TITLE: **Randomized Double-Blind Phase 2 Trial of Ibrutinib versus Standard Treatment for COVID-19 Illness Requiring Hospitalization with Safety Lead-In**

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1. PROTOCOL SYNOPSYSIS

IND Sponsor	The Ohio State University
Protocol Title	Randomized Double-Blind Phase 2 Trial of Ibrutinib versus Standard Treatment for COVID-19 Illness Requiring Hospitalization with Safety Lead-In
Protocol Number	Protocol
Phase of Development	Phase 2 Randomized Adaptive Trial
Rationale	The SARS-CoV-2 virus, a novel coronavirus represents a serious human to human pathogenic virus and represents a current WHO pandemic pathogen. The clinical syndrome manifested by SARS-CoV-2 is termed COVID-19 with a common presentation of fever (89%), cough (68%), CT abnormalities (86%) and lymphocytopenia (84%) with nausea (5%) and diarrhea (4%) being uncommon. Severe disease that requires admission occurs in 20% and a subset of these patients require ICU care (6%), intubation (2.3%) or die (1.4%). The death rate from COVID-19 in different populations has ranged from 2.4% in China to 7.2% in Italy. Death rate from COVID-19 increases proportionally with older age, being highest among older patients and also those who are immunocompromised or have other co-morbidities or lymphocytopenia. Among hospitalized cancer patients with COVID-19 in China, a 38% frequency of mechanical ventilation or death occurred compared to 8% among patients without cancer. The systemic and pulmonary pathogenesis derived from clinical cases of ICU hospitalized COVID-19 cases and autopsy series demonstrate increased levels of plasma inflammatory cytokines including TNF-alpha, IL-6, and IL-2, and IL-10 and neutrophilic infiltration, macrophages, monocytes, minimal lymphocytes (CD4+ T-cells predominantly) and type 2 pneumocytes with viral particles. Other risk factors for severe COVID-19 illness is the presence of neutrophilia, organ dysfunction (elevated LDH), coagulation abnormalities, thrombocytopenia, and lymphocytopenia suggesting both findings observed in hemophagocytic syndrome, and immune deficiency. To date, there have been no studies published that follow immune response serially in patients with SARS-CoV-2 infection and COVID-19 syndrome. Several studies have demonstrated cross comparative studies of moderate versus severe COVID-19 syndrome where differential decline in CD4 and CD8 cells occurs with increasing features of both exhausted T-cells (increased PD1, LAG3, CTLA4, and decreased intracellular gamma-interferon) and inflammatory cytokines. These findings mimic other chronic virus and parasitic infections where inability of CD4 T-cells to generate cytotoxic gamma-interferon and T-

	cell exhaustion contributes to failure of the host organism to clear viral infections. Application of a therapeutic that enhances Th1 polarization, diminishes T-cell exhaustion and decreases TNF and IL6 production by both T-cells and monocytes would represent a potential novel therapeutic approach to COVID-19 syndrome. In contrast to immune suppression predicting higher infection rate and morbidity with COVID-19, once this syndrome is active therapies directed at diminishing inflammation including corticosteroids, IL-6 neutralizing antibodies, and hydroxychloroquine or hydroxychloroquine with azithromycin have demonstrated anecdotal benefit among ill patients. Patients recovering from COVID-19 syndrome demonstrate evidence of humoral neutralizing antibodies and SARS-CoV-2 specific T-cells. Additionally, ill patients treated with plasma derived from patients who have developed COVID-19 and recovered with evidence of immune response have had evidence of clinical improvement. This provides evidence that strategies that can disrupt the acute inflammatory response associated with respiratory failure while preserving immune function could serve to effectively treat patients with COVID-19. Cancer based targeted therapies often seek to shut down inflammatory cytokine release while not compromising innate or adaptive immune response. Examples of this include application of targeted agents directed at graft versus host disease while at the same time maintaining anti-leukemic activity in the setting of allogeneic stem cell transplant. One such example of this is Ruxolitinib, a JAK2 inhibitor that was recently FDA approved for the use of acute graft versus host disease. JAK2 inhibitors also demonstrate profound reduction in cytokine production in myelofibrosis and other inflammatory diseases. Similarly, work by OSU investigators and then others has demonstrated ibrutinib, an irreversible inhibitor of BTK and ITK, has chronic graft versus host therapeutic potential in pre-clinical models and does not inhibit graft versus leukemia effect. As an irreversible ITK inhibitor, Ibrutinib has been shown to polarize CD4 cells to a Th1 phenotype in human CLL cells favoring gamma interferon production and in murine models enabling clearance of pathogens such as listeria monocytogenes and leishmania. By enhancing T-cell function, ibrutinib has been shown to enhance other T-cell based therapies including TLR agonists, PD1 blockade, and CAR-T cells. The combination of CAR-T cells and ibrutinib in addition to being highly active was shown to also potentially diminish cytokine release syndrome as compared to an earlier report of administering CAR-T cells alone in CLL. This was recapitulated experimentally in a murine model of CAR-T cell mediated cytokine release syndrome where ibrutinib improved survival by decreasing this complication while not abrogating T-cell expansion or killing. Finally, in work performed by our own group in CLL we demonstrated that

	ibrutinib via ITK inhibition diminishes both activation induced death and reversed features of immune exhaustion, a common pathway that T-cells become depleted in the setting of cancer or chronic viral infections. These favorable immune modulating features of ibrutinib establish it as a potential therapy to enhance Th1 polarization, diminished exhaustion, and improved T-cell immune response toward SARS-CoV-2. Despite being an immune modulator, ibrutinib has not been administered clinically to treat infectious disease or abrogate inflammatory toxicity mediated by immune hyperactivation in the lung. However, there is significant pre-clinical data implicating BTK activation in acute pulmonary injury and subsequent ARDS. BTK activation has been demonstrated to be an essential component of lung injury induced by infectious pathogens, sepsis, and hemorrhagic lung injury that is mediated by excessive inflammatory macrophages and neutrophils. Genetic knock down of BTK impaired this lung injury. Subsequent pharmacologic studies with ibrutinib have confirmed this. Specifically, ibrutinib in the setting of murine pneumococcal pneumonia has also been shown to negatively influence both monocyte and granulocyte migration into the lung and also alveolar macrophage activation, cytokine release and plasma leakage. Antibiotic mediated killing of bacteria was not impaired. A similar study with seasonal influenza A virus demonstrated ibrutinib administered intranasally to mice starting 72 h after lethal infection with influenza A diminished weight loss and led to significant improved overall survival. Additionally, ibrutinib treatment had a dramatic effect on morphological changes to the lungs including decreased alveolar hemorrhage, interstitial thickening, and the presence of alveolar exudate concomitant with diminished inflammatory mediators TNF-alpha, IL-1beta, IL-6, and MCP-1. This murine study suggests that ibrutinib may be an effective therapy for not only influenza-induced lung injury but for treating other viral pathogens mediating lung dysfunction via excessive inflammation. Collectively, these data support ibrutinib may diminish the lung pathology mediated by the SARS-CoV-2 virus and justify application of this approach for clinical investigation in patients with COVID-19 syndrome. Collectively, we put forth that ibrutinib as an agent that may 1) diminish the excessive innate immune inflammatory pulmonary response to SARS-CoV-2 infection that causes need for intubation and often death; 2) helps to prevent/reverse the severe compromise of adaptive immune system by ameliorating lymphocytopenia, reducing exhaustion as measured by checkpoint molecule expression (PD-1/CTLA4 etc.), and preserving the Th1/Tc1 function. This ultimately will help to protect against HLH/MAS like symptoms, where deficiency in T cells or NK cells plays a key role and 3) Enhance or at least not compromise viral clearance based upon data by our group with listeria and Leishmania major and others with influenza.

	This clinical trial proposal seeks to test this hypothesis by administering ibrutinib therapy for hospitalized COVID-19 patients with a history of cancer. Here we will determine if ibrutinib effectively diminishes the high observed frequency of respiratory failure or death. If preliminary data suggest this approach shows promise in high risk cancer patients, we would broaden the eligibility to non-cancer patients after discussion with the Food and Drug Administration.
Objectives	**Primary Objectives** Safety Lead-In • To determine the feasibility and tolerability of administering Ibrutinib in COVID-19 infected patients Phase 2 o To determine whether ibrutinib administration plus standard of therapy (Arm A) in cancer patients can diminish respiratory failure or death due to COVID-19 as compared to control population receiving placebo plus standard therapy (for example antiviral such as remdesivir or others, chloroquine, hydroxychloroquine, cytokine blocking peptides or small molecules) (Arm B). Respiratory failure is defined as any of the followings: ▪ Endotracheal intubation and mechanical ventilation ▪ Extracorporeal membrane oxygenation ▪ High-flow nasal cannula oxygen delivery (i.e., reinforced nasal cannula delivering heated, humidified oxygen with fraction of delivered oxygen ≥0.5 and flow rates of ≥30 l/min) ▪ Noninvasive positive pressure ventilation ▪ Clinical diagnosis of respiratory failure without initiation of one of above measures only when clinical decision-making is driven solely by resource

limitation or if patient has DNI (Do Not Resuscitate) status.

Secondary Objectives

- To determine time to clinical resolution of need for supplemental oxygen (i.e. maintenance of oxygen saturation of 93% or greater on room air with ambulation).
- To determine rate of ICU admission and length of ICU admission for patients treated with ibrutinib (Arm A) versus control population receiving standard therapy (Arm B)
- To determine rate of shock requiring vasopressor support for patients treated with ibrutinib (Arm A) versus control population receiving standard therapy (Arm B)
- To determine the rate of secondary infection (bacterial, fungal, viral) for patients treated with ibrutinib (Arm A) versus control population receiving standard therapy (Arm B)
- To determine the time to hospital discharge for patients treated with ibrutinib (Arm A) versus control population receiving standard therapy (Arm B)
- To determine grade 3 or higher toxicity observed in patients treated with ibrutinib (Arm A) versus control population receiving standard therapy (Arm B)
- To determine time to mechanical ventilation, the number of days of mechanical ventilation per patient and total observed in patients treated with ibrutinib (Arm A) versus control population receiving standard therapy (Arm B)
- To determine the overall survival at 3 and 12 months post-enrollment.

Exploratory Objectives

- To examine the impact of baseline clinical features (e.g. type of cancer, active therapy), duration of symptoms prior to admission and laboratory features (e.g. T cell count) on outcome for patients treated on this therapeutic study
- To determine the time to defervescence (oral temperature<100.5 degrees F for a 48 hour time period) among patients treated with

	ibrutinib (Arm A) versus control population receiving standard (Arm B) therapy • To determine the proportion of patients with viral clearance at end of ibrutinib therapy, time of hospital discharge and follow up thereafter among patients treated with ibrutinib (Arm A) versus control (Arm B) treatment • To determine the time and proportion of patients who develop IgM and IgG levels toward SARS-CoV-2 treated with ibrutinib (Arm A) versus control treatment (Arm B) • To examine immune cell subsets for absolute number, activation, exhaustion markers, and presence of maturation arrest (NK cells) at baseline and over time among patients treated with ibrutinib (Arm A) versus control (Arm B) treatment • To examine T-cell repertoire over time among patients treated with ibrutinib (Arm A) versus control (Arm B) treatment • To determine the influence of epigenetic age, clonal hematopoiesis, and monoclonal B cell lymphocytosis (MBL on treatment outcome • To determine serial change in inflammatory markers as CRP, ferritin, D-Dimer and cytokines including IL6, IL1B, and TNF-alpha serum levels over time among patients treated with ibrutinib (Arm A) versus control (Arm B) treatment.
Trial Design	This study is a Phase 2 randomized double-blinded trial using a group sequential design with a lead-in cohort to better define safety and tolerability of ibrutinib combined with standard therapies for COVID-19 in a high-risk cancer population. The lead-in cohort and randomized trial define two separate components of the study. **<u>Safety Lead-in Cohort</u>** This study will begin with a 12 patient lead-in component to establish safety and better characterize toxicity prior to the randomized component. For safety purposes, patients will be enrolled in cohorts of 3 for the first 6 patients, and patients will receive ibrutinib at a dose of 420 mg daily. Dose limiting toxicity (DLT) will be evaluated during the first 14 days of treatment. DLT would be considered to be any of the following: • Grade 4 hematologic toxicity that persists for 3 or more days that is considered at least possibly related to ibrutinib.

	• Grade 3 or higher non-hematologic toxicity that are considered at least possibly related to Ibrutinib with the exception of nausea, vomiting, diarrhea, or electrolyte abnormality, unless these persist for at least 3 days despite maximal supportive care • Any grade 3 or higher fungal or bacterial infection (excluding line infection, catheter-associated UTI, or C difficile infection), cardiac toxicity (with the exception of hypertension) or bleeding regardless of the attribution. We note, though, that many patients in the hospital that develop infection of any grade will be treated with IV antibiotics, and that per CTCAE criteria, those graded 3 or higher would be those where IV antibiotics are indicated, not only for those where IV are chosen due to convenience. • Grade 3 or higher hemorrhage regardless of attribution, or Grade 2 hemorrhage that is considered at least possibly related to ibrutinib and is considered to be significant by the treating physician in collaboration with the PI. • Non COVID-19 related neutropenic fever Enrollment to this dose level will stop if 2 of the first 3 evaluable patients or if at least 33% of subsequent evaluable patients (i.e, 2/6, 3/9, or 4/12) have DLT. If unacceptable toxicity is observed, Ibrutinib will decrease to 280 mg daily, and another 12 patient lead-in will be evaluated at this lower dose level following the same stopping rules. If toxicity is acceptable, the study will proceed to the randomized component. Patients who do not receive 14 days of Ibrutinib for reasons other than toxicity or DLT will be replaced for the purposes of the safety and tolerability assessment. **<u>Randomized Double-Blind Phase 2 Study</u>** The main study is a randomized, double-blind placebo-controlled trial. Following completion of the safety lead-in, patients in the phase 2 portion will be randomized in a 1:1 fashion to receive ibrutinib plus standard treatment (Arm A) versus placebo plus standard treatment (Arm B) for COVID-19. Patients may receive any additional therapies that are not prohibited in the section on concomitant medications. In this trial, cycles will be 7 days in length. Study drug will continue for 2 cycles (14 days).

Accrual Expectations, N	78
Inclusion/ Exclusion Criteria	**Inclusion Criteria** 1. Hospitalization for confirmed PCR positive COVID-19 infection 2. Active cancer, defined as a solid malignancy either undergoing active therapy, receiving therapy within 1 year, or a hematologic malignancy under active therapy or observation. 3. Age ≥ 18 4. Patients with evidence of pulmonary involvement who meet any of the followings; presence of infiltrates on chest X-ray or CT scan or need for supplemental oxygen < 8L nasal cannula or pulse oximetry < 94% on room air. 5. Biochemical values within the following limits: a. Creatinine clearance ≥ 25 ml/min by Cockcroft-Gault equation b. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x ULN 6. Hematology values must be within the following limits (no need to hold growth factors or blood products transfusion): a. Absolute neutrophil count (ANC) ≥ 1000/mm^3 independent of growth factor support b. Platelets ≥50,000/mm^3 7. Ability to swallow capsules or receive opened capsule content via nasogastric or enteral feeding tube as described in 7.2 8. Ability to provide informed consent indicating that they understand the purpose of and procedures required for the study, including biomarkers, and are willing to participate in the study. If a patient is unable to provide informed consent (e.g. does not possess decisional capacity), a legally authorized representative may provide consent for the patient. 9. Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for

	subjects participating in clinical trials. Men must agree to not donate sperm during and after the study. For females, these restrictions apply for 1 month after the last dose of study drug. For males, these restrictions apply for 3 months after the last dose of study drug. 10. Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at Screening. Women who are pregnant or breastfeeding are ineligible for this study. **Exclusion Criteria** 1. Patients with new-onset malignancy requiring urgent initiation of systemic chemotherapy 2. Active uncontrolled systemic bacterial or fungal or other viral infection 3. Requires anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) 4. Currently receiving BTK inhibitor therapy 5. Actively receiving anti-cancer therapy (other than hormonal therapies). All anti-cancer therapy (except hormonal therapies) must be stopped at the time of screening; can be resumed as soon as ibrutinib is discontinued. Significantly T cell suppressive chemotherapy (defined as requiring PJP prophylaxis per standard guidelines) is not allowed for 3 months prior to enrollment. 6. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification 7. Requirement for mechanical ventilation at screening 8. Known bleeding disorders (e.g., Von Willebrand's disease, platelet storage pool disorders, or hemophilia) 9. Stroke or intracranial hemorrhage within 6 months of screening. 10. Major surgery or non-healing wound within 4 weeks of enrollment. 11. Concomitant administration of prohibited medications (See Appendices 12.)

	13. Known history of human immunodeficiency virus (HIV), or active hepatitis B or C infection 14. Disease significantly affecting gastrointestinal function and/or inhibiting small intestine absorption (malabsorption syndrome, resection of the small bowel, poorly controlled inflammatory bowel disease, etc.). 15. Requires chronic treatment with strong CYP3A inhibitors or inducers. See appendix A for complete list of medications 16. Participation in another clinical trial for COVID 19 (antiviral based trials accepting co-enrollment, emergency use or compassionate use or expanded access protocols are allowed)
Length of Study	Patients will be followed for 12 months or until death or withdrawal of study consent for further follow-up. Following hospitalization, study visits may be by telephone or video encounters. Patients will need to return to OSU for laboratory studies as outlined in the study calendar.
Treatment Algorithm	Phase 2: Patients will be randomized 1:1 to ibrutinib plus standard treatment (Arm A) versus placebo plus standard treatment (Arm B)
Investigational Product **Dose/Route/ Regimen**	Ibrutinib or Placebo 420 mg or 280 mg Doses described above will be given daily by mouth for 7 day cycles.
Standard of care	Patients will receive supportive care or directed therapies based on our institutional COVID-19 treatment recommendations. See appendix C for details. This is an evolving matter and continuous updates to these recommendations will take place as new data arise. Details of supportive or targeted therapy will be reported for each patient.
Study Assessments	**Biomarker and Correlatives** The following biological specimens will be collected in this study and will be used to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drug response including efficacy and/or adverse events. Biomarker samples may be used for potential assay development of companion diagnostics. Tests will include • Measurement of viral clearance in each treatment arm; • Measurement of immune cell subsets for absolute number, activation, exhaustion markers, and presence of maturation arrest (NK cells) at baseline and over time among patients treated with ibrutinib (Arm A) versus control (Arm B) treatment

	• Measurement of T-cell repertoire and IgM, IgA, IgG response to SARS-CoV-2 over time among patients treated with ibrutinib (Arm A) versus control (Arm B) treatment; • Measurement of epigenetic age, clonal hematopoiesis, and MBL on treatment outcome • Measurement of serial change cytokines including (but not limited to) IL6, IL1B, TNF-alpha, IL-10 serum levels over time among patients treated with ibrutinib (Arm A) versus control (Arm B) treatment
Statistics/ **Sample Size Estimate**	Safety Lead-In: 12 patients will be enrolled as part of the safety lead-in cohort. Enrollment to a dose level will stop if 2 of the first 3 evaluable patients or if at least 33% of subsequent evaluable patients (i.e, 2/6, 3/9, or 4/12) have DLT. Randomized Phase 2: Allowing for roughly 10% over-accrual, we plan to randomize 66 high-risk patients with cancer to the two arms of the study in a 1:1 ratio utilizing a permuted block schedule. Randomization will be stratified on age (<60 years vs ≥ 60 years) and presence of comorbidities (yes vs no) (comorbidities defined in Appendix C). The primary endpoint is the proportion of randomized patients with respiratory failure or death during hospitalization for COVID-19 infection within 30 days of registration. Based on the study in China, we assume that the event rate is 40% and that it can be reduced to 15% when Ibrutinib is given in addition to standard care for COVID-19. With 60 patients and using a standard group sequential design, there is 82.8% power to detect a reduction in the event rate under the alternative hypothesis and constraining the one-sided type I error to 20%. Power was calculated using a z-test for the difference in two proportions, pooled variance, and adjustment for small sample sizes with the Casagrande-Pike-Smith correction (EAST v6.5; Cytel, Inc). There will be an interim analysis when 50% of randomized patients have been followed for 30 days from registration. The study will be stopped early if at the interim analysis the observed event rate is higher in the ibrutinib arm (Arm A) than in the control arm (Arm B). At the final analysis, data will be analyzed using a one-sided Fisher's exact test and a promising signal declared if p≤0.20 and the event rate is lower in the experimental arm.

	Although the actual reduction in the event rate could be larger than 25%, it could also be as low as 20% and still be quite meaningful. Furthermore, there is uncertainty in the event rate of the control arm. For these reasons, we have incorporated increased flexibility at the time of the interim analysis to potentially increase the sample size if conditional power indicates promising results, and will thus implement an adaptive group sequential design (Chen, DeMets, Lan; 2004). At the interim analysis, there are 4 possible outcomes: 1) the futility criteria are met and the trial stops early; 2) the conditional power is unfavorable (<50%), and enrollment continues to the full 60 patients without an increase in sample size; 3) the conditional power is in a promising zone (defined as conditional power ≥50% and < 82.8%), and sample size may be re-estimated with the original sample size updated to boost the power to a target of 82.8%, subject to a maximum sample size of 120; or 4) the conditional power is favorable (≥82.8%), and enrollment continues to the full 60 patients without an increase in sample size. When using this procedure, no adjustment to the final test statistic or critical value from the original design is required to control the Type I error rate. In addition, if the conditional power is in the promising zone, we can choose not to increase the sample size beyond what was originally planned or by a flexible amount without penalty. Operating characteristics using the adaptive group sequential design is presented for four different scenarios: Scenario 1: Event rates in the ibrutinib and control groups are 15% and 40% Scenario 2: Event rates in the ibrutinib and control groups are 25% and 50% Scenario 3: Event rates in the ibrutinib and control groups are 20% and 40% Scenario 4: Event rates in the ibrutinib and control groups are 30% and 50% For each scenario, the power and expected sample size is also provided for the standard group sequential design. For example, under Scenario 4, the power of the adaptive group sequential design has increased by 11.7% at the cost of corresponding average sample size increases of 11 patients. It is important to note that under the standard group sequential design, the power would have been only 64.7%. For the adaptive group sequential design, the conditional power falls in the promising zone 21.0% of the time, and for these simulations, the re-estimated sample size on average is 101 resulting in a boost in power to 89.2%.

Operating characteristics were calculated based on 10,000 simulations. For the purposes of the simulations, an efficacy boundary was defined using an alpha-spending function with Gamma(-30), a very conservative boundary to reflect the absence of an interim stopping rule for superiority. All sample size and power calculations used EAST v6.5 (Cytel, Inc).

Scenario	Interim Outcome	Probability of Interim Outcome	Power Conditional on Interim Outcome	Expected Sample Size
1	Futility	3.5%	0%	30
	Unfavorable	13.1%	71.8%	60
	Promising	13.0%	97.8%	111
	Favorable	70.4%	97.9%	60
	All Trials / GSD*	100%	91.0% / 82.8%	66 / 58
2	Futility	5.0%	0%	30
	Unfavorable	13.8%	62.2%	60
	Promising	16.7%	95.3%	103
	Favorable	64.6%	96.5%	60
	All Trials / GSD	100%	86.8% / 78.7%	66 / 57
3	Futility	8.0%	0%	30
	Unfavorable	19.8%	56.9%	60
	Promising	15.9%	92.1%	112
	Favorable	56.3%	94.7%	60
	All Trials / GSD	100%	79.3% / 68.0%	66 / 55
4	Futility	9.0%	0%	30
	Unfavorable	19.0%	52.0%	60
	Promising	21.0%	89.2%	101
	Favorable	51.1%	93.7%	60
	All Trials / GSD	100%	76.4% / 64.7%	66 / 55

All based on 10000 Simulations; GSD = standard group sequential design

Publication of the results of this study will occur for the safety lead-in cohort (report 1) and then the randomized phase 2 patient group (report 2).

2. Study Objectives

2.1. Primary Objective

Safety run-in

- To determine the feasibility and tolerability of administering Ibrutinib in COVID-19 infected patients

Phase 2

- To determine whether ibrutinib administration plus standard care for COVID-19 (Arm A) in cancer patients can diminish respiratory

failure or death as compared to untreated control population receiving placebo plus standard care (antiviral such as remdesivir or others, chloroquine, hydroxychloroquine, cytokine blocking peptides or small molecules) (Arm B). Respiratory failure is defined as any of the followings:

- Endotracheal intubation and mechanical ventilation
- Extracorporeal membrane oxygenation
- High-flow nasal cannula oxygen delivery (i.e., reinforced nasal cannula delivering heated, humidified oxygen with fraction of delivered oxygen ≥0.5 and flow rates of ≥30 l/min)
- Noninvasive positive pressure ventilation
- Clinical diagnosis of respiratory failure without initiation of one of above measures only when clinical decision-making is driven solely by resource limitation or if patient has DNI (Do Not Resuscitate) status.

2.2 Secondary Objectives

- To determine time to clinical resolution of need for supplemental oxygen (i.e. maintenance of oxygen saturation of 93% or greater on room air with ambulation) or need for supplemental oxygen above baseline for those on home oxygen.
- To determine rate of ICU admission and length of ICU admission for patients treated with ibrutinib (Arm A) versus control population receiving standard therapy (Arm B)
- To determine rate of shock requiring vasopressor support for patients treated with ibrutinib (Arm A) versus control population receiving standard therapy (Arm B)
- To determine the rate of secondary infection (bacterial, fungal, viral) for patients treated with ibrutinib (Arm A) versus control population receiving standard therapy (Arm B)
- To determine the time to hospital discharge for patients treated with ibrutinib (Arm A) versus control population receiving standard therapy (Arm B)
- To determine grade 3 or higher toxicity observed in patients treated with ibrutinib (Arm A) versus control population receiving standard therapy (Arm B)
- To determine time to mechanical ventilation, the number of days of mechanical ventilation per patient and total observed in patients treated with ibrutinib (Arm A) versus control population receiving standard therapy (Arm B)
- To determine the overall survival at 3 and 12 months post-enrollment.

Exploratory Objectives

- To determine the time to defervescence (oral temperature<100.5 degrees F for a 48 hour time period) among patients treated with ibrutinib (Arm A) versus control population receiving standardtherapy (Arm B)

- To examine the impact of baseline clinical features (e.g. type of cancer, active therapy), duration of symptoms prior to admission and laboratory features (e.g. T cell count) on outcome for patients treated on this therapeutic study

- To determine the proportion of patients with viral clearance at end of ibrutinib therapy, time of hospital discharge and follow up thereafter among patients treated with ibrutinib (Arm A) versus control (Arm B) treatment

- To determine the time and proportion of patients who develop IgM and IgG levels toward SARS-CoV-2 treated with ibrutinib (Arm A) versus control treatment (Arm B)

- To examine immune cell subsets for absolute number, activation, exhaustion markers, and presence of maturation arrest (NK cells) at baseline and over time among patients treated with ibrutinib (Arm A) versus control (Arm B) treatment

- To examine T-cell repertoire over time among patients treated with ibrutinib (Arm A) versus control (Arm B) treatment

- To determine the influence of epigenetic age, clonal hematopoiesis, and monoclonal B cell lymphocytosis (MBL) on treatment outcome

- To determine serial change in inflammatory markers as CRP, ferritin, D-Dimer and cytokines including IL6, IL1B, and TNF-alpha serum levels over time among patients treated with ibrutinib (Arm A) versus control (Arm B) treatment

3. Study Endpoints

3.1. Primary Endpoints

Proportion of patients who develop respiratory failure (as defined elsewhere in the protocol) or death during hospitalization for COVID-19 infection within 30 days of registration

3.2. Secondary Endpoints

- Time from study initiation to 48 hours fever-free (<100.5 degrees F orally)
- Duration of hospitalization
- Time in ICU
- Time to ICU admission
- Number of days requiring supplemental oxygen (or supplemental oxygen above baseline levels)
- Total days of mechanical ventilation
- Time to mechanical ventilation
- Shock and need for pressure support

- Incidence of any infection (viral, fungal, bacterial) including opportunistic infections
- Time to clinical resolution
- Grade 3 or higher toxicity
- Viral clearance at the end of therapy
- Time to viral clearance
- Overall survival at 3 and 12 months

4. BACKGROUND

4.1 SARS-CoV-2 and COVID-19:

The SARS-CoV-2 virus, a novel coronavirus originated from Wuhan China and represents a serious human to human pathogenic virus. SARS-Co-OV-2 has a variable phenotype ranging from asymptomatic carrier state to rapidly progressive acute respiratory distress syndrome. The clinical syndrome manifested by SARS-CoV-2 is termed COVID-19. Both the infectiveness and pathogenic nature of this respiratory droplet transmitted RNA virus greatly exceeds that of influenza, likely as a consequence of no prior human exposure or available vaccine. SARS-CoV-2 has rapidly spread throughout the world and was recently by the WHO as a pandemic pathogen. Notably, SARS-COV-2 has common presentation of fever (89%), cough (68%), CT abnormalities (86%) and lymphocytopenia (84%) with nausea (5%) and diarrhea (4%) being uncommon. Severe disease that requires admission occurs in 20% and a subset of these patients require ICU care (6%), intubation (2.3%) or die (1.4%).[1] The death rate from COVID-19 in different populations has been different from China (updated data, 2.4%) to Italy (7.2%).[2,3]. Death rate from COVID-19 increases proportionately with older age, being highest among older patients and also those who are immunocompromised or have other co-morbidities or lymphocytopenia [1,3-5]. Among hospitalized cancer patients with COVID-19 in China, a 38% frequency of mechanical ventilation or death occurred compared to 8% among patients without cancer[6]. The systemic and pulmonary pathogenesis derived from clinical cases of ICU hospitalized COVID-19 cases and autopsy series demonstrates increased levels of plasma inflammatory cytokines including TNF-alpha, IL-6, and IL-2, and IL-10 and neutrophilic infiltration, macrophages, monocytes, minimal lymphocytes (CD4+ T-cells predominately) and type 2 pneumocytes with EM viral particles. [7,8] Other risk factors for severe COVID-19 illness include the presence of neutrophilia, organ dysfunction (elevated LDH), coagulation abnormalities, thrombocytopenia, and lymphocytopenia suggesting both findings observed in hemophagocytic syndrome that often accompanies immune deficiency and dysregulation [1,9,10].

4.2 Immune Response to SARS-CoV-2:

To date, there have been no studies published that serially follow immune response in patients with SARS-CoV-2 infection and COVID-19 syndrome. Several studies have demonstrated cross comparative studies of moderate versus severe COVID-19 syndrome where differential decline in CD4 and CD8 T-cells occurs with increasing features of both exhausted T-cells (increased PD1, LAG3, CTLA4, and decreased intracellular gamma-interferon) and inflammatory cytokines[11-13].. These findings mimic other chronic virus and parasitic infections where inability CD4 T-cells to generate cytotoxic gamma-

interferon and T-cell exhaustion contributes to failure of the host organism to clear viral infections. Application of a therapeutic that enhances Th1 polarization, diminishes T-cell exhaustion and decreases TNF and IL6 production by both T-cells and monocytes would represent a potential novel therapeutic approach to COVID-19 syndrome.

In contrast to immune suppression predicting higher infection rate and morbidity with COVID-19, once this syndrome is active therapies directed at diminishing inflammation including corticosteroids, IL-6 neutralizing antibodies, and hydroxychloroquine or hydroxychloroquine with azithromycin have demonstrated anecdotal benefit among ill patients. Patients recovering from COVID-19 syndrome demonstrate evidence of humoral neutralizing antibodies[14,15] and SARS-CoV-2 specific T-cells. Additionally, ill patients treated with plasma derived from patients who have developed COVID-19 and recovered with evidence of immune response have had evidence of clinical improvement[16]. This provides evidence that strategies that can disrupt the acute inflammatory response associated with respiratory failure while preserving immune function could serve to effectively treat patients with COVID-19.

4.3 Cancer Strategies to Diminish Inflammatory, but not Immune Response:

Cancer based targeted therapies often seek to shut down inflammatory cytokine release while not compromising innate or adaptive immune response. Examples of this include application of targeted agents directed at graft versus host disease while at the same time maintaining anti-leukemic activity in the setting of allogeneic stem cell transplant[17,18]. One such example of this is Ruxolitinib, a JAK2 inhibitor that was recently FDA approved for the use of acute graft versus host disease. JAK2 inhibitors also demonstrate profound reduction in cytokine production in myelofibrosis and other inflammatory diseases[19]. Similarly, work by OSU investigators and then others has demonstrated ibrutinib, an irreversible inhibitor of BTK and ITK that is FDA approved for marketing for treatment of chronic lymphocytic leukemia (CLL), mantle cell lymphoma, marginal zone lymphoma, and Waldenstrom's macroglobulinemia, has chronic graft versus host therapeutic potential in pre-clinical models and does not inhibit graft versus leukemia effect[20-22]. As an irreversible ITK inhibitor, Ibrutinib has been shown to polarize CD4 cells to a Th1 phenotype in human CLL cells favoring gamma interferon production and in murine models enabling clearance of pathogens such as listeria monocytogenes and Leishmania Major [23,24]. By enhancing T-cell function, ibrutinib has been shown to enhance other T-cell based therapies including TLR agonists[25], PD1 blockade[26], and CAR-T cells[27-29]. The combination of CAR-T cells and ibrutinib in addition to being highly active was shown to also potentially diminish cytokine release syndrome as compared to an earlier report of administering CAR-T cells alone in CLL[30,31]. This was recapitulated experimentally in a murine model of CAR-T cell mediated cytokine release syndrome where ibrutinib improved survival by decreasing this complication while not abrogating T-cell expansion or killing[32]. Finally, in work performed by our own group and others in CLL demonstrated that ibrutinib via ITK inhibition diminishes both activation induced death and reversed features of immune exhaustion, a common pathway that T-cells become depleted in the setting of cancer or chronic viral infections[33,34]. These favorable immune modulating features of ibrutinib establish it as a potential therapy to enhance Th1 polarization, diminished exhaustion, and improved T-cell immune response toward SARS-CoV-2. Given the availability clinically of both less selective irreversible BTK

inhibitors such as ibrutinib and more selective inhibitors (Zanabrutinib, acalabrutinib, and others), the question becomes which target is essential for immune modulation. Using the genetic XID BTK kinase inactive mouse, several groups have demonstrated favorable immune modulation including resistance to multiple organisms including Leishmania Major and other pathogens due to Th1 polarization and enhanced immune response[35-37]. Our work and that of others in CLL patients suggest that even more selective BTK inhibitors such as acalabrutinib which lack inhibition of ITK have similar immune modulating potential in the setting of CLL[33]. As such, from available work we would expect selective BTK inhibitors to be immune modulating, whereas dual inhibitors of BTK and ITK to have both immune modulatory and also ability to expand immune cell subsets based upon reversal of activation induced death by T-cells.

4.4 Targeting BTK as an Anti-infectious Strategy:

Despite being an immune modulator, BTKi of any kind (selective BTK or BTK/ITK) has not been administered clinically to treat infectious disease or abrogate inflammatory toxicity mediated by immune in the lung. However, there is significant pre-clinical data implicating BTK activation in acute pulmonary injury mediated by macrophages and neutrophils and subsequent acute respiratory distress syndrome. BTK activation has been demonstrated to be an essential component of lung injury induced by infectious pathogens, sepsis, and hemorrhagic lung injury that is mediated by excessive inflammatory macrophages and neutrophils [38-40]. Elegant genetic knock down of BTK impaired this lung injury [39,40]. Subsequent pharmacologic studies with ibrutinib have confirmed this. Specifically, ibrutinib in the setting of murine pneumococcal pneumonia has also been shown to negatively influence both monocyte and neutrophil influx into the lung and also alveolar macrophage activation, neutrophil influx, cytokine release and plasma leakage. Antibiotic mediated killing of bacteria was not impaired[41]. A similar study with seasonal influenza A virus demonstrated ibrutinib administered intranasally to mice starting 72 h after lethal infection with influenza A diminished weight loss and led to improved overall survival (37). Additionally, ibrutinib treatment had a dramatic effect on morphological changes to the lungs including decreased alveolar hemorrhage, interstitial thickening, and the presence of alveolar exudate concomitant with diminished inflammatory mediators TNF-alpha, IL-1beta, IL-6, KC, and MCP-1. This murine study suggests that ibrutinib may be an effective therapy for not only influenza-induced lung injury but for treating other viral pathogens mediating lung dysfunction via excessive inflammation[42]. Ibrutinib and potentially other irreversible BTK inhibitors that target BMX irreversibly as well may also have added advantage at diminishing inflammation induced by macrophages and monocytes as shown by both genetic and pharmacologic studies where this kinase regulates TLR4 activated expression of IL-6 or other pathways involving STAT [43-45]. Collectively, these data support ibrutinib or even a more selective BTKi may diminish the lung pathology mediated by the SARS-CoV-2 virus and justify application of this approach for clinical investigation in patients with COVID-19 syndrome.

4.5 Risk Mitigation for Targeting BTKi in COVID-19 syndrome:

Concern for administering ibrutinib or even more selective BTK inhibitors for the treatment of COVID-19 syndrome includes 1) impairment of humoral or cellular immune

response to SARS-COV-2 virus; 2) overlapping cardiac toxicity that might occur with viral induced cardiac symptoms and also therapeutics such as chloroquine and hydroxychloroquine; 3) increased bleeding given the presence of thrombocytopenia with severe cases; 4) increase in alternative infections arising from the anti-inflammatory response to ibrutinib and other BTKi. A small study examining the response of CLL patients on ibrutinib vaccinated against influenza A demonstrated protective titers in up to 74% of patients[46]. In a prospective study performed by our own group in early stage CLL not requiring therapy, ibrutinib was administered concurrently with prenar-13 vaccine and compared to sequential prevnar 13 followed by ibrutinib. In the concurrent arm, 15/16 patients showed a significant increase in antibody titer following vaccination whereas in in the sequential arm 3/13 patients had an increase in antibody titer. Additionally, long-term treatment with both ibrutinib and acalabrutinib does not significantly impair humoral function and results in elevated serum IgA levels among non-heavily pretreated patients[47,48]. This trial will include monitoring of IgM and IgG response to SARS-CoV2 among recovering patients as one of the secondary endpoints to assure diminished response is not noted. With short exposure to ibrutinib (14 days for most), we do not anticipate this will occur and believe the risk population justifies this inclusion. While cardiac toxicity consisting predominately of hypertension or atrial fibrillation and much lesser frequency of ventricular tachycardia and rare cardiomyopathy[49-52]. The risk of atrial fibrillation is approximately 3-10% and occurs over an extended period of time. Prolongation of QT is uncommon with ibrutinib. To minimize risk we will exclude patients with recent myocardial infarct, symptomatic congestive heart failure, and also poorly controlled or patients at high risk for ventricular arrhythmias. Patients with COVID-19 are in the hospital and can be closely monitored for both arrhythmia and functional cardiac problems. Given the short period of ibrutinib treatment (14 days for most), the cardiac risks seem justifiable given the high mortality associated with hospitalized COVID-19 patients with cancer. While serious bleeding has uncommonly been observed with ibrutinib therapy[53-55], efforts to risk mitigate this by pausing therapy for surgical procedures and also avoiding anticoagulation with warfarin and other agents has greatly diminished this risk. The pathology of lung and organ failure in COVID-19 syndrome can involve microthrombi that ibrutinib may have some protective effect against. Indeed, a collective experience by our group at OSU with ibrutinib demonstrated that CLL patients had a very low level of venous or arterial thrombosis as compared to historical controls[56]. To mitigate risk of serious CNS bleeding we will exclude patients with recent stroke (hemorrhagic), congenital or acquired bleeding diathesis. Patients will be monitored for bleeding and if excessive events are noted the study will be put on hold and re-evaluated. Finally, the concern for secondary infection with ibrutinib must be considered in the context of significant clinical experience with this agent in different lymphoid malignancies where over time the frequency of infections significantly diminishes. However, heavily pre-treated patients and those who have received steroids concurrently are probably more at risk[57,58]. Given the short duration of ibrutinib in this trial (14 days for most patients), we do not anticipate that the risk of such infections will be high. We will monitor for these and adjust the trial if observed.

4.6 Summary:

Collectively, this trial seeks to test the hypothesis that BTK inhibitors such as ibrutinib or other even more selective BTKi may 1) diminish the excessive innate immune inflammatory pulmonary response to SARS-COR-2 infection that causes need for intubation and often death; 2) helps to prevent/reverse the severe compromise of adaptive immune system by ameliorating lymphocytopenia, reducing exhaustion as measured by checkpoint molecule expression (PD-1/CTLA4 etc.), and preserving the Th1/Tc1 function. This ultimately will help to protect against HLH/MAS like symptoms, where deficiency in T cells or NK cells plays a key role and 3) Enhance or at least not compromise viral clearance based upon data by our group with listeria and Leishmania major and others with influenza A. This clinical trial proposal seeks to test this hypothesis that by administering ibrutinib therapy for hospitalized COVID-19 patients with a history of cancer or a pre-cancer associated with high risk of infectious morbidity (monoclonal B-cell lymphocytosis, MGUS, and smoldering multiple myeloma, aplastic anemia, and myelodysplasia). Here we will determine if ibrutinib effectively diminishes the high observed frequency of need for mechanical ventilation or death. A randomized phase 2 study of hospitalized patients with COVID-19 syndrome and cancer/pre-cancer syndromes comparing active intervention with ibrutinib (Arm A) + standard of care versus standard of care (Arm B). Cancer patients are chosen for this trial initially as they are at higher risk of poor outcome from SARS-CoV-2. The dose of ibrutinib is chosen based upon the extensive CLL experience of the 420 mg and our own data demonstrating significant T-cell modulation when administered in this manner. Therapy will be given for 14 days with the potential of re-starting therapy if recurrent pulmonary symptoms recur. This trial includes extensive risk mitigation to decrease potential risk of administering ibrutinib in this setting. If preliminary data suggest this approach shows promise, we would consider broadening the eligibility to non-cancer patients at a later time in consultation with the FDA as a second cohort.

5. PATIENT SELECTION

5.1. Inclusion Criteria

1. Hospitalization for confirmed PCR positive COVID-19 infection
2. Active cancer, defined as a solid malignancy either undergoing active therapy, receiving therapy within 1 year, or a hematologic malignancy under active therapy or observation.
3. Age ≥ 18
4. Patients with evidence of pulmonary involvement who meet any of the followings; presence of infiltrates on chest X-ray or CT scan or need for supplemental oxygen < 8L nasal cannula or pulse oximetry < 94% on room air.
5. Biochemical values within the following limits:
    a. Creatinine clearance ≥ 25 ml/min by Cockroft-Gault equation

b. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin

c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x ULN

6. Hematology values must be within the following limits (no need to hold growth factors or transfusions):

   a. Absolute neutrophil count (ANC) ≥ 1000/mm^3 independent of growth factor support

   b. Platelets ≥50,000/mm^3

7. Ability to swallow capsules or receive opened capsule content via nasogastric or enteral feeding tube as described in 7.2

8. Ability to provide informed consent indicating that they understand the purpose of and procedures required for the study, including biomarkers, and are willing to participate in the study. If a patient is unable to provide informed consent (e.g. does not possess decisional capacity), a legally authorized representative may provide consent for the patient.

9. Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not donate sperm during and after the study. For females, these restrictions apply for 1 month after the last dose of study drug. For males, these restrictions apply for 3 months after the last dose of study drug.

10. Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at Screening. Women who are pregnant or breastfeeding are ineligible for this study.

5.2 Exclusion Criteria

1. Patients with new-onset malignancy requiring urgent initiation of systemic chemotherapy.

2. Active uncontrolled systemic bacterial or fungal or other viral infection

3. Requires anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon)

4. Currently receiving BTK inhibitor therapy

5. Actively receiving anti-cancer therapy (other than hormonal therapies). All anti-cancer therapy (except hormonal therapies) must be stopped at the time of screening; can be resumed as soon as ibrutinib is stopped. Significantly T cell suppressive chemotherapy (defined as requiring PJP prophylaxis per standard guidelines) is not allowed for 3 months prior to enrollment.

6. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by

the New York Heart Association Functional ClassificationRequirement for mechanical ventilation at screening

7. Requirement for mechanical ventilation at screening
8. Known bleeding disorders (e.g., Von Willebrand's disease, platelet storage pool disorders, or hemophilia)
9. Stroke or intracranial hemorrhage within 6 months of screening.
10. Major surgery or non-healing wound within 4 weeks of enrollment.

Concomitant administration of prohibited medications (See Appendices

11.)
12. Known history of human immunodeficiency virus (HIV), or active hepatitis B or C infection
13. Disease significantly affecting gastrointestinal function and/or inhibiting small intestine absorption (malabsorption syndrome, resection of the small bowel, poorly controlled inflammatory bowel disease, etc.).
14. Requires chronic treatment with strong CYP3A inhibitors or inducers. See appendix A for complete list of medications
15. Participation in another clinical trial for COVID 19 (antiviral based trials accepting co-enrollment, compassionate or emergency use or expanded access protocols are allowed)

5.3. Inclusion of Women and Minorities

All genders, races, and ethnic groups are eligible for this trial and encouraged to participate.

6. REGISTRATION PROCEDURES

6.1. Informed Consent

The patient must willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. The consent process will either take place in-person or over a phone/video conferencing application. Any questions or clarifications will be addressed by the clinical research coordinator, a co-investigator, or a specific designee previously approved by the OSU Institutional Review Board (IRB) using forms approved by the IRB.

6.2. Registration

This is a single center trial conducted at The Ohio State University (OSU). Dr. Zeinab El Boghdadly, the lead clinical investigator, will coordinate protocol management with

assistance from Drs. Jennifer Woyach and John Byrd, who will also have access to and responsibility for regulatory matters. All patients for whom questions arise relative to eligibility for the study should be discussed with one of the principal investigators prior to entry onto the study.

Patients will be registered by a clinical research coordinator, as per CTO standard practice. Because of the highly infectious nature of COVID-19 and need to conserve personal protective equipment, the study will be discussed with the patient by a study PI or co-I through a video or telephone conference, prior to the research coordinator initiating the consent process. It is expected that most study laboratories will be available from standard of care procedures prior to study enrollment, and these can be used for screening studies as long as they are obtained within 3 days of screening. Patients with a positive SARS-CoV-2 PCR result performed at any facility within 10 days of screening do not need to be retested given the known prolonged shedding nature of the viral infection.

Patients will be registered after meeting all entry requirements, clearance by the Protocol Coordinator, and signing of the informed consent.

Following registration, patients should begin protocol treatment within 48 hours. Issues that would cause treatment delays should be discussed with the Principal Investigator as soon as possible.

7. TREATMENT PLAN

7.1. Overview and Design of Study

7.1.1 Phase 1b

This study will begin with a 12 patient lead-in cohort to establish safety and better characterize toxicity prior to the randomized component. For safety purposes, patients will be enrolled in cohorts of 3 for the first 6 patients, and patients will receive ibrutinib at a dose of 420 mg daily. Dose limiting toxicity (DLT) will be evaluated during the first 14 days of treatment.

DLT would be considered to be any of the following:

- Grade 4 hematologic toxicity that persists for 3 or more days that is considered at least possibly related to ibrutinib.
- Grade 3 or higher non-hematologic toxicity that are considered at least possibly related to Ibrutinib with the exception of nausea, vomiting, diarrhea, or electrolyte abnormality, unless these persist for at least 3 days despite maximal supportive care
- Any grade 3 or higher fungal or bacterial infection (excluding line infection, catheter-associated UTI, or C difficile infection), cardiac toxicity (with the exception of hypertension) or bleeding regardless of the attribution. We note, though, that many

patients in the hospital that develop infection of any grade will be treated with IV antibiotics, and that per CTCAE criteria, those graded 3 or higher would be those where IV antibiotics are indicated, not only for those where IV are chosen due to convenience.

- Non COVID-19 related neutropenic fever

Further enrollment to this dose level will stop if 2 of the first 3 evaluable patients or if at least 33% of subsequent evaluable patients (i.e, 2/6, 3/9, or 4/12) have DLT. If unacceptable toxicity is observed, Ibrutinib will decrease to 280 mg daily, and another 12 patient lead-in will be evaluated at this lower dose level following the same stopping rules. If toxicity is acceptable, the study will proceed to the randomized component. Patients who do not receive 14 days of Ibrutinib for reasons other than toxicity or DLT will be replaced for the purposes of the safety and tolerability assessment.

7.1.2 Randomized Double-Blind Phase 2 Study

In the phase 2 portion of the study, patients will be randomized in a 1:1 fashion to receive ibrutinib plus standard care for COVID-19 versus placebo plus standard treatment for COVID-19. The study is double blinded and each patient will be assigned a randomization number by the James blind pharmacy. The patient, treating physicians, study personnel, and outcome assessors will all remain blinded to group assignment until after the database is locked and blinded analysis is completed.Only the unblinded statistician and the pharmacy staff have access to the unblinded randomization list.
Patients may receive any additional therapies that are not prohibited in the section on concomitant medications. In this trial, cycles will be 7 days in length. Ibrutinib therapy will continue for 2 cycles (14 days). Dose of study drug should be held or modified for adverse events as outlined in **Section 7**.
Patients who develop respiratory failure but are determined by the principal investigator to have clinical benefit from treatment may continue on for the full course of treatment.

7.2. Ibrutinib and Placebo Administration

The sponsor will provide both ibrutinib and matching placebo. Study participants will be dispensed ibrutinib daily (ARM A) and matching capsule placebo (ARM B) through the investigational pharmacy at OSU.The matching placebo will be identical in size and shape, but do not contain ibrutinib.

Ibrutinib or placebo will be administered as capsules (3x140mg capsules) orally once daily with water. The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and should not

be crushed and patients should not attempt to open capsules or dissolve them in water. Patients requiring mechanical ventilation who cannot swallow capsules can have capsules crushed under water and administered through nasogastric or orogastric tube in collaboration with OSU pharmacy as outlined in Appendix B. Each dose of study drug should be taken at approximately the same time every day.

Patients may NOT consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit during the study.

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose. Missed doses will not be made-up. If vomiting occurs no replacement dose is to be given.

If patients are discharged from the hospital prior to completing the course of study drug, the remainder drug to complete two cycles of therapy will be sent home with the patient at discharge and a pill diary will be used.

Medication administration records will be used to determine compliance with study therapy.

7.3. Concomitant Medication Use Guidelines For Study Participants

Warfarin is excluded throughout the trial as is grapefruits and grapefruit juice, starfruit, and Seville oranges. Cancer therapy is also prohibited during the study. Medications allowed with caution are found in Appendices

A. All concomitant medications need to be documented in the electronic medical record.

Standard of Care COVID 19 Therapy

All standard of care therapy for COVID 19 that is not specifically prohibited in the protocol is acceptable and encouraged. Current standards of care can be found in Table 2 of Appendix C. It is acknowledged that standards of care are likely to change during the course of the study. Standard of care therapy should be considered in the context of toxicities expected with ibrutinib, and therapies that are expected to have overlapping toxicities should be used with caution.

Anticoagulants and Anti-platelet agents

Laboratory studies have shown that *in vitro* ibrutinib can prevent platelets from aggregating normally. While serious bleeding has been uncommon in patients treated to date, it is possible that treatment with the study drug could increase the risk of bruising or bleeding, particularly in subjects receiving oral anticoagulants or antiplatelet agents. Besides warfarin, which is prohibited, patients on the study may receive any other anticoagulants or antiplatelet agents at prophylactic or therapeutic doses. Subjects receiving anticoagulants and/or antiplatelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding or bruising and ibrutinib should be withheld in the event of any significant

bleeding events. Patients receiving both therapeutic anticoagulation and anti-platelet agents should be considered at higher risk for bleeding.

Inhibitors or inducers of CYP3A

As ibrutinib is primarily metabolized by CYP3A. Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure, these should be avoided as possible. Avoid grapefruit and Seville oranges during ibrutinib treatment as these contain moderate inhibitors of CYP3A. Strong inhibitors of ibrutinib should be avoided during the course of the trial. Dose adjustment of ibrutinib due to concomitant use of CYP3A inhibitors should follow Table 1 below as applicable. See Appendices
A for a summary of cautionary medications.

Table 1: Ibrutinib Dose Modification Guidance for Co-Administration with CYP3A Inhibitors

Co-administered Drug	**Recommended Ibrutinib Dose for the Duration of the Inhibitor Use[a]**	**Recommended Ibrutinib Dose for the Duration of the Study IF THE STARTING STUDY DOSE IS 280 mg**
Mild CYP3A inhibitors	420 mg once daily. No dose adjustment required.	280 mg daily. No dose adjustment required
Moderate CYP3A inhibitors	280 mg once daily.	140 mg once daily
Voriconazole 200 mg twice daily Posaconazole suspension 100mg once daily, 100 mg twice daily, or 200 mg twice daily	140 mg once daily.	70 mg once daily
Posaconazole at higher doses[b]	70 mg once daily.	Discontinue ibrutinib
Other strong CYP3A inhibitors	Avoid concomitant use and consider alternative with less CYP3A inhibitory potential. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib. If the benefit outweighs the risk and long-term dosing is required (more than seven days), reduce ibrutinib dose to 140 mg once daily for the duration of the inhibitor use.	Avoid concomitant use and consider alternative with less CYP3A inhibitory potential. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib. If the benefit outweighs the risk and long-term dosing is required (more than seven days), reduce ibrutinib dose to 140 mg once daily for the duration of the inhibitor use.

a. Monitor for adverse reactions to ibrutinib (IMBRUVICA) and interrupt or modify dose as recommended (see Dosage and Administration).

b. Posaconazole at higher doses (posaconazole suspension 200 mg three times daily or 400 mg twice daily, posaconazole IV injection 300 mg once daily, posaconazole delayed-release tablets 300 mg once daily).

A list of common CYP3A inhibitors and inducers is provided in **Appendix A.** For further information, please refer to the current version of the ibrutinib IB and examples of inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/.

Tocilizumab has the potential to reduce ibrutinib concentrations, and thus should be used with caution

7.4 Supportive Medications

Colony Stimulating Factors

Colony stimulating factors including filgrastim (G-CSF; Neupogen) and peg-filgrastim (peg-GCSF; Neulasta) may be employed for primary and secondary prophylaxis according to American Society of Clinical Oncology (ASCO) Guidelines.

Corticosteroids

Use of corticosteroids is currently recommended for patients with COVID 19 and hypoxia, [59] Use of dexamethasone (or equivalent corticosteroid) at doses of 6 mg daily for 10 days is allowed. Further use of corticosteroids for COVID 19 is discouraged but use for management of unrelated chronic medical illnesses (e.g. COPD exacerbation) will be allowed at doses equivalent to ≤20 mg prednisone daily.

Anti-Emetics

Prophylactic and other antiemetic therapy will be given at the discretion of the treating physician but should not routinely include corticosteroids.

Antimicrobial Prophylaxis

Prophylaxis for varicella zoster virus (VZV), herpes simplex virus (HSV), or pneumocystis pneumonia (PJP) prophylaxis is allowed, but not required or recommended.

7.5. Perioperative/Periprocedural Management

The following guidance should be applied during the perioperative period for patients who require surgical intervention or an invasive procedure while receiving ibrutinib:

For any planned surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held for at least 7 days prior to the intervention and should be held at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed and without serosanguinous drainage or the need for drainage tubes.

For planned minor procedures (such as needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. It is not necessary to hold ibrutinib for bone marrow biopsies, intubation or central line placements.

For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure or 3 days for an urgent minor procedure, or at the discretion of the investigator.

7.6. Duration of Treatment

Study treatment will continue for a total of 2 cycles (14 days). Therapy will also be discontinued if

- Toxicity requiring unacceptable dose suspension or reduction as outlined in Section 7.1**.**
- Patient voluntarily withdraws from the study
- The treating physician decides it is no longer in the best interest of the patient to continue study treatment

7.7. Duration of Follow-up

Patients will be followed for up to 12 months or until death or withdrawal of consent from study assessments and all further follow-up. Patients who discontinue therapy should continue to be followed for study assessments according to the study calendar. Following hospitalization, study visits will be telephone or video encounters. Patients will need to return to OSU when feasible for laboratory studies as outlined in the study calendar and in line with institutional criteria for discontinuation of isolation at the outpatient setting.

7.8. Criteria for Removal from Study

Patients will be removed from the study if they die or if they withdraw consent from study assessments and all further follow-up. Discontinuation of therapy alone is not sufficient for removal from study. Date of study removal and reason will be documented in the case report form.
For subjects who withdraw consent, there must be clear documentation of whether the subject withdraws consents to treatment only (i.e. agrees to follow-up) or withdraws consent to treatment and follow-up.

7.9. Duration of Study

The study will end 12 months after the final patient is enrolled.

8. DOSE DELAYS AND MODIFICATION (Only Applicable to Safety lead-in patients who do not have DLT, and Phase 2 Patients

8.1. Guidelines for Dose Suspension or Modification Due to Adverse Events

Adverse events (AEs) will be assessed and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Laboratory toxicities will be formally evaluated on days 8, 15, 22, and 29, unless determined to be clinically irrelevant by the principal investigator. These labs will be done ± 3 days.

Treatment with study drug should be interrupted for any grade 3 or higher non-hematologic toxicity with at least possible association to ibrutinib, with the exception of electrolyte abnormalities, nausea, vomiting, or diarrhea, alopecia, or hypertension that can be managed with supportive medications.

Treatment with study drug should be interrupted for any grade 4 hematologic toxicity (or increase in grade by 2 levels if baseline toxicity exists) with at least possible association to ibrutinib with the exception of neutropenia that can be managed with growth factors, anemia/thrombocytopenia responsive to transfusion, or lymphocytosis/lymphocytopenia.

Once the toxicity has resolved to grade 1 or baseline, study drug can be restarted at the original dose. If toxicity recurs, the dose should be held and then decreased by one dose level as outlined in Table 2.

If drug needs to be held > 14 days and still considered possibly drug-related, study drug should not be restarted.

Table 2: Dose De-Escalation Schedule for Toxicity

Dose De-Escalation Schedule for Toxicity	
Dose Level	Study drug
Level 1 – Starting Dose	**420 mg/day (Days 1-14)**
Level 2	280 mg/day
Level 3	140 mg/day
Level 4	Discontinue

8.2. Dose modification of study drug (Ibrutinib or placebo) for Hepatic Impairment

Patients who develop grade 2 increase in bilirubin or ALT/AST should have study drug dose reduced to 2 capsules (equivalent to 280 mg daily) for either arms. If liver function tests return to grade 1 levels, study drug can be increased to 3 capsules (equivalent to 420 mg daily). Patients who develop grade 3 or higher increase in bilirubin or AST/ALT or who have evidence of hepatic failure should have study drug discontinued permanently.

8.3 **Unblinding Procedures**

Unblinding can be done only in cases of an emergency leading to a life threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions. As well, unblinding would be considered in a situation where knowledge of the arm would determine whether a procedure

could be performed emergently (because of risk of bleeding). In any case of unblinding, the patient will be discontinued from the protocol drug.

9. ADVERSE EVENT ASSESSMENT AND REPORTING

9.1. Safety Assessment Overview and Monitoring Timeframe

To monitor the toxicity of study treatment and ensure safety of subjects enrolled in this interventional study adverse events (AEs) will be assessed at each study visit and described and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. In general, AEs and serious adverse event (SAEs) should be reported as a diagnosis instead of symptoms if possible at the time of reporting.

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e. start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug, and actions taken.

The study period during which all AEs and SAEs must be reported begins after the patient is randomizes and ends at 30 days post completion of treatment. After this period investigators should only report SAEs that are attributed to prior study treatment.

Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The INSTITUTION and PRINCIPAL INVESTIGATORS shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe.

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to study drug (ibrutinib or placebo) are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study drug.

All (serious and non-serious) adverse events reported for study drug should be followed-up in accordance with clinical practice.

9.2. Definition of an Adverse Event (AE)

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed

intervention regardless of attribution. The event does not necessarily have a causal relationship with that treatment or usage.

This includes the following:

- An exacerbation or an unexpected increase in frequency or intensity of a pre-existing condition (other than condition under investigation) including intermittent or episodic conditions.
- Significant or unexpected worsening or exacerbation of the condition/indication under investigation.
- A suspected drug interaction.
- An intercurrent illness.
- Any clinically significant laboratory abnormality.

An AE does not include:

- Anticipated day-to-day fluctuations of any pre-existing conditions including the disease under study.
- Signs and symptoms of the disease under study that do not represent a significant worsening or exacerbation.
- Expected progression of the disease under investigation.

9.3. Definition of a Serious Adverse Event (SAE)

An AE that meets one or more of the following criteria/outcomes is classified as serious:

- Death.
- Life threatening.
- Disabling/incapacitating.
- Results in new hospitalization or prolongs a hospital stay.
- A congenital abnormality.
- Other serious medical events may also be considered SAEs if it is an important medical event that may not be immediately life threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment may jeopardize the patient or may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above.

Death for any reason must be reported as a SAE.

A SAE does not include:

- Progression of the underlying infection or syndrome (COVID-19).
- Hospitalization for a routine clinical procedure or treatment as required by the protocol.

- Hospitalization for non-medical reasons (i.e., social admissions, hospitalizations for social, convenience, or respite care).

9.4. Definition of an Unlisted (Unexpected) Adverse Event

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ibrutinib, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

9.5 Definition of an Adverse Event of Special Interest

Adverse events of special interest are events that Janssen is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- Major Hemorrhage
  Major hemorrhage is defined as any hemorrhagic event that is Grade 3 or greater in severity or that results in 1 of the following: intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization.
- Intracranial Hemorrhage
  Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest.
- Other Malignancies
  In addition to all routine AE reporting, all new malignant tumors, including solid tumors, skin malignancies and hematologic malignancies, are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

Any adverse event of special interest should be recorded on a Serious Adverse Event Report Form and be reported to Janssen within 24 hours of becoming aware of the event.

9.6. Adverse Event Grading and Attribution

All patients must be carefully monitored for AEs, including clinical laboratory tests. AEs should be assessed in terms of their seriousness, intensity, and relationship to the study drug. For consistency, events are to be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If CTCAE criterion does not exist for a particular AE, the investigator should use the grade or adjectives as described below:

- Grade 1: Mild. Does not interfere with patient's usual function.
- Grade 2: Moderate. Interferes to some extent with patient's usual function.
- Grade 3: Severe. Interferes significantly with patient's usual function.
- Grade 4: Life-Threatening. Results in a threat to life or in an incapacitating disability.

The investigator will make a judgment regarding whether or not the AE was related to study drug, as outlined in **Table 5** For the purpose of safety analyses all AEs that are classified as possibly related will be considered treatment-related events.

Table 5. Criteria for Attribution of Adverse Events

Attribution	Criteria
Not related	The lack of a temporal relationship of the event to study treatment makes a causal relationship not reasonably possible, or other drugs, therapeutic interventions, or underlying conditions provide a sufficient explanation.
Possibly related	The temporal relationship of the event to study treatment makes a causal relationship reasonably possible, and the event is equally explained by exposure to the study treatment than by other drugs, therapeutic interventions, or underlying conditions.

9.7. Reporting of SAEs and Special Reporting Situations

Overview

As the sponsor of the Study, Institution and Principal Investigators shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. Safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

The institution and principal investigator will provide safety information to Janssen on adverse events, special situations including pregnancies and product quality complaints.

Management of Safety Data

This Study has been designated as an interventional study. As such, all adverse events, special situations including pregnancies and product quality complaints will be reported as described in this exhibit from the time a subject has signed and dated an Informed Consent Form (ICF) until 30 days after the last documented use of a product under study within the

study. All subsequent AEs and SAEs will be collected after this period if the Principal Investigator considers the AE/SAE to be causally-related to the use of the study drug.

9.7.1. All Adverse Events (AEs)

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of therapy. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

9.8 Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

9.9. Data and Safety Monitoring

This study will be monitored both by the investigators and The OSU Data and Safety Monitoring Committee (DSMC), a multidisciplinary board that will monitor the safety and conduct of this trial to ensure patient safety, data quality, and data timeliness. The outcome of the DSMC review of the Lead-in component of the study will be shared with PCYC/Janssen.

The OSU Comprehensive Cancer Center DSMC is composed of a multidisciplinary team with expertise reviewing clinical trial data and adverse events. Information to be provided to the committee may include: up-to-date participant accrual; dosing information; all grade 2 or higher adverse events that have been reported across all sites as well as a summary of all deaths occurring within 30 days of the last day of the treatment period. In addition to safety results, all response/efficacy information (including laboratory results, scans etc.) will be reviewed to better assess the risk/benefit of the study intervention. Should any major concerns arise, the DSMC, after meeting in a closed session, will offer recommendations regarding whether or not to suspend or amend the study.

The DSMC will review all serious adverse events in real time. Outside of concerns regarding adverse events (including SAEs reviewed by the DSMC), the DSMC will review safety data at the next DSMC meeting after the first 12 patients have completed therapy and thereafter every time 30 additional patients have completed therapy (e.g. 12 patients, 42 patients, 78 patients) or every 3 months, whichever comes more quickly. .

The study investigators will conduct continuous review of data and will hold weekly teleconferences to discuss toxicities throughout the course of the trial. Any disagreement among the Co-Investigators as to the safety of the trial will be escalated to the DSMC. Frequency and severity of adverse events will be reviewed by the principal investigator and compared to what is known about the agent from other sources; including published literature, and scientific meetings to determine if the trial should be terminated before completion.

All reportable Serious Adverse Events (SAE) will also be reported to the OSU Cancer IRB as per the policies of the IRB.

10. PHARMACEUTICAL INFORMATION

10.1. Ibrutinib (PCI-32765, Imbruvica™)

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). It is a white to off-white solid with the empirical formula C25H24N6O2 and a molecular weight 440.50. Ibrutinib is freely soluble in dimethyl sulfoxide, soluble in methanol, and practically insoluble in water. The chemical name for ibrutinib is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1Hpyrazolo[3,4 d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one.

10.1.1. Formulation and Storage

Ibrutinib and placebo will be supplied as capsules. Capsules are provided as a hard gelatin capsule containing 140mg of ibrutinib or placebo.

Bottles should be stored at room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F to 86°F).

The investigational pharmacy at OSU will dispense a 14 day supply of capsules on day 1. This supply will be used to administer daily doses while the patient is admitted. If a patient is discharged before the completion of the 14 days of therapy, the remaining supply will be sent home with the patient along with a pill diary.

10.1.2. Administration

The study drug will be administered in the form of 3 capsules orally once daily (either placebo or ibrutinib). The Ibrutinib arm will receive 420mg (3 X 140-mg capsules) orally once daily. The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and patients should not attempt to open capsules or dissolve them in water. Patients requiring mechanical ventilation who cannot swallow pills can have capsules opened and administered through nasogastric or orogastric tube in collaboration with OSU pharmacy. In this case, please see preparation worksheet (Appendix B). Each dose of study drug should be taken at approximately the same time every day.

Patients may NOT consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit during ibrutinib treatment.

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed doses. If vomiting occurs no replacement dose is to be given.

10.1.3. Overdosage

Any dose of study drug administered in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as a SAE in the appropriate time frame and documented as clinical sequelae to an overdose, and would lead to unblinding.

There is no specific experience in the management of ibrutinib overdose in patients. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST

and ALT) after a dose of 1680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

10.1.4. How Supplied

Ibrutinib and matched placebo will be supplied by Janssen.

11. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Correlative laboratory studies for this trial will focus on the modulation of immune response to SARS-CoV-2, clearance of virus, and modulation of immune cells in response to ibrutinib, and select senescence markers (i.e. clonal hematopoiesis, epigenetic age, and others) that are examined to be predictive of outcome. These results, using descriptive analyses, will be correlated between the ibrutinib plus supportive care and the placebo arm, and baseline values and change in values will be correlated with the primary or secondary outcomes. Samples will be collected at the following times:

- Screening
- Day 2 immediately pre-dose
- Cycle 2 Day 1
- End of Ibrutinib (±3 days)
- 1, 3, 6, and 12 months post study entry (±14 days)

In order to prevent viral transmission, patients who are discharged from the hospital will have follow-up labs collected at the OSU outpatient laboratory if they meet criteria for discontinuation of isolation at the outpatient setting. If they do not meet criteria for safe discontinuation of isolation per OSU guidelines, laboratory studies will not be obtained, and this will not be considered a protocol deviation. Samples for assays not performed in the clinical pathology laboratories (CPL) will be sent to the Experimental Hematology Laboratory (EHL) for analysis.

These samples will be used for the following assays:

- Measurement of viral clearance using PCR (from nasal pharyngeal swab in viral media) and serologic antibody testing (CPL):
- Measurement of immune cell subsets for absolute number, activation and exhaustion markers, and maturation using clinical immunome panel (CPL, EHL) at baseline and over time
- Measurement of senescence including epigenetic age (EHL), targeted sequencing for the presence of clonal hematopoiesis (EHL), and others at baseline (this will be done on residual DNA from material derived from immunophenotype/T-cell repertoire)
- Measurement of B/T-cell repertoire and IgM, IgA and IgG response to SARS-CoV-2 (CPL/EHL)

- Measurement of cytokines including IL6, IL1β, TNF-α, and serum alternative multi-cytokine panel to be performed broadly in EHL (CPL/EHL)
- Measurement of serial and post-treatment T-cells to isolate and expand SARS-CoV2 specific T-cells, B-cells and other immune senescent changes (EHL)

Samples for the EHL will be collected and in some cases processed by the clinical trials processing laboratory (CTPL).

We will also collect samples to evaluate ibrutinib pharmacokinetics (PK). This will include trough measurements after the first dose (day 2 pre-dose) and at steady state. For this, approximately 5 mL of blood will be collected in sodium heparin (green top) tubes, placed on ice and immediately centrifuged at 1,200 x g for 10 minutes to isolate plasma. Plasma will be frozen in two separate vials and stored in a -70°C (or less) freezer. Each sample will be labeled with the protocol number, patient number, reference time point relative to the protocol, date and time the sample was obtained.

To perform these analyses, the following samples will be collected at each time point:

Assay	Screening	Day 1 24 hours (prior to second ibrutinib dose)	C2D1 (prior to ibrutinib dose)	End of Rx	1 month From start	2 month From start	3 month From start	6 month From start	12 month From start
Serologic antibody testing	CPL 1 EDTA (3ml)		CPL 1 EDTA (3ml)	CPL 1 EDTA (3ml)	CPL 1 EDTA (3ml)	CPL 1 EDTA (3ml)	CPL 1 EDTA (3ml)	CPL 1 EDTA (3ml)	CPL 1 EDTA (3ml)
C5b-9 level	CPL 1 EDTA (3ml)		CPL 1 EDTA (3ml)	CPL 1 EDTA (3ml)	CPL 1 EDTA (3ml)				
Epigenetic age/clonal hematopoiesis/COVID T-cells, cytokines	CTPL 5 (8 ml ACD)		CTPL 5 (8 ml ACD)	CTPL 5 (8 ml ACD)	CTPL 5 (8 ml ACD)		CTPL 5 (8 ml ACD)		CTPL 5 (8 ml ACD)
Ibrutinib PK	CTPL 1 NaHep (5 mL green top)	CTPL 1 NaHep (5 mL green top)	L 1 NaHep (5 mL green top)						

To protect patient identity, samples sent to EHL will be coded and stored with a subject identification number. The key linking the subject identification number to the individual patient identifying information will be available only to investigators and qualified honest brokers. This key will be password protected. Samples not immediately used will be stored in the Experimental Hematology Laboratory. Any remaining tissue will be stored for future use in the CLL Experimental Hematology Laboratory. Future use will be only that which relates specifically to the biology of COVID-19 and treatment with ibrutinib

12. STUDY CALENDAR[A]

	Screening	Cycle 1 Day 1[I]	Cycle 2 Day 1[I]	End of Treatment (day 14 + up to 3 days if outpatient)	1 month post enrollment [J]	2 months post enrollment [J]	3 months post enrollment [J]	6 months post enrollment [J]	12 months post enrollment [J]
Informed Consent	X								
Medical History	X		X		X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X[K]	X[K]	X[K]	X[K]
Physical Exam	X	X	X	X					
Vital Signs[B]	X	X	X	X					
EKG[C]	X	X	X	X					
CBC with differential	X	X	X	X	X	X	X	X	X
Serum Chemistry,[D]	X	X	X	X	X	X	X	X	X
PT/PTT/INR, D-dimer, fibrinogen, LDH	X	X	X	X	X				
Hepatitis B,C Screening[E]	X								
CRP, ferritin, troponin	X	X (daily)	X (daily)	X	X				
IL6, IFNγ, TNF	X		X	X					
Serum or Urine Pregnancy Testing	X								
Flow cytometry (Immunome)	X		X	X					
Total serum IgG, IgA, and IgM	X			X		X	X	X	X
Nasopharyngeal SARS-CoV-2 PCR[F]	X			X	X (if negative will stop	X (if negative will stop	X (if negative will stop		X (if negative will stop further testing)

					further testing)	further testing)	further testing)		
Peripheral Blood for Correlative Laboratory Studies[G]	X	X	X	X	X	X	X	X	X
Ibrutinib or placebo		X							

A. All research coordinator contact (consent, adverse events, concomitant medications) will be either by phone or over videoconference. Physical examination will be performed by the inpatient treatment team and does not have to be study personnel. For study participants who are discharged prior to completing 14 days, no daily labs will be performed at the outpatient setting and C2D1 labs will be performed on the day of discharge. Study participants will follow institutional inpatients/outpatient isolation initiation and discontinuation measures.
B. Should include Oxygen saturations and O2 requirement. Consider continuous cardiac monitoring, especially for patients receiving concomitant medications with cardiac effects
C. Consider continuous cardiac monitoring, especially for patients receiving concomitant medications with cardiac effects. All patients receiving hydroxychloroquine will be placed on telemetry as part of our standard institutional practice guidelines.
D. Includes chem 10 and liver function panel. Should consider doing chemistry panel and CBC daily.
E. Includes hepatitis C Ab, hepatitis B antibody, surface antigen, and core antigen. Patients with positive surface antigen or core antibody should have hepatitis B DNA tested. Those with a positive core antibody and negative surface antigen may start treatment while awaiting hepatitis B DNA result given its long turnaround time. If the latter is positive, the study drug will be stopped.
F. Will use currently available clinical methods, which may evolve during the course of the study. A positive COVID 19 PCR test at any facility within 10 days of screening is allowed.
G. Please see section 11 for details on required samples. The correlative samples will be collected from standard clinical material that comes through the flow cytometry laboratory under Dr. Gerard Lozanski. Material (plasma, DNA, RNA) will be transferred to the EHL for studies not performed in clinical pathology.

H. Ibrutinib will be administered daily for patients on the ibrutinib arm (Arm A) for a total of 2 cycles (14 days). Placebo will be administered to patients on the standard care arm (ARM B)

I. During study drug administration, CBC and BMP should be collected daily. Liver function tests should be performed at least twice weekly.

J. Post-discharge evaluations may be conducted by phone or videoconference. Laboratory studies will be obtained in the OSUCCC outpatient labs if patient meet criteria for discontinuation of isolation. Patients who are unable to return to OSU will be allowed to have labs performed locally and correlative/COVID related samples shipped to OSU if possible. This has to be approved by the study team. Labs can be performed ± 7 days for timepoints after day 14.

K. Toxicity will continue to be assessed during phone assessments every other week in patients who do not have all toxicities that are possible drug-related resolved at the 1 month follow-up point.

13. STATISTICAL CONSIDERATIONS

This study will enroll high-risk cancer patients testing positive for COVID-19, to be treated with ibrutinib plus standard of care therapy for COVID-19 or placebo plus standard of care therapy for COVID-19. There will be two components of the trial: 1) a safety lead-in component to evaluate the feasibility and tolerability of administering ibrutinib with standard therapy for COVID-19 and 2) a double-blinded randomized component to assess efficacy of ibrutinib with standard therapy for COVID-19 versus placebo plus standard therapy for COVID-19.

Safety Lead-in Cohort

This study will begin with a 12 patient lead-in cohort to establish safety and better characterize toxicity. Patients will receive Ibrutinib at a dose of 420mg daily. For safety purposes, patients will be enrolled in cohorts of 3 for the first 6 patients, with a pause in study enrollment after each cohort to assess for dose-limiting toxicity (DLT). DLT will be evaluated during the first 14 days of treatment.

DLT would be considered to be any of the following:

- Grade 4 hematologic toxicity that persists for 3 or more days that is considered at least possibly related to ibrutinib.
- Grade 3 or higher non-hematologic toxicity that are considered at least possibly related to Ibrutinib with the exception of nausea, vomiting, diarrhea, or electrolyte abnormality, unless these persist for at least 3 days despite maximal supportive care
- Any grade 3 or higher fungal or bacterial infection (excluding line infection, catheter-associated UTI, or C difficile infection) or cardiac toxicity (with the exception of hypertension) regardless of the attribution. We note, though, that many patients in the hospital that develop infection of any grade will be treated with IV antibiotics, and that per CTCAE criteria, those graded 3 or higher would be those where IV antibiotics are indicated, not only for those where IV are chosen due to convenience.

- Grade 3 or higher hemorrhage regardless of attribution, or Grade 2 hemorrhage that is considered at least possibly related to ibrutinib and is considered to be significant by the treating physician in collaboration with the PI.

- Non COVID-19 related neutropenic fever

Enrollment to this dose level will stop if 2 of the first 3 evaluable patients or if at least 33% of subsequent evaluable patients (i.e, 2/6, 3/9, or 4/12) have DLT. If unacceptable toxicity is observed, Ibrutinib will decrease to 280 mg daily, and another 12 patient lead-

in will be evaluated at this lower dose level following the same stopping rules. If acceptable toxicity is observed, the study will proceed to the randomized component. Patients who do not receive 14 days of Ibrutinib for reasons other than toxicity or DLT will be replaced for the purposes of the safety and tolerability assessment.

Randomized Phase 2

The main study is a randomized, double-blind placebo-controlled trial. The primary endpoint of the phase 2 component is the proportion of randomized patients with respiratory failure or death during hospitalization for COVID-19 infection within 30 days of registration. Respiratory failure is defined as any of the following: 1) endotracheal intubation and mechanical ventilation, 2) extracorporeal membrane oxygenation, 3) high-flow nasal cannula oxygen delivery (i.e., reinforced nasal cannula delivering heated, humidified oxygen with fraction of delivered oxygen ≥0.5 and flow rates of ≥30 l/min), noninvasive positive pressure ventilation, or 4) clinical diagnosis of respiratory failure without initiation of one of above measures only when clinical decision-making is driven solely by resource limitation or if patient has DNI (Do Not Resuscitate) status. Patients will be randomized to each treatment arm in a 1:1 ratio utilizing a permuted block schedule. Randomization will be stratified on age (<60 years vs ≥ 60 years) and presence of comorbidities (yes vs no) (comorbidities defined in Appendix C).

Design and Sample Size: Based on a study in China, we assume that the event rate is 40% with standard care and that the event rate can be reduced to 15% when Ibrutinib is added to standard care for COVID-19. With 60 patients and using a standard group sequential design, there is 82.8% power to detect a reduction in the event rate under the alternative hypothesis and constraining the one-sided type I error to 20%. Power was calculated using a z-test for the difference in two proportions, pooled variance, and adjustment for small sample sizes with the Casagrande-Pike-Smith correction (EAST v6.5; Cytel, Inc). There will be an interim analysis when 50% of randomized patients have been followed for 30 days from registration. The study will be stopped early if at the interim analysis the observed event rate is higher in the ibrutinib arm (Arm A) than in the control arm (Arm B). We will plan to over-accrue by about 10% for a total accrual goal of 66 patients.

Although the actual reduction in the event rate could be larger than 25%, it could also be as low as 20% and still be quite meaningful. Furthermore, there is uncertainty in the event rate of the control arm. For these reasons, we have incorporated increased flexibility at the time of the interim analysis to potentially increase the sample size if conditional power indicates promising results, and will thus implement an adaptive group sequential design (Chen, DeMets, Lan; 2004).

At the interim analysis, there are 4 possible outcomes: 1) the futility criteria are met and the trial stops early; 2) the conditional power is unfavorable (<50%), and enrollment continues to the planned sample size without an increase in sample size; 3) the conditional power is in a promising zone (defined as conditional power ≥50% and < 82.8%), and sample size may be re-estimated with the original sample size updated to boost the power to a target of 82.8%, subject to a maximum sample size of 120; or 4) the conditional power is favorable (≥82.8%), and enrollment continues to the planned

sample size without an increase in sample size. When using this procedure, no adjustment to the final test statistic or critical value from the original design is required to control the Type I error rate. In addition, if the conditional power is in the promising zone, we can choose not to increase the sample size beyond what was originally planned or by a flexible amount without penalty.

Operating characteristics using the adaptive group sequential design is presented for four different scenarios:
Scenario 1: Event rates in the ibrutinib and control groups are 15% and 40%
Scenario 2: Event rates in the ibrutinib and control groups are 25% and 50%
Scenario 3: Event rates in the ibrutinib and control groups are 20% and 40%
Scenario 4: Event rates in the ibrutinib and control groups are 30% and 50%

For each scenario, the power and expected sample size is also provided for the standard group sequential design. For example, under Scenario 4, the power of the adaptive group sequential design has increased by 11.7% at the cost of corresponding average sample size increases of 11 patients. It is important to note that under the standard group sequential design, the power would have been only 64.7%. For the adaptive group sequential design, the conditional power falls in the promising zone 21.0% of the time, and for these simulations, the re-estimated sample size on average is 101 resulting in a boost in power to 89.2%.

Operating characteristics were calculated based on 10,000 simulations. For the purposes of the simulations, an efficacy boundary was defined using an alpha-spending function with Gamma(-30), a very conservative boundary to reflect the absence of an interim stopping rule for superiority. All sample size and power calculations used EAST v6.5 (Cytel, Inc).

Scenario	Interim Outcome	Probability of Interim Outcome	Power Conditional on Interim Outcome	Expected Sample Size
1	Futility	3.5%	0%	30
	Unfavorable	13.1%	71.8%	60
	Promising	13.0%	97.8%	111
	Favorable	70.4%	97.9%	60
	All Trials / GSD*	100%	91.0% / 82.8%	66 / 58
2	Futility	5.0%	0%	30
	Unfavorable	13.8%	62.2%	60
	Promising	16.7%	95.3%	103
	Favorable	64.6%	96.5%	60
	All Trials / GSD	100%	86.8% / 78.7%	66 / 57
3	Futility	8.0%	0%	30
	Unfavorable	19.8%	56.9%	60
	Promising	15.9%	92.1%	112

	Favorable	56.3%	94.7%	60
	All Trials / GSD	100%	79.3% / 68.0%	66 / 55
4	Futility	9.0%	0%	30
	Unfavorable	19.0%	52.0%	60
	Promising	21.0%	89.2%	101
	Favorable	51.1%	93.7%	60
	All Trials / GSD	100%	76.4% / 64.7%	66 / 55

All based on 10000 Simulations; GSD = standard group sequential design

Primary Endpoint Analysis: All randomized patients will be included in the primary endpoint analysis and analyzed in the treatment arm to which they were randomized (ITT population). The data will be analyzed using a one-sided Fisher's exact test and a promising signal declared if $p \leq 0.20$ and the event rate is lower in the experimental arm. Since the primary endpoint is to be measured within the first 30 days of registration, we do not expect that primary endpoint information will be missing. However, if there is data missing, the patient will be considered a treatment failure.

Sensitivity analyses include comparison between treatment arm when adjusting for stratification factors and other important variables such as type of cancer or more refined categories of standard of care therapy via logistic regression. If there are events for respiratory failure based on clinical diagnosis without an objective measure and driven solely by resource limitation or if patient has DNI (Do Not Resuscitate) status, a sensitivity analysis will compare arms excluding patients with these events. Sensitivity analyses will be performed for the ITT population and for eligible patients who receive their assigned therapy without a major protocol violation.

Adverse Event Stopping Rules: If there is no concerning safety signal in the lead-in cohort, and the study is able to continue to the randomized component as planned, we have included a plan for comparing toxicity at the interim analyses (first 30 patients across both arms). Accrual will be temporarily suspended to this study and discussion of the data with co-investigators and the data safety monitoring board will occur if we observe adverse events that satisfy the following criteria:

- If the percentage of grade 3/4 all-cause adverse events is at least 15% higher in the ibrutinib arm than in the standard of care arm. This would also include grade 2 hemorrhage if considered significant by the treating physician in collaboration with PI.
- If the percentage of grade 4 all-cause adverse events is at least 15% higher in the ibrutinib arm than in the standard of care arm
- If the percentage of grade 5 treatment-related adverse events is at least 5% higher in the ibrutinib arm than in the standard of care arm

We note that the above stopping rules may be adjusted at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend

accrual because of unexpected adverse event profiles that have not met the specified rules above.

Secondary Endpoints: At the final analysis, all adverse events will be summarized by grade, type, and attribution (regardless of attribution and treatment-related) for each arm. Time-to-event endpoints such as time to discharge and overall survival will be estimated for each arm using the method of Kaplan-Meier. Medians estimates and/or estimates at specific time points will be provided with 95% confidence intervals. The proportion of patients with viral clearance at the time of hospital discharge will be estimated with 95% confidence intervals for each arm. For all biomarkers, descriptive statistics (e.g., means, medians, standard deviations, interquartile range) and graphical displays will be used to characterize central tendency and variability over time. Values will be log transformed as appropriate to reflect biologic plausibility. We will evaluate for statistical trends over time among the biologic measurements, with multiple measurements per patient, using mixed effects models. Lastly, associations between baseline characteristics and the primary endpoint will be evaluated with logistic regression, adjusting for arm. These analyses will be largely descriptive, as a result of a limited sample size.

14. RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

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Appendices

Appendix A: INHIBITORS AND INDUCERS OF CYP3A

NOTE: Itraconazole and ketoconazole can be replaced with voriconazole for study subjects.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	carbamaze
indinavir	nevirapine
nelfinavir	barbiturates
ritonavir	glucocorticoids
clarithromycin	modafinil
Itraconazole	oxcarbazepine
Ketoconazole	pioglitazone
nefazodone	troglitazone
saquinavir	pioglitazone
suboxone	**Strong CYP3A inducers**
telithromycin	avasimibe
cobicistat	carbamazepine
boceprevir	phenobarbital
mibefradil	phenytoin
telaprevir	rifabutine
troleandomycin	rifampin
posaconazole	St. John's Wort
voriconazole	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
isavuconazole	
crizotinib	
darunavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Seville orange juice	
verapamil	
imatinib	
Weak inhibitors:	
cimetidine	
fluvoxamine	
All other inhibitors:	
chloramphenicol	
delavirdine	
gestodene	
mifepristone	
norfloxacin	
star fruit	

Appendix B: Preparation Worksheet for NG or OG Tube Administration of Ibrutinib

PREPARATION WORKSHEET FOR IBRUTINIB

Preparation Worksheet for Ibrutinib for each dose that is prepared.

IP Preparation Steps for Ibrutinib 140 mg

Preparation Date: ____dd/ ____mmm/ _____yyyy

Subject No. _____

____ ____HH: ____mm

Preparation area:

PREPARATION OF THE DRUG PRODUCT

INSTRUCTIONS	RECORD	
1. Confirm the preparation area is clean and cleaning is performed according to site procedure.	_____/_____ Performed by Date	
2. Ensure the dispensing labels are prepared		
3. Remove 3 capsules from the bottle.	Medication Kit Number: _____	
4. Record the time the capsules are removed from the bottle.	dd / mmm / yyyy HH: mm	
5. Open the 3 capsules and place their contents into a glass beaker. Tap the capsule bodies and caps against the side of the beaker to remove any excess material remaining within the capsule bodies and caps.		
6. Prepare a glass beaker filled with 30 mL of water, add to the beaker with the capsule contents, and swirl/mix until the contents are uniform.	Volume of water in beaker (mL): _____	
7. Allow the dispersion to stand for at least 15 minutes.	Standing Start: HH: mm	Standing End: HH: mm
8. Affix an 18 gauge needle to a 60 mL syringe, briefly swirl the beaker, and draw the dispersed capsule contents into the syringe.		

9. Prepare a glass beaker filled with 10 mL of water, add to the empty container to rinse, and draw up into the same syringe.	Volume of water in beaker (mL): _____	
10. Prepare a glass beaker filled with 10 mL of water, add to the empty container to rinse a second time, and draw up into the same syringe, leaving air between solution and plunger.	Volume of water in beaker (mL): _____	
11. Invert the syringe several times to ensure capsule material remains suspended and does not stick to the sides of the syringe.		
12. Draw the plunger back slightly to evacuate the tip. Close the syringe with a tip cap.		
13. Shake the syringe vigorously for approximately 1 min and allowed to stand for at least 30 minutes to allow for complete dispersion prior to dose administration.	Standing Start: ___HH: mm	Standing End: __HH: mm
14. Fill in the variable text fields of the previously prepared dispensing labels and affix the label on the barrel of the syringe.		
15. Calculate expiry: Expiry time is 4 **hours** after the capsules are removed from the bottle.	Expiry date: dd / mmm / yyyy HH: mm	
16. Place the syringe in a tray or a suitable container in a horizontal position.		
Attestation of Dose Preparation steps 1-16	_____/_____ Performed by Date	_____/_____ Checked by Date
The prepared syringe is ready to be provided to the dose Administrator		

Appendix C: Institutional guidelines for management of COVID-19

Treatment Setting	Treatment Recommendations Regardless of Age, Comorbidities, or Immunocompromised Status
Outpatient Setting	Supportive Care
Inpatient Setting*	**Mild Disease** – Without pneumonia and requiring <4L of new O2
	Supportive Care
	Moderate Disease – Pneumonia requiring hospitalization, not meeting criteria for severe disease OR no evidence of pneumonia, but requiring ≥4L of new O2
	Consider Treatment**
	Severe Disease – Requiring mechanical ventilation OR impending respiratory failure requiring intubation (RR>30 breaths/min; O2 saturation ≤93% on room air; PaO2/FiO2 ratio <300mmHg)
	Consider Treatment

*Treatment requires approval 24/7 – see Appendix C
**Strongly consider treatment if duration of illness ≥ 7 days

Table 1: Treatment Recommendations for Highly Suspected / Confirmed COVID-19		
Setting / Severity of Illness	**Description**	**Treatment**
Outpatients	All outpatients	Supportive care
Inpatients Mild Disease	Inpatients without pneumonia and SpO2 > 94% on room air	
Inpatients Severe Disease	Inpatients with SpO2 ≤ 94% on room air; requiring supplemental oxygen, mechanical ventilation, or ECMO	Consider treatment and/or enrollment in clinical trial(s)
Treatment recommendations regardless of age, comorbidities, or immunocompromised status		

Table 2: Adjunctive Antimicrobial Therapies to Consider in Patient Meeting Criteria for Treatment			
Medication	**Dose**	**Indication for Use**	**Additional Information**
Remdesivir	**200 mg IV for 1 day** **Then 100 mg IV daily for 4 – 9 days (Refer to Table 5 in Appendix A)** No adjustment for renal impairment/ ECMO	• Non-FDA-approved agent available via emergency use authorization	• See Appendix A for additional information on how to obtain this product • Baseline and daily serum creatinine and hepatic function labs required • Avoid combination therapy with hydroxychloroquine/ chloroquine due to in vitro antagonism • The clinical relevance of in vitro CYP drug-drug interactions has not been established.

Comorbidities: obesity, asthma, chronic heart, lung, kidney, or liver disease; poorly controlled diabetes mellitus; pregnancy; or active malignancy

Please refer to https://osu.app.box.com/s/sgvwyweea5xx7mjoghfimcaeakpq52hv for most updated version of institutional COVID 19 guidelines

Table 2: Adjunctive Antimicrobial Therapies to Consider in Patient Meeting Criteria for Treatment

Medication	Dose	Indication for Use	Additional Information
Remdesivir	• **200 mg IV x 1 day** • **Then 100 mg IV daily x 4-9 days** • No adjustment for renal impairment/ ECMO	• Non-FDA-approved agent available via compassionate use, expanded access, and emergency use authorization	• See Appendix A for additional information on how to obtain this product • Baseline and daily hepatic function labs required
Hydroxychloroquine (Plaquenil®) PO Suspension (intubated) or Tablets (not intubated)	• **400 mg BID x 1 day** • **Then 200 mg PO BID x 4 days** • No adjustment for renal impairment • If inadequate supply, may substitute chloroquine 500 mg PO x 5-10 days (Appendix B) • May extend course up to 10 days based on clinical response	• Consider use in patients who do not meet criteria for remdesivir or while awaiting remdesivir	• May cause QTc prolongation (See Appendix B) • Tablets cannot be crushed – use suspension for tube administration
Convalescent Plasma	• Refer to Convalescent Plasma Expanded Access Program Workflow for information regarding eligibility, patient consent, and the approval process for COVID-19 patients in whom this therapy is *recommended by an Infectious Disease provider*		
Non-Antimicrobial Medications	• Additional recommendations for non-antimicrobial medications associated with complications and comorbidities linked to COVID-19 (e.g. IVIG, tocilizumab, corticosteroids, ACEI/ARBs, NSAIDS, etc.) refer to the Inpatient Evaluation and Management Guideline for COVID-19		

*The appendix in the tables refer to an external document