MSK PROTOCOL COVER SHEET

A Phase II Study of IL-6 Receptor Antagonist Tocilizumab to Prevent Respiratory Failure and Death in Patients with Severe COVID-19 Infection (COVID)

Principal Investigator/Department: Boglarka Gyurkocza, MD / Medicine

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Objectives: The primary objective of the study is to evaluate the impact of tocilizumab administration on progression of respiratory failure due to severe COVID-19 infection. The secondary objectives of the study include evaluations of mortality, ventilator free days for both cohorts of patients, safety, change in levels of interleukin-6 (IL-6), C-reactive protein (CRP), ferritin, chest imaging, coagulation parameters and antibody formation and SOFA score.

Patient Population: Patients (pts) with documented severe COVID-19 infection, who will be treated in two concurrent cohorts: Cohort #1: pts who manifest dyspnea, pulse oxygenation $\leq$ 93% on room air or with respiratory rate >/= 30 breaths/min, elevated IL-6 level and fever or suspected respiratory infection, who have not been intubated, and Cohort #2: pts who have been intubated and demonstrate an elevated IL-6 level.

Study Design: This is a phase II study investigating the efficacy and safety of IL-6 receptor antagonist tocilizumab in reducing the rates of progressive respiratory failure and death in patients presenting with severe COVID-19 infection. Outcomes of the two cohorts will be evaluated separately. Standard clinical tests will be obtained before each administration and at termination from the study. Clinical parameters related to cytokine release syndrome (CRS) will be evaluated before each tocilizumab administration and at end of study.

Treatment Plan: Patients will undergo evaluation with designated tests. They will be treated with tocilizumab 8 mg/kg intravenous (i.v.) at time of enrollment. If there are no clinically significant adverse effects (i.e. safety issues), and clinical condition persists, the patient can receive a second dose at 24hr -5 days.

In the case of refractory or worsening respiratory failure, patients will be discontinued from this study and can be managed with other investigational therapy or standard of care per MSKCC.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

To evaluate the impact of tocilizumab administration on progression of respiratory failure in patients infected with severe COVID-19.

Secondary Objective:

1. Overall survival
2. Protocol-defined therapeutic response to tocilizumab, as specified in Section 13.1
3. Mechanical ventilation-free days (for both cohorts) at 4weeks.
4. To assess the safety of tocilizumab in patients with severe COVID-19 infection.
5. To assess treatment impact on CRP, IL-6 and cytokine levels, ferritin, lymphocyte

phenotypes, coagulation parameters, immunoglobulin levels and antibody levels.

6. To assess the impact on supplemental oxygen requirement, chest imaging and fever.
7. To assess SOFA scores following tocilizumab administration in patients with severe COVID19 admitted to ICU who are intubated, on mechanical ventilation (cohort #2, Appendix 1)
8. To assess ability to produce antibody against SARS-CoV-2

3.0 BACKGROUND AND RATIONALE

3.1. Coronavirus Disease 2019 (COVID-19)

Coronavirus disease 2019 (COVID-19) is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) resulting in symptoms of fever, cough and shortness of breath. SARS-CoV-2 is a highly pathogenic coronavirus that infects the upper and lower respiratory tract, causing a mild or highly acute respiratory syndrome (ARS). Data from China have indicated that about 20% of patients developed severe disease. Severe disease (severe pneumonia) in adolescents and adults is defined by the World Health Organization as fever or suspected respiratory infection plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 =< 93% on room air ("Clinical management of severe acute respiratory infection [SARI] when COVID-19 disease is suspected. Interim guidance issued on 13 March 2020). Older adults, particularly those with serious underlying health conditions, are at higher risk of death than younger individuals. A minority of patients presented with respiratory failure, septic shock and multi-organ dysfunction, resulting in a fatality of approximately 4.1%[1].
In a series of 41 patients with laboratory-confirmed SARS-CoV-2 infection who required hospital admission the most common symptoms at onset of illness were fever (98%), cough (76%), and myalgia or fatigue (44%); less common symptoms were sputum production (28%), headache (8%), hemoptysis (5%), and diarrhea (3%)[2]. Dyspnea developed in 55% of patients (median time from illness onset to dyspnea 8.0 days [IQR 5·0–13·0]). 63% of 41 patients had lymphopenia. All 41 patients had pneumonia with abnormal findings on chest CT. Complications included ARS (29%), RNAaemia (15%), acute cardiac injury (12%) and secondary infection (10%). Of the 41 patients, 13 (32%) were admitted to an ICU and six (15%) died. In this series, when compared with non-ICU patients, ICU patients had higher plasma levels of IL2, IL7, IL10, IP10, MCP1, MIP1A, and TNFα.

3.2 Associated Cytokine Release Syndrome (CRS)

The pathophysiology of unusually high pathogenicity for SARS-CoV and has not been completely understood. Early studies have shown that increased amounts of proinflammatory cytokines in serum (e. g, IL1B, IL6, IL12, IFN-γ, IP10, and MCP1) were associated with pulmonary inflammation and extensive lung damage in patients with severe ARS[3]. In a case study, Xu et al. reported lung biopsies of a patient with COVID19 showing bilateral diffuse alveolar injury with cytomyxoid fibroma exudate, and subsequent peripheral flow cytometry analysis revealed a decrease in CD4 and CD8 cells, but an increase in the Th17 cell population[4]. Th17 cells are helper T cells differentiated from Th0 cells mainly stimulated by IL-6 and IL-23[5].

The SARS-CoV-2 binds to alveolar epithelial cells, then the virus activates the innate immune system and adaptive immune system, resulting in the release of a number of cytokines, including IL-6. In addition, due to the activity of these pro-inflammatory factors, vascular permeability increases, leading to a release of fluid and blood cells into the alveoli, resulting in dyspnea and even respiratory failure[6-8].

Consistent with others, Zhang et al. reported high levels of pro-inflammatory cytokines in most of the severe COVID-19 patients requiring ICU admission, including high levels of erythematosus sedimentation rate (ESR), C-reactive protein (CRP), and high levels of IL-6,TNFα, IL-1β, IL-8, IL2R, etc., which were associated with acute respiratory distress syndrome (ARDS), hypercoagulation and disseminated intravascular coagulation (DIC), manifested as thrombosis, thrombocytopenia, and gangrene of the extremities. Based on these data, they concluded that CRS might have exacerbated the lung damage as well as contributed to other fatal complications[9]. Siddiqi et al. proposed a 3-stage clinical classification model, recognizing that COVID-19 illness exhibited three grades of increasing severity which corresponded to distinct clinical findings, response to therapy and clinical outcome (Siddiqi et al., J Heart Lung Transplant, 2020). A small proportion of COVID-19 patients would transition into the third and most severe stage of illness, which manifested as an extra-pulmonary systemic hyperinflammatory syndrome. In this stage, markers of systemic inflammation appeared to be extremely elevated.

Based on the above, we hypothesize that CRS plays an important role in severe cases of COVID-19, so neutralizing key inflammatory factors in CRS will be of great value in reducing mortality in severe cases.

3.3 Role of IL-6 blockade

Interleukin-6 (IL-6) is an important member of the cytokine network and plays a central role in acute inflammation[10]. When IL-6 was first identified, it was characterized according to its ability to promote the population expansion and activation of T cells, the differentiation of B cells, and regulation of the acute-phase response[11-17].

Almost all stromal cells and cells of the immune system produce IL-6, and while IL-1b and tumor-necrosis factor are major activators of IL-6 expression, other pathways such as Toll-like receptors, prostaglandins, adipokines, stress responses and other cytokines can also promote its synthesis. IL-6 is controlled at multiple levels by microRNAs (for example, let-7a), RNA-binding proteins (for example, Lin28B and Arid5a), RNases (for example, regnase-1) and circadian control factors such as the product of the 'clock gene' *Per1* (refs. 18–20). Normal physiological concentrations of IL-6 in human serum are relatively low (1–5 pg/ml), but these are rapidly elevated in disease settings and in extreme circumstances, such as meningococcal septic shock. Thus, IL6 expression is subject to both homeostatic basal regulation and rapid induction in the context of infection, autoimmunity or cancer in which increases in IL-6 are often a better predictor of disease activity than is CRP[18-20].

IL-6 plays a central role in cytokine storm and in acute inflammation. IL-6 is a multi-effective cytokine with anti-inflammatory and pro-inflammatory effects. There are three main pathways of IL-6 signal transduction[10,21] see Figure 1.: 1. classical signal transduction (Figure 1A), 2. trans signal transduction (Figure 1B) and 3. trans presentation (Figure 1C).

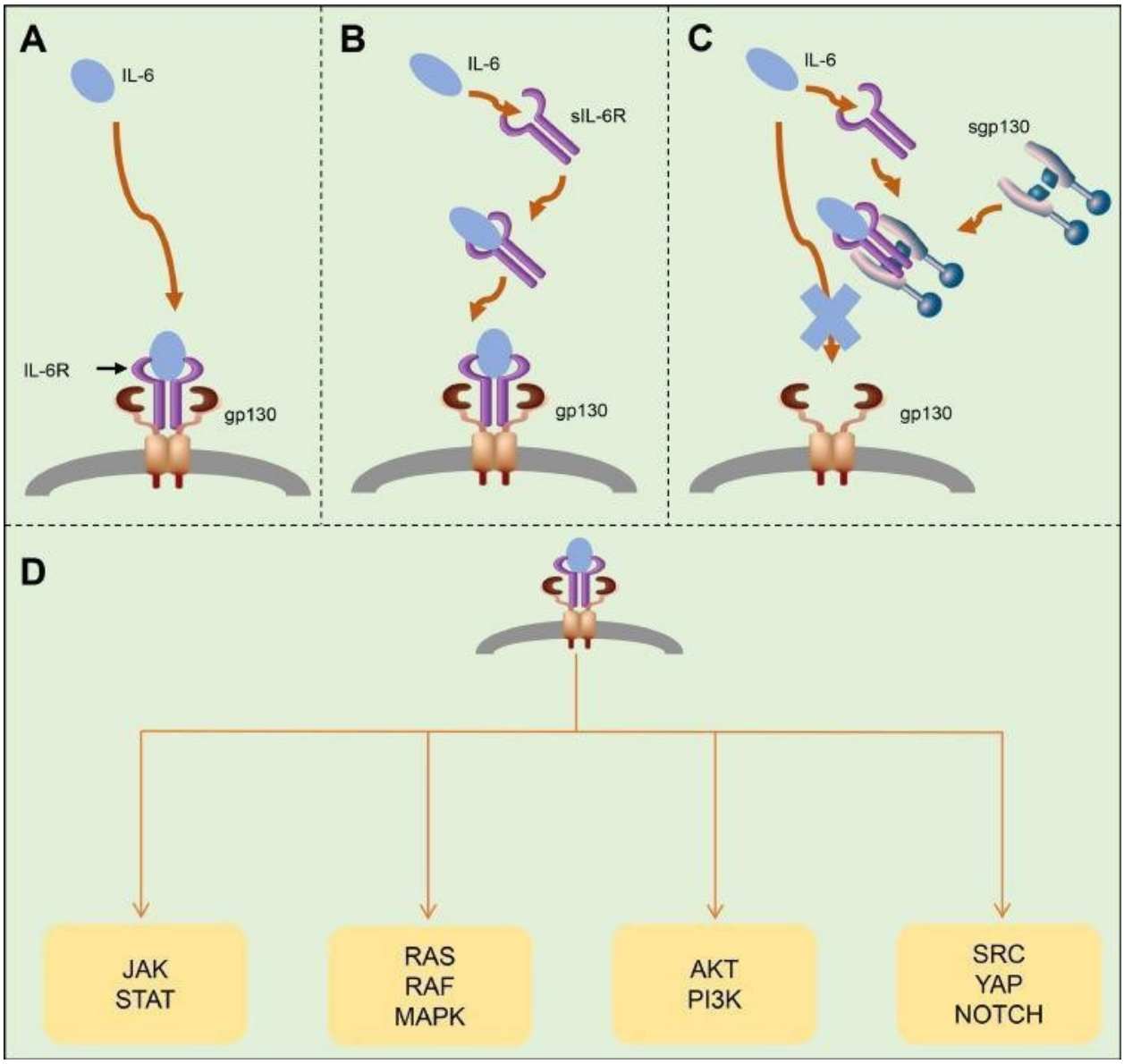

Figure 1. Signal transduction pathway of IL-6. (A) classical signal transduction; (B) trans signal transduction; (C) trans presentation; (D) The next step is to activate the JAK-STATA (STAT1, STAT3 and, to a lesser extent, STAT5) pathway, in addition, RAS-RAF pathway, SRC-YAP-NOTCH pathway, and AKT-PI3K pathway also being activated. So as to promote complex biological functions such as proliferation, differentiation, oxidative stress, immune regulation and so on adapted from Zhang et al.[1].

In the classical signal transduction pathway[22], IL-6 binds to its receptor IL-6R to form a complex, and then binds to the membrane protein gp130 to initiate intracellular signal transduction. IL-6R exists not only in a transmembrane form, but also in a soluble form. IL-6 binds to these two forms and then interacts with gp130 to trigger downstream signal transduction and gene expression[23-25]. In the trans signal transduction pathway, the binding affinity of sIL-6R to IL-6 is similar to that of IL-6R, and this

complex binds to gp130, which initiates intracellular signal transduction. In the classical signal pathway, many cells cannot respond to IL-6 signal because they do not express IL-6R, but some of these cells can be stimulated by sIL-6R-IL-6 complex to respond to IL-6 signal and cause cell signal transduction[26,27]. The trans presentation signal is suppressed by extracellular sgp130, and sgp130 can form a complex with sIL-6R to prevent sIL-6R from binding to membrane-bound gp130[28]. The next step is to activate the JAK-STATA (STAT1, STAT3 and, to a lesser extent, STAT5) pathway, in addition, the RAS-RAF pathway, the SRC-YAP-NOTCH pathway[29], and AKT-PI3K pathway (Figure 1D)[1].

Effects of IL-6:

A. Effect on B lymphocytes[11]: IL-6 can induce B cells to proliferate, differentiate and produce antibodies. IL-6 is especially needed when B cells are activated by antigen and differentiate to produce IgM, IgG and IgA antibodies.
B. Effect on T lymphocytes[30]: IL-6 is the terminal helper factor of cytotoxic T lymphocytes (CTL), which can induce CTL activity and make immature thymocytes develop into CTLs. In addition, IL-6 is a pro-inflammatory regulator of T cells. IL-6 can promote Th17 cell lineage proliferation/differentiation and function, inhibit the induction of regulatory T cells (Treg), and promote the development of a self-reactive pro-inflammatory CD4 T cell response. IL-6 combined with TGF-β can promote the development and function of Th17 cells, which are related to the occurrence and development of many self-inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, etc.[31,32].
C. Effect on hepatocytes[18,33]: IL-6 proteins can induce hepatocytes to synthesize acute phase reactive proteins at the gene transcription level, such as serum amyloid A (SAA) and CRP.
D. Effect on hematopoietic stem cells[34]: IL-6 can cooperate with other cytokines to promote the growth of early bone marrow stem cells, enhance the differentiation of blood cells and promote their colony formation.
E. Participates in the occurrence of immune abnormalities[35]: hypergammaglobulinemia, myocardial myxoma, bladder cancer and chronic rheumatoid arthritis.
F. Participates in the occurrence and development of cardiovascular diseases [36]: myocardial ischemia, coronary atherosclerosis, angina pectoris, congestive heart failure, and hypertension.

3.4. Rationale for Dose Selection and Administration Schedule of IL-6 receptor antagonist Tocilizumab

Tocilizumab is a recombinant humanized monoclonal antibody against human interleukin 6 (IL-6) receptor of immunoglobulin IgG1 subtype. Tocilizumab specifically binds soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits sIL-6R and mIL-6R-mediated signal transduction. It has been approved for the treatment of rheumatoid arthritis [37] and systemic juvenile idiopathic arthritis[38]. In addition, it has also been reported that tocilizumab treatment was associated with improvement in lymphadenopathy and laboratory markers of inflammation in patients with Castleman disease[39], also, generated clinical responses and normalized acute-phase responses in

Crohn's disease[40]. It is worth noting that tocilizumab is effective in the treatment of severe CRS including in patients treated with chimeric antigen receptor T cell (CAR-T) therapy[41,42] such as that associated with CART cell therapy. The recommended dose of tocilizumab is 8mg / kg intravenous drip (i.v.) every 4 weeks, for adults with rheumatoid arthritis, which can be used in combination with methotrexate or other anti-rheumatic drugs. In patients with liver enzyme abnormalities, or decreased neutrophil or platelet counts, the dose of tocilizumab can be reduced to 4mg/kg. For systemic juvenile idiopathic arthritis (sJIA) patients, the dose of tocilizumab was 12mg/kg (body weight<30kg) and 8mg/kg (body weigh≥30kg). Intravenous drip every 2 weeks is recommended, and the drip time is more than 1 hour.

The safety of tocilizumab was studied in 5 phase III double-blind controlled trials in patients older than 18 years of age with active rheumatoid arthritis, including during extended follow up[43].

The total control population included all patients in the double-blind period of each core study from randomized grouping to the first change of treatment regimen or the completion of a 2-year treatment period. Among them, the double-blind control period of 4 studies was 6 months, and the other double-blind control period was 2 years. In these trials, 774 patients received tocilizumab 4mg/kg combined with methotrexate (MTX) and 1870 patients received tocilizumab 8mg/kg combined with MTX or other disease-modifying antirheumatic drugs (DMARDs). A total of 288 patients were treated with tocilizumab 8mg/kg alone. In one 6-month controlled trial, the incidence of infection events in patients with tocilizumab 8mg/kg + DMARD and placebo + DMARD was 127 cases/100 patient-year and 112 patient-year/100 patient-year, respectively. Among the total exposed population, the overall incidence of infection events in the tocilizumab + DMARD group was 108 cases / 100 patient year. The 6-month controlled trial also showed that the incidence of severe infection (bacteria, viruses and fungi) in the 8mg/kg + DMARD group was 5.3/100 patient-year, while that in the placebo + DMARD group was 3.9/ 100 patient-year. In the monotherapy trial, the incidence of severe infection was 3.6 cases/100 patient-year in the tocilizumab group and 1.5 cases /100 patient-year in the MTX group.

On August 30, 2017, tocilizumab (8 mg/kg for patients with weight >= 30 kg) was approved in the United States for severe life-threatening CRS caused by chimeric antigen receptor T-cell (CAR T) immunotherapy. Per package insert, tocilizumab doses exceeding 800 mg per infusion are not recommended in rheumatoid arthritis or CRS patients.

Wei Haiming, et al. conducted a retrospective study observing the efficacy of tocilizumab in treating severe or critical COVID-19 patients [unpublished][9]. Along with the basic anti-virus treatment, tocilizumab was administered to 20 patients as 400 mg once i.v. Within a few days, the fever returned to normal and other symptoms improved remarkably. 75% had improved oxygenation with 90.5% showing improvement in CT scans. In addition, the percentage of peripheral lymphocytes returned to normal in 52.6% patients. While the study is limited by small patient numbers, the data suggest tocilizumab might be an effective treatment in patients with severe COVID-19 infection.

With regard to the safety of tocilizumab in the treatment of patients with severe COVID-19, a preprinted study (Xiaoling et al. http://chinaxiv.org/abs/2020 03.0 0 026) evaluated 21 patients. The mean age was 56.8 ±16.5 years, range 25 to 88 years. There were no complications associated with tocilizumab and no history of illness deterioration or death. Overall, the risk of secondary infection with tocilizumab seemed low, based on preliminary data from China.

As of now, several clinical trials have been registered on safety and efficacy of tocilizumab in the treatment of severe COVID-19 pneumonia in adult inpatients, including a multicenter, randomized controlled trial for the efficacy and safety (ChiCTR2000029765), a single arm multicenter study on tocilizumab (ChiCTR2000030796), and combination of tocilizumab and other drugs (ChiCTR2000030442 and ChiCTR2000030894).

Based on the above data, we propose a study to investigate the efficacy of tocilizumab in reversing respiratory failure and preventing death in Covid-19 infected patients at MSKCC. First, CRS is believed to play a role in the clinical deterioration of infected patients. Second, tocilizumab is an effective treatment for CRS in other conditions. Lastly, there is no effective treatment for respiratory failure and CRS in Covid-19 infected patients.

3.5 Remdesivir received emergency use approval from the U.S. Food and Drug Administration (FDA)

Remdesivir, a pro-drug of an RNA polymerase inhibitor was identified early as a promising therapeutic candidate for COVID-19, because of its ability to inhibit SARS-CoV-2 in vitro[44]. On May 1st, 2020, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for the investigational antiviral drug remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease. While there is limited information known about the safety and effectiveness of using remdesivir to treat people in the hospital with COVID-19, the investigational drug was shown in a clinical trial to shorten the time to recovery in some patients[45]. The emergency use authorization allows for remdesivir to be distributed in the U.S. and administered intravenously by health care providers, as appropriate, to treat suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease. Severe disease is defined as patients with low blood oxygen levels or needing oxygen therapy or more intensive breathing support such as a mechanical ventilator. The current protocol (protocol 20-185) is exploring the potential benefit of interleukin-6 blockade in the context of severe COVID-19 pneumonia. As remdesivir, targets a fundamentally different part of the pathophysiologic process, there is continued rationale to explore this objective.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a phase II study investigating the efficacy and safety of tocilizumab in reducing progression of respiratory failure and death due to severe COVID-19 infection. There will be 2 cohorts with 20 patients enrolled in each arm of the study. Progression of respiratory failure in cohort #1 will be defined as a sustained increase in oxygen requirement or need for intubation/mechanical ventilation. In cohort #2 progression of respiratory failure will be defined as a need for increasing respiratory support (e.g. FiO2 or PEEP, please see Section 13.0). Each arm will be evaluated for efficacy and safety separately.

4.3 Intervention

Patients will first be evaluated based on standard clinical diagnostic studies as noted in Section 9.0. Patients meeting criteria for severe infection will receive tocilizumab 8 mg/kg i.v. at enrollment. Dose will be capped at 800 mg per infusion. Patients who are not intubated will be assessed separately from the cohort of patients who are intubated. Standard medical monitoring including BP, temperature and oxygenation will be maintained as per MSKCC protocol. If there is no improvement or toxicity, a second dose can be given 24 hrs to 5 days later.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENT

Description: Tocilizumab is a humanized anti-human IL-6 receptor antibody of the IgG1 subclass. The medication is made by grafting the complementary determining regions of a mouse anti-human IL-6 receptor mAb onto human IgG1. Tocilizumab binds to both the membrane-bound and soluble forms of human IL-6 receptor (IL-6R), thereby inhibiting the action of the cytokine/receptor complex and interfering with the cytokine's effects.

Supply

Solution, Intravenous [preservative free]:

Tocilizumab: 80 mg/4 mL (4 mL); 200 mg/10 mL (10 mL); 400 mg/20 mL (20 mL) [contains polysorbate 80]

Tocilizumab will be supplied by MSK specialty pharmacy.

Storage

Store intact vials, prefilled syringes, and autoinjectors at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect vials, prefilled syringes, and autoinjectors from light (store in the original package until time of use); keep prefilled syringes and autoinjectors dry. Solutions diluted for IV infusion in NS may be stored at 2°C to 8°C (36°F to 46°F) or room temperature for up to 24 hours; solutions diluted for IV infusion in ½ **NS** may be stored at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature for up to 4 hours; protect from light

6.1 CRITERIA FOR PARTICIPANT ELIGIBILITY

6.2 Participant Inclusion Criteria

1. Patient or designated proxy willing and able to provide informed consent prior to enrollment in the study.
2. COVID-19 PCR positive on nasopharyngeal swab
3. Aged ≥18 years old
4. Patient hospitalized with newly diagnosed, documented severe COVID-19 infection: with respiratory rate >/= 30 breaths/min OR peripheral capillary oxygen saturation (SpO2) ≤ 93% on room air for non intubated pts.
5. Fever of 38.5 C or suspected respiratory infection
6. IL-6 level >/= 80 pcg/ml
7. Cohort #1 – non intubated
   Cohort #2 –intubated
8. Women of childbearing potential must have a negative serum or urine pregnancy test
9. Patients receiving ongoing steroid therapy are eligible
10. Patients will be allowed to receive concurrent or sequential treatment with remdesivir

6.3 Participant Exclusion Criteria

1. Patients with uncontrolled systemic fungal and bacterial infections
2. Patients with latent tuberculosis.
3. Patients with known hypersensitivity to tocilizumab or any component of theformulation

4. Concurrent initiation of steroid therapy is not allowed
5. Patients with uncrontrolled malignant disease, with a life expectancy of 3 months or less

7.0 RECRUITMENT PLAN

Patients hospitalized with documented severe COVID-19 infection who are febrile (> 38.5C) or have suspected respiratory infection, with respiratory rate >/= 30 or have a pulse oxygenation at least <u>≤</u> 93% on room air (non intubated pt) or are intubated, and lL 6 level >/= 80 pcg/ml . These patients/healthcare proxies will be approached for participation in the study and consented. This study will be offered to eligible patients regardless of gender, race, or ethnicity. Physicians will discuss with the patient/ healthcare proxy his/her diagnosis, prognosis, risks and benefits of participation, as well as treatment alternatives which will include standard treatment options and other available investigational studies. All patients/proxies will be required to sign an IRB approved informed consent form prior to enrollment on study.

7.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

8.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.

3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

9.1 PRE-TREATMENT/INTERVENTION

The following tests are required at within 48 hrs prior to receiving tocilizumab:

- Standard vital signs
- CBC with differential count and comprehensive chemistry panel.
- Lymphocyte phenotyping (including CD3, CD4, CD8, Cd19, CD56+16, CD45RA and CD45; "lymphocyte subsets") and immunoglobulin levels
- PT/PTT/INR/fibrinogen/d-dimer
- Cytokine panel including IL-1 beta, IL-6, IL-10 and TNF-alpha ("cytokine panel-1") and C-reactive protein, and ferritin
- Radiologic imaging of the lungs
- Sequential Organ Failure Assessment (see https://www.mdcalc.com/sequential-organ-failure-assessment-sofa-score#evidence) for patients admitted to the ICU, who are intubated and receive mechanical ventilation
- SARS-CoV-2 antibody testing (specimen will be saved, and test may be performed at a later time).

10.1 TREATMENT/INTERVENTION PLAN

- All enrolled patients will be monitored for signs and symptoms of CRS based on American Society for Transplantation and Cellular Therapy guidelines that were developed to monitor for CRS following immune effector cell therapy (Appendix 2.), and SOFA (Appendix 1.) will be performed on enrollment, prior to second dose, on d7 of enrollment, and at time of discontinuation from the study.
- Patients will receive 8mg/kg i.v. once on day of enrollment. Dose will be capped at 800 mg per infusion.

- If there are no clinically significant adverse effects, defined as grade 3-5 toxicities probably or definitely related to tocilizumab, from the first dose and patients are not demonstrating signs of improvement, they may receive a second dose between 24 hrs to 5 days later at 8mg/kg i.v. This dose will be also capped at 800 mg per infusion.
- If patients are not deemed suitable for a second dose 24 hrs to 5 days later, patients will be removed from the study and managed per MSK standard of care or may be offered another investigational agent.
- In patients admitted to the ICU, who are intubated and are on mechanical ventilation if there is progression of the SOFA score to a score >4, the treatment will be considered a failure and the study will be terminated.
- Patients will be followed for the first 30 days and at 3-6 months for survival and efficacy.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

Peripheral blood samples for standard clinical tests will be collected from patients according to the schedule listed in Table 1 below.

Table 1: Scheduled Assessments

Tests	Screening	0[1]	1	3-5	7	11-15	23-30[2]	3-6 months[2]
Informed consent	X							
Physical exam	X	X	X	X	X	X	X	X
Pulse oxygenation	X	X	X	X	X	X	X	
Lung radiologic imaging	X			X	X			
CRP, ferritin	X		X	X	X	X	X	
CBC, COMP	X	X	X	X	X	X	X	X
IL-1 beta, IL-6, IL-10, TNF-alpha (Cytokine panel-1)	X	X		X	X	X		
CD3, Cd4, CD8, CD19, CD56+16, CD45RA, CD45 (Lymphocyte Subset)	X				X	X	X	X
Coagulation studies[2]	X		X	X	X	X	X	
SOFA score	X		X	X		X		
Immunoglobulins/SARS-CoV-2 Ab	X					X	X	X
Research PBMC Sample		x			x	x	x	x
Research Plasma Sample		x			x	x	x	x

[1]If Screening and day 0 tests would fall within 24 hrs of each other, day 0 testing may be omitted

[2]Studies will be obtained in approx. timeframe as they are able to return to clinic.

[2]Coagulation studies include PT, PTT, fibrinogen and D-dimer levels

Blood samples are to be draw n *prior to* the infusion of tocilizumab.

12.1 CRITERIA FOR REMOVAL FROM STUDY

A subject will be withdrawn from the study for any of the following reasons:

- Progressive disease as defined above.
- Lost to follow up
- Withdrawal of consent for study participation
- The investigator believes that for safety reasons (eg, AE) it is in the best interest of the subject to stop treatment
- Death
- Principal Investigator/MSKCC terminates the study

Patients removed from the study prior to receiving tocilizumab on study will be replaced.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Criteria for Therapeutic Response/Outcome Assessment

Criteria for Toxicity

Toxicity will be graded in accordance with Common Toxicity Criteria version 5.0 (CTCAE 5.0) developed by the National Cancer Institute, November 27th, 2017 (http://ctep.cancer.gov). The only toxicities captured will be all grade 4-5 toxicities deemed probably or definitely related to the treatment with the drug.
CRS will be graded according to the ASBMT consensus grade definitions [24].

Criteria for Therapeutic Response

- Decrease in fevers to <38.5 C for 24hrs in febrile patients

Plus one of the following (in patients not receiving steroids); patients who are receiving steroids will need to meet one of the following criteria:

- A decrease in the SOFA score by ≥1 category for 24 hrs or longer in patients admitted to the ICU who are intubated and require mechanical ventilation (cohort #2)
- Decrease in oxygen requirement that persists greater than 48h. The decrease in oxygen requirement (supine FiO2) that persists for > 48 hrs refers to the highest FiO2 level used on either noninvasive (e.g. nasal cannula, high-flow nasal cannula, nonrebreather mask) or invasive mechanical ventilation.
- Increase in ventilator free days of at least 1 day by day 14.

Progressive disease:

- Persistent fever of ≥ 38.5 C in patients not receiving steroids

Plus one of the following in patients not receiving steroids; if patients receiving steroids develop any of the following they will be considered to have progressive disease:

- Increase in the SOFA score to ≥ 4 category inpatients admitted to the ICU who are intubated and require mechanical ventilation (cohort #2)
- Need for intubation (cohort #1) or increase in mechanical ventilation support (cohort #2). Increase in mechanical ventilation support will be defined as the sustained (at least 12-24 hrs) need for a higher supine FiO2 or PEEP during any 24 hr period.
- Patients with increased in oxygen requirement (cohort #1) or need in increase in mechanical ventilation (cohort #2) after receiving first dose of tocilizumab, who then receive another investigational agent will be treated as "progression of disease/study failure"

14.0 BIOSTATISTICS

This is a phase II protocol to study tocilizumab in two separate cohorts of patients. The first cohort of patients are those who have dyspnea, pulse oxygenation ≤ 93% on room air or >50% lung involvement on imaging within 12-48 h, elevated IL-6 level and fever who have not been intubated. The second cohort are those who have been intubated and have an elevated IL-6 level.

Cohort 1

The primary endpoint for this cohort is progression of respiratory failure (binary yes/no while hospitalized). Progression of respiratory failure will be defined as a sustained increase in oxygen requirement (FiO2) or need for intubation/mechanical ventilation. Patients who receive off-protocol COVID19-directed therapy for respiratory symptoms will be deemed as having progression of respiratory failure at that time. Patients who die while hospitalized will be treated as a study failure (progression of respiratory failure, e.g. requiring intubation). There are very limited data to use as a historical benchmark for this endpoint in the patient population. Therefore, the aim is to estimate the 14-day time-to-progression without a formal corresponding hypothesis test. A total of 20 patients will accrue into this cohort. The endpoint will be estimated using Kaplan-Meier methodology, though we note it is highly unlikely that any patient will be lost to follow up before 14 days. With 20 patients and assuming no loss to follow up, we can approximate the precision by treating the endpoint as binary, which would have maximum half-width of +/- 0.23.

A safety run-in will be implemented in this cohort. If more than 1 patient in the first 6 develops a grade 4 or 5 CTCAE toxicity definitely related to tocilizumab, accrual to this cohort will be suspended and all safety data will be reviewed by the study team, IRB, and DSMC.

Cohort 2

The primary endpoint for this cohort is 14-day time-to-progression of respiratory failure or death. Progression of respiratory failure for this cohort will be defined as an increase in mechanical ventilation support. Patients who receive an off-protocol therapy for respiratory symptoms will be deemed as having progression of respiratory failure at that time. Similar to cohort 1, there are very limited data to use as a historical benchmark in the patient population. Therefore, the aim is to estimate the 14-day time-to-progression without a formal corresponding hypothesis test. A total of 20 patients will accrue into this cohort. The endpoint will be estimated using Kaplan-Meier methodology, though we note it is highly unlikely that any patient will be lost to follow up before 14 days. With 20 patients and assuming no loss to follow up, we can approximate the precision by treating the endpoint as binary, which would have maximum half-width of +/- 0.23.

A safety run-in will be implemented in this cohort. If more than 1 patient in the first 6 develops a grade 4 or 5 CTCAE toxicity definitely related to tocilizumab, accrual to this cohort will be suspended and all safety data will be reviewed by the study team, IRB, and DSMC.

Secondary Objective:

- 30-day time-to-progression of respiratory failure or death will be estimated using Kaplan-Meier methodology. This will be estimated separately for the two cohorts.
- 30-day and 3-month overall survival will be estimated using Kaplan-Meier methodology. This will be estimated separately for the two cohorts.
- The proportion who achieve a protocol-defined therapeutic response, as specified in Section 13.1, along with an exact 95% confidence interval will be reported. This will be estimated separately for the two cohorts.
- The number of ventilator-free days alive within the first 30 days will be estimated and summarized using descriptive statistics. This will be estimated separately for the two cohorts.
- The safety of the study drug will be summarized using descriptive statistics separately for the two cohorts.
- The change from baseline in the levels of CRP, IL-6 and cytokine levels, ferritin, lymphocyte phenotypes, coagulation parameters, immunoglobulin levels and antibody levels will be summarized and visually displayed. A Wilcoxon signed rank test may be used to assess these changes. This will be estimated separately for the two cohorts.
- To estimate the proportion of patients who separately have 1) a decrease in fever <38 for 24hrs, 2) a 50% improvement in lung radiologic imaging, 3) a decrease in oxygen requirement that persists greater than 48h
- To estimate the proportion of patients who have an increase in SOFA score by > 1 category.
- To estimate the proportion of patients who have an antibody against SARSCoV-2 detected.

15.0 TOXICITIES/RISKS/SIDE EFFECTS

The possible discomforts, side effects, and risks related to tocilizumab treatment in this particular population of patients are not all known. Most side effects are not serious. Some may be serious and may require treatment or additional testing. Such side effects can result from a patient's disease, the drug being studied, other drugs, other diseases, or a combination of these. These side effects may or may not have been due to tocilizumab.

This section describes which and how frequently side effects occurred in subjects treated with tocilizumab.

It is unclear, but based on mechanism of action, possible, that tocilizumab will impede the ability to make an anti-SARS-CoV-2 antibody. It is unknown whether these antibodies would provide protection against future infections. Monitoring immunoglobulin levels and SARS-CoV-2-specific antibodies is a secondary objective of the trial.

Tocilizumab is in general well tolerated. It may cause infusion related reactions, headache, dizziness and skin rash. Other potential side-effects include increase in liver function tests, diarrhea, abdominal pain, and increased serum cholesterol.
Rare side effects include allergic reaction, increased risk of infection, low blood pressure, cough, and pneumonia.

Incidence as reported for adults unless otherwise noted. Incidence as reported for monotherapy and combination therapy. Combination therapy refers to use in rheumatoid arthritis with nonbiological disease-modifying antirheumatic drugs or use in systemic juvenile idiopathic arthritis or polyarticular juvenile idiopathic arthritis in trials where most patients (~70% to 80%) were taking methotrexate at baseline.

>10%:

- Endocrine & metabolic: Increased serum cholesterol (19% to 20%; children and adolescents: ≤2%)
- Hepatic: Increased serum alanine aminotransferase (≤36%), increased serum aspartate aminotransferase (≤22%)
- Local: Injection site reaction (SubQ: Children and adolescents: 15% to 44% [higher incidence occurred in weight ≥30 kg]; adults: 7% to 10%)
- Miscellaneous: Infusion-related reaction (4% to 20%)

1% to 10%:

- Cardiovascular: Hypertension (6%), peripheral edema (<2%)
- Dermatologic: Skin rash (2%)
- Endocrine & metabolic: Hypothyroidism (<2%), increased LDL cholesterol (9% to 10%; children and adolescents: ≤2%)

- Gastrointestinal: Diarrhea (children and adolescents: ≥5%), gastric ulcer (<2%), gastritis (1%), oral mucosa ulcer (2%), stomatitis (<2%), upper abdominal pain (2%), weight gain (<2%)
- Hematologic & oncologic: Leukopenia (<2%), neutropenia (children and adolescents <30 kg, grade 3: 26%; children and adolescents ≥30 kg, grade 3: 4%; adults, grade 3: 3% to 4%), thrombocytopenia (1%)
- Hepatic: Increased serum bilirubin (<2%)
- Immunologic: Antibody development (children and adolescents: ≤6%; adults: <2%; neutralizing, adults: ≤1%)
- Infection: Herpes simplex infection (<2%)
- Nervous system: Dizziness (3%), headache (7%)
- Ophthalmic: Conjunctivitis (<2%)
- Renal: Nephrolithiasis (<2%)
- Respiratory: Bronchitis (3%), cough (<2%), dyspnea (<2%), nasopharyngitis (7%), upper respiratory tract infection (7%)

Frequency not defined:

- Cardiovascular: Hypotension
- Endocrine & metabolic: Increased HDL cholesterol
- Gastrointestinal: Nausea
- Hematologic & oncologic: Malignant neoplasm
- Hypersensitivity: Angioedema
- Otic: Otitis media

Pregnancy
There are no adequate and well-controlled studies of tocilizumab in pregnant women. Pregnant and breastfeeding women are excluded from participation in this study. Female patients of childbearing potential must undergo a pregnancy test during study initiation, prior to receiving intervention.

It is very important both that women taking part in this study, and that partners of men taking part do not become pregnant during the study conduct**.** During this study and for 3 months after the last dose of study drug, both men and women of childbearing potential must use proven birth control methods (such as birth control pills, intrauterine device, barrier method combined with gel or foam with spermicide, avoiding sex, or proof of a woman having her tubes tied or a man having his sperm tubes cut or blocked). Participants must not donate sperm or eggs during the study, or for 3 months after the last dose of study drug.

CTCAE Version 5 will be utilized for toxicity evaluation.

15.1 Serious Adverse Event (SAE) Reporting

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

- Death
- A life-threatening adverse event

- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- 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 participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

16.0 PROTECTION OF HUMAN PARTICIPANTS

Risks: The standard of care for patients eligible for this study is generally management for individual symptoms using standard of care tocilizumab. Administration of tocilizumab has the potential of causing toxicities that would not occur if just the standard of care medication for each individual symptom was administered.

Benefits: Administration of tocilizumab will potentially improve the signs and symptoms of COVID-19 infection and potentially avoid further respiratory failure and death.

Possible toxicities / side effects: Please see Section 15.0. Toxicities for tocilizumab listed are based on those previously reported for the medication in previous clinical trials.

Costs: Patients will be charged for routine care including hospital charges, physician visits, routine laboratory, radiologic, and pathologic studies required for monitoring of their condition. Patients will be billed for tocilizumab.

Alternatives: Alternative treatment options include standard of care management for individual symptoms, or participation in other investigational studies.

Eligibility Exceptions: There will be no exceptions to the eligibility requirements for this protocol without the authorization of the Institutional Review Board of Memorial Hospital.

Protocol Amendments and Study Termination: All protocol amendments will be reviewed and approved by the Institutional Review Board of Memorial Hospital before they are implemented.

Incentives: No incentives will be offered to patient/subjects for participation in this study. Participation is voluntary.

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have

received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

16.2 Data Management

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization and coordinating the activities of the protocol study team.

The data collected for this study will be entered into Medidata. Source documentation will be available to support the computerized patient record.

All grade 4-5 toxicities deemed definitely, probably, or possibly related to the treatment drug, and all grade CRS will be reported. Serious adverse events will be reported for 30 days after the last dose of study drug.

16.3 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.4 Data and SafetyMonitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA

and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

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18.0 APPENDICES

Appendix A: Sequential Organ Failure Assessment (SOFA) based on Ferreira et al. JAMA 2001

Variable	Points
PaO_2/FiO_2, mmHg	
≥400	0
300-399	+1
200-299	+2
100-199 and mechanically ventilated	+3
<100 and mechanically ventilated	+4

Platelets, ×10³/µL	
≥150	0
100-149	+1
50-99	+2
20-49	+3
<20	+4
Glasgow Coma Scale	
15	0
13–14	+1
10–12	+2
6–9	+3
<6	+4
Bilirubin, mg/dL (µmol/L)	
<1.2 (<20)	0
1.2–1.9 (20-32)	+1
2.0–5.9 (33-101)	+2
6.0–11.9 (102-204)	+3
≥12.0 (>204)	+4
Mean arterial pressure OR administration of vasoactive agents required (listed doses are in units of mcg/kg/min)	
No hypotension	0
MAP <70 mmHg	+1
DOPamine ≤5 or DOBUTamine (any dose)	+2
DOPamine >5, EPINEPHrine ≤0.1, or norEPINEPHrine ≤0.1	+3
DOPamine >15, EPINEPHrine >0.1, or norEPINEPHrine >0.1	+4
Creatinine, mg/dL (µmol/L) (or urine output)	
<1.2 (<110)	0

1.2–1.9 (110-170)	+1
2.0–3.4 (171-299)	+2
3.5–4.9 (300-440) or UOP <500 mL/day)	+3
≥5.0 (>440) or UOP <200 mL/day	+4

Interpretation:

SOFA Score	Mortality if initial score	Mortality if highest score
0-1	0.0%	0.0%
2-3	6.4%	1.5%
4-5	20.2%	6.7%
6-7	21.5%	18.2%
8-9	33.3%	26.3%
10-11	50.0%	45.8%
12-14	95.2%	80.0%
>14	95.2%	89.7%

Mean SOFA Score	Mortality
0-1.0	1.2%
1.1-2.0	5.4%
2.1-3.0	20.0%
3.1-4.0	36.1%
4.1-5.0	73.1%
>5.1	84.4%

Appendix B: ASTCT Consensus Grading for Cytokine Release Syndrome

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)