Cleveland Clinic

Cancer Advances

Cleveland Clinic Cancer Center | Summer 2017

Mapping Mutations —

Largest Genomic Assessment of MDS Identifies Dynamics of Clonal Evolution

Ranked No. 7 in America for cancer care by *U.S. News & World Report*.

Dear Colleagues,

Welcome to the latest edition of *Cancer Advances*. Since our last issue, our new cancer outpatient tower has opened and is buzzing with activity. Intellectually, I knew that the building design would enhance the function of our multidisciplinary teams and elevate the patient experience. But it's only as I've become accustomed to working in the space that I deeply understand how much it reflects who we are as Cleveland Clinic Cancer Center. The space expresses the empathy and collaboration that are so central to our cancer programming.

The building reflects our emphasis on patient comfort and convenience. The foremost thing we can do to alleviate patient anxiety is to provide prompt access to treatment, something we're studying at both our own institution and across the nation.

It reflects our efforts to ensure that the treatments provided are leading-edge and based on the highest-quality research. The articles in this issue illustrate the strength and value of many of our programs, including our Leukemia & Myeloid Disorders and Colorectal Cancer programs. Advances in radiotherapy dosing and therapy timing and sequencing are providing patients with less toxic, more effective treatments.

Finally, the building represents setting the standard for cancer care, both within our programs as best practices and care paths, and nationally with leadership in research and in clinical practice guidance.

As I walk to my office each morning, the space reminds me of the gravity and significance of what we do, and how much of it depends on the exchange of ideas and the synergy a shared, purposeful space can provide. I hope that in this space, in these pages, you find reason to collaborate with us to benefit your patients. Our doors are open.

Sincerely,

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Mapping Mutations —

Largest Genomic Assessment of MDS Identifies Dynamics of Clonal Evolution

Symptom management and disease remission remain the goals of treatment for patients living with myelodysplastic syndrome (MDS). However, approximately one-third of patients progress to acute myeloid leukemia (AML), and early identification of high-risk patients can help improve treatment recommendations to slow or stop that progression.

Identification of those patients at highest risk for contracting AML relies heavily on clinical and pathology data, rather than any molecular or genomic clues that might help providers better anticipate which patients stand to benefit from more aggressive treatment options.

Jaroslaw Maciejewski, MD, PhD, Chairman of the Department of Translational Hematology and Oncology Research at Cleveland Clinic Cancer Center, recently co-authored a paper in *Nature Genetics* that represents the world's largest inventory of genomic alterations throughout disease progression in patients with MDS.

"These successions have meaning for treating oncologists in terms of both how to approach treatment and what to communicate to patients," says Dr. Maciejewski. "We have mapped a series of mutational paths that myelodysplastic syndromes can take toward either aggressive cancers or manageable chronic conditions."

Results confirmed what Dr. Maciejewski and many others have suspected — progression is not straightforward, but rather a complex and shifting landscape with a handful of critical mutations that move the disease in one direction or another.

"Disease progression in MDS patients is not merely shaped by simple rounds of linear evolutions as previously described, but is also accompanied by frequent clone sweeping of existing subclones, in which driver mutations are thought to play critical roles," Dr. Maciejewski and collaborators wrote.

The sequencing study identified 16 driver mutations that steer overall disease progression and map to clinical presentation.

(continued on page 4)

Dr. Maciejewski is Chairman of Cleveland Clinic Cancer Center's Department of Translational Hematology and Oncology Research, a staff physician in the Department of Hematologic Oncology and Blood Disorders and Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

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(continued)

Two mutational paths, two very different outcomes

A series of mutations enriched in secondary acute myeloid leukemia (sAML) (rather than high-risk MDS) tended to be newly acquired and associated with faster sAML progression and a shorter overall survival than wild type.

Study authors classified these seven enrichments as type-1 mutations, which indicate a higher-risk disease, frequently drive MDS toward sAML and are associated with poor clinical outcomes. Type-1 mutations are *FLT3, PTPN11, WT1, IDH1, NPM1, IDH2* and *NRAS.*

Other mutations had a weaker impact on disease progression toward sAML, even in patients currently classified as having high-risk MDS. The study classified these as type-2 mutations, which include *TP53, GATA2, KRAS, RUNX1, STAG2, ASXL1, ZRSR2* and *TET2*.

In both type-1 and type-2, MDS remained a progressive disease. The study helps elucidate whether the disease is likely to develop into cancer or display increasing degrees of MDS-related morbidities.

Additionally, both types demonstrated patterns of propeller or driver mutations, which tended to set the course for disease progression, regardless of other genomic alterations happening within the malignancy.

These driver mutations appear to be sequential, Dr. Maciejewski says, leading the disease through a stepwise progression.

"Some of the mutations are dominant — they commandeer disease progression and set the stage for the next step in disease," he says.

Clinical impact and drug development

The study included whole-exome and/or targeted sequencing of 699 patients. Of those, the study performed longitudinal analysis of 122 patients to follow the disease progression from a mutational perspective.

Furthermore, the study included data from previously sequenced patients, for a total of 2,250 cases evaluated for mutational enrichment patterns.

"The novelty of this paper is that we have sequenced enough patients to help understand the drivers that push patients from MDS to leukemia," Dr. Maciejewski says. "It's important to have a critical mass of patients, which helps characterize impact and influence of the less common mutations."

Armed with study results, physicians and drug developers may be able to move forward with new solutions for patients with MDS.

"This is the largest genomic data set for MDS, and it is our hope that our team — and others — can take this information to design new clinical trials and develop new targeted therapies," says Dr. Maciejewski.

Using a molecular profiling approach to treatment could have multiple benefits. Profiling could help not only identify targets for existing therapy but also inform whether disease should be monitored or treated aggressively.

Dynamics of clonal evolution

Many questions remain unanswered, and future studies are likely to seek a more detailed understanding of the mutational interactions at each juncture and their correlation with clinical outcomes.

For instance, clone sweeping is commonly seen during disease progression, but type-1 mutations may not cause it, according to the study, which found that type-1 mutations tend to have a smaller clonal burden than other mutations.

Researchers reported 74 type-1 mutations in sAML samples, of which only 25 (34 percent) were involved in clone sweeping, whereas the remaining 49 (66 percent) were found in one or more subclones.

The authors speculated that the diagnosis of sAML is closely associated with the evolution of a new subclone, instead of the dominant clones in the preceding MDS phase.

"If a patient develops a type-2 mutation versus a type-1, their treatment might be less aggressive," says Dr. Maciejewski. "However, without more clinical data, we don't yet know."

The ultimate goal is genomic prognostics that would empower treating physicians to make better-informed decisions earlier in the disease management process, improving overall outcomes and diminishing the burden of uncertainty for patients.

Maciejewski Receives $5.5 Million Outstanding Investigator Award

The groundbreaking research efforts of Jaroslaw Maciejewski, MD, PhD, over two decades to decode the complex mechanisms of bone marrow failure syndromes (BMFS) have earned him the National Heart, Lung, and Blood Institute's Outstanding Investigator Award.

The prestigious multiyear grant is meant to spur innovation by providing stable, long-term funding for a research program rather than an individual project. It is awarded to an investigator whose research record demonstrates the ability to make major scientific contributions, mentor others, advance the field and impact clinical care.

"The selection of Dr. Maciejewski for the Outstanding Investigator Award is proof that he is one of a handful of true leaders in the field of genetics, leukemias and bone marrow failure states," says Brian J. Bolwell, MD, FACP, Chairman of Taussig Cancer Institute. "He has the keenest scientific mind of anyone I have ever met. What sets him apart is his ability to marry scientific knowledge with clinical medicine, which very few researchers can do."

The molecular basis of bone marrow failure syndromes

Dr. Maciejewski, Chairman of Cleveland Clinic Cancer Center's Department of Translational Hematology and Oncology Research, has focused on understanding the molecular basis of BMFS. Specifically, he has worked to characterize somatic and germline alterations of genes involved in hematopoietic cell proliferation, differentiation and regulation of metabolic processes, and to identify the consequences of those mutations.

Dr. Maciejewski's molecular profiling of various forms of BMFS using systematic next-generation sequencing has identified many new pathogenic genomic lesions and has enabled him to define new disease phenotypes and redefine existing ones. For example, in 2015 he and an international team identified acquired mutations normally found in leukemia in a large proportion of patients with aplastic anemia, which previously had been considered a nonmalignant condition. The mutations may indicate an early leukemic stage.

Developing genomic-based targeted therapies

Dr. Maciejewski's intent is to use the improved molecular understanding of BMFS to develop genomic-based targeted therapies with the potential for cure, and biomarkers comparable to *BRCA1/2* mutations in breast cancer that can identify at-risk BMFS patients for early intervention.

"BMFS constitute a major, high-mortality medical problem, and their incidence is likely to rise as life expectancy increases," Dr. Maciejewski says. "The need to develop new therapies and diagnostic tools is great. Further understanding the pathogenesis of BMFS will bring important progress to many basic problems of hematopoiesis. I'm grateful to have the support to continue this work."

Dr. Maciejewski is the author or co-author of more than 320 scientific publications and participates in numerous international research collaborations. He previously received four National Institutes of Health research project (R01) grants.

Multigene Panel Testing Reveals **Mutations** in **Early-Onset CRC Patients**

Colorectal cancer (CRC) is the third most frequently diagnosed cancer in the U.S. While the overall incidence of CRC has decreased over the past 20 years, the incidence of early-onset CRC in the U.S. has been increasing for reasons that are not understood, says Matthew Kalady, MD, Co-Director of Cleveland Clinic Cancer Center's Colorectal Cancer Program. He is co-author of a recent *JAMA Oncology* study that used multigene panel testing to closely examine genetic mutations among CRC patients younger than 50. The researchers found that 16 percent of these patients tested positive for one or more genetic mutations, which could have important ramifications regarding heightened cancer risk for both patients and their relatives.

Gene	Associated Syndrome or Cancer(s)	Overall Penetrance	Patients with Mutation, No. (%)	(95% CI)
Any pathogenic or likely pathogenic mutation			72 (16)	(12.8-19.8)
Genes associated with colon cancer			59 (13.1)	(10.2-16.7)
MLH1	Lynch syndrome	High	13 (2.9)	(1.6-5.0)
MSH2	Lynch syndrome	High	16 (3.6)	(2.1-5.8)
MSH2/monoallelic *MUTYH*	Lynch syndrome/colon cancer	High/low	1 (0.2)	(0.01-1.4)
MSH6	Lynch syndrome	Moderate	2 (0.4)	(0.08-1.8)
PMS2	Lynch syndrome	Moderate	5 (1.1)	(0.4-2.7)
APC	Familial adenomatous polyposis (FAP)	High	5 (1.1)	(0.4-2.7)
APC p.I1307K	Colon cancer	Low	4 (0.9)	(0.3-2.4)
MUTYH				
Biallelic	*MUTYH*-associated polyposis	High	4 (0.9)	(0.3-2.4)
Monoallelic	Colon cancer	Low	7 (1.6)	(0.7-3.3)
SMAD4	Juvenile polyposis syndrome	High	1 (0.2)	(0.01-1.4)
APC/*PMS2*	FAP/Lynch syndrome	High/ moderate	1 (0.2)	(0.01-1.4)
Genes not traditionally associated with colon cancer			13 (2.9)	(1.6-5.0)
BRCA1	Hereditary breast-ovarian cancer syndrome	High	2 (0.4)	(0.08-1.8)
BRCA2	Hereditary breast-ovarian cancer syndrome	High	4 (0.9)	(0.3-2.4)
ATM	Breast cancer, pancreatic cancer	Moderate	3 (0.7)	(0.2-2.1)
ATM/*CHEK2*	Breast cancer, pancreatic cancer	Moderate	1 (0.7)	(0.01-1.4)
PALB2	Breast cancer, pancreatic cancer	Moderate	2 (0.4)	(0.08-1.8)
CDKN2A	Melanoma, pancreatic cancer	High	1 (0.2)	(0.01-1.4)

Table. Germline mutations identified and associated syndromes

Other studies have demonstrated the feasibility, cost-effectiveness and timeliness of multigene panel testing for hereditary mutations. However, this study is the first in which researchers used multigene panel testing to study potentially important mutations among patients with early-onset CRC.

The researchers tested 450 patients under the age of 50 for 25 cancer susceptibility genes. Among the study participants, 8.2 percent had another malignancy in addition to CRC. The multigene panel testing revealed a total of 75 mutations present in 72 of the patients (16%; 95% CI, 12.8%-19.8%). In 61 of these 72 patients, the mutations occurred in moderate- to high-penetrance genes, while in the other 11 patients, the mutations occurred in low-penetrance genes (Table).

Rethinking the standard approach

Importantly, 24 of the 72 patients with identified mutations did not meet established criteria for genetic testing for the gene(s) in which their mutation(s) appeared. "One-third of the 72 people who had mutations would not have been tested in routine practice," says Dr. Kalady. With multigene panel testing, physicians have the potential to identify many more mutations of possible clinical significance.

For example, Dr. Kalady says that under today's guidelines, the standard approach for a patient

with suspected Lynch syndrome (a hereditary CRC syndrome characterized by multiple cancers at a younger age) would be to test the tumor for germline mutations in the mismatch repair (MMR) genes.

Although currently most young CRC patients have their tumors tested for Lynch syndrome, Dr. Kalady says that the new study's findings strongly suggest that the standard, limited genetic testing is insufficient. "The take-home clinical translation is that 16 percent of people under 50 with CRC who undergo multigene panel testing will be found to have something abnormal," he says. "They might have a gene predisposing them for other cancers, which we wouldn't find without the multipanel test."

His group's study of early-onset CRC patients was part of a larger study run by the Ohio Colorectal Cancer Prevention Initiative (OCCPI) that included all CRC patients in Ohio. OCCPI is a statewide program involving 51 hospitals that screens newly diagnosed CRC patients and their biological relatives for Lynch syndrome, which is caused by the presence of an MMR mutation in one of four genes and which heightens risk for not only CRC, but also uterine, ovarian, stomach and other cancers.

Study identifies actionable therapeutic targets

The reasons for the current upswing in the incidence of early CRC are not clear, says Dr. Kalady, who adds that many researchers suspect that lifestyle or dietary factors may contribute. Early-onset CRC can serve as a warning flag for a predisposition to other inherited cancers, and early identification of hereditary cancer syndromes can make an important difference for both patients and their relatives in terms of risk assessment and clinical decisions about treatment. In this study, the researchers' identification of MMR tumor status as well as genetic mutations provided actionable therapeutic targets to be included in their treatment plans.

Furthermore, the 16 percent prevalence of gene mutations in this sample of early-onset CRC patients is likely an underestimation. First, there are probably undiscovered CRC-susceptibility genes. Also, certain gene variants that were not counted as mutations in the present study may, in time, prove to be pathogenic.

Genetic counseling imperative

Dr. Kalady says that when sending early-onset CRC patients for multigene panel testing, physicians should ensure that the patient meets with a genetic counselor to understand the implications of the test results and avoid undue stress.

He also mentions one important caveat about the more widespread use of multigene panel testing in early-onset CRC patients. Although the cost of this testing has decreased and is covered by most insurance plans, the ability to interpret the test results is currently limited, he says. The tests often reveal a mutation or variant of unknown significance, one that is clearly abnormal but whose clinical importance is not yet fully understood. In this study, 178 variants of uncertain significance were found in 145 patients (33.3 percent).

Over time, as researchers identify and classify new variants, multigene panel testing will gain even more clinical utility. "A variant might not be of unknown significance anymore," Dr. Kalady says, adding that "it can be reclassified as causative."

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Time to Treat Is Increasing, Associated with Worsened Survival

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After reviewing nearly 3.7 million patient records, Cleveland Clinic researchers have shown that an increase in time to treatment initiation (TTI) for new cancer diagnoses adversely affects outcomes. The team studied trends in TTI for common solid tumors treated with curative intent, determinants of delayed TTI and impact on overall survival. They found that TTI has lengthened significantly in recent years.

Researchers utilized population-based, prospective data from the National Cancer Database for newly diagnosed U.S. patients with certain early-stage solid-tumor cancers from 2004 to 2013. TTI was defined as days between diagnosis of cancer and first treatment (surgery, systemic or radiation therapy).

The study population of 3,672,561 patients included those who had breast, prostate, colorectal, non-small cell lung (NSCLC), renal and pancreatic cancers. Median TTI increased from 21 days in 2004 to 29 days in 2013. Determinants of delays included care at academic centers and change in treating facility. Increased TTI was associated with worsened overall survival (OS) for stages I and II breast, lung, renal and pancreatic cancers, and stage II colorectal cancers, with an increased mortality of 1.2 to 3.2 percent per week of delay, adjusting for comorbidities and other variables.

Prolonged TTI of greater than six weeks was associated with substantially worsened OS. Five-year OS for stage I NSCLC was 56 percent for TTI of less than or equal to six weeks, versus 43 percent for TTI greater than six weeks. Five year OS for stage I pancreatic cancer was 38 percent versus 29 percent, respectively.

"In addition to its impact on outcomes, delayed TTI can cause unnecessary stress and anxiety for patients," says Brian J. Bolwell, MD, FACP, Chairman of Taussig Cancer Institute and senior author of the research. "Coordinating care is difficult, particularly in academic cancer centers, but once you take the time to identify all the hurdles and address each of them, progress in TTI is achievable."

Cleveland Clinic cancer programs have made reducing TTI for cancer patients a priority, an effort that began two years ago. Overall TTI initially was similar to that of other major cancer centers, and it has now decreased 17.5 percent overall, with Cleveland Clinic's largest cancer programs (breast, colorectal and lung) showing the greatest reduction. The organization's goal is to reduce TTI further, to less than 20 days.

"Physicians need to commit to multidisciplinary care and form integrated practice units that focus on patients," says Alok A. Khorana, MD, Co-Director of Cleveland Clinic Cancer Center's Upper Gastrointestinal and Colorectal Cancer programs and the study's first author. "TTI needs to be measured and emphasized, and we must understand what is important to each individual patient and not assume we already know."

VELO SANO. Bike to cure.

VeloSano Participants and Donors Accelerate Cleveland Clinic Cancer Research

In its three-year history, VeloSano has raised nearly $9 million for cancer research at Cleveland Clinic.

The cycling event, which takes place in and around Cleveland each July, allows individuals and teams ranging from casual riders to avid cyclists and virtual participants to pedal sponsored rides of 12 to more than 200 miles over two days. One hundred percent of the funds raised is applied to cancer research projects, laboratory expenses and personnel recruitment within Cleveland Clinic.

A $1 million donation from Cleveland Clinic Trustee Stewart A. Kohl and his wife, Donna, established VeloSano in 2013. The couple were veterans of the Pan-Mass Challenge, a Massachusetts cancer bike-a-thon, and had seen the impact it had on riders, the community and collective efforts to fight cancer.

The inaugural VeloSano Bike to Cure ride in 2014 raised nearly $2 million, and the ride brought in another $3 million in 2015. VeloSano 2016 raised $3.37 million.

Proceeds from the event are distributed in two ways:

1. **VeloSano Pilot Awards** provide seed funding for cancer research activities across Cleveland Clinic. Utilizing a competitive application and peer-review selection process, the Pilot Awards support projects with a high likelihood of obtaining future extramural funding. The focus of these one-year grants is to build on Cleveland Clinic Cancer Center's recent advancements in cancer genetics, epigenetics, and basic and translational tumor immunology.
2. **VeloSano Impact Awards** are distributed by the event's Medical Chairman, Brian J. Bolwell, MD, FACP, to satisfy the critical needs of Cleveland Clinic Cancer Center. Impact Awards address strategic priorities that will advance investigational abilities in cancer research and ensure that caregivers and patients have access to the best medical talent and technology available.

Sixteen Pilot Awards and five Impact Awards were allocated using 2016 VeloSano funds.

PILOT Awards: Epigenetic control of the 14q32 miRNA megacluster is a determinant of therapeutic refractory lymphoid malignancies **Alexandru Almasan, PhD** | Mycobiome-microbiome profiling in oral wash and normal-tumor pairs of oral cavity squamous cell carcinomas **Charis Eng, MD, PhD** | Increased macropinocytosis by tumor-associated endothelial cells requires integrin α3β1/CD151 and promotes angiogenesis **Candece L. Gladson, MD** | The microbiome and neoadjuvant therapy in HER2-positive breast cancer **Stephen Grobmyer, MD** | Molecular basis of relapse in diffuse large B cell lymphoma **Neetu Gupta, PhD** | Targeting the interaction between the drivers of lethal cancer progression as a novel treatment strategy for prostate cancer **Hannelore Heemers, PhD** | Epigenetic histone modifications track the pathogenesis of colitis-associated cancer in primary human organoids **Emina Huang, MD** | Coenzyme A synthase: A novel target for rectal cancer radiation sensitivity **Matthew F. Kalady, MD** | Development of a cancer stem cell targeting strategy via disrupting cell-cell communication **Justin Lathia, PhD** | Genome organizer-mediated repression of LINE-1 retrotransposition during inflammation **Michelle S. Longworth, PhD** | High molecular weight kininogen: A novel tumor suppressor **Keith McCrae, MD** | Targeting the SET-SETBP1-PP2A oncogenic nexus by small molecules to prevent cancer progenitor cell growth and induce terminal differentiation and death **James Phillips, PhD** | An intrabody approach to define the value of protein disulfide isomerase (PDI) inhibition in oncology **Frederic J. Reu, MD** | Determining the role of aberrant glucocorticoid metabolism in enzalutamide-resistant prostate cancer **Nima Sharifi, MD** | Targeting HDL metabolism to prevent progression to lethal prostate cancer **Jonathan D. Smith, PhD** | Targeting macrophage migration inhibitory factor (MIF) to treat multiple myeloma **Qing Yi, MD, PhD**

IMPACT Awards: Quantification of therapeutic responses in pediatric and AYA Hodgkin lymphoma patients via detection of circulating tumor DNA **Rabi Hanna, MD** | Brain metastases research program **Manmeet Ahluwalia, MD** | Chronic myelomonocytic leukemia **Jaroslaw Maciejewski, MD, PhD** | Colon cancer metastasis **Xiaoxia Li, PhD** | Cancer thrombosis **Alok Khorana, MD**

A Paradigm Shift in CLL Treatment:

Optimal Sequencing of Targeted Therapies

Dr. Hill is Director of Cleveland Clinic Cancer Center's Lymphoid Malignancies Program and staff in the Department of Hematology and Medical Oncology.

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The emergence of B-cell receptor (BCR) and B-cell lymphoma 2 (BCL-2) inhibitors has transformed the treatment of chronic lymphocytic leukemia (CLL). With each development and study, we move closer to chemotherapy-free treatments for this most common leukemia. Brian T. Hill, MD, PhD, Director of Cleveland Clinic Cancer Center's Lymphoid Malignancies Program, is on the forefront of these developments as the field begins to determine how best to utilize these newer but increasingly popular treatments.

B-cell receptor inhibitors

Researchers continue to gain a deeper understanding of the role of the BCR signaling pathway in the development and maintenance of B-cell malignancies. The downstream effects of BCR activation include the activation of intracellular transduction molecules with kinase function. These kinases ultimately influence cell survival, proliferation, function and differentiation.

Ibrutinib, the first Bruton tyrosine kinase (BTK) inhibitor developed, was initially approved for patients with relapsed CLL and/or del(17p). Its use has been expanded to all CLL patients, including those previously untreated.

Idelalisib was developed to inhibit PI3K, another BCR pathway critical to CLL survival. It is approved in combination with rituximab for patients with relapsed CLL.

While ibrutinib and idelalisib are kinase inhibitors (KIs), venetoclax functions by inhibiting the anti-apoptotic effects of BCL-2. It has been approved for patients with CLL with del(17p).

Indications for all these therapies are expected to expand with the anticipated results of front-line Alliance (NCT01886872) and ECOG (NCT02048813) studies comparing chemo-immunotherapy to ibrutinib-based therapy, as well as other studies with venetoclax in combination with monoclonal antibodies.

"These therapies are relatively new," says Dr. Hill, "and while we knew anecdotally that many patients discontinued the therapies for many reasons, we didn't have data on why or to what effect, or if a certain sequence of these drugs affected efficacy or discontinuation rates."

Real-world outcomes of CLL patients treated with KI therapy

In a study published in *Blood* in late 2016, Dr. Hill and colleagues from 10 U.S. academic medical cancer centers, including first author Anthony R. Mato, MD, at the Hospital of the University of Pennsylvania, sought to answer these questions in relation to ibrutinib and idelalisib. "We found that toxicity was the most common reason for discontinuation for both ibrutinib and idelalisib," says Dr. Hill (Table).

For patients discontinuing because of toxicity, an alternative KI was the most common follow-up therapy and was associated with an estimated progression-free survival (PFS) of 11.9 months. Among those patients who discontinued because of CLL progression, PFS was considerably shorter (seven months), suggesting that novel therapies should be considered before switching KIs.

Table. Most common reasons for discontinuation of ibrutinib or idelalisib

	Ibrutinib % (N)	Idelalisib % (N)
Toxicity	51 (73)	52 (18)
CLL progression	28 (40)	31 (11)
RT	8 (11)	6 (2)
Cellular therapies (chimeric antigen receptor T cell or allogeneic stem cell transplantation)	2 (3)	0 (0)
Unrelated death/other	11 (16)	11 (4)

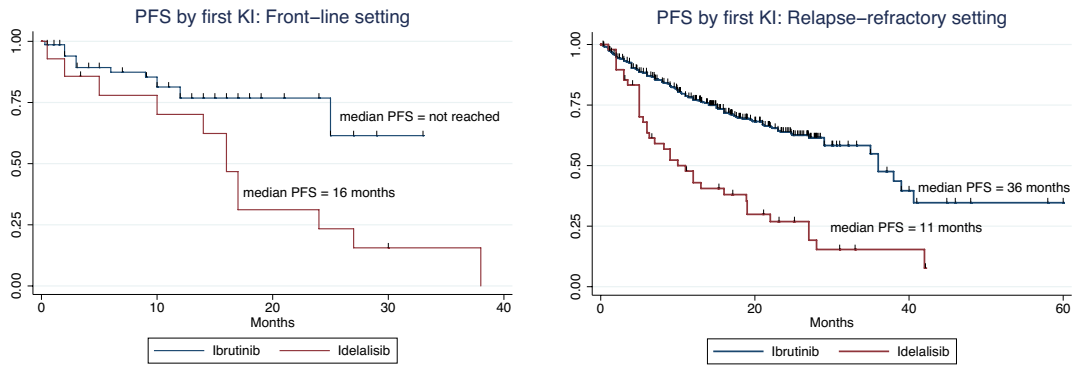

Figure. **PFS** (left) **by first kinase inhibitor (ibrutinib versus idelalisib) in the front-line setting. PFS** (right) **by first kinase inhibitor (ibrutinib versus idelalisib) in the relapsed-refractory setting.**

Republished with permission from Mato AR, Hill BT, Lamanna N, et al. Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multi-center study of 683 patients. Ann Oncol. *Published online Jan. 27, 2017.*

"Interestingly, we found that over 50 percent of patients who discontinued their first KI during the study period did so due to toxicity," says Dr. Hill. "In the studies that led to the FDA approval of these drugs, progression of disease, not toxicity, was the major reason for discontinuation. For patients who discontinue a KI due to disease progression, our data suggest subsequent treatment with cellular therapies, stem cell transplantation, venetoclax or clinical trials with novel agents is likely to be of more benefit than a second KI."

Do outcomes depend on sequence?

"In our initial study, KI choice did not appear to impact progression-free or overall survival," says Dr. Hill (PFS [HR 0.3, 95% CI, 0.08-1.2]; OS [HR 0.4, 95% CI, 0.08-2.1]). "We and others have found a high overall response rate (ORR) for patients treated with venetoclax after KI discontinuation, and we decided to investigate this finding further."

In a multicenter study of 683 CLL patients published in *Annals of Oncology* in January 2017, the consortium, including Drs. Mato and Hill, as well as Allison Winter, MD, a Cleveland Clinic Cancer Center fellow, reported a strong preference for one sequence — ibrutinib followed by idelalisib — for patients in all settings: front-line (HR 2.8, 95% CI, 1.3-6.3, $P = 0.01$), relapsed-refractory (HR 2.8, 95% CI, 1.9-4.1, $P < 0.001$), del(17p) (HR 2.0, 95% CI, 1.2-3.4, $P = 0.008$) and complex karyotype (HR 2.5, 95% CI, 1.2-5.2, $P = 0.02$) (Figure).

"We also found that if initial kinase inhibitor therapy failed, treatment with an alternate KI or venetoclax was superior to existing chemo-immunotherapy combinations," says Dr. Hill. "It also appears that using venetoclax after ibrutinib failure is slightly superior to using it after idelalisib failure."

The study is the largest on KI discontinuation and clinical outcomes after discontinuation, and it describes for the first time beyond anecdotal reports what happens when a patient switches from one KI to another.

Implications for patient care

The introduction of targeted therapies for CLL marks a move away from a chemotherapy paradigm, and this work offers insight into how best to use and sequence these agents both for individual oncologists and for leaders setting guidelines in the field. "Sequence is important because we want to maximize patient outcomes and minimize toxicity," says Dr. Hill, "but it's also important to establish the algorithms and care paths that are becoming central in the transition to value-based care. As we develop these best practices, the results of these studies are influencing our approach at Cleveland Clinic."

Sunitinib Treatment Breaks Feasible for Metastatic Renal Cell Carcinoma

A recent Cleveland Clinic Cancer Center study demonstrates that periodic sunitinib treatment breaks balance toxicity with clinical benefit and are a feasible option for patients with metastatic renal cell carcinoma (mRCC).

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Other Cleveland Clinic authors of this study include Laura S. Wood, MSN, RN, OCN; Paul Elson, ScD; Kimberly D. Allman, CNP; Jennifer Beach, RN; Allison Martin, PA-C; Beth R. Zanick, BS, RN; Petros Grivas, MD, PhD; Tim Gilligan, MD; and Jorge A. Garcia, MD.

"This disease is largely incurable, and patients are on chronic therapy," says Brian I. Rini, MD, Director of Cleveland Clinic Cancer Center's Genitourinary Cancer Program and senior author of the study. "With chronic sunitinib therapy comes the challenges of cumulative toxicity and costs." This prospective phase 2 trial is the first to investigate renal cell carcinoma treatment in which interruptions and reinitiations were based on tumor burden reduction and tumor growth.

Clinical efficacy uncompromised in previously untreated patients

Researchers treated patients who had undergone no prior systemic treatment with 50 mg sunitinib once per day for the first 28 days of a 42-day cycle. Unless toxicity or disease progression became unacceptable, patients were treated for four cycles (Figure). During this phase, the median tumor burden reduction was 1.7 cm (range, -6.1 to 5.2 cm).

Of the 37 patients who completed four cycles, 20 were eligible for subsequent intermittent therapy. Treatment interruptions were based on a reduction in tumor burden (median duration, 8.3 weeks), and treatment was reinitiated upon tumor growth (median retreatment period, 12.0 weeks). Data from these patients show that extended breaks from treatment are feasible and result in clinical efficacy similar to that found in prior studies exploring sunitinib treatment in mRCC.

"We achieved our primary endpoint of this study and discovered that intermittent sunitinib dosing was feasible for many patients," says Moshe C. Ornstein, MD, MA, a Cleveland Clinic Cancer Center fellow and lead author of the study. "We were also encouraged by our other results, including response to treatment and progression-free and overall survival."

After the first four cycles of therapy, the objective response rate was 46 percent. At the time of study analysis, median progression-free survival was 22.4 months (95% CI, 5.4 to 37.6 months) and median overall survival was 34.8 months (95% CI, 14.8 months to not applicable).

"In most patients who did the intermittent dosing, we saw a sawtooth-type pattern in which tumor burden was reduced during treatment and increased during treatment breaks," says Dr. Rini. "Some patients were even able to extend treatment breaks to over three years, while some were transitioned back to the standard schedule based on tumor burden." Overall, patients were spared a median of nine treatment cycles each, resulting in reduced toxicity, better quality of life, equivalent or better clinical outcomes, and an approximate cost savings of over $160,000 per patient.

Intermittent therapy in metastatic cancers

The intermittent therapy concept has also been studied in metastatic colorectal cancer given the neurotoxicity of front-line therapy oxaliplatin. Intermittent reintroduction of this agent into the combination regimen at a prespecified time or at disease progression resulted in decreased neuropathy and improved overall outcomes. The current study, published in the *Journal of Clinical Oncology* in early 2017, is unique in its discontinuation of all therapies during treatment breaks and its interruptions of treatment based on decreased tumor burden.

Data from this single-site study cannot be generalized to other agents, but the maintained efficacy of sunitinib after treatment breaks is encouraging. Some have hypothesized a "rebound effect" of rapid tumor growth due to increased VEGF levels after discontinuation of anti-VEGF

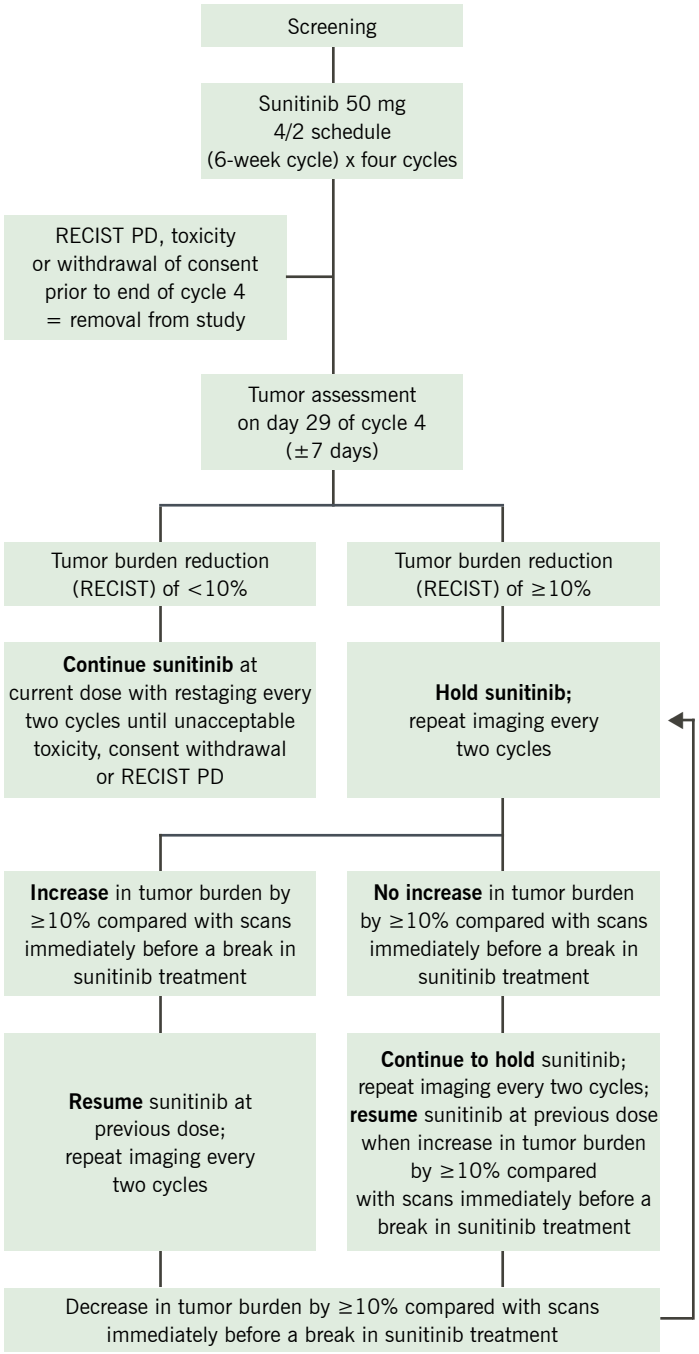

Figure. **Study schema.**

therapy. Though data do not support this idea with respect to sunitinib for the treatment of mRCC, more studies are needed to determine feasibility and efficacy with other VEGF-receptor tyrosine kinase inhibitors.

"There's more work to do," says Dr. Rini, "but we are hopeful and encouraged that intermittent sunitinib treatment will spare some patients unnecessary toxicity and cost, improve their quality of life and not compromise their clinical outcomes."

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InterContinental Hotel
Cleveland, OH
For information contact Sheryl Krall at kralls2@ccf.org or 216.444.7924.

November 8, 2017
Breast Cancer Update: From Screening Through Treatment to Survivorship
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November 11, 2017
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Radiation Oncology Gets a Dose of **Precision Medicine**

For the first time in this era of precision medicine, physicians can optimize radiation therapy dosage based on a patient's tumor genomics.

Dr. Scott is associate staff in Cleveland Clinic Cancer Center's Department of Translational Hematology and Oncology Research and Department of Radiation Oncology.

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The new genomic-adjusted radiation dose (GARD) technology, co-invented by Jacob Scott, MD, of Cleveland Clinic and Javier Torres-Roca, MD, of Moffitt Cancer Center, offers treatment teams a simple and reliable tool to match radiation dosage with a tumor's molecular profile. It is currently being commercialized through a company founded by Dr. Torres-Roca called Cvergenx.

"Radiation therapy has been one-size-fits-all when it comes to the dose of the radiation given," says Dr. Scott, a physician-scientist in Cleveland Clinic's Department of Translational Hematology and Oncology Research. "Radiation oncologists have made a lot of progress in shaping dosage — minimizing side effects and sparing healthy tissue — but the field has largely been left out of the genomics revolution sweeping through cancer care."

GARD combines LQ and RSI

GARD represents the world's first validated and scalable answer to this problem and offers radiation therapists an easy-to-interpret recommendation for radiation dosing, based on an individual patient's genomic likelihood of response to treatment.

GARD's scoring combines two well-validated algorithms — the linear-quadratic (LQ) model and the gene-expression-based radiosensitivity index (RSI), developed by Dr. Torres-Roca and colleagues — when calculating the recommended dosage.

While the LQ model offers well-known clinical efficacy in identifying equivalent dosing strategies, it cannot account for an individual tumor's genomic predisposition to respond to radiation. The RSI, however, evaluates expression levels of 10 different genes that have been found to affect a tumor's response to radiation.

Combining information gleaned from a patient's gene expression and the LQ model results in a spectrum of GARD scoring, in which higher values correlate with a higher likelihood of clinically relevant response to radiation therapy (Figure).

(continued on page 16)

(continued)

The Lancet Oncology article provides a detailed description of how GARD has been tested, which includes more than 8,200 primary tumor tissue samples from 20 disease sites enrolled in the Total Cancer Care® protocol. The study also includes 263 samples from the Erasmus Breast Cancer Cohort, 77 from the Karolinska Breast Cancer Cohort, 60 from the Moffitt Lung Cancer Cohort, 40 from the Moffitt Pancreas Cancer Cohort and 98 from The Cancer Genome Atlas glioblastoma patient cohort.

In these tests, GARD independently predicted clinical outcomes in breast cancer, lung cancer, glioblastoma and pancreatic cancer. Additionally, the rate of five-year distant-metastasis-free survival was longer in patients of the Erasmus Breast Cancer Cohort whose GARD scores were higher than in those with low GARD values.

In short, test results offer a strong correlation between GARD scoring, which can be affected through changes in radiation dose, and clinical outcomes.

Long overdue

Targeted chemotherapies and immunotherapies are sweeping through cancer care as researchers, drug developers and physicians seek new ways to treat the individual tumor, rather than the disease site.

As optimistic as many are about the future of this burgeoning field of precision medicine, about half of all cancer cures in the United States come from radiation therapy, but only $1 is spent on radiation oncology research for every $20 spent on cancer drug studies.

Dr. Scott hopes GARD and other initiatives like it will pave the way for more funding and support to work on customizing radiation therapy using the same genomics tools available in the rest of the oncology landscape.

"As we bring radiation therapy into the era of precision medicine, we have an opportunity to make significant gains in this field that will help millions of patients," says Dr. Scott.

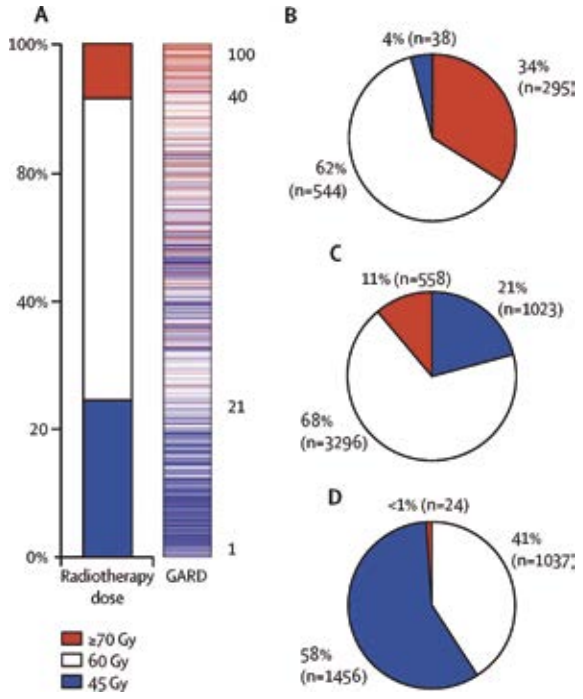

Figure. **A framework for genomic-adjusted radiation dose (GARD).**

(A) The left plot shows the proportion of patients in each radiotherapy dose group. On the right plot, GARD values for each individual patient are presented ranked from the highest to lowest value; each line represents an individual patient; color relates to dose assigned. Nine patients in the cohort had a GARD higher than 100; these patients were assigned a GARD of 100.

Pie charts show dose assignments for patients in GARD score groups: (B) high (89.41-100 percentile); (C) middle (30.41-89.4 percentile); and (D) low (0-30.4 percentile). GARD=genomic-adjusted radiation dose.

Figure and legend republished with permission from Elsevier from Scott JG et al. A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study. Lancet Oncol. *2017;18:202-211.*

Icon Comes to New Cancer Center Building

The new Taussig Cancer Center building houses Ohio's first Leksell Gamma Knife® Icon™ radiosurgery technology. Icon offers the most precise brain radiosurgery capabilities of any currently available technology.

The addition of this new technology further enhances patient care, research and education at Cleveland Clinic Cancer Center. Since 1997, the center has performed over 6,000 cases using Gamma Knife for brain tumor treatment. Cleveland Clinic is also one of the few centers to offer a weeklong Gamma Knife training course, which has trained hundreds of physicians and medical physicists. In addition, the center is active in scientific and clinical research, has ongoing clinical trials for patients with brain metastases, and holds an annual international symposium on radiosurgery.

Upgraded features benefit patient care

Icon's front-mounted, cone-beam CT scanner allows the physician to verify the patient's head position prior to treatment. This verification enables physicians to treat tumors in locations close to critical structures such as the optic apparatus and brain stem, and to replace rigid frames that screw into a patient's skull with a mask as a stereotactic reference.

The mask "offers a better patient experience for some patients and allows us to divide treatments over multiple sessions, which is useful for some complex cases," says John Suh, MD, Chair of the Department of Radiation Oncology and Associate Director of the Gamma Knife Center. The presence of high-definition motion management, which uses an infrared camera, monitors any patient motion during treatment.

"It's a very exciting time in oncology, in particular, radiation oncology," says Dr. Suh. "We plan to create the future of cancer care in the new Taussig Cancer Center by providing timely, compassionate, innovative and comprehensive cancer care."

First ASCO **Pancreatic Cancer Treatment Guidelines** Should Improve Care

Dr. Khorana is Co-Director of Cleveland Clinic Cancer Center's Upper Gastrointestinal and Colorectal Cancer programs and a staff member in the Department of Hematology and Medical Oncology. He is a Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

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Pancreatic cancer is increasingly impacting cancer-related mortality in the United States and is slated to become one of the leading causes of cancer deaths by the end of this decade.

There are no screening programs for early detection. Overall five-year survival is 7.2 percent. Recent insights into the biology of pancreatic cancer have led to novel therapeutics, and combination regimens have produced incremental

Highlights from the first set of comprehensive guidelines from ASCO include:

▶ **Potentially curable** pancreatic cancer

- Establishes two primary categories for recommended therapies: primary pancreatectomy vs. preoperative therapy groups
- Focuses on initial assessment, workup after diagnosis, appropriate adjuvant regimen, palliative care timing and surveillance

▶ **Locally advanced** pancreatic cancer

- Recommends that all patients with this presentation undergo a full assessment of psychological status, social support and symptom burden early in the process
- Examines emerging data on stereotactic body radiation therapy to inform recommendations for initial treatment approach, selection and radiation therapy timing

▶ **Metastatic** pancreatic cancer

- Details when to choose FOLFIRINOX vs. gemcitabine/nab-paclitaxel vs. gemcitabine alone for first-line treatment
- Recommends against the routine use of PET scans

improvement in median survival, but key clinical issues remain, including:

- The definition of resectable cancer
- Neoadjuvant versus adjuvant therapeutic approaches
- The role of radiation therapy and newer radiation technology
- Appropriate treatment of locally advanced disease
- Sequencing of treatment in metastatic disease

To help address these knowledge gaps, the American Society of Clinical Oncology's (ASCO) Clinical Practice Guidelines Committee initiated the Pancreatic Cancer Working Group. The group commissioned three expert panels to produce new pancreatic cancer guideline documents for potentially curable (likely resectable), locally advanced and metastatic clinical presentations.

"The three published papers represent ASCO and the oncology community's effort to standardize care of patients with pancreatic cancer in the three most common types of presentation," says oncologist Alok A. Khorana, MD, Co-Director of Cleveland Clinic Cancer Center's Upper Gastrointestinal and Colorectal Cancer programs and co-chair of the panel that prepared the guidelines for potentially curable pancreatic cancer. Because patients with pancreatic cancer are often older and have significant symptoms, each panel embedded geriatric oncology and palliative medicine experts within the process.

Oncologist Davendra Sohal, MD, MPH, Director of Cleveland Clinic Cancer Center's Clinical Genomics Program, co-chaired the panel that produced the metastatic pancreatic cancer guidelines. "Though we have seen more promising treatments in recent years, the prognosis for patients diagnosed with metastatic pancreatic cancer remains poor," says Dr. Sohal. "The panel's guidelines ensure that palliative care services are an important consideration in clinical decision-making." The five-year overall survival for patients with metastatic pancreatic cancer is 2 percent.

"These guidelines have been formulated with consensus from a variety of providers across multiple disciplines as well as patient advocates," Dr. Khorana says. "The manuscripts focus on providing appropriate care across the continuum for this illness, with an emphasis on early involvement of palliative care and patient-centered approaches that include treatment decision-making in the context of medical comorbidities. The guidelines also identify the existence of major knowledge gaps and call for additional federal and philanthropic funding to help increase the options available for this difficult illness."

Dr. Sohal is Director of Cleveland Clinic Cancer Center's Clinical Genomics Program and associate staff in the Department of Hematology and Medical Oncology.

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CHAIRMAN'S **Q&A**

Brian J. Bolwell, MD, FACP, Talks About **Leading Through Change**

Dr. Bolwell is Chairman of Taussig Cancer Institute.

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The U.S. Department of Health and Human Services Agency for Healthcare Research and Quality has over 2,000 metrics for clinical quality. How do you address so many metrics at one time?

When you sit in front of a patient and try to help them, it's hard to imagine there are actually 2,000 things to measure. But I do think many of the metrics make sense, especially those dealing with quality, like the incidence of deep venous thrombosis after surgery.

As a leader, I focus on how to get a team of people from point A to point B. I think if you tell a team they need to meet 55 different metric goals, that tends to be rather overwhelming. There's a finite number of things on which I can ask them to focus, and if we do those very well, it's likely that many other things will follow.

I think of the analogy of a golf swing. It's actually very difficult to swing well. I remember someone telling me years ago that if you finish a swing in balance and you're pointing to the target, you've probably made a pretty good swing. Similarly, I think if we can focus on a handful of things and do them well, it's pretty likely that we're doing a whole bunch of other things well too.

What metrics does Cleveland Clinic Cancer Center prioritize and why?

We focus on three priorities that I think are fundamental. Quality and safety are number one. Number two is treating people well, and number three is access.

You have to lead with quality and safety. Very early in my career, I was running the bone marrow transplant program, and we heard about a couple of catastrophic events that had happened at another center in which patients received fatal doses of chemotherapy. It turned that organization on its head, and it certainly changed the way we order chemotherapy here. When I began leading this center, our goal was to eliminate harm events from chemotherapy, and by working together with our nursing colleagues, we've actually lowered our chemotherapy harm events to zero for the past five years.

The second thing is treating people well, and that starts with our own work family. I think if we ensure that everyone in our work environment is treating the entire team with respect, then it's highly likely we'll treat patients and their families well.

Finally, we are incredibly focused on access. I think the time it takes for a person to receive their first therapy after diagnosis is a surrogate marker for the amount of empathy in a culture. It's a cultural thing. People need to be seen; we get them in and see them. We know they're anxious and scared, and respect that with prompt access. I'm happy with the progress we've made on time-to-treat metrics thus far. I think improving access cascades to many other measures.

Reimbursement tied to specific metrics is just one example of the tumultuous changes occurring in healthcare in general and in oncology in particular. As a leader, how do you promote the well-being of your colleagues in such an environment?

The whole field of oncology is changing very, very rapidly. I think that for most of us, simply keeping up is a challenge. I think step one is to communicate with staff. Be transparent about what is going on in the organization and outside the organization. People need to know why we're being asked to do whatever the task at hand might be.

Another focus is teamwork. I think the shift to value-based care has caused disruptive change, but the emphasis on integrated teams has been a particularly helpful change. That's the whole key to value-based care. But by nature, most physicians are pretty independent. Teamwork was not a qualification to get into medical school or residency, and it's not something with which everyone is comfortable.

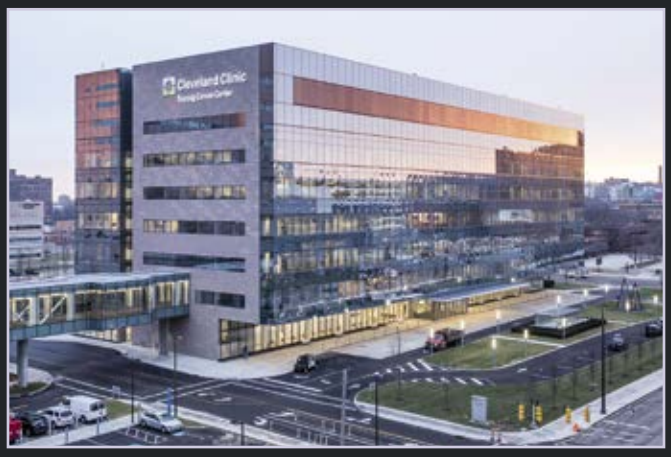
Our care paths are a good example of a response to value-based care that has fostered teamwork. To analyze what treatments work best, what should be the standard of care, we involved team members from different institutes, different locations, in different positions. The goal was to adopt a standard of care, but we also created a sense of teamwork that fosters collaboration and gets people working together on a task, which is important to creating an environment in which people feel comfortable and fulfilled in their daily work.

What enables you to lead through this time of change?

A while ago I was fortunate to undergo formal leadership training, which included an extensive report of my colleagues' perceptions of me and my leadership style. It was basically a 20-page report in which they told me everything I did wrong, but it was incredibly useful. Openness to constructive criticism is key. It was eye-opening; I learned and changed a lot.

I've read about 40 books on the topic of leadership, and I've gravitated to something called serving leadership, which just makes sense to me. It means that I have three goals. Set a clear vision, which is harder than it sounds. Hire wonderful people, and enable them to succeed. And then remove the barriers. I think that's a big part of how I can contribute to the team's well-being. Anytime you work in a large organization, there are barriers, political or otherwise. My job is to remove those and let people do their jobs.

As a leader, if I can focus on those three things, and if as a cancer center we can focus on quality and safety, respect for one another, and access, then no matter how the external environment demands change, we will succeed.



Tour Cleveland Clinic's New Cancer Center with *The Washington Post*

An interactive media experience with *The Washington Post* shows how the new Cleveland Clinic Cancer Center maximizes multidisciplinary care and prioritizes the patient experience. See Brian J. Bolwell, MD, FACP, Chairman, Cleveland Clinic Taussig Cancer Institute, discuss why proximity matters in enhancing the function of a multidisciplinary team, and how architects, patients and physicians designed the new building to facilitate team-based care. Also hear from John Suh, MD, Chair of Radiation Oncology, and Pauline Funchain, MD, medical oncologist, in virtual tours of the radiation and infusion suites as well as other patient areas. Videos, panoramic images and other immersive media are available on *The Washington Post*'s website or at clevelandclinic.org/empathybydesign.

Sharifi Honored by Clinical Research Forum

Cleveland Clinic physician-researcher Nima Sharifi, MD, was recognized as a Top Ten Clinical Research Achievement awardee by the Clinical Research (CR) Forum, a national organization of senior researchers and thought leaders from the nation's leading academic health centers.

Dr. Sharifi was selected for his research published in the October 2016 edition of *The Lancet Oncology*, which showed for the first time that patients with advanced prostate cancer are more likely to die earlier from their disease if they carry a specific testosterone-related genetic abnormality.

The Top Ten Clinical Research Achievement Award winners were chosen based on the degree of innovation and novelty involved in the advancement of science; contribution to the understanding of human disease and/or physiology; and potential impact on the diagnosis, prevention and/or treatment of disease. The CR Forum hosted its sixth annual awards ceremony in April at the National Press Club in Washington, D.C.

Dr. Sharifi's research found that a specific, inherited polymorphism in the *HSD3B1* gene renders standard therapy for metastatic prostate cancer less effective. Men involved in the study were treated with androgen deprivation therapy (ADT) for metastatic prostate cancer. While the treatment is widely successful in many patients, eventually prostate tumors are able to circumvent ADT, and patients become resistant to the treatment because the tumors make their own androgens.

Dr. Sharifi's work was supported by Cleveland Clinic, the U.S. Department of Defense Congressionally Directed Medical Research Programs, the Gail and Joseph Gassner Development Funds, a Howard Hughes Medical Institute Physician-Scientist Early Career Award, the Prostate Cancer Foundation, an American Cancer Society Research Scholar Award, and additional grants from the National Cancer Institute (R01CA172382, R01CA190289 and R01CA168899).

A **Path to Reverse Enzalutamide Resistance** in Advanced Prostate Cancer

A Cleveland Clinic research team has discovered a biological pathway that could ultimately help men overcome resistance to androgen receptor antagonist therapy in advanced prostate cancer.

The study is the latest in a line of significant androgen-related research with the potential to impact prostate cancer treatment from Nima Sharifi, MD, who holds appointments in Cleveland Clinic's Lerner Research Institute Department of Cancer Biology, Glickman Urological & Kidney Institute and Taussig Cancer Institute.

Resistance inevitably develops

While metastatic prostate cancer responds initially to medical or surgical castration in virtually all men, the disease eventually progresses to castration-resistant prostate cancer (CRPC). In 2015, most of the estimated 26,100 prostate cancer deaths in the U.S. were due to the metastatic castration-resistant form of prostate cancer.

For more than 70 years, androgen deprivation therapy (ADT) has been the gold standard for systemic treatment of prostate cancer. Prostate cancer cell growth depends on androgen stimulation of the cell's androgen receptor (AR), which drives expression of AR-induced oncogenes. With gonadal suppression, ADT dramatically reduces serum testosterone levels, resulting in AR deactivation and inhibition of tumor growth.

After one to two years, however, most patients' tumors evolve from castration-sensitive to CRPC, as a result of tumors' acquisition of androgen synthesis capability.

Dr. Sharifi's previous research found that prostate cancer patients with an inherited gene variant that enhances androgen synthesis are highly likely

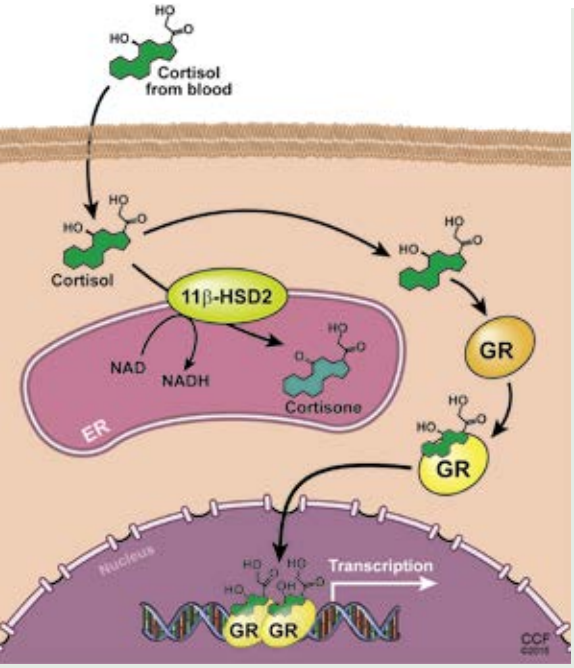


Figure. **Glucocorticoid receptor (GR) stimulation with enzalutamide resistance in prostate cancer is tightly regulated by glucocorticoid metabolism in target tissues.** Stimulation of GR by cortisol in humans is limited by 11β-HSD2, which oxidizes and converts cortisol to inactive cortisone. In mice, 11β-HSD2 converts active corticosterone to inactive 11-dehydrocorticosterone.

Reprinted with permission Li J, Alyamani M, Zhang A, Chang KH, Berk M, Li Z, Zhu Z, Petro M, Magi-Galluzzi C, Taplin ME, Garcia JA, Courtney K, Klein EA, Sharifi N. Aberrant corticosteroid metabolism in tumor cells enables GR takeover in enzalutamide resistant prostate cancer. eLife. *2017;6:e20183.*

to develop tumors with more rapid resistance to ADT and have faster cancer progression and significantly reduced survival. Results from this research suggested that a variant of the *HSD3B1* steroidogenic enzyme gene could be a powerful new biomarker capable of identifying patients with aggressive disease who warrant early escalated therapy with next-generation anti-androgens.

Enzalutamide is one such potent next-generation AR antagonist that can prolong survival for metastatic CRPC patients. "In prostate cancer, we know that a hormone-receptor complex instructs cells to proliferate," says Dr. Sharifi. "Enzalutamide blocks this interaction, rendering androgens inactive."

However, most men eventually develop resistance to the drug, leading to disease lethality.

Metabolic switch

Dr. Sharifi's research team discovered a complex cascade of events — a "metabolic switch" — that occurs when androgen receptors are blocked with enzalutamide. Results show that enzalutamide treatment causes levels of the enzyme 11β-HSD2 to plummet, which in turn creates a surplus of cortisol in tumor cells. This excess cortisol activates its own receptor-protein complex, which then assumes the role of the disabled androgen receptor, prompting the tumor to increase production of androgens (Figure).

Since simply blocking cortisol from its receptor is not compatible with life, Dr. Sharifi's team searched for an alternative means of turning off this metabolic switch. In their mouse xenograft tumor and human tissue models, results suggested that blocking 11β-HSD2 protein loss or reinstating 11β-HSD2 expression in the tumor reverses enzalutamide resistance.

A step closer, but further study needed

The team's findings were published in *eLife* in early 2017. Dr. Sharifi is hopeful that further research can elucidate a pharmacologic solution that prevents or reverses enzalutamide resistance.

"This is a major discovery that demonstrates how tweaking changes in metabolism induced by hormonal therapy can offer major benefits to patients in prostate and possibly other cancers," Dr. Sharifi explains. "We need additional studies to determine how to safely increase 11β-HSD2 in patients, but we are a step closer to finding answers and hopefully prolonging the lives of men who are in the unfortunate situation of being resistant to all current therapies."

Dr. Sharifi is staff in Cleveland Clinic's departments of Hematology and Medical Oncology, Cancer Biology, and Urology. He holds the Kendrick Family Endowed Chair for Prostate Cancer Research and is Associate Professor of Molecular Medicine at Cleveland Clinic Lerner College of Medicine.

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Recent Advances and **Next Steps** in Advanced Urothelial Carcinoma

By Petros Grivas, MD, PhD, and Pedro Barata, MD, MSc

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On Twitter: @PGrivasMDPhD

Dr. Barata is an experimental therapeutics fellow at Cleveland Clinic Cancer Center.

Bladder cancer is the fourth most common cancer in men and the fifth most common in general, and was responsible for more than 16,300 deaths in 2016 in the U.S. alone. It is the most expensive cancer to treat from diagnosis to death and is a significant burden to patients, families and healthcare systems. Urothelial carcinoma is the most common type of bladder cancer.

Until recently, the standard therapy among patients with advanced urothelial carcinoma was cisplatin-based combination chemotherapy, including dose-dense methotrexate, vinblastine, adriamycin and cisplatin (ddMVAC), as well as cisplatin/gemcitabine. Altogether, these regimens yield response rates of 50 to 70 percent but are usually short-lived, with median progression-free survival (PFS) and overall survival (OS) of 7 to 8 months and 14 to 15 months, respectively.

Carboplatin-based regimens have typically been used in those who cannot tolerate cisplatin. A proportion of patients may not receive chemotherapy due to medical comorbidities and poor performance status. Historically, chemotherapy for platinum-refractory disease with vinflunine and docetaxel has resulted in low response rates with a relatively short median OS of approximately 6-8 months.

Checkpoint therapy and bladder cancer

Recent developments in cancer immunology have provided new therapeutic approaches. Several antibodies that block immune checkpoints (e.g., cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] and programmed cell-death protein 1 [PD-1]/PD-1 ligand 1 [PD-L1] pathways) have been developed. These antibodies have yielded major advances across multiple malignant neoplasms by unleashing the antitumor activity of T cells to target inhibitory pathways and thus reverse immunosuppression.

The first four FDA-approved agents for patients with metastatic urothelial cancer who relapse during/after platinum-based chemotherapy are atezolizumab, a PD-L1 inhibitor; nivolumab, a PD-1 inhibitor; and durvalumab and avelumab, PD-L1 inhibitors. All four agents appear to have comparable efficacy (15 to 20 percent response rates) and safety profiles, as well as kinetics of response.

Both rapid and durable responses were noted in these trials. Furthermore, the safety profile was very favorable, with less than 20 percent of grade 3/4 treatment-related adverse events. While the accelerated approvals were granted to address unmet needs, confirmatory studies are required to grant full approval of these drugs, including the IMvigor211 phase 3 trial comparing atezolizumab to chemotherapy, which did not meet its primary endpoint.

Results have been published from the large, randomized phase 3 trial of pembrolizumab (KEYNOTE-045) in 542 patients with relapse during/after a platinum-based regimen. The trial randomized patients to the anti-PD1 agent or chemotherapy (vinflunine or taxane) and showed longer median OS (10.3 months vs. 7.4 months, HR 0.73) and higher response rate (21.1 percent vs. 11.4 percent) with pembrolizumab. The estimated duration of response was also greater with pembrolizumab, which was better tolerated than chemotherapy. The FDA is actively reviewing these data.

While cisplatin-based combination chemotherapy has been proven to offer clinical benefit based on randomized controlled trials, approximately half of patients may be ineligible for cisplatin therapy because of poor performance status, renal impairment, notable hearing loss or neuropathy, or NYHA class III/IV heart failure.

In the first cohort of the phase 2, single-arm IMvigor210 trial, cisplatin-ineligible patients with advanced urothelial cancer were treated with atezolizumab. With a median follow-up of 17.2 months, the overall response rate was 23 percent. Median OS was 15.9 months, with 70 percent of responses ongoing.

Pembrolizumab was also assessed in the front-line setting in the phase 2 KEYNOTE-052 trial. With a median follow-up of eight months, results were also very promising with a response rate of 24 percent, and 83 percent of patients with ongoing responses at six months; treatment was well-tolerated, as with other studies.

Questions for the future

Questions remain for the future of bladder cancer treatment. What is the preferred agent? Can biomarkers help us select patients with a high chance of response compared with those who may not benefit? What about promising combinations/sequences? Can we use an anti-PD-1 agent if there is progression on anti-PD-L1, and vice versa? Can we pursue treatment breaks in responders? The absence of head-to-head comparison studies along with the comparable outcomes reported in different studies makes the answers to these questions difficult to discern. Level of evidence, frequency/logistics of administration and cost are relevant factors.

Because we have tangible examples of outliers who respond positively to treatment, a very challenging need is the development of predictive biomarkers to help select patients more likely to respond. So far, we have been treating all patients without the need to test a priori for a companion diagnostic biomarker, such as tumor tissue PD-L1 expression. It is likely that response to checkpoint inhibitors is a much more complex process, involving PD-L1 status, genomic/transcriptomic subtype, tumor microenvironment, tumor mutational load and specific "neoantigens," numerous host immune system factors, and possibly host microbiome, among others. Tumors with higher mutational load are more likely to respond, as shown in the IMvigor210 trial, supporting the role of tumor mutations in the development of neoantigens and subsequent T-cell response. Also, luminal II molecular subtype (based on The Cancer Genome Atlas classification) was strongly associated with response to atezolizumab. Our interdisciplinary team of many scientists and clinicians is actively pursuing translational biomarker studies to answer such important questions with scientific rigor.

More clinical and translational research is needed to better understand immunologic mechanisms, test novel immune targets and combine them with existing and future therapies, and develop better biomarkers that help us offer the right treatment to the right patient at the right time. We have many open clinical trials for patients in different stages of urothelial/bladder cancer and are hopeful for continued advances in the field.

New Staff

Joycelin Canavan, MD
Radiation Oncology
Mansfield, OH

Anupama Doraiswamy, MD
Hematology and Oncology
Weston, FL

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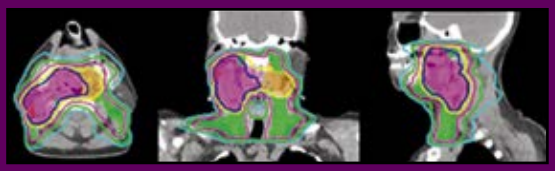

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Cancer Advances provides information from Cleveland Clinic cancer specialists about innovative research and diagnostic and management techniques.

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Taussig Cancer Center / CA
Cleveland Clinic
9500 Euclid Ave.
Cleveland, OH 44195

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The Cancer Center's more than 450 physicians, researchers, nurses and technicians care for thousands of patients each year and provide access to a wide range of clinical trials. Cleveland Clinic Cancer Center unites clinicians and researchers based in Taussig Cancer Institute and in Cleveland Clinic's 26 other clinical and special expertise institutes, as well as cancer specialists at our regional hospitals, health centers and at Cleveland Clinic Florida. Cleveland Clinic is a nonprofit academic medical center ranked as the No. 2 hospital in the country (*U.S. News & World Report*), where more than 3,400 staff physicians and researchers in 140 specialties collaborate to give every patient the best outcome and experience.

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