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Guidance for Development of Chemopreventive Agents

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Approaches to the development and marketing approval of cancer chemopreventive agents have been described by a Working Group from the National Cancer Institute and the Food and Drug Administration in a recent publication [1]. The approaches described do not constitute regulatory requirements, but rather are a summary of the participants' consensus views. It was noted that each potential chemopreventive drug will present unique characteristics such that the fine points of development must be considered on a case-by-case basis. The examples of chemopreventive approaches given primarily involve intraepithelial neoplasia (dysplasia), since the majority of human cancers are epithelial in origin. However, in the future, the approaches may be applied to dysplasia in mesenchymal tissue as well, such as in premalignant lesions of connective and hematopoietic tissues leading to sarcomas, leukemias, and lymphomas.

A strategy was developed to identify candidate drugs, with examples that illustrate how drugs can be characterized for efficacy through *in vitro* transformation modulation and mechanistic assays, and animal tumor modulation models of carcinogenesis. To qualify an agent for clinical study, sufficient evidence was recommended as follows: (1) one or more animal tumor modulation efficacy studies with statistically significant reduced tumor incidences, reduced tumor multiplicities and/or increased tumor latencies, and determination of the concentration-effect relationship, (2) one or more tumor modulation efficacy studies with statistically nonsignificant but dose-associated positive trends of reduced tumor incidences, reduced tumor multiplicities and/or increased tumor latencies, supported by at least one *in vitro* chemopreventive transformation modulation study and/or *in vitro* chemoprevention-related mechanistic study, including characterization of *in vitro* concentration-effect relationship, (3) at least one statistically significant *in vivo* surrogate endpoint modulation study, wherein the surrogate endpoint is validated reasonably to predict an *in vivo* tumor endpoint in the relevant organ, supported by at least one *in vitro* chemopreventive transformation modulation study and/or *in vitro* chemoprevention-related mechanistic study, including characterization of *in vitro* concentration-effect relationship, or (4) strong and compelling evidence of chemopreventive efficacy from epidemiological studies involving the specific agent and target tissue (Table I).

Requirements and recommendations for safety evaluation in toxicology testing were outlined (Table II) and the evaluation of pharmacokinetic and pharmacodynamic drug effect and potential surrogate endpoint biomarkers in Phase I trials was considered. As for investigational drugs for other indications, preclinical toxicity studies should be conducted in two species, rodent and non-rodent, and should include clinical observations, clinical chemistry, hematology, urinalysis, and pathology (gross and micro-

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TABLE I. Preclinical Efficacy Studies for Initiation of Phase I–II Clinical Trials for Chemopreventive Investigational Drugs [1]

I. Recommended – At least one (1) of the following efficacy studies (*i.e.*, A.1., A.2., A.3., or B. below):

A. *In vivo* tumor modulation:

1. Completion of, at least, one (1) *in vivo* tumor modulation efficacy study with a statistically significant reduced tumor incidence and/or reduced tumor multiplicity and/or increased tumor latency in relation to control, and determination of the concentration-effect relationship.

2. Completion of, at least, one (1) *in vivo* tumor modulation efficacy study with a statistically nonsignificant but dose-associated positive trend, in relation to control, of reduced tumor incidence and/or reduced tumor multiplicity and/or increased tumor latency **and** supported by at least one (1) *in vitro* chemopreventive transformation modulation study(s) and/or *in vitro* chemoprevention-related mechanistic study(s), including characterization of *in vitro* concentration-effect relationship.

3. Completion of, at least, one (1) statistically significant *in vivo* surrogate endpoint modulation study, wherein the surrogate endpoint is validated reasonably to predict an *in vivo* tumor endpoint in the relevant organ, **and** supported by at least one (1) *in vitro* chemopreventive transformation modulation study(s) and/or *in vitro* chemoprevention-related mechanistic study(s), including characterization of *in vitro* concentration-effect relationship.

B. Epidemiology:

Existence of strong and compelling evidence of chemopreventive efficacy from epidemiological studies involving the specific agent and target tissue.

II. Additional studies to be considered:

A. For A.1. & A.2. above, efficacy studies in two (2) or more tumor model systems for different organs or in two (2) or more models of the same organ system.

B. For A.3. above, efficacy studies in two (2) or more *in vivo* surrogate endpoint modulation studies.

C. For I.B. above, supporting data from *in vitro* transformation modulation and/or *in vitro* biochemical mechanistic study(s), including characterization of *in vitro* concentration-effect relationship.

Tables I–IV: Previously published in Kelloff, G.J., Johnson, J.R., Crowell, J.A., Boone, C.W., DeGeorge, J.J., Steele, V.E., Mehta, M.U., Temeck, J.W., Schmidt, W.J., Burke, G., Greenwald, P., and Temple, R.J. Approaches to the development and marketing approval of drugs that prevent cancer. *Cancer Epidemiol. Biomarkers Prev.* 4: 1–10, 1995. Reprinted with permission.

TABLE II. Preclinical Safety Studies for Initiation of Phase I–II Clinical Trials for Chemopreventive Investigational Drugs [1]

I. Required:

A. Toxicity studies conducted in two species, rodent and non-rodent.

1. Assess clinical observations, clinical chemistry, hematology, urinalysis, pathology (gross and microscopic inspection of major organs and tissues).

2. Be of sufficient duration to support the proposed clinical trials (*i.e.*, of equal or preferably greater duration than the proposed clinical trial or up to 6 months in rodents and 12 months in dogs).

3. Use route of therapeutic administration equivalent to the intended clinical route. If not appropriate or not possible, provide rationale for route used.

4. Use drug substance as prepared for clinical trial.

B. Genotoxic potential should be assessed in a battery of assays.

C. Segment I reproductive performance and effect on fertility in rat and Segment II teratology study in rat and rabbit should be conducted as early as possible, prior to large clinical trials or trials of long duration, and in accordance with the ICH and the Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs.

D. Combinations of chemopreventive drugs should be evaluated in at least one study of appropriate duration in the most appropriate species for interactions in pharmacokinetics, toxicity, enzyme effects, or other relevant parameters.

II. Recommended:

A. The clinical formulation should be used in all *in vivo* toxicity studies when possible.

B. Pharmacokinetics and metabolite profiles should be examined in conjunction with toxicity studies to aid in interpretation of findings and evaluation of relevance to humans.

C. Pharmacologically guided Phase I clinical starting dose, dosing interval, and dose-escalation strategy should be based upon consideration of concentration-effect relationship shown in preclinical efficacy and toxicity studies.

scopic inspection of major organs and tissues). The toxicology studies should be of sufficient duration to support proposed clinical trials (*i.e.*, of equal or preferably greater duration than the proposed clinical trial or up to 6 months in rodents and 12 months in dogs). These studies should use a route of therapeutic administration equivalent to the intended clinical route and should test the drug substance that would be used in clinical trials. Genotoxic potential should be assessed in a battery of assays, and Segment I reproductive performance and effect on fertility in rat and a Segment II teratology study in rat and rabbit should be conducted as early as possible, prior to large or long clinical trials, and in accordance with the International Conference on Harmonization of Technical Requirements for Registration for Pharmaceuticals for Human Use (ICH)[1] and the Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs. Combinations of chemopreventive drugs should be evaluated in at least one study of sufficient duration in the most appropriate species to detect interactions in pharmacokinetics, toxicity, enzyme effects, or other relevant parameters. Importantly, the Working Group recommended that pharmacokinetics and metabolite profiles be examined in conjunction with toxicity studies to aid in interpretation of findings and evaluation of relevance to humans (Table III). Further, a pharmacologically guided Phase I clinical starting dose, dosing interval, and dose-escalation strategy should be based upon consideration of concentration-effect relationship shown in preclinical efficacy and toxicity studies. Prior to clinical trials longer than one year, chronic toxicity studies should be completed in two species (6 months in rodent, 12 months in non-rodent) with parameters assessed as above. Before Phase III studies, all special toxicity studies (neurotoxicity, cardiotoxicity, *etc.*, as appropriate) should be completed, and at least one rodent carcinogenicity bioassay should be initiated prior to large Phase III studies (completion of one carcinogenicity study should be strongly considered).

As discussed below, multiple parameters need to be considered for chemopreventive drugs investigated in clinical trials (see Table IV). Phase I clinical trials should include single-dose studies in both fasting and non-fasting normal subjects to characterize single-dose pharmacokinetics (*i.e.*, absorption, distribution, metabolism, elimination) and acute toxicity. The single-dose studies might also include placebo control and pharmacodynamic evaluation of dose response for modulation of selected drug effect or surrogate endpoint biomarkers. Subject follow-up upon completion of treatment would include evaluation of modulation of marker status. Also, repeated daily dose studies should be conducted using multiple dose levels for a period of 1–3 months in normal subjects or up to 12 months in subjects at increased risk of cancer(s), for which the drug demonstrates efficacy in preclinical evaluation, to assess multiple dose pharmacokinetics and chronic toxicity. Participation of normal subjects for more than one month can be considered based on available information (toxicity, clinical experience, *etc.*) for each drug on a case-by-case basis.

Phase II trials should emphasize the evaluation of surrogate endpoint biomarkers that are highly correlated to cancer incidence and may serve as an estimate of cancer incidence reduction. In the event that a clearly defined and standardized surrogate endpoint biomarker had not been identified, a randomized, blinded, parallel dose-response chronic dosing study (Phase IIa) for 3 months or more in subjects at high risk for cancer at the site of investigation would be recommended using dosing levels shown to be safe in prior Phase I studies. Such a study would serve as a basis for a Phase IIb study; the objectives of the Phase IIa study are to evaluate measurements of candidate biomarkers (drug effect and/or surrogate endpoint) and the dose-response relationship of biomarker modulation and tolerance to modulation, to standardize assays and quality control procedures, and to characterize chronic dosing toxicity. The Working Group concluded that at least one Phase IIb study would be required prior to Phase III trials. This would be a randomized, blinded, placebo-controlled chronic dosing study for three months or more in subjects at high risk for cancer at the site of investigation at one or more dosing levels shown to be safe and effective in modulating biomarkers. Objectives of the Phase IIb study are to establish dose-surrogate endpoint marker response and chronic dosing toxicity and to select a safe and effective dose based on surrogate endpoint marker response and chronic dosing toxicity.

Phase III studies would be randomized, blinded, placebo-controlled clinical trials with the objectives of demonstrating a significant reduction in incidence or delay in occurrence of cancer, validating surrogate endpoints, further assessing drug toxicity, and further characterizing the relationship of dose and/or pharmacokinetics to efficacy and toxicity. In Phase III trials, the interim analysis of a validated surrogate endpoint of cancer incidence may facilitate timely and cost-effective marketing of efficacious drugs. In case of formulation differences, Phase III trials would establish the bioequivalence between the to-be-mar-

[1]Please See Appendix A: Abbreviations at end of Supplement.

TABLE III. Preclinical Safety Studies for Initiation of Clinical Trials Beyond One Year in Duration for Chemopreventive Investigational Drugs [1]

I. Required:

A. Completion of chronic toxicity studies in two species (6 months in rodent, 12 months in non-rodent) with parameters assessed as above.

B. All special toxicity studies (assessing neurotoxicity, cardiotoxicity, *etc.*, as appropriate) before Phase III.

C. Initiation of at least one of the rodent carcinogenicity bioassays prior to initiation of large Phase III studies. Completion of one study should be strongly considered.

II. Required for New Drug Application (NDA):

A. Segment III perinatal and postnatal development study in rat prior to submission of the NDA.

B. Completion of two rodent carcinogenicity bioassays prior to NDA submission.

TABLE IV. Phase I–III Studies of Chemopreventive Investigational Drugs [1]

Phase I			
I.	Required:	A.	Single-dose studies in both fasting and non-fasting normal subjects to characterize single-dose pharmacokinetics (*i.e.*, absorption, distribution, metabolism, elimination) and acute toxicity.
		B.	Repeated daily dose studies using multiple dose levels for a period of 1–3 months in normal subjects **or** up to 12 months in subjects at increased risk for cancer(s), for which the drug demonstrates efficacy in preclinical evaluation, to assess multiple dose pharmacokinetics and chronic toxicity. Participation of normal subjects for more than one month will be considered based on available information (toxicity, clinical experience, *etc.*) for each drug on a case-by-case basis.
II.	Recommended:		Under I.A. above, include placebo control and pharmacodynamic evaluation of dose response for modulation of selected drug effect or surrogate endpoint biomarkers. Subject follow-up upon completion of treatment will include evaluation of modulation of marker status.
Phase II			
I.	Recommended IIa:		In the event that a clearly defined and standardized surrogate endpoint biomarker is not identified, then a randomized, blinded, parallel dose-response chronic dosing study will be conducted for 3 months or more in subjects at high risk for cancer at the site of investigation using dosing levels shown to be safe in prior Phase II studies. As a basis for the IIb study, the objectives are to evaluate measurements of candidate biomarkers (drug effect and/or surrogate endpoint) and the dose-response relationship of biomarker modulation and tolerance to modulation, to standardize assays and quality control procedures, and to characterize chronic dosing toxicity.
II.	Required IIb:		Randomized, blinded, placebo-controlled chronic dosing study for 3 months or more in subjects at high risk for cancer at the site of investigation at one or more dosing levels shown to be safe and effective in modulating biomarkers. Study objectives are to establish dose-surrogate endpoint marker response and chronic dosing toxicity and to select a safe and effective dose based on surrogate endpoint marker response and chronic dosing toxicity.
Phase III			
Randomized, blinded, placebo-controlled clinical trials.			
The objectives are to:			
		1.	Demonstrate a significant reduction in incidence or delay in occurrence of cancer.
		2.	Validate surrogate endpoints.
		3.	Assess drug toxicity.
		4.	Characterize the relationship of dose and/or pharmacokinetics to efficacy and toxicity.
		5.	In case of formulation differences, establish the bioequivalence between the to-be-marketed formulation and the

keted formulation and the formulation used in pivotal clinical trials.

REFERENCE

1. Kelloff, G.J., Johnson, J.R., Crowell, J.A., Boone, C.W., DeGeorge, J.J., Steele, V.E., Mehta, M.U., Temeck, J.W., Schmidt, W.J., Burke, G., Greenwald, P., and Temple, R.J. Approaches to the development and marketing approval of drugs that prevent cancer. *Cancer Epidemiol. Biomarkers Prev.* 4: 1–10, 1995.