THE CANCER LETTER

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Turmoil in Texas

DePinho Recommended AVEO Stock on CNBC Six Days After FDA Said New Trial Was Needed

By Paul Goldberg

MD Anderson President Ronald DePinho touted the stock of his biotech on a CNBC show for investors six days after FDA indicated that a long list of fundamental problems had made that company's drug a lost cause.

AVEO Pharmaceuticals Inc., the company DePinho co-founded, met with FDA officials on May 12, 2012, sources in Houston said to The Cancer Letter. At the meeting, agency officials reportedly enumerated a list of problems that would require a new clinical trial to resolve.

Nonetheless, in his appearance on "Closing Bell with Maria Bartiromo" on May 18, DePinho, who at the time served on the company's board of directors, described the AVEO agent tivozanib as a "very effective drug that has a superior safety profile" that constitutes "massive advances in our ability to really do something about a disease that has long been very refractory."

Contacted by The Cancer Letter earlier this week, DePinho said he wasn't aware of FDA's views on the approvability of tivozanib when he appeared on CNBC. "I was not involved with the discussions with FDA," he said to The Cancer Letter. "I suggest you contact AVEO."

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Sequestration

$293 Million NCI Cut To Drop Success Rate

By Matthew Bin Han Ong

NCI Director Harold Varmus announced May 7 that sequestration will decrease the institute's budget by $293 million for the rest of fiscal 2013—a 5.8 percent cut.

"This decrease is attributable in large part to sequestration (a 5.1 percent decline), with the remainder due to further reductions mandated by [the Department of Health and Human Services] to support various departmental obligations," Varmus wrote in an email to grantees and contractors.

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Obituary

Emil Frei, Pioneer of Combination Therapy

Emil "Tom" Frei III, an oncologist who developed the first complete cures for cancers with combination chemotherapy, died April 30 at his home in Oak Park, Ill. He was 89.

Frei was the emeritus director and emeritus physician-in-chief of Dana-Farber Cancer Institute. He previously held senior leadership positions at NCI and MD Anderson Cancer Center.

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TIVO-1 Results Uninterpretable Says FDA in Pre-NDA Meeting

(Continued from page 1)

An AVEO spokesman didn't respond to an email. The company said it wouldn't communicate with investors or the press until July 28, the deadline for FDA to make its decision.

Last week, the FDA Oncologic Drugs Advisory Committee voted 13:1 to recommend against tivozanib's approval for advanced renal cell carcinoma, concurring with FDA that a new clinical trial would be required (The Cancer Letter, May 3).

Tivozanib's problems included a higher overall survival on the comparator arm, which could suggest inferiority. The company failed to convince the committee that the problem was caused by a crossover.

The trial was designed to measure progression-free survival as a primary endpoint, and overall survival as a secondary endpoint. The survival deficit didn't reach statistical significance, but the agency doesn't require statistical significance on safety endpoints.

"A pre-NDA meeting was held in May 2012," FDA said in the briefing document it prepared for the tivozanib application. "Here, the FDA expressed concern about the adverse trend in overall survival in the single phase III trial and recommended that the sponsor conduct a second adequately powered randomized trial in a population comparable to that in the U.S."

The Cancer Letter requested that the agency release the exact date of the pre-NDA meeting, but the agency denied the request.

The question of what DePinho knew—or could have been expected to know—raises a number of concerns, ethicists say. Moreover, the statements DePinho made on CNBC could make him the focus of investigations in suits filed by AVEO's shareholders.

"If you are in the media touting a drug, but you have every reason to think it's not effective and is unlikely to be approved, it may not violate the law, it is a mountain of ethically-suspect behavior," said Arthur Caplan, director of the Division of Medical Ethics and the William F. and Virginia Connolly Mitty Professor of Bioethics at New York University Langone Medical Center.

"You can't put commercial messages out in good conscience, knowing that the regulatory agency is exceedingly unlikely to be satisfied with the data you have submitted on the drug," Caplan said.

"The question starts to become: What is the push to get on the business media to talk about the drug when you have an enormous conflict of interest in terms of your own interests in the drug? Are you the best spokesperson for it? Is that the best role for you to be playing?

"Given other responsibilities and duties, I would say no."

Contacted soon after DePinho's appearance on CNBC, AVEO officials said the MD Anderson president wasn't speaking for the company.

"AVEO had nothing to do with Dr. DePinho getting booked on CNBC," Rob Kloppenburg, AVEO vice president of corporate communications, said at the time. "We think the best thing to do would be to discuss the impetus for the interview with his representatives at MD Anderson."

Contacted by The Cancer Letter at the time, DePinho acknowledged that his stock tip was inconsistent with his role as a state employee (The Cancer Letter, June 1, 2012).

Sources at MD Anderson said DePinho was in frequent contact with AVEO. He was frequently seen wearing a jacket with the company logo, and he talked often about the promise of tivozanib. A sample of the drug was prominently displayed in his office, insiders said.

Clearly, the company would have had the data—including survival data—in time for the May 12 pre-NDA meeting, experts in clinical trials say. These are formal meetings, based on data packets that are submitted to the agency well in advance, usually six weeks to a month before the meeting is scheduled.

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"I can't imagine anyone expecting that a negative trend would flip to the positive side," said an individual with extensive experience in conducting large clinical trials and presenting data to FDA. "FDA has been clear that when PFS is the primary endpoint, all the tendencies of the data must be positive. Neutral might be acceptable if there was a huge toxicity, or some other advantage in addition to PFS."

FDA has the authority to decline to accept a filing.

However, when this happens, the agency's reasons for refusing to file aren't released to the public. In cases where the agency wants to make a point, it accepts the filing and consults ODAC.

Several clinical trialists consulted by The Cancer Letter said they were surprised by the company's claim that the data weren't mature enough for presentation at scientific meetings, including the 2012 annual meeting of the American Society of Clinical Oncology.

"What strikes me most is that senior management waited over two months from May 12 to Aug. 2 to make a formal statement about the issue—while the stock gyrated," an expert in clinical trials said. "Of course, one has to wonder what role the board had in these decisions—hard to imagine that management did this alone."

Patients with advanced renal cell carcinoma usually die quickly, which means that overall survival data don't take long to mature.

Filings show that in 2011, DePinho and Chin sold a substantial amount of AVEO stock—50,000 shares for a total of $770,000—before the projected date of completion of the trial, as noted by www.clinicaltrials.gov.

On May 30, 2012, less than two weeks after his CNBC appearance, DePinho exercised 12,500 shares in the company's stock options for a total of $159,750.

Now, with DePinho off the board, the company no longer discloses his trades. Responding to questions from The Cancer Letter, DePinho acknowledged that he has been selling AVEO stock.

"When I joined MD Anderson, I held board positions and equity stakes in a number of private companies," DePinho said to The Cancer Letter. "In the case of AVEO, I had a 10b5-1 plan in place. Since that time, I have been unwinding those positions by divesting stock, including AVEO, resigning all board positions, and establishing a blind trust to manage any holdings that still remain. Under the UT System conflict of interest plan, I could not acquire additional stock."

The DePinho family's holdings aren't yet in the blind trust that was mandated by the UT System last October, he said.

"I have submitted plans for establishing a blind trust to the UT System, and as soon as final approval is received, intend to transfer to it all of my remaining AVEO equity," he said.

The UT System Chancellor Francisco Cigarroa, said he remains confident in DePinho's leadership.

"The UT System Board of Regents continues to express its confidence and strong support for President Ron DePinho and his leadership of UT MD Anderson," Cigarroa said in a statement.

"The board relies on the chancellor and executive vice chancellor for health affairs to evaluate presidents, and both executive vice chancellor Ken Shine and I are unequivocally united in our support for President DePinho.

"It is our understanding that President DePinho never participated in a meeting between the FDA and AVEO, nor do we have any evidence whatsoever to suggest that he had access to any FDA information at the time of the CNBC interview.

"Today, UT MD Anderson is leading the country's cancer clinical trials with nearly one-third of the 71 FDA approved drugs in testing and development. Under the leadership of President DePinho, UT MD Anderson continues to accelerate progress on working to reduce cancer mortality rates, and we are proud of him and his extraordinary faculty and researchers in their quest to make cancer history."

Matthew Bin Han Ong contributed to this story.

Transaction Date	Options Acquired	Securities Disposed	Proceeds	Total Units Remaining
May 30, 2012	12,500	-	$159,750	-
June 1, 2011	12,500	-	$235,875	-
May 10, 2011	-	10,000	$165,375.5	442,524
April 28, 2011	-	40,000	$604,433	452,524

DePinho and Chin's transactions in AVEO stock. The company has not reported the couple's trades since DePinho stepped off the board Dec. 31, 2012. Chin remains on AVEO's scientific advisory board.

The Tivozanib Timeline

December 2008, May 2009

End-of-phase II meetings between AVEO Pharmaceuticals Inc. and FDA result in agreement concerning the design of the phase III trial of tivozanib for advanced renal cell carcinoma.

During the December 2008 meeting, the agency and AVEO discuss several study designs and FDA states that "a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive may be considered for regulatory decision."

FDA also states that "a statistically significant improvement in OS is not required for regulatory approval, but a pre-specified OS analysis plan is still helpful in the regulatory decision making process."

In the May 2009 meeting, the agency and AVEO discuss the final phase III protocol. Crossover design is not discussed and is not included in the phase III study itself (a later protocol added the crossover). See the FDA briefing documents for ODAC.

According to clinicaltrials.gov, the study's estimated completion date—defined as final collection date for primary outcome measure—is December 2011.

June 9, 2011

Ronald DePinho, co-founder of AVEO and member of the company's board of directors, is named president of MD Anderson Cancer Center. His wife, Lynda Chin, an AVEO co-founder, joins MD Anderson as a senior scientist.

April 16, 2012

AVEO says the TIVO-1 pivotal trial demonstrates tivozanib's safety and efficacy. In a press release, William Slichenmyer, the company's chief medical officer, states: "We believe that the efficacy and safety profile consistently demonstrated by tivozanib and recently validated in our phase III TIVO-1 trial represent an important step forward in the treatment of patients who have advanced RCC. We are pleased with the opportunity to collaborate with tivozanib study investigators on publishing these positive phase II data in the Journal of Clinical Oncology, and look forward to advancing our work with our global partners at Astellas to bring tivozanib to patients who can benefit from this therapy."

April 20, 2012

DePinho asks for a waiver from the UT System to allow him to stay involved in commercial activities. The waiver would cover his service on the board of AVEO (The Cancer Letter, Oct. 26, 2012).

May 12, 2012

At the pre-NDA meeting, FDA officials say the agency "expressed concern about the adverse trend in overall survival in the single phase III trial and recommended that the sponsor conduct a second adequately powered randomized trial in a population comparable to that in the U.S."

According to the agency, the final analysis of OS showed a trend toward a detrimental effect on OS with tivozanib; HR=1.25, p=0.11. Median OS was 28.8 mos. in the tivozanib arm and 29.3 mos. in the sorafenib arm. See the FDA briefing documents for ODAC. The agency declined to release the exact date of the pre-NDA meeting, but sources in Houston say the meeting occurred on May 12, 2012.

May 16, 2012

An AVEO press release states that "overall survival data are not yet mature." The press release reports progression-free survival data: "Based on independent radiological reviews, tivozanib demonstrated a statistically significant improvement in PFS with a median PFS of 11.9 months compared to a median PFS of 9.1 months for sorafenib in the overall (Intent To Treat) study population (HR=0.797, 95% CI 0.639–0.993; P=0.042). Objective response rate for tivozanib was 33 percent compared to 23 percent for sorafenib. The efficacy advantage of tivozanib over sorafenib was consistent across subgroups in the study."

May 18, 2012

DePinho—who, at the time, was on the AVEO board of directors—appears on the CNBC program "Closing Bell with Maria Bartiromo." He recommends investment in the company and its drug, stating that AVEO "has utilized, has exploited science-driven drug discovery, and it's about to announce, or has announced already publicly, and will present in detail at ASCO, a very effective drug that has a superior safety profile for renal cell cancer, a major unmet need. So these are massive advances in our ability to really do something about a disease that has long been very refractory."

The appearance is posted on the CNBC website, and a transcript can be downloaded from The Cancer Letter.

DePinho and his family hold 590,440 shares in AVEO, company filings show. For three days preceding DePinho's appearance on CNBC, AVEO's stock price had been falling, trading at $11.28 per share just before DePinho goes on camera. The DePinhos' holdings are worth $6.66 million.

June 1, 2012

Contacted by The Cancer Letter, DePinho apologizes for praising AVEO stock on the CNBC program. Offering investment advice is inconsistent with his position as an employee of the state of Texas (The Cancer Letter, June 1, 2012). Following DePinho's appearance, the share price started to climb back up, trading at about $12.73 when the market closed on May 31, making the DePinho holdings worth about $7.5 million.

June 2, 2012

At the annual meeting of the American Society of Clinical Oncology, Robert Motzer, an attending physician on the Genitourinary Oncology Service at Memorial Sloan-Kettering Cancer Center and the principal investigator on the study, presents the TIVO-1 data. He says the overall survival data would be presented at a later date.

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Aug. 2, 2012

AVEO acknowledges the survival deficit. A press release contains a "regulatory update," which states:

"The FDA has expressed concern regarding the OS trend in the TIVO-1 trial and has said that it will review these findings at the time of the NDA filing as well as during the review of the NDA. AVEO is conducting additional analyses to be included in the NDA submission that demonstrate that the OS data from TIVO-1 are consistent with improved clinical outcomes in RCC patients receiving more than one line of therapy; analyses that the company believes will directly address this issue. AVEO is continuing to work toward submitting the NDA by end of the third quarter; however, there is a chance that the additional OS analyses may cause the submission to move into the fourth quarter."

Sept. 28, 2012

AVEO submits an application for tivozanib for the treatment of advanced renal cell carcinoma. According to a press release, the application is supported by a single phase III trial, a randomized phase II trial, and an extension/crossover study.

Oct. 10, 2012

DePinho receives a waiver, which enables him to continue to serve on the AVEO board of directors (The Cancer Letter, Oct. 26, 2012). The waiver requires him to place the stocks of AVEO and other firms in a blind trust.

Dec. 20, 2012

AVEO announces that DePinho would step off the board effective Dec. 31, 2012. His wife, Chin, continues to serve on the company's scientific advisory board.

May 2, 2013

ODAC votes 13:1 against approval of tivozanib, concurring with the agency that a deficit in overall survival on the experimental arm is unacceptable (The Cancer Letter, May 3). Post-ODAC, the company is trading at just above around $2.50, which means that if the DePinho holdings in AVEO remained the same, they would be worth less than $1.5 million.

Sequestration

$293 Million Cut to NCI Budget Will Lower Grant Success Rate

(Continued from page 1)

The cuts to NCI exceeded previous estimates by about $74 to $84 million—a sizable reduction, given that the institute has also been losing spending power due to flat budgets and inflation (The Cancer Letter, March 22).

"We can now expect to fund slightly more than 1,000 new and competing grants—less, but only a bit fewer, than the nearly 1,100 funded in each of the past couple of years," Varmus said.

NCI success rates for individuals competing for new research project grants have declined over the last decade from the mid-20s to about 13 or 14 percent in 2011 and 2012 (The Cancer Letter, April 26).

"The already low success rates for grant applicants may decline a small degree, but we believe that we have achieved a fair compromise, given the size of the budget reduction overall, our commitments to current grantees, and our several fixed costs," Varmus wrote.

"Although I recognize that there may be resistance in Congress to returning our budget to FY2012 levels or better, it is encouraging to note that the president has proposed a significant increase above FY2012 for the FY2014 NIH budget."

The text of Varmus's May 7 email follows:

A message that I sent to you in March [The Cancer Letter, March 8] outlined the general approach that the NCI planned to take to absorb an anticipated reduction in our FY2013 budget. At that time, I promised to provide more information once we received firm figures for the remainder of this fiscal year.

Now that the Congress and the Administration (including the Office of Management and Budget, the Department of Health and Human Services, and the NIH Director's Office) have weighed in, the NCI has learned that our budget for the current year will be approximately $4.78 billion, $293 million less than in FY2012, a reduction of 5.8 percent.

This decrease is attributable in large part to sequestration (a 5.1 percent decline), with the remainder due to further reductions mandated by DHHS to support various Departmental obligations.

As in the strategy I outlined previously, we have responded to this situation by reducing funds for virtually all sectors of the NCI portfolio in order to limit the impact of the reductions on the most vulnerable part of the budget—our capacity to issue new and competing research project grants.

This is not easily accomplished. Over 20 percent of our budget is comprised of fixed costs—such as salaries for NCI personnel, rents, utilities, Clinical Center expenses, etc.—and cannot be reduced. (And we have also decided not to reduce salaries for NIH trainees.)

That means that the other components of the budget must absorb the entire reduction, lowering their allocations by an average of over 7 percent.

To do this, we have had to make appreciable reductions in ongoing (non-competing) grants (about 6 percent), centers and other research programs (6.5 percent), and research and development contracts (8.5 percent).

Similar or even larger reductions were applied to

the discretionary parts of other budgets, such as research management and support and the intramural program, in both of which salaries constitute most of the expense.

As a result of these decisions, we can now expect to fund slightly more than 1,000 new and competing grants—less, but only a bit fewer, than the nearly 1,100 funded in each of the past couple of years.

The already low success rates for grant applicants (recently in the range of 13 to 14 percent) may decline a small degree, but we believe that we have achieved a fair compromise, given the size of the budget reduction overall, our commitments to current grantees, and our several fixed costs.

As in past years, a fuller account of the FY2013 budget will soon be posted on the NCI website to provide additional details.

Needless to say, no one at the NCI is happy about these reductions, but they are now unavoidable for FY2013. I believe that our goals should be to manage as best we can within these limits, to use the nearly $4.8 billion at our disposal as effectively as possible to make progress against cancer, and to look for opportunities to improve our fortunes in the next year or two.

Although I recognize that there may be resistance in Congress to returning our budget to FY2012 levels or better, it is encouraging to note that the President has proposed a significant increase above FY2012 for the FY2014 NIH budget.

Those of us who must govern the NCI in this difficult year thank you for your attention to this matter and ask for your support of our efforts to cope with it.

In Brief

AUA and ASTRO Publish Prostate Cancer Guideilnes

THE AMERICAN UROLOGICAL ASSOCIATION released a clinical practice guideline for prostate cancer screening, updating the association's best practice statement on prostate-specific antigen and suggests that the greatest benefit to PSA screening appears to be in men 55 to 69 years old.

The association also published a joint guideline with **The American Society for Radiation Oncology** on radiation therapy after prostatectomy for patients with and without evidence of prostate cancer recurrence.

The PSA guideline was announced during the association's annual meeting in San Diego. It does not address detection of prostate cancer in symptomatic men. The association recommends that men aged 55 to 69 talk with their physician about the benefits and harms of testing and engage in shared decision-making. The guideline recommends screening every two years instead of annually.

The guideline states that PSA screening in men under 40 is not recommended, nor is routine screening in men at average risk who are between the ages of 40 to 54 years. It also recommends against routine PSA screening in men over 70, or any man with less than a 10-15 year life expectancy.

The ASTRO-AUA guideline recommends that physicians offer adjuvant radiation therapy to patients with adverse pathologic findings at the time of prostatectomy because of demonstrated reductions in recurrence and progression.

The guideline also recommends that clinicians define biochemical recurrence as a detectable or rising PSA value after surgery that is ≥ 0.2 ng/ml, with a second confirmatory level of ≥ 0.2 ng/ml; and that clinicians should consider restaging an evaluation in a patient with a PSA recurrence.

The PSA guideline is available on the AUA website, and a PDF of the AUA-ASTRO guideline can be downloaded from the International Journal of Radiation Oncology • Biology • Physics.

Obituary

Emil "Tom" Frei III, Pioneer of Combination Chemotherapy, Dies

(Continued from page 1)

Frei's breakthrough work began in 1955, with his arrival at NCI—he was recruited by the institute's director, Gordon Zubrod, to do research in childhood leukemia. Within a year, he was named chief of the NCI's Leukemia Section and later, chief of medicine.

Dissatisfied with the short-term acute lymphoma leukemia remissions produced by single-drug therapies, Frei and his colleagues began testing combinations of two or more agents to attack multiple aspects of leukemia cell growth.

"It was known that these drugs were cell-killers: some of them were derived from mustard gas," NCI Director Harold Varmus said May 3 to the New York Times. "They were developed initially as toxic agents, not different from drugs that were used in warfare."

With his colleague Emil Freireich, now at MD Anderson, Frei demonstrated that treatment with multiple chemotherapy agents could produce lasting remissions in children with acute lymphocytic leukemia.

At the time, this disease had been uniformly fatal,

and single chemotherapy drugs could only bring it into temporary remission.

By combining as many as four drugs in a five-year treatment plan, Frei and his colleagues had increased the survival rate for pediatric leukemia to about 40 percent by 1965.

"If you give 60 percent of each dose, it's the same as giving 100 percent of one or the other," said Freireich to the New York Times. "But the effect on the tumor is additive."

Today, the long-term survival rate for childhood leukemia is more than 80 percent, and combination chemotherapy is the foundation for treating many adult and pediatric cancers.

The Frei-Freireich collaboration also resolved chemotherapy-induced bleeding with infusions of blood platelets—allowing chemotherapy to be administered safely in larger, more effective doses.

"Dr. Frei and his colleagues saved the lives of literally millions of cancer patients by championing the then novel idea of combination chemotherapy for cancer over 40 years ago, and then developing effective combination regimens for previously incurable cancers," Dana-Farber President Edward Benz said in a statement.

Frei moved to MD Anderson in 1965, where he served as associate scientific director of clinical research and as chair of the Department of Experimental Therapeutics.

In 1972, he joined Dana-Farber as physician-in-chief, succeeding the institute's founder, Sidney Farber. A year later, he became director of Dana-Farber and professor of medicine at Harvard Medical School.

With Dana-Farber colleagues Arthur Skarin and George Canellos, Frei developed a therapy for adults with non-Hodgkin lymphoma—one of the first chemotherapy regimens to produce a significant cure rate for the disease.

He joined fellow Dana-Farber researchers in pioneering the use of chemotherapy, surgery, and radiation therapy as a primary treatment for osteogenic sarcoma, a bone cancer of young adults. In the mid-1970s, he and his associates developed and tested drug combinations that boosted survival rates for breast cancer patients. He also worked with Dana-Farber investigators to pioneer the use of bone marrow transplants for various types of cancers.

"In addition to his pioneering work, Dr. Frei led the Dana-Farber Cancer Institute in its earliest days, nurturing the Institute through a remarkable period of excellence and growth," Benz said. "His leadership was essential in establishing Dana-Farber as one of the world's most outstanding centers for cancer research, prevention, and treatment."

For a generation of workers in the Longwood Medical Area, Frei was a familiar sight, pedaling his bike to and from Dana-Farber.

Frei was born in St. Louis on Feb. 21, 1924, and grew up surrounded by artists and musicians.

His paternal grandfather founded the Emil Frei Art Glass Company in St. Louis, specializing in the design and manufacture of stained-glass windows. This company provided the glass panel in Dana-Farber's Yawkey Center for Cancer Care, which features illustrations of chemical compounds and words like hope, courage, and inspiration.

Frei's interests took a turn for science when, in his early teens, he read a book called Rats, Lice, and History by Hans Zinsser. The book planted the seeds of a lifelong passion for scientific discovery and a career-long search for a cure for cancer.

Drafted for active military duty in 1943 for World War II, Frei served under the V-12 Program until 1945. The U.S. Navy sent him to Colgate University for pre-medical studies.

He was admitted to Yale University Medical School in 1944 and received his MD in 1948. He performed his internship at St. Louis University Hospital and was a commissioned officer in the Navy Medical Corps from 1950-52, serving in Korea.

Over the course of his career, Frei published more than 500 papers in scientific and professional journals and was the recipient of numerous awards and honors. In 1972, he was awarded the Albert Lasker Medical Research Award in recognition of his scientific contributions.

He most recently lived in Chicago.

Frei was married to Elizabeth (Smith) Frei from 1948 until her death in 1986. He later was married to Adoria (Brock) Frei from 1987 until her death in 2009.

Frei is survived by his five children, Mary, Emil (and his wife, Lauren), Alice, Nancy, and Judy (and her husband, Larry Howe), and by 10 grandchildren.

"Tom Frei was one of a handful of physicians who developed combination chemotherapy for cancer and produced the first cures of childhood leukemia," said David Nathan, president of Dana-Farber from 1995 to 2000.

"His was a massive contribution to medicine. Patients and trainees will remember him with deep respect."