

# *Anticancer Drug Clinical Trial Guideline*

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## ***Anticancer Drug Clinical Trial Guideline***

### **1. Introduction**

*This guideline is in order to guide clinical studies for antitumor agents, including what should be considered in different clinical phases. The guideline provides the principle of research objective, execution and efficacy evaluation. Investigators should also consult other relevant guidance issued by SFDA and GCP requirements.*

### **2. The Overall Consideration of Clinical Trial**

*As most of other types of agent, the clinical trial of antitumor agent is also divided into phase I, phase II and phase III trials. The main purpose of phase I is to evaluate the tolerance of specific agent to patients and provide information on recommend dosing design for later stage studies. Phase II trial mainly focus on preliminary evaluation on drug efficacy and safety. The purpose of phase III is to further validate the efficacy based on results of Phase II trial and provide enough evidence to obtain final approval.*

*However given the basic mechanism of tumor is quite different from other illness, the clinical trial phases could be non-fixed procedures. This means that phase III trials may also include some exploratory studies, while the validation research can be a part of phase II. Considering usually Phase III trial need to provide enough patient survival rate benefit information, which usually cause significantly prolonged trial turn-around, a new model of adjusting trial plan during a clinical study has been used more and more recently (adaptive design). The critical point on clinical trial study design is to plan the next phase of clinical trials based on thorough consideration and summary of all previous trial results (or pre-clinical tests), in order to rule out non-effective or highly toxic drug and/or select the appropriate drugs to proceed to large population clinical trials at the earliest stage, in order to bring new anticancer agent to the market to benefit oncology patients.*

*The following critical issues need to be fully considered when designing the overall development plan of clinical study according to the specific characteristics of tumor disease and antitumor agents.*

#### **2.1 The Selection of Patients**

*Due to commonly high toxic property of chemotherapy agents, in phase I clinical trial, cancer patients, instead of healthy volunteers should be chosen. The trial will not only focus on tolerance observation, the efficacy of the agents should also be observed and evaluated.*

*Cancer patients shall be applied for the 1st line standard treatment first. Patients can take part in the clinical trial only if the standard treatment fails or after recurrence after treatment. For ethical reasons, usually the new antitumor drug will not be considered as 1st line therapy until the efficacy of the drug as 2nd or 3rd line treatment has been fully validated. In addition, as in this stage of studies, the efficacy of test drug sometimes were compromised by the drug resistance caused by previous treatment, the efficacy of the test drug to drug resistant tumor species is recommended to be explored during preclinical studies and in its early stage clinical trials.*

Also due to the fact that some chemotherapy drugs have been demonstrated to be effective on preventing cancer recurrence after surgery, combination therapy of test drug with some other cancer therapies (e.g. radiotherapy) could also provide useful information on various potential indications of specific drug.

## **2.2 Dose Regimen Design**

Usually antitumor efficacy and safety are related to the dose regimen. The different dose regimen (such as different dose interval and speed) may produce different dose limited toxicity (DLT) and maximal tolerated dose (MTD). For cytotoxic drugs, to achieve the best efficacy the dose regimen should be fully investigated to achieve maximized efficacy, while maintain acceptable toxicity tolerance...

## **2.3 The Selection of Tumor Types**

Antitumor drugs may not only be effective on one type of tumor. Also it is impossible to be efficacious to all kinds of tumor. Therefore it is recommended to choose various tumor types (usually include the known sensitive tumors as well as a few non-determined tumors) to obtain preliminary indications of the tumor sensitivity in phase I/II clinical trial. Then select the most sensitive tumor type in phase III clinical trial.

## **3. The General Portfolio of Clinical Trial**

### **3.1 Phase I Clinical Trial**

Phase I trial is commonly required to the new API that has been first entered trials in human. The main purpose of phase I is to evaluate the DLT and MTD, as well as recommended dose regimen.

The pharmacology, acute toxicity, repeated drug toxicity and other necessary toxicity researches in animals should be finished before starting phase I clinical trial. The safety should be well forecasted through all preclinical studies.

#### **3.1.1 Study Purpose**

The main purpose is to explore MTD, DLT and recommend dose regimen for phase II clinical trials. Meanwhile, it will study a new drug's pharmacokinetic characteristics, getting parameters of pharmacokinetics, observing the preliminary efficacy, and analyzing of PK/PD (pharmacokinetics/pharmacodynamics).

#### **3.1.2 The Selection of Patients**

Selection of patients for phase I clinical trials should on the following basic standards:

- a. Patients have been diagnosed as malignant cancer;
- b. Standard treatment is no longer effective and the use of new drug may be beneficial. If the potential indicated can be expected, the recruitment of trial patients should bear corresponding tumor type.
- c. The patients should have no serious hematopoietic dysfunction or any dysfunction in heart, lung, liver and kidney or immunodeficiency. The patients whose performance status ECOG should between 0 and 1 or KPS >

70 .

- d. *No previous treatment effects should interfere with current study. It should be at least 4 weeks after the last chemotherapy or other treatments*
- e. *The life expectancy for any patient should be more than 3 months so that safety and efficacy follow up can be preformed.*

*As cytotoxic drugs usually cause various side effects and treatment in healthy people can not reflect safety and efficacy. To avoid unnecessary damage in healthy volunteer, Phase I trial of cytotoxic drug selects cancer patients. For non-cytotoxic drug, such as hormones and tyrosine kinase inhibitor, selection of healthy people as patients is allowed.*

*Considering ethics, the tumor patients who can be treated with regular treatment shouldn't be selected in phase I clinical trials, but advanced cancer patients who fails by standard treatment or no standard treatment are usually candidates. Due to the fact that the physical conditions of patients are usually poor, and patients had various treatments with side effect before the clinical trial, the results of trial may be affected by these factors. Therefore selection of patients in this stage of clinical trial need to be very cautious.*

*In order to explore efficacy of the test drug in different tumor types, at this stage multiple cancer patients are recommended to be recruited,*

*As for molecular targeted drugs, the targeting bio-marker can also be helpful for patient screening during recruitment process.*

### **3.1.3 Dosing Design**

*Dose regimen of anti-tumor drugs is the key factor that determine efficacy and safety. In phase I clinical trial, appropriate dose regiment and tolerance should be explored.*

#### **3.1.3.1 Initial Dose**

*Because the therapeutic index of most anti-tumor drugs is narrow, and high initial dose will lead to severe toxicity, even death of patients, which may cause fail results for a good antitumor drug candidate. However, if the initial dose was set too low, the trial duration would be delayed and cause unnecessary study. In addition, from the ethics point of view, it shouldn't make more patients expose to ineffective dose treatment. So the initial dose should be carefully selected according to the results of non-clinical pharmacology, toxicology and pharmacokinetics/toxicokinetics.*

*For cytotoxic drugs, initial dose of phase I clinical trials should be 1/10 MTD dose of rodents in non-clinical trials or 1/6 MTD dose of non-rodents with unit  $\text{mg}/\text{m}^2$ . Meanwhile, it should inspect the toxicity and reverse reaction of MTD dosage in other species of animal. For non-cytotoxic drugs, as it has lower toxicity, initial dose of phase I clinical trials can be 1/5 of non-rodents' NOAEL (no observation in the dose of adverse reactions) or higher. It will be acceptable that initial dose in domestic clinical trials refers to international clinical trials data if it is available and considered to be reliable. But the differences between human species should also be considered.*

*It should be noted, when developing the drug combination therapy, the interaction between two drugs may cause subsequently increase on toxicity. In general, the toxicity of combination therapy could be predicted according to the toxicity of individual component when anti-tumor activity depends on theoretical speculation. If the PK interaction can be neglected, and dose-reflect/toxicity is unknown, the initial dose should be designed as 1/2 of in individual component recommended dose. It also could be designed as entire dose of recommended dose in one individual component while decreasing the other component dose (50% or*

lower). Besides, drug administration order is very important. The efficacy and safety will be affected by drug administration order and interval. All the factors mentioned above must be considered when designing the dose regimen.

So far, there has no standard method to assess ratio of each component in combination therapy and optimize benefit-risk. So it is acceptable to consider the higher active component at first when optimizing dose regimen.

### **3.1.3.2 Dose Escalation**

The exposure – effect/ toxicity curve of pre-clinical trials and individual differences should be considered when designing the dose escalation research. In general, improved Fibonacci method will be used, after initial dose, 100%, 67%, 50%, 33%...increasing in order. Currently, there are other methods to design dose escalation. So the rationality and decided dose regimen should be clarified clearly. The rate of dose escalation should be adjusted based on drug characteristics. The methods and rationality of the dose escalation regimen should be clarified in study protocol. And the definition of MTD and LDT should be detailed described. Avoiding more patients to use invalid drug, it should select less patients who reach evaluation requirements in each dose group. In general, the patient's number should be 3 or more than 3 at least. If there is no toxicity or light toxicity, the patients number less than 3 would be accepted. If it appears significant toxicity, the patient's number should be increased. 3 more patients should be increased if more than 3 degree side effect is found in one patient of one group. Go into next group if there is no one case. If it appears side effect again, dose escalation should be stopped. It is allowed to move into next dose group only when the information is sufficient.

Comparing with single dose research, it will need more patients in each dose group of combination therapy.

In principle, it shouldn't do dose escalation research in one patient. But increasing dose in one patient is permitted if it appears light toxicity or occasionally unobvious toxicity to decrease the no active drug dose in patient. But it should have pre-clinical toxicology test results to show the compound will not accumulate.

It needs enough observation time if the test drug toxicity delays occur. Usually, the observation time of dose escalation trial should be 3-5 weeks after treatment. If toxicity is tolerance, patient would be treated again after recovery. And it is better to take at least 2 circle treatments in one dose level to observe efficacy.

For cytotoxic drug, dose escalation should be stopped when it reach MTD. The obvious MTD couldn't be observed for non-cytotoxic drug because the toxicity is low. If there is no better efficacy while increasing the dose, but accompanied with obvious toxicity creasing, it should choose the lower dose to continue the study.

### **Administration Route and Interval**

The administration route can be chosen according to pre-clinical research results or phase II clinical purpose. Treatment interval should be designed according pre-clinical trial results, drug toxicity ratio of tumor/ normal tissue, human tolerance and pharmacokinetics.

It will be helpful to refer to similar drugs. Cytotoxic drug can be explored various dose regimens according to regular treatment, generally including single dose, once a week, daily dose. The repeat drug administration interval could be determined by results of toxicity recovery time of single dose. Usually, the repeat drug administration interval would be 3-4 weeks.

### **3.1.4 Toxicity Reaction Observation and Evaluation**

*The category and the severity of the side effects evaluation should follow standard international common drug toxicity reaction standards. ([Common Toxicity Criteria, CTC] in The American National Cancer Institute [NCI], appendix 3)*

*The evaluation of side effects at least should include clinical symptoms, physical examination, the urine and blood work, imaging examination. Particular attention should also focus on clinical observed side effects from similar drugs from the same family and specific check-up should be included accordingly. The administration local instinction should also be recorded. According to the evaluation system that has been well established to evaluate and grade various side effects, as well as making judgment on the correlation between side effects and test drug, the reversibility of each observed toxicity, dose and the duration of the designed therapy.*

*The evaluation of side effects not only includes the test drug evaluation, it also should include the evaluation of other factors related to observed toxicity, such as organ dysfunction, drug combination therapy etc. These factors will also need to be further discussed in the future in the II/III phase of clinical trial.*

*If there is any fetal case in the trial, the detailed case report should be provided. The detailed evaluation of death cause and the relation between the case and the trial study need to be thoroughly reported, if necessary an autopsy should be carried out.*

### **3.1.5 Pharmacokinetic Study**

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*Pharmacokinetic mainly studies the description of human body drug pharmacokinetics characteristics, deciding major pharmacokinetics parameters. The design of experiments should include drug absorption, distribution, metabolism and excretion as a whole picture. Special focus should be put on the evaluation pharmacokinetics parameters and administration dose, safety and clinical efficacy (exposure-efficacy correlations). It is recommended to establish group PK/PD analysis model, this will help explain the toxic effects, optimize design of the administration dose regimen.*

*Imaging can be used to study the test drug distribution in tumor and, when necessary, advanced imaging technology can be used for whole body drug distribution study.*

*Because the drugs may be used for different disease status, or different patient age populations, so it may need to carry out some special pharmacokinetics studies, such as liver and kidney dysfunction, old age or children. The trial should also include factors that may interfere with the test drug absorption, distribution, excretion and metabolism, such as food effect, drug interaction, the different ethnic groups. These studies can be selected to be carried out at different trial stages, according to clinical requirements.*

*Pharmacokinetic study can be either carried out alone, or with tolerance studies. But for human pharmacokinetic studies, letter of consent from each patient should be mandatory.*

### **3.1.6 Drug Efficacy Evaluation**

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*Because antitumor drugs usually recruit cancer patients in the study, so phase I clinical trials can obtain preliminary observation on drug efficacy, and provide reference for later phase studies. The evaluation of anticancer efficacy should follow the international evaluation standard (RECIST STANDARD, Appendix 4). At the circumstance that the permission of the patients, obtain samples of body fluid and blood/serum, tissues. Using bio-marker to predict the efficacy is also recommended in this stage of trial. Such as molecular targeting antitumor drug efficacy can be predicted through specific marker. If the investigators believe the patients can tolerate extra treatment and it is benefit to the patients, continued administration can be proceed to further evaluate the drug efficacy, even after designed therapy has been completed.*



*It should be noted, due to the small sample size in this Phase I study, it is usually considered the obtained data cannot thoroughly evaluate the efficacy of the test drug. Therefore using data from Phase I to evaluate drug efficacy should be very cautious.*

### **3.1.7 Study Termination**

*For the cytotoxic drugs, if DLT \ MTD and toxic targeted organ has all been determined, the study can be considered as completion.*

*If the patients have following situations during study, the trial for this patient should be terminated immediately: 1) There is evidence to show that progression of disease; 2) Appear unacceptable adverse effects; 3) Patients require to stop; 4) Investigator decide to terminate a treatment*

*If the following conditions happen, it is recommended to terminate the whole trial or re-design the study: Termination of multiple patients; The incidence and severity of side effects demonstrate the treatment bring more risk than benefit to patients; difficulty to recruit patients; Poor quality of data, data inaccurate and incomplete.*

### **3.1.8 Interpretation of Phase I Trial Results**

*After phase I clinical trials, the design of the study, results and data should be summarized and used to be analyzed together with preclinical study results to obtain decision on whether or not the research purpose has been achieved and any potential concerns. The report should include the following factors: 1) Maximum tolerated dose (MTD) or Dose limiting toxicity(DLT); 2) Observed toxicity category, occurrence rate, , severity, prevention and detox protocol, and correlation with dose regimen, etc; 3) Preliminary efficacy results, such as ORR (Objective Response Rate), or results from some bio-markers; 4) Pharmacokinetics parameter and PK/PD values; 5) Targeted Phase II trial patients, recommended dose regimen and administration method. If current phase I clinical trial is difficult to provide enough support data for the following phase II trial, other phase I trial or non-clinical studies should be performed.*

## **3.2 Phase II Clinical Trial**

*Phase II trial is a more thorough exploration on test drug efficacy in one or more than one tumor types, after phase I clinical trial decided the major toxicity organs of the test drug and it is within commonly acceptable toxicity limits.*

*Phase II trial antitumor drugs in considered as one of the critical steps in a drug development process. The following aspects of information should be obtained during this phase of trial:*

- a. A judgment on whether or not the text drugs has antitumor activity;*
- b. A judgment on which type of tumor is most sensitive to the test drug for further development;*
- c. A judgment on which type of tumor is NOT sensitive to the test drug and should be excluded in any further development.*

*In summary, a well designed phase II trial should be able to exclude non-sensitive tumors, while determine sensitive tumor types as potential indication for further development. In this way Phase II trial should provide sufficient supporting information for trial design of Phase III trial.*

### **3.2.1 Study Purpose**

*The main purpose of Phase II is to examine whether or not the drug has antitumor efficacy, explore the antitumor spectrum of test drug, and at the same time a more thorough study on drug adverse effects It should be noted, in addition to the*

common adverse effects, some drug related rare side effects, accumulation toxicity, and toxicity caused by repetitive administration should also be evaluated. The prevention and processing method of side effects should also be suggested and examined.

Phase II trial should also further explore and optimize dose regimen that used in phase I trial, including dose, dose interval, duration of the therapy, the possibility of combination therapy with radiation and other chemotherapy drugs, etc. Also it should further clarify the correlation between the test drug therapy efficacy and induced toxicity.

### **3.2.2 Study Design**

Due to the fact that phase II trial is a exploratory study, not verification study, as well as malignant tumor unlikely would heal without treatment, the efficacy (any shrink in terms of the size of tumor) can be considered as the contribution of the test drug therapy. . Therefore phase II trial usually does not have to be a random, controlled design. However if a standard therapy is available, it is recommended to use standard therapy as control group in order to check the superiority of the test drug at earliest clinical trial stage. Another major purpose for Phase II trial is to exclude some non-sensitive tumor types, or patients with certain type of tumor bears high side effect ratio, to avoid more patients receive non-effective treatment. Therefore Multi-stage design of the trial is usually employed in this stage of study to help recognize any treatment that is found to be inappropriate to specific recruited patients and terminate the study as early as possible.

Combination therapy may not be able to well demonstrate the efficacy and toxicity contribution of the test drug and therefore it is recommended to use singly drug treatment in Phase II trial, in order to well demonstrate the test drug efficacy and toxicity profile. In case single drug is not suitable or not ethically appropriate, a random phase II trial should be performed in order to evaluate the necessity of combination therapy that will be carried out in Phase III.

### **3.2.3 The Selection of Patients**

The selection criterion of Phase II patients is similar to that for Phase I. In addition, patients should at least have one identified tumor type as well as well accepted parameter for efficacy evaluation, in order to obtain preliminary efficacy results of test drug.

For some specific tumor types, such as brainstem glioblastoma, in which case pathology examination/cell study may cause serious effects on patients, the trial design can use clinical symptom, radiology results and or laboratory test to obtain efficacy data.

The selection of Phase II trial tumor type should follow preliminary results on efficacy from Phase I. It should also be considered through the susceptibility of any type of tumor cell according to similar category of drug with the text drug, as well as in vitro cell study results. Regularly, Phase II trial should select more tumor types instead of only one or two tumors in order to obtain more information for Phase III trial and decrease the risk of Phase III trial.

The plan of patient recruitment should be well designed, to minimize the number of patients required to obtain required study purpose. The trial design should include at certain criteria, the trial should be terminated (in case the efficacy has shown to be low or the toxicity is too high). However if the study shows a good efficacy potential, Phase III trial can be started before the Phase is completed.

The final criteria of the efficacy should be designed according to scientific theory, mostly will be according to the type of tumor and the total patient population, If from Phase II that the efficacy has been determined it is not effective on certain type of tumor, the conclusion should be made that this type of cancer is not a suitable indication of this test drug.

### **3.2.4 Dosing Design**

*Phase II trial should further explore and optimize the dosing regimen of test drug, based on information obtained from Phase I trial. Two or more doses could be started simultaneously. The detailed dosing regimen should also be explored, such as dose level, dosing intervals, total therapy duration as well combination therapy strategy. In this trial study, all pharmacological factors that could interfere with efficacy or safety should be considered and studied. The dose should also be designed and adjusted considering the case of side effect and toxicity. It should be noted, during the clinical trial, patients should not be administered any other drug that may cause interference on efficacy or safety of text drug. Drug that may have interaction with test drug should also be avoided during the trial design.*

### **3.2.5 Drug Efficacy Evaluation**

*ORR (Objective Response Rate) is defined as the rate of patients that has obtained certain degree of tumor shrink and maintain this decrease in a certain period of time. It is a preliminary indication on the anti-cancer efficacy and is commonly used as a critical parameter to evaluate the drug efficacy in Phase II trial.*

*The clinical trial should be designed according to international standards, (e.g. RECIST) to record ORR. In common, imaging is used for this purpose. However to certain type of tumor, imaging may not be the best option, such as the measurement of tumor size on the surface can use caliper instead. When multiple tumor sites exists, a representative parameter can be used to evaluate the ORR parameter. If there is new or more tumor sites becomes available during the study, these sites should also be evaluated.*

*Even though ORR has been considered as a good parameter to evaluate the antitumor efficacy of test drug, it may not well represent overall survival rate. In order to provide more information to better understand pharmacological effect of test drug and decrease the risk of later stage clinical trial, PFS (progress free survival) and OS (Overall survival) as well as some other parameters that could provide good information on clinical benefit, such as quality of patient life, clinical symptom etc should also be included in the trial, if possible.*

### **3.2.6 Safety Inspection and Evaluation**

*Besides regular safety evaluation parameters, Phase II trial should also focus on main toxicities that has been observed during Phase I trial and preclinical animal studies. Also the toxicities that have been observed in similar drugs should also be evaluated. The correlation between dose regimen and side effects as well as the recovery after the termination of therapy should also be evaluated. The optimized dose should bear good efficacy under conditions either the patients tolerate the dose regimen or the patients can obtain good recover after the designed therapy.*

### **3.2.7 Study Termination**

*If the sensitive tumor type and optimized dose regimen has been obtained, Phase III trial can be started. However if Phase II could not provide good evidence of the text drug for indicated indication, the clinical trial of the test drug should be terminated.*

*In addition if the following situation has been occurred on specific patient during Phase II trial, the patient should also be terminated for further studies:*

*Evidence shown obvious cancer development even after designed therapy*

*Patients cannot tolerate the therapy or accumulative toxicity has been observed and induce not possible to keep the therapy*

*The patient request to stop the treatment*

*P.I. think the therapy should be terminated on specific patient*

### **3.2.8 Interpretation of Phase II Trial Results**

*The summary of Phase II study should include the follow factors: ORR*

*The conclusion whether or not the drug is benefit to patients and if the drug should be moved to Phase III trial based on ORR.*

*According to ORR, decide most sensitive tumor type and Medium sensitive tumor type, to decide the recommended indication for Phase III study.*

*If OS, quality of patient life or other clinical parameters have been evaluated in the trial, these should also be summarized. However the major focus on Phase II is to obtain preliminary evaluation on anticancer efficacy, therefore OS is not mandatory for this stage. The observation and evaluation on OS can be done during Phase III trial stage.*

*Summary on optimization of dose level, dose interval, duration of therapy as well as combination therapy that can be used for design of Phase III trial.*

*Summary on SAE regarding category, possible consequence, case percentage, recovery time as well as reversibility, correlation between dose regimen and SAE, clinical treatment for major SAE should be presented. The adjustment of dose regimen according to side effects should also be summarized for Phase III trial.*

### **3.3 Phase III Clinical Trial**

*Phase III clinical trial is considered as verification study, through large sample size, random, controlled study, the drug efficacy and safety factors should be fully evaluated to the selected patient population chosen from Phase II to final evaluate the benefit of the test drug.*

*Due to the fact that Phase III trial usually is very costly and long turn-around, following factors should be seriously evaluated before the decision to move any test drug to Phase III trial:*

*Good supporting data on drug mechanism and targeted pharmacological effect*

*Good supporting data on sufficient anti-cancer activity*

*Acceptable pharmacokinetics profile, for oral drug for example, good bioavailability and relatively long half-life*

- a. The intended indication has the demand for a new therapy*
- b. SAE can be well controlled and treated, if happens*
- c. The Purpose of Phase III study*
- d. Fully evaluate the benefit that targeted patient can obtain after new therapy*
- e. Fully evaluate the toxicity profile of test drug, especially some rare cases of SAE that cannot observe during previous trials due to the sample size. The evaluation should include benefit V.S. risk evaluation.*

#### **3.3.1 Study Purpose**

*Phase III trial should be random design in order to minimize any bias from P.I during the study. Due to the fact that Phase III trial usually choose OS as the critical parameter, while usually age, status of the cancer as well as previous other treatment usually cause interference on OS, the balance between each group during study design is very important. The randomized design including all these factors will be helpful for further evaluation of the data obtained from this stage of trial.*

### **3.3.2 Study Design**

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*Due to the fact that most of anticancer drugs are cytotoxic drug, as well as the method of administration varies (e.g. oral, injection of intravenous infusion), double-blind method may not be suitable.*

*However for non-cytotoxic drug, due to the lower toxicity, double-blind method maybe suitable. If double-blind is not used for the study, the termination point, sensitivity analysis and other method to minimize the bias during the study should be used for adjustment.*

*It has been well recognized that using blank control in this type of study is not ethically appropriate. Usually the control group should use standard treatment. The efficacy of test drug should be superior or non-inferior than clinical standard treatment. The selection of control group should be based on the theory that the duration of therapy is similar with the designed therapy in order to facilitate evaluation. If a standard treatment is not available, placebo can be used. In this case superiority need to be obtained comparing to the placebo group.*

*Parallel study design is the most popular method. Cross-over study is usually not recommended for anti-cancer drugs. When multiple treatments are included in the same study, Factorial design ANOVA should be used for analysis. However, if the treatments have interactions (e.g. antagonism OR overlapping toxicity), this analysis should not be used.*

*When previous study data is used as control, theoretical analysis and evaluation should strictly followed SYSTEMATIC REVIEW PROCESS guideline. It should be noted, due the fact that the difference of diagnosis technique, imaging technique, patient care etc. under different studies, using previous study data as control may cause significant misleading results wrong conclusion.*

*If combination therapy is chosen for Phase III study, the combination therapy of Test drug + Drug A (a clinical treatment drug) can be compared with drug A alone. Another option could be using the test drug to replace a drug that already considered as good combination therapy with Drug A.*

### **3.3.3 The Selection of Patients**

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*Phase III clinical trials should select the patients with tumor type which has already been proved effective exactly in phase II, and should also meet the condition of phase II trial. It need large sample, randomized, controlled group to confirm the efficacy and safety for each tumor type. The design of sample size for each tumor type should according to statistics and expected difference of the primary endpoint.*

*The estimate of sample size is determined by endpoint. If the endpoint is overall survival, disease-free survival, no progress survival, disease progress time or the time to treatment failure, the sample size should be designed according to survival analysis.*

### **3.3.4 Dosing Design**

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*The design of phase III dosage regimen should according to the results of phase II. Drug circles are usually not fixed. Generally, it should continue until disease progression or not tolerance toxicity appeared. The treatment circle for some*

adjuvant treatments before or after surgery and most radical chemotherapy treatment are usually fixed. In this situation, the study should be terminated when the fixed treatment ending.

### 3.3.5 Drug Efficacy Evaluation

The purposes of early clinical trials (phase I/II) are evaluating safety and confirming the biological activity, such as ORR. The main purpose of phase III is evaluating clinical benefit. So clinical benefit is the support of drug approved, such as the extension of overall survival or the alternative endpoint that has been established to predict clinical benefit.

The common endpoint for antitumor drug include overall survival, disease-free survival, progression-free survival, time to disease progress, time to treatment failure, reports the results of the subjects and quality of life, objective remission rate and biomarkers, etc. Different endpoint has advantages and disadvantages. The investigator should choose primary and secondary endpoint according to the drug classes, cancer types, the current situation and the developing goal of clinical treatment. It will compare the advantage and disadvantage of different endpoint and some other issues.

#### a. OS, Over Survival

Overall survival is defined as the time from randomization until death from any cause (For patients failing to follow-up before the endpoint, the latest time should be defined as dead time). Overall survival is considered as the most reliable cancer endpoint. This endpoint is precise and easy to measure and document by the date of death. OS is often as the first choice of phase III endpoint. Demonstration of a statistically significant improvement in overall survival can be considered to be clinically significant if the toxicity profile is acceptable, and has often supported new drug approval.

Difficulties in performing and analyzing survival studies include long follow-up periods in large trials and subsequent cancer therapy potentially confounding survival analysis.

#### b. Endpoints Based on Tumor Assessments

DFS (Disease Free Survival): is defined as the time from randomization until recurrence of tumor or death from any cause. The most frequent use of this endpoint is in the adjuvant setting after definitive surgery or radiotherapy. DFS has been the primary basis of approval for adjuvant breast cancer hormonal therapy, adjuvant colon cancer, and adjuvant cytotoxic breast cancer therapy. DFS can be a surrogate for clinical benefit or it can provide direct evidence of clinical benefit. This determination is based on the magnitude of the effect, its risk-benefit relationship, and the disease setting. However, in disease settings where survival benefit has been already established, it is unlikely that DFS can be considered a clinical benefit.

Compare with OS, DFS need shorter time and smaller samples size. Important considerations in evaluating DFS as a potential endpoint include the estimated size of the treatment effect and proven benefits of standard therapies. The protocol should carefully delineate both the definition of DFS and the schedule for follow-up studies and visits.

Unscheduled assessments can occur for many reasons and differences between study arms in the frequency, timing, or reason for unscheduled assessments can introduce bias. Bias can be minimized by blinding patients and investigators to the treatment assignments. The potential effects of bias due to unscheduled assessments can be evaluated by a comparative analysis of the total number of events over the follow-up period regardless of when the events occurred.

PFS (Progress free survival) is defined as the time from randomization until objective tumor progression or death. PFS can reflect tumor growth and be assessed before the determination of a survival benefit. For a given sample size, the magnitude of effect on PFS can be larger than the effect on overall survival. The role of PFS as an endpoint to support licensing approval

varies in different cancer settings. Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit of the new treatment compared to available therapies.

*TTP (Time to progress) is defined as the time from randomization until objective tumor progression; In TTP analysis, deaths are censored, either at the time of death or at an earlier visit representing informative censoring (nonrandom pattern of loss from the study). However, in situations where the majority of deaths are unrelated to cancer, TTP can be an acceptable endpoint.*

*ORR (Objective response rate) is defined as the proportion of patients with tumor size reduction of a predefined amount and for a minimum time period. ORR includes CR (complete response) and PR (partial response). ORR is usually as one endpoint of phase II clinical trial, but it is not a primary endpoint of phase III. ORR is not appropriate for low objective remission rate drug.*

*TTF (Time to failure) is defined as a composite endpoint measuring time from randomization to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death. TTF is not recommended as a regulatory endpoint for drug approval. TTF does not adequately distinguish efficacy from these additional variables. A regulatory endpoint should clearly distinguish the efficacy of the drug from toxicity, patient or physician withdrawal, or patient intolerance.*

### **c. Endpoints Involving Symptom Assessment**

*Symptomatic improvement is considered a clinical benefit. Drug approvals have used patient symptom assessments and/or physical signs representing symptomatic improvement (e.g., weight gain, decreased effusion) as the primary efficacy endpoint. However, measures of global health-related quality of life (HRQL) have not served as primary efficacy endpoints in oncology drug approvals. For the improvement of signs and symptoms or QOL assessments to be used as primary endpoints to support cancer drug approval, the SFDA should be able to distinguish between improvement in tumor symptoms and lack of drug toxicity. An apparent effectiveness advantage based on a global HRQL instrument can simply indicate less toxicity rather than effectiveness.*

*Time to progression of cancer symptoms, an endpoint similar to TTP, is a direct measure of clinical benefit rather than a potential surrogate. As discussed earlier, problems in measuring progression (e.g., missing assessments) also exist in evaluating time to symptomatic progression. Because few cancer trials are blinded, assessments can be biased. A delay between tumor progression and the onset of cancer symptoms can occur. Often alternative treatments are initiated before achieving the symptom endpoint, confounding this analysis. Many cancer trials are performed in patients who may have minimal cancer symptoms. In addition, tumor symptoms can be difficult to differentiate from drug toxicity.*

*A composite symptom endpoint should have components of similar clinical importance and the results should not be exclusively attributed to one component. For example, drugs have been approved for treatment of patients with cancer metastases to the skeleton based on a composite benefit endpoint. Skeletal-related events are defined as pathological fractures, radiation therapy to bone, surgery to bone, and spinal cord compression.*

*Selection of the appropriate population can be critical for documenting symptom benefit. Patients symptomatic at study baseline can be evaluated with a categorical symptom response analysis. In asymptomatic patients at baseline, a time-to-first-symptom analysis can be used. If patients discontinue the study drug or begin a new drug, symptomatic progression can still be assessed if follow-up is continued until documentation of the first symptom.*

*Missing data and infrequent assessments can complicate the evaluation of symptom data especially in open-label studies. Withdrawing treatment because of drug toxicity or tumor progression is one cause of missing symptom data. Ideally, when patients stop treatment, data collection forms should continue to gather information to inform the analysis. Data collection on multiple symptoms should be addressed prospectively regarding multiplicity and the necessary statistical adjustments should be specified in the SAP.*

#### **d. Biomarkers**

Generally, biomarkers assayed from blood or body fluids have not served as primary endpoints for cancer drug approval, although paraprotein levels measured in blood and urine have been used as part of myeloma response criteria. Further research is needed to establish the validity of available tests and determine whether improvements in biomarkers predict clinical benefit.

#### **3.3.6 Observation and Evaluation of Toxicity**

Besides regular safety research, investigator should pay attention to observe toxicity and rare toxicity of phase I/II trial and non-clinical trials.

#### **3.3.7 Interim Analysis**

Interim analyses are frequently undertaken in Phase III trials, but early stopping whether for futility or difference is a sensitive issue. If the majority of the total number of expected events in the long term has been observed and a difference has been documented, this is normally accepted as an indicator that the study is reasonably mature and that the study results will remain stable over prolonged follow-up. The interpretation of interim analyses conducted on a less mature data set may be problematic. In cases where the treatment effect has been underestimated in the planning of the study, this may create a dilemma if statistically convincing effects in terms of overall survival have been demonstrated too early. Interim analyses based on events of progression are not encouraged.

#### **3.3.8 Trial Terminate and Suspend**

The trial should be terminated or suspended if the following situation happened: 1) The expected number of events did not reach the request; 2) If results show test group is obviously better than control group, the control group patients should be turned to test group; 3) If expected or unintended adverse events rate is too high.

#### **3.3.9 Interpretation of Phase III Trial Results**

Summary should include the following contents:

State clearly the benefit that the drug brought to patients, such as overall survival, tumor recurrence time, time to progress, shrink the tumor volume, improved clinical symptoms and improve life quality, etc.

The endpoint concerned time should be observed accurately as far as possible. The review density should be sufficient. And survival analysis method should be used to evaluate in order to make full use of information.

State the acute toxicity, subacute toxicity, chronic toxicity, volume toxicity, rare toxicity of drugs, and the drug related incidence of toxicity reaction, severity level, duration, whether reversible, clinical consequences and processing method, etc.

Evaluate the risk-benefit by efficacy combined with safety. In situation of lacking standards treatment, investigator should compare test drug with placebo. Otherwise, test drug should be compared with standards treatment. Usually expect to demonstrate the clinical advantage of test drug, such as prolonging the survival time or improve the quality of life.

To investigate whether the drug is effective for particular people, it is necessary to make further stratified analysis. The detail of stratified analysis must be in the trial plan. Post hoc exploratory analysis results can't be basis of approval.



*Generally, the antitumor drugs permission must be based on phase III clinical research results, must have positive clinical benefit result, must establish good risk-benefit relationship. But because of the characteristics of the cancer, patients need to an effective therapy. If waiting for trial to complete all, some patients may lose the opportunity to treatment. If there is no effective treatment for the indications, or clinical trial data suggests test drugs significantly better than existing treatment, registration can be applied in advance. But the subsequent complete research results must be submitted within the time prescribed to finally confirm the clinical efficacy.*

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