National Cancer Institute

Meeting Summary

P-4 Chemoprevention Trial Assessment Group Meeting

Hyatt Regency Bethesda
Bethesda, MD
March 23, 2007

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
National Cancer Institute
National Institutes of Health

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Contents

Summary of Issues/Recommendations From the NCAB P-4 Subcommittee

1. The ultimate value of the study will be determined by whether it provides sufficient positive data to change the practice of preventive medicine. To date, the prevention trials in breast cancer have provided positive results with both tamoxifen and raloxifene, but despite their ability to decrease the numbers of tumors by 50%, neither has been widely adopted, probably because of concerns about side effects and the relatively low risk for a major segment of the female population of interest. Prior studies have not defined a survival benefit, and the cost-benefit analysis of the P-1 trial predicted a surprisingly high expenditure ($1.3 million) for each year of life saved. Thus, if we are to undertake another such study, in a relatively low-risk population, we need to be sure that (1) the expected risk-benefit ratio is clearly defined by the study, (2) the U.S. Food and Drug Administration (FDA) agrees with the design and the planned collection of data as a "registration" trial, and (3) the company in question (Novartis) is backing the study.

2. Regarding these three key points, at the meeting, it was not clear that the risk/benefit ratio for AIs would be clearly defined by this study. The AIs have the potential for serious toxicity in at least two areas, bone and lipids/heart attacks. These toxicities may not become evident in the first 5 years of the trial. Thus while the cancer prevention impact may become clear quite early in the trial, it may take 5-10 years to assess the drug's safety and its impact on mortality. There is no placebo control group for comparative assessment of these important toxicity rates. Secondly, regular toxicity assessment is planned only for the first 5 years on study. Thereafter, late-occurring toxicities will be monitored through voluntary reporting, as events happen. This may well be inadequate for purposes of registration. Regarding points 2 (FDA) and 3 (Novartis) above, both the FDA and Novartis need to reassure the NCI that the trial design has their full support as a registration effort.

3. The costs of the trial are not clear. NSABP says the price is $55 million for 5 years, not counting indirects. NCI says the total cost is likely to be $110 million or higher, if one takes into account the need for longer followup. This figure needs to be clarified. In addition we need to know what Novartis is actually willing to contribute to the trial. If it is aimed at registration, the company should fund a major part of the cost.

4. Everyone agrees that the greatest need is for identification of biomarkers that define a high-risk population. The proposed trial does not incorporate a strategy for defining such markers, and uses a selection strategy based primarily on age and prior breast pathology. Many of our advisers were reluctant to see the NCI embark on a 10-year trial with basically a 15-year-old approach, Drug A versus Drug B, in an unselected population.

5. There were various suggestions for amending the trial, including one that proposed a look at shorter durations of therapy for the two agents in a 2 × 2 design. It is unclear whether the addition of randomization steps would add to the cost of the trial, and might lead to both less toxicity and lower efficacy in the new arms.

6. The trial should become a platform for research on identifying higher risk subgroups. Key to this effort is the collection of tumor tissue and normal cells (whole blood) for molecular studies. These samples must be available to outside investigators. NSABP should establish a transparent process, with outside representation and NCI participation ensuring access to samples for qualified investigators.

These are the primary concerns expressed at the meeting. It will be important to add the missing information for our discussion in June, particularly a clear definition of the cost, and the support of the FDA and Novartis in aiming for registration. To summarize, while virtually all the participants thought that interesting and useful information would come from the trial, as proposed, there was uncertainty that the trial would lead to registration. Even if the trial meets its goal regarding tumor prevention, as currently designed, it was the dominant opinion that, because of concerns about toxicity, its effect on the practice of preventive medicine might be modest.

Meeting Summary
P-4 Chemoprevention Trial Assessment Group Meeting

Executive Summary

The goal of the P-4 Chemoprevention Trial Assessment Group that met on March 23, 2007, was to provide the National Cancer Institute's (NCI) National Cancer Advisory Board (NCAB) with input and suggestions on addressing barriers facing chemoprevention research in the context of current advances in molecular science, the regulatory climate for cancer chemopreventive agents, and the public acceptance of chemoprevention. The Group was encouraged to utilize this background to offer guidance and suggestions on the P-4 trial to the NCAB, given its size, duration, and central role in the NCI's breast cancer chemoprevention program.

Given the makeup of the group of experts assembled, there was a range of often divergent views on the best path forward in chemoprevention. A number of important issues and questions were raised and a robust discussion of the P-4 chemoprevention trial. The following summary presents the wide-ranging opinions and views, in both the group discussions and the breakout groups that met to consider general questions and provide suggestions and guidance as requested.

The P-4 Chemoprevention Trial, developed by the National Surgical Adjuvant Breast and Bowel Project (NSABP), is a double-blind trial designed to compare raloxifene with letrozole in risk-eligible postmenopausal women. The NSABP has 50 years of clinical trial experience and is supported by more than 200 centers in the United States, Canada, and Puerto Rico, plus an additional 300 satellite institutions.

As designed, the trial does not have a placebo arm. When fully accrued, the trial will enroll 12,800 postmenopausal women over a 4-year period, followed by a 3-year analysis period. The trial will include women who have a Gail score >1.66% for a 5-year risk of breast cancer, and participants will be stratified by age, relative risk, race, and history of lobular carcinoma in situ (LCIS). Patients will receive either raloxifene or letrozole (all participants will receive an active agent) for 5 years and will be given breast exams, mammograms, lipid panels, and bone mineral density assessments during the trial.

Specimens from the P-4 trial will be placed into the NSABP Human Specimen Banks. Currently, correlative studies embedded in the trial include quality of life, serum and tissue collection, cognition, and a Biomarker Modulation Study (reported on at the meeting), to be performed by the Southwest Oncology Group (SWOG).

Discussions during the meeting emphasized the difficulty of estimating the total cost of the trial, depending on followup and outcomes. The P-4 trial is proposed as a 5-year study at a budget of $54 million. Given the experience on the P-1 and P-2 trials, it is expected that the P-4 trial will require 10 to 13 years to complete; the total cost, while currently unknown, will likely exceed $100 million. The NSABP stated that Novartis will donate $30 million for the trial to aid in recruitment and adherence at local sites, and the drugs will be donated by Novartis and Eli Lilly.

Summary of Major Suggestions. The P-4 Chemoprevention Trial Assessment Group held far-ranging general discussions and more focused deliberations in three breakout groups. Each of the reports from the breakout groups was also followed by a general discussion. Summaries of the presentations, general discussions, and breakout group input are presented in the summary that follows. The Group focused on a number of topics affecting the field of chemoprevention today and, in that context, thoughtfully discussed the pros and cons of the proposed P-4 trial. Although a large number of issues and questions were discussed, a selected number of key areas captured a great deal of the deliberations of the overall Group

and the smaller breakout groups. The following summary attempts to capture these major focus areas and the suggestions that emerged during the course of the meeting:

- One of the major areas discussed at this meeting was the critical role of the populations chosen for study in chemoprevention trials as part of a larger strategy to move the field forward. Better tools to assess risk are critical to the future advancement of cancer chemoprevention. The NCI should make every effort to utilize all aspects of contemporary molecular biology and genetics to improve our ability to predict individual cancer risk through the development of new tools. New programs need to be designed and funded in this area.

  Until risk can be more accurately estimated, the Group suggested that investigators do everything possible to choose populations that are at sufficient risk to more clearly rationalize risk-benefit to patients and the regulatory bodies. Specifically for the P-4 trial, the Group suggested that other parameters, such as breast density, be included as a factor for estimating risk, and that higher risk populations, such as ductal carcinoma in situ (DCIS) patients, be the population of choice for a seminal study of breast cancer chemoprevention.

- The field of chemoprevention needs trials that will serve as incentives to both patients and the private sector to enter into the studies and the field, respectively. In that regard, it was suggested that patients would benefit most from the P-4 trial if it were performed as a registration trial. It would possibly require a placebo arm and clear data to define toxicity to undertake P-4 as a registration trial, but since it was stated that the NCI and the NSABP are in discussions with the U.S. Food and Drug Administration (FDA), a registration-directed trial should clearly be explored.

- Cancer chemoprevention trials are long and very expensive, and there is very little incentive for the industry to invest in and pursue this area. Approaches to trial design that could speed the trial process for studies such as the P-4 trial are critical to advancing the field. Other designs should be considered specifically for the P-4 trial. Suggestions included performing the P-4 trial using a 1-year 2×2 design or performing a series of smaller trials with clear endpoints.

- One of the major deterrents to breast cancer patients participating in cancer chemoprevention trials such as P-4 is the fear of side effects. In many instances, these fears are responsible for a significant dropout rate and impact the ultimate uptake of the results. The NCI must focus a portion of its chemoprevention program on better approaches to identify patient populations that are likely to suffer side effects in cancer chemoprevention trials. The NCI should focus on defining and supporting programs that use current and emerging technologies (e.g., pharmacogenomics) to stratify patients on the basis of their risk for the potential side effects (e.g., bone loss, cardiovascular events, etc.) of chemoprevention drugs, especially those associated with aromatase inhibitors (AIs). Given that the future uptake of these types of agents may depend heavily on how well the P-4 trial manages the question of side effects, studies should be embedded in the trial to inform these questions.

- The future of cancer chemoprevention will depend significantly on the engagement of the basic and translational science communities. To accomplish this will require the development of the highest quality biorepositories that are broadly available for qualifying biomarker and other studies. It is suggested that the P-4 trial develop such biorepositories and utilize a transparent process to make them broadly available to support meritorious studies.

- Contemporary advances in genomics, proteomics, imaging, and a number of related fields offer the opportunity to capitalize on cancer chemoprevention clinical trials through correlative studies. For example, single nucleotide polymorphism (SNP) analysis could be used to identify patients at risk for side effects, and combinations of markers could conceivably be developed to predict response. In chemoprevention, we must build a scientific base for biomarkers that will correlate with outcome.

Endpoints could also be validated through nesting in treatment trials as an example of a better use of resources. The P-4 trial should give careful consideration to correlative studies (individuals will develop breast cancer, so the transition can be studied) that can be incorporated early in the trial and plan for longer studies as the biorepository develops.

- Recent advances in molecular biology, molecular genetics, advanced technologies, and bioinformatics have set the stage for performing shorter more potentially meaningful clinical trials through the use of biomarkers. Biomarkers are very likely the single biggest hope for chemoprevention trials in terms of addressing issues.

- The low penetration of the findings from the P-1 and P-2 trials strongly suggests that the P-4 trial will likely result in a similar outcome. This issue can be addressed only by asking the best questions in the right populations that maximize risk-benefit for patients and ensure minimum side effects. Communication and public education are also critical to helping the general population understand the value of these types of agents, especially in the presence of knowledge of risk. The plan for the P-4 trial should include a plan for communication with and education of the patient population at every phase of the trial, including the breast cancer clinical community, survivor groups, and other interested parties.

  The NCI should also undertake appropriate research studies to better understand why the uptake of these breast cancer chemopreventive agents by patients is so low. These findings could be used to create science-based education and communication strategies on risk-benefit for the affected communities.

- Breast cancer chemoprevention trials such as P-4 are very expensive. Given the stated importance of the P-4 trial to at-risk populations of postmenopausal women and its central role in the NCI's chemoprevention program, it is critical that a business plan—or similar forward-looking document that presents a credible estimate of the expected cost and duration of the trial—be completed before the trial is initiated. Best estimates of cost, dropout rates, and expected outcomes should be utilized to develop this plan.

- There is a definite need for a strategic plan in cancer chemoprevention research. We should not continue to simply build on the paradigm of continuing to build on prior chemoprevention trials. A more strategic approach is to define what the field needs to progress rapidly in the next 10 years and design studies to address those challenges.

The detailed summaries of the deliberation of the P-4 Chemoprevention Trial Assessment Group are presented in the following meeting summary.

Meeting Summary
P-4 Chemoprevention Trial Assessment Group Meeting

Welcome and Overview

Martin D. Abeloff, M.D., Director, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Dr. Abeloff began by welcoming participants and thanking them for participating in this important meeting. He then noted that the considerable progress in the early detection and systemic therapy of breast cancer during the past few decades has resulted in a steady, incremental decrease in age-adjusted mortality. According to an NCI projection for 2015, the mortality rate from breast cancer is expected to decrease by 50% compared with that in 1990. Dr. Abeloff said that the cancer community has reached a pivotal point from which to build on these incremental successes. Two major chemoprevention trials, the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 and P-2, have informed the proposed NSABP P-4 trial that will be discussed at this meeting. Praising the 44 meeting participants for their extensive and varied expertise in chemoprevention research, Dr. Abeloff charged attendees with assessing the optimal strategies for chemoprevention trials based on current knowledge of breast cancer chemoprevention and the state of the science. He noted that the proceedings from this meeting will be presented in a report to a subcommittee of the NCI's NCAB.

National Cancer Advisory Board Role

Bruce A. Chabner, M.D., Chair, NCAB Subcommittee, Clinical Director, Massachusetts General Hospital Cancer Center, Professor, Harvard Medical School

Dr. Chabner began by noting that the NCI first addressed the chemoprevention of breast cancer nearly 20 years ago in the context of assessing the safety and efficacy of tamoxifen in the P-1 trial. He added that this pivotal trial set the paradigm for many contemporary solid-tumor chemoprevention efforts, and, in terms of practice, the field of breast cancer chemoprevention has progressed relative to that of other solid tumors. Nonetheless, challenges remain with the design and implementation of clinical trials in this area (e.g., choice of agent and endpoints and risk/benefit and cost analyses). Dr. Chabner stressed that attendees should consider the field holistically when discussing the P-4 trial, in both the context of its advantages and disadvantages and potential alternative approaches to identifying high-risk patients. He noted that the NCAB Subcommittee is committed to listening carefully to the pertinent scientific and intellectual issues related to the P-4 trial and to providing the NCAB and ultimately the NCI Director the best advice possible to accelerate progress based on the state of the science in breast cancer chemoprevention.

At this point, Dr. Paulette Gray requested that participants declare perceived and actual conflicts of interest, which were captured in the conflict-of-interest forms required of all attendees.

NCI Director's Perspective and Charge to the Group

John E. Niederhuber, M.D., Director, National Cancer Institute, National Institutes of Health

Dr. Niederhuber began by thanking the participants for agreeing to convene on such short notice. He said that he has been involved in breast cancer treatment for several decades and would like to base decisions regarding the allocation of NCI resources on the best scientific knowledge available. Dr. Niederhuber added that he has discussed P-4 extensively with scientists, oncologists, patients, and advocates, including the trial's design in the context of the current state of the science, advanced technologies, and the knowledge base in breast cancer. He expressed concern about several aspects of the trial, including its design, the risks associated with aromatase inhibitors (AIs), and whether the trial's outcome would

provide new knowledge and benefit to patients. Dr. Niederhuber asked the attendees to assess the potential investment of resources in the trial and to consider possible approaches to advancing the overall field of breast cancer chemoprevention. He expressed some concern that the trial design might not reach a conclusion in a manner commensurate with the many rapidly advancing fields of science and technology and noted that he is currently reviewing the NCI review and decision-making process for trials such as P-4. Dr. Niederhuber stressed that it is imperative to pursue every opportunity to support the best science in a competitive fashion using rigorous review. In closing, he said that the NCI would like to know what participants think about the state of the science, evolving technologies, and strategies to optimize the investment of NCI resources with respect to future chemoprevention research.

Overview of Status of Chemoprevention Trials (SERMs and Aromatase Inhibitors) and Proposed P-4 Trial

D. Lawrence Wickerham, M.D., Associate Chairman, National Surgical Adjuvant Breast and Bowel Project

Dr. Wickerham began by describing the NSABP P-4 trial in the context of the preceding prevention trials for breast cancer and noted that P-4 will accrue 12,800 postmenopausal women over a 4-year period, followed by a 3-year analysis period. Participants will be stratified by age, relative risk, race, and history of lobular carcinoma in situ (LCIS) and will receive either raloxifene or letrozole for 5 years.

Dr. Wickerham indicated that the NSABP has 50 years of clinical trial experience and is supported by more than 200 centers in the United States and Canada, plus an additional 300 satellite institutions. In 1981, the NSABP conducted the B-14 trial to assess the safety and efficacy of adjuvant therapy with tamoxifen in node-negative disease. Tamoxifen was found to reduce the risk of breast cancer in the contralateral breast, and this outcome led to the development in 1998 of the P-1 study (n=13,000), which compared tamoxifen to a placebo in otherwise healthy individuals who had an increased risk for breast cancer (e.g., history of LCIS, elevated Gail score). Tamoxifen proved efficacious, with a 49% overall reduction in invasive breast cancers and a 50% reduction in noninvasive breast cancers relative to the placebo. Unblinding of this trial led to 1,500 women in the placebo group crossing over to tamoxifen therapy. This trial, however, clearly showed that tamoxifen was associated with significant side effects, including thrombotic risks and an elevated risk of endometrial cancer. A significant long-term benefit from tamoxifen was then established in the International Breast Intervention Study (IBIS)-1 trial, which compared the agent to a placebo, with a median followup of 96 months.

Studies were then conducted to compare tamoxifen with raloxifene, which was approved for the treatment of osteoporosis based on data from the Multiple Outcomes of Raloxifene (MORE) study. This trial demonstrated that raloxifene reduced the risks of newly diagnosed invasive breast cancer and estrogen-receptor (ER)-positive invasive breast cancer relative to a placebo by 72% and 84%, respectively. Based on these results, the NSABP conducted the 5-year Study of Tamoxifen and Raloxifene (STAR), which was also called the P-2 trial, in risk-eligible, postmenopausal women (n=19,742). The average followup in this study was 47.3 months. The trial indicated that raloxifene was not as effective as tamoxifen in preventing noninvasive cancers (e.g., LCIS and ductal carcinoma in situ [DCIS]), although raloxifene resulted in fewer endometrial cancers and fewer thromboembolic events. The average annual rate and number of strokes were comparable, and there was no significant difference in quality-of-life (QOL) endpoints between the two treatment groups. The trial demonstrated that raloxifene was a viable option for postmenopausal women, with the added practicality that it may already be prescribed for osteoporosis in this population.

Data from six trials (e.g., Arimidex and Tamoxifen Alone or in Combination [ATAC], Breast International Group [BIG] 1-98, Italian Tamoxifen Anastrozole [ITA], Intergroup Exemestane [IES], Austrian Breast and Colorectal Cancer Study Group [ABCSG]/Arimidex-Nolvadex [ARNO], and

MA-17) of adjuvant hormonal therapy with steroidal (e.g., exemestane) or nonsteroidal (e.g., letrozole, anastrozole) AIs have demonstrated reductions in contralateral breast cancers. In the adjuvant setting, AIs were superior to tamoxifen or a placebo after 5 years. Letrozole in particular proved to be well tolerated, and the MA-17 trial showed no statistical difference in the discontinuation rates for letrozole versus placebo. These results have led to the IBIS-II and MAP-3 trials, which compared placebo to anastrozole and exemestane, respectively, in postmenopausal women at increased risk for breast cancer. However, all AIs cause myalgia and arthralgia, side effects (plus cholesterol) that will be monitored during the P-4 trial.

Informed by these precedent studies, P-4 is a double-blind trial to compare raloxifene with letrozole in risk-eligible postmenopausal women. All participants will receive an active agent; there is no placebo arm. The trial will include women who have a Gail score >1.66% for the 5-year risk of breast cancer. Dr. Wickerham noted that, if the Gail score cutoff were raised to 2.5-3.0, minority women would be disproportionately excluded from participation, and the ability to carry out cross-trial comparisons would be impacted. Participants in the P-4 trial will receive breast exams, mammograms, lipid panels, and bone mineral density assessments during the trial 5 years from entry. Correlative studies embedded into the trial include QOL, serum and tissue collection, cognition, and the Southwest Oncology Group (SWOG) Biomarker Modulation Study.

Specimens from the P-4 trial will be placed into the NSABP Human Specimen Banks, which are open to access by NSABP members and nonmembers and contain extensive specimens from the P-1 and P-2 trials. Dr. Wickerham stated that the availability of specimens is promoted at national meetings and through the NCI Specialized Programs of Research Excellence (SPOREs) Advisory Board. Applications are accepted from academia and industry, and review policies have met guidelines issued by the Office for Human Research Protections and the NCI. Central pathology reviews have been completed for all invasive breast cancer cases in the banks.

Dr. Wickerham indicated that the P-4 trial has been approved by the NCI for a proposed 5-year direct budget of $54 million. The NSABP will assume the full cost of specimen storage and analysis. He added that the P-4 trial represents a public-private partnership; Eli Lilly and Novartis have agreed to provide the study agents and placebos. Novartis has also pledged $30 million to aid in recruitment and adherence at local sites. Dr. Wickerham noted that both companies will lose their patents before completion of the trial.

Although the P-4 trial does not enroll premenopausal or ER-negative women, it does represent the next logical step in the series of trials for the chemoprevention of breast cancer. Moreover, the design embeds the collection and distribution of biological materials using established methods, and sites have potential participants ready to enroll. In closing, Dr. Wickerham noted that the NSABP has a history of completing chemoprevention trials on time and under budget.

Discussion

At this point, Dr. Abeloff opened the floor for questions and a discussion of issues related to chemoprevention and the P-4 trial. The key topics of the discussion are summarized below:

Cost

Attendees asked several questions about the total cost of the P-4 trial in light of the revised budget estimates presented by Dr. Wickerham. Dr. Wickerham responded that the NSABP has an indirect cost rate of approximately 10%. The direct cost of $54 million provided in the presentation includes the budget for the prevention sites of enrollment by the members. He also noted that Novartis has pledged $30 million to support the trial. Dr. Wickerham's estimate for the cost of the trial was $66 million in total Federal funding over the next 5 years. It was noted, however, that it would be difficult to present a total

estimate of the entire study because it will likely extend beyond 5 years, and a 5-year projection was all that was required of the NSABP to meet application guidelines. Dr. Wickerham added that the P-4 accrual phase is projected to take 4 years, followed by a period of analysis that, while dependent on the number of events, is projected to take 3 years.

With respect to prior chemoprevention trials, attendees expressed concern that the P-4 trial may extend 10 or more years in duration. It was noted that it is difficult to estimate the total costs of such trials in advance, since the NCI continues to invest in trials as outcomes emerge (e.g., the STAR trial). One attendee asked whether the NSABP had done an estimate of cost savings, assuming that letrozole proves to be the superior agent. It was noted that the P-4 trial design features components that will allow such an analysis, but the analysis itself is not embedded in the trial.

Another participant expressed concern about the total health care costs for study participants in excess of those costs incurred by participating in the trial (e.g., cardiovascular disease and osteoporosis in postmenopausal women). The prescription of an AI raises concerns about the potential impact on bone health, which may add to the total cost. It was noted that the study as designed is amenable to insured participants who can afford to maintain bone health. However, the P-4 trial uses a standard-of-care-based protocol, and funds have been made available to provide partial support to economically disadvantaged individuals. It was noted that some of these issues represent a challenge for all clinical trials.

Trial Design (General Considerations)

On the basis of previous breast cancer chemoprevention studies that compare selective ER modulators (SERMs) and AIs, it was estimated that a 40% reduction could be afforded by letrozole in the P-4 trial. The trial uses the standard methodology of previous treatment trials and has built in a reassessment of sample size. It was noted that invasive breast cancer was the primary endpoint of the P-1 and P-2 trials. One discussant noted that it will be important to assess the global index of side effects, benefits, and toxicity. It was noted that the option exists to unblind the P-4 trial once a sufficient result has been obtained, although there are service problems with this approach.

One participant commented on the perception that the NSABP is reluctant to release materials from its prospective, hypothesis-driven trials. In response, Dr. Wickerham noted that the organization remains committed to promoting the availability of materials and to acting as a responsible, active steward of the resources.

Identification of Biomarkers of Risk

Attendees inquired about insight gained from the P-1 and P-2 trials with regard to biomarkers of increased risk. Dr. Wickerham responded that the P-4 trial will incorporate some biomarker-based substudies (e.g., the SWOG Modulation Study [n=400]) that will utilize the trial's specimen resources. This strategy does not require reconsent from trial participants. The PA-3 trial has currently accrued approximately half of its patients. One attendee asked when data will be available from the clinical trials that compare steroidal to nonsteroidal AIs, such as the PA-3 trial that compares anastrozole, letrozole, and exemestane.

Rationale for Trial

One attendee expressed concern that the P-4 trial fails to address the population of ER-negative breast cancer patients. It was noted that other studies in this area that are conducted by the NCI and the pharmaceutical industry are not ready to move into Phase III studies. Another participant asked about information that can be gained from a prevention trial that cannot be obtained through treatment trials. It was noted that patients who have DCIS represent a high-risk population for contralateral breast cancers.

Recommended Additional Studies

This topic was opened with the comment that the P-4 trial should be considered in terms of the "ABC" paradigm—agent, biomarker, and cohort. Although AIs show great promise as potential preventive agents, parallel biomarker and cohort studies are needed to reduce and narrow the target population. It was suggested that results from the Women's Health Initiative, IBIS-II, PA-3, P-1, and P-2 studies indicate that the model to determine who should receive intervention will likely be complex and will require the incorporation of genomic data. Presumably, a predictive biomarker-based model could be applied to the P-4 population to examine subsets of high-risk patients utilizing P-4 biospecimens. Given the P-4 design, biomarkers may be difficult to validate, but several participants suggested that biospecimens could be collected and biomarkers validated using nested case-control studies within the trial design. The NCI currently funds many large biomarker initiatives that may have relevance to P-4 (e.g., Early Detection Research Network [EDRN] and the Clinical Proteomics Technologies for Cancer Initiative teams are investigating breast cancer). It was suggested that KI-67 should be considered as a potential marker because it is part of the embedded SWOG study.

Risk Estimates

Risk assessment was discussed by the group in terms of available resources for risk calculations. It was suggested that major areas that hold the greatest promise for refining risk assessment in chemoprevention trials include genomic data and mammographic density. It was noted that the embedded SWOG study will correlate mammographic density with changes in tissue biopsies, DNA, and serum. Furthermore, it was suggested that adding mammographic density to the calculation of risk may offset the problem of exclusion of African American women. Since the definition of race affects the Gail score, embedded studies may help determine who will benefit from treatment.

The issue of women who develop breast cancer after receiving an AI suggests that additional research is required to assess the relationship between risk and menopausal status. It was suggested that the NCI chemoprevention program develop several biomarkers and models to predict risk for individuals, with sufficient statistical certainty to support their use in trials. Finally, it was agreed that since AIs and SERMs have significant side effects, the design of the P-4 trial must make every effort to include studies to identify patients who will suffer serious problems with bone loss, cardiovascular problems, and so on. For all these studies, the highest quality biorepositories will be required to answer these key questions.

Other Issues and Concerns

Participants raised a series of far-ranging concerns and issues, which are summarized below:

- Respondents discussed the timeframe for the P-4 trial, noting that mortality and the total health benefit beyond breast cancer must be assessed.
- Concern was expressed that the absolute benefit of an AI over tamoxifen has not been adequately assessed over time. Given that most invasive breast cancers are ER-positive, patients have yet to be followed for a sufficient amount of time to determine the full effect of ER status on lesion development.
- Several participants commented on the lack of a placebo arm in the P-4 trial design. While there are no data to disfavor a placebo arm, comparing one active agent to another does not allow for true assessment of the end-organ effects of the agents. A placebo-controlled treatment arm establishes predictiveness, and biomarkers are confounded in the absence of a placebo arm. There are currently no adjuvant trials that provide comparative data on the end-organ effects of AI use.
- It was noted that 25% of women dropped out of the initial tamoxifen trial, suggesting that long-term use of an agent has behavioral issues associated with clinical penetration.

- Conversely, since the benefits may last for a period following stoppage of the agent, as seen with IBIS data, although the end-organ effects may not be known, short-term intervention may confer a longer term benefit.
- It was suggested that a 2×2 study for 1 year be considered for P-4 versus the current design, noting that the trial may be improved overall if it were of shorter duration

Charge to Breakout Groups

Martin D. Abeloff, M.D., Director, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (Moderator)

Dr. Abeloff noted that P-4 is the flagship trial for chemoprevention in terms of scope and expenditure. Yet there remains a perception that specimen access is limited and that insufficient hypothesis-generated, prospective studies are being carried out. He charged participants with considering these issues in the context of building a scientific base for chemoprevention that engages the broadest possible community and utilizes the best science. Three breakout groups were convened to generate suggestions for the NCI's NCAB P-4 Trial Subcommittee, considering the P-4 trial in the larger context of investments in an overall chemoprevention research portfolio. The results of these discussions follow.

Discussion and recommendations made to the Subcommittee by these breakout groups appear below. Full summaries of the breakout groups' discussions can be found in Appendices I, II, and III.

Breakout Group Reports, Discussion of Group Input, and Suggestions for the NCAB Subcommittee

Martin D. Abeloff, M.D., Director, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (Moderator)

Group 1 Summary

This group suggested that the size of this trial, like other recent efforts in "big science," requires a formal mechanism to engage in broad discussions early in the trial design process to vet the needs of individual stakeholders.

The group also recognized that resources generated during the conduct of a trial of this magnitude can be mined for a wide range of research studies; therefore, it may be appropriate in trials such as P-4 to include an arm that may be of limited immediate value to the trial but will support and inform other studies.

The group noted that currently there are no genetic markers of susceptibility for the population of high-risk patients identified for the P-4 trial, but there is potential opportunity to better estimate risk based on the rapid evolution of imaging technologies. This may be especially important, as there are indications that prevention of contralateral breast cancer may not serve as a robust surrogate for primary prevention.

The issue of the numbers of women who may be removed from the trial because of side effects was also discussed. Following the theme of risk assessment, individual susceptibility factors may play a role in the side-effect profiles of these agents and should be considered in the conduct of the trial. It was also pointed out that letrozole may produce side effects of sufficient health impact to influence a patient's decision for use. However, some participants argue that the rigor with which side effects are captured in adjuvant trials is actually less robust than that generally applied in prevention trials.

The discussion turned to the potential clinical utility of steroidal AIs in the next 10 years, given projected changes in the field. Within the class of AIs, preclinical data suggest that letrozole is only marginally

better than anastrozole, but it was suggested that patients who cannot tolerate the drug may be those who would benefit most from its use (i.e., women with low estrogen levels).

The group provided the following general suggestions for future chemoprevention studies (see slides):

- Consider entering into international collaborations with partners that are experienced in trial design (e.g., Quintiles).
- Explore alternative trial designs that demonstrate the efficacy of the study agent, and also include selected studies in patients who are at high risk for side effects of the drug or other symptoms.
- For these chemoprevention trials, promote additional openness and transparency regarding study design, process, and availability of specimens and data.
- To open the design of these trials, formalize discussion early in the process, possibly through a working group; such a group could consider long-term issues without the onus of generating a consensus statement.
- Consider new and innovative approaches to involving industry in the support of chemopreventive trials.
- Formalize and implement mechanisms to allow trial designs to be modified to address embedded studies and biomarker profile studies.
- Consider designing these trials with future applications in mind (e.g., data and specimen archives, foundational research for future experiments).

Group 2 Summary

The group discussed two overarching issues: the P-4 trial addresses an important question—breast cancer chemoprevention; and the NCI must demonstrate inclusive and innovative leadership with respect to cancer prevention. However, additional partners across the community should be considered as contributors of specific components to such trials. Concern was also expressed in this group that delay of the P-4 trial may significantly impact the ability to carry out the trial and impact future trials.

Furthermore, the group suggested that reinforcing the importance of chemoprevention in the community through an educational campaign would be very helpful. Pharmaceutical companies must become more engaged in cancer prevention. All stakeholders, including patients, advocates, and scientists, should be invited to participate from the outset in a discussion of risk-benefit.

Participants generally agreed that prospective tissue collection is essential to successfully applying biomarkers to stratify risk, although risk analysis remains complex. The group emphasized that large-scale trials are necessary to develop biorepositories that can support future research applications (e.g., marker validation, SNP analysis). A clear and widely publicized process must be in place to ensure that biospecimens thus collected will be available for future research.

Group 2 detailed the following limitations of previous chemoprevention trials:

- Inadequate representation from minority populations
- Inadequate attention to ethical considerations and dissemination of information
- Sample sizes that confound selection of appropriate patients

While the therapeutic effect of these agents has been clearly demonstrated, there was concern that the cancer community may not be looking appropriately (scientifically) at questions related to prevention. Participants advocated recruiting minority populations at the community level—recognizing that we must learn how to define much better those at high risk—so that accrual requirements can be reduced.

The group expressed concern about the following issues related to the P-4 trial:

- The trial does not incorporate state-of-the-science methodologies.
- The outcome may not provide new information.
- The trial has no placebo arm.

The group also discussed the biospecimens collected for the trial. They noted that many women who participate in prevention trials have undergone breast biopsies, and biorepositories should bank normal samples (e.g., tissue, aspirates, serum, and adjacent tissue) along with cancerous tissue. This resource should be made available for analysis to both basic and clinical scientists. The group suggested that the NCI issue a Request for Applications (RFA) at a later date for researchers who are interested in using the specimens to support correlative studies.

With respect to risk stratification, the group suggested using pharmacogenomic studies to stratify risk populations and to incorporate biomarkers and prospective stratification by means other than the Gail score. Such strategies may enable accrual requirements for prevention trials to parallel those for treatment studies.

With respect to overall trial design, the group offered several suggestions, including the following:

- Embed formally a duration hypothesis in the trial design.
- Create a 2×2 design examining 1-year and 2.5-year trial periods (to reduce costs by using fewer investigational agents without affecting sample size).
- Consider additional questions that can be asked within this study (e.g., duration, sequence) that would provide additional insight at no extra cost.
- Issue an RFA prior to funding this trial to ensure that all ideas are brought forward in a competitive fashion.

Group 3 Summary

Group 3 expressed a generally unfavorable view of the cost-benefit for this trial relative to the spectrum of prevention-related questions. Although the NSABP is qualified to conduct a trial of this scope, the group felt that the trial represents only an incremental move forward for the field of chemoprevention. The major recommendation from this group was that the P-4 investigators develop a clear strategic approach, working with industry, to develop a registration strategy that will ensure provider and reimbursement support.

Reasons given by the various participants for not supporting this trial as presented included competing opportunity costs, delayed outcome data, and a predictable conclusion. The group felt that the consequences of the trial had not been adequately addressed; that is, will the results be consequential when they emerge?

In addition to pursuit of a registration strategy for P-4, other alternative strategies suggested for prevention trials included conducting smaller trials that investigate more innovative approaches, addressing front-end and back-end issues (not just the main question of the trial), engaging industry in these efforts, and asking multiple questions in any trial of the scope of P-4. The group also suggested that the opportunity to investigate prevention endpoints in the context of adjuvant clinical trials remains an untapped resource.

The group concluded by noting that the field requires a strategic approach that critically assesses both scientific and behavioral issues. Moreover, the clarification of risk assessment must be a critical focus of

any prevention strategy and the trials that support it. While the group did not feel that the P-4 trial was poorly designed, there was consensus that smaller trials could catalyze the gathering of knowledge and move the prevention field forward in a more cost-efficient manner.

General Discussion Following Breakout Reports

As in the earlier discussions, participants focused on several key issues regarding breast cancer chemoprevention and the trial under discussion as follows:

P-4 as a Registration Trial. It was noted that the P-4 trial would have maximal benefit if it is pursued as a registration trial. However, the attendees pointed out that the lack of a placebo arm will hamper trial registration, which is a concern given the trial's public health ramifications. An alternative may be to design trials that allow companies to acquire a label, but trials of this type of design require a clear delineation of relative toxicity profiles.

All chemopreventive trials exist with social context, and to its credit, the NSABP has followed the example of Eli Lilly in the STAR trial by submitting P-4 to the U.S. Food and Drug Administration (FDA).

Predictability of Trial Outcome. The P-1 trial established that observations regarding the prevention of contralateral breast cancer translated well to prevention trials; the P-1 trial was a seminal trial in that regard. It was noted that the results of the six trials that have compared AIs with tamoxifen in the adjuvant setting (e.g., BIG I-98, ITA, IES, ABCSG-8, ARNO 95, and ATAC) were remarkably homogeneous, indicating that AIs are significantly better than tamoxifen. Based on these data, there is a 90% chance that letrozole will be more effective than raloxifene in the P-4 trial.

On the positive side for P-4, the trials highlighted did not provide robust data on the toxicity of letrozole over time, which would be informed by P-4.

Risk Assessment in Cancer Prevention Trials. It was stated that although the concept of breast cancer prevention has been "marketed," the data do not support the concept. Risk reduction and prevention are not the same thing, and mortality data have not yet been developed. It was also noted that elementary tools are available to assess risk, and the P-4 trial would not improve our current understanding of risk. Instead of large trials such as this, smaller intervention trials should be tailored to provide an increased understanding of risk. In addition, there is no guarantee that the public will accept this approach to chemoprevention even if a massive education campaign were undertaken.

Correlative Studies. Several attendees noted that the P-4 trial will provide biospecimens that will facilitate translation to the clinic. The trial will provide a valuable community resource: well-curated, annotated data from a group of women following set protocols with followup analysis. For early detection of cancer, it is critical to have specimens that precede the development of disease, and if P-4 specimens are collected yearly and made broadly available, they could be a valuable resource.

It was noted that biomarkers have been discussed in the context of embedding these studies in adjuvant and prevention trials, although to date no biomarkers have been validated in this manner. Cost and feasibility have generally been barriers to launching parallel qualitative trials within the context of larger trials. However, it was suggested that the P-4 investigators should consider how a pilot study could be embedded into the larger trial—assuming that there are biomarkers that merit validation.

Impact of the P-4 Trial. During this session, the group spent some time discussing the potential impact of the trial and expressed concern that the consequences of this question have not been adequately addressed. Additional consideration is required to determine whether women will use the agent and

whether insurance companies will pay for the drug when it is used in a chemopreventive setting. Despite the impact issue, several participants thought that the trial would have an impact on the field—but the impact was not clearly defined.

One participant commented that if the trial is not funded, potential consequences include the additional expense required to restart the trial at a later date if so desired. The trial features the agents that are current standard of care, and it is speculative to assume that another agent with similar global impact will emerge in the next 7 years.

Funding for Chemoprevention Trials. Attendees discussed general strategies to fund chemoprevention trials, including collaborative government-industry partnerships and issuance of an RFA. These should all be considered for the P-4 trial.

Although there is no blueprint for funding a prevention trial, only a few organizations can carry out studies of the magnitude of the P-4 trial, and the NSABP has a track record in performing these trials.

Response and Next Steps

John E. Niederhuber, M.D., Director, National Cancer Institute, National Institutes of Health

Dr. Niederhuber thanked participants and respondents for their insight on the field of cancer chemoprevention, and the P-4 trial in particular. He noted that the NCI will take the input from the NCAB and this meeting and apply it to all aspects of the Institute's prevention efforts. Dr. Niederhuber noted that the state of the science is moving rapidly and that the NCI is committed to ensuring that the best science is applied to preventing cancer. He stated that future cancer researchers will look back and see clearly that this was a period of unprecedented opportunity. Dr. Niederhuber noted also that budgetary constraints are clearly a major issue that will no doubt impact the funding of long-range projects. He concluded by observing that the NCI will consider all comments put forth at this meeting and will act appropriately with regard to supporting the field of chemoprevention.

The meeting was adjourned.

Appendix I
P-4 Chemoprevention Trial Assessment Group

Summary of Breakout Group 1

General Discussion

The session opened with a request that the discussion not be framed in terms of the issues and questions surrounding chemoprevention that are independent of the P-4 trial. Overall, it was suggested that the trial should be viewed as an example from which to comment on ways to advance the field of chemoprevention.

Given these opening remarks, participants suggested the following actions with respect to the design, review, and implementation of future large-scale prevention trials:

- Formalize discussion early in the process, possibly through a working group. Such a group can consider long-term issues without the onus of generating a consensus statement.
- Consider ways to involve industry in the support of chemoprevention trials early in the process.
- Formalize and implement mechanisms to allow trial designs to be modified to address embedded studies and biomarker profile studies.
- Design these trials with future applications in mind (e.g., data and specimen archives, foundational research for future experiments).

Major challenges inherent in chemoprevention trials include the following:

- Toxicity of agents may influence their prophylactic use.
- Minority and other populations may not accept these types of chemopreventives.
- Use of agents may be limited to high-risk populations.

One attendee noted that the rational design of biomarker-based studies is necessary to support validation of these markers. In Phase III trials, markers must be validated before they can be proposed for widespread use. A nested case-control approach offers the advantage of involving patients who have developed cancer and those who have not within the same trial. The specimen bank proposed with the P-4 trial offers a tremendous resource that may complement emerging applications such as imaging, which is not useful in very early breast cancer but has application for DCIS and mammographic density. It was noted also that the long-term positive effect of these agents after stoppage of therapy suggests that nonhuman animal models should be revisited in conjunction with clinical studies.

Another participant commented that the outcome of P-4 may be predicted from precedent trials. While it has been demonstrated that tamoxifen is superior to placebo, a small placebo arm may provide biomarker information. However, a placebo arm is not appropriate to answer the central question of this trial. Letrozole appears to have the greatest impact in properly selected individuals and thus represents an appropriate clinical consideration in appropriate individuals. Moreover, the protocol describes creating appropriate specimen banks, and new studies can be added on an ancillary basis as the study proceeds. Additionally, it was noted that there are no biomarkers that predict the risk of developing breast cancer; therefore, a population of women at risk of developing longer term breast cancer should be selected to test candidate therapeutic agents.

It was noted that it is plausible to collect appropriate specimens in a large study without conducting a concomitant in-depth analysis for biomarkers. The value of such a resource lies in its establishment of an infrastructure to support future studies, once markers have been identified and validated. Biomarkers could conceivably be validated concurrently with the P-4 trial if funding is provided; and it was observed

that the NSABP has extensive expertise in the collection and storage of biospecimens and is open to specific suggestions in this regard.

Participants discussed concerns that the research community may not know about specimen resources from NSABP trials or the process required to apply for them. The group agreed that a clear description and transparent process for specimen access and use are needed to counteract a perception of opacity. It was noted that the NSABP has been active in engaging SPORE directors about available resources. It was suggested that the NCI design a way to disseminate information about biospecimens available through its sponsored projects. It was observed that the NCI has currently posted an RFA for specimens to be used in multi-institutional trials that use peer-group approval followed by secondary approval from a study section. It was recommended that this process be streamlined.

The group discussed a range of issues related to side effects and chemoprevention trials. Although contralateral breast cancer may be a good SERM marker, it is not totally predictive. Side effects differ among healthy individuals who take these agents, and many healthy individuals ultimately are removed from these trials because of side effects. It was suggested that common toxicity criteria be established. Individual susceptibility factors may play a role in the side-effect profiles of these agents; in particular, letrozole may have side effects so dramatic that they impact a patient's decision for use. It was observed that adjuvant treatment often diminishes concerns about side effects, since it becomes difficult to differentiate side effects. It was noted that the rigor with which side effects are captured in adjuvant trials falls short of that found in prevention trials.

It was noted that a trial of the scope of P-4 allows the statistical power to assess the role of SNPs in susceptibility, thus providing an opportunity to identify patients who will likely experience side effects. Ultimately, such a strategy could result in the construction of haplotype maps with respect to the metabolism of drugs. By contrast, many prevention trials are too underpowered to definitively identify individuals susceptible to side effects.

Participants also discussed the utility of steroidal AIs in light of projected changes in the field within the next 10 years. They observed that there will not likely be a new drug to replace hormone inhibition of breast cancer in that time. Preclinical data suggest that, within the class of AIs, letrozole is marginally better than anastrazole. However, the patients who cannot tolerate the drug may be those who would benefit most from its use (e.g., women with low estrogen levels).

Attendees offered the following suggestions with respect to recruiting at-risk women into prevention trials:

- Advertise the trial process and proposed directions.
- Emphasize that chemoprevention for breast cancer is the leading edge of chemoprevention. This may offset some of the setbacks that the field has encountered in light of data on nonsteroidal anti-inflammatory drugs and colon cancer.
- Improve integration between consortia and other groups that sponsor large-scale initiatives.

It was observed that implementing many of the suggestions from this meeting would ultimately make the trial more expensive. One individual noted that the design was reasonable and supportable and wondered what might be funded if the trial did not proceed. There was also speculation that the trial may result in a reduced prevalence of breast cancers for trial participants, leading to the premature cessation of the trial and the subsequent loss of information on cardiovascular disease and osteoporosis. Mortality would make an ideal endpoint, but this approach would make the trial longer and more expensive.

Participants also discussed international partnerships in large-scale prevention trials. It was noted that the expense is usually less, although data quality is often reduced. Also, political and data regulatory issues

may arise. It may be wise to involve international partners that are established in trial design (e.g., Quintiles) in future trial preparations.

National Cancer Institute
Chemoprevention Meeting

"P-4 Chemoprevention Trial Assessment Group"

Breakout Group #1

Question #1

Formalize discussion early in the process for "big science" (e.g., working groups)

Develop and formalize mechanisms to modify trial to meet scientific needs of other groups

Sample banks and data are key resources

Question #2

Consider different strategies (e.g, optical density imaging vs. mammography)

Consider using nested case/control studies for biomarkers

High-risk cohort selection needed but no proven markers

Does placebo group offer critical biomarker information?

Question #3

Does prevention of contralateral breast cancer serve as surrogate for primary prevention?

Genetic risk assessment

Molecular endpoints

Consider international collaborations for future studies

Question #4

Studies of efficacy

Studies of selected high-risk patients

Emphasis on symptoms and adverse events

Question #5

Consensus about more openness about process and availability of specimens/data

Appendix II
P-4 Chemoprevention Trial Assessment Group

Summary of Breakout Group 2

National Cancer Institute
Chemoprevention Meeting

"P-4 Chemoprevention Trial Assessment Group"

Breakout Group #2

Question #1

- We have learned that accrual to and retention in large prevention trials possible
- We learned that women are willing to comply with preventive treatment
- We learned that pharmaceutical companies could be convinced to focus on prevention
- We learned that public relations can interfere if not appropriately addressed – previous trials not prepared for the media response
- We learned that stakeholder (e.g., patients, advocates, scientists) should be invited to participate from the beginning
- We learned that it is important to educate clinicians and the public
- We learned that it was useful to prospectively collect tissue
- We learned that we could successfully apply biomarkers to stratify risk
- We learned that breast cancer prevention is possible, but the risk analysis is complicated

Question #1

- Limitations:
  - We did not adequately address minority populations
  - We did not adequately address ethics and dissemination of information
  - We still cannot select patients appropriately (reduced sample size)

Question #1

- Ongoing messages about chemoprevention and estrogen from the WHI study color the uptake of these agents, although penetrance of hormones (OCs) is very high because every women sees herself at risk
- The therapeutic effect of these agents has been clearly demonstrated but we may not be looking at the right aspects of prevention
  - Better definitions of risk
  - Collections of various types of tissue

Question #1

- This is both a physician and patient issue
- Advocates/members of the public need to be involved from the very beginning
- Recruitment of minority populations is best facilitated from the community level
- Large trials are necessary for the development of biorepositories that can be available for future analysis (validation of markers, SNPs, etc.)
- We still need to learn how to define those at high risk, thereby reducing accrual requirements

Question #1

- Assurances must be made that tissues, etc. would be widely available for future research – a clear and widely known process must be in place to ensure that these precious resources are well utilized

Question #2

- Validation of biomarkers remains a priority and we must look in the right places to do effect risk assessment
- Concern that this trial doesn't incorporate the science of today and that the outcome won't matter – are there studies that can be embedded to alter this perception?
- Are the drugs appropriate? Should there be a placebo arm?

Question #2

- Many women who go on prevention trials have had breast biopsies and biorepositories should include the normal samples (tissue,aspirates, serum, adjacent tissue, etc.) as well as the cancers

Question #2

- This resource should be used as an opportunity to integrate basic and clinical sciences to deliver prevention – what can we accomplish for this investment?
  - We need to think about the continuum...when do we intervene?
  - Make sure samples from this study would be available and then later issue an RFA for correlative studies

Question #2

- How we integrate the ongoing biomarker activities (e.g., SPORE, EDRN) with this trial?
- We are in a process that will set the stage for future studies requiring fewer participants

Question #2

- Now that we know we are going to get breast cancer reduction, what else should we be asking to accelerate the research by getting the right people on study and we are preparing for the next question?

Question #3

- In order to do this kind of research you need exquisite clinical annotation and samples
  - Plasma/serum
  - Lymphocytes
  - Tissue (including surrounding and normal samples)
  - Mammography repository

Question #3

- Defining high risk populations, moderate risk populations, etc. through pharmacogenic studies
- Incorporation of biomarkers and prospective stratification other than Gail score
- The goal is to have prevention trials that have similar accrual requirements as treatment studies

Question #3

- Have we optimized what we have already learned from P-1 and P-2? How many women should we expose to hormonal manipulation before we know who might benefit?
- Tissue, including the surrounding tissue, gives clues as to who will develop breast cancer (growing out live cells)
- It would be possible to develop mathematical models in real time to go beyond the Gail models

Question #4

- The clinical question must drive the study. This is an important clinical question and would not be done by the pharmaceutical industry.
- The key information that will come for this trial will give the comparison of chemoprevention agents – hopefully with biologic information to differentiate – and will provide access to samples

Question #4

- Formally embed a duration question in P-4 and create a 2x2 design examining 1-year and 5-year administration – sample size would not be affected but the cost is less because less drug is required

Question #4

- Are there additional questions that we can ask within this study – duration, sequence, etc. – that would provide the opportunity to essentially get more for your money?
- How can we use these resources to get the most we can for prevention?
- Embedded studies are still largely in the discovery phase and we should be clear on what discovery phase medicine is.

Question #5

- Before a large investment such as this is made, an RFA should be issued to ensure that all ideas are brought forward in a competitive fashion
- what is done for large prevention trials should be done for all large scientific programs – competition should be required

Summary

- Most people feel that this trial addresses an important question and should go forward.
- Breast cancer prevention is very important and the NCI must demonstrate leadership of prevention in the community This is an important question.
- We don't want to be here 8 years from now with the same questions.

Summary

- Additional partners across the community should be looked to as contributors for specific components of these types of trials or for other trials that might be done
- Delay in this trial may significantly impact our ability to do this and/or future large scale prevention trials
- In order to complete these trials we need to reinforce the importance of chemoprevention in the community – ~~education campaign~~

Summary

- Most people feel that this trial addresses an important question and should go forward
- Breast cancer prevention is very important and the NCI must demonstrate leadership of prevention in the community

Appendix III
P-4 Chemoprevention Trial Assessment Group

Summary of Breakout Group 3

Several issues served as focus points for group 3 and were important areas of discussion for the group as follows:

- **This is not a science problem.** It is a classic situation of decision-making being separated from resource allocation. During times of tight budgets, such decisions become both harder and more critical.
- **We are on the cusp of change in research.** Focus is moving toward more biological approaches to disease research. It is sometimes hard to get researchers to become accustomed to this new way of doing business. For example, in chemoprevention there is little information about individual risk, even though this is a huge issue in prevention.
- **Opportunity costs.** The question may not be, is this study worth $50-$100 million, but rather what other things could be done with that money, and are they a better return for our investment?
- **Answers may already be known.** Based on plenary conversations, it seemed that the outcomes were rather "pedestrian" and predictable. In addition, there are so many other "interesting" questions out there in cancer prevention that are not being answered: it may be more productive to pursue those instead.
- **FDA concerns.** Since this is not a registration trial, as it is written now, the likelihood that the FDA would approve any prevention indication based on this research is rather low.

Group Discussion

In response to the charge to the group, participant discussion focused on the following topics:

Registration. While it was agreed that an up-front registration was a real and significant obstacle to getting FDA approval, it was recognized that a registration plan could be implemented later. One participant suggested that Novartis, at the very least, develop a proposal for registration before study implementation. It was also noted that since this is a "global responsibility," there is a greater need for registration and that perhaps other private industry should also be enrolled in this effort.

Study expectations. The group discussed whether it would be realistic to assess the study's value only by its direct health impact or whether it would still be worthwhile if the study served as an intermediate step. Specifically, the study could serve to prove that a good tool is available, which could then be followed by efforts to home in on the target population and details such as sequencing, dose, duration, schedule, etc. Some concerns were expressed on whether this was the most efficient approach for determining the answers to these research questions. It was also noted that many of the previous studies did not reap immediate success but served as building blocks for continued efforts that eventually did have some positive impact.

Infrastructure. Some attendees viewed the study as necessary to maintain the current research infrastructure, a resource that took a lot of investment to build. Most agreed that this aspect alone was not worth the study cost but was an important added factor that should not be overlooked. There was also discussion that perhaps the large infrastructure could be a liability and that a smaller, more streamlined system for research could possibly be more beneficial.

Prevention versus treatment. It was noted that prevention is quite different from treatment in terms of receiving FDA approval, gaining acceptance from the public, etc. This is a very complicated field that requires a different approach; for example, better information (confidence) in pinpointing individualized

risk and overall impact on women's health in terms of a risk-benefit is a more critical issue for prevention.

It was mentioned that intervention versus prevention might be an easier objective to address. For example, high-risk women might be more amenable to the intervention. A woman with less than 10% risk would probably not participate. It was agreed, however, that moving outside treatment (whether prevention or intervention) is a good direction for research.

Timeframe. The patient advocate representatives were concerned that the larger study would take too much time to provide any tangible results and that perhaps smaller studies might push the research field faster. There were also questions about the absolute impact of the study and whether good measures to assess impact even exist. Other attendees added that because this study had such a long process, other smaller studies might "trump" the results; if that were the case, could this study be modified to build on the new state-of-the-art information?

Front-end and back-end assessments. One attendee noted that in addition to examining the process, it is critical to look at front-end issues (e.g., risk assessment). For example, what is the risk if the person does not see a doctor regularly, as is often the case? Also, in terms of the back end, is the study cost-effective, and are people continuing with the program? For example, those who end up dropping out need to be assessed to determine why (e.g., are they part of a vulnerable population that developed sensitivity to the medication, or were there cost factors, etc.?). Is there a followup (e.g., pill counting) to determine whether study participants are actually following through? If the percentage of noncompliance is high, this would have a direct impact not only on the study results but also on its cost.

Need for a strategic plan in terms of prevention research. Rather than using a paradigm of merely building on existing studies, participants suggested that a more outcome-driven approach might be better; that is, the field would determine what we want to know over the next 10 years and then design studies that will help us answer those challenges or questions.

Auxiliary trials. While the group agreed that auxiliary trials would be beneficial to the study, it was noted that such studies often are difficult because of complexity and expense.

Lack of a placebo arm. There was concern about the lack of a placebo arm in terms of both FDA approval and study impact.

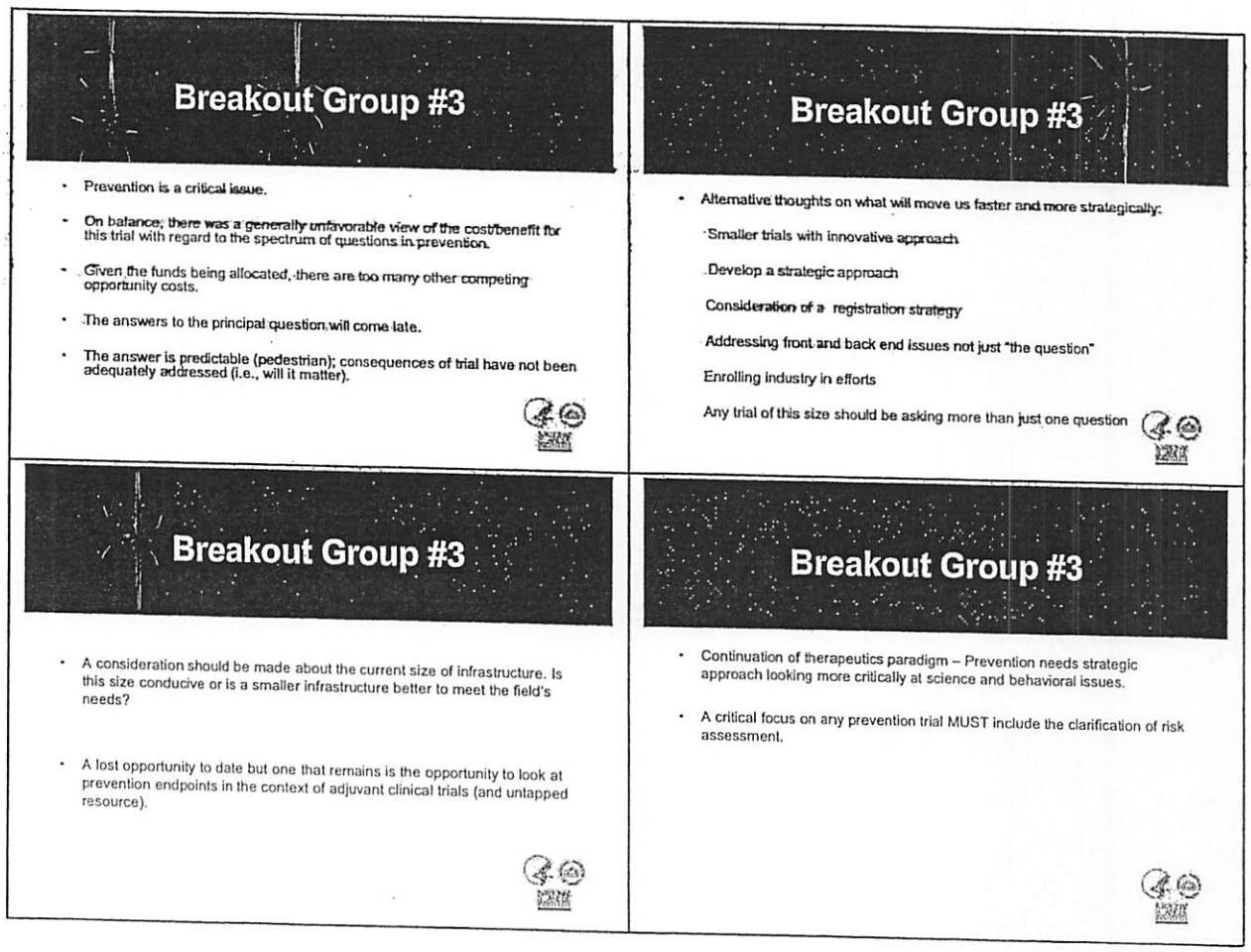
Individual risk. There are still many unknowns, and, given the importance of consideration of individual risk for any prevention approach, many more advances need to be made in this area before any prevention protocol could be implemented for the general public.

Discussion Summary

Overall impressions and suggestions from this group included the following:

- There are too many exciting advances in science that suggest that the funds could be better spent. We also need to look at the infrastructure and how to change the playing field.
- The answer to the question posed in the trial will not come for years and is predictable. This is a large investment for such a pedestrian question.
- There is a need for progress in cancer chemoprevention, but we need a strategic approach.
- This protocol is written like a treatment protocol. We need to take a tougher look at the science and the risk-benefit. We should look at outcome studies (e.g., compliance and uptake) because these are critical issues. Front-end and back-end issues are just as important as questions "in the middle."

- Prevention is important. Risk assessment is important. However, to move the field faster, we need smaller, more targeted trials. We can proceed more rapidly rather than waiting 8 to 12 years for results; the tradeoffs do not seem worth it.
- This trial has a low yield for the dollars spent. Opportunity costs are a big issue. As an alternative, perhaps focus on risk assessment and smaller, faster trials. Tissue access is needed for risk assessment. We need to think about a registration strategy and have a discussion with industry partners.
- The impact factor would be low; the money would be better spent elsewhere.
- Results are predictable, and the consequences of the outcomes are not addressed. A smaller more efficient structure and innovative design would facilitate asking several more relevant questions. A large study such as this asks one major question and there is no guarantee that in 7 to 10 years, it will even be a relevant question.
- A smaller infrastructure will allow the question to be answered; the current infrastructure needs to become "stealth" versus "stellar"!
- The value of the trial is questionable for the cost, but the infrastructure of the NSAB should be maintained; perhaps they can be more efficient.
- Whatever it takes, we need to encourage research in prevention, but prevention research must focus on risk assessment.



National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

P-4 Chemoprevention Trials Assessment Group

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