion rate can be increased by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. Subsequent infusions should be initiated at 175 mg/hour. In the absence of IARS, the rate may be increased by 100 mg/hour every 30 minutes, to a maximum of 400 mg/hour. Patients who do not experience an IAR during the first 4 isatuximab infusions may have their need for subsequent premedication reconsidered at the Investigator's discretion in consultation with the Study Chairs to avoid unnecessary sedation.

e. HOW SUPPLIED

1. Isatuximab vials will be provided by Sanofi and distributed by:

   Sanofi US Services Inc.
   55 Great Valley Parkway
   Malvern, PA 19355
   USA

2. Isatuximab C1P2F2 (cell 1, process 2, formulation 2) drug product is presented as a concentrate for solution for infusion in vials containing 20 mg/mL (500 mg/25 mL) isatuximab in 20 mM histidine, 10% (w/v) sucrose, 0.02% (w/v) polysorbate 80, pH 6.0 buffer.

3. Isatuximab is supplied for parenteral administration as a sterile, nonpyrogenic, injectable, 20 mg/mL concentrate for solution for infusion, essentially free of particulates, and is packaged in 30 mL glass vials fitted with elastomeric closure. Each vial contains a nominal content of 500 mg of isatuximab C1P2F2. The fill volume has been established to ensure removal of 25 mL. Isatuximab are single-use vials. Unused portion must be discarded.

f. STORAGE, PREPARATION & STABILITY

1. Isatuximab will be stored between +2 and +8°C and protected from light upon receipt. Shelf-life of isatuximab is currently 24 months. Refer to the **S1702** training slides for temperature excursion information.

2. Isatuximab concentrate for solution for infusion will be diluted in an infusion bag with 0.9% sodium chloride solution or 5% dextrose solution to achieve the appropriate drug concentration for infusion.

   Infusion via a central line is preferred if available. In case of patients with local intolerance after peripheral IV infusion, decision to use central line is left to investigator decision. The final infusion volume corresponding to the dose of isatuximab will be administered by IV infusion for the period of time that will depend on total dose administered.

3. Dilution should be performed in an aseptic condition per local guidelines. Select appropriate diluent bag volume of NaCl 0.9% and/or Dextrose 5% solutions that are polyolefin (PO), polyethylene (PE) or polypropylene (PP), or polyvinyl chloride (PVC) with DEHP to ensure diluted product concentration is between 0.8 and 5.3 mg/mL. Doses ≥ 3,300 mg must be diluted in Dextrose 5% solution. Bag sizes between 250 mL and 1,000 mL can be used to prepare the infusion solutions; bags of 250 mL, 500 mL, or 1,000 mL are recommended for this study. Add appropriate amount of isatuximab into the bag and gently homogenize by inverting the bag. Follow local procedures for priming of tubing and filter and for use of a secondary line. Prepared solutions for infusion are stable at room temperature for 16 hours.

4. Prior to dosing, each patient's dose will be individually prepared by the study pharmacist and labeled with protocol number, patient number, and treatment description. The patient's weight should be measured prior to each cycle; however dose should only be changed if the patient has > 10% change in weight.

5. To calculate the exact volume of concentrated solution needed for the dose, apply the following equation:

   Vdose (mL) = [Dose (mg/kg) x Body weight (kg)]/20 (mg/mL)

   Example: for a 70 kg patient dosed at 20 mg/kg:
   Vdose is (20 x 70)/20 = 70 mL of Isatuximab

6. To calculate the number of vials needed for the dose follow these steps:

   1. Patient dose (vials) = Vdose (mL)/25 mL
   2. If result is obtained with decimals, it should be rounded up to the nearest upper unit

   Example: for a 70 kg patient dosed at 20 mg/kg the calculated patient dose is 2.8 vials, then 3 vials should be used to obtain the volume of concentrated solution.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering: Isatuximab may be ordered by completing and submitting the **S1702** Drug Order and Acknowledgment of Receipt Form per the instructions on the form. The form can be found on the protocol abstract page of the SWOG website (www.swog.org) or on the protocol abstract page of the CTSU website (www.ctsu.org).

2. Drug Handling and Accountability

   a. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return or disposal of all drugs received from the supplier using the NCI Drug Accountability Record Form (DARF) available at http://ctep.cancer.gov.

   b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF.

   c. Sites must also document drug receipt (including temperature excursion information) and the acknowledgment must be returned to Sanofi per the instructions on the **S1702** Drug Order and Acknowledgment of Receipt Form. The form can be found on the protocol abstract page of the SWOG website (www.swog.org) or on the protocol abstract page of the CTSU website (www.ctsu.org).

3. Drug Disposition Instruction

   a. Used vials and expired vials should be destroyed on site per institution SOP and documented accordingly on DARF in a timely manner. Unused vials should be destroyed on site per institution SOP and documented accordingly on the DARF upon study closure and the last enrolled patient has completed treatment.

   b. Drug expiration: (If packaging does not have expiration date, check with insert from company when available. If packaging has expiration date, indicate drug expiration date on the DARF under

Manufacturer and Lot # and use the drug lots with shorter expiration date first).

4. Contact Information

Questions about drug orders or shipping should be directed to the Sanofi US Services Inc at CS-US-Shipment-Requests@sanofi.com.

4.0 STAGING CRITERIA

Staging criteria not applicable.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. For each criterion requiring test results and dates, please record this information on the Onstudy Form or on the AL Baseline Tumor Assessment Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 or myelomaquestion@crab.org prior to registration. **NCI policy does not allow for waiver of any eligibility criterion http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm.**

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14 or 28, or 35 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patient must have relapsed or refractory primary systemic AL Amyloidosis, histologically-confirmed by positive Congo red stain with green birefringence on polarized light microscopy, OR characteristic appearance by electron microscopy AND confirmatory AL amyloid typing (mass spectrometry-based proteomic analysis or immunofluorescence). If there is question regarding diagnosis, consult Study Chairs prior to submission via e-mail to terri.parker@yale.edu and vaishali.sanchorawala@bmc.org. Pathology report must be submitted as indicated in Section 14.4a.

b. Patient must have measurable disease as defined in Section 10.1 within 28 days prior to registration. Serum β2 microglobulin, Serum Quantitative Immunoglobulins (IgG, IgA, and IgM), serum free kappa and lambda, SPEP with M-protein quantification, and urine immunofixation electrophoresis must be obtained within 28 days prior to registration.

c. Patient must demonstrate a difference in the involved serum free light chains (kappa or lambda) versus the uninvolved serum free light chain of ≥ 4.5mg/dL within 28 days prior to registration.

d. Patient must have objective organ involvement defined by ONE (or more) of the following. All disease for involved organs must be assessed at baseline (defined as within 28 days prior to registration) and must be documented on the AL Baseline Tumor Assessment Form. Note that the following organ disease assessments are required **if there is suspected involvement of the organ(s)**. Only one organ is required to be involved for the patient to be eligible for the study. Assessment of

each organ at baseline is not required if organ involvement is not suspected (see Section 9.0 for post-activation requirements).

1. Kidney: Albuminuria greater than or equal to 500 mg per day on a 24-hour urine specimen, OR prior kidney biopsy (at time of diagnosis) showing amyloid deposition;

2. Heart: Mean left ventricular wall thickness on echocardiogram greater than or equal to 12 mm in the absence of hypertension or valvular heart disease, OR NT-pro BNP greater than 332 pg/mL provided that patient does not have impaired renal function (as defined by calculated creatinine clearance less than 25 mL/min), OR prior cardiac biopsy (at time of diagnosis) showing amyloid deposition with past documented or presently noted clinical symptoms and signs supportive of a diagnosis of heart failure in the absence of an alternative explanation for heart failure;

3. Liver involvement: Hepatomegaly (total liver span >15cm) as demonstrated by CT, ultrasound, or MRI OR elevated alkaline phosphatase (ALP) greater than 1.5 times the upper limit of normal, OR prior liver biopsy (at time of diagnosis) showing amyloid deposition;

4. Gastrointestinal tract: For patients with suspected baseline GI involvement (prior biopsy showing amyloid deposition AND symptoms such as GI bleeding or persistent diarrhea [> 4 loose stools/day on most days over a consecutive 28-day period]), a 24-hour fecal fat test must be obtained at baseline.

5. Autonomic or peripheral nervous system: Orthostatic symptoms including dizziness or light-headedness with standing, nausea, early satiety, diarrhea or constipation, abnormal sensory and/or motor findings on neurologic exam, or gastric atony by gastric emptying scan. Patients suspected to have neurologic involvement, must have neurologic assessment including orthostatic measurements at baseline. NIS score at baseline is also suggested as a clinical tool for measurement of peripheral neuropathy, but it is not required. NCS/EMG studies are not required and can be obtained as clinically indicated. Orthostatic measurements must be repeated on 2 separate occasions (at least 1 day apart; e.g., Day -3 and Day -1).

6. Soft tissue: Macroglossia, or soft tissue deposits (including lymphadenopathy, recurrent peri-orbital purpura, peri-articular, skin or other soft tissue) requiring therapy. Imaging (CT, MRI, or ultrasound) is not required but may be performed as clinically indicated to measure soft tissue involvement.

e. Patients must not have active symptomatic multiple myeloma, as defined by 2015 IMWG criteria (CRAB criteria; bone marrow plasmacytosis > 60%). kappa: lambda ratio >100 is acceptable only if the clinical symptoms and sign are attributable only to amyloidosis and not multiple myeloma (Hgb < 8g/dL). *(15)*

5.2 Prior/Concurrent Therapy Criteria

a. Patient must be relapsed or refractory to **at least** one prior line of therapy (such as: transplant, radiation, or chemotherapy).

b. Patients must have completed other systemic therapy ≥ 14 days or investigational drug ≥ 28 days prior to registration, surgery (other than biopsies) ≥ 21 days prior to registration, and any autologous stem cell transplant (ASCT) ≥ 100 days prior to registration.

c. Patients must not have received any supplements which have been known to have some anti-amyloidogenic effect (such as: doxycycline; curcuramin; prednisone; dexamethasone; epigallocatechin gallate [EGCG]) within 14 days prior to registration.

d. Patients must not have any known allergies to isatuximab or other monoclonal antibody therapies.

e. Patients must not have received daratumumab within 56 days prior to registration nor have been refractory to daratumumab.

f. Patients must not be eligible for autologous stem cell transplantation as determined by the treating investigator or if the patient declined/refused.

5.3 Clinical/Laboratory Criteria

a. Patients must have a complete medical history and physical exam within 28 days prior to registration.

b. Patients must be ≥ 18 years of age.

c. Patients must have adequate hepatic function within 28 days prior to registration, as defined by the following:

Total bilirubin ≤ 2.0 x IULN (institutional upper limit of the norm) (patients with Gilbert's Syndrome must have a total bilirubin less than 3.0 mg/dL)

AND
SGOT/AST and SGPT/ALT ≤ 4.0 x IULN

d. Patients must have adequate renal function, as defined by:

- Creatinine clearance (CrCl) ≥ 25 mL/min., as measured by a 24-hour urine collection or as estimated by the Cockcroft and Gault formula. The serum creatinine value used in the calculation must have been obtained within 28 days prior to registration.
  Estimated creatinine clearance =

$$\frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$$

e. Patients must have bone marrow aspirate and biopsy within 35 days prior to registration. The following are required:
- quantitative percent clonal plasma cell involvement,
- standard immunophenotyping,
- immunohistochemistry,
- cytogenetics,
- fluorescent in situ hybridization (FISH) (via participating site local laboratory) to assess for del 17p; t11;14; t4;14, t14;16; and del 13q.

Additionally, FISH and cytogenetic testing (normal – XY; and all abnormalities) are required to have been performed and to be reported, even if "no results" was achieved (i.e. due to too few cells in specimen). If FISH was performed, then the patient is eligible. If FISH was not performed, then patient is not eligible. Central pathology analysis will not be required, however the local pathology report and FISH/Cytogenetic data must be submitted in Medidata RAVE.

f. Patients must have adequate bone marrow function as defined by the following within 28 days prior to registration: ANC ≥ 1,000 cells/mcl without growth factor support, AND platelets ≥ 75,000 cells/mcl.

g. Patients must have hemoglobin ≥ 8 g/dL within 28 days prior to registration. Patients may have received transfusion if greater than 7 days prior to registration.

h. Patients must have adequate cardiac function as defined by the following:
- New York Heart Association (NYHA) < Class IV heart failure (see Section 18.2); and
- LVEF by ECHO ≥ 35% within 28 days prior to registration; and
- NT-proBNP ≤ 8500 pg/mL within 28 days prior to registration.

i. Patients must have a Zubrod Performance Status ≤ 2.

j. Patients must not have any clinically significant uncontrolled systemic illness, including but not limited to uncontrolled, active infection requiring intravenous antibiotics, unstable angina pectoris, myocardial infarction within the past 6 months, uncontrolled cardiac arrhythmias, uncontrolled hypertension, or uncontrolled diabetes mellitus.

Uncontrolled diabetes: Patients who have a diagnosis of diabetes must have an Hb A1C < 7% within 28 days prior to registration. The same criterion will be used in patients with confirmed diagnosis of diabetes mellitus who have been on a stable dietary or therapeutic regimen for this condition in the last three months.

Uncontrolled blood pressure and hypertension: All blood pressure measurements within the 28 days prior to registration must be SBP ≤ 160 and DBP ≤ 100. An exception can be made by a healthcare provider for a patient with a single blood pressure elevation who upon rechecking has a blood pressure within the parameters above.
- See ACCF/AHA.AMA-PCPI joint statement

k. Females of childbearing potential 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. Females of childbearing potential (FCBP) must also agree: (1) to have a pregnancy test prior to the start of each treatment cycle and (2) to either commit to continued abstinence from heterosexual intercourse or to use effective contraception while receiving study drug and for at least 12 weeks after receiving the last dose of study drug. Females are considered to be of "childbearing potential" if they have had menses at any time in the preceding 24 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, she is responsible for beginning contraceptive measures. 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 for the study duration and for 12 weeks after the discontinuation of treatment.

l. Patients with evidence of Hepatitis B Virus (HBV) are eligible provided there is minimal hepatic injury and the patient has undetectable HBV on suppressive HBV therapy. Patient must be willing to maintain adherence to HBV therapy. Patients with previously treated and eradicated Hepatitis C Virus (HCV) who have minimal hepatic injury are eligible.

m. Patients who are known to be HIV-positive at registration are eligible if at time of registration they meet all other protocol eligibility criteria in addition to the following:

1. Patient has undetectable HIV viral load by standard PCR clinical assay;

2. Patient is willing to maintain adherence to combination antiretroviral therapy;

3. Patient has no history of AIDS defining condition (other than CD4 cell count < 200 mm^3);

4. Patient is otherwise likely to have a near normal lifespan if not for the presence of relapsed/refractory amyloid.

n. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for at least two years.

5.4 Specimen Submission Criteria

Patients must be offered participation in specimen banking as outlined in Section 15.1. With patient consent, pretreatment specimens must be collected and submitted via the SWOG Specimen Tracking System as outlined in Section 15.1.

Instructions for obtaining a SWOG Patient ID prior to patient registration are available in Section 15.1c.2.

5.5 Regulatory Criteria

a. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

b. As a part of the OPEN registration process (see Section 13.4c for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

There are no stratification factors.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Terri Parker at 203/737-7059 or Dr. Vaishali Sanchorawala at 617/638-8265.

For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials".

7.1 General Treatment Instructions

a. Infusion associated reactions (IARs) (mostly Grade 1-2 and manageable) are very common with the first isatuximab dose administration, even in patients who had received prophylaxis (see Section 7.1b). Extensive clinical experience with approved monoclonal antibodies indicates that mild-to-moderate infusion reactions (either allergic, or consisting of cytokine release, which mimics hypersensitivity reactions) are common, particularly during the first infusion; the cytokine release syndrome associated with monoclonal antibodies consists of a pseudo allergic Type B (non-immunoglobulin E mediated) reaction. The IARs associated with isatuximab have been occurring most commonly at the first administration, are not dose dependent, and the patients do not appear to sustain sequelae. Infusion-associated reactions generally do not cause therapy discontinuation and tend not to recur at subsequent administrations of isatuximab, but if an IAR is observed, the patient must also be informed of the potential risk of recurrent allergic reactions at subsequent infusions.

b. In an attempt to mitigate the incidence and severity of IARs, it is recommended that the initial infusion rate should not exceed 175 mg of isatuximab per hour. In the absence of an IAR after 1 hour of infusion, the infusion rate can be increased by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. Subsequent infusions should be initiated at 175 mg/hour. In the absence of IAR's, the rate may be increased by 100 mg/hour every 30 minutes, to a maximum of 400 mg/hour.

NOTE: This drug requires infusion mg/hour

In the event of a Grade 2 hypersensitivity reaction, the isatuximab infusion should be interrupted and may subsequently resume after recovery, at a slower infusion rate, under close monitoring and with supportive care as needed. See Section 8.5 for guidelines for management of infusion-related reactions.

Prior to restarting the infusion, patients may receive additional medication per the judgment of the Investigator. Recommended medications consist of diphenhydramine 25 mg IV and methylprednisolone 100 mg IV (or equivalent). In the event of a Grade 3 or 4 hypersensitivity reaction, treatment with isatuximab is to be immediately and permanently discontinued.

Vital Sign Monitoring
Blood Pressure is collected at baseline. Vitals below will be performed per drug safety monitoring.

First infusion: Prior to infusion obtain vital signs (BP, HR, temp, oxygen saturation by pulse oximeter). Repeat every 15 minutes for the 1st hour, then every 30 minutes and with each rate change for the duration of the infusion and continue for 30 minutes after the end of the infusion.

Second infusion: Prior to infusion obtain vital signs (BP, HR, temp, oxygen saturation by pulse oximeter). Repeat every 30 minutes and with each rate change for the duration of the infusion and continue for 30 minutes after the end of the infusion

Third and subsequent infusions: Prior to infusion obtain vital signs (BP, HR, temp, oxygen saturation by pulse oximeter). Repeat every 30 minutes and with each rate change for the duration of infusion and at the end of infusion.

c. Potential Interference with Blood Bank Serologic Tests:

The CD38 protein is weakly expressed on the surface of red blood cells. Because of this, anti-CD38 antibodies in patients' plasma can lead to pan-reactivity and thus interfere with various blood bank serologic tests. To avoid potential problems with blood transfusion, the American Association of Blood Banks recommends that patients being treated with anti-CD38 antibodies have blood type and screen tests performed at baseline, after treatment, and each time before blood infusion.

Type and screen patients and notify institutional blood bank before the first administration of the drug and repeat prior to any blood product transfusion. RBC antigen screen is recommended but not required, as per institutional blood bank protocol, and a card with blood type will be carried by the patient throughout the study (see Appendix 18.6). Baseline type and cross should be used for transfusions, as post-treatment blood type does not change but appears different due to presence of the CD38 antibody.

d. Strongly recommend that blood pressure is controlled prior to beginning infusion on Day 1, Cycle 1, as per American Heart Association standards, preferable SBP ≤ 140 and DBP ≤ 90. Blood pressure must be SBP ≤ 160 and DBP ≤ 100 on Day 1 Cycle 1.

7.2 Pre-Medication

a. Primary prophylactic treatment with diphenhydramine 25 to 50 mg IV (or by mouth), methylprednisolone 100 mg IV (or equivalent), ranitidine 50 mg IV (or equivalent), and acetaminophen 650 to 1000 mg orally 15 to 30 minutes (and never longer than 60/ minutes) should be administered to all patients prior to the isatuximab infusion to minimize the incidence and severity of IAR commonly observed with monoclonal antibodies. In the event of interruption of infusion due to mild or moderate hypersensitivity reaction, patients should additional pre-medication, as indicated in Section 7.1b (above).

Patients who do not experience an IAR during the first 4 isatuximab infusions may have the need for subsequent premedication reconsidered at the discretion of the treating physician (in consultation with the Study Chairs) to avoid unnecessary sedation. Please contact the Study Chairs at: terri.parker@yale.edu and vaishali.sanchorawala@bmc.org for documentation and consultation on changes in subsequent pre-medication.

Prophylactic treatment is commercially available and will not be supplied by the study.

b. Antiviral and proton pump inhibitor

All patients should receive an antiviral (such as acyclovir 800 mg orally daily) for the duration of the study.

A proton-pump inhibitor will be used to prevent peptic disease. Prevacid (lansoprazole) 15 mg orally daily or equivalent is recommended.

These medications are commercially available and will not be supplied by the study. The treating physician will provide an outpatient prescription for these medications.

7.3 Treatment

Agent	Cycle(s) [1]	Day(s)	Dose	Route
Isatuximab	1	1, 8, 15, 22	20 mg/kg	IV
Isatuximab [3]	2 – 24	1, 15	20 mg/kg	IV

[1] Note: One cycle = 28 days
[2] Patient will continue on therapy until completion of 24 Cycles of therapy or until one of the criteria in Section 7.4 is met, whichever occurs first.
[3] For Cycles 2-24, C1D1 weight should be used for dosing, unless there is a > 10% change in weight.

7.4 Organ Evaluation Guidelines

Please refer to Section 5.1d for eligibility requirements and Section 9.0 for additional timepoints.

a. Cardiac

Cardiac organ evaluation must include clinical NYHA evaluation, 2d echocardiogram, and serum NT pro-BNP and troponin I or T measurements. Echocardiogram results including LVEF, intraventricular septum wall thickness, and left ventricular posterior wall thickness, and if possible (though not essential) global longitudinal strain (GLS). It is recommended that baseline and subsequent echocardiograms are performed at the same location.

b. Renal

Renal evaluation must include 24-hour urine, including: Total Protein, UPEP with M-Spike, Urine Protein Immunofixation and Creatinine clearance; serum creatinine. If a 24-hour urine specimen is being collected, the UPEP and urine IFE can be obtained via the 24-hour urine. If a 24hour urine is not required, then a urine random/spot urine sample is adequate for the UPEP and urine IFE on day 1 of each cycle.

c. Autonomic Neuropathy

Assessment must include clinical assessment of symptoms (nausea, diarrhea, early satiety) and orthostatic blood pressure and pulse rate evaluations. See Appendix 18.7 for instructions on obtaining orthostatic blood pressure. Pulse should be recorded at the same time as each blood pressure measurement.

d. Peripheral Neuropathy

To be assessed clinically. Neurologic Impairment Score (NIS) score is suggested as a tool for measurement of peripheral neuropathy but is not required. If baseline nerve conduction study/electromyogram (NCS/EMG) were obtained for evaluation of peripheral nervous system, they must be followed as part of the organ response assessments. See Appendix 18.2 for NIS form.

e. Soft Tissue / Lymph Nodes:

To be assessed clinically; however, if imaging was used at baseline it is suggested that follow-up assessments also be by imaging.

f. Liver:

Imaging (CT, US or MRI) to document size of liver, serum alkaline phosphatase (ALP)

g. Gastrointestinal:

Clinical assessment of GI bleeding, diarrhea; 24-hour fecal fat test

h. Serum Chemistry:

Must include: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine/ CrCl, glucose, total protein, albumin, calcium, total bilirubin, alkaline phosphatase, uric acid, and SGOT/AST and SGPT/ALT.

7.5 Criteria for Removal from Protocol Treatment

a. Hematologic progression of disease or symptomatic deterioration (as defined in Sections 10.2 and 10.7). Organ progression (as defined in Section 10.4) in the absence of hematologic progression does not necessitate removal from treatment.

b. Unacceptable toxicity.

c. Treatment delay >14 days, unless approved by the Study Chair, as indicated in Section 8.3b. Treatment must not be delayed for any reason > 42 days. For treatment delay of >14 days, see Section 8.3b.

d. The patients may withdraw from the study at any time for any reason.

e. 24 cycles of treatment completed as planned.

f. Development of overt myeloma.

7.6 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.7 Follow-Up Period

All patients will be followed until 4 years after registration or until death, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE Version 5.0 for toxicity and serious adverse event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page https://ctep.cancer.gov. All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

8.2 Supportive Care

Blood product transfusion, intravenous albumin, intravenous fluids and electrolyte replacement, antiemetics, antidiarrheal medication, g-csf, anti- hypersensitivity medications are all allowable as per institutional standards and Section 3 of the protocol.

8.3 Dose Delays

a. No dose reduction is authorized for isatuximab.

b. Cycle delay up to 14 days is allowed, as indicated in Table 1 below.

Any additional delay (beyond 14 days) must be determined in consultation with the Study Chair(s), and documented via email to: terri.parker@yale.edu and vaishali.sanchorawala@bmc.org. The decision to continue treatment will be based on potential for continued clinical benefit, as determined jointly by the treating physician(s) and Study Chair(s). Treatment may not be delayed for any reason for more than 42 consecutive days.

c. Within a cycle, an isatuximab administration can be delayed for up to +/-3 days. If the dose cannot be administered within +/- 3 days, the isatuximab dose will be omitted. If one dose of isatuximab is administered within these windows, the interval between the next infusions should be maintained to 1 week or 2 weeks respectively

Only 1 omission per cycle is permitted. Further omissions must be discussed on a case by case basis with the Study Chair, documented by email to: terri.parker@yale.edu and vaishali.sanchorawala@bmc.org.

d. If a patient experiences several AEs and there are conflicting recommendations, follow the most conservative dose delay.

Table 1: Dose Delays for Isatuximab

Treatment-related Adverse Event	Grade of Event	Management for Isatuximab
Neutropenia	≤ Grade 1	No change.
	Grade 2	No change.
	Grade 3	Hold isatuximab until ≤ Grade 2.
	Grade 4	Off protocol therapy.
	[1] G-CSF may be used per treating physician discretion and institutional guidelines. See Section 8.4.	
Anemia[1]	≤ Grade 1	No change.
	Grade 2	Hold isatuximab until < Grade 2.
	Grade 3	Hold isatuximab until < Grade 2.

Treatment-related Adverse Event	Grade of Event	Management for Isatuximab
	Grade 4	Off protocol therapy.
	[1] Dose delay is not required for anemia, unless deemed necessary by the treating physician. Transfusions and/or erythrocyte stimulating agents are allowable.	
All other events	≤ Grade 1	No change.
	Grade 2	Hold isatuximab until < Grade 2 OR patient returns to baseline (where patient had a predetermined abnormal baseline).
	Grade 3	Hold isatuximab until < Grade 2 OR patient returns to baseline (where patient had a predetermined abnormal baseline).
	Grade 4	Off protocol therapy.

8.4 White Blood Cell Growth Factors

If used, white blood cell growth factors, including biosimilars, must be used per ASCO guidelines http://jco.ascopubs.org/content/24/19/3187.full and NCCN Guidelines® Myeloid Growth Factors http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf.

8.5 Guidelines for the Management of Infusion Reactions (IRs)

Patients should routinely receive premedications prior to isatuximab infusion to reduce the risk and severity of IARs commonly observed with monoclonal antibodies. Infusion associated reactions are defined as AEs related to isatuximab with onset typically within 24 hours from the start of the infusion.

Patients presenting Grade 2 IAR(s) with infusion interruption may subsequently resume isatuximab at half of the initial infusion rate under close monitoring and supportive care as needed. These patients must be informed of the potential risk of recurrent infusion reactions upon rechallenge. For further infusions, patients may receive additional premedication per the judgment of the Investigator. Additional recommended premedications include diphenhydramine 25 mg IV (or equivalent) and methylprednisolone 100 mg IV.

Once a Grade 2 IAR leading to interruption has improved to Grade ≤1, the infusion may be restarted at half the original infusion rate. If symptoms do not recur after 30 minutes, the infusion rate may be increased in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

Patients presenting Grade 3 or 4 isatuximab IAR(s) must have isatuximab permanently discontinued and appropriate supportive therapy should be administered. The IAR(s) and the therapy administered must be documented in the eCRF.

Table 2 - Management of infusion associated reactions

CTCAE Version 5.0 criteria definition	Intervention recommendation
Mild (Grade 1) Infusion interruption or intervention not indicated	Continuation of isatuximab infusion per the judgment of the Investigator following close direct monitoring of the patient's clinical status. Isatuximab infusion may be stopped at any time if deemed necessary. If stopped, IAR will be classified as Grade 2 as per CTCAE Version 5.0.
Moderate (Grade 2) Therapy or infusion interruption indicated, but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Stop isatuximab infusion. Give additional premedication with diphenhydramine 25 mg IV (or equivalent) and/or methylprednisolone 100 mg IV (or equivalent) as needed. Isatuximab may be resumed only after patient recovery, with slower infusion rate and with close monitoring.
Severe or life-threatening **(Grade 3 or 4)** Grade 3: prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Grade 4**:** life-threatening consequences; urgent intervention indicated	Stop isatuximab infusion. Give additional premedication with diphenhydramine 25 mg IV (or equivalent) and/ or methylprednisolone 100 mg IV (or equivalent) and/or epinephrine as needed. Definitive treatment discontinuation.
Note: infusion should be completed within 16 hours from the end of infusion preparation or a new infusion should be prepared with the remaining dose to be administered the same day. Abbreviations: AE = adverse event; IAR = infusion associated reaction; IV = intravenous; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs = nonsteroidal anti-inflammatory drugs.	

8.6 Dose Delay Contacts

For treatment or dose delay questions, please contact Dr. Terri Parker at 203/737-7059 or Dr. Vaishali Sanchorawala at 617/638-8265.

8.7 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

REQUIRED STUDIES	PRE-STUDY (w/in 28 days prior to registration, unless otherwise noted)	Cycle Length = 28 days (+/- 3 days)					Off TX Pre-Progression FU	Post Progression FU
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles up to 24 Cycles		
PHYSICAL								
History and Physical Exam [O]	X	X	X	X	X	X		
Height	X							
Weight	X	X	X	X	X	X		
Performance Status	X	X	X	X	X	X		
Toxicity Notation		X (Days 1, 8, 15, 22)	X (Days 1, 15)	X (Days 1, 15)	X (Days 1, 15)	X (Days 1, 15)	X[Q]	X[Q]
NYHA Assessment [K]	X	X	X	X	X	X	X	
Vital Signs [N]	X	X	X	X	X	X	X	
Clinical autonomic neurologic evaluation [A, H]	X	X (every 2 cycles, +/- 7 days)		X (every 2 cycles, +/- 7 days)		X (every 2 cycles, +/- 7 days)	X (every 6 months, +/- 21 days)	
Clinical peripheral neurologic evaluation [A, H, K]	X	X (every 2 cycles, +/- 7 days)		X (every 2 cycles, +/- 7 days)		X (every 2 cycles, +/- 7 days)	X (every 6 months, +/- 21 days)	
Clinical GI evaluation [A, H, K]	X	X (every 2 cycles, +/- 7 days)		X (every 2 cycles, +/- 7 days)		X (every 2 cycles, +/- 7 days)	X (every 6 months, +/- 21 days)	
LABORATORY								
Type and screen and blood bank notification [E]	X							
CBC w/ differential, Platelets [C]	X	X (Days 1, 8, 15, 22)	X (Days 1, 15)	X (Days 1, 15)	X (Days 1, 15)	X (Days 1, 15)		
Serum Chemistry [C, J, K]	X	X (Days 1, 8, 15, 22)	X (Days 1, 15)	X (Days 1, 15)	X (Days 1, 15)	X (Days 1, 15)		

REQUIRED STUDIES	PRE-STUDY (w/in 28 days prior to registration, unless otherwise noted)	Cycle Length = 28 days (+/- 3 days)					Off TX Pre-Progression FU	Post Progression FU
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles up to 24 Cycles		
TSH, free T4, free T3 [J]	X							
HIV, HBV, HCV [R]	X							
PT/PTT/INR [L, P]	X	X	X	X	X	X		
RESPONSE ASSESSMENT								
Serum β2 microglobulin, LDH, uric acid [J]	X							
Serum Quantitative Immunoglobulins (IgG, IgA, and IgM)	X							
SPEP with M-protein quantification	X	X	X	X	X	X	X	
Serum free kappa and lambda light chains	X	X	X	X	X	X	X	
Serum Immunofixation	X	X	X	X	X	X		
Urine Protein Electrophoresis [K]	X	X	X	X	X	X		
Urine Immunofixation Electrophoresis [K]	X	X	X	X	X	X		
Troponins (T or I) [A,L]	X	X	X	X	X	X	X	
NT-pro-BNP [L]	X	X	X	X	X	X	X	
Urine or Serum Pregnancy [F]	X	X	X	X	X	X		

REQUIRED STUDIES	PRE-STUDY (w/in 28 days prior to registration, unless otherwise noted)	Cycle Length = 28 days (+/- 3 days)					Off TX Pre-Progression FU	Post Progression FU
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles up to 24 Cycles		
24-hour urine [A, H, K]	X	X (If obtained w/in 28 days prior to C1D1, tests need not be repeated.)		X		X	X	
Bone Marrow Aspirate or Biopsy, including FISH, Cytogenetics and Immunophenotyping	X (w/in 35 days)							
24-hour fecal fat [A,G]	X	X (If obtained w/in 28 days prior to C1D1, tests need not be repeated.)			X (every 3 cycles, +/- 7 days)	X (every 3 cycles, +/- 7 days)	X (every 6 months, +/- 21 days)	
X-RAYS AND SCANS								
Ultrasound, MRI or CT for Disease Assessment of liver, soft tissue or lymph nodes [A,I]	X	X (If obtained w/in 28 days prior to C1D1, tests need not be repeated.)				X (every 6 months, +/- 21 days)	X (every 6 months, +/- 21 days)	
12-lead EKG	X	X (Days 1, 15)	X					
2D ECHO [G, K]	X	X (If obtained w/in 28 days prior to C1D1, tests need not be repeated.)			X (every 3 cycles, +/- 7 days)	X (every 3 cycles, +/- 7 days)	X (every 6 months, +/- 21 days)	
SPECIMEN SUBMISSION								
Optional Peripheral Whole Blood, Serum. Bone Marrow Aspirate	X							

REQUIRED STUDIES	PRE-STUDY (w/in 28 days prior to registration, unless otherwise noted)	Cycle Length = 28 days (+/- 3 days) Cycle 1	Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles up to 24 Cycles	Off TX Pre-Progression FU	Post Progression FU
and Biopsy Core for Banking [B]								

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org) and on the CTSU website (www.ctsu.org).
Forms submission guidelines are found in Section 14.0. Click here for footnotes.

NOTE Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines on the allowed protocol visits/treatment window as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf. SWOG Best Practices allows for a +/- 3 day window for 28 day cycles.

Footnotes for Calendar 9 (Isatuximab)

A Tests are to be performed per Section 5.1d for suspected organ involvement. If baseline test was performed and abnormality present, the tests will be repeat until off tx prior to progression.
B See Section 15.1.
C Prior to treatment on each day of isatuximab, or within 3 days prior to each administration.
E See Section 7.1c for type and screen requirements. See Appendix 18.6 for sample type and screen card.
F For women of childbearing potential, prior to beginning treatment at each cycle (or up to 3 days prior to Day 1).
G If required: Day 1 of Cycles 1, 4, and 7, then every 3 cycles (+/- 7 days) during treatment, then every 6 months (+/- 21 days) hematologic progression.
H If required: Day 1 of Cycles 1, 3, 5, then every 2 cycles (+/- 7 days) until completion of treatment, then every 6 months (+/- 21 days) until hematologic progression.
I If required: Every 6 months during and after treatment until hematologic progression, then as clinically indicated.
J TSH with reflex to free T4, and free T3 uric acid and LDH are required only when clinically indicated; however, baseline testing is encouraged to assess for thyroid involvement, if suspected.
K See Section 7.4 for a detailed description of organ evaluation and 24 hour urine collection assessment criteria, including serum chemistry panel requirements. All evaluations will continue at specified intervals until one of the criteria for removal from protocol treatment has been met (see Section 7.5).
L If required: Day 1 (+/- 3 days) of each cycle.
M See treatment plan Section 7.3.
N See Sections 5.1d.5 and 7.1b.
O Must include assessment of soft tissue and lymph nodes, if present at baseline; see Section 7.4e.
P May be either INR or PT and PTT. Whichever is performed at baseline should be used throughout treatment.
Q Assessments should continue until resolution of all acute adverse events.
R Only required per Section 5.3 Eligibility.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Measurable disease

For the purpose of measuring hematologic response, measurable disease is defined as:

a. Positive monoclonal serum immunofixation electrophoresis or urine immunofixation electrophoresis,

and/or

b. Serum free light chain ratio outside of normal range (normal range: 0.25 – 1.65)

10.2 Hematologic Response and Progression

Confirmation must be made by verification on two consecutive determinations.

a. Hematologic response: *(16,17)*

1. Complete Response (CR):
CR is defined as laboratory values within the normal range free light chain (FLC) ratio (0.25 – 1.65) and negative serum and urine immunofixation (as per institutional laboratory values).

2. Very Good Partial Response (VGPR):
A VGPR is defined as the difference between involved and uninvolved FLCs [dFLC] < 4.0 mg/dL.

3. Partial Response (PR):
Partial Response is defined as a dFLC decrease of ≥ 50%, but remaining > 4.0 mg/dL

b. Hematologic progression: 50% increase from nadir, or from baseline (if there was no response) in any ONE OR MORE of the following: *(18)*

1. Serum M-protein: 50% increase in Serum M protein to a value greater than 0.5 g/dL.

2. Urine M protein: 50% increase in Urine M protein to a value greater than 200 mg/day (a visible peak must be present)

3. Free light chain increase of 50% to a value greater than 10 mg/dL

c. Stable Disease:
Patients who do not meet criteria for objective response or progression (see Sections 10.2a and 10.2b) will be termed to have stable disease.

10.3 Organ Response *(19)*

Response to therapy in terms of improvement in organ dysfunction will be defined based on functional improvement in one or more involved organ systems. Only 1 parameter is required to satisfy the organ response criteria. In order to be classified as a confirmed organ response, confirmation must be made by verification on a second consecutive assessment at least 4 weeks after the first observation of response.

a. Liver response requires either:

1. A 50% decrease in (or normalization of, <1.5 IULN) alkaline phosphatase level, or

2. A reduction in the span of the liver by at least 2 cm by radiographic determination.

b. Renal response is defined as either: *(20)*

1. A 30% decrease in urine total albumin; or

2. A decrease to less than 500 mg/24 hours urine total protein without renal progression (where renal progression is defined in Section 10.4a.1).

c. Gastrointestinal response is defined as either:

1. Reduction in 24-hour fecal fat excretion by ≥ 50% in patients with steatorrhea; or

2. ≥ 50% reduction in number of loose stools per day in patients with diarrhea.

d. Cardiac response is defined as either: *(21)*

1. NT-proBNP response (>30% decrease and at least 300 pg/mL decrease is needed from the baseline result if NT- proBNP ≥ 650 pg/mL at baseline) or

2. NYHA class decrease from 1 to 0; 2 to 1 or 0 or from 3 to 1 (2 class decrease if baseline NYHA III). (That is, If NYHA is 1 or 2, a 1-class level drop is required. If NYHA is a 3, a 2-class level drop is required.)

e. A neurologic response is defined as:

1. Clear improvement in neuropathy (peripheral or autonomic) in the opinion of the treating investigator. For peripheral neuropathy, the Neuropathy Impairment Tool – Lower Limbs (NIS-LL) must be used to assess response.

   The NIS (LL is a scoring system graduated from 0 points (the normal finding) to a maximum of 88 points (the absence of all motor, sensory, and reflex activity in the lower extremities). The scale is additive of all deficits (64 potential points for muscle strength, 8 points for reflexes, and 16 points for sensory function) in the lower extremities. A NIS-LL score demonstrating a decrease from baseline of ≥ 2 points is indicative of organ response. *(22)*

   See Section 18.2.

2. For autonomic neuropathy, a clear improvement in the opinion of the investigator including improvement in orthostatic blood pressure (systolic blood pressure (SBP)) readings and symptoms of dizziness and nausea on 2 separate occasions.

a. Orthostatic hypotension is defined as a decrease in systolic blood pressure of 20 mm Hg or a decrease in diastolic blood pressure of 10 mm Hg within three minutes of standing when compared with blood pressure from the sitting or supine position. Orthostatic symptoms include dizziness, lightheadedness, nausea

f. Soft tissue/lymph nodes: There is no reliable method for assessing soft tissue responses. Determination of soft tissue response will be performed by the site investigator in conjunction with the PI/Medical Monitor. Examples of soft tissue responses would include decreased size and thickness of tongue, or improved tongue mobility, on physical examination (for macroglossia); objective decrease in size of soft tissue deposits on examination or imaging.

10.4 Criteria for Organ Progression

Progression will be defined based on objective evidence of worsening of organ dysfunction due to AL amyloid.

a. Any ONE of the following criteria must be met to be termed as organ progression for the purpose of this study:

1. Renal: A 50% increase (at least 1 g/day) of 24-hour urine protein to > 1 g/day OR 25% worsening of serum creatinine or creatinine clearance (Cockcroft-Gault method).

2. Hepatic progression is defined by either:

a. A 50% increase of alkaline phosphatase level above lowest level, or

b. An increase in liver span by at least 2 cm (radiographic determination).

3. Gastrointestinal: Worsening of diarrhea with an increase 50% of previous movements per day (not attributable to the study drug or an alternative explanation in the opinion of the treating physician) or 24-hour fecal fat increase by 50%.

4. Cardiac: An increase in cardiac wall thickness by 2 mm or an increase in NYHA class by one grade with a decreasing ejection fraction of 10%, or an increase in NT-proBNP by > 30% and >300 pg/mL or an increase in troponin T or I by $\geq$ 33%.

5. Neurologic: Clearly progressive neuropathy (peripheral or autonomic) that in the opinion of the treating investigator is unrelated to study drug.

a. For peripheral neuropathy, the Neuropathy Impairment Tool – Lower Limbs (NIS-LL) must be used to assess progression.

The NIS (LL is a scoring system graduated from 0 points (the normal finding) to a maximum of 88 points (the absence of all motor, sensory, and reflex activity in the lower extremities). The scale is additive of all deficits (64 potential points for muscle strength, 8 points for reflexes, and 16 points for sensory function) in the lower extremities. A NIS-LL score demonstrating an

increase from baseline of ≥ 2 points is indicative of organ progression. *(23)*

See Section 18.2.

b. Clear worsening of orthostatic vital signs (SBP) and symptoms of dizziness or nausea on 2 separate occasions.

6. Soft tissue/lymph nodes: Clearly progressive macroglossia or symptomatic soft tissue deposits.

10.5 Time to Hematologic Response

From date of registration to date of first documentation of hematologic PR, VGPR, or CR as defined in Section 10.2.

10.6 Overall Survival

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.7 Progression-Free Survival

From date of registration to date of first documentation of progression, symptomatic deterioration (as defined below), or death due to any cause. Patients last known to be alive and progression-free are censored at date of last contact.

Symptomatic Deterioration: The global deterioration of health status requiring discontinuation of treatment without objective evidence of progression.

10.8 Performance Status
Patients will be graded according to the Zubrod performance status scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3.	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

11.0 STATISTICAL CONSIDERATIONS

11.1 Two-Stage Design

The primary goal of this study is to test the hypothesis that the rate of confirmed overall hematologic response (CR+VGPR+PR) to treatment is at most 10% versus the alternative that the true hematologic response rate is 30% or greater.

A two-stage design will be used for patient accrual, with a total of 35 eligible patients who are evaluable for hematologic response per the definition in Section 11.2b below. *(24)* Patients who received at least one dose of study drug will be considered evaluable. Initially, 20 eligible, evaluable patients will be accrued. If one or fewer hematologic partial or better responses are observed in the first 20 patients, this treatment will be considered insufficiently active in this population and further accrual will be terminated. If two or more confirmed, partial or better responses are observed, then an additional 15 eligible, evaluable patients will be accrued. If at least 8 out of the total 35 patients have a confirmed response, the treatment may be recommended for further testing in subsequent studies. An estimated 39 patients will be enrolled to this study (including 35 eligible and evaluable patients, with 20 enrolled to Stage 1 and 15 enrolled to Stage 2, and with an additional 4 patients enrolled overall to account for ineligible and unevaluable patients).

With an estimated accrual rate of 1-2 patients per month, it is anticipated that the study will reach full accrual in 20 to 40 months.

11.2 Sample size and Power Justification

a. Assuming the number of hematologic responses is binomially distributed this design has a significance level of 2% and a power of 87% for detecting a true overall hematologic response rate of at least 30% versus the null hypothesis response rate of 10% of less.

b. All eligible patients who receive any study treatment will be considered to be evaluable for response and toxicity, and will be included in the analysis.

c. Patients who go off study or die prior to the first response assessment will be considered as non-responders.

11.3 Analysis of Primary Endpoint

The primary endpoint of this study is overall confirmed hematologic response rate (ORR), which includes partial response (PR), very good partial response (VGPR) and complete response (CR) as defined in Section 10.2.

Hematologic response will be reported with a binomial confidence interval. All eligible patients who received at least one day of treatment, including those that go off study or die prior to the first response evaluation, will be included in the calculation of response rates. The null hypothesis of a response rate of 10% or lower will be evaluated as described above, with potential adjustments to the critical values once the exact number of patients is determined.

11.4 Analysis of Secondary and Other Endpoints

Toxicity will be evaluated using the CTCAE Version 5.0 items. All eligible patients that have initiated treatment will be considered evaluable for toxicity analyses. The maximum Grade for each toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. Assuming 35 eligible, evaluable patients, any toxicity event seen with at least 5% probability is likely to be observed at least once (83% chance). With 35 eligible patients, response rates and rates of individual toxicities can be estimated to within +/- 17% (95% confidence interval).

Organ response will be evaluated in the subset of patients with evaluable organ involvement using current criteria Organ involvement will be considered evaluable if it qualifies based on the criteria defined in Section 10.3. There may be eligible patients whose organ involvement is based upon a feature (such as amyloid deposition or certain types of soft tissue involvement) that does not have an associated response/progression

definition. These patients will not be evaluated for organ response. The proportion of patients with organ response will be estimated as the number of patients with documented organ response out of the number of patients with documented evaluable organ involvement at baseline.

OS and PFS will be estimated using the Kaplan-Meier method.

11.5 Safety Analysis

There is no formal Data and Safety Monitoring Committee for this study. Accrual reports are generated weekly and study-specific accrual is monitored by the Study Chair, Study Statistician and the Disease Committee Chair.

There will be a run-in to ensure safety of this treatment combination. Ten patients will initially be treated. The following adverse events of special interest are specified as a potential safety concern, if a patient experiences one of them in the 1st cycle of treatment. If two or fewer patients experience any of the toxicities listed below during the first cycle of treatment, then accrual will continue as planned. If three or more patients experience at least one of these toxicities during the first cycle of treatment, the trial will be temporarily closed to accrual pending a decision as to whether to continue accrual. If accrual is re-opened, a protocol revision will include justification for continued accrual and for any treatment regimen modifications. If accrual is proceeding quickly, enrollment will be paused until all ten patients in the initial safety cohort have completed one cycle of treatment or experienced one of the events listed below.

Events to be monitored during safety run-in:

- Grade 3 and 4 infusion-associated reaction (IARs) defined as anaphylactic reaction, hypertension, or dyspnea.
- Grade 4 cardiac event (including CHF and arrhythmias) (or > 2 NYHA grades higher than patient baseline)
- Grade 4 neutropenia or thrombocytopenia that does not resolve to < Grade 3 within 10 days
- Grade 4 infection.
- Grade 4 gastrointestinal ileus, or obstruction.
- Grade 4 LFT abnormalities (AST, ALT, Bilirubin)

Reports summarizing adverse events, serious adverse events (SAEs) and treatment administration are provided monthly to the Study Chair and Study Statistician for monitoring. In addition, all SAEs, which by definition require expeditious reporting, are reviewed and processed by the Adverse Event Coordinator at the SWOG Operations Office and a physician reviewer based on data provided via the NCI CTEP-AERS system. Cumulative study-specific SAE reports are provided to the Study Chair and Study Statistician upon occurrence of an event. Formal reports summarizing the study are prepared for all SWOG members every 6 months.

12.0 DISCIPLINE REVIEW

This study will not utilize discipline review.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than 5 working days prior to planned start of treatment).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) <https://ctepcore.nci.nih.gov/rcr >. Documentation requirements per registration type are outlined in the table below

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and

IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR Help Desk by email at < RCRHelpDesk@nih.gov >.

b. CTEP Associate Registration Procedures

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For ques-tions, please contact the ***CTEP Associate Registration Help Desk*** by email at ctepreghelp@ctep.nci.nih.gov.

c. CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

1. IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

2. Downloading Site Registration Documents:

Site registration forms may be downloaded from the **S1702** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the SWOG link to expand, then select trial protocol **S1702** Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

3. Requirements For **S1702** Site Registration:

- CTSU Transmittal Sheet (optional)
- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4. Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office, via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

5. Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 888/823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website www.swog.org and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, you must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login https://login.imedidata.com/selectlogin using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members’ website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU help Desk at 888/823-5923 or by e-mail at ctsucontact@westat.com .

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site http://swog.org and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION:

Submit the following:

Onstudy Form

AL Baseline Tumor Assessment Form

Pathology report, confirming AL amyloidosis (as defined in Section 5.1)

If organ involvement was assessed by biopsy, submit the pathology report documenting the involvement (see Section 5.1d).

If patient has involvement of the liver or lymph nodes, submit radiology reports (ultrasound, CT, or MRI) to assess liver and lymph node size at baseline.

See Section 15.0 for specimen submission requirements.

b. WITHIN 35 DAYS AFTER REGISTRATION:

Submit the following:

S1702 Cytogenetics and FISH Analysis Form.

Institutional Flow Cytometry Report for Immunophenotyping and **S1702** Immunophenotyping Form

Institutional Cytogenetics Report, FISH Analysis Report, and Bone Marrow Aspirate and Biopsy Report

c. WITHIN 14 DAYS AFTER EACH CYCLE OF TREATMENT:

Submit the following:

S1702 Treatment Form

S1702 Adverse Event Form

AL Follow Up Tumor Assessment Form

d. WITHIN 30 DAYS OF DISCONTINUATION OF TREATMENT:

Submit the following:

Off Treatment Notice

S1702 Treatment Form

S1702 Adverse Event Form

AL Follow Up Tumor Assessment Form

e. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit the **S1702** Treatment Form and **S1702** Adverse Event Form (if the patient was still on protocol treatment),

Submit the AL Follow Up Tumor Assessment Form

f. EVERY 6 MONTHS FOR 4 YEARS AFTER REGISTRATION:

Submit the following:

Follow Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported).

g. WITHIN 14 DAYS OF SECOND MALIGNANCY:

Submit the following:

Follow Up Form

h. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death **and a final S1702** Treatment Form and **S1702** Adverse Event (if the patient was still on protocol treatment) or Follow-Up Form (if the patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 Translational Medicine and Banking (**OPTIONAL**)

Specimens for translational medicine and banking (submitted to the SWOG Biospecimen Bank– Solid Tissue, Myeloma and Lymphoma Division-Lab #201) (optional for patient):

a. With patient's consent, specimens (**peripheral whole blood, serum**, **bone marrow aspirate and bone marrow biopsy core**) must be collected prior to initiation of protocol therapy. Collection instructions are outlined in Section 15.1b and shipping instructions are outlined in Section 15.1c. (See also Section 9.0):

1. Tissue (frozen bone marrow biopsy core): Pretreatment (within 35 days prior to registration).

2. Blood (whole blood and serum) must be fresh drawn prior to treatment on Cycle 1, Day 1.

b. Specimen Collection Instructions:

1. Peripheral Whole Blood:

a. Fill one 4 mL lavender **plastic** EDTA tube completely with 4mL peripheral blood.

b. **Do NOT centrifuge**. **Immediately after collection**, mix by gently inverting the tube at least 8 to 10 times.

c. Clearly and appropriately label the sample tube (per instructions in the STS).

d. **Within 30 minutes of collection (after gently mixing), freeze** the blood in an upright position at -80ºC for storage until shipment. If freezer is not immediately available, samples must be stored on dry ice until shipment.

2. Bone Marrow Aspirate:

a. Collect 3 – 4 mL of bone marrow aspirate into a sodium heparin (NaHep, green top) tube.

b. Mix gently by inverting the tube 8 to 10 times. Do not centrifuge and do not freeze.

* Note that marrow specimens should be submitted within 24 hours of draw for viability.

3. Bone Marrow Biopsy Core:

a. Biopsy core specimen should be 1 – 2 cm in length.

b. Snap-freeze immediately after resection.

* Note that marrow specimens should be submitted within 24 hours of draw for viability.

4. Serum:

a. Collect 5 – 7 mL of blood into a red top tube.

b. Allow blood to clot (30 – 60 minutes) before processing. Refer to processing instructions on the SWOG website (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures.

5. Additional specimen collection, labelling, and shipment instructions for the serum, bone marrow aspirate and bone marrow biopsy core specimens can be accessed on the SWOG Specimen Submission webpage: www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures.

6. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

c. Specimen Labeling

1. Blood, serum, and bone marrow labels should include:
   - SWOG patient number
   - Patient initials
   - Collection date (date the specimen was collected from the patient)
   - Laterality (bone marrow only – e.g. left, right)

2. Tissue specimen labels should include:
   - SWOG patient number*
   - Patient initials
   - Collection date (date the specimen was collected from the patient)
   - Collection site (e.g., lymph node)
   - Specify if the tissue is from Primary (P) or Metastatic (M)
   - Surgical Pathology ID (SPID) and Block number (e.g., A2, 3E, 2-1, etc.)

   * To obtain a SWOG Patient ID prior to patient registration, go to the SWOG specimen tracking system (https://crawb.crab.org/TXWB/ctsulogon.aspx) and select "Specimen Tracking." Use the "Log a Specimen" link from the Specimen Tracking Home page. Use the "No Patient ID yet?" link and enter demographic information for the patient on the next page. This will assign a SWOG patient ID number and will remain the patient's ID number. **If the patient does register to the study, it is important to remember to use this patient ID number on the OPEN system so the specimens will match with the correct patient.** Specimens will be destroyed if the patient is not subsequently registered to the study.

d. SHIPPING SAMPLES

1. SWOG Specimen Tracking System (STS)

   All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site http://swog.org and logon to the Members Area. After you have logged on using your SWOG roster ID number and password, click on the CRA Workbench link to access the home page for CRA Workbench website. Non- SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://spectrack.crab.org (select the option "SWOG – SWOG – CTSU"). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

   A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the

specimen bag if it has one, or in a separate resealable bag. The Specimen Submission Form is NOT required when the online system is used.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://spectrack.crab.org/Instructions); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of **peripheral whole blood, serum**, **bone marrow aspirate and bone marrow biopsy core samples** for SWOG Biospecimen Bank for Translational Medicine and banking is identified as follows:

Lab #201: SWOG Biospecimen Bank
Solid Tissue, Myeloma and Lymphoma Division
Phone: 614-722-2865
Contact: SWOG Bank Coordinator
Email: bpcbank@nationwidechildrens.org

2. Federal guidelines for the shipment of blood products:

   a. The tube must be wrapped in an absorbent material.

   b. The tube must then be placed in an AIRTIGHT container (like a resealable bag).

   c. Pack the resealable bag and tube in a Styrofoam shipping container.

   d. Pack the Styrofoam shipping container in a cardboard box.

   e. Mark the box "Biohazard".

e. Obtaining SWOG Patient ID Prior to Patient Registration

To obtain a SWOG patient ID for purposes of specimen submission prior to registration, use the SWOG specimen tracking system (https://crawb.crab.org/TXWB/ctsulogon.aspx). Select “Specimen Tracking,” then click the “Log a Specimen” link from the Specimen Tracking Home page, and then the “No Patient ID yet?” link. Enter demographic information for the patient on the next page. This will assign a SWOG patient ID number and will remain the patient’s ID number. If the patient does register to the study, it is important to remember to use this patient ID number on the OPEN system, so the specimens will match with the correct patient. Specimens will be destroyed if the patient is not subsequently registered to the study. Note that patients must sign consent prior to specimen submission.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent
The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review
This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability
An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Monitoring
This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, all adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

Confidentiality
Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to SWOG by telephone at 210-614-8808, or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table 16.1.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in this study isatuximab (SAR650984). If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse events that Occur on Studies under an Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] Isatuximab (SAR650984).

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or Section 16.1f.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 and Early Phase 2 Studies Utilizing an Agent under a non-CTEP-IND:**

1. **Group-specific instructions.**

Supporting Documentation Submission - Within **5 calendar days** submit the following to the SWOG Operations Office by fax to 210-614-0006 or mail to the address below:

- Printed copy of the first page of the CTEP-AERS report
- Copies of clinical source documentation of the event
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center, copies of Off Treatment Notice and/or Notice of Death.

2. The adverse events listed below also require expedited monitoring for this trial:

- ≥ Grade 3 infusion-associated reactions (IARs);
- Acute IARs Grade 3 or 4. An IAR is an AE related to isatuximab typically with onset within 24 hours from the start of isatuximab infusion
- Symptomatic overdose (serious or nonserious) with study treatment
- An overdose (accidental or intentional) with the study treatment is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as:
- Increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.
- Of note, asymptomatic overdose has to be reported as a standard AE.

3. For study arm(s) [applicable study arm(s)], the adverse events listed below do **not** require expedited reporting via CTEP-AERS: None.

g. Reporting Secondary Malignancy, including AML/ALL/MDS

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

2. Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. **Reporting Pregnancy, Pregnancy Loss, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Pregnancy Loss** Pregnancy loss defined in CTCAE as "Death in utero"**. Pregnancy loss** should be reported expeditiously as **Grade 4 "pregnancy loss" under the Pregnancy, puerperium and perinatal conditions** SOC.

A pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

3. **Death Neonatal** Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth.

   A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERs recognized this event as a patient death.

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

i. Sanofi-Direct Additional SAE Reporting Requirements

1. Pregnancy reporting:

   In the event that the partner of a study participant becomes pregnant while the participant is on study treatment, additional reporting of pregnancy information to Sanofi is requested.

   In the event of such a pregnancy, the site must make reasonable efforts to obtain consent from the study participant's partner for pregnancy reporting. The additional consent is the responsibility of the site and must take place according to local Institutional Review Board requirements. A sample consent template is included as Appendix 18.4.

   If consent is obtained, information about the pregnancy and the outcome of the pregnancy must be reported via the Sanofi Exposure During Pregnancy (EDP) Form. The form must be submitted directly to Sanofi according to the instructions on the form included in Appendix 18.5.

   Institutional support for this additional data collection and submission may be obtained by submitting the Pregnancy Reporting Reimbursement Form, which is located on the protocol abstract page of the SWOG website (www.swog.org) or the CTSU website (www.ctsu.org). Note that this additional support is available ONLY to institutions submitting the Sanofi Exposure During Pregnancy Form in the event that a female partner of a study participant becomes pregnant. Pregnancy and outcome information submitted via CTEP-AERS performed in accordance with NCI guidelines as part of regular adverse event reporting requirements is not reimbursed.

2. Additional information

   Reporting information provided in the protocol takes precedence over information provided in the supplemental reporting requirements.

17.0 BIBLIOGRAPHY

1 Gertz MA. Immunoglobulin light chain amyloidosis: 2011 update on diagnosis, risk-stratification, and management. Am J Hematol 86(2): 180-6, 2011. PMID: 21264900.

2 Cibeira MT, Sanchorawala V, Seldin DC, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. Blood 118(16):4346-52, 2011. PMID: 21828140.

3 Palladini G, Perfetti V, Perlini S, et al. The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL). Blood 105:2949-5, 2005. PMID: 15572585.

4 Sanchorawala V, Skinner M, Quillen K, et al. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation. Blood 110(10):3561-3, 2007. PMID: 17673601.

5 Dispenzieri A, Buadi F, Laumann K, et al. Activity of pomalidomide in patients with immunoglobulin light-chain amyloidosis. Blood, 119(23), 5397-5404, 2012. PMID: 22493299.

6 Kastritis E, Anagnostopoulos A, Roussou M, et al. Treatment of light chain (AL) amyloidosis with the combination of bortezomib and dexamethasone. Haematologica. 92(10):1351-8, 2007. PMID: 18024372.

7 Reece DE, Sanchorawala V, Hegenbart U, et al. Weekly and twice-weekly bortezomib in patients with systemic AL amyloidosis: results of a phase 1 dose-escalation study. Blood 114:1489–97, 2009. PMID: 19498019.

8 Mikhael JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood. 10;119(19):4391-4, 2012. PMID: 22331188.

9 Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet. 2016 Apr 9;387(10027):1551-60. Epub 2016 Jan 7. PMID: 26778538.

10 Sher T; Fenton B, Gertz, M, et al. First report of safety and efficacy of daratumumab in two cases of advanced immunoglobulin light chain amyloidosis. Blood. http://dx.doi.org/10.1182/blood-2016-06-722496. 2016.

11 Stanford U. (Kaufman GP, et al: Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. Blood, 2017).

12 Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. Am J Hematol. Aug;79(4):319-28, 2005. PMID: 16044444.

13 Bortezomib with or without dexamethasone in primary systemic (light chain) amyloidosis.. J Clin Oncol. Feb 20;28(6):1031-7. doi: 10.1200/JCO.2009.23.8220. Epub 2010 Jan 19, 2010. PMID: 20085941.

14 Palladini G, Hegenbart U, Milani P, et. al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood. Oct 9;124(15):2325-32. doi: 10.1182/blood-2014-04-570010. Epub 2014 Aug 12, 2014. PMID: 25115890.

15 Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. Jan;23(1):3-9. doi: 10.1038/leu.2008.291. Epub 2008 Oct 30, 2009. PMID: 18971951.

16 Comenzo RL, Reece D, Palladini G, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. Leukemia 26, 2317–2325; doi:10.1038/leu.2012.100, 2012. PMID: 22475872.

17 Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, April 18-22, 2004. Am J Hematol. Aug;79(4):319-328. 2005. PMID: 16044444.

18 Comenzo RL[1], Reece D, Palladini G, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis, 2012.100. leu. Epub Apr 5, 2012. PMID: 22475872.

19 Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, April 18-22, 2004. Am J Hematol. Aug;79(4):319-328. 2005. PMID: 16044444.

20 Palladini G, Hegenbart U, Milani P, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood. Oct 9;124(15):2325-32. 2014. PMID: 25115890.

21 Palladini G, Dispenzieri, A, Gertz MA. New Criteria for Response to Treatment in Immunoglobulin Light Chain Amyloidosis Based on Free Light Chain Measurement and Cardiac Biomarkers: Impact on Survival Outcomes. J Clin Oncol. Dec 20;30(36):4541-9. 2012. PMID: 23091105.

22 Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology. 79(8):785-92; 2012. PMID: 22843282.

23 Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology. 79(8):785-92; 2012. PMID: 22843282.

24 Green S. and Dahlberg S. Planned versus attained design in Phase II clinical trials. Statistics in Medicine 11:853-862, 1992

18.0 APPENDIX

18.1 New York Heart Association Classifications

18.2 Neuropathy Impairment Scale – Lower Limbs

18.3 SWOG Biospecimen Bank Appendix

18.4 Sanofi-Direct Pregnancy Reporting Consent

18.5 Sanofi Exposure During Pregnancy (EDP) Form

18.6 Isatuximab Type and Screen Card

18.7 Measuring Orthostatic Blood Pressure

18.1 New York Heart Association Classifications

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability To Work**
I	None	None	None	Full Time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

18.2 Neuropathy Impairment Scale – Lower Limbs

The NIS (LL is a scoring system graduated from 0 points (the normal finding) to a maximum of 88 points (the absence of all motor, sensory, and reflex activity in the lower extremities). The scale is additive of all deficits (64 potential points for muscle strength, 8 points for reflexes, and 16 points for sensory function) in the lower extremities.

Instructions: Complete each assessment outlined below and assign a score for the right side and for the left side.

S1702 Patient ID: ___ ___ ___ __ ___ ___

Date of Visit: _____

□ Registration □ Cycle ___, Day 1 □ Post-Treatment (Pre-Hematolgic Progression)	□ Post-Adverse Event Follow-up □ Unscheduled Visit

Assessment	***Right***	***Left***	***Sum***
Muscle Weakness Score each assessment as: 0: normal, 1: 25% weakened, 2: 50% weakened, 3: 75% weakened, 4: paralysis			
Hip Flexion (iliopsoas)			
Hip Extension (gluteus max.)			
Knee Flexion (biceps femoris)			
Knee Extension (quadriceps)			
Ankle Dorsiflexors (tibialis ant. +)			
Ankle Plantar Flexors (gastroc. soleus)			
Toe Extensors			
Toe Flexors			
Reflexes Score each, assessment as: 0: normal, 1: reduced, 2: absent			
Quadriceps femoris			
Triceps surae/gastroc. soleus			
Sensation: Great Toe (terminal phalanx) Score each assessment as: 0: normal, 1: reduced, 2: absent			
Touch pressure			
Pinprick			
Vibration			
Joint position			
Total Score:_____			

Source: Dyck PJ, Litchy WJ, Lehman KA, et al. Variables influencing neuropathic endpoints: the Rochester Diabetic Neuropathy Study of Healthy Subjects. *Neurology*. 1995e45(6):1115(21.

Performed by (Print Name): _____

_____ Date:_____/_____/_____
Signature dd mm yyyy

18.3 SWOG Biospecimen Bank Appendix

Specimen Receipt, Processing, and Storage

The SWOG Biospecimen Bank will receive frozen serum, frozen blood, snap-frozen bone marrow biopsy, and fresh bone marrow aspirate.

The Bank will accession and barcode frozen specimens for long-term storage; serum and frozen blood will be stored in a -80°C freezer for long-term storage, and the bone marrow biopsy will be stored in a liquid nitrogen vapor phase freezer.

The fresh bone marrow aspirate will be processed using a ficoll-hypaque gradient, and the resulting cells wil be sorted (CD138 +/-), aliquoted into 1 x 10^7 cells per vial, and stored in a liquid nitrogen vapor phase freezer until distribution.

Distribution of Specimens from the SWOG Biospecimen Bank to TM Investigators:
At the end of the study, the Bank will receive a list of specimens for distribution.

Frozen Whole Blood will be shipped to the SWOG Biospecimen Bank for extraction, and then forwarded to Sanofi for genotyping analysis.

18.4 Sanofi-Direct Pregnancy Reporting Consent

* NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

- This template Sanofi-direct pregnancy reporting consent is provided as a tool to be used in the event that the female partner of a male study participant becomes pregnant while the study participant is on study treatment. This consent is not mandatory for female partners of all male patients, only those who will submit additional pregnancy information to Sanofi. Sites may use local pregnancy reporting consent forms providing that they include adequate information as provided in this document, and pregnancy reporting consent is obtained in some written and IRB approved form prior to reporting pregnancy information to Sanofi. *Note that patients consent to pregnancy prevention as part of the clinical trial consent, so pregnancy events are not expected during the trial.*

- This template has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. It is suggested that sections of this document that are in bold type be used in their entirety.

* These notes for investigators are instructional and should not be included in the informed consent form given to the prospective participant.

Sanofi-Direct Pregnancy Reporting Consent for Female Partners of Male Study Participants

What is the purpose of this consent form?

You are the partner of a male study participant that took the drug isatuximab as part of the study **S1702**, and you have become pregnant. Sanofi, the drug's manufacturer, is trying to learn more about how the drug affects the developing baby and the pregnancy. They would like to collect information about you, your pregnancy, the baby's development during the pregnancy, and the outcome of the pregnancy. This will help them to better inform future patients and the partners of future patients who receive the drug about what their pregnancy risks might be. The purpose of this consent form is to ask your permission for the study doctor/nurse to collect this information and provide it to Sanofi. If you accept, your medical information regarding the pregnancy may be shared with people or groups associated with the study.

Procedures

Study participants should not father a child during the study treatment, or for up to 12 weeks after the study is over. The participant's consent form for the treatment study discussed this in more detail. Information on your sex life habits might be collected.

If a participant fathers a child during the study treatment or for up to 12 weeks after the study is over, they are asked to notify the study doctor within 24 hours of finding out that their partner is or might be pregnant. The pregnant female partner will be asked to provide information about the pregnancy and the baby for at least one year after the birth.

The information Sanofi will ask for is as follows:

- What are the first date of your last menstrual period and estimated date of conception?
- When during your pregnancy was the first exposure to the drug?
- Do you have any other risk factors that would affect the pregnancy (high blood pressure, diabetes, history of abnormal pregnancy, etc.)?
- Did you smoke, drink alcohol, or use any illegal drugs during the pregnancy?
- How many previous pregnancies and children have you had, and were there any problems?
- Outcome of the pregnancy (birth, stillbirth, miscarriage, etc.)?
- Was the baby born with any abnormalities?
- Is the baby male or female, and what is his/her length, weight and head measurement?

Your personal identifying information will not be provided to Sanofi. Your partner's SWOG patient ID will be the only identifying information sent. Sanofi will not have access to the secure study database for **S1702** that links SWOG patient IDs to patient identifying information.

If you consent, the study doctor/nurse will gather this information on a form and send it to Sanofi. The information will be sent over a secure system. The doctor/nurse may need to ask you questions to get the necessary information. Sanofi will put your information into a database with the information from others who have provided pregnancy information, and analyze it to see if and how the drug has affected the reported pregnancies. They will need to collect this information throughout your pregnancy and for a year after your baby is born – at the time you initially learn of the pregnancy, at the time of any event during the pregnancy, at the end of the pregnancy, and a year after the baby is born.

You will be told about any new information that might change your decision to be in this follow-up.

You may be asked to sign a revised consent form if this occurs.

If you do not sign this consent, it will not affect your or your partner's treatment on the **S1702** study.

By signing this consent form, you are agreeing to allow the information about you, your pregnancy, and your baby's development during the pregnancy and up to a year after your baby is born to be sent to Sanofi.

What possible risks are there?

Since this follow-up is observational only, no physical risk is expected.

If you provide this information, you may be asked sensitive or private questions about you and your pregnancy and sexual activity which you normally do not discuss. You may have some emotional discomfort from answering these questions.

There is also a possible risk that your personal or medical information or your child's personal or medical information might be compromised. Secure programs and procedures are in place to protect your personal information, your personal information is not provided to Sanofi, and we will do our best to make sure that personal information is kept private. However, we cannot guarantee total privacy. There is a chance that some of this personal or medical information may be given out as required by law. If any information that is sent to Sanofi is published or presented at scientific meetings, your name and personal identifying information will not be used.

What possible benefits can I expect?

This is not a treatment study. You are not expected to receive any direct medical benefits from this follow-up.

The information from this follow-up may lead to a better knowledge and treatment in the future for pregnant women and fetuses who could be exposed to isatuximab.

You will not be paid for your participation in this follow-up.

What are the costs?

You will not have any costs for being in this follow-up.

This follow-up will not cover any costs related to your pregnancy, delivery or care of your child. You and/or your medical/hospital insurance carrier will still be billed for your regular medical care expenses as they normally would.

Can I stop providing information?

Your participation in this follow-up is voluntary. You can decide to stop providing information to Sanofi at any time. However, information that has already been sent cannot be taken back. If you decide to stop, no further information about you, your pregnancy, or the pregnancy outcome will be sent to Sanofi.

Your decision will not result in any penalty or loss of benefits to which you or your child are entitled.

Your participation in this follow-up may be stopped at any time by your doctor or the sponsor without your consent for any reason.

Who can answer my questions about this?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

Signature

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in this follow-up.

Partner's signature_____

Date of signature_____

18.5 Sanofi Exposure During Pregnancy (EDP) Form

Complete whenever an embryo or fetus has been exposed to isatuximab.

Submit via e-mail as soon as pregnancy of female partner of male patient has been diagnosed.

E-mail: corina.oprea@sanofi.com and derya.cetiner-ext@sanofi.com

Pregnancy

First Date of Late Menstrual Period (DD-MM-YYYY): _____

Estimated Date of Conception (DD-MM-YYYY): _____

Relevant History

Risk factors for adverse pregnancy outcomes including environmental or occupational exposures, e.g. hypertension, diabetes, etc. Family history of congenital abnormality/genetic diseases, consanguinity (or any family relation or lineage) between parents (specify degree):

1) Did mother smoke during pregnancy?

☐ No ☐ Yes: Number per day? _____

2) Did the mother drink alcohol during the pregnancy?

☐ No ☐ Yes: Frequency? _____

3) Did the mother use illicit drugs during the pregnancy?

☐ No ☐ Yes: Frequency? _____

Obstetrical History
Number of previous pregnancies/children. Outcome of previous pregnancies (live birth, miscarriage, elective termination, late fetal death, ectopic pregnancy, molar pregnancy). Previous maternal pregnancy complications. Previous fetal/neonatal abnormalities and type. History of sub-fertility.:

Exposure to Products: Maternal
Were any drugs (e.g., OTC, medical prescription) taken by the mother during the pregnancy?

☐No

☐Yes, please specify (for each drug):

Drug Name:
Indication:
Start Date:
Stop Date:
Reason for Stopping:
Dose:
Formulation:
Frequency:

Drug Name:
Indication:
Start Date:
Stop Date:
Reason for Stopping:
Dose:
Formulation:
Frequency:

Drug Name:
Indication:
Start Date:
Stop Date:
Reason for Stopping:
Dose:
Formulation:
Frequency:

Drug Name:
Indication:
Start Date:
Stop Date:
Reason for Stopping:
Dose:
Formulation:
Frequency:

(Include Product Indication; Start Date \ Stop Date; Reason for stopping; Dose; Formulation and Frequency for each drug taken)

Outcome of Pregnancy Date of outcome (DD-MM-YYYY): _____

Check one

☐Full term live birth ☐Preterm live birth ☐Stillbirth

☐Spontaneous abortion/miscarriage ☐Induced abortion ☐Unknown

Gestational age at birth in weeks, (if known): _____

Infant

Check one

☐Normal ☐Congenital Malformation/Anomaly**

☐Other neonatal problem** ☐Unknown

☐Other neonatal problem/abnormality (include dysmaturity, neonatal illness, hospitalization, drug therapies) Specify:_____

Apgar Score: 1min _____ 5min _____

☐Male ☐ Female

Birthweight_____grams

Or, if birthweight in grams unknown: Birthweight ☐ lb ☐oz

Length at birth: in cm Head Circumference at birth: _____☐ in ☐cm

*****Complete also the Serious Adverse Event section of the report, specifying the diagnosis as the Serious Adverse Event***

18.6 Isatuximab Type and Screen Card

Patient Last Name: _____**First Name:** _____

Subject/Patient Date of Birth: I_ ._ I_ ._ I_ ._ ._ ._ I

I am being treated with **ISATUXIMAB, which may interfere with type and screen test results.**

Since: I_ ._ I_ ._ I_ ._ ._ ._ I (MM/DD/YYYY) **Until : I_ ._ I_ ._ I_ ._ ._ ._ I** (MM/DD/YYYY)

The blood bank should be aware that you are receiving an anti-CD38 treatment (isatuximab) before any red blood cells transfusion:

Before starting isatuximab my blood test results collected on ___/ _/ ___ were (MM/DD/YYYY)

Blood type: _____
Indirect Coombs test (antibody screen): _____

Contact details of institution where the blood tests were performed: _____
_____
_____
_____

Note to Transfusion Services: Treatment with anti-CD38 antibodies can result in interference with blood bank serologic tests. Please review the bulletin from the American Association of Blood Banks for more information on this potential interference (http://www.aabb.org/programs/publications/bulletins/Documents/ab16-02.pdf#search=anti%3DCD38).

18.7 Measuring Orthostatic Blood Pressure

Instructions:

1. Have the patient lie down for 5 minutes.
2. Measure and record blood pressure and pulse rate.
3. Have the patient sit for 1-2 minutes.
4. Measure and record blood pressure and pulse rate.
5. Have the patient stand for 1-2 minutes (stand by patient for safety).
6. Measure and record blood pressure and pulse rate.

A drop in blood pressure of > 20 mm Hg, or in diastolic blood pressure of >10 mm Hg, or experiencing lightheadedness or dizziness is considered abnormal.

Note: The remainder of this form is provided as a tool and may be used and maintained in the patient chart; however, sites are not required to use or maintain this form.

Recording Measurements

Patient ID: Date: Time:

You do not need an order for measuring Orthostatic Blood Pressure. Position		**Time**	**Blood Pressure and Heart Rate**	**Associated Symptoms**
Lying down		**5 minutes**	**BP_____/_____ HR_____ BP _____/_____**	
Sitting		**1-2 minutes**	**HR_____ BP_____/_____ HR_____**	
Standing		**1-2 minutes**	**HR_____ BP_____/_____ HR_____**	

Symptoms of Orthostatic Hypotension	**Patients Most at Risk**
Dizziness, feeling faint	Older patients (approx. 20% of people > 65)
Light headedness	HI Bleed/Anemic
Blurred vision	Dehydration
Disorientation and confusion	Surgical patients
Weakness/fatigue/falling	Diabetics
Chest pain	Heart disease

Expectation: Perform Orthostatic BP on all high-risk patients at least once per shift.

Adapted from Tip Sheet available at

http://www.hret-hiin.org/Resources/falls/16/measuring_orthostatic_blood_pressure_tip_sheet_3.7.16.pdf.