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## *In the Know*

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**June 2006**

from

**The Duke Patient/Family Resource Center**

The Duke Patient/Family Resource Center is

- A lending library offering books, audio and video tapes, magazines and free brochures dealing with cancer and certain blood disorders and with issues of coping, survivorship, caregiving, and grieving
- Open 8:30 to 5:00 every day the Morris Clinics are open
- Located in the White Zone, first floor, of the Morris Cancer Clinic, Room 15123.
- Our phone number is 919-684-6955. Our email address is [FamilyLibrary@mc.duke.edu](mailto:FamilyLibrary@mc.duke.edu)



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### **Contents:**

#### **Targeted Drugs**

The hoopla these days in the cancer world focuses on the newest generation of cancer treatments known as targeted drugs. Names like Herceptin®, Gleevec®, and Avastin® have already become familiar as their use spreads from breast cancer, leukemia, and colorectal

cancer to a much wider range of cancers. Now the floodgates are opening and drugs like Nexavar® and Sutent® are making headlines in connection with kidney cancer, Rituxin® in connection with lymphoma, and Revlimid® and Velcade® in connection with multiple myeloma. To quote from a recent New York Times article, "About 400 cancer drugs from 178 companies are in clinical trials, according to the Pharmaceutical Research and Manufacturers Association. That is twice the number of drugs in trials for illnesses like [Alzheimer's](#) disease and [depression](#) and nearly three times as many as for heart attack and stroke." [NYTimes June 5, 2006]

What is meant by "targeted," one wonders, and are these drugs doing so well that there should be a flood of them entering into clinical trials? Let's first put them in context.

**Groping vs. targeting.** Start with targeting. All cancer drugs are "targeted" in a sense because all have been selected specifically for their effect on cancer cells. They target the cancer cell, in other words. But for most old line chemotherapies, "selected" is the appropriate term rather than "targeted," because most were groped out in the lab by observing their effects either on tumors in lab rats or on cancer cells in a petri dish. In fact the very first chemo, mustard gas, was discovered inadvertently when those who succumbed after an horrendous harbor explosion involving the gas during WWI were found to have lost most of the white blood cells in their bodies. Aha! thought scientists: Let's try this on leukemia! It worked. Sort of.

As in the case of nitrogen mustard, the derivative of mustard gas, any tested substance with an observed anti-cancer cell effect eventually gets tried on human cancer patients. Refinements follow.

But in no real sense were these earlier drugs *designed* to interfere with cancer in a specific way. In many cases, the actual mechanism of their action was initially unknown. It was enough that they did interfere with cancer cells. Thinking centered around the fact that since not just cancer cells, but all rapidly dividing cells in the body (the linings of the gastrointestinal tract, hair follicles, bone marrow, etc.) were impacted, chemotherapies were going primarily to rapidly dividing cells. In other words, some aspect of cell behavior, such as spending a lot of time in the division process, was being singled out by these drugs.

With the rise of molecular cell biology and the genetic sciences, the interpretation of a drug's effects has shifted dramatically. With new insights into the internal workings of cells and their stored DNA, the mechanism of action of many drugs became a lot more specific. If you google up a chemo drug nowadays, doxorubicin (Adriamycin®) for example, you will find its mechanism of action described in molecular biological language, e.g. "the drug wedges between the bases of DNA and blocks DNA synthesis and transcription." For Taxol® (paclitaxel), "the drug binds to microtubules and prevents their breakdown." In fact I was unable to find older, more primitive explanations of chemotherapy anywhere on the Web.

The same knowledge that made older drugs better understood, has also made possible the rise of designer drugs: drugs specifically designed with a target in mind, something in the workings of cancer cell molecules that can be disrupted so that the progress of the cancer grinds to a halt. These drugs are the truly "targeted" therapies.

**Examples of targeted drugs.** One famous example is Gleevec® (imatinib mesylate), which was designed to treat chronic myeloid leukemia (CML). In CML, a mutation in white blood cells causes two genes normally separate to be fused together. This fused gene in turn produces an aberrant tyrosine kinase receptor. Tyrosine kinase is an enzyme that plays an important role in cell division; there are several different versions of it. Circulating in the body it latches onto "receptors" embedded in white blood cells and in doing so sets off a signal to begin cell division. With an aberrant receptor, unfortunately, the cell receives a continuous signal to divide. Thus more and more white blood cells proliferate in the blood

stream and this is the cancer. Gleevec® intervenes in this process by blocking the aberrant receptor so that it cannot receive any incoming tyrosine kinase. The cell shuts down and even politely commits "cell suicide" (apoptosis), the recourse of a genetically normal cell when it becomes hopelessly damaged.

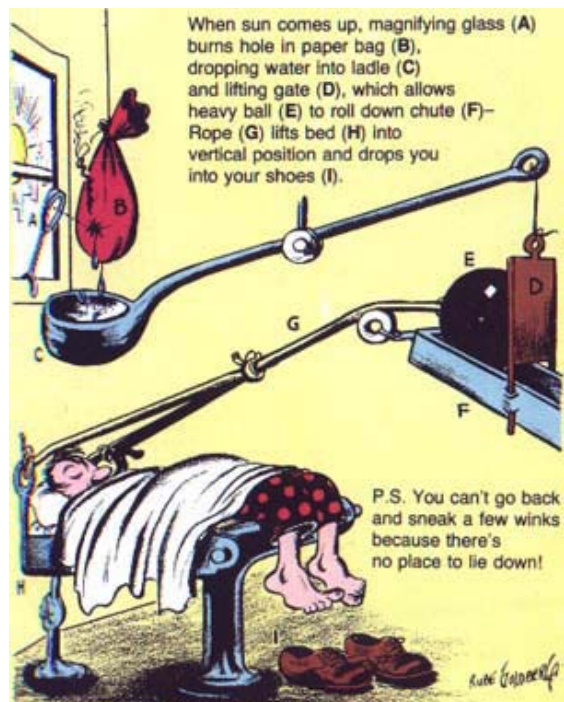
If this receptor blocking trick sounds familiar, it is because there exists an earlier and still standard form of targeting used in regard to the hormone sensitive cancers, like breast cancer and prostate cancer. The sex hormones are "growth factors" for many of the cells in our bodies, those cells related to reproductive function and secondary sex characteristics. The different sites of hormone stimulation, e.g. breast, uterus, testicles, etc. have cell receptors to which the sex hormone attaches, triggering cell division. Normally, we wouldn't want these hormones to be put out of commission.

But certain breast and prostate cancers feed on these hormones, using them to stimulate round-the-clock cell proliferation. In this case, people are quite willing to shut their hormones down. Indeed, one of the main treatments for advanced prostate cancer is sometimes called simply, "the androgen blockade." Androgen is the precursor to testosterone and estrogen. Other types of hormones are used to quell the production of androgen in the man's body, and his subsequent loss of testosterone not only shuts down the majority of those hungry prostate cancer cells but also prevents the bulking up of his muscles and lowers, or even erases, his sex drive. It's a trade-off.

With breast cancer targeting, the design and discovery process followed a slightly different course. Tamoxifen, one of the earliest estrogen interference drugs, sits on and thus blocks the estrogen receptors on breast tissue cells, including breast tissue cancer cells. No estrogen can occupy the blocked receptors, so the signal to go into cell division never arrives. Paradoxically, however, tamoxifen seems to work as well as estrogen in setting off the signal for uterine cells to divide! Each type of sex cell seems to have its own hormone signaling system. Shutting down cancer in one sex cell type might increase the risk of it in another. Drug designers have therefore taken to shutting down estrogen at its source, the precursor molecule androgen. The latest "hormone" drugs for breast cancer, termed "aromatase inhibitors" bind to an enzyme, aromatase, rather than to a receptor, and interfere with the conversion of androgen to estrogen. Femara® (letrozole) and Arimidex® (anastrozole) are examples of aromatase inhibitors.

You can see by this last example that there's still a certain amount of serendipity and groping going on. Even with a designed drug, there can be unexpected bad effects, as when tamoxifen was found to increase the risk of uterine cancer. But there can also be certain unexpected good effects. Herceptin® (trastuzumab), designed merely to target the excessive Her2/neu genes in certain breast tumors, has been found to also act as an angiogenesis inhibitor, blocking the signals that a tumor uses to cause blood vessels to grow toward it and give it a blood supply. This indicates that Herceptin® might be useful in a broader range of cancers. Similarly, Gleevec® was found to interfere with yet another enzyme in a different cancer: gastrointestinal stromal tumor. This rare stomach cancer is now enjoying its first really effective form of treatment.

**Pathways: the underlying concept.** The idea that the life and behavior of all cells is controlled by molecular signaling - within the cell, between cells, and between the cell and its microenvironment - is the master concept underlying the rise of targeted drugs. Cells are viewed as having signaling "pathways." One signal sets off another, which sets off another, etc. in what may seem to be an elaborate Rube Goldberg scheme that eventually arrives at a result. (Some randomly chosen pathway diagrams from Google Images will appear later in this newsletter).



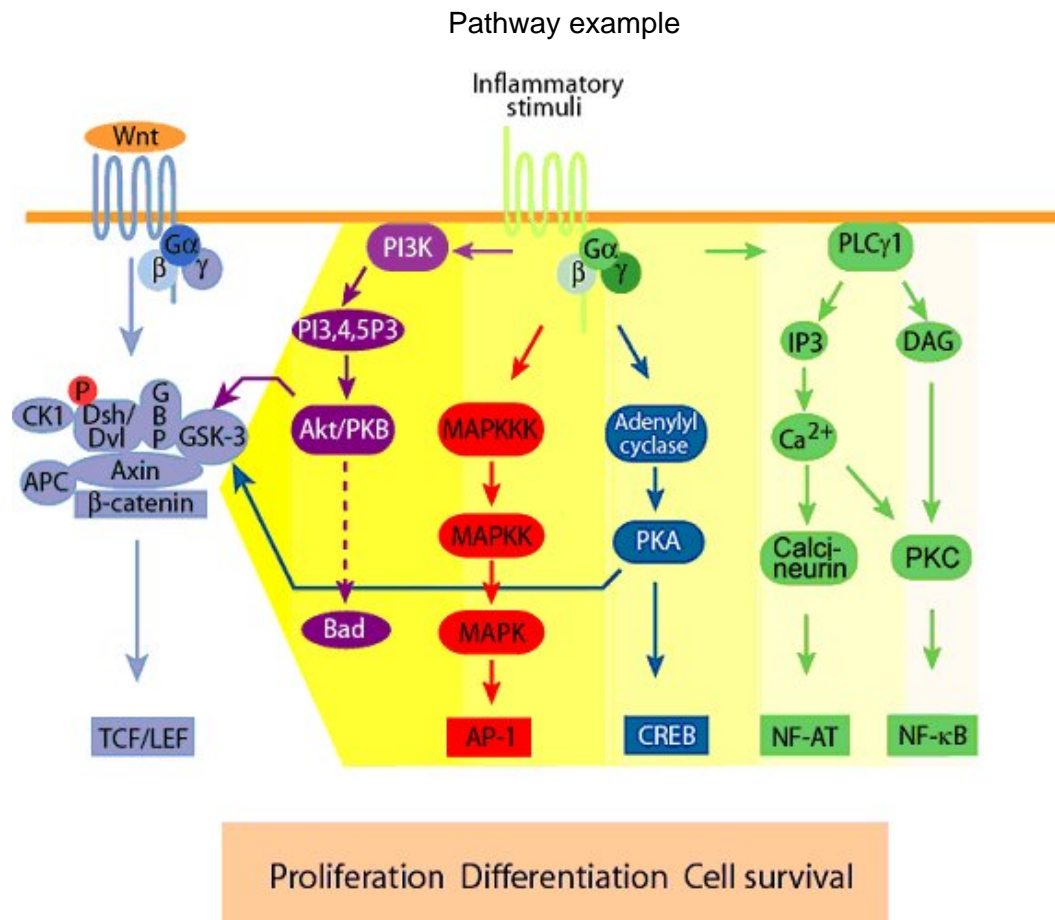
Intervene at any point along a pathway and you alter the results for the entire cell, and perhaps for that cell's neighbors or even for organs distantly located. In fighting cancer, the trick is to find pathways that are being over-utilized by cancer cells or utilized in an aberrant way and aim the drug at the excess or at the aberrance. This way the damage to normal cells is kept to a minimum.

The most heavily targeted pathways are those involved in cell division (e.g. Gleevec®, Herceptin®, tamoxifen), and those involved in signaling blood vessels to grow in the direction of the cancerous cells (Avastin® (bevacizumab), Erbitux® (cetuximab), Tarceva® (erlotinib). Some drugs cover both angles: Herceptin®, apparently. Also Nexavar® (sorafenib), one of the new treatments for renal cell cancer is billed as both a tyrosine kinase inhibitor, and an angiogenesis (blood vessel growth) inhibitor. Another targeting approach involves having the drug latch onto a certain type of cell, and in doing so signal the immune system to attack the cell. One highly effective treatment for B cell lymphoma, Rituxan® (rituximab), binds directly to the B cells and causes the immune system to attack them. Here is a case where the designer drug acts as an artificial immune system, primed to wipe out a cancer.

**Weighing the advantages/drawbacks of targeted drugs:** The most important thing about any new cancer drug is that it fight the cancer more effectively than the pre-existing treatments. Probably the next most important thing is that it be better "tolerated" - i.e. have fewer serious side effects - than pre-existing treatments. These two factors are often weighed against each other. If the drug is substantially effective, patients will put up with side effects, even rather severe ones. If it is only moderately effective, but causes little discomfort and inconvenience, patients will certainly want to try it and doctors to prescribe it. Moderate effectiveness includes holding the cancer steady, even though failing to shrink it. Lastly, if the cancer in question has no very impressive treatment and/or has not responded well to the treatments that do exist for it, patients and their doctors may opt for the new, promising drug.

We need to add one more caveat before working out a report card for the targeted drugs mentioned. Because of the very specific way that targeted drugs attack a cancer, it stands to reason that genetic differences in patients or in patients' tumors (tumors have their own scrambled genetic plan) may influence whether the targeted drug will work. Herceptin®, for

instance, was specifically designed to help breast cancer patients whose tumor "over-expressed" (made too many copies of) the gene for Her2/neu receptors. Only about 30% of breast cancers over-express the Her2/neu gene, but the resulting cancers are unusually aggressive. With the appearance of Herceptin®, these 30% of breast cancer patients started to win back life-span. The remaining 70% of breast cancer patients, however, were not helped by Herceptin®.



Cascade of signals set loose in the WNT pathway as a result of an inflammatory signal. The WNT pathway is associated with several cancers.

**Effectiveness of targeted drugs:** We'll take just the three blockbusters - Gleevec®, Herceptin®, and Avastin®, since they have the longest track records, and report what degree of effectiveness each was found to have against which cancers. What follows will be quotes from the websites devoted to clinical trial results and our comments on these quotes.

#### Herceptin® for Her2/neu positive breast cancer

When used in combination with chemotherapy, Herceptin was shown to improve overall response rates from 29 percent (in women treated with chemotherapy alone) to 45 percent with the addition of Herceptin. The median time to disease progression was increased to 7.2 months in women treated with chemotherapy plus Herceptin compared with 4.5 months in women treated with chemotherapy alone.

When used in combination with paclitaxel, Herceptin was shown to improve overall response rates from 15 percent (in women treated with paclitaxel alone) to 38 percent with the addition of Herceptin. The median time to disease progression was increased from 2.5 months in women receiving paclitaxel alone to 6.7 months in women receiving both paclitaxel and Herceptin.

In a trial evaluating Herceptin alone in women with metastatic breast cancer, 14 percent of women who had failed one or two prior chemotherapy regimens had objective tumor responses with tumor shrinkage of 50 percent or greater in response to Herceptin treatment. Tumor response to Herceptin was also shown to be durable, with a median duration of response of 9.1 months. Median survival in this single-arm study was 13 months.

Remember that "median" means the middle of the range of responses: half of the women in the above trials survived more than 13 months, while half survived less than 13 months. Those who survived more than 13 months would include women who survived for years.

Some may be dismayed to find that usually the targeted drug is being tested in combination with a chemotherapy of some sort, rather than replacing chemotherapy. Partly this is the logic of clinical trials. One does not want to deprive test subjects of at least one part of the current "standard of care" treatment while having them test the new drug. There are no "sugar pills" in cancer drug trials. The so-called placebo is always the treatment that is the standard of care for the day. True, there are some patients for whom taking the new drug solo is medically appropriate, but these are typically in the minority and confining tests to just those patients would cause the trial to be excessively delayed waiting for enough numbers to give valid results.

Another reason for combinations is that combination treatments - "drug cocktails" - are becoming more common as the standard of care in every area of cancer. In essence, hitting the cancer from two or more directions simultaneously is a more effective way of beating it back. With the targeted drugs often having fewer severe side effects, they can be combined more readily into one-two punch combination therapies. Indeed, after the trials are finished, it will usually be the winning "cocktail" that becomes the new standard of care for medically appropriate patients rather than just the new drug by itself. In the most recent clinical trials on Herceptin®, for example, it is reported that the rate of cancer recurrence was cut by 52% when the drug was paired with one of the standard chemos, like Taxol®.

Even more specific reasoning regarding "cocktails" may emerge as the new drugs mechanisms of action are better understood. As we shall see below, an altered understanding of the mechanisms of action of Avastin® is emerging as different trials continue.

#### Gleevec® on CML

The study--known as the International Randomized Study of Interferon and ST1571[Gleevec]--involved 1,106 patients in 16 countries. Patients were randomly assigned to receive either Gleevec or conventional therapy with interferon and low-dose cytarabine. The research team was led by Stephen G. O'Brien, M.D., of the University of Newcastle in the United Kingdom.

At 18 months of follow-up, 92 percent of patients on Gleevec had no progression of disease, compared with 73.5 percent of patients on conventional therapy. Eighty-five percent of patients on Gleevec had a major cytogenetic response (a significant reduction in the number of cancerous cells), compared with 22 percent of patients on conventional therapy.

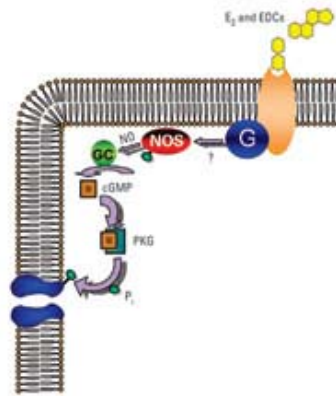
#### Gleevec® on Gastrointestinal Stromal Tumor (GIST)

The study, conducted at four sites in the U.S. and Finland, including Portland, looked at 147 GIST patients who had failed surgical or chemotherapy treatment for the disease and began taking Gleevec. Within weeks to months, 53.7 percent of patients had a partial response, including shrinkage of tumors, and another 27.9 percent of patients had no further progression of the disease.

"In essence, three-quarters of patients in this study were doing better, a remarkable result considering that this type of cancer typically ravishes the body very quickly and kills patients within months," said co-principal investigator Charles Blanke, M.D., associate professor of medicine in the Oregon Health & Science University School of Medicine and the Portland Veterans Affairs Medical Center.

It needs to be added that the long term follow-up on the Gleevec® trials, the follow-up that would show whether Gleevec® actually prolonged the lives of the tested patients in contrast to earlier therapies, has not to our knowledge been published.

#### Pathway example



Hypothetical model of the molecular pathway involved in E2-induced  $[Ca^{2+}]_i$  regulation in cells.

#### Avastin® on Colorectal Cancer

##### The Study

About 800 patients with previously untreated metastatic colorectal cancer were randomly divided into two groups. One group received IFL (also known as the Saltz regimen) plus bevacizumab [Avastin®] while the other received IFL plus a placebo (a dummy substance). IFL consists of irinotecan, 5-fluorouracil (5-FU), and leucovorin.

##### Results

Patients who received IFL plus bevacizumab survived a median of 20.3 months while those on IFL plus placebo had a median survival of 15.6 months. Cancer did not progress for a median of 10.6 months in the bevacizumab group compared to 6.2 months in the other group. Tumors shrank by at least half in 45 percent of the patients who received bevacizumab versus 35 percent in the other group.

"This is the first phase III trial of an anti-angiogenesis strategy to treat human cancer," said lead investigator Herbert Hurwitz, M.D., of Duke University Medical Center. "The results are clinically meaningful."

Here we are looking at an even more impressive survival advantage than that of Herceptin® with metastatic breast cancer. Avastin® is one of the first tested of the "anti-angiogenesis" drugs. It targets one of the factors, VEGF, that tumors employ to signal to the vascular system to send new blood vessels growing toward the tumors. Without the ability to recruit a blood supply, the typical tumor stalls in its growth and stays quite tiny.

Over the course of trials of Avastin® in combination with different chemotherapies,

however, it appears that Avastin® greatly increases the usual killing effect of the chemotherapy with which it is paired. Since the chemo is arriving at the tumor through the blood vessels, this effect could not be obtained if Avastin® immediately shut down the tumor's blood supply. It is possible that initially, and for a short while, Avastin® actually enhances the tumor's blood supply! All the more reason for always pairing it with a chemotherapy.

With these three targeted drugs, we are seeing quite encouraging effectiveness stories, though not as encouraging as the over-excited media reported when the first trials were completed. Two of them, however, Herceptin® and Avastin®, will probably always be paired with a chemotherapy, at least for the initial rounds of treatment, thus the day has not yet dawned when we can consign those harsh chemotherapies to the dustbin of history. These means that whatever side effects the new drug has will be added to the side effects of its chemo partner, or partners, in a complex mixture.

**Side effects of targeted drugs.** If the media led you to believe that targeted drugs have no side effects, well guess again. There may be some and some may even be quite serious. Breastcancer.org, for instance, gives the following portrait of Herceptin® side effects:

Herceptin causes flu-like symptoms in about 40% of the women who take it. These symptoms may include fever, chills, muscle aches, or nausea. These side effects generally become less severe after the first treatment. Other side effects, including low white or red blood cell counts, diarrhea, and infections, are seen in some women receiving Herceptin in combination with chemotherapy, but are rarely seen in women taking Herceptin alone.

#### Serious heart side effects

Less commonly, Herceptin can damage the heart's ability to pump blood effectively. Find out more about the benefits and side effects of Herceptin. Rarely (about 5% of the time), the heart damage is bad enough that women experience stroke or life-threatening congestive heart failure—a condition in which the heart can't pump effectively. Slightly more often (about 7% of the time), Herceptin causes mild heart failure.

Women who experience mild or more serious heart damage can stop taking Herceptin and start taking heart-strengthening medications. This often brings heart function back to normal.

One chemo with which Herceptin® is almost never paired nowadays is doxorubicin (Adriamycin®) because this particular chemo is itself associated with heart damage.

On the side effects of Gleevec®, Novartis, the drug maker reports:

Of the approximately 1700 patients in these studies, the most common side effects were [fluid retention](#) (swelling around the eyes or legs) (54%-76%), [diarrhea](#) (30%-60%), [nausea](#) (43%-73%), vomiting (15%-58%), fatigue (30%-48%), [muscle cramps](#) (28%-62%), [muscle or bone pain](#) (11%-49%), abdominal pain (23%-27%), and [rash](#) (26%-47%). In most cases, these side effects were managed with other medications without having to reduce the dose of Gleevec or stop treatment. In a small percentage of patients with side effects, the dose of Gleevec was reduced or treatment was stopped temporarily. Discontinuation of Gleevec therapy because of side effects occurred in 4% to 8% of patients.

[http://www.gleevec.com/info/page/safety\\_info](http://www.gleevec.com/info/page/safety_info)

Finally, Avastin® which is typically combined with one or more chemotherapies, produces a range of side effects that include hypertension, blood clots, bowel perforation, and insidious kidney damage. RXList.com put together the following table on Avastin side effects. It compares the control group patients (Arm 1) of all trials with the Avastin® receiving group of patients (Arm 2). The comparison is only of the more serious - Grade 3-4 - "adverse events" that appeared in the trials. For example, among patients receiving only chemo, 74% experienced adverse events. A rocky road already. Adding in Avastin®, we find that 87% experienced adverse events.

[http://www.rxlist.com/cgi/generic3/avastin\\_ad.htm](http://www.rxlist.com/cgi/generic3/avastin_ad.htm)

<b>Table 4 NCI-CTC Grade 3 and 4 Adverse Events in Study 1 (Occurring at Higher Incidence (<math>\geq 2\%</math>) in AVASTIN vs. Control)</b>		
	Arm 1 IFL+Placebo(n=396)	Arm2 IFL+AVASTI (n=392)
<b>Grade 3-4 Events</b>	295 (74%)	340 (87%)
<b>Body as a Whole</b>		
Asthenia	28 (7%)	38 (10%)
Abdominal Pain	20 (5%)	32 (8%)
Pain	21 (5%)	30 (8%)
<b>Cardiovascular</b>		
Deep Vein Thrombosis	19 (5%)	34 (9%)
Hypertension	10 (2%)	46 (12%)
Intra-Abdominal Thrombosis	5 (1%)	13 (3%)
Syncope	4 (1%)	11 (3%)
<b>Digestive</b>		
Diarrhea	99 (25%)	133 (34%)

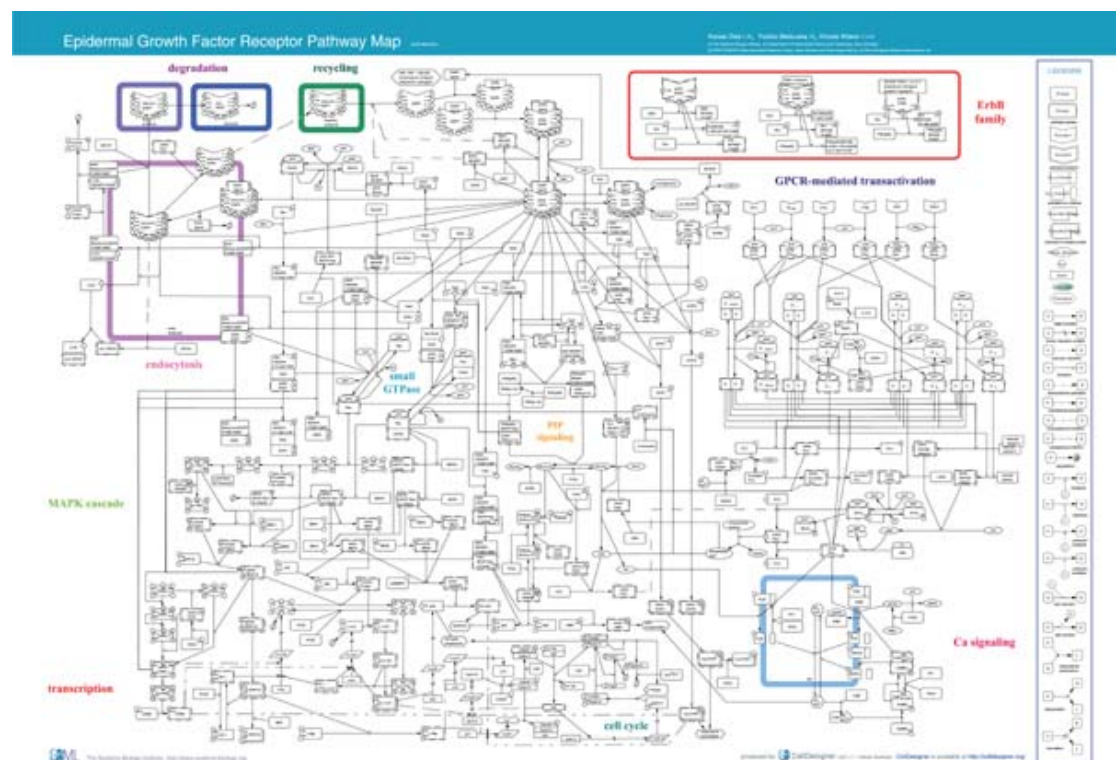
Constipation	9 (2%)	14 (4%)
<b>Hemic/Lymphatic</b>		
Leukopenia	122 (31%)	145 (37%)
Neutropenia"	41 (14%)	58 (21%)
<p><sup>a</sup> Central laboratories were collected on Days 1 and 21 of each cycle. Neutrophil counts are available in 303 patients in Arm 1 and 276 in Arm 2.</p>		

The National Cancer Institute says of Avastin®, "It is important to note that there are general toxicities associated with bevacizumab therapy, including bleeding, arterial clots (which could lead to stroke and heart attack), bowel perforation, wound healing difficulties, and hypertension."

Bear in mind that the targeting of the particular cell pathway that cancer cells are over-using or abusing will to some extent effect normal cells as well. Normal tissues of the body, if wounded, will need to produce new vascularization so that wound healing can take place. If the patient is on Avastin®, this becomes more difficult (though not impossible).

Moreover, any given molecular pathway could underlie an important biological function that scientists did not realize was involved. The suspicion now is that VEGF, the blood vessel growth factor targeted by Avastin®, may also have the additional function of tidying up existing blood vessels so that clots do not form. Blocking it thus makes the patient more clot prone. The pathway diagram below gives you a hint of how complex these situations can be.

### Pathway example



The epidermal growth factor pathway is the target of several new cancer drugs, Erbitux® being one example.

**Can targeted drugs hold the cancer in check forever?** Those who support the model of cancer as an (almost) manageable chronic disease, like diabetes, are prone to argue that one of these days there will be pills we pop every morning that keep our cancer from bothering us as we go about our lives. The cancer may be still there, but it is held in check in the same way that drugs nowadays can hold off the ravages of diabetes or atherosclerosis, or even HIV. Indeed with every improvement in cancer treatment buying more time for patients with metastatic disease, it would seem we are moving steadily toward the manageable chronic disease situation.

But there is one big fly in the ointment when it comes to cancer, which is that cancer itself is an evolving entity. Cancer cells regularly reproduce mutated, imperfect, copies of themselves, causing the tumor burden in the patient's body to become more and more genetically diverse. Genetic diversity is what keeps saving the cancer from extinction. There will always be a cell or two left in the patient's body after treatment that, because of its genetic uniqueness, did not succumb to the chemo or the radiation. The unique cell then becomes the mother of a new line of treatment resistant tumors.

This problem has not been solved by the targeted drugs. A pathway or two may be blocked, but there are always others. Science writer Sharon Begley, writing on targeted drugs, remarks that "tumors seem to have more pathways than field mice in a meadow." [Wall St. Journal, Sept 10, 2004] So, indeed, there are targeted drug failures that started out as targeted drug successes. The tumors seem to find another growth factor, or blood vessel signaler, to turn to in their onward march and after a while scans start revealing that some of the tumors are beginning to expand again rather than to shrink. One must take into account also that a side effect such as hypertension or kidney damage, can build up to life-threatening levels over time and require that the drug be discontinued. In any case, the day will come when the targeted drug becomes a spent bullet just like a standard chemo.

This so far being the case, the world has not yet had to come to grips with the full implications of maintaining millions of people for years and years on drugs that cost \$100,000 per year, or more. That pill you pop every morning to keep your cancer in check, if it ever arrives, had better cost less than three bucks a pop.

What the targeted drugs are offering, and this not to be sneered at, is greater flexibility and more options in tailoring treatment to maximum effect, whether this be prolonging the lives of patients with metastatic disease or actually extinguishing a cancer caught early and still genetically uncomplicated. The more leeway the oncologist has to hit the cancer from several directions at once, the more likelihood that a success will be achieved. The biggest impact by these new drugs on the cancer mortality rate will probably begin to show up when the drugs have gone beyond their initial careers as tumor-shrinkers in patients with metastatic disease and become recurrence-preventers for patients with early-stage disease. Herceptin® may be paving the way in this regard. (See below)

**Expanding the big four into new areas.** Avastin® is now in trials for breast cancer, kidney cancer, lung cancer, ovarian cancer and pancreatic cancer. It flunked initial trials on ovarian cancer and breast cancer, but with altered methodology, it is now considered promising for these cancers once again. Herceptin® is now in trials for early breast cancer and is showing considerable effectiveness in forestalling recurrence. It has been tried on certain lung cancers and salivary gland cancer without effect. Gleevec® is in trials for other leukemias, metastatic breast cancer, advanced small cell lung cancer, kidney cancer, pancreatic cancer, sarcoma,

glioblastoma, chordoma, hypereosinophilic syndrome, and for certain types of thyroid and thymic cancers. Rituxan® is in trials for other lymphomas and is enjoying a new career against auto-immune diseases, where it is in trials for rheumatoid arthritis.

**Other named targeted drugs effective against cancer.** The following is a list of other targeted drugs that are far enough down the pipeline to have names instead of numbers and that have shown efficacy against some cancers.

- Erbitux® (cetuximab). Approved for metastatic colorectal cancers and for squamous cell head-neck cancer. In trials for pancreatic cancer, non-small cell lung cancer, and other head-neck cancers.
- Tarceva® (erlotinib). Approved for some non-small cell lung cancers and metastatic pancreatic cancer. In trials for adenocarcinoma of the lung, kidney cancer, colorectal cancer, pancreatic cancer, ovarian cancer, head-neck cancer, and glioblastoma multiforme (a deadly brain cancer).
- Iressa® (gefitinib). Approved for certain types of non-small cell lung cancer. In further trials for lung cancer and for head-neck cancer.
- Sutent® (sunitinib). Approved for kidney cancer and as second line treatment of GIST in patients for whom Gleevec® failed. In further trials for kidney cancer, and for cancers associated with Von-Hippel-Lindau syndrome (a genetic proneness to certain cancers).
- Nexavar® (sorafenib). Approved for kidney cancer. In trials for melanoma, primary liver cancer, non-small cell lung cancer, certain leukemias, and a wide range of adult solid tumors.
- Velcade® (bortezomib). Approved for multiple myeloma that has not responded to other treatments.
- Campath® (alemtuzumab). It is mainly used to treat people with B-cell chronic lymphocytic leukemia (CLL). It is sometimes used as part of research trials to treat other types of leukemia.
- Bexxar® (tositumomab). Approved for non-Hodgkin's lymphoma that has not responded to other treatments.
- Zevalin® (ibritumomab). Approved for non-Hodgkin's lymphoma that has not responded to other treatments.
- Tykerb® (lapatinib). Just emerging from clinical trials on Her2/neu positive breast cancer, and expected to be a backup drug when Herceptin® fails.

**Summarizing.** The targeted drugs signal a new, more promising era in cancer treatment, including new hope for patients suffering from rare and poorly understood cancers. One should not expect that these drugs will be free of the problems associated with most earlier treatments, i.e. side effects and the rise of drug resistance in one's cancer. Nor do they mean that we have seen the last of the older style chemotherapies, because some of these are experiencing a new career as combination partners with the new targeted drugs. However, with the added flexibility that these drugs offer the oncologist, and with this, the increased chance of extinguishing early-caught cancers, it seems likely that the cancer mortality rate will begin to drop on many fronts.

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