FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Oncologic Drugs Advisory Committee

Tuesday, December 16, 2008

8:00 a.m. to 3:30 p.m.

Hilton Washington, D.C. North Gaithersburg
620 Perry Parkway
Gaithersburg, Maryland

Oncologic Drugs Advisory Committee
December 16, 2008

Hilton Washington DC North/Gaithersburg
The Ballrooms, 620 Perry Parkway, Gaithersburg, MD

Meeting Roster

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Meeting Roster

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Meeting Roster

TEMPORARY VOTING MEMBERS (Continued)

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OODP, OND, CDER, FDA

Robert O'Neill, Ph.D.
Director, Office of Biostatistics (OB)
Office of Translational Science (OTS), CDER, FDA

Ruthann Giusti, M.D.
Medical Officer, Division of Biologic Oncology
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Robert Becker, M.D., Ph.D.
Chief Medical Officer, Office of In-Vitro
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Center for Devices and Radiological Health (CDRH), FDA

FOOD AND DRUG ADMINISTRATION
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AGENDA

December 16, 2008

8:00 a.m.	Call to Order Introduction of Committee	**Janice Dutcher, M.D.** Acting Chair, ODAC
	Conflict of Interest Statement	**Nicole Vesely, Pharm.D.** Designated Federal Official, ODAC

The committee will discuss biologic license application (BLA) 125084, trade name ERBITUX (cetuximab), ImClone Systems, Incorporated, and BLA 125147, trade name VECTIBIX (panitumumab), Amgen, Incorporated, in the context of K-ras as a predictive and/or prognostic biomarker in oncology drug development. The discussion at this meeting will focus on general considerations for clinical trial designs involving the use diagnostic tests and conducting retrospective analyses .

8:10 a.m.	Opening Remarks	**Richard Pazdur, M.D.** Director, Office of Oncology Drug Products (OODP), Office of New Drugs (OND), CDER, FDA
8:15 a.m.	**FDA Presentation** Regulatory History	**Ruthann Giusti, M.D.** Medical Officer, Division of Biologic Oncology Products, OODP, OND, CDER, FDA
8:30 a.m.	**Sponsor Presentation** Role of K-ras Mutation Status In Optimizing Selection of Colorectal Cancer Patients for Treatment with Erbitux® (Cetuximab)	**ImClone Systems Inc.** **Hagop Youssoufian, M.D.** Senior Vice President, Clinical Research and Development ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company
9:00 a.m.	**Sponsor Presentation** Introduction and Overview	**Amgen, Inc.** **Paul Eisenberg, M.D., MPH** Senior Vice President, Global Regulatory Affairs & Safety Amgen Inc.
	KRAS as a Predictive Biomarker for Vectibix®(panitumumab) Monotherapy	**David Reese, M.D.,** Executive Director Global Clinical Development Amgen Inc.

FOOD AND DRUG ADMINISTRATION
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AGENDA

December 16, 2008
(continued)

9 : 30 a.m.	**FDA Presentation**	
	Prospective vs. Non-Prospective Design in Companion Drug/Diagnostic Studies	**Robert Becker, Jr., M.D., Ph.D.** Chief Medical Officer, Office of In Vitro Diagnostics (OIVD), CDRH
	Some Considerations for Statistical Design, Analysis, and Interpretation for Biomarker Classifier Based Clinical Trials in Establishing Efficacy in Support of Regulatory Marketing and Promotional Claims	**Robert O'Neill, Ph.D.** Director, Office of Biostatistics (OB), Office of Translational Sciences (OTS), CDER, FDA
10:30 a.m.	*Break*	
10:45 a.m.	Questions to the Presenters	
11:30 a.m.	Open Public Hearing	
12:30 p.m.	*Lunch*	
1:30 p.m.	Questions to ODAC and ODAC Discussion	
3:00 p.m.	*Break*	
3:15 p.m.	Questions to ODAC and ODAC Discussion	
4:00 p.m.	Adjourn	

C O N T E N T S

P R O C E E D I N G S

DR. DUTCHER: Good morning. We're going to get started.

My name is Janice Dutcher. I'm chairing this special meeting of the ODAC Committee. I need to read some statements at the beginning.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings.

However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch.

Thank you.

We're going to go around the table and ask members of the committee to introduce themselves.

As I said, my name is Janice Dutcher. I'm at Montefiore Medical Center in New York, New York Medical College.

DR. GREM: I'm Jean Grem. I am from the University of Nebraska Medical Center in Omaha.

DR. RICHARDSON: Ron Richardson, Mayo Clinic, Rochester, Minnesota, a medical oncologist.

DR. DUTCHER: Yes. Please say your discipline, as well. Thank you.

MS. MASON: I'm Jenny Mason, Virginia Mason. I'm the Executive Director of the Inflammatory Breast Cancer Research Foundation and a nurse.

MS. DE LUCA: Jo-Ellen De Luca. I'm your patient advocate.

DR. D'AGOSTINO: Ralph D'Agostino from Boston

University, statistician.

DR. FUNKHOUSER: Bill Funkhouser from Chapel Hill, North Carolina, at UNC, in atomic pathology.

DR. MORTIMER: Joanne Mortimer, Medical Oncologist, City of Hope.

DR. NETTO: George Netto from Johns Hopkins University, pathology, molecular pathology and oncology.

DR. RAGHAVAN: Derek Raghavan, Cleveland Clinic, medical oncology.

DR. CURT: Gregory Curt, medical oncology, AstraZeneca, industry representative to ODAC.

DR. PAZDUR: Richard Pazdur, Office of Oncology Drug Products, FDA.

DR. KEEGAN: Patricia Keegan, FDA.

DR. BECKER: Robert Becker, Center for Devices and Radiological Health, FDA.

DR. GIUSTI: Ruthann Giusti, medical oncology, medical officer, Office of Oncology Drug Products, FDA.

DR. ZHOU: Andrew Zhou from University of Washington, biostatistician.

DR. SIMON: Richard Simon, National Cancer Institute. I'm chief of the Biometric Research Branch.

DR. PRZYGODZKI: I'm Ron Przygodzki. I'm a molecular genetic pathologist and I'm the director in Biomedical Labs and Research Development in the Veterans Affairs.

DR. LINK: Michael Link, pediatric oncologist, Stanford.

DR. HARRINGTON: David Harrington, statistician, Dana-Farber Cancer Institute.

DR. LYMAN: Gary Lyman, medical oncologist and health outcomes researcher from Duke University.

DR. WILSON: Wyndham Wilson, intramural program, National Cancer Institute, medical oncologist.

MS. VESELY: Nicole Vesely, designated federal official, ODAC.

The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting

members are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC Section 208(3), Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special and regular government employees with potential personal

financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of ImClone Systems' Erbitux and Amgen's Vectibix regarding types of studies and data needed to establish KRAS mutational status as predictive of response to drug therapy or as a prognostic biomarker in colon cancer. This topic is a particular matter involving specific parties.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, conflict of

interest waivers have been issued in accordance with 18 USC Section 208(b)(3) to the following participants: Dr. Jean Grem for imputed interest in three Eastern Oncology Cooperative Group sponsored trials and one Cancer and Leukemia Group B sponsored trial. The magnitude of the funding for each trial is between zero and $50,000.

Dr. David Harrington for an imputed interest in a cooperative group related to a competing product. The magnitude of the subcontract is between $50,001 and $100,000.

Dr. Derek Raghavan for an imputed interest in the sponsor of one of the products to be discussed. The magnitude of the contract is between $50,001 and $100,000.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents which are posted on FDA's Website at www.fda.gov/ohrms/dockets/default.htm.

Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of

Information Office, Room 6-30 of the Parklawn Building.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Gregory Curt is participating in this meeting as a non-voting industry representative, acting on behalf of all regulated industry.

Dr. Curt's role at this meeting is to represent industry interests in general and not any particular company. Dr. Curt is employed by AstraZeneca.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to

advise the committee of any financial relationships that they may have with any firms at issue.

We also just wanted to remind everyone to please silence your cell phones if you have not already done so. And I would also like to identify the FDA press contact, Karen Riley.

Thank you.

And we did also want to make one announcement that there will be a fire alarm test at 11:00 a.m. this morning. It will last approximately 30 seconds. There's no need for us to leave the room, but not to alarm anyone, it will just be a test.

DR. DUTCHER: All right. We're going to proceed with the meeting.

The first agenda item is the opening remarks by Dr. Pazdur.

DR. PAZDUR: Good morning. The selection of a drug based on a biomarker profile is desirable because it may limit drug exposure to patients who will benefit from drug treatment, may avoid drug use in patients who may be harmed by drug treatment, or may enhance safe use by optimizing drug dosing.

In the ideal case, the development of the assay methodology for a biomarker should be an integral part of the clinical drug development program. The clinical studies required to establish the drug's efficacy and those needed to establish the prognostic and/or predictive value of the biomarker should occur in tandem.

However, there are multiple examples of retrospective or post hoc biomarker assessment. The worst example involves a retrospective reanalysis of a failed clinical trial, that is, a trial that did not meet its primary endpoint. An attempt to salvage the trial is made by examining non-pre-specified subgroups.

The FDA discourages such practice and this practice should not be considered during this advisory meeting discussion. However, FDA also recognizes that there may be legitimate reasons for the lack of consideration of biomarkers early in drug development, primarily due to advances in the scientific knowledge of a drug or disease occurring during drug development.

In today's meeting, the FDA seeks guidance regarding how to incorporate new scientific information

without compromising our mandate to ensure that the marketed drugs show substantial evidence of efficacy and are safe.

The FDA and commercial sponsors during this meeting will present a recent example of retrospective biomarker analyses intended to support changes to product labeling.

ImClone, the license-holder for Erbitux, and Amgen, the license-holder for Vectibix, will describe the results of retrospective analyses assessing efficacy outcomes determined by KRAS genomic status. We have asked these sponsors to present this data to provide a context for the questions and discussions posed to the committee.

The KRAS presentations provide a real world situation faced by the FDA in which considerations of the type and extent of data needed to support labeling claims must be made. The issues posed to the committee during the afternoon discussions deal with general considerations of incorporating retrospectively identified biomarkers in regulatory decisions rather than the specifics of the KRAS example.

As previously stated, an ideal scenario is one in which the relationship of the biomarker to the potential action of the drug is recognized early. Indeed, such a relationship might be the motivation for starting the drug's development. In this setting, many milestones for development of the in vitro diagnostic, or IVD, might be reached in an orderly manner.

The identity of the biomarker should be established early, along with reliable means for its measurements. If the biomarker has an impact on the natural course of the disease, being prognostic, such a relationship might be elucidated.

Through preclinical studies and early clinical trials, support might grow for the applicability of the biomarker as an indicator of drug effect. Formulation of an intended use of the biomarker might emerge and resources are committed to complete the analytical validation of a fully specified in vitro diagnostic.

When a definitive efficacy trial for an investigational drug is undertaken, its design might incorporate a test of the IVD so that conclusions can

be drawn concerning both the drug's safety and efficacy and the effectiveness of the in vitro diagnostic. With a trial that is successful from all perspectives, the drug will be approved and the test will be clinically validated and approved for prediction of the drug effect.

For many reasons, the ideal situation is unusual. When a definitive efficacy trial has been conducted and completed without reference to the biomarker, there may be an intense interest to retrospectively examine the biomarker in available clinical trial specimens.

The follow-up of patients accrued to an efficacy trial is already at hand. The patients who accrue to the completed trial include both patients who were, quote, "positive" and patients who were also negative for the biomarker of interest, a likely requirement for gaining insight on a predictive claim for the in vitro diagnostic.

There are many issues to be addressed with the strategy of retrospectively examining biomarker data. Some of the points of discussion should include

the following.

First, the chance of erroneously concluding that there is a real treatment effect, when, in fact, it is not true, or the chance of concluding there is no treatment effect, when, in fact, one actually exists, are two critical concerns for the design and interpretation of study results of any clinical trial.

There are many examples of sub-population findings that are spurious. To address this problem, it is necessary to control the chances of making these false conclusions, usually by pre-specifying the hypotheses and the number of subgroups for which a treatment effect in a sub-population is sought as a primary objective of the trial.

Secondly, an additional issue to be discussed with the anticipated use of retrospective analysis is the concept of replication, that is, the likelihood for reproducing a treatment effect identified in a subpopulation in a single trial in another independent trial.

A third consideration in using retrospective biomarker analysis is that the required sample size for

the biomarker negative population should be sufficient to detect a treatment effect, if it exists, considering that the effect may not be of the same magnitude as in the biomarker positive subpopulation.

The minimum performance characteristics, for example, sensitivity, specificity, reproducibility, of the assay used to define patient subgroups and the consequences of the performance for correct decision-making and inferences from the study should be understood. In addition, the proportion of patients whose biomarker specimens are available for analysis needs to be considered in any request for a retrospective analysis of a completed trial.

Clarity on whether the biomarker is being considered a prognostic and/or predictive marker and the consequences of these definitions on study design planning, sample size and the ability to draw conclusions must be understood.

Lastly, there should be an understanding if randomization has been preserved in a retrospective analysis, especially if small sample size subpopulations identified after completion of the

clinical trial are utilized.

In today's meeting, we will discuss the concept of a, quote, "prospective/retrospective study." A working definition follows.

In a completed or post-interim analysis trial, biomarker samples were collected prior to treatment initiation, whether or not full ascertainment. The hypothesis is prospectively specified prior to diagnostic assay testing. However, the clinical outcome data without biomarker information have been collected, un-blinded and analyzed. The biomarker data analysis might arguably be prospectively performed; however, this is a retrospective analysis.

In essence, in a prospective/retrospective study, the classification factor or biomarker is not known at the time of study initiation and the study is, at first, not analyzed with that factor as part of the hypothesis. The initial hypothesis and endpoints of the study are not changed, except if pre-specified as part of a planned adaptive study design.

The control of false positive conclusions from the study are appropriately dealt with. The

randomization is not stratified on a biomarker status as one of the hypotheses to be tested. Biomarker should be ascertained at baseline on all subjects randomized to treatment groups, ideally.

The FDA is seeking ODAC's deliberations on issues raised in using biomarkers after trials have been initiated or completed. In particular, the committee should discuss the conditions where a prospective/retrospective clinical study design may provide evidence for treatment effects that are limited to biomarker classified subpopulations, thereby being judged as evidence of a predictive marker.

In addition, if a retrospective analysis can be performed to show benefit in a subset and it is considered acceptable that randomization on a biomarker status was not done, what level of evidence should be considered for reproducibility of the finding?

As stated previously, our purpose of presenting KRAS data is to provide an illustrative example of the complexities in decision-making regarding retrospective analyses. We view these discussions at today's ODACs to be an educational

dialogue, examining the incorporation of new scientific information without compromising our mandate to ensure that marketed drugs show substantial evidence of efficacy and are safe.

Thank you.

DR. DUTCHER: Thank you, Dr. Pazdur.

Dr. Ruthann Giusti will present the FDA's presentation and regulatory history.

DR. GIUSTI: Good morning. As Dr. Pazdur has previously alluded to, the selection of a drug based on a genomic biomarker profile has the potential to limit drug exposure to patients who are most likely to benefit from the drug, to avoid or modify drug use in patients who are most at risk of developing drug-related toxicities, and to optimize drug dosing based on pharmacogenomic models of drug activation and elimination.

In the ideal case, the development of the genomic biomarker is an integral part of the clinical development. The assay methodology for the assessment of the biomarker is well characterized prior to initiation of the randomized trial. The clinical trial

required to establish the efficacy of the drug and those required to establish the prognostic and predictive value of the genomic biomarker then can proceed in tandem.

FDA strongly endorses this prospective and scientifically guided approach to drug development as part of the critical path initiative. This approach permits labeling considerations to be data driven based on clinical trial results.

However, increasingly, examples can be cited of the reanalysis of clinical trials data to explore efficacy in a subset of patients retrospectively defined by a genomic biomarker, and FDA acknowledges that there may be legitimate reasons for failure to assess a genomic biomarker during the course of drug development, the primary reason being that scientific advances may outpace drug development and require a redefinition of the original study question. However, this is distinct from a post-hoc subgroup analysis in an attempt to salvage a failed clinical trial. This is a practice that is to be discouraged and one that the FDA cannot endorse.

To provide a context for today's meeting, FDA presents a real world example. Two anti-EGFR antibodies have been approved for use in the United States for the treatment of patients with metastatic colorectal cancer.

These are ImClone's cetuximab and Amgen's panitumumab. Based on retrospective analyses assessing efficacy as a function of KRAS mutation subset, both ImClone and Amgen propose to include information concerning drug use in the subset of patients with metastatic colorectal cancer whose tumors express wild-type KRAS.

The basis for these proposals is the apparent lack of efficacy of cetuximab and panitumumab in patients whose tumors express a mutated version of KRAS. This observation has been made in the retrospective analyses of several completed randomized trials.

While the example for today's discussion involves KRAS, FDA seeks general guidance from ODAC this morning concerning how to incorporate new and evolving scientific information from retrospective

biomarker analyses into product labeling, this without compromising FDA's legal mandate, which is to ensure that marketed drugs show substantial evidence of efficacy and are reasonably safe.

FDA hasn't advised ImClone and Amgen that the optimal approach is to conduct a trial prospectively designed to assess efficacy in patients who are randomized based on KRAS genomic status, as determined using a validated assay. However, the results of recently completed retrospective analyses have been widely disseminated and there is a perception within the oncology community that the lack of efficacy of the anti-EGFR therapies in patients whose tumors express a mutated KRAS is well established, and conducting a prospectively designed trial at this point in time may no longer be feasible.

So given these practical constraints, FDA has indicated that submission of a retrospective analysis could be considered if the following conditions are met.

These conditions are that the trial is adequate, well controlled and well conducted; that the

sample size is large enough to approximate random allocation for factors not used as stratification variables for randomization; that an evaluable biomarker result is obtained on a high number of randomized participants to minimize selection bias; that the biomarker assay has acceptable performance characteristics in terms of sensitivity, specificity and precision under the conditions proposed for clinical use; the genomic analysis is performed by individuals who are masked to treatment assignment and to the clinical outcome in the original trial; and, finally, that an acceptable plan for the biomarker analysis has been pre-specified.

With these conditions in mind, I will now review the randomized trials that have been retrospectively submitted to the FDA in which efficacy in the KRAS genomic subgroups has been assayed.

It must be noted that FDA has not reviewed any of these studies in detail or verified the results of any of the retrospective KRAS analyses that will be presented today.

In April 2008, ImClone submitted summary

results from four large completed randomized clinical trials of cetuximab in which available tumor tissue was obtained and then retrospectively tested for KRAS genomic status.

These trials include two trials of chemotherapy with or without cetuximab in first line metastatic colorectal cancer, the CRYSTAL and the OPUS trials, the EPIC trial of irinotecan with or without cetuximab in second line metastatic colorectal cancer, and the NCIC trial of best supportive care with or without cetuximab in third line therapy.

The primary study endpoint was met in only two of these trials, the CRYSTAL trial and the NCIC trial.

In this slide, and in subsequent slides, those trials in which the primary study endpoint was met have been highlighted. The NCIC study is the only trial of an anti-EGFR antibody to have shown an overall survival benefit in metastatic colorectal cancer.

These four studies have been retrospectively analyzed to assess efficacy by treatment arm and by KRAS genomic status. In these studies, the percent of

the originally randomized study population assessed for KRAS genomic status ranged from 23 percent in the EPIC trial to 69 percent in the NCIC and the OPUS trials. Both direct sequencing and PCR-based methodologies were used for retrospective KRAS testing.

Amgen has submitted summary results from the retrospective analysis of two large randomized studies in metastatic colorectal cancer, the 408 trial of best supportive care with or without panitumumab in the third line treatment of metastatic colorectal cancer and the PACCE trial of chemotherapy with bevacizumab with or without panitumumab in first line metastatic colorectal cancer. The primary endpoint for both of these trials was progression-free survival.

In the 408 trial, the primary endpoint for the analysis was met, which resulted in the accelerated approval of panitumumab. The PACCE trial failed to meet its primary endpoint and the study was terminated when statistically inferior progression-free survival was observed in the panitumumab treated patients.

As part of an active biomarker exploration program, Amgen acquired tissue on patients enrolled in

the 408, as well as other ongoing trials. In the 408 trial, tissue availability was required for study entry and, consequently, KRAS genomic status was available in a large proportion of both of these trials, over 90 percent in the 408 trial and 82 percent from patients enrolled in the PACCE trial.

Both studies used a PCR-based assay to assess KRAS genomic status. And while the assay used to demonstrate KRAS subgroup was the prototype of the DxS assay, the analytical performance of this assay had not been characterized at the time. And the PACCE trial, which failed to meet its primary endpoint, had the largest number of patients tested for KRAS mutation status of any of the retrospectively analyzed trials.

Even with a high rate of KRAS mutation ascertainment, the number of patients within each subgroup can be relatively small. For example, here, despite KRAS mutation ascertainment in 92 percent of the randomized population in the 408 trial, the number of patients, when stratified by KRAS mutation and treatment assignment, is approximately 100 patients in each subgroup.

What general observations can be made about the retrospective KRAS studies?

Summary data from the retrospective KRAS analyses from six randomized studies in metastatic colorectal cancer have been presented to the FDA.

The pre-specified primary endpoint for the studies were met in only three of these trials, the CRYSTAL, the NCIC, and the 408 trial. These studies were heterogeneous with respect to the line of therapy, additional treatments administered, and in the percent of the originally randomized study population assessed for KRAS. None of the studies were assessed using KRAS assay methodology with well characterized analytical performance.

Six studies were reported in which a time to event endpoint was the primary endpoint. The direction of interaction of effects favored the wild-type KRAS group in three studies, the CRYSTAL, the NCIC and the 408 trial.

In these three trials, the originally defined primary study endpoint was met. In two trials, the EPIC and the PACCE trials, the direction of interaction

of effects did not favor the wild-type KRAS subgroup. And in the PACCE trial, the direction of interaction of effects favored the KRAS mutated subgroup. These two trials failed to meet their primary originally defined study endpoint.

The direction of and the interaction of effects also favored KRAS in the OPUS -- the KRAS wild-type subgroup in the OPUS trial, in which the primary endpoint was response rate. However, this study did not meet its primary endpoint.

In five of the six trials in which the retrospective KRAS analysis reported progression-free survival results, the direction of the interaction of effects favored the KRAS wild-type subgroup.

In three of these trials, the CRYSTAL, the NCIC, and the 408 trial, the study met the originally defined primary study endpoint. The other three trials failed to meet the originally defined study endpoint.

In the retrospective KRAS analysis, the direction of the interaction of effects favored the KRAS wild-type subgroup in both the EPIC and the OPUS trial and, as previously stated, the direction of the

interaction of effects favored the KRAS mutated subgroup in the PACCE trial.

Looking at the report of overall survival as an endpoint in the retrospective analysis, the direction of interaction of effects favored the wild-type KRAS subgroup in two studies, the CRYSTAL and the NCIC.

In the 408 and EPIC trials, the retrospective KRAS analysis for overall survival, the interaction of effects was neutral, and, in the PACCE, favored the KRAS mutated subgroup. Overall survival results were not provided for the OPUS trial.

What then is the potential to obtain additional data to address the question of efficacy of EGFR antibodies within KRAS defined genomic subsets?

Amgen has completed enrollment of two large randomized trials and plans retrospective testing of treatment effects by KRAS status in these studies. These include a randomized study of FOLFOX with or without panitumumab in first line metastatic colorectal cancer and a study of FOLFIRI with or without panitumumab in second line therapy.

The CALGB and NCCTG are currently actively accruing two randomized trials. However, both trials have recently been modified to limit enrollment to patients with KRAS wild-type tumors through completion of the trial.

This slide shows the accrual to these studies at the time the decision was made to modify the inclusion criteria. KRAS mutation testing of all four of these trials will be done with the to be commercialized DxS test kit.

Representatives from ImClone and Amgen will present data concerning their retrospective analyses and following these presentations, FDA will have two additional presentations.

Dr. Robert Becker will discuss the optimal approach to drug biomarker co-development, which includes the prospective development of assay method qualification and clinical validation.

Dr. Robert O'Neill will then discuss the limitations associated with the use of retrospective subset biomarker data.

We note again that the purpose of today's

discussion is not to render an opinion on the action FDA should take on any given application. This can only be completed upon a full review of the study data. Rather, today, FDA asks ODAC to consider the following four general questions.

First, when is it appropriate to limit the use of a drug to a subset based on a retrospective analysis of one or more studies that were not initially designed for this purpose?

Secondly, when is a prospective study designed explicitly for the purpose of examining treatment effects in a predefined subgroup needed to establish treatment effects in this group?

Third, what properties of clinical studies originally designed for non-selected populations make such studies unsuitable for demonstrating efficacy in a biomarker subgroup?

And when is it acceptable to limit future enrollment to a biomarker selected subgroup of an actively accruing clinical trial based on data external to that trial?

And, finally, we ask ODAC to consider the

importance of timing and rigor in determining the analytical performance of the companion diagnostic test.

Thank you.

DR. DUTCHER: Thank you very much.

We're going to move on to the sponsors' presentations. The first presentation will be by ImClone.

Dr. Youssoufian?

DR. YOUSSOUFIAN: Good morning, ladies and gentlemen, and thank you, Dr. Pazdur and Dr. Giusti, for outlining these critical issues so well.

My name is Hagop Youssoufian from ImClone Systems and, as of several weeks ago, a wholly-owned subsidiary of Eli Lilly and Company.

I have the pleasure of representing our extended family today, as well as our development partner, Bristol-Myers Squibb, in this discussion. We've been working in collaboration with the scientific community and the FDA to refine the use of Erbitux in patients with colorectal cancer. KRAS testing gives us this opportunity. And as we describe our data today,

it is with the belief that the level of evidence justifies its rapid implementation to identify the most appropriate candidates for Erbitux therapy.

In this presentation, I will review the large and consistent body of evidence on the predictive value of KRAS for Erbitux therapy in colorectal cancer.

Secondly, I will touch on the impact of the new KRAS data, which has been nothing less than transformational in both academia and the medical community.

Patients with KRAS mutated colorectal cancer, as Dr. Giusti outlined, are no longer eligible for clinical trials utilizing Erbitux. This development has profound implications for the conduct of prospective conformational studies.

Thirdly, we believe that the current labeling of Erbitux should be revisited, and I will reflect on ongoing discussions with the FDA to arrive at appropriate next steps.

Briefly, Erbitux is a recombinant chimeric monoclonal antibody that was first approved by the FDA in 2004. Currently, Erbitux is indicated in EGFR

expressing colon cancer as monotherapy or in combination with irinotecan, but without KRAS selection, and in head and neck cancer.

The development of Erbitux has always included a search for meaningful biomarkers. Although I mentioned that EGFR expression by immunohistochemistry is specified in our label for colon cancer, most experts would agree that this is not fully reliable. KRAS, by contrast, is a great example of a biomarker that represents the convergence of a molecular concept and clinical data.

From the work of Bert Vogelstein, it's been known for over two decades that mutations in KRAS represent early events in the pathogenesis of colon cancer and are, thus, relevant to both early and advanced disease. But more directly to the point, KRAS plays a pivotal role in the antitumor effect of anti-EGFR monoclonal antibodies.

This is illustrated on this slide. In the wild-type state, the binding of cetuximab to EGFR can shut down receptor-mediated signaling. However, mutations in KRAS place the system in a perpetually

active state that is no longer responsive to cetuximab. Hence, it follows from the biology that cetuximab should work primarily in KRAS wild-type tumors.

In over the past two years, there's been a profusion of reports demonstrating correlations between KRAS status and efficacy. This slide summarizes several such reports that come from a variety of sources and geographies. This is not an exhaustive list.

It is apparent that the response rates of patients with KRAS wild-type tumors are superior to those with KRAS mutated tumors. Collectively, these large differences between wild type and mutant tumors and the consistency among different studies began to suggest that KRAS is a strong predictor of Erbitux efficacy. It's also remarkable just how rapidly the new KRAS data in colon cancer permeated the medical community.

In the case of Erbitux, several milestones are worth noting.

In April of 2008, we submitted pharmacogenomic data to the FDA through the mechanism

of voluntary genomic data submission, or VGDS.

In May and June, there were a number of presentations of novel data in both front line and refractory settings.

As a consequence of these developments, NCI CTEP issued an action letter to cooperative groups requiring exclusion of patients with KRAS mutant colon cancer from clinical trials of Erbitux-containing regimens.

And within this timeframe, the European indication of Erbitux in colon cancer was also revised to target KRAS wild-type tumors only. This was followed by a publication in the *New England Journal* and by the NCCN issuing revised guidelines for KRAS-based treatment with Erbitux.

Again, as Dr. Giusti outlined, the VGDS included pharmacogenomic data from four company-sponsored randomized trials, shown here. Although KRAS analysis was done retrospectively, archive tissue had to be available prospectively for EGFR testing, which was then retrieved for KRAS testing, and this was possible in 23 to 69 percent of

the cases. A common reason for our inability to obtain tissue was the lack of informed consent.

The analysis was also planned prospectively, with a specific marker, KRAS, and pre-specified cut points. We also communicated data and performance characteristics of two assay methodologies, indicated here, that we used and compared those methods against a test being developed by DxS.

The DxS test uses allele-specific PCR and this test is currently undergoing review by the FDA. The correlation in a limited number of samples that we tested was high.

So I will now review these studies in greater detail.

The NCIC CO.17 study forms by far the most important foundation for how we think about the clinical activity and validity of KRAS in Erbitux.

In this study, 572 patients with EGFR-positive refractory colorectal cancer were randomized to Erbitux with best supportive care or best supportive care alone. The primary endpoint was overall survival. Patients were not selected by KRAS

status. Nevertheless, in this KRAS unselected population and for the first time, there was a significant improvement in survival, with a median of 6.1 months and 4.6 months in favor of Erbitux, translating to a 23 percent reduction in the risk of death.

The NCIC made a concerted effort to collect archived tissue for KRAS analysis. These samples, again, were obtained at the time of diagnosis and eventually retrieved from 69 percent of the randomized patients, stored in a central repository maintained by the NCIC, and then analyzed for mutations by Bristol-Myers Squibb. The mutation frequency was 42 percent, which is consistent with the data and the literature.

Now, in an effort to make the analysis as rigorous as possible, it's important to take note of the following.

First, KRAS analysis was performed in a blinded fashion by a different party, BMS, and in accordance with a statistical analysis plan written before the mutation data was analyzed.

Second, every randomly assigned patient for whom KRAS data was available was included in the analysis.

And third, the focus of the analysis was KRAS. This was not an unspecified, broad exploratory program.

Baseline demographic features were comparable between the overall and the KRAS evaluable populations and within the KRAS subsets. Therefore, the data from the KRAS subset should be a faithful reflection of that of the total study population.

This slide shows the survival curves in the KRAS evaluable population. Aside from the demographic comparability, the KRAS evaluable and the ITT populations were also comparable with regard to outcome, in this case, the median survival times and hazard ratios.

Now, for the key efficacy data within the KRAS subset. This was analyzed by treatment arm.

In the KRAS wild-type group, the median survival was 9.5 months with Erbitux versus 4.8 months without Erbitux and the hazard ratio was 0.55 and the

P value, less than 0.0001. By contrast, there was little, if any, effect attributable to Erbitux in the mutant population. A formal interaction test between KRAS status and Erbitux treatment yielded a P value of 0.01, indicating that KRAS status is a significant predictor of survival with Erbitux treatment.

Now, given the overall survival advantage already attributable to Erbitux in the unselected population, the near doubling of survival with the inclusion of KRAS information demonstrates a striking enhancement of Erbitux activity that is clearly attributable to Erbitux -- I'm sorry -- to KRAS.

We then asked whether a KRAS evaluable dataset that represents 69 percent of the primary analysis population is sufficiently robust to support this conclusion. To do so, we made several extreme assumptions about the missing data. I will give two examples.

If we assume that all of the missing data were from the KRAS mutant population, the interaction test remains significant. Conversely, if the KRAS wild-type population was the culprit for all missing

data, the interaction is also strong. These results essentially imply that the KRAS data from the KRAS evaluable population are so robust that even with extreme assumptions, an evaluable sample size that is large and otherwise satisfies the criteria that were outlined previously is very likely sufficient to justify our conclusions.

Besides survival, KRAS status also consistently affected other efficacy endpoints. For PFS, in the KRAS wild-type background, the effect size increased from a median of 1.9 months in the control group to 3.8 months with Erbitux, amounting to a statistically significant 60 percent reduction in the progression risk. No such effect was noted in the KRAS mutant population. This interaction test was highly significant.

Although not shown here, there were no responders in the best supportive care group and only a single responder in the KRAS mutant group treated with Erbitux. All other responders were in the KRAS wild-type group treated with Erbitux.

These data demonstrate robust internally

consistent effects with Erbitux that are essentially restricted to patients harboring wild-type tumors.

While I won't discuss the safety data, by and large, safety and tolerability were comparable between the ITT and the KRAS populations, indicating that KRAS selection enhances the already favorable risk-benefit profile of Erbitux.

Importantly, the role of KRAS as a prognostic marker can also be assessed cleanly in this setting without a potential confounding effect by chemotherapy. And as shown here, there were no differences in survival between the wild-type and mutant populations, indicating that KRAS is largely, if not purely, a predictive marker of efficacy.

In summary, the NCIC data demonstrate convincing, robust effects on the KRAS-dependent efficacy of Erbitux in colon cancer. By virtue of the fact that this was a monotherapy study, these data, we believe, are the cleanest possible demonstration of the impact of KRAS on Erbitux therapy.

Next, I will go on to describe additional combination studies in the first and second line

settings that were also outlined by Dr. Giusti that confirm and extend these data.

CRYSTAL was a first line study of approximately 1,200 patients that compared in a randomized fashion the benefit of adding Erbitux to FOLFIRI in chemotherapy naive EGFR-positive metastatic colon cancer. This was a positive trial in that the primary endpoint of PFS, as assessed by an independent review committee, was met. Survival was a secondary endpoint. Since the submission of VGDS, our development partner, Merck Serono, has provided survival information and updated the KRAS data.

In the KRAS unselected population, there was a statistically significant improvement in PFS, with a median of 8.9 months versus eight months in favor of Erbitux. Note the hazard ratio of 0.85 to which I will return shortly.

Here, again, tissue for KRAS analysis was obtained from archived material and the analysis performed in a blinded fashion and under carefully defined standard operating procedures. The tissue collection rate was 45 percent and reasons for not

having a higher yield were very similar to those of the NCIC study. The 36 percent frequency of KRAS mutation was also similar. Baseline demographic characteristics between the ITT and the KRAS population, as well as within the KRAS evaluable subsets, were comparable.

First, and not shown on this slide, beside the demographic comparability, in the KRAS evaluable population, the hazard for PFS was 0.82 in favor of Erbitux and you'll recall the hazard of 0.85 in the ITT population, again, indicating comparability between these populations and suggesting that selection bias is limited.

As shown here, within the KRAS evaluable subsets, the benefit of adding Erbitux to FOLFIRI was limited to the KRAS wild-type population. The hazard in this case was 0.68 compared to 0.85 in the ITT population. Again, no benefit was apparent in the KRAS mutant population with Erbitux above chemotherapy. There was a strong association between KRAS status and Erbitux treatment with a P value of 0.07. Parenthetically, we've also performed sensitivity analyses of missing data scenarios similar to the NCIC

study and the outcome, again, supports the predictive value of KRAS in this setting.

With regard to secondary endpoints, the median survival times in the ITT population were 19.9 months with Erbitux versus 18.6 months without Erbitux, and this was not significant.

In the KRAS subtype, shown here, the median survival times in the wild-type subset were 24.9 months and 21.1 months with and without Erbitux, respectively, which remained non-significant. But even here, it appears that any potential impact of Erbitux on survival might occur in the wild-type setting.

The overall response rate in the KRAS wild-type setting was improved to an extent greater than that in the ITT population, 59 percent versus 43 percent, without a similar effect in the mutant population. The interaction test was significant.

Therefore, as in the NCIC monotherapy study, the impact of KRAS is notable consistently across most, if not all, efficacy endpoints and, in this case, the KRAS dependency of Erbitux appears to be relevant to front line therapy in combination with FOLFIRI.

The notion that KRAS is a predictive marker of Erbitux efficacy, even in the setting of combination therapy, is supported by OPUS, a Phase II study, in which 337 unselected patients were randomized to first line treatment with FOLFOX alone or in combination with Erbitux. The overall response rate, the primary endpoint was not met.

The strategy of tissue collection and KRAS analysis were quite similar to those of other studies. The tissue collection yield in this case was 69 percent with a breakdown for wild-type and mutant populations consistent with the other studies. The demographic variables were comparable across all populations.

With the benefit of KRAS selection, the response rate increased to 61 percent in the Erbitux arm compared to 37 percent in the control arm, which was significant. By contrast, patients with KRAS mutations derived no such benefit.

Similarly, for PFS, which was identical for both arms in the KRAS unselected population, an improvement could be demonstrated only in patients with wild-type tumors, with a 43 percent risk reduction in

progression and a P value of 0.016. The interaction between KRAS status and each of these endpoints was significant. Although this is a much smaller study, the results are consistent with both the NCIC study and CRYSTAL in the sense that the efficacy of Erbitux is enhanced in the KRAS wild-type milieu.

This slide summarizes the main efficacy endpoints from these three studies. Two met their primary endpoints in the ITT population, while OPUS did not. In all three studies, the ITT and KRAS populations were comparable, both by baseline and key efficacy characteristics.

KRAS selection led to notable enhancements of the primary analysis outcomes, which were validated by interaction tests, as well as the enhancements in secondary efficacy endpoints in many cases, indicating internally consistent results.

This last study that I wish to discuss is EPIC, a second line Phase III study included in the VGDS that randomized about 1,300 patients with EGFR-positive colorectal cancer to Erbitux plus irinotecan or irinotecan alone. It failed to meet its

primary endpoint of overall survival, but it is instructive to look at this study mostly to point out concerns that we all share about the adequacy of some retrospective data.

Areas of concern, which were highlighted before, included the following. Per protocol, tissue for KRAS testing could only be obtained from U.S. patients, about 23 percent of the overall population, which differed from the overall population on certain baseline characteristics.

Moreover, with regard to the primary efficacy endpoint, the survival outcomes, shown here, in the ITT and the KRAS evaluable populations were inconsistent and, in fact, trended in different directions. This may have been impacted by differences in crossover rates.

Although the other outcomes may be directionally consistent in the two populations, this study serves to illustrate, perhaps too obviously, that not all retrospective data can be given equal weight and that distinctions must be made between studies with larger sample retrievals and internally consistent

results, such as the randomized studies I have presented earlier and others that lack those features.

I will now describe the impact of these data on current research and clinical practice.

Following the 2008 ASCO meeting, NCI CTEP issued an action letter to their investigators requiring temporary suspension and amendments to Erbitux-containing colon cancer trials. Three major trials, shown here, all combination studies, were affected.

Our companies endorsed this action for sponsored trials and, at the same time, Merck Serono and the European cooperative groups amended the PETACC-8 adjuvant trial and a first line trial, COIN.

All of this was done rapidly in a highly collaborative fashion. I'd like to use the intergroup N-0147 adjuvant trial to illustrate this collaborative dynamic.

The NCCTG proposed the amendment to limit eligibility to KRAS wild-type tumors, changed the primary analysis population to patients with wild-type KRAS tumors, increased the sample size with power

calculations sufficient to detect a treatment effect in the KRAS wild-type population, and incorporate KRAS testing using the DxS kit.

At the same time that protocol changes were being discussed with sponsors in CBER, CDRH was evaluating the technical aspects of the assay itself and agreed with DxS on a set of criteria that defined technical success. So thanks to these efforts, accrual on the amended study resumed quickly.

The status of the other studies is as shown. COIN had already completed accrual, but the analysis plan was revised to focus on the KRAS wild-type subset.

In time, these studies could provide additional data relevant to today's discussion, but their incremental value is unlikely to alter the substantial body of knowledge that we believe is already established.

The impact of KRAS testing is also increasingly apparent at the community level. Only last month, the NCCN issued new guidelines for colorectal cancer that reflect these new realities, to not only recommend KRAS testing in the workup of all

patients with metastatic cancer, colon cancer, but also recommend Erbitux and Vectibix as single agents and Erbitux in combination with irinotecan for patients with wild-type KRAS tumors.

So in summary, although the current labeling of Erbitux makes no mention of KRAS, we believe that these data provide strong support to consider a labeling change. The data are reproducible and consistent.

With regard to the attributes of the sponsored studies, we used all the mechanisms available to us to carry out the tissue collection and the analysis in a highly rigorous fashion.

I would again emphasize the following. The cooperative groups and the sponsors spared no effort to collect tissue. The NCIC and the CRYSTAL studies were well conducted and well controlled, that were positive studies.

The sample sizes of the KRAS evaluable populations are sufficiently large to ensure comparability of the KRAS evaluable and the ITT populations both with respect to baseline

characteristics and overall outcome.

The analyses were performed in a blinded fashion. There is consistency across different assays with regard to their performance characteristics and the additional validation work for DxS assay is in progress.

Given these developments, prospective comparisons of Erbitux activity in patients with wild-type versus mutant tumors and stratified at randomization by KRAS status are no longer possible.

So for all of these reasons, we believe the timing is right to discuss a labeling change with the FDA and, at a minimum, incorporate the NCIC KRAS data in the labeling, perhaps in the clinical study section of that label.

In closing, we strongly believe that these data are clinically relevant and compelling and the recent change in the NCCN guidelines is but one affirmation. It's especially gratifying that all of this is anchored firmly in science. And so I'd like to end with an essential point.

While these data open a new era in the

treatment of colorectal cancer, we as sponsors cannot effectively communicate them to practitioners without a labeling change. A labeling change would certainly make it congruent with state-of-the-art medical practice.

We have submitted a meeting request to the FDA and very much look forward to a continued dialogue in the near future. In due course, our hope is that we will be able to convey this information to physicians in the most compliant and responsible way to enable them to make the best risk-benefit assessments for their patients.

Thank you very much.

DR. DUTCHER: Thank you very much.

We're going to go on to the second sponsor presentation and another FDA presentation, and then we'll have questions of the presenters.

Dr. Eisenberg is going to be presenting for Amgen.

DR. EISENBERG: Dr. Dutcher, members of the committee, thank you.

I'll be making some brief comments on behalf

of Amgen and then Dr. David Reese, a medical oncologist in our Global Development Group, will walk through the data with respect to KRAS and our data with panitumumab monotherapy and combination therapy.

First of all, we appreciate the opportunity to present our data today. Our data with respect to the response of patients with colorectal cancer to panitumumab with KRAS mutations, we believe, is compelling and are supportive of the importance of KRAS as a predictive biomarker.

We also appreciate the opportunity to have a discussion, as FDA has framed it, around the general technical considerations that one must consider in evaluating the use of biomarkers in the treatment of patients with cancer, particularly in an era where emerging science almost always will be outpacing our ability to test the results in rigorous clinical trials in the manner that we ideally would consider appropriate.

I think it's also important, and it was implicit in the comments, actually explicitly stated by the other sponsor, that the sponsors and FDA are,

obviously, interested in communicating benefit-risk to patients and, clearly, the information we obtain from biomarker data is an important component of that.

One component, as the committee is being asked to address, are the technical considerations to validate a biomarker. Another component, and one I think that is reflected in the comments regarding how clinical practice has already changed, is the fact that medical judgment regarding weight of evidence plays an important role in making decisions ultimately as to how to conservatively communicate potential risks and potential benefits. It's an important topic, one which we take seriously.

With regard to the KRAS data, Amgen's position is quite clear. We believe that there is a predictive value to the KRAS mutation status and the treatment of patients with colorectal cancer with panitumumab as monotherapy should be restricted to patients with wild-type KRAS or, that is, KRAS without activating mutations. This is reflected in our product label outside the U.S. We believe it should be reflected in the U.S. label to avoid treatment of

patients who are highly unlikely to benefit as a consequence of having activated mutations. Clearly, the committee's deliberations, discussion will guide both FDA and the sponsors in the most appropriate way to communicate this to patients.

I'd like to now briefly provide you an overview of what Dr. Reese will cover in greater detail regarding the basis of our studies, which, as noted by Dr. Giusti, were part of a program which allowed us to have a very high ascertainment of KRAS status, because we anticipated that there would be emerging data that would inform the use of panitumumab in patients with colorectal cancer and, therefore, included in our trials, informed consent to allow collection of samples as a criteria for entry and, therefore, a high ascertainment of KRAS on archived samples from the clinical program.

With regard to the KRAS analyses, we have data from both Phase II and Phase III studies. However, again, importantly, reflective of the comments FDA has made regarding level of evidence, we'll discuss the 408 study, which has already been alluded to, which

was the pivotal registration study, that is, the randomized control study that led to accelerated approval of panitumumab as monotherapy for treatment of patients with metastatic colorectal cancer.

There was a pre-specified analysis plan, that is, after initial validation, which Dr. Reese will review for you, of the potential value of KRAS mutations in determining response. A pre-specified analysis plan was prepared prior to a blinded analysis of all of the samples in the hypothesis testing study, which were samples from the 408 study.

In addition, there was a fair amount of work done to identify a reliable assay. You've heard mention of the DxS assay. We have worked with DxS and are happy to discuss that, if the panel wishes to identify that assay, and then to use a single assay. And, again, I believe Dr. Giusti appropriately noted that in her presentation, a PCR-based assay to assess KRAS status in the samples that were archived from 408.

All of our studies, the hypothesis testing studies, as well as generation studies, have been very consistent with regard to the high negative predictive

value, that is, that KRAS activating mutations predict non-response in virtually all patients in which that has been evaluated in the clinical programs with panitumumab in the monotherapy setting.

Now, we recognize -- and, clearly, the science outpaced the clinical study. So the predictive value regarding KRAS potential in determining response to panitumumab, those data emerged after the 408 study was fully enrolled and, in fact, had been completed and analyzed.

However, the work going on to validate KRAS was occurring in parallel to the completion of that study. And we also recognize the importance that when a recommendation is made regarding benefit-risk to patients, it has to be implementable; that is that there has to be an FDA-approved test to allow a clinician to have a high degree of certainty that if we're making a recommendation to a patient, it's on the basis of high evidence scientifically regarding the test validity.

Outside the U.S., that test is available. It is the DxS test, and FDA is currently working with DxS

to evaluate what the requirements would be for that to be available in the U.S., though we would note that there are other means through clear labs, pathology labs, for testing for KRAS and, in fact, KRAS testing clinically has been implemented, but recognize the challenges FDA has in assuring that that clinical implementation meets the reliability standards, and I'm sure they'll revisit that in their presentation.

But ultimately, we believe the use of KRAS as a predictive marker will improve the benefit-risk profile for panitumumab monotherapy decisions regarding treatment of patients with colorectal cancer. And I'll have Dr. Reese now walk through the data that support our position.

DR. REESE: Good morning. My name is Dave Reese. I'm a medical oncologist in the Clinical Development Group at Amgen, and I'm pleased to be here with you today to share some of our data regarding KRAS as a predictive biomarker for panitumumab.

This is a diagram that many of you will be familiar with, illustrating EGFR signaling pathways. When ligand binds to the EGFR, the receptor homo or

heterodimerizes. This causes intracellular tyrosine phosphorylation and subsequent activation of a number of downstream signaling pathways.

The RAS-MAP kinase pathway is one of the most important effectors of EGFR signaling in colorectal cancer. RAS was identified as a human oncogene more than 25 years ago, when it was recognized that point mutations in the molecule render it constitutively active. Our understanding of this biology subsequently gave rise to the hypothesis that upstream inhibitors of EGFR, such as EGFR antibodies, would be ineffective in tumors in the presence of RAS mutations.

With the availability of panitumumab and cetuximab, a number of investigators began examining KRAS as a potential predictive biomarker. Shown here are representative studies. In these trials, patients had received panitumumab or cetuximab alone or in combination with chemotherapy.

As you can see in the middle of the slide, approximately 30 to 50 percent of tumors bore KRAS mutations, and, on the right of the slide, you can see that the large majority of responses clustered in

patients with KRAS wild-type tumors. Some of the responses reported in these studies in patients with KRAS mutant tumors may have been due to concomitant chemotherapy that some of these patients were receiving. Well, these data, as they emerged, really prompted us to focus on KRAS as a predictive biomarker in the panitumumab development program.

This slide overlays key milestones from our biomarker program, as well as the pivotal 408 study that led to accelerated approval for panitumumab.

Shown at the bottom of the slide are key events in the panitumumab development and regulatory pathway. The 408 pivotal monotherapy trial completed enrollment early in 2005 and ultimately formed the basis for accelerated approval for panitumumab at the end of 2006.

Beginning in 2004, as shown on the top of the slide, we began exploring multiple biomarkers, multiple targets across tumor indications within the panitumumab program. With the emergence of Phase II data regarding KRAS, we elected to focus on this potential predictive biomarker and, first, performed an analysis of our

Phase II studies.

These analyses, on which we've provided additional information in the briefing book, comprised about ten percent of all patients enrolled in our Phase II trials and indicated that responses were reported only in patients with KRAS wild-type tumors. Those data, in concert with data from the literature, then prompted us to perform a comprehensive analysis of the pivotal 408 trial for KRAS as a predictive biomarker.

As you can see by the overlay of these timelines, and as Dr. Pazdur has pointed out, this is a real world example of how knowledge of a biomarker may emerge in parallel with the development program of a molecule.

Prior to conducting the analysis on our Phase III study, we needed to select a KRAS assay. Our goal here was really to identify an assay that could be used in a high throughput fashion on routinely available clinical specimens, specifically, formal and fixed paraffin-embedded tumor samples that would be normally obtainable from patients.

When thinking about KRAS testing, there are a few important points to bear in mind. First, more than 95 percent of activating KRAS mutations affect Exon 2, specifically codons 12 and 13.

Prior to analyzing our Phase III data, we performed a comparison study using 40 commercially available tumor samples that were sent to a variety of independent laboratories to compare their assays against bidirectional DNA sequencing performed at Amgen. Bidirectional DNA sequencing is often regarded as the gold standard in these sorts of cases.

Prior to the analysis of specimens in our Phase III trial, the performance characteristics of the specific assay that we selected, the DxS mutation test kit, were determined by the manufacturer and, also, independently validated in the central independent laboratory performing testing on our specimens. As you can see in the table at the bottom of this slide, the DxS assay compared to bidirectional sequencing produced concordant results in 39 out of 40 tumors.

I'd now like to turn to a description of our Phase III monotherapy data.

This is the study schema, illustrating the design for the 408 trial that led to accelerated approval for panitumumab in 2006.

In this trial, patients with advanced chemotherapy refractory colorectal cancer were randomized to panitumumab or best supportive care. An important design feature of this trial was an optional crossover to panitumumab among patients initially assigned to best supportive care at the time of disease progression. In fact, more than three-quarters of patients crossed over to panitumumab at a median time to crossover of between seven and eight weeks. The primary endpoint of this trial was progression-free survival.

These are the PFS curves from the 408 study that led to accelerated approval in 2006. As you can see, panitumumab significantly improved progression-free survival compared to best supportive care with a hazard ratio of 0.54.

Well, with the emergence of the KRAS hypothesis, we believed that the 408 study provided an opportune setting to assess KRAS as a potential

predictive biomarker. The protocol had required tumor samples for EGFR assessment. These were archived with the specific intent of performing correlative biomarker analyses in the future. In addition, based on an anticipated high KRAS ascertainment rate, we believed that the sample size would be sufficient to provide balance between treatment arms. Importantly, KRAS was the only biomarker tested in this particular exercise; in other words, we were not examining a panel of biomarkers, but, rather, KRAS alone.

Finally, statistical calculations had indicated that we should have high power to test whether KRAS was a predictive biomarker for progression-free survival.

A statistical analysis plan was developed and finalized prior to knowledge of any patient's KRAS status. The objectives of this plan were, first, to test whether the relative improvement in PFS was greater in patients with KRAS wild-type tumors as opposed to those with KRAS mutant tumors. Then we would test specifically the treatment effect on PFS, response and overall survival in the KRAS wild-type

stratum. An important feature of this statistical analysis plan is that the analysis was designed to control the overall Type I error rate for the set of planned comparisons within the KRAS analysis.

What did we find? KRAS was ascertained in an independent laboratory, blinded to treatment assignment and clinical outcome. We obtained tumor samples from 96 percent of all patients enrolled in the trial. KRAS testing was successful in a very high proportion of those. Ultimately, KRAS results were available for 92 percent of all patients enrolled in the initial study.

As you can see at the bottom of the slide, the distribution of wild-type to mutant KRAS status is as one would expect from the prior literature; 57 percent of patients had KRAS wild-type tumors.

Baseline demographic and tumor characteristics were well balanced between treatment arms when broken out by tumor KRAS status and treatment assignment. Specifically, there were no imbalances for known prognostic factors, such as age or performance status.

This is probably the most important slide that I'll share with you today. This shows progression-free survival curves broken out by tumor KRAS status and treatment assignment. On the left, in patients with KRAS wild-type tumors, panitumumab significantly improved progression-free survival with a hazard ratio of 0.45. In contrast, in patients with KRAS mutant tumors, there was no difference in progression-free survival with a hazard ratio of 0.99. As you can see, the PFS curves here largely overlap. A quantitative interaction test evaluating a treatment by KRAS interaction was highly significant, with a P value of less than 0.0001.

Consistent with the progression-free survival data were data from tumor response. Shown on this slide are waterfall plots that graph the maximum percent change in individual tumors from individual patients. A green bar below the line indicates a decline in tumor size. A blue bar above the zero line indicates an increase in tumor size.

As you can see in the upper left corner, 61 percent of patients with KRAS wild-type tumors

receiving panitumumab experienced some degree of tumor shrinkage. Declines in tumor size were quite unusual in all three other groups. The partial response rate was 17 percent among patients with KRAS wild-type tumors receiving panitumumab. It was zero percent in all other groups.

Well, we've shared with you efficacy data. What about safety data, an important consideration when we're evaluating overall risk-benefit.

This shows selected adverse events of interest to EGFR inhibitors broken down by tumor, KRAS status, and treatment assignment.

The first thing to note when assessing these data is that patients with KRAS wild-type tumors receiving panitumumab received, on average, double the number of infusions as those with KRAS mutant tumors receiving panitumumab.

There were some increases in the KRAS wild-type group in specific events, such as skin rash, diarrhea, or hypomagnesaemia. These are well described side effects of EGFR inhibitors.

When we attempted to control for drug

exposure and analyze safety, for example, by looking across the first eight weeks of therapy, as you can see, the numerical differences between these groups become much smaller.

We do not believe that there are any intrinsic differences in the safety profile of panitumumab between patients with KRAS wild-type tumors and those with KRAS mutant tumors. There is nothing about the biology of the disease that would lend us to that speculation.

Well, once we had completed our Phase III analysis, we wished to extend our understanding of KRAS as a potential predictive biomarker. We performed a pooled analysis of four monotherapy studies that had been performed in the panitumumab development program. The four trials comprising this analysis had very similar eligibility criteria and all were conducted in patients with advanced chemotherapy refractory disease. KRAS was tested with the same methodology, the DxS kit, in the same independent central laboratory, blinded to clinical outcome, in each of these studies. A high rate of KRAS ascertainment was achieved within each

study and overall, as I'll show you in a moment. Finally, each study had consistent outcomes by KRAS status.

These are the results from the pooled analysis. The four studies included in this analysis included the 408 pivotal trial, this is the study I've just shown to you; the 194 trial, this was the crossover trial available to patients in the pivotal trial initially assigned to best supportive care; and, two large Phase II monotherapy studies, the 167 and 250 trials. These trials were performed in patients whose tumors expressed high or low or negative EGFR, respectively. A total of 715 patients were ultimately included in these analyses, representing a KRAS ascertainment rate of 90 percent across all of these studies.

The objective response rate was 14 percent in patients with KRAS wild-type tumors and zero percent in patients with KRAS mutant tumors. In fact, among 320 patients in the panitumumab development program, for whom we have data and who have KRAS mutant tumors, no objective responses have been recorded.

Finally, I'd like to conclude with a glimpse of some of our plans for the future. These have been mentioned by Dr. Giusti earlier, and I'd like to take you through a few of the details regarding these trials. They specifically focus on panitumumab in the combination chemotherapy setting and in evaluation of KRAS as a predictive biomarker.

This table illustrates the currently ongoing or completed trials that are controlled studies that will evaluate panitumumab in combination regimens and have incorporated KRAS analysis into the study designs.

As Dr. Giusti has shown you, the 181 and 203 studies are fully enrolled, Phase III trials in the second and first line settings, respectively. In these trials, patients are randomized to a chemotherapy regimen with or without panitumumab. We expect data from these studies in 2009.

The 141 or SPIRIT trial is a randomized Phase II study in which patients with second line colorectal cancer receive FOLFIRI chemotherapy with either panitumumab or bevacizumab. This trial is currently enrolling. With the availability of some of

the data you heard earlier in the day, this trial has been amended to enroll patients only with KRAS wild-type tumors.

Finally, you've heard brief mention of the 249 or PACCE study. This was a trial that examined chemotherapy with bevacizumab, with or without panitumumab. This trial was terminated prematurely when outcomes were reported to be inferior on an interim analysis in the panitumumab arms. We've provided additional data on this trial in the briefing book and would be happy to take you through some of that during the question-and-answer session, if you so desire.

I'd like to turn now and describe the ongoing pivotal trials.

As I noted, the 181 and 203 studies are fully enrolled and we believe these will provide relatively comprehensive information about KRAS as a predictive biomarker for panitumumab in the combination chemotherapy setting.

The 181 trial is being conducted in patients with second line colorectal cancer. They are

randomized to receive FOLFIRI chemotherapy with or without panitumumab. This trial completed enrollment in the early part of this year, with just under 1,200 patients participating. We anticipate that data from this trial will be available in 2009.

The statistical analysis plan for this study, after consultation with the FDA and European regulatory authorities, has been amended to focus the analysis on an outcomes by KRAS analysis. Likewise, the 203 study, which is being conducted in the first line setting, randomizes patients to FOLFOX chemotherapy with or without panitumumab.

This trial was also initiated and largely enrolled as our Phase III data became available and prior to any of the cetuximab combination therapy data being available. We have also amended the statistical analysis plan for this trial to focus on an outcome by KRAS analysis. Together, these two trials enroll nearly 2,400 patients and we believe will provide a relatively definitive answer to the role of KRAS as a predictive biomarker in the combination chemotherapy setting for panitumumab.

In conclusion, I'd like to note that we all share a number of goals in being here today. First, we wish to avoid toxicity of drugs in patients who are unlikely to benefit from those drugs. We believe that in the monotherapy setting, our data are compelling and consistent and that patients with KRAS mutant tumors are very unlikely to derive benefit from therapy. We are committed to enhancing benefit from therapy and trying to get the right drug to the right patient at the right time.

We have an obligation to ensure that KRAS testing is available. We are working closely with the FDA, our diagnostic partner, and our collaborators to ensure that this happens as soon as possible. We believe we have an obligation to provide reliable information to physicians and patients, specifically, through the label.

Based on the totality of the evidence that we've presented, we believe that in the monotherapy setting, the use of KRAS as a predictive biomarker will improve the risk-benefit profile for panitumumab in patients with advanced colorectal cancer.

It's been a privilege to be here with you today. We hope these data are of some value to the agency and the committee as we debate the optimal development of biomarkers in oncology.

Thank you.

DR. DUTCHER: Thank you very much.

We now have two presentations by FDA regarding design issues and study issues.

Dr. Becker will begin, followed by Dr. O'Neill.

DR. BECKER: So this is an unusual example of inter-center participation in an advisory council meeting, and I think it reflects a welcome and growing collaboration on important questions such as those that you'll be considering today.

Good morning. I will present some issues concerning drug device development from the perspective of medical device regulation. I will touch on the risk-based approach that CDRH takes to regulation of medical devices as this applies to companion diagnostics.

I will discuss some aspects of medical

devices for predictive claims for companion diagnostics; that is, their use to distinguish patients who will benefit by treatment with a drug from patients who will not.

I will discuss best approaches to the analytical validation of the companion diagnostic. These topics will connect up with topics in retrospective testing of clinical trial specimens in order to clinically validate a drug-device pair.

Authority for FDA's regulation of medical devices in the United States stems from the 1976 medical device amendments to the Federal Food, Drug and Cosmetic Act. The standard for legal marketing is that such devices are safe and effective, meaning there is reasonable assurance that probable benefits outweigh any probable risks, and that use of the device will provide clinically significant results. These assurances involve assessments of risk.

One element of risk for in vitro diagnostic devices, or IVDs, is whether use of a device explicitly drives a clinical decision. Important new devices are now emerging in which the result from a single

laboratory test can rule in or rule out the use of a specific potentially effective therapy for a life-threatening disease. For companion diagnostics, the risk for the test is equivalent to the risk for the drug whose use is guided by the test result. Such usage requires availability of an FDA-approved test for the biomarker. Companion diagnostics are at the heart of personalized medicine, with some uses that Dr. Giusti has already described. Taken together, these uses are meant to identify patients for whom drug selection and dose ensure a satisfactory risk-benefit ratio.

It is worthwhile to consider how biomarkers can be helpful in this regard. Within broad classes of ailment, we generally narrow the scope in which drugs are studied. In cancer, for example, the focus may be specific to an organ or tissue, such as colon or lung or lymphoid. Further subdivision is commonly done; for example, small cell versus non-small cell cancers in lung.

The point is that these narrowings usually follow extensive study and clinical confirmation and

serve to distinguish diseases that differ for features like pathophysiologic mechanism, aggressiveness or response to therapy.

In an important sense, each addition to our growing portfolio of biomarkers can serve to further sub-classify disease, with a caveat that the time and study needed to understand many biomarkers' significance have not yet been achieved before a drug trial starts. Therefore, care is needed in applying biomarkers for patient management. Incomplete understanding of what the biomarker means can lead to misperceptions about the best population for use of the drug.

An example is in the selection of patients for drug clinical trials. A trial designed under the expectation that effectiveness of the drug depends on expression of a biomarker might establish a benefit for the studied subpopulation; that is, a biomarker positive group. However, such a trial does nothing to establish the biomarker's meaning. The presupposition that biomarker positive patients are enriched for responders remains a presupposition.

By itself, such a trial leaves the promise of personalized medicine unfulfilled, since we obtain only half an answer to the question of optimal drug use, absent evidence establishing that biomarker negative patients will not significantly benefit from the drug. We really want to know whether biomarker expression distinguishes patients who will benefit from patients who will not benefit from the drug. This can be a complex question to resolve, partly because there are two ways in which the biomarker's expression might have medical significance.

In one way, the biomarker predicts which patients will benefit from the drug. For example, patients who express the biomarker will benefit and patients who do not express the biomarker will not benefit. This is the essence of a predictive biomarker claim and it requires comparison of the drug effect in one biomarker defined group with the drug effect in another biomarker defined group.

It is also feasible that the biomarker's expression simply denotes the aggressiveness of the disease without regard to how the disease is treated.

This is the essence of a prognostic biomarker claim, by which the outcomes among a group of patients are associated with the biomarker status. Prognostic claims are not framed in terms of drug effect since different treatments are not part of the outcome comparisons.

For illustrative purposes, via a set of sketches, let us presume that a new targeted drug has beneficial effect compared to standard therapy for some population. Perhaps a beneficial effect can be detected even in an unselected population, as depicted in this panel.

What follows are illustrations of three of the many ways in which predictive and prognostic effects might occur.

In the first example, a biomarker is predictive for benefit in that marker positive patients benefit from the targeted drug, while marker negative patients do not.

As another illustration, it is also feasible that a biomarker is simply prognostic, with no predictive value. It is prognostic in that marker

positive patients do better than marker negative patients. However, the drug effect does not differ between the marker positive and marker negative patients. Therefore, the biomarker has no predictive effect and may be ineffective in assessing who should or should not receive the drug.

It is also feasible that a marker is neither predictive nor prognostic if the benefit from the targeted drug does not vary between marker positive and marker negative patients and there is no difference in outcome between marker positive and marker negative patients within treatment groups.

Examples of both success and challenges in development of oncology drugs and companion diagnostic tests are seen in our experience with receptor targeted monoclonal antibodies and the IVDs for related biomarkers.

Accrual of HER2 positive patients to the pivotal Herceptin trials is widely credited with having drastically shortened the time and expense needed to demonstrate drug effect in marker positive patients. Since marker negative patients were not studied, we do

not know well Herceptin's effect or lack of effect in such patients. The HER2 biomarker test requires expert visual interpretation of images and there are concerns in recent years about the consistency with which those interpretations are made. Further complications arise with availability of multiple assays spanning multiple technologies for presence of the HER2 protein or amplification of the gene for it.

Lastly, the demonstration of safety and efficacy for Herceptin in settings beyond the original advanced stage cancer trials has relied on the same HER2 tests and decision points as before. There is little knowledge, and none reviewed by FDA, concerning different performance of the HER2 assays for the various drug indications.

Erbitux and Vectibix both came to market in the United States on the basis of trials that accrued marker positive patients; that is, patients whose tumors expressed epidermal growth factor receptor. As with HER2 testing, the biomarker assay requires visual interpretation of complex images. The readout for EGFR is perhaps even more challenging than for HER2 because

the cut point was set at expression of the marker by just one percent of the tumor cells.

Over the last two years or so, there are reports of responses to cetuximab by patients who did not meet marker positive criteria, and these have raised uncertainty about whether the biomarker is helpful in discriminating patients who will or will not respond to the drug.

The lessons to be drawn from these precedents have been discussed and debated. The benefit is that important new drugs are on the market. From the medical device perspective, it is beneficial to have biomarker assays marketed subject to quality system practices, including post-market monitoring. However, the claims for the devices are quite limited. In particular, predictive claims are not established for distinguishing patients who will benefit or not benefit from the drugs.

Experience so far provides imperfect, but important precedence. Looking forward, questions remain concerning the extent of knowledge that is needed for adequate analytical and clinical validation

of paired drugs and diagnostic devices.

Studies done ahead of a clinical drug trial can establish a biomarker's role in the pathophysiology of disease, perhaps including insights on disease prognosis. This information might give ample incentive for developing the drug to target the biomarker. However, it cannot directly address whether a particular biomarker test set for a particular cutoff to distinguish marker positive from marker negative disease distinguishes patients who will or will not benefit from the drug.

This is the setting for our questions today about the use of data from retrospective analyses of clinical trials. In peeling off patient subsets from clinical trials, developers of drugs and IVDs will aim to establish claims for the biomarkers to guide the use of the drugs. Insight and consensus are needed about the extent of knowledge that is sufficient for analytical and clinical validation of such uses.

I'll now discuss how and when, relative to pivotal clinical trials, knowledge about satisfactory performance characteristics for the biomarker test

should be obtained. In a broad sense, this knowledge concerns the analytical validation of the medical device.

There are hurdles that must be cleared in order to interpret data from pivotal clinical trials competently, regardless of whether the trials accrue patient subpopulations or all comers. One hurdle is that practical problems in obtaining the right kind of specimen might occur. Pre-analytical variables, though often neglected, have a large effect on results from many tests. Clearly, alteration or degradation of the biomarker during specimen acquisition, storage or processing can raise implications about the meaning of test results.

Also important are the effects of sub-sampling the specimen for analysis and variation in biomarker presence or state with different kinds of samples or prior treatment of the patient.

Another hurdle is that the analytical performance characteristics of the biomarker measurement process might be insufficient to distinguish benefitting from non-benefitting patients.

It is essential to understand and control the analytical sensitivity, specificity, accuracy and precision of the test.

For IVDs operating at very low levels of the analyte, a stable limit of detection is critically important. Reproducibility of analytical results across different laboratories is a requirement for medical devices that are fielded widely. In essence, we need confidence that patient classifications according to a biomarker cut point are consistent and correct.

Other hurdles concern the biology of the marker itself and the drug's interaction with the biomarker or alternatives to interaction with it. Presence of the biomarker analyte beyond the cells of therapeutic interest may cloud the meaning of biomarker measurements. Some biomarkers might vary widely in their expression without proportional implications for the effect of the drug. Finally, the biomarker might relate to only one of several modes by which the drug can act.

All of these considerations should be

resolved before the biomarker is brought into a pivotal clinical trial to establish use of the biomarker in guiding drug therapy.

All that I've said so far readily applies when a new drug and a new biomarker test travel together through a co-development effort. However, there are various ways in which product development can diverge from the idealized concurrent path.

One way is when there is late recognition of the biomarker or its putative relevance to drug effect so that a new test bears on the use of a previously studied drug. This is the case with the anti-EGFR monoclonal antibody drugs and KRAS testing discussed today.

Another situation is when a biomarker that has been previously well characterized and reduced to a test approved for clinical use seems relevant to development of a new drug. FDA has seen this situation in evaluating next in class drugs targeted at a previously studied biomarker. An example was the review coordinated between CDER and CDRH for the new drug application for Vectibix and the pre-market

approval supplement of the Dako pharmDx EGFR immunohistochemistry assay. Vectibix carried indications very similar to Erbitux and the Dako test was unchanged from the version previously studied with Erbitux. The PMA supplement review for the unchanged Dako test was uncomplicated and rapid.

It is also feasible that a previously studied drug will be reevaluated in the context of a previously studied IVD test; for example, when the drug and the test must be reviewed for a new indication. Changes in indication have occurred already; for example, when Herceptin was evaluated for use in adjuvant therapy of breast cancer.

It is an open question whether the companion diagnostic gives equivalent performance in selecting different kinds of patients for Herceptin treatment. To date, re-review of the companion diagnostic has not been undertaken for such a situation.

These variant co-development situations may ultimately prove to be more common than classical concurrent development of new drugs and devices. It is important to recognize and accommodate these

challenges, the challenges that they raise.

In cases like today's example with anti-EGFR monoclonals and KRAS, analytical validation of the new IVD test may come very late in the development process and it is tempting for clinical validation plans to rely on the analysis of specimens that were retained from ongoing or already completed clinical trials.

I'll speak more about the analytical validation timing and then briefly about some retrospective trial analysis issues that will be treated in more detail by Dr. O'Neill.

FDA strongly recommends that sponsors complete the analytical validation of their IVD test product before applying the test to specimens in the clinical trials that would be submitted for review of the drug and the test.

This is not to say that the device must be locked down for specifications and performance very early in the development program. Test performance depends partly on recognizing what analytical performance characteristics are needed and designing the test to meet these needs. Substantial and often

iterative effort is spent during test development to ensure that the test design yields analytical performance characteristics that support the test's clinical performance. Interim data may prompt changes in test design, followed by another round of analytical validation studies. The expense of these efforts motivates sponsors to time them carefully.

It is essential to recognize that changes in the design of the test and its analytical performance characteristics become very suspect if they are prompted by results from testing pivotal trial specimens. Such changes are likely to raise the need for additional clinical trials to establish the performance characteristics of the test for use with the drug.

Some test developers consider taking a non-final version of the test into the clinical trial, intending to reduce the test to a final version later, in order to demonstrate clinical validity using pivotal trial specimens.

Even assuming that final configuration of the test is not contaminated by insights from the pivotal

trial material, this strategy carries significant risks. One is that the final configuration of the test might simply perform unacceptably worse than did the earlier test version. Another risk is that the specimens from the pivotal trial will be unavailable or unsuitable for testing with the final device, so that performance cannot be directly assessed. Bridge studies using specimens somehow like those from the clinical trial are a markedly less desirable approach to validation.

There are special issues if a non-final version of the IVD test is used as a gate in accruing patients to the pivotal trial, as in, for example, a trial confined to marker positive patients. Here is why.

In accruing only patients who are marker positive, according to a prototype IVD assay, patients in blocks B and D go off study. When the final version of the device is applied, patients in block C are also removed from the analysis. This is not a problem if the two device versions are perfectly concordant, since then no patient will be in block B or block C.

To the degree that the two versions are not concordant, either or both of these blocks will be populated. Patients in block A will be the only ones carried through the statistical analysis in a marker positive study. Such patients might not be representative of the patients in blocks A and B, who will receive the drug if the drug and the final device are approved.

An alternative would be to consider patients who test positive with either version of the device as positive for the biomarker. However, this does not match the manner in which patients will be tested post-approval since only the final IVD will be approved and performance characteristics of the test will be skewed by including block C patients in the analysis.

Summarizing my points on analytical validation. Regardless of the co-development path needed for a drug-device pair, it is highly desirable to complete the specification and analytical validation of the IVD before using the device to test clinical trial samples. Strategies for very late analytical validation, depending on like performance between the

final test and an earlier version, might raise significant review issues.

As discussed already, trials that assess efficacy of the drug in both marker positive and marker negative patients are most informative. If the trial, nevertheless, is designed to accrue only a subset of, say, marker positive patients, then it is especially desirable to avoid accruing patients based on one version of the device with the intent of completing the clinical validation using a second version of the device.

You've previously seen this graphic depicting an idealized pathway for developing the companion diagnostic test along with the drug. Such a development path provides for early identification of the biomarker. It provides for exploration of the biomarker's relevance to the disease and for relevant measurement of the biomarker itself. It provides for early assessment concerning relevance of the biomarker to use of the drug and it provides for final assessment of the drug and the analytically validated device in pivotal trials.