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ODAC Recommends Approval Of Paxene; Will IVAX Break Into $1 Billion Market?

The FDA Oncologic Drugs Advisory Committee Sept. 19 unanimously recommended approval for a version of paclitaxel produced IVAX Corp. of Miami for refractory advanced AIDS-related Kaposi's sarcoma.

The committee's recommended approval for the drug, trade name Paxene, less than three months after it recommended approval for Taxol, the original paclitaxel agent, as a treatment for the same indication (**The Cancer Letter**, July 4).

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In Brief

Lombardi Comprehensive Designation Renewed; Yale Plans Breast Cancer Lab

LOMBARDI CANCER CENTER has received a renewal of its status as an NCI-designated Comprehensive Cancer Center. Lombardi Cancer Center is part of Georgetown University Medical Center in Washington, DC. . . . **YALE CANCER CENTER** plans to establish the Marcia Israel Laboratory for Earlier Diagnosis of Breast Cancer with a donation from Marcia Israel, a Los Angeles philanthropist. The laboratory will begin preliminary research by October, the center said. . . . **PETER HO**, former senior investigator in the NCI Cancer Therapy Evaluation Program, Investigational Drug Branch, joined the Oncology Therapeutics Area of Novartis AG, of East Hanover, NJ. . . . **JEFF HUMPHREY**, former clinical associate in the NCI Medicine Branch, was named associate director, clinical cancer research, at Bristol-Myers Squibb Pharmaceutical Research Institute in Wallingford, CT. . . . **RACHEL HUMPHREY**, also a former clinical associate at NCI, was named associate director, oncology and cardiopulmonary research, at Bayer Pharmaceuticals in West Haven, CT. . . . **DEREK RAGHAVAN** was named professor of medicine and urology, and chief of the Division of Medical Oncology at the University of Southern California School of Medicine. He also was appointed the associate director for clinical research and coordinator of the Genitourinary Cancer Program at the USC/Norris Comprehensive Cancer Center. Raghavan is the former chief, Departments of Solid Tumor Oncology and Investigational Therapeutics at Roswell Park Cancer Institute and professor of medicine and urology at the State University of New York, Buffalo. . . . **DOROTHEE**

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ODAC Recommends Approval Of Paxene For Refractory KS

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Since Taxol, the Bristol-Myers Squibb version of paclitaxel, was the first of the two drugs to receive approval, it received the orphan drug status, which entails seven years of market exclusivity for KS.

Obtaining the approval recommendation from ODAC was only the first of two obstacles for IVAX. To bring Paxene to market, IVAX would have to convince FDA that the drug is superior to or chemically distinct from Taxol for the KS indication (**The Cancer Letter**, Aug. 15).

If Paxene gets on the market for KS, a disease that affects a small number of patients, the approval would open the doors for off-label use and the loss of market exclusivity for Bristol.

Taxol currently accounts for about $1 billion a year in worldwide sales for BMS. The stakes are, in fact, even higher. The entire system of market exclusivity for orphan drugs could come into question should the Paxene versus Taxol contest spill out of FDA and into the courtrooms and Capitol Hill hearing rooms.

Given that Paxene v. Taxol is a game of strategy, it is natural that the questions ODAC members were not asked were at least as significant as the questions asked. Thus, many observers noted that FDA chose not to seek the committee's guidance on establishing distinctions between the Paxene and Taxol as treatment for KS.

Granted, the question would have been unanswerable, considering that the two drugs were never compared in side-by-side trials and that objective response in KS is an elusive concept. However, the glaring absence of such questions to ODAC means that FDA plans to resolve the orphan drug issue on the staff level.

Since the committee's guidance was sought only on the relatively straightforward issue of whether Paxene is approvable, the committee members, in effect, became observers of the more contentious issue. Of course, the committee members could do more than observe: they could ask questions, presumably to assess the strategies of the sponsors and to gauge the position of FDA officials.

"What about a patient who has already received Taxol for this indication, and has progressed, and is not responding?" Robert Ozols, senior vice president, medical science, at Fox Chase Cancer Center, asked before the final vote to recommend approval. "Are we saying that they should be candidates for Paxene?

"Are they the same drug?" Ozols continued. "Are they different drugs? Are we going to say that they are different [formulations] of drugs? That they have different have different properties? That they have different responses, toxicities?"

"That's not fundamentally different from what you make of a situation whenever there are two manufacturers who make the same active moiety in two different drug products," said Robert Temple, head of the FDA Office of Drug Evaluation I. "Usually, when you failed one thing, you wouldn't try the generic. I must say we have not actually told people that, but we thought that was fairly clear."

The session revealed that IVAX officials are in a disagreement with the FDA staff over the quality of life advantage the company claims in its NDA.

The FDA review of the application stated that the company's measurement of the quality of life advantage was based on a prospective study and therefore is not valid. "The results of the analyses of the Symptom Distress Scale components, and therefore the total SDS score, should be interpreted with caution due to lack of a control group in the study," the agency said in its review.

"The impact of these data cannot be adequately assessed [and] no claims for improvement can be validly made," the review said. "The approval decision should be made only on the clinical

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considerations in this application."

The company said the improvement in the patients' assessment of their quality of life, measured at every third course, was statistically significant at cycles 4, 7, and 10. "Very few patients were lost between baseline and cycle 4, indicating that the improvement seen at cycle 4, at least, is due to bias," said Ken Duchin, an official of Baker Norton Pharmaceuticals, an IVAX unit that is developing Paxene.

Quality of life measurement is particularly important in KS since assessment of tumor responses can be open to interpretation, Duchin said. "Thus, it is possible for a patient not to be scored as having a tumor response, despite having clear evidence of clinical benefit," he said at the meeting.

The measurement was obtained using a combination of the Karnofsky Performance Status, photographs, and a 15-point scale in which patents were asked to assess their well-being and symptoms of their disease.

"We understand and deeply respect the FDA review, and we understand their comments," said Samuel Broder, former NCI Director, who is the IVAX senior vice president, research and development. "Our position is that we do not agree with their assessment.

"Recognizing all of the potential limitations, the simple bottom line is that a prospective study with statistically significant results, at least for certain parameters and at certain time points, must constitute an improvement over previous attempts to make these quality of life assessments.

"So, with respect to FDA, on this specific point, we disagree," Broder said.

The IVAX data are based on a study of 89 patients who received 100 mg/m^2 over three hours every two weeks.

According to the company, 2% of the patients exhibited complete response, 44% exhibited partial response, 33% had stable disease, 6% progressed and 16% were not evaluable. FDA analysis of the data showed no complete response, 42% partial response, 18% stable disease, and 25% progressive disease. The remainder—16%—were not evaluable.

According to FDA analysis limited to eligible patients, partial response rate was 46%. Median response duration was 128 days, and median time to progression was 164 days.

The company said Paxene's toxicity profile was consistent with that of Taxol. "Paxene exhibited no higher incidences for any of the toxicities seen with Taxol, and in some cases, the rate may be lower," Duchin said.

The FDA evaluation, presented by reviewer Ken Kobayashi, said the data from the phase II trial in refractory KS do not make such comparisons possible. The study demonstrates objective tumor response, but is inadequate to evaluate such secondary endpoints as duration of response, time to progression, and survival, Kobayashi said.

The relatively small size of the IVAX study drew criticism from Michael Marco, director of opportunistic diseases at the Treatment Action Group, who served as a patient representative on the panels that approved both Taxol and Paxene for KS.

"I think we need to start holding companies to a higher standard, and ask for larger patient studies when they come to us in the future," Marco said. While the 89-patient Paxene study appears small, it represented the largest population of patients ever used to test a KS drug, IVAX officials said.

Two Taxol studies presented data from the treatment of 85 patients, of whom 59 (19 in one study and 40 in another) failed prior chemotherapy, IVAX officials said. The study that led to the approval of Doxil used data from 77 patients who failed prior chemotherapy.

It is unlikely that Paxene's formulation, which differs from that of Taxol, would be a factor in FDA's decision on the orphan drug issue. The agency made that position clear in the letter that extended the orphan drug status to Taxol.

"Please note that it is paclitaxel and not its formulation that has received orphan designation," the agency wrote in a letter to Bristol.

IVAX is developing Paxene in partnership with NaPro Biotherapeutics of Boulder, CO.

ODAC Gives Okay To Photofrin For Microinvasive NSCLC

The FDA Oncologic Drugs Advisory Committee last week recommended approval of Photofrin (porfimer sodium) photodynamic therapy for the treatment of microinvasive non small cell lung cancer in patients for whom surgery and radiation are contraindicated.

Ten committee members voted to recommend approval of Photofrin at the Sept. 18 meeting. Two members abstained from the vote.

Photofrin was developed by QLT PhotoTherapeutics Inc. (Nasdaq: QLTIF) of

Vancouver, and is marketed in the US by Sanofi Pharmaceuticals Inc.

QLT presented data from three single-arm trials using Photofrin to treat microinvasive NSCLC and endobronchial carcinoma in situ. The study group included 100 patients with early stage non small cell lung cancer.

The indication group included 24 patients with superficial lung cancer for whom surgery and radiation therapy were contraindicated. Inoperable patients had either prior resection, poor pulmonary function, or were non-resectable due to tumor location. Patients not able to receive radiation therapy had previous high dose XRT treatment, poor pulmonary function, multifocal disease, or a poor medical condition.

QLT reported a median survival of 5.7 years for patients who received Photofrin. Median time to tumor recurrence in the indication group was 3.4 years.

Thirty-one percent of the overall study group, and 29 percent of the indication group died of cancer during the trial, the company said.

FDA asked the committee to vote on whether the 24 indication patients represented a group with no standard therapeutic option; and whether Photofrin should be approved for microinvasive NSCLC and endobronchial carcinoma in situ.

The committee voted 10-1, with one abstention, to accept the 24 indication patients as having no standard therapeutic option.

ODAC voted 7-4 against recommending approval of Photofrin for the treatment of endobronchial carcinoma in situ, due to an absence of histological review data to prove existence of in situ cancer in the study group. Committee members also raised concerns over whether carcinoma in situ should be treated at all. One member of the committee abstained.

QLT PhotoTherapeutics also presented data comparing Photofrin photodynamic therapy to Nd: YAG laser therapy in the treatment of advanced stage endobronchial NSCLC.

The company presented data from two prospective, randomized trials comparing efficacy in reduction of tumor size, and palliation of symptoms in patients with partially obstructing endobronchial cancer.

In its review, FDA found the data to be incomplete and potentially biased. Reviewer Grant Williams said tumor size was not collected in many patients, courses of Photofrin were defined differently from the YAG courses, and luminal response data for Photofrin was not always meaningful.

Williams said there was a significantly larger amount of missing data from the YAG arm than from the Photofrin arm.

The data QLT presented did show efficacy and evidence of patient benefit, Williams said.

FDA asked ODAC to vote on whether the studies were adequate and well controlled trials demonstrating the efficacy of Photofrin in the treatment of advanced endobronchial NSCLC. Ten members voted no with two abstentions.

Committee members said they were hesitant to recommend against the drug, but were obligated to based on the lack of data.

Many members said they were sure the drug was effective, but did not want to set a precedent of recommending FDA approval of drugs that presented inadequate trial data.

"We are all grappling with what level of confidence we have in the data," said Richard Schilsky, director of the University of Chicago Cancer Research Center. "We keep coming back to the phrase 'we don't know.' We don't know how good this treatment is, and we don't know how toxic it is.

"If we don't know these two things, I don't know how we can recommend this treatment be sold in American medicine," Schilsky said.

Photofrin has been approved in the US for the treatment of advanced-stage esophageal cancer. The drug was approved for lung and esophageal cancer in France and the Netherlands; for esophageal and bladder cancer in Canada; and for early-stage lung, esophageal, gastric, and cervical cancers in Japan.

In Brief:

Macks Receive Recognition

(Continued from page 1)

HERLYN will receive **t**he Brain Tumor Society's Daniel R. Schrier Chair of Research. Herlyn is a scientist in the Wistar Institute Tumor Immunology Program. Herlyn will receive $78,000 for research on active specific immunotherapy. . . . **SEN. CONNIE MACK**, his wife **Pricilla Mack**, and Washington news anchor **Andrea Roane** will receive Congressional Families Action for Cancer Awareness Awards for their commitment to cancer research.

Report Finds NIH Not At Fault In P-32 Ingestion By Postdoc

Two researchers complete a day of work in their NCI lab. One of the two picks up a Geiger counter and proceeds to monitor radiation.

As the counter gets closer the other researcher, his pregnant wife, the count rate increases. She has been exposed to radiation. After monitoring several items of his wife's clothing, the researcher suspects internal contamination.

Thus, at 6 p.m., June 29, 1995, the NIH radiation safety and emergency officials responded to a call from a man who claimed that his wife had ingested phosphorus-32.

That was the beginning of a legal and regulatory tangle in which two postdoctoral fellows, a couple from China, claimed that NIH failed to secure radioactive materials, and made transparent insinuations that the woman's contamination was caused by their supervisor in a quest to force her to abort the fetus and continue to devote her efforts to research.

The story has had its day in the newspapers and on the CBS news program 60 Minutes (**The Cancer Letter**, Nov. 3, 1995). Also, it came under scrutiny of investigators of the Office of Investigations of the Nuclear Regulatory Commission, the Federal Bureau of Investigation, the NIH Police Department and the HHS Office of the Inspector General.

Last week, NRC ruled that the contamination was not the result of breaches in safety and security procedures on part of NIH and said that the NIH subsequent handling and investigation of the incident was appropriate. The petition for NRC enforcement action was filed by the postdoctoral researchers, Wenli Ma and Wenling Zheng.

In a decision dated Sept. 17, Carl Paperiello, director of the NRC Office of Nuclear Material Safety and Safeguards, said the NIH radiation safety and security procedures were indeed lax in several instances. However, NRC officials said NIH has tightened its safety and security procedures uncovered after the incident and paid a $2,500 fine assessed last year. Thus, no new penalties would be warranted, wrote Carl Paperiello, director of the NRC safety office.

Now, let us return to the scene of Ma's contamination:

Her husband and collaborator Zheng uses a Geiger counter…

Why?

The report of the investigation states that the couple did not use any radioactive materials that day. Moreover, for months prior to June 29, they were working exclusively with phosphorus-33, a much lower energy beta-emitter than P-32. The energy of the particles it emits is too low to be readily detected by a Geiger counter.

After the counter detects radioactivity near Ma, and after Zheng apparently rules out external contamination, NIH emergency officials received a call from a man with a heavy accent who said that his wife had "injected" P-32.

The first mystery was solved immediately: Zheng meant "ingested." Another, question was harder to answer: How did Zheng know that his wife had ingested P-32, as opposed to another radioisotope?

In the report written by the NRC Office of Investigations to summarize the multi-agency investigation, several NIH officials stated that they remembered distinctly that Zheng reported that Ma had ingested P-32. That, in fact, was the case.

"The survey meter used by Zheng only reflects that radiation is present," the investigation report states. "It would not reflect that Ma was contaminated with a specific isotope. This is even more puzzling because Ma and Zheng routinely utilized P-33, not P-32."

According to the investigation report, questions about Zheng's discovery and reporting of Ma's contamination have been posed to the couple through their lawyers, but no answer has been received.

The report states that "evidence developed during the investigation does not identify individual(s) responsible for the contamination incidents" at NIH. An item called "supplemental information" offers a clue about the investigators' conclusions:

"On Oct. 24, 1996, results of this investigation, including information regarding Zheng, were presented by the FBI to the US Attorney's Office for the District of Maryland. The cognizant Assistant US Attorney advised that due to the lack of physical evidence and any corroborating statements concerning Zheng's involvement, he would decline prosecution of this case."

Zheng did not expose his wife to radiation, his attorney David Marshall said to **The Cancer Letter**. "It is outrageous that the investigators for NRC would suggest in any way that Dr. Zheng was responsible

for this," said Marshall, an attorney with the firm of Bernabei & Katz. "That's not what the record in the case demonstrates at all."

Marshall characterized the investigation as an effort to "whitewash" the government's role in the case.

"The NRC report reflects the continuing cover-up of the government's responsibility for Dr. Ma's injuries," Marshall said. "I don't trust the FBI investigation of this at all. From the beginning, NIH and FBI steered this investigation away from their responsibility for Dr. Ma's contamination, and have suggested in this report that Dr. Zeng might be responsible."

Marshall said Ma and Zheng, whose visa and employment at NIH were extended by six months last August, are considering further legal action.

In addition to alleging "Zheng's involvement" in the contamination, the report of the investigation further chips away at the issue that gave the story its international appeal: the allegation that John Weinstein, Ma's and Zheng's supervisor at NCI, insisted that the couple abort the baby so they could devote themselves fully to their work.

In interviews with the investigators, Weinstein said he regarded Ma's pregnancy as a personal matter and made no recommendations either for or against its termination. In fact, Weinstein said it was Zheng who brought up the subject of abortion.

"According to Weinstein, Zheng said they wanted to have an abortion," the investigation report states, paraphrasing Weinstein's interview with FBI. Evidence presented to FBI is not quoted directly, in accordance with that agency's policy.

"Zheng was concerned about having an abortion in the US, with the violence which has occurred at abortion clinics," the report continued. "Weinstein said Zheng was concerned with the way some people in the US feel about abortions. Zheng told Weinstein that he and Ma were acquainted with another Chinese woman who had gone to the clinic and had an abortion performed.

"The abortion, which was performed by an `Indian,' apparently resulted in serious complications for this woman," Zheng reportedly said to Weinstein.

"In relating this conversation, Weinstein said Zheng said the words to the effect that it was not the right time to have a baby," the report states.

In a written statement quoted in the report, Robert Zoon, NIH radiation safety officer, said that following the Ma's contamination, Zheng "volunteered" that Ma's pregnancy was an accident, and that the couple were concerned about having a baby in a foreign country and the possibility that caring for a baby would adversely affect their fellowship.

According to Zoon's account, Zheng said that Weinsten was "not very happy" with Ma's pregnancy, and that had they been in China, termination of pregnancy would have posed few problems. "Here in America, they were concerned about the views on abortion," Zheng reportedly said to Zoon.

Attorney Marshall said Zheng had made general statements about abortion, but only in response to suggestions that his wife terminate her pregnancy. "NIH management pressured them to have an abortion," Marshall said. "It's not true that they considered having an abortion."

Weinstein's reaction to the NRC decision and the investigation documents appears on page 7.

In his decision, Paperiello said NIH could have done nothing to prevent another, apparently related exposure, in which 26 employees were contaminated with P-32 after drinking from a water fountain in the proximity of Weinstein's lab. Zheng was among those contaminated in that incident, which was discovered days after Ma's contamination.

"There is no evidence that NIH contributed directly or indirectly to the deliberate misuse of the licensed material involved, and NIH could not reasonably foresee that an employee or employees would maliciously misuse radioactive material as was done in this case," Paperiello wrote in his decision.

Following the contaminations, NRC conducted a series of inspections which revealed a number of violations of requirements for security and control of radioactive materials, as well as requirements for radiation safety training, inventory control, monitoring, and the issuance, use and collection of dosimetry.

At this time, the commission would seek no additional fines against NIH, Paperiello wrote in his decision.

"We think the NRC decision essentially confirms our claims that Dr. Ma was intentionally contaminated by somebody using NIH materials, and that these materials were used by an NIH employee," Zheng's and Ma's attorney Marshall said. "The NRC's failure to impose a substantial fine on NIH allows NIH to continue putting its employees and

the public at risk."

Following the release of the NRC decisions, NIH officials said the standards for security and use of radioactive materials have been enhanced and are now "among the most stringent such standards found in research institutions."

"NIH welcomes the NRC conclusions that NIH actions taken in responding to and investigating the June 1995 contamination incident were appropriate," NIH said in a statement. "It is particularly significant that NRC concluded that the contamination of Dr. Ma and the water cooler was not the result of faulty compliance with security requirements for radioactive materials."

In his decision, Paperiello said the abdominal pains Ma claims to have experienced at the time of contamination were unrelated to the exposure.

Based on NRC estimates of safety significance of the exposures, Ma would face no deterministic or stochastic effects, and the child would face no deterministic effects. The child's excess risk of developing cancer was estimated as 0.33%. The natural risk of childhood cancers is about 0.1%.

"Thus, the probability that the exposed fetus will not develop a radiation-induced childhood cancer is 99.67%," Paperiello wrote.

The text of Paperiello's decision is available on the NRC web site (http://www.nrc.gov/OPA/). The text of the investigation report will be available next week on **The Cancer Letter** web site (http://www.cancerletter.com).

Weinstein: Investigation Report Ends A Personal Nightmare

The following is the text of a statement by John Weinstein, a principal investigator in the NCI Laboratory of Molecular Pharmacology:

My wife and I are very grateful for the joint efforts of the NRC, FBI, DHHS, NIH police, and U.S. Attorney's Office in producing these two massive and comprehensive documents, which finally set the record straight. We are particularly gratified to see the "Agent's Analysis" beginning on page 79 of the Office of Investigations report. It succinctly puts the entire matter in its proper perspective—exonerating me completely, point by point.

We are also pleased that the NRC has denied the petition to suspend or revoke NIH's radioisotope license. Granting the petition would have crippled NIH's important research on cancer, on AIDS, on heart disease, on Alzheimer's, and on a host of other diseases. Anyone who has a friend or family member with one of those afflictions should breathe a sigh of relief. NIH has been called correctly the "crown jewel" of biomedical research for the entire world—and a source of pride for all Americans.

Despite all of the accusations and insinuations, we are pleased that Dr. Ma and her child are not expected to suffer any medical effects from the contamination. Although Dr. Ma and Dr. Zheng appear to have misinterpreted my many attempts to support them personally and in their careers, I did in fact do my very best for them, both before the contamination and in its immediate aftermath. Others have amply attested to that fact—and to my personal concern for the welfare of all postdoctoral fellows who train in the laboratory. In particular, my dedication to international cooperation and my enthusiasm for ethnic diversity in the research group are well documented.

It's time to look forward, not back. I look forward to devoting full, undisrupted attention to my research on cancer. This is an extraordinary moment in the history of medical science, and our research group is in a position to contribute. My wife and I look forward together—with a sense of immense relief—to the end of this personal nightmare. We want to express our deep appreciation to our many good friends and colleagues, in the scientific community and elsewhere, for their heartwarming support over the past two years. That has been the silver lining to this otherwise sorry affair.

Cooperative Groups:

Three Insurers Agree To Cover Patient Care Costs In Studies

Three health insurance plans in the Midwest have agreed to pay the cost of patient care for their members who participate in NCI-approved cooperative group clinical trials, the groups and the insurers said last week.

Together, the three insurers cover more than 200,000 members in Wisconsin and Minnesota, NCI said in a Sept. 19 statement.

The agreements are the first negotiated with regional insurers by cooperative groups that primarily study adult cancers. Security Health Plan, of Marshfield, WI, and Mayo Health Plan, of Rochester, MN, were two of the plans joining the agreement.

Robert Comis, chairman of the Eastern Cooperative Oncology Group, said a third firm has agreed to cover patient care costs, but did not want to make a pubic announcement yet.

"This is a first step in what we hope will be a long series of discussions with insurers in every region," Comis said to **The Cancer Letter**. "We are working on three levels, with health plans that have committed publicly, those that are extremely interested but are not ready for a public announcement, and health plans that are beginning to talk to us."

EGOG began to meet with insurers a year ago to discuss barriers to patient entry onto clinical trials, Comis said. Other cooperative groups joined the effort. The agreements apply to any NCI-approved clinical trial sponsored by a cooperative group.

Other details of the agreement are under discussion, including methods of review and certification of group institutions, Comis said.

Patient care costs generally include any medical care a patient would normally receive for management of the disease, whether or not the patient is enrolled in a study.

Security Health Plan, a health maintenance organization associated with the Marshfield Clinic, has always covered patient care costs of any of its 90,000 members who enter cooperative group trials, said William Maurer, medical director of the organization. "Not only will we be able to provide our members with the opportunity to access the state-of-the-art in cancer care today, but by working with the cooperative groups we can improve the standards of care for the future," Maurer said.

Mayo Health Plan, covering 5,000 people in Southeastern Minnesota, is an HMO associated with the Mayo Clinic. "This [agreement] will almost certainly provide immediate patient benefits as well as contributing to long-term research in the battle against cancer," said Hugh Smith, MHP medical director.

Michael O'Connell, a Mayo Clinic oncologist and chairman of North Central Cancer Treatment Group, said the group system offers insurers a high level of quality control. "With this agreement, the patient benefits from the opportunity to access the highest quality cancer care available and everyone else benefits from our ability to raise cancer treatment standards to the next level," O'Connell said.

The agreements have the potential to remove several barriers to patient entry onto clinical trials, Comis said. These barriers include the time a physician must spend arranging for patient entry and approval from the insurer.

"The ultimate arrangement would be that when a doctor or nurse has a patient from one of these health plans and has determined that the patient would be a candidate for a clinical study, the patient could be streamlined through the entry process," Comis said. "It would be easier for the patient to get on a study, easier for the payer to know what kind of study, and easier for the physician, who won't have to spend an undue amount of time on the entry process.

"We hope this will lead to an increase in the number of cancer patients on clinical studies," Comis said.

There is little data on the frequency that patients are denied entry to trials due to payment issues, Comis said. A recent survey of ECOG physicians found that 25 percent say that dealing with payers and getting patients on trials are major barriers to their participation in research, Comis said.

"There is no question that it has become increasingly difficult for physicians to participate in clinical trials on a national level," Comis said. "All of us do clinical investigation, to some extent, on a margin. The more time you take to put a patient on a study, the more time it takes to monitor data, the more that margin is squeezed."

For the payers, an obstacle to working with the cooperative groups has been the language of clinical trials, Comis said. "Phase I, II, III, IV makes an artificial distinction between what the treatment is," he said. The groups looked for another way to describe what they do.

In their announcements, Security and Mayo said the agreement provides coverage of patient care costs "for studies of leading treatment alternatives."

The groups learned that they have what payers want, Comis said. "In the group system, we have a dynamic treatment strategy for every major cancer, a well-defined package that is agreed upon by the experts," he said. "We have quality control, centralized review, auditing procedures, and we publish and present data. We have all the characteristics that health plans and the payer community are interested in seeing develop."

Last year, the Blue Cross and Blue Shield Association and two pediatric cooperative groups agreed on payment of patient care costs for children in BC/BS plans (**The Cancer Letter**, April 19, 1996).