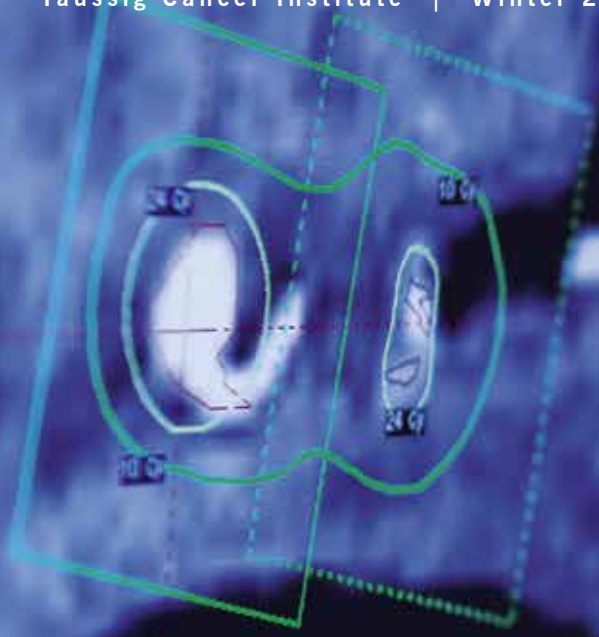
Cleveland Clinic

Cancer Consult

Taussig Cancer Institute | Winter 2015



Research Confirms Gamma Knife as an Option for More Brain Metastases

Also Inside:

Ranked as one of the top hospitals in America for cancer care by *U.S. News & World Report*.

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Dear Colleagues,

Welcome to the latest issue of *Cancer Consult*. As the new year begins, we have much exciting news to share with you.

From monoclonal antibodies to cytokines and prototype vaccines, Taussig Cancer Institute has a long history of developing and testing novel immunotherapies for cancer. As you will read on p. 6, we are working on the next generation of immunotherapeutics. Lead investigator Brian I. Rini, MD, FACP, of our Department of Hematology and Medical Oncology describes the promise that broadly applicable immune checkpoint inhibitors are showing in early trials of patients with metastatic renal cell carcinoma as well as cancers of the lung and skin.

Elsewhere in this issue are more examples of Cleveland Clinic's robust portfolio of leading-edge cancer research, including:

- Our verification of the safety and efficacy of Gamma Knife® radiosurgery in patients with extensive brain metastases.
- Our discovery of a new genetic variation in a known family of proteins — vascular endothelial growth factors — that has the ability to inhibit tumor growth and angiogenesis.
- Our plans for a translational research program to develop targeted therapies for advanced biliary tract cancers, and similar work to provide personalized treatments for recurrent pediatric cancers.

Those and other efforts by Cleveland Clinic researchers and clinicians are helping shape the future of cancer care. Soon that care will take place in an innovative new setting on our main campus.

Construction is underway on Cleveland Clinic's new cancer building, a seven-story, 377,000-square-foot facility that will unite all our outpatient oncology services in a single location. The $277 million structure, which we have been planning for more than two years and which will open in 2017, represents a fundamental transformation in the way we deliver care. On p. 24 you can learn more about its design and rationale.

I am proud of the new building, but am even more so of the outstanding staff of clinicians, researchers and other caregivers who will occupy it. Let me introduce you to the newest member of that stellar group. Marc Ernstoff, MD, is the new Director of our Melanoma Program. Many of you know Dr. Ernstoff from his groundbreaking research in immunotherapy for solid tumors, and from his long and prestigious tenure at Dartmouth College's Geisel School of Medicine, the Dartmouth-Hitchcock Medical Center and the Dartmouth-Hitchcock Norris Cotton Cancer Center. We are glad to have Dr. Ernstoff on our team.

I welcome the opportunity to collaborate, to discuss ideas and to answer questions. If we can help you with a patient's care or a clinical issue, please let me know.

Sincerely,

Brian J. Bolwell, MD, FACP
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Research Confirms **Gamma Knife** as an Option for More Brain Metastases

With earlier diagnosis and improved therapies extending cancer patients' lives, the incidence of brain metastases is increasing.

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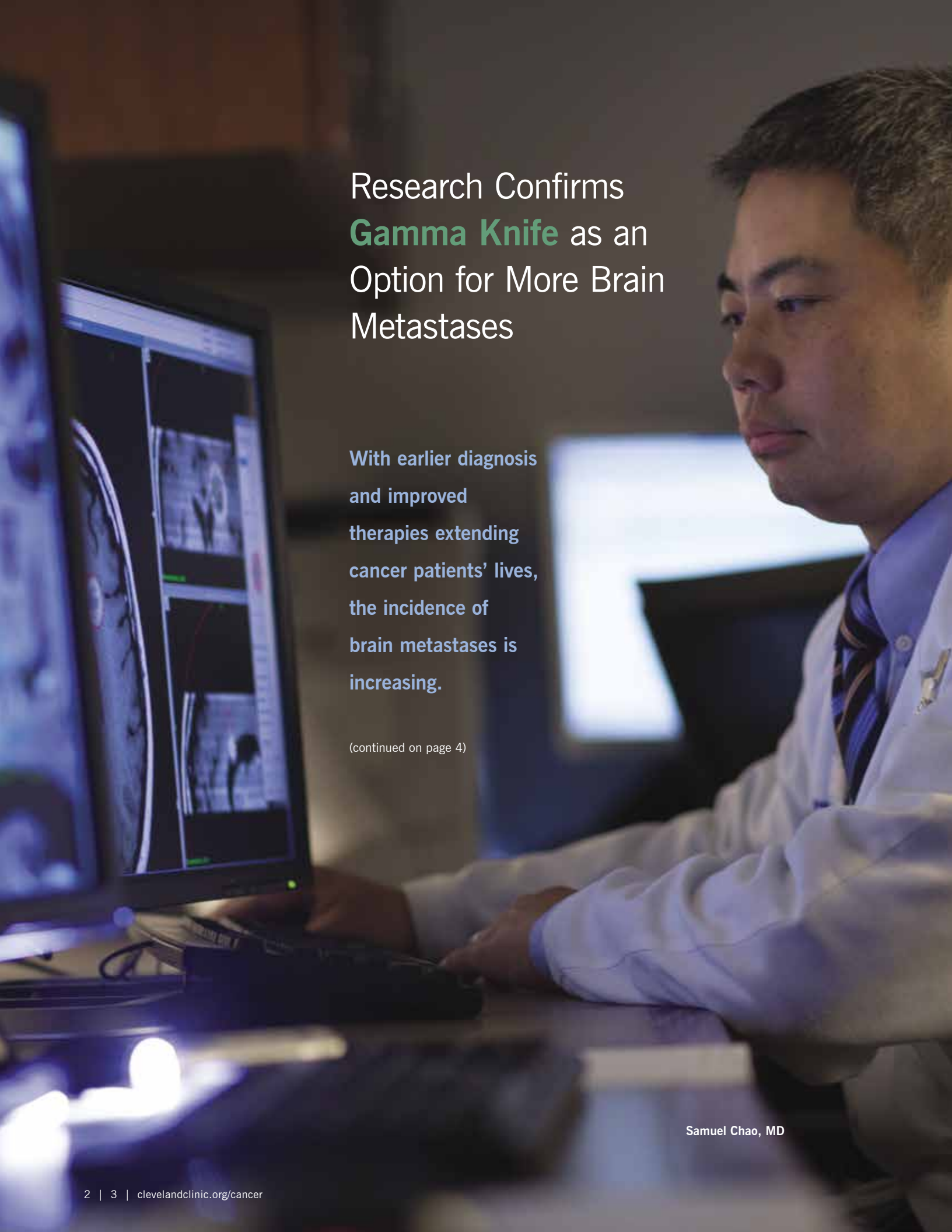


Samuel Chao, MD

Gamma Knife

(continued)

Dr. Chao is a staff member of Cleveland Clinic's Department of Radiation Oncology and of the Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center. He can be reached at chaos@ccf.org or 216.445.7876.

Gamma Knife® stereotactic radiosurgery is a standard treatment approach for patients with one to four brain metastases. Whole-brain radiation therapy (WBRT) has been the primary therapeutic modality for patients with five or more brain metastases, although there is debate about what constitutes optimal treatment.

The Gamma Knife technology's improved automation and precision have enabled radiation oncologists and neurosurgeons to treat patients with multiple brain metastases with increasing confidence. However, Gamma Knife's role in this higher-metastases realm has not been well-defined, and a limiting factor has been patient comfort during lengthier sessions.

Cleveland Clinic researchers have verified the safety and efficacy of Gamma Knife surgery (GKS) for upfront and salvage treatment in patients with five or more brain metastases. They also have confirmed the safety and efficacy of a higher-than-standard isodose line, which makes shorter treatment sessions possible.

The findings, published in the *Journal of Neurosurgery,*[1] reinforce GKS as a viable additional treatment option for patients with extensive intracranial disease burden of five or more metastases.

A subsequent study published in *Neurosurgery*[2] determined that prescribing the radiation dose to a higher isodose line is safe and effective while decreasing treatment time. Although the research examined higher isodose lines in patients with one to three brain metastases, the concept can be applied to patients with more brain metastases.

"We can treat five or more brain metastases in less time," says Cleveland Clinic Taussig Cancer Institute radiation oncologist Samuel Chao, MD, a co-author of both studies. "This allows for improved patient comfort without compromising safety or tumor control, given how effective Gamma Knife radiosurgery is in treating brain metastases."

Survival Impacts

The researchers retrospectively reviewed the impact of GKS — used as either a sole upfront treatment, a boost to upfront WBRT or a salvage treatment — on the survival outcomes of adult patients with five or more brain metastases. The cohort consisted of 170 patients treated between 1997 and 2010 at Cleveland Clinic's Gamma Knife Center.

The study found that:

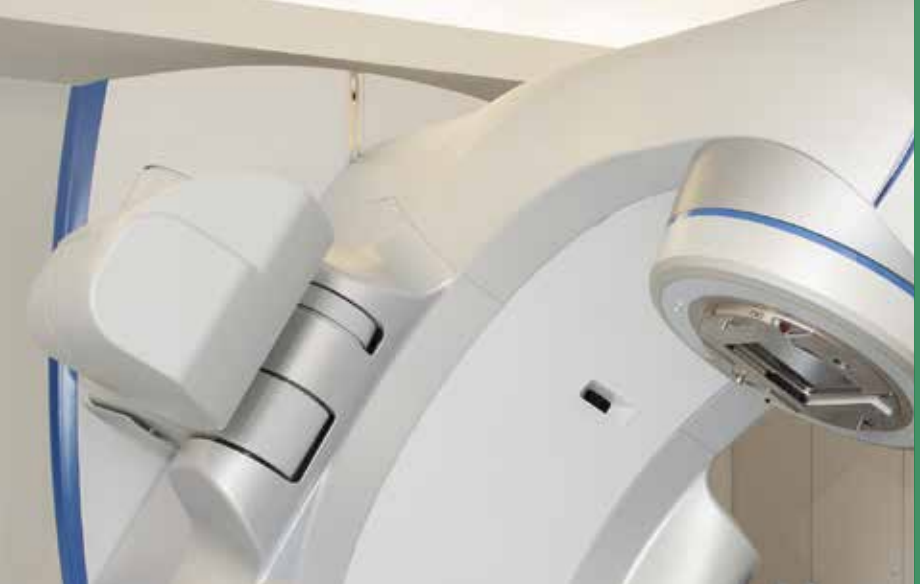
- Median survival times were 6.4 months after upfront GKS, 6.5 months after GKS to boost upfront WBRT and 6.8 months after salvage GKS ($p > 0.05$).
- Estimated six-month and one-year survival rates were 56 percent and 26 percent, respectively.
- Estimated six-month and one-year progression-free survivals were 25 percent and 13 percent, respectively.
- Imaging-verified disease progression occurred in 51 percent of patients during the follow-up period (which lasted a median of 6.2 months after GKS). There were isolated local recurrences in 3 percent of patients, local and distant recurrences in 8 percent and isolated distant recurrences in 40 percent.
- Eighty-seven percent of patients died during the follow-up period. Systemic disease progression was the primary cause of death in 39 percent; neurological progression was the cause in 26 percent.

KEY POINTS

Whole-brain radiation therapy has been the primary treatment method for patients with five or more brain metastases.

Gamma Knife stereotactic radiosurgery's improved automation and precision suggest it could be an effective therapeutic modality for multiple brain metastases.

Cleveland Clinic researchers have verified the safety and efficacy of Gamma Knife surgery as a viable upfront and salvage treatment option for patients with five or more metastases.



In addition to the Gamma Knife system, Cleveland Clinic recently added an EDGE™ Radiosurgery Suite, building out a comprehensive line of aggressive radiation therapy options, especially for extracranial sites such as spine, lung, liver, kidney and prostate.

- Independent predictors of poor prognosis after GKS were a low Karnofsky Performance Scale score at time of treatment, concurrent extracranial metastases to multiple organs, age older than 60 and a high intracranial tumor burden (> 10 cm^3).

Based on the results, the Cleveland Clinic researchers concluded that GKS alone or as a WBRT boost is a reasonable upfront treatment option for patients with five-plus metastatic brain tumors who haven't already undergone WBRT. Postponing WBRT by using GKS alone could help avoid neurocognitive decline in patients likely to have extended survival, the researchers reported.

Shortened Treatment Duration

In 2007, Cleveland Clinic acquired the Leksell Gamma Knife Perfexion™ system, the latest version of the technology, allowing for efficient treatment of multiple lesions in one setup. A potential drawback of treating more brain metastases than in the past, however, is that patients require a longer GKS session — three to four hours to irradiate six to 10 lesions.

That can be extremely uncomfortable, especially for patients with physical disabilities or limitations caused by their disease, says Dr. Chao.

Employing a higher than normal isodose level could potentially achieve the same results with shorter treatment duration.

Radiation oncologists and neurosurgeons have typically prescribed to a 50 to 60 percent isodose line in GKS.

Isodose levels of 70 to 80 percent have been applied for many years in linear accelerators to safely and effectively treat intracranial and extracranial tumors, but these levels had not been verified with GKS. Dr. Chao wanted to explore this possibility, including the potential for side effects and the impact on local control.

"We had hypothesized that we could use the higher isodose line in GKS for multiple metastatic brain tumors without compromising control or causing side effects, especially given its successful use with linear accelerators. The *Neurosurgery* study confirms it," says Dr. Chao.

Six to 10 lesions can be treated in two to three hours with the 70 to 80 percent isodose line. The Perfexion system's automated alignment provides additional safety with the higher isodose levels compared with manually aligned systems, Dr. Chao says. Patients are more comfortable, spend less time in treatment and, most important, have a new therapeutic option to consider in GKS.

While WBRT is still an appropriate upfront choice for some patients with multiple brain metastases, those who receive their lifetime maximum exposure have lacked further recourse. GKS provides a salvage opportunity, as well as an alternative for upfront treatment or as a WBRT boost.

References

1. Mohammadi AM, Recinos PF, Barnett GH, Weil RJ, Vogelbaum MA, Chao ST, et al. Role of Gamma Knife surgery in patients with 5 or more brain metastases. *J Neurosurg.* 2012;117 Suppl:5-12.
2. Shiue K, Barnett GH, Suh JH, Vogelbaum MA, Reddy CA, Weil RJ, Angelov L, Neyman G, Chao ST. Using higher isodose lines for gamma knife treatment of 1 to 3 brain metastases is safe and effective. *Neurosurgery.* 2014;74(4):360-364.

Immune Checkpoint Blockade Shows Promise as Novel Therapy for Cancer

Immune checkpoint blockade (ICB) research is one of the most exciting recent developments in immunotherapy for cancer, and Cleveland Clinic researchers are at the center of it. The use of nivolumab, alone or in combination with other agents, has shown significant promise in early trials of patients with metastatic renal cell carcinoma (mRCC), as well as cancers of the lung and skin.

Dr. Rini is a staff member of Cleveland Clinic's Department of Hematology and Medical Oncology and an Associate Professor of Medicine at the Cleveland Clinic Lerner College of Medicine. He can be reached at rinib2@ccf.org or 216.444.9567.

Brian I. Rini, MD, FACP, of Cleveland Clinic's Taussig Cancer Institute, is one of the lead investigators in international studies examining the efficacy of immune checkpoint inhibitors against mRCC.

"Taussig Cancer Institute has taken a leadership role in the development of novel immunotherapies for cancer," says Dr. Rini. "Building on a long history of clinical and laboratory excellence in immunology and immunotherapy, we are poised to develop the next generation of immunotherapeutics to extend the lives of cancer patients."

ICB's purpose is to temporarily inhibit modulating mechanisms in the patient's immune system and to bring the full force of the immune system to bear against cancer cells. In a healthy person, these modulating systems protect bodily tissue from the actions of immune factors. The challenge for oncologists has been that malignant tissue is able to exploit these mechanisms and to become less susceptible to the disease-fighting abilities of activated T cells and other immune components, including CTLA-4, PD-1, LAG-3 and TIM-3.

Restoring Immune Activity with Nivolumab

Dr. Rini and his colleagues have completed some trials — and are conducting others — involving nivolumab, an antibody that inhibits expression of the programmed death-1 (PD-1) receptor and its principal ligand, PD-L1. PD-L1 expression has been clinically associated with poor prognosis in mRCC patients.

Nivolumab is a human IgG4 PD-1 immune checkpoint inhibitor. It has been shown to restore T-cell immune activity. Patients with mRCC treated with the agent have shown positive objective responses in a phase 1 trial (N = 296) whose results were published in the *New England Journal of Medicine*.[1]

This group found that the objective responses to nivolumab were durable in patients with advanced non-small-cell lung cancer, melanoma and RCC. At one-year follow-up, 20 of 31 patients exhibited objective responses that lasted one year or longer. There was also a strong correlation between PD-1/PD-L1 expression and response to immune blockade. Of the 17 patients with PD-L1-negative tumors, none had an objective response to ICB with nivolumab. In contrast, 9 of 25 patients with PD-L1-positive tumors had an objective response.

The researchers concluded that "anti-PD-1 antibody produced objective responses in approximately 1 in 4 to 1 in 5 patients with non-small-cell lung cancer, melanoma or renal cell cancer."

Other ICB Study Results

Several other promising study results have been presented as abstracts at recent annual meetings of the American Society of Clinical Oncology (ASCO). Cleveland Clinic conducted some of this research.

In general, the results have revealed high objective response rates and tolerable side-effects when compared with treatment with vascular endothelial growth factor (VEGF) inhibitors (bevacizumab,

Brian I. Rini, MD, FACP

KEY POINTS

Immune checkpoint blockade (ICB) has demonstrated promising early results in patients with advanced renal cell, lung and skin cancers.

ICB agents temporarily inhibit modulating mechanisms in a patient's immune system, enabling a robust immune response against cancer cells.

Clinical trials involving nivolumab, an antibody that inhibits expression of the programmed death-1 (PD-1) receptor and its principal ligand, PD-L1, have shown its ability to restore T-cell immune activity and produce objective, durable response rates in patients with advanced non-small-cell lung cancer, melanoma and renal cell carcinoma.

sunitinib and pazopanib) and with mammalian target of rapamycin (mTOR) inhibitors (everolimus and temsirolimus).

In contrast, one study presented at ASCO found that up to 31 percent of patients with heavily pretreated mRCC were responsive to PD-1/PD-L1 blockade. The responses have been durable and associated with relatively little grade-3 toxicity.

In a phase II dose-ranging trial presented at ASCO, the researchers, including Dr. Rini, observed significant anti-tumor activity following treatment with nivolumab. In a group of patients (N = 168) with pretreated mRCC, all three dosages (0.3 mg/kg, 2 mg/kg and 10 mg/kg) were associated with objective responses of long duration. The median duration of objective response was 18.2 months for the 0.3 mg/kg group, which was not reached in the groups receiving the higher dosages. Rates of grade 3-4 treatment-related adverse events were ≤ 17 percent in all three groups. There were no instances of grade 3-4 pneumonitis.

A phase I trial of nivolumab in combination with ipilimumab, also presented at ASCO by a group that included Dr. Rini, showed similarly promising results. Patients were randomly assigned to one of two arms in this trial: nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (arm N3+I1; N = 6) or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (arm N1+I3; N = 9). Durations of response were 4.1+ to 22.1+ weeks in the N3+I1 arm and 6.1+ to 18.3+ weeks in the N1+I3 arm. Stable disease was observed in 39 percent of patients in N3+I1 and 33 percent of patients in N1+I3. Responses to treatment occurred by week 6 (first tumor assessment) in 67 percent of patients in both groups.

Cleveland Clinic researchers are also involved in international studies of two other checkpoint inhibitors: pembrolizumab and MPDL3280A. Study of these two compounds is ongoing, but early results suggest they have the potential for clinical efficacy.

Dr. Rini intends to continue with this promising ICB research, investigating ways to further reduce adverse treatment-related side effects, identify optimal dosages and dosing schedules, and discover other chemotherapeutic agents that act synergistically with immune checkpoint inhibitors.

Reference

1. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med.* 2012;366(26):2443-2454.

How has genomic analysis of tumors affected cancer therapy?

Because we know more about the genomic nature of tumors, we're thinking of cancers in a different way. Historically we've classified cancers by their anatomic location. Today we're increasingly looking at what genomic abnormalities are associated with a given patient's cancer. Different cancers may share pathway abnormalities, regardless of their anatomic site of origin. And we now have a menu of drugs designed to act on these genomic abnormalities. It's a very exciting time. Personalized cancer medicine is real. It's not theoretic; it's happening today in clinic. New therapies for cancers that have been difficult to treat, such as lung cancer, are extending survival and improving quality of life for a large number of patients.

In addition to the benefits of having all this new cancer genomic information, are there challenges?

The genomic information we have right now outstrips our tools. We only have so many available drugs. A large number of genomic abnormalities exist, so it may not be realistic to have a drug for every one.

The second challenge is how we should conduct clinical research in this space. Historically we took hundreds of patients with a given disease and randomized them to treatment A or treatment B. With sophisticated genomic analysis it will be a challenge to identify 100 patients with the exact same DNA fingerprint to compare treatment A with treatment B. So we've got to think about clinical research in a different way.

How will that genomic variability among patients affect clinical trial design and the evaluation of results?

The numbers of patients enrolled in a particular trial are probably going to be smaller than they used to be. Some pharmaceutical companies have adopted a way to conduct a clinical trial in which patients with multiple cancers, such as lung cancer, breast cancer, colon cancer, etc., are all eligible to receive a new treatment that targets a specific genomic pathway if their cancer has that abnormality detected. The primary purpose is to study results of the drug against all cancers with a specific genomic target. This is different than the traditional model of clinical research, which only looks at one disease such as colon cancer. With the new approach, you know that initially you're looking for a small number of patients, but if you show any clinical efficacy, especially in a clinical situation where there are very few therapeutic options, then that's reason enough to propel that study into a more advanced phase 2 or phase 3 trial.

I think the challenge will be to convince our insurance colleagues that the gold standard of a very large prospective randomized trial may not always be necessary to show proof of principle with targeted therapies.

There's also the issue of cost.

It's approaching $100,000 for a patient to have a complete course of targeted therapy. That's part of the societal equation we've also got to figure out, because the cost is going up logarithmically, not linearly. Does that mean in 10 years it's going to cost $1 million for a course of targeted therapy? Obviously if that's the case it's not feasible. The economics just don't work.

I think the answer is forming new collaborations. We're going to have to figure out how to collaborate with pharmaceutical companies, insurance companies, clinical researchers and providers, and Washington, D.C., meaning the Food and Drug Administration, the National Cancer Institute and the Centers for Medicare & Medicaid Services. The historical lack of alignment among these parties will not work with personalized medicine because the outcome will be too complicated and expensive.

How are you translating what you're learning from cancer genomic analysis into clinical care?

Genomic testing is not one test. One can examine a specific panel of a finite number of genes; alternatively, one can analyze the entire genome. How extensive clinical

Brian J. Bolwell, MD, FACP, Talks About **Personalized** Cancer Care

genomic testing should be in routine clinical practice is an unanswered question at present.

We have identified a practical approach that involves an extensive analysis, but is limited to 350 or so genes that have known actionable items associated with them.

We have taken the approach that we want to prospectively collect information on all patients who have high-level sequencing performed on their tumor. We started by having a feasibility trial in which every patient who had such an analysis was part of a clinical trial. That is evolving into a routine clinical practice algorithm in which we have a way to track genomic data.

It's important to build genomic information into care path development. Cleveland Clinic has spent a great deal of time developing treatment algorithms or care paths, which I think is the wave of the future. The more we get into population-based management and bundling for reimbursement, the more important it is to have standardization, to reduce variability and adhere to principles that optimize clinical outcomes and are cost-effective.

If the oncology community can do that collectively, on a national scale, it will be easier to form the collaborations needed to try to advance the science of genomic medicine.

How does Cleveland Clinic deal with the complexity and uncertainty of genomic sequencing information?

One of our lessons learned is the importance of a genomics tumor board. If sophisticated genomic analysis is performed, the clinician will get a report that is frequently confusing. It's filled with detail and potential recommendations that are difficult to prioritize. So every week 10 to 20 physicians in our cancer center get together and go over every one of these reports to try to make it a little clearer. We devise a specific treatment recommendation and deliver that to the clinician who ordered the test. Having that consensus opinion has been invaluable.

What are you doing to ensure that treatments are available for the genomic abnormalities that tumor sequencing identifies?

Internal drug development is something that Cleveland Clinic is known for. Our technology development arm, Cleveland Clinic Innovations, has been in existence for quite a while to facilitate the infrastructure and process of developing new therapies, such as precision-based medicines for cancer. Taussig Cancer Institute recently hired a medicinal chemist who's basically exclusively working on making drugs that can attack genomic targets identified by our scientists to try to yield clinical benefit.

What do you think cancer care will look like in 15 or 20 years?

I think there's a pretty good chance that it's going to be routine to have very extensive and sophisticated genomic analysis of a given patient's tumor. It's likely that there will be a much more complete menu of targeted drugs, and maybe other things that can manipulate these genomic abnormalities in a favorable way.

One possibility is making a cancer cell behave normally. By definition, a cancer cell wants to keep making cancer cells and messes up the cells around it. If you can trigger a cancer cell to still have a genomic abnormality associated with it but to act like a normal cell and not grow uncontrollably, you can manage somebody's cancer. If you can differentiate the cancer into acting normally, that's a whole new field that has great promise. That's one of the things we're working on here. Some results have been very, very exciting.

Bringing **Precision Medicine** to **Biliary Cancers**

Biliary tract cancers — including intra- and extrahepatic cholangiocarcinomas, and gallbladder cancer — are aggressive malignancies with poor clinical outcomes.

By Alok Khorana, MD, and Davendra Sohal, MD, MPH

Dr. Khorana is a staff member of Cleveland Clinic's Department of Hematology and Medical Oncology and Director of the Taussig Cancer Institute's Gastrointestinal Malignancies Program. He can be reached at khorana@ccf.org or 216.636.2690. On Twitter: @aakonc

Dr. Sohal is a staff physician in the Department of Hematology and Medical Oncology and Director of the Taussig Cancer Institute's Clinical Genomics Program. He can be reached at sohald@ccf.org or 216.444.8258.

Most patients present with advanced disease, and current management options are limited to chemotherapy agents such as gemcitabine and cisplatin, with modest benefit.

In many other cancers, physician-scientists have been able to improve clinical outcomes by identifying molecular aberrations in tumors and by conducting clinical trials of novel therapies aimed at those molecular targets.

There are several obstacles, however, to studying biliary tract malignancies:

- They are a group of relatively uncommon cancers.
- Tissue biorepositories are rare or non-existent.
- Federal funding for scientific research is limited.
- Patients present late in the course of the disease, making enrollment in clinical trials difficult.

Surmounting the Obstacles to Biliary Cancer Research

At Cleveland Clinic's Taussig Cancer Institute, we are building a research program to overcome these hurdles. With the Frank and Nancy Porter family's creation of the Porter Family Genomics Fund, we are able to initiate a comprehensive research program in biliary malignancies that will be quickly translatable into innovative clinical trials.

Alok Khorana, MD

Our initial focus is the creation of a robust biorepository of tumor tissue specimens collected both retrospectively and prospectively from patients seen at Cleveland Clinic. We will utilize these biospecimens to develop an easily reproducible platform to study molecular alterations in biliary tract cancers.

Dealing with the Scarcity of Tumor Tissue Samples

In the past, we have been limited because traditional clinical specimens contain only small amounts of tumor tissue. Most diagnoses of biliary tract cancers are made using fine-needle aspiration samples or bile duct brushings collected during procedures such as endoscopic ultrasound or endoscopic retrograde cholangiopancreatography.

Partnering with Case Comprehensive Cancer Center scientists who have extensive experience in clinical genomics, we have identified tumor sequencing platforms that can allow us to identify DNA and RNA changes in archived biliary tract cancer specimens obtained during routine clinical care. Our collaborators will use leading-edge high-throughput next-generation sequencing

KEY POINTS

Biliary tract cancers are aggressive and difficult to treat successfully.

Attempts to improve outcomes have been hampered by the cancers' relative rarity, the advanced stage of most tumors upon presentation, and the scarcity of tissue biorepositories and research funding.

Cleveland Clinic is building a comprehensive biliary cancer research and targeted treatment program to overcome these obstacles.

techniques and bioinformatics methods that can surmount the usual problems of quantity and quality of tumor tissue.

Next, we envision being able to correlate these molecular findings with clinical data to understand the impact of various molecular alterations on clinical outcomes. We are therefore also building a robust clinical data set to complement potential molecular findings.

In addition, comparisons between biliary tract cancer specimens and non-neoplastic biliary tissues, such as specimens obtained during cholecystectomies, will allow us to further home in on alterations that play a critical role in cancer development and progression. Thus, we will be able to create a catalog of clinically relevant molecular alterations in biliary tract cancers.

Davendra Sohal, MD, MPH

Employing Clinical Trials of Targeted Therapies

Finally, we plan to apply this knowledge to clinical trials of novel targeted therapies. We already have a unique clinical genomics program at the Cancer Institute. As part of this program, we perform extended genomic sequencing of clinical specimens from patients with advanced solid tumors. Results are reviewed at a dedicated Genomics Tumor Board — a weekly meeting of clinical and translational oncologists.

Participants review each result in detail and make recommendations for targeted therapy — on-label drugs, off-label use or clinical trials — which are communicated to treating physicians.

We have a portfolio of clinical trials of targeted therapies encompassing many genomic alterations of known clinical value and many solid tumor histologies. We will build on our experience with this initial broad program, with a focus on obtaining novel agents and innovative trials specifically for our patients with biliary malignancies.

We are privileged to have the support of patient survivors and advocates such as Lisa Craine and her foundation, "Craine's Cholangiocarcinoma Crew."

Soon we hope to utilize modern tumor sequencing methods and novel targeted therapies in conjunction with a well-established program of patient identification, tumor sequencing, and coordinated patient access and enrollment into clinical trials of targeted therapies based on their individual tumor genome. This effort will bring individualized therapies and precision oncology to each of our patients with biliary malignancies.

Targeted Pediatric Cancer Treatment: ‘Every Patient Teaches Us Something’

When Cleveland Clinic pediatric oncologist Johannes Wolff, MD, talks about his novel approach to targeted cancer therapy for treatment-resistant malignancies, you won’t hear him discussing general categories of tumors and their overall responses.

Dr. Wolff is Chairman of Cleveland Clinic Children’s Department of Pediatric Hematology-Oncology and Blood & Marrow Transplantation. He can be reached at wolffj@ccf.org or 216.445.3588.

“The whole concept is to get away from the classical, old-fashioned diagnoses given by pathologists looking at tumors through a microscope,” he says. “Instead of separating them into categories based on pathology, we’re looking at tumor marker expression in each patient. We’re focusing on truly individualized treatment.”

With smaller numbers of tumors overall in the pediatric population versus adults and therefore fewer standardized protocols, personalized medicine takes on an even greater importance. “Every patient teaches us something,” Dr. Wolff says.

Creating a Treatment Road Map

Dr. Wolff, who joined Cleveland Clinic in late 2013 as Chair of the Department of Pediatric Hematology-Oncology and Blood & Marrow Transplantation, so far has about 10 patients with treatment-resistant, often recurrent tumors who are undergoing highly specialized targeted therapy. Sometimes the tumors are rare and/or aggressive, and no standard therapy exists. Many tend to be neurological.

KEY POINTS

The paucity of standardized protocols for pediatric cancers heightens the importance of individualized, targeted therapy.

Cleveland Clinic is providing targeted pediatric oncology care and is conducting research to analyze outcomes, with the goal of creating treatment algorithms related to specific tumor markers and drug selection.

He creates a personalized therapeutic road map for each patient based on genomic, proteomic and/or related testing to target and attack the tumor’s unique molecular abnormalities. Such testing provides valuable information — for example, hundreds of genetic hot spots have the potential for mutation in the cancer genome.

In keeping with pediatric oncology’s tradition of multidrug therapy, Dr. Wolff’s synergistic, holistic approach combines novel agents with well-established treatments. “We take everything that can help the patient — including biologics and traditional chemotherapy — and combine multiple drugs in a unique way,” he says.

Moving the Needle with Targeted Therapy

Dr. Wolff first became interested in targeted therapy about a decade ago, prompted by a desire to improve the 80 percent overall success rate in treating pediatric cancers, as measured by clinical trials.

While targeted therapy originated in adult oncology, those patients typically receive only one or two drugs based on a single tumor marker. “With much larger numbers of adult patients within one diagnosis category, targeted therapy is still protocol-driven with off-the-shelf options,” he says.

“In pediatric oncology, we are getting away from the diagnoses and are looking only at the markers and using highly individualized multiple-drug therapies,” Dr. Wolff says. “We don’t have enough patients to break down diagnoses into smaller groups to write protocols. I write a new multidrug protocol for every single patient based on the treatment targets that the tumor expresses.”

Some of those patients and their families have journeyed far to receive care. At least two have

moved to Ohio from other states, and another travels from Europe.

Dr. Wolff says that while not all molecular test results are actionable, he has always been able to recommend a treatment for patients whose tests provide some tumor marker information.

"The days are over of having 10 drugs available to treat a patient's cancer, trying all of them and having nothing left," Dr. Wolff says. "There hasn't been a time in the past five to 10 years when I didn't have anything to give. However, the issue of determining when the toxicity is worth it remains, and those decisions still need to be made."

Measuring Outcomes

The success of targeted therapy is assessed using typical criteria such as survival, event-free survival, quality of life and long-term sequelae. While it's too soon to measure outcomes in Dr. Wolff's Cleveland Clinic patients, he has many success stories involving patients he previously treated.

"Patients and their families often come to us after being told there's nothing else that can be done, and they are very thankful to have targeted therapy as an option," he says. "With targeted therapy, we've had individual patients who lived much longer than expected, or who are still living after being told they would die."

Building a Treatment Algorithm

Cleveland Clinic's Institutional Review Board recently approved Dr. Wolff's research project to analyze the outcomes of targeted therapy in pediatric patients. The goal is to create treatment algorithms related to specific tumor markers and drug selection.

However, obtaining funding for the research remains an issue. "This type of treatment is so out of the box that traditional funding agencies hesitate to fund it," he says.

Dr. Wolff points to the importance of ongoing research and evaluation when it comes to such innovative therapy.

"Now that we have more patients, there are more data to pull out of the medical record for analysis," he says. "We need to assess what's worked in which patients so the next patients have an even smarter choice of drugs."

"I write a new multidrug protocol for every single patient based on the treatment targets that the tumor expresses."

Johannes Wolff, MD

Can a **VEGF-A Variant** Help Halt the Spread of Cancer?

The vast majority of cancer-related deaths are attributable to metastasis. That makes slowing or halting tumor growth and migration a critical target in the ongoing study and treatment of cancer.

Dr. Fox is a staff member of Cleveland Clinic's Department of Cellular and Molecular Medicine and the Department of Cardiovascular Medicine. He can be reached at foxp@ccf.org or 216.444.8053.

The ability to interdict the metastatic process could revolutionize oncological intervention and outcomes. That's why recent progress by Cleveland Clinic researcher Paul Fox, PhD, reported in the journal *Cell*, is attracting attention. His discovery[1] of a new variation in a known family of proteins — an alteration that has the ability to inhibit tumor growth and angiogenesis — affirms the adage that sometimes big things come in small packages.

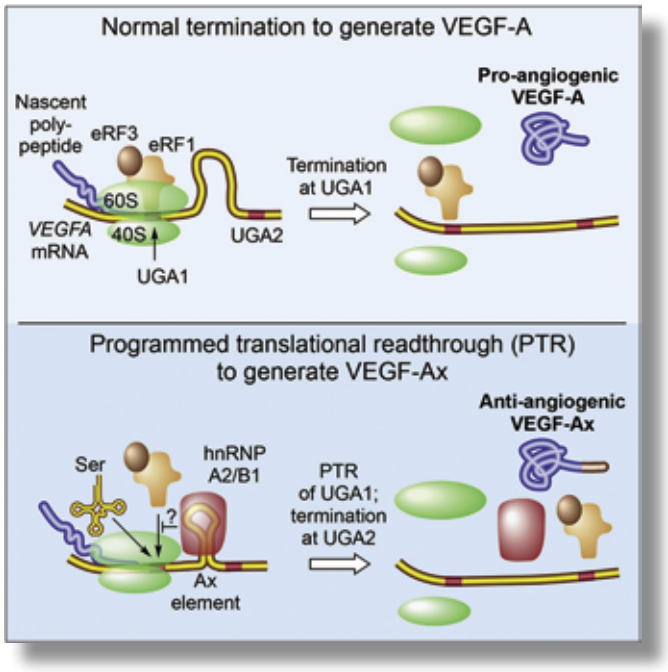


Figure 1. **Generation of VEGF-A and VEGF-Ax.**
Reprinted from *Cell*. 2014;157(7):1605-1618. Eswarappa SM, Potdar AA, Koch WJ, Fan Y, Vasu K, Lindner D, Willard B, Graham LM, DiCorleto PE, Fox PL. Programmed translational readthrough generates antiangiogenic VEGF-Ax. Copyright 2014, with permission from Elsevier.

A Double-Edged Sword

Dr. Fox's work relates to vascular endothelial growth factor A (VEGF-A), which is essential for the normal development of blood vessels and the proliferation of endothelial cells. It also plays a part in wound healing, inflammation, and female reproduction and menstruation.

VEGF-A also is involved in pathological processes: It has long been known to stimulate angiogenesis in solid tumors, increasing the likelihood of growth and metastasis. Scientists worldwide have examined whether blocking VEGF-A can serve as a therapeutic tool against cancer. In fact, such therapies currently exist to treat colon and kidney cancers, and researchers are investigating their efficacy against other neoplasms.

Alteration Reverses Angiogenic Behavior

A team led by Dr. Fox, of Cleveland Clinic's Lerner Research Institute, has uncovered a variant of VEGF-A that might provide additional guidance for developing novel and effective cancer treatments.

The new protein is generated when a ribosome ignores a stop codon's instruction for a gene to terminate the translation of its genetic code. This process, known as a programmed translational read-through, transforms VEGF-A into a slightly altered variant, which Dr. Fox and his colleagues named VEGF-Ax ("x" is for extended). The new isoform contains a unique 22-amino-acid C terminus extension.

This tiny transformation causes a not-so-tiny effect: It appears to reverse the behavior of its parental form, VEGF-A. That means that it halts rather than promotes angiogenesis and tumor growth.

Paul Fox, PhD

KEY POINTS

Finding ways to slow or stop tumor growth and migration is a critical goal in oncology research.

Vascular endothelial growth factor A (VEGF-A), a protein essential for normal blood vessel development and wound healing, also can stimulate angiogenesis in solid tumors, increasing the likelihood of growth and metastasis.

Cleveland Clinic researchers recently discovered a VEGF-A variant called VEGF-Ax that, when administered to mice with human xenograft tumors, significantly reduced tumor progression and tumor-associated angiogenesis.

Future research will expand on animal study findings.

Dr. Fox's team found that administering recombinant VEGF-Ax to nude mice with human xenograft tumors significantly reduced tumor progression and tumor-associated angiogenesis.

"It is truly remarkable that a small addition in a protein sequence leads not just to a protein with a different function, but one with a function completely opposite to the original," Dr. Fox says. "In the context of cancer, the small extension changes a very bad protein into a very good one."

From Mice to Men?

The initial discovery of VEGF-Ax occurred in animal models, but it may prove relevant to humans through future studies. The end goal could be an injectable VEGF-Ax to slow tumor growth as a direct therapy.

Dr. Fox notes some potential indirect benefits as well, such as the utility of VEGF-Ax as a biomarker to inform treatment decisions.

For example, conventional anti-VEGF-A therapy would not only inhibit VEGF-A's tumor-stimulating properties, but would unfortunately also block the beneficial, anti-angiogenic effects of VEGF-Ax. Thus, if a tumor is producing a large amount of VEGF-Ax, clinicians might want to avoid such a treatment.

"This is also instructive to clinicians who are researching VEGF therapy and may want to start thinking about therapies that will block regular VEGF-A but not this new extended form," Dr. Fox says.

The next stage in research will focus on expanding findings from animal studies. For instance, it is unclear whether toxicity is an issue. Acquiring additional data on VEGF-Ax dosage and frequency of administration is imperative. Despite such questions, Dr. Fox remains cautiously optimistic about the discovery's implications.

"Is this likely to lead to a cancer cure? Who knows," he says. "Is it likely to improve the therapies being used against cancer? I think there's a pretty good chance that this will be an important contribution to our understanding of how to apply anti-angiogenic therapy."

Reference

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Debunking the Myths of Chemotherapy in Prostate Cancer

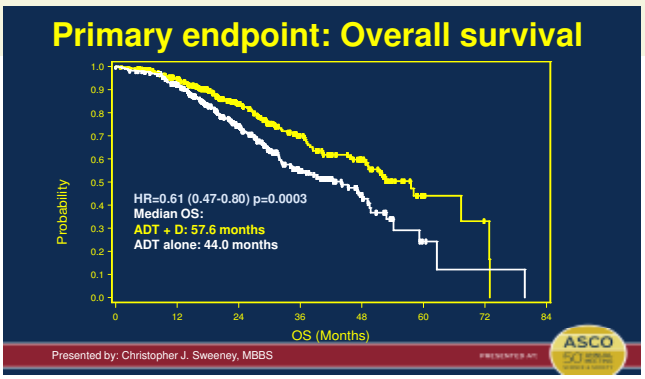

Figure 1. **Overall survival results from the CHAARTED trial.** Data presented at the 2014 American Society of Clinical Oncology Annual Meeting and reused with permission of study chair and presenting author Christopher Sweeney, MBBS, Associate Professor of Medicine, Harvard Medical School/Dana-Farber Cancer Institute.
ADT = androgen deprivation therapy, D = docetaxel

By Jorge A. Garcia, MD, FACP

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During the past five years, treatment options for men with advanced prostate cancer (PCa) have changed dramatically with the introduction of immunotherapy, novel adrenal and androgen receptor targeted agents, and the use of alpha emitters.[1]

Despite the uniqueness of some of these approaches, the role of chemotherapy in the management of this disease has gained momentum with the recent results from a large North American intergroup trial. ECOG 3805, also known as the ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED), evaluated the role of upfront chemotherapy in men with metastatic disease who need androgen deprivation therapy (ADT).[2]

KEY POINTS

Chemotherapy's use in prostate cancer has been hampered by myths regarding its side effects and potential negative impact on quality of life, its questionable activity in prostate cancer, and the belief that chemotherapy should be reserved until other therapies are exhausted.

Recent clinical trial results have changed perceptions about systemic chemotherapy in castration-resistant prostate cancer and bolstered the case for upfront use in selected men with advanced disease.

The Evolving View of Chemotherapy in PCa

Historically, the use of chemotherapy in PCa has faced significant challenges. Among these, the issue of who should have responsibility for patient oversight has been the biggest one. Should patients with advanced disease be managed by urologists or medical oncologists? When should a urologist refer a patient to a medical oncologist?

Although these questions can be answered in many ways, there is now recognition that men with advanced PCa benefit from a multidisciplinary treatment approach. Fueling the debate is the fact that chemotherapy has traditionally been reserved for men with advanced disease who become castration-resistant — a patient population managed by medical oncology.

Myths surrounding chemotherapy relate to its side effects and potential detrimental impact on quality of life (QOL), its supposedly questionable activity in PCa, and the perception that it should be used as the last treatment choice after everything else has failed. It certainly did not help that trials in the late 1990s evaluating mitoxantrone-based chemotherapy in castration-resistant disease failed to show survival benefit.[3,4]

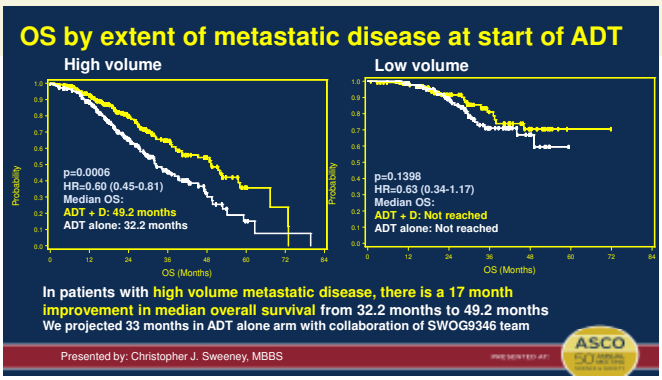

Figure 2. **Overall survival results from the CHAARTED trial by the extent of metastatic disease at the start of androgen deprivation therapy.** Data presented at the 2014 American Society of Clinical Oncology Annual Meeting and reused with permission of study chair and presenting author Christopher Sweeney, MBBS, Associate Professor of Medicine, Harvard Medical School/Dana-Farber Cancer Institute.

Chemotherapy Improves Overall Survival in Castration-Resistant Prostate Cancer

Perhaps one of the most important years for PCa was 2004, when two well-conducted randomized phase 3 clinical trials (SWOG 9916 and TAX 327) evaluating docetaxel-based chemotherapy in men with metastatic castration-resistant prostate cancer (mCRPC) led to the Food and Drug Administration's approval of this regimen in CRPC.

Treatment with docetaxel not only improved overall survival (OS) but led to effective tumor burden reduction, prostate specific antigen (PSA) declines and improvement in QOL in those men with symptomatic disease.[5,6] In fact, the median OS in the long-term follow-up analysis for the TAX 327 is 19.2 months for docetaxel-treated patients versus 16.3 months for those receiving mitoxantrone.[7] As important was the fact that the side effect profile was manageable and similar to that of chemotherapy agents in other solid tumors.

More recently the utility of second-line chemotherapy with cabazitaxel, a semisynthetic taxane derivative developed for its activity in patients with resistance to docetaxel, was demonstrated in the international TROPIC trial. That phase 3 trial evaluated this novel taxane against mitoxantrone in mCRPC patients who progressed on docetaxel. Men treated with

(continued on page 18)

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Debunking Myths

(continued)

cabazitaxel had an increased OS compared with those treated with mitoxantrone (hazard ratio [HR] 0.70, 95% CI 0.59-0.83, median survival 15.1 vs. 12.7 months).[8]

The results of these trials have clearly changed the thinking about systemic chemotherapy in CRPC and have debunked some of the myths that discouraged this approach for many years.

Now the issues we face are of even greater magnitude. An improved understanding of the biology of CRPC coupled with the availability of newer agents has challenged the approach that one treatment fits all. As a result, questions about patient selection, the appropriate timing for treatment, the mechanisms of resistance and the best treatment sequence are the focus of additional research.

Should Chemotherapy Be a Last Treatment Choice?

The simple answer to this complex question is NO. Some of the most dramatic findings ever published on PCa are the recent results of ECOG 3805, a randomized phase 3 study of ADT +/- 6 cycles of docetaxel chemotherapy in men with hormone-naïve metastatic PCa.[2] Cleveland Clinic participated in the ECOG 3805 trial.

Jorge A. Garcia, MD, FACP

The rationale for the trial's design was simple: Attack de novo testosterone-independent clones early, allowing ADT to keep PCa in remission longer.

More than 790 men with metastatic PCa in need of ADT were randomized to either ADT alone or chemotherapy and ADT. Patients were stratified based on extent of metastases (high vs. low volume), age, Eastern Cooperative Oncology Group performance status, use of agents to prevent skeletal-related events, use of anti-androgens and prior adjuvant ADT. The primary end point was OS. Standard secondary end points included rate of PSA undetectability at six and 12 months, time to CRPC, safety, and QOL at 12 months.

The OS for the entire cohort was 57.6 months versus 44 months favoring the docetaxel + ADT arm (HR 0.61; $p = 0.003$). Similarly, the OS in men with high-volume disease (defined as visceral disease and/or four or more bone metastases with at least one beyond the pelvis and vertebral column) was 49.2 months versus 32.2 months in favor of the chemotherapy + ADT arm (HR 0.60; $p = 0.0006$). Nearly twice as many patients achieved an undetectable PSA at six and 12 months in the chemotherapy arm (27.5% vs. 14% and 22.7% vs. 11.7 percent respectively; $p < 0.0001$), and the time to CRPC was also greater for those in the combination arm (14.7 months vs. 20.7 months; $p < 0.0001$).

Patients in the chemotherapy arm experienced more toxicities compared with those on ADT alone; however, these toxicities were docetaxel-related and similar to those commonly observed when this agent is utilized in the CRPC setting.

These data continue to support the importance of chemotherapy in men with PCa. They debunk the myth that late treatment is better and clearly establish the use of upfront chemotherapy for selected men with advanced disease (even prior to the development of castration-resistant disease) as a new standard of care.

Guidelines Set for Blood Cell Mobilization and Collection Prior to Transplant

Hien Duong, MD

KEY POINTS

Because of varying resources, hospitals historically have used differing protocols and algorithms to mobilize peripheral blood progenitor cells (PBPC) for autologous and allogeneic hematopoietic cell transplantation.

A Cleveland Clinic-led task force has developed evidence-based guidelines for mobilizing and collecting PBPC safely.

The guidelines address clinical questions such as which growth factor is optimal, what chemotherapy and dose are most effective, and when to initiate leukapheresis. They also contain recommendations for special patient populations and comorbidities.

There are many effective ways to mobilize peripheral blood progenitor cells (PBPC) for autologous and allogeneic hematopoietic cell transplantation. These regimens include growth factor alone or in combination with chemotherapy, both of which can be enhanced with plerixafor, a fairly new option.

Historically, hospitals have applied differing PBPC mobilization protocols and algorithms depending on their available resources. This is because mobilization requires coordination among multiple departments (apheresis, transfusion medicine, flow cytometry), and not every hospital has similar access to or availability of these departments.

Because of the imperative needs to mobilize and collect PBPC safely, adequately and cost-effectively for transplant, and to standardize practices, the American Society of Blood and Marrow Transplantation (ASBMT) established a task force led by Cleveland Clinic hematologist/oncologist Hien Duong, MD, to develop and publish evidence-based guidelines.

Impact of Plerixafor

With the Food and Drug Administration's approval of plerixafor as a mobilizing agent in 2008, a large body of studies and abstracts detailed mobilization and improved efficiency in collection of PBPC under varied circumstances.

Dr. Duong and the ASBMT Practice Guidelines Committee began the process of guideline development with a thorough literature review of these publications. The group defined recommendations intended to improve practices at PBPC-handling facilities, whether at small or large hospitals, and with varying resources.

Scope of Guidelines

The guidelines address clinical questions such as which growth factor is optimal, what chemotherapy and dose are most effective, and when to initiate leukapheresis. They also contain recommendations for special patient populations and comorbidities.

The detailed guidelines were peer reviewed by a national expert base representing small and large hospitals and approved by the ASBMT before being published in *Biology of Blood and Marrow Transplantation.*

"We lay out the known risks and benefits, advantages and disadvantages, of each mobilization strategy," says Dr. Duong. "We also recommend target cell doses for collection and infusion for transplant. We present data on how cell collection can most safely and effectively be done."

The standardized algorithms address the optimal resource accessibility and may help smaller transplant programs justify investment in necessary service enhancements. The guidelines include a list of frequently asked questions to provide additional comprehensive guidance.

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HIGHLIGHTS
from the
ASH
ANNUAL MEETING

Physicians and investigators from Cleveland Clinic's Taussig Cancer Institute made major contributions to the American Society of Hematology (ASH) 2014 Annual Meeting in San Francisco, describing their research in oral and poster presentations. Here are abstracts from four of the presented papers. (Cleveland Clinic authors are listed in bold.)

A Novel Mechanism of Cellular Activation Mediated by Antiphospholipid Antibody-Induced Extracellular Vesicles

Meifang Wu, MD; Suman Kundu, MBA; Venkaiah Betapudi, PhD; and **Keith R McCrae, MD**

Introduction: Antiphospholipid syndrome (APS) is characterized by thrombosis and/or recurrent fetal loss in the presence of persistently elevated antiphospholipid antibodies (APLA). Elevated levels of endothelial cell-derived extracellular vesicles (EV) are present in the plasma of patients with APLA, and APLA, particularly those directed against β2-glycoprotein I (β2GPI), stimulate EV release from endothelial cells (EC). However, the constituents or activity of these EV are not well-studied.

Objective: To determine whether EV derived from anti-β2GPI-antibody-treated EC activate quiescent EC, and to define the mechanism.

Methods: EV released by EC in response to exposure to β2GPI and either anti-β2GPI antibodies or control immunoglobulin G (IgG) were isolated by ultra-centrifugation. EC treated in this manner, as well as released EV and EV-free conditioned medium, were analyzed for interleukin-1β (IL-1β) content. Both EC and EV were also probed for expression of components of the *NLRP3* inflammasome. The ability of EV isolated from treated cells to activate EC in an autocrine/paracrine manner was assessed through measurement of E-selectin expression on the EC surface as well as phosphorylation of *IRAK4*. To define the mechanism of EC activation by EV, EC were pretreated with several inhibitors of the IL-1β signaling pathway, or with siRNA against *IRAK4, TLR2, TLR4, TLR7* and *TLR9*, or EV. We also examined the effect of pretreating EV with RNase A before addition to EC.

Results: EV released from EC in response to anti-β2GPI antibodies, but not control IgG, were enriched in mature IL-1β and induced EC activation. However, the ability of these EV to activate EC was not inhibited by a neutralizing IL-1 antibody, IL-1 receptor antagonist or IL-1 receptor siRNA. To define the signaling cascade activated by EC-derived EV, we examined downstream components of the IL-1 receptor (IL-1R)/toll-like receptor (TLR) pathway, finding that activation was associated with and dependent upon phosphorylation of *IRAK4*. To determine which members of the IL-1R/TLR family mediated *IRAK4* phosphorylation and cellular activation in response to APLA-induced EV, we inhibited the expression of *TLR2, TLR4, TLR7* and *TLR9* using specific siRNAs. Inhibition of *TLR7*, but not other TLRs, blocked EC activation in response to EV. Since a ligand of *TLR7* is single-stranded RNA (ssRNA), we also pretreated EV with RNase A, which inhibited activation to a similar extent as *TLR7* knockdown. Finally, we also observed that anti-β2GPI antibodies increased the expression of EC *TLR7*.

Conclusions: APLA/anti-β2GPI antibodies cause EC activation and inflammasome formation, leading to release of IL-1β enriched EV. These EV induce EC activation; however, activation is mediated primarily through interactions of EV-associated ssRNA with *TLR7* rather than through an IL-1β receptor-dependent pathway. These EV may contribute to vascular activation in an autocrine/paracrine manner and contribute to the prothrombotic phenotype in APS.

DDX41 Is a Tumor Suppressor Gene Associated with Inherited and Acquired Mutations

Chantana Polprasert, MD; Isabell Schulze; **Mikkael A Sekeres, MD, MS; Hideki Makishima, MD, PhD; Bartlomiej P Przychodzen; Naoko Hosono, MD, PhD; Jarnail Singh, PhD; Richard A Padgett, PhD; Xiaorong Gu, PhD;** Eckhard Jankowsky, PhD; **Michael Clemente, MS; Brittney Dienes; Sudipto Mukherjee, MD, MPH;** Utz Krug, MD; Hans-Ulrich Klein, PhD; Martin Dugas, MD; Wolfgang E Berdel, MD; Kenichi Yoshida, MD, PhD; Yuichi Shiraishi, PhD; Kenichi Chiba, PhD; Hiroko Tanaka, BA; Satoru Miyano, PhD; Seishi Ogawa, MD, PhD; Carsten Müller-Tidow; and **Jaroslaw P Maciejewski, MD, PhD**

Familial myelodysplastic syndrome (MDS) is rare and usually occurs at a young age. Distinguishing familial from sporadic disease at the typical late age of disease onset is difficult. While investigating the genetic background in familial acute myeloid leukemia (AML) cases, we identified five families characterized by germline (GL) mutations in the DEAD-box RNA helicase *DDX41* gene. In one family, a father, son, daughter and paternal grandmother were affected.

Sequencing revealed a GL *DDX41* mutation (c.419insGATG, p.D140fs; prevalence in controls < .0001%) cosegregating with the disease. This mutation was recurrent in three other AML families, while in another family containing identical twins with congruent MDS, a c.T1187C mutation (not detected in controls) was identified. Further screening (N = 1052) identified 15 patients with GL *DDX41* alterations. We previously reported recurrent somatic (c.G1574A, p.R525H) *DDX41* mutations in MDS. Further analysis revealed that somatic and GL mutations coincided, with 50% of patients carrying GL mutations having biallelic lesions of *DDX41,* suggesting a strong predisposition to second allele lesions. Isolated recurrent somatic p.D140fs was found in another 12 patients. In total, 25 cases had *DDX41* mutations: 15 GL and 17 somatic, of which seven were biallelic. In addition to *DDX41* mutations, we observed 15 somatic mutations (5% of all cases) in other members of the DEAD/H-box RNA helicase family *(DDX11,17,23,53,50,60* and *DHX29,32,33,34,37,58).* GL *DDX41* mutations could be considered founder lesions, while somatic *DDX41* mutations were ancestral in some cases and secondary in others. GL and somatic *DDX41* mutations were more commonly associated with normal karyotype (81% vs. 47%; p =.02), while biallelic cases lacked other typical AML mutations. Among 112 patients treated with lenalidomide, all 8 of the $DDX41^{MT}$ cases responded

(p =.006) per International Working Group criteria. The most frequent mutations coincident with *DDX41* lesions involved *TP53* and *RUNX1.*

DDX41 is expressed in myeloid cells, consistent with a function in hematopoiesis. GL mutations were predominantly out-of-frame insertions early in the gene, likely functionally equivalent to deletions. Deletion of *DDX41* is found in 26% of all del5q cases. Such deletions of the *DDX41* locus lead to haploinsufficient expression, which is also observed in 5% of diploid cases. *DDX41* appears to be an essential gene, as the inactivating GL c.419insGATG mutation was not found among del5q35.3 patients and no $DDX41^{-/-}$ pups have been observed to date in the offspring of *DDX41* knockout mice. For somatic $DDX41^{R525H}$, we showed decreased ATPase activity in vitro, suggestive of a possible dominant negative effect.

Lentiviral shRNA *DDX41* knockdown (40%-50%) in K562 cells enhanced proliferation compared to mock transduced cells. Forced *DDX41* overexpression in U937 cells, which express low levels of *DDX41,* inhibited growth. Overexpression of either WT or $DDX41^{R525H}$ in HEK293 cells led to the p.R525H mutant increasing soft agar colony formation compared to $DDX41^{WT}$ or $DDX41^{KD}$ cells. Previous data suggested that *DDX41* is a component of the catalytic spliceosome and becomes stably associated at a late step (Complex C) immediately prior to catalysis of the first splicing reaction. We have also verified this result through proteomic analysis of complexes associated with epitope tagged *DDX41.* The coprecipitated proteins included many mature spliceosomal components, but few that are associated with early forming complexes, suggesting that *DDX41* is distinct from other MDS-associated splicing factors that function early in the pathway. In $DDX41^{KD}$ HEK293 cells (80% reduction), using qRT-PCR analysis of the spliced to unspliced RNA ratio, we demonstrated that splicing of a subset of introns is indeed significantly reduced. In patient samples with $DDX41^{MT}$, using deep RNA NGS, we found that multiple alternative exons were altered in their inclusion frequency.

In summary, we identified GL mutations in *DDX41* that are associated with the development of hereditary MDS/AML. The strong family history and late onset suggest high penetrance and long latency. GL *DDX41* defects strongly predispose to somatic *DDX41* mutations. Our results indicate that *DDX41* lesions lead to altered splicing of many genes likely responsible for downstream leukemogenic effects of $DDX41^{MT}$. *DDX41* mutations, along with hemizygous *DDX41* deletions, constitute a new type of leukemogenic defect and highlight a new class of tumor suppressor genes.

A Novel Prognostic Model in Heavily Treated Patients with Myelodysplastic Syndromes (MDS)

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Background: The Revised International Prognostic Scoring System (IPSS-R) was developed to risk-stratify untreated patients (pts) with MDS. It has since been validated in pts treated with a single line of drug therapy, and has been modified in untreated pts to include mutational data; however, these approaches do not reflect typical MDS pts who receive different types of treatment in different sequences. We propose a prognostic model that incorporates mutational data and predicts outcome in pts with primary and secondary MDS regardless of their initial or subsequent treatments.

Methods: Clinical and mutational data of 333 pts with newly diagnosed MDS who were treated at our institution between 1/2000 and 1/2012 were analyzed. The IPSS-R was calculated at diagnosis. Survival was calculated from the date of diagnosis to last follow-up or death. A panel of 62 gene mutations obtained by next-generation targeted deep sequencing was selected based on the frequency observed in a separate cohort of MDS patients analyzed by whole exome sequencing. A Cox proportional multivariate analysis including age, IPSS-R score and mutations that are present in ≥ 10 pts was used to select independent prognostic factors. The fit of the proposed model to the data was assessed using the Akaike information criterion (AIC).

Results: Median pt age was 68 years (range, 20-87); 214 pts (64%) had de novo MDS, 39 (12%) had antecedental hematologic disorders, 37 (11%) had secondary MDS, and 43 (13%) had chronic myelomonocytic leukemia (CMML). Pts received between zero and seven lines of therapy: 15% did not receive any treatment, 85% received at least one treatment, 40% received ≥ two treatments, 20% received ≥ three treatments and 14% of pts eventually underwent hematopoietic cell transplant (HCT). First-line therapies included growth factors (30%), azacitidine +/- combination (32%), decitabine +/- combination (7%), single-agent lenalidomide (5%), investigational agents (5%), induction chemotherapy with cytarabine and an anthracycline (7+3, 2%), and immunosuppressive therapy (4%). With a median follow-up of 38 months (mo) (range, 0.4-128.5), 70 pts (21%) progressed to AML, and the median overall survival (OS) was 35.1 mo (range, 0.4-128.5). Per IPSS-R risk groups, median OS for very low was 35

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mo, low 35 mo, intermediate 22 mo, high 19 mo and very high 12 mo. Among the 62 gene mutations, 25 were present in ≥ 10 pts: *TET2* (17%), *ASXL1* (15%), *SF3B1* (14%), *STAG2* (11%), *DNMT3A* (11%), *RUNX1* (10%), *U2AF1* (9%), GPR98 (8%), *ZRSR2* (7%), *BCOR* (6%), *TP53* (5%), *NF1* (5%), *EZH2* (5%), *APC* (5%), *SUZ12* (5%), *BCORL1* (4%), *CBL* (4%), *PRPF8* (4%), *NRAS* (3%), *CUX1* (3%), *DDX54* (3%), *IDH2* (3%), *KDM6A* (3%), *PHF6* (3%) and *SETBP1* (3%). A Cox proportional hazard analysis including age, IPSS-R score and the 25 gene mutations listed above identified the following as independent prognostic factors: age, IPSS-R, *ASXL1, BCOR, BCORL1, EZH2, IDH2, SF3B1* and *TP53.* The linear predictive Cox model score obtained using the fitted coefficients of each prognostic factor was: *ASXL*1 0.65 + *BCOR* X 0.92 + *BCORL*1 X (-1.65) + *EZH2* X 0.71 + *IDH2* X (-1.0) + *SF3B1* X (-0.59) + *TP53* X 1.24 + Age X 0.04 + IPSS-R score X 0.43. Four prognostic groups were proposed: low (score 0-3.4, 80 pts, median OS 47.3 mo), intermediate-1 (score 3.5-4, 69 pts, median OS 30.2 mo), intermediate-2 (score 4.1-5.4, 131 pts, median OS 19.9 mo) and high (score ≥ 5.5, 53 pts, median OS 12.2 mo), $p < 0.001$. The new model demonstrated a markedly better fit, reflected in an AIC of 2026, compared with 2058 for the IPSS-R.

Conclusion: We propose a new mathematical model that incorporates age, IPSS-R score and several gene mutations that can accurately predict OS in pts with primary and secondary MDS as well as CMML regardless of initial or subsequent treatments, including HCT. This model also highlights the importance of mutational data along with clinical data for risk stratification in MDS.

In Analogy to AML, MDS Can Be Subclassified by Ancestral Mutations

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Somatic mutations constitute key pathogenetic elements in myelodysplastic syndrome (MDS). Unbiased whole exome sequencing (WES) and deep next-generation sequencing (NGS) led to discovery of new somatic mutations and to the recognition of (1) tremendous diversity of mutations and their combinations and (2) individual intratumor heterogeneity and clonal hierarchy. Chromosomal lesions further increase the complexity of molecular defects.

While in MDS molecular defects are acquired in order, observations made in acute myeloid leukemia (AML) highlight the importance of ancestral events — e.g., t(8;21), inv16 or t(15;17) and other lesions that are used as the basis for nosological subclassification. Thus, it is the identity of individual ancestral events or their classes rather than the spectrum of secondary events or the distribution of mutations that will allow for molecular, functionally relevant and diagnostically useful classification within MDS. This would explain why only a few somatic mutations have been found to be prognostically important, as their position in the clonal hierarchy has not been accounted for. With this in mind, we applied WES (N = 206) and targeted deep NGS (N = 836) and studied 100 samples serially with analyses focused on ancestral events.

Globally, through WES we identified and validated 2,386 mutational events in 1,458 genes. Of these, 112 genes were mutated at significant frequencies ($p < 0.05$); groups of affected genes involved in splicing, transcription, DNA methylation, histone modification and others were distinguished. On average, nine somatic events per MDS case, 10.7 in secondary acute myeloid leukemia (sAML) and 12.5 in MDS/myeloproliferative neoplasms (MPN) were found. Resequencing in combination with single nucleotide polymorphism-array karyotyping provided information on variant allelic frequency (VAF) adjusted for corresponding zygosity of mutations; 99% of cases displayed clear intratumor heterogeneity due to multiple clones defined by hierarchically acquired somatic mutational patterns.

Using cross-sectional analyses, the highest mean VAF could be interpreted as consistent with the ancestral nature of the mutations, as seen for instance in a proportion of *TET2* and *SF3B1* mutant cases. In contrast, the lowest mean VAF indicated secondary events, as occur in *NPM1* and RAS pathway mutations. Similar conclusions were made based on cross-sectional analyses showing a similar distribution of ancestral but not secondary events in MDS and sAML. All gene mutations were categorized into those that are predominantly ancestral and those that are facultatively secondary. The most frequent founder mutations were identified *(TET2, DNMT3A, SF3B1, ASXL1, TP53, U2AF1, RUNX1, SRSF2)* and used to subclassify approximately 80% of patients, with the remainder containing more infrequent ancestral mutations. While in a combined fashion (as both founder and secondary events) many of these mutations were not predictive of prognosis, they gained relevance when only cases affected by ancestral mutations were used for prognostication. Thus, some of the mutations, when present as secondary events, may not be predictive.

Founding mutations may determine subsequent clinical and molecular features. While other frequently affected genes, *SF3B1* or *ASXL1*, are not associated with a significant increase in the number of concomitant mutations, cases with *TET2* mutations showed significantly more frequent mutations per case than those with wild-type *TET2* (14.6 vs. 9.1; $p = 0.001$). Moreover, ancestral *TET2* mutations were associated with concomitant mutations due to high C-to-T transitions, possibly because reduced 5-hydroxymethylcytosine might create the specific mutator milieu.

Most important is the association not of any type, but of ancestral mutations with certain pathomorphologic features and outcomes. Founding *TET2* mutations are associated with MPN/MDS while secondary *TET2* mutations are present in MDS. Ancestral *DNMT3A* mutations determine a rapid progression to AML, whereas subclonal *DNMT3A* mutations are also found in high-risk MDS. RAS pathway mutations are ancestral in chronic myelomonocytic leukemia and secondarily positive in the late stage of MDS (sAML). Specific ancestral events may determine subsequent mutational events, and while both types of mutation may affect the clinical phenotype, the initial events are less diverse and more subtype-specific. In conclusion, WES clarified the distinct landscape and ordering of the somatic mutational spectrum in MDS.

Medical Innovation Summit Focuses on **Personalized** Cancer Care

Each year since 2002, Cleveland Clinic has hosted the Medical Innovation Summit, a multiday international conference that brings together executives, government officials, investors, entrepreneurs and clinicians to discuss how to achieve game-changing healthcare innovations.

The theme of the 2014 summit in October was cancer treatment and the advent of personalized precision medicine. Cleveland Clinic's Taussig Cancer Institute is a leader in the delivery of personalized, genomic-based cancer care and the development of targeted therapies.

Nearly 1,700 attendees from 34 states and 17 countries participated in Medical Innovation Summit sessions exploring the promises and challenges of personalized cancer care. Oncogenomics has the potential to significantly improve the efficacy of cancer treatments and to inform early-intervention and prevention strategies, panelists said. It also raises formidable medical, economic, technological and ethical issues that will require innovative solutions if early advancements are to continue.

Highlights and major discussion points from the summit (videos of individual sessions are available at summit.clevelandclinic.org):

Obtaining actionable information from tumor genomic analyses Whole-tumor sequencing produces huge volumes of data about genetic variation and abnormalities, but determining which of that actually affects cancer progression is currently challenging. "We're really in the infancy of understanding how to interpret the oncogenetic tests out there," said panelist Brian Rini, MD, a Cleveland Clinic medical oncologist who treats advanced genitourinary cancers and is leading clinical trials of experimental targeted therapies. "How to bring all that data down to a decision-making point for an individual patient is something the field has struggled with for the last decade." In many cases, "we have guesses as to what's actionable, but we don't really know until we treat. And we don't have drugs against all those therapeutic targets." Added Matthew Robson, MD, the Clinical Head of Translational Clinical Oncology for the pharmaceutical company Novartis: "We're learning a lot more about not just what the tumor is like at diagnosis, but the impact of targeted therapeutics on the tumors. The genetic data in understanding resistance is very important because tumors change over time. We're seeing some really great results for targeted therapies, but the problem is that single-target therapies aren't producing the sort of durabilities we'd like to see. Genetic data is absolutely crucial to helping us understand how we can combine or sequence targeted agents to prolong patients' lives. The tension between lots of data and how we interpret it and what's actionable is going to be something to watch."

Personalized medicine's impact on clinical trials Targeted experimental cancer therapies that may have potentially greater efficacy than traditional drugs, but in smaller patient populations, are prompting a reconsideration of how clinical trials are conducted and what constitutes successful outcomes for regulators and insurers. For example, with genomic analysis of tumors, "lung cancer is being partitioned into smaller and smaller diseases," said panelist Alan Wright, MD, the Chief Medical Officer of Roche Diagnostics. "That trend is going to continue. It's going to require a drastic rethinking of what the evidentiary standards are and how to develop statistics to approve novel therapies." Panelist Angela Davies, MD, the Chief Medical Officer of Champions Oncology Inc., which develops targeted cancer therapies, sees a move away from "all-comer" phase 1 clinical trials that enroll any patient with disease progression. "Many of the phase 1 trials I'm working on now are focused on specific patient populations where a biomarker must be present to enroll. Or there are tumor type-specific phase 1 trials where efficacy and molecular specificity is being explored at the same time. The focus is safety, but also efficacy and the ability to transition to a phase 1b or even a single-arm phase 2 trial in a highly selected population. I'm hopeful that is going to mean a much shorter timeline for drug development and our ability to deliver that benefit to a broader number of patients much sooner."

Increasing the appropriate use of genetic and genomic testing for cancer risk assessment and prevention Based on current guidelines, approximately 12 million people ought to undergo diagnostic testing to determine their risk of hereditary cancers, said panelist Mark Capone, President of Myriad Genetics Inc. Yet in the 18 years that the company has marketed such tests, it has processed less than 10 percent of that number. "Insurance companies pay for the tests, but there is a massive educational awareness gap that continues to exist in this country" among patients and physicians, Capone said. A potential solution is Cleveland Clinic's MyFamily, a web-based application to collect information about a patient's family health history and assess individual risk for heritable and genetic disease. The algorithm-based tool is meant to support clinical decision-making regarding a patient's genetic risk and the appropriateness of conducting genetic testing. It will be available to all Cleveland Clinic primary care physicians by early 2015, said MyFamily inventor Charis Eng, MD, PhD, who chairs Cleveland Clinic's Genomic Medicine Institute.

Data access and advanced analytical computing needs The computational demands of genomic analysis and the need to access, share and compare large amounts of patient data across divergent electronic medical records systems for population-based care management pose major challenges. "As we collect bigger data, we're going to have to have ways to understand the bigger data," said Toby Cosgrove, MD, CEO and President of Cleveland Clinic. "Total knowledge in healthcare is doubling every two years. The data is going to overwhelm us. That's where artificial intelligence can help." One example: At the innovation summit, Cleveland Clinic and IBM announced a new collaboration involving Watson, the advanced computing system currently enrolled at Cleveland Clinic Lerner College of Medicine. Researchers at Cleveland Clinic's Genomic Medicine Institute will use Watson's cognitive learning skills and cloud computing capabilities to catalog patients' tumor DNA, then search millions of clinical records and research studies to identify potential targeted treatments.

Top 10 innovations Each year at the Medical Innovation Summit, Cleveland Clinic experts unveil a list of the 10 medical innovations they predict will have the biggest impact on clinical care in the next 12 months. Three of the 10 on the list for 2015 are cancer-related: antibody-drug conjugates, immune checkpoint inhibitors and intraoperative radiation therapy for breast cancer.

Above right: Brian I. Rini, MD, FACP

New Cancer Facility Designed for Collaboration, Improved Patient Outcomes

When Cleveland Clinic's $276 million, 377,000-square-foot cancer building opens in 2017, some of its features will be immediately apparent: the flow of patients, the abundance of natural light, and the combination of clinical care with support services.

In February 2015, cancer services at Cleveland Clinic Florida will also have a new home with the opening of the Maroone Cancer Center.

It, along with the expanded Pauline Braathen Neurological Center, will be housed in the five-story, 143,000-square-foot Egil and Pauline Braathen Center on Cleveland Clinic Florida's Weston campus. The Maroone Cancer Center will include advanced diagnostic, radiosurgery and radiotherapy capabilities; a leading-edge, family-friendly chemotherapy infusion suite; and expanded patient support and cancer education services.

A deeper look will reveal a facility designed expressly to improve patient outcomes through a collaborative, disease site-specific approach to cancer care.

The idea: Patients benefit from their oncologists, surgeons, radiation oncologists, social workers and other team members working in close proximity. They also benefit from having an infusion suite close to their doctor's clinic, negating the need for multiple appointments and — along with many other efficiencies — ultimately bringing healthcare costs down.

Such cancer care is already the norm at Cleveland Clinic, but having it scattered in 10 locations across the main campus presents challenges for practitioners and patients. The new multidisciplinary cancer building, with 126 exam rooms and 98 treatment rooms, aims to incorporate all services under one roof.

"The new cancer building will create a seamless, personalized experience for patients," said Brian J. Bolwell, MD, FACP, Chairman of Cleveland Clinic's Taussig Cancer Institute.

The new building will have space dedicated to phase 1, 2 and 3 clinical trials — with a special emphasis on supporting phase 1 trials.

Brian J. Bolwell, MD, FACP

Coordinating Care, Expanding Clinical and Research Space

Multidisciplinary work has existed for years, but organizing multidisciplinary groups by disease — teams focused around breast cancer, head and neck cancer, and other specific cancer types — will receive new emphasis in the cancer facility.

Each disease group will have its own dedicated clinical practice area on a floor of the new facility. Likewise, each practice area will have space for subspecialized nurses, social workers and other key team members, plus exam and procedure rooms. Even though this will be an outpatient facility with surgeries performed elsewhere, surgeons will have the space and equipment needed to perform consults with patients on-site. And because genetic counseling improves patient outcomes, there will be space dedicated to this practice, as well as genetics and genomics testing.

The facility will provide a new, centralized home for existing high-level treatment technology, including six linear accelerators and a Gamma Knife® suite.

Beyond clinical services, the facility will house critical support such as registered dietitians, prosthetics, wig services and a spiritual center.

"Everyone who has a diagnosis of cancer is scared," Dr. Bolwell said. "We want to do everything we can to alleviate that anxiety. We have to provide many different ways to help patients and their families deal with not just the medical aspects of their disease but the psychological ones too."

Enhanced space matters as much for researchers as it does for care teams, Dr. Bolwell notes. The new building will have space dedicated to phase 1, 2 and 3 clinical trials — with a special emphasis on supporting phase 1 trials.

A Place of Light and Hope

The new cancer building's design is the result of two years of planning, visits to other cancer facilities and more than 400 meetings involving clinicians, caregivers and the Boston architecture team of William Rawn Associates.

"The building will be bright, spacious and serene," said Toby Cosgrove, MD, CEO and President of Cleveland Clinic, at the September 29th groundbreaking. "It will be a place of light, confidence and hope. It will raise the treatment of cancer to a new level of comfort and convenience, providing the most effective care in the most productive surroundings. It will set a new national standard for outpatient cancer treatment in the 21st century."

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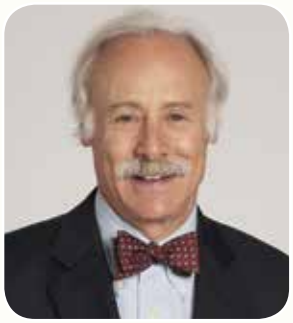

Marc Ernstoff, MD, has recently joined Cleveland Clinic as Director of the Melanoma Program.

Dr. Ernstoff's research has focused on the immunobiology of melanoma and its implications for therapy. His early work while at the Yale Comprehensive Cancer Center pioneered the role of interferons as therapies and led to the first FDA-approved immune therapy for solid cancers: adjuvant high-dose interferon for high-risk primary melanomas.

During his career, Dr. Ernstoff helped establish the first medical oncology program at Pittsburgh Cancer Institute (PCI), where he served as Medical Director of the Genitourinary Tumors Study Group and Director of the Hematology-Oncology Fellowship Program from 1986 to 1991. He successfully competed for the first National Cancer Institute (NCI) T32 training grant for Hematology/Oncology Fellows awarded to PCI.

Prior to accepting his new position at Cleveland Clinic, Dr. Ernstoff spent 23 years on the faculty at Geisel School of Medicine at Dartmouth College and held leadership roles at Dartmouth-Hitchcock Medical Center and the NCI-designated Norris Cotton Cancer Center. He served as Associate Director, Clinical Research, and Director of the Melanoma Program at the cancer center, and as Section Chief of Hematology/Oncology at Dartmouth-Hitchcock. Most recently he held the O. Ross McIntyre Chair of Medicine Professorship.

Dr. Ernstoff received his medical degree from New York University School of Medicine. He completed an internal medicine residency at Bronx Municipal Medical Center and The Hospital of The Albert Einstein College of Medicine, and a medical oncology fellowship at Yale University School of Medicine.

He is a member of the American Association for Cancer Research, the American Society of Clinical Oncology and the American Society of Clinical Oncology Program Committee.

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Cancer Consult provides information from Cleveland Clinic Taussig Cancer Institute specialists about innovative research and diagnostic and management techniques.

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Cleveland Clinic Taussig Cancer Institute annually serves more than 28,000 cancer patients. More than 250 cancer specialists are committed to researching and applying the latest, most effective techniques for diagnosis and treatment to achieve long-term survival and improved quality of life for all cancer patients. Taussig Cancer Institute is part of Cleveland Clinic, an independent, nonprofit, multispecialty academic medical center.

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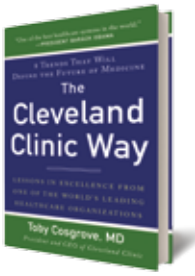

The Cleveland Clinic Way

By Toby Cosgrove, MD,
CEO and President of Cleveland Clinic

Great things happen when a medical center puts patients first. Visit **clevelandclinic.org/ClevelandClinicWay** for details or to order a copy.

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Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,000 physicians and scientists represent 120 medical specialties and subspecialties. We are a main campus, 18 family health centers, eight community hospitals, more than 75 northern Ohio outpatient locations (including 16 full-service family health centers), Cleveland Clinic Florida, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City and Cleveland Clinic Abu Dhabi.

In 2014, Cleveland Clinic was ranked one of America's top hospitals in *U.S. News & World Report*'s annual "Best Hospitals" survey. The survey ranks Cleveland Clinic among the nation's top 10 hospitals in 13 specialty areas, and the top hospital in heart care (for the 20th consecutive year) and urologic care.

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