Dear Colleagues and Friends:

Welcome to the latest issue of Cancer Consult. On behalf of everyone at Taussig Cancer Institute, I am pleased to share with you the innovative treatments and groundbreaking research conducted at our facilities each and every day.

In this issue, we include excerpts from select presentations given by our staff at the recent American Society of Clinical Oncology (ASCO) annual conference. We also discuss a new paradigm in translational research brought on by the discovery of the MET mutation in certain lung cancers. In addition, we provide you with an up-to-date review of the cancer research being conducted in our labs.

One of the cornerstones of cancer therapy is multidisciplinary care and research. At Cleveland Clinic, we employ this approach because it leads to the best possible outcomes for our patients. As such, we have included a collaborative study with our Glickman Urological & Kidney Institute on the long-term effectiveness of brachytherapy to treat prostate cancer as well as a summary of breakthroughs in cancer genomics identified by researchers in our Genomic Medicine Institute. Discoveries such as these can improve diagnostic screening guidelines for at-risk patients and help guide more individualized courses of treatment.

Cleveland Clinic is committed to producing and reporting quality outcomes. I encourage you to review our cancer 2011 Outcomes, one of a series of books that is published annually and are available at clevelandclinic.org/outcomes.

We are continually inspired by our patients to challenge the status quo, developing new ways to treat cancer today with an ultimate goal of eradicating it. We hope you find this publication valuable to your practice.

Sincerely,

Brian J. Bolwell, MD
Chairman, Taussig Cancer Institute

Jay P. Ciezki, MD (right), staff physician in the Department of Radiation Oncology, and Steven Campbell, MD, PhD (left), staff urologist, during a brachytherapy procedure.
Brachytherapy Experience Informs Study of Long-Term Effectiveness of Procedure

Story on page 4
Informed by this large experience in the procedure, in February of this year, Jay P. Ciezki, MD, staff physician in the Department of Radiation Oncology, presented an abstract on the subject at the annual Genitourinary Cancers Symposium. Dr. Ciezki’s paper may have surprised some members of the audience, as it reported the results of a study that had found external beam radiotherapy to be the most toxic and costly treatment for localized prostate cancer, and brachytherapy the least toxic and costly. Both methods of treatment are known to be equally effective in curing prostate cancer. This conclusion was based on an analysis of the long-term toxicity and associated costs of treating prostate cancer with prostatectomy, external beam radiotherapy, and brachytherapy, from the large Surveillance, Epidemiology and End Results (SEER)/Medicare Database.

“We noticed rather quickly from examining our own data that the brachytherapy patients had far fewer side effects than the external beam patients,” says Dr. Ciezki. “The outcome in terms of cancer cure was the same, and depending on how you look at it, maybe even a little bit better with brachytherapy. But we wondered if this would match external data.”

For sheer volume of information, the SEER database was the most logical to harvest. It contains data on 26 percent of the U.S. population, and includes 16 years of follow-up on prostate cancer. Since treatment-related toxicity is typically reported only for a period of at most five years after therapy in most other studies, SEER was an ideal source.

“Disease progression can impact quality of life and so can the side effects of treatment.”

Jay P. Ciezki, MD

Last fall, Cleveland Clinic acknowledged two milestones in the treatment of prostate cancer: 15 years of brachytherapy with its 4,000th patient treated.

To refer a patient to Dr. Ciezki, email ciezki@ccf.org or call 216.445.9465.
Dr. Ciezki’s group queried SEER for patients with prostate cancer treated with radical prostatectomy, external beam radiotherapy or brachytherapy between 1991 and 2007. Billing codes were examined for the initial treatment and for any toxicity-related interventions. These codes were selected because they are reasonably accurate, says Dr. Ciezki, while diagnostic codes are notoriously inaccurate.

The queries yielded a total of 137,427 patients with prostate cancer, with a median follow-up of 71 months. Approximately 43 percent had been treated with radical prostatectomy, 44 percent with external beam radiotherapy, and 12 percent with brachytherapy.

The study paid particular attention to the most common GI toxicity, cauterization for rectal bleed, and the most common GU toxicity, dilation of urinary stricture.

“These are the sorts of toxicities that you’re not going to see reported in most journals,” says Dr. Ciezki. “They are Grade 3 and higher, so serious they require surgery.” SEER does not contain comprehensive data on the less serious side effects that are the typical subject of most other reports in the medical journals, he says.

The data indicated that patients treated with external beam radiotherapy accumulated side effects at a much higher rate than did those treated with brachytherapy or surgery. The cost per year associated with the initial treatment, as well as with follow-up treatment for side effects, was more than twice as great with external beam as it was for either of the other two modalities.

Intensity modulated radiation therapy (IMRT) is often touted as a safe successor to “standard” external beam radiotherapy, but it’s not so, says Dr. Ciezki.

“IMRT is doing quite badly in prostate cancer therapy,” he says. The technique is newer, so it has shorter follow-up, but still far more side effects. “Just because something is new doesn’t mean it’s better,” says Dr. Ciezki.

The SEER database supported this conclusion.

“We’ve always seen the arguments for external beam as false,” says Dr. Ciezki, “and we’ve reacted by assessing our outcomes with all modalities and focusing on using those that demonstrate superior results. This has led us to use brachytherapy more often than external beam radiotherapy for prostate cancer,” he said. He reflected on the early years.

“When we started our program in 1996, we used a more cumbersome process for planning and treating our brachytherapy patients. Now, we use a single-session approach that we pioneered, where the planning and implantation are performed in one setting.”

“Prostate cancer is very unlikely to kill a patient, but it is likely to impact quality of life in two ways,” says Dr. Ciezki. “Disease progression can impact that quality, and so can the side effects of treatment. That’s what this paper is all about.”

A second study currently in press examines the screening issues associated with prostate cancer.

“We thought that a lot of the national dialogue on this also missed the point,” says Dr. Ciezki. “It focused on prostate cancer screening as a way to prevent death from prostate cancer, when in fact death from prostate cancer is relatively uncommon. We thought that one should instead look at the real clinical problem, which is the metastatic burden of the screened population, and ask how that burden changes over time.”
Charis Eng, MD, PhD, has dedicated her career to understanding genes that play a role in inherited cancers and translating those findings to the improved clinical care of patients. She is the Sondra J. and Stephen R. Hardis Chair and founding director of Cleveland Clinic's Genomic Medicine Institute and founding director of its clinical component, the Center for Personalized Genetic Healthcare.

In 1997, she led the research team that discovered the relationship between PTEN, one of the body's many tumor suppressor genes, and Cowden syndrome (CS), a rare disorder characterized by noncancerous, tumor-like growths and an increased risk of developing certain cancers.

Approximately 25 percent of patients with CS have inherited PTEN mutations that prevent the gene from effectively controlling cell growth, leading to the formation of tumors. Recently, Dr. Eng's team has found other genes (SDHx and KLLN), which when altered, cause CS in the absence of PTEN alterations. She also found that PTEN is one of the most frequently somatically altered genes in a variety of cancers. More recently, she helped to investigate the extent and magnitude of cancer risks associated with PTEN alterations.

Cancer Incidences, Thyroid Cancer and CS

For example, incidences of thyroid cancer are rising rapidly. Over the past five years it has mysteriously been the fastest-growing diagnosis in women and the second-fastest in men. However, because germline PTEN alterations have been found to be associated with CS and patients with CS have a high risk of breast, thyroid and other cancers, Dr. Eng and colleagues compared incidence of and clinical and histological characteristics of thyroid cancer in 2,723 patients with CS or CS-like disease.

The results, published in the December 2011 issue of *Journal of Clinical Endocrinology & Metabolism*, showed that thyroid cancer risk is elevated in individuals with CS or CS-like disease. Compared with the general population in this country, the age- and sex-adjusted standardized incidence rates of thyroid cancer in those with PTEN mutations were 183 in male carriers and 57 in female carriers. While the rarer follicular thyroid cancer is almost fourfold over-represented in those with PTEN mutations, the trend is reversed favoring papillary thyroid cancer in those with PTEN or SDHx mutations.

The study also indicated that patients with PTEN mutations had an earlier onset of thyroid cancer than previously believed. In the past, based on retrospective data and expert opinion, thyroid screening was not recommended until the late teens. Dr. Eng and colleagues noted six cases in PTEN mutation carrying patients under 18 years old, leading them to suggest that thyroid surveillance should begin when a PTEN mutation is identified, even in children. Led by Cleveland Clinic, which has a multidisciplinary clinical center for PTEN/Cowden syndrome care, many centers have changed their thyroid surveillance because of this study.

Genetic Interactions

Dr. Eng's investigations also have focused on the role that PTEN plays in connection with other genes, specifically androgen receptors, which have been found to be a common component in both prostate and breast cancers but appear to have an opposite effect.

In a study, published in the Oct. 21, 2011 issue of *Oncogene* Dr. Eng and colleagues focused on the interaction between androgen receptors (AR) and PTEN. The researchers found an interesting contradiction: increased AR expression and decreased PTEN
expression predict a poor clinical outcome in prostate cancer, while increased AR and increased PTEN expression correlate with better disease-free survival in breast cancer. Looking at the interaction between AR and PTEN, they concluded that AR inhibits PTEN expression in prostate cancer cells, but stimulates expression in breast cancer cells.

The results have implications for gender-specific disease management, Dr. Eng says. Where treating prostate cancer revolves around blocking AR, breast cancer treatment will have a better outcome if circulating androgen is increased.

**Lifetime Risk and Screening Recommendations**

The fact that patients with germline PTEN mutations are at an increased lifetime risk of certain cancers intrigued Dr. Eng and her colleagues. To better understand and document this phenomenon, Dr. Eng and her team published a recent and only prospective cohort study on the topic in the January 15, 2012 issue of *Clinical Cancer Research*. In the study, Dr. Eng and her team looked at age-related risk and genotype-phenotype associations, finding that patients with PTEN mutations are at an increased risk for colorectal cancer, kidney cancer and melanoma, in addition to breast, endometrial and thyroid cancers, for which they discovered a much higher lifetime risk than had been previously estimated.

On the basis of the results, Dr. Eng and her colleagues have recommended a comprehensive approach to surveillance and management of these patients. “So suddenly instead of just screening for breast and thyroid cancers, we need to screen for these four other cancers,” she says. “The study also shows where the age of risk is so we know when to start.”

The paper is altering clinical practice because the new data impact cancer risk assessment, genetic counseling and management. “When these results were published, we immediately shared our paper and recommendations with our medical colleagues around the country and the world who look after such patients so that they could change their clinical screening and the way they look after these patients and their families,” she says.
Clinical Trials Lead the Way to Advances in Hematology

Through our affiliation with Case Western Reserve University’s Case Comprehensive Cancer Center, Cleveland Clinic recently joined the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). As a Clinical Center, we participate in large multi-institutional trials addressing hematopoietic cell transplantation.

Current BMT CTN studies are:

A Multi-Center, Phase III, Randomized Trial of Reduced Intensity Conditioning (RIC) and Transplantation of Double Unrelated Umbilical Cord (dUCB) versus HLA-Haploidentical Related Bone Marrow (haplo-BM) for Patients With Hematologic Malignancies

Patients with hematologic malignancies who are eligible for allogeneic bone marrow transplantation (BMT) can receive a graft from an HLA-matched sibling or a suitably matched unrelated adult HLA donor. For the up to one-third of patients who lack a suitably matched relative, however, identifying a suitably matched unrelated donor from the National Marrow Donor Program takes a median of four months; some patients succumb to the disease while waiting for a donor.

Several small studies have shown that partially HLA-mismatched related bone marrow (haplo-BM) and dUCB are valuable sources of donor cells for RIC BMT, extending this treatment modality to patients who lack other donors.

This trial will compare progression-free survival (PFS) at two years post-randomization between two groups of 410 patients (with acute lymphoblastic leukemia/lymphoma, acute myelogenous leukemia, Burkitt’s lymphoma in remission or lymphoma) who receive unrelated double-cord blood unit transplantation versus HLA-haploidentical related bone marrow transplantation. Confirming the safety and efficacy of dUCB and/or haploidentical-related bone marrow transplant would allow access to BMT for essentially all patients in need. The central hypothesis of this trial is that PFS at two years after RIC haplo-BMT is similar to the PFS after RIC dUCB BMT

A Randomized, Multi-Center, Phase III Study of Allogeneic Stem Cell Transplantation Comparing Regimen Intensity in Patients With Myelodysplastic Syndrome or Acute Myeloid Leukemia

For patients with MDS and AML, which mostly affect people over 65 years and are the most common indications for allogeneic transplant, pre-transplant high-intensity myeloablative conditioning (MAC) regimens pose a high risk of toxicity, a major cause of non-relapse mortality (NRM). Reduced intensity conditioning (RIC) regimens, which are used in patients who are deemed unfit for MAC regimens, are associated with decreased transplant-related toxicity and mortality but also with increased malignancy relapse. However, the data is confounded by patient-selection bias as older, more infirm patients are often chosen for RIC regimens.
This study will compare 18-month overall survival between two groups of patients aged 18 to 65 with acute myeloid leukemia or myelodysplasia receiving MAC versus RIC regimens. The study will test the hypothesis that the intensity of the conditioning regimen will decrease treatment-related mortality without increasing relapse so that overall survival will be improved. The results are important to the transplant community and may change current practice patterns.

Within the Case Comprehensive Cancer Center, the following study of busulfan dosing is being conducted:

**Personalized Monitoring of Intravenous Busulfan Dosing for Patients with Lymphoma Undergoing Autologous Stem Cell Transplantation**

Brian T. Hill, MD, PhD, Principal Investigator

For 30 years, busulfan has been used as part of the preparative regimen for HCT to treat lymphoma and other hematologic cancers. Due to variability in individual patients’ metabolism of busulfan and the relatively narrow therapeutic window, the plasma exposure at a given busulfan dose based on weight or body surface area (BSA) results in toxicity (over-dosing) or suboptimal therapeutic benefit of disease (under-dosing). The focus of this nonrandomized, single-arm pilot study is to determine the feasibility of real-time personalized therapeutic dose monitoring (TDM) for once-daily IV busulfan administration as part of a preparative regimen for patients with lymphoma undergoing autologous HCT. If TDM is shown to improve patient outcomes and increase progression-free survival, it could become the standard of care for busulfan dosing in lymphoma treatment.

Cleveland Clinic’s Taussig Cancer Institute recently entered into an adult medical oncology affiliation with Cadence Health in Winfield, Ill., the newly named health system created through the merger of Central DuPage Hospital and Delnor Hospital. This is Cleveland Clinic’s first national affiliation in adult medical oncology.

“Our affiliation with Cadence Health will help enhance patient care by providing the latest treatments available, along with greater access to clinical trials,” says Brian J. Bolwell, MD, Chairman of the Taussig Cancer Institute. “We will work together to achieve the highest standards of care and the best outcomes for our patients.”

The affiliation is similar to Cleveland Clinic’s heart surgery affiliation established in 2010 with Central DuPage Hospital — one of eight heart surgery affiliations Cleveland Clinic has entered into nationally.

Once the adult medical oncology program affiliation is fully implemented by late 2012, Cadence Health patients will have access to treatment protocols, clinical trials, and additional research opportunities that are offered through Cleveland Clinic.

The agreement was announced in February 2012.

“Cadence Health patients already have local access to comprehensive cancer care and state-of-the-art technology, including a world-class proton therapy center,” says Luke McGuinness, Chief Executive Officer of Cadence Health. “The new affiliation with Cleveland Clinic will raise the bar even higher for regional cancer care, bringing our patients the expertise of one of the leading cancer centers in the world. We are eager to build on our successful relationship with this top healthcare provider and offer more advanced care to our patients.”
MET Signaling Pathway Provides Vast Research Opportunities

A unique MET mutation detected in lung cancer has paved the way to what may be a new paradigm in translational research to understand non-kinase domain mutations and MET kinase targeted therapy.

“We believe that MET receptor tyrosine kinase is a novel target in lung cancer,” says Patrick Ma, MD, Director of Aerodigestive Oncology Translational Research, “and is important for therapeutic intervention in human cancer.”

In 2003, the first preclinical prototype MET inhibitors were identified, and the MET receptor was subsequently validated as an “actionable” cancer target. Studies since that time have shown that the MET pathway is activated in many solid and hematological malignancies, including lung cancer, often associated with poor prognosis. MET can be altered through ligand or receptor overexpression, genomic amplification, MET mutations and alternative splicing.

Since that time, MET has become better understood. The natural ligand for MET is hepatocyte growth factor (HGF), also called scatter factor because it induces epithelial cell-cell repulsion (scattering). Aberrant HGF stimulation of MET in human cancer can occur by aberrant autocrine (intratumoral), paracrine (micro-environmental) or endocrine (circulatory) loop signal activation.

Upon HGF binding to the Sema domain, MET dimerizes leading to autophosphorylation of intracellular tyrosine residues. MET activation results in the recruitment and activation of downstream adaptor proteins and kinase targets resulting in a multitude of effects such as increased cell proliferation, cell cycle progression,
MET Signaling Pathway Provides Vast Research Opportunities

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scattering, motility, migration, invasion, survival, extracellular matrix remodeling and changes in metabolism. Thus, MET signaling contributes to tumor growth, scattering, motility, invasiveness, and metastasis, thereby playing important roles in mediating tumor MET dependence and progression.

Therapeutic intervention strategies to block and inhibit MET receptor oncogenic signaling cascade include blocking ligand-receptor interaction, preventing receptor dimerization, blocking MET kinase intrinsic activity and inhibiting specific downstream signal transducers.

Critical to embryogenic development of the placenta, liver, kidney, neurons and muscle, in vivo MET receptors trigger a unique biological response that leads to invasive growth. While found in numerous human solid and hematological malignancies, studies have shown that over 70 percent of lung cancer tissue expressed MET, and 40 percent showed MET receptor overexpression. Phospho-MET expression is found to be the highest in lung cancer among other common solid malignancies.

Since MET is found in abundance in stem and progenitor cells, but in lower levels in mature cells, it stands to reason that the concept of a cancer stem cell is key. In theory, MET is a potential marker of an expanding cell population that is changing yet retains stem cell properties; in prior studies, Dr. Ma and his fellow researchers have found that MET expression co-localizes at the lung bronchioalveolar duct junction where the bronchioalveolar stem cells were identified.

Studies taken together indicate that a logical path for investigation is to develop clinical studies of MET

Banking Protocol Enables Research Options

The possibilities afforded with a translational research lab right next door became more extensive when Dr. Patrick Ma joined Cleveland Clinic less than two years ago.

Dr. Ma is the Director of Aerodigestive Oncology Translational Research in the Department of Translational Hematology and Oncology Research, or THOR. He is also a staff physician in Solid Tumor Oncology specializing in thoracic oncology. He decided upon his arrival to establish a blood and tissue collection protocol that would enable patients to donate blood and redundant tumor tissue to THOR for the purposes of advancing research in cancer diagnosis and novel therapy.

Armed with IRB approval (#07-267), Dr. Ma worked on a protocol that would not only fully inform patients about how such a protocol would apply to their specific case, but would allow patients to feel invested in the future of cancer research. Cancer researchers are excited about the project as well because it provides a “library” of samples that represent the depth and breadth of cancers treated by a high-volume center such as Taussig. The initiative has also facilitated collaborative research with Thoracic Surgery, Pulmonary Medicine and Pathology, and with researchers in the Lerner Research Institute and Genomic Medicine Institute.

“We’ve had a wonderful response from patients,” says Dr. Ma. “In less than a year, we’ve had more than 100 patients sign up for and consented to the protocol. We have started using this invaluable research resource in our translational research initiatives in cutting-edge areas such as circulating tumor cell, cancer genomics, proteomics and metabolomics. In the future, we aim to continue this important endeavor to put the blood and redundant tissue to productive use in our labs to impact clinical outcomes in our cancer patients.”

For more information, contact Dr. Patrick Ma at map@ccf.org or 216.445.5545.
inhibitors, alone and in combination with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) in lung cancer both as primary or secondary strategies to prevent or overcome EGFR-TKI resistance.

In studies, both in vitro and in vivo, Dr. Ma and colleagues recently demonstrated that some drug-sensitive lung adenocarcinoma cells with mutant EGFR sensitizing to erlotinib (EGFR-TKI) remarkably exhibited a very early, within the first 6 to 9 days of drug exposure, “adaptive” tumor resistance to escape the EGFR-TKIs, with 100-fold more resistant phenotype, thereby implicating a model of “minimal residual disease.” Importantly, their research team also demonstrate similar early “adaptive” resistance in the H1975 cells (that harbor the erlotinib-resistant T790M EGFR mutation) against dual irreversible EGFR TKI plus MET inhibitor. Ma says that this early effect is important to note and intriguing to pursue because it indicates that according to his studies, the role of MET in acquired EGFR-TKI resistance might be more relevant in the late stages of resistance development but not necessarily so in the early emergence of an adaptive drug-resistance state.

Currently, more than a dozen MET inhibitors targeted to human cancers, including lung cancer, are at various stages of clinical trial studies, from preclinical to Phase III trials.

Included in this work is a global Phase III trial that Dr. Ma is involved in as principal investigator, that is drawing to a close. The MARQUEE (Met inhibitor ARQ 197 plus Erlotinib vs Erlotinib plus placebo in NSCLC) trial is compiling strong and extensive evidence of efficacy in combining ARQ197 (tivantinib, MET inhibitor) and Erlotinib (EGFR inhibitor), to shut down tumors.

“It's gratifying to see all the work devoted to this area of research coming to clinical fruition. It is particular exciting to see that in two separate recent Phase II studies using MET inhibitors, significant prolonged time-to-new-metastasis was observed, lending strong support to the notion of inhibiting MET signaling to impact tumor invasion and metastasis, which account for majority of human cancer morbidities and mortalities,” says Dr. Ma.

While the role of MET/HGF in cancer growth and invasion has been well-studied, he continues, and current work in trials is promising, MET inhibition strategies still deserve further studies.

Cleveland Clinic Highlights of ASCO Annual Meeting 2012

The ASCO Annual Meeting, which was held from June 1-5, 2012 in Chicago, brought together more than 25,000 oncology professionals from a broad range of specialties, who explored the theme of the meeting — “Collaborating to Conquer Cancer.”

Cleveland Clinic had a presence in the genitourinary, lung and breast cancer tracks, with the following significant presentations:

Oral presentation:
Abstract #4503
Axitinib for first-line metastatic renal cell carcinoma (mRCC): Overall efficacy and pharmacokinetic (PK) analyses from a randomized Phase II study
Brian Rini, MD

Axitinib is a potent, selective, second-generation inhibitor of vascular endothelial growth factor receptors with efficacy in mRCC. Due to PK and pharmacodynamic variability, some patients have suboptimal drug exposures at the standard 5-mg twice daily (BID) dose. Prior analyses indicated higher drug exposure enhanced efficacy; thus, dose titration based on individual tolerability may optimize exposure and improve outcomes. A randomized Phase II trial evaluated the efficacy and safety of axitinib dose titration from 5 mg BID to a maximum of 10 mg BID in first-line mRCC in three groups, totaling 203 patients.

As of April 30, 2012 ORR was 43% in groups A+B and 59% in group C. Median progression-free survival was 14.5 months in groups A+B and 16.4 months in group C. Patients with drug exposure above therapeutic threshold on Cycle 1 Day 15 had longer mPFS and higher ORR than those with subtherapeutic exposure.

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Known as the MDS Clinical Research Consortium, the five-year, $16 million initiative is sponsored by the Aplastic Anemia & MDS International Foundation and supported by the Edward P. Evans Foundation.

This is the first privately funded MDS research consortium in the U.S. Mikkael Sekeres, MD, MS, Director of Taussig Cancer Institute’s Leukemia Program, will co-chair the Consortium with Guillermo Garcia-Manero, MD, of MD Anderson Cancer Center.

Centralized clinical operations (data collection and management, biostatistics, clinical trial accrual and supervision of research protocols) will be housed at Quantitative Health Sciences at Taussig. A portion of the grant will be set aside to fund this function.

The consortium will be administered by the Aplastic Anemia & MDS International Foundation.

Programs selected as part of the consortium are based at U.S. academic medical centers that serve a high volume of MDS patients, maintain a current and historical patient database, and have a current and retrospective MDS patient cohort of sufficient size to have a very significant track record of participation in MDS-related clinical trials.

The other five participating institutions are the Dana Farber Cancer Institute; MD Anderson Cancer Center, H. Lee Moffitt Cancer Center and Research Institute, Weill Medical College of Cornell University and the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins.

The consortium will fill a major gap in MDS-related clinical research by providing a new “critical mass” of dedicated institutions to support the evaluation of promising new therapies, epidemiological studies, and translational studies leading to new treatments and classifications for these diseases. It will also sponsor a yearly, dedicated MDS fellowship slot at each institution.

“This consortium is the first clinical research network created to support the infrastructure that makes MDS clinical research happen by enabling

For more information about the consortium, contact Dr. Mikkael Sekeres at sekerem@ccf.org or 216.445.9353.

For more information on the Aplastic Anemia & MDS International Foundation, visit aamds.org.
the collaboration of the leading MDS centers in the U.S. “ says Dr. Sekeres.

“One of the greatest challenges in research of rare diseases like MDS is having enough patients to conduct meaningful clinical trials. No single center can do it alone. This uniquely collaborative effort overcomes that barrier,” says John Huber, Executive Director of the Aplastic Anemia & MDS International Foundation. “To have these six leading MDS research centers working together in this way is unprecedented.”

Education Toolkit Equips Providers for Journey to Health

Mikkael Sekeres, MD, MS, is no stranger to helping patients and caregivers understand the intricacies of MDS. He also devotes a significant portion of his time to creating resources for providers and patients about this group of blood disorders. His introduction to and work with the Aplastic Anemia & MDS International Foundation has resulted in a unique and ongoing partnership.

Over the past decade, Dr. Sekeres has worked with the foundation on a provider toolkit on the group’s website, aamds.org. The toolkit provides simple, clear instructions on how to manage the disease, and a wide variety of resources to help doctors provide the best care for those with this complex diagnosis. Resources, such as videos, webinars and information packets make the toolkit user-friendly and appropriate for different educational uses.

Dr. Sekeres says that the site’s educational materials were not created in a vacuum. In fact, he says that the direction for the patient toolkit came from MDS patients.

“The content we put in the toolkit all came out of an Internet survey we administered to approximately 350 MDS patients about their understanding of their disease,” he says. “We revamped the educational materials based on where we saw gaps in knowledge, and then published the results in The Oncologist.”

In part, the MDS Consortium grant can be attributed to the educational work of the foundation. When Edward P. Evans was diagnosed with MDS in 2010, he sought information on his condition, and found the aamds.org website. Prior to Mr. Evans’ death that same year, he directed that a portion of his estate be allocated for research in MDS, particularly clinical research.

“Community hematologists and oncologists are who the patients see,” says Dr. Sekeres. “This toolkit provides benefits to both the patient and the physician who may desire a depth of information about MDS.”

The toolkit can be found at aamds.org/treating-mds-toolkit.

Cleveland Clinic Highlights of ASCO Annual Meeting 2012
(contd)

Abstract #95358
Physiology of chemotherapy induced fatigue and cognitive dysfunction in early stage breast cancer
Halle C. F. Moore, MD; Guang H. Yue, PhD; Lisa A. Rybicki; Vlodek Siemionow, PhD

Cognitive impairment is a poorly understood and worrisome potential complication of adjuvant chemotherapy (CT). We sought to evaluate electroencephalography (EEG) as a means to measure neurophysiologic function in women receiving CT for early breast cancer.

Women planning to undergo CT for operable breast cancer and age-similar controls were evaluated at baseline, during CT and at one year with neurophysiologic assessments. Testing included a brief fatigue inventory, brief mental fatigue assessment, a Processing Speed Index derived from the Digit Symbol Coding and Symbol Search subtests of the Wechsler Adult Intelligence Scale, and a sustained elbow flexion physical task. EEG recordings were obtained at rest and after the cognitive and physical tasks. Data were analyzed using repeated measures of analysis of variance.

Our study found that patient-perceived mental and physical fatigue during chemotherapy corresponded to significant changes in EEG brain activity patterns but not to cognitive testing or physical endurance testing. EEG may offer a sensitive means to measure alterations in brain function associated with CT.
Selected Publications


Arsenic and ATRA have revolutionized the treatment of what used to be a mostly lethal disease, acute promyelocytic leukemia (APL, PML-RARA). Although the mechanism by which ATRA induces cell cycle exit in APL is generally accepted as being via differentiation, there has been confusion and controversy regarding the actions of arsenic. This short report resolves this controversy, by demonstrating unequivocal cell cycle exit by molecular differentiation pathways of APL cells treated with non-apoptosis-inducing concentrations of arsenic.


The use of etoposide (VP-16) for stem cell mobilization has been reported as a significant risk factor for the development of therapy-related myelodysplasia/therapy-related AML (tMDS/AML) after transplantation. This study compares the safety and effectiveness of VP-16+G-CSF (VP+G) to G-CSF alone for PBPC mobilization in a group of patients with non-Hodgkin's lymphoma and Hodgkin's lymphoma who underwent autologous transplantation. The addition of etoposide significantly improves the effectiveness of mobilization at the cost of an increased incidence of neutropenic fever though with no mortalities. There is no evidence of increased incidence of tMDS/AML in patients receiving VP+G compared with those mobilized with G-CSF alone.


External beam radiation therapy is the standard treatment for men who present with clinically localized prostate cancer. The purpose of this review was to provide clarification on the appropriateness criteria and management considerations for the treatment of prostate cancer with external beam radiation therapy. Modern external beam radiation therapy series demonstrate favorable biochemical control rates for these patients, and morbidity profiles were also shown to be favorable with modern techniques such as 3-dimensional conformal radiation therapy and intensity-modulated radiation therapy.
Cleveland Clinic Partners on Phase II of NO1 Clinical Trials Pipeline

Ohio State, an NO1 contract holder, sought to improve its application by expanding into a consortium to include other academic centers. The NO1 contract allows researchers to work together to conduct novel clinical trials with respect to many solid tumors and hematologic neoplasms. Approximately 10 trials are active in NO1 at present, with more pending activation.

The benefit to participating institutions is access to a range of novel agents being developed by a variety of pharmaceutical companies that are working with the NCI, addressing both liquid and solid tumor cancers. Studies that will be conducted at Cleveland Clinic will enroll patients with a broad range of neoplastic conditions.

Robert Dreicer, MD, Cleveland Clinic’s PI for the NO1 collaboration, says that one of the additional opportunities provided by the NO1 contract is for career development of younger faculty who will submit proposals for clinical trials to the NCI. “The best outcome would be that our young faculty develop studies that are vetted and felt worthy by their colleagues in the NO1 consortium and ultimately approved by the NCI leading to cutting-edge Phase II clinical trials.”

In fact, several letters of intent have been submitted by Cleveland Clinic faculty to the consortium and are working their way through the process to the NCI. “Ultimately,” Dr. Dreicer says, “this collaboration will increase access to novel compounds for patients with a number of different types of malignancies.”

Cleveland Clinic currently participates in a U01 collaboration led by Case/University Hospitals within the Case Comprehensive Cancer Center, making Cleveland Clinic one of the few entities in the country to participate in both contracting mechanisms.

“For more information about the collaboration, contact Dr. Dreicer at dreicr@ccf.org or 216.445.4623.”

“Ultimately, this collaboration will increase access to novel compounds for patients with a number of different types of malignancies.”

Robert Dreicer, MD
Clinical Trials Enrolling Patients

At any given time, Taussig Cancer Center has several hundred cancer clinical trials under way on the main campus and at some Cleveland Clinic regional facilities. Here is a representative sample of trials that are currently accepting patients:

**RENAL CELL CARCINOMA**

**DUKE 2810**
Randomized Phase II study of Everolimus (Afinitor) vs. Sunitinib (Sutent) in patients with metastatic clear cell Renal cell carcinoma (ASPiEN)

**Objective:** The primary endpoint will be a comparison of progression-free survival (PFS) between the treatment arms following therapy initiation.

**PROSTATE CANCER**

**NCI 1811**
Randomized, double-blind, placebo-controlled Phase II study of ARQ 197 (tivantinib) in men with asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer

**Objective:** To determine progression-free survival (PFS) in men with minimally symptomatic or asymptomatic metastatic castrate resistant, chemotherapy-naive prostate cancer treated with ARQ 197.

**COUG 1811**
Multicenter, open-label, single-arm, Phase II study of Abiraterone Acetate Plus Prednisone in subjects with advanced prostate cancer without radiographic evidence of metastatic disease

**Objective:** To demonstrate that abiraterone acetate plus prednisone effectively decreases PSA in subjects with non-metastatic CRPC who have a rising PSA despite castrate levels of testosterone.

**MDS**

**ARRY 1Z11**
Phase I Study of ARRY-614 in patients with low or intermediate-1 risk myelodysplastic syndromes

**Objective:** To determine the recommended Phase II schedule (once-daily [QD] or twice-daily [BID] dosing) and dose of ARRY-614 administered as a semi-solid suspension (formulated) capsule in patients with low or intermediate-1 risk myelodysplastic syndromes (MDS)
MYELOFIBROSIS

INCT 1Z11
Open label assessment of safety and efficacy of Ruxolitinib (INCB018424) in subjects with primary myelofibrosis, post essential thrombocytopenia - myelofibrosis and post polycythemia vera-myelofibrosis who have platelet counts of 50 x 10^9 / L to 100 x 10^9 / L

Objective: To determine the effects of ruxolitinib on spleen volume and symptomatic burden in patients with primary myelofibrosis (PMF), post polycythemia vera-myelofibrosis (PPV-MF) and post essential thrombocytopenia-myelofibrosis (PET-MF) who have baseline platelet counts of 50 x10^9/L to 100 x10^9/L. Also to determine the safety and tolerability of ruxolitinib in patients with PMF, PPV-MF and PET-MF who have Baseline platelet count of 50 x10^9/L to 100 x10^9/L.

LEUKEMIA

NOVA 1909
Phase 1/b, open-label, multi-center, dose-escalation study of oral Panobinostat (LBH589) administered with 5-Azacitidine (Vidaza®) in adult patients with myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML) or acute myeloid leukemia (AML)

Objective: To determine the MTD of oral panobinostat in combination with a fixed dose of 5-Aza in adult patients with IPSS INT-2 or high risk MDS, CMML, or AML. End-points for primary objectives: incidence of DLT.

In addition, Cleveland Clinic offers an online tool for physicians, patients and caregivers to search for clinical trials. This web-based clinical trials database lists all the trials being managed by oncologists in the Taussig Cancer Institute.

To search the database, visit clevelandclinic.org/cancerclinicaltrials.

For information about clinical trials, call the Cancer Answer Line at 866.223.8100.
24/7 REFERRALS

Referring Physician Hotline
855.REFER.123 (855.733.3712)

Hospital Transfer
800.553.5056

On the Web at: clevelandclinic.org/refer123

About Cleveland Clinic

Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, 2,800 physicians represent 120 medical specialties and subspecialties. We are a main campus, 18 family health centers, eight community hospitals, Cleveland Clinic Florida, the Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City, and Cleveland Clinic Abu Dhabi.

In 2012, Cleveland Clinic was ranked one of America’s top four hospitals in U.S. News & World Report’s annual “America’s Best Hospitals” survey. The survey ranks Cleveland Clinic among the nation’s top 10 hospitals in 14 specialty areas, and the top hospital in three of those areas.

RESOURCES FOR PHYSICIANS

Referring Physician Center and Hotline
Cleveland Clinic’s Referring Physician Center has established a 24/7 hotline — 855.REFER.123 (855.733.3712) — to streamline access to our array of medical services. Contact the Referring Physician Hotline for information on our clinical specialties and services, to schedule and confirm patient appointments, for assistance in resolving service-related issues, and to connect with Cleveland Clinic specialists.

Physician Directory
View all Cleveland Clinic staff online at clevelandclinic.org/staff.

Track Your Patient’s Care Online
DrConnect is a secure online service providing real-time information about the treatment your patients receive at Cleveland Clinic. Establish a DrConnect account at clevelandclinic.org/drconnect.

Critical Care Transport Worldwide
Cleveland Clinic’s critical care transport teams and fleet of vehicles are available to serve patients across the globe.

• To arrange for a critical care transfer, call 216.448.7000 or 866.547.1467 (see clevelandclinic.org/criticalcaretransport).

• For STEMI (ST elevated myocardial infarction), acute stroke, ICH (intracerebral hemorrhage), SAH (subarachnoid hemorrhage) or aortic syndrome transfers, call 877.379.CODE (2633).

Outcomes Data
View clinical Outcomes books from all Cleveland Clinic institutes at clevelandclinic.org/outcomes.

Clinical Trials
We offer thousands of clinical trials for qualifying patients. Visit clevelandclinic.org/clinicaltrials.

CME Opportunities: Live and Online
The Cleveland Clinic Center for Continuing Education’s website offers convenient, complimentary learning opportunities. Physicians can manage CME credits using the myCME.com Web portal available 24/7. Visit ccfcme.org.

Executive Education
Cleveland Clinic has two education programs for healthcare executive leaders — the Executive Visitors’ Program and the two-week Samson Global Leadership Academy immersion program. Visit clevelandclinic.org/executiveeducation.

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