Circulating Tumor Cell (CTC) caught in the act of dividing. Orange cell is in mitosis and has mixed androgen receptor (AR) signaling activity. Green cell is a contaminating white blood cell.

Massachusetts General Hospital Cancer Center researchers developed an assay that preliminary evidence shows may help target men who will benefit from new second-line treatments for metastatic prostate cancer. The assay is based on Circulating Tumor Cells (CTCs) captured with a microfluidic device called the HBCTC-chip (Herringbone CTC-chip), which was invented at Mass General Hospital in 2010. If validated, the assay would provide a noninvasive and rapid blood test to monitor treatment response at a stage when time is of the essence. This work was featured in the November 2012 issue of Cancer Discovery.

Approximately 90 percent of the 217,000 cases of prostate cancer diagnosed in the United States each year are localized and amenable to cure, but the remainder—for reasons yet unknown—develop metastatic disease. Androgen deprivation therapy is initially effective for metastatic prostate cancer, but within several years, the majority of these men become resistant to the therapy. Potent secondary hormonal therapies are being introduced into the clinic for these cases of castration-resistant prostate cancer, but effectiveness varies from patient to patient, suggesting different biomolecular pathways to drug resistance.

To guide therapeutic decisions, there is a need for a biomarker to assess whether the new drugs are reaching their target. Serum PSA is not a reliable marker of treatment benefit in the setting of castration-resistant prostate cancer. Prostate cancer primarily metastasizes to bone and can only be sampled invasively, which is not ideal for measuring treatment response.

The goal of the Mass General Cancer Center research team was to find a biomarker that is reliable to help predict treatment response for castration-resistant prostate cancer. According to David Miyamoto, MD, PhD, Mass General radiation oncologist and researcher in cancer genetics and one of the primary

continued on the next page
CTC-Chip Assay Shows Promise to Personalize Metastatic Prostate Cancer Treatment

authors of the study, the team’s approach was to look at CTCs. CTCs are shed into the bloodstream by cancers and potentially can be analyzed to more accurately understand the biology of the tumor as a response to therapy.

Using the CTC-chip to capture these rare CTCs from patients’ blood samples, the research team conducted molecular analyses and developed an assay that shows promise as a biomarker. If preliminary results are successfully validated, the Evans Assay (named in recognition of support from the Evans Foundation) may help individualize a patient’s prostate cancer treatment, as well as provide new scientific insights into the role of the androgen receptor pathway in prostate cancer progression.

Applying the CTC-Chip to Prostate Cancer Studies

This avenue of research was made possible by the invention of the first-generation CTC-chip at Massachusetts General Hospital. Mehmet Toner, PhD, a bioengineer at Massachusetts General, and Daniel A. Haber, MD, PhD, director of the Massachusetts General Cancer Center, led a large team of engineers, cancer clinicians, and scientists who developed the first-generation CTC microchip. The CTC-chip uses a microfluidic design to isolate CTCs in a patient’s blood with a sensitivity that had not been seen before. Massachusetts General researchers tested the device across several different cancer types, including prostate, breast, pancreas, and colorectal cancers, and published their findings in *Nature* in 2007. The original team members included molecular biologist Shyamala Maheswaran, PhD; medical oncologist Lecia Sequist, MD; and engineer Sunitha Nagrath, PhD.

Members of the team that developed the CTC-chip then collaborated with Shannon Stott, PhD, an engineer; Richard J. Lee, MD, PhD, a Cancer Center medical oncologist; and Dr. Miyamoto to develop new imaging technologies to more specifically detect and analyze prostate cancer CTCs. Researchers first analyzed blood samples from both localized and metastatic patients to ascertain whether CTCs were present in both and if they were useful to monitor treatment responses. In cases of metastatic disease, researchers observed that the numbers of CTCs after initiation of therapy tended to drop, indicating a response to treatment. In localized prostate cancer, researchers were also able to detect CTCs in a subset of patients, but after radical prostatectomy, CTCs for the majority had disappeared, reports Dr. Miyamoto.

That promising work was published in *Science Translational Medicine* on March 31, 2010, and prompted the team to expand their focus. Previously, the focus had been on the significance of numbers of CTCs in the blood and then was expanded to include the molecular signaling events within CTCs. Technological advances made in 2010 to the CTC-chip made it possible to examine signaling activity at the single-cell level. The second-generation Herringbone CTC-chip (*hCTC-chip*), developed by a team of engineers led by Dr. Stott (*Proceedings of the National Academy of Sciences*, 2010), has improved sensitivity and is transparent. The transparency enabled researchers to perform a combination of high-resolution imaging and sophisticated molecular analysis. The CTCs became the means for trying to understand the molecular events in the tumors in response to therapies, Dr. Miyamoto explains.

The growth and survival of prostate cancer cells are highly dependent on signals received from androgens through the androgen receptor (AR) protein. Androgen deprivation therapy, the first line of therapy for metastatic prostate cancer, works by depriving the androgen receptor of its signal. That therapy is highly effective in most patients initially, but within several years, nearly all of these cancers become resistant.

One of the leading hypotheses for why the cancer becomes castration-resistant is that AR signaling becomes reactivated despite the low levels of serum testosterone during androgen deprivation therapy, according to Dr. Miyamoto. As of 2010, there have been several new drugs introduced into the clinic that inhibit AR signaling by different mechanisms than first-line androgen deprivation therapy. These

Key Points

- Mass General Cancer Center researchers developed an assay that isolates and analyzes cancer cells circulating in a patient’s blood.
- Researchers can use that assay (Evans Assay) to detect and follow changes in androgen receptor signaling before and after treatment.
- The analysis of androgen receptor signaling could potentially guide choice of treatment for patients with metastatic prostate cancer.
- The CTC-chip’s future usefulness may extend to early detection of prostate cancer and for identifying who should be treated before the cancer has metastasized.
drugs include abiraterone acetate, MDV3100, ARN-509, and TAK-700. The U.S. Food and Drug Administration approved abiraterone acetate in 2011 and MDV3100 in 2012 for the treatment of castration-resistant prostate cancer.

Dr. Miyamoto and his colleagues traced AR signaling changes in CTCs before and after administering hormonal agents, including abiraterone acetate. To measure the activity of AR signaling within the individual cells, researchers established a quantitative immunofluorescence assay (Evans Assay) based on the expression of AR-regulated genes. The assay provided a clear measure of whether the AR pathway had been reactivated after resistance to androgen deprivation therapy. The team perfected this assay in prostate cancer cell lines and then applied it to CTCs obtained from men with metastatic prostate cancer.

Findings on Treatment Response
Dr. Miyamoto reports that in patients who had not yet had androgen deprivation therapy, the AR cell signaling pathway was predominantly turned on in the CTCs. After the initiation of androgen deprivation therapy, the signaling was turned off, which is precisely what is expected if the therapy is effective.

In contrast, researchers found that men with castration-resistant prostate cancer had highly variable AR signaling responses in their CTCs, before and after treatment. Before treatment, some men had CTCs with androgen receptor signaling turned on (AR-on cells), others had AR-off cells, and still others had AR-mixed populations. That variability was present when looking at different patients, as well as when looking at different sets of cells isolated from any one patient.

Mixed signaling was also observed after treatment with abiraterone acetate. The presence of AR-mixed CTCs—revealing a confusion in the AR signaling pathway, which abiraterone acetate targets—was associated with an adverse treatment outcome. There was also decreased overall survival in another subpopulation of castration-resistant prostate cancer patients: those whose percentage of AR-on cells increased after initiating abiraterone acetate treatment. Neither of these subpopulations responded to the drug.

The 2012 Cancer Discovery study is proof of principle that it is possible to monitor AR signaling in patients with metastatic prostate cancer, according to Dr. Miyamoto. Using CTC-chip technology to isolate CTCs from patients with metastatic prostate cancer, the researchers did this in real time, repeatedly and noninvasively, and observed changes in AR signaling as a result of therapy.

Dr. Miyamoto emphasizes that these early results indicate that changes in AR signaling may be correlated with patient prognosis. Before the Evans Assay will be clinically useful, however, it must be validated in a larger clinical trial, which Drs. Miyamoto and Lee are initiating at the Cancer Center.

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Biomarkers Are Changing Glioblastoma Prognosis and Management

Glioblastoma is the most common and aggressive type of malignant primary brain tumor. Current glioblastoma treatment options are not highly effective at prolonging survival; with standard multimodal treatment, median survival for primary glioblastoma is approximately 15 months. Because of this, it is increasingly recognized that more personalized glioblastoma treatments will need to be developed to target the specific molecular characteristics of different tumors.

Researchers now recognize that multiple glioblastoma subtypes exist, with distinct molecular traits. Indeed, the first recognition that there were different molecular subtypes of glioblastoma came from research at Massachusetts General Hospital that was published in 1993. The identification of these and subsequently discovered glioblastoma biomarkers is providing neuro-oncologists at the Massachusetts General Hospital Cancer Center with key prognostic input and important information toward developing long-term treatment plans.

Historically, the relatively small number of patients affected by glioblastoma has presented a challenge to achieving the critical mass needed to carry out adequately powered clinical studies. This challenge multiplies when a tumor is further divided into subtypes based on molecular analysis. However, physician researchers at the Mass General Cancer Center have made it a priority to position themselves as a key referral center for these cases and can effectively and rapidly enroll patients in clinical trials that match their tumor characteristics.

Genetically Complex Tumors
Certain glioblastomas will have varying genetic markers in different regions of the tumor; a recurrent tumor may also have different characteristics from a primary tumor. The coexistence of multiple tumor markers can make treatment decisions complex, with patients often requiring a combination of carefully targeted therapies.

One study conducted by Mass General Cancer Center researchers identified up to three unique receptor tyrosine kinases (RTKs) coamplified in approximately 5 percent of glioblastoma tumors. These mosaic molecular changes were identified in tumors that had not received prior chemoradiation or RTK inhibitory treatment.

To prospectively detect the range of genomic alterations present in each tumor, Mass General Cancer Center physicians use a broad-based cancer genotyping platform, based on SNaPshot technology. The analysis is a high-throughput tumor genotyping program that, along with other molecular diagnostic tests, is part of standard postsurgical evaluation of patients with newly diagnosed primary and secondary glioblastomas. The diagnostic test evaluates tumor DNA for more than 100 well-characterized cancer mutations, several of which are relevant for glioblastoma prognosis and/or management. In addition, other molecular diagnostic tests assess for gene amplification, translocation, and methylation. The information obtained from this profiling is used to develop prognostic projections and to match patients to relevant treatment protocols and clinical trials.

Methylated vs. Unmethylated MGMT
One key prognostic biomarker for glioblastoma is the methylation status of the promoter (a regulatory region) of a gene known as methylguanine-DNA methyltransferase (MGMT). MGMT is a DNA-repair enzyme and mediator of patient resistance to chemotherapy. Following surgical resection, the tumor specimen is evaluated to determine
Key Points

- Glioblastoma research is shifting toward more specialized clinical trials that subdivide patients based on their tumor’s molecular characteristics.
- Increasingly, biomarker assessment is a prerequisite for clinical trial enrollment in patients with glioblastoma.
- Glioblastoma patients at the Mass General Cancer Center receive broad-based cancer genotyping, based on SNAPSHOT technology, and a standard panel of other molecular diagnostic tests as part of postsurgical evaluation; many of these markers are relevant for glioblastoma prognosis and/or treatment.
- Mass General is one of only a few sites nationwide with the expertise and infrastructure to direct patients with glioblastoma toward the most appropriate clinical trial.
- Mass General is at the forefront of implementing new imaging techniques that may identify glioblastoma biomarkers more rapidly and noninvasively.

whether the MGMT gene promoter is methylated or unmethylated. Activated (unmethylated) MGMT can mediate resistance to chemotherapy; therefore, individuals with methylated, or inactivated, MGMT have improved survival rates. The percentage of glioblastoma patients with methylated MGMT has ranged from 45 percent to 58 percent.

There are other benefits to knowing a patient’s MGMT status. According to Tracy T. Batchelor, MD, executive director of Mass General Cancer Center’s Stephen E. and Catherine Pappas Center for Neuro-Oncology, it has historically been challenging to interpret a patient’s first MRI after completion of chemotherapy and radiation. During this time, it can be unclear whether changes to MRI readings are due to progressive tumor development or tissue destruction, a sign of effective treatment. However, knowing that a patient’s MGMT is methylated provides a strong indicator that any early observable MRI changes are treatment-related.

Knowledge of a patient’s MGMT status is increasingly becoming a prerequisite for clinical trial enrollment.

Currently, there are two international trials evaluating patient outcomes based on MGMT status (one trial is enrolling only patients with methylated MGMT, while the other is recruiting patients with unmethylated MGMT).

EGFR Amplification

Amplification of the epidermal growth factor receptor (EGFR) gene, observable via the clinical molecular profiling panel used by Mass General, is one of the most common gene mutations in glioblastoma. According to Andrew S. Chi, MD, PhD, an instructor in Neurology at Mass General, nearly one-half of glioblastoma tumors harbor EGFR amplification, and the EGFR gene can be present in tumors in huge copy numbers relative to normal cells. This amplification may drive tissue growth in a subset of glioblastoma patients. EGFR amplification is an attractive candidate for therapeutic intervention because solid preclinical data exists in glioblastoma and abundant evidence of the efficacy of EGFR-inhibitory treatment exists for other cancer types.

The Mass General Cancer Center is currently participating in a multicenter phase 2 clinical trial of dacomitinib, a potent and irreversible inhibitor of the EGFR receptor, in patients whose tumors have progressed following standard therapy. One advantage of dacomitinib is that unlike other EGFR inhibitor drugs tested in glioblastoma, it has some degree of central nervous system penetration. In addition, since this clinical trial is only enrolling patients with EGFR amplification, it is expected that its results will provide critical information to determine whether EGFR amplification is a true biomarker for treatment decision making.

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FISH analysis of cells from a single tumor shows coamplification of two different receptor tyrosine kinases (shown in red and green).
**IDH1 Mutation**

Another key prognostic mutation that molecular analysis provides information on is the isocitrate dehydrogenase 1 (IDH1) gene. IDH1 mutations occur in approximately 12 percent of glioblastoma patients and are particularly common among young patients and glioblastomas that developed from prior lower-grade tumors. The presence of mutated IDH1 is associated with improved overall survival (3.8 vs. 1.1 years for patients with normal IDH). This suggests that patients with mutated IDH1 are a clinically discrete patient subgroup, although it is not yet clear whether any relationship exists between IDH1-mediated survival time and specific therapeutic approaches. However, it is likely that researchers’ understanding of this relationship will progress rapidly over the next several years. IDH1-inhibitory treatments are currently being developed, and animal trials are now under way.

In the near future, Mass General may be able to use a less invasive approach to identify IDH1 mutations. The metabolite 2-hydroxyglutarate (2HG) accumulates in gliomas with IDH1 mutations; 2HG can be used as a biomarker for the presence of mutated IDH1. In 2012, Ovidiu Andronesi, MD, PhD, and colleagues from Mass General published the results of a pilot study that used optimized in vivo spectral editing magnetic resonance spectroscopy (MRS) and two-dimensional correlation spectroscopy (COSY) to noninvasively identify 2HG accumulation in patients with IDH1 mutations in *Science Translational Medicine*. With this approach, investigators were able to noninvasively obtain detailed IDH1 molecular characterization profiles prior to surgical resection, with important implications for tumor diagnostic workup and treatment decision making. This new technological approach may open new ways to select patients for clinical trials, as well as track the effects of specific therapies on glioblastomas with IDH1 mutations.

*Figure A (left) shows an MRI scan of a patient with a malignant glioma harboring an IDH1 mutation. The characteristic 2HG cross-peak in the Hα-Hβ region (area within the red rectangle) is highlighted. Figure B (right) shows a patient with a glioblastoma lacking the IDH1 mutation. This region does not include any Hα-Hβ region cross-peak.*

**The Role of 1p and 19q Codeletions in Anaplastic Oligodendroglioma Prognosis and Treatment**

Research conducted collaboratively by Mass General’s Department of Pathology and investigators at the London Regional Cancer Centre (Ontario) at the University of Western Ontario more than a decade ago is contributing now to breakthroughs in glioma management. The RTOG 9402 study, presented at the 2012 American Society of Clinical Oncology (ASCO) meeting in Chicago, evaluated the long-term benefits of chemotherapy plus radiotherapy (CT+RT) compared with RT alone in patients with anaplastic oligodendroglioma, another glioma type. Combined treatment was associated with improved progression-free survival (2.5 vs. 1.7 years, p=0.003). However, investigators also found that the presence of 1p and 19q chromosomal codeletions, the most common chromosomal abnormality in oligodendroglioma, was associated with dramatically improved overall survival in both pure and mixed tumors, regardless of treatment modality (8.7 vs. 2.7 years, p<0.001).

The potential prognostic role of 1p and 19q status was first identified by David Louis, MD, chief of the Department of Pathology, Mass General, and senior author of this article. The authors observed that 50 to 70 percent of anaplastic oligodendrogliomas showed a loss of the 1p/19q chromosomal arms and posited that this information might be useful to both predict treatment response and develop prognostic assessments.

An earlier report on the RTOG 9402 study, summarizing patient outcomes after a minimum three years of follow-up, found no survival...
difference regardless of treatment approach, although significant benefit was observed for progression-free survival. The 2012 study, however, represented 11 years of patient follow-up and confirmed improved survival rates for patients with 1p/19q codeletions, independent of treatment used (CT+RT: 14.7 years; RT: 7.3 years, p=0.03), as well as a significant survival benefit with CT+RT compared with RT alone.

Fourteen years after the relationship between 1p/19q in anaplastic oligodendroglioma was first identified, updated results from the RTOG 9402 study results have fully validated the original observations of Louis and J. Gregory Cairncross, MD. Testing for 1p and 19q codeletions now plays a pivotal role in anaplastic oligodendroglioma decision making and is part of the standard profile generated by physicians at the Mass General Cancer Center.

Clinical Impact
According to Dr. Batchelor, glioma research is shifting toward more specialized clinical trials that subdivide patients into groups based on molecular tumor characteristics. In other words, the era of identifying and testing targeted therapies for glioblastoma is officially under way. Dr. Chi emphasizes that the Mass General Cancer Center has developed a practical yet robust platform to genotype gliomas in a short time frame. This not only makes it possible to incorporate molecular profiling into standard clinical evaluation but has also facilitated a more rational, targeted approach to enrolling patients in early-stage clinical trials. Mass General is one of only a few sites nationwide that is able to direct patients with glioblastoma toward the most appropriate clinical trial.

Currently, when glioblastoma tumors recur or progress during standard therapy, very few effective and/or low-toxicity second-line treatments are available for patients. However, the work that the Mass General Cancer Center is conducting to identify biomarkers and determine their prognostic and predictive roles will likely drive the next wave of therapeutic innovation for glioblastoma patients.

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Biliary tract cancers (BTCs) encompass both cholangiocarcinoma, which is further subdivided into intrahepatic, perihilar, or distal cholangiocarcinoma, and carcinoma arising from the gallbladder. Although BTCs are generally grouped together due to their anatomic proximity, growing evidence from their clinical behavior and response to therapy suggests that these cancers may differ substantially. New research from staff at the Massachusetts General Hospital’s Translational Research Laboratory (TRL) and Massachusetts General Hospital Cancer Center’s Tucker Gosnell Center for Gastrointestinal Cancers may provide one major genetic explanation. In a paper published in January 2012 in *The Oncologist*, the research team discovered that a significant number of cholangiocarcinomas possess a genetic mutation in the gene encoding for the isocitrate dehydrogenase (IDH)1 or IDH2 enzyme. These mutations were found only in intrahepatic cholangiocarcinoma (ICC) tumors—or cancers arising in the bile duct within the liver. About 25 percent of ICC tumors had mutations in either the *IDH1* or *IDH2* gene.

Spearheaded at Mass General by Andrew X. Zhu, MD, PhD, director of hepatobiliary research at the Tucker Gosnell Center for Gastrointestinal Cancers; A. John Iafrate, MD, PhD, co-executive director of the TRL; and Darrell R. Borger, PhD, co-director of the TRL, in collaboration with several groups including those with new drug development expertise, this research represents the first time that mutations in the gene encoding for the metabolic enzyme IDH1 or IDH2 were detected in cholangiocarcinoma.
gene mutations that were evaluated with this genotyping platform, including PIK3CA, KRAS, NRAS, and AKT1. The IDH mutation was not detected in a single extrahepatic bile duct or gallbladder tumor. This result strongly suggests that IDH1 and IDH2 gene mutations are clinically relevant in ICC and represent a novel therapeutic target in this malignancy.

Developed by the TRL (also led by Leif W. Ellisen, MD, PhD, and Dora Dias-Santagata, PhD), the clinically validated Mass General SNaPshot platform allows for a molecular stratification of cancer patients and in some cases allows for placement of patients into trials of novel agents that target specific mutated gene products. Reimbursed by insurance, this analysis is routinely available to Mass General oncologists who find that mutational profiling information can be relevant for the treatment of their patients. With this technique, many mutations can be interrogated simultaneously.

Researchers do not yet have a complete understanding of the underlying genetic mechanisms of cholangiocarcinoma, and clinical trials targeting various oncogenic alterations have been disappointing in the treatment of the disease. This could be because the most appropriate subset of cholangiocarcinoma patients was not chosen. Or it could indicate that the gene mutations that were evaluated with this genotyping platform, including PIK3CA, KRAS, NRAS, and AKT1. The IDH mutation was not detected in a single extrahepatic bile duct or gallbladder tumor. This result strongly suggests that IDH1 and IDH2 gene mutations are clinically relevant in ICC and represent a novel therapeutic target in this malignancy.

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Key Points

- Cholangiocarcinoma (bile duct cancer) subtypes have largely been indistinguishable by histological or genetic mutational analysis.
- New research from Mass General and collaborators finds that mutations in the gene encoding for the isocitrate dehydrogenase 1 or 2 enzyme are present in cholangiocarcinomas but not in other types of biliary tract cancers.
- Nearly 25 percent of intrahepatic cholangiocarcinomas contain mutations in IDH1 or IDH2.
- The end product of mutated IDH enzymatic activity, 2-hydroxyglutarate, may represent an oncometabolite contributing to cholangiocarcinoma tumor development.
- Mass General researchers are collaborating with pharmaceutical partners to expedite clinical trial activity of new IDH inhibitors in patients with IDH mutations.
More than 12,000 people in the United States are diagnosed with BTCs each year, and the overall five-year survival rate is poor, even for those diagnosed with local disease. Standard chemotherapy involving gemcitabine and cisplatin remains inadequate, and clinicians are eager to identify subgroups of cholangiocarcinoma patients with well-defined molecular signatures. Cholangiocarcinoma is the second most common form of liver cancer, with incidence and mortality rates that have been increasing over time. Further understanding of the mutant IDH enzyme and identification of those with genetically susceptible disease offers the possibility of improved targeted treatment.

**IDH Detected in Other Cancers**

IDH mutations have previously been described in a very limited number of cancer types. Recurrent mutations were first found in 2008 in glioblastomas and have since been identified in about 70 percent of low-grade gliomas or secondary glioblastomas, 20 percent of acute myeloid leukemia cases, and more than 50 percent of central chondrosarcoma tumors. Outside of that, IDH mutations are rare in all other cancer types that have been tested to date. As a result, the patient population with these mutations appears to be very confined.

The identification of the IDH1/2 mutations in cholangiocarcinoma was a fortuitous discovery. Researchers at the TRL added the IDH1 test to the standard SNaPshot panel to serve as a prognostic indicator for neuro-oncologists treating patients with glioma. Consistent evidence suggests the presence of IDH1 mutation in glioma is associated with a better prognosis. Neuro-oncologists wanted to use the IDH test to identify glioma patients with this mutation in order to better optimize the management of these patients.

As it became apparent that IDH1/2 gene mutations were being detected in cholangiocarcinoma patients during routine SNaPshot clinical testing, the TRL team retrieved past tumor samples from pathology archives for more extensive analysis with hundreds of patient samples. Since the 2012 Mass General paper was published, two other groups have published independent findings suggesting that IDH mutations might be associated with better prognosis in cholangiocarcinoma. To further assess whether these mutations can be associated with any additional clinical variables, Dr. Zhu and Dr. Borger have initiated a research partnership with multiple institutions, particularly The Johns Hopkins University, to conduct a larger study of hundreds of patient samples. They will be investigating IDH1/2 mutational status, patient characteristics, and histological markers, among other variables, to see if IDH mutant cases have a more favorable outcome and are associated with other clinical and pathologic variables.

**Focus on IDH End Product**

Normal IDH1 and IDH2 enzymes function to convert isocitrate to alpha-ketoglutarate. However, mutant IDH produces 2-hydroxyglutarate (2-HG) as the end product. This metabolite accumulates to very high levels in tumors with the mutation. In the

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**Borger et al. Figure 1**

There are distinct differences in the gene mutation signature of cholangiocarcinomas versus gallbladder tumors. The novel finding of IDH1 and IDH2 gene mutations in a subset of cholangiocarcinoma patients may suggest a new direction for therapeutic targeting.
Mass General analysis, 2-HG was found to accumulate to levels up to 250-fold above normal. While it is believed to act as an oncometabolite, the exact means by which 2-HG contributes to the tumorigenic process remains under active investigation. There is growing evidence that an important mechanism involves the ability of 2-HG to interfere with the activity of enzymes known as dioxygenases, which have a number of cellular functions. Some of these dioxygenases are key epigenetic regulators, and high intracellular levels of 2-HG can inhibit their function and promote DNA and histone methylation. The result is that the expression of many genes can be simultaneously silenced. If some of those genes are important regulators of differentiation, survival, or proliferation, silencing them could contribute to driving tumorigenesis.

2-HG may also represent a disease biomarker, since it is a direct product of mutant IDH1 and IDH2 activity in tumor cells. At high levels within the tumor, an active question being addressed by the Mass General group is whether 2-HG enters the bloodstream, where it offers the potential for use as a measure of disease burden over the course of treatment. This can provide a new approach to gauge how well a therapy is working for a particular patient.

On Track for IDH Inhibition

The natural progression of this research between clinicians and pharmaceutical companies is to explore the role of IDH inhibitors. Drs. Zhu, Iafrate, Borger, and colleagues at Mass General are working closely with a couple of pharmaceutical partners with the goal of bringing IDH inhibitors into the first-in-human clinical trials. The recent paper revealing the IDH gene signature discovery in cholangiocarcinoma is an example of how Mass General approaches genetic studies in a very purposeful collaborative manner in order to bring new findings into the clinical realm as quickly and efficiently as possible.

Through the Mass General TRL, IDH1 mutational analysis has been standard practice for a couple of years. Testing for IDH2 mutations is now available as well. To date, a base of more than 100 patients has already been identified with IDH mutation, representing a pool of potential candidates for evaluation of IDH inhibitors. Also, the infrastructure is in place to support ongoing clinical trial accrual based on IDH status. As such, Mass General is considered among one of the leading institutions ready to participate in first-in-human studies as new drugs become available.

Though it is not yet possible to know when new IDH-targeted drugs will enter the clinic, the partnership of research and clinical expertise at Mass General, coupled with pharmaceutical drug developers, is an example of how the Mass General TRL focuses on efforts with the highest chance of providing a direct clinical benefit. In the case of IDH1/2 mutations in bile duct cancer, the hope is to expand treatment options and offer access to early phase 1 studies in patients with genetically appropriate tumors.

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Celebrating 10 Years of Proton Therapy on the Mass General Campus and Approval for Program Expansion

The 10th anniversary of proton beam therapy on the Massachusetts General Hospital campus was celebrated in September. Guests at the event included Victoria Kennedy, wife of the late Sen. Ted Kennedy, who received proton therapy as a Mass General patient. More than 5,500 patients have received proton therapy in the past 10 years, and staff delivers more than 14,000 treatments annually.

“The Proton Therapy Center is a beacon of hope to many. Our goal in the years ahead is to add a second machine so that we can provide this treatment to every patient who needs it,” says Jay Loeffler, MD, chief of the Department of Radiation Oncology at Mass General.

In fact, Mass General is well on its way to achieving this goal. In October, the Massachusetts Department of Public Health unanimously approved Mass General’s application for a second proton treatment machine to be located in the Lunder Building. The addition of a second cyclotron represents an important step in improving patients’ access to this critical treatment. In addition, the second unit will provide essential backup capabilities for patients already receiving treatment in cases of downtime affecting either cyclotron. The second cyclotron will also increase Mass General’s ability to conduct clinical research trials and provide further educational opportunities for clinicians.

Mass General’s Sara Kelly Honored as One of Boston Business Journal’s 40 Under 40

This past fall, Sara Kelly, senior managing director of development at the Massachusetts General Hospital Cancer Center, was selected by the Boston Business Journal (BBJ) as one of its 40 Under 40 honorees for 2012. For 15 years, the BBJ has honored hundreds of impressive entrepreneurs and rising business leaders at their 40 Under 40 reception and awards presentation.

Judges reviewed more than 300 nominations, considering professional accomplishments and community involvement. Honorees were selected as business and civic leaders who collectively represent the next wave of talent and commitment in the Boston economy. “Boston’s economy increasingly is being driven by the energy of the next generation of entrepreneurs and executives,” said Chris McIntosh, publisher of the BBJ. “Our 40 Under 40 honorees represent that remarkable wave of talent.”

Mass General Cancer Center to Launch New Website to Connect Users with Clinical Trials of Targeted Cancer Therapies

The Mass General Cancer Center recently developed and is launching an industry-leading website that connects users with the Cancer Center’s innovative clinical research in the field of targeted cancer therapies.

The website features an interactive tool that enables users to search for targeted cancer therapy clinical trials. Users can input as much information as available, searching by disease type, gene, or mutation. Search results are customized to the user and highlight clinical trials that are available at Mass General Cancer Center. The user-friendly format is designed to guide both patients and physicians through what can be an increasingly complex field with unique opportunities.

The hope is that the site will enable users to easily access clinical trial information on targeted cancer therapies, dramatically improving their access to targeted cancer treatment options.

An official launch date will be released soon. Visit massgeneral.org/cancer for the announcement and to learn more information on targeted cancer clinical trials at Mass General Cancer Center.
Mass General Cancer Center’s Henri and Belinda Termeer Center for Targeted Therapies Opens for Clinical Operation

On December 3, Mass General Cancer Center’s Henri and Belinda Termeer Center for Targeted Therapies opened for clinical operation. This dedicated center for phase 1 and 2 clinical trials is located in a newly renovated suite within the Cancer Center’s Yawkey Center for Outpatient Care. The mission of the center is to improve access to new cancer therapies for as many patients as possible and to speed the cycle of discovery. The center brings together many existing resources across the Cancer Center and the hospital to maximize scientific and clinical collaboration. The center was designed to ensure continuity of the patient experience for patients participating in clinical trials. Physicians from each disease center are integrated within the Termeer Center, and the center is staffed by specially trained physicians, nurses, and research staff.

Keith T. Flaherty, MD, has been named the director of the Henri and Belinda Termeer Center for Targeted Therapies. A melanoma specialist and renowned leader in targeted therapies, Dr. Flaherty joined the team in the Center for Melanoma at Mass General in 2009 as the director of Molecular Therapeutics. In addition to his leadership role in the Termeer Center, Dr. Flaherty will continue seeing patients in the Center for Melanoma. The Termeer Center was made possible by a generous gift from Henri and Belinda Termeer.

Keith T. Flaherty, MD, consults with a patient.

David P. Ryan, MD, Appointed as Mass General’s New Chief of Hematology/Oncology

Massachusetts General Hospital’s Department of Medicine and the Mass General Cancer Center are proud to announce the appointment of David P. Ryan, MD, to the position of chief of the Division of Hematology/Oncology at Mass General, effective October 1. Dr. Ryan has served as associate chief of Hematology/Oncology and clinical director of the Cancer Center since 2009. As chief of Hematology/Oncology, Dr. Ryan will succeed José Baselga, MD, PhD, with whom he has worked closely for the past two years.

Dr. Ryan is an authority on the treatment of gastrointestinal cancers, serving as the clinical director of the Cancer Center’s Tucker Gosnell Center for Gastrointestinal Cancers. His expertise has been recognized by membership in leading national committees, including clinical task forces for the National Cancer Institute and the National Comprehensive Cancer Center Network. He currently chairs Partners Healthcare’s Colon Cancer Care Redesign Initiative. Known as one of our institution’s most outstanding, caring, and compassionate clinicians, Dr. Ryan was the recipient of the Cancer Center’s the one hundred award in 2009 and was featured in a 2008 PBS special, The Truth About Cancer. He is known as an exceptional clinical teacher and mentor to medical house staff, clinical oncology fellows, and junior faculty.

As Clinical Director of the Cancer Center, Dr. Ryan oversees the operations of 24 multidisciplinary disease centers, which include participants from various Mass General departments and divisions, including Hematology/Oncology, Surgery, Radiation Oncology, Imaging, Pathology, Psychiatry, and many more. The exceptional clinical success of our integrated Cancer Center is a testament to his skills and leadership.

Dr. Ryan completed his medical residency and chief residency at Columbia Presbyterian Hospital, followed by clinical oncology training within the DF/PCC fellowship program, a joint program between Mass General Cancer Center and Dana-Farber/Brigham and Women’s Cancer Center. He has been on the Mass General faculty since 1998. As Chief of the Division of Hematology/Oncology, he will succeed Dr. Baselga as incumbent of the Bruce A. Chabner, MD, Chair in Hematology/Oncology at Mass General, named after Dr. Chabner, a pioneer in the field of cancer therapeutics at the National Cancer Institute, who led the Mass General Division of Hematology/Oncology from 1995 to 2006.

David P. Ryan, MD
New Physicians Join the Cancer Center

**Clinical Area**

<table>
<thead>
<tr>
<th>Clinical Area</th>
<th>Name</th>
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<tr>
<td>Thoracic</td>
<td>Christopher G. Azzoli, MD</td>
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<tr>
<td>Neuro-Oncology</td>
<td>Priscilla Brastianos, MD</td>
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<tr>
<td>Sarcoma</td>
<td>Gregory Cote, MD, PhD</td>
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<tr>
<td>Gynecologic Oncology</td>
<td>Donald Dizon, MD</td>
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<tr>
<td>Breast</td>
<td>Dejan Juric, MD</td>
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<td>IMAGING</td>
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<td>Abdominal Imaging and Intervention</td>
<td>Sheela Agarwal, MD</td>
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<td>Abdominal Imaging and Intervention</td>
<td>Tarik K. Alkasab, MD</td>
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<tr>
<td>Abdominal Imaging and Intervention</td>
<td>Avinash Kambadakone, MD</td>
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<tr>
<td>Neurological Imaging</td>
<td>Hillary R. Kelly, MD</td>
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<tr>
<td>Abdominal Imaging and Intervention</td>
<td>Arun Krishnaraj, MD</td>
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<td>Musculoskeletal Imaging and Intervention</td>
<td>Frank Simeone, MD</td>
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<td>NEUROSURGERY</td>
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<td>Tumor and Vascular Neurosurgery</td>
<td>Brian Nahed, MD</td>
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<td>PATHOLOGY</td>
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<td>Breast and Gastrointestinal</td>
<td>Amy Ly, MD</td>
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<td>PSYCHIATRY</td>
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<td>Psychiatric Oncology</td>
<td>Kelly Irwin, MD</td>
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<td>RADIATION ONCOLOGY</td>
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<td>High Throughput Drug Screening</td>
<td>Cyril H. Benes, PhD</td>
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<td>Computational Biology</td>
<td>Gad Getz, PhD</td>
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<td>Proteomics and Mass Spectrometry</td>
<td>Wilhelm Haas, PhD</td>
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<td>Bioengineering and Cell Imaging</td>
<td>Shannon Stott, PhD</td>
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<tr>
<td>SURGERY</td>
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<td>General/Gastrointestinal Surgery</td>
<td>James M. Becker, MD</td>
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<td>SURGICAL ONCOLOGY</td>
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<td>Immunotherapy Research</td>
<td>Soldano Ferrone, MD, PhD</td>
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<td>UROLOGY</td>
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<tr>
<td>Gastrointestinal</td>
<td>Dicken Ko, MD</td>
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**Physician Awards and Honors**

- Nick Dyson, PhD, Raul Mostoslavsky, MD, PhD, and Anders Naar, PhD, were named as three of eight Mass General Research Scholars for 2012. The recipients each receive an unrestricted five-year grant to support innovative research projects.
  The Research Scholars Program grant was launched in 2011 by the hospital’s Executive Committee on Research and the Research Advisory Council through a $10 million challenge grant from an anonymous donor. The program is designed to give forward-thinking Mass General investigators the flexibility to pursue research into unexpected areas.
- Cancer Center scientist Dejan Juric, MD, was honored by the American Association for Cancer Research as a recipient of the 2012 Aflac Incorporated Scholar-in-Training Awards. The award will help fund research on a next-generation PI3K alpha-specific inhibitor, including pharmacokinetic studies and initial efficacy results in a first-in-human clinical trial.
- Miguel Rivera, MD, was named a 2012 recipient of a Hyundai Scholar by Hyundai Hope on Wheels. Dr. Rivera received funding for a research project to apply cutting-edge genomic technologies to the analysis of primary bone tumors in children. This multidisciplinary project will provide novel insights into pediatric bone cancer biology and reveal new opportunities for therapeutic intervention.
- Vinod Vathipadiekal, PhD, was honored by the American Association for Cancer Research as a 2012 recipient of the Bristol-Myers Squibb Oncology Scholar-in-Training Award. This award will help fund Vathipadiekal’s research of the gene expression profile of chemoresponse in papillary serous tumors of the ovary. To date, the study has identified POLH and REV3L as potential biomarkers and therapeutic targets.
- Juanjuan Yang, PhD, received one of the American Association for Cancer Research’s 2012 Aflac Incorporated Scholar-in-Training Awards. The award will help fund research on the regulation of the glutamine-to-lipid pathway activated by hypoxia-inducible factor (HIF). It will link metabolic signatures to deficiency of the Von Hippel-Lindau (VHL) gene frequently mutated in kidney cancer.

**Continuing Medical Education Credits**

For physicians and health care professionals who value the highest standards of clinical care, the Massachusetts General Hospital Academy dedicates itself to providing world-renowned postgraduate education that improves clinical practice and leads to better lives for patients and their families.

For more information, or to register for a free course, visit MGHAcademy.org.
## 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/cancer/trials.

<table>
<thead>
<tr>
<th><strong>Bone Marrow Transplant</strong></th>
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<tbody>
<tr>
<td>10-057 Sequential Myeloablative Autologous Stem Cell Transplantation Followed by Allogeneic Non-Myeloablative Stem Cell Transplantation for Patients With Poor Risk Lymphomas Phase 2 Yi-bin Chen, MD 617-726-1124</td>
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<tr>
<th><strong>Breast Cancer</strong></th>
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<tr>
<td>11-299 A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial Comparing Capecitabine Plus Sorafenib vs. Capecitabine Plus Placebo in the Treatment of Locally Advanced or Metastatic HER2-Negative Breast Cancer Phase 3 Steven Isakoff, MD, PhD 617-726-4920</td>
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<tr>
<th><strong>Gastrointestinal Cancers</strong></th>
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<tr>
<td>11-164 A Phase 1b Clinical Trial of LDE225 in Combination With Fluorouracil, Leucovorin, Oxaliplatin, and Irinotecan (FOLFIRINOX) in Previously Untreated Locally Advanced or Metastatic Pancreatic Adenocarcinoma, With an Expansion Cohort at the Recommended Phase 2 Dose Phase 1b Eunice Kwak, MD, PhD 617-726-8478</td>
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<tr>
<th><strong>Gynecologic Cancers</strong></th>
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<tr>
<td>11-399 A Randomized Phase 2 Non-Comparative Study of the Efficacy of PF-04691502 and PF-05212384 in Patients With Recurrent Endometrial Cancer Phase 2 Michael J. Birrer, MD, PhD 617-724-4800</td>
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<th><strong>Head and Neck Cancers</strong></th>
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<tr>
<td>11-337 Re-Differentiation of Radioidine-Refractory BRAF V600E-Mutant Papillary Thyroid Carcinoma With OSE218436: A Pilot Study Pilot Stephen Rothenberg, MD 617-724-4000</td>
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<tr>
<th><strong>Hematology</strong></th>
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<tr>
<td>11-471 A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel-Group Trial With an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Oral E5501 vs. Eltrombopag, in Adults With Chronic Immune Thrombocytopenia (Idiopathic Thrombocytopenic Purpura) Phase 3 David Kuter, MD 617-726-8743</td>
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<th><strong>Leukemia</strong></th>
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<tr>
<td>12-202 A Phase 1 Study of Lenalidomide plus Chemotherapy With Mitoxantrone, Etoposide, and Cytarabine for the Reinduction of Patients With Acute Myelogenous Leukemia Phase 1 Karen Ballen, MD 617-726-6799</td>
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<tr>
<th><strong>Lymphoma</strong></th>
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<tr>
<td>11-462 Brentuximab Vedotin Plus AVD in Non-Bulky Limited-Stage Hodgkin’s Lymphoma Phase 2 Jeremy S. Abramson, MD 617-726-8743</td>
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<tr>
<th><strong>Melanoma</strong></th>
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<tr>
<td>12-088 A Phase 1/2 Trial of Leflunomide in Combination With Vemurafenib in Patients With V600 Mutant Metastatic Melanoma Phase 1/Phase 2 Keith T. Flaherty, MD 617-726-1941</td>
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<tr>
<th><strong>Multiple Myeloma</strong></th>
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<tr>
<td>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 Relapsed/Refractory Multiple Myeloma Phase 1/Phase 2 Noopur Raje, MD 617-724-4000</td>
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<tr>
<th><strong>Neuro-Oncology</strong></th>
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<tr>
<td>09-468 An Open-Label, Phase 2 Trial of Orally Administered PF-02298804 in Adult Patients With Relapsed/Recurrent Glaucoma (GBM) Phase 2 Andrew S. Chi, MD, PhD 617-643-5530</td>
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<tr>
<th><strong>Pediatric Cancers</strong></th>
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<td>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</td>
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<tr>
<th><strong>Sarcoma</strong></th>
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<tr>
<td>11-470 Phase 2 Study of the PARP Inhibitor, Olaparib, in Adult Patients With Recurrent/ Metastatic Ewing’s Sarcoma Following Failure of Prior Chemotherapy Phase 2 Edwin Choy, MD 617-643-0230</td>
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<tr>
<th><strong>Targeted Therapies</strong></th>
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<tr>
<td>11-217 A Phase 1, Open-Label, Dose Escalation Study of MGA271 (Fc-Optimized Humanized Anti-B7-H3 Monoclonal Antibody) in Patients With Refractory B7-H3-Expressing Neoplasms or Neoplasms Whose Vasculature Expresses B7-H3 Phase 1 Keith T. Flaherty, MD 617-726-1941</td>
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<tr>
<th><strong>Thoracic Cancers</strong></th>
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<tr>
<td>10-452 A Phase 1, Multicenter, Open-Label Dose Escalation Study of LDK378, Administered Orally in Adult Patients With Tumors Characterized by Genetic Abnormalities in Anaplastic Lymphoma Kinase (ALK) Phase 1 Alice Shaw, MD, PhD 617-724-4000</td>
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CtC-Chip Assay Shows Promise to Personalize Metastatic Prostate Cancer Treatment

Next Steps
In addition to conducting a large clinical trial to validate the assay, Cancer Center researchers are investigating the other biomolecular pathways that drive castration-resistant prostate cancer. Dr. Miyamoto and his colleagues are currently investigating the pathways being activated in the CTCs of the subpopulation of men whose AR signaling is off or mixed, for example. As more is learned, the goal is to further increase the accuracy of predicting which drugs will work for which patients.

Researchers are also studying the potential usefulness of the untreated CTC-chip both in the early detection of prostate cancer and for identifying which localized cancers need treatment and which can be followed by active surveillance. Usefulness of the untreated CTC-chip for either goal would be a major breakthrough in prostate cancer detection and treatment.

Selected References


Contributor
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55 Fruit Street/LH 200
Boston, MA 02114

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Printed with Ultraviolet (UV) inks

Volume 3, Number 1, Winter 2013

ADVANCES at the MASS GENERAL CANCER CENTER