IMMUNONCOVID-20

A prospective, controlled, randomized, multicenter study to compare the efficacy of a chloroquine analog (GNS561), an anti PD-1 (nivolumab) and an anti-interleukine-6 receptor (tocilizumab) versus standard of care in patients with advanced or metastatic cancer and SARS-CoV-2 (COVID-19) infection.

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SPONSOR (ID)	Centre Léon Bérard (ET20-076)
EudraCT number	2020-001373-70
	Version 1.1 dated Mar 31st 2020

PROTOCOL APPROVALS

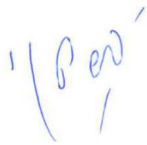
Institutional Review Board (CREC)	Approval Date	
	Reference	
Competent Authority : ANSM	Approval Date	Mar 31st 2020
	Reference	2020-001373-70
Ethic Committee : CPP IDF6	Approval Date	
	Reference	
ICMJE-approved registry: Clinicaltrial.gov	Date	Apr 2nd 2020
	Reference	NCT04333914

PROTOCOL AGREEMENTS

I understand that the clinical trial entitled "ImmunONCIVD-20 - A prospective, controlled, randomized, multicenter study to compare the efficacy of a chloroquine analog (GNS561), an anti PD-1 (nivolumab) and an anti-interleukine-6 receptor (tocilizumab) versus standard of care in patients with advanced or metastatic cancer and SARS-CoV-2 (COVID-19) infection..",

Will not start without the prior written approval of a properly constituted Institutional Review Board/Ethics Committee (CPP) and competent authority (ANSM). No changes will be made to the study protocol without the prior written approval of the sponsor and the Ethics Committee and Competent Authority.

I have read, understood, and agreed to abide by all the conditions and instructions contained in this protocol. I agree to comply with the French national regulations and ICH Harmonized Tripartite Guideline for Good Clinical Practice for conducting clinical trials and local regulations and will conduct the above study under these standards.

Title	**IMMUNONCOVID-20** **A prospective, controlled, randomized, multicenter study to compare the efficacy of a chloroquine analog (GNS561), an anti PD-1 (nivolumab) and an anti-interleukine-6 receptor (tocilizumab) versus standard of care in patients with advanced or metastatic cancer and SARS-CoV-2 (COVID-19) infection.**
Protocol version	**Version 1.1 dated Mar 31st 2020**
Coordinating investigator	**Dr Philippe CASSIER, MD**  23/03/2020
Associated investigator	**Dr Virgine AVRILLON, MD**  23/03/2020
Sponsor's representative	**Dr David PEROL, MD, Head of Clinical Research Department**  23/03/2020

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ABREVIATIONS

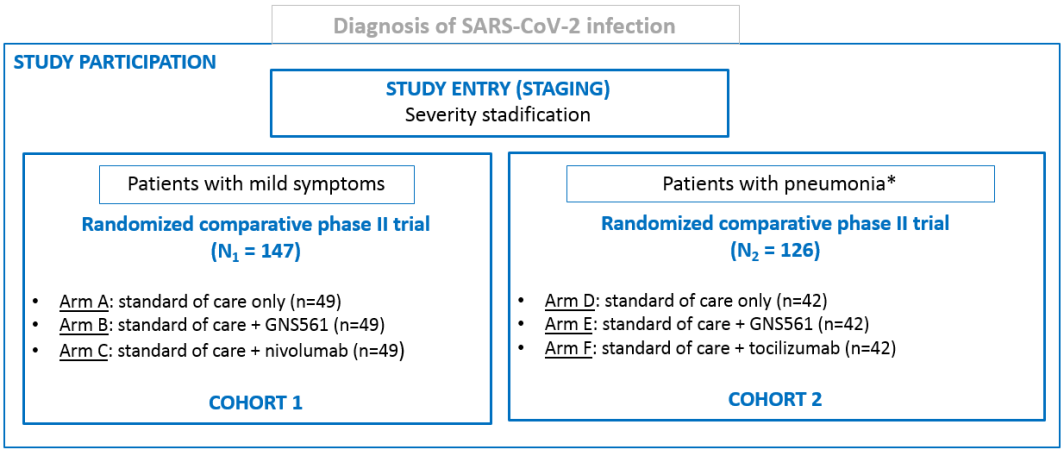
AE	Adverse Event
ANC	Absolute Neutrophil Count
ANSM	Agence Nationale de Sécurité des Médicaments et des produits de santé
CLB	Centre Léon Bérard
CNIL	Commission Nationale de l'Informatique et des Libertés
CPP	Comité de Protection des Personnes
CRF	Case Report Form
CT	Computed Tomography
DARF	Drug Accountability Record Form
DPO	Data Protection Officer
DRCI	Direction de la Recherche Clinique et de l'Innovation
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EOT	End of Treatment
EudraCT	European drug regulatory authorities clinical trials
FU	Follow-Up
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
IB	Investigator Brochure
ICF	Informed Consent Form
ICI	Immune Checkpoint Inhibitors
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational Product
ITT	Intent-to-treat
IV	Intravenous
LT	Limiting Toxicity
MedDRA	Medical Dictionary for Regulatory Authorities
MR-001	Méthodologie de Référence
MRI	Magnetic resonance imaging
NCA	National Competent Authority
NCI-CTC	National Cancer Institute – Common Terminology Criteria
OS	Overall Survival

PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein ligand 1
PP	Per Protocol
PS	Performance Status
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper Limit of the Normal

SYNOPSIS

Title	**IMMUNONCOVID-20** – A prospective, controlled, randomized, multicenter study to compare the efficacy of a chloroquine analog (GNS561), an anti PD-1 (nivolumab) and an anti-interleukine-6 receptor (tocilizumab) versus standard of care in patients with advanced or metastatic cancer and SARS-CoV-2 (COVID-19) infection.
Sponsor	Centre Léon Bérard, Lyon, France
Study identification	Sponsor ID: ET20-076 EudraCT number: 2020-001373-70 NCT: TBD
Version	1.1 dated Mar 31st 2020
Study coordination	Coordinating investigator **Dr Philippe CASSIER**, Centre Léon Bérard, Lyon Dr Virginie AVRILLON, Centre Léon Bérard, Lyon Coordinating centre: Direction de la Recherche Clinique et de l'Innovation, Centre Léon Bérard, Lyon
Participating sites	French Comprehensive anticancer center and Universitary hospitals.
Therapeutic indication	Patients with advanced or metastatic cancer who have Sars-CoV-2 infection not eligible to a resuscitation unit.
Study objectives	The main objective is **to compare versus standard of care short-term mortality rates** in advanced or metastatic cancer patients who are positive for COVID-19 treated with a chloroquine analog (GNS561), an anti-PD1 (nivolumab) or an anti-IL-6R antibody (tocilizumab). The primary endpoint will be the **28-day survival rate**, defined by the proportion of patients still alive 28 days after randomization. The 28-day survival rate will be described in each arm of each cohort. The secondary objectives will be to describe in each arm of the study: • Time to clinical improvement • Clinical status at days 7, 14 and 28 • Mean change in clinical status from baseline to days 7, 14 and 28 • Overall survival • Length of stay in Intensive Care Unit and in Resuscitation Unit • Duration of mechanical ventilation or high flow oxygen devices • Duration of hospitalization • Rate of throat swab negativation at days 7, 14 and 28 • Quantitative SARS-CoV-2 virus in throat swab at days 7, 14 and 28 • Quantitative SARS-CoV-2 virus in blood at days 7, 14 and 28 • Rate of secondary infection by other documented pathogens (bacteria, fungi) • Biological parameters (hematological parameters and markers of inflammation) • Safety of experimental treatments. And to perform Cost-Effectiveness Analyses (CEA) with Incremental Cost-Effectiveness Ratios (ICERs) expressed in cost per Life Year Gained.
Study design	This is a **muticenter clinical program including a staging phase and 2 different therapeutic cohorts** according to the patient's level of symtoms. Patients with mild symtoms of COVID-19 will be included in Cohort 1; patients with moderate or severe symtoms will be included in cohort 2.

A total of 273 patients will be included in the IMMUNONCOVID-20 program (Cf. study scheme below).



* : Pneumonia must be confirmed by chest imaging, and an oxygen saturation (Sao2) of 94% or less while they are breathing ambient air or a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) (Pao2:Fio2) at or below 300 mg Hg

Figure : Overview of study design

In cohort 1 randomization will be stratified on patient age (<70 vs. ≥70 years old) and in cohort 2 on the basis of respiratory support methods at the time of enrolment: hospitalization associated or not with oxygen support with nasal duct or mask (<5 on the WHO-ISARIC seven-category ordinal scale) *versus* non-invasive mechanical ventilation or high flow oxygen therapy or invasive mechanical ventilation (≥5 on the WHO-ISARIC seven-category ordinal scale).

In the experimental arms of cohort 1, patients will be treated either with oral GNS561 during 14 consecutive days or with a single intravenous administration of nivolumab.

In the experimental arms of cohort 2, patients will be treated either with oral GNS561 during 14 consecutive days, or with a single intravenous administration of tocilizumab.

In experimental arms, a first step for safety assessment will be initiated only at CLB. The **enrolment rules in experimental arms** are determined to identify a safety signal that would occur in a large fraction of advanced or metastatic cancer patients with COVID-19. According to binomial law, among 3 patients or 6 patients treated with a given experimental arm there is a 90% probability of observing for at least one of these patients a LT if this event occurs in at least 54% and 32% of treated patients, respectively.
For each experimental arm, the enrolment of the first 3 or 6 patients will be done in the coordinating center only (CLB), and will be carried out as follows:

- **GNS561 arms: the same rules will be applied in COHORT 1 and in COHORT 2.**
  The enrolment of the first 3 patients in both cohorts will be done without minimum time interval between each inclusion. Among the first treated 3 patients of each cohort with a minimum follow up time of 48 hours:
  - If no LT is observed, enrollment will be opened to all participating centers up to 49 patients into COHORT 1 and 42 patients into COHORT 2. If more than two (>2) LT are observed in a given cohort, GNS561 arm will be stopped in this cohort.
  - If only one (1) LT is observed in one cohort or another, 3 additional patients will be included into this cohort. If less or equal than 2 (≤2) LT are observed among the 6 first treated patients with a minimum follow up time of 48 hours, enrollment will be opened to all participating centers up to 49 patients into COHORT 1 and 42 patients into COHORT 2.

	- **Anti-PD1 arm** (COHORT 1): the enrolment of the first 3 patients in the coordinating center only (CLB) will be done with a minimum of 72 hours between each inclusion. Among the first 3 patients treated with a minimum follow up time of 48 hours:
	  ○ If no LT is observed, enrollment will be opened to all participating centers up to 49 patients into COHORT 1. If more than two (>2) LT are observed, anti-PD1 arm will be stopped.
	  ○ If one (1) LT is observed, 3 additional patients will be included in the coordinating center. If less or equal than 2 (≤2) LT are observed among the 6 first treated patients with a minimum follow up time of 48 hours, enrollment will continued in all participating centers up to 49 patients into COHORT 1.
	- **Anti-IL6R arm** (COHORT 2): the enrolment of the first 3 patients will be done without minimum time interval between each inclusion. Among the first treated 3 patients with a minimum follow up time of 48 hours:
	  ○ If no LT is observed, enrollment will be opened to all participating centers up to 42 patients into COHORT 2. If more than two (>2) LT are observed, anti-IL6R arm will be stopped.
	  ○ If one (1) LT is observed, 3 additional patients will be included in the coordinating center. If less or equal than 2 (≤2) LT are observed among the 6 first treated patients with a minimum follow up time of 48 hours, enrollment will be opened to all participating centers up to 42 patients into COHORT 2.
	
	In each experimental arm, after the initial enrolment of 3 or 6 patients with a minimum of 48 hours of follow-up time per patient, a **steering committee meeting will be held to review the available safety/efficacy data and make a decision regarding additional recruitment in each cohort**, according to predefined stopping rules, based on safety data and outcomes reported in the first patients.
	The steering committee will be composed of the coordinating and associated investigators, representatives of the coordinating center (medical monitor, statistician, and project manager) and principal investigators of the participating sites.
	
	In patients from cohort 1, the anticancer treatment may be continued (as per investigator's decision). In patients from cohort 2, anticancer treatment must be temporarily interrupted before randomization and at least up to 28 days after the date of randomization.
	
	In both cohorts, patients will be followed-up continuously until the hospitalization discharge and then weekly for a minimum period of 28 days after the randomization. After this 28-day follow-up visit, respiratory symptoms and treatment-emergent averse events will be collected weekly in the clinical database for 1 additional month and then at 3 months and 6 months after the date of randomization.
	
	In each cohort, the data cut-off will be 2 months after the last randomization. All efficacy analyses will be performed on the intent-to-treat populations. The end of the study will be defined as the end 2-month follow-up visit of the last patient randomized. Vital status will be updated once for all patients at the end of the study.
	
	The end of the study will be defined as the data cut-off of the last cohort still active.

Study population	**Inclusion criteria** I1. Age 18 or older at the time of enrolment.

I2. Histologically or cytologically confirmed diagnosis of advanced or metastatic hematological or solid tumor (hematological or solid tumor, any type and any localization).

I3. Documented diagnosis of COVID-19 (diagnostic test performed in a certified laboratory) or symptoms of COVID-19 associated with radiological signs of pneumonia as described by Shi et al.

I4. **Cohort 2**: patients with pneumonia confirmed by chest imaging, and an oxygen saturation (Sao2) of 94% or less while they are breathing ambient air or a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) (Pao2:Fio2) at or below 300 mg Hg.

I5. Patient not eligible for a transfer to Resuscitation Unit (either due to underlying medical condition – including cancer – or due to lack of available bed).

I6. Life-expectancy longer than 3 months.

I7. Adequate bone marrow and end-organ function defined by the following laboratory results:

- Bone marrow:
  - Hemoglobin ≥ 7.0 g/dL,
  - Absolute Neutrophils Count (ANC) ≥ 1.0 Gi/L,
  - Platelets ≥ 100 Gi/L;
- Hepatic function:
  - Total serum bilirubin ≤ 1.5 x ULN (except patients with Gilbert's syndrome who must have total serum bilirubin ≤ 3.0 x ULN),
  - AST and ALT ≤ 5 ULN
- Renal function:
  - Serum creatinine ≤ 2.0 x ULN or Cr. Cl. ≥ 30ml/min/1.73m² (MDRD or CKD-EPI formula);

I8. Willingness and ability to comply with the study requirements;

I9. Signed and dated informed consent indicating that the patient has been informed of all the aspects of the trial prior to enrolment (in case of emergency situation, please refer to protocol section 13.1 PATIENT INFORMATION AND INFORMED CONSENT);

I10. Women of childbearing potential (Appendix 2) are required to have a negative serum pregnancy test within 72 hours prior to study treatment start. A positive urine test must be confirmed by a serum pregnancy test;

I11. Women of childbearing potential and male patients must agree to use adequate highly effective contraception (Appendix 2) for the duration of study participation and up to 6 months following completion of therapy;

I12. Patient must be covered by a medical insurance.

Non-inclusion criteria

E1. **For cohort 1 only** : Patient currently receiving therapy with an anti- PD-1, anti- PD-L1, or anti-CTLA4.

E2. **For cohort 2 only:** Patient currently receiving therapy with an anti- IL-6 or anti-IL-6R.

E3. Contraindication to treatment with nivolumab (**cohort 1 only**) or to tocilizumab (**cohort 2 only**) as per respective SPC, including known hypersensitivity to one of these study drugs or severe hypersensitivity reaction to any monoclonal antibody.

E4. Patient known to have intolerance or hypersensitivity to chloroquine or any quinoline derivates (e.g., quinine, chloroquine, mefloquine).

	E5. Patient has active autoimmune disease that has required systemic treatment in the past 3 months before the date of randomisation or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids at doses higher than 10 mg/d prednisone equivalents or immunosuppressive agents. Note 1: Patients with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Patients that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Patients with hypothyroidism stable on hormone replacement or Sjögren's syndrome will not be excluded from the study. Note 2: Patients may receive corticosteroids as required for the management of SARS-CoV-2-related symptoms. **E6.** Patient requires the use of one of the following forbidden treatment during the study treatment period: ▪ Major surgery. ▪ Live vaccines. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever and BCG. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed. **E7.** Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to the date of randomisation unstable arrhythmias or unstable angina, Known Left Ventricular Ejection Fraction (LVEF) < 50%. Note: Patients with known coronary artery disease, congestive heart failure not meeting the above criteria must be on a stable medical regimen that is optimized in the opinion of the treating physician and in consultation with a cardiologist if appropriate. **E8.** Patient has Active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening), Active hepatitis C (Patients positive for hepatitis C virus (HCV) antibody are eligible only if PCR is negative for HCV RNA at screening) or Human Immunodeficiency Virus (HIV) infection (HIV 1/2 antibodies). **E9.** Prior allogeneic bone marrow transplantation or solid organ transplant in the past. **E10.** Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator. **E11.** Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. **E12.** Pregnant or breastfeeding patient, or expecting to conceive children within the projected duration of the trial, starting with the screening visit through 6 months after the last dose of study drugs.
Study treatments	**Cohort 1:** • Arm A: Standard of care only • Arm B: Standard of care + GNS561 400mg qd loading dose orally for 2 days then, 200mg qd orally for a total treatment duration of 14 consecutive days • Arm C: Standard of care + Nivolumab : 0.3mg/Kg, intravenously, single infusion at Day 1 **Cohort 2:** • Arm D: Standard of care only • Arm E: Standard of care + GNS561 400mg qd loading dose orally for 2 days then, 200mg qd orally for a total treatment duration of 14 consecutive days • Arm F: Standard of care + Tocilizumab : 400mg flat dose, intravenously, single infusion at Day 1

Sample size	**COHORT 1** **N=147 (49 per arm)** The sample size was calculated in order to provide a relevant power to compare each of the 2 experimental arms (anti-PD1 and GNS561) vs control arm. Same hypotheses are used for each of the two comparisons, namely: anti-PD1 therapy and GNS561 would be considered as efficient in cancer patients with mild symptoms from infection by SARS-CoV-2 if they will reduce mortality rate at 28 days from the expected level of 25% with standard of care to 5%. According to these hypotheses, 49 patients in each arm are required to achieve a power of 80% for detecting a statistically significant difference using a 1:1:1 randomization ratio. Each comparison will be performed using a two-sided test at a 2.5% level, in order to keep a global alpha risk of 5%. **COHORT 2** **N=126 (42 per arm)** The sample size was calculated in order to provide a relevant power to compare each of the 2 experimental arms (anti-IL6 and GNS561) vs control arm. Same hypotheses are used for each of the two comparisons, namely: anti-IL6 therapy and GNS561 would be considered as efficient in cancer patients with severe infection by SARS-CoV-2 if they will reduce mortality rate at 28 days from the expected level of 40% with standard of care to 10% *(Liang W et al Lancet Oncol 2020)*. According to these hypotheses, 42 patients in each arm are required to achieve a power of 90% for detecting a statistically significant difference using a 1:1:1 randomization ratio. Each comparison will be performed using a two-sided test at a 2.5% level, in order to keep a global alpha risk of 5%. **Pooled analysis in COHORT 1&2** In addition, a pooled analysis of patients randomized into GNS561 and standard of care arms from COHORTS 1&2 will also be performed to assess the efficacy in the whole population. The total number of patients randomized in the GNS561 and control arms in Cohorts 1+2 would be equal to 91 per arm (49+42). This pooled sample size would provide a power higher than 90% to detect a difference between a standard of care arm 28-day survival rate of 70% and a GNS561 arm 28-day survival rate of 90% with a 5% two-sided significance level. No multiple adjustment will be applied for this pooled analysis, as this analysis will be considered as confirmatory.
Expected study timelines	First patient in: Early April 2020 Last patient in: June 2020 Last patient Last visit: Aug. 2020 Blind review and database lock: Sep. 2020 Statistical report: Sep. 2020 Publication: Sep. 2020

1. BACKGROUND

1.1 OVERVIEW OF STUDY DISEASE & MEDICAL NEED

1.1.1 Epidemiology

Since December 2019, the novel coronavirus (SRAS-COV2, causing an emerging infectious disease called Covid-19) has spread quickly worldwide.

As of March 25th 2020, more than 413,000 cases and 18,000 deaths have been reported over 197 countries (WHO data). The overall case-fatality rate is about 2.3% but reaches 8.0% in patients aged 70 to 79 years and 14.8% in those aged >80 years (1). Most cases have been diagnosed between 30 and 79 years of age, and the main symptoms of COVID-19 include febrile respiratory infection, respiratory difficulties and, in most severe cases, acute respiratory distress, acute renal insufficiency or multi-visceral deficiency leading to death. Pneumonia in previous viral epidemics (e.g. H1N1) has been reported more frequently in patients with hematologic malignancies than in patients with solid tumors (55% versus 25%) and the 30-day mortality was higher in patients with pneumonia (up to 26%) (2, 3).

France is now facing the COVID-19 wave with more than 11,000 cases, as of March 20th 2020 (4).

1.1.2 Diagnosis and current treatment

No therapeutics have yet been proven effective for the treatment of severe illness caused by SARS-CoV-2. Current management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality (5).

The current standard of care for patients with respiratory symptoms is mainly symptomatic with support in respiratory function: oxygen supplementation, non-invasive ventilation, invasive ventilation, antibiotherapy, vasopressive support, renal-replacement therapy, extracorporeal membrane oxygenation.

The natural history of COVID19 remains unclear, and although interhuman transmission is the main mode of spread (6), the details of this process remain unknown (7). The median incubation period has been reported to be 4 days, ranging from 2 to 7 days. The median age of the patients in several series is around 50 years and ranges from 30 to 80 years, indicating that symptomatic cases are mostly seen in adults, but without a clear increased incidence in older adults. The most common symptoms are fever, cough and other respiratory symptoms as well as fatigue, while gastrointestinal symptoms, such as nausea, vomiting or diarrhea are uncommon (1). Among admitted patients, the median duration of hospital stay was 12 to 13 days but was increased in patients with severe forms, including SARS-CoV-2 associated pneumonia (8, 9). Mortality for patients admitted to ICU for SARS-CoV-2related acute respiratory distress syndrome (ARDS) has been reported in the range of 40-80%, the later being reported for patients requiring mechanical ventilation (8, 10), while duration of ICU admition has been reported to be particularly prolonged as well.

Thus, there is an urgent need for an effective treatment to treat symptomatic patients but also to decrease the burden of the number of patients hospitalized.

1.2 CURRENT THERAPEUTIC STRATEGIES UNDER INVESTIGATION

Recently, a combination of anti-viral treatments (lopinavir and ritonavir) failed to improve the clinical outcome of adult patients with COVID-19. Other alternatives starts to be explored, including chloroquine and antibodies targeting the interleukin-6 receptor (sarilumab, tocilizumab) or the Human Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) (gimsilumab).

1.2.1 Chloroquine and Hydroxychloroquine

Based on evidence showing that chloroquine and its derivatives may induce lysosome-mediated cell death, many researchers have focused on chloroquine effects in cancer therapy (11-15).
Chloroquine and hydroxychloroquine were developed as an antimaliarial agents but have been shown to have antiproliferative effects that may be relevant to cancer, immune-modulatory effects that have led to its widespread use as therapy of systemic lupus erythematosus and have also been shown to have anti-viral effects. The cellular target of CQ and HCQ has only recently been shown to be palmitoyl-protein thioesterase 1 (PPT1) (16), and inhibition of PPT1 mediates the lysosome acidification inhibition induced by CQ and HCQ as well as their derivatives. This effect on lysosome inhibits the pH-dependent replication steps of several viruses including members of the flaviviruses, retroviruses, and coronaviruses, including SARS-CoV-2 (17-20).
This mainly preclinical rational has led recently to the use of HCQ by Gautret et al in an open-label non-randomized clinical trial assessing the efficacy of hydroxychloroquine and azithromycin as a treatment of COVID-19 (21). In this small, non-randomized trial 26 patients with PCR-confirmed (on nasopharyngeal sample) COVID-19, received hydroxychloroquine 600mg/day. Of these, 6 also received azithromycin, based on their clinical presentation. Outcomes in this group were compared to those of 16 control patients. The primary outcome was viral clearance at 6 days post-inclusion measured with PCR. Six patients were withdrawn from the analysis due incomplete data and the authors reported that patients in the active arm were more likely to have achieved viral clearance (70%; 14/20) than those in the control arm (12.5%; 2/16; $p < 0.001$). The small size of this trial, the lack of randomization and of a covariate adjusted analysis, the fact that patients were inappropriately withdrawn from the analysis limit the conclusions that can be drawn from this study (22).
The most common adverse events observed with CQ and HCQ are gastrointestinal symptoms (mainly nausea), visual disturbances but are in general mild and do not require dose modifications (23, 24). Another potential interest of CQ and HCQ in COVID-19 is to limit the tissue damage associated with excess inflammation through their immunomodulatory effects (25).

1.2.2 Targeting Hyperinflammation

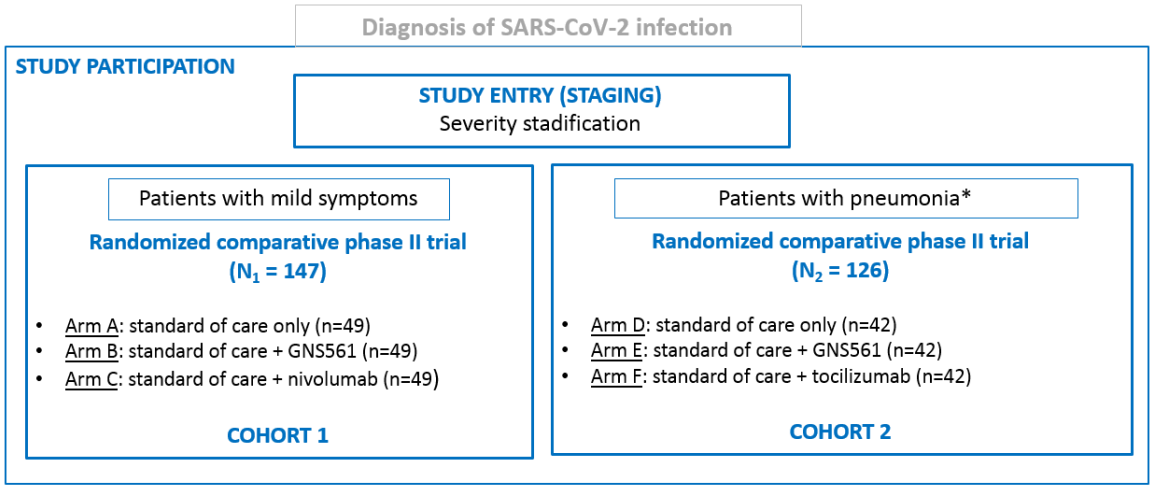
Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome. And authors have recently recommended the identification and treatment of hyperinflammation using existing, approved therapies with proven safety profiles to address the immediate need to reduce the rising mortality (26).
Secondary haemophagocytic lymphohistiocytosis (sHLH) is an under-recognised, hyperinflammatory syndrome characterised by a fulminant and fatal hypercytokinaemia with multiorgan failure. In adults, sHLH is most commonly triggered by viral infections and occurs in 3·7–

4·3% of sepsis cases. Cardinal features of sHLH include unremitting fever, cytopenias, and hyperferritinaemia; pulmonary involvement (including ARDS) occurs in approximately 50% of patients. A cytokine profile resembling sHLH is associated with COVID-19 disease severity, characterised by increased interleukin (IL)-2, IL-7, granulocyte colony stimulating factor (GCSF), interferon-γ inducible protein 10 (IP10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1-α (MIP1α), and tumour necrosis factor-α (TNFα) (27).
Early studies have shown that increased amounts of proinflammatory cytokines in serum (eg, IL1B, IL6, IL12, IFNγ, IP10, and MCP1) were associated with pulmonary inflammation and extensive lung damage in SARS patients (28). In patients presenting with SARS-CoV-2 infection Wang et al. showed that IL6 and IL10 were elevated and this feature was higher in patients with lower SpO2 at admition (29), suggesting that excessive inflammation may be responsible for lung damage and poor clinical outcome in this disease as well.

Interleukine 6 (IL-6) is a cytokine that can be secreted by several cell types during infectiion, inflammation and cancer. It binds to a membrane-bound receptor, IL-6R, which is devoid of signaling domain and thus must bind to gp130 for signaling. IL-6R is expressed on hepatocytes, some leukocytes and epithelial cells. In addition, a soluble form of IL-6R (sIL-6R) can also bind and signal using gp130, thus allowing IL-6 to act on cells that express gp130 but not IL-6R (phenomenon known as IL-6 trans-signaling). In addition, a third mode of IL-6 signalling, called IL-6 trans-presentation has been described and involves the provision of the IL-6 signal by dendritic cells during the antigen-specific interaction with T cell, resulting in the commitment of the T cell to a highly tissue-destructive phenotype (30).

1.3 STUDY PROPOSAL

Our proposal is to conduct a **muticenter clinical program including a staging phase and 2 different therapeutic cohorts** according to the patient's symtoms. Patients with mild symtoms of COVID-19 will be included in Cohort 1; patients with moderate or severe symtoms will be included in cohort 2. A total of 273 patients will be included in the IMMUNONCOVID-20 program (Cf. study scheme below).



* : Pneumonia must be confirmed by chest imaging, and an oxygen saturation (Sao2) of 94% or less while they are breathing ambient air or a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) (Pao2:Fio2) at or below 300 mg Hg

Overview of study design

In cohort 1 randomization will be stratified on patient age (<70 vs. ≥70 years old) and in Cohort 2 on the basis of respiratory support methods at the time of enrollment: hospitalization associated or not with oxygen support with nasal duct or mask (<5 on the WHO-ISARIC seven-category ordinal scale) vs. non-invasive mechanical ventilation or high flow oxygen therapy or invasive mechanical ventilation (≥5 on the WHO-ISARIC seven-category ordinal scale).
In the experimental arms (B and C) of cohort 1, patients will be treated either with oral GNS561 during 14 consecutive days or with a single intravenous administration of nivolumab.
In the experimental arms (E and F) of cohort 2, patients will be treated either with oral GNS561 during 14 consecutive days, or with a single intravenous administration of tocilizumab.
In each experimental arm, safety analysis will be performed following the enrolment of 3 to 6 patients (see statistical section for details).

1.4 STUDY TREATMENTS :OVERVIEW AND DOSE SELECTION

1.4.1 Nivolumab

Nivolumab (Opdivo®, Bristol-Myers Squibb Pharma, a fully human immunoglobulin G4 PD-1 immune checkpoint inhibitor antibody), is approved as a single agent for the treatment of several advanced/metastatic solid tumor types resistant or relapsing after standard treatment types including melanoma, non-small cell lung cancer (NSCLC); renal cell carcinoma (RCC), and squamous cell carcinoma of the head and neck. To treat advanced cancer patients, the recommended dose is 240mg, Q2W.

The PD effects of nivolumab in subjects with cancer were studied by assessing receptor occupancy (RO), peripheral immune cell population modulation, systemic cytokine modulation, and change in absolute lymphocyte count (ALC) in studies MDX1106-03 and/or CA209009. Peripheral RO of PD-1 is saturated at doses 0.3 mg/kg dose levels as measured on $CD3^+$ cells from frozen and fresh PBMCs (Nivolumab IB).

The choice of this low dose of nivolumab is based on the following:

1) Avoid exacerbation of immune system activation potentially leading to immune-mediated AEs (including pneumonitis) but to use minimal dose able to saturate PD1 receptor occupancy.
2) The goal here is to relieve T lymphocyte exhaustion for a limited duration to combat infection, without the need for prolonged saturation of RO. Thus the “minimal” pharmacodynamically active dose is selected for this study.

1.4.2 GNS561

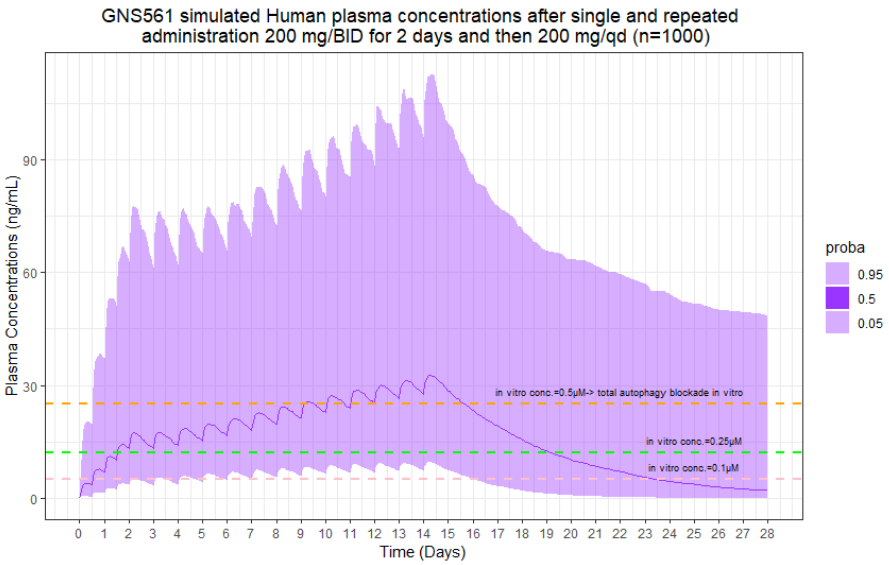
GNS561 is an orally available chloroquine analog currently in development for oncology indications (First in human trial is ongoing NCT03316222). GNS561 is expected, based on its similarity to chloroquine and hydroxychloroquine and its known mode of action, to have activity against coronaviruses. Indeed, previous studies have shown that infection y coronaviruses induced autophagy and that the autophagy machinery was required to initiate Coronavirus replication. In

addition, in vitro studies have shown that GNS561, by affecting autophagy at late stage, inhibits the pH-dependent replication steps of several viruses including members of the flaviviruses, retroviruses, and coronaviruses, including SARS-CoV-2. Preliminary results indicate that GNS561 inhibits SARS-CoV-2 replication with an EC50 value is the low micromolar range: at 1µM GNS561 lead to 44% virus inhibition versus 26% for hydroxychloroquine (GNS561 investigator brochure addendum).

GNS561 shows inhibition of the autophagy flux properties with a LC3-II Baf/No Baf = 1.2 at a concentration of 0.5 µM in vitro in cancer cell lines. At this concentration, the autophagic flux is totally blocked in vitro. Based on this data, the ones from the distribution study GNS561PKEP0263 where the lung to plasma ratio is estimated to be 2880 and from a monocompartimental pharmacokinetics model with a time dependant clearance describing GNS561 plasma concentrations developed from the preliminary pharmacokinetics data from the clinical study GNS561CLIQ0211, the proposed dosing protocol is defined as a 200 mg of GNS561 twice a day (morning and evening after a meal) for 2 days (4 administrations total) followed by 200 mg q.d. for the following twelve days.

At this dosing regimen, simulations shows a low GNS561 residual plasma exposure (median) of approximately 13 (day 2) to 28 (day 15) ng/mL. These low concentrations may however allow at least a 2.5 µM exposure (corresponding to a 25, 10 and 5 multiplicative factor compared to in vitro concentrations) from day 2 in the pulmonary unbound fraction (with the following assumptions: lung/plasma ratio is the same in human and rat and is constant over time and dosing regimen, and the lung unbound fraction is the same as the plasma unbound fraction). These concentrations are believed to allow the inhibition of autophagy in vivo which will inhibit the entry and replication of the virus.

Preliminary data from the first clinical centers experimenting GNS561 reveal linear plasma concentration allowing the dose extrapolation to support different dosing regimen. The residual plasma concentrations (Ctrough) estimated by our model are 13.3/20.7 ng/mL on D2, 19.6/27.4 ng/mL on D7 and 28.6/38.8 ng/mL on D14 (median and mean resp.). These concentrations are correlated with important unbound pulmonary concentration leading to an unbound lung conc. to in vitro concentration mean ratio of approximately **42, 17 and 8.5 as soon as D2** after the beginning of the treatment for in vitro concentrations of 0.1, 0.25 et 0.5 µM respectively. This ratio increases to **up to 79, 32 and 16 on D14 resp.** for the in vitro concentration mentioned above.
The figure below shows the simulated plasma concentration (5-95 percentiles in purple shade) after 200 mg bis in die for 2 days followed by 200 q.d administration of GNS561 for 12 days. The horizontal lines represent the extrapolated plasma concentration to be achieved to reach a GNS561 lung unbound fraction concentration of 10 times the in vitro concentration (0.1, 0.25 and 0.5 µM).



Given these data regarding activity and the expected long tissular half life of GNS561, a loading dose of GNS561 400 mg qd with be given on days 1 and 2, followed by 200 mg qd for 12 days to provide sufficient exposure in humans for efficacy.

Of note, in the ongoing Phase I dose escalation (NCT03316222), the tested dose at 200mg and 300mg bid have shown good tolerance, with mostly manageable gastrointestinal AE (https://www.genosciencepharma.com/wp-content/uploads/2019/10/0319-Poster-AASLD.pdf).

Based on mechanism of action of the drug and premilinary results of ongoing clinical trial in humans, the potential adverse events are:

- **Gastrointestinal disorders**: nausea, vomiting and diarrhea.
- **Hepatobiliary disorders**: increased transaminase levels.

1.4.3 Tocilizumab

Tocilizumab is an anti-IL-6 receptor antibody was initially developed for the treatment of rheumatoid arthritis and other forms of inflammatory arthritis in the late 1990's and was initially approved in these indications. In addition, tocilizumab has been more recently approved by the FDA to treat cytokine release syndrome (CRS) associated with the use of chimeric antigen receptor T-cell in oncology indications and is currently used to treat CRS associated with other forms of immunotherapy such as T-cell engaging bispecfic antibodies (32) (NCT03866239). In the treatment of CRS, tocilizumab has been shown to be highly active and although the optimal timing of tocilizumab in this indication is still debated, emerging evidence suggest that earlier use of tocilizumab leads to overall reduced toxicities and better outcome (33). In this indication, the use of tocilizumab has not been associated with discernible toxicity.

The recommended dose in individuals weighing 30 kg or more is 8 mg/kg but flat doses of 400 and 800 mg have been used (https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/interim-recommendations-for-the-use-of-tocilizumab-in-the-management-of-patients-with-severe-covid-19.pdf). A recent retrospective report using 400 mg flat dose showed striking efficacy in 20 patients with severe SARS-CoV-2 related pneumonia. Based on this preliminary report and because of possible drug-shortage of tocilizumab we plan to use a single flat dose of 400 mg, with the possibility to give a second dose if no response is observed after 24h.

2. OBJECTIVES

2.1 STUDY OBJECTIVES

2.1.1 Primary objective

The main objective is **to compare short-term mortality rates** in advanced or metastatic cancer patients who are positive for COVID-19 treated with a chloroquine analog (GNS561), an anti-PD1 (nivolumab) or an anti-IL-6R antibody (tocilizumab) versus standard of care.

The primary endpoint will be the **28-day survival rate**, defined by the proportion of patients still alive 28 days after randomization.

The 28-day survival rate will be described in each arm of each cohort.

2.1.2 Secondary objectives

The secondary objectives will be to describe in each arm of the study:

- Time to clinical improvement
- Clinical status at days 7, 14 and 28
- Mean change in clinical status from baseline to days 7, 14 and 28
- Overall survival
- Length of stay in Intensive Care Unit and in Resuscitation Unit
- Duration of mechanical ventilation or high flow oxygen devices
- Duration of hospitalization
- Rate of throat swab negativation at days 7, 14 and 28
- Quantitative SARS-CoV-2 virus in throat swab at days 7, 14 and 28
- Quantitative SARS-CoV-2 virus in blood at days 7, 14 and 28
- Rate of secondary infection by other documented pathogens (bacteria, fungi)
- Biological parameters (hematological parameters and markers of inflammation)
- Safety.

And to perform Cost-Effectiveness Analyses (CEA) with Incremental Cost-Effectiveness Ratios (ICERs) expressed in cost per Life Year Gained.

2.2 STUDY ENDPOINTS

2.2.1 Primary endpoint

The primary endpoint will be **the 28-day survival rate**, defined by the proportion of patients still alive 28 days after randomization.

If vital status at 28 days post randomisation is not available due to early transfer in an external resuscitation unit, patients will be considered as failure at the date of the transfer.

Comparison of each experimental arm (**GNS561 then Anti-PD1 for cohort1 and GNS561 then Anti-IL6R for cohort2)** to control arm will be performed using a chi-square test if applicable, a Fisher exact test otherwise. Statistical test will be performed at a two-sided 2.5% alpha level.

2.2.2 Secondary endpoints

- **Time to clinical improvement** defined as the time from randomization to an improvement of two points (from the status at randomization) on a seven-category ordinal scale or live

discharge from the hospital, whichever comes first. Clinical status will be assessed at baseline then weekly using the WHO-ISARIC seven-category ordinal scale consisting of the following categories: 1, not hospitalized with resumption of normal activities; 2, not hospitalized, but unable to resume normal activities; 3, hospitalized, not requiring supplemental oxygen; 4, hospitalized, requiring supplemental oxygen; 5, hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 6, hospitalized, requiring ECMO, invasive mechanical ventilation, or both; and 7, death.

- **Clinical status at D7, D14 and D28** will be assessed using the WHO-ISARIC seven-category ordinal scale.
- **Mean change in clinical status from baseline to days 7, 14 and 28** will be assessed using the WHO-ISARIC seven-category ordinal scale.
- **Overall survival** will be defined by the time from date of randomization until date of death, regardless of the cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.
- The **length of stay in Intensive Care Unit** (from the date of admission in the Unit to the date of discharge)
- **The duration of mechanical ventilation or high flow oxygen devices** (from the date of intubation to the stop date of **mechanical ventilation or high flow oxygen**)
- **The duration of hospitalization** (from the date of hospitalization to the date of definitive discharge for live patients)
- The **rate of throat swab negativation at D7, D14 and D28**
- **The viral RNA load in throat swab and blood samples at D7, D14 and D28**
- **The rate of secondary infection by other documented pathogens** (bacteria, fungi) at D7, D14 and D28 if available.
- The **biological parameters** changes from baseline. The following parameters will be studied: neutrophils, lymphocytes, platelets, hemoglobin, CRP, pro-calcitonine and pro-inflammatory cytokine (IL6).
- The **safety profile:**
  - Treatment-Emergent Adverse Events, Serious Adverse Events, Suspected Unexpected Serious Adverse Reactions, New Safety Issues described using the NCI-CTC AE classification v5.
  - Number of participants with a discontinuation or temporary suspension of study drugs (for any reason).
- Incremental Cost-Effectiveness Ratios (ICERs) expressed in cost per Life Year Gained.

2.3 OVERVIEW OF STUDY DESIGN

This is a **muticenter clinical program including a staging phase and 2 different therapeutic cohorts** according to the patient's symtoms. Patients with mild symtoms of COVID-19 will be included in Cohort 1; patients with moderate or severe symtoms will be included in cohort 2.

A total of 273 patients will be included in the IMMUNONCOVID-20 program.

In cohort 1, 147 patients will be centrally randomized (1:1:1 ratio) to receive:

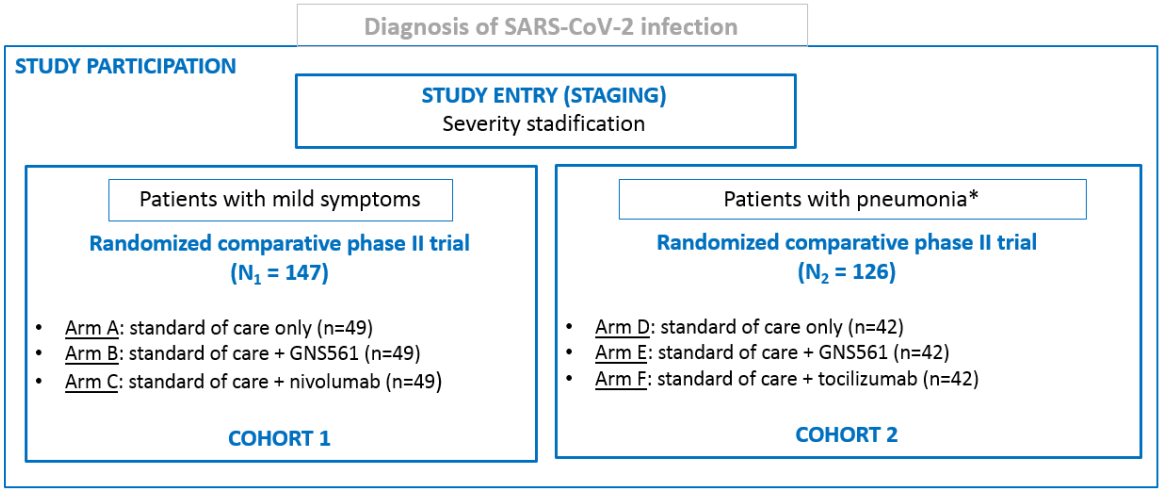
- Arm A: Standard of care
- Arm B: Chloroquine analog (GNS651)
- Arm C: Anti-PD-1 (nivolumab)

Randomisation will be stratified on patient's age: <70 vs. ≥70 years old.

In cohort 2, 126 patients will be centrally randomized (1:1:1 ratio) to receive :

- Arm D: Standard of care
- Arm E: Chloroquine analog (GNS561)
- Arm F: Anti-IL-6 (tocilizumab)

Randomisation will be stratified on the basis of respiratory support methods at the time of enrollment: hospitalization associated or not with oxygen support with nasal duct or mask (<5 on the WHO-ISARIC seven-category ordinal scale) vs. non-invasive mechanical ventilation or high flow oxygen therapy or invasive mechanical ventilation (≥5 on the WHO-ISARIC seven-category ordinal scale).



* : Pneumonia must be confirmed by chest imaging, and an oxygen saturation (Sao2) of 94% or less while they are breathing ambient air or a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) (Pao2:Fio2) at or below 300 mg Hg

Overview of study design

In the experimental arms (B and C) of cohort 1, patients will be treated either with oral GNS561 during 14 consecutive days or with a single intravenous administration of nivolumab.

In the experimental arms (E and F) of cohort 2, patients will be treated either with oral GNS561 during 14 consecutive days, or with a single intravenous administration of tocilizumab.

The **enrolment rules in experimental arms** are determined to identify a LT signal that would occur in a large fraction of advanced or metastatic cancer patients with COVID-19. According to binomial

law, among 3 patients or 6 patients treated with a given experimental arm there is a 90% probability of observing for at least one of these patients a LT if this event occurs in at least 54% and 32% of treated patients, respectively.

For each experimental arm, the enrolment of the first 3 or 6 patients will be done in the coordinating center only (CLB), and will be carried out as follows:

- **GNS561 arms: the same rules will be applied in COHORT 1 and in COHORT 2.**
  The enrolment of the first 3 patients in both cohorts will be done without minimum time interval between each inclusion. Among the first treated 3 patients of each cohort with a minimum follow up time of 48 hours:
    - If no LT is observed, enrollment will continued in all participating centers up to 49 patients into COHORT 1 and 42 patients into COHORT 2. If more than two (>2) LT are observed in a given cohort, GNS561 arm will be stopped in this cohort.
    - If only one (1) LT is observed in one cohort or another, 3 additional patients will be included into this cohort. If less or equal than 2 (≤2) LT are observed among the 6 first treated patients with a minimum follow up time of 48 hours, enrollment will continued in all participating centers up to 49 patients into COHORT 1 and 42 patients into COHORT 2.
- **Anti-PD1 arm** (COHORT 1): the enrolment of the first 3 patients in the coordinating center only (CLB) will be done with a minimum of 72 hours between each inclusion. Among the first treated 3 patients with a minimum follow up time of 48 hours:
    - If no LT is observed, enrollment will continued in all participating centers up to 49 patients into COHORT 1. If more than two (>2) LT are observed, anti-PD1 arm will be stopped.
    - If one (1) LT is observed, 3 additional patients will be included in the coordinating center. If less or equal than 2 (≤2) LT are observed among the 6 first treated patients with a minimum follow up time of 48 hours, enrollment will continued in all participating centers up to 49 patients into COHORT 1.
- **Anti-IL6R arm** (COHORT 2): the enrolment of the first 3 patients will be done without minimum time interval between each inclusion. Among the first treated 3 patients with a minimum follow up time of 48 hours:
    - If no LT is observed, enrollment will continued in all participating centers up to 42 patients into COHORT 2. If more than two (>2) LT are observed, anti-IL6R arm will be stopped.
    - If one (1) LT is observed, 3 additional patients will be included in the coordinating center. If less or equal than 2 (≤2) LT are observed among the 6 first treated patients with a minimum follow up time of 48 hours, enrollment will continued in all participating centers up to 42 patients into COHORT 2.

In each experimental arm, after the initial enrolment of 3 or 6 patients with a minimum of 48 hours of follow-up time per patient, a **steering committee meeting will be held to review the available safety/efficacy data and make a decision regarding additional recruitment in each cohort**, according to predefined stopping rules, based on tolerance data and outcomes reported in the first patients.

The steering committee will be composed of the coordinating and associated investigators, representatives of the coordinating center (medical monitor, statistician, and project manager) and principal investigators of the participating sites.

In patients from cohort 1, the anticancer treatment may be continued (as per investigator's decision). In patients from cohort 2, the anticancer treatment must be temporarily discontinued before randomization and at least up to 28 days after the date of randomization.
In both cohorts, patients will be followed-up continuously until the hospitalization discharge and then weekly for a minimum period of 28 days after the randomization. After this 28-day follow-up visit, respiratory symptoms and treatment-emergent averse events will be collected weekly in the clinical database for 1 additional month and then at 3 months and 6 months after the date of randomization..
In each cohort, the data cut-off will be 2 months after the last randomization. All efficacy analyses will be performed into the intent-to-treat populations. The end of the study will be defined as the 6-month follow-up visit of the last patient randomized. Vital status will be updated once for all patients at the end of the study.
Nota Bene: beyond recovery from COVID-19, anticancer treatment may be reintroduced as per investigator's decision.

2.4 STUDY DURATION

The duration of participation for a patient ranges from 3 (last patient in) to 9 months (first patient in), including:

- A treatment and active follow-up period of 28 days (or until the hospitalization discharge, whichever occurs last);
- A follow-up period of 5 months (overall follow-up of 6 months);
- A long-term follow-up period until the end of the study.

Considering a 3-month accrual period and a maximum follow-up of 6 months for the last patient, the overall study duration is expected to be 9 months.

3. BENEFIT AND RISK ASSESSMENT

The benefit and risk assessment is based on the following:

- **The unmet and urgent medical need for patients with COVID-19 infection**. There is no approved treatment for the COVID-19. The "Guidance on the Management of Clinical Trials during the COVID 19 (Coronavirus) pandemic (version 1.0 dated Mar 20th 2020)" reports that "absolute priority should be given to clinical trials on treatments for COVID-19 and COVID19-related illnesses, or trials on serious diseases with no satisfactory treatment option". Even if hydroxychloroquine migth significalty decrease the viral load, its translation in clinical benefit remains to be confirmed.**The medical and scientific rationale that sustains our proposed strategies**. There is biological rationale to treat patients with hyperinflammation with anti-iL-6 or anti-IL-6R. Preclinical and clinical data support that GNS561 might be of clinical interest and is safe.
- The confirmed safety of the selected dose for each IMP.
- An initial safety run will be conductec for each experimental arms. There will be a close monitoring of safety concerns and a sequential recruitment will be implemented to take into consideration the tolerance of previous patients for each study drug. At first, all patients will be recruited at Centre Léon Bérard to have a better and quick management of all the data and safety concerns.
- A steering committee will be in charge of reviewing on real time gathered data from the patients randomized in participating sites. It will be responsible of determining whether the benefit / risk ratio remains favourable.
- After the end of participation in the study, anticancer treatments will be reintroduced as per investigator's discretion.
- Based on preclinical data and previous clinical experience, the proposed study design, the doses selection, and the safety monitoring plan described in this protocol, **the Sponsor considers that adequate risk mitigation measures are included in this protocol and that the benefit-risk profile is favourable** to proceed with the proposed clinical study.

4. STUDY POPULATION

The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. Selection criteria have been set according to the Reference Safety Information of Investigational Medicinal Products. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or patient's safety.

4.1 INCLUSION CRITERIA

Patients eligible for inclusion in this study have to meet **ALL** the following criteria:

I1. Age 18 or older at the time of enrolment.

I2. Histologically or cytologically confirmed diagnosis of advanced or metastatic hematological or solid tumor (hematological or solid tumor, any type and any localization).

I3. Documented diagnosis of COVID-19 (diagnostic test performed in a certified laboratory) or symptoms of COVID-19 associated with radiological signs of pneumonia as described by Shi et al. (34);

I4. **Cohort 2**: patients with pneumonia confirmed by chest imaging, and an oxygen saturation (Sao2) of 94% or less while they are breathing ambient air or a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) (Pao2:Fio2) at or below 300 mg Hg.

I5. Patient not eligible for a transfer to Resuscitation Unit (either due to underlying medical condition – including cancer – or due to lack of available bed).

I6. Life-expectancy longer than 3 months.

I7. Adequate bone marrow and end-organ function defined by the following laboratory results:

- Bone marrow:
  - Hemoglobin ≥ 7.0 g/dL,
  - Absolute Neutrophils Count (ANC) ≥ 1.0 Gi/L,
  - Platelets ≥ 100 Gi/L;
- Hepatic function:
  - Total serum bilirubin ≤ 1.5 x ULN (except patients with Gilbert's syndrome who must have total serum bilirubin ≤ 3.0 x ULN),
  - AST/ALT ≤ 5 ULN
- Renal function:
  - Serum creatinine ≤ 2.0 x ULN or Cr. Cl. ≥ 30ml/min/1.73m² (MDRD or CKD-EPI formula);

I8. Willingness and ability to comply with the study requirements;

I9. Signed and dated informed consent indicating that the patient has been informed of all the aspects of the trial prior to enrolment (in case of emergency situation, please refer to protocol section 13.1 PATIENT INFORMATION AND INFORMED CONSENT);

I10. Women of childbearing potential (Appendix 2) are required to have a negative serum pregnancy test within 72 hours prior to study treatment start. A positive urine test must be confirmed by a serum pregnancy test;

I11. Women of childbearing potential and male patients must agree to use adequate highly effective contraception (Appendix 2) for the duration of study participation and up to 6 months following completion of therapy;

I12. Patient must be covered by a medical insurance.

4.2 NON-INCLUSION CRITERIA

E1. **For cohort 1 only** : Patient currently receiving therapy with an anti- PD-1, anti- PD-L1, or anti-CTLA4.

E2. **For cohort 2 only:** Patient currently receiving therapy with an anti- IL-6 or anti-IL-6R.

E3. Patient presents a contraindication to Nivolumab treatment (**cohort 1 only**) or to tocilizumab (**cohort 2 only**) as per respective SPC, including known hypersensitivity to one of these study drugs or severe hypersensitivity reaction to any monoclonal antibody.

E4. Patient known to have intolerance or hypersensitivity to chloroquine or any quinoline derivatives (e.g., quinine, chloroquine, mefloquine)

E5. Patient has active autoimmune disease that has required systemic treatment in the past 3 months before the date of randomisation or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids at doses higher than 10 mg/d prednisone equivalents or immunosuppressive agents.

Note 1: Patients with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Patients that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Patients with hypothyroidism stable on hormone replacement or Sjögren's syndrome will not be excluded from the study.

Note 2: Patients may received corticosteroids as required for the management of SARS-CoV-2-related symptoms.

E6. Patient requires the use of one of the following forbidden treatment during the study treatment period:

- Major surgery.
- Live vaccines. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever and BCG. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

E7. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to the date of randomisation unstable arrhythmias or unstable angina, Known Left Ventricular Ejection Fraction (LVEF) < 50%.

Note: Patients with known coronary artery disease, congestive heart failure not meeting the above criteria must be on a stable medical regimen that is optimized in the opinion of the treating physician and in consultation with a cardiologist if appropriate.

E8. Patient has Active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening), Active hepatitis C (Patients positive for hepatitis C virus (HCV) antibody are eligible only if PCR is negative for HCV RNA at screening) or Human Immunodeficiency Virus (HIV) infection (HIV 1/2 antibodies).

E9. Prior allogeneic bone marrow transplantation or solid organ transplant in the past.

E10. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration

of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.

E11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

E12. Pregnant or breastfeeding patient, or expecting to conceive children within the projected duration of the trial, starting with the screening visit through 6 months after the last dose of study drugs.

5. STUDY TREATMENTS

Treatment arms will be randomly allocated by investigational sites using a randomization platform. Treatments will be allocated using an Iteractive Web Response System (IWRS).

In the randomized clinical program, the information delievered on GNS561 administration and management guideline are the same in cohort 1 and cohort 2.

5.1 STANDARD OF CARE

All patients of the study will receive standard of care, regardless of the cohort and the arm allocated by randomization.
With regards to the respiratory symptoms and medical resoures at investigational site, the following should be given according to the patient's condition: oxygen supplementation, non-invasive ventilation, invasive ventilation, antibiotherapy, vasopressor support, renal replacement therapy, or extracorporeal membrane oxygenation.
Additional care and medications should be administered in the patient's best interest.

5.2 OVERVIEW ON STUDY DRUGS

5.2.1 Nivolumab

Name (code)	Nivolumab (OPDIVO®)
Therapeutic Class	Human monoclonal antibody (IgG4 kappa immunoglobulin) targeting PD-1.
Mode of Action	PD-1 checkpoint inhibitor that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2.
Formulation	Sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid) and polysorbate 80 (Tween□□80), at pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup.
Composition	Each vial contains Nivolumab 100 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP.
Stability	Refer to label on the vial.
Packaging	10 mL Type I flint glass vials, single use, stoppered with butyl rubber stoppers and sealed with aluminum seals. Each vial contains 100 mg of Nivolumab.
Storage	Unopened vials: 2° to 8°C. Protect from light and freezing.

	After preparation, store the Nivolumab solution for infusion either: 1) at room temperature for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or 2) under refrigeration at 2°C to 8°C for no more than 24 hours from the time of infusion preparation.
Route of administration	Intravenous (IV).
Dosage regimen	0.3mg/kg.
Duration of treatment	1 single dose at Day 1.

5.2.2 GNS561

Chemical Name (other names)	2-(4-chlorobenzylamino)-4-(4-tert-butylaminopiperidin-1-yl)quinolone
Therapeutic Class	Palmitoyl-protein thioesterase 1 (PPT1) inhibitor
Mode of Action	GNS561 binds to PPT1 and induces lysosomal permeabilization, cytosolic release of cathepsins, inhibition of late stage autophagic flux, activation of caspases and induction of apoptosis
Formulation	White opaque hard gelatin capsules containing.
Composition	Each capsules contains 200 mg GNS561, in size 4 or 0el (elongated), respectively. Each capsule contains GNS561, lactose monohydrate, crospovidone XL, hydroxypropylcellulose, magnesium stearate, and titanium dioxid).
Stability	See expiry date on the vials
Packaging	White high density polyethylene bottles without desiccant and closed with a polypropylene cap. 30 capsules per bottle.
Storage	15-25°C.
Route of Administration	per os. Capsules are to be taken every day with a glass of water following a meal (preferably at the same time each dosing day)
Dosage regimen	400mg qd loading dose orally for 2 days then, 200mg qd orally for a total treatment duration of 14 consecutive days.
Missed Doses	If for any reason a treatment is not given within the allowed treatment window (± 12h) it will be cancelled (i.e., missed for that time point), and treatment will be resumed at the next dosing day.

Duration of treatment	14 days.

5.2.3 Tocilizumab

Chemical Name (other names)	RoActemra
Therapeutic Class	Humanised IgG1 monoclonal antibody against the human interleukin-6 (IL-6) receptor produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.
Mode of Action	Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling.
Formulation	Vials of 80 mg of tocilizumab* in 4 mL (20 mg/mL), or 200 mg of tocilizumab* in 10 mL (20 mg/mL), or 400 mg of tocilizumab* in 20 mL (20 mg/mL).
Composition	Each 80 mg vial contains 0.10 mmol (2.21 mg) sodium. Each 200 mg vial contains 0.20 mmol (4.43 mg) sodium. Each 400 mg vial contains 0.39 mmol (8.85 mg) sodium. List of excpients : Sucrose, Polysorbate 80, Disodium phosphate dodecahydrate, Sodium dihydrogen phosphate dehydrate, Water for injections
Stability	See expiry date on the vials
Packaging	Vial (type I glass) with a stopper (butyl rubber) containing 4 mL, 10 mL or 20 mL concentrate. Pack sizes of 1 and 4 vials.
Storage	2°C–8°C. Do not freeze.
Route of Administration	Intravenous
Dosage regimen	400 mg flat dose.
Duration of treatment	1 single dose at Day 1.

5.3 PREPARATION AND ADMINISTRATION OF STUDY DRUGS

5.3.1 Recommendations for Nivolumab

Aseptic technique must be strictly observed throughout the preparation procedure preferably in a biologic safety cabinet or an isolator since no anti-microbial preservative is present in the solution.

Vials should be used for specific patients and should not be shared between patients.

As with any biologics, allergic like reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available (i.e. resuscitation equipment; oral and intravenous antihistamines (as per institutional practice and for

example: e.g. ranitidine 50 mg IV, clemastine 2 mg IV, dexchlorphenyramine 5 mg IV, chlorphenamine 4 mg PO, 10 to 20 mg IV. as required) and if necessary hydrocortisone (IV up to 500 mg as required)), and study personnel must be trained to recognize and treat anaphylaxis.
The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

Nivolumab should be injected as a 30-min IV infusion and not as an IV push or bolus injections.

Nivolumab injection 100 mg/10 mL (10 mg/mL) is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter.
Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.
Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection, USP to protein concentrations as low as 1 mg/mL. Instructions for dilution and infusion of Nivolumab injection are be provided in the pharmacy Manual.

5.3.2 Recommendations for GNS561

GNS561 should be given once a day every day with a glass of water following a meal (preferably at the same time each dosing day) at the following dose :

- Day 1 - Day 2 (loading dose) : 400mg (2 capsules) once daily
- Day 3 - Day 14 : 200mg (1 capsule) daily

Prophylaxis : Nausea has been the main limiting adverse event seen at higher doses in the on-going dose-seeking study and is manageable with ondansetron. Patients should be given prophylaxis with ondansetron 8 mg orally approximately 30 minutes before GNS561, at least on day 1 and 2.

5.3.3 Recommendations for tocilizumab

Study drug should be inspected visually for particulate matter or discolouration prior to administration. Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted.
Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 100 mL infusion bag, equal to the volume of tocilizumab concentrate required for the patients dose, under aseptic conditions. The required amount of tocilizumab concentrate (0.4 mL/kg) should be withdrawn from the vial and placed in the 100 mL infusion bag. This should be a final volume of 100 mL. To mix the solution, gently invert the infusion bag to avoid foaming.

After dilution, tocilizumab should be administered as anintravenous infusion over 1 hour.

After dilution, the prepared solution for infusion is physically and chemically stable in sodium chloride 9 mg/mL (0.9%) solution for injection at 30ºC for 24 hours. From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C–8°C, unless dilution has taken place in controlled and validated aseptic conditions.

5.4 DOSE MODIFICATIONS

Due to single administration at day 1, there is no dose modification for Nivolumab and Tocilizumab. In case of vomiting despite optimal prophylaxis, GNS561 should be discontinued.

5.5 CONCOMITANT TREATMENTS

All treatments being taken by the patient at the time of consent signature until the 28-day follow-up visit, are regarded as concomitant treatments.

5.5.1 Permitted concomitant treatments

Supportive treatment as medically indicated for the patient's well-being may be prescribed at the Investigator's discretion. Every medication or treatment taken by the patient during the trial must be recorded in the eCRF.

5.5.2 Prohibited concomitant treatments

The following concomitant treatments are not permitted during the study treatment period:

- Cohort 2 only : any investigational agent or anticancer therapy other than the protocol specified therapies.
- Cohort 2 only : any concurrent chemotherapy, immunotherapy, monoclonal antibody, biologic (monoclonoal antibody or others biologic agent), any targeted therapy for cancer treatment, other than any stated in the protocol. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever and BCG. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Immunosuppressive medications, including corticosteoids, may be used to manage dyspnea and other SARS-CoV-2-related symptoms at the discression of the treating investigator (and should be recorded in the CRF). For patients in the GNS561 arm : The medications listed in Table below should be contra-indicated while some of them may be used with caution (Antacids, Proton pump inhibitors, Loperamide) while taking GNS561. The grapefruit and its juice are contra-indicated.

Medications that May Interact with GNS561

Generic Name	
Antacids	Ketoconazole
Boceprevir	*Loperamide*
Bupropion	Mitotane
Carbamazepine	Nefazodone
Cimetidine	Nelfinavir
Cinacalcet	Paroxetine

Clarithromycin	Phenytoin
Cobicistat	Posaconazole
Conivaptan	*Proton pump inhibitors*
Dabigatran	Quinidine
Diltiazem	Rifampin
Duloxetine	Ritonavir
Enzalutamide	St. John's wort
Fexofenadine	Talinolol
Fluoxetine	Telaprevir
Fluvoxamine	Terbinafine
H2 antagonists	Troleandomycin
Idelalisib	Vinblastine
Itraconazole	Voriconazole

- **For patients in the GNS561 arm :** Proton pump inhibitors, H2-antagonists, and antacids are not prohibited but must not be taken at the same time as GNS561; a wash-out period of 6 hours is recommended.

5.6 STUDY DRUGS MANAGEMENT

5.6.1 Ordering and site supplies

Nivolumab and tocilizumab will be provided by the investigational sites.

GNS561 will be provided free of charge by Genoscience (Marseille) and supplied to participating centers. The first supply will be managed by the Sponsor. Additional Study drug requests will be addressed to the Sponsor using the specific *Request form* (See Pharmacy Manual). GNS561 must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated staff have access in accordance with the applicable regulatory requirements. Upon receipt, Study drug should be stored according to the instructions specified on the drug labels and in the Pharmacy Manual.

5.6.2 Labelling and packaging

Study drugs will be labelled with specific and regulatory required labels according to GCP and GMP.

5.6.3 Compliance and On site Accountability

Study drugs shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate Drug accountability record form (DARF – See Pharmacy Manual) of study drugs is maintained with information related to drug receipt (if applicable), drug dispensing and destruction (See Pharmacy Manual for specific forms).

The study site personnel will keep a record of all study drugs dispensed to and returned by the patients throughout the study. Deviation(s) from the prescribed dosage regimen should be reported to the sponsor.

A copy of the DARF is available in the Pharmacy Manual. These records must be available for inspection by the Study Monitor.

Under no circumstances will the Investigator supply study drugs to a third party, allow the study drugs to be used other than as directed by this Clinical Trial Protocol, or dispose of study drugs in any other manner.

6. ASSESSMENTS & SCHEDULE

The following schedule of study assessments applies for patients from both cohorts, regardless of the randomization arm.

6.1 ASSESSMENT TO BE PERFORMED AT SCREENING

The investigator or designee staff will have to proceed to the following information/procedures during the screening visit:

- Inform the patient of the treatments, the objectives and the design of the study, answer to questions and sign with him/her the informed consent form. **The investigator must not start any study-related procedure before Informed Consent Form (ICF) is signed and dated by both the patient (and impartial witness, if applicable) and the investigator**.
- Check the eligibility criteria list and perform the following exams:

Screening/Baseline assessments

TYPE OF ASSESSMENT	TIMING
General demography and Relevant medical history Demography (age, gender) A complete history of COVID-19 (including, date of diagnosis, start date of symtoms, concomitant treatments…) 7-items WHO ordinal scale (respiratory supplementation)	Within 72 hours before randomization
Complete physical examination (as per routine practice) Major review of body systems (general appearance, skin, neck including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities) Vital signs (blood pressure, temperature, pulse, respiratory rate and oxygen saturation) Weight and height Performance Status (PS) will be measured using the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale (Appendix 4**).**	Within 72 hours before randomization
Concomitant treatments and symptoms Assessment of baseline signs and symptoms (concomitant disease), concomitant infections Prior/concomitant therapies	Within 72 hours before randomization
Laboratory tests (as per routine practice) Hematology: white blood cells, differential white blood cell count (including absolute neutrophils and lymphocytes counts), hemoglobin, and platelet count Coagulation panel: pro-thrombin time or INR, a partial thromboplastin, fibrinogen Biochemistry: glucose, urea, serum creatinine, creatinine clearance (calculated according to Cockcroft –Gault or MDRD for > 65 years formula), sodium, potassium, calcium, phosphorus, bicarbonate, chloride, albumin, total protein, albumin, total bilirubin (direct and indirect), alkaline phosphatase, AST, ALT, CRP, procalcitonine	Within 72 hours before randomization

Proinflammatory cytokine: IL6 Cardiac assessment : troponin	
Pregnancy tests (if applicable) Serum or urine pregnancy tests If urinary test is positive, a serum test should be performed	Within 72 hours before randomization
Imaging Diagnostic chest CT	14 days
Cardiac function Electrocardiogram (12-lead ECG), including QTcf interval	Within 72 hours before randomization

Procedure for randomization

As soon as screening assessments are completed and the patient's eligibility is confirmed, the investigator, or its designee, will proceed to the randomization via the on-line secure platform (https://clb-lyon.ennov.com/CSOnline/) in which the stratification criteria will be provided.

A confirmation e-mail of randomization will be automatically sent to the investigational staff and the coordinating centre. It will remind patient's identification in the study.

6.2 ASSESSMENTS TO BE PERFORMED DURING THE 28-DAY FOLLOW-UP PERIOD

Patients should be followed-up until the 28-day follow-up visit or until the hospitalization discharge whichever occurs last.

Post-randomization assessments

TYPE OF ASSESSMENT	TIMING
Physical examination (as per routine practice) Major review of body systems (general appearance, skin, neck including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities) Vital signs (blood pressure, temperature, pulse, respiratory rate and oxygen saturation) Weight	Weekly (and as clinically indicated)
Respiratory disease Assessment respiratory signs and symptoms 7-items WHO ordinal scale (respiratory supplementation) and type of respiratory supplementation Viral clearance (throat swab or bronchoalveolar lavage, blood sample)	Weekly (and as clinically indicated)
Laboratory tests[a] (as per routine practice) Hematology: white blood cells, differential white blood cell count (including absolute neutrophils and lymphocytes counts), hemoglobin, and platelet count Coagulation panel: pro-thrombin time or INR, a partial thromboplastin, fibrinogen Biochemistry: glucose, urea, serum creatinine, creatinine clearance (calculated according to Cockcroft –Gault or MDRD for > 65 years formula), sodium, potassium, calcium, phosphorus, bicarbonate, chloride, total protein, albumin, total protein, total bilirubin (direct and indirect), alkaline phosphatase, AST, ALT, CRP, procalcitonine. Proinflammatory cytokine: IL6	Weekly (and as clinically indicated)
Cardiac function Electrocardiogram (12-lead ECG), including QTcf interval.	**If clinically indicated only**
Hospitalization Type of hospitalization and change of hospitalization Date of discharge	**Continuously**
Safety assessments Limiting toxicities (first 3 patients of each arm) Tolerance (NCI CTC AE version 5.0)	**Continuously**

6.3 PATIENT FOLLOW-UP (BEYOND THE 28-DAY FOLLOW-UP PERIOD)

Beyond the 28-day follow-up visit, patients will be followed-up weekly for 1 additional month, then at 3 months and 6 months after the date of randomization to assess respiratory symptoms and any treatment-emergent adverse event.

Vital status will be updated once for all patients in each cohort at the time of the LPLV.

7. TREATMENT, STUDY AND SITE DISCONTINUATION

Study drugs should be administered as per protocol whenever possible in accordance with the investigator's judgment and patient consent. However, patients have the right to voluntary discontinue (i.e. Permanently stop) study drugs or withdraw from the study at any time for any reason. In addition, the investigator has the right to discontinue a patient from study drugs or withdraw a patient from the study.

7.1 STUDY TREATMENT DISCONTINUATION

Patient may discontinue from GNS561 in case one of the following criteria is met:

- Patient refuse to continue the study treatment;
- The treatment duration has been completed as per protocol (i.e. 14 days);
- Patient's willingness to stop the treatment;
- Any unacceptable toxicity, either as per investigator's judgment;
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator;
- Patient non-compliance, as defined as unable or unwilling to complete the required study dosing or assessments;
- Death.

Any study treatment discontinuation should be fully documented in the CRF with date and reason.

7.2 PREMATURE PATIENT WITHDRAWAL

Patient may prematurely discontinue from the study for the following reasons:

- Withdrawal of consent; it should be distinguished in patient's medical file whether the patient refuses to continue the study procedures (withdrawal from the treatment) or if he/she refuses subsequent data collection in his/her patient's file (withdrawal from the study). Data collected prior to the consent's withdrawal remain in the study database and will be considered for safety analyses.
- Death.
- Early termination of the study for any reason.

A subject who discontinues study participation prematurely for any reason is defined as a dropout if the subject has already been administered at least 1 dose of study drugs.
A patient who discontinues, for any reason, study participation before randomization is considered as a screening failure.

7.3 STUDY DISCONTINUATION

The Sponsor could stop the study at any time. Reasons for stopping the study may include, but are not limited to, the following:

- The incidence of severity of AE in this or other study indicate a potential health hazard to patients;
- Patients enrolment is unsatisfactory;
- If any information leads to doubt as to the benefit/risk ratio of the clinical trial.

In all cases (decided by the Sponsor or by the Investigator), the appropriate EC and NCA should be informed according to applicable regulatory requirements.

7.4 SITE DISCONTINUATION

The Sponsor has the possibility to replace a site at any time. Reasons for replacing a site may include, but are not limited to the following:

- Slow recruitment (i.e. no inclusion after a reasonable period of time mutually agreed upon), despite the Investigator has received from the Sponsor all IP, means and information necessary to perform the Clinical Trial;
- Inaccurate or incomplete data recording;
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to non-compliance with the Clinical Trial Protocol, breach of the applicable laws and regulations or breach of the ICH guidelines for Good Clinical Practice.

In any case, the sponsor will notify the Investigator of its decision by written notice.

The investigator has also the right to stop the study at any time. He/She must notify (30 days' prior notice), the sponsor of his/her decision and give the reason in writing.

8. SAFETY

ICH Good Clinical Practices (GCP) requires that both investigators and sponsor follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

8.1 DEFINITIONS

The following standard definitions for adverse events will be used:

Adverse event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

Serious adverse event (SAE): any untoward medical occurrence or effect that at any dose:

- results in death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital abnormality or birth defect;
- is a significant medical event (i.e. that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above).

Limiting toxicities (LT) are defined as any of the following AEs grading using NCI-CTCAE v5.0 occurring during the LT period (i.e. 48 hours or 72 for nivolumab arms) and assessed as related to study drug:

- Hematological toxicity:
  - Grade ≥ 4 neutropenia (ANC < 500/µL).
  - Grade ≥ 3 febrile neutropenia.
  - Grade ≥ 4 thrombocytopenia.
- Any Grade ≥ 3 major organ adverse event with the following exceptions:
  - Grade 3 fatigue.
  - Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the patient is asymptomatic.
  - Grade 3 or 4 lymphopenia.
  - Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days.
  - Grade ≥ 3 Diarrhea adequately managed with supportive care measures.

Suspected Unexpected Serious Adverse Reaction (SUSAR) is any untoward and unintended adverse reaction to an IP, not mentioned or differing in terms of nature, intensity, frequency or clinical course from that listed in the SmPC of nivolumab and tocilizumab or in the latest version of IB of GS561 and results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is medically significant and/or is a suspected transmission of an infectious agent.

New Safety Issues: Any new data that could lead to reevaluate the ratio between the benefits and the risks of the research, or that could be sufficiently important to consider modifications of the research

documents, the research management and the drug utilization or, to suspend, to interrupt or to modify the protocol of the research or of similar researches.

8.2 REPORTING OF ADVERSE EVENTS

General Guidelines for reporting of Clinical AE

Study drugs related AE of any grade (NCI CTCAE v5) and all SAE, regardless of the relationship to the IP, occuring from the signature of the ICF until 28 days after the last treatment administration for a patient are to be recorded on the corresponding CRF pages or screen.

As far as possible, the AE should be described using medical terms: diagnosis or single syndrome should be reported instead of symptoms.

For all AE reported, the Investigator should specify:

1. ***Whether the event is serious or not***. The severity is related to the intensity whereas a serious AE is defined by the criteria described in Section 11.1. A severe AE should not be always considered as serious, and a serious AE may not be of severe intensity.
2. ***The date of onset and its duration (start and end dates)***. The Investigator should follow up the outcome of any AEs until the return to normal or consolidation of the patient's condition. Once resolved, the details should be recorded in the CRF: **only the worst grade of a specific event should be recorded.** All AE still evolving at the end of the study are to be followed up by the investigator until their resolution or stabilization.
3. ***The intensity*** (using NCI CTCAE v.5 (Appendix 3)),
4. ***Action taken with respect to IP*** (no action taken; IP dosage adjusted/temporarily interrupted; investigational product permanently discontinued due to this AE, concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization), corrective treatment/therapy given, additional investigations performed, outcome.
5. ***The relationship*** between an investigational product and an AE, using the EVCTM (EudraVigilance Clinical Trial Module) criteria :
   - Not related: AEs which are felt to be due to extraneous causes and not related to the administration of study drug.
   - Related: AEs which are felt to be related to the drug administration. Relationship to drug is related if :
     - The event follows a reasonable temporal sequence from administration of the drug and could not be explained by the known characteristics of patient's clinical state, environmental or toxic factors;
     - The event disappears or decreases upon cessation of drug or reduction in dose (and if applicable, reappears on rechallenge of drug);
     - The event follows a known response pattern to the suspected drugs.

Nota bene: Signs and symptoms that are present prior to the first study drug administration are to be recorded on the medical history pages included in the CRF. They are to be recorded as AE as soon as one of the following changes occurs: increased intensity, relationship, action taken regarding study drug.

8.3 REPORTING OF SAE

The investigator must report to the pharmacovigilance of the sponsor: SAE, AE following misuse or overdose, and pregnancies occurring or observed during the course of the study and within 28 days after the last administration of the IP, whatever their relationship to the study treatment. This have to be done **without delay after the investigator becomes aware of the event**.

SAEs occurring more than 2 months after study treatment completion need to be reported only if a relationship to the investigational product (e.g. secondary malignancy) is suspected by the investigator.

In case of SAE, the investigator will have to:

1. Fill and sign an SAE or AESI report form
2. Collect any additional document necessary for SAE assessment (such as hospitalization report, biological results)
3. Assess the seriousness and causality of the event with the investigational product using the EVCTM criteria: related *versus* not related (see section 11.2)
4. Send the SAE form without delay and additional documents:
   - Either by fax to :
     - The pharmacovigilance of the sponsor - 🖷 +33 (0)9 81 40 42 80
     - Copy to the coordinating centre - 🖷 +33 (0)4 78 78 27 15
   - Or by e-mail to anne.millaret@ctvigilance.fr

A complete description and medical diagnosis shall be provided. In case of incomplete information, the investigator will have to provide follow-up information (outcome, more precise medical details, results of investigations, copy of discharge summary, etc) as soon as possible, again using the SAE Report Form (follow-up) to the pharmacovigilance of the sponsor and to the study monitor. When this information is passed on, care must be taken to continue to respect patient anonymity. The study monitor or pharmacovigilance of the sponsor may contact, or visit the investigator, in order to obtain details.

All SAE must be followed by the investigator until resolution or stabilization, and a final assessment sent to pharmacovigilance of the sponsor as a SAE Report Form (SAE FU).

Nota bene: The following events **are not** to be considered as SAE:

- Progression of the underlying disease
- Hospitalisation (1 night or more) or hospitalisation prolongation for one of the following reasons:
  - Planned hospitalisation for routine intervention
  - Hospitalisation or intervention requested by the protocol
  - Hospitalisation for explorations not related to a modification of the patient health
  - Hospitalisation for comfort or for social reasons (for example: hospitalisation of an elderly person due to dependence on his partner who was hospitalised)
  - Hospitalisation not related to a patient health worsening and not related to the study objectives (for example: plastic surgery)
  - Hospitalisation for standard monitoring of a pre-existing disease or medical condition that did not worsen

Nota bene: Misuse or overdose of the study treatment will have to be considered as SAE, even if they don't meet the seriousness criteria.

8.4 PREGNANCY

Serum or urine pregnancy testing will be done for patients of childbearing potential at the screening visit, and when in case of pregnancy suspicion during the entire study period.

Pregnancy of the patient or his partner must be reported to the pharmacovigilance but it should not be reported as an SAE in the eCRF.

If the investigator has been informed that a female patient is pregnant during the study period trial and up to 6 months after the last study drug administration:
1. The investigational product should be immediately discontinued and the planned safety assessments (i.e. the end of study) should be performed
2. The investigator must immediately notify the study monitor, complete the SAE Report Form, and send it by fax to the pharmacovigilance of the sponsor or by e-mail to anne.millaret@ctvigilance.fr.
3. Follow-up of the pregnancy will be mandatory until the outcome has been determined. At the completion or termination of the pregnancy, the investigator must complete a SAE Report Form (follow-up) and fax it to the pharmacovigilance of the sponsor.

- *Pregnancy of a male patient's partner*

Male participants will have to report immediately if his partner becomes pregnant. During the study and up to 6 months after le last study drug administration.

1. The investigator must immediately notify the study monitor, complete the SAE Report Form, and send it by fax to the pharmacovigilance of the sponsor.
2. The investigator must document in the patient's medical file that the couple gives authorization to disclose information on pregnancy follow-up and outcome.

The investigator must provide all details on pregnancy follow-up and outcome, using the SAE report form.

8.5 RESPONSIBILITIES OF THE SPONSOR

The sponsor will have to collect reports of SAE and their follow-ups from the Investigator. The Sponsor will have to collect, from the notifying investigator, all the information necessary for the evaluation of the cases.

The sponsor will have to report any suspected SUSAR potentially related to the study treatment to the EMA Eudravigilance database and the Competent Authorities within the requested period, i.e. **without delay** for death and life-threatening SUSAR and until 15 days for the other SUSARs. The information's follow-up must be transmitted within a new delay of 8 days for all SUSARs.

The evaluation of expectedness is based on knowledge of the adverse reaction on the reference document: the current reference document is the latest version of the IB of GNS561 and the SmPC of nivolumab and tocilizumab.

The sponsor will also have to inform the Ethics review committee of any SAE with the potential to modify the benefit/risk ratio of the present study.
The sponsor will be responsible for reporting the Development Safety Update Report (Annual Safety report) to Competent Authority and to EC.

The Sponsor will be responsible to alert the Principal Investigator in case of identification of a New Safety Issue and will propose urgent security measures to be applied.

The Sponsor will be responsible for reporting of New Safety Issues and measures to be proposed **without delay** to Competent Authorities and to EC. Additional relevant information concerning the New Safety Issues must be reported within 8 days.

The Sponsor shall notify the Principal Investigators of any information which might affect the patient's safety.

9. STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

9.1.1 COHORT 1 (n=147)

The sample size was calculated in order to provide a relevant power to compare each of the 2 experimental arms (anti-PD1 and GNS561) vs control arm. Same hypotheses are used for each of the two comparisons, namely: anti-PD1 therapy and GNS561 would be considered as efficient in cancer patients with mild symptoms from infection by SARS-CoV-2 if they will reduce mortality rate at 28 days from the expected level of 25% with standard of care to 5%. According to these hypotheses, 49 patients in each arm are required to achieve a power of 80% for detecting a statistically significant difference using a 1:1:1 randomization ratio. Each comparison will be performed using a two-sided test at a 2.5% level, in order to keep a global alpha risk of 5%.

9.1.2 COHORT 2 (n=126)

The sample size was calculated in order to provide a relevant power to compare each of the 2 experimental arms (anti-IL6 and GNS561) vs control arm. Same hypotheses are used for each of the two comparisons, namely: anti-IL6 therapy and GNS561 would be considered as efficient in cancer patients with severe infection by SARS-CoV-2 if they will reduce mortality rate at 28 days from the expected level of 40% with standard of care to 10% (35). According to these hypotheses, 42 patients in each arm are required to achieve a power of 90% for detecting a statistically significant difference using a 1:1:1 randomization ratio. Each comparison will be performed using a two-sided test at a 2.5% level, in order to keep a global alpha risk of 5%.

9.1.3 Pooled analysis in COHORT 1&2

In addition, a pooled analysis of patients randomized into GNS561 and standard of care arms from COHORTS 1&2 will also be performed to assess the efficacy in the whole population. The total number of patients randomized in the GNS561 and control arms in Cohorts 1+2 would be equal to 91 per arm (49+42). This pooled sample size would provide a power higher than 90% to detect a difference between a standard of care arm 28-day survival rate of 70% and a GNS561 arm 28-day survival rate of 90% with a 5% two-sided significance level. No multiple adjustment will be applied for this pooled analysis, as this analysis will be considered as confirmatory.

Sample size calculation was performed using NQuery version 7.0, module PTT0.

9.2 ANALYSIS POPULATION

For statistical considerations, patients will be considered as part of the following described population:

- The Intent-to-treat (ITT) population, defined as all patients randomized in the trial, regardless of whether they actually received treatment. The treatment groups will be analyzed as randomized.
- The safety analysis set is defined as all randomized patients having received at least one dose of study treatment, whether withdrawn prematurely or not. Patients will be analyzed according to the treatment initiated (and not according to the randomisation arm).

Baseline characteristics and efficacy data will be described on the ITT population. The safety analysis set will be used for safety analyses.

9.3 STATISTICAL ANALYSIS

All statistical methods will be based on the International Conference on Harmonisation (ICH) E9 document "Statistical Principles for Clinical Trials".

Patient characteristics and baseline data will be sumarized using descriptive analyses. Qualitative variables will be presented using frequency and percentage distributions. The number of missing data will be given, but will not be considered for the calculation of proportions. Quantitative data will be described using the number of observations, mean, standard deviation, median, minimum and maximum values, as well .

In each cohort, 2 comparisons are planned : **GNS561 vs control then Anti-PD1 vs control for cohort1 and GNS561 vs control then Anti-IL6Rvs control for cohort2.**

Statistical analyses will be performed using SAS® software version 9.4 (SAS Institute, Cary, NC, USA, 2003) or later.

9.3.1 Safety run-in phase

The primary endpoint is the number of limiting toxicities (LTs) occurring during the first 48 hours of treatment. LTs are defined as the occurrence of any of the following events evaluated as related to study drug:

- Hematological toxicity:
  - Grade ≥ 4 neutropenia (ANC < 500/µL).
  - Grade ≥ 3 febrile neutropenia.
  - Grade ≥ 4 thrombocytopenia.
- Any Grade ≥ 3 major organ adverse event with the following exceptions:
  - Grade 3 fatigue.
  - Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the patient is asymptomatic.
  - Grade 3 or 4 lymphopenia.
  - Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days.
  - Grade ≥ 3 Diarrhea adequately managed with supportive care measures.

The safety profile will be summarized with descriptive statistics (appropriate proportions with their 95% confidence interval).

The analysis of the run In phase will be performed after 48 hours of follow-up of the first 3rd or 6th patients randomized in each Cohort/Experimental arm. Safety data will be reviewed by the steering committee regarding each Cohort/Arm independantly:

- If 0/3 patients exposed to experimental treatment (**GNS561 cohort1, GNS561 cohort2, Anti-PD1 or Anti-IL6R arms)** experienced limited toxicities related to treatment, the safety data will be considered acceptable and enrolment/randomization will continue.
- If 1/3 patient experienced limited toxicities, 3 additional patients will be included in this Cohort/Arm and safety will be re-evaluated after 6 patients.
  - If 1 additional patient experienced LT (i.e. 2/6 patients with LT), this treatment arm will be stopped in this cohort.

- If no additional patient experienced LT (i.e. 1/6 patients with LT), the safety data will be considered as acceptable and enrolment/randomization will continue.

- If ≥ 2/3 patients experienced a LT, no further enrollment/randomization will be allowed for this Cohort/Arm.

An additional safety rule will be applied to Anti-PD1 arm (COHORT 1): the enrolment of the first 3 patients in the coordinating center only (CLB) will be done with a minimum of 72 hours delay between each treatment initiation.

The steering committee meeting will be held to review the available safety/efficacy data and make a decision regarding additional recruitment in each Cohort/Arm, according to predefined stopping rules, based on tolerance data and outcomes reported in the first patients. The steering committee will be composed of the coordinating investigator, representatives of the coordinating center (medical monitor, statistician, and project manager) and principal investigators of the participating sites.

9.3.2 Study endpoints

- **Primary endpoint**

The primary endpoint will be the 28-day survival rate, defined by the proportion of patients still alive 28 days after randomization.
If vital status at 28 days post randomisation is not available due to early transfer in an external resuscitation unit, patients will be considered as failure at the date of the transfer.
Comparison of each experimental arm (**GNS561 then Anti-PD1 for cohort1 and GNS561 then Anti-IL6R for cohort2)** to control arm will be performed using a chi-square test if applicable, a Fisher exact test otherwise. Statistical test will be performed at a two-sided 2.5% alpha level.

- **Secondary endpoints**

- **Time to clinical improvement** will be defined as the time from randomization to an improvement of two points (from the status at randomization) on the seven-category ordinal scale or live discharge from the hospital, whichever comes first. Failure to reach clinical improvement or death before day 28 will be censored at last evaluation or date of death if occurred. The time to clinical improvement will be estimated by treatment arm using the Kaplan-Meier method and compared between experimental and control arms using a Log-rank test at a two-sided 5% alpha level. Hazard ratios with 95% confidence intervals will be calculated by Cox proportional-hazards model.
- **Clinical status on the seven-category ordinal scale at D7, D14 and D28** will be described by treatment arms. Depending on the number of patients by category, class groupings can be made in order to be able to perform a valid statistical test. Statistical test will be performed at a two-sisded 5% alpha level.
- **Mean change in the ranking on the ordinal scale from baseline to D7, D14 and D28** will be calculated by treatment arm. Experimental treatment arms will be compared to control arms using a T test if applicable or a nonparmetric wilcoxon test otherwise at 5% alpha level. Graphical evolution over time will be presented by treatment arms using boxplot.
- **Overall survival** will be defined by the time from date of randomization until date of death, regardless of the cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.
  Duration of follow-up in all patients will be estimated using the reverse KM estimator (36) and will be described in terms of median.

OS will be estimated by treatment arm using the Kaplan-Meier method, and will be described in terms of median survival along with the associated 2-sided 95% CIs for the estimates. The survival rate will be described at different time with the associated 2-sided 95% Cis. Comparison between experimental and control arms will be performed using Log-rank test stratified on randomization stratification factor. Statistical test will be performed at a two-sided 5% alpha level. Hazard ratios with 95% confidence intervals will be calculated by Cox proportional-hazards model.

- The **length of stay in Intensive Care Unit** (from the date of admission in the Unit to the date of discharge), **duration of mechanical ventilation or high flow oxygen devices (from the date of intubation to the stop date of mechanical ventilation or high flow oxygen) and duration of hospitalization** (from the date of hospitalization to the date of definitive discharge for live patients) the will be calculated for each patient. Median duration in each experimental treatment arm will be presented and compared to control arm using a nonparmetric wilcoxon test a 5% alpha level.
- The **rate of throat swab negativation and rate of secondary infection by other documented pathogens** (bacteria, fungi) will be presented by treatment arm and timepoints (7, 14 and 28 if available). Comparison of each experimental arm to control arm will be performed using a chi-square test if applicable, a Fisher exact test otherwise. Statistical test will be performed at a two-sided 5% alpha level.
- The **viral RNA load** in throat swab and blood samples at D7, D14 and D28 and **biological parameters** will be graphically described in each arm. Mean curves +/- SD will be plotted over time. Absolute and relative relative variations compared to baseline will be plotted. for neutrophils, lymphocytes, platelets, hemoglobin, and pro-inflammatory cytokine (IL6)
- The **safety profile** (Treatment-Emergent Adverse Events, Serious Adverse Events, Suspected Unexpected Serious Adverse Reactions, New Safety Issues) will be described using the NCI-CTC AE classification v5. Descriptive statistics will be provided by treatment arm for characterizing and assessing patient tolerance to treatment. The AE, grade ≥3 AEs, AEs related to treatment and Serious AE will be described per System Organ Class and Preferred Term.
- The number of participants with a discontinuation or temporary suspension of study drugs (for any reason) will be describe by treatment arms.

- **<u>Pooled analysis</u>**

Data of **GNS561 and control** arms of the 2 cohorts will be pooled together in order to confirm results observed separately. Primary endpoint, clinical status at D7, D14 and D28, time to clinical improvement and overall survival will be analysed in this population. All statistical tests will be adjusted on cohort parameter and performed at a 5% two-sided alpha level.

9.3.3 Health economics evaluation

Cost-Effectiveness Analyses (CEA) will be conducted alongside the trial comparing standard of care, chloroquine analog, anti-PD-1/PD-L1 in cohort 1 and standard of care, chloroquine analog, and Anti-IL-6 in cohort 2. The Cost-Effectiveness Analyses (CEA) will be also performed on the pooled analysis comparing GNS561 and standard of care arms from COHORTS 1&2. Based on the primary endpoint, Incremental Cost-Effectiveness Ratios (ICERs) will be expressed in cost per Life Year Gained. The timeframe will be 28 days and the viewpoint will be the French National Insurance.

- Identification, measurement, and evaluation of costs : costs will be calculated based on the individual-level use of hospital services over the study period (cf. secondary endpoints length of stay in Intensive Care Unit, duration of hospitalization). Using the Diagnosis-related group (i.e. les Groupes Homogènes de Malades), hospital stays will be evaluated based on the latest

costs available (Etudes Nationales de Coûts (ENC) or tariffs if costs are not available). Acquisition costs for the most expansive drugs (e.g. anti-PD-1/PD-L1) will be based on the list of common units of dispensation for supplementary medicines (liste des unités communes de dispensation prise en charge en sus). Costs of medical transport: data will be derived from the French Court of Audit's report on medical transport expenses covered by the French National Health insurance. Due to the short time horizon, costs will be not discounted. Mean total costs will be calculated for each arm of both cohorts. Descriptive statistics with arithmetic mean costs and standard deviations will be used to present treatment costs. For both cohorts, difference in total costs (GNS561 vs control then Anti-PD1 vs control for cohort1 and GNS561 vs control then Anti-IL6Rvs control for cohort2) will be reported. In both cohort, one-way analysis of variance (ANOVA) will be used to compare the arithmetic mean cost in the three treatment arms. In cases of violation of parametric assumptions, nonparametric bootstrap method will be adopted.

- Multiple regression analyses will also be performed to examine the relationship between costs and a range of potentially explanatory patient (age, sex, comorbidities, etc.) and tumor characteristics (localization, type, etc.) including treatment arm and cohort.
- Effectiveness: the primary endpoint, i.e. 28-day survival rate, will be used.
- Incremental Cost-Effectiveness Ratios (ICERs) expressed in cost per Life Year Gained calculation: in both cohort three alternatives (i.e. arms 1, 2 and 3) are available. Hence, multiple pairwise comparisons (1 vs. 2, 1 vs. 3, 2 vs. 3) can be made each providing different incremental costs and effectiveness resulting in different ICERs. First of all, strongly dominated altervatives (i.e. more costly and less effective) -if any- will be ruled out and then ICERs will be calculated based on comparisons of moving to increasingly costly and increasingly effectives alternatives (37). ICERs will be then positioned within the cost-effectiveness plane where the horizontal axis represents the difference in effects and the vertical axis the difference in costs (38). The uncertainty surrounding the ICERs will be captured by a probabilistic analysis using non-parametric bootstrap methods. Simulated bootstrap samples will be generated by independent draws with replacement from pairs constituted by the mean cost difference and the mean effectiveness difference. These pairs will be represented by a scatter of points corresponding to an estimate of their joint distribution. Confidence regions for these pairs will be represented by ellipses, the outer ellipse defining the confidence region of the pair at the 95% level and the inner ellipse at the 50% level. For still greater robustness, in addition to the confidence ellipses described, uncertainty around the ICER will be taken into account by calculating the probability that it belonged to each of the quadrants of the cost-effectiveness plane. One-way sensitivity analyses will be illustrated graphically using tornado diagrams (39). Finally, the cost-effectiveness plane with multiple alternatives will be made.

In a context of lack of data regarding the 2019 coronavirus disease (COVID-19), this trial-based economic evaluation will provide useful and complementary information for decision makers.

10.DATA COLLECTION, MANAGEMENT & QUALITY CONTROL

10.1 STUDY REMOTE MONITORING

All personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information.

According to the ICH guidelines for GCP and local law requirement, the study monitor must check the Case Report Forms (CRF) entries against the source documents. All along the clinical trial, the sponsor will perform study monitoring according to the predefined monitoring plan.

Following a risk-based approach, all electronic CRF will be centrally analysed. Then, when deemed absolutely necessary and possible, source Data Verifications (SDV) will be performed on-site, tailored on central monitoring findings.

Medical files will be fully reviewed by the monitor for all patients to identify any event related to the primary endpoint. In addition, a particular attention will be paid to consent procedures, selection criteria and safety concern.

A monitoring (remote or on-site) report will be written for each visit to document the progress of the clinical trial and give an account of all emergent problems.

The sponsor will help the investigators to conduct the study in compliance with the clinical trial protocol, Good Clinical Practices (GCP) and local law requirements.

In addition to the monitoring, investigational sites will be contacted at regular intervals either by phone or by e-mail, by a representative of the coordinating centre (i.e. the study monitor) to review study progress, investigator's and patient's compliance with clinical trial protocol, and any emergent problems.

10.2 DATA ENTRY AND DATA MANAGEMENT

Data entry and data management will be performed by the investigational site's staff and the coordinating centre (DRCI, Centre Léon Bérard), respectively, using the ENNOV clinical solution (compliant with the regulatory requirements).

It is the responsibility of the Investigator to maintain adequate and accurate CRFs for each enrolled patient.

Data entry will be performed by investigators (or the investigator's designee) on an electronic Case Report Form (eCRF) (https://clb-lyon.ennov.com/CSOnline/) using personal login and password.

Queries will be generated automatically in the eCRF for erroneous and missing data. It will be answered by investigational site's staff in compliance with source data and saved in the eCRF.

The study monitor will ask the investigational site's staff to modify any erroneous, forgotten, inconsistent or unclear data. All database modifications will be explained (if necessary) and recorded in the audit trail.

If the data are modified by another person than the investigator, the authorization of this person will be documented on the delegation form.

Adverse events will be coded according to the MedDRA®.

10.3 AUDIT AND INSPECTIONS

For the purpose of ensuring compliance with the Clinical Trial Protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that auditors/inspectors are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

12. STUDY COMMITTEES

12.1 STEERING COMMITTEE

A steering committee will be established to oversee the conduct of the study and to make any necessary recommendations as needed. It will be composed of:

- The coordinating investigators: Dr Philippe CASSIER and Dr Virginie AVRILLON;
- The methodologist/statistician and the project manager of the trial (DRCI, CLB);
- The principal investigators of the main centres.

It will be regularly informed of the inclusion rate and of any emergent problems, and will decide of potential amendments. At the end of the study, it will review the activity and safety data.
The Steering committee is also empowered to propose the inclusion (or non-inclusion) of any participating centre and has final decision on the iDSMB recommendations.
Meetings are scheduled before the start of accrual, at any time during the trial if needed or upon request of one members or by sponsor.

In each experimental arm, after the initial enrolment of 3 or 6 patients with a minimum of 48 hours of follow up time per patient, a **steering committee meeting will be held to review the available safety/efficacy data and make a decision regarding additional recruitment in each cohort**, according to predefined stopping rules, based on tolerance data and outcomes reported in the first patients.
Special attention will be paid to the first 3 to 6 patients treated by **Anti-PD1 in cohort 1**. Steering members will be informed daily during the first 72 hours following treatment administration of patient's general condition as well as any medically significant adverse event and its relation to treatment administration that appears during the day.

12.2 INDEPENDENT DATA SAFETY MONITORING BOARD

Not applicable

12.3 RADIOLOGICAL TUMOR ASSESSMENT

Not applicable

13. ETHICAL AND REGULATORY ASPECTS

This Clinical Trial will be conducted in accordance with the World Medical Association (WMA) Declaration of Helsinki principles, laid down by the 18th WMA Assembly (Helsinki, 1964) and subsequent amendments, and the current ICH guidelines for GCP.
This Clinical Trial will be also conducted in compliance with French and European laws and regulations in force, as well as any applicable guidelines.
The trial will be registered on the European Medicine Agency (EMA) databases and on other sites, as appropriate.

13.1 PATIENT INFORMATION AND INFORMED CONSENT

Prior to a patient's participation in the clinical trial, the investigator shall fully inform the patient of all aspects of the clinical trial that are relevant to the patient's decision to participate as required by local laws and regulations in force. Such information shall be prepared in writing, be available to the patient and shall be given for the patient to consider his/her decision to participate in the clinical trial.
Informed consent is documented by means of a written, dated and signed ICF. The written ICF should be signed with name and date personally filled-in by the patient and by the investigator after ensuring that the patient has understood the information.
A copy of the signed and dated written ICF will be provided to the patient.
The investigator must not start any study-related procedure before ICF is duly signed and dated by both, patient and investigator.
The ICF must be revised whenever there are substantial changes to the study protocol/procedures or when new information becomes available that may affect the willingness of the patient to participate. Patients must be re-consented to the most current version of the ICF during their participation in the study (see 15.9. Protocol amendments). In case of consent withdrawal, protocol dispositions will be followed as stated in section 9.2 "Premature patient withdrawal".

In case of emergency situations, when trial participants are incapable of giving their informed consent (for example because they are under intensive medical care), informed consent of these patients or their representatives or trusted person will need to be acquired later, as soon as feasible. The patient, if any, their representatives or the trusted person mentioned are informed as soon as possible and their consent, when required, is requested for the possible continuation of this research. In these cases, the investigator is expected to record why it was not possible to obtain consent from the participant prior to enrollment.

Alternative ways of obtaining such consent of patient's representative should be considered during the pandemic e.g. contacting the patient's representative via e-mail and obtaining written consents. It is allowed to obtain a dematerialized consent sent by e-mail for the patient's representatives Any consent obtained this way should be documented and confirmed by way of normal consent procedures at the earliest opportunity when the trial participants or representaitves will be back at the regular sites.

13.2 NATIONAL COMPETENT AUTHORITY (NCA) AND ETHICS COMMITTEE (EC)

Prior to its implementation, this Clinical trial will receive the authorization from the National Competent Authority (ANSM – Agence Nationale de Sécurité du Médicament et des produits de santé) and the approval/favourable opinion from the appropriate EC (designated Comité de Protection des Personnes).
During the Clinical Trial, any substantial modification (i.e. any change to any aspect of the clinical trial which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and

robustness of the data generated) shall only be implemented if it has been approved, in accordance with the regulation in force, by the appropriate EC and/or Competent Authority depending on the modification.

13.3 DATA PROTECTION

Personal data will be collected and processed in accordance with Regulation (EC) No 2018/1725 and national data protection legislation implementing Regulation (EU) 2016/679 (General Data Protection Regulation), respectively.

The Coordinating centre (DRCI Centre Léon Bérard) committed to the Commission Nationale de l'Informatique et des Libertés (CNIL) to comply to the reference methodology 1 (Méthodologie de Référence MR-001): statement registered under #1994173 the 27/09/2016.

The personal data processing from this clinical trial falls within the scope of the MR-001.

Arrangements to comply with the applicable rules on the protection of personal data are implemented by the sponsor and coordinating centre, including but not limited to:

- Personal data are collected and processed for the sole purpose of this clinical trial;
- Contracts signed between sites, investigators and sponsor include clauses on personal data protection;
- Patients will be identified by a code number and their initials excluding any directly identifying personal data. The matching list is kept on the site by the investigator;
- All the data concerning the patients will be recorded in the eCRF throughout the study. Data entry will be performed online by investigators and authorised staff only. Access to the eCRF is protected with personal access codes;
- Access to the personal data, under sponsor's responsibility and within the legal frame, is restricted to the sponsor and persons acting on its behalf, investigators and their team as well as persons in charge of quality assurance and sponsor's study monitors under required conditions;
- The sponsor is responsible for the collected data processing. In agreement with the European regulations concerning data protection, the General Data Protection Regulation (GDPR), patient's data are carried out in research and public interest. Data will be transferred to French Authorities in conditions ensuring appropriate security, integrity and confidentiality. Personal data will not be transferred outside the European Union. If patients have any question concerning their data protection, they can contact the investigator or the Data Protection Officer (DPO) at the following address: dpd@lyon.unicancer.fr. If a patient is not satisfied by the reply obtained, he/she can contact the CNIL using the following link: https://www.cnil.fr/
- In case a patient wants to withdraw from the study, the data collected prior to his/her withdrawal will be processed and will not be deleted. However, no further data will be collected in the database.
- Patients will be fully informed in the ICF on the study related personal data collecting and processing (nature, purpose, data recipients, use of already collected data in case of study exclusion or withdrawal of consent), their right of access, rectification, opposition, erasure, processing restriction and data portability. The investigator is the contact person on those matters. He/she will then forward the request to the sponsor.
- Once the project completed, patients' data will be retained for a maximum of 2 years after the last scientific publication linked to the research project. Then, they will be archived for a maximum of 25 years.

13.4 RESPONSIBILITIES OF THE SPONSOR

The Sponsor takes the responsibility for the initiation, for the management and for setting up the financing of the clinical trial, including but not limited to:

- To register the trial in EMA databases and get an European drug regulatory authorities Clinical Trials (EudraCT) number;
- To submit the protocol to the appropriate EC and NCA for approval/authorisation before its implementation as well as if any substantial modification occurs throughout the study;
- To subscribe an insurance for compensation for any damage suffered by a subject resulting from participation in the clinical trial which is appropriate to the nature and the extent of the risk;
- To insure the suitability of individuals and sites involved in conducting the clinical trial;
- To provide to the investigators all required information and documents to conduct properly the clinical trial;
- To insure that the clinical trial is conducted in compliance with the protocol and good clinical practice;
- To adequately monitor the conduct of the clinical trial in order to verify that the rights, safety and well-being of subjects are protected, that the reported data are reliable and robust, and that the conduct of the clinical trial is in compliance with the requirements of the regulation and laws in force;
- To insure arrangements for traceability, storage, return and destruction of investigational medicinal product(s), depending on the nature of the clinical trial;
- To notify EMA, NCA and principal investigators for any SUSAR occurred, in and outside France, with the investigational product(s) or procedure(s) as well as to provide relevant additional information;
- To notify the appropriate EC, NCA and principal investigators of any New Safety Issue, in the requested delay;
- To notify the appropriate EC, NCA and principal investigators of serious breaches (i.e. likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial) as well as of all unexpected events which may affect the benefit-risk balance of the clinical trial, but are not SUSAR;
- To notify the appropriate EC, NCA and principal investigators of urgent safety measures where an unexpected event is likely to seriously affect the benefit-risk balance;
- To communicate the annual security report (Development Safety Update Report [DSUR]) to the NCA, the appropriate EC and principal investigators;
- To keep a clinical trial master file at all times containing the essential documents relating to the clinical trial, relevant to sponsor's responsibility, and to archive its content during the minimum legal length after the end of the trial;
- To declare the start and end of the trial and communicate a summary of the results to the EMA, NCA and appropriate EC within requested time limits.

13.5 RESPONSIBILITIES OF THE INVESTIGATOR

The investigator is a qualified medical doctor who takes responsibility for the conduct of a clinical trial at a clinical trial site whereas the principal investigator is the responsible leader of a team of investigators.

The principal investigator shall:

- Demonstrate the suitability of the clinical trial site with the conduct of the study (facilities, recruitment potential, personnel qualification, availability…);

- Ensure compliance of the clinical trial at a clinical trial site with the protocol and requirements of the laws and regulations in force as well as any applicable guidelines, including GCP;
- Identify (if necessary) investigators to assist in the conduct of the clinical trial. Qualification of the investigators will be documented in a current curriculum vitae and other relevant documents;
- Assign tasks among the members of the team of investigators in a way which is not compromising the safety of subjects and the reliability and robustness of the data generated in the clinical trial at that clinical trial site. All investigators shall be appointed and listed in a timely manner;
- Under her/his responsibility, clinical research technicians provide administrative and logistic support to the study; assist in the auditing of source records and the documentation of eCRFs.
- To keep a clinical trial master file at all times containing the essential documents relating to the clinical trial, relevant to investigator's responsibility, and to archive its content during the minimum legal length after the end of the trial;

Responsibilities of the investigators include, but are not limited to:

- To ensure compliance with all procedures required by the clinical trial protocol, data collection and GCP;
- To collect subject's written informed consent form;
- To complete eCRF for each enrolled patient, to validate collected data in the eCRFs and if necessary to date, correct and sign DCF (Data Clarification Form);
- To store data and identification of enrolled patients in accordance with current legislation, for the minimal length after the end of the study
- To record and document AE or laboratory abnormalities identified in the protocol as critical to the safety evaluation and report them to the sponsor in accordance with the reporting requirements and within the periods specified in the protocol;
- To notify immediately any SAEs to the Sponsor's Pharmacovigilance (Dr Anne Millaret) and the coordinating centre (DRCI);
- To accept potential visits of control by monitors and inspectors mandated by the sponsor or the NCA.

13.6 CONFIDENTIALITY

All information disclosed or provided by the Sponsor, or produced during the Clinical Trial, including, but not limited to, the Clinical Trial Protocol, the CRFs, and the results obtained during the course of the Clinical Trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

The submission of the Clinical Trial Protocol and other necessary documentation to the Ethics Committee and/or competent authority is mandatory but the EC/CA members have the same obligation of confidentiality.

The Investigator and the Sub-Investigators shall use the information solely for the purposes of this Clinical Trial, to the exclusion of any use for their own or for a third party's account.

Furthermore, the Investigator and the Sponsor agree to adhere to the principles of personal data confidentiality in relation to the patients, Investigator and its collaborators involved in the study.

13.7 PROPERTY RIGHTS

All information and documents provided by the sponsor, as well as all the results/data which arise directly or indirectly from the clinical trial are the sole and exclusive property of the sponsor. The investigator shall not mention any information or the product in any application for a patent or for any other intellectual property rights.

13.8 PROTOCOL AMENDMENTS

Any modification of the protocol has to be agreed by the principal investigator and the sponsor in the form of a written amendment.

Any amendment which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial requires authorisation/favourable opinion by NCA and/or appropriate EC prior to its implementation unless there are overriding safety reasons.

In some instances, an amendment may require a change to the ICF. The investigator must receive an EC favourable opinion concerning the revised ICF prior to implementation of the change and patient's signature should be collected again if applicable and as soon as possible.

13.9 INSURANCE

The sponsor has subscribed an insurance policy in compliance with local laws covering its responsibility for all the participants for any injury that might be caused by the clinical trial (SHAM 18 rue Edouard Rochet 69372 LYON Cedex 08 – police 142883). The insurance of the Sponsor does not relieve the Investigator and the collaborators from maintaining their own liability insurance policy.

14. REPORTING AND PUBLICATIONS

A study report will be prepared under the responsibility and according to the standards of the sponsor, provided that all CRFs have been completed. It will include the study objectives, the methodology, statistical analysis and raw data listings, and the conclusions of the study. It will also include all the list of AE that occurred during the study and data concerning all the patients included in the study. It will be submitted to the coordinating investigator for review and signature. The clinical study report will be prepared and will be available for health authorities within one year after the end of the study.

The manuscript of the publication will be prepared within the 6 months following the publication of the final clinical study report by the principal investigator, or upon agreement.

Investigators are informed that the sponsor reserves all rights to data generated from this study. Written approval from the sponsor must be obtained prior to any publication or presentation of data from this study.

The sponsor is not allowed to use investigator's name in any publication without a prior written consent.

The investigator is not allowed to use sponsor's name in any publication without a prior written consent.

The principal investigator agrees to publish the results. No publication can be done without the principal investigator and the Sponsor approval; the funding source will be mentioned in the acknowledgments section. The final decision for the publication of the study will be taken by the principal investigator, statisticians and the sponsor.

Any publication or communication (oral or written) will be defined by mutual agreement between the investigators according to international guidelines (http://www.icmje.org/). All the authors who participated actively to the conception of the study, its development and writing of results will be cited, i.e.:

- The coordinating investigators, the investigator of the translational program, and all investigators who have included and followed patients. The order of citation will be established according to the number of inclusions in the study.
- The contributors of the coordinating centre team (DRCI) who participated in the drafting of the protocol and the statistical analysis of the study.
- The Centre Léon Bérard will be cited as Sponsor of the study.

15.REFERENCES

(1) Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020.

(2) Angeles-Sistac D, Martin-Onraet A, Cornejo-Juarez P, et al. Influenza in patients with cancer after 2009 pandemic AH1N1: An 8-year follow-up study in Mexico. Influenza Other Respir Viruses 2020;14(2):196-203.

(3) Dignani MC, Costantini P, Salgueira C, et al. Pandemic 2009 Influenza A (H1N1) virus infection in cancer and hematopoietic stem cell transplant recipients; a multicenter observational study. F1000Res 2014;3:221.

(4) https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/articles/infection-au-nouveau-coronavirus-sars-cov-2-covid-19-france-et-monde. 2020.

(5) Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020.

(6) Buckee CO, Balsari S, Chan J, et al. Aggregated mobility data could help fight COVID-19. Science 2020.

(7) Lipsitch M, Swerdlow DL, Finelli L. Defining the Epidemiology of Covid-19 - Studies Needed. N Engl J Med 2020;382(13):1194-6.

(8) Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020.

(9) Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020.

(10) Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA 2020.

(11) Piao S, Amaravadi RK. Targeting the lysosome in cancer. Ann N Y Acad Sci 2016;1371(1):45-54.

(12) Boya P, Gonzalez-Polo RA, Poncet D, et al. Mitochondrial membrane permeabilization is a critical step of lysosome-initiated apoptosis induced by hydroxychloroquine. Oncogene 2003;22(25):3927-36.

(13) Zhang Y, Liao Z, Zhang LJ, Xiao HT. The utility of chloroquine in cancer therapy. Curr Med Res Opin 2015;31(5):1009-13.

(14) Fu W, Li X, Lu X, et al. A novel acridine derivative, LS-1-10 inhibits autophagic degradation and triggers apoptosis in colon cancer cells. Cell Death Dis 2017;8(10):e3086.

(15) Xu R, Ji Z, Xu C, Zhu J. The clinical value of using chloroquine or hydroxychloroquine as autophagy inhibitors in the treatment of cancers: A systematic review and meta-analysis. Medicine (Baltimore) 2018;97(46):e12912.

(16) Rebecca VW, Nicastri MC, Fennelly C, et al. PPT1 Promotes Tumor Growth and Is the Molecular Target of Chloroquine Derivatives in Cancer. Cancer Discov 2019;9(2):220-9.

(17) Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis 2003;3(11):722-7.

(18) Keyaerts E, Vijgen L, Maes P, Neyts J, Van RM. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun 2004;323(1):264-8.

(19) Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30(3):269-71.

(20) Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov 2020;6:16.

(21) Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;105949.

(22) Dahly D, Gates S, Morris T. Statistical review of Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. 2020.

(23) Berende A, ter Hofstede HJ, Vos FJ, et al. Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease. N Engl J Med 2016;374(13):1209-20.

(24) Van Gool WA, Weinstein HC, Scheltens P, Walstra GJ. Effect of hydroxychloroquine on progression of dementia in early Alzheimer's disease: an 18-month randomised, double-blind, placebo-controlled study. Lancet 2001;358(9280):455-60.

(25) Savarino A. Use of chloroquine in viral diseases. Lancet Infect Dis 2011;11(9):653-4.

(26) Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020.

(27) Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506.

(28) Wong CK, Lam CW, Wu AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol 2004;136(1):95-103.

(29) Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis 2020.

(30) Garbers C, Heink S, Korn T, Rose-John S. Interleukin-6: designing specific therapeutics for a complex cytokine. Nat Rev Drug Discov 2018;17(6):395-412.

(31) https://www.fda.gov/media/72309/download. 2005.

(32) Frey NV, Porter DL. Cytokine release syndrome with novel therapeutics for acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2016;2016(1):567-72.

(33) Gardner RA, Ceppi F, Rivers J, et al. Preemptive mitigation of CD19 CAR T-cell cytokine release syndrome without attenuation of antileukemic efficacy. Blood 2019;134(24):2149-58.

(34) Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020.

(35) Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020;21(3):335-7.

(36) Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17(4):343-6.

(37) Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the economics evaluation of health care programmes. 4th Edition, New-York: Oxford University Press 2015.

(38) Black WC. The CE plane: a graphic representation of cost-effectiveness. Med Decis Making 1990;10(3):212-4.

(39) Eschenbach T. Engineering Economy: Applying Theory to Practice. Oxford University Press (2nd Edition) 2010.

Appendix 1 – Reference safety Information

The Reference Safety Information for **GNS561 is the last version of the Investigational Brochure**.

The last version of the **Summary of Product Characteristics of Opdivo (nivolumab) and RoActemra (tocilizumab)** are available on the EMA website :

- https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf
- https://www.ema.europa.eu/en/documents/product-information/roactemra-epar-product-information_en.pdf

Appendix 2 - Child-bearing potential and effective contraception

- **Child-bearing potential**

Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.
Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

Female patient of child-bearing potential

Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception (Table below) from the time of screening throughout the total duration of the drug treatment and up to 6 months after the last dose of study drug. Non-sterilised male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Male patients with a female partner of childbearing potential

Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and up to 6 months after the last dose of study drug. However, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation up to 6 months after the last dose of study treatment.
Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table below).

- **Contraception**

Highly effective methods of contraception, defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described in the table below. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Highly Effective Methods of Contraception (<1% Failure Rate)

• Barrier/Intrauterine methods	• Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant® • Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • Injection: Medroxyprogesterone injection: e.g. Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based

[a] This is also considered a hormonal method

Blood and sperm donation

Patients should not donate blood or sperm while participating in this study and for at least 6 months following the last infusion of study drug.

Appendix 3 - Common Terminology Criteria for Adverse Events (CTCAE) V5.0

Refer to NCI CTC AE v.5.0 online at the following NCI website:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.

When 2 criteria are available for similar toxicities, the one resulting in the more severe grade should be used.

The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.

An accurate baseline prior to therapy is essential.

Appendix 4 - ECOG Performance Status (PS) scale

ECOG PS	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in "A practical Guide to EORTC studies". p108, March 1994, Leuven, Belgium.

(*) ECOG = Eastern Cooperative Oncology Group