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Advisors Reaffirm Survival As Standard For Full FDA Approval Of Cancer Drugs

In a unanimous vote last week, the FDA Oncologic Drugs Advisory Committee reaffirmed the extension of survival as the gold standard for full approval of cancer drugs.

Though the pharmaceutical industry systematically pressures the agency to accept lower standards, particularly the measurement of the time to disease progression, the committee vote June 7 indicates that ODAC intends to look for some tangible patient benefit as a requirement for full approval of cancer drugs.

While full approval—the ultimate prize bestowed by the advisory

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In Brief:

FDA Deputy Commissioner Friedman Named Senior VP, Clinical Affairs, At G.D. Searle

MICHAEL FRIEDMAN, deputy commissioner for operations at FDA, has been appointed senior vice president, clinical affairs, for G. D. Searle & Co., effective in July. Searle, based in Skokie, IL, is the pharmaceutical sector of Monsanto Co. Friedman will be responsible for directing strategy and implementation of clinical research. He also will advise the development of novel nutritional product candidates within the Monsanto Life Sciences program. Friedman served as acting commissioner of FDA for a year and nine months, and was a leading candidate to become commissioner. Prior to joining FDA, Friedman spent 12 years at NCI, directing cancer research and therapy programs, and eight years on faculty at the University of California, San Francisco Medical School. Friedman's appointment follows the retirement of **John Alexander**, who led Searle's worldwide clinical trial development programs since 1991. In December 1998, FDA approved the Searle arthritis drug Celebrex. More than five million prescriptions have been written for the drug since its approval, the company said. In 1998, Monsanto reported sales of $8.6 billion and invested approximately $1 billion in research and development. . . . **HHS SECRETARY DONNA SHALALA** on Friedman's departure: "When you think of the Food and Drug Administration's mission to promote and protect the public health, you think of Mike Friedman," Shalala said in an official statement earlier this week. "Mike has spent his professional life working to improve the quality of health care delivered to people in the United States and around the world. In doing so, he has distinguished himself as a leader not only within

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Time To Progression Viewed As Surrogate For Survival

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committee and FDA—is likely to be out of reach for sponsors who are unable to prove patient benefit, the committee is likely to remain generous with another prize, accelerated approval.

In another unanimous (12-0) vote, ODAC said that time to progression can be regarded as a reliable surrogate for accelerated approval, which is contingent on the sponsor's completion of studies aimed to demonstrate patient benefit.

Though the accelerated approval designation is widely used by the agency, no drug approved through this mechanism has been pulled off the market based on failure by the sponsors to prove patient benefit, and several drugs have gone on to receive full approval.

Committee discussion pointed to another area of extraordinary uncertainty: the measurement of quality of life. Trials that produce credible quality of life data would be extremely expensive, said Richard Schilsky, director of the University of Chicago Cancer Center and the incoming ODAC chairman.

"If someone is willing to make the investment to do it right, I think that would provide exceptionally valuable data," Schilsky said at the meeting. "I am concerned that these studies will be missing a lot of data points because of the complexity of evaluations that would have to be done, and at the end of the day, it would be difficult to have data that would be of the quality that we would like."

Though unusual, the FDA decision to ask ODAC to examine the approval criteria is not unprecedented. The questions were narrowly framed to apply to new cytotoxic drugs for initial treatment of metastatic breast cancer. However, the agency and the reviewers stated repeatedly that the committee recommendations would have broader implications.

"This is one of the most important matters the committee has considered, because it involves not just a single drug or application, but all future applications for this use," said John Johnson, oncology drugs clinical team leader at FDA, in his presentation to the committee. " In addition, any committee recommendation may be extended to other kinds of cancer."

The implications are even broader, several informed observers said. With cytostatic drugs in the development pipeline, the agency and its advisors will inevitably have to develop the standards for approval of drugs that do not cause tumor regression.

This broader agenda was clearly visible to Stephen Carter, a pharmaceutical industry consultant who has missed few ODAC meetings since that committee's formation in 1973, presented applications for five new drugs developed by Bristol-Myers Squibb Co., and is currently consulting with companies that develop cytostatic drugs.

"Cytostatic compounds probably will not cause objective regressions, and therefore time to progression is really the only meaningful surrogate for these kinds of compounds, and basically any pharmaceutical company that's developing these compounds is going to use time to progression as their phase II 'Go/No-Go' criterion," Carter said to **The Cancer Letter**.

"In a circumstance in which accelerated approval is justified, clearly time to progression is going to have to be the basis of that accelerated approval with these newer agents," Carter said.

The Rationale For Survival

FDA official Johnson said the agency does not recognize increased time to progression as sufficient grounds for full approval of cytotoxic drugs because its value to the patient is not always clear.

Moreover, increased time to progression is usually modest, and is vulnerable to investigator bias. Survival, by contrast, is 100 percent accurate,

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Johnson said. If time to progression is to be substituted for survival, survival gains that were made in the past could evaporate.

"The FDA wants assurance that these survival gains are not lost when a new drug is introduced," Johnson said. "There are only two real endpoints in cancer clinical trials: either prolongation of life or a better life," Johnson said. "All other efficacy endpoints must be surrogates for one of these."

In recent years, the gold standard of survival has been challenged on many fronts. Patients whose disease progresses while in clinical trials often move on to secondary therapies, some of which are beginning to affect survival.

Johnson said these effects could be statistically adjusted. In fact, such analysis is now being performed to assess the effect of CPT-11 in advanced colorectal cancer. "In one recent protocol, the sponsor proposed that the primary efficacy analysis be a survival analysis adjusted for secondary use of CPT-11," Johnson said.

Another challenge comes from study designs including one that led to the approval of the breast cancer drug Herceptin. In the Herceptin studies, patients randomized into the standard treatment arm are allowed to cross over into the experimental arm if their treatment failed.

"If the test drug is not marketed, the protocol should prohibit this," Johnson said. "If the test drug is marketed, the FDA looks at the response rate, response duration and time to progression after crossover to estimate the likelihood of an effect on survival.

"Crossover from the control treatment to the test drug does not always obscure the survival effect of the test treatment," Johnson said.

A trial of Herceptin as the initial treatment of metastatic breast cancer showed a five-month median survival advantage despite the fact that 65 percent of control patients crossed over to Herceptin.

"It appears that the test drug may have less effect when given as second-line treatment," Johnson said. "The Herceptin randomized controlled trial supports the idea that the main problem is not our test methodology, but the lack of good new agents to test."

[See page 6 for the text of Johnson's remarks.]

"Time to Progression"

ODAC is sorting through these endpoints without the benefit of reliable studies comparing survival and time to progression.

Oncologist Sandra Swain, a consultant to the committee, said uncertainty begins with the definitions. Currently, most studies calculate time to progression from the date of randomization until either progressive disease or death, Swain said**.** However, this definition is not used uniformly.

"The term 'time to treatment failure' was used in the 1970's through 1990s," said Swain. "I found that the rules are often not prospectively defined. It makes reading the literature difficult, because frequently the investigators do not define what exactly they mean by either treatment failure or progression."

The quality of data presented to ODAC has been uneven, said Swain, a former member of the committee.

"I noticed, having been on [ODAC] recently, many of the companies are bringing time to treatment failure data to the committee," Swain said. "This to me is a waste basket endpoint in that it calculates from the date of randomization until almost anything you can think of: progressive disease, death, withdrawal due to an adverse event, patient refusal, patient being lost to follow-up, or further anti-tumor therapy.

"It can be anything, and it doesn't give you a handle on biological activity or the clinical efficacy of the drug being tested, so I don't believe that this endpoint should be used as a primary endpoint," Swain said.

In a review of literature, Swain found that generally the survival benefit with most cytotoxic drugs is modest, ranging between two and six months, and that time to progression appears to be correlated with survival.

Looking over approval of breast cancer cytotoxic drugs approved by FDA, Swain noted that FDA and ODAC in recent years have used response and time to progression data as a basis for both full and accelerated approval of second-line breast cancer therapies.

Thus, in 1994, Taxol (paclitaxel) was given full approval for the second-line treatment of breast cancer, based on a randomized study comparing two doses of the drug. The primary endpoint in the studies was time to progression. The sponsor, Bristol-Myers Squibb, presented survival data that did not demonstrate a statistically significant survival advantage.

In 1996, Taxotere (docetaxel) was given accelerated approval based on response data. Two

years later, the sponsor, Rhone-Poulenc Rorer, returned with survival data and was given full approval.

Also in 1998, Herceptin (trastuzumab), a monoclonal antibody sponsored by Genentech Inc., was given full approval based on a response rate and time to progression. In the data presented, survival was a secondary endpoint. Thus, at least in the case of Herceptin, the FDA Center for Biologics Evaluation and Research accepted time to progression as a primary endpoint.

Another breast cancer drug, Xeloda (capecitabine), sponsored by F. Hoffmann-LaRoche Ltd., was given an accelerated approval based on response rate data.

"I think time to progression is an acceptable endpoint which may confer patient benefit," Swain said.

However, time to progression endpoint cannot be viewed in isolation, Swain said. "Time to progression may not be a surrogate for patient benefit if you have a very toxic therapy," she said. "You have to have a therapy that is either nontoxic or has toxicity that allows to maintain the quality of life. Toxicity certainly must be taken into consideration, and it cannot outweigh any kind of benefit that we may see."

Among materials cited by Swain was a "White Paper" on breast cancer drugs, published in the Journal of Clinical Oncology in 1991.

"The clinical usefulness of a drug must reflect the relationship of risk to benefit for specific clinical conditions," the document states. "The primary aim of cancer treatment is prolongation of life, but the demonstration that a new agent causes tumor regression and improves patients' clinical condition also supports approval of a new agent, even in the absence of improved survival.

"In breast cancer, a large fraction of recurrences are symptomatic, making improved disease-free survival a valid surrogate for improved quality of life," the document states.

"Surrogate:" A Matter of Definitions

ODAC member Richard Simon said time to progression may not be a true surrogate for patient benefit since data do not link time to progression to symptomatic improvement or deterioration.

"I think 'surrogate' is a very strong statement," said Simon, chief of the NCI Biometric Research Branch. "It means it represents an effect on what it's a surrogate of. I don't think we have that body of data."

Swain agreed.

"Intuitively, we think that if time to progression is increased, the patient is going to benefit, and symptoms are going to be lessened," Swain said. "I agree that the statement is strong. If you noticed, in my presentation I did not make that statement at all. I didn't say it was a surrogate, because I think you need hard data for that, and I don't think we have it."

ODAC member Schilsky said the most persuasive argument for using time to progression in place of survival is that survival data are vulnerable to being distorted by secondary therapies.

"What I wonder about is whether there is any evidence whether that is the case," Schilsky said. "In second-line therapies, in virtually all the studies, survival advantage was pretty minimal. That raises the question in my mind whether second-line therapy has much potential to confound interpretation of results.

"So far, I am not persuaded that theoretical concerns about confounding interpretation of survival is actually a real concern based upon data that we actually have available to look at," Schilsky said.

Also, Schilsky said the advantage of relying on time to progression was not immediately apparent from the data presented. "The data that Sandy [Swain] presented was persuasive that time to progression correlates with survival, [but] in virtually every case where there is a time to progression advantage shown, there was also a survival advantage.

"So it's not clear that there is an advantage to time to progression over survival, except the fact that we may get to that endpoint a little sooner," he said.

Of Margins And Biases

Committee members Simon and Stacy Nerenstone pointed to potential disadvantages of using time to progression instead of survival.

"My own view is that if you accept time to progression as the primary endpoint, then trials will be done in that way, and women will never know whether there is a real survival benefit to the treatment that has been approved," Simon said.

While time to progression may appear to be worthwhile to a clinician, measuring it would be subject to statistical bias, said Nerenstone, associate clinical professor of oncology at the Helen and Harry Gray Cancer Center at the Hartford Hospital.

"We are talking about a very small amount of time difference," Nerenstone said. "It's very dangerous to say that a drug shows statistical improvement when these are open studies and when there are clearly apparent biases of physicians who enroll patients on these trials. [Let's say] Mrs. Jones comes in. She has a new backache. Are you going to immediately get a bone scan?

"We are talking about investigator biases that are going to be able make the difference between the drug that may or may not statistically improvement in time to progression," Nerenstone said.

When the margins are so small, the question of patient benefit becomes more difficult to answer, said ODAC chairman Janice Dutcher, an oncologist at Our Lady of Mercy Medical Center in the Bronx.

"The issue is, does a one-month difference have meaning to people?" Dutcher asked. "If it's six months, and survival is better, too, it's wonderful. But we haven't seen data that suggest that there are big incremental differences by any of these measures with the kind of drugs we've been seeing in the disease we've been talking about.

"I think that time to progression would be wonderful. If it's a year, that would be great. But I think this committee would want to be flexible in terms of looking at information presented to them, and attempt to tease out an improvement," Dutcher said.

Quality of Life: The Elusive Bottom Line

Ultimately, reliable measurement of the quality of life emerged as the bottom-line issue in the committee's discussion.

Measurement—and improvement—in the quality of life also happens to be one of the few issues on which nearly all patient groups agree.

"Women make different decisions about the tradeoff between quality of life and prolongation of life," said Helen Schiff, a member of SHARE, a New York-based patient advocacy group.

"It's a terrible choice to make, but, unfortunately, that is where breast cancer treatment is at right now," Schiff said to the committee. "We need the information on both of these endpoints—quality of life and survival—to make one of the most important decisions of our life: How and when to die.

"Perhaps these two endpoints should be combined into quality-of-life-adjusted survival."

Another advocate, Robert Erwin, of the Marti Nelson Cancer Research Foundation, said FDA should maintain its gold standard of survival and accept time to progression as the primary endpoint only in cases where approval can be explicitly tied to quality of life. "I believe that maintaining the current accelerated approval mechanism combines the best features of free market incentives with rational consumer protection," Erwin said.

The committee asked FDA officials to meet later this year to consider the issues involved in defining and measuring the quality of life.

Though the issues involved in measuring the quality of life are exceedingly complicated, such measurements can be carried out if they are given a higher priority by drug sponsors and clinical trials cooperative groups, said ODAC member Nerenstone.

"I think drug companies and even cooperative groups that had trouble getting [quality of life] studies done because [quality of life] has always been relegated to a third point," Nerenstone said. "It's not the [primary endpoint].

"It needs to be improved, and people need to pay more attention to it. It's very expensive. You have to have that data manager making sure that baseline characteristics are filled out. You need to make sure that the forms are done, and you need to make sure that the patients understand that these are not optional," Nerenstone said.

"It's part of the whole study design."

Survival v. Quality of Life

ODAC member Kim Margolin, an oncologist at City of Hope National Medical Center, said defining quality of life is an extraordinary challenge.

"Those of us who haven't had cancer and those of us who had demonstrate the fact that it is very hard for one person or a group of people to estimate what the components of quality of life of another group of people would be," Margolin said.

The theoretical and logistical issues involved in correlating patient benefit with improved survival and time to progression are extraordinarily complicated and woefully misunderstood, said ODAC member George Sledge, a professor at the departments of medicine and pathology at Indiana University School of Medicine. His remarks follow:

"The question in mind is whether time to progression represents a decent surrogate endpoint for either overall survival or quality of life. If it doesn't represent a decent surrogate endpoint for either of these, I am not entirely sure what it is we are measuring.

"One of the problems I have is that I am not

sure quality of life and overall survival are always the same endpoint. If you look at Eastern Cooperative Oncology Group study 1193, in that trial, the only patients who had an improved quality of life were patients who started out symptomatic and then responded to therapy," said Sledge, who served as chairman of the phase III study of Adriamycin v. Taxol v. Taxol, Adriamycin and G-CSF. The study was presented at the 1999 annual meeting of the American Society of Clinical Oncology.

"If you started out without symptoms, your quality of life got worse.

"If you started out with symptoms and didn't respond, your quality of life got worse.

"In an American cooperative group trial, when we are talking about patients entering the trial, it's very difficult to have a quality of life benefit for most of the patients who enter the trials.

"The big problem is that you are only likely to see quality of life improvement in patients who are symptomatic. Most US trials require patients to have a performance status of zero to two [on the ECOG or Zubrod scale, ranging from asymptomatic to moderately symptomatic and in bed for less than half a day.]

"Most patients who go on trials have the performance status of zero to one [from asymptomatic to mildly symptomatic and fully ambulatory], so you are automatically introducing an a priori bias against being able to see the quality of life endpoint for most of the patients who are going on a clinical trial.

"Overall survival is most likely to be improved in patients who start asymptomatic, with small-bulk, small-volume disease. So, quality of life and overall survival aren't necessarily the same endpoint.

"So if you are then to ask what is time to progression a surrogate for, I'd say from what I heard this morning, we don't have striking data that it's a surrogate for either survival or quality of life.

"My overall feeling is that this is a tremendously understudied area, an area where we don't have any striking data to allow us to make a conclusion about whether or not this represents an acceptable surrogate for either of these endpoints."

Three Drug Recommendations

Turning to the three drug applications presented at the two-day meeting, ODAC made the following recommendations:

—The committee recommended approval for Ellence (epirubicin hydrochloride injection) as a component of adjuvant therapy for patients with axillary nodal tumor involvement following resection of primary breast cancer.

Studies presented by the drug's sponsor, Pharmacia & Upjohn, sought approval for the anthracycline compound for both adjuvant therapy and first-line treatment of metastatic disease. However, the committee recommended against the metastatic disease indication. The drug, marketed as Farmorubicin outside the U.S., is used in more than 80 countries to treat a variety of cancers, including breast cancer.

—The committee recommended accelerated approval of a supplemental New Drug Application for Doxil (doxorubicin HCl liposomal injection) in the treatment of metastatic carcinoma of the ovary in patients refractory to both paclitaxel- and platinum-based chemotherapy.

The committee recognized tumor shrinkage as a plausible surrogate endpoint for clinical benefit. Ultimately, the sponsor, Alza Corp. of Palo Alto, CA, will have to produce data pointing to a clinical benefit.

Doxil, a liposomal formulation of doxorubicin, has been granted orphan drug status for ovarian cancer, which provides for seven years of market exclusivity upon approval. Accelerated approval entitles the sponsor to orphan drug benefits.

The drug is approved for the treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy. The product was launched by Sequus Pharmaceuticals Inc., which merged with Alza earlier this year.

—The committee approved a supplemental New Drug Application for Ethyol (amifostine) for the reduction of moderate-to-severe, post-operative radiation-induced xerostomia in patients undergoing radiation treatment for head and neck cancer.

Ethyol is indicated for reducing the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian or non-small cell lung cancer. The drug is sponsored by U.S. Bioscience of West Conshohocken, PA.

Endpoints: The FDA View

Following is the text of the presentation to ODAC by John Johnson, oncology drugs clinical team leader at FDA:

This morning's topic is considerations on the use of time to progression as the primary efficacy endpoint in randomized controlled trials of cytotoxic

drugs for initial treatment of advanced metastatic breast cancer.

This is one of the most important matters the committee has considered, because it involves not just a single drug or application, but all future applications for this use. In addition, any committee recommendation may be extended to other kinds of cancer.

Before we decide where we are going, it is a good idea to review where we are and the reasons we are there. My assignment this morning is to review the FDA's present efficacy requirements for marketing approval of a drug for this use and to explain the rationale for those requirements.

The present FDA efficacy requirement for marketing approval for this use is a favorable effect on survival demonstrated in a randomized controlled trial. The favorable effect can be superiority to a control or equivalence to an effective standard regimen. The FDA's reasons for requiring a favorable effect on survival fall into two categories—safety and efficacy.

First, cytotoxic drugs have substantial toxicity. Usually, only a minority of patients have a tumor response and most tumor responses are only partial. Time to progression effects are usually modest. In view of the toxicity of cytotoxic drugs, the FDA has not considered tumor response rate or time to progression as adequate bases for marketing approval.

The second reason related to drug toxicity for requiring survival data is that survival in a randomized controlled trial can be viewed as a safety endpoint. In some patients it is not clear whether the cause of death is drug toxicity or tumor progression or both. Survival is the net effect of deaths from both tumor and drug toxicity. Actually for this purpose a survival effect is not necessary. We only want assurance that the new treatment is not worse.

The reason related to efficacy for requiring a survival effect is that effective cytotoxic drug regimens prolong life. Dr. Craig Henderson, a former ODAC chairman, in a presentation on this issue to the committee at an earlier meeting, estimated that effective doxorubicin-based combination drug regimens prolong life by about six months, compared to no treatment. The FDA wants assurance that these survival gains are not lost when a new drug is introduced.

By far the most common criticism of the requirement for a survival effect is that secondary drug therapy after tumor progression might obscure any survival effect of the test drug. One would expect that a drug used after tumor progression would have the same survival effect in both treatment groups and would thus not obscure the survival effect of the test drug.

The effect of secondary treatment on survival can be analyzed. Usually, there is a particular drug we are concerned about. We can determine the proportion of patients in each treatment group that got the drug after tumor progression. Usually, it will be the same in each treatment group. If there is an imbalance, the next step is to assess whether the drug had a survival effect. If so, an adjusted analysis can be done.

Recently this type of analysis has started to occur in clinical studies in advanced colorectal cancer. For many years no one thought that available secondary therapies were likely to have a substantial survival effect in advanced colorectal cancer.

After CPT-11 became available and was shown to prolong life when given after progression as secondary therapy for advanced disease, investigators started including analyses for the effect of secondary CPT-11 use in their protocols. In one recent protocol the sponsor proposed that the primary efficacy analysis be a survival analysis adjusted for secondary use of CPT-11.

The potential effect on the survival analysis of crossing over patients after tumor progression from the control treatment group to the test treatment is more serious. If the test drug is not marketed, the protocol should prohibit this. If the test drug is marketed, the FDA looks at the response rate, response duration and time to progression after crossover to estimate the likelihood of an effect on survival.

Crossover from the control treatment to the test drug does not always obscure the survival effect of the test treatment. In the recent randomized controlled trial of Herceptin in initial treatment of metastatic breast cancer a five-month median survival advantage was shown even though 65 percent of control patients crossed over to Herceptin.

It appears that the test drug may have less effect when given as second-line treatment. The Herceptin randomized controlled trial supports the idea that the main problem is not our test methodology, but the lack of good new agents to test. In this case it was not difficult to detect a good new agent even in the face of a suboptimal study design.

[Let us compare] survival and time to

progression as efficacy endpoints. Survival is assessed every day and is 100 percent accurate for the event and nearly 100 percent accurate for the day of the event. Time to progression is assessed only every two to six months and is much less accurate for the event and even less accurate for the time of the event. The importance of survival is unquestioned while the importance of time to progression is less certain. Survival is both a safety and an efficacy endpoint. Time to progression is only an efficacy endpoint.

Of course, if death is counted as tumor progression, then time to progression is also a safety endpoint. But I do not believe we should do this, because death and progression are qualitatively different.

Also in most protocols, this only serves to cover-up the failure to do adequate testing to detect progression. In favor of time to progression, it is faster and a time to progression effect is not obscured by secondary therapy after progression.

If time to progression were used as the primary efficacy endpoint, time to progression would probably require more complete assessment and more frequent assessment than is presently done. Would pharmaceutical companies be willing to provide the additional resources?

Incomplete assessment at baseline is an occasional problem. More frequent problems are incomplete assessments at follow-up visits. In some protocols only selected sites of known disease may be followed.

In other protocols all known disease sites may be followed, but not other sites where new disease is likely. For example a patient with lung metastases may be followed with a chest x-ray. No disease was present in the liver at baseline, so the liver is not followed.

The liver fills up with metastases while the lung disease remains stable. The patient dies without any documented tumor progression. This is then compounded by scoring the patient as progressed on the date of death, which means she is scored as progression free until the date of death. This is obviously not believable. Other problems are missed assessments and infrequent assessments.

If time to progression were used as the primary efficacy endpoint, what would be the effect on the requirement for survival data? There are three possible scenarios:

—In the first scenario pharmaceutical companies may stop their studies and submit the NDA when data on time to progression is obtained. There would never be any survival data. This scenario is unacceptable to everyone with whom I have discussed it at the FDA .

—The second scenario would be accelerated approval based on time to progression, with survival data required later to convert the accelerated approval to regular approval.

—The third scenario would be regular approval based on time to progression with a commitment to submit survival data later for inclusion in the labeling.

In summary, there are only two real endpoints in cancer clinical trials. Either prolongation of life or a better life. All other efficacy endpoints must be surrogates for one of these.

So for time to progression to be used as the primary endpoint in randomized controlled trials for initial treatment of metastatic breast cancer, time to progression must be a surrogate for a better life or a longer life.

In Brief:

Shalala Thanks Friedman

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the ranks of government, but in the medical, academic, science and research communities as well.... I would like to personally thank Mike for his outstanding leadership as FDA's acting commissioner from February 1997 through November 1998. His stewardship during that period was much more than keeping the trains on track. Mike inspired the agency to move forward and keep focused on its mission. And he did so with enthusiasm, intelligence and collegiality. For that, we are sincerely grateful. On behalf of everyone at HHS, I applaud Mike for his exemplary service and wish him all the best in his future endeavors. We will miss him." . . . **FDA COMMISSIONER JANE HENNEY** on Friedman's departure: "The nation owes an enormous debt of gratitude to Dr. Michael Friedman. After his career as an academic researcher and many years as head of the Cancer Treatment Evaluation Program at the National Cancer Institute, Mike joined the Food and Drug Administration at a crucial time. As acting commissioner, Mike worked tirelessly with Congress on the FDA Modernization Act of 1997, negotiated the reauthorization of the prescription drug user fee program, and pushed ahead with other public health measures."

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