REGULATION OF THE INDONESIAN FOOD AND DRUG AUTHORITY
NUMBER 36 OF 2019
ON
GUIDELINES FOR EFFICACY AND SAFETY ASSESSMENTS OF ANTI-CANCER DRUGS

BY THE BLESSINGS OF ALMIGHTY GOD

CHAIRPERSON OF INDONESIAN FOOD AND DRUG AUTHORITY,

Considering :
a. that in order to protect the public from the circulation of Anti-cancer Drugs which do not meet the requirements, it is necessary to assess the aspects of safety, efficacy, and quality in the implementation of registration;
b. that in order to ensure the Anti-cancer Drugs have complied with the efficacy and safety aspects, it is necessary to issue a guideline governing the procedures for efficacy and safety assessments of anti-cancer drugs;
c. that based on the considerations as referred to in point a and point b, it is necessary to issue a Regulation of the Indonesian Food and Drug Authority on Guidelines for Efficacy and Safety Assessments- Efficacy and Safety Assessments of Anti-cancer Drugs;

Observing :
1. Presidential Regulation Number 80 of 2017 on Indonesian Food and Drug Authority (State Gazette of the Republic of Indonesia of 2017 Number 180);
2. Regulation of the Indonesian Food and Drug Authority Number 26 of 2017 on Organization and Work

Procedures of Indonesian Food and Drug Authority (State Bulletin of the Republic of Indonesia of 2017 Number 1745);

3. Regulation of the Chairperson of Indonesian Food and Drug Authority Number 24 of 2017 on Criteria and Procedures for Drug Registration (State Bulletin of the Republic of Indonesia of 2017 Number 1692) as amended by Regulation of the Indonesian Food and Drug Authority Number 15 of 2019 on Amendment to Regulation of the Chairperson of Indonesian Food and Drug Authority Number 24 of 2017 on Criteria and Procedures for Drug Registration;

HAS DECIDED:

To issue: REGULATION OF THE INDONESIAN FOOD AND DRUG AUTHORITY ON GUIDELINES FOR EFFICACY AND SAFETY ASSESSMENT OF ANTI-CANCER DRUGS.

Article 1

In this Authority Regulation:

1. Drug means a finished product including Biological Product, which is a substance or combination of substances used to affect or investigate the physiological system or state of pathology in order to establish diagnosis, prevention, treatment, recovery, and improvement of health, and contraception for humans.
2. Anti-cancer Drug means a drug intended for the therapy and treatment of cancer.
3. Applicant means Pharmaceutical Industry that has obtained licensing in Pharmaceutical Industry in accordance with the provisions of legislation.
4. Evaluator means an employee within Indonesian Food and Drug Authority who based on an appointment letter and an assignment letter from the authorized official has duty to evaluate and/or assess for Drug registration submitted by the Applicant.

Article 2

(1) Guidelines for Efficacy and Safety Assessments of Anti-cancer Drugs serves as a reference for:
   a. The Evaluator in conducting an evaluation and/or an assessment of Efficacy and Safety of Anti-cancer Drugs; and
   b. The Applicant in completion of registration requirements of Anti-cancer Drugs.

(2) The provisions as referred to in section (1) are carried out in the context of drug registration.

(3) The Guidelines as referred to in section (1) include:
   a. assessment principles;
   b. non-clinical assessments; and
   c. clinical studies.

(4) The Guideline as referred to in section (3) is listed in the Annex as an integral part of this Regulation.

Article 3

The implementation of these guidelines considers the provisions of legislation on the following activities:

a. criteria and procedures of drug registration;
b. assessment of new development drugs;
c. assessment of biosimilar products; and/or
d. assessment of bioequivalence study.

Article 4

Monitoring of the safety of Anti-cancer Drugs is conducted based on the provisions of legislation on pharmacovigilance.

Article 5

Assessment for application of Anti-cancer Drug registration that has been submitted prior to the enforcement of this Regulation is carried out based on the provisions of legislation on the following activities:

a. criteria and procedures of drug registration;
b. assessment of new development drugs;
c. assessment of biosimilar products; and/or
d. assessment of bioequivalence study.

Article 6

This Regulation comes into force on the date of its promulgation.

In order that every person may know hereof, it is ordered to promulgate this Regulation by its placement in the State Bulletin of the Republic of Indonesia.

Issued in Jakarta
on 30 December 2019

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,

signed

PENNY K. LUKITO

Promulgated in Jakarta
on 30 December 2019

DIRECTOR GENERAL OF LEGISLATION
OF MINISTRY OF LAW AND HUMAN RIGHTS
OF THE REPUBLIC OF INDONESIA,

signed

WIDODO EKATJAHJANA

STATE BULLETIN OF THE REPUBLIC OF INDONESIA OF 2019 NUMBER 1687

Jakarta, 28 July 2022
Has been translated as an Official Translation
on behalf of Minister of Law and Human Rights
of the Republic of Indonesia
DIRECTOR GENERAL OF LEGISLATION AD INTERIM,

DHAHANA PUTRA

ANNEX TO
REGULATION OF THE INDONESIAN FOOD AND DRUG AUTHORITY
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GUIDELINES FOR EFFICACY AND SAFETY ASSESSMENTS OF ANTI-CANCER DRUGS

I. INTRODUCTION

A. Background

A malignant tumor or cancer is a condition that can generally be life-threatening. The mortality rate from this disease is still relatively high and existing therapies have relatively limited benefits but have huge side effects. Therefore, public are still expecting the invention of anti-cancer drugs that are more effective and safer for patients.

Prior to circulation to public, it is necessary to ensure the efficacy, safety and quality of anti-cancer drugs, especially new anti-cancer drugs, both as new active substances and for the purpose of new cancer indications. In order to ensure the efficacy and safety of anti-cancer drugs, it is necessary to carry out a series of assessment stages (depending on the purpose of anti-cancer drug registration), starting from non-clinical data assessment, pharmacokinetic clinical data assessment, biomarkers, exploratory clinical studies and confirmatory clinical studies. For drugs that have been distributed in other countries, a post-marketing safety data assessment (Periodic Safety Update Report/PSUR) is required in the country that has approved the drugs.

B. Objective

These guidelines for Efficacy and Safety Assessments of Anti-cancer Drugs aims in providing guidance for Efficacy and Safety Assessments of Anti-cancer Drugs and is intended for complementing the existing Regulation of Indonesian FDA on Criteria and Procedures

for Drug Registration. General principles which are not stated in these guidelines refers to the aforementioned Regulation.

C. Guidelines Benefit

In the process of assessing the efficacy and safety of anti-cancer drugs, these guidelines can serve as a guide in the comprehension of non-clinical and clinical study data that must be available to support new registrations and variations of new indications of drugs, including biological products, for the treatment of cancer with adequate data.

These guidelines can also be a guide for researchers, cancer study groups, Contract Research Organizations (CROs), etc., that will design and conduct study that can later be used in applying for the marketing authorization of anti-cancer drugs.

D. Scope

These guidelines contain general principles for assessing aspects of the efficacy and safety of anti-cancer drugs in the context of granting marketing authorizations/approvals in Indonesia. These guidelines explain the requirements for non-clinical and clinical data that must be submitted to support claims for indications, posology, and information related to safety of use. They also explain important aspects of each stage of the efficacy and safety assessments, including an assessment of the information obtained from non-clinical and clinical data. The data consist of toxicological, pharmacodynamic, pharmacokinetic data, dosage determination, and efficacy and safety assessments based on clinical trials that meet the methodological requirements to generate the necessary clinical evidence.

These guidelines apply to small molecules and biotechnology (biopharmaceutical) products regardless of route of administration. Radiopharmaceuticals are not covered in these guidelines, but some principles can be adapted. These guidelines do not apply to the assessments of quality aspects. Along with the dynamics of scientific and technological advances, these guidelines will further be developed to accommodate the development of science and technology in the future.

II. ASSESSMENT PRINCIPLES

A. Registration Documents

The completeness of the anti-cancer drug registration document refers to Regulation of the Indonesian FDA on Criteria and Procedures for Drug Registration which is determined based on the category of drug registration.

B. Assessment of New Anti-cancer Drug Registration

This section covers efficacy and safety assessments for new drugs, new biological products, and drugs with new indications and posologies.

1. Efficacy Assessment

In efficacy assessment, the determination of the sample size must be based on the primary hypothesis to be tested. This primary hypothesis must include the outcome variable being measured and the difference to be achieved compared to the comparator. The power to be achieved to test for differences in outcomes is at least 80% with a 95% confidence interval or another appropriate statistical significance. For the non-inferiority test, a minimum power of 90% is used with a one-sided hypothesis. The hypothesis is prioritized to answer the non-inferiority test. If this is not possible, a differentiating hypothesis can be used (either in terms of differences in clinical effects, pathological responses (cellular, molecular, or chemical), or biomarkers.

Guidance on sample sizes in clinical trials of anti-cancer drugs for very rare cases must consider aspects related to clinical, pathological, molecular, cellular, radiological or laboratory responses.

2. Safety Assessment

The anti-cancer drug safety assessment is based on safety studies on non-clinical, clinical trials and the latest post-marketing periodic safety update reports (PSUR) and data reported by patients (Patient Reported Outcome/PRO).

C. Assessment of Biosimilar Anti-cancer Drugs

Specifically for biosimilar anti-cancer drugs, an assessment is

carried out in accordance with the existing Regulation of Indonesian FDA on the Assessment of Biosimilar Products.

D. Assessment of Generic Anti-cancer Drugs

Specifically for generic anti-cancer drugs, an assessment is carried out in accordance with the existing Regulation of the Indonesian FDA on Procedures of Bioequivalence Study.

III. NON-CLINICAL ASSESSMENT

A. Studies to Support Non-clinical Assessment

Non-clinical studies that must be included are pharmacological studies (pharmacodynamics, pharmacokinetics) and safety studies including general toxicity and specific toxicity (reproductive, genotoxicity, carcinogenicity, immunotoxicity, photosafety).

1. Pharmacodynamics Studies

Pharmacodynamics studies include initial characterization of the mechanism of action of drug compounds, schedule dependencies, and antitumor activity. An appropriate model must be selected based on the target and mechanism of action, but it is not necessary to study using the same tumor type intended for clinical evaluation.

This study may serve as a guide to a schedules and dose-escalation schemes; providing information for the selection of animals for testing; assisting in initial dose selection and selection of biomarkers, and if relevant, for justification of drug combinations. Understanding the secondary pharmacodynamic effects of drugs can contribute to safety assessments in humans.

The selection of animal models or other suitable testing systems needs to be considered in order to obtain scientifically valid information. The selection factors include pharmacodynamic response, pharmacokinetic profile, species, strain, sex and age of test animals, susceptibility, sensitivity, and reproducibility of the assay system and other available information about the substance. If available, human data (e.g. in vitro metabolism) may be considered in the selection of the assay system.

2. Pharmacological Safety Studies

Assessment of the effect of drugs on the function of vital organs (including the cardiovascular, respiratory and nervous systems) can be included in general toxicological studies. Detailed clinical observations after adequate dose selection and electrocardiographic measurements on non-rodents are considered sufficient.

3. Pharmacokinetics

Assessment of limited pharmacokinetic parameters (e.g. peak plasma levels, Area Under the Curve (AUC) and half-life) in animal species used for non-clinical studies can be used as a basis for dose selection, schedule and dose escalation during phase I studies. Further information on the absorption, distribution, metabolism and excretion of drugs in animals are usually obtained in parallel with clinical developments.

4. General Toxicology

Toxicological studies to determine the No Observed Adverse Effects Level (NOAEL) or No Effect Level (NOEL) are not required to support the clinical use of an anti-cancer drug. Since drug toxicity can be strongly influenced by the administration schedule, the estimated administration schedule in clinical studies must be assessed in toxicological studies. This is then discussed in points B.3 (Duration and Schedule of Toxicological Study to Support Initial Clinical Trials) and B.4 (Duration of Toxicological Studies to Support Extension of Clinical Development and Development Duration).

The potential for recovery from toxic effects needs to be assessed to understand whether serious side effects are reversible or irreversible. If there is severe toxicity on clinical exposure and recovery cannot be based on scientific assessment, a study covering a terminal non-dosing period is required. The scientific assessment includes the extent and severity of pathological lesions and the regenerative capacity of the organ systems that exhibit these effects. Assessment until complete recovery is not considered essential.

For small molecules, general toxicity tests are usually carried out on rodents and non-rodents. In certain circumstances, on a case-by-case basis, alternative approaches may be taken (e.g. for genotoxic

drugs targeting rapidly dividing cells, repeated dose toxicity studies on a single rodent species might be considered sufficient, provided that the rodent is the relevant species). Toxicokinetic assessment is performed if necessary.

5. Reproductive Toxicology

Studies of embryofetal toxicity of anti-cancer drugs must be available when applying for marketing authorization, but these studies are not considered essensial to support clinical trials of treatment of patients with advanced cancer. Embryofetal toxicity studies are not considered essensial for genotoxic drugs and drugs to target rapidly dividing cells (e.g. crypt cells, bone marrow) or drugs belonging to a group of drugs that cause developmental toxicity.

For small molecules, embryofetal toxicological studies are usually carried out in two species. If the results of studies in one species indicate that the drug causes embryofetal death or teratogenicity, confirmatory testing in a second animal species is no longer required. Alternative approaches such as literature assessment, placental transfer assessment, direct or indirect effects of biopharmaceuticals, or other factors, can be considered with scientific justification. Fertility studies and early embryonic development are not required for advanced anti-cancer drugs. The information available from general toxicological studies regarding the effects of drugs on the reproductive organs can be used as a basis for assessing fertility disorders. In general, pre- and post-natal toxicological studies are also not required for advanced anti-cancer drugs.

6. Mutagenicity/Genotoxicity

Genotoxicity studies are not considered essential to support clinical trials in advanced cancer. If the drug is used at an early stage, a mutagenicity study is required.

7. Carcinogenicity

Carcinogenicity studies are not required for advanced anti-cancer drugs. If the drug is used for an early stage, a carcinogenicity study is required.

8. Immunotoxicity/Immunogenicity

For most anti-cancer drugs, the components of a general toxicology study design are considered sufficient to assess immunotoxic potential and support marketing. For immunomodulatory drugs, additional endpoints (such as immunophenotyping by flow cytometry) may be included in the study design.

9. Photosafety Testing

An initial assessment of the phototoxic potential must be conducted based on the photochemical properties of the drug and information from other drugs in the same class. If an assessment of these data indicates a potential risk, appropriate protective measures must be taken during the outpatient study. If photosafety risk cannot be evaluated based on nonclinical data or clinical experience, a photosafety assessment consistent with the principles in ICH M3 (R2) must be available prior to application for marketing authorization.

B. Non-clinical Data to Support Clinical Trial Design and Marketing

1. Estimation of Start Dose in Humans

The selection of start dose for first administration in human must be scientifically justified using all available non-clinical data (pharmacokinetics,pharmacodynamics, toxicity), and the selection is based on various approaches. A common approach for many small molecules, the start dose is 1/10 of the severe toxic dose occurring in 10% of rodents (Severe Toxic Dose/STD 10). If the most suitable species is non-rodent, the initial dose is 1/6 of the highest non-severely toxic dose (HNSTD). HNSTD is defined as the highest dose level shown not causing death, life-threatening toxicity, or irreversible findings.

For many small molecules administered systemically, the change from animal dose to human dose is based on normalization of body surface area. For small molecules and biopharmaceuticals, dose changes based on body weight, AUC, or other exposure parameters are appropriate. For biopharmaceuticals with immune agonist effects, the start dose selection uses the Minimal Anticipated Biological Effect Level (MABEL).

2. Dose Escalation and Highest Dose in Clinical Trials

In general, the highest dose or exposure tested applied in non-clinical trials does not limit the dose escalation or the highest dose tested in clinical trials in cancer patients. If a steep dose-response or exposure-response curve is observed for severe toxicity in non-clinical toxicology studies, or if there are no preceeding markers of severe toxicity, a dose escalation that is lower than the usual (2-fold) dose escalation must be considered.

3. Toxicological Test Duration and Schedule to Support Initial Clinical Trials

Although in phase I clinical trials, drug administration can be continued according to the patient's response, there is no need for new toxicological studies with a duration that exceeds the duration of the complete toxicological test.

The non-clinical study design selected must be appropriate to accommodate the different drug administration schedules used in the initial clinical trial. It may be that the schedule for administration in clinical trials is not always the same as for toxicological tests, but the information obtained from toxicological study must be sufficient to support clinical dosing and administration schedules and to identify potential toxicity. For instance, factors to consider are half-life in test animals and projected half-life in humans, exposure assessment, toxicity profile, receptor saturation, etc.

Table 1 shows examples of non-clinical treatment schedules that are commonly used in the development of anti-cancer drugs and can be used for small molecules or biopharmaceuticals. In cases where the available toxicological information does not support a change in the clinical administration schedule, it is necessary to perform additional toxicological study on one species.

Table 1. Sample of anti-cancer Drug Treatment Schedule to Support Initial Clinical Trials

Clinical Treatment Schedule	**Sample of Non-clinical Treatment Schedule 1,2, 3, 4**
Once every 3-4 weeks	Single dose
Every day for 5 days every 3 weeks	Every day for 5 days
Every day for 5-7 days, 1 week interval	Every day for 5-7 days, 1 week interval (2-dose cycle)
Once a week for 3 weeks, 1 week off	Once a week for 3 weeks
Twice or three times a week	Twice or three times a week for 4 weeks
Every day	Every day for 4 weeks
Every week	Once a week for 4-5 doses

[1] Table 1 describes the stages of drug administration. Timing of toxicity assessment in preclinical studies must be scientifically justified based on the expected toxicity profile and clinical treatment schedule. For instance, animal sacrifice must be considered shortly after the drug administration stage to check for early toxicity and animal sacrifice at a later stage to check for late onset toxicity.

[2] The administration schedule described in the table does not specify the recovery period.

[3] The treatment schedule described in this table must be modified for molecules with broad pharmacodynamic effects, long half-lives or potential for anaphylactic reactions. In addition, the possibility of immunogenicity must be considered.

[4] The treatment schedule described in this table must be modified for molecules with broad pharmacodynamic effects, long half-lives or potential for anaphylactic reactions. In addition, the possibility of immunogenicity must be considered.

For studies using non-rodent animals, the dose group usually consists of a minimum of 3 animals/sex/group, with an additional 2 animals/sex/group for recovery. Studies are usually conducted on both sexes, or must be justified if the study uses only one sex.

4. Duration of Toxicology Studies to Support Continued Clinical Development and Development Duration

Non-clinical data to support phase I and clinical phase I are usually sufficient for moving to phase II and serve as second or first-line therapy in patients with advanced cancer. In order to support the development of anti-cancer drugs for patients with advanced cancer, results from repeated dosing studies of 3 months following the intended clinical schedule must be provided prior to commencing Phase III studies. For most drugs intended for the treatment of patients with advanced cancer, a 3-month non-clinical study is considered sufficient to support marketing. When considering changes to the clinical schedule, an assessment of the existing clinical data must be conducted to justify the change.

5. Drug Combination

Pharmaceutical preparations that are planned to be used in combination must be well studied individually in the toxicological assessment. Data to support rational combinations must be prepared before commencing clinical studies. In general, toxicological studies assessing the safety of drug combinations intended for giving treatment for patients with advanced cancer are not warranted.

6. Non-clinical Studies to Support Study in Pediatric Population

The general principle for assessing most Anti-cancer drugs in pediatric patients is to determine the dose in a first place, with relatively safe dose in the adult population, and then assess some of these doses in early pediatric clinical studies. The recommendations for non-clinical studies outlined in this document also apply to the pediatric population.

Studies in juvenile animals to support cancer treatment in the pediatric population are commonly not performed. Conducting

studies in juvenile animals is considered only if safety data in humans and previous animal studies are deemed insufficient for safety evaluation in the pediatric age group.

C. Other Considerations

1. Conjugated Products

A conjugated product is a drug that is covalently bound to a carrier molecule, such as a protein, lipid or sugar. The safety of conjugated materials is a major concern. The safety of unconjugated materials, including the linkers used, may have been partially evaluated. Data on the stability of the conjugate in the plasma of test animals and humans must be available. Toxicokinetic evaluation must assess both aspects, namely conjugated compounds and unconjugated compounds after administration of conjugated substances.

2. Liposomal Products

A complete evaluation of the liposomal product is not necessary if the non-encapsulated material is well recognized. The safety assessment must include a toxicological evaluation of the liposomal product as well as a limited evaluation of the non-encapsulated drug and its carrier (e.g. single-group studies of toxicological studies). The principles described herein may also apply to other similar carriers.

3. Evaluation of Drug Metabolites

In some cases, metabolites that have been identified in humans have not been qualified in non-clinical studies. For these metabolites, separate evaluation is generally not required for advanced cancer patients.

4. Evaluation of Impurities

Standards of impurities must have negligible risk, according to the provisions of the Criteria and Procedures for Drug Registration. If the impurities exceed the required limit for anti-cancer drugs, it must be accompanied by adequate justification. The justification includes the type of disease being treated and the

patient population, the nature of the parent drug (pharmacological properties, genotoxicity and carcinogenic potential, etc.), duration of treatment and the impact of reducing impurities in manufacturing.

Furthermore, the qualification assessment may consider the dose or concentration tested in a non-clinical study relative to the clinical dose. For impurities that are genotoxic, several approaches are used in determining impurity limits based on increase in lifetime risk of cancer. However, this limit is not for the treatment of advanced cancer patients, and the aforementioned justification is applied to consider setting a higher impurity limit. Impurities that are metabolites that have appeared in animal and/or human studies are generally acceptable.

For generic anti-cancer drugs, the active substance must have the same type and impurity limit as the innovator drug. When applied differently, identification of the impurities must be carried out with the impurity limit as required. Generic anti-cancer drugs to be registered in Indonesia must use active substances that have been approved in at least 1 (one) country with a well-known evaluation system in accordance with the Criteria and Procedures for Drug Registration.

IV. CLINICAL STUDIES

A. Exploratory Study

The exploratory study is a phase I/II clinical study.

1. Cytotoxic Compound

This section refers to conventional cytotoxic substances, i.e. compounds that induce lethal and irreversible cellular damage after short-term exposure through interference with DNA replication, mitosis, etc. The activity indicators that are considered suitable for these compounds are toxicity and tumor response.

Conceptually, this section is also relevant for targeted cytotoxic compounds such as toxin-coupled monoclonal antibodies. However, in this setting, tumor antigen expression and prodrug activation pathways must also be considered. As with non-cytotoxic compounds, it is recommended to conduct non-clinical and clinical studies aimed at characterizing the

prerequisites for activity/resistance and to identify markers of resistance.

a. Phase I Study, Dose Determination Test and Dosage Schedule in Monotherapy

The main objective is to determine the Dose Limiting Toxicity (DLT) and the dose to be applied for further studies. The initial dose may use the same dose or a dose based on body surface area (BSA). Where available, the use of pharmacodynamic endpoints may also assist in dose selection.

1) Main Objectives

a) Identifying the Maximun Tolerated Dose (MTD), DLT and recommended doses for Phase II to determine the schedule and route of drug administration.

b) Characterizing the frequent side effects and dose-related target organ toxicity and drug administration schedule. Severity, duration and reversibility must be determined.

c) Initial characterization of pharmacokinetics, including dose and time-dependencies. If necessary, characterization of the relationship of PK/PD with the target effect and side effects and exposures obtained by different routes of administration is also carried out.

2) Patient Eligibility

This study is recommended to be carried out in cancer patients for whom alternative therapies are not available.

3) Administration Route and Schedule

The selection of route and the first dose administered to humans must be justified based on non-clinical data. In most cases, the first administration in human studies is recommended intravenously to eliminate variability related to bioavailability.

In order to obtain a drug administration schedule, experience with this class of compounds is very useful. Non-clinical data regarding cycle dependence and ex vivo cytotoxicity ratio of tumor/normal tissue may also be useful.

4) Dose Escalation

For drugs with minimum or insignificant toxicity, dose escalation can be applied to the same patient.

5) Toxicity Assessment

Minimum requirements for side effect assessment include symptom assessment, physical examination, electrocardiogram (ECG), blood and urine laboratory tests, and radiological examination, if relevant. Pre-clinical data are used as a guide for further testing. If there are no QTc-associated signs in preclinical studies or class products, no specific QTc study is required, but inclusion of the ECG as part of routine monitoring is recommended. Toxicity is assessed according to generally recognized systems (e.g Common Terminology Criteria for Adverse Events/CTCAE).

b. Phase II Therapeutic Exploratory Study, Monotherapy

Phase II studies observe the activity of a single compound on various tumor types, or specific tumor types, or the activity and feasibility of combination or multimodality regimens.

This section focuses on studies which main objective is to estimate the antitumor activity of a single compound in patients with a particular tumor type in order to identify compounds that will be used for confirmatory studies.

1) Study design and objectives

Phase II studies may use a variety of study designs and preliminary studies must provide initial evidence of drug activity and tolerability. It is recommended to use a randomly allocated control

group, especially if only one pivotal confirmatory study is expected.

Study objectives:

a) Assessing response probabilities (and other relevant efficacy parameters) in the target tumor type and making conclusion on the importance of follow-up studies (investigating early stages of disease, combination, compared with standard therapy).

b) Researching pharmacogenomics and biomarker characteristics, if necessary.

c) Further characterizing the dose and dependence on the dosing schedule with respect to drug safety and activity.

d) Further characterizing Adverse Drug Reaction (ADR)

e) Further characterizing PK and PK/PD

f) If necessary, further characterizing the optimal route of administration.

2) Selection and Number of Patients

The definition of disease stated as the target of treatment, the previous therapy (if any), and the stage of disease must be specified in details according to diagnostic criteria which have been internationally agreed. In this case, it is desirable to use sensitive antitumor activity measurement parameters such as functional imaging.

3) Dosage and Administration Schedule

Dosage and administration schedule must be clearly defined.

a) Guidance must be provided to explain dose reduction in relation to the severity of the observed toxicity.

b) If necessary, include a guide explaining the dose escalation of the drug if the toxicity is low.

4) Activity Assessment

The Objective Response Rate (ORR) must be documented in accordance with international standards (e.g Response Evaluation Criteria in Solid Tumors (RECIST), Volumetric RECIST, or World Health Organization (WHO) criteria. Modification of these criteria is possible in certain situations, but must be justified. In assessing ORR, the Intention-to-Treat (ITT) principle must be adhered to. In single arm studies, the ORR in a per protocol analysis may be reported as the main parameter. It is recommended to conduct an external independent review of tumor response, according to study objectives.

Response duration, Time to Progression (TTP) or Progression-Free Survival (PFS), confirmed ORR and Overall Survival (OS) must typically be reported. The use of tumor biomarkers and other dynamic activity measurements is also recommended. In haematological malignancies, disease-specific response criteria are unavoidable in most cases, and complete harmonization has not been achieved for some diseases. For patients with symptomatic disease at the beginning of the study, an assessment of symptom control is recommended, if a randomized phase II study is performed.

2. Non-cytotoxic Compound

This refers to a very heterogeneous group of compounds, ranging from antihormonal compounds to antisense compounds, signal transduction inhibitors, angiogenesis inhibitors, or cell cycle inhibitors, immunomodulators, etc. Common elements influencing clinical trial design are that toxicity may not be an appropriate parameter in dosing and schedule studies, and ORR may not be an appropriate parameter for measuring anti-tumor activity.

In contrast to cytotoxic chemotherapy, non-cytotoxic compounds are generally given continuously so that the toxicity profile tends to be different where DLT can appear for the first time

after repeated cycles of therapy. Therefore, the tolerability and toxicity profiles can be used to determine the Recommended Phase 2 Dose (RP2D) in addition to DLT and MTD.

Therefore, the early stages of clinical drug development are more complex and must be adapted to the pharmacology assumptions of individual compounds as defined in non-clinical studies. The rather strict boundary delimitation between phase I and phase II studies, as is true for conventional cytotoxic compounds, may be less relevant as a parameter of anti-tumor activity, e.g biomarker measurements may be required in advance for dosage determination and administration schedule.

On the other hand, most of the elements for cytotoxic drugs have also contained some relevance, for instance restrictions regarding patient eligibility, recommended route of administration, assessment of toxicity and anti-tumor activity, etc. However, this issue will not be discussed further in this section.

a. Phase I, Dose Determination Test and Administration Schedule for Monotherapy

Non-clinical study data and, if available, data from healthy subjects, may be used to develop a study design to be applied to patients, for instance eligibility criteria and initial dose as well as specific toxicity caused by the drug and sufficient observation period in order to see the toxicity. In accordance with the guidelines for cytotoxic compounds, these studies must normally be applied to cancer patients who have not obtained standard therapies. Subjects who are refractory to conventional cytotoxic compounds may also be resistant to several other compounds, resulting in the use of no other drugs. This will certainly affect the possibility of defining the relationship between dosage/concentration and effect.

PD parameters may include biochemical parameters (receptor binding, enzyme inhibition, downstream events, and other parameters defined in non-clinical studies), imaging studies, proteomics and immunological measurements (antibody or T cell response). It is recommended to conduct a population PK/PD study. For cytostatic compounds in non-

clinical study, it may be necessary to extend the exposure/contact time in clinical trial in order to obtain evidence of tumor shrinkage. If an early and unexpected tumor shrinkage is found, this may indicate that further studies are needed to establish the mechanism of this early response.

Although drug development for compounds with a single main activity target, such as mutated BRAF, is easier to apply, the pharmacological rationale underlying compounds that have multiple targets (poly-targets) are expected to be reflected in exploratory study programs, as for selected biomarkers aiming at identifying suitable target population for the treatment.

1) Main Objectives

a) Measurements of tolerability, safety, PK and if possible PD are relevant goals.

b) As with conventional cytotoxic drugs, it is recommended to use tumor markers and sensitive imaging techniques in combination with conventional methods to delineate possible anti-tumor activity.

2) Patient Eligibility

Based on the toxicological and tolerability findings, as well as the pharmacological assumptions of the drug in pre-clinical trials, initial trials are sometimes possible in healthy volunteers. Eligibility criteria and number of patients must be established according to the study objectives, also taking into account the variability of PK and PD at the dose and administration schedule chosen for further study.

If pharmacologically unjustified, the results of analyzes of accessible tumor biopsies (primary lesions and/or metastatic lesions) are expected to play an important role in studies conducted to identify suitable target populations for confirmatory studies.

3) Dose Escalation

Until now, it is relatively difficult to find tumor selectivity for most compounds. Given that drug safety may not always be related to dose, tolerability and toxicity are still important measures in the study of determining the dose and schedule of administration. If dose escalation to MTD is not sufficient to determine the recommended dose, then dose escalation can be based on relevant pharmacodynamic and safety data in animal studies as well as human PK/PD data from initial and follow-up dose cohorts. Mechanism-based PK/PD modeling may also be useful to guide decision making.

For drugs that work on specific molecular targets (target-mediated biologic pathways), the dosing strategy should not only focus on safety, but also on determining the optimal therapeutic dose. One example is escalating the dose until the target-mediated biologic pathway is achieved with minimum toxic effects. The results of pharmacokinetic/pharmacodynamic observations as well as clinical response (e.g. tumor response or PFS) can be used as additional safety endpoint data to determine therapeutic dose.

The concept of determining MTD and DLT must also be considered in order to determine the relevant toxic effects and determine the dose given in phase 2 studies. Most of the Molecularly Targeted Agent (MTA) and immunomodulating therapy are given continuously and/or long-term (with or without off-treatment period). Some specific toxic effects often appear after the first cycle of drug administration, such as in the form of peripheral neuropathy. Acute toxicity in Cycle 1 which is generally used as a benchmark may not always be found. Therefore, in the definition of DLT and MTD, consideration must be given to the possible long-term toxicity that may affect tolerability and therapeutic dose.

In clinical trials of phase I MTA, more than half of the patients have probably shown grade 3 to 4 toxicity

after the first cycle. Differences between acute toxicity occurring after the first cycle, sustained toxicity affecting tolerability, and delayed severe toxicity needs to be noted and reported.

Dose escalation can be carried out even if an adverse event occurs after the first cycle. However, consideration must be given to the optimal dose requirement while avoiding continuous dose escalation or subsequent dose reductions. Adverse events that occur in each cycle of therapy must be reported. The dose applied in phase 2 must be based on a thorough assessment of likelihood occurrences of adverse events.

Dose estimation of MTA in long-term therapy may use a time-to-event assessment method on an ongoing basis which also considers the toxicity that occurs during the therapy. In order to use this method, the DLT specified in the protocol must cover all the toxicities occured, not only those found after the first or second cycle.

4) Toxicity Evaluation

The general principles are as discussed in point A.1.a (Phase I study, Dosage Determination Studies and Dosage Schedules in Monotherapy), but the known pharmacological reactions associated with adverse reactions are more diverse and must be considered in research planning. For instance, for immune check point inhibitors, autoimmune reactions or immune-related reactions may be included; while other anti-angiogenic compounds side effects may include vascular events, hypertension and proteinuria.

b. Phase II, Therapeutic Exploratory Study for Monotherapy

1) Study Design and Activity Parameter

Although the ORR has drawbacks regarding patient selection, etc., it is a fairly convincing parameter of anti-tumor activity, considering that for most tumors, spontaneous regression fulfillment criteria for at least a partial response are rare.

It is recommended to use a control group that is allocated randomly, as to ascertain whether the selected biomarker is prognostic and/or predictive. However, for exploratory purposes, studies without comparisons can be carried out as long as the results can be interpreted. In these circumstances, the Guidelines on cytotoxic compounds need to be applied.

However, TTP and PFS are principally a function of the tumor growth rate and the activity of anti-tumor compounds. Also, when the presence of progressive disease is an inclusion criterion, tumor growth rate is difficult to define in most patients, and historical data are even more difficult to interpret. Therefore, the interpretation of TTP/PFS data without a randomly allocated comparison is problematic.

Especially in breast cancer, Clinical Benefit Response Rate (CBR), i.e. Complete Response (CR), Partial Response (PR), and absence of progression within 6 months, are parameters of anti-tumor activity that have been established, and can be used for comparisons between studies, although it gives the same major problem as TTP/PFS.

2) Exploratory Study with Time-related Endpoint

There may not be an ideal but feasible exploratory study design for compounds that are assumed to control tumor growth. Here are some design alternatives, with their advantages and disadvantages, that are acceptable from a regulatory perspective. Regardless of the study design, it is recommended that only patients with documented tumor progression can participate in the study.

a) Dose comparison studies with randomized designs (e.g comparing the lowest dose that is still likely to be pharmacologically active, with a higher dose); if they showed a difference in TTP/PFS, they would provide evidence of drug activity, but not in absolute terms.

b) Single arm study with randomized withdrawal of therapy, in patients with non-progressive disease after receiving experimental therapy for a certain period of time. Carry-over effects may occur in some compounds.

c) In patients who have received previous treatment, a comparison of TTP/PFS in the patient himself (intra-patient) may provide evidence of drug activity. In this design, the final TTP of the previous treatment is compared with the TTP/PFS of the experimental treatment. It is recommended to recruit patients with secondary and primary resistance to previous therapy. This is to ensure that the study population is relevant. It also needs be noted that patients with initial failure (primary resistance) to previous therapy may exhibit TTP inversion due to fluctuations in tumor growth rates and the variability associated with imaging techniques. For certain indications, intra-patient comparisons can also be justified in naive patients, i.e. patients who are followed-up without therapy until they experience progression, followed by experimental therapy until progress is made.

d) Randomized phase II study, vs active compound (or placebo/Best Supportive Care if justified) in selected populations. It needs to be noted that in the TTP/PFS comparison, pure growth-inhibiting compounds are "preferred" over compounds that stimulate tumor shrinkage, given that progression is defined by associating it with the best tumor response. Therefore, as the tumor progresses, the tumor burden in patients who fail with pure growth-inhibiting compounds will be higher than in patients with tumor shrinkage.

e) If there is no more suitable techniques applied, TTP/PFS and CBR without internal comparator must be accepted as measures of anti-tumor

activity in phase II study. In this case, it is recommended to conduct a systematic literature review, including the methodology.

In principle, a statistical approach similar to the phase II study with ORR as the outcome parameter could be used. However, early termination criteria are often difficult to determine. The number of patients must be sufficient to obtain an estimate of the percentage of patients who are progression-free at a predetermined point in time. Assessing the rate of tumor progression in the no-therapy group is not easy, while the expected outcome is not easy to define.

For these situations, it is recommended to use ORR and tumor progression, and carried out by an independent team. An increase in tumor size due to inflammation, known as "pseudoprogression", may be an early marker of the activity of certain compounds. If this is known from previous studies, assessment of pseudoprogression must be planned and included in the protocol. Assessment of ORR and TTP as parameters of drug activity must still be carried out even though assessments in the form of tumor markers/PD have been used in-paralel.

The use of HRQoL instrument or symptom control is necessary in randomized design studies. For a window of opportunity study and if sensitive pharmacological effect measures are available (e.g tumor imaging and/or biomarkers) and the target population has been identified with tumors that are likely to be sensitive, a comparative study with placebo is necessary.

Measurements related to ORR that have not been fully validated but considered sensitive are acceptable for exploratory purposes, dose comparisons, and subject exclusion from studies if there is no drug activity shown. However, this must still be recorded, discussed in the analysis, and reported. Nevertheless, in the study

protocol criteria for progressive disease, it is advisable to determine whether incorporation (e.g biomarkers, or imaging, or symptoms) can be used in the study.

3. Immunomodulatory Compounds and Monoclonal Antibodies (MoAb)

This section is primarily intended to provide guidance regarding exploratory studies and also cover some aspects relevant to confirmatory studies.

a. Monoclonal Antibodies

Monoclonal antibodies can affect tumor cells directly, for instance through Antibody-Dependent Cell-mediated Cytotoxicity (ADCC) and/or blocking signals at growth factor receptors/antiapoptotic receptors, or indirectly through targeting growth factors to tumors or tumor supporting structures, or by blocking inhibitory T cell signals (e.g anti-CTLA4, anti-PD-1, and anti-PD-L1).

In vitro non-clinical studies must be carried out to determine the primary activity of MoAb. This study may include relevant examinations of:

1) Binding to target antigen: tumor cells or plasma must be screened for over-expression of the target, and the relationship between target expression and its activity must be investigated.
2) Unwanted targets. Tumor specificity may not be attainable, but it is possible to screen 'unwanted' targets by using in vitro, which would facilitate a safety assessment.
3) Fab-related functions (e.g neutralization of soluble ligands, receptor activation or blockade)
4) Fc-related functions (e.g ADCC, complement-dependent cytotoxicity (CDC); complement activation).

Target-mediated disposition can be seen with MoAb. Adequate characterization of disproportionate behavioral form of PK with this dose may not be possible until late-phase studies, when studying patients with tumors whose targets vary widely. Therefore, continuous assessment of PK MoAb is

recommended during clinical development programmes, which often involve different tumor types and stages.

MoAb clearance is commonly affected by FcRn IgG cycling, Anti-Drug-Antibodies (ADA) immunogenicity and can also be influenced by factors in the patient's health status (e.g albumin, soluble receptor or ligand, type and severity of disease, tumor burden, etc.). Knowledge of these factors can support comprehension of the nature of MoAb exposure and response. Experience with MoAb immunogenicity in other areas of clinical medicine must be considered in terms of assay selection, markers for loss of activity, and potential safety concerns.

b. Immunomodulatory Compounds including Tumor Vaccines

Immune therapy, including therapeutic cancer vaccines, aims at inducing specific anti-tumor immunity against existing malignancies. Such immune therapy is generally intended to induce adaptive T and B cells and innate immune responses in cancer patients. The properties of the drugs used vary widely, including synthetic peptides, recombinant proteins, virus-like particles, immunomodulatory antibodies, gene therapy, and cell-based products. Since it is difficult to impair tolerance to tumor antigens which are usually derived from self-antigens, cancer vaccines are commonly combined with pharmacologically active adjuvants such as cytokines or toll-like receptor agonists. Another approach to impair immune tolerance is by blocking inhibitory T cell signals, namely with monoclonal antibodies. The activation and proliferation of T cells results in both desirable and unwanted immunostimulatory effects: wanted anti-tumor effects and the emergence of immune toxicities such as colitis and endocrine insufficiency.

Non-clinical in vivo and in vitro proof-of-concept studies must be provided to justify start dose and planned schedule for phase I study. Additionally, and on a case-by-case basis, rationale for start dose can be supported by using 'Minimal Anticipated Biological Effect Level (MABEL)' approach and

with non-clinical and clinical data of related compounds. It is acknowledged that for products relying on human-specific antigens that need to be presented to Major Histocompatibility Complex (MHC) molecules, predictive animal models are frequently not available. However, animal models using homologous antigens or animals that are human MHC transgenics may become options for non-clinical pharmacological and toxicological studies, where available. There must be information on the differential expression of target antigens in tumors and healthy tissues in humans. In the absence of relevant and predictive animal models, in vitro studies on human cells, such as the in vitro T-cell priming assay may be suitable to demonstrate proof-of-concept.

The purpose of initial clinical study is to establish safety and the dose and schedule that induces the desired immune response. Dose finding studies are generally required to establish phase II dosing recommendations. Monitoring of the immune response, i.e. the induction of antigen-specific T cells or the presence of a humoral response, is important to establish an appropriate dose and schedule. To achieve this goal, various monitoring assays may be required and must be explored carefully. The analysis method must be described in details in the clinical trial protocol.

Tumor biopsies taken before and after drug administration are expected to play an important role in assessing the level and type of immune activation in target tissues, and can be an early marker for potential anti-tumor activity. Induction of tumor response in patients with high tumor burden can serve as formidable obstacle to overcome, and may result in the inclusion of patients with minimal or low tumor burden. An example is the treatment of NSCLC (NonSmall Cell Lung Cancer) patients after complete tumor resection, where cancer immunotherapy can be assessed in an adjuvant setting. Another example is a patient with non-resectable NSCLC who has responded to chemotherapy. Clinical study designs using experimental therapies in patients with limited and measurable disease must be

justified with caution. As with other anti-tumor substances, evidence of anti-tumor activity is important before initiating confirmatory studies.

Oncology patients usually discontinue treatment when the disease progresses. Induction of an effective immune response and clinical response may take more time to develop (delayed effect) compared to classical cytotoxic compounds. Thus, patients may experience disease progression before the onset of biologic activity or clinical effects. Discontinuation of active cancer immunotherapy in cases of slow progression may not be appropriate. In such situations, a detailed definition of “slowly progressive disease” and/or withdrawal criteria is expected to be included in the study protocol, and close monitoring of the patient is required. The definition of “slowly progressive disease” must be guided by the course of the disease being studied. The revised criteria for the definition of progression are acceptable if there is appropriate justification, in confirmatory studies, but OS is the recommended outcome measure. Potential toxicities, such as the induction of autoimmune reactivity (cellular and humoral) and the induction of tolerance, must be monitored carefully during clinical development.

4. Combination Therapeutic Study

a. Combination of Conventional Cytotoxic Compounds

The selection of patients with alternative therapies must consider the documented activity of each component of the combination regimen. The exploratory study included the establishment of MTD and RP2D for the combination drug, as well as initial assessment of antitumor activity in terms of ORR and PFS/TTP. While the level of antitumor activity for the new combination is determined based on assumptions, the toxicity may be predictable on the basis of the individual components. If PK interactions can be excluded, and based on the dose-response/toxicity profile, dosing studies can be initiated at about half the recommended monotherapy dose for each compound. It is also possible to start at the full

recommended monotherapy dose for one compound and a reduced dose (<50%) for the other compound. Since the order of administration may be important in terms of potential PK interactions and anti-tumor activity, this must be taken into account in the study design.

There is no uniform method to balance the dose intensity between the components of a combination regimen to optimize the risk-benefit. Thus, it is agreed that priority in terms of dose intensity must be given to the compound with the highest monotherapeutic activity. If one component is regard as an acceptable treatment regimen in monotherapy, randomized phase II study comparing monotherapy with combination regimens can provide informative data. For confirmatory studies, comparisons with the best available evidence-based comparison regimen are expected.

b. Combination with Non-cytotoxic Drugs

Chemotherapy regimens to be combined with non-cytotoxic substances are chosen as the "best" regimen, unless there are strong biologic or pharmacological reasons. If the dose intensity/systemic exposure of the chemotherapy regimen is not changed, it can be assumed that all patients will receive appropriate therapies. Therefore, there is no need to limit patient eligibility from this perspective.

When previous non-clinical and clinical experience suggests that PD markers, etc. can provide information in terms of anti-tumor activity, it must be part of the study plan. This includes investigating whether the expression of the target non-cytotoxic compound is affected by therapy with the cytotoxic agent, and vice versa if necessary.

Given the predictability of additional activity in nonclinical models, randomized phase II study comparing experimental regimens with chemotherapy regimens alone are considered important. For this study, it is recommended that conventional antitumor activity data (ORR/TTP) be supplemented with tumor markers and parameters sensitive to, e.g. tumor metabolic activity, as needed.

If the additional activity of a non-cytotoxic compound to a chemotherapy regimen has been demonstrated, the need for further randomized phase II study when investigating for new indications may not be warranted. However, this must be justified, as the importance of target expression and inhibition may differ in other tumor types.

If target expression for non-cytotoxic compounds can be affected differently by different chemotherapy regimens, it is advisable to study target expression during therapy with new chemotherapy regimens before undertaking add-on study. Research aimed at understanding the mechanisms and prerequisites for additional effects is highly recommended, as they may improve the characterization of the target population in other future studies.

For some non-cytotoxic compounds, the combination is needed not only to optimize anti-tumor activity, but is actually needed to determine its activity. For such compounds, for instance the target saturation in monotherapy and non-clinical toxicity data for the combination can be used to establish an appropriate starting dose and schedule. Otherwise, dose/schedule exploratory studies and therapeutic exploratory studies may be continued as for the monotherapy regimen.

If supported by non-clinical biological and/or pharmacological data and strong preliminary proof-of-principle clinical data, two new compounds can be combined in a co-development program. The following three scenarios can occur:

1) Uni-enhancement, is a scenario in which one component of combination B, which has no anti-tumor activity or has minimal activity, but increases the anti-tumor activity of another component of combination A (e.g through prevention of resistance). B's contribution needs to be enforced with data from an appropriate non-clinical model. In phase II, comparison with standard control therapy is recommended, whereas phase II monotherapy data for B may be considered unnecessary. A suitable

phase II design could be one randomized three-group study AB vs A vs standard control therapy.

2) Co-enhancement, can be used when both components of the combination show (moderate) antitumor activity, and when combined the antitumor activity is greatly increased. In phase II, the new combination must be compared with the components of the combination as monotherapy at the effective dose, and standard control therapy: AB vs A vs B vs standard control therapy. Depending on the outcome of phase II, one or two monotherapy groups may not be needed in phase III. If the monotherapy group of one component combination is part of phase III (A+B vs B vs standard comparator), the same monotherapy may not need to be included in phase II (A+B vs A vs standard control therapy).

3) Synthetic lethality, is a scenario which the two components of the combination have no anti-tumor activity or minimal anti-tumor activity, but show potent activity as a combination. If non-clinical and clinical studies indicate "inactivity" at dose/exposure levels well above the combined dose and the combination is clearly active, contributions of both components may not be required for phase II and phase III studies. The need for both components of the combination needs to be proven for new indications, considering that the same target may have different effects on different malignancies.

c. Evaluation of Toxicity and Tolerability in Studies for Combination Dosage Establishment

If there is no suitable pharmacodynamic endpoint for dose optimization, then dosage establishment is essentially dependent on toxicity and tolerability. The study design for dosage establishment depends on the drug class. For instance, if it is necessary to extend the duration of therapy, DLT needs to be observed to determine the dosage limit that gives the desired clinical effect, with tolerable side effects.

B. Phase III, Confirmation Study

Confirmation study must be designed with the aim to establish a risk-benefit profile of the test drug in the target population in accordance with clinical practice. Confirmation study are conducted to determine whether the test drug has better efficacy than existing therapeutic options or has comparable efficacy but with a better safety profile.

1. Design

a. Patient Population

For diagnosis, criteria for initiation of treatment, eligibility, response criteria, and choice of comparison therapy are determined based on scientific evidence and/or general knowledge and current treatment guidelines. The heterogeneity of the study population (performance status, co-morbidities, organ dysfunction, etc.) in the study needs to be reduced in order to improve the study's ability to detect differences between study groups. Patients must be selected based on appropriate tumor characteristics, e.g stage, grade, target expression, and other biomarkers important for tumor prognosis and/or sensitivity, previously received therapy (responsive/resistant/refractory), performance status, co-morbidities, and organ dysfunction. Stratification also needs to be carried out based on other important and recognized prognostic variables.

If several variables (including phenotype and genotype) have certain effects on the outcome, then these variables must be mentioned in the clinical trial protocol including the statistical analysis plan. The calculation of the sample size must consider these variables. For instance, if it is known that the response of an Anti-cancer drug will be different in individuals with a certain phenotype, then the clinical trial protocol must be stated and statistical analysis designed to show that the response between the two phenotypes is significantly different.

Considering that phase III clinical trials are confirmatory study, the variables that will be used to measure therapeutic outcomes must be defined and included in the clinical trial

protocol. For an illustration, if a targeted therapy is being observed, then the variable that shows the target expression must be supported by the same histological diagnostics. If the clinical trial will involve subjects with different histological diagnostics, then a clinical trial with a different protocol must be carried out.

It is possible that the target indication includes such a small group of patients that an "exceptional" condition applies. If an Anti-cancer drug is indicated for a patient who does not respond to or is intolerant of standard drug therapy, combining the two groups in one study is permitted only if (1) it occurs in very rare disease or (2) there are no other therapy options.

b. Comparative Therapy

Preferred comparator drugs are drugs that have been registered in Indonesia. Exceptions are given for drugs used for diseases that do not have standard therapy or are classified as orphan drugs.

Among the best available comparators, regimens with the same cycle length must be selected so that tumor assessment can be scheduled at the same time. If the goal is not to improve tolerability and toxicity, a regimen with the same toxicity as the test regimen is selected. A double-blind design can be done if the side effects are comparable. Placebo can be used in add-on studies (in active comparison or Best Supportive Care (BSC)).

It is preferable to use active comparators that have shown an effect in terms of clinical response. If there is no recognized comparison regimen, the BSC can be used, but a documented active comparison is preferred, for example in terms of response rate. If a single comparison regimen is recognized as a comparator, the regimen that provides the best clinical outcome must be selected for a comparator.

A scientific evidence-based therapy generally refers to the primary therapy that provides the best benefit. In certain conditions, a type of malignancy may fail to respond to several lines of therapy. In this situation, clinical trials can be carried

out in a single arm on patients who have shown good performance status (Eastern Cooperative Oncology Group (ECOG) 0 and 1), and are intended for the treatment of life-threatening diseases. If the test drug is used as a single drug or in combination, the test regimen must be compared with a "best available" comparator based on the benefit/risk ratio, not just on efficacy.

The superiority criterion must be demonstrated when a test drug is added to a recognized regimen, rather than the recognized regimen. A drug is classified as superior if it has shown a clinically and statistically significant difference.

c. One-Way Cross-Over

One-Way Cross-Over during disease progression mayonly be performed if it is believed that the treatment options provided are of greater benefit to the subject. If such a One-Way Cross-Over is required, there must be sufficient evidence that the PFS, OS, and other important secondary endpoint data are convincing enough to achieve the clinical trial objectives and draw adequate conclusions. In such circumstances, OS analysis may be carried out on the basis of the planned secondary or co-primary analysis.

Subjects who have progressed to therapy group A (comparator drug) may be given the right to switch to therapy group B (test drug), as long as the test drug proves to be beneficial. In this situation, data analysis must include the subject's data when switching to the test drug (e.g staging, ECOG, duration of treatment at cross-test, cardiovascular, laboratory parameters). However, in this condition, it is not permitted to calculate the OS.

d. Randomization and Stratification

Randomization and stratification must adhere to the general principles of clinical trials. In many cases, double-blind designs are not feasible because of obvious differences in toxicity between study regimens or safety reasons. If studies are to be conducted in a non-blind manner, there are implications for the selection of study endpoints, assessment by independent teams, sensitivity analyzes and other methods

must be undertaken to limit potential bias with respect to study dissimilarities.

e. Endpoints

Confirmatory study must demonstrate that the test drug has clinical benefit. There must therefore be sufficient evidence to demonstrate that the selected primary endpoint can provide a valid and reliable clinical benefit in the patient population described in the inclusion criteria.

Acceptable primary endpoints are OS, PFS, DFS (Disease Free Survival) and ORR. OS is the most reliable cancer endpoint. Other primary endpoints, such as TTP or TTF (Time to Treatment Failure), are possible by submitting justification.

OS is the time measured from randomization of subjects to the occurrence of death from any cause, and it is measured in the ITT population. OS is measured in a randomized controlled trial with comparators. Historical trials are not commonly used to calculate OS.

It needs to be noted that the calculation of OS is often constrained by the presence of several confounding variables that can affect the results of OS analysis, for instance, due to long follow-up and the presence of co-morbidities. Clinical trials can also use PFS/DFS as the primary endpoint. However, the secondary endpoint must be an OS, and vice versa.

If OS is reported as a secondary endpoint, estimates of the effect of treatment on OS must ensure that there are no relevant negative effects at this endpoint, commonly by showing a trend towards superiority. In situations where there is a large effect on PFS, or if there is a long expected survival after progression, and/or a clearly favorable safety profile, precise OS estimates may not be required for approval.

If the OS is reported as the primary endpoint, consistency is expected as a regards effect on PFS. If inconsistency is expected, for example in the case of certain immuno-modulating therapies, an explanation in the study protocol is required.

However, the extension of PFS/DFS has shown that the drug is beneficial for patients. The selection of the primary endpoint must be based on the relative toxicity of test drug, and also the expected survival after disease progression, available next-line therapy and the prevalence of the condition. Regardless of the primary endpoint chosen, it needs to be emphasized that the magnitude of the effect of treatment on all relevant outcomes is the basis for the risk-benefit assessment.

In some conditions, events of progression will be observed at a slow rate, making frequent assessment of events of progression a burden to the patient. The event rate at pre-determined time and at fixed time can be used as the primary outcome in this case. If the event rate at one point is selected for the primary analysis, it is recommended that all patients have been in the study for that time period. PFS, in the time to event analysis, must be reported as a secondary endpoint when a fixed time point assessment is used as the primary outcome.

The tumor resistance profile to drugs is influenced by therapy. This may be relevant for next-line therapeutic activity. This is most clearly seen when adjunctive/long-term therapy is compared with no treatment or placebo, e.g. first-line ovarian cancer, NSCLC and certain haematological conditions. Progress while the subject is undergoing therapy indicates that at least there has been resistance to the therapy or regimen. This is different from progress when not treated. Resistance to next-line therapy may differ between the test drug group and the control group, where one may experience cross-resistance with the next drug.

In the event that an intervention is intended to benefit from maintenance therapy or to increase the number of induction cycles, such a study must be designed with the aim of demonstrating a survival benefit in the patient. If this is not possible, other endpoints such as PFS in next-line therapy (PFS2) can be used. This situation must be described in the study, especially with regard to drugs or regimens for next-line therapy after progress.

If the test drug used for adjunctive therapy can be applied as the sole drug at the time of relapse, it is recommended that initial treatment, i.e. adjunctive therapy, be compared with deferred therapy, i.e. therapy at the time of progression.

It is not possible to describe next-line therapy in the study protocol and to follow patients with scheduled assessments until PFS2. In these cases the timing of next-line therapy can be used as a proxy for PFS2. The possible increase in variability in the "PFS2" assessment will be taken into account in the comparison of PFS2 control against PFS2 test.

In this case, the data completeness must be ensured, in general, early progression "on or off" therapy is associated with more aggressive disease i.e. biasing of early PFS2 results in favor of groups showing inferior PFS1 results. In patients with tumor-associated symptoms at baseline, symptom control, if associated with anti-tumor effects, is a valid measure of therapeutic activity validity and may serve as a primary endpoint in end-line therapy studies, provided that possible sources of bias are minimized. In certain cases, time to symptomatic tumor progression may also be a sufficient primary measure of benefit to the patient.

Secondary Endpoints and Exploration Analysis

In addition to OS or PFS as primary endpoints, other parameters such as ORR and tumor stability must also be reported, e.g. for 3 or 6 months. Especially in palliative conditions, to assess HRQoL/PRO, generally accepted instruments can be used (point 4.2. Health Related Quality of Life (HRQoL).

f. Immunogenicity

Anti-cancer drugs classified as biological products are required to include data on immunogenicity as a primary or secondary outcome.

Immunogenicity is the ability of a therapeutic protein product to induce an immune response against that protein and other similar proteins or to cause unwanted clinical events related to an immune response.

For Anti-cancer drugs in the form of protein compounds, such as monoclonal antibodies, the immune response to therapeutic proteins poses problems in patient safety and product efficacy. Unwanted immune responses to therapeutic protein products can neutralize their biological activity and result in adverse events, not only by inhibiting their efficacy, but also by cross-reacting with endogenous proteins and causing loss of physiological function. Since most of the adverse effects originate from the elicitation of an immune response to a therapeutic protein product mediated by humoral mechanisms, antibodies to the therapeutic protein product are the main criterion in measuring the immune response to this class of products.

The resulting immune response to therapeutic protein products can range from the absence of clinical manifestations to serious adverse events, including life-threatening complications such as anaphylactic reactions or neutralization of efficacy.

Antibodies to therapeutic protein products are divided into neutralizing and non-neutralizing antibodies. Neutralizing antibodies bind to specific functional parts of the therapeutic protein product and neutralize its activity. Non-neutralizing antibodies will bind to parts of the therapeutic protein product that are not functional parts and cause various effects on efficacy and safety.

The long-term persistence of neutralizing antibodies needs to be investigated in long-term clinical studies. In general, for chronically administered products, immunogenicity data of one year or more must be collected and assessed, unless a shorter duration can be justified scientifically. In some cases, a longer assessment may be required, depending on the frequency and severity of the consequences. Such studies can be carried out after marketing authorization approval.

Under certain conditions, antibody responses, regardless of clinical response, must be followed in series, until the levels return to baseline. For therapeutic protein

products that lose their efficacy, regardless the duration of treatment, it is important to assess whether the loss of efficacy is antibody-mediated.

Anti-cancer drugs in the form of protein compounds or biological products, such as monoclonal antibodies, must always be investigated for their immunogenicity before obtaining marketing authorization. Immunogenicity studies must be investigated in both animals and humans, as animal data usually cannot predict immune responses in humans.

In immunogenicity studies, manufacturers need to justify antibody testing strategies including selection, assessment, and characterization of antibody determination methods; exact sampling time, including the start time. Factors that must also be considered are sample volume and sample processing/storage as well as the selection of statistical methods for data analysis. The antibody determination method needs to be validated for the intended purpose. An assay method for screening with sufficient sensitivity must be used for antibody detection. Neutralization determination methods must also be available for further antibody characterization, if any. The possible influence of other antigens on the antibody determination method must be taken into account. The detected antibodies need to be further characterized and their potential clinical implications regarding safety, efficacy and pharmacokinetics need to be evaluated.

For instance, antibody isotypes must be determined if they predict safety (e.g. the incidence of IgE antibodies correlates with the occurrence of allergic and anaphylactic responses). The observation period required for immunogenicity testing depends on the desired length of therapy and the expected time for antibody formation. This must be stated and explained by the manufacturer. In the case of chronic administration, one year's data are generally sufficient to obtain marketing authorization in assessing the incidence of antibody formation and possible clinical implications. If deemed clinically relevant, the development of

antibody titers, their suitability over time, potential changes in the character of the antibody response and their possible clinical implications must be assessed before and after marketing. As pre-marketing immunogenicity data are often limited, further characterization of the immunogenicity profile may require post-marketing. This is especially done if serious adverse events associated with rare antibodies are not detected in the pre-marketing stage.

2. Efficacy

a. Treatment for Curative Purposes

The main objective of developing new therapies, e.g in patients with high-grade lymphoma, germ cell tumors or in adjuvant conditions, is to increase cure rates and survival or reduce toxicity relevantly without loss of efficacy. However, in some cases, and because of the complexity of administering therapy, for example in Acute Myeloid Leukemia (AML), the effect of the test drug on this endpoint may be difficult to demonstrate.

The test drug is expected to be rarely used as a single therapy, but will be used as an add-on to an established or modified regimen, or as a substitute for a compound that is part of an established regimen. In this case, adjunctive therapy can be considered as an add-on therapy if it is considered not to have been established.

In the treatment of acute leukemia, failure to achieve CR, recurrence and death without recurrence are counted as events in the EFS analysis. Patients who do not achieve a CR during the predefined induction phase will be considered to have an event at time 0.

If EFS is the primary endpoint, study data are analyzed only when they are sufficiently mature, i.e. if plateau EFS is predicted to be stable or if additional disease recurrence is rare. In patients with high-grade lymphoma or solid tumors, PFS can be used as an outcome. Not achieving at least PR after a set period/number of cycles can be considered as treatment failure and therapy is continued only for those

achieving at least PR. In the primary analysis it was recommended that patients who do not achieve PR will not be followed up or on next-line therapy until progression or death.

If cure rate improvement is the goal of therapy, it is recommended that DFS at a predetermined time point be used as the outcome (see above for timing).

1) Reduced Toxicity Expected

In the majority of cases, the substitution design is predictable, meaning that the A in the prescribed regimen (AB) is replaced with the test drug X (XB). From a regulatory perspective, non-inferior designs are acceptable and in the vast majority of cases, EFS or PFS are the accepted primary endpoints.

In cases where induction is followed by consolidation and/or adjunctive therapy, the confounding effect of therapy given after the end of the trial therapy may make endpoints other than PFS or EFS more appropriate. This means that the CR (and CR + PR) after the end of the experimental therapy can be the accepted primary endpoint if further therapy is scheduled.

CR is defined on the basis of established clinical criteria, but supporting evidence in the case of Minimal Residual Disease (MRD) e.g. by molecular criteria must be sought. As for other biomarkers, intra- and inter-laboratory variability must be minimized through standardization.

2) Increased Toxicity Expected

Substitution or add-on designs can be used. In most cases, the advantage in terms of EFS, PFS, or the appropriate OS, must be demonstrated and the benefits in terms of extended time to event must be sufficiently large to balance the increased toxicity.

The large increase in CR after induction therapy is associated with trends in PFS or EFS, and survival, may be sufficient if the treatment schedule is administered after the end of the trial therapy tends to confound the overall outcome. This is of particular relevance if the target population is small.

3) Major Increase Toxicity Expected

The objective must be to demonstrate an increased cure rate or OS improvement. In some cases, such as in small study populations, large increases in EFS or PFS and supporting data compatible with favorable trends in survival may be sufficient.

b. Treatment administered with the intent to achieve long-term disease control

Typical conditions include initial-line therapy in advanced breast cancer, colorectal cancer, low-grade lymphoma and chronic leukemia for which established comparative therapies are available and the next-line treatment options are effective.

1) Reduced Toxicity Expected

Non-inferior designs are acceptable and PFS is considered a suitable primary endpoint. In the case of a relevant reduction in toxicity, mature survival data may be submitted after the marketing authorization release if justified by study data.

2) Increased Toxicity Expected

The objective must be to demonstrate superiority at least in terms of PFS. Survival data must be available at the time of registration. Mature survival data cannot be expected in all follow-up cases after consent for survival. If the absence of an increase in treatment-related mortality is not definitively established, mature survival data must be available for safety efficacy assessment prior to drug authorization approval.

3) Major Increase in Toxicity Expected

The main objective is to demonstrate improved survival. In individual cases, this may not be achievable because of the expected good prognosis with regard to survival and the availability of many next-line regimens, including test therapy at disease progression and a small target population. If PFS is the primary endpoint chosen for the study, thorough justification is required. Discussion of the planning stages is also necessary for

the assessment of mortality that may be associated with therapy. Although only the main benefit in terms of prolongation of PFS is received, if possible the number of patients included must be sufficient to obtain an estimate of OS.

c. Palliative Therapy

This refers primarily to last-line conditions where the prognosis for survival is poor and when it is difficult to identify a documented comparative therapy. In other cases, patients are deemed unsuitable for intensive and potentially curative therapy as defined by well-defined criteria. In cases where there is no established comparative therapy, the investigator's best choice or BSC with or without placebo is acceptable.

In studies conducted with BSC as a comparative therapy, studies must aim to demonstrate OS prolongation and/or symptom control of global improvement or HRQoL and efforts are needed to reduce possible bias. Studies in this population require that the treatment is well tolerated.

If the comparator regimen is known to be active but not established, superiority in terms of PFS may be acceptable. In this case, the following will be taken into account in the risk-benefit assessment i.e. evidence showing the activity of the comparative therapy, the magnitude of the benefit of the PFS trial regimen over the comparison regimen, tolerability/toxicity profile, survival after progression and prevalence of the condition.

It is acknowledge that a patient may be considered suitable only for palliative therapy at baseline due to poor performance status, but may respond well so that further therapy can be given with curative intent, including reduced intensity of Hematopoietic Stem Cell Transplantation (HSCT). The management of the patient in this condition must be defined in the analysis plan.

3. Special Consideration

a. Hematopoietic Stem Cell Transplantation, Methodological Consideration

If allogeneic HSCT is a future treatment option, it is important to determine how the transplantation must be handled in the analysis plan. It is fully recognized that the criteria for HSCT (patient eligibility, Human Leukocyte Antigen (HLA) compatibility, conditioned regimen, graft versus host disease prevention, etc.) vary between institutions and regions. However, these criteria must be defined in the protocol and the reasons for performing or not performing the HSCT must be written down by the Case Report Form (CRF).

Although transplantation-related mortality is a problem and long-term benefits require prolonged follow-up, it is commonly expected that patients who underwent HSCT are followed for OS and EFS since randomization. Patients may be censored at the time of conditioning for HSCT for sensitivity analysis.

Since treatment given before transplantation can affect the outcome of HSCT, the proportion of patients who underwent HSCT is not considered a matched primary outcome, even if all patients responding well to treatment are scheduled for transplantation.

Autologous stem cell transplantation has received less attention from an assessment perspective and can be viewed as an intensified consolidation therapy in which the consequences for short-term mortality and possible long-term benefits are less pronounced than after HSCT. However, heterogeneity in performing autologous transplantation must be avoided wherever possible, and censoring may not be performed.

b. (Neo) Adjuvant Sensitizer Therapy

In the adjuvant setting, the ultimate goal is to increase cure rates. While the effect on DFS is considered relevant to the individual patient, it is important to consider in study planning whether it is necessary to demonstrate a beneficial effect on cure rates, i.e. in analyzes performed when recurrence rates have reached a plateau.

Since the use of adjuvant therapy may limit treatment options at the time of relapse, OS data must be reported. For established adjuvant therapy areas, e.g. breast cancer and colorectal cancer, and if the benefit-risk is considered favorable for the trial regimen based on DFS and available safety and survival data, including PFS on next-line therapy after disease recurrence, the mature survival data can be reported after approval. In some cases, and because of major toxicity concerns, beneficial effects on OS must be demonstrated.

The objectives of neoadjuvant therapy may include improving overall outcome (OS, DFS/PFS), enabling surgery and organ preservation (e.g. more conservative surgery). If organ preservation is the main objective, at least non-inferior DFS/PFS must be documented. As for adjuvant therapy, a defined number of cycles is often given. With delay in study objectives, it is acceptable that treatment be discontinued if tumor shrinkage is not observed after the defined treatment period. When pathological CR at the time of surgery was reported as a secondary endpoint, patients with discontinued treatment must be considered as non-responders.

c. Drug Resistance Modifiers, Chemoprotective Agents and Radio/Chemotherapy

In principle, the confirmatory study design for testing drug resistance modifiers and chemo/radio sensitizers (A) is clear and simple; AB must be demonstrated to be more active than the established regimen (B) in terms of antitumor activity and the benefits-risks of the combination must be shown to be favorable. If there is a PK interaction, or a PD interaction unrelated to anti-tumor activity, an adjustment in the dose of B in the combination group may be necessary to make comparison an AB versus B for the same at similar overall toxicity. If an overall PK interaction effect is evident captured from a by change in the plasma levels of B (e.g. no change in distribution), a dose adjustment of B in order to compare AB vs. B at the same similar exposure of B is preferred.

For chemoprotective agents, it must be demonstrated that normal tissue is more protected from toxicity than tumor tissue. For most cytotoxic compounds, it is easier to detect dose-related differences in toxicity than in efficacy. This means that in most cases very large studies with tight confidence intervals around anti-tumor activity measurements are needed to prove that normal tissue protection is achieved without loss of anti-tumor activity. Co-primary endpoints are required needed, testing the hypothesis testing to of improved safety and non-inferior anti-tumor activity. In some cases, it may be easier to demonstrate conclusively a difference in tissue protection by increasing the dose of the cytotoxic compound in the test group in order to demonstrate an improvement in anti-tumor activity without a rise in increased toxicity.

However, if it can be demonstrated conclusively that there is no PK interaction and that the chemoprotective compound cannot interact with the tumor, for example in the absence of the target in tumor cells, it may be acceptable to simply demonstrate decreased reduced toxicity without a formal non-inferiority testing of tumor protection.

d. Tumor Prevention

In concept, the situation is somewhat similar to the adjuvant condition. Individuals at risk must be defined so that the observed reduction in the risk of tumor events outweighs the side effects of therapy. For tumor prevention it is possible to select tumors with altered biological behavior, comparative data on tumor phenotype/genotype are expected and data on tumor response to therapy or OS may be needed. In planning this study, regulatory scientific advice is recommended.

4. Methodological Consideration

One single study devoted to a particular indication is common. A consent based on a pivotal study required evidence of efficacy at levels exceeding the standard criteria for statistical significance. This is particularly the case with non-inferiority studies, in studies with PFS as the primary endpoint and

comparisons with investigator's best choice/BSC. It is recognized that supporting evidence from confirmatory studies performed on other indications must be taken into account in the assessment. The supporting value of these studies may vary and it is necessary to discuss the relevance of these findings in relation to the registration of these new indications.

a. Adaptive Design

If a phase II/III study is designed to answer only the single, non-complex questions in a phase II study, for appropriate dosing at the confirmation stage, an adaptive design is acceptable.

For more complex problems, e.g. setting defining the right proper target population, or other problems, e.g. re-estimation of sample size and cut-off for biomarker-positive tumor samples, etc., an adaptive design approach based on scientific principles can be considered if it proves to be beneficial. In this situation, an independent efficacy/safety supporting study is required as part of the marketing authorization application.

b. Interim Analysis

In phase III clinical trials, interim analyzes are often performed to decide whether the study can be discontinued (because it has been shown to provide significant benefit in the test drug group). Discontinuation of the study for this reason may also be performed if the effect of the drug on a rapidly progressing tumor is relatively the same as for a less aggressive tumor. If a large number of long-term events (tumor progression) have been identified and there is evidence of a difference between the two groups, the study is considered adequate and the effect is assumed to be constant and will not change the outcome of the study if continued. Interim analysis results interpretation is not recommended if based on studies that have not been able to prove a difference in effect between the test drug group versus the control group.

In cases where treatment effects have been underestimated in study planning, this can create a dilemma if statistically convincing effects in terms of OS have been

demonstrated before a representative and mature dataset is available. Other monitoring committee decisions could be investigated in this regard such as limiting the continuation of the study to an underrepresented subset to which the observed effects cannot be extrapolated. Analysis according to tostratifying stratification factors of importance for prognosis can provide insight as well as a similar analysis with respect to PFS.

c. Event Analysis Time and Assessment of Response and Progress

For studies with PFS/DFS as the primary endpoint, study visits are vital. Adherence to the schedule stated in the protocol is essential and deviations must be reported (Annex 1). As discussed above (exploratory studies with time-related endpoints), the comparison of PFS between predominantly tumor-shrinking compounds and predominantly growth-inhibiting compounds may favor the latter due to tumor burden at the time of progression. There has been no regulatory experience regarding comparisons with clearly differentiated results in terms of ORR and PFS and no established method to adjust them. If exploratory studies indicate that this is a problem then alternative endpoints such as OS must be considered.

Differences in mode of action between the test and control drugs can generate problems, with regard to the measurement of tumor burden and anti-tumor activity, an early example of tumor swelling. If such problems are foreseeable, which may require deviation from the standard approach (RECIST, WHO), it is recommended that agreement be reached with the regulatory agency before starting the pivotal study. If tumor screening techniques cannot be used for an independent decision, it is advisable to discuss available alternatives with the regulatory agency.

Pseudo-response must always be considered as a possibility when tumor-associated edema is a problem, as in high-grade gliomas, updated response and progression criteria must be submitted where available. If these criteria have not

been established, then scientific suggestions and advice with the aim of discussing imminent alternative methods are necessary.

d. Non-inferiority Studies

Guidelines for the design, implementation and analysis of non-inferiority studies are provided in other guiding guideline documents, but certain topics deserve special attention in the field of oncology. For PFS endpoints, which can be considered as composite endpoints, discussion of the non-inferiority margin must consider the effect of the comparison drug thoroughly, but conclusions must include discussion of each type of event (death, new metastases, target lesion progression, clinical progression), including a description of the regimen effect of comparator drugs. If differences in progressive disease profiles are to be expected, these must be considered at the planning stage, with conservative margins and an adequate sample size, to obtain the number of events required to draw reliable conclusions.

Given the importance of the sensitivity study to assess non-inferiority clinical trials, where the test and comparator groups are assumed to have similar activity, it is necessary to plan a previous subgroup analysis, for instance excluding patients with poor prognostic factors at baseline such as poor Performance Status (PS), comorbidities, etc. since it is more difficult to detect differences in activity between therapeutic regimens within this group of patients. A per-protocol analysis must be defined so that protocol deviations, compliance issues, etc. do not reduce the possibility of detecting discrepancies. This analysis was conducted with the aim of showing consistency.

e. Analysis Based on Patient Grouping According to Therapy Results Outcome of Treatment

Comparison of time-to-event variables (such as OS or PFS) by grouping patients according to the results of post-randomization therapy is problematic. Since the outcomes such as tumor response, dose, toxicity or patient compliance are interactions between therapy, patient and tumor, the contribution of therapy cannot be separated.

However, certain unexpected outcomes such as a marked improvement in survival despite dose reduction due to toxicity, or the absence of long-term survival in treatment-responsive patients, may be informative. The search for unexpected findings can be a reason for an exploratory analysis.

The duration of response comparing groups of patients with different therapies may be considered informative. Data must be reported with Confidence Interval (CI) values for each study group, but significance tests comparing response durations between groups may not be performed because comparisons between groups were not randomized. The "response time" in which patients with no response were grouped as zero duration could be statistically compared between study groups.

f. Studies for Very Rare Tumors or in Relatively Small Populations

For some very rare tumors or tumors with very specific indications, either because of the tumor phenotype or associated expression of certain targets, it is sometimes not possible to recruit a sufficiently large number of patients. Randomized studies with sufficient power to detect clear differences in anti-tumor activity are also difficult to conduct.

In certain situations, a relatively small sample size with a randomized design with a comparator is the accurate option. In other circumstances, TTP/PFS analysis between patients can also be used as a study option. It can also be in the form of comparison of TTP on previous therapy with TTP or death in the group receiving the test drug. For instance, a cancer X has been receiving therapy A or a combination of A and B. The test drug was given to the experimental group who also received therapy A or a combination of A and B. Then, the TTP values between the two were compared.

In relation to that matter, the protocol must clearly describe the conditions that can be analyzed. Superiority must be shown, for instance, in the form of differences in the percentage of TTP achievement in subjects with condition X

versus subjects with condition Y in the same treatment group. Thus, if a study is conducted on drugs for cancer patients whose occurrence is very rare, the evaluation of these anti-cancer drugs can be carried out with supporting data from phase 2 clinical trials which are equipped with strong justification.

In a small target population, all evidence regarding efficacy and safety must be considered. This includes clinical response rates, response duration and outcomes such as HSCT rates, MRD measurements to determine response rates and disease recurrence. Time to endpoint events such as PFS and OS must be reported although it is known that formal statistical significance cannot always be expected, even if the test drug has better efficacy. In the absence of a general solution to the problem of how to document the benefits-risks in such cases, scientific advice is needed.

g. Use of External Control

The use of external controls (including historical controls) and concluded that "the inability to control bias limits restricts the use of external control designs, in situations where the therapeutic effect is dramatic and the course of disease is predictable". In this case, prospective confirmation in a randomized study, with a comparator drug was not only rejected by the investigator, patient or ethics committee, but was also not required.

5. Specific Population

a. Elderly and Frail

When elderly patients are to be treated with a new drug in clinical practice, the clinical study program must include a large number of patients, including patients with co-morbidities, in order to assess the benefits-risks of the drug. For some drugs, the safety of the drug needs to be established in healthy patients prior to confirmatory studies in elderly patients, but justification is needed in this case.

As a note, the eligibility criteria are not barriers to obtain elderly patients but investigators need specific

encouragement and support to include these patients. More efforts need to be made to collect data in Marketing Authorization Applications (MAA); however, if the benefit-risk cannot be assessed with certainty in elderly patients or those with frequent co-morbidities in the target population, then this must be reflected in the marking and post-marketing studies are necessary.

Data from elderly patients must be available for pharmacokinetic analysis, e.g. as part of a population pharmacokinetic analysis. The description of the safety profile must include a profile of the severity of the adverse event and its consequences, such as decreasing the dose of the drug, delaying the dose or starting concomitant therapy. An evaluation of the therapeutic effect consistency and safety profile in the elderly patient population, including appropriate age groups, with a younger population is expected to be available.

Certain drugs may be specifically suitable for the treatment of elderly patients because of the drug's PK profile such as low sensitivity to the affected organ. In such cases, studies in elderly patients are needed. It has been difficult to find suitable comparative therapies and outcomes other than PFS/OS. In this case it is advisable to reach an agreement with Indonesian FDA for a drug development program. frail patients, whether elderly or not, with PS disorders are a vulnerable group of subjects and are rarely included in clinical studies. Clinical studies for this patient group are supported from a regulatory perspective.

b. Children

Malignancies in children include cancers that are specific to children (e.g. nephroblastoma) and other malignancies that are not specific to the paediatric population (e.g. osteosarcoma, acute leukaemias, malignant lymphomas and brain tumors).

When malignancy cases occurring in both adult and paediatric populations have similar biological or clinical characteristics, factors to be considered include possible

differences between childhood and adult tumors in terms of genotype/phenotype properties of the tumor, pre-clinical activity of the new compound, pharmacokinetics/pharmacodynamics tumor markers in humans and available treatment options.

The pharmacokinetic profile is one of the basis for establishing dosage recommendations to different age groups in the paediatric population. It is therefore important to include a sufficient number of subjects to represent the proposed age range. Another factor, such as body weight, may be useful for further optimization of the initial dosing regimen. Measurement of markers for efficacy and toxicity can provide more information regarding the concentration-response/toxicity relationship.

The design of clinical trials in children is generally similar to that of clinical studies in adults. Designing a phase 1 clinical trial in children with cancer needs to consider the following points:

1) Phase I study of anti-cancer drugs for children must assess the therapeutic effect of the drug, not just an evaluation of toxicity.
2) Paediatric patients participating in a phase 1 study must have adequate physiological status to ensure that the organ-specific toxicity observed in the study is related to the substance under investigation, and can identify and differentiate from the patient's underlying organ dysfunction. Besides, the Patient must also have adequate performance status, as measured by the appropriate performance status scale for paediatrics.
3) Dosage for paediatric patients is usually defined in mg/kg of body weight. Various dose escalation strategies were evaluated with the aim of minimizing the number of dose levels required to achieve MTD or determining the effective dose that could be used in phase 2.
    a) The start dose used in paediatric phase 1 study is generally 80% of the MTD determined in adults. For dose escalation, a dose increases of 20-30% is used.

b) If there are no adult MTD data and there is no unacceptable individual toxicity, intra-patient dose escalation is performed.

c) DLT may differ between patients with different treatment histories. This also needs to be considered in determining the dose.

d) In general, only the first course of therapy is used to determine DLT, but patients may continue the study for multiple treatment courses as long as there is no progressive disease, the patient may receive all the benefits of the treatment objectives (e.g. pain relief, disease stabilization or response). These data can be used as preliminary evidence of cumulative toxicity.

4) Pharmacokinetic data obtained in phase I study in children can be used to compare systemic exposures between adult and paediatric patients. In phase I/II, it is necessary to consider pharmacokinetic evaluation in the paediatric population, among others, to identify age groups with dissimilar drug exposures and dosing requirements. Inter-individual variation and individual data must be described to identify subgroups of patients requiring alternative dosing regimens.

5) Relevant pharmacodynamic variables should be measured as early as possible, to determine the pharmacokinetic relationship (e.g. AUC) with toxicity/efficacy, which is then used as a consideration for drug dose selection in the subsequent clinical study phase.

6) For certain anti-cancer drugs, individual patient doses can be determined by the Maximum Tolerated Systemic Exposure (MTSE). If higher exposures are required for paediatric patients than therapeutic exposures in adults, the pharmacokinetics in children must be evaluated with respect to possible non-linearity; In addition, the safety limits established for drug exposure in pre-clinical studies must be re-calculated and evaluated.

Pharmacokinetic data for various age groups must be

investigated, especially the peak age of cancer incidence in these children.

c. Gender

For some tumors and/or therapies, gender-related differences in anti-tumor activity have been reported. Differences in therapy due to the influence of gender need to be considered in the study design. On the other hand, if the proportions of women and men reflect disease prevalence, the sponsor provides exploratory sub-group analysis data (efficacy and safety) by gender.

d. Patients with Impaired Organ Function

In general, the recommendations for anti-cancer drugs are the same as for other drugs according to existing clinical pharmacology guidelines. Matters that need to be considered include, among others, dose reduction in subjects with certain organ disorders. On one side, reducing the dose can reduce the risk of unwanted side effects. However, on the other hand, it is necessary to prove that this dose reduction has no effect on the clinical effect of the drug. Especially when the test drug indications are intended for patients with impaired organ function.

6. Safety

a. Basic Concept

Adverse Events (AE) are all unwanted clinical events that occur in clinical trials without regard to a causal relationship. In clinical trials, adverse events must be recorded and assessed for severity. ADR is based on causality relationship. In clinical trials, information about Adverse Drug Reaction (ADR) must be proven to have a causal relationship either directly or indirectly related to drug use. ADR manifestations can be clinical, laboratory, or radiological. As with adverse events, ADR must also be recorded and assessed for severity. After a causality assessment, some adverse events will be designated as ADRs. Determination of an event as ADR or AE can refer to the applicable clinical safety data management guidelines, namely regulations issued by Indonesian FDA or

other internationally applicable guidelines such as ICH E2A34.

The concept of Treatment-Emergent AEs (TEAEs) denotes adverse events that were not present at baseline (pre-treatment) or have increased in severity during the treatment.

The standard classification system for adverse events in oncology follows internationally acceptable standards, such as the toxicity criteria from the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). Tolerability can also be assessed by using Patient Reported Outcomes (PRO).

Tolerability of a drug is generally defined as the ADR that is still acceptable to the patient. During the treatment process, the ADR found may affect the patient's quality of life or activities of daily living. Tolerability can affect the delivery of drug at intended dose and schedule. Information regarding tolerability can be obtained from the outcomes of dose adjustments and discontinuation of the drug.

The importance of ADR affecting tolerability compared infrequent severe or life-threatening ADR differs depending on the state of the disease. This needs to be considered in planning the treatment programs. In the palliative setting, infrequent severe or fatal ADR, may still be considered an acceptable risk as long as the drug can still improve the patient's quality of life. Whereas in the neoadjuvant setting is considered as inappropriate.

b. Safety in Oncology Context

In oncology, the causality between adverse events in relation to the investigational drug is generally difficult to determine because of the frequent overlapping symptoms of the underlying malignant disease and the toxicity of anti-cancer therapy. This condition is emphasised if the study design does not use a random method.

More serious ADRs are likely to appear during the first and second treatment cycles, and then decrease as tolerance develops. Under certain conditions, cumulative toxicity may arise as a result of long-term treatment. However this is not sufficient to describe that the product is safe.

With the growing variety of anti-cancer drugs such as cytotoxic, targeted therapy and immunotherapy, both different dosage regimens and modes of action will result in different toxicity and tolerability profiles. Therefore, planning for the collection, analysis, and reporting of safety data must be considered.

Conventional cytotoxic drugs are usually administered at weekly or longer intervals and cause acute but transient toxicity, followed by recuperation before the next treatment cycle. On the other hand, targeted drugs and immunomodulators are usually given continuously/every day so that the toxicity profile is different, either delayed or more or less constant. Tolerability can be a major issue for some products, while for others it can lead to potentially life-threatening reactions. Both types of toxicity must be investigated comprehensively. Co-administration of anti-cancer from different pharmacological groups is often applied, adding the complexity that requires further research.

Some classes of anti-cancer drugs such as MoAb in long-term administration can cause an immunogenicity reaction that reduces the clinical effect of therapy. This condition may go unobserved because there are no side effects but it increases the risk of a poor outcome.

c. Study Design from a Safety Perspective

1) General Recommendation

From a planning perspective, it is important to consider how the study design impacts the safety information obtained. The recommendation is stated as follows:

If in a clinical trial, the therapeutic regimen in the randomized group is different, the study design must describe procedures for obtaining information regarding side effects (e.g. by telephone), so that all adverse events can be recorded. It is always advisable to carry out comparative clinical trials. This is based on the fact that when the study was conducted on only one group of subjects (single arm), the AE data was often hampered

with the symptoms of the disease. For example, in hematology products, the most common adverse events that occur are myelosuppression, infection, and bleeding, which are similar to symptoms of the underlying hematological malignancy.

2) Extended Safety Data Collection

In some clinical trials, the group that received the test drug was able to stay longer in the group in which they were randomized. This is because of the clinical benefits obtained during therapy with the test drug. The condition might be different with the comparator group which may not last long enough in the group.

Adverse events can occur in this group and often go unobserved by researchers. Therefore, safety data in this group must be recorded and reported completely in order to be interpreted correctly to prevent bias. Another impact that may occur is when the observation of AE is stopped to the comparator group; then the research may unknowingly cause an adverse effect on this group, such as in the form of progressive or deteriorating disease.

PRO measurements can be considered for clinical trials of Anti-cancer drugs. Although the study was declared complete and there was a significant difference in outcome between the two groups, this does not guarantee that adverse events will no longer be found. It may be necessary to record and report adverse events or ADR data that will occur some time after the study is discontinued or after a decision on next-line therapy has been made.

3) Safety Database

All safety data of an Anti-cancer drug must be collected from all relevant studies including studies on other indications. The amount of safety data collected must be sufficient for a risk-benefit assessment of the specific target population studied. Baseline data must include the quantity and severity.

If the safety data available is not sufficient when the drug is being approved for a particular indication,

then comprehensive data can be collected at the specified time. If the adverse events that occur are thought to be related to the risk of fatal drug effects, the outcome measurement (primary endpoint) should be in the form of OS whenever feasible.

4) Studies to Demonstrate Improved Safety

Several clinical trials of anti-cancer drugs aim to demonstrate that the safety aspect of the test drug is better than its comparator. If this aim is to be achieved, clinical trials must be designed to include and explain the advantages of safety aspects of the drug in details, including the calculation of sample size. Therefore, sample size is determined by frequency or risk of adverse events (which is commonly inconsistent).

In order to avoid bias in the assessment of toxicity and tolerability outcomes, the toxicity assessment should be comprehensive and may not only focus on one side effect, such as neuropathy.

d. Collection, Analysis, and Reporting of Safety Data

All drug toxicity data, including cumulative toxic effects, must be recorded in details. It is not permitted to exclude some adverse events that are considered to be related to the disease in the analysis, since it will eliminate the opportunity to find an association between adverse events and drugs. If the aim of the clinical trial is to prove a cure, a long-term follow-up is necessary. Delayed toxic effects generally occur only a few years after treatment (including the appearance of a second primary malignancy and toxicity to other organs such as the cardiovascular and central nervous system).

All applications for marketing authorization must include cumulative adverse events data from all pivotal clinical trials conducted at a certain time, namely 3 months, 6 months and 1 year, to prove the safety aspect of the drug. A clinical trial may be conducted in a short term (e.g. 6 months) or long term (e.g. 5 (five) years). For short-term clinical trials, monitoring of adverse events must be more frequent and intense, for instance once a week for the first 2 (two) months

and then every 2 (two) weeks. As for long-term clinical trials, the observation of adverse events can be carried out more frequently at first and then followed by a less frequent observation afterwards (namely, every month for the first 6 (six) months followed by every 3 (three) months after that period).

Adverse events that lead to dose reduction, interruption or discontinuation must be reported. For instance, abnormal laboratory results must be reported, e.g. cytopenias or elevated liver enzyme levels leading to a dose adjustment or interruption of the drug.

1) Temporal Perspective

In addition to standard adverse events reporting, which is based on cumulative frequency with toxicity levels, other measures are needed to understand the safety profile of Anti-cancer drugs. There needs to be information regarding how the process of adverse events occurs and its prevalence and severity, which may change over time during the treatment process.

For major adverse events, attention must also be paid to effects that are common in the treatment cycle and affect their tolerability and safety. For instance, short-term fatigue or severe diarrhea may have little effect on tolerability, whereas long-term fatigue or moderate-grade diarrhea may have a major impact and require special examination. It is necessary to measure the incidence and prevalence of adverse events per treatment cycle, and the time to event, as well as the duration and severity of adverse events. Supporting documents need to contain or present the PRO.

A time-adjusted analysis of adverse events needs to be carried out. One example is the determination of Adverse Events based on different date or time of events. Another example is the incidence per 100 patient-years, which may suggest a certain pattern. In reality, the number of adverse events is seldom constant so that it is often difficult for statistical

analysis (requires an exponential distribution assumption), resulting a summary description of the adverse events needs to be provided to facilitate the assessment, especially if there are significant differences in observation time between treatment groups. Kaplan-Meier analysis needs to be carried out on certain adverse events by considering censoring of events (subjects who cannot be monitored for various reasons/loss to follow-up). However, not all adverse events need to be reported in details. Selection criteria may include, namely, adverse events leading to discontinuation of treatment, dose reduction or interruption of treatment, severe adverse events and all adverse events that affect tolerability or the benefit-risk ratio.

2) Dose Reduction and Other Consequences

One of the most important things that need to be in the risk-benefit assessment is the extent to which dose reduction can overcome adverse events. It is also necessary to report on the use and preventive measures, such as the use of antiemetics or growth factors. Information regarding the relationship between the profile of adverse events and drug exposure is also necessary. Longitudinal PK/PD data which also analyzes dose adjustment could be useful for further consideration.

Additional data as consequences of adverse events that need to be recorded include the severity and type of infection due to neutropenia, the frequency and duration of hospitalisation, the use of other necessary measures (e.g. transfusion) and the outcome of hospitalisation including recovery rate and fatality rate (severity condition requiring life-saving or potentially causing death). For patients undergoing more intensive cytotoxic/immunosuppressive therapy, it is necessary to monitor the frequency of occurrence of infection and the cause of infection (viral, bacterial

or fungal). For compounds that are suspected or known to cause long-term immunodeficiency, monitoring for opportunistic infections must be carried out for up to 1 year after completion of therapy.

For immunomodulatory drugs such as checkpoint inhibitors, it is necessary to monitor the potential for adverse events related to the immune system, such as diarrhea, colitis, rash, mucositis, liver toxicity, pituitary, pneumonitis and other endocrine disorders.

3) Causality Assessment

Causality assessment is a critical step in establishing drug safety profile. The principles of causality assessment as outlined in the Summary of Product Characteristics must be applied by considering the following provisions:

a) Adverse Events unrelated with the product information should not be included.

b) The conclusion that AE is an ADR may not be based on the researcher's assessment.

Although the investigator's assessment of causality to the patient may not be altered and must be reported, it is the applicant who applies for marketing authorization to submit a product safety profile based on a thorough evaluation of pre-clinical and clinical safety data.

This is based on the fact that when the pivotal study is carried out and used for the first marketing authorization application, information on the safety profile of the product is still very limited. Therefore, investigators' assessments of the association of adverse events with the test drug in these early studies were more prone to error than those in approved drug studies.

Adverse Events may be overlapping with the symptoms of the disease itself. In this situation, researchers tend to not report adverse events due to

drugs, so these symptoms are not recorded as adverse events (underestimated). In other situations, overestimation can also happen, for instance recording an adverse event that is actually related to the disease but is considered an adverse event due to drugs.

Therefore, although researchers often provide useful clinical information, the frequency of adverse events is the least biased in causality assessment. If there is no significant difference in the frequency of adverse events between treatment groups, making it difficult to conclude as a drug-induced adverse event, then the applicant must conduct a causality assessment using a medical-pharmacological assessment.

If the pharmacological mechanism cannot explain the causal relationship between variables plausibly, it is necessary to do positive dechallenge and rechallenge (the drug is stopped and observed whether the symptoms disappear, then the drug is given back and observed whether the effect reappear). If both conditions do not take place, the applicant must provide sufficient information to ensure the evaluation process. If the available data is still inadequate, then the Adverse Event may not be concluded as a drug-related Adverse Event until sufficient data is obtained.

In fact, oncology drugs are often given in combination. Through study design, it is usually not possible to find the causality of adverse events on one individual drug, because adverse events can be influenced by other combined drugs. However, efforts to prove a causal relationship may not hinder the main objective of the study. For instance, when an adverse event is not assuredly caused by a drug, it does not conclude that the drug is relatively safe because it must be proven by the supporting data that display a causality relationship.

e. Abnormalities of Laboratory Examination Results

If the results of laboratory tests that are reported as adverse events are not considered clinically relevant by the researcher, the real data of laboratory results obtained in clinical trials can serve as a more objective measurement. Both laboratory data and supporting clinical data must be included in the report.

Data related to longitudinal analysis including the effects of dose adjustments and time-dependent analysis must be reported. Data about the initial condition of each patient that can affect the causality assessment of the occurrence of adverse events must be considered and analyzed. For instance, if a large proportion of patients who have liver metastases, it is unlikely to conclude that the liver enzymes elevations is entirely caused by the drug. Therefore, an additional analysis is needed to compare elevated liver enzymes in the group with liver metastases versus the group without liver metastases.

f. Safety Data in relation to Radiation Therapy

Since radiation therapy is the standard therapy in malignant tumors, it can be expected that the patient will receive a radiation therapy. In a palliative therapy, the radiation therapy is conducted concurrently with or within a time frame close to drug administration. Safety information for concurrent or sequential use of drugs with radiotherapy must be collected throughout the study, including radiation recall data. Subjects requiring radiation therapy while enrolled in clinical trials of a novel agents or a combination thereof must be withdrawn from the study. If information on safety and tolerability with radiation is needed, it is necessary to carry out a well-designed study, with radiation as concomitant therapy, and the administration schedule is adjusted to non-clinical toxicology studies.

The collection and reporting of safety data must be aimed at radiotherapy-specific items such as radio sensitization and "radiation recall". The detailed information on radiotherapy is essential for retrospective understanding in the event of

unforeseen radiosensitivity reactions, and for providing recommendations for the precaution of subjects requiring radiation therapy due to disease progression when enrolled to clinical trials of a novel agent or combination who will be usually withdrawn from study therapy, as progression is commonly seen as the “stopping rule”, unless the study design incorporates other pre-defined measures to handle such events. In haematological malignancies, bone marrow failure is often the major presenting symptom and can be aggravated by a treatment. In this case, dose reduction due to haematological toxicity may not be indicated.

If the aim of the study is to demonstrate improved safety, the protocol must specify how this should be accomplished. It is unacceptable to focus on a single toxic effect. Outcomes must provide unbiased information regarding overall toxicity and tolerability, as well as for specific types such as neuropathy, where clinically relevant improvement is expected. With limited experience with the aforementioned types of studies, European Union regulatory advice must be taken into account. Where necessary, pharmacogenomics can be used to identify patients at high risk of severe toxicity.

g. Use of Patient Reported Outcomes in Safety Assessment

Data derived from patient-reported outcomes (PRO) can be used as supporting data to assess the tolerability and safety profile of anti-cancer drugs. This information is also useful for evaluating the effect of dose reduction on adverse events.

h. Safety Reporting in Specific Population and Pharmacogenomics

If possible, it is advisable to collect samples prospectively for pharmacogenomic assessment regarding drug safety issues.

1) Paediatric Population

For studies in the paediatric population, adverse events must also include reporting of possible effects related to organ maturation, growth and development, including hormonal development. In this context, non-clinical studies can be an important source of information for risk-benefit assessment at the time of marketing authorization approval. Some long-term effects that require follow-up after the marketing authorization has been granted, still need to be monitored and reported.

Other safety data that need to be evaluated in paediatric studies include different toxicity profiles between adults or paediatric age groups. In particular circumstances, where it is not possible to obtain clinical data through clinical trials in a particular paediatric age group, it may be possible to use mathematical modeling and simulation as an approach to assessing safety.

2) Elderly Patients and Other Risk Factors

If the proposed drug is also targeted at the elderly population or vulnerable group of patients, then the safety profile data in this subgroup must be reported. Likewise, groups of subjects with certain conditions such as patients with brain metastases or patients with poor performance status must be included and reported in an attempt to prove the safety profile in both groups. This will be useful to be included in the product information. This group does not need to be included in the benefit and safety analysis.

i. Presentation of ADR in Product Information

In oncology, it is somewhat difficult to distinguish clinical symptoms due to disease or drugs (e.g. fatigue, weight loss, gastrointestinal symptoms, and myelosuppression). On the other hand, it may be difficult to determine the role of anti-cancer drug toxicity, especially if given in combination. In this context, the delivery of information about the toxicity of an anti-cancer drug is challenging. Therefore, the Applicant

needs to refer to the provisions related to the preparation of the Summary of Product Characteristics, for instance information on warnings, contraindications in pregnancy and lactation.

For adverse events that meet the causality requirements, they are recorded in a tabulated list which is arranged based on the category of the affected organ system as well as the type of side effect and the frequency for each category. For instance, side effects on the Central Nervous System (CNS) include headache, dizziness, and vertigo. Furthermore, the frequency of each occurrence is explained.

The product information must describe that the ADR frequency listed could be from other drugs which are a combination given together or are a symptom of the disease. Other aspects that need to be reported include ADR where observations are made at a certain median time, namely 6 months, so the ADR data is explained based on observations during the median time of 6 months.

Inclusion of information about the frequency of occurrence of toxicity based on the degree of severity needs to be done to make it easier for clinicians to make decisions about various risks that may occur.

An example to this case is regarding how many percent of patients experiencing mild, moderate, and severe toxicity. It is necessary to include data on ADR in each treatment group. ADR data can be selected based on certain criteria, such as ADR leading to discontinuation, reduction or interruption/temporary interruption of drug dosage, serious reactions, and other reactions likely to affect tolerability or benefit-risk ratio. If possible, some ADR data can be displayed separately based on each existing study, bearing in mind, the design of each study may be different. However, the data will be easier to interpret if it comes from a pooled analysis of several studies (as long as the accuracy and reliability can be accounted for).

Another information that needs to be displayed is related to several aspects, such as the frequency of ADR based on

time (for example, the effect of nausea appears more frequently in the fourth cycle of therapy), the duration of the occurrence of ADR, abnormal values in unbiased laboratory test results.

C. Post-Marketing Studies

Post-marketing studies are conducted after drug marketing authorization approval to obtain additional information about the efficacy, safety, and use of the drug. The studies are conducted for the following purposes:

1) Measuring the potential risk;
2) Evaluating the risks of drugs used in certain patient populations, for instance pregnant women, certain age groups, patients with kidney or liver disorders or comorbidities or other relevant drugs;
3) Evaluating the risk after long-term use of the drug;
4) Proving the absence of risk;
5) Assessing patterns of drug use to add information related to drug safety or risk management effectiveness (e.g. gathering information on indications, off label use, dosage, treatment with other drugs or medication errors that may affect safety, as well as studies that provide information regarding the estimated impact on public health);
6) Measuring the effectiveness of risk management activity.

The implementation of post-marketing studies can refer to international guidelines, such as ICH E8.

CHAIRPERSON OF THE INDONESIAN FOOD AND DRUG AUTHORITY,

signed

PENNY K. LUKITO