NON-INTERVENTIONAL (NI) STUDY PROTOCOL

POST MARKETING SURVEILLANCE STUDY TO OBSERVE SAFETY AND EFFICACY OF INLYTA®

Compound Number:	AG-013,736	
Compound Name:	INLYTA® capsules 1mg, 5mg (Axitinib)	
Study Number:	A4061075	
Version and Date:	Final	04 September 2012
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	Amendment 7	30 January 2019
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ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADL	Activities of Daily Living
AE	Adverse Event
SAE	Serious Adverse Event
CRF	Case Report Form
eCRF	Electronic Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete Response
PR	Partial Response
SD	Stable Disease
PD	Progressive Disease
EIU	Exposure in Utero
FGF	Fibroblast Growth Factor
IRB/IEC	Institutional Review Board/Independent Ethics Committee
MFDS	Ministry of Food and Drug Safety
LPD	Local Product Document
LSLV	Last Subject Last Visit
NCI CTC	National Cancer Institute Common. Terminology Criteria
ODC	Obvious Data Correction
ORR	Objective Response Rate
PCD	Primary Completion Date
PDGF	Platelet-derived Growth Factor

PFS	Progression-free survival
PV	Pharmacovigilance
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
SAP	Statistical Analysis Plan
SOP	Standard Operating System
SRSD	Single Reference Single Document
TTP	Time to progression
VEGF	Vascular Endothelial Growth Factor

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1. RATIONALE AND BACKGROUND

Renal cell carcinoma (RCC) accounts for 85% of kidney cancers, and is a collection of different types of tumors that arise from the renal epithelium. Renal cell carcinoma (RCC) is diagnosed in approximately 170,000 patients worldwide annually, resulting in 82,000 deaths.

Early stage disease does not typically produce significant clinical signs or symptoms, consequently 25-30% of newly diagnosed patients present with advanced (including locally invasive or advanced) or unresectable disease. The 5-year survival rate for advanced RCC is estimated to be ≤10%.

Most RCCs are highly vascularised tumors that over-express a number of growth factors, including VEGF (Vascular endothelial growth factor), PDGF (Platelet-derived growth factor) and fibroblast growth factor (FGF). The clear cell RCC subtype represents approximately 85% of the RCC population and frequently displays allelic loss on chromosome 3p, accompanied by mutational inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene. VHL-associated RCC are known for their vascularity and these tumors produce high levels of vascular endothelial growth factor (VEGF). In addition, recent studies suggest that in sporadic clear cell RCC, increased expression of VEGF is closely correlated with neovascularization, which is a prerequisite of tumor growth and metastasis.

INLYTA®, a substituted indazole derivative, is an oral, potent, and selective inhibitor that blocks signal transmission via vascular endothelial growth factor receptor (VEGFR-1, -2 and -3) which is related to vascularization of tumors and tumor proliferation.

INLYTA® was first approved as new medicine on 22 Aug 2012. As required for any new medication approved by Ministry of Food and Drug Safety (MFDS), safety and efficacy information of new medication should be provided at minimum 3000 subjects administered in the setting of routine practice during the initial 6 years after the approval. However, based on MFDS's review upon Pfizer Korea's request, additional 3 years of study period has been granted to collect safety and efficacy information of minimum of 100 subjects.

2. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to monitor usage of INLYTA® in real practice including adverse events on INLYTA®.

3. RESEARCH METHODS

3.1. Study design

Observational, non-interventional drug and multi-center study in which subjects will be administered as part of routine practice at Korean health care centers by accredited physicians. At least 3000 subjects should be enrolled in this study based on the Article 6 of "Basic Standards for the Re-examination of New Medicines" notified by MFDS. However, with additional 3 years of study period,at least 100 subjects who are being treated with Inlyta within the approved indication will be studied for total of 9 years according to the review result by the MFDS per Pfizer's request to adjust the number of subjects. The study can be performed in Korean health care centers where INLYTA® is prescribed for advanced renal cell carcinoma (aRCC) after failure of one prior systemic therapy which is the indication for INLYTA® and where post-marketing study is allowed by institutions.

To achieve the target sample size, the study is being conducted in prospective study design and retrospective study design.

Patients to whom INLYTA® is first administered or patients who are already on INLYTA® during the study period should be enrolled in the study. Observation should be done from treatment initiation of INLYTA® for at least 28 calendar days. There are no visits or activities mandated by this study and routine observation will be done during INLYTA® treatment.

3.2. Study population

All subjects enrolled should meet the usual prescribing criteria for INLYTA® as per the Local Product Document (LPD) and should be entered into the study at the physician's discretion.

3.2.1. Inclusion criteria

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

1. Patients diagnosed as advanced renal cell carcinoma (aRCC) after failure of one prior systemic therapy.

2. Patients to whom INLYTA® is first administered or patients who are already on INLYTA® during the study period

3. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

3.2.2. Exclusion criteria

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

1. Any patient who does not agree that Pfizer and companies working with Pfizer use his/her information
2. Patients with hypersensitivity to axitinib or to any other component of INLYTA®
3. Patients under 18
4. Pregnant women

3.3. Data sources

The followings are data sources for the study:

1. Medical records
2. Laboratory test results

3.4. Variables

Variable	Role	Data source(s)	Operational definition
Demographic Characteristics	Baseline characteristics	Medical records	*
Basic Laboratory data	Baseline characteristics	Laboratory test results	*
Concomitant medication	Baseline characteristics	Medical records	*
Efficacy result by physician	outcome	Medical record	*

AE events	outcome	Medical record	*

*Refer to 3.5.4.Investigating Matters

Detail instruction of variable will be included Statistical Analysis Plan (SAP) and CRF.

3.5. Study procedures

3.5.1. Study Duration

As specified in the product license given by MFDS, this study was to be conducted for 6 years from the approval date of 22 Aug 2012 to 21 Aug 2018. On May 2018, MFDS has granted 3 additional years for the study, for total of 9 years for the study period.

3.5.2. Study Treatment

The use and dosage recommendations for INLYTA® will take place on the basis of the approved LPD and will be adjusted solely according to medical and therapeutic necessity.

3.5.3. Endpoints

3.5.3.1. Safety Endpoints

The clinical nature, incidence, duration, and severity of adverse events; discontinuation due to adverse events; outcome and possible causality will be monitored in this study.

3.5.3.2. Efficacy Endpoints

- Tumor response based on RECIST 1.1
- ORR
- PFS within limited follow-up period
- TTP

3.5.4. Investigating Matters

This means that the physician should enroll all subjects to whom INLYTA® is prescribed for the first time after contract is executed and who agree that Pfizer Korea and companies working with Pfizer Korea use his/her information by signing the ‘data privacy statement’.

Data for patients who are currently on INLYTA® will be collected as much as possible following the categories for patients who are prescribed with INLYTA® for the first time.

3.5.4.1. Reporting of the study

Final study report will include analysis for patients prescribed with INLYTA® for the first time, for patients who are already on INLYTA® at the time of enrollment, and for all enrolled patients.

3.5.4.2. Demographic Information

- Name of Institution: Record the name of institution.
- Name of Physician: Record the name of physician engaged into this study.
- Department: Record the medical department, practicing the study.
- Subject ID: Record 4 digit number per subject registration sequence.
- Confirmation of Data Privacy Statement: If all agreement for using subject's personal and medical information, signature and date are obtained by subject or legally authorized representative, then check the box of 'yes'. If not, check 'no' which means that case is excluded from this study.

3.5.4.3. Subject Status

- Initial of Subject: Record the name of subject with English initials.
- Date of birth: Record the date of birth of the subject.
- Sex: Check either 'male' or 'female'.
- Classification: Check either 'outpatient' or 'inpatient'.
- Height/Weight: Record by cm / kg unit.
- Allergic history: Check either 'yes' or 'no'. If 'yes', then record the allergen and the according symptom.

3.5.4.4. Diagnosis

- Diagnosis: check the aRCC and classify cell component, 'clear cell' or 'other'.
- Date of diagnosis: Record the date the subject was initially diagnosed as advanced RCC
- Metastasis: Check either 'yes' or 'no'. If 'yes', check the metastasis site. If 'other', specify.
- Primary lesion surgery: Check whether the subject had prior cancer surgery (nephrectomy)

or not. If the subject had the surgical procedure, record the surgical date.

- Prognostic criteria: Record the value of all risk factors for MSKCC and Heng criteria and record the value of serum LDH both at diagnosis and at initiation of treatment of INLYTA [1), 2), 3)].

  - MSKCC risk factors

Karnofsky performance status < 80%
< 1 y between diagnosis and start of first systemic therapy
Corrected serum calcium > 10 mg/dL
Hemoglobin < lower limit of normal
LDH > 1.5 times upper limit of normal

  - Heng risk factors

Karnofsky performance status < 80%
< 1 y between diagnosis and start of first systemic therapy
Corrected serum calcium > 10 mg/dL
Hemoglobin < lower limit of normal
Neutrophils > upper limit of normal
Platelets > upper limit of normal

3.5.4.5. Medical History

Check the box next to 'yes' or 'no' for past/present disease. If 'yes', record the full name of the disease as appears in the medical terminology dictionary (written by the Korean Medical Science Association). then select the box next to 'past' or 'present' in the line of according disease category. If the disease does not exist in the form, record the full name of the disease in the 'others' category as appears in the medical terminology dictionary (written by the Korean Medical Science Association).

3.5.4.6. Prior Chemotherapy/Immunotherapy and Radiation Therapy

Prior to administrating INLYTA®, if the subject received other chemotherapy / immunotherapy or received radiation therapy to treat, advanced RCC, record them. First, check among 'yes', 'no' or 'unknown'. If 'yes', record the followings.

<Chemotherapy/Immunotherapy>

- Name of chemotherapy/immunotherapy drug: Record generic name.
- Duration of administration: Record the start date and stop date of the chemotherapy/ immunotherapy.

<Radiation therapy>

- Site of radiation therapy: Record the site of radiotherapy.
- Duration of radiation therapy : Record the start date and stop date of the radiation therapy.

3.5.4.7. Concomitant Medication

The physician records the medication especially all anti-hypertensive drugs and any drug related to CYP3A4/5(including transfusion) which has been administered at the point of being enrolled in this study or which are administered newly after being enrolled. Check either 'yes' or 'no', if 'yes', record in detail.

- Name of drug: Record the name of drug.
- Total daily dose: Record the total daily dose.
- Duration of administration: Record the start date and stop date of the concomitant medication (year/ month / day). If the medication is being continued at the completion of the study, record the start date only.
- Purpose of administration: Record the purpose in detail.

3.5.4.8. Administrative Status for Study Drug

INLYTA® is provided by the physician's prescription and Pfizer Korea will not provide drug for this study.

Record the following with regard to administrative status for the study drug.

- Duration of administration: Record the start date and stop date of the medicated drug (year / month / day). If the medication is being continued at the completion of the study, check the box next to 'ongoing'.
- A single dose: Record the dose (in mg) of study drug. In case of dose titration up or down, record each dose with the periods respectively.
- Daily dosing frequency: Record dosing frequency per day.
- Reason for dose adjustment: Record any remarks if applicable

Refer to LPD for posology and method of administration.

3.5.4.9. Safety

3.5.4.9.1. Adverse Event

Every observed and reported adverse event, regardless of the causal relationship with the study drug, must be recorded on an adverse event section in case report forms. The query pattern of experience of adverse event to the subjects is as follow;
Patients who are prescribed with INLYTA® for the first time during the study period: "Have you had any health problem since last visit?"
Patients who are already on INLYTA® at the time of enrollment: all safety information will be collected from medical chart since the date of treatment initiation.
For adverse events repeating before and after administrating the study drug, record the the date adverse event was first experienced and the date adverse event resolved. Background information on INLYTA® can be obtained from the current version of the local product document, which is the single reference safety document (SRSD) for information relating to INLYTA®.

Check either 'yes' or 'no' in adverse event section. If 'yes', record in detail.

- Adverse events: Record the name of adverse event. If possible, specify diagnosis, not individual symptoms. Record the name according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
- Date of onset: Record the date of onset. Record approximate date if an actual date is unknown.
- Date of resolution: Record the date of resolution. Record approximate date if an actual date is unknown.

- Severity: Severity evaluation of adverse event must be done according to the NCI CTC grade.
  - The physician will use the following definitions of severity in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 to describe the maximum intensity of the adverse event:

Grade	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

If the severity of an adverse event changed, the adverse event must be entered separately. Record stop date of previous severity and onset date of new severity – along with completion of all other items.

- Seriousness: Check either 'yes' or 'no'. If 'yes', record the appropriate number for the category of seriousness.

  A serious adverse event is any untoward medical occurrence in a subject administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

  (1) results in death;
  (2) is life-threatening;
  (3) requires inpatient hospitalization or prolongation of hospitalization;
  (4) results in persistent or significant disability/incapacity(substantial disruption of the ability to conduct normal life functions);
  (5) results in congenital anomaly/birth defect.

  Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a serious adverse event. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with severity Grade 5.

Lack of efficacy should be reported as an adverse event when it is associated with a serious adverse event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a subject exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

In case of serious adverse event, Drug Safety Unit in Pfizer Pharmaceuticals Korea is to be notified promptly by the physician.

Check the following at the end of the study or after the resolution of adverse event.

- Outcome: The evaluation of outcome will include: Record the date of recovery in case of 'Recovered' or 'Recovered with sequelae'.
  - Recovered
  - Recovered with sequelae
  - Recovering
  - Not recovered
  - Unknown

- Causality of adverse event to the study drug: The causal relationship of adverse event to the study drug must be allocated by the physician according to the following criteria.

(1) Certain
- It follows a reasonable time sequence from administration of the drug (before and after the study medication).
- It could not be explained by other drugs, chemical substance or accompanying diseases.
- It has clinically reasonable reaction on cessation of the drug.
- It has pharmacological or phenomenological reaction to re-administration of the drug, where necessary.

(2) Probable/likely
- It follows a reasonable time sequence from administration of the drug (before and after the study medication).
- It could not be explained by other drugs, chemical substance or accompanying diseases.
- It has clinically reasonable reaction on cessation of the drug.

(No information on re-administration)

(3) Possible
- It follows a reasonable time sequence from administration of the drug.
- It could also be explained by other drugs, chemical substance or accompanying diseases.
- It lacks information or has unclear information on discontinuation of the drug.

(4) Unlikely
- It is not likely to have a reasonable causal relationship from administration of the drug. Rather, it seems to be temporary.
- It could also be reasonably explained by other drugs, chemical substances or latent diseases.

* Other causality of adverse event: If the adverse event is not related to the study drug, physicians should indicate the most appropriate cause from the followings and record in detail.

1. Disease under the study
2. Other disease (please specify)
3. Concomitant treatment drug or non-drug (please specify)
4. Others (please specify)

(5) Conditional/unclassified
- It needs more data to make an appropriate assessment or its additional data are being reviewed.

(6) Unaccessible/unclassifiable
- Lack of sufficient information or conflicting information hampers accurate causality assessment or supplementation or confirmation.

(7) Not applicable

- Action: Check relevant action.

A. Discontinuation (Permanently, Temporarily or delayed) B. Dosage reduced
C. Dosage increased D. No Change E. Unknown F. Not Applicable

3.5.4.9.2. Laboratory Test

Laboratory test is not mandatory because this study is a non-interventional study. If physician performed a laboratory test (e.g. TSH, T4, CBC, LDH and corrected Calcium) under their usual practice, the results can be collected.

- Name of laboratory test: Record the item of laboratory test.
- Date for laboratory test: Record the date with year / month / day.
- Test result before / after medication: Record the test result.

If abnormal objective lab result is clinically significant related to adverse event, it has to be recorded in adverse event section of a case report form.

3.5.4.10. Efficacy Assessment

The determination of antitumor efficacy will be based on objective tumor assessments made according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 of unidimentional evaluation. Progression-free survival (PFS) is defined as the time from first dose of study medication to first documentation of objective tumor progression, or to death due to any cause, whichever occurs first. And Time To Progression(TTP) is defined as the time to progression is one way to see how well a new treatment works. PFS will be assessed using the Kaplan-Meier method. Estimate of the PFS curves from the Kaplan-Meier method will be presented.

- Date of Tumor Assessment: Record the actual date that the scan was performed.
- Overall response: Check in ***ONE*** box indicating the overall tumor assessment based on RECIST Tumor Assessment Criteria.

Refer to [Appendix 4] for RECIST 1.1 Tumor Assessment Criteria.

3.6. Power and sample size

Per MFDS regulation, at least 3000 subjects were required for the study initially. However, based on the decision from MFDS on April 26, 2018, at least 100 subjects who are eligible according to '3.2 Study population' will be observed for total of 9 years

3.7. Data sources

3.7.1. Case report forms

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record (eCRF; electronic case report form) 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 shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

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 are correctly recorded. Any corrections to entries made in the CRFs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry. For studies using electronic data capture systems, an audit trail of any corrections to original data entry must be ensured.

In many cases, the source document is the subject medical chart. In these cases, data collected on the CRFs must match the data in the chart.

In some cases (e.g., subject interview), 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.

3.7.2. Record retention

To enable evaluations and/or inspections audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents copies of all CRFs, safety reporting forms source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

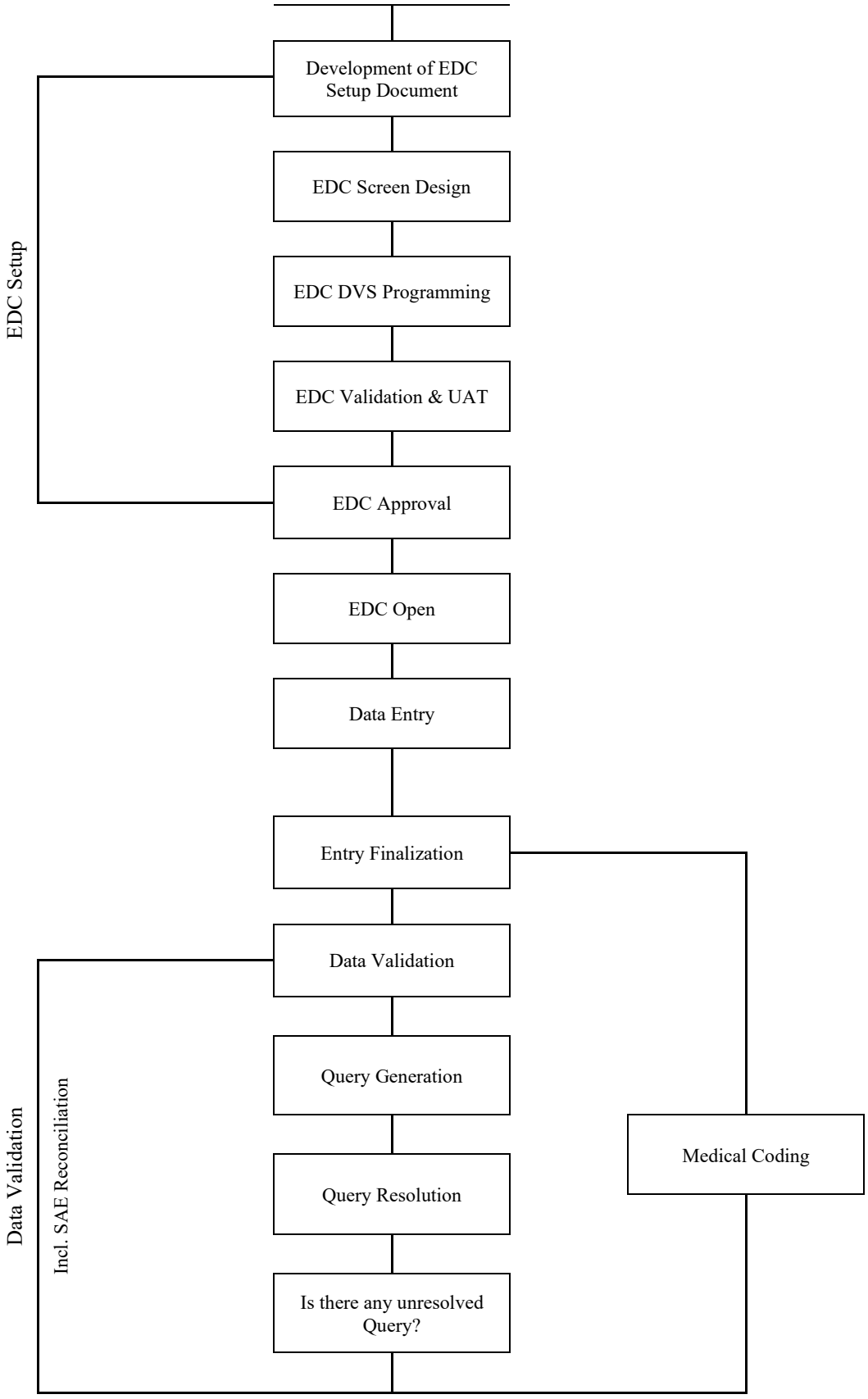
If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

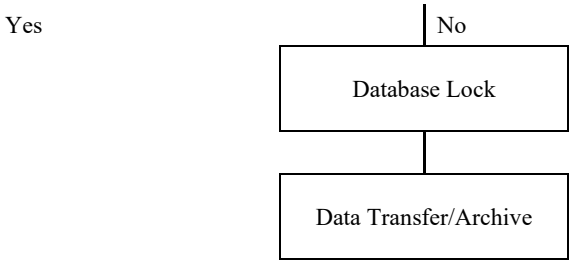
The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

3.8. Data management

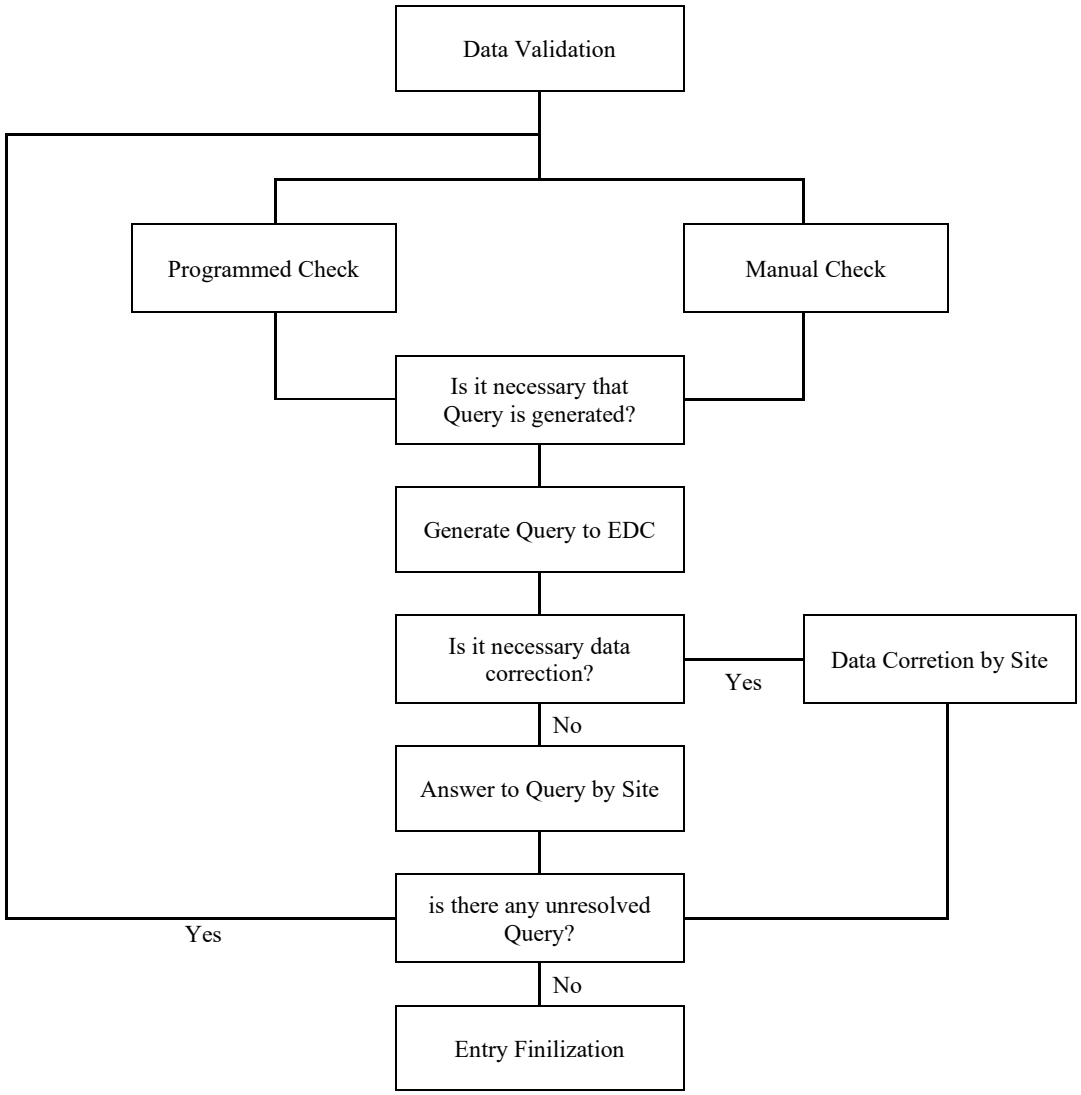
CRF data collected by the investigator will be entered into the clinical database. AEs and Medical history will be coded using World Health Organization - Adverse Reaction Terminology. Concomitant medication will be coded via ATC code. Statistical analysis will be carried out with SAS software version 9.4 or a more recent version.

Preparation & Planning


Development of EDC Setup Document
EDC Screen Design
EDC DVS Programming
EDC Validation & UAT
EDC Approval
EDC Open
Data Entry
Entry Finalization
Data Validation
Query Generation
Query Resolution
Is there any unresolved Query?
Medical Coding
EDC Setup
Data Validation
Incl. SAE Reconciliation



<figure1> Data management flow chart



<figure2> Data validation flow chart

3.9. Data analysis

Analysis will be performed for the pooled data collected by each investigator during the re-examination period. Total number of centers participating, total number of cases enrolled and retrieved, and total number of cases included in the analysis will be presented in summary tables. Evaluation of data will primarily consist of summary displays (eg, descriptive statistics, tables, and graphs).

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

3.9.1. Assessment Parameters

3.9.1.1. Parameters on Safety

- Safety parameters will be evaluated.
- Incidence of adverse events categorized according to physical organ and disease symptoms
- Sub-analysis may be performed using factors considered to affect safety. If required, Chi-square test (X^2 test) or Fisher's exact test (if the expected frequency for each cells under 5 is more than 20%) will be used for subgroup analysis.
- Clinically significant abnormalities from laboratory tests (if any). If data are applicable, paired t-test, descriptive analyses and other statistical methods will be used.

3.9.1.2. Efficacy Parameters

- The four *ORR categories (by RECIST) : CR, PR, SD, PD
- The two period scale: PFS, TTP
- Efficacy parameters will be descriptively summarized. If necessary, For the ORR and PFS, sub-analysis may be performed using factors considered to affect efficacy. If required, X^2-test or Fisher's exact test (if the expected frequency for each cells under 5

is more that 20%) paired t-test, analysis by repeated measurement, Kaplan-Meier curve, Long-rank test and other statistical methods will be used.

* ORR(Objective Response Rate) : the proportion of patients who have a partial or complete response to therapy

3.9.2. Interim Analysis

As required by MFDS regulations, the periodic report should be submitted to MFDS every 6 months for the first two years and then annual report should be submitted to MFDS for the third, fourth and fifth year. The final report for the date collected until August 21, 2018 should be submitted in the sixth year, by November 21, 2018. For the additional study period, periodic report should be submitted to MFDS every 6 months, and the final report of the entire study period should be submitted by November 21, 2021. Interim analysis will be performed in time for the report submission.

Analysis will be performed for safety group and efficacy group for patients who are prescribed with INLYTA® for the first time and for patients who are already on INLYTA® separately, and for all enrolled patients.

- Safety group: Subjects who have been administered INLYTA® at least once and evaluated with safety-related endpoints at least once.
- Efficacy group:ITT (Intent-to-treat) group - subjects to whom INLYTA® is administered INLYTA®at least once.

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.

3.10. Quality control

Quality assurance audits will be performed at study centers by Pfizer's own independent quality assurance group or by the clinical research organization. These audits will be conducted according to Pfizer's procedures and the guidelines for Good Pharmacoepidemiology Practices (GPP).

3.11. Strengths of the research methods

- Large scale non interventional real world study for evaluating efficacy and safety of investigational drug

3.12. Limitations of the research methods

- Regulatory- required study for maintaining license and exclusivity.
- SAP and number of enrolled subjects are ruled by PMS guideline of MFDS, not specific to disease and/or drug characteristics.

4. PROTECTION OF HUMAN SUBJECTS

4.1. Subject Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staffs have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred

to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

4.2. Subject Consent

The informed consent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/independent ethics committee (IEC) before use, and available for inspection.

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 the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The investigator, or a person designated by the investigator, will obtain the written data privacy statement 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 data privacy statement. The investigator further must ensure that each study patient or his or her legally acceptable representative, or parent(s) is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a patient's legally acceptable representative/parent(s), the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/IEC. If the investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/IEC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (e.g., minor,

decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (e.g., parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

4.3. Subject withdrawal

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

If the subject 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 before such withdrawal of consent.

4.4. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The study protocol will be submitted to MFDS prior to the study. The ethical consideration on this study will be evaluated by the IRB/ IEC in each clinical site prior to the study, if the site has an approval process for this PMS study according to the local standard operation procedure of the site.

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 by the investigator. Copies of IRB/IEC approvals should be forwarded to Pfizer.

4.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Pharmaceutical Research and Manufactures Association(PhRMA) guidelines and Korea PMS regulations and/or guidelines.

5. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

5.1. Requirements for the study

5.1.1. REQUIREMENTS

The table below summarizes the requirements for recording safety events on the case report form and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	Recorded on the case report form	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below).

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or

life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

5.1.2. Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of Inlyta or the time of the patient's informed consent if s/he is already exposed to Inlyta, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient changes his/her mind about participation, failed screening criteria), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to Inlyta, the SAE also must be reported to Pfizer Safety.

5.1.3. Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to Inlyta, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that Inlyta caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether Inlyta caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that Inlyta did not cause the event, this should be clearly documented on the case report form and the NIS AEM Report Form.

5.2. DEFINITIONS OF SAFETY EVENTS

5.2.1. Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Lack of efficacy;

- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

5.2.2. Serious adverse events

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a serious adverse event. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with severity Grade 5.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

5.2.3. Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) Inlyta, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to Inlyta (maternal exposure).

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to Inlyta prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with Inlyta, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to Inlyta in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

<u>Exposure during breastfeeding</u>

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE :

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
  - An identifiable reporter;
  - A suspect product;
  - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

5.3. COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the physician is aware of any new information which might influence the evaluation of the benefits and risks of INLYTA®, Pfizer should be informed immediately.

In addition, the physician will inform Pfizer immediately of any urgent safety measures taken by the physician to protect the study subjects against any immediate hazard, and of any serious breaches of this NI study protocol that the physician becomes aware of.

5.4. SINGLE REFERENCE SAFETY DOCUMENT

Background information on INLYTA® can be obtained from the current version of the local product document, which is the single reference safety document (SRSD) for information relating to INLYTA® in this study.

6. STUDY DISCLOSURE

Pfizer fulfils its commitment to publicly disclose clinical trial results through posting the results of this study on www.clinicaltrials.gov. Pfizer posts the results of all studies that is has registered on ClinicalTrials.gov regardless of the reason for registration.

The results are posted in a tabular format called Basic Results.

- For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:
- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, FDA-approved products, Pfizer posts results within one year of the primary outcome completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last subject, last visit (LSLV).

- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days after US regulatory approval. or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);

- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year after such discontinuation of the program (if there are no plans for outlicensing or within two years if outlicensing plans have not completed).

- Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

7. LIST OF FIGURES

1. <Figure 1> Data Management Flow Chart

2. <Figure 2> Data Validation Flow Chart

8. REFERENCES

1) Robert J. Motzer, Jennifer Bacik et al. Interferon-Alfa as a Comparative Treatment for Clinical Trials of New Therapies Against Advanced Renal Cell Carcinoma. J Clin Oncol 2001, 20:289-296. 2001
2) Tarek M. Mekhail, Rony M. et al. Validation and Extension of the Memorial Sloan-Kettering Prognostic Factors Model for Survival in Patients With Previously Untreated Metastatic Renal Cell Carcinoma. J Clin Oncol 2005, 23:832-841.
3) Daniel Y.C. Heng, Wanling Xie, et al. Prognostic Factors for Overall Survival in Patients With Metastatic Renal Cell Carcinoma Treated With Vascular Endothelial Growth Factor–Targeted Agents: Results From a Large, Multicenter Study. J Clin Oncol 2009, 27:5794-5799.

APPENDIX 1. RESPONSIBLE PARTIES

Protocol Contact

Name, degree(s)	Title	Affiliation	Address
PPD	Korea Oncology Medical Lead	PPD	PPD Korea

Country Coordinating Physicians

NA

APPENDIX 2. AMENDMENTS

Amendment number	Date	Country(ies)	Site(s)	Rationale for amendment	Protocol section(s) changed
1	03 May 2016	South Korea		-Sample size reduction -Safety reporting language	Section 3.2 Section 5 Appendix 1
2	03 Jan 2018	South Korea		Adverse events reporting criteria change	Section 3.5.4
3	19 Mar 2018	South Korea		Change in study design	Section 3.1 Setion 3.5 Section 3.6 Section 4 Section 5
4	20 Apr 2018	South Korea		Change in study design	Section 3.1 Section 3.2. Section 3.5 Section 3.6 Section 5
5	16 May 2018	South Korea		Change in study design and minimum number of cases	Section 1 Section 3.1 Section 3.2. Section 3.5 Section 3.6 Section 3.7 Section 3.8 Section 3.10 Section 4

6	15 Jun 2018	South Korea		Change in study duration, sample size	Section 1 Section 3.1 Section 3.2 Section 3.5 Section 3.6 Section 3.7 Section 3.8 Section 3.10 Section 4 Section 5

APPENDIX 3. MILESTONES

Milestone	Planned date
Start of data collection	Dec 2012
End of data collection	21 Aug 2018
Interim reports	21 Apr 2013 21 Oct 2013 21 Apr 2014 21 Oct 2014 21 Oct 2015 21 Oct 2016 21 Oct 2017 21 Apr 2019 21 Oct 2019 21 Apr 2020 21 Oct 2020

	21 Apr 2021
Study result report (initial 6years) Final study report (initial 6years + additional 3 years)	21 Nov 2018 21 Nov 2021

APPENDIX 4. RECIST 1.1 TUMOR ASSESSMENT CRITERIA 1.1

At baseline, individual tumor lesions will be categorized by the physician as either measurable or not, according to the criteria summarized below:

Measurable Lesions

Lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm for lesions other than lymph nodes and assessed by CT scan (CT scan slice thickness no greater than 5 mm).

10 mm for lesions assessed clinically by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

20 mm for lesions assessed by chest X-ray.

15 mm in short axis for lymph nodes when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Non-measurable Lesions

Non-measurable lesions include small lesions (longest diameter <10 mm or pathological lymph nodes with a ≥10 but <15 mm short axis) as well as truly non-measurable lesions. Truly non-measurable lesions include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam and not measurable by reproducible imaging techniques.

Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

Special Considerations Regarding Specific Lesions

Bone lesions:

Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic lesions:

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Solitary lesions:

If a measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Recording Tumor Measurements

All measurable lesions up to a maximum of 2 lesions per organ and up to 5 in total and representative of all involved organs should be identified as **target lesions** and measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions should be selected on the basis of their size (lesions with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The longest diameter will be recorded for each target lesion. The sum of the longest diameter of all target lesions will be calculated and recorded as the baseline sum diameter to

be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment.

One exception to the above described approach is related to pathological lymph nodes. Pathological lymph nodes are defined as measurable lesions and may be identified as target lesions if the criterion of a short axis of ≥15 mm by CT scan is met. Only the short axis of these nodes will contribute to the baseline sum. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Definition of Tumor Response

Target Lesions

Response in target lesions is defined as follows:

Complete Response (CR): disappearance of all target lesions.

Partial Response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also

demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered a sign of progression.

Stable Disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the CRF.

Non-Target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Response in non-target lesions is defined as follows:

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Cytology, histology

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in germ cell tumors). When effusions are known to be a potential adverse effect of treatment (eg, taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response or stable disease and progressive disease.

For patients having effusions or ascites, only cases having cytological proof of malignancy should be recorded on the CRF. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the CRF.

New Lesions

The appearance of new malignant lesions indicates PD. New lesion should be unequivocal (eg, not attributable to differences in imaging technique, or change in imaging modality or findings not attributable to tumor). If a new lesion is equivocal, for example due to its small size, continued therapy and follow-up assessment will clarify the etiology of the disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

The use of FDG-PET is sometimes reasonable to complement a CT scan assessment of a PD (particularly for possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up;

No FDG-PET at baseline and a positive FDG-PET at follow- up: if the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Confirmation of Tumor Response

Confirmation of response is required for non-randomized trials with primary endpoint of response, but is not required in randomized studies since the control arm serves as appropriate means of interpretation of data.

Determination of Overall Response by the RECIST 1.1 Criteria

When both target and non-target lesions are present, individual assessments will be recorded separately. The overall assessment of response will involve all parameters as depicted in Table 1.

Table 1. Response Evaluation Criteria in Solid Tumors

Target lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = complete response, PR = partial response, SD = stable disease,			
PD = progressive disease, and NE = inevaluable.			

Best overall response

The best overall response is determined once all the data for the patient is known. Best response in trials in which confirmation of complete or partial response is not required (ie, randomized trials) is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be the best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

When confirmation of CR and PR is required (ie, non-randomized trials with primary endpoint of response), the best overall response is defined according to the tumor response along the study. Complete or partial responses may be claimed only if the criteria for each are met at a following time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 2.

Table 2. Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR

PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.		
[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.		

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.