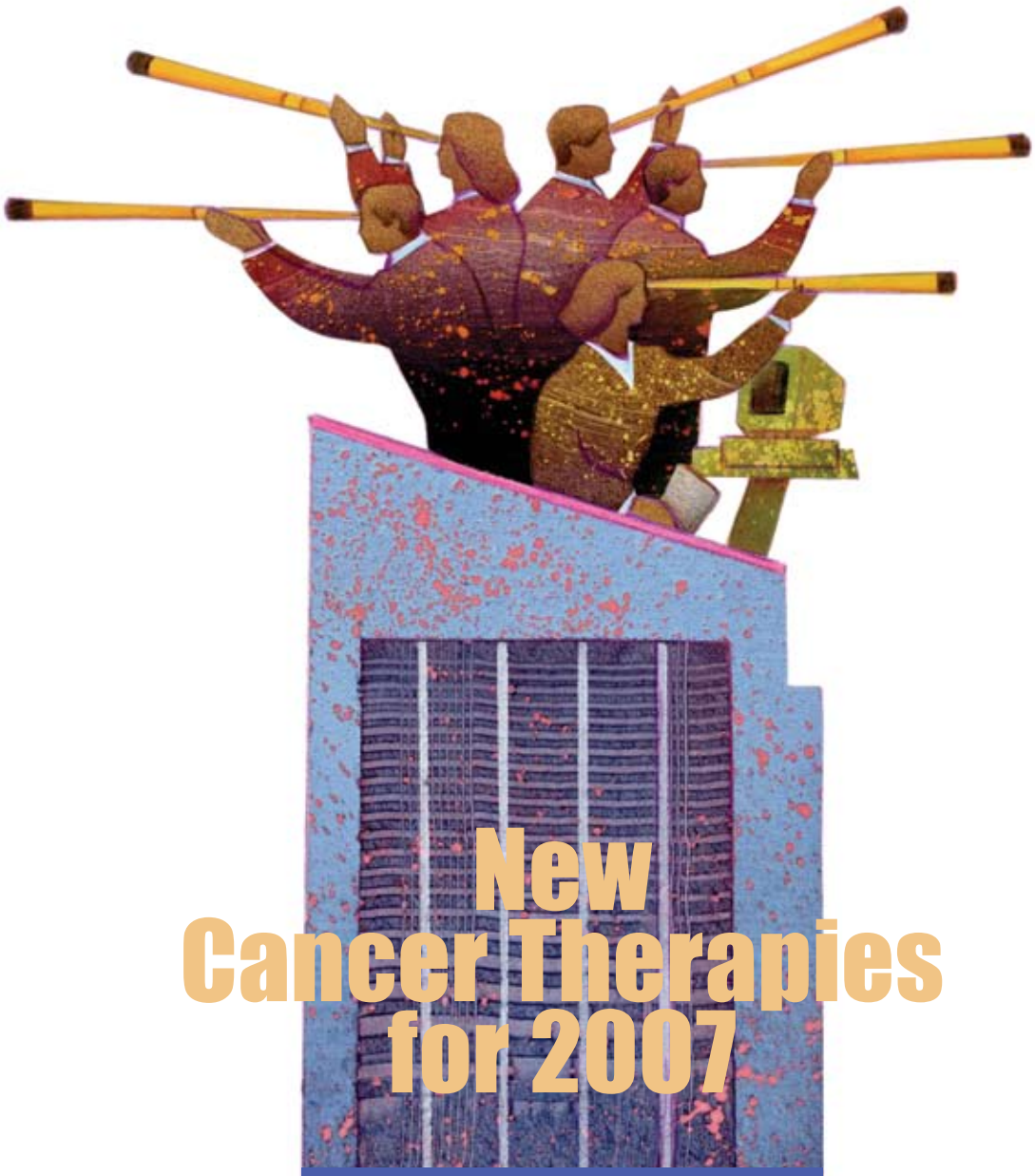

New Cancer Therapies for 2007

Looking to the Future

by Byron Peters, RPh

We are living in an era of exciting drug development for cancer therapies. As 2007 unfolds, we will likely see another year in which breakthrough anticancer therapies will reach the market. These emerging new cancer therapies may include new uses and/or roles for existing therapies, new dosages and/or new delivery methods of existing therapies, new formulations of existing agents, and, of course, new compounds. All of these agents will have an impact on the world of oncology and cancer care. This impact will be felt by numerous groups, including providers (oncologists, nurses, pharmacists), oncology administrators and practice managers, payers, pharmaceutical companies, and, most important, by patients with cancer.

The approval process of the Food and Drug Administration (FDA) is a critical element in determining which therapies will come to market in 2007 and which agents will not. Some of the new therapies may qualify for FDA "fast track" designation allowing them to receive approval sooner. Despite the frequent criticisms voiced against the FDA and complaints that its approval process takes too long to bring new therapies to the market, patients in the United States still tend to have an advantage over their European counterparts. A recent report revealed that Europeans wait longer for new cancer therapies to be approved than Americans. In some cases, that wait can be four times as long.[1]

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Although it is impossible to know for certain which drugs in clinical trials will receive FDA approval in 2007, three facts can be ascertained:

- Recently approved agents will continue to increase in usage in 2007
- Recently approved agents will find new roles expanding their use in patients
- Some anticancer drug therapies that are in clinical trials will receive FDA approval.

One way to predict which anticancer therapies will be new or "popular" in 2007 is to look at some of the recently approved oncology agents and the types of therapies they represent. Recent FDA approvals fall into two main categories of anticancer therapies: traditional cytotoxic agents and newer targeted therapies.

Cytoxic Agents

An example of a traditional cytotoxic chemotherapy drug recently approved by the FDA is decitabine (Dacogen®). An analogue of the natural nucleoside 2'-deoxycytidine, decitabine is believed to exert its antineoplastic effects via hypomethylation of DNA and inhibition of DNA methyltransferase.[2] Decitabine is indicated for patients with myelodysplastic syndrome, whether previously treated or not. Although the FDA considers myelodysplastic syndrome a rare disease, in the last five to ten years the number of cases in the United States has tripled to nearly 30,000 per year.[3] The approved dose of decitabine is 15 mg/m^2 IV over 3 hours, repeated every 8 hours for 3 days. Another emerging popular dose of decitabine is 20 mg/m^2 IV over 1 hour, once a day for 5 days.[4] This cytotoxic drug should continue to increase in use in 2007.

Another cytotoxic drug that recently received FDA approval is nelarabine (Arranon®). Nelarabine is a pro-drug of the deoxyguanosine analogue ara-G and undergoes several reactions until it is converted to ara-GTP. Accumulation of ara-GTP in leukemic blasts leads to inhibition of DNA synthesis and cell death.[5] Nelarabine is indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma who have not responded to or who have relapsed following treatment with at least two chemotherapy regimens. The recommended adult dose of nelarabine is 1,500 mg/m^2 IV over 2 hours on days 1, 3, and 5 repeated every 21 days. Nelarabine represents a new alternative for patients suffering from these diseases.

While traditional cytotoxic drugs have been responsible for significant cures and effective disease management in cancer patients for years and will remain an important weapon in the oncologists' arsenal, increasing knowledge about the biology of cancer at the cellular level has helped researchers identify key cellular targets. The identification of these targets has, in turn, helped spur the development of drugs focused at these targets, known as "targeted therapies."

Targeted Therapies

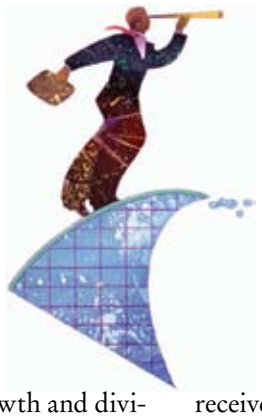
Targeted cancer therapies use drugs that block the growth and spread of cancer cells by interfering with specific molecules that are responsible to some degree for tumor growth and/or tumor spread. (Typically, this "interference" occurs either inside the cell or on the surface of the cell.) By focusing on a very specific target (or molecular target), the hope is that these therapies may prove more efficacious than traditional cytotoxics. A targeted approach is likely to result in less systemic toxicity and fewer side effects compared to traditional chemotherapy drugs. With the hope of fewer side effects, comes the expectation that these new drugs may result in therapies that are better tolerated, potentially having a positive impact on the patient's quality of life. (Note, however, that targeted therapies can also have severe side effects for patients.)

Targeted therapies may not always be used as "replacement therapy" for existing drugs, but rather, these agents may be used as adjunctive therapy. Thus, targeted therapy anticancer drugs are being studied in clinical trials as single agents (alone), or in combination with cytotoxic chemotherapy, or with other targeted therapy drugs. Targeted therapies may be administered in a sequence or they may be given all together.

In addition to the pharmacologic benefits these drugs may offer patients, many targeted therapies are being formulated as oral agents for patient convenience. A look at the current clinical development pipeline for breast cancer drugs shows how popular targeted therapies have become. Of the breast cancer drugs in development, 68 percent are targeted therapies, 22 percent are cytotoxic agents, and 10 percent are hormonal agents.

Although many different types of targeted therapies have either received FDA approval or are in various stages of research development, these new agents have some common characteristics. Specifically, these drugs have been shown to interfere with the growth and division of cancer cells through varied mechanisms and at various stages in the growth, development, and spread of cancer. Some of these mechanisms involve various signaling processes while others involve certain proteins. Targeted therapies fall into two major categories (each with subtypes): those that focus on *internal* components and functions of cancer cells, and those that focus their effects *outside* of cancer cells and target receptors on the cell's surface.

The "internal" group contains many subtypes, which are categorized by their specific cellular effects. Both groups



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have demonstrated success inhibiting cell growth and division, as well as interfering with the spread of cancer mediated by angiogenesis (the formation of new blood vessels). This process provides cancer cells with oxygen and certain nutrients, contributing to the spread of cancer cells that will invade surrounding tissue. The result is metastatic disease, which carries with it a poor prognosis for the patient. Targeted therapies that block or inhibit angiogenesis are known as anti-angiogenesis agents.[6]

Internal Approach

Signal transduction within the cell is an important process that facilitates cell proliferation, differentiation, and apoptosis. Targeted therapies that interfere with the signaling pathway are called signal transduction inhibitors (STIs). Tyrosine kinases are a group of enzymes that play a critical role in maintaining cell growth and differentiation via the signaling pathway in normal cells. When mutations occur within the tyrosine kinases, however, these enzymes may play an important role in the pathogenesis of cancer.[7] Targeted therapies that act against these enzymes are known as tyrosine kinase inhibitors (TKIs).

As a result of the Human Genome Project, more than 90 tyrosine kinases have been identified. The human epidermal growth factor receptor (HER) family of receptor tyrosine kinases is made up of four types of receptors:[8]

1. Epidermal growth factor receptor (EGFR), also known as HER1 or ErbB1
2. HER2, also known as ErbB2 or neu
3. HER3, also called ErbB3
4. HER4, which is referred to as ErbB4.

Low-molecular-weight tyrosine kinase inhibitors (also known as small-molecule inhibitors) have been shown to be very effective antitumor agents. Several of these small-molecule TKIs have demonstrated very good oral bioavailability and thus have been formulated into oral targeted therapies. Overall, these oral agents have been well tolerated by patients. The small size of these molecules may allow them to find their way into hard to reach locations making them attractive choices for some diseases. Researchers are also developing TKIs that target two receptors instead of one. These compounds are referred to as "dual TKIs."

The FDA has recently approved several small-molecule TKIs. The most recent of these is dasatinib (Sprycel®), which is an oral inhibitor of multiple kinases. Dasatinib is approved for treating adults in all phases of chronic myeloid leukemia with resistance or intolerance to imatinib or other therapy. Dasatinib is also approved for adults with Philadelphia chromosome positive acute lymphoblastic leukemia who are resistant or intolerant to prior therapy.[9] Another new oral TKI is sorafenib (Nexavar®), which received FDA approval for advanced renal cell carcinoma. Clinical trials of sorafenib demonstrated a progression-free survival that was twice as long compared to placebo.[10] Sunitinib (Sutent®) is yet another TKI that is approved for advanced renal cell carcinoma and for the treatment of gastrointestinal stromal tumors at a dose of 50 mg per day. Sunitinib has been shown to reduce tumor cell proliferation and inhibit angiogenesis.

Other TKIs that have received FDA approval include:

- Imatinib (Gleevec®) for the treatment of Ph+ chronic myelogenous leukemia and gastrointestinal stromal tumors
- Gefitinib (Iressa®) for the treatment of metastatic non-small cell lung cancer
- Erlotinib (Tarceva®), a dual TKI recently approved for second-line treatment of NSCLC and first-line treatment of pancreatic cancer when combined with gemcitabine.

Another group of chemotherapy drugs that exert an "internal approach" to attacking cancer cells are the drugs that induce apoptosis. Usually, cell death is accomplished by interfering with various proteins and special enzymes known as proteosomes. One recently approved targeted therapy that inhibits proteosomes is bortezomib (Velcade®). Bortezomib is FDA approved to treat multiple myeloma patients who have failed to respond to other therapies.[11]

External Approach

The "external" approach of targeted therapies usually involves targeting key antigens on the surface of various cancer cells. This method is best accomplished through the use of monoclonal antibodies that have been created specific to various antigens found on the surface of certain cancer cells. Inhibition of these cell-surface receptors can lead to disruption of the cellular signal transduction pathway that can stop tumor cell growth. In addition, the effects against these cell-surface growth factors can prevent the growth and spread of cancer cells. Monoclonal antibodies are sometimes used in combination with anticancer drugs, radioisotopes, or other toxins. Lastly, monoclonal antibodies may also help to enhance a patient's immune response to cancer.

Over the past two decades, tremendous advances have occurred in the development of monoclonal antibodies for cancer chemotherapeutic agents. Scientists have now developed fully humanized monoclonal antibodies using transgenic mice. This advance has virtually eliminated immunogenicity issues with monoclonal antibodies and dramatically reduced the incidence of infusion-related reactions from monoclonal antibodies in clinical practice. In 2007, we will likely see an increase in the number of fully humanized monoclonal antibodies that reach the market as targeted therapies for cancer.

A number of new traditional cytotoxics show promise for the treatment of cancer.

In the targeted approach to managing cancer, monoclonal antibodies continue to pay a key role. Some popular monoclonal antibodies for cancer treatment that have received FDA approval include:

- Panitumumab (Vectibix®) is the most recent monoclonal antibody directed against EGFR, to receive FDA approval. The drug is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma, however, it is a fully humanized monoclonal antibody that should yield a lower incidence of infusion-related reactions.[12]
- Rituximab (Rituxan®), a chimeric monoclonal antibody that binds specifically to the antigen CD20 on the surface of normal and malignant B-lymphocytes. The drug is indicated for CD20-positive, B-cell non-Hodgkin's lymphomas of various types.[13]
- Trastuzumab (Herceptin®), a humanized monoclonal antibody that binds to the HER2/ErbB2 receptor on the cell surface of breast cancer cells. The HER2 gene is amplified and the protein is overexpressed in approximately 25 to 30 percent of all breast cancers.[14] Trastuzumab has demonstrated significant clinical activity as a single agent and in combination with cytotoxic chemotherapy in HER2-positive breast cancer.
- Alemtuzumab (Campath®)
- Gemtuzumab (Mylotarg®)
- Cetuximab (Erbitux®), a chimeric monoclonal antibody that specifically binds to the extracellular domain of the human epidermal growth factor receptor (EGFR).[15] EGFR is expressed in many solid tumors including head and neck, colon, and rectal cancers where it is expressed in about 80 percent of cases.[16] Cetuximab is indicated for locally or regionally advanced head and neck cancer, recurrent or metastatic head and neck cancer, and EGFR-expressing, metastatic colorectal carcinoma. The management of colorectal cancer as a result of targeting the EGFR receptor with monoclonal antibodies represents a major advance in therapy.[17]
- Bevacizumab (Avastin®), a humanized monoclonal antibody that inhibits the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab binds to VEGF and prevents the interaction of VEGF with its receptors on the cells surface. This inhibition of the protein VEGF leads to a reduction of microvascular growth and inhibits metastatic disease progression. Bevacizumab is indicated for first-line treatment of patients with metastatic colorectal carcinoma and patients with non-squamous non-small cell lung cancer.[18]

Essential for the growth and metastases of solid tumors, angiogenesis is characterized by oncogene-driven tumor expression of pro-angiogenic factors including VEGF, basic fibroblast growth factor, platelet-derived growth factor (PDGF), and transforming growth factor-beta. Recently, data in breast cancer patients have demonstrated that an increase in VEGF expression has been associated with poor prognosis.[19] Clinical studies have shown that bevacizumab, when used alone or in combination with cytotoxic chemotherapy in women with advanced breast cancer, is safe, effective, and improved overall response.[20] This drug may be one of the targeted therapies we see emerging in 2007 with additional indications for use in other cancers with an over-expression of VEGF.

New Drugs in the Pipeline

A number of new traditional cytotoxics show promise for the treatment of cancer.

Pixantrone (BBR-2778). An anthracycline, the molecule pixantrone is being studied for its effects in the treatment of aggressive non-Hodgkin's lymphoma and breast cancer. The hope is that pixantrone's low incidence of cardiotoxicity, ease of administration, and overall tolerability will be advantages for patients some day. The drug is being studied as a single agent and in combination with other cytotoxics.

Satraplatin. This third generation oral platinum drug has demonstrated positive results in Phase III clinical trials of patients with hormone-refractory prostate cancer. Early data suggest anti-tumor activity comparable to cisplatin and carboplatin with less cross-resistance (e.g., resistance to a particular drug and subsequently, other similar drugs in the same class).

Trabectedin (Yondelis®). This drug binds to DNA and interacts with DNA repair enzymes to disrupt the cell cycle. It has demonstrated good clinical activity in Phase III trials of patients with ovarian cancer.

New Formulations or Delivery Methods in the Pipeline

Several already-approved cancer therapy molecules are in Phase III clinical trials for new formulations or delivery methods.

Vincristine sulfate liposomes injection (VSLI). Also known as Marqibo® or Onco TS, the chemotherapy drug vincristine is encapsulated in a sphingosomal drug delivery system (a proprietary type of liposomal carrier) to increase effectiveness and reduce side effects. Phase III trials in relapsed, aggressive non-Hodgkin's lymphoma have demonstrated positive results.

Paclitaxel poliglumex. Xyotax® is a compound that combines the chemotherapy drug paclitaxel with a biodegradable, water-soluble polyglutamate polymer. The agent is intended to provide a more effective treatment by delivering an increased amount of paclitaxel to cancer cells. Phase III clinical trials in patients with non-small cell lung cancer

The Impact of New Therapies

New anticancer therapies affect the entire continuum of care: patients and providers, manufacturers, and payers.

Patients and Providers. While new therapies mean more treatment options for the patient and the oncologists' repertoire, they may have a profound impact on practices and administrators who manage the practices. If the new therapy is an oral agent that replaces an existing infusion treatment, it will lead to fewer infusions, which could impact treatment room workload and revenues. Since an increasing number of oral therapies are coming to market, some oncology practices may choose to explore oral dispensing opportunities.[1] Anticancer therapies that represent a novel delivery technique or preparation methodology will impact oncology nurses and/or pharmacists. Oncology nurses may also be affected by a new therapy if it involves special monitoring requirements, supportive care requirements, and patient education requirements.

Manufacturers. Approval of new anticancer treatments affect the pharmaceutical industry in multiple ways.

Companies bringing a new drug to market have the promise of increased revenues and profits. The financial gain realized by the drug manufacturer may be reinvested into future research and development that may lead to additional new cancer breakthroughs. The company may use these new revenues to fund educational programs for oncology professionals, as well as educational materials for cancer patients.

For pharmaceutical companies without a new drug, any new cancer drug in the marketplace raises several concerns. First, a new product by a competitor may lead to reduced sales of an existing drug and, subsequently, decreased revenue. Not all responses are negative; some pharmaceutical companies may respond by trying to develop a new agent that competes or is an improvement over the new product that just entered the market. In this scenario, the patients become the beneficiaries.

Payers. This group definitely feels the financial impact of new anticancer therapies. As new therapies reach the market, their corresponding "price tags" continue to increase adding a greater burden to payers. One recent article reported that the cost of new cancer drugs could be several times higher than existing products with similar indication.[2] Other reports contend that the benefits of some of these new cancer therapies justify their price by virtue of the fact that the patient's quality of life may be improved and/or toxicities may be reduced.[3]

Payers and oncologists must work together when making treatment decisions involving expensive new therapies to assure appropriate utilization of resources. While cancer patients can pressure physicians to use any drug, at any cost, at any point in their disease process, oncologists should provide patients with realistic expectations and subsequently appropriate treatment decisions involving the new therapies.[4] A tool that can help payers and clinicians is the development of evidence-based approaches to new therapy utilization and decision-making.[5] With reimbursement in decline, appropriate utilization of new drugs will be critical.

References

[1]Buller J. Dispensing pharmacy in a community oncology practice: success. *Oncologistics*. 2006: First Quarter;9-12.

[2]Garattini S, Bertele V. Efficacy, safety, and cost of new anticancer drugs. *Br Med J.* 2002: 325(7358); 269-271.

[3]Calvert H, Jodrell DI, Cassidy J, Harris AL. Efficacy, safety, and cost of new anticancer drugs: pessimistic conclusion was not justified. *Br Med J.* 2002: 325(7375); 1302.

[4]Jennett B, Buxton M. When is treatment for cancer economically justified? Discussion paper. *J Royal Society of Med.* 1990:83;25-28.

[5]Foy R, So J, Rous E, Scarffe JH. Perspectives of commissioners and cancer specialists in prioritizing new cancer drugs: impact of the evidence threshold. *Br Med J.* 1999; 318(7181): 456-459.

have demonstrated good responses, as have clinical trials in women with ovarian cancer.

Oral topotecan. Hycamtin® is another example of a different dosage form or delivery method of a marketed cytotoxic drug. Phase III clinical trials have shown effectiveness in both small and non-small cell lung cancer. Oral topotecan has been studied as a single agent and in combination with cisplatin. This oral dosage form may offer a treatment option for patients who live long distances from a cancer center, making it difficult for them to receive intravenous therapy.

New Indications in the Pipeline

Several anticancer agents already on the market may have possible new indications this year.

Bevacizumab combined with paclitaxel for women with recurrent or advanced stage breast cancer. Phase III data suggest an added benefit in response when bevacizumab is added to paclitaxel therapy.

Bortezomib is presently FDA-approved for the treatment of patients with multiple myeloma who have already been treated with two other types of chemotherapy. However, results from clinical trials suggest that bortezomib may be effective as first-line therapy for patients with multiple myeloma.

New Targeted Therapies in the Pipeline

As previously discussed, targeted therapies will likely provide the majority of new drugs brought to market in this year.

One targeted therapy that is showing great promise in clinical trials is ***lapatinib (Tykerb®).*** Lapatinib is an epidermal growth factor receptor (EGFR) and ErbB2 (HER2/neu) dual TKI under clinical investigation for the treat-

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ment of breast and lung cancer. It has actually arrested the development of breast cancer in some patients with metastatic disease.[21] In a Phase III clinical trial, lapatinib combined with capecitabine produced a greater than 50 percent increase in time to progression compared to capecitabine alone in women with refractory, advanced, or metastatic breast cancer.[22] Lapatinib may offer women with HER2 positive breast cancer another treatment option.

Nilotinib (AMN107) is a TKI that selectively inhibits Bcr-Abl (a fusion protein), which is the causative abnormality in CML. Nilotinib was designed to overcome imatinib-resistance or intolerance in Ph+ chronic myelogenous leukemia in chronic phase, accelerated phase, and myeloid and lymphoid blast crisis. Nilotinib appears to be a more selective and potent inhibitor of Bcr-Abl than imatinib.[23]

Zactima (ZD6474 or Zactimatm®) is an oral multitargeted TKI with potent activity against the VEGF receptor on endothelial cells as well as EGFR-thymidine kinase and ret TK. Zactima has demonstrated anti-tumor activity by inhibiting tumor growth, invasion, and metastases. Zactima has been studied in clinical trials for the treatment of non-small cell lung cancer. This once-a-day oral therapy may provide a treatment option for elderly patients with non-small cell lung cancer due to its favorable toxicity profile.

The Future is Today

While many unknowns remain regarding which drugs will receive FDA approval and which drugs will receive new indications this year, we can safely predict that more chemotherapeutic agents will be available to oncologists in 2007 than in 2006. We can be certain that usage of various recently approved chemotherapy drugs will increase in 2007 as the number of cancer patients increases and clinicians become familiar with the new drugs. We can also be assured that covered treatment indications will increase in 2007, either through FDA approval or by an addition to the compendia listing.

We also know that the future will be challenging. Insurers and patients will be challenged to pay for these newer and more expensive therapies as they reach the market. Oncology clinicians may have some tough decisions to make, selecting the best therapies for their patients that also meet with approval from payers. In the end, we know that cancer patients will ultimately reap the benefits of these technological advancements and improved understanding of the biology of cancer.

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References

[1]Brower V. Fast tracking drugs in patients. *European Molecular Biology Organization.* 2002; 3(1): 14-16.
[2]Dacogen product information. MGI Pharma, Inc. Bloomington, MN. May 2006.
[3]Palacio M. FDA approves decitabine for treatment of myelodysplastic syndromes. *Hem/Onc Today.* June 2006; 16.
[4]Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol.* 2005;23:792-799.
[5]Arranon product information. GlaxoSmithKline. Research Triangle Park, NC. October 2005.
[6]Weiner LM, Borghaei H. Targeted therapies in solid tumors: monoclonal antibodies and small molecules. *Hum Antibodies.* 2006;15(3):103-111.
[7]Paul MK, Mukhopadhyay AK. Tyrosine kinase—role and significance in cancer. *Int J Med Sci.* 2004; 1(2):101-115.
[8]Lin NU, Winer EP. New targets for therapy in breast cancer: small molecule tyrosine kinase inhibitors. *Breast Cancer Res.* 2004; 6(5):204-210.
[9]Fuerst ML. FDA approves dasatinib for imatinib resistance & intolerance 3 weeks after enthusiastic recommendation from ODAC. *Oncology Times.* July 10, 2006. 9.
[10]Lohr LK. Sunitinib and sorafenib represent new treatment options for renal cell cancer. *Hem/Onc Today.* June 2006; 6.
[11]Velcade product information. Millennium Pharmaceuticals, Inc. Cambridge, MA. March 2006.
[12]Vectibix product information. Amgen, Inc. Thousand Oaks, CA. September 2006.
[13]Rituxan product information. Biogen IDEC, Inc. and Genentech, Inc. South San Francisco, CA. March 2006.
[14]Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER2/ *neu* oncogene. *Science.* 1967;235:177-182.
[15]Erbitux product information. Imclone Systems Incorporated. Branchburg, NJ. March 2006.
[16]Slevin M, Payne S. New treatments for colon cancer. *Br Med J.* 2004;329:124-126.
[17]Vincenzi B, Schiavon G, Silletta M, Santini D, Tonini G. The new era in the treatment of advanced colorectal cancer patients: the role of monoclonal antibodies. *Expert Opin Emerg Drugs.* 2006;11(4):665-683.
[18]Avastin product information. Genentech, Inc. South San Francisco, CA. October 2005.
[19]Yu JL, Rak JW. Host microenvironment in breast cancer development: inflammatory and immune cells in tumor angiogenesis and arteriogenesis. *Breast Cancer Res.* 2003;5(2):83-88.
[20]Miller KD. E2100: A randomized phase II/III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer. May 16, 2005. Scientific presentation: American Society of Clinical Oncologists 41st Annual Meeting, Orlando, Fla.
[21]Moy B, Goss, PE: Lapatinib: current status and future directions in breast cancer. *Oncologist.* 2006;11(10):1047-1057.
[22]Geyer CE, et al. Lapatinib (Tykerb) plus capecitabine delays progression of HER2 positive breast cancer. June 3, 2006. Scientific presentation: American Society of Clinical Oncologists 42nd Annual Meeting, Atlanta, Ga.
[23]Weisberg E, Manley PW, Breitenstein W, et al. Characterization of AMN107: a selective inhibitor of native and mutant Bcr-Abl. *Cancer Cell.* 2005;7:129-141.