A PHASE II RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED CLINICAL TRIAL OF HYDROXYCHLOROQUINE FOR PROPHYLAXIS AGAINST COVID-19 IN PATIENTS RECEIVING RADIOTHERAPY

MSK PROTOCOL

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Please note: All listed above must have completed the mandatory Human Subjects Education and Certification and Good Clinical Practice Certification Programs.

OneMSK Sites	
Site Name	Site's Role
Manhattan	All Protocol Activities
Basking Ridge	All Protocol Activities
Bergen	All Protocol Activities
Commack	All Protocol Activities
Monmouth	All Protocol Activities
Westchester	All Protocol Activities
Nassau	All Protocol Activities

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Patients receiving radiotherapy are at high risk for infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), due to frequent and close contact with healthcare workers and other patients, older age, and compromised immune systems. Following infection, these patients are at high risk for severe infectious complications that can require hospitalization critical care, and can potentially lead to death. This is a phase II placebo-controlled, double-blinded, randomized study evaluating hydroxychloroquine as prophylaxis against coronavirus disease 19 (COVID-19) among patients with no history of SARS-CoV-2 infection who are receiving radiotherapy for cancer.

The primary eligibility criteria is based on a symptom screen and risk factors for prior COVID-19 exposure or infection. Clinical criteria include: no history of SARS-CoV-2 infection; no COVID-19-like symptoms (Temp >38.0C in addition to sore throat, cough, shortness of breath, wheezing, chest tightness, body aches/myalgias, chills, diarrhea, or anosmia) within 14 days of enrollment; and no close contacts with confirmed SARS-CoV-2 patients within 14 days. The patient must meet clinical criteria to enroll. The clinical criteria is based on the standard MSKCC COVID-19 screening guideline plus several additional criteria, such as no history of anosmia and diarrhea. Patients with symptoms and negative COVID-19 PCR or negative COVID-19 serology will be allowed to enroll.

At the time of protocol writing, COVID-19 testing capabilities at MSKCC include SARS-CoV-2 PCR. A serologic assay for anti-SARS-CoV-2 IgG and IgM is being validated and will become available prior to protocol opening. \We also allow optional laboratory-based criteria to be accounted for in our enrollment criteria. We have obtained a set of Standard Q COVID-19 IgM/IgG rapid immunochromatographic tests manufactured by SD Biosensor and distributed to us for the trial by Henry Schein Inc. Additional optional criteria also includes the rapid Standard COVID-19 Ag test manufactured by SD Biosensor and distributed to us for the trial by Henry Schein Inc. Any of the above tests, when available, must be negative prior to enrollment. Thus, the rapid antigen and serology tests are optional, and will only be done if personal protective equipment (PPE) is available and if testing does not interfere with available resources at MSKCC.

Patients who meet all eligibility criteria will be randomized 1:1 to receive hydroxychloroquine 400mg daily versus placebo at the start of radiation therapy. Every patient on trial must be scheduled to receive at least 10 radiation treatments prior to initiation of hydroxychloroquine or placebo. Patients will receive hydroxychloroquine concurrently with at least 10 radiation treatments and will then continue hydroxychloroquine or placebo for 14 days after completion of radiotherapy. Our primary objective is to compare the cumulative incidence of SARS-CoV-2 infection within 9 weeks of randomization for patients receiving radiotherapy with prophylactic hydroxychloroquine versus placebo. We will randomize n=132 patients. If the protocol accrues

100 patients within the first 28 days of activation, it will be amended to expand to n=166, as described in the biostatistics section. Proton therapy is permitted for this protocol at ProCure and NYPC.

Figure 1.1 Schema

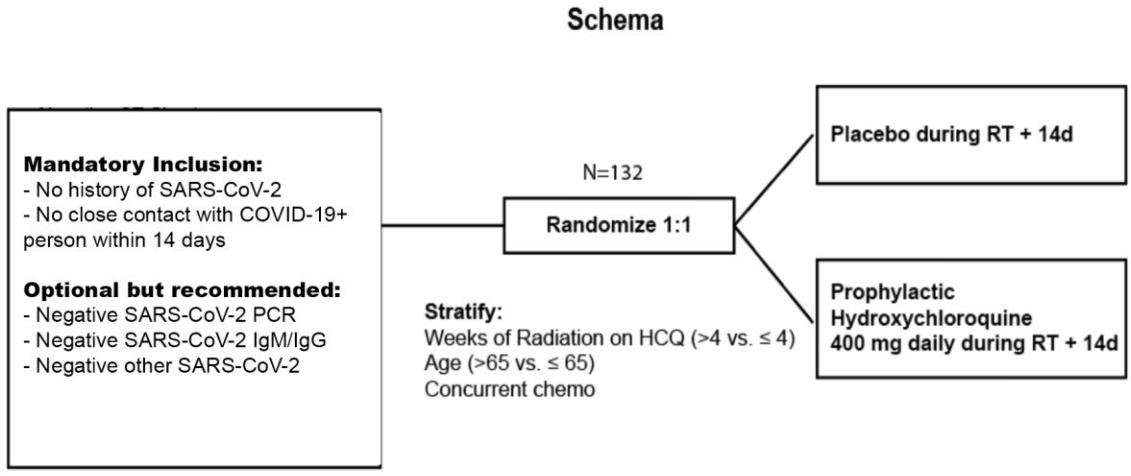
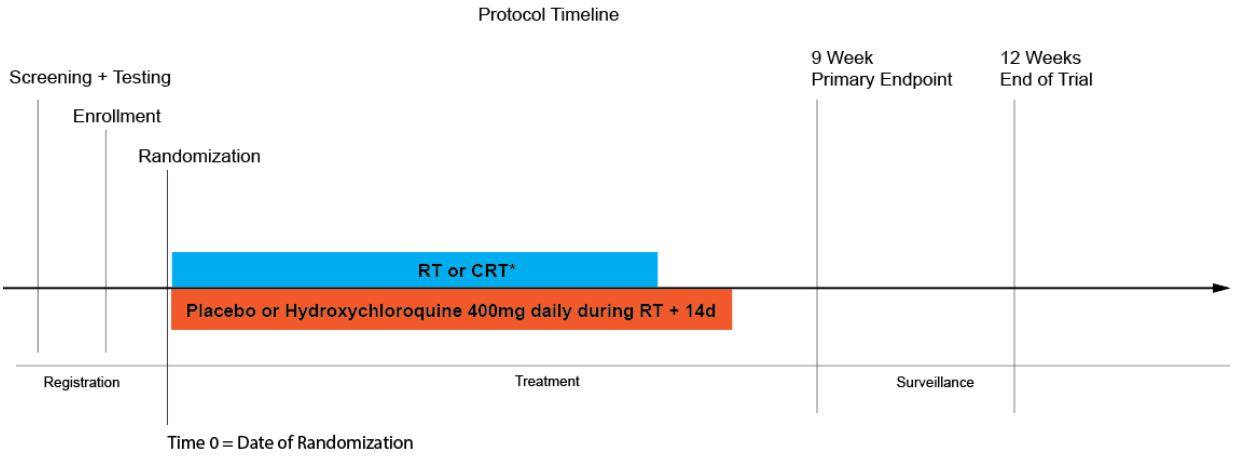


Figure 1.2: Protocol Timeline



* Patients currently receiving radiaiton can be enrolled provided they receive at least 10 fractions of RT with concurrent hydroxychloroquine or placebo.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

2.2 Primary Objectives:

- To compare the cumulative incidence of SARS-CoV-2 infection (Section 13.1) within 9 weeks from randomization in patients receiving radiotherapy with prophylactic hydroxychloroquine versus placebo.

2.3 Secondary Objectives:

- To compare the cumulative incidence of severe COVID-19 or death (Section 13.1) within 12 weeks of randomization in patients receiving radiotherapy with prophylactic hydroxychloroquine versus placebo.
- To compare the cumulative incidence of symptomatic COVID-19 (Section 13.1) within 9 weeks of randomization in patients receiving radiotherapy with prophylactic hydroxychloroquine vs placebo.
- To compare the cumulative incidence of acute grade ≥3 toxicity in patients receiving radiotherapy with prophylactic hydroxychloroquine versus placebo within 12 weeks of randomization.

2.4 Correlative studies (if specimen is available):

- To evaluate the baseline prevalence of anti-SARS-CoV-2 antibodies in patients receiving radiation and chemoradiation without history of symptomatic COVID-19
- To correlate the qualitative Standard Q COVID-19 IgM/IgG rapid immunochromatographic test manufactured by SD Biosensor with quantitative SARS-CoV-2 serology tests (assays being validated in MSKCC Laboratory Medicine) in patients where banked serology is available.
- To correlate the rapid Standard COVID-19 Ag test manufactured by SD Biosensor and distributed to us for the trial by Henry Schein Inc. with the SARS-Co-V-2 RT PCR, only in patients where RT-PCR data is available.
- In patients who are serology negative, to compare the cumulative incidence of symptomatic COVID-19 within 9 weeks from randomization to prophylactic hydroxychloroquine versus placebo
- In patients who are serology negative, to compare the cumulative incidence of severe COVID-19 within 12 weeks from randomization to prophylactic hydroxychloroquine versus placebo
- Collected serum will be stored for future studies

3.1 BACKGROUND AND RATIONALE

3.2 SARS-CoV-2 and Cancer

SARS-CoV-2 is a highly contagious novel coronavirus that is the cause of COVID-19, a disease associated with high rates of viral pneumonia, morbidity, and mortality, particularly in

susceptible populations. As of 3/26/2020, the World Health Organization reports 489,718 confirmed cases and 22,171 deaths. In the United States, 40-50% of the population is conservatively projected to become infected. SARS-CoV-2 disproportionately impacts patients who are elderly, immunocompromised, male, and those with comorbidities.[2–4]

The cancer patient population is at high risk of infection due to frequent exposures to the healthcare workers, other patients, and immunosuppression from their cancer. Once infected, cancer patients face high rates of severe infections requiring hospitalization, critical care, ventilator support, and ultimately high rates of death. The mortality rate in cancer patients is the highest among any reported subset. Liang et al. report a 34% risk of intensive care unit requirements, ventilation use, and death among SARS-CoV-2 patients with cancer compared to 8% of SARS-CoV-2 patients without cancer.[4] Moreover, among cancer patients – those who undergo surgery or receive cytotoxic chemotherapy within one month of infection were at the highest risk. In Italy, cancer patients comprised 4.6% of the population[5] but represented 20% of all COVID-19 related deaths.[6]

3.3 Preclinical Efficacy of Chloroquine and Hydroxychloroquine in Coronaviruses

Chloroquine and hydroxychloroquine are quinine compounds that are well tolerated and widely used for decades for both malaria prophylaxis and treatment as well as in the management of chronic rheumatological diseases, such as rheumatoid arthritis and systemic lupus erythematosus. Importantly, chloroquine has broad-spectrum antiviral properties and is a potent inhibitor of coronaviruses including SARS-CoV-1, inhibiting viral fusion and replication *in-vitro*.[7–9] Mechanistically, chloroquine interferes with sialic acid biosynthesis – which coronaviruses utilize as moieties for ligand recognition. In SARS-CoV-1, chloroquine also impacts the glycosylation of a viral cell surface receptor, angiotensin-converting enzyme 2 (ACE2).[10] Additionally, chloroquine has been demonstrated to interfere with viral-endosomal membrane fusion in SARS-CoV-1, increasing endosomal pH, and abrogates the release of the viral genome. Hydroxychloroquine is a derivative of chloroquine that is associated with decreased toxicity and has demonstrated antiviral activity against SARS-CoV-2 *in vitro*.[11] Based on *in vitro* data, hydroxychloroquine is also thought to inhibit viral replication by preventing glycosylation of the ACE2 receptor, glycosylation of the viral spike protein used for infecting the host cell, and by reducing the acidification of intracellular organelles, which is essential for viral membrane fusion.[11] Thus, chloroquine and hydroxychloroquine have the potential to therapeutically inhibit viral fusion and replication in SARS-CoV-2.

3.4 Rationale for Clinical Investigation

Hydroxychloroquine is an inexpensive and well-tolerated drug with a well-established safety profile. It has known anti-viral activity and is highly efficacious for malaria chemoprophylaxis. With regard to SARS-CoV-2 clinical data, Chinese investigators published a narrative description of 100 SAR-CoV-2 patients treated on a clinical trial with chloroquine and report: rapid decline in fever, improved clinical findings on thoracic imaging, and decreased recovery

time.[7, 12, 13] As a result of favorable toxicity profile and potential efficacy, many on-going trials are testing hydroxychloroquine as a treatment for COVID-19. Emerging data demonstrate that hydroxychloroquine is well tolerated in patients with COVID-19 and may be associated with reduced viral load; however, the ability of hydroxychloroquine to prevent infection in a high-risk population remains unknown.[14] Therapeutic and/or prophylactic use has been recommended internationally by an expert consensus group of the Department of Science and Technology of Guangdong Province in China, the Dutch Center of Disease Control, and the Italian Society of Infectious and Tropical disease. Notably, hydroxychloroquine is undergoing expedited review for use in SARS-CoV-2 by the United States Food and Drug Administration.[12, 13, 15] To date, only one randomized clinical trial of hydroxychloroquine has demonstrated a benefit. 62 patients hospitalized for mild COVID-19 viral pneumonia were randomized 1:1 to hydroxychloroquine 200mg twice daily for 5 days. The authors reported that hydroxychloroquine was associated with shorter time to remission of fever and cough and greater improvements in radiographic CT findings based on serial scans. Importantly, all four patients that decompensated and developed "severe" viral pneumonia were in the control group.[16]

In light of the current public health emergency, and widespread infection risk, we are in urgent need of effective risk reduction strategies for our cancer patients as we await effective therapeutic options. Patients receiving daily radiation treatments for cancer in SARS-CoV-2 endemic areas are at increased exposure risk. These patients are also at high risk for infection due to treatment-related immunosuppression. Therefore, in the setting of the current pandemic, we propose a clinical trial investigating the use of daily prophylactic hydroxychloroquine in cancer patients undergoing radiation therapy. We hypothesize that prophylactic hydroxychloroquine will reduce the risk of symptomatic SARS-CoV-2 infection, hospitalizations, and disease morbidity in the high-risk cancer population receiving radiation therapy.

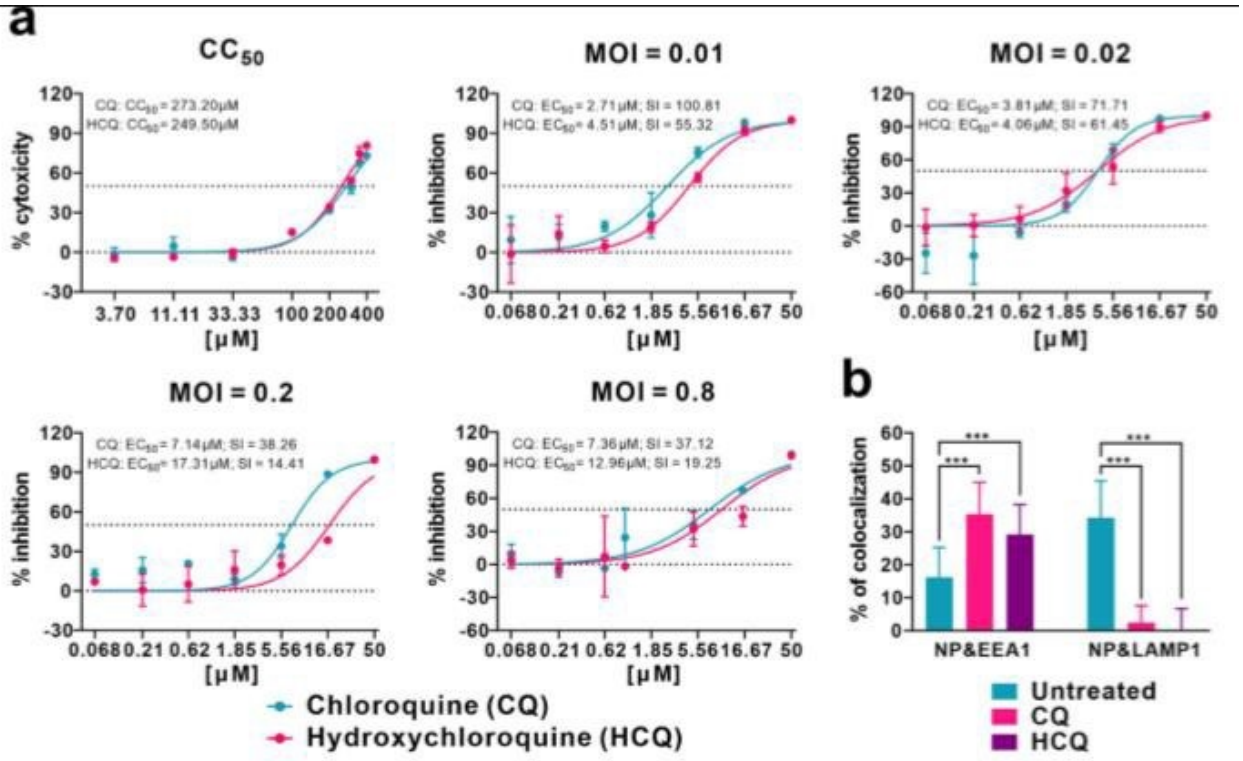
3.5 Rationale for hydroxychloroquine dosing of 400mg daily

Liu et al. recently studied the *in vitro* efficacy of both chloroquine and hydroxychloroquine on inhibition of the SARS-CoV-2 virus in African green monkey kidney VeroE6 cells.[11] They evaluated the dose-response curve for chloroquine and hydroxychloroquine across a range of multiplicities of infection (MOI) (ratio of viral particles to cells) of SARS-CoV-2 (0.01, .02, 0.2, and 0.8) and concentrations of drug (0-50 μM) (**Figure 3.4.1**). Efficacy was measured using quantification of cell copy numbers 4 hours post-infection. Across the MOI range, the 50% maximal effective concentration (EC_{50}) of hydroxychloroquine were 4.51, 4.06, 17.31 and 12.96μM. The ECs_{50} for chloroquine were similar across the range, although chloroquine appeared to have a lower EC_{50} for MOI=0.2. Strikingly, the selectivity index (50% cytotoxic concentration / 50% effective concentration) was 55 and 61 at MOI 0.01 and 0.02, respectively, but decreased to 14.41 and 19.25 at higher concentrations of 0.2 and 0.8. Thus hydroxychloroquine may be more effective earlier in the disease, when the concentration of viral particles is low. Dosages of hydroxychloroquine 5-6.5mg/kg/day yield blood concentrations of approximately 500 ng/ml, or equivalently 1.15 μM, but concentrations in the tissue - particularly

the lungs - can reach 200-700x the blood concentration in the steady-state. Similarly, Wang and colleagues identified an EC_{50} for chloroquine of 1.13 for an MOI of 0.05.[9] Based on this data, the proposed dosing of 400 mg daily will provide a concentration that is efficacious for SARS-CoV-2.

Additionally, hydroxychloroquine 400 mg daily is an FDA approved dose for the treatment of rheumatoid arthritis and systemic lupus erythematosus. The safety of long-term administration, over a time-frame of months to years, is well studied in the rheumatologic population. These experiences suggest hydroxychloroquine has a favorable safety profile at a 5-6.5mg/kg/day dose level for a period of months to years.

Figure 3.4.1: In vitro viral inhibition dose response curves.



3.6 Rationale for Duration of Hydroxychloroquine Prophylaxis

The SARS-CoV-2 pandemic has resulted in this virus being endemic in the New York/New Jersey region. Patients undergoing radiation therapy are at increased exposure risk due to daily visits to waiting rooms, therapy machines, and frequent clinic visits for up to 7-weeks of daily radiation. Indeed, the SARS-CoV-2 experience in China reports that 41.3% of admissions are due to hospital-acquired transmission.[17] Thus the daily medical visits required for radiation

treatment administration also place cancer patients at significant risk of viral exposure. Our proposed trial attempts to mitigate infection risk through prophylactic use of hydroxychloroquine.

The principle of prophylactic use of hydroxychloroquine for cancer patients is analogous to its use in chemoprophylaxis of falciparum malaria, in which travelers to regions where malaria is endemic take chloroquine during travel and 2-4 weeks post exposure.[18] Similarly, cancer patients undergoing radiation are subject to repeat viral exposure risks with every visit. Given that patients are at risk of infection until their last fraction of radiation, and that the viral incubation period ranges from 3-14 days - we propose use of prophylactic hydroxychloroquine use during radiation therapy as well as 14 days after for potential post-exposure prophylaxis.[19]

3.7 Hydroxychloroquine in combination with radiation and chemotherapy in cancer

Rosenfeld et al. reported a phase I/II trial of hydroxychloroquine with radiation and temozolomide for glioblastomas. The phase I portion used a 3+3 design with escalating oral doses from 200 mg to 800 mg in 200 mg increments. 3/3 subjects treated at the 800mg dose developed dose-limiting toxicity, primarily in the form of grade 3 neutropenia and thrombocytopenia, including 1 patient who developed sepsis. None of 3 patients treated at the 600 mg phase I level developed a grade 3 toxicity. In the phase II expansion, which included 75 patients treated with 600 mg by mouth once daily, the risk of grade 3 and 4 thrombocytopenia and neutropenia was 15%, which is similar to what is observed in standard practice without hydroxychloroquine. This study also describes pharmacokinetics of hydroxychloroquine at 600 mg by mouth once a day which is in keeping with what is expected in patients treated with rheumatologic conditions. The radiotherapy was tolerated with expected toxicities.[20]

Eldredge et al. conducted a phase I clinical trial of chloroquine (250mg daily) with concurrent whole brain radiotherapy. Radiotherapy was given to a total dose of 37.5 Gy in 2.5 Gy daily fractions, which is an equivalent dose of 41.25 Gy when given in 2 Gy fractions. The authors noted no grade 3 or greater toxicities during treatment, and no greater than expected skin toxicity, neurocognitive toxicity, or radiation necrosis.[21]

Hong et al. treated 50 patients on a phase II study of hydroxychloroquine 400 mg by mouth twice daily with short-course chemoradiation (5 Gy x 5 vs. 3 Gy x 10) with concurrent capecitabine 825mg/m^2 BID, followed by surgical resection and adjuvant gemcitabine. The investigators found the hydroxychloroquine to be well tolerated, without a meaningful impact on disease-free survival.[22]

Rangwala et al. treated 40 patients on a phase I protocol of dose-dense temozolomide with increasing doses of hydroxychloroquine ranging from 200mg to 1200mg daily. No MTD was reached for hydroxychloroquine and the authors recommended a dosage of 600mg twice daily. Importantly, the dose-dense schedule of temozolomide in this study was intermittent, which may

explain why treatment with higher doses of hydroxychloroquine were tolerated than in the study by Rosenfeld and colleagues. The most common toxicities observed in this group were grade 2 fatigue (55%), anorexia (28%), nausea (48%), constipation (20%), and diarrhea (20%). Treatment up until 400mg of hydroxychloroquine was relatively well tolerated with lymphopenia being the primary toxicity (3/7), as would be expected with dose-dense temozolomide.[23]

Goldberg et al. treated 27 patients with non-small cell lung cancer in a 3+3 phase I dose-escalation study with hydroxychloroquine with or without erlotinib. Hydroxychloroquine was given at 400mg, 600mg and 1000mg dose levels. Grade 3+ toxicities on this trial were uncommon, and none were considered related to hydroxychloroquine. No DLTs were observed in either arm, so the maximum tolerated dose was 1000mg of hydroxychloroquine.[24]

Boone and colleagues conducted a phase I/II trial of hydroxychloroquine (1200mg/day) and gemcitabine (1500mg/m^2) as neoadjuvant therapy for pancreatic cancer. 35 patients were enrolled, and no dose-limiting toxicities were observed.[25] The same investigators performed a subsequent randomized controlled trial of nab-paclitaxel (1000mg/m^2) and gemcitabine (125mg/m^2) alone, with or without hydroxychloroquine (600mg twice daily) from day 1 until the day before planned. The investigators randomized 64 patients (30 chemo alone, 34 chemo + hydroxychloroquine). No differences in toxicity were identified, and the authors identified higher rates of partial pathologic response (55.9% for chemo + hydroxychloroquine vs. 10% for chemo alone), and near complete response (20.6% in chemo + hydroxychloroquine vs. 0% for chemo arm). Treatment with hydroxychloroquine was associated with increased evidence of autophagy and tumor immune infiltration in the resection specimens.[26] Similarly, Karasic and colleagues reported on 112 patients randomized to gemcitabine/nab-paclitaxel +/- hydroxychloroquine 600mg twice daily. Hydroxychloroquine was associated with higher neutropenia (42.6% vs. 22.6%), fatigue (7.4% vs. 0%), nausea (9.3% vs. 0%), peripheral neuropathy (13.0% vs. 5.7%), visual changes (5.6% vs. 0%), and neuropsychiatric symptoms (5.6% vs. 0%).[27]

Chloroquine and hydroxychloroquine have been studied extensively using in vitro studies of cancer as inhibitors of autophagy, as well as modifiers of the radiation treatment effect. Clinical data in human subjects is more sparse, but several phase I and II trials have been performed that have evaluated the safety of combining hydroxychloroquine with chemotherapy, radiotherapy, and chemoradiotherapy. The dose-limiting toxicities of hydroxychloroquine or chloroquine in these settings has primarily been related to cytopenias, which have primarily been observed with very high doses of hydroxychloroquine (600 - 1200 mg per day). Given the limited amount of bone marrow that is included in modern radiation fields and the low proposed dose of hydroxychloroquine, we do not expect significant excess toxicities with this approach.

3.7 Risk of Infection Over Time

For the purpose of this trial, we estimate that among radiotherapy patients in the New York City Metropolitan area who do not have a history of SARS-CoV-2 infection or suspected SARS-CoV-

2 infection, 40% will become symptomatically infected with SARS-CoV-2 over a course of fractionated radiotherapy. Predictions are variable with large confidence intervals, and there is significant uncertainty due to dependencies on government actions related to social distancing and testing.

As of 3/26/2020, New York state had 33,033 confirmed cases, 1,603 hospitalized cases with 366 deaths, for a hospitalization rate among confirmed cases of approximately 15% in the general population.[28] These data fit an exponential model ($\log_{10}$ transform, least squares regression R^2=0.98). In such a model, the population risk increases from approximately 1% to 20% over the course of a week, and increases from 20% to 100% over the course of another week (**Figure 3.7.1**).

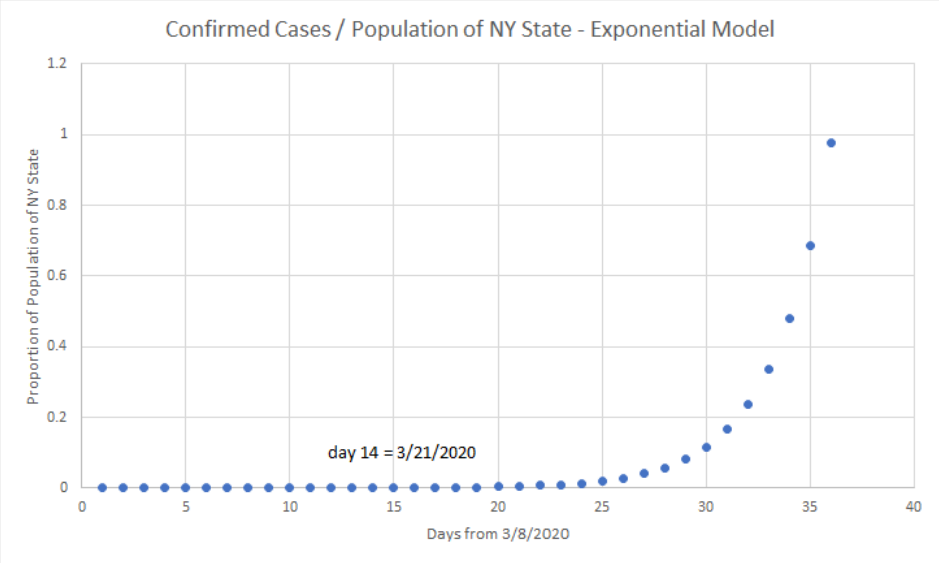


Figure 3.7.1 Exponential Model of Confirmed Cases in New York state over 5 weeks (Data from https://covidtracking.com/data)

At the time of this writing, mandatory social distancing is in effect, which may "flatten the curve". In the Chinese experience with strict police enforcement and testing, the peak in detected cases did not occur until 1 week after lockdown, and approximately half of the new cases occurred after lockdown.[29] Further, New York state does not have a true lockdown, but rather a "PAUSE" policy which may not be as effective as strict *cordon sanitaire* as was implemented in Wuhan, Hubei Province, China. Thus, despite efforts to reduce the number of new infections, the risk of becoming infected over 2-7 weeks of daily radiotherapy likely exceeds 40%.[13] (**Figure 3.7.2**) If social distancing is effective at reducing infection rates, as it has been in some countries, the pattern of infections may become more cyclical.[30]

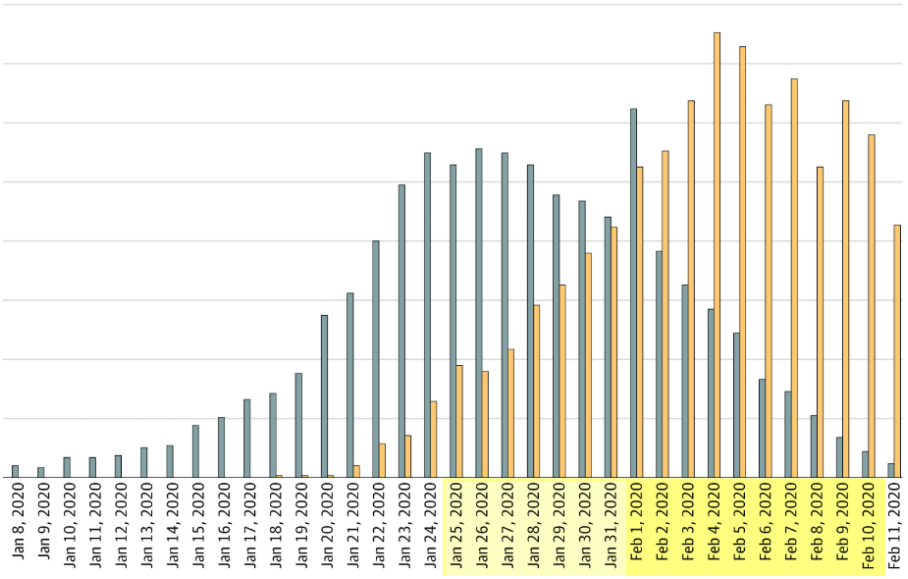


Figure 3.7.2. Pattern of COVID-19 diagnoses in early 2020 from Wu et al., JAMA 2020.[29] Timeline of confirmed COVID-19 cases in China (yellow) and the corresponding dates of symptom onset (blue).On Jan 22, 2020, the Hubei government declared a class 2 response to a public health emergency, leading to restricted travel and enforced social distancing. The rate of new symptomatic cases decreased rapidly thereafter (blue), but the peak of diagnosed cases (yellow) did not occur until several days later.

Direct estimates on the risk of SARS-CoV-2 infection in this population are not yet available, but the infection risks among healthcare providers may provide a reference for the risk of infection among cancer patients receiving radiotherapy. Radiotherapy patients are treated on a daily basis over the course of several weeks. In addition to time spent in the radiotherapy clinic, they may also require supportive care, hydration, amongst other appointments. They may spend significant time in shared spaces with other patients, such as waiting areas, cafeterias, or locker rooms, or may share equipment, such as X-ray machines, CT scanners, hospital chairs. All of these exposures place them at high risk of exposure to SARS-CoV-2 from other patients and staff. Compared with healthcare providers, radiotherapy patients are often older and have compromised immune systems from cancer and cancer-related treatment. Unlike healthcare providers, cancer patients do not have access to personal protective equipment.

The rate of infection with SARS-CoV-2 is high amongst front-line healthcare providers out of all studied groups. In China, 3,300 healthcare providers developed confirmed SARS-CoV-2.[31] In Italy, 20% of all confirmed infections were in healthcare providers, despite comprising a far smaller proportion of the population (4.6%).[6] Wang et al. found the attack rate (number of new cases in a population at risk / number of people in that population) per day was 3.5 times higher in healthcare workers compared to the general population (**Figure 3.7.3**).[32] Furthermore, the

authors estimate that at least 59% of true infections were not diagnosed (**Figure 3.7.4**), suggesting that a much larger proportion of healthcare workers were infected. Li and colleagues estimated that nearly 86% of cases were not documented, and therefore not reported in official statistics.[33] Together, these data suggest that nearly 50% of healthcare workers could be infected over the course of a few months.

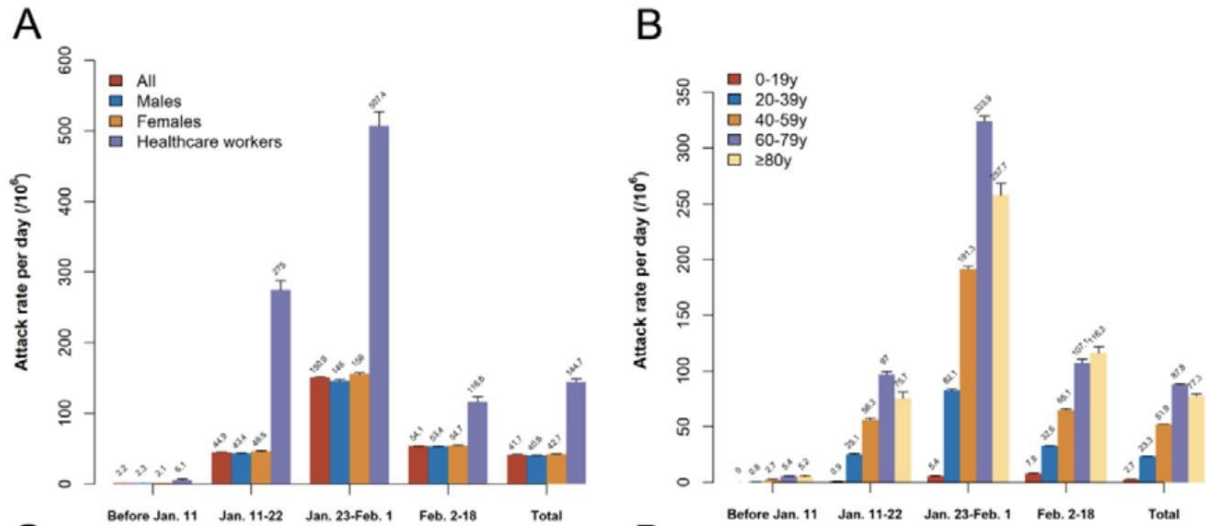


Figure 3.5.3 Attack rate of SARS-CoV-2 by sex and healthcare worker status (A) and age (B) over different periods during the Chinese Wuhan epidemic. (Figure from Wang et al. MedRxiv preprint)[32]

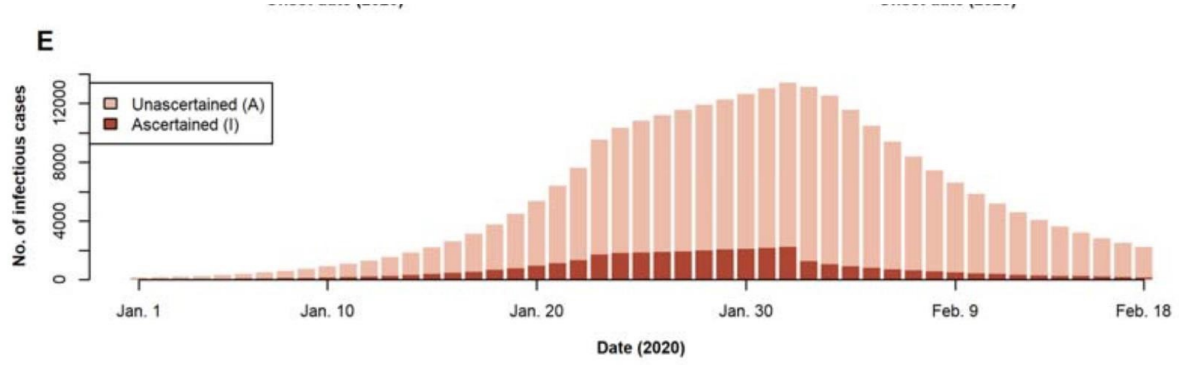


Figure 3.7.4 Laboratory confirmed cases vs predicted number of unconfirmed cases in China based upon epidemiologic modeling suggests that confirmed cases represent a small fraction of total infections.(Figure from Wang et al. MedRxiv preprint)[32]

Radiotherapy patients may face similar rates or potentially greater rates of infection compared to healthcare workers, since they face similar daily exposures, but are older, have compromised

immune systems, and lack personal protective equipment. Whereas the large majority of younger patients are asymptomatic or only mildly symptomatic, the proportion of deaths and severe cases among older patients and those with comorbidities suggests this proportion will be much higher in our cancer population. For instance, in a long-term care center in Washington State, USA, 81/120 (67.5%) of residents, with median age of 81 (range 54-100) and 34/180 (18.9%) of employees were diagnosed with COVID-19 by 3/9/2020. Among 120 residents, 56.8% were hospitalized and 27.2% died. Early genomic-epidemiologic studies suggest that these infections developed over an approximately 2-month period between January and March 2020.[34]

Based on these data, we estimate that the true risk of symptomatic infection over 9 weeks for a patient who tests negative at enrollment will be at least 40%. This estimate is in keeping with estimates from the governmental organizations including California, New York, and Germany.[35, 36]

3.8 Estimate of effect size for hydroxychloroquine

There are no known estimates of effect size for hydroxychloroquine for COVID-19 prophylaxis, and the available evidence is limited to in vitro data and data in patients who are acutely ill with COVID-19. Given in vitro data showing efficacy at lower MOI, we hypothesize that hydroxychloroquine will prevent 50% of infections, reducing the infection rate from 40% to 20%.

3.9 Rationale for use of SARS-Cov-2 PCR, Rapid Standard COVID-19 Antigen and Serology tests

Rationale for use of SARS-CoV-2 RT-PCR and Rapid Standard COVID-19 Antigen testing:

SARS-CoV-2 nucleic acid RT-PCR is currently the standard method of diagnosis of active infection, and RT-PCR is a standard method used in diagnostic virology.[37] Respiratory tract specimens are obtained from nasopharyngeal swabs, induced sputum, or bronchoalveolar lavage, and RNA is subsequently extracted for amplification. In January 2020, Corman et al. published a validated diagnostic workflow evaluating n=297 clinical samples, demonstrating a sensitivity of up to 3.8 copies per reaction with a 95% detection probability, with high specificity and no cross reaction with other evaluated viruses.[37] However, there are several assays used across institutions internationally with a range of sensitivity/specificities, and there have been reports of sensitivity issues due to inadequate nasal swabs, cross-reactivity against SARS-CoV-1, and concerns with regard to the limit of detection. Concerns regarding sampling are due to concern that viral load in the upper respiratory tract is lower than in lower respiratory tract and variable amount of viral shedding at different stages of infection.[38]

MSKCC utilizes a validated, CLIA certified RT-PCR for SARS-CoV-2. However, in the setting of resource shortages (including personal protective equipment for staff obtaining respiratory

samples and test kit/reagent availability) we will follow MSKCC COVID-19 testing policy and only test when available and appropriate.

The commercial rapid antigen test in this protocol utilizes a nasopharyngeal or oropharyngeal swab specimen and is a chromatography based immunoassay. If present in the specimen, extracted antigen binds to anti-COIVD-19 IgG antibody conjugated with color particles in the test device. The assay result can be read in 30 minutes, allowing for rapid assessment of active SARS-CoV-2 infection. A swab is included in the test kit. Similar to the RT-PCR for SARS-CoV-2 test where PPE is required, we will only administer this test when we have the appropriate PPEs so that we do not pose an infection risk for our staff. This test is also optional and dependent on institutional resources.

Rationale for use of SARS-CoV-2 Serology: Standard Q COVID-19 IgM/IgG rapid immunochromatographic test or Validated Assays by MSKCC Laboratory Medicine

While SARS-CoV-2 RT-PCR is the current standard for measuring active infection, it relies on expression of viral RNA and is not a reliable method of evaluating prior infection. Serologic assays, such as ELISAs and lateral flow immunoassays detect IgM and IgG antibodies against the SARS-CoV-2 virus in patient serum. Quantification of IgM and IgG can also help to distinguish between the acute and convalescent phase following SARS-CoV-2 exposure, and thus also potentially give additional data with regard to long-term immunity. Therefore, the benefit of these serologic tests is that the presence of antibodies to SARS-CoV-2 can indicate prior exposure, give data with regard to current immunity, as well as identify asymptomatic carriers, and diagnosis patients with symptomatic infection who have mounted an immune response. While these assays are standardly used in virology, the assays specific for SARS-CoV-2 are currently being validated.[39] Zhao et al. reported results from serial plasma samples obtained from n=173 patients with symptomatic SARS-CoV-2 infection. Significantly, 93% of patients had an IgA, IgM, or IgG antibody seroconversion rate in n=173 patients, with nearly 100% seroconversion of total antibody 1 mo after onset of illness, where as <40% of patients did in the first 7 days of illness.[40] Thus this data indicates that the assay has excellent sensitivity >7 days after symptom onset.

MSKCC's department Laboratory Medicine is currently validating several serologic assays. However given that this resource will be limited, in this trial we have another optional commercial serology test, the Standard Q COVID-19 IgM/IgG rapid immunochromatographic test ,manufactured by SD Biosensor and distributed to us for the trial by Henry Schein Inc. The serologic assay allows for rapid testing of SARS-CoV-2 IgM and IgG antibodies within 15 minutes, using 10 uL of whole blood, serum, or plasma.[39] This product is registered with the FDA and has a sensitivity of 81.8% and Specificity of 96.6% in all patients tested, as well as 92.2% sensitivity and 96.6% specificity in specimens tested 8-10 days after the date of symptom onset. We will utilize this rapid serology test to evaluate for prior SARS-CoV-2 exposure in combination with clinical assessment of patient symptoms at the time of enrollment. If a patient

becomes symptomatic during the trial, we will follow MSKCC guidelines for testing for symptomatic patients. We will also obtain Standard Q COVID-19 IgM/IgG rapid immunochromatographic test and when there is available PPE that does not interfere with institution resources, we will obtain the rapid antigen test. These tests can be utilized as confirmatory tests for our primary endpoint, but are optional and are dependent on available institutional resources. .

Initial serology will enable identification of patients who had prior exposure to the SARS-CoV-2 virus, who subsequently seroconverted. With pre- and post serology data in patients who provide optional research laboratory, we will be able to answer several key questions: 1) whether patients who do not develop symptomatic COVID-19 during the trial can seroconvert, and 2) how this is influenced by hydroxychloroquine vs. placebo.

Rationale for Optional Research CT Chest Imaging:

Due to a shortage of test kits during the outbreak in Wuhan, China, diagnoses of COVID-19 were rendered based upon clinical suspicion and CT chest. Characteristic CT changes associated with COVID-19 have previously been described,[41] and vary relative to the time frame relative to symptom onset as well as the severity of illness.[42, 43] In some cases, CT changes may precede RT-PCR.[44]

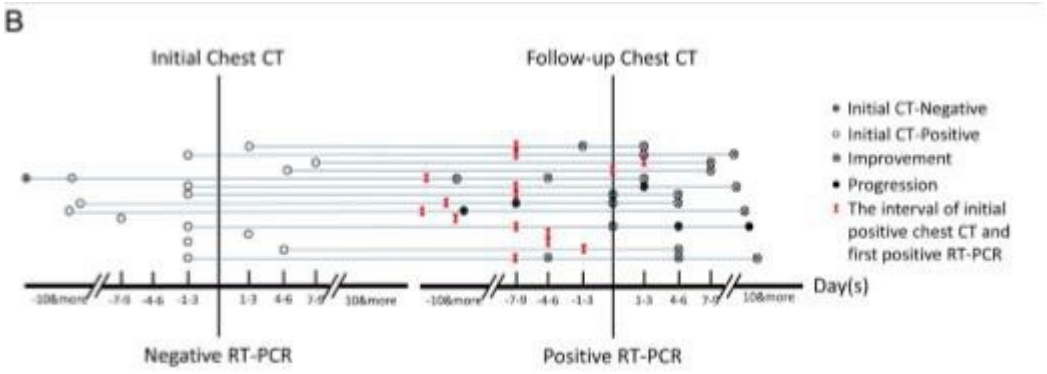


Figure 3.9.1 In a subset of patients with initially negative RT-PCR who subsequently developed a positive RT-PCR, most patients had suspicious CT findings on their original CT Chest.[44]

Studies from China suggest that CT Chest has high sensitivity for COVID-19, but low specificity when using RT-PCR as a reference. Because RT-PCR also has limited sensitivity, especially early in the disease course, many "false positive" CT scans may actually reflect a false negative RT-PCR test. Fang et al. reported on a series of 51 patients who were diagnosed with COVID-19 by RT-PCR who had CT Chest within 3-days of diagnosis. Within this hospitalized, symptomatic cohort, the sensitivity of CT imaging of the chest was 98%, compared with 71% for initial RT-PCR. All patients were eventually diagnosed with COVID-19 by RT-PCR. The average

time from symptom onset to testing was 3 +/- 3 days for both RT-PCR and CT Chest.[45] In a separate study from Wuhan, Ai et al. reported on a series of 1014 cases who underwent both CT Chest and RT-PCR for SARS-CoV-2. Using RT-PCR as a reference, the sensitivity of CT Chest was 97% and the specificity was 25%, with an overall accuracy of 25%. Interestingly, of 308 patients with initially negative RT-PCR based on oropharyngeal swab, 81% of were subsequently felt to have likely or probable COVID-19 with a false negative on initial RT-PCR.[44]

The diagnostic performance of CT chest is strongly dependent on the time from treatment onset. Wang and colleagues reported a longitudinal radiographic study of 90 patients who underwent a cumulative 366 CT scans during their hospitalization for COVID-19. Among 10 scans that were obtained on the day of symptom onset, 60% were normal. However, the percentage of normal scans in confirmed SARS-CoV-2 cases decreased to approximately 14% for scans obtained 1-5 days after symptom onset. <5% of scans were normal 6-11 days after symptom onset.

Due to concerns regarding a resource shortage, an optional research CT Chest will help to establish a baseline for future comparison. Given that part of our cancer workup often times includes a baseline CT chest, we do not require additional chest CTs at baseline strictly for the purpose of this trial. Due to the relatively high sensitivity, patients with symptoms and a positive CT Chest will be excluded from the study.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a randomized (1:1), double-blind, placebo-controlled phase II clinical trial in subjects ≥18 years old scheduled to receive at least 10 radiation treatments. Patients undergoing neoadjuvant radiation, adjuvant radiation, definitive radiation alone, and chemoradiation are eligible. Subjects will be randomized to either prophylactic hydroxychloroquine or placebo. The study will be conducted at Memorial Sloan Kettering (inclusive of Memorial Hospital, MSK Bergen, MSK Westchester, MSK Monmouth, MSK Basking Ridge, MSK Nassau, MSK Koch, and MSK Commack). Proton therapy is permitted for this protocol at ProCure and NYPC. The study will enroll 132 patients meeting the outlined inclusion and exclusion criteria with a planned expansion to 166 patients if there is rapid accrual in the first 28 days.

4.3 Intervention

4.3.1. Baseline Assessment

All patients will undergo baseline history, electrocardiogram, SARS-CoV-2 symptom screen as per standard MSKCC policy (**Appendix 18.2**), and laboratory studies as part of an initial assessment for protocol eligibility. Telemedicine visits are permitted; the baseline physical

exam is optional. Baseline QTc intervals will be calculated from the diagnostic EKG. All patients will provide consent. Remote consent is permitted to reduce exposure risks.

Testing capabilities for SARS-CoV-2, demand on laboratory medicine resources, and demand on healthcare system resources are in flux, and tests may become unavailable during the course of the study. Therefore, we have obtained additional rapid Standard Q COVID-19 IgM/IgG rapid immunochromatographic test kits manufactured by SD Biosensor and distributed to us for the trial by Henry Schein Inc. If resources are available, patients are recommended to undergo negative Standard Q COVID-19 IgM/IgG rapid serologic testing. If rapid IgM/IgG serology is negative, patients will also undergo rapid standard COVID19 Antigen test if MSKCC resources allow (see Section 4.2.2) . Use of these assays will be optional, and also be dependent upon institutional resources.

4.3.2. SARS-CoV-2 PCR Testing and rapid Standard COVID19 Antigen test

- Patients who develop symptoms during the protocol will be referred for SARS-CoV-2 PCR testing per MSKCC policy. Testing requirements are subject to change per MSKCC policy. We will adhere to MSKCC policy. When possible, these patients will also undergo a Standard Q COVID-19 Ag test.
- For MSKCC COVID-19 PCR: This assay will only be conducted in accordance with MSKCC guidelines and only if PPE resources are available. A nasopharyngeal swab will be collected. Specimens will be stored at 2-8 degrees C for up to 72 hours after collection. They will be shipped to Memorial Sloan Kettering Laboratory Medicine on an ice pack, per MSKCC SARS-CoV-2 CLIA certified testing protocol. Samples will be processed and RNA will be extracted. RNA will be reverse transcribed into cDNA and amplified through a real-time PCR instrument. Probe will anneal to a target sequence located between forward and reverse primers. Taq polymerase will degrade the probe, and the fluorescent signal will be generated by separation of the reporter and quencher dye. Fluorescent intensity will be monitored during each cycle and compared to housekeeping gene expression. Detection of viral RNA will be determined based on a predetermined expression threshold.
- For STANDARD Q COVID-19 Antigen test: A nasopharyngeal or oropharyngeal specimen will be collected using a sterile swab. The swab with collected specimen will be inserted into an extraction buffer tube and swirled at least five times. The swab is removed while squeezing the sides of the tube to extract the liquid from the swab. The filter cap will be screwed onto the tube. 4 drops of extracted specimen from the tube will be dropped into the test device. The test result will be read in 30 minutes per the package instructions. Antigen testing will only be done if PPE resources are available.

Patients who develop COVID-19-like symptoms (as defined by MSKCC Screening criteria), and test positive for COVID-19 IgM/IgG by the rapid serology assay, or test positive for the rapid

COVID19 Antigen test, or who test positive forSARS-CoV-2 by PCR, at an outside facility will be declared positive for SARS-CoV-2 and will not reflexively be referred for repeat SARS-CoV-2 at MSKCC. All MSKCC COVID-19 PCRs will only be done according to policy. COVID-19 serology assays and antigen testing will be done only if institutional resources permit.

Furthermore, given the possibility of resource constraints, we will follow MSKCC policy which is subject to change on which patients are considered positive for SARS-CoV-2.

See section 4.2.9 for management of patients who test positive for SARS-CoV-2 by RT PCR or Rapid antigen test.

4.3.3. SARS-CoV-2 Serologic Testing

Optional serology testing will be done at two points for each patient using the qualitative Henry Schein Standard Q COVID-19 IgM/IgG Rapid Test:

- Initial enrollment for all patients (optional testing)
- Optional second time point will be one of the following:
    - 8-20 days after patients on-treatment develop symptoms concerning for COVID-19 and are presumed positive per criteria specified in the protocol
    - 9 weeks following treatment if a patient never develops symptoms concerning for COVID-19 during prophylaxis
- Collection of capillary whole blood specimen: Using a capillary tube, 10 microliters of capillary whole blood will be collected through a finger prick. The collected whole blood will be added to the test device well. 3 drops (90 microliters) of buffer will be placed into the test device. Tests will be read in 10-15 minutes. Tests will be interpreted as positive if IgM and/or IgG is detected.

Research correlative serum (optional) will be collected at two points for each patient for analysis in our correlative objectives seeking to quantify SARS-CoV-2 IgG/IgM in validated ELISA at MSKCC. Serology will be banked and will not be processed immediately by laboratory medicine to conserve resources:

- Initial enrollment for all patients
- Second time point will be one of the following:
    - 8-20 days after patients on-treatment develop symptoms concerning for COVID-19 and are presumed positive per criteria specified in the protocol
    - 9 weeks following treatment if a patient never develops symptoms concerning for COVID-19 during prophylaxis

Processing of research serum: 8-10 mL of whole blood will be aseptically collected in a serum separator tube. Blood will be allowed to clot for 30 minutes at room temperature and the sample will be centrifuged at 2000g for 10 minutes in a 4 degrees C centrifuge. The

supernatant (serum) will be immediately transferred into a sterile polypropylene tube. Samples can be maintained at 2-8 degrees C for <48 hours while awaiting transport. Samples will be banked in aliquots at -20 degrees C for future analysis in collaboration with MSKCC Laboratory Medicine.

4.2.5. Randomization Timing Instructions

Following enrollment patients will undergo randomization to placebo or hydroxychloroquine as outlined in Section 7. For patients who have not yet started radiation, randomization will take place no greater than 2 business days prior to radiation treatment start. Patients who develop COVID-19 symptoms (Temp >38.0C in addition to sore throat, cough, shortness of breath, wheezing, chest tightness, body aches/myalgias, or chills, diarrhea, or anosmia) after enrollment but prior to randomization will need to undergo repeat assessment (SARS-CoV-2 serology, antigen testing, or PCR) before starting hydroxychloroquine. We will adhere to the MSKCC screening guidelines. These guidelines are subject to change and we will add any additional new screening guidelines to this protocol. For patients who have already started radiation at the time of enrollment, randomization will take place immediately after enrollment. Patients, providers, and clinical research staff will be blinded to the randomization. Randomization will occur 2 business days prior to the first fraction of radiation. For patients who have already started their radiation treatment course at the time of enrollment, please note again that there must be enough fractions remaining in their treatment course to allow for a minimum of 10 fractions with hydroxychloroquine or placebo after randomization to be eligible for this trial.

4.2.6. Drug administration

Hydroxychloroquine will be administered at a weight-based dose:

- Weight ≥ 60 kg: 400 mg daily (7 days/week) administered in 2 tablets, 200 mg/tab
- Weight <60 kg:
    - Mon, Wed, Fri, Sun: 400 mg daily administered in 2 tablets, 200 mg/tablet
    - Tues, Thurs, Sat: 200 mg daily administered in 1 tablet, 200 mg/tablet

Dose reduction to 200 mg daily (7 days/week) will be done for patients with Grade 3 renal or hematologic adverse events, until the toxicity has resolved to grade 1. These dose reductions are safety measures as hydrochloroquine is renally excreted and immunomodulatory. If randomized to placebo, patients will be given an equivalent number of weight-based placebo tablets. In the event that the patient is unable to swallow the tablets (i.e. due to dysphagia, PEG dependence), MSKCC pharmacy will provide an oral suspension of equivalent dosage. See Section 10.3.2 for details on drug or placebo administration.

For patients who have not yet started radiation therapy at the time of enrollment, drug administration will start on the same day as the first fraction of radiation. For patients who have

started radiation therapy at the time of enrollment, drug administration will start upon receipt, such that there are a minimum of 10 radiation treatments concurrent with hydroxychloroquine. Treatment with daily (7 days/week) hydroxychloroquine or placebo, as per randomization, will continue for the duration of radiation therapy for all patients and continue for 14 days after the completion of radiation therapy. A weekly supply of drug or placebo will be provided to patients at MSK pharmacies. The patient will continue the drug until they test positive by SARS-CoV-2 criteria or meet positive criteria as determined in Section 13.1. If there are radiation treatment interruptions ≥ 3 days, for non-COVID-19 related reasons the drug or placebo will be held. The study drug/placebo will be self-administered by the patient. Subjects will not be monitored during dose administration. A medication diary will be provided for the patient to document self-administration.

4.2.7. Radiation therapy:

Standard radiation therapy will be prescribed and administered as per the patient's radiation oncologist. Eligible radiation therapy regimens for patients who have not started radiotherapy at the time of enrollment regimens consist of a minimum of 10 fractions. Patients who are already undergoing radiation therapy at the time of the start of treatment for this protocol must have at least 10 remaining radiation fractions following enrollment and randomization, such that hydroxychloroquine is administered with 10 radiation treatments. Neoadjuvant, definitive, adjuvant, palliative, and hypofractionated regimens are allowed as long as the number of fractions meets the aforementioned requirements. Fractions in the radiation course can be administered daily, every other day, or twice daily as long as the number of fractions meets the aforementioned requirements. Radiation therapy will be performed with external beam ionizing radiation as per standard of care in accordance with institutional practice. Proton therapy is permitted for this protocol at ProCure and NYPC. At the time of CT simulation, the CT will include the entire thorax with breath hold and thin cuts, as protocoled in conjunction with Radiology and Radiation Oncology. The radiation simulation order will specify that the patient is enrolled on a clinical trial, and under simulation comments the following language should be included: "Extend CT simulation to include thorax, breath hold, thin cuts. No additional contrast or immobilization needed." Dose to targets and organs at risk must be minimized and must satisfy institutional guidelines. Image guidance will be at the discretion of the treating radiation oncology in accordance with institutional practice. Patients who screen positive based on MSKCC symptom criteria and/or test positive on SARS-CoV-2 PCR or serology test - will have their radiation treatment course determined per department guidelines (Appendix 18.2). Radiation treatments may be either with proton radiotherapy or standard radiotherapy.

4.2.8. Chemotherapy:

The addition of concurrent chemotherapy to radiation will be determined by the patient's medical oncologist as per standard of care and disease management team practice at MSKCC. Biologic agents and immunotherapy given concurrently with radiation must be in line with MSKCC

radiation oncology department practice. Standard of care laboratories associated with the patient's chemotherapy regimen will be obtained as per the patient's medical oncologist.

4.2.9. Symptom screening and toxicity assessments:

In addition to the mandated institutional policy for all patients entering an MSKCC building for radiation to undergo COVID-19 screen with every treatment, patients enrolled on the trial will undergo symptom screening by clinical nursing staff, the patient's medical provider, or the PI/Co-PIs (Screening, week 1, and week 12). This can be done remotely via telemedicine. Risk factors and symptoms associated with SARS-CoV-2 will be assessed through the Screening and Toxicity form in Appendix 18.1.

Patients will undergo standard of care weekly clinical radiation oncology status checks with assessments based on body site as per standard of care at Memorial Sloan Kettering. Telemedicine/remote status checks as well as telemedicine-based research screens are permitted and encouraged. Patients must be assessed for initiation of QTC prolonging agents (Appendix 18.3). Principal investigators and research staff should be notified for patients who screen positive. Principal investigators and research staff should be notified for any grade ≥3 adverse events, QTC>500, if patients are started on any QTC prolonging agents, and hospital admissions.

If a patient screens positive for COVID-19, the Principal Investigators must be notified of the date of symptom onset, the testing ordered, and the outcomes of the test (SARS-CoV-2 Rapid IgM/IgG serology, COVID-19 Antigen, or COVID-19 PCR, MSKCC Elisa based Serology test). The principal investigators should be notified of all hospitalizations or deaths for any reason.

4.2.10. On-treatment or post-treatment SARS-CoV-2 testing:

Patients who screen positive as defined in Appendix 18.2 will undergo standard MSKCC SARS-CoV-2 testing, with sample collection and testing methods as previously outlined. We will adhere to MSKCC policy in the determination of which patients are positive for SARS-CoV-2. Patients with negative symptom screens throughout their treatment course will complete a course of hydroxychloroquine or placebo (as specified by randomization) for the duration of radiotherapy and for 14 days post-radiation, and undergo post-treatment SARS-CoV-2 testing as described and following MSKCC policy.

4.2.11. SARS-CoV-2 positive patients:

Patients enrolled on the trial who test positive for SARS-CoV-2 will no longer continue the study intervention, but will continue to be followed for study purposes. Patients who are enrolled on trial who develop symptoms suspicious for COVID-19 and who have a positive test for COVID-19 prior to randomization will be removed from trial and replaced.

SARS-CoV-2 infection management will be as per Memorial Sloan Kettering infectious disease team standard of care/policy. The patient's radiation treatment course will be determined per Memorial Sloan Kettering Radiation Oncology Department policy for SARS-CoV-2 positive patients.

4.3 Estimated Duration of Subject Participation

Enrolled patients will be treated with hydroxychloroquine or placebo daily (7 days/week) for the duration of radiation therapy plus 14 days after the completion of radiation. All subjects will be followed for SARS-CoV2 infection status, hospitalizations, toxicity, and survival weekly during radiation and at 9 weeks after start of drug, unless the patient meets criteria for trial removal, or the Principal Investigator elects to end the study. Patients will be followed for development of COVID-19 symptoms, diagnosis of COVID-19, hospitalization (for any reason), critical or supportive care, or death. If a patient develops grade 4 toxicity or is admitted to a hospital, the patient's treatment arm will be unblinded at the discretion of the PI or co-PIs.

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

5.2 Hydroxychloroquine

5.2.1. Description:

Hydroxychloroquine sulfate is a white or practically white, crystalline powder, freely soluble in water; practically insoluble in alcohol, chloroform, and in ether. The chemical name for hydroxychloroquine sulfate is 2-[[4-[(7-Chloro-4-quinolyl) amino]pentyl] ethylamino]ethanol sulfate (1:1). Its structural formula is: The molecular weight of hydroxychloroquine sulfate is 433.95, and molecular formula is C18H26ClN3O.H2SO4. Hydroxychloroquine tablets contain 200 mg hydroxychloroquine sulfate, equivalent to 155 mg base, and are for oral administration. Inactive Ingredients: Dibasic calcium phosphate USP, hypromellose USP, magnesium stearate NF, polyethylene glycol 400 NF, polysorbate 80 NF, corn starch, titanium dioxide USP, carnauba wax NF, shellac NF, black iron oxide.

5.2.2. Pharmacokinetics:

Following a single 200 mg oral dose of hydroxychloroquine to healthy males, the mean peak blood concentration of hydroxychloroquine was 129.6 ng/mL, reached in 3.26 hours with a half-life of 537 hours (22.4 days). In the same study, the plasma peak concentration was 50.3 ng/mL reached in 3.74 hours with a half-life of 2963 hours (123.5 days). Urine hydroxychloroquine levels were still detectable after 3 months with approximately 10% of the dose excreted as the parent drug. Results following a single dose of a 200 mg tablet versus i.v. infusion (155 mg), demonstrated a half-life of about 40 days and a large volume of distribution. Peak blood concentrations of metabolites were observed at the same time as peak levels of hydroxychloroquine. The mean fraction of the dose absorbed was 0.74. After administration of single 155 mg and 310 mg intravenous doses, peak blood concentrations ranged from 1161

ng/mL to 2436 ng/mL (mean 1918 ng/mL) following the 155 mg infusion and 6 months following the 310 mg infusion. Pharmacokinetic parameters were not significantly different over the therapeutic dose range of 155 mg and 310 mg indicating linear kinetics. Following chronic oral administration of hydroxychloroquine, significant levels of three metabolites, desethylhydroxychloroquine (DHCQ), desethylchloroquine (DCQ), and bidesethylhydroxychloroquine (BDCQ) have been found in plasma and blood, with DHCQ being the major metabolite. The absorption half-life was approximately 3 to 4 hours and the terminal half-life ranged from 40 to 50 days. The long half-life can be attributed to extensive tissue uptake Reference ID: 4047416 rather than through decreased excretion. Peak plasma levels of hydroxychloroquine were seen in about 3 to 4 hours. Renal clearance in rheumatoid arthritis (RA) patients taking hydroxychloroquine for at least six months seemed to be similar to that of the single dose studies in volunteers, suggesting that no change occurs with chronic dosing. Range for renal clearance of unchanged drug was approximately 16 to 30% and did not correlate with creatinine clearance; therefore, a dosage adjustment is not required for patients with renal impairment. In RA patients, there was large variability as to the fraction of the dose absorbed (i.e. 30 to 100%), and mean hydroxychloroquine levels were significantly higher in patients with less disease activity. Cellular levels of patients on daily hydroxychloroquine have been shown to be higher in mononuclear cells than polymorphonuclear leukocytes.

5.2.3. Supply:

Hydroxychloroquine and placebo will be provided by Rising Pharmaceuticals. Hydroxychloroquine will be provided in 200mg tablets. Hydroxychloroquine will be stored, prepared, and administered per MSKCC guidelines. Placebo will be manufactured for the purpose of this blinded study with the same size, shape, color, and identification code as the hydroxychloroquine. Placebo will be manufactured with ingredients that constitute hydroxychloroquine without the active ingredients. The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of hydroxychloroquine.

5.2.4. Formulation, Packaging, and Storage

Hydroxychloroquine tablets are white, to off-white tablets. Each tablet contains 200 mg of hydroxychloroquine. Dispense in a light-resistant container as defined in USP/NF. Keep out of the reach of children. Store at room temperature, allow excursions between 15 and 30 degrees C.

6.1 CRITERIAFOR SUBJECT ELIGIBILITY

6.2 Participant Inclusion Criteria:

- Age ≥ 18
- ECOG 0-3

- For patients who have not started radiation at the time of screening: patients are required to have a plan in place for a minimum of 10 radiation treatments with or without concurrent systemic therapy
- For patients who have already started radiation at the time of screening: patients must complete enrollment such that they are able to receive at least 10 radiation treatments with hydroxychloroquine.
- §Disease Site
- Mandatory inclusion criteria:
    - No COVID-19 symptoms within 14 days of enrollment:
        - (Temp >38C in addition to sore throat, cough, wheezing, chest tightness, shortness of breath, body aches, chills, diarrhea, and anosmia)
        - If symptoms are present within 14 days of enrollment, patients with a negative COVID-19 PCR or COVID-19 serology assay are eligible for inclusion.
    - No close contact with confirmed COVID-19 person
        - Close contact defined as:
            - Within 6 feet for prolonged period
            - Cohabitating
- Optional laboratory criteria (Recommended if available)
    - Negative pre-treatment SARS-CoV-2 rapid antigen test result (within 1 week of enrollment)
    - Negative pre-treatment SARS-CoV-2 PCR test result (within 1 week of enrollment) using MSKCC laboratory or outside laboratory assay
    - Negative pre-treatment Standard Q COVID-19 IgM/IgG rapid serology result (within 1 week of enrollment)
    - Blood serum for SARS-CoV-2 serology tests (being validated by MSKCC)

§Disease site meets following criteria:

- Head and Neck / High-Risk Skin Cancer
- Lung Cancer
- Breast Cancer
- Prostate Cancer
- Central Nervous System Tumors
- Gastrointestinal System Cancer
- Gynecologic cancer
- Other disease sites permitted at PI discretion

See section 9.1 for management guidelines regarding discordant RT-PCR and CT Chest criteria

6.3 Participant Exclusion Criteria:

- Previous positive test for SARS-CoV-2

- Previous positive serology test for SARS-CoV-2
- Recent Chest CT meeting CT exclusion criteria
- Live in a skilled nursing facility with COVID-19 symptoms (Temp >38 C in addition to sore throat, cough, wheezing, chest tightness, shortness of breath, body aches or chills, diarrhea, anosmia)
- Known hypersensitivity to hydroxychloroquine or 4-aminoquinoline derivatives
- Pre-existing retinopathy
- Known chronic kidney disease, stage 4 or 5, or receiving dialysis
- Breast Feeding
- Tamoxifen
- Absolute neutrophil Count <1,000/ml at registration
- Concurrent use of any other quinine derivative
- Antiarrhythmic medications: amiodarone, sotalol, dofetilide, procainamide, quinidine, flecainide
- Glucose-6-phosphate dehydrogenase deficiency
- Pre-treatment corrected QT interval (QTc) ≥470 milliseconds**
- Prisoners
- Inability to participate
- Psoriasis
- History of suicidal ideation

* CT Criteria for Enrollment Exclusion (Optional - only for patients who received a diagnostic CT as part of standard of care or a thoracic CT as part of radiation simulation):

All patients with COVID-19 typical radiographic findings on CT Chest as defined by the RSNA will be excluded. Patients with any NEW COVID-19 indeterminate radiographic findings on CT Chest that are concerning for COVID-19 will be excluded. COVID-19 indeterminate features are permitted if they can be demonstrated as STABLE on prior (>14 calendar days) CT Chest or PET/CT. If no prior comparison is available AND any intermediate or typical feature is present, the patient is not eligible.

- COVID-19 Atypical Features
    - Isolated lobar or segmental consolidation without GGO
    - Discrete small nodules (centrilobular, “tree-in-bud”)
    - Lung cavitation
    - Smooth interlobular septal thickening with pleural effusion
- COVID-19 Indeterminate Features
    - Multifocal, diffuse, perihilar, or unilateral GGO with or without consolidation lacking a specific distribution and are non-rounded or non-peripheral
    - Few very small GGO with a non-rounded and non-peripheral distribution
- COVID-19 Typical Features

- Peripheral, bilateral GGO with or without consolidation or visible intralobular lines ("crazy paving")
- Multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines ("crazy paving")
- Reverse Halo sign or other findings of organizing pneumonia

** If pre-treatment QTC can be decreased to <470, the patient can be re-considered for trial.

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's radiation oncology team; the site protocol investigator, or a research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The site principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. This initial contact can be done via a telemedicine visit or telephone encounter. The recruitment process outlined presents no more than minimal risk to the privacy of patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; (4) maintaining information in a screening log of patients approached (if applicable), and (5) reviewing CT imaging and calling patients to confirm details regarding COVID-related testing, complications, or symptoms.

The limited waiver will apply only to MSKCC.

7.1. Research Participant Registration

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

7.2 CRDB Blinded Randomization

This is a double blind randomized comparison of hydroxychloroquine or placebo. After eligibility is established and consent is obtained, patients will be registered through the Clinical Trials Management System (CTMS) and then randomized using the Randomization Module in the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted block, age (>65 vs. ≤ 6 weeks), duration of radiation therapy with concurrent hydroxychloroquine or placebo (>4 vs. ≤4 weeks), receipt of concurrent chemotherapy (yes vs. no). Since this is a double blind study, the patients' treatment assignments can be viewed in the CRDB only by the hospital pharmacists who are dispensing the study drugs. All data will be collected and analyzed at MSKCC. Compiled data will be submitted to the biostatistician on study (Dr. Zhigang Zhang) for analysis.

7.3 Breaking the Blind

At all times, treatment and randomization information will be kept confidential and will not be released to the patient, investigator, the study staff, or the sponsor's study team until following the conclusion of the study, with the exception described in this section.

At the initiation of the study, the study site will be instructed on procedures for breaking the blind. Blinding codes should be broken only in emergency situations for reasons of patient safety. If the patient has an adverse event that may be considered hydroxychloroquine mediated, treatment for the adverse event should be administered as if the patient is receiving hydroxychloroquine. Whenever possible, the investigator should contact the principal investigator before breaking the blind. The method will be either a manual or electronic process. When the blind of a patient has been broken, the reason must be fully documented. If the blind is broken, the investigator should promptly inform the study PI. The patient for whom the blind has been broken will be discontinued from the study treatment.

If a patient develops grade 4 toxicity or is admitted to a hospital, the treatment arm will be unblinded at the PI or co-PIs discretion.

8.1 INFORMED CONSENT PROCEDURES

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

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of the study and the likely follow-up required
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

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

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

9.1 PRETREATMENT EVALUATION/INTERVENTION

Within 60 days of starting treatment, the following tests need to be done:

- Complete History
- Physical Examination (not required)
- Vital Signs (pulse, blood pressure), including weight
- Performance Status
- Record of concomitant medications
- Signed informed consent (electronic permitted)
- Electrocardiogram with QTc calculation
- Comprehensive Panel, including liver function tests (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium).
- Complete Blood Count (including platelets)
- G6PD Deficiency testing

- Women of childbearing potential must have negative pregnancy test per radiation oncology standard of care
- Research blood draw (this should be performed on the same day as initial SARS-CoV-2 testing): Peripheral blood samples will be collected in 1 serum separator tube (for serologic testing).
- Optional pre-treatment SARS-CoV-2 testing: IgM/IgG rapid serology, within 1 week of randomization. The rapid serology test is negative and there are available PPE, a rapid Standard COVID19 antigen test will be performed if institutional resources permit.
- Screening risk assessment for prior COVID-19 infection, COVID-19 household contacts, or COVID-19 symptoms (Temp >38C in addition to sore throat, cough, shortness of breath, wheezing, chest tightness, body aches or chills, anosmia, diarrhea) within 1 week of randomization

9.2 Management of patients based on Rapid serology and Antigen testing

- Patients who are COVID-19 IgM and IgG negative when possible should undergo Rapid COVID-19 antigen testing to enroll on the trial.
- Patients who are COVID-19 IgM and IgG negative, who then undergo Rapid COVID-19 antigen testing but are found to be COVID-19 antigen positive will not be enrolled on the trial. Antigen testing suggests active infection and patients will be advised to take safety measures as if COVID-19 positive.
- Patients who are COVID-19 IgM and/or IgG positive do not meet criteria for the trial. Their serology indicates COVID-19 exposure and out of caution will be advised to take safety measures as if COVID-19 positive.
- If at any time during the trial patient is tested with MSKCC COVID-19 PCR for a clinical reason, a positive result from the PCR will supersede all point of care serology and antigen testing. Patients in this circumstance will be presumed positive and will either not be enrolled on the study or will discontinue study drug.
- All patients who are presumed positive will be managed per MSK Infectious disease policy and their radiation treatment course will be in accordance with MSK Radiation Oncology Department policy

10.1 TREATMENT/INTERVENTION PLAN

10.2 Dosing Instructions and Schedule

10.2.1. Hydroxychloroquine Dosing Instructions and Schedule

Hydroxychloroquine will be administered at the following weight-based dose:

- Weight ≥ 60 kg: 400 mg daily (7 days/week) administered in 2 tablets, 200 mg/tab
- Weight <60 kg:
    - Mon, Wed, Fri, Sun: 400 mg daily administered in 2 tablets, 200 mg/tablet

- Tues, Thurs, Sat: 200 mg daily administered in 1 tablet, 200 mg/tablet
- If randomized to placebo, patients will be given the equivalent tabs and schedule, based upon weight

For patients who have not yet started radiation therapy at the time of enrollment, drug or placebo will be administered within 48 hours of the first fraction of radiation. For patients who have started radiation therapy at the time of enrollment, drug or placebo administration will be upon receipt of medication. Hydroxychloroquine or placebo will continue until 14 days after the completion of radiation treatments. A weekly supply of drug or placebo will be provided to patients. Drug will be self-administered by the patient. Subjects will not be monitored during dose administration. A medication diary will be provided for the patient to document self-administration and to list daily dosages of medication.

10.1.2 Radiation Dosing Instructions and Schedule

Radiation therapy will be started after simulation as per MSKCC department timeline. Patients will undergo a standard of care course of radiation at the discretion of the treating radiation oncologist. Radiation dose to target and organs will be in accordance with MSKCC institutional guidelines.

10.1.3 Chemotherapy Dosing Instructions and Schedule

In patients who are receiving chemotherapy, immunotherapy, or biologic therapy with radiation - chemotherapy will be as per standard of care in accordance with institutional practice and at the discretion of the treating medical oncologist. Administering concurrent radiation with systemic agents must be in accordance with MSKCC radiation oncology department practice.

10.2 Concomitant Medications and Therapies

All medication that is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the investigator.

10.2.1 Permitted concomitant therapy includes:

- Standard therapies for concurrent medical illness
- Supportive care for any underlying illness
- Palliative (limited-field) radiation therapy is permitted
- Treatment with nonconventional therapies (such as acupuncture), and vitamin/mineral supplements are permitted provided the therapy does not interfere with the study endpoints, in the opinion of the investigator
- Bisphosphonates or denosumab

- Subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and INR/PTT are considered stable by the treating physician.

10.2.2. Excluded Concomitant Medications

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications are considered exclusionary during the study. The Principal Investigator must be notified if a subject receives any of these during the study.

- Antiarrhythmic medications: amiodarone, sotalol, dofetilide, procainamide, quinidine, flecainide

The study team must document if QT prolonging medications are administered at any time during the study period. Efforts should be made to avoid QT prolonging medications if acceptable alternatives are available. See QT prolongation section in 15.7

Precautions should be taken with the following medications listed in Section 15.4. Patients will not be excluded based on these medications but patients will be monitored cautiously with a minimum of q2 week laboratory evaluation and weekly symptoms/toxicity screen.

10.3 Hydroxychloroquine Dose Modification and Discontinuation

10.3.1 Initial Hydroxychloroquine Dose

- Patients will be initiated on a weight based dose (As outlined 10.1).
- Patients currently on any medications that have the potential to interact with Hydroxychloroquine (drug interactions) will not undergo dose modifications and will be monitored on treatment.

10.3.2. Hydroxychloroquine Dose Modifications and Discontinuation During Treatment

For subjects who do not tolerate the protocol-specified dosing schedule due to toxicity that is relevant to hydroxychloroquine administration or any toxicity that may be impacted by hydroxychloroquine, dose modifications and interruptions are recommended in order to allow subjects to continue the study treatment. The dose modifications for the hydroxychloroquine-specific scenarios (QTc prolongation, acute kidney injury, and cytopenias) are outlined below.

Toxicities will be graded according to CTCAE version 5.0 of the NCI Common Terminology Criteria for Adverse Events CTCAE version 5.0 is identified and located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

For subjects who develop QTc prolongation during therapy. The following hydroxychloroquine dose modification guidelines are recommended:

QTc Prolongation	**Recommended management or dose modification**
QTc>500 msec based on an average value of triplicate ECGs	-Assess the quality of the ECG, QT value, and repeat if needed -Test serum potassium, calcium, phosphorus, and magnesium. If abnormal, correct per routine clinical practice to within normal limits. -Review concomitant medication and identify any association with QT prolongation*. -If a QTc prolonging agent is identified continue hydroxychloroquine at the current dose, but withhold the agent if medically feasible and recheck QTc in 5-10 days. -If persistent QTc >500 msec or if no other QTc prolong agent is identified, remove patient from study

*QTc prolonging medications include: haloperidol, ziprasidone, quetiapine, thioridazine, olanzapine, risperidone, amiodarone, sotalol, dofetilide, procainamide, quinidine, flecainide, macrolides, fluoroquinolones, amitriptyline, imipramine, citalopram, methadone, sumatriptan, ondansetron, cisapride. Following trial enrollment will have QTC rechecked 1 week after initiation of the QTC prolonging agent. Notify Principal investigators if QTc prolonging medications are initiated after enrollment.

For subjects who develop **acute kidney injury** during therapy. The following dose modification guidelines are commended:

Grade	Recommended Management	Dose modification
1-2	-Monitor creatinine weekly -If creatinine returns to baseline resume routine creatinine monitoring per protocol -Promote hydration and cessation of nephrotoxic drugs	Maintain current dose of hydroxychloroquine
3	-Monitor creatinine every 2-3 days -Promote hydration and cessation of nephrotoxic drugs -Consult nephrology	Reduce hydroxychloroquine dose to 200 mg daily and restart at initial dose once CrCl recovered or returns to Grade 1.
4	-Monitor creatinine daily -Consult nephrology -Promote hydration and cessation of	-Discontinue hydroxychloroquine and remove from study

	nephrotoxic drugs	

For patients who develop **cytopenias** during therapy. The following dose modification guidelines are recommended.

Grade	Recommended Management	Dose modification
1-2	-Monitor CBC w/diff weekly -Management per medical oncology	Maintain current dose of hydroxychloroquine
3	-Monitor CBC w/diff daily-weekly per provider discretion -Consider holding immunosuppressive agents -Management per medical oncology	Reduce hydroxychloroquine dose to 200 mg daily and restart at initial dose once cytopenia returns to Grade 1.
4	-Management per medical oncology -Consider holding immunosuppressive agents	-Discontinue hydroxychloroquine and remove from study

11.1 EVALUATION DURING TREATMENT/INTERVENTION

11.2 Study Calendar

Study Week (from randomization)	**Pre Study[a]**	**Wk 1**	**Wk 2**	**Wk3**	**Wk4**	**Wk5**	**Wk 6**	**Wk7**	**Wk8**	**Wk9**	**Wk 12**	**Off Study**
Informed Consent	x											
Concurrent Meds	x											
Vital Signs	x											
Weight	x											
EKG	x	x	b	b	b	b	b	b				
AE evaluation (non-RSA, tele- assessment)[c]	x	x								x	x	
CBC with diff, plts[d]	x	x	%%	%%	%%	%%	%%	%%	%%			
Comprehensive Panel	x	x	%%	%%	%%	%%	%%	%%	%%			

Optional Rapid COVID-19 IgG/IgM testing +/- COVID-19 rapid antigen testing [f]	x	**								x		
Research blood (optional): SARS-CoV-2 serology[g]	x	##								x		
Symptom Screening Questionnaire (non-RSA)[h]	x											

[a]See Section 8.0 for the timing of these tests/evaluations prior to start of therapy
[b]Following baseline and week 1 EKG. EKGs will be monitored weekly for the duration of the radiation treatment course. Patients are eligible for more frequent EKGs if a patient is started on any QTc prolonging agents during therapy(Haloperidol, ziprasidone, quetiapine, thioridazine, olanzapine, risperidone, amiodarone, sotalol, dofetilide, procainamide, quinidine, flecainide, macrolides, fluoroquinolones, amitriptyline, imipramine, citalopram, methadone, sumatriptan, ondansetron, cisapride)
[c]Adverse effect evaluation can be done telephonically.
[d]CBC with diff, plts and Comprehensive Metabolic Panel will be allowed weekly as per standard of care for patients receiving concurrent chemotherapy with radiation. For patients receiving radiation therapy alone, labs will be collected at the specified time points.
[e]Comprehensive Metabolic Panel = albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
[f] Rapid COVID-19 IgM/IgG serology testing will be done for patients who screen as negative by clinical symptoms. Patients to be managed by results per Section 9.1. If Rapid COVID-19 IgM/IgG serology is negative, when possible patients will also undergo Rapid COVID-19 Antigen testing. This testing is optional but recommended.
[g]Research Blood Draw must be done via SST.
[h]See Appendix 18.2 for symptom screening questionnaire. This can be administered electronically, telephonically, or in person at the time of screening. During radiation therapy, patients are symptom-screened for fever, cough, and COVID-19 contact prior to entering the building.
**Rapid COVID-19 IgM/IgG serology testing +/- Rapid COVID-19 antigen testing (as per Section 9.1) will be completed for patients on treatment who develop clinical symptoms suspicious for COVID-19.
Research SARS-CoV-2 serology banking (optional but recommended): If patients presumed COVID-19 positive per protocol, research blood draw to occur 8-20 days after initiation of symptoms
%% Periodic CBC and CMP will be obtained per standard of care for patients receiving concurrent chemotherapy. Dose adjustments for hydroxychloroquine must be made based upon these assessments (Section 10.3).

Note: Efforts should be made for telephone evaluations should be done when appropriate.

12.1 CRITERIA FOR REMOVAL FOR STUDY

Patients should permanently discontinue treatment with hydroxychloroquine or placebo in the event of:

- Patients who test positive for SARS-CoV-2* will discontinue study therapy and be followed
- Severe, unexpected toxicities/side effects such as (CTCAE v.5.0 grade 3 or 4) that cannot be managed by dose delay
- Dose delay of greater than 14 days from the intended day of the next scheduled dose
- Pregnancy: in the case of a patient becoming pregnant during the trial, hydroxychloroquine must be immediately stopped and the patient must be follow-up until birth or other termination of pregnancy. Counseling on birth defect risk must be offered.
- QTc >500 and medically unable to discontinue QTc prolonging agent
- If the treating physician determines that it is in the best interest of the patient to stop the study drug.
- Participant non-compliance with the defined by the study design
- Participant's right to withdraw consent for continued participation, and/or death. In case a patient withdraws his/her consent for taking drug, it is of utmost importance for the robustness and integrity of the trial results that his/her safety data be recorded at the end of the 9-week period.

* A patient will be declared positive for SARS-CoV-2 according to the outcomes outlined in section 13.

Patients who discontinue from this trial are not allowed to be re-enrolled. For patients who stopped the trial before enrollment, their data will be part of the description of the screening population, and will be replaced.

13.1 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.2 Criteria for Therapeutic Response/Outcome Assessment

Definitions:

SARS-CoV-2 Positive:

Patients who meet testing criteria will be referred for confirmatory testing and will be considered SARS-CoV-2 Positive if:

- Rapid COVID-19 IgG/IgM serology testing result: positive for IgM and/or IgG (For symptomatic patients -his test should be administered >7 days from the onset of symptoms to ensure enough time has passed for antibody response)
- MSKCC COVID-19 serology as result is positive for IgM and/or IgG (For symptomatic patients - this test should be administered >7 days from the onset of symptoms to ensure enough time has passed for antibody response)
- Rapid COVID-19 antigen positive
- MSKCC COVID-19 PCR positive
- Outside laboratory COVID-19 PCR positive

If patients do not screen positive for symptoms during the duration of therapy, and are COVID-19 IgG/IgM serology negative at 9 weeks will be considered negative for COVID-19.

Mild Symptomatic COVID-19:
Patients who are symptomatic (Appendix 18.2) and who are considered SARS-CoV-2 positive but who do not meet criteria for severe COVID-19, critical COVID-19 will be considered to have mild symptomatic COVID-19.

Severe COVID-19:
Patients who are positive for SARS-CoV-2 (as defined above) who develop a new oxygen requirement attributable to COVID-19, tachypnea (RR > 20), or those who require hospitalization due to COVID-19 will be considered to have severe COVID-19.

Critical COVID-19 / Death:
Patients who are positive for SARS-CoV-2 (as defined above) who require care in the intensive care unit (ICU) or who die of COVID-19 related morbidity will be considered to belong to this category.

Symptom and treatment toxicity will be evaluated mid-radiation treatment course, post-radiation, and at 9 weeks. This will also capture high grade toxicity and hospitalization events.

13.3 Criteria for Study Endpoint Evaluability

Any patients who are enrolled and subsequently test positive for SARS-CoV-2 by RT-PCR (outside RT-PCR test results allowed) at any point during the 9 weeks following enrollment will be an event that is considered in the 9-week SARS-CoV-2 infection rate primary endpoint.

Patients who subsequently test SARS-CoV-2 positive who require oxygenation, hospitalization, or death within 12 weeks will be included in our secondary endpoint measuring SARS-CoV-2 infection morbidity.

Withdrawal or patients who or lost to follow-up without subsequently testing SARS-CoV-2 positive/death, or those who are removed due to toxicity will be censored.

14.0 BIOSTATISTICS

The primary objective of this study is to compare the rate of infection with SARS-CoV-2 at 9 weeks from randomization in patients receiving radiotherapy or chemoradiotherapy with prophylactic hydroxychloroquine versus placebo. Patients will be declared to be infected if they have a positive test for SARS-CoV-2 using the MSKCC or other approved assay with or without symptoms of infection (defined in Section 18.1). Patients who test positive using any other assay may be required to undergo confirmatory testing. This requirement may be waived at the discretion of the principal investigator. In order to ascertain the 9-week end-point, efforts will be made to test asymptomatic patients who did not undergo SARS-CoV-2 testing at 9 weeks after the start of radiation treatments.

Based upon a baseline estimated SARS-CoV-2 infection rate of 40% in a New York City metropolitan setting in the control arm, and an estimated 20% risk of SARS-CoV-2 infection in the experimental arm (i.e., H0 p=40% vs. H1: p=20%), we estimate a sample size of 132 patients will be needed with a one-sided proportion test with alpha of 0.05, power of 0.80, and 1 early assessment when 50% of the end-points have been met. Patients will be randomized between the two treatment arms in a 1:1 ratio. Patients will be stratified by age (>65 vs. ≤ 65) , concurrent chemotherapy (yes vs. no), and weeks of radiation (>4 vs. ≤4). At the early assessment, when half of the endpoints have been collected, Lan-Demets spending function will be utilized and the trial will be stopped for futility if p-value>0.37 or efficacy if p-value<0.0055. At the final analysis we will reject the null hypothesis when p-value<0.048.

The design of using a one-sided test with alpha=0.05 for this randomized trial has been extensively discussed. Due to the urgent nature of the study and the fast-changing situation of COVID-19, precisely estimating the enrollment rate is difficult while completing the study in a timely fashion is of paramount importance. We thus assume, based on clinical experience and knowledge of COVID-19, an enrollment rate of 50 patients per month across all MSKCC sites. This means that it will take approximately 3 months to randomize 132 patients. The implementation of a one-sided test is based on multiple existing studies showing the promising effect of hydroxychloroquine. The early assessment with both futility and efficacy boundaries will be conducted to reduce study participants' exposure to an inferior treatment. If the accrual within the first 28 days is ≥100 patients, the trial will be amended to expand the accrual (at which time we will not have conducted the interim analysis due to the fact that the endpoint requires 9 weeks to collect). We will consider lowering the type 1 error rate to 0.025 with power still at 0.8. This will require a sample size of 166. At the early assessment when half of the endpoints have been collected, the trial will be stopped for futility if p-value>0.29 or efficacy if p-value<0.0015. At the final analysis we will reject the null hypothesis when p-value<0.024. The

usual intention-to-treat analysis will be applied. All patients who drop out for any reason, are lost to follow-up, are removed from protocol, or die of any cause without known 9-week infection status will be declared positive.

Sample size and power calculations were completed using software R 3.6.0 and EAST 6.5.

For secondary objectives:

To compare the likelihood of symptomatic COVID-19 infection or death (defined in section 13.1) within 9 weeks from randomization, we will apply a two-sided, two-sample proportion test on evaluable patients for this objective. That is, for each arm, the denominator will be those enrolled on each arm, while the numerator is the number of such patients who have symptomatic COVID-19 infection within 9 weeks of randomization.

To compare the likelihood of severe COVID-19 infection or death (defined in section 13.1) within 12 weeks from randomization, we will apply a two-sided, two-sample proportion test on evaluable patients for this objective. That is, for each arm, the denominator will be those enrolled on each arm, while the numerator is the number of such patients who have severe COVID-19 infection requiring hospitalization or death within 12 weeks of randomization.

To evaluate acute toxicity associated with administration of daily (7 days/week) hydroxychloroquine during radiation or chemoradiation for each arm, all acute toxicities will be collected and documented by grade, type and location. Once the treatment arm is unblinded, we will tabulate and summarize the toxicities for the hydroxychloroquine arm. For this analysis, all randomized subjects who received at least one dose of study drug will be included.

For the correlative endpoints:

Baseline prevalence of anti-SARS-CoV-2 antibodies will be summarized as sample proportion with confidence intervals. In patients who are serology negative, we will compare the symptomatic COVID-19 infection rate within 12 weeks from randomization between the two arms using a 2-sample, 2-sided proportion test. The rate of severe COVID-19 infection or death within 12 weeks from randomization will be compared similarly. Serum samples will be stored for future studies.

15.1 TOXICITIES/SIDE EFFECTS

15.2 Serious Adverse Event (SAE) Reporting

During radiation, chemoradiation, and hydroxychloroquine administration, adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events - Version CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site: http://ctep.cancer.gov/protcolDevelopment/electronicapplications/ctc.htm.

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

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

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

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

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

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
- An explanation of how the AE was handled
- A description of the participant's condition
- Indication if the participant remains on the study

- If an amendment will need to be made to the protocol and/or consent form and whether the SAE is an unanticipated problem

15.3 External SAE Reporting

No additional SAE reporting information is required by the drug supplier.

15.4 Attribution of the AE:

- **Definite** - The AE is **clearly** related to the study treatment
- **Probable** - The AE is **likely** related to the study treatment
- **Possible** - The AE **may be r**elated to the study treatment.
- **Unlikely** - The AE is **doubtfully** related to the study treatment.
- **Unrelated** - The AE is **clearly** not related to the study treatment.

Reproductive risks: There is a risk of sterility and/or birth defects associated with this study. Subjects must use birth control while on this study. Women should not breastfeed while on this study.

15.5 Drug Interactions with Hydroxychloroquine

- Digoxin: Concomitant hydroxychloroquine and digoxin therapy may result in increased serum digoxin levels: serum digoxin levels should be closely monitored in patients receiving combined therapy.
- Insulin or antidiabetic drugs: Hydroxychloroquine may enhance the effects of a hypoglycemic treatment
- Drugs that prolong QT interval and other arrhythmogenic drugs: Hydroxychloroquine prolongs the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias. Also, there may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine is used concomitantly with other arrhythmogenic drugs.
- Mefloquine and other drugs known to lower the convulsive threshold: hydroxychloroquine can lower the convulsive threshold.
- Antiepileptics: The activity of antiepileptic drugs might be impaired if co-administered with hydroxychloroquine.
- Methotrexate: Combined use of methotrexate with hydroxychloroquine has not been studied and may increase the incidence of adverse effects.
- Cyclosporin: An increased plasma cyclosporin level was reported when cyclosporin and hydroxychloroquine were co-administered.
- The following interactions have been observed on treatment with the structurally related substance chloroquine phosphate, and therefore cannot be ruled out for hydroxychloroquine.
    - Praziquantel: Chloroquine has been reported to reduce the bioavailability of praziquantel.

- Antacids and kaolin: Antacids and kaolin can reduce absorption of chloroquine; an interval of at least 4 hours between intake of these agents and chloroquine should be observed.
- Cimetidine: Cimetidine can inhibit the metabolism of chloroquine, increasing its plasma level. Concomitant use of cimetidine should be avoided.
- Ampicillin: In a study of healthy volunteers, chloroquine significantly reduced the bioavailability of ampicillin.

15.6 Hydroxychloroquine - Potential Adverse Events

Uncommon adverse events (1-10%):

- **Ocular:** Risk of ocular adverse events are low in the setting of short duration of daily hydroxychloroquine administration. However, rare irreversible retinal damage has been observed in some patients who received hydroxychloroquine sulfate. Significant risk factors for retinal damage include daily doses of hydroxychloroquine sulfate greater than 6.5 mg/kg (5 mg/kg base) of actual body weight, durations of use greater than five years, subnormal glomerular filtration, use of some concomitant drug products such as tamoxifen citrate and concurrent macular disease. In a series of 1207 patients, 1 (0.08%) patient treated with hydroxychloroquine was found to have retinal toxicity after 7 years of daily hydroxychloroquine at 6.98 mg/kg.[46] At doses as high as 1000mg per day, as has been explored in cancer trials, more rapid onset retinitis has been observed.[47]

Frequency Not Defined Adverse Events:

- **Cardiac Effects, including Cardiomyopathy and QT prolongation:** Hydroxychloroquine prolongs the QT interval. Ventricular arrhythmias and torsades de pointes have been reported in patients taking hydroxychloroquine. Postmarketing cases of life-threatening and fatal cardiomyopathy have been reported with use of hydroxychloroquine as well as with use of chloroquine. Patients may present with atrioventricular block, pulmonary hypertension, sick sinus syndrome or with cardiac complications. ECG findings may include atrioventricular, right or left bundle branch block. Chronic toxicity should be considered when conduction disorders (bundle branch block/atrio-ventricular heart block) or biventricular hypertrophy are diagnosed.
- **Worsening of psoriasis and porphyria:** Hydroxychloroquine use in patients with psoriasis may precipitate a severe attack of psoriasis. When used in patients with porphyria the condition may be exacerbated.
- **Proximal Myopathy and Neuropathy:** In patients undergoing long-term hydroxychloroquine therapy - skeletal muscle myopathy or neuropathy leading to progressive weakness and atrophy of proximal muscle groups, depressed tendon reflexes, and abnormal nerve conduction, have been reported.
- **Neuropsychiatric events, including suicidality**: Suicidal behavior has been rarely reported in patients treated with hydroxychloroquine.

- **Hypoglycemia:** Hydroxychloroquine has been shown to cause severe hypoglycemia including loss of consciousness that could be life threatening in patients treated with or without antidiabetic medications.
- **Hepatic/Renal Disease**: Hydroxychloroquine should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs.
- **Hematologic Effects/Laboratory Tests:** Rarely severe blood disorders such as aplastic anemia, agranulocytosis, leukopenia, or thrombocytopenia, can appear.
- **Dermatologic Effects**: Bleaching of hair, alopecia, pruritus, skin and mucosal pigmentation, photosensitivity, and skin eruptions (urticarial, morbilliform, lichenoid, maculopapular, purpuric, erythema annulare centrifugum, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, and exfoliative dermatitis).

15.6 Principles of Adverse Event Management

A reduction in dosage may be necessary in patients with QTc prolonging medications, renal dysfunction, hepatic dysfunction, or hematologic dysfunction due to underlying comorbidities or medication/chemotherapy known to affect these organs. General criteria for dose reduction is as outlined in Section 10.3.

QTc Assessment and Prolongation:
Baseline and weekly post initiation of hydroxychloroquine EKG will be completed for QTC monitoring for the duration of radiation therapy. Patients with QTC >470 milliseconds at baseline will be excluded. Reconsideration of trial enrollment can be considered if QTC prolonging medications can be optimized and repeat EKG demonstrated QTC <= 470.

Following initiation of hydroxychloroquine, patients please follow the following guidelines for management as outlined in Section 10.3.

Renal Insufficiency:
Hydroxychloroquine is renally excreted and dose modification may be needed in the setting of renal insufficiency. Prior to the start of treatment, concomitant medications must be reviewed for the potential risk of inducing nephrotoxicity and modified if clinically possible. Guidelines for on treatment renal insufficiency are as outlined in Section 10.3.

Nausea/Vomiting: Preferred antiemetic agents include non-QTC prolonging medications such as promethazine or lorazepam (if the patient has no allergy or contra-indication). After a trial of these medications, other anti-emetics can be considered with QTC monitoring 1 week after anti-emetic initiation. Principal investigators should be notified if any QTC prolonging medications are initiated.

Dermatitis: Grade 1 or 2 dermatitis may be managed conservatively. Use fragrance-free detergents/soap and moisturiser. Mild dermatitis may be treated with emollients and topical corticosteroids at the clinician's discretion. Grade 3 or higher dermatitis should be monitored carefully and a dermatology consult should be obtained. Pruritis is also a common side effect associated with hydroxychloroquine. Consider antihistamine initiation, promethazine, or a prednisone 10 mg single daily dose.

Cytopenias and myelosuppression: Patients undergoing concurrent chemotherapy as well as radiation therapy with radiation may experience cytopenias during the treatment course. Refer to Section 10.3 for guidance and dosing adjustment considerations.

Ocular: For individuals with significant risk factors (daily dose of hydroxychloroquine sulfate greater than 5.0 mg/kg base of actual body weight, subnormal glomerular filtration, use of tamoxifen citrate or concurrent macular disease) monitoring should include referral for annual examinations. For individuals without significant risk factors, annual exams can be deferred in the setting of short-term use.

Hypoglycemia: Hydroxychloroquine may enhance efficacy of insulin and antidiabetic drugs. Patients presenting with clinical symptoms suggestive of hypoglycemia during treatment with hydroxychloroquine should have their blood glucose checked and treatment reviewed as necessary. A decrease in dose of insulin or antidiabetic drugs may be required.

16.1 PROTECTION OF HUMAN PARTICIPANTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

Inclusion of Women and Minorities: Patients of all races, both male and female, will be accepted into the protocol. ; we also take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. The proposed study population is as described.

Exclusion of Pregnant Women: Lactating and pregnant women are excluded because of risks associated with radiotherapy to the developing fetus

Children have been excluded from this study as the study population is adults with solid tumor malignancy.

Participants may not receive the study drug off protocol, with the exception of symptomatic patients who developed confirmed COVID-19 infection and receive hydroxychloroquine for the purpose of treatment off protocol.

Benefits: It is possible that this treatment will result in reduced SARS-CoV-2 infection rates. It is not known, of course, whether these or any other favorable events will occur.

Costs: The patient will be responsible for the costs of standard medical care, including, CT scans, all drug administration fees and all hospitalizations, as well as for complications of treatment. Hydroxychloroquine will be supplied to patients by Rising Pharmaceuticals at no cost. Patients will not be responsible for the costs of blood procurement obtained for research purposes.

Incentives: No incentives will be offered to patients/subjects for participation in the study.

Alternatives: Patients may be eligible for standard of care therapy or other investigational studies.

16.2 Privacy

Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (e.g., qualified monitors) may review patients' records and pathology slides, as required.

16.3 Data Management

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

The data collected for this study will be entered into a secured database at Memorial Sloan-Kettering Cancer Center. Source documentation will be available to support the computerized patient record. Data will be stored in Medidata.

16.4 Quality Assurance

Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits may be conducted by the study team, at a minimum of two times per year, or more frequently if indicated.

16.5 Data and Safety Monitoring

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

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-In-Chief, Clinical Research.

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

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

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

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

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18.1 APPENDICES

18.2 COVID19 Symptom Questionnaire for patients and Testing Algorithm for Providers

Within the last 14 days have you had:

Have you had any difficulty breathing while not moving that is new or gotten worse?	Yes or No
Have you had any new wheezing?	Yes or No
Have you had any new chest tightness?	Yes or no
Have you had any new coughing?	Yes or No
Have you had a sore throat?	Yes or No
Have you had a temperature of 100.4 degrees Fahrenheit (or 38.0 degrees Celsius) or higher?	Yes or No
Have you had any new body aches?	Yes or No
Have you lost your sense of smell?	Yes or No
Have you had diarrhea (at least 3 episodes of watery or loose stool within 24 hours)?	Yes or No

INTERIM TESTING ALGORITHM FOR SARS-CoV-2 (COVID-19) Testing Criteria at MSK

The following template is designed to assist MSK staff in determining if they **should consider** testing patients for COVID-19. **This guidance is no substitute for sound clinical judgment and/or direct patient assessment.** These strategies do not apply for employees. Questions regarding employee testing should be referred to EHWS. Expect this guidance to change as the pandemic evolves. **An RVP to evaluate for routine circulating respiratory viruses should be sent prior to or concurrently with COVID-19 testing.**

Clinical Features	Risk Factors?	Considerations in Cancer patients	COVID-19 Testing?
Asymptomatic (No acute respiratory symptoms)	No	No	No
Acute Respiratory Symptoms or Influenza-like Illness • **Signs and symptoms DO NOT prompt ER/UCC/SCC evaluation**	No	Patient is not in active cancer-related therapy	Use clinical judgment
Acute Respiratory Symptoms or Influenza-like Illness	No	Patient is receiving active cancer therapy, including immunotherapy, chemotherapy, or radiation to thorax	Yes
Acute Respiratory Symptoms or Influenza-like Illness • **Signs and symptoms prompt ER/UCC/SCC evaluation**	**Wide-spread COVID transmission *** **OR** **Any of the following in last 14 days:** Travel to affected area** Close contact with confirmed COVID-19 case*** Skilled nursing facility admission	No	Yes
Acute Respiratory Symptoms or Influenza-like Illness • **Patient requires Hospitalization**	-----	------	Yes
Unexplained Acute Respiratory Symptoms or Influenza-like Illness • **Hospitalized patient with clinical and microbiologic evaluation**	-----	------	Yes

* wide spread community transmission as identified by CDC.
**CDC defined affected travel areas
***Close contact with confirmed COVID-19 case: defined as being within ~6 feet of a COVID-19 case for 10 minutes or longer
Acute respiratory infection symptoms (also known as influenza like illness or ILI) include new cough, shortness of breath, myalgias, wheezing or chest tightness, or sore throat, etc. Fever may not always be present in our high-risk patient population.

18.2. MSKCC Radiation Oncology Department Guidelines for Radiation Therapy in COVID19-positive or COVID19 suspected patients (as of 3/24/2).

- **COVID positive patients:**
  - Outpatients - will take direction of the Department of Health about Quarantine and follow Workflow A below.
  - Inpatients - DEcision for treatment to be made based on Workflow B below.
- **Patients at risk for COVID who are symptomatic:** This category includes patients who are symptomatic (Temp >38C in addition to sore throat, cough, shortness of breath, wheezing, chest tightness, body aches or chills, diarrhea, anosmia), regardless of risk of exposure
  - **Non-urgent radiation treatment (can hold treatment for 2-4 days):** Mandate test before treatment, and hold treatment until treatment results. We anticipate that at the current testing capability, which is continuously increasing, this timeframe should only be 1-4 days.
  - **Urgent radiation treatment (e.g. cannot hold treatment for 2-4 days)**: Treat based on clinical judgement (of the treating radiation oncologist) as above (as if positive).
- **Patients who are at high risk for COVID due to exposure but who are symptomatic (including those in self-quarantine)**
  - Current MSKCC policy as of 3/24/20 has not made SARS-CoV-2 testing available yet for these patients. If a patient notifies the clinic/attending that they had an exposure and are not symptomatic:
    - **Non-urgent per treating attending (can hold treatment for 2-4 days).** Please hold treatment until 5 days after reported exposure. If the patient develops symptoms during this time, follow policy in #2 above. If asymptomatic 5 days after exposure, resume treatment with a mask until day 14 after exposure.
    - Urgent per treating attending (e.g. cannot hold treatment for 2-4 days). Attending of record to discuss with service chief, disease site director, and departmental leadership per steps 2-7 in Workflow A below. If treated without break, the patient will be added to the schedule at the end of the day with appropriate protective measure taken.
- **Workflow A: COVID19-positive outpatients:**
  - When a staff member is informed that a patient is COVID19 positive, e-mail the a) service chief, b) attending of record and c) radiation therapy chiefs, at zzPDL_RAO-chief_RTTs.
  - The attending of record and service chief will arrange to contact the patient and inform them to not come into the department until a decision is made about continuing treatment, over the next business day.

- Treating physician to discuss case with disease site director, including urgency of treatment and clinical implications of holding until COVID19 negative.
- Case to be reviewed on COVID19 daily huddle call in afternoon (typically 3:30), to determine whether the patient should continue treatment or be given a treatment break. This wall will include: a) the disease site director of the case in question, b) operational leadership team (Dr. Powel, Dr. Cahlon, service chiefs), and c) managers from therapy, nursing, and our APP team. The primary attending will also be invited to the huddle to discuss the case and can opt to participate if they would like.
- Decision regarding treatment will be communicated to the patient and other treating physicians by the primary attending and schedule adjusted accordingly. The primary attending and disease site director will be responsible for determining a fractionation scheme to account for treatment breaks and to minimize the negative impact on outcome.
- Patients who receive radiation will be treated at the end of the day with appropriate cleaning and precautions.
- Over time, and depending on the number of COVID19+ patients, we hope to develop an algorithm with each disease site so that each case will not require a full discussion.

- **Workflow B: COVID19-positive inpatients at Memorial Hospital;**
  - When a staff member is informed that a patient is COVID19 positive, e-mail the: a) service chief, b) attending of record and c) radiation therapy chiefs, at zzPDL_RAO_chief_RTTs
  - If a decision regarding treatment can be deferred until the daily departmental huddle, follow the workflow above.
  - If the clinical situation is emergent, the primary physician should speak with the disease site director, service chief, and department leadership for a prompt decision.
  - If the consensus is that emergent treatment is needed, the service chief and attending of record will arrange for the patient to be treated at the end of the day, with appropriate cleaning and precautions.

18.3 QT Prolonging agents

Haloperidol, ziprasidone, quetiapine, thioridazine, **olanzapine**, risperidone, **amiodarone**, sotalol, dofetilide, procainamide, quinidine, flecainide, macrolides, fluoroquinolones, amitriptyline, imipramine, citalopram, methadone, sumatriptan, **ondansetron**, cisapride. Please check uptodate with the addition of any new medications to determine whether it is a QTc prolonging agent.

18.4 Management Algorithm for Positive Screen

- The study PI or CoPIs must be notified by email or phone
- Patients who have a positive symptom screen will undergo testing per MSKCC COVID19 testing protocol.
    - If patient is SARS-CoV2 positive by SARS-CoV-2 PCR at MSKCC or any outside laboratory facilities
        - Subsequent prescriptions of study drug will be canceled
        - The patient should be instructed to discontinue study and undergo management per MSKCC Infectious Diseases Guidelines in conjunction with the treating team.
        - Patient's remaining radiation treatment course will be completed per MSKCC Radiation Oncology Department guidelines for COVID19 positive patients
    - If patients is SARS-CoV2 negative, patient will continue on the protocol
- Patients who have had no change in symptom screen symptoms with interval negative test will not be retested