Major international clinical trials spearheaded by physician-scientists at the Massachusetts General Hospital Cancer Center are revealing the power of new targeted anti-cancer therapies—administered as a single agent or in combination—and helping accelerate approval of these new drugs by the U.S. Food and Drug Administration (FDA).

Breast Cancer

In October 2011, José Baselga, MD, PhD, chief of the Division of Hematology/Oncology at Mass General and associate director of the Mass General Cancer Center, presented the results of an international phase 3 clinical trial for women with advanced breast cancer at the annual meeting of the European CanCer Organisation (ECCO) in Stockholm, Sweden. The clinical trial, known as BOLERO-2, was designed to assess the impact of treating women with metastatic estrogen-receptor (ER)-positive breast cancer with a combination of two drugs, everolimus, a drug previously used to treat advanced kidney cancer and some pancreatic cancers, and exemestane, an aromatase inhibitor (hormonal therapy).

At the ECCO meeting, Dr. Baselga reported that the BOLERO-2 trial was halted in July 2011 when an interim analysis showed that women receiving the combination therapy experienced significantly longer progression-free survival than women receiving exemestane alone. In fact, the combination therapy halted the progression of metastatic breast cancer in women for a median of 11 months, compared with about four months for women receiving exemestane alone. Dr. Baselga said that this study is probably “the most positive trial ever” for women.

continued on the next page

New Drugs Fight Metastatic Cancer to Extend Disease-Free Survival

The new Henri and Belinda Termeer Center for Targeted Therapies represents a paradigm shift from traditional clinical cancer research to a focus on genotype-based targeted therapies, clinical trials at early stages in the disease process, and the application of targeted drugs across multiple tumor types. See page 14 for more on this story.

INSIDE

6 Achieving the Promise of Anti-Angiogenic Therapies
8 New Procedure Transforms Surgery for Some Rectal Cancer Patients
10 Reducing Treatment Toxicity for Head and Neck Cancer Patients
13 News Briefs from the Massachusetts General Hospital Cancer Center

massgeneral.org/cancer
New Drugs Fight Metastatic Cancer to Extend Disease-Free Survival

with ER-positive breast cancer who have stopped responding to conventional hormonal therapy.

Everolimus works by targeting a protein called mTOR, which belongs to the family of enzymes known as PI3 kinases, or PI3Ks. In healthy cells, mTOR is involved in cell growth, cell proliferation, protein synthesis, and many other functions. In tumor cells, the mTOR pathway goes awry, leading to excess proliferation and failure to respond to normal growth regulatory mechanisms.

The BOLERO-2 clinical trial, which involved 724 patients from 24 countries, represents an important milestone in the development of therapies that specifically block growth-promoting pathways in cancer cells. Many of the side effects of conventional chemotherapy drugs result from their tendency to destroy all cells in the body engaged in rapid cell division, including normal cells in the gut and bone marrow. Targeted therapies are expected to have fewer side effects and to be more effective than conventional cancer therapies.

Dr. Baselga’s presentation in Stockholm demonstrates the leadership role played by Mass General Cancer Center physicians and scientists in today’s revolution in cancer medicine. Another important milestone in the development and use of targeted therapies occurred in August 2011, with the FDA’s approval of the drug crizotinib.

**Lung Cancer**

Alice T. Shaw, MD, PhD, thoracic oncologist in the Center for Thoracic Cancers at the Mass General Cancer Center, led the expansion of the crizotinib trial that ultimately resulted in the drug’s accelerated approval for a type of advanced non-small-cell lung cancer (NSCLC) defined by a chromosomal rearrangement of the anaplastic lymphoma kinase (ALK) gene. This phase 1 trial was initially led by Eunice Kwak, MD, PhD, and Jeffrey Clark, MD, both medical oncologists in the Tucker Gosnell Center for Gastrointestinal Cancers at the Mass General Cancer Center.

On average, patients with ALK-positive NSCLC are younger than other lung cancer patients and are more likely to be nonsmokers. The ALK gene, located on chromosome 2, normally plays a role in the development of certain brain cells and then lies dormant. With the translocation, however, the short arm of chromosome 2 breaks apart and inverts on itself, fusing a part of the ALK gene to another gene, EML-4, causing ALK to become stuck in the “on” position. The ALK fusion gene becomes a driver of cancerous growth.

In June 2011, at the annual meeting of the American Society of Clinical Oncology (ASCO), Dr. Shaw reported on findings from a phase 1 study of crizotinib in ALK-positive NSCLC patients; the one-year survival rate of these patients was 74 percent. In a subset analysis comparing crizotinib-treated patients with those who had never received crizotinib, the two-year survival rate was 55 percent in the crizotinib group, compared with 12 percent among those who received standard chemotherapy. Preliminary findings from the ongoing phase 2 study, reported in July 2011, confirm that crizotinib is highly active in patients with ALK-positive NSCLC.

**Accelerated Approval**

Historically, the time between the start of a phase 1 clinical trial and FDA approval of a drug is eight to 10 years. With crizotinib, the drug’s approval came just four years after the discovery by Japanese researchers that some NSCLC tumors carried the ALK mutation. The accelerated clinical trials and FDA approval of crizotinib (see the timeline below) represent a paradigm shift in cancer drug discovery, based in

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**Timeline for PF-02341066 – Crizotinib**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>2006</td>
<td>Phase 1 study started</td>
</tr>
<tr>
<td>2007</td>
<td>ALK Mutant NSCLC Nature paper published (by Japanese investigators)</td>
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<tr>
<td>2008</td>
<td>7/08 – ALK cohort opens at the recommended phase 2 dose (led by Dr. Shaw)</td>
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<tr>
<td>2009</td>
<td>9/09 – Phase 3 study started</td>
</tr>
<tr>
<td>2010</td>
<td>1/10 – Phase 2 study started (led by Dr. Shaw)</td>
</tr>
<tr>
<td>2011</td>
<td>8/11 – Crizotinib receives FDA approval</td>
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Timeline for FDA approval of crizotinib.
large part on the ability to start with a population of patients whose cancers are driven by a molecularly defined genetic mutation—such as the ALK translocation.

Crizotinib’s approval demonstrates that targeted therapies may be able to move to market faster than traditional chemotherapy drugs. Typically, clinical trials preceding FDA approval of a drug have occurred in three phases: a phase 1 trial involving a small number of patients to assess the safety of a new drug candidate; a phase 2 trial with 100 or more patients to gauge whether a drug actually accomplishes its objective; and a much larger and longer phase 3 clinical trial—often randomized—to determine whether a drug is better, as good as, or worse than standard therapies.

Just four months after the Japanese scientists published their findings in the journal Nature about the link between some lung cancers and the ALK translocation, Dr. Shaw, Dr. Kwak, Dr. Clark, and their colleagues began enrolling patients with ALK-positive NSCLC into the ongoing phase 1 clinical trial of crizotinib. Because of the match between the drug and the target, and because NSCLC generally has a very poor prognosis, the researchers did not have to wait long to observe dramatic results. In fact, crizotinib moved directly from the phase 1 study to concurrent phase 2 and 3 studies, and then on to FDA approval—without waiting for phase 3 results—a dramatic acceleration of the development time from laboratory to routine use (as advocated for in an early 2011 New England Journal of Medicine editorial by Bruce Chabner, MD, director of clinical research at the Mass General Cancer Center).

If the researchers had not had access to genetic testing, the results would have been quite different. Only 4 to 5 percent of patients with NSCLC carry the ALK translocation. Thus, testing crizotinib in the broad population of patients with NSCLC would have been unlikely to show positive results, or it would have taken much longer for positive results to emerge from the background of drug failures in patients whose tumors did not carry the ALK translocation.

**Routine Cancer Genotyping**

The Mass General Cancer Center is uniquely suited to advance the development of targeted therapies because it provides routine analysis of tumor genomes for many types of cancer, including lung cancer. In the Cancer Center’s Translational Research Laboratory, a collaborative team of pathologists and oncologists, led by John Iafrate, MD, PhD, and Leif W. Ellisen, MD, PhD, developed a new diagnostic test—based on a technology called “SNaPshot”—to produce highly accurate gene sequencing results using archived formalin-fixed paraffin-embedded (FFPE) tumor specimens.

Key Points

- The BOLERO-2 clinical trial showed that women with metastatic estrogen-receptor (ER)-positive breast cancer fared significantly better on a combination of two drugs, everolimus and exemestane, than on exemestane alone.

- Crizotinib’s accelerated approval was based on data from phase 1 and early phase 2 studies. The phase 1 trial showed an overall one-year survival rate of 74 percent in lung cancer patients with NSCLC and the ALK gene rearrangement.

- Careful patient selection combined with expanded phase 1 clinical cohorts and concurrent phase 2 and 3 clinical trials at Mass General will help expedite the development of targeted therapies for all cancer patients.

- The Mass General Cancer Center is developing and testing a variety of combinations of targeted therapies to overcome the problem of drug resistance, which often develops in response to therapy with a single targeted agent.

- The Henri and Belinda Termeer Center for Targeted Therapies, the Translational Research Laboratory (for genomic analysis of tumors), and the Center for Molecular Therapeutics (for drug discovery in cancer cell lines) together provide a uniquely powerful framework for developing and testing new targeted therapies.

continued on the next page
While several centers have initiated tumor sequencing projects for the purpose of generating research databases, Mass General is among the first to develop a broad tumor analysis platform accurate enough for clinical decision making. For example, clinical FFPE tumor specimens vary greatly in size (number of tumor cells) and DNA quality, yet the Mass General test provides sensitive and specific information about 15 genes and more than 130 specific mutations likely to have an impact on cancer progression and therapy. The Mass General test for broad-based tumor mutation analysis has been widely acclaimed and was licensed by a commercial entity to allow oncologists outside of academic medical centers access to the test.

The Henri and Belinda Termeer Center for Targeted Therapies

Two other factors have made the Mass General Cancer Center a leader in targeted therapies: its expertise in conducting first-in-human clinical trials and its capacity to test new anti-cancer drugs. Daniel A. Haber, MD, PhD, director of the Mass General Cancer Center, reports that the number of patients enrolled in phase 1 clinical trials at the Cancer Center has tripled since Dr. Baselga’s arrival in July 2010 from Spain, where he was founding director of the Vall d’Hebron Institute of Oncology and president of the European Society of Medical Oncology. Dr. Baselga heads the Cancer Center’s new Henri and Belinda Termeer Center for Targeted Therapies (see News Briefs, page 14) designed to provide the best possible environment for state-of-the-art cancer clinical trials.

Glenn Siegmann, MS, RPh, administrative director of clinical and translational research at the Mass General Cancer Center, works with physician-scientists to design and conduct clinical trials. He says that the Termeer Center will provide a crucial setting for many new developments in cancer research, including the use of expanded cohorts for phase 1 clinical trials. With expanded cohorts, drugs are tested in clusters of patients whose tumors carry the same genetic mutation even though they may have arisen in different body tissues. For example, mutations in the BRAF gene have been found in malignant melanoma, as well as in some cases of lung cancer, colorectal cancer, non-Hodgkin’s lymphoma, and thyroid cancer. The use of expanded cohorts for drug testing can reveal the relative importance of a particular gene mutation in different forms of cancer and the likely impact of blocking that mutation in the course of a patient’s disease.

Some of the drugs used in novel clinical trials in the Termeer Center will be identified through Mass General’s Center for Molecular Therapeutics, a facility that maintains more than 1,000 cancer cell lines to screen drugs and drug combinations for activity against different subgroups of tumors. Others will come through the Cancer Center’s numerous collaborations with leading pharmaceutical and biotechnology companies.

Combination Therapies

Maintaining an active cancer drug discovery program at Mass General is critical because in almost all cases, tumors in people with advanced cancer develop resistance to individual targeted therapies over time. When one pathway driving unregulated growth is blocked, another will eventually take its place.

**Genotyping in the Translational Research Laboratory**

The Translational Research Laboratory provides rapid, personalized genomic testing as an important component of routine care for newly diagnosed lung cancer patients, thereby increasing the physician’s ability to select the right targeted therapies based on molecular alterations in a patient’s tumor.
To overcome this problem, many groups at the Mass General Cancer Center are developing combination therapies to block drug resistance before it occurs. For example, Keith T. Flaherty, MD, director of the Developmental Therapeutics Program at Mass General, led early clinical trials of a drug called vemurafenib, which was approved by the FDA in August 2011 for metastatic melanoma. Vemurafenib targets a mutation in the BRAF gene, a key component of the RAS-RAF pathway involved in normal cell growth and development. About half of all melanoma tumors and 8 percent of all solid tumors carry a mutated BRAF gene. The BRAF mutation acts like a stuck accelerator, causing uncontrolled growth and prolonged survival of cancer cells. Vemurafenib blocks activity of the mutant BRAF gene and triggers programmed cell death.

In phase 1 and 2 clinical trials, vemurafenib produced sufficient tumor shrinkage to define a clear response in about 60 percent of patients, but within a year most tumors became resistant to the drug. Mass General is now pursuing studies of more than a half dozen multi-drug combinations to circumvent the resistance problem. One major effort employs a BRAF inhibitor plus a drug that inhibits a different kinase enzyme called MEK; activation of the MEK gene pathway is one of the mechanisms that enables tumor cells to overcome the inhibitory effects of vemurafenib. Dr. Flaherty and his collaborators presented data from a phase 1 study of the BRAF inhibitor/MEK inhibitor protocol at the ASCO meeting in June 2011. The data showed that the combination was safe, well-tolerated, and produced a promising response rate as high as 77 percent when both drugs were given at full doses.

Similarly, Jeffrey A. Engelman, MD, PhD, director of the Center for Thoracic Cancers at the Mass General Cancer Center, is pursuing strategies combining new inhibitors of the epidermal growth factor receptor (EGFR) with other targeted therapies in lung cancer. EGFR inhibitors have been available for several years for lung cancer, but resistance remains a concern. The team is focusing on combining new EGFR inhibitors with inhibitors of the cMET pathway in patients with EGFR-mutated lung cancers.

Finally, Dr. Baselga and Beverly Moy, MD, MPH, clinical director of the Cancer Center’s Gillette Center for Breast Cancer, are conducting multiple clinical trials of drug combinations in breast cancer patients. In December 2011, Dr. Baselga presented the results of one trial, known as CLEOPATRA, at the San Antonio Breast Cancer Conference. The phase 3 clinical trial compared a three-drug regimen consisting of pertuzumab (the first drug designed to block the pairing of key cell-surface receptors on breast cancer cells), Herceptin, and the chemotherapy drug docetaxel with a regimen of Herceptin and docetaxel alone. In a study of more than 800 women with HER2-positive metastatic breast cancer, those who received the two targeted therapies (pertuzumab and Herceptin) plus chemotherapy experienced significantly longer progression-free survival than women who received only chemotherapy and Herceptin alone.

Selected References


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Advancing the Promise of Anti-Angiogenic Therapies

At the end of the past century, new theories about how a tumor grows and subverts blood vessels to achieve a growth advantage over adjacent normal tissues generated tremendous excitement. Researchers began the search for anti-angiogenic factors that could eradicate tumors by starving them of their blood supply. Unfortunately, subsequent clinical trials were disappointing; not only did anti-angiogenic drugs generally fail to cure cancer; the survival benefits from anti-angiogenic drugs approved by the U.S. Food and Drug Administration (FDA) turned out to be only modest.

Massachusetts General Hospital scientist Rakesh K. Jain, PhD, and his collaborators have been at the forefront of efforts to understand why the promise of anti-angiogenic drugs has not been fulfilled and how such drugs can be used effectively in combination with other therapies to improve patient survival. Dr. Jain, director of the Edwin L. Steele Laboratory for Tumor Biology at Mass General and Andrew Werk Cook professor of Tumor Biology (Radiation Oncology) at Harvard Medical School, has made important advances in understanding the complex micro-environment of tumor tissues. He and his collaborators have demonstrated that manipulating the blood vessels in tumors can be exploited to improve cancer therapy but in a different way from that proposed originally by Judah Folkman, MD, the visionary physician-scientist from Children’s Hospital Boston who first described the importance of angiogenesis in cancer.

Simultaneously, Othon Iliopoulos, MD, assistant professor of medicine at Harvard Medical School, director of the Cancer Genetics Laboratory, and clinical director of the Von-Hippel Lindau Disease/Family Renal Cell Cancer Clinic at Mass General, is unraveling the pathways that regulate how tumor cells respond to hypoxia in their environment to produce angiogenic factors. His discoveries, like those in the Jain Laboratory, are revealing new targets for anti-cancer drugs.

Hypoxia and VEGF

Healthy tissues carefully regulate the balance of growth-promoting and growth-limiting signals to ensure proper development of blood vessels throughout the body. In cancer, these signals become unbalanced; growth-promoting factors, such as vascular endothelial growth factor (VEGF), are overexpressed by cancer cells, leading to the formation of dilated, irregular, and highly permeable blood vessels around the tumor.

One result of this irregular growth of blood vessels is that blood flow and oxygenation varies tremendously from one part of the tumor to another. Diminished oxygen levels in some parts of the tumor (a condition known as hypoxia) cause some tumor cells to switch on a special metabolic pathway that enables them to survive in a quiescent state. Hypoxic tumor cells do not divide rapidly like other tumor cells, and thus they are generally resistant to conventional chemotherapy and radiation. In addition, tumor cells in a hypoxic state rapidly accumulate genetic mutations and are more likely to metastasize than other tumor cells.

Dr. Folkman’s original theory led to clinical trials of drugs such as the humanized monoclonal antibody bevacizumab, which was designed specifically to block VEGF activity. The hope was that these drugs would starve cancer cells of oxygen and nutrients by shutting down their blood supply. Unfortunately, bevacizumab alone failed to produce significant improvement in patient survival. However, subsequent clinical trials revealed that combining bevacizumab with standard chemotherapy drugs could prolong life. This is paradoxical because chemotherapy requires an intact blood supply to deliver drugs to tumors and the original goal of anti-angiogenic drugs was to destroy blood
vessels. Dr. Jain proposed a new theory to resolve this paradox.

Instead of destroying the tumor vasculature with high doses of anti-angiogenic drugs, Dr. Jain says, one could use them to “normalize” the tumor vasculature—making it more like that of healthy tissue—by using lower doses of anti-angiogenic drugs. As a result, tumor cells are less likely to undergo the metabolic shift to hypoxic growth and—with improved tumor blood flow—more likely to respond to concurrent chemotherapy, radiation therapy, and immune therapy (see the top of page 6).

Dr. Jain and his colleagues at the Massachusetts General Hospital Cancer Center first examined the role of bevacizumab in normalizing tumor blood vessels in patients with rectal carcinoma. They found that the benefits of normalization were transient, presumably because cancer cells began producing higher amounts of other vascular growth factors to replace VEGF. Studies of the anti-VEGF drug cediranib in patients with glioblastoma (conducted by the Jain group in collaboration with Mass General Cancer Center neuro-oncologist Tracy Batchelor, MD, MPH, and radiologist A. Gregory Sorensen, MD) showed that the normalization effect begins within 24 to 48 hours, but the duration of the normalization window varies tremendously from one glioblastoma patient to another. Once the window shuts, the tumor vasculature again grows in disarray, re-creating conditions favorable for the development of dangerous, quiescent cancer cells.

Dr. Jain says that early clinical studies of patients provided the foundation for a variety of new projects in his laboratory, including efforts to (1) identify alternative pathways used by tumors to escape anti-angiogenic therapy; (2) find ways of extending the normalization window; (3) seek out biomarkers and other tools capable of monitoring when normalization begins and ends following the administration of anti-angiogenic drugs; and (4) search for predictive biomarkers to identify patients who would benefit from anti-angiogenic therapy.

**New Anti-Angiogenic Pathways Identified as Targets**

While VEGF appears to be an important growth-promoting molecule affecting vascular changes associated with cancer, many other molecules have similar effects. To identify additional targets for anti-cancer drug regimens, Dr. Jain and his colleagues have gathered data on the activity of 40 known growth factors and related molecules in patients receiving anti-VEGF therapy for a variety of different types of cancer. This large net captured six potential targets for further investigation.

One of these targets was a protein called SDF1α, which was present at increased levels in virtually all patients involved in the study. Dr. Jain is now working with pharmaceutical companies to develop strategies for targeting the SDF1α receptor in patients with colorectal cancer who have failed to respond to anti-VEGF therapies. Drugs that block the SDF1α pathway may be used alone, in combination with anti-VEGF agents, or in combination with conventional cancer therapies, such as radiation. The focus on SDF1α also has yielded a possible marker to help physicians predict cancer prognosis; high SDF1α levels appear to be correlated with rapid progression of disease.

In another recently published study, Drs. Jain, Sorensen, and Batchelor reported that glioblastoma patients whose blood vessels were most normalized one day after taking cediranib experienced the longest survival. In a follow-up study—presented at an MRI conference—they reported that these long-surviving patients exhibit increased tumor blood flow. These two findings provide the most compelling evidence in humans to support Dr. Jain’s “vascular normalization” hypothesis. Dr. Jain stresses, however, that improved distribution of blood to the tumor plays a more significant role than increased flow. The goal, he says, is to reverse hypoxia and return the cellular environment to a normal state. Simply increasing blood flow to areas already receiving adequate flow does not accomplish that goal. Success depends on increasing blood flow to hypoxic regions.

**Looking Upstream: Targeting the Conductor of the Hypoxic Response**

Dr. Iliopoulos uses a complementary approach to explore the biochemical mechanisms underlying cancer angiogenesis and to validate new targets for anti-cancer drug development. His work focuses on a transcription factor called hypoxia-inducible factor (HIF), which regulates pathways involved in angiogenesis, metabolism, and metastasis (see the bottom of page 6), the three key functions required for cancer progression.

Dr. Iliopoulos describes HIF as the conductor of the hypoxic response and explains that it represents an appealing target for cancer therapy because it is active in virtually every type of cancer cell, yet it is inactive in normal, well-oxygenated cells. HIF regulates the overexpression of VEGF in cancer cells as well as the activity of many other growth-promoting pathways. Dr. Iliopoulos suggests that targeting the conductor rather than individual players in the orchestration of the hypoxic response may make it more difficult for cancer cells to escape destruction.

Recently, the Iliopoulos Lab identified and validated eight novel small molecules that inhibit one member of the HIF family—namely, HIF-2α. Because these molecules inhibit all the downstream targets of HIF, they should impede the cancer cell’s ability to find alternative mechanisms not only for promoting abnormal growth of blood vessels, but also for shifting metabolic pathways and enhancing metastasis. These molecules have been tested in animal models as well as in cell lines, and Dr. Iliopoulos and his colleagues continued on page 16.
New Procedure Transforms Surgery for Some Rectal Cancer Patients

Massachusetts General Hospital surgeons are pioneering the use of new scar-less, minimally invasive surgical procedures for the treatment of rectal cancer and other conditions. This form of surgery, called natural orifice transluminal endoscopic surgery (NOTES), uses the natural orifices of the body—mouth, anus, and vagina—to gain entry into body cavities. Potential benefits of the NOTES approach for rectal cancer include less pain, no visible scarring, more rapid recovery and the possibility of shorter hospital stays. Additional advantages also may include reduced anesthesia requirements and avoidance of complications associated with abdominal surgeries through large abdominal incisions, such as wound infections and hernias.

Mass General surgeon Patricia Sylla, MD, traveled to Barcelona in November 2009 to perform the first-in-human laparoscopic-assisted NOTES rectal cancer resection. The 76-year-old female patient, who had received presurgical chemotherapy and radiation therapy, was discharged on the fourth postoperative day and has had her temporary ileostomy (diversion of the small intestine to a surgically-created skin opening for evacuation of the bowel) closed; she has remained free of cancer. Conventional rectal cancer resections generally involve hospital stays of six to 10 days and usually require a temporary ostomy.

Since that initial NOTES procedure, Mass General has become the site of the sole IRB-approved clinical trial of NOTES in the Eastern United States for removal of adenocarcinoma of the rectum. Surgical entry is made through the anus and rectum, followed by excision of the tumor and surrounding tissue through the same orifice. Eligible patients must have cancers of the low to mid-rectum staged at T1, T2, or T3—with no evident lymph node involvement and no visible breach of the wall of the rectum on imaging. Exclusion criteria include a prior history of colorectal cancer, sphincter incontinence, and metastatic disease.

Mass General Leadership in Advanced Gastrointestinal Surgery

David W. Rattner, MD, chief of the Division of Gastrointestinal and General Surgery at Mass General, has been a leader in the international effort to advance natural orifice surgery in a carefully controlled fashion since 2005. At that time, he was president of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and one of a group of 12 distinguished surgeons in the U.S. who formed the National Orifice Surgery Consortium for Assessment and Research (NOSCAR). The NOSCAR mission is to fund research and develop new natural orifice surgical techniques and instrumentation. NOSCAR is sponsoring the NOTES rectal cancer randomized prospective human clinical trial at Mass General.

Dr. Rattner performed the first NOTES surgery in New England in May 2009, when he removed the gallbladder of a young woman through vaginal excision. All NOTES gallbladder cases at Mass General are performed as part of another IRB-approved clinical trial. Mass General surgeons are about to launch a third NOTES clinical study for patients with achalasia, an esophageal motility disorder involving the smooth muscle layer of the esophagus and the lower esophageal sphincter (LES) that requires surgical intervention.

Dr. Sylla’s role in advancing minimally invasive surgical approaches to rectal cancer was recognized in March 2011, when she received a prestigious two-year research fellowship from the highly competitive Harvard Catalyst Program for Faculty Development and Diversity. Her research project focuses on evaluating the safety and efficacy of NOTES for rectal cancer.

NOTES using TEM and Laparoscopy: A Hybrid Procedure

The NOTES rectal cancer procedure pioneered by Drs. Rattner and Sylla and their colleagues is a hybrid approach using transanal endoscopic microsurgery (TEM) and laparoscopy. Developed in the 1980s, TEM is a minimally invasive procedure that uses a set of specialized instruments designed to excise polyps and other rectal lesions via rectal entry, rather than cutting through the abdominal wall to reach the rectum. However, TEM is intended to remove only small polyps and other lesions in the rectum; it is not meant to extend as far as the abdominal cavity. With NOTES, surgeons can remove not only polyps or tumors but also surrounding tissues, including the

Key Points

- NOTES for rectal cancer is a surgical approach using the anus as the point of surgical entry, tissue excision, and exit, eliminating the need for abdominal incisions.
- Potential benefits of NOTES include smaller incisions, less pain, reduced anesthesia, shorter hospital stays, and faster postsurgical recovery.
- Mass General Cancer Center is now enrolling eligible patients with early-stage rectal cancer in the first NOTES clinical trial in the Eastern United States for rectal cancer.
- Advances in instrumentation design and increased clinical training will allow the application of NOTES to larger patient populations in the future.
lymph nodes, blood vessels, and as long a section of the rectum as is necessary for a successful cancer operation.

In rectal cancer, the lymph nodes most likely to be affected by the disease are those confined to the fatty tissue around the rectum called the mesorectum. One of the goals of successful rectal cancer surgery is to remove the rectum and entire mesorectum as one intact specimen (total mesorectal excision). This reduces the likelihood of any cancer cells remaining in the body. When a tumor is located deep within the pelvis, near the anus, performing a total mesorectal excision using conventional abdominal surgery is technically very difficult. The approach through the anus with NOTES allows surgeons to visualize and remove the rectum and mesorectum more easily. Patients who enroll in the NOTES rectal cancer study at Mass General will have NOTES combined with laparoscopy, allowing for a total mesorectal excision.

While NOTES for rectal cancer is still in its early days, surgeons familiar with other NOTES procedures expect that postsurgical infection rates at the cancer site will be similar to that of conventional rectal cancer surgery. Dr. Rattner reports that among the approximately 5,000 published cases of NOTES for gallbladder removal, the infection rates have been similar to those of laparoscopic gallbladder removal.

Progress in Instrumentation

Dr. Sylla says that over time, broader application of NOTES for rectal cancer surgery will depend on the development of specialized instruments to perform the surgery. Early NOTES procedures for rectal cancer employed existing laparoscopic instruments; however, surgeons working in the narrow rectal opening find they need longer, more flexible tools for reaching high into the colon and rectum to reconnect tissue segments. Mass General surgeons, in collaboration with other members of NOSCAR, are leading efforts to develop specialized tools for NOTES rectal cancer surgery. Drs. Rattner and Sylla are actively testing these tools in the laboratory.

As the technology improves, surgeons will likely continue to rely on laparoscopy to assist with visualization and instrument manipulations. Currently, about 15 to 20 percent of rectal cancer surgeries in the U.S. are performed using laparoscopic assistance. The other 80 to 85 percent are performed through larger abdominal incisions. At Mass General, the rate of laparoscopy for rectal cancer is higher, on average 35 to 40 percent.

Going forward, laparoscopy is likely to remain an adjunct to NOTES surgery for rectal cancer. When NOTES for gallbladder excision was introduced at Mass General, surgeons used two or three laparoscopic ports to ensure patient safety. With increased practice, surgeons successfully completed the surgery using just one or two abdominal ports. Today, most transvaginal gallbladder excisions are performed using just one laparoscopic port. One might expect a similar path with NOTES for rectal cancer as surgical instrumentation improves and surgeons become more proficient with established protocols.

Collaborative Environment at Mass General Essential for NOTES

Dr. Rattner cautions that the use of NOTES for rectal cancer requires proficiency with colorectal surgery, minimally invasive techniques, and endoscopy. Surgeons should have extensive experience with TEM for resection of polyps and early tumors. In addition, NOTES requires a highly collaborative environment, like that at Mass General, where surgeons, radiologists, oncologists, and pathologists work together closely to achieve consensus on cancer staging, tumor location, and patient selection criteria. This close collaboration helps ensure that the patient receives the best possible, individually tailored cancer care.

Selected References


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Massachusetts General Hospital Cancer Center physicians are among the most experienced in the United States at treating rare cancers of the head and neck. They routinely manage significant volumes of cancer subtypes that other centers may see only once or twice a year. This volume enables them to conduct state-of-the-art clinical trials to improve survival and reduce the toxicities and resultant symptoms typically associated with the treatment of advanced head and neck cancers, including dry mouth, swallowing problems, hearing loss, and vision impairment.

Mass General’s multidisciplinary team—that includes surgical oncologists from the Massachusetts Eye and Ear Infirmary—provides advanced radiation therapy, medical oncology, and surgery, as well as specialty rehabilitative services to offer the finest in complete patient care. For example, radiation oncologist Annie Chan, MD, director of the Head and Neck Radiation Oncology Research Program at Mass General, is leading two clinical trials to assess the use of proton beam therapy in patients with nasopharyngeal and sinonasal cancers.

Nasopharyngeal carcinoma is the most common cancer originating in the nasopharynx, the uppermost part of the pharynx, behind the nose, where the nasal passages and auditory tubes join the remainder of the upper respiratory tract. It accounts for less than 1 percent of malignancies overall in the United States and Western Europe. However, it is more common in people of Asian, Mediterranean, and African descent. Sinonasal malignancy is an uncommon but aggressive cancer of the nasal cavity and/or paranasal sinuses.

Minimizing Side Effects of Radiation Therapy

Mass General, in collaboration with the Harvard Cyclotron Laboratory at Harvard University, became the first hospital in the U.S. to use fractionated proton beam therapy to treat head and neck cancers as early as 1991. Today, it is one of only two institutions nationwide conducting prospective clinical trials on proton beam therapy for the treatment of nasopharyngeal and sinonasal cancers.

Proton beam is a type of external beam radiation treatment. The characteristics of...
Key Points

- Mass General radiation teams have used proton beam therapy to treat head and neck cancers for almost two decades.

- Proton beam therapy may reduce the acute and long-term side effects of treatment for head and neck cancer by minimizing damage to healthy tissues.

- Prospective clinical studies at Mass General are exploring the use of proton beam therapy for the treatment of nasopharyngeal and sinonasal cancers.

- Speech, language, and swallowing specialists are using new technologies to improve the swallowing function for cancer patients.

- Medical oncologists at Mass General provide state-of-the-art personalized therapies for patients with BRAF-induced thyroid cancer.
In the near future, Dr. Chan says, head and neck cancer patients at Mass General will also have access to a more advanced form of proton therapy called intensity modulated proton therapy (IMPT). IMPT is expected to have even greater potential for sparing normal tissues than 3-D proton therapy (see page 10; label C).

Advanced Technology in Assessing and Rehabilitating Swallowing Function After Treatment

Other specialists in the multidisciplinary Center for Head and Neck Cancers also focus intently on improving the quality of life for people diagnosed with this disease. In 2005, observations made by speech and swallow specialists, who are integral members of every patient’s care team in the head and neck center, led to a change in radiation treatment planning that has reduced the rate of esophageal stricture after treatment.

More recently, Tessa Goldsmith, associate director of the Department of Speech, Language and Swallowing at Mass General, noticed that patients with human papillomavirus (HPV)-positive oropharyngeal cancer treated with chemoradiation therapy were less likely to experience post-therapy swallowing problems than patients with HPV-negative disease. She wondered whether it might be possible to reduce the use of prophylactic gastrostomy (feeding tubes) in patients with HPV-positive disease. To find the answer, Goldsmith is conducting a prospective clinical trial combining videofluoroscopy and pharyngeal manometry (a technique for assessing pressure changes in the throat) to compare swallow outcomes in HPV-positive and HPV-negative patients.

Clinically, some patients perceive swallowing difficulties even when there is no physiologic evidence for impairment. Goldsmith says that information from video swallow studies and manometry provides these patients with techniques to improve swallowing function and can help them overcome fears of swallowing that may have arisen during therapy.

Advanced Chemotherapy for Head and Neck Cancer Patients

On the medical oncology front, Dr. Wirth and other Mass General oncologists are assessing new targeted therapies for head and neck cancers, especially those not linked to HPV infection. While the incidence of HPV-positive cancers has been rising, patients with HPV-negative disease—often associated with tobacco and alcohol use—have a worse prognosis. Patients with HPV-positive cancers have a five-year disease-free survival rate of 85 to 90 percent; the five-year survival rate for patients with HPV-negative head and neck cancers is 25 to 40 percent.

Dr. Wirth recently opened a phase 1 trial that combines a new targeted drug, CUDC-101, with standard chemoradiation in an attempt to improve the cure rate for poor-prognosis head and neck cancers. A separate study, available at multiple sites, including Mass General, focuses on thyroid cancers found to carry a mutation on the BRAF oncogene; the study uses vemurafenib, a BRAF-inhibitor that has proven effective for some patients with melanoma.

Selected References


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The Wonder of Lunder—Enhancing Oncology Care

In June 2011, Massachusetts General Hospital celebrated the opening of the new Lunder Building—a 530,000-square-foot 14-floor facility offering the latest in medical technology and architectural design. The building includes expanded areas for radiation oncology and inpatient cancer care at the heart of the main campus.

The new James M. and Ruth P. Clark Center for Radiation Oncology, located on the lowest two floors of the Lunder Building, features linear accelerators with sophisticated enhancements for state-of-the-art radiation therapy. The center’s open floor plan was designed specifically to facilitate collaboration among caregivers from multiple specialties engaged in radiation therapy, and to provide space for increased supportive services for patients, ranging from yoga classes to nutrition counseling.

The Lunder Building’s new W. Gerald Austen, MD Inpatient Care Pavilion reflects similar attention to detail. Lunder floors 9 and 10 have been designated as medical oncology floors. All patient rooms on Lunder 10 are set up for protective isolation for bone marrow transplant patients and others with similar needs. The entire unit maintains a positive pressure environment in which the airflow is carefully managed to help minimize and prevent infection. Lunder 9 and 10 also include an exercise room specifically designed for oncology inpatients, an infusion suite, and a satellite pharmacy for inpatients.

FDA Approves Denosumab for Patients with Prostate Cancer

On September 16, 2011, the U.S. Food and Drug Administration (FDA) granted approval for denosumab as a treatment to increase bone mass in patients who are at high risk of fracture from androgen deprivation therapy (ADT) for nonmetastatic prostate cancer or from adjuvant aromatase inhibitor therapy for breast cancer. In men with nonmetastatic prostate cancer, denosumab reduced the incidence of vertebral fracture.

The FDA decision regarding prostate cancer was based on an international randomized double-blind placebo-controlled phase 3 clinical trial led by Matthew R. Smith, MD, PhD, director of the genitourinary malignancies program at the Mass General Hospital Cancer Center. Dr. Smith and his colleagues enrolled 1,468 men who had been treated with ADT for nonmetastatic prostate cancer, and who were either older than 70 years of age or considered at risk of developing fractures based on bone density measurements or medical history.

Study results showed that bone mineral density measurements were significantly higher in the denosumab group, versus a placebo group. In addition, at 36 months, the proportion of men with new vertebral fracture was 1.5 percent in men treated with denosumab compared with 3.9 percent in men treated with placebo.

Awards and Honors

- Michael R. Stratton, PhD, director of the Wellcome Trust Sanger Institute and joint head of the Cancer Genome Project at the Sanger Institute, received the sixth annual Massachusetts General Hospital Award in Cancer Research in April 2011. Dr. Stratton is an international authority in the cancer genetics field.
- In April 2011, Daniel A. Haber, MD, PhD, director of the Mass General Cancer Center, was elected to the American Academy of Arts and Sciences, one of the nation’s most prestigious honorary societies and a leading center for independent policy research.
- Jeremy S. Abramson, MD, director of the Center for Lymphoma was named to the Jon and Jo Ann Hagler Chair in Lymphoma at the Mass General Cancer Center in June 2011.
- In September 2011, the American Academy of Child & Adolescent Psychiatry named Paula K. Rauch, MD, founder and director of Mass General Cancer Center’s Marjorie E. Korff Parenting At a Challenging Time (PACT) Program, as recipient of the 2011 Simon Wile Leadership in Consultation Award. The award recognizes outstanding leadership and continuous contributions in the field of liaison child and adolescent psychiatry.
- Two prominent Mass General physicians were elected to the Institute of Medicine (IOM) in October 2011: Jay S. Loeffler, MD, chief, Department of Radiation Oncology at Mass General, and James H. Thrall, MD, chief, Department of Imaging. Election to the IOM is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service.
- Cancer researchers J. Keith Young, MD, PhD, Andrea McClatchey, PhD, and Lee Zou, PhD, received three of the five Massachusetts General Hospital Research Scholar Awards for 2011.

New Physicians Join the Cancer Center:

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<thead>
<tr>
<th>Clinical Area</th>
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<tr>
<td>HEMATOLOGY ONCOLOGY</td>
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<td>Breast Cancer</td>
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<td>NEUROSURGERY</td>
<td>Dan Cahill, MD</td>
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Milestone Gift Establishes the Henri and Belinda Termeer Center for Targeted Therapies

A gift of $10 million from Henri and Belinda Termeer, announced on September 13, 2011, will enable the Mass General Cancer Center to expand its efforts in the important new field of targeted cancer therapies. Through the creation of the Henri and Belinda Termeer Center for Targeted Therapies, the former chief executive of Genzyme Corporation and his wife, both longtime supporters of the hospital, are advancing the Cancer Center’s effort to cut the average time for cancer drug development from 10 years to five.

José Baselga, MD, PhD, chief of the Division of Hematology/Oncology and associate director of the Cancer Center, will lead the Termeer Center, which will offer a comprehensive translational research program to develop and test treatments designed to attack specific genetic mutations responsible for an individual patient’s tumor. The new center will speed the discovery and delivery of new targeted therapies and significantly expand the number and range of clinical trials available to patients.

Henri Termeer serves on the hospital’s Board of Trustees and Belinda Termeer is a director on the Cancer Center’s Leadership Council.

For more information about the Henri and Belinda Termeer Center for Targeted Therapies, visit massgeneral.org/targetedtherapy.

Breast Cancer Reduced by More than Half in Postmenopausal Women

At the 2011 annual meeting of the American Society of Clinical Oncology (ASCO), Paul E. Goss, MD, director of the breast cancer research program at the Mass General Hospital Cancer Center, announced that the hormone-blocking drug exemestane reduced breast cancer cases by more than half in postmenopausal women enrolled in an international study.

“We proved that exemestane reduced the risk of invasive breast cancer by 65 percent,” said Dr. Goss, lead author of the study that was published in the New England Journal of Medicine.

The seven-year study followed 4,560 postmenopausal women from the United States, Canada, Spain, and France who had at least one risk factor for breast cancer. The women were randomly assigned to two groups: one that received a placebo and one that took exemestane. After three years, there were 11 invasive breast cancers among the women receiving exemestane compared with 32 in the placebo group. Additionally, there were fewer precursor lesions found in women receiving the drug.

Women who received exemestane experienced more hot flashes, fatigue, sweating, and insomnia than those who received the placebo. Other potential side effects, including bone fractures, osteoporosis, and cardiovascular effects, were the same in both groups. Only a small percentage of women who might benefit from risk-reducing drugs for breast cancer currently take them.

Keith D. Lilemoe, MD, Appointed to Lead Department of Surgery

Keith D. Lilemoe, MD, a world-renowned general surgeon who specializes in pancreatic and biliary surgery, began his tenure as Mass General’s surgeon-in-chief and chief of the Department of Surgery this past May. Prior to his new role, Dr. Lilemoe spent 27 years at Johns Hopkins in Baltimore and most recently led the Department of Surgery at Indiana University Hospital in Indianapolis. Lilemoe succeeds Andrew L. Warshaw, MD, who led the department for 14 years.
Selected Open Clinical Trials

The Massachusetts General Hospital Cancer Center conducts nearly 400 clinical trials in collaboration with DF/HCC. Selected Mass General trials currently enrolling patients are listed here. For a complete list, go to: massgeneral.org/trials.

**GYNECOLOGIC CANCERS**

**09-286** A Phase 2, Multicenter, Single-Arm Study Evaluating Carboplatin/Gemcitabine in Combination With BSI-201 in Patients with Platinum-Resistant Recurrent Ovarian Cancer  
Phase 2  
Michael J. Birrer, MD, PhD  
617-724-4800

**HEAD AND NECK CANCERS**

**10-308** A Phase 2 Study Of Proton Beam Therapy For Locally Advanced Sinonasal Malignancies  
Phase 2  
Annie W. Chan, MD  
617-726-7559

**HEMATOLOGY**

**2009 P002612 TMH-08** A Randomized Trial to Determine if There Is a Clinically Important Difference Between the Effect of Shorter Storage-Age RBCs vs. Longer Storage-Age RBCs on Clinical Outcome and Mortality Risk (RECESS)  
Phase 2  
Christopher P. Stowell, MD  
617-726-2815

**LYMPHOMA**

**10-271** A Phase 2 Trial of Ofatumumab for Initial Systemic Treatment of Indolent B-Cell Lymphomas  
Phase 2  
Jeremy S. Abramson, MD  
617-726-8743

**MELANOMA**

**10-056** An Open-Label, Dose-Escalation, Phase 1 Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of the BRAF Inhibitor GSK2118436 in Combination with BRAF Mutant Metastatic Melanoma  
Phase 1  
Keith T. Flaherty, MD  
617-726-1941

**MULTIPLE MYELOMA**

**11-053** A Phase 1/2, Open-Label, Multicenter Study of ACY-1215 Administered Orally as Monotherapy and in Combination With Bortezomib and Dexamethasone for the Treatment of Relapsed or Refractory Multiple Myeloma  
Phase 1/2  
Noopur Raje, MD  
617-724-4000

**NEURO-Oncology**

**09-468** An Open-Label, Phase 2 Trial of Orally Administered PF-00299804 in Adult Patients with Relapsed/Recurrent Glioblastoma (GBM)  
Phase 2  
Andrew S. Chi, MD, PhD  
617-643-5530

**PEDIATRIC CANCERS**

**09-273** Reduced-Duration Stanford V Chemotherapy With or Without Low-Dose Tailored-Field Radiation Therapy for Favorable Risk Pediatric Hodgkin’s Lymphoma  
Phase 2  
Alison M. Friedmann, MD  
617-726-2737

**SARCOMA**

**09-352** A Phase 1/2 Study of PCI-24781 in Combination With Doxorubicin for Treatment of Advanced Sarcomas Following Failure of Prior Anthracycline Therapy  
Phase 1/2  
Edwin Choy, MD  
617-643-0230

**TARGETED THERAPEUTICS**

**10-262** A Phase 1A, Multicenter, Open-Label Dose Escalation Study of Oral BYL719, in Adult Patients with Advanced Solid Malignancies, Whose Tumors Have a Mutation of the PIK3CA Gene  
Phase 1  
José Baselga, MD, PhD  
617-726-2606

**THORACIC CANCERS**

**11-126** A Phase 2, Double-Blind, Placebo-Controlled Study of IPI-504 and Docetaxel in Previously Treated Patients With Stage IIIIB or IV Non-Small Cell Lung Cancer  
Phase 2  
Rebecca Heist, MD  
617-726-4000
have shown that they are well tolerated; results in preclinical animal models have also demonstrated that inhibition of HIF leads to cancer suppression. In addition to providing therapeutic opportunities, understanding of HIF expression in human solid tumors and blood cancers also may have strong predictive value for judging the likely course of disease. The Iliopoulos Lab has used the molecules it identified as HIF inhibitors as chemical probes to dissect the HIF pathway at the molecular level. This work, combined with proteomic studies of blood and tumor samples from patients with renal cell carcinoma (RCC), has led to the identification of a set of biomarkers for measuring tumor activity. These biomarkers may serve as early warning signals for the presence of RCC, as well as surrogate markers for disease activity in patients enrolled in clinical trials.

At the Mass General Cancer Center, improved understanding of the effects of anti-angiogenic agents in patients and of the cellular pathways involved in new vessel formation has created multiple opportunities for the development of drugs and diagnostic tools. Research in the Jain, Iliopoulos, and other labs at the Mass General Cancer Center will continue to build on this knowledge to improve patient care.

Achieving the Promise of Anti-Angiogenic Therapies

Selected References


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Continued from page 7