

**Off Label Drugs In Cancer Care:
The Truth Is Somewhere In Between**

Len Lichtenfeld, MD, MACP
Deputy Chief Medical Officer
May 21, 2008





The Bottom Line:

Cancer medicine IS an off-label specialty



Then...

- Few drugs
- Almost all intravenous
- Few successes
- No internet
- No outpatient chemotherapy



Now... The Landscape Has Shifted

- Many drugs
- Many combinations
- Targeted therapies
- Oral drugs
- Internet
- Explosion in studies and reports



Off-label, 1977 Vintage

VP-16

Off Label, 2008 Vintage

The screenshot shows a Windows Internet Explorer browser window displaying the Dr. Len's Cancer Blog. The address bar shows the URL <http://www.cancer.org/asp/blog/Comments.aspx?id=196>. The page features the American Cancer Society logo and a navigation menu with links for Home, Community, Get Involved, Donate, Contact Us, and Site Index. A search bar is also present. The main content area displays a blog post titled "ESAs: The Evidence Mounts They May Be Harmful" by Dr. Len Lichtenfeld, posted on 2/26/2008 at 3:59 PM. The post discusses a research paper from the Journal of the American Medical Association regarding erythropoiesis-stimulating agents (ESAs) and their potential harm to cancer patients. The sidebar includes a keyword search box with "Breast Cancer" entered, and a "Recent Entries" section listing posts from 5/16/2008, 5/12/2008, and 5/8/2008. The Windows taskbar at the bottom shows the Start button, several open applications, and the system clock indicating 1:27 PM on Tuesday, 5/20/2008.

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ESAs: The Evidence Mounts They May Be Harmful

Posted on 2/26/2008 3:59 PM by Dr. Len Lichtenfeld

A research paper in today's issue of the [Journal of the American Medical Association](#) provides unfortunately impressive evidence that [erythropoiesis-stimulating agents](#), or ESAs, are in fact dangerous to the health of cancer patients.

The drugs, known by their trade names [Procrit](#) and [Aranesp](#), have been the focus of intense scrutiny by patients, patient advocates, researchers, the press, politicians, the [Centers for Medicare and Medicaid Services](#) and others for much of the past year.

The current report, authored by a group of researchers from many well-regarded universities, shows that without a doubt ESAs lead to a much higher incidence of venous thromboembolism when patients treated with these drugs are compared to those who are not treated with ESAs.

The paper also reports that survival is shortened for cancer patients treated with ESAs, although the results are not quite as dramatic.

ESAs have been important drugs in the treatment of patients with cancer.

They first came to market in the early 1990s. For those of you who aren't familiar with cancer treatment at that time, we had great concerns about the safety of the blood supply. Transfusions will always have risks, but in those years the risks were magnified by the fact

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1:27 PM
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Agreement:

- Oncologists feel the PDR has little or no influence
- The proportion who reports that the PDR is very useful has declined drastically over the past 11 years
- Online access to medical libraries' databases is more credible now than 11 years ago



The Realities:

- Medical knowledge regarding appropriate cancer treatments has exceeded the capabilities of any one physician to keep up to date
- Internet access has increased, as has access to medical information (the ASCO effect)
- However, not all information is readily accessible and it is certainly not well organized



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Herceptin Shows Benefits in Early Stage Breast Cancer

Recurrences Cut in Half, Survival Improved

Article date: 2005/04/27
Herceptin (trastuzumab), a drug used to treat some types of advanced [breast cancer](#), also appears to help some women with early stages of the disease, according to two studies. The results were so promising that the National Cancer Institute (NCI) stopped the research ahead of schedule to make the findings public.



In the studies, women who received [Herceptin](#) along with chemotherapy had half the risk of the cancer returning as women treated only with chemotherapy. They also lived longer.

Even though Herceptin works in only 20% -30% of breast cancers, experts

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ORIGINAL ARTICLE

Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer

Edward H. Romond, M.D., Edith A. Perez, M.D., John Bryant, Ph.D.,
Vera J. Suman, Ph.D., Charles E. Geyer, Jr., M.D., Nancy E. Davidson, M.D.,
Elizabeth Tan-Chiu, M.D., Silvana Martino, D.O., Soonmyung Paik, M.D.,
Peter A. Kaufman, M.D., Sandra M. Swain, M.D., Thomas M. Pisansky, M.D.,
Louis Fehrenbacher, M.D., Leila A. Kutteh, M.D.,
Victor G. Vogel, M.D., Daniel W. Visscher, M.D., Greg Yothers, Ph.D.,
Robert B. Jenkins, M.D., Ph.D., Ann M. Brown, Sc.D., Shaker R. Dakhil, M.D.,
Eleftherios P. Mamounas, M.D., M.P.H., Wilma L. Lingle, Ph.D.,
Pamela M. Klein, M.D., James N. Ingle, M.D., and Norman Wolmark, M.D.



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Who Pays Depends on Who You Are and Where You Live

Posted on 5/4/2006 7:36 PM by Dr. Len Lichtenfeld

[An article in the Wall Street Journal](#) earlier this week caught my attention.

It discussed the current use of the targeted therapy [Herceptin](#) as an adjuvant treatment for breast cancer, and how is faring in the marketplace both in the United States and in Europe.

The article highlighted for me the stark contrasts between how we approach the availability of new medicines and new indications for established medicines in this country and in the rest of the world.

Those differences are real, and have implications for the type of health care and health insurance "system" we are willing to accept in this country.

Herceptin is probably the first real targeted therapy drug. **[It is a drug that, until recently, was used solely to treat women who had recurrent breast cancer, and whose breast cancer tissue contained a gene called "HER 2."](#)** It is a very expensive drug.

February 16, 2006

British Clinic Is Allowed to Deny Medicine

By [SARAH LYALL](#)

LONDON, Feb. 15 — When her local health service refused to treat her [breast cancer](#) with the drug Herceptin, 54-year-old Ann Marie Rogers sued. But on Wednesday, a High Court judge ruled against her.

In his decision the judge, David Bean, said that although he sympathized with Ms. Rogers's predicament, the health service in Swindon, where she lives, had been justified in withholding the drug.

"The question for me is whether Swindon's policy is irrational and thus unlawful," Justice Bean wrote. "I cannot say it is."

The ruling has potentially serious implications for patients across the taxpayer-financed National Health Service.

Despite health officials' contention that decisions about treatment are based solely on clinical effectiveness, critics contend that with drugs growing ever more expensive, cost has become an increasingly important factor. They also say patients are at the mercy of the so-called postcode lottery, in which treatments are available in some postal zones but not others.

"This drug could save the lives of 1,000 women a year," Jeremy Hughes, chief executive of the lobbying group Breakthrough Breast [Cancer](#), said of Herceptin. "It is unfair and cruel for women like Ann Marie Rogers to know that it is money and their postcode that stands between them and this potentially life-saving treatment."

Herceptin, made by Roche, is currently licensed for use in late-stage breast cancer. Although some studies have shown that it is also effective in treating HER-2

Court Backs Briton's Right to a Costly Drug - New York Times - Windows Internet Explorer

http://www.nytimes.com/2006/04/13/world/europe/13britain.html?_r=1&sq=herceptin%20in%20breast%20cancer&st=nyt

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The New York Times
nytimes.com

April 13, 2006

Court Backs Briton's Right to a Costly Drug

By [SARAH LYALL](#)

LONDON, April 12 — An appeals court here declared Wednesday that a local health service had acted illegally in withholding a potentially lifesaving drug from a woman with [breast cancer](#).

The decision, by the Court of Appeal, overturns a lower court ruling and means that the woman, Ann Marie Rogers, will now receive a full course of the drug, Herceptin, from her health service, in Swindon. The ruling has potentially wide implications for breast cancer treatment throughout the taxpayer-financed National Health Service, where the availability of medicines can depend on where people live.

"It's pretty clear that the judgment provides guidance to all N.H.S. authorities," Yogi Amin, a lawyer for Mrs. Rogers, said in an interview. "For patients, it means that if a doctor properly prescribes the drug, the local health authority can't issue a blanket refusal on the grounds of cost or regulatory reasons."

A year's treatment with Herceptin can cost tens of thousands of dollars.

Mrs. Rogers, 54, went to court when her local health service, Swindon Primary Care Trust, refused to treat her breast cancer with Herceptin even after her doctor had prescribed it. The drug, made by Roche, is licensed for use in late-stage breast cancer, but some studies

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FDA Expands the Use of Trastuzumab (Herceptin) for Early Stage Breast Cancer After Primary Therapy

On November 16, 2006, the U.S. Food and Drug Administration granted approval to trastuzumab (Herceptin, Genentech) as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel for the adjuvant treatment of women with node-positive, HER2-overexpressing breast cancer. The approval is based on evidence of a significant prolongation in disease-free survival in women receiving Herceptin and chemotherapy compared to those receiving chemotherapy alone.

An integrated interim analysis of 3752 women from two NCI-Cooperative Group trials (NSABP B31 and NCCTG N9831) were reviewed. Both studies restricted enrollment to women whose breast cancer demonstrated 3+ overexpression by immunohistochemistry or gene amplification (FISH). All women received standard adjuvant chemotherapy [four 21-day cycles of doxorubicin and cyclophosphamide (AC) followed by paclitaxel administered weekly or every 3 weeks for a total of 12 weeks]. As appropriate, women also received hormonal therapy and local radiotherapy. Patients were randomized to receive either no additional therapy or to receive Herceptin at 4 mg/kg on the day of paclitaxel initiation and subsequently at 2 mg/kg weekly for a total of 52 weeks.

Disease-free survival (DFS), defined as the time from randomization to recurrence, occurrence of contralateral breast cancer, other second primary cancer, or death, was the

SFGate.com [Print This Article](#) [Back to Article](#)

More ^{SFGate} good news for Genentech drug Avastin helps those with breast cancer, clinical study shows

Bernadette Tansey, Chronicle Staff Writer
Saturday, April 16, 2005



Genentech Inc.'s pioneering colon cancer drug Avastin, already showing potential as a lung cancer treatment, delivered significant benefits to breast cancer patients in clinical trial results announced Friday by the company and the National Cancer Institute.

In positive data that emerged earlier than expected from the late-stage study, Avastin delayed the worsening of metastatic breast cancer when combined with chemotherapy.

Health experts emphasized that Avastin, a humanized monoclonal antibody, is not a cure for breast cancer. But its ability to control the disease for a longer period is a significant advance, said institute Director Dr. Andrew von Eschenbach.

"This is an important step in our journey to ultimately eliminate the suffering and death due to cancer," he said.

Genentech shares leapt more than 18 percent Friday, gaining \$10.72, or 18.28 percent, to close at \$69.35.

The jump in the share price was the second in just over a month related to the success of Avastin in a major cancer category. On March 14, the South San Francisco biotech giant reported that Avastin lengthened the average survival of lung cancer patients

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Avastin And Breast Cancer: It's Not Over Yet

Posted on 12/6/2007 6:06 PM by Dr. Len Lichtenfeld

The decision yesterday by the [FDA's Oncology Drug Advisory Committee](#) to [recommend that Avastin \(bevacizumab\) not be approved for the treatment of metastatic breast cancer](#) is one more step in a discussion that has significant implications not only for the use of Avastin in breast cancer, but also how this type of decision-making is going to influence cancer treatment in the future.

[Avastin is a type of drug that we call "targeted therapy."](#) These newer drugs generally target a specific process in a cancer cell that can then influence the function of the cell and lead to its death. In the case of Avastin, the targets are the blood vessels that cancers need to grow. Avastin interferes with that process, and has been demonstrated to be effective in a number of cancers, including colon and lung cancers.

[In April, 2005, the National Cancer Institute announced that a clinical trial of Avastin](#) with chemotherapy used in the treatment of women with recurrent breast cancer (compared to a "control" group that received only the chemotherapy) resulted in such positive results that the oversight committee monitoring the study ordered it to be stopped and the results released immediately.

This study showed that women who received the combination therapy extended the time for the cancer to progress by an average of four months, according to one news report. The design of the study had anticipated about two months of improvement.

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Imagine If It Had NOT Been Approved...

The screenshot shows a Windows Internet Explorer browser window displaying the Dr. Len's Cancer Blog. The address bar shows the URL: <http://www.cancer.org/asp/blog/Comments.aspx?id=195>. The page features the American Cancer Society logo and a navigation menu with links for Home, Community, Get Involved, Donate, Contact Us, and Site Index. The main content area displays an article titled "Avastin In Breast Cancer: The FDA's Dilemma" posted on 2/25/2008 at 11:12 AM by Dr. Len Lichtenfeld. The article discusses the FDA's decision to provide accelerated approval for Avastin in the first-line treatment of HER-2 negative metastatic breast cancer. The text includes: "The FDA's decision late Friday afternoon to provide 'accelerated approval' for the use of Avastin in the first line treatment of HER-2 negative metastatic breast cancer was the culmination of a lot of handwringing and head scratching on the part of many people. From my vantage point, the FDA made the right decision in a difficult situation. That said, this is not the end of this story. I have previously written about Avastin and the decision of an FDA advisory panel several months ago to (closely) vote not to approve the drug for this indication. That decision by the panel members had to be a difficult one. Metastatic breast cancer is a disease that is treatable, but not considered curable. Every time we have a new drug that may offer benefit to women in this circumstance, it is important that we make certain that we are providing an effective therapy that will indeed help those in need. The Avastin situation is of interest for a number of reasons. When determining if new cancer drugs are effective, the FDA generally wants to see evidence that the group treated with the drug lives longer than the group that receives the standard therapy. In this case, Avastin was added to the chemotherapy drug Taxol, a well". The browser's taskbar at the bottom shows the start button, several open applications, and the system tray displaying the date and time as 11:38 AM Tuesday 5/20/2008.



Where we are today:

- What will not work is “I am the doctor, I make my own judgments, therefore what I want is what I will do.”
- Individual physician variability/lack of standardization
- There is no nationwide reference for uniform chemotherapy regimens/doses
- Costs are becoming an increasing concern

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Update on survival from the original phase II trial of bevacizumab and irinotecan in recurrent malignant gliomas.

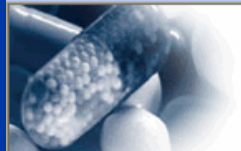
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Meeting: [2008 ASCO Annual Meeting](#)

Abstract No: 2021

Citation: *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 2021)

Author(s): S. A. Wagner, A. Desjardins, D. A. Reardon, J. Marcello, J. E. Herndon, II, J. A. Quinn, J. N. Rich, S. Sathornsumetee, H. S. Friedman, J. J. Vredenburgh

Abstract: **Background:** Recurrent grade III-IV malignant gliomas have a dismal prognosis and effective salvage therapies are limited. **Methods:** From 4/05-2/06, a phase II trial was conducted at Duke University using bevacizumab and irinotecan in patients with recurrent malignant gliomas. 2 cohorts were enrolled that included 33 grade III and 35 grade IV patients. The first cohort received bevacizumab at 10mg/kg plus irinotecan (dose based on patient's anticonvulsant) every two weeks. The second cohort received bevacizumab at 15mg/kg every 21 days and irinotecan on days 1, 8, 22, and 29. **Results:** Overall response rates for both grade III and IV were 59% (grade III 61%, grade IV 57%). 6 month PFS and OS for grade III were 59% and 79% and for grade IV 43% and 74% respectively. In 12/07, we evaluated all patients enrolled in the trial to determine the 2 yr OS. From the 2 cohorts, 22% (15/68) of the patients are still alive (11 grade III, 4 grade IV). For the grade IV patients, the 2yr OS is 15%. All four of the grade IV patients completed 9 cycles of therapy. Two (2/4) progressed (8mo and 17mo) and both reinitiated bevacizumab and irinotecan with radiographic response. The other two have been progression free since the end of treatment (11mo and 18mo). Surprisingly, both of these patients had only partial resections at the time of diagnosis. For the grade III patients, the 2 yr OS is 33%. All but one patient has progressed; ranging from 1 to 14 months. 4 patients are currently on bevacizumab-based therapy. 1 on carboplatin, 2 on etoposide and 1 on bevacizumab alone for radiation necrosis. The remaining patients are on metronomic temozolomide (2), etoposide (1), and a phase I clinical trial (2). 2 patients are currently being followed off therapy. The one patient who did not progress only received a partial cycle on study and had to discontinue secondary to TTP and has been off treatment for the last 21 months. **Conclusions:** The combination of bevacizumab and irinotecan provides a clinically meaningful treatment option for patients with recurrent malignant gliomas.



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Bevacizumab



Agent	Brand Name(s)	Disease	Pharmacologic Class	Histology	FDA Disease Indication attention to boxed warning(s).	Route(s)	ICD-9 Code	NCCN Recommended Use	NCCN Category
Bevacizumab				High-grade gliomas; Glioblastoma multiforme	Bevacizumab, in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for first-line or second-line treatment of patients with metastatic carcinoma of the colon or rectum. Bevacizumab, in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer. Bevacizumab, in combination with paclitaxel is indicated for the treatment of patients	IV	191.0-191.9	Recurrence or palliative therapy in 2A combination with irinotecan for glioblastoma multiforme for the following indications: <ul style="list-style-type: none"> diffuse or multiple recurrent disease resectable local recurrent disease without carmustine polymer unresectable local recurrent disease 	

Thank you!

