

SARS-Cov-2 infection Screening in Cancer Patients

NEO-SCREEN-COVID

ID-RCB Number n°2020-A01098-31

Sponsor

Centre Antoine Lacassagne
33 avenue de Valombrose
06189 NICE CEDEX 2



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PROTOCOL SUMMARY

SARS-Cov-2 infection Screening in Cancer Patients

NEO-SCREEN-COVID

n° ID-RCB : 2020-A01098-31

Number of recruiting centers and number of subjects

Number of centers	1
Number of patients	500

Study rational

Since December 2019, outbreak of COVID-19 caused by a novel virus SARS-Cov-2 has spread rapidly around the world and became a pandemic issue. Cancer patients seem to be at higher risk of infection and evolution to severe forms related to immunosuppression, according to the first published data from Chinese experience. However, the role of confounding factors such as age and smoking habits cannot be independently assessed. Supplementary data from a large retrospective Italian cohort suggest that the proportion of cancer patients with severe form of COVID-19 could be lower than expected. In addition, the proportion of asymptomatic SARS-Cov-2 infected cancer patients is unknown.

Based on academic and expert's recommendations, most of cancer units have already modified cancer treatment during the pandemic, in order to limit the number of outpatient visits / inpatient admissions and then reduce or avoid cross infection of COVID-19, although the negative impact on patient's outcome (cancer recurrence or mortality) has not been established.

Thus, a large screening for SARS-Cov-2 infection in treated cancer patients could help to:

- Define an accurate prevalence of COVID-19 immunization in this population
- Aggregate data on the relationship between clinical characteristics in cancer patients and COVID-19 risk.
- Provide information about asymptomatic COVID-19 cases.
- Organize effectively cancer units to separate infected and non-infected patients.

The RT-PCR gold-standard test for COVID-19 on nasal and pharyngeal swabs has limitations, as the test is not universally available, turnaround times can be lengthy, and reported sensitivities vary. It does not provide information about immunization status.

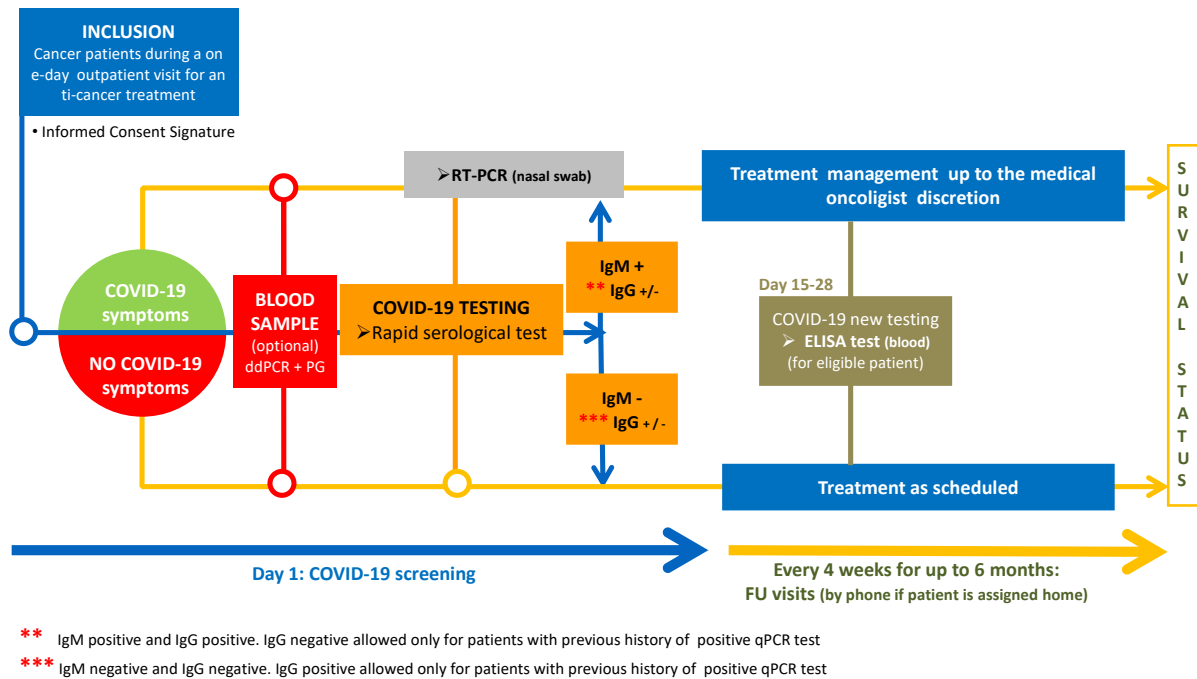
Serological assays may be important for understanding the epidemiology of emerging SARS-Cov-2, including the burden and role of asymptomatic infections.

Thus, the development of new devices or techniques for accurate diagnosis of SARS-CoV-2 infections, of fast and safe use, that could be spread in the local hospitals and clinics, would be a major advance for identifying and treating patients. In addition, information about the immunization of fragile people, such as cancer patients, could help to plan a safe strategy for anti-cancer treatment schedule and for the end of quarantine.

Methodology

This is a prospective, non-randomized, monocentric study assessing the prevalence of a SARS-Cov-2 infection in cancer patients.

Consecutive cancer patients that require at least one visit for anti-cancer treatment in a one-day outpatient care units will be tested by using a rapid serological test (Servbio ref C4650) with a drop of blood from a finger prick.



Objectives

Main objective

The primary objective is to evaluate the prevalence of COVID-19 with a rapid serological test in a cohort of consecutive cancer patients that require at least one visit for anti-cancer treatment in a one-day outpatient care units.

Secondary objectives

1. To evaluate patient's and health care professional's perception about the rapid serological test
2. To evaluate the concordance of COVID-19 positivity by the rapid serological test compared to the gold-standard RT-PCR on nasal swab for eligible patients
3. To evaluate the concordance of COVID-19 positivity by the rapid serological test compared to a classic serological test (ELISA method) from whole blood
4. To evaluate the proportion of the patients who will have at least one positive testing among all the methods applied.
5. To evaluate the number of patients who will get at least one new testing after the rapid serological test has been performed.
6. To compare the clinical and biological characteristics between positive and negative tested COVID-19 patients.
7. To describe the outcome of COVID-19 positive patients
8. To evaluate the impact of COVID-19 rapid serological test on the anti-cancer treatment schedule

Ancillary study (optional)

- Detection of SARS-Cov-2 viral load with ddPCR

In order to explore the accuracy of new minimally invasive diagnostic tools and to fully understand the timing of infection, patients will have a blood and saliva sample collection for additional COVID-19 testing by using ddPCR.

- Pharmacogenetic study

A specific blood sample, along with a specific informed consent for pharmacogenetics, will be collected in order to further perform analyses of germinal polymorphisms of genes directly involved in the binding and introduction of SARS-Cov-2 within host cells. Cell entry of SARS-Cov-2 depends on the binding of the viral spike (S) protein to ACE2 cellular receptor, as well as to S protein activation by host cell proteases such the serine protease encoded by TMPRSS2. Both ACE2 and TMPRSS2 genes present functional polymorphisms that may affect gene expression. Cao et al conducted a comparative genetic analysis of ACE2 in different populations and found a difference in the distribution and allelic frequency of ACE2 polymorphisms between Asians and Caucasians. They also suggested that these SNPs could modulate ACE2 expression in tissues, which may bring different susceptibility to SARS-CoV-2.

Study population

Inclusion criteria

To be eligible for participation in this trial, the subject should fulfill the following criteria:

1. Age $\geq$ 18-years old;
2. Patient treated for histologically proven cancer;
3. Patient that require at least one visit for anti-cancer treatment in a one-day outpatient care units
4. Patients that have previously been tested positive with a RT-PCR test from nasal swab that have been authorized to come to the hospital (after recovery or a 14-days quarantine period, according to local guidelines) can be included.
5. Patient willing and able to provide written informed consent/assent for the trial;
6. Patient affiliated with a health insurance system.

Exclusion criteria

The subject should not enter into the study if any of the following criteria are fulfilled:

1. Patient not able to give free consent
2. Patient not able to understand the protocol;
3. Patient not able to undergo the COVID-19 test
4. Vulnerable persons as defined by article L1121-5 - 8:
 - a. Pregnant women, women in labour or breast-feeding mothers, persons deprived of their freedom by judicial or administrative decision, persons hospitalized without their consent by virtue of articles L. 3212-1 and L. 3213-1 and who are not subject to the provisions of article L. 1121-8
 - b. Persons admitted to a social or health facility for reasons other than research
5. Adults subject to a legal protection order or unable to give their consent.

Evaluation criteria

Primary endpoint

The rate of prevalence will be defined as the ratio of the number of positive patients to the number of patients tested based on the rapid serological test (presence of IgM and/or IgG).

Secondary endpoints

1. The assessment of the perception of the rapid serological test for patient and health care professional will be measured in terms of (cf Appendix 6):

- Pain: The pain assessment will be performed using a visual analog scale (VAS). The score will be graded between 0 (absence of pain) to 10 (maximum pain)
- Simplicity: The assessment of the satisfaction of care will be carried out using a Likert scale with 4 modalities. The score will be graded between “Poor” to “Very Good”.
- Rapidity: The assessment of the satisfaction of care will be carried out using a Likert scale with 4 modalities. The score will be graded between “Poor” to “Very Good”.
- Satisfaction with care: The assessment of the satisfaction of care will be carried out using a Likert scale with 4 modalities. The score will be graded between “Poor” to “Very Good”.

Pain, simplicity, rapidity and satisfaction with care assessments will be evaluated immediately after the COVID-19 rapid serological test.

2. The concordance rate of COVID-19 positive and COVID-19 negative serological rapid test on whole blood compared to the gold-standard RT-PCR on nasal swab for corresponding patients will be evaluated in term of diagnostic performance (sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratio and area under the ROC curve).

3. The concordance rate of COVID-19 positive and COVID-19 negative serological rapid test on whole blood compared to an ELISA serological test on whole blood, for corresponding patients, will be evaluated in term of diagnostic performance (sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratio and area under the ROC curve).

4. The proportion of COVID-19 positive patients among population of cancer patients will be defined as the rate of patients with at least one positive test among all the methods applied (rapid serological test and/or serological ELISA test and/or RT-PCR and/or ddPCR).

5. The proceedings of additional COVID-19 testing for corresponding patients will be described in terms of:

- Time interval between the tests
- Type and results of the subsequent tests

6. The clinical and biological characteristics between positive and negative COVID-19 will be compared in term of (Cf 7.2):

- Age, gender, BMI, performance status, smoking history, alcohol consumption, medical history and concomitant medication
- Clinical characteristics: clinical stage, location, type of treatment.
- Biological: blood group, hematology, coagulation parameters and serum clinical chemistry.

7. The outcome of COVID-19 positive patients will be described by evaluating the rate of hospital admission for severe COVID-19 form and rate of death.

8. The impact of COVID-19 testing on the anti-cancer treatment schedule will be evaluated in term of:

- number and duration of medical treatment delay
- number of treatment discontinuation

Description of specific procedures

COVID-19 status will be assessed using several tests.

1. Rapid serological test (antibody test): mandatory

The COVID-19 sign IGM/IGG (Servibio, ref C4650) test is a rapid qualitative immunochromatographic test for the detection of immunoglobulins G (IgG) and M (IgM) in human whole blood (used with a drop of blood from a finger prick).

The test will be performed at time of inclusion by the investigator or a designated nurse, according to the developer notice.

2. Serological ELISA test (antibody test): mandatory for eligible patients

The ELISA test is an immune-enzymatic method to detect the presence of antibody against SARS-Cov-2. The test will be performed 15 to 28 days after the inclusion for eligible patients.

1. SARS-Cov-2 RT-PCR test from nasal swab (viral load): for eligible patients (suggestive symptoms) according to local guidelines.

The PCR test is currently the gold-standard for COVID-19 diagnosis.

Sample of a mixture of mucuous and saliva will be collected from the upper respiratory tract using a nasopharyngeal swab technique. Viral RNA will be tested for SARS-CoV-2 using a real-time reverse-transcription polymerase chain reaction (RT-PCR) assay.

The test will be performed according to local guidelines at the discretion of the investigator.

Statistical analysis plan

Determination of sample size

A total of 500 patients assessable are necessary, considering about 5% of non-assessable tests results or patients withdrawing their consent.

Calculation carried out using the David Sample software "Sample Size Software" (Single Proportion - Large Population)

Statistical analysis

The characteristics of the diagnostic variables will be assessed using conventional measures: True Positive (VP), False Positive (FP), True Negative (VN), False Negative (FN), Positive Predictive Value (VPP), Negative Predictive Value (VPN), Sensitivity, Specificity, ROC Curve (Receiver Operating Characteristic) and calculation of the ROC Under-Curve Area (ASC) with its 95% confidence interval.

Biological collection samples

To support future scientific research, as well as identifying characteristics that may predict, among various parameters a higher frequency and/or severity of COVID-19, 36 ml peripheral blood will be collected at time of inclusion.

Out of these 36 ml of blood:

- 9 ml (EDTA tube) will be dedicated to SARS-Cov-2 ddPCR testing
- 4 ml (EDTA tube) will be stored for the pharmacogenetics study (ACE2 and TMPRSS2 polymorphisms).

Planned schedule

Accrual period	30 weeks
Patient Follow-up	6 months
Overall duration of the trial (follow-up included)	14 months
Duration of patient participation	6 months

Study procedures

	Selection/Inclusion	COVID-19 Screening	Follow up		Survival follow-up ^f
	Day 1		Day 7 to 28	At least every 4 weeks for up to 6 months	
Informed consent	X				
Eligibility criteria verification	X				
Inclusion	X				
Medical History, Blood group, Smoking status, alcohol consumption and vaccination (influenza/BCG) history	X				
Ethnicity	X				
Characteristics of cancer and anti-cancer treatment (clinical stage, location and type of treatment)	X				
Collection of clinical data related to COVID-19 (symptoms, history...)	X		X	X	
Clinical evaluation^a (PS, Physical Exam, T°, height, weight, age, BMI)	X		X ^a	X ^a	
Concomitant medication	X		X	X	
Laboratory assessment^b	X		X	X	
SRAS-Cov 2 testing (rapid serological test and/or RT-PCR and/or digitalPCR and/or ELISA) ^{c,d}		X ^c	X ^d	X ^d	
Blood and saliva sample collection	X				
Satisfaction questionnaire	X				
Medical consultation (phone call or physical)^e			X	X	

a-e. Visits will be held on site (or by phone if the patient is not able to come to the institution) at least every 4 weeks during 6 months.

b. Laboratory assessment includes: Hb, platelet, leukocytes, neutrophils, lymphocytes, LDH, CRP, Procalcitonin, Sodium, potassium, ASAT, ALAT, GGT, PAL, Bilirubin, calcium, protein, albumin. Blood proteins electrophoresis will be performed at inclusion.

c. SRAS-Cov-2 testing: At inclusion, rapid serological test +/- digitalPCR (blood and saliva) +/- RT-PCR test will be performed.

d. Depending on the symptoms and COVID-10 history, patient will be retesting by an ELISA serological test 15 to 28 days following the inclusion for eligible patients. Any retesting performed to the patient during the study will be recorded into the eCRF.

f. Collection (date and status) from patient's medical file gathered in the framework of the patient's standard care. COVID-19 infection/Alive or not/Cause of death will be reordered until 12 month after the last FU.

List of abbreviations

ACE	Angiotensin-converting enzyme
AE	Adverse Event
ALT	Alanine Amino Transférase
ANC	Absolute Neutrophil Count
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
AST	Aspartate Amino Transferase
BRC	Biological Resources Center
CAL	Centre Antoine Lacassagne
CBC	Complete Blood Count
CDC	Center for Disease Control
COVID	coronavirus infectious disease
CPP	Comité de Protection des Personnes
CRA	Clinical Research Associate
CRF	Case Report Form
CRID	Clinical Research and Innovation Delegation
D	Day
DEBDS	Department of Epidemiology, Biostatistics and Health Data
DeIRCI	Delegation of Clinical Research and Innovation
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FU	Follow Up
ICH	International Conference on Harmonization
Ig	Immunoglobulin
NCI CTC-AE	National Cancer Institute Common Toxicity Criteria-Adverse
PAS	Statistical Analysis Plan
PBMC	Peripheral blood mononuclear cells
PS	Performans Status
RNA	Ribonucleic acid
RT-PCR	Reverse-transcription polymerase chain reaction
ddPCR	droplet-digital polymerase chain reaction
SAE	Serious Adverse Event
SARS-Cov-2	Severe acute respiratory syndrome coronavirus 2
SNP	Single nucleotide polymorphism
TMPRSS2	Transmembrane Serine Protease 2
VAS	Visual analog scale

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The Sponsor, the Centre Antoine Lacassagne, declares that the trial entitled «SARS-Cov-2 infection Screening in Cancer Patients » - NEO-SCREEN-COVID will be conducted in compliance with the Protocol, with the French modified Law N°2012-300 dated March 5th, 2012, relative to research involving human persons, with the French Public Health Code, to its decrees and orders currently in force, to Good Clinical Practices (ICH E6 R2).

1 BACKGROUND AND RATIONALE

1.1 Study rationale

Since December 2019, outbreak of COVID-19, caused by a novel Severe Adult Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) has spread rapidly around the world and became a pandemic issue. In the general population, the majority of infected cases will have no to mild symptoms and will recover within few days with symptomatic measures. However, several risk factors have already been identified and may increase the frequency and/or the severity of the disease: older age, as well as medical comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, high blood pressure and cancer (1).

Further retrospective Chinese published cohort studies have identified cancer as a suspected specific risk factor. The prevalence of COVID-19 patients with cancer ranged from 0.79% to 2.2%, which was higher than the prevalence of both overall diagnosed COVID-19 patients reported over the same time period and the incidence of cancer in the Chinese population (2-4). This could be related to the closer medical follow-up of cancer patients.

More concerning, Liang et al. observed that patients with cancer had a higher risk of severe events or death compared to non-cancer patients (38% vs 8%, $p=0.0003$) (4). Zhang et al. reported a first estimate of the probability of dying in infected cancer patients, with a mortality rate (28.6%) (3) that was more than 10 times higher than that reported in all COVID-19 patients in China (2.3%) (1). The recent use of anticancer therapies within 14 days of infection (including chemotherapy, immunotherapy and radiation) was an independent predictor of death or other severe events ($HR>4$) (3). It is hypothesized that patients with cancer may be susceptible to an infection during a viral epidemic owing to their immunocompromised status, especially under cancer treatment.

Conversely, a large retrospective study on 1591 SARS-Cov-2 infected patients admitted in intensive care units in Italy showed that “only” 8% of the patients had a medical history of cancer. Moreover, the mortality rate of the entire cohort was 26% (5), which was quite similar to that observed in the previous described Chinese cancer patient’s cohort (3).

Thus, no firm conclusions can be drawn on the relationship between cancer and COVID-19.

One other concern is the transmission pathway(s) of COVID-19. Zhang et al. reported that a high proportion of patients acquired the infection while already in the hospital for cancer treatment (28.6%), thus implicating the hospital environment as a source of spread of the virus, as patients with cancer are often recalled to the hospital for treatment and monitoring (3).

Moreover, the proportion of asymptomatic infected people is a major question under investigation, to prevent from COVID-19 propagation. Recently, some authors have suggested this proportion to range from 50 to 78% in an unselected population (6, 7). Even in patients that will finally have symptoms, the pre-symptomatic transmission could range from 48 to 77% (8).

There is no clear information about the proportion of asymptomatic COVID-19 cancer patients.

Academic and experts’ recommendations have already proposed to organize and protect specific cancer units without COVID-19 patients if possible, and at least to prioritize cancer treatment during the pandemic in order to limit the number of outpatient visits / inpatient admissions and then reduce or avoid cross infection of COVID-19 (9, 10).

These early and mostly quickly published data are important but some questions remain unanswered. Most of these retrospective studies included small cohorts with a large amount of heterogeneity: various cancer types with different biological behaviors, highly variable disease courses (from months to years), and diverse treatment strategies, that may not be ideally representative of the whole population with cancer. Thus, current evidence remains insufficient to explain a conclusive association between cancer and COVID-19 (11).

Other authors have also highlighted the risk of delaying or modifying cancer treatment. In this COVID-19 outbreak, the major risk for patients with cancer is the inability to receive necessary medical services (both in terms of getting to hospital and provision of normal medical care once there). As cancer patients have been identified “at risk”, some clinical trials are being delayed, enforced quarantine complicates hospital attendance for repeat appointments and continuity in care. Recognition and treatment delays of emergencies or severe adverse effects are possible concerns and might affect their survival (12). There is clear evidence that treatment postponement can adversely affect outcomes for certain indications such as delaying radiotherapy for head and neck cancer patients, or adjuvant chemotherapy for colorectal and breast cancer. Treatment delay may also affect outcomes for many other indications (10), which constitutes part of the so-called “distraction effect” (13).

To avoid the distraction effect, an exhaustive screening should be offered to every patient that requires healthcare in anti-cancer institutions, in order to protect non-infected patients and create specific units for infected ones.

Moreover, to build clinical studies that will bring representative results about the impact of cancer and anti-cancer-treatments on COVID-19 incidence and/or severity, we need to assess large clinical and biological characteristics of cancer patients with (COVID-19+) and without (COVID-19-) SARS-CoV-2 infection.

A special attention should be given to comedications, as non-cancer treatments (like anti-inflammatory, steroids and angiotensin-converting enzyme (ACE) inhibitors) have been identified as predictive of a worse outcome in COVID-19 patients (14, 15).

In the same way, smoking (which is a well-known risk factor involved in many cancer types) is also suspected to drive COVID-19 incidence and severity and could be a confounding factor. Tobacco use significantly increases the gene expression of angiotensin-converting enzyme 2 (ACE2), the binding receptor for SARS-CoV-2, which could explain the elevated susceptibility to COVID-19 in smokers. Furthermore, cigarette smoking is the leading cause of chronic obstructive pulmonary disease, which has been identified as an independent risk factor in severe COVID-19 cases (11).

According to the World Health Organization, the current gold standard for the diagnosis of SARS-CoV-2 infection is based on the real-time fluorescent quantitative PCR (RT-PCR) assay of nasal and pharyngeal swabs (16). Nevertheless, RT-PCR is known to have some limitations: the test is not universally available, turnaround times can be lengthy, and reported sensitivities vary (17).

RT-PCR test does not provide information about immunization, that should be only assessed with a serology test. Serological assays are not routinely used for diagnosis of COVID-19 due to the lack of commercial reagents, but they may be important for understanding the epidemiology of emerging SARS-CoV-2, including the burden and role of asymptomatic infections (18).

Thus, the development of devices for accurate diagnosis of SARS-CoV-2 infections, of fast and safe use, that could be spread in the local hospitals and clinics, would be a major advance for identifying and treating patients. In addition, information about the immunization of fragile people, such as cancer patients, could help to plan a safe strategy for anti-cancer treatment schedule and for the end of quarantine.

1.2 Research hypothesis

In order to assess COVID-19 prevalence in cancer patients, a simple serological test should be easy to perform and accurate to be implemented for a large-scale screening. Serological immunochromatographic approach could be considered as appropriate to this purpose.

In addition, this screening may enhance the knowledge about clinical and biological characteristics of SARS-Cov-2 infected cancer patients.

1.3 Overall Risk/Benefit Assessment

1.3.1 Expected benefit

A screening for SARS-Cov-2 infection in cancer patients could help to define an accurate prevalence of COVID-19 in this population and aggregate data to better understand the relationship between cancer and COVID-19.

Systematic COVID-19 detection may help to effectively organize cancer units to separate COVID-19 (+) and COVID-19 (-) patients, to avoid COVID-19 (-) patients to get infected during their visit for treatment.

The use of a simple and rapid serological test, assessable with a drop of blood from a finger prick could provide a rapid diagnostic orientation and better comfort in use for patients.

1.3.2 Foreseeable risks

Risks for patients are non-significant: the only procedure for this research is blood samples withdraw (up to 36 ml).

1.4 Study population

Patient treated for histologically proven cancer that accepts to undergo a rapid serological test for COVID-19 detection.

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2 STUDY OBJECTIVES

2.1 Primary objective

The primary objective is to evaluate the prevalence of COVID-19 with a rapid serological test in a cohort of consecutive cancer patients that require at least one visit for anti-cancer treatment in a one-day outpatient care units.

2.2 Secondary objectives

1. To evaluate patient's and health care professional's perception about the rapid serological test

2. To evaluate the concordance of COVID-19 positivity by the rapid serological test compared to the gold-standard RT-PCR on nasal swab for eligible patients
3. To evaluate the concordance of COVID-19 positivity by the rapid serological test compared to a classic serological test (ELISA method) from whole blood
4. To evaluate the proportion of the patients who will have at least one positive testing among all the methods applied.
5. To evaluate the number of patients who will get at least one new testing after the rapid serological test has been performed.
6. To compare the clinical and biological characteristics between positive and negative tested COVID-19 patients.
7. To describe the outcome of COVID-19 positive patients
8. To evaluate the impact of COVID-19 rapid serological test on the anti-cancer treatment schedule

2.3 Ancillary analyses (optional)

- Detection of SARS-Cov-2 viral load with ddPCR

Published data, although of a low level of evidence, show a sensitivity of 56 to 83 % for the COVID-19 RT-PCR (19). Interestingly, the droplet-digital PCR (ddPCR) method known to be far more sensitive than conventional RT-PCR, has been shown to be superior for clinical detection of SARS-CoV-2, especially in patients with low viral load, with a limit of detection up to 500 times lower than that of RT-PCR (20, 21). Such a high sensitivity of ddPCR open the possibility to detect SARS-CoV-2 RNA in other biological specimens known to present lower viral loads, such as blood, saliva or feces that could be easily collected and prevent from an unpleasant nasal swab (18).

In order to explore the accuracy of new minimally invasive diagnostic tools, patients will have a blood and saliva sample collection for additional COVID-19 testing by using ddPCR. Also, combined with serological test, this strategy could help to fully understand the evolution of the infection over time.

- Pharmacogenetic study

A specific blood sample, along with a specific informed consent for pharmacogenetics, will be collected in order to further perform analyses of germinal polymorphisms of genes directly involved in the binding and introduction of SARS-Cov-2 within host cells. Cell entry of SARS-Cov-2 depends on the binding of the viral spike (S) protein to ACE2 cellular receptor, as well as to S protein activation by host cell proteases such the serine protease encoded by TMPRSS2 (22). Both ACE2 and TMPRSS2 genes present functional polymorphisms that may affect gene expression. Cao et al conducted a comparative genetic analysis of ACE2 in different populations and found a difference in the distribution and allelic frequency of ACE2 polymorphisms between Asians and Caucasians. They also suggested that these SNPs could modulate ACE2 expression in tissues, which may bring different susceptibility to SARS-CoV-2 (23).

3 STUDY ENDPOINTS

3.1 Primary endpoint

The rate of prevalence will be defined as the ratio of the number of positive patients to the number of patients tested based on the rapid serological test (presence of IgM and/or IgG).

3.2 Secondary endpoints

1. The assessment of the perception of the rapid serological test for patient and health care professional will be measured in terms of (cf Appendix 6):

- Pain: The pain assessment will be performed using a visual analog scale (VAS). The score will be graded between 0 (absence of pain) to 10 (maximum pain)
- Simplicity: The assessment of the satisfaction of care will be carried out using a Likert scale with 4 modalities. The score will be graded between “Poor” to “Very Good”.
- Rapidity: The assessment of the satisfaction of care will be carried out using a Likert scale with 4 modalities. The score will be graded between “Poor” to “Very Good”.
- Satisfaction with care: The assessment of the satisfaction of care will be carried out using a Likert scale with 4 modalities. The score will be graded between “Poor” to “Very Good”.

Pain, simplicity, rapidity and satisfaction with care assessments will be evaluated immediately after the COVID-19 rapid serological test.

2. The concordance rate of COVID-19 positive and COVID-19 negative serological rapid test on whole blood compared to the gold-standard RT-PCR on nasal swab for corresponding patients will be evaluated in term of diagnostic performance (sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratio and area under the ROC curve).

3. The concordance rate of COVID-19 positive and COVID-19 negative serological rapid test on whole blood compared to an ELISA serological test on whole blood, for corresponding patients, will be evaluated in term of diagnostic performance (sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratio and area under the ROC curve).

4. The proportion of COVID-19 positive patients among population of cancer patients will be defined as the rate of patients with at least one positive test among all the methods applied (rapid serological test and/or serological ELISA test and/or RT-PCR and/or ddPCR).

5. The proceedings of additional COVID-19 testing for corresponding patients will be described in terms of:

- Time interval between the tests
- Type and results of the subsequent tests

6. The clinical and biological characteristics between positive and negative COVID-19 will be compared in term of (Cf 7.2):

- Age, gender, BMI, performance status, smoking history, alcohol consumption, medical history and concomitant medication
- Clinical characteristics: clinical stage, location, type of treatment.
- Biological: blood group, hematology, coagulation parameters and serum clinical chemistry.

7. The outcome of COVID-19 positive patients will be described by evaluating the rate of hospital admission for severe COVID-19 form and rate of death.

8. The impact of COVID-19 testing on the anti-cancer treatment schedule will be evaluated in term of:

- number and duration of medical treatment delay
- number of treatment discontinuation

4 STUDY POPULATION

4.1 Overview

Patient treated for histologically proven cancer that accepts to undergo a rapid test for SARS-Cov-2 infection.

4.2 Inclusion criteria

To be eligible for participation in this trial, the subject should fulfill the following criteria:

1. Age $\geq$ 18-years old;
2. Patient treated for histologically proven cancer;
3. Patient that require at least one visit for anti-cancer treatment in a one-day outpatient care units
4. Patients that have previously been tested positive with a RT-PCR test from nasal swab that have been authorized to come to the hospital (after recovery or a 14-days quarantine period, according to local guidelines) can be included.
5. Patient willing and able to provide written informed consent/assent for the trial;
6. Patient affiliated with a health insurance system.

4.3 Exclusion criteria

The subject should not enter into the study if any of the following criteria are fulfilled:

1. Patient not able to give free consent
2. Patient not able to understand the protocol;
3. Patient not able to undergo the COVID-19 test
4. Vulnerable persons as defined by article L1121-5 - 8:

- a. Pregnant women, women in labour or breast-feeding mothers, persons deprived of their freedom by judicial or administrative decision, persons hospitalized without their consent by virtue of articles L. 3212-1 and L. 3213-1 and who are not subject to the provisions of article L. 1121-8
- b. Persons admitted to a social or health facility for reasons other than research
- c. Adults subject to a legal protection order or unable to give their consent.

5 STUDY DESIGN

5.1 Experimental design

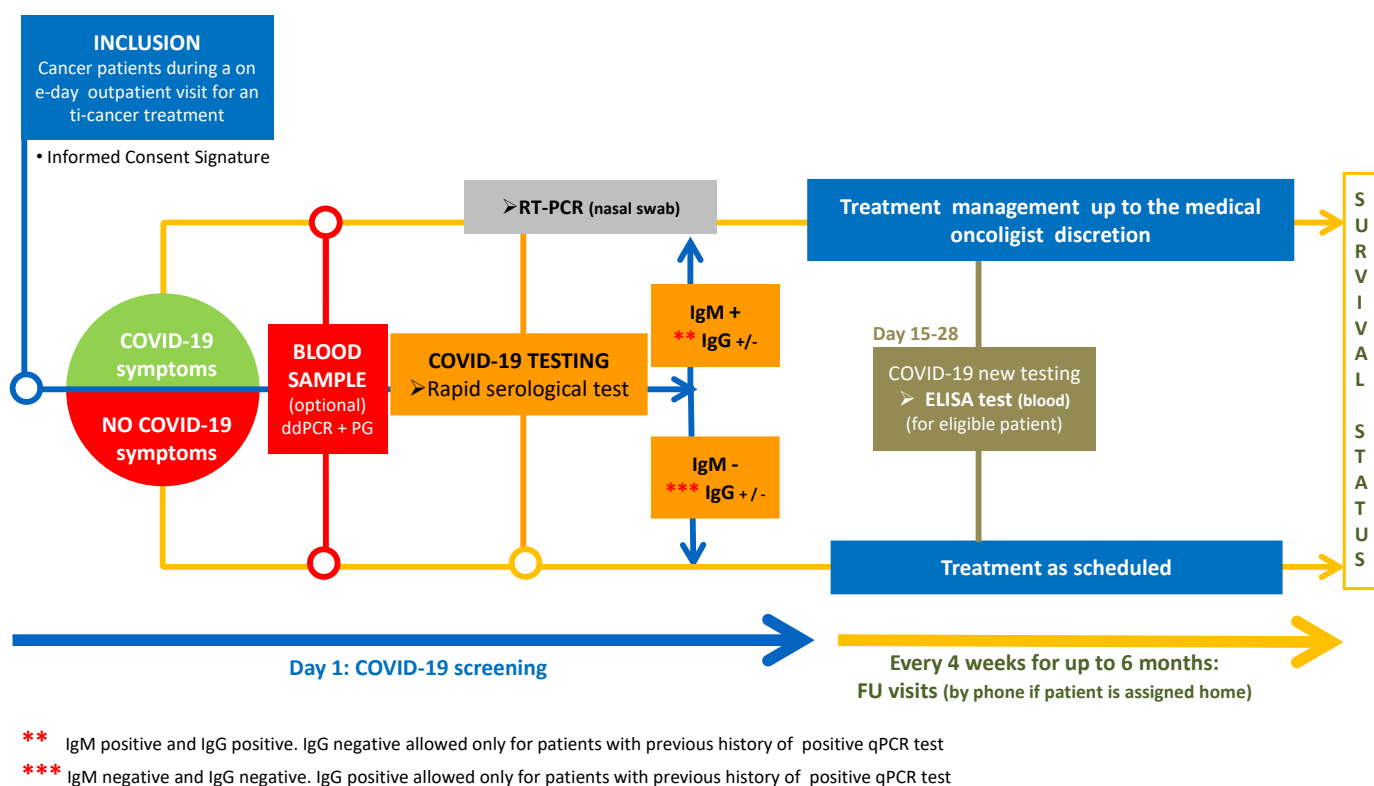
This is a prospective, non-randomized, monocentric study assessing the prevalence of a SARS-Cov-2 infection in cancer patients.

Consecutive cancer patients that require at least one visit for anti-cancer treatment in a one-day outpatient care units will be tested by using a rapid serological test (Servibio, ref C4650) with a drop of blood from a finger prick.

- a. If the patient has suggestive symptoms of COVID-19 at arrival, local procedures will apply for isolation, and RT-PCR testing from nasal swab. The rapid serological test will be done concomitantly.
If the rapid serological test is negative, patient will be proposed to get a new serological testing 15 to 28 days later (ELISA technique).
- b. If the patient has no suggestive symptom of COVID-19 at arrival and no history of previous COVID-19 testing, the rapid test will be done in the one-day care unit, before anti-cancer treatment.
 - I. In case of negative rapid test: the patient will receive anti-cancer treatment as scheduled
 - II. In case of IgG and/or IgM positive rapid test: local procedures will apply for isolation and RT-PCR testing from nasal swab. The decision to receive or not anti-cancer treatment will depend on the medical oncologist decision.
- c. If the patient has no suggestive symptom of COVID-19 at arrival and a history of a previous COVID-19 (+) RT-PCR testing (authorization to come to the hospital after recovery and/or a 14-days quarantine period, according to local guidelines), the rapid test will be done in the one-day care unit, before anti-cancer treatment.
 - I. In case of negative rapid test: the patient will receive anti-cancer treatment as scheduled.
The patient will be proposed to get a new serological testing 15 to 28 days later (ELISA technique).
 - II. In case of IgG positive rapid test: the patient will receive anti-cancer treatment as scheduled.
 - III. In case of IgM positive rapid test: local procedures will apply for isolation and RT-PCR testing from nasal swab. The decision to receive or not anti-cancer treatment will depend on the medical oncologist decision.
The patient will be proposed to get a new serological testing 15 to 28 days later (ELISA technique).

Patients that have previously been tested positive with a RT-PCR test from nasal swab and that have been authorized to come to the hospital (after recovery or a 14-days quarantine period, according to local guidelines) will be able to get a rapid serological test in the study.

Study design:



5.2 Patient recruitment

During a physical examination, the principal investigator or co-investigator will provide potential patients with a verbal description of the study, including explanation regarding the potential risks and benefits of participating in the study.

Potential patients will be asked to read the consent form and to sign and date it once all of their questions have been answered and they voluntarily agree to participate in the study. A copy of the signed informed consent form will be provided to the patient.

It is expected that 500 patients will be recruited into the study during a 6 weeks inclusion period.

5.3 Inclusion procedure

Once the informed consent signed, and if all eligibility criteria are met, the investigator or a member of his team will register directly the patient on the data capture system through the internet network using the following address

<https://www.centreantoinelacassagne-csonline.org/csonline/> (or in case of no access, send the registration request by email at dr-ci-inclusions@nice.unicaner.fr).

For each patient who signed the informed consent a study number will be allocated. Only the first initial of the first name and last name, the month and years of birth of the registered patients will be known.

When the patient's inclusion is completed, an email notification will be sent to the investigating center and the Clinical Research and Innovation Delegation (CRID) team at the sponsor center to notify them of the inclusion of a new patient.

5.4 Description of temporary or permanent discontinuation of the research

The study may be prematurely terminated or suspended if the Sponsor and the principal investigator judge it necessary:

- under the guidance of the Independent Data Monitoring Committee (IDMC)
- If specific stopping rules as defined in part 5.5 are met
- upon the request of the Research Ethics Boards due to:
 - Poor enrolment
 - Inadequate data quality, completeness, and timeliness.

5.5 Description of end of follow-up, withdrawn of trial and latest news

Patients may be withdrawn from the study for any of the following reasons:

- If the patient decides to do so, at any time and irrespective of the reason (consent's withdrawal)
- If the investigator or sponsor judges it necessary for safety, behavioral, administrative reasons, or under exceptional circumstances for reasons to be precisely justified.
- Patient loss to follow-up.
- Death.
- Study termination by Sponsor.

In this case, no further evaluation should be performed and no additional data should be collected.

The investigator must perform every effort to contact patients lost to follow-up. Attempts to contact such patients must be documented in the patient's records. Patients who did not complete the study and for whom no endpoint data are available will be considered as lost to follow-up.

5.6 End of study

The end of study will take place six months after the date of the last follow-up visit of the last participant.

5.6.1 Latest news

Collection (date and status) will be made exclusively using the source data from the patient's medical file gathered in the framework of the patient's standard care. A collection of the following data will be performed until 12 months after the last follow-up, according to the previous described objectives:

- COVID-19 infection (date, type of test performed),
- Alive or not,
- Date and cause of death.

6 STUDY PROCEDURES

6.1 COVID-19 testing

COVID-19 status will be assessed using several tests.

6.1.1 Rapid serological test (antibody test): mandatory

The COVID-19 sign IGM/IGG (Servibio, ref C4650) test is a rapid qualitative immunochromatographic test for the detection of immunoglobulins G (IgG) and M (IgM) in human whole blood (used with a drop of blood from a finger prick). It allows rapid and effective detection of SARS-Cov-2 virus infection in just 10 minutes.

Characteristics of the test provided by the developer are:

- Diagnostic sensitivity: 90%
- Diagnostic specificity: 94%
- Interpretation time: 10-15 minutes

The test will be performed by the investigator or a designated nurse, according to the developer notice (Appendix 5).

6.1.2 Serological ELISA test (antibody test): mandatory for eligible patients

The ELISA test is an immune-enzymatic method to detect the presence of antibody against SARS-Cov-2.

This test will be processed from a whole blood sample (6ml on a dry tube) with a specific assay for eligible patients.

6.1.3 SARS-Cov-2 RT-PCR test from nasal swab (viral load): for eligible patients (suggestive symptoms) according to local guidelines.

The PCR test is currently the gold-standard for COVID-19 diagnosis.

Sample of a mixture of mucuous and saliva will be collected from the upper respiratory tract using a nasopharyngeal swab technique. It takes about 10 min to be collected. After extraction, viral RNA will be tested for SARS-CoV-2 using a real-time reverse-transcription polymerase chain reaction (RT-PCR) assay.

The testing process can take up to 6 hours to get the result.

The test will be performed according to local guidelines at the discretion of the investigator.

6.2 Creation of a dedicated biobank

Collecting and storing samples of blood from patients for research purposes are necessary to support future scientific research, as well as identifying characteristics that may predict, among various parameters a higher frequency and/or severity of COVID-19.

After patients have signed the informed consent form, 36 ml peripheral blood will be collected at time of inclusion as described below:

- 18 ml on EDTA tubes
- 9 ml on heparinized tube
- 9 ml on dry tube.

Out of these 36 ml of blood:

- 9 ml (EDTA tube) will be dedicated to SARS-Cov-2 ddPCR testing
- 4 ml (EDTA tube) will be stored for the pharmacogenetics study (ACE2 and TMPRSS2 polymorphisms).

These tubes will immediately be sent to the Biological Resources Center (CRB) of the Centre Antoine Lacassagne (CRB-CAL) to be recorded in the MBioLIMS® sample management software and then processed (under adequate safety conditions) and stored for additional ancillary analyses.

In accordance with the revised 2004 Bioethics law now set up the conservation and use of these samples, in particular by informing the patient and by seeking his consent or by exercising his right of opposition according to the terms of obtaining samples. This law also provides that at the end of the biological study, without opposition from the patient and if the samples have not been fully used, they may be the subject of scientific research (s) later.

6.3 Ancillary analyses

6.3.1 SARS-Cov-2ddPCR test from saliva and blood (viral load)

The development of other SARS-Cov-2 detection techniques, such as the very sensitive droplet-digital PCR (ddPCR) test for identifying viral RNA, and its application not only to nasopharyngeal swabs, but also to biological samples with lower viral loads (like blood or saliva) could provide very useful additional diagnostic tools.

The ddPCR test will be developed in the Oncopharmacology laboratory of the Centre Antoine Lacassagne, according to current recommendations of the American Center for Disease Control (CDC) using SARS-Cov-2 N1 and N2 target genes. To this end, we will use the 2019-nCoV CDC ddPCR Triplex Probe Assay kit (ref dEXD28563542 BioRad, currently available) designed to specifically detect N1 and N2 target genes.

For these patients, SARS-Cov-2 ddPCR testing will be performed:

- On viral RNA extract from a saliva sample
- On viral RNA extract from whole blood sample.

Saliva samples will be collected using specific collection devices suitable for stabilization and transportation of viral RNA from saliva (ref RE-100 Oragene-RNA, DNA Genotek).

6.3.2 Pharmacogenetics study

Analyses of germinal polymorphisms of genes directly involved in the binding and introduction of SARS-Cov2 within host cells will be investigated. Cell entry of SARS-Cov-2 depends on the binding of the viral spike (S) protein to ACE2 cellular receptor, as well as to S protein activation by host cell proteases such the serine protease encoded by TMPRSS2 (22). Both ACE2 and TMPRSS2 genes present functional polymorphisms that may affect gene expression. Cao et al conducted a comparative genetic analysis of ACE2 in different populations and found a difference in the distribution and allelic frequency of ACE2 polymorphisms between Asians and Caucasians. They also suggested that these SNPs could modulate ACE2 expression in tissues, which may bring different susceptibility to SARS-CoV-2.

Analyses of ACE2 and TMPRSS2 gene polymorphisms will be performed by means of high throughput genotyping on Mass Array (Agena); alternatively, the whole coding regions will be sequenced by NGS.

7 SCHEDULE OF ASSESSMENTS AND STUDY VISITS

7.1 Duration of patient participation

The duration of study participation will be 6 months from the date of consent signature, including:

- Inclusion on day 1 (day of consent signature)
- SARS-Cov-2 screening (day 1)
- Follow-up period (from day 1 until 6 months, at least every 1 to 4 weeks)

A flow chart (see appendix 1) provides a summary of required study evaluations.

7.2 Selection/inclusion visit (Day 1)

During a consultation with the investigator when patient attends for treatment at the one-day care unit, information concerning the organization and the aims of the investigation will be provided to the subject (the information note should be read and given to the patient).

The patient could take the necessary time to consider the risk and benefits associated with his participation in the study.

In compliance with article 1121.11, before any signing of the free and informed consent by patients and before any procedure forming part of the study, patients must undergo a prior medical examination adapted to the research.

For patients who signed their participation consent form and meet all eligibility criteria for the trial, the following assessments will be performed:

- Clinical evaluation with Performance Status (PS), physical exam, vital signs (temperature, weight, height, age, BMI)
- Collection of clinical data regarding viral symptoms, history of a previous COVID-19 testing (date and type of testing, results) and possible contact with SARS-Cov-2 infected people.
- Medical history of relevant severe disease
- Previous vaccination (influenza / BCG)
- Characteristics of cancer and anti-cancer treatment: clinical stage, location, type of treatment.
- Smoking status, alcohol consumption
- Concomitant medication, with specific attention to corticosteroids, non-steroidal anti-inflammatory drugs, aspirin, immunosuppressive agents, RAAS inhibitors, hydroxychloroquine and/or macrolides within 15 days before inclusion,
- Blood group
- Laboratory assessment
 - Hemoglobin, platelet, leukocytes, neutrophils, lymphocytes
 - LDH, CRP, Procalcitonin,
 - Sodium, potassium, ASAT, ALAT, GGT, PAL,
 - Bilirubin, calcium, protein, albumin,
 - Blood proteins electrophoresis
- Questionnaire for satisfaction evaluation
- SRAS-Cov-2 test: rapid serological test (and RT-PCR test according to local guidelines).
- Blood and saliva sample collection for ddPCR testing and pharmacogenetics
- Ethnicity (for pharmacogenetic ancillary study)

7.3 Patient management

7.3.1 Visit 1/SARS-Cov-2 screening (day 1)

- a. If the patient has suggestive symptoms of COVID-19 at arrival, local procedures will apply for isolation, and RT-PCR testing from nasal swab. The rapid serological test will be done concomitantly.

If the rapid serological test is negative, patient will be proposed to get a new serological testing 15 to 28 days later (ELISA technique).

- b. If the patient has no suggestive symptom of COVID-19 at arrival and no history of previous COVID-19 testing, the rapid test will be done in the one-day care unit, before anti-cancer treatment.
 - I. In case of negative rapid test: the patient will receive anti-cancer treatment as scheduled
 - II. In case of IgG and/or IgM positive rapid test: local procedures will apply for isolation and RT-PCR testing from nasal swab. The decision to receive or not anti-cancer treatment will depend on the medical oncologist decision.
- c. If the patient has no suggestive symptom of COVID-19 at arrival and a history of a previous COVID-19 (+) RT-PCR testing (authorization to come to the hospital after recovery and/or a 14-days quarantine period, according to local guidelines), the rapid test will be done in the one-day care unit, before anti-cancer treatment.
 - I. In case of negative rapid test: the patient will receive anti-cancer treatment as scheduled.
The patient will be proposed to get a new serological testing 15 to 28 days later (ELISA technique).
 - II. In case of IgG positive rapid test: the patient will receive anti-cancer treatment as scheduled.
 - III. In case of IgM positive rapid test: local procedures will apply for isolation and RT-PCR testing from nasal swab. The decision to receive or not anti-cancer treatment will depend on the medical oncologist decision.
The patient will be proposed to get a new serological testing 15 to 28 days later (ELISA technique).

7.3.2 Visit 2 (day 7 to 28)

When COVID-19 negative patients come back to the one-day care unit for the next treatment administration (between d7 and d28), the following procedures will be performed:

- Clinical evaluation with Performance Status (PS), physical exam, vital signs (temperature, weight)
- Collection of clinical data regarding viral symptoms and possible contact with SARS-Cov-2 infected people.
- Concomitant medication with specific attention to corticosteroids, non-steroidal anti-inflammatory drugs, aspirin, immunosuppressive agents, RAAS inhibitors, hydroxychloroquine and/or macrolides uptake
- Information about cancer treatment
- Laboratory test
 - Hemoglobin, platelet, leukocytes, neutrophils, lymphocytes
 - LDH, CRP, Procalcitonin,
 - sodium, potassium, ASAT, ALAT, GGT, PAL, TP, TCA,
 - Bilirubin, calcium, protein, albumin,
- Serological ELISA test for eligible patients within 15 to 28 days after inclusion,
- Patients will be able to get a new COVID-19 test according to local guidelines. The date, type and results of every additional testing will be recorded

Patients that have been tested COVID-19 positive at one of the initial tests will be advised to stay at home for at least 14 days and will be contacted by phone.

The followings items will be discussed and recorded:

- Clinical assessment
- Collection of clinical data regarding viral symptoms

- Concomitant medication with specific attention to corticosteroids, non-steroidal anti-inflammatory drugs, aspirin, immunosuppressive agents, RAAS inhibitors, hydroxychloroquine and/or macrolides uptake,
- Information about cancer treatment
- Laboratory test
 - Hemoglobin, platelet, leukocytes, neutrophils, lymphocytes
 - LDH, CRP, Procalcitonin,
 - sodium, potassium, ASAT, ALAT, GGT, PAL, TP, TCA,
 - Bilirubin, calcium, protein, albumin,

Patients with a positive test (whatever the technique) will ideally get a new COVID-19 test after 15 to 28 days according to local guidelines.

The date, type and results of any additional testing will be recorded.

If a patient has been admitted to the hospital, the COVID-19 treatment and outcome will be recorded.

7.4 Follow-up visits

Visits will be held on site (or by phone if the patient is not able to come to the institution) at least every 4 weeks during 6 months.

The following procedures will be performed:

- Clinical evaluation with Performance Status (PS), physical exam, vital signs (temperature, weight)
- Collection of clinical data regarding viral symptoms and possible contact with SARS-Cov-2 infected people.
- Concomitant medication with specific attention to corticosteroids, non-steroidal anti-inflammatory drugs, aspirin, immunosuppressive agents, RAAS inhibitors, hydroxychloroquine and/or macrolides uptake,
- Information about cancer treatment
- Laboratory test
 - Hemoglobin, platelet, leukocytes, neutrophils, lymphocytes
 - LDH, CRP, Procalcitonin,
 - sodium, potassium, ASAT, ALAT, GGT, PAL, TP, TCA,
 - Bilirubin, calcium, protein, albumin,
- The date, type and results of any additional COVID-19 testing will be recorded.

7.5 End of study

The end of study will take place six months after the date of the last follow-up visit of the last participant.

7.5.1 Latest news

Collection (date and status) will be made exclusively using the source data from the patient's medical file gathered in the framework of the patient's standard care. A collection of the following data will be performed until 12 months after the last follow-up, according to the previous described objectives:

- COVID-19 infection (date, test performed),
- Alive or not,
- Date and cause of death.

8 STATISTICAL ANALYSIS

All statistical analyses will be performed at alpha risk=5% in bilateral hypothesis by the statistician of the Center Antoine Lacassagne using R.3.6.1 and SAS 9.4 software for windows.

8.1 Determination of sample size

The primary objective is to evaluate the prevalence of COVID-19 by using a rapid serological test in a cohort of consecutive cancer patients that require at least one visit for anti-cancer treatment in a one-day outpatient care units.

A recently analysis conducted at the Antoine Lacassagne Center between 16 March 2020 and 10 April 2020 in a population of 300 persons (patients and health care professionals) revealed a rate of 10% of people diagnosed positive at COVID-19 using a routine RT-PCR test (Publication in progress). These first results are consistent with the results published by Kissler et al. in April 2020 (24).

The number of subjects is estimated on the basis of a confidence interval for the rate of patients diagnosed with COVID-19.

Considering the following hypotheses:

- Confidence interval = 95%
- Confidence interval width = 4%
- Proportion, $\pi_{\text{Plan}} = 10\%$

Considering about 5% of non-assessable tests results or patients withdrawing their consent, a total of 500 patients assessable are necessary to satisfy these assumptions.

Calculation carried out using the David Sample software "Sample Size Software" (Single Proportion - Large Population)

8.2 Statistical analysis plan

Demographics, baseline disease characteristics and baseline laboratory results will be summarized using descriptive statistics for all treated patients.

Qualitative data will be presented as absolute frequency, relative frequency, confidence interval 95 % and percentage of missing data. These data will be compared according to the Chi2 test or Fisher exact test when necessary. A multivariate analysis could be performed using a logistic regression model with Odds ratio corresponding to the studied variables.

Quantitative data will be presented as frequency histogram, median, range, mean, standard deviation and percentage of missing data. These quantitative data will be compared according to Student T test or Wilcoxon test when needed. We will use the Pearson (parametric case) or Spearman (non-parametric case) coefficient to measure the dependence between two quantitative variables. A multivariate analysis could be performed using linear regression methods.

The characteristics of the diagnostic variables will be assessed using conventional measures: True Positive (VP), False Positive (FP), True Negative (VN), False Negative (FN), Positive Predictive Value (VPP), Negative Predictive Value (VPN), Sensitivity, Specificity, ROC Curve (Receiver Operating Characteristic) and calculation of the ROC Under-Curve Area (ASC) with its 95% confidence interval.

8.3 Interim analysis

No interim analysis is planned as part of the Initial Statistical Analysis Plan. Continuous monitoring of safety and efficacy data will be carried out throughout the study.

8.4 Method for missing, unused or invalid data

The missing data will be described precisely and an analysis of the probable cause of each missing data will be performed. In some cases, these data can be extrapolated by simple methods (LOCF, average, median) or more complex if necessary (multiple imputation).

8.5 Choice of subjects to be included in the analysis

Two populations of analyzes will be identified

- Intent-To-Treat Efficacy (ITT): The ITT population corresponds to all the patients included in the study
- The FAS population corresponds to all patients included in the study, excluding patients with a major violation of the protocol (defined as at least 1 inclusion and/or non-inclusion criteria not met).

A flow chart representing the number of eligible patients, the number of patients included and the number of patients analysed will be presented.

A description of the patients who left the study and the reason for leaving the study will be presented.

8.6 Management of changes made to the initial statistical analysis plan

All changes to the initial statistical analysis plan (SAP) must be described in detail, justified and discussed in an updated version of the SAP. Such changes may also include exploratory additional analyses not originally scheduled.

After verification of the database, the data will be exported by the Data Manager to the biostatistician.

9 HANDLING OF ADVERSE EVENTS

9.1 Adverse Event definition

In accordance with the International Conference of Harmonisation (ICH), an AE is any untoward medical occurrence in a patient participating in a clinical research. The event does not necessarily have to have a causal relationship with this treatment to be known as an AE. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the medical device and/or medicinal (investigational) product, whether or not considered related to them. Pre-existing conditions which worsen during a study are to be reported as AEs.

In regard with the nature of the study objectives, diagnostic performance and prevalence, all AE related to the cancer treatment will not be reported.

All adverse event occurring and related to the study procedure should be registered in the eCRF from the date of informed consent signature to 30 days after the last follow up visit.

An abnormal laboratory value will not be assessed as an AE unless that value is considered by the investigator of clinically relevant in the context of this study.

It is considered as serious adverse event (SAE), any event that:

- results in **death**,
- is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe),
- requires in patient **hospitalization or prolongation of existing hospitalization** (see clarification in the paragraph below on planned hospitalizations),
- results in **persistent or significant disability / incapacity** (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions),
- induces a **congenital anomaly / birth defect or abortion**,
- is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), whether pathogenic or non-pathogenic, is considered an infectious agent.

The terms invalidity and incapacity correspond to any clinically relevant physical or psychic handicap, transient or permanent, with impacts on the physical condition/activity and/or the quality of life of the patient.

Any clinical event or laboratory result that is considered as serious by the investigator and that does not correspond to any of the serious adverse event criteria listed above is considered as medically relevant. That which can put the patient at risk and/or require a medical intervention to prevent the development of any serious adverse event previously cited (e.g.: overdosing, a second cancer, pregnancy in partners of patients and new events can be considered medically relevant).

The following are not considered to be serious adverse events:

- Hospitalization < 24h
- Hospitalization already scheduled before study entry and/or which is part of the protocol (biopsy, chemotherapy, etc)
- Progression of the cancer or disease under study is not reported as a SAE unless it is considered to be procedure-related by the investigator,
- Death related to the progression that occurs after the notification period as defined in the protocol.

A distinction is made between the expected and unexpected serious adverse event

Pursuant to Article L. 1123-10 Code of Public Health the notion of "new safety issue" is introduced and translated as:

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. A new safety issue could lead the sponsor and the investigator to take urgent safety appropriate measures.

9.2 Definition of expected serious adverse reaction

An expected serious adverse reaction is an event already mentioned in the most recently version of in the most recent version of the technical file for the study procedure.

9.3 Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is an event that is not mentioned in the technical file in its nature, intensity or evolution or frequency.

9.4 Intensity criterion

The intensity criterion must not be confused with the seriousness criterion that is utilized to define the obligations of declaration.

Severity criterion: The criterion for severity (intensity) must not be confused with the seriousness criterion which is the guide for defining the reporting requirements.

The severity of adverse events will be estimated according to the extract from the CTC-AE version 5.0 classification (appendix 2). The severity of adverse events not listed in this classification will be assessed according to the following qualifiers:

- Mild (grade 1): does not affect the patient's normal daily activity
- Moderate (grade 2): disrupts the patient's normal daily activity
- Severe (grade 3): prevents the patient from carrying out his normal daily activity
- Very severe (grade 4): requires resuscitation / is life-threatening
- Death (grade 5)

9.5 Handling of serious adverse events

The investigator must immediately inform, without delay, as soon as he is aware of it, the CRID pharmacovigilance unit by email at drci-sae@nice.unicanter.fr of any SAE, whether or not related to the research, which occurs during the study or in the 30days following the last administration of the study procedure.

All delayed serious adverse events (that occur more than 30 days after the end of the study or after the designated follow-up period) that are reasonably considered to be linked to the ongoing research must be declared without delay. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Notification must be carried without delay after the sponsor-investigator's observation or awareness of the event, by email to the CRID Pharmacovigilance unit: drci-sae@nice.unicanter.fr using the form, located in the investigator file, completed as precisely as possible, dated and signed by the investigator.

For each event, the investigator will note:

- The event's description, as clearly as possible and in accordance with the medical terminology,
- The intensity,
- The date of the event's beginning and end,
- The measures undertaken and whether or not the use of a correcting treatment was necessary,

- If the trial's procedure was interrupted,
- Its evolution will be followed until remission or recovery of the prior state or stabilization of possible sequels,
- The causality between the observed event a constraint linked to the research protocol (e.g. a period without treatment, complementary examinations requested within the framework of the research protocol, etc...),
- The causality relating to the procedure(s) used in the trial, the treated pathology, another type of pathology, or another treatment,
- Current and previous concomitant treatments (other than those used to treat the event),
- Previous diseases and medical histories,
- Complementary examinations (blood test, biopsy, etc.),
- The concomitant treatments used to treat the event.

The investigator must also attach a serious adverse event report every time it is applicable:

- A copy of the hospitalization report or of the prolongation of hospitalization,
- A copy of the autopsy report,
- A copy of the results of all complementary examinations, including the relevant negative results and providing the normal laboratory values,
- Any other document that is relevant in the investigator's opinion.

All these documents must be anonymised.

Additional information can be requested (by fax, email, telephone or visit) by the monitor and/or the CRID Vigilance department using a data clarification form.

The collection of adverse events will be done through the Electronic Case Report Form (eCRF). The investigators will be asked to collect the data and in particular the information related to the tolerance on a continuous basis on the eCRF, this will allow the promoter to follow in real time the declared adverse events.

Before the activation of each participating center, training in protocol, safety and specific procedures will be carried out with the investigators and their teams during the site initiation visit of the study.

The obligations described in this section of the protocol, in terms of the serious adverse event report (SAE) by the investigators, will be specified.

The description of the expected adverse event and the adverse events reporting system (serious or non-serious) will also be discussed.

All the SAEs will be evaluated by the CRID Pharmacovigilance unit of the Centre Antoine Lacassagne, including the verification of the severity criterion, the causality and the unexpectedness and will be entered into a dedicated vigilance database.

Any new security information will be sent to investigators via e-mail or newsletters.

In addition to the ongoing safety assessment, a project meeting will be organized every 3 months with the Coordinator Investigator to discuss the progress of the test and verify all information received since the previous meeting and to confirm continuity of study under the same conditions.

9.6 Sponsor's responsibilities

For all SAEs, the sponsor evaluates the causality relationship with the research protocol, concomitant treatments and / or any other cause, as well as the expected / unexpected nature of any serious adverse reaction.

The sponsor will have to report all SUSARs to the ANSM according to the regulatory deadlines,

without delay for the SUSARs having caused a death or threatening the vital prognosis and within 15 days for the other SUSARs. Any follow-up information must be sent within 8 days for all SUSARs.

The sponsor will have to inform the ANSM of any SAE or new fact that has the potential to modify the benefit and risk ratio of the study.

The sponsor will be responsible for reporting the annual safety report (DSUR -Development Safety Update Report) of the study to the ANSM and to the Ethics Committee (EC).

The sponsor will be responsible to alert the principal investigator in case of identification of a new safety issue and will propose emergency measures to be applied.

The sponsor will be responsible for declaring any new safety issue, as well as the emergency measures to be applied, without delay to the ANSM and the Concerned EC. All relevant monitoring information must be declared within an additional 8 days.

The sponsor must inform the principal investigators of the study of any new safety information.

9.7 SAE follow-up

The investigator is responsible for appropriate medical follow-up of patients until the resolution or stabilization of the event or until the death of the patient. This can sometimes mean that the follow-up continues after the patient has left the trial.

The investigator shall send additional information to the CRID Pharmacovigilance unit using an SAE declaration form (by ticking the Follow-up n°X box to specify that it is a follow-up and not an initial report) as soon as he is aware of the event. He shall also submit the last follow-up at the resolution or stabilization of the SAE.

The investigator must keep the documents concerning the suspected serious adverse event in order to supplement the information previously submitted if necessary.

The investigator must respond to requests for additional information from the CRID Vigilance department in order to document the initial observation.

10 QUALITY ASSURANCE

10.1 The Case Report Form

In compliance with the standard *modus operandi* implemented at the Centre Antoine Lacassagne, the Case Report Form for this trial was only devised once the protocol had received the approval of all the persons who had participated in the drafting of this text.

Participation of the DEBDS data manager at Centre Antoine Lacassagne has been essential in order to:

- create the digital case report form, which will be regarded as the Data Base, on the Ennov Clinical developed by the ENNOV group;
- ensure quality control and the export of patient-related data.

Traceability of accesses and data modifications is ensured by the Ennov Clinical software by means of an audit trail. Access is obtained exclusively via identifiers and passwords specific to each user, who will enjoy particular rights according to his/her role.

The Ennov Clinical software developed by the ENNOV company meets the stringent requirements laid down by the Food and Drug Administration (FDA) guidelines, chapter 21 CFR Part 11.

The data base will be hosted by the ENNOV data centers on secured servers (two back-up sites on geographically distinct sites). Before the data are processed by the Biostatistician at CAL, the data manager will proceed to check the data by means of coherence tests (queries) and will ensure the resolution of any detected incoherencies.

All data will be anonymized and will be handled in the strictest confidence.

10.2 Trial monitoring

In order to guarantee the authenticity and credibility of the data in compliance with Good Clinical Practices (ICH E6R2), the Sponsor will install a quality assurance system.

In accordance with the monitoring plan of the study, the Clinical Research Associate will visit each of the study center during the study:

- on initiation of the trial
- once or several times in the course of the study depending on the inclusion rate;
- at the end of the study.

Remote monitoring will be also performed according to the monitoring plan.

The aims of these visits are:

- to check on observance of the protocol, of the BCP, and of current laws and regulations,
- to verify the consent and eligibility of each of the patients taking part in the research,
- to verify the concordance and coherence of the data in the Case Report Form with the source documents,
- to ensure, where necessary, that the persons likely to participate in the research are not already part of a separate research program which might prevent them from concluding the trial for which they are candidates. The monitor will also ensure that the patients have not participated in any research program for which an exclusion period is currently required.
- to check the declarations of Severe Undesirable Events,

The Clinical Research Associate will have access, on receiving the consent of the subjects concerned, to the individual data strictly required by these control measures. The data will be subject to professional secrecy.

All visits will be followed by a monitoring report (traceability of the visits).

10.3 Audit and inspection

The investigator should understand that source document for this study should be made available to appropriately qualified personal from the Centre Antoine Lacassagne Development Quality Assurance Unit or its designees or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

The investigators agree to comply with the demands of the Sponsor and of the Competent Authority regarding the auditing and inspection of the study for at least 10 years following completion of the study.

An audit can be conducted at any stage of the study, from the development of the protocol to the publication of the results and the filing of the data or the products used during the study.

10.4 Data processing and research-related documents

Data processing will be processed under the responsibility of the Data Protection Officer of Centre Antoine Lacassagne. He delegates the data processing to the Doctor Emmanuel CHAMOREY, Biostatistician at the Centre Antoine Lacassagne. The data will remain the property of the Centre Antoine Lacassagne, the Sponsor of the research.

According to the revised version of the Informatics and Liberty law of June 20th, 2018 and its application decrees, and to the deliberations of the CNIL 2018-153 dated, May 3rd 2018 and the regulation EU 2016/679 of the European parliament on General Data Protection Regulation (GDPR) enforced on May 25, 2018, the Centre Antoine Lacassagne has committed to follow the reference methodology MR001 issued by the French National Commission on Informatics and Liberty.

If the data required for biomedical research within the centers undergo data processing or are managed by computer-based systems, each Center:

- a) will ensure and document the compliance of the computer systems used in the research with requirements it laid down in terms of integrity, accuracy and reliability of the data, and adherence to the anticipated performances (i.e., validation)
- b) will implement and ensure follow-up of the standardized operative procedures regarding the usage of these systems
- c) will ensure that the design of these systems will allow the data to be modified in such a way that the modifications are documented and that no acquired data are deleted (i.e., safeguard a trace of the data audit and of the modifications)
- d) implement and ensure the follow-up of a security system to prevent any unauthorized access to the data
- e) ensure that processing of data of a personal nature undertaken in the framework of the research is performed in the conditions stipulated by law N° 78-17 dated January 6 1978 regarding informatics, files and liberty modified by law N° 2004-801 dated August 6 2004 and by the regulatory texts issued for its application.

If the data are modified during processing, it must always remain possible to perform a comparison between the original data and observations and the data following modification.

The system used to identify the subjects consenting to the research must be free of all ambiguity and must permit identification of all data gathered for each of these subjects, while preserving the confidentiality of the information relative to the subjects and in accordance with modified law N°78-17 and the General Data Protection Regulation (GDPR) enforced on May 25, 2018.

All documentation relative to the trial (protocol, consents, clinical reports, requests for correction; investigator file, etc.) as well as the original documents (laboratory results, X-rays, accounts of consultation, clinical examination reports, etc.) is considered to be confidential and will be archived in a safe place.

For each center, and in virtue of the decree of November 8th 2006, the Chief Investigator will keep the data together with a list identifying patients for a minimum period of 15 years following the end of the study. After this period, the center will not destroy the said documentation until the written agreement of the Sponsor has been obtained.

11 ETHICAL AND REGULATORY ISSUES

- The clinical trial should be conducted in compliance with:
- The Good Clinical Practices recommended by the International Conference on Harmonization (ICH E6 R2, on 2017, June 14th),
- The modified Law Number 2012-300 dated March 5th, 2012 relative to research involving human beings in the French Public Health Code, to its decrees and orders currently in force
- The Law “Informatique et liberté” Number 78-17 dated January 6th, 1978, modified by law Number 2018-493 dated June 20th 2018 relative to the protection of physical persons regarding the processing of personal data,
- the General Data Protection Regulation (GDPR) enforced on May 25, 2018.

11.1 The Ethics Committee and the Competent Authority

Before conducting biomedical research on human beings, the Sponsor is obliged to submit the research program to:

- The Ethics Committee which delivered a favourable opinion on (date),
- The Competent Authority for information on (date).

11.2 Information and participant consent

In compliance with articles L1122-1 and 2 of the French Code of Public Health, prior to the conduct of biomedical research on a human being, free, informed, written consent of that person must be obtained after he/she has been given full information by the Investigator during a consultation and after a sufficient period of reflection.

The information document and the consent form intended for the patient will comprise all the items defined by the modified Public Health law Number 2012-300 dated March 5th, 2012 relative to research involving the human person, modified by decree Number 2016-800 dated June 16th, 2016. The two documents have been drafted in simple terms understandable to the patient. Both documents (information leaflet and consent form) will be kept in the Investigator file held at the Investigating Center, and two copies of each will be delivered to the patient.

The consent form must be dated and signed personally by the participant in the research and the Investigator.

Once the patient has been properly informed and has signed both copies, along with the Investigator, the original will be kept in the Investigator file held at the Investigation Center and the duplicate will be handed to the patient by the Investigator.

The patient will be free to agree to, or refuse, conservation of his/her biological samples.

11.3 Sponsor's responsibilities

In accordance with law 2004/806 in the French Code of Public Health, the Sponsor of the clinical trial is the “natural or legal person instigating the research, and which will ensure the management of the research and verify that the necessary funding will be forthcoming”.

The Sponsor's main responsibilities are as follows:

- To obtain a specific study insurance,
- To register the trial on the European data base and to obtain an a Study number,
- To obtain clinical trial authorization for the initial project and substantial possible modifications from the Ethics Committee and the Competent Authority; opinion from the Ethics Committee,
- To keep informed the directors and investigators in the different investigating centers,
- To declare the start and end of the trial to the Competent Authority,
- To declare to the competent authority all suspected unexpected adverse events relative to one of the investigational treatments and to transmit this information to the Ethics Committee from the beginning to the end of the trial,
- To alert the ANSM, the Ethics Committee and the principal investigators, in case of new safety issues and to transmit the urgent safety appropriate measures to be applied,
- To draft the annual safety report containing all the adverse events occurring during the trial and send it to the competent authority and to the Ethics Committee ,
- To draft the final trial report,
- To inform the Competent Authority, the Ethics Committee and the participants in the research of the trial results,
- To archive all documents of the trial, in a suitable place, for a minimum period of 15 years following the end of the research.

11.4 Investigators' responsibilities

The principal investigator in each center involved commits to conduct the clinical trial in compliance with the protocol approved by the Ethics Committee and by the Competent Authority and with existing regulations, and notably the modified law Number 2012-300 dated March 5th, 2012 relative to research involving the human person, modified by decree Number 2016-800 dated June 16th, 2016 and the Good Clinical Practices (ICH E6 R2).

The Investigator will make no change in the protocol without the written permission of the Sponsor and without obtaining authorization regarding the proposed modifications from the Ethics Committee and the Competent Authority.

The Principal Investigator will be responsible for:

- Informing the Sponsor of his/her curriculum vitae, and of that of his/her co-researchers,
- Identifying the members of his/her team involved in the trial and to define the responsibilities of each (CRA, radiology manipulator, etc.),
- Ensuring recruitment of patients in the manner he/she committed to,

Each investigator will be responsible for:

- For observing the confidentiality of the trial,
- For gathering the patient's informed consent regarding the research, personally dated and signed by the patient, before any specific trial selection procedure is performed,
- To monitor the patients included as specified in this protocol,
- To regularly update the Case Report Form for each of the patients included in the trial
- To make available the patients' source documents to the CRA mandated by the Sponsor to enable the CRA to compare these data with those committed to the clinical case report and to establish their validity,
- To correct, date and sign any corrections made at the request of the CRA mandated by the Sponsor for each of the included patients,
- To declare, as soon as he/she becomes aware of it, any unexpected or expected adverse event to the trial Sponsor by completing the adverse event declaration form,
- To agree to regular visits either from the CRA mandated by the Sponsor or by possible auditors designated by the Sponsor or by inspectors appointed by the competent authorities,

All documentation relative to the trial (protocol, consents, clinical reports, investigator files, etc.), along with the source file for each participant in the trial, will be considered confidential and must be kept in a safe place,

The principal investigator will safeguard the data as well as a list identifying the patients for a period of at least 15 years following the end of the study.

12 CONFIDENTIALITY AND PROPERTY RIGHTS

All information communicated or obtained and all data and results produced during the conduct of the trial legally belong to the Centre Antoine Lacassagne, which will enjoy free usage of the same. The trial cannot be the topic of any written or oral presentation other than with the Sponsor's agreement.

The Investigator commits him/herself, and all individuals involved in the conduct of the trial, to guarantee the confidentiality of all the information supplied by the Centre Antoine Lacassagne until publication of the findings of the trial. This confidentiality requirement will not apply to information supplied by the Investigator to patients in the framework of their participation in the trial nor to previously-published information.

The Investigator commits to not publish, divulge or use, in whatever form, directly or indirectly, the scientific or technical information relative to the trial.

Nevertheless, in accordance with article R 5121-13 of the French Code of Public Health, the center and the Investigator will be authorized to convey information relative to the trial to:

- The Minister with responsibility for health,
- The Public Health Medical Inspectors,
- The Public Health Pharmacy Inspectors. The General Manager and the Inspectors of the ANSM.

13 PUBLICATION OF STUDY RESULTS

All information and results derived from this trial will be considered confidential, at least until such time as appropriate analysis and verification have been concluded by the Sponsor, the coordinating investigators and the trial statistician.

All publications, abstracts or presentations including results from the trial must be submitted for approval to the Sponsor, the coordinating investigators and the trial statistician.

Authorship and Rank will be subject to a prior agreement between the author and a validation by the investigator coordinator. Authorship and Rank must be specified in every statistical report on the study data.

Any formal publication of the study in which input of Centre Antoine Lacassagne personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Centre Antoine Lacassagne personnel. Authorship will be determined as following:

- for original papers in a journal, the first author will be the investigator coordinator or any person involved in the study and chosen by the investigator coordinator.
- All investigators having included at least 5% of evaluable patients in the study will be included as authors.
- Other will be mentioned in the acknowledgements section (list of participants) of the article.
- Rank will be attributed according number of evaluable patient with respect to primary endpoint.
- Other authors will be ranked according to their effective contribution to the paper (Vancouver rules).
- Statistician will be in third position upon agreement with the investigator coordinator or any other position on the investigator coordinator decision.

The Clinical Research Department and the Antoine Lacassagne Biological Resource Center will be included in the affiliation of the principal investigator. The correct affiliation of the Centre Antoine Lacassagne is Centre Antoine Lacassagne - University Côte d'Azur.

14 APPENDIXES

14.1 Appendix 1 – Flow chart

	Selection/Inclusion	COVID-19 Screening	Follow up		Survival follow-up ^f
	Day 1		Day 7 to 28	At least every 4 weeks for up to 6 months	
Informed consent	X				
Eligibility criteria verification	X				
Inclusion	X				
Medical History, Blood group, Smoking status, alcohol consumption and vaccination (influenza/BCG) history	X				
Ethnicity	X				
Characteristics of cancer and anti-cancer treatment (clinical stage, location and type of treatment)	X				
Collection of clinical data related to COVID-19 (symptoms, history...)	X		X	X	
Clinical evaluation ^a (PS, Physical Exam, T°, height, weight, age, BMI)	X		X ^a	X ^a	
Concomitant medication	X		X	X	
Laboratory assessment ^b	X		X	X	
SRAS-Cov 2 testing (rapid serological test and/or RT-PCR and/or digitalPCR and/or ELISA) ^{c d}		X ^c	X ^d	X ^d	
Blood and saliva sample collection	X				
Satisfaction questionnaire	X				
Medical consultation (phone call or physical) ^e			X	X	

a-e. Visits will be held on site (or by phone if the patient is not able to come to the institution) at least every 4 weeks during 6 months.

b. Laboratory assessment includes: Hb, platelet, leukocytes, neutrophils, lymphocytes, LDH, CRP, Procalcitonin, Sodium, potassium, ASAT, ALAT, GGT, PAL, Bilirubin, calcium, protein, albumin. Blood proteins electrophoresis will be performed at inclusion.

c. SRAS-Cov-2 testing: At inclusion, rapid serological test +/- digitalPCR (blood and saliva) +/- RT-PCR test will be performed.

d. Depending on the symptoms and COVID-10 history, patient will be retesting by an ELISA serological test 15 to 28 days following the inclusion for eligible patients. Any retesting performed to the patient during the study will be recorded into the eCRF.

f. Collection (date and status) from patient's medical file gathered in the framework of the patient's standard care. COVID-19 infection/Alive or not/Cause of death will be reordered until 12 month after the last FU.

14.2 Appendix 2 – Classification CTCT-AE version 5.0

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

14.3 Appendix 3 – WHO performance status

GRADE	PERFORMANCE STATUS – WHO CLASSIFICATION
0	Normal activity
1	Asthenia experienced but maintains activity considered normal by the patient (professional, etc.)
2	Autonomous outpatient, reduced activity and remains in bed or seated less than 50% of his/her wakeful time
3	Major limitations on activity, partial autonomy and remains in bed or seated more than 50% of his/her wakeful time.
4	Total disability, remains in bed 100% of his/her wakeful time.

14.4 Appendix 4 – Insurance Certificate

