Non-Interventional Multi-Center Study for Molecular Diagnostic Technologies Validation in NSCLC Patients Protocol N° X9001083

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1 LIST OF ABBREVIATIONS

ABL	Abelson murine leukemia
AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
ATP	Adenosine Triphosphate
AUC	Area Under the plasma Concentration-time curve
BCR	Breakage Cluster Region
cfDNA	cell free DNA
CTCAE	Common Terminology Criteria for Adverse Event
c-Met	Mesenchymal-epithelial transition factor
CYP	Cytochrome P450
DCR	Disease Control Rate
DR	Duration of Response
EML4	Echinoderm Microtubule-Assosciated Protein-Linked 3
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
FDA	Food and Drug Administration
HDFE bottle	High Density Polyethylene Bottle
HGF/R	Hepatocyte Growth Factor/Receptor
INR	International Normalized Ratio
IRR	Independent Radiology Review
KRAS	Kirstin Rat Sarcoma
MedDRA	Medical Dictionary for Regulatory Activities
ORR	Objective Response Rate
OS	Overall Survival

PFS	Progression-Free Survival
PRO	Patient Reported Outcome
QLQ-LC13	Quality of Life Questionnaire Lung Cancer module 13
QOL	Quality of Life
QT	Time from the beginning of the QRS complex to the end of the T wave in the electrocardiogram
QTc	QT interval, Corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	c-ROS oncogene 1, receptor tyrosine kinase
RT-PCR	Reverse Transcription Polymerase Chain Reaction
TTR	Time to Tumor Response
VEGF	Vascular Endothelial Growth Factor
VHL	Von Hippel-Lindau

2 RESPONSIBLE PARTIES

The Precision Medicine Center of Excellence of Pfizer Chile (CEMP in Spanish), based in Santiago, Chile will be responsible for the execution of the non-interventional protocol.

The mission of the Center (CEMP) is to deliver technical and operational excellence in Precision Medicine R&D and molecular diagnostic development in Latin America for the benefit of cancer patients all over the world.

The other involved parties will be the hospital Centers that will be providing samples, the diagnostics test providers (Vysis ALK Break Apart FISH or Ventana ALK IHC) and the sequencing providers both in Chile and Brazil.

Their main responsibilities will be the following:

CEMP, through CRO ICON, will be responsible for sample collection and transportation from hospital centers to the FISH/Ventana ALK test providers, the sequencing providers and/or CEMP facilities. Thus, CEMP will receive clinical data informed consents, tissue and blood samples coming from hospitals, and data results of FISH/Ventana ALK and NGS from research centers.

In Brazil, AC Camargo Cancer Center (ACC), as a FISH/Ventana ALK and NGS sequencing provider, will perform nucleic acid extraction from both kind of samples (tissue and blood). ACC will also perform genomic analysis using a PGM device. Biodata (.vcf and .pdf files) coming from the sequencers will be processed and raw data will be supported in a Data Center. ACC will be responsible for the storage of the remaining tissue and the nucleic acid from blood in Brazil.

In Chile, CEMP Genomic Laboratory and the sequencing center Genoma Mayor will perform nucleic acid extraction from both kind of samples (tissue and blood). Also, they will perform genomic analysis using a PGM device and process the biodata coming from the sequencers and will store the raw and processed data accordingly. CEMP will be responsible for the storage of the remaining tissue and the nucleic acid from blood in Chile.

In both countries, the NGS service providers (ACC, Genoma Mayor and Genomic Laboratory at Pfizer) will work as a parallel sequencing facility.

The reference hospital centers will be responsible for collecting the patient identification according to the inclusion criteria, gathering the clinical data and due diligence to obtain the inform consent from patients. They will obtain and process the tissue and blood samples according to guidelines and perform the histopathological analysis. Some of the hospital Centers will perform the FISH/Ventana ALK test if technology and expertise is available. If not, samples will be sent to the designated FISH/Ventana ALK provider in Brazil or Chile.

ABSTRACT

Non-Interventional Multi-Center Study for Molecular Diagnostic Technologies Validation in NSCLC Patients

To identify patients who can respond to targeted therapies, it is imperative that new molecular diagnostics be developed and deployed.

The research lines planned for the CEMP-Chile are aimed at data generated to validate NGS (Next Generation Sequencing) and blood detection for ALK and/or ROS translocations. These patients may be eligible for ALK and/or ROS inhibitor treatment; however treatment and follow-up on care is out-of-scope of this protocol.

Study Objectives and Endpoints:

Primary objective

- To determine concordance between the Vysis ALK Break Apart FISH test or the Ventana ALK IHC test and Thermofisher NGS technology.
- Validation of more sensitive, less invasive and state of the art screening platforms for NSCLC.

CCI [redacted]

Study Design

This is a non-interventional multi-center diagnostic study to validate novel diagnostic technologies, such as Next Generation Sequencing (NGS) from both tissue and blood compared to the current gold standard tests.

As a non-interventional study, patients will not be treated or affected as part of the protocol.

This study will determine the correlation between the Vysis ALK Break Apart FISH test or the Ventana ALK IHC test of NSCLC tumors and next generation sequencing NGS analysis from tissue and blood derived nucleic acids. The study involves the collection and analysis of FFPE tumor tissue and blood of NSCLC patients to be analyzed with a Thermo Fischer NGS Oncomine fusion panel assay.

A positive correlation with these novels technologies will mean an efficient, more accurate test, which could impact a greater number of cancer patients around world.

The endpoint of this Project will be to analyze 30 positive ROS1 and 120 positive ALK samples to validate the diagnostic method.

Given an estimated prevalence of ROS1 at 1-2% and ALK at 3-5% for NSCLC, an initial set of 1000 patients will be screened. An interim analysis will be performed at the first 1000 NSCLC samples to evaluate prevalence rates (tentatively 10 ROS1+ and 40 ALK+).

For the majority of molecular tests, it is expected that at least 50 positive patient samples be utilized for validation, and ideally at least 10 positives representing each variant being detected[1]. Given the low prevalence of ROS1 which has 16 unique variants and recent analysis demonstrating that in 30 ROS1+ patient samples, there is representation of the 3 dominant variants suitable for analytical validation[2], it is necessary to screen at least 3000 NSCLC samples for identifying positive samples for both ROS1 and ALK that should be sufficient for analytical validation of the NGS platform. If anticipated prevalence rates at the 3000 sample mark do not align with determined prevalence rates at this stage and/or 30 positive ROS1 and 120 positive ALK samples are not obtained, an additional 3000 patients will be screened for a potential total of 6000 patients. The overall screening will occur at 3 or more sites. Patients will only participate in the study for the initial sample collection period.

The study will be completed in approximately 48 months.

Study Treatment
None.

3 AMENDMENTS AND UPDATES

None.

4 MILESTONES

Milestone	Planned date
Start of data collection Initiation of NSCLC FFPE tissue collection	June 30, 2015
End of data collection Completion of 6000 FFPE samples, 6000 blood samples	June 30, 2019
Interim study report Data analysis of the first 1000 samples processed by NGS will be assessed	October 31, 2016
Interim study report Data analysis of the first 3000 samples processed by NGS, and first 1000 blood samples will be assessed	October 31, 2017
Final study report Data analysis of the last 6000 samples processed by NGS, 3000 blood samples will be assessed	December, 31, 2019

5 RATIONALE AND BACKGROUND

A. Molecular Diagnostics

Two of the most relevant areas of today's health care diagnostics are "in vivo" imaging and "in vitro" diagnostics. The first includes such technologies as X-Rays, ultrasonic waves, magnetic resonance, or radio-nuclear methods that generate images of the body and its organs. The second areas include tests performed on a sample taken from the body (blood, tissue, sputum, urine, etc.)[1].

Molecular diagnostics belongs to a subset of in vitro diagnostics. It describes a certain type of diagnostic tests that assess a person's health literally at a molecular level, detecting and measuring specific genetic sequences in deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) or the proteins they express. This allows identifying on whether a specific person is predisposed to have a disease, whether they actually have a disease, or whether a certain treatment option is likely to be effective for a specific disease.

Molecular diagnostics has revolutionized biological and biomedical research becoming a growing part of a successful health care system, providing critical information that health care providers and patients need to make the right medical decisions[2]. It often provides objective, quantitative measurements that inform every stage of care—prevention, detection, diagnosis, treatment, and successful management of health conditions.

Personalized medicine, where understanding the underlying molecular mechanisms of diseases allows physicians to evolve to an individual more effective therapy is a derivative of molecular discovery. [3] The ultimate power of personalized medicine is the feasibility to treat smaller groups with therapies tailored to their molecular profile.

When specific proteins or genetic sequences have a known association with a specific health condition or disease, they are often referred to as "biomarkers" because they are markers of that condition or disease.[4] The detection of Cancer biomarkers can be useful in establishing a specific diagnosis and also in establishing a specific diagnosis.

World advances in increasing automation are enabling the development of cutting-edge molecular diagnostics to be performed, better detecting biomarkers and as a result stimulating the understanding the mechanism of diseases that will foster the discovery of the next breakthrough targeted therapies.[5]

Therefore the research around new diagnostics technologies that will enhance the overall effectiveness of therapies in the treated population is essential to increase the proportion of patients with favorable outcomes.

B. Lung Cancer

Non-small cell lung cancer (NSCLC) is a common cause of cancer mortality throughout the world. In 2007, there were 1.5 million new lung cancer cases diagnosed worldwide, including around 733,100 cases in the South American Region.[6]

Approximately 85% of lung cancer is histologically defined as non-small cell and the remaining 14% as small cell. The majority of patients with NSCLC present with inoperable locally advanced (Stage IIIB) or metastatic (Stage IV) disease for which no curative treatment is yet available. In newly diagnosed patients with good performance status, platinum-based doublet-combination chemotherapies are associated with a median overall survival (OS) of 7.4 to 9.9 months. [7, 8, 9, 10, 11, 12] Therefore, newer agents with novel mechanisms of action are still desperately needed for this serious life-threatening disease. [15,16]

The rapid and efficient identification of key driver genes in non-small-cell lung cancer (NSCLC) is becoming increasingly important.[17] Clinical screening efforts have revealed that the most common mutations in lung cancer specimens involve *EGFR and KRAS*, along with 10 other genes that show a prevalence of mutation in 5% or less of tumors. The *ALK* gene is rearranged in around 3%-5% of patients with NSCLC and has been the focus of intense basic and clinical research, suggesting that the frequency of the gene rearrangement is similar in Asian and Western patients.

ROS1 is a receptor tyrosine kinase of the insulin receptor family. Chromosomal rearrangements involving the ROS1 gene were originally described in glioblastomas, where ROS1 (chromosome 6q22) is fused to the *FIG* gene (chromosome 6q22 immediately adjacent to ROS1), [16] and have been shown to be transforming in transgenic mice.[17] More recently, ROS1 fusions were identified as potential driver mutations in an NSCLC cell line (HCC78; *SLC34A2*-ROS1) and an NSCLC patient sample (*CD74*-ROS1). [18] These fusions led to constitutive kinase activity and were associated with sensitivity in vitro and in vivo to crizotinib. As of December 2013, 16 different variants have been found.[16, 17, 18]

The present study is designed to advance the molecular testing methodologies to identify ALK+ and ROS1+ NSCLC patients. Advanced next generation sequencing screening methodologies will be used to identify NSCLC patients whose tumors contain a *ROS1* gene inversion or translocation or an ALK translocation.

A parallel test for ALK+ by either the Abbott ALK FISH test or the Ventana ALK IHC test is necessary to validate the NGS test in all samples. A parallel test for ROS1+ by either the Kreatech FISH test or the D4D6 ROS1 IHC test may be necessary to validate the NGS test in all samples.

6 RESEARCH QUESTION AND OBJECTIVES

This investigation intends to validate molecular diagnostics technologies on ALK+/ROS1+ NSCLC tumor diagnostic; more accurate and precise methods than the existing companion diagnostics (FISH Vysis ALK Break Apart FISH test or the Ventana ALK IHC test).

CEMP Genomic Laboratory together with its sequencing providers (ACC in Brazil, Genoma Mayor in Chile) will process NGS data from tissue and blood and compare it against histopathological and FISH/Ventana ALK results. With this comparison CEMP will be able to determine if NGS technologies are suitable to be considered as accurate diagnostic methods.

The main question that will be addressed in this project is the significant global demand to develop improved molecular diagnostics for cancer, for both translational/clinical applications, as well as companion diagnostics to personalize oncology medicines, in order to increase the overall effectiveness of therapies to patients which may benefit the most, with significant value add to both payers (public healthcare and/or healthcare insurance) and drug manufacturers.

Accordingly, next generation molecular diagnostics should leverage scientific advancements to become less invasive, require less amount of patient tissue for testing and of greater sensitivity to cancer-specific genetic indicators, whether inherited, mutated, or transcribed.

The primary disease focus of this project is to examine novel technologies for NSCLC patient screening for detection of ALK and ROS1 positive patients.

The project will address this technical issue through two research lines:

1) Development of an ALK/ROS fusion specific next generation sequencing panel;
2) Detection of tumor-derived nucleic acids in the blood of patients diagnosed with NSCLC.

7 RESEARCH METHODS

NGS translocation detection platform

The current study design aims to validate the NGS ALK/RET/ROS detection platform; archival or prospective tumor tissue specimens will be collected from previously diagnosed NSCLC patients enrolled on the study and analyzed for the presence or absence of ALK/RET/ROS translocations.

The data from these assays in combination with the subsequent outcome data collected from the clinical sites will be used to define a diagnostics strategy for the NGS platform.

Circulating nucleic acid (CNA) analyses

For the CNA analysis, two blood tubes will be from all patients at baseline and at time of progression (if possible). One blood tube will be used for RNA analysis. A second blood tube will be used for DNA analysis. Both preparations will be processed and stored frozen until extraction and NGS protocols are defined for this analysis (2016).

Protocols for FFPE processing and blood collection will be provided (See Appendix 1).

Additional tests on the tumor tissue and blood samples can be performed. These may include other tests for the ALK gene fusion or other lung cancer biomarkers according to the state-of-art on this area.

7.1 Study design

This is a non-intervention multi-center study where tissue and blood of NSCLC patients will be collected. Patients will not be treated as part of this protocol and will only participate in the study for the initial samples and clinical parameters collection period.

Up to 6000 patients are expected to be screened in the study overall at 3 or more sites.

Samples should include:

1. Archived or tumor tissue as formalin-fixed paraffin-embedded (FFPE) tissue block or 10 unstained slides containing serial 5-micron tumor tissue sections.
2. Blood samples collected in the provided StepCheck tubes. One 8ml tube for DNA collection, one 8mL tube for RNA collection.

The study will evaluate the strength of NGS technology as diagnostics methods for ALK+ and or ROS1+ tumors.

The strength of the study is based on the fact that NGS technology has an adequate sequencing quality (Q>30) and coverage, which ensures the accuracy of results. Given the low prevalence of ALK and ROS rearrangements, it is necessary to sample up to 6000 samples to obtain at least 30 ROS1+ for adequate concordance against other platforms. This is critical for the diagnostic evaluation results, making it eligible as a good diagnostic method.

Besides this, the clinical data will be correlated to the NGS data. This will provide demographics correlations and give information about the incidence of the markers in the Chilean and Brazilian people.
The study will be completed in approximately 48 months.

7.1.1 .Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Female or male, 18 years of age or older.
2. Patients with histologically or cytological proven diagnosis of NSCLC, pathologically identified as adenocarcinoma.
3. Patient naïve in lung cancer treatment
4. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all the pertinent aspects of the study prior to enrollment.
5. Patients must give consent to the research use of their archived or tumor FFPE tissue, and if available, 2 blood tubes.

7.1.2 Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Prior chemotherapy treatment.

7.2 Variables

The variables that can impact in the project are non-existence of clinical data, of properly taken samples, misdiagnosis of adenocarcinoma, insufficient blood volume, improper sample storage and transportation, insufficient number of slides for the RNA extraction, inadequate preparation and handling of FFPE, inadequate amounts or bad quality of the RNA derived from FFPE or blood samples, variability in FISH/Ventana ALK testing due the operator or the equipment itself.

7.3 Data sources

The primary data sources for variables relevant to the study objectives will include medical records, patient interviews and molecular profiling.

Data resulting from health or investigator records provided in case report forms will be described under the statistical analysis plan.

7.4 Study size

The results regarding the presence or absence of specific gene fusions (ALK and/or ROS1) after applying NGS will be confirmed using certified and validated test for clinical use, which will allow the specificity of NGS test for the analyzed gene. In all participant subjects the presence of gene ALK and ROS1 variation will be analyzed which will allow to estimate the sensitivity in the NGS test.

The specificity of the NGS trial will be calculated based on cases with a particular gene fusion where a result has been obtained through a certified test. Thus, the specificity will be equal to the confirmed cases through certified test divided by the total of NGS identified mutated cases number. The sensitivity will be calculated dividing the number of cases with a confirmed gene fusion by an ALK and/or ROS1 certified test by the number of the same cases in which the fusion was identified by NGS.

The gene fusion in ROS1 has been selected as the primary variation for the statistical analysis plan, since is the less frequent variation in lung cancer (COSMIC Sanger Database) with a prevalence of 1-2%. The confidence intervals for sensitivity and specificity will be calculated according to the efficiency method of the marker (efficient score method, Newcombe, 1998, Wilson, 1927). [19, 20]

This study expects to analyze a total of 30 tumors with alterations in the ROS1 gene and 120 alterations in ALK. Thus, for a precision up to 80% (either specificity or sensitivity), will be enough information to stablish a sensitivity and specificity estimation of the NGS trial within 0.1 points and 0.05 points (wide of 95% of the confidence interval) respectively.

Given an estimated prevalence of ROS1 at 1-2% and ALK at 3-5% for NSCLC, an initial set of 1000 patients will be screened.

An interim analysis will be performed at the first 1000 NSCLC samples to evaluate prevalence rates. If anticipated prevalence rates do not align with determined prevalence rates at this stage, an additional 2000 patients will be screened for a potential total of 3000 patients.

A subsequent interim analysis will be performed at the 3000 NSCLC samples to evaluate prevalence rates. If anticipated prevalence rates do not align with

determined prevalence rates at this stage, an additional 3000 patients will be screened for a potential total of 6000 patients. The overall screening will occur at 3 or more sites. Patients will only participate in the study for the initial sample collection period.

The study will be completed in approximately 48 months. Since it's a non-interventional multi-center study involving the collection and analysis of FFPE tumor tissue and blood of NSCLC patients, patients will not be treated as part of the protocol.

7.5 Data management

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required.

The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry."

In most cases, the source documents are the hospitals or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

7.6 Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor.

The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

7.7 Quality control

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate.

The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

7.8 Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports).

The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

7.9 Other aspects

Not applicable.

8 PROTECTION OF HUMAN SUBJECTS

8.1 Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form and one copy will be given to the patient or his/her representative.

8.2 Patient withdrawal

Patients may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected if no withdrawal of consent is requested.

8.3 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC.

All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

8.4 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonization guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

9 PUBLICATION OF STUDY RESULTS

Since the objective of Pfizer's Center of Excellence is to lead the research in precision Medicine, publications with Study Researchers will be promoted, whether or not the results are favorable to the study.

Since the Study is part of a multi-center study, Study Researchers agree that publications are to be a joint publications, even after the study is finished.

To ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Study Researchers will provide Pfizer an opportunity to review any proposed joint publication or other type of disclosure before it is submitted or otherwise disclosed.

Study Researchers will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 60 days before they are submitted for publication or otherwise disclosed.

Study Researchers will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

For all publications relating to the Study, the Center of Excellence will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

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APPENDIX 1. LIST OF STAND ALONE DOCUMENTS.

Document reference	Title
OCP Fusion including DNA/RNA extraction	NGS SOP for FFPE processing
Streck cell free RNA BCT	Blood (RNA) tube collection and storage
Streck cell free DNA BCT	Blood (DNA) tube collection and storage