Cleveland Clinic

# Cancer Advances

Cleveland Clinic Cancer Center | Summer 2019

## Developing Targeted Agents for Molecular Subtypes of Leukemia

## Dear colleagues,

Welcome to the latest edition of *Cancer Advances*. The programs and projects described in this issue reflect Cleveland Clinic Cancer Center's emphasis on high-impact, translational cancer research and innovative therapies. The work highlighted here is the result of dozens of talented clinicians and researchers working together to advance patient care.

Our cover story offers a glimpse into the drug discovery work of our Department of Translational Hematology and Oncology Research (p. 2), led by Drs. Jaroslaw Maciejewski and Yogen Saunthararajah. We also highlight the results of two clinical trials recently published in the *New England Journal of Medicine* by the leaders of our Genitourinary and Gastrointestinal Malignancies programs, Drs. Brian Rini (p. 6) and Alok Khorana (p. 7).

We continue to offer the most advanced treatments to our patients, like CAR T-cell therapy for large B-cell lymphoma (p. 10), hyperthermic intraperitoneal chemotherapy for advanced ovarian cancer (p. 18), and an aggressive, three-pronged approach to perihilar cholangiocarcinoma (p. 12).

And we are innovating in cancers that traditionally offered limited treatment options for patients. Dr. Manmeet Ahluwalia offers his thoughts on four of our promising bench-to-bedside initiatives in glioblastoma (p. 14), and Dr. Davendra Sohal details how we've harnessed the power of molecular profiling to improve survival in patients with pancreatic cancer (p. 9). The many projects awarded funds from VeloSano 5 (p. 22) promise to offer meaningful innovations for our patients, from photoacoustic immunotherapy to noninvasive detection of hepatocellular carcinoma.

While these advances are important for our patients, the paramount thing we can do to ease their anxiety is to treat their cancer as quickly as possible. As you will read on page 16, we have continued our efforts to reduce time-to-treat for our patients and have made tremendous progress — and national impact — since we began.

As always, I welcome the opportunity to discuss the research projects and treatment initiatives underway at Cleveland Clinic Cancer Center and the possibilities for collaboration. Don't hesitate to reach out with ideas, questions, concerns or suggestions.

Sincerely,

**Brian J. Bolwell, MD, FACP**
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# **Targeted Agents in Development** for Molecular Subtypes of Leukemia

## Investigators making strides in cancer drug discovery

Several novel therapeutic agents for the treatment of hematologic malignancies are in development at Cleveland Clinic Cancer Center. Physician-scientists in Lerner Research Institute's Department of Translational Hematology and Oncology Research are leading drug discovery projects focused on the development of new, selective anticancer agents that inhibit the function of specific genes or proteins that cancer cells rely on to survive and resist the stress triggered by conventional chemotherapy.

"Our current focus in the area of myeloid neoplasia is on development of targeted agents for molecular subtypes of leukemia defined by specific mutations and improvement of hematopoietic stem cells [HSCs] in various diseases," says Jaroslaw Maciejewski, MD, PhD, Chair of the Department of Translational Hematology and Oncology Research (THOR).

Together with his collaborators James Phillips, PhD; Babal Kant Jha, PhD; Valeria Visconte, PhD; and Yogen Saunthararajah, MD; Dr. Maciejewski directs Cleveland Clinic's cancer drug discovery efforts. The portfolio of drugs is growing, and multiple patents have been filed.

"As practicing hematologists, we see an urgent need to have better drugs available. Our clinical practice and patients provide a constant inspiration for the drug discovery efforts," says Dr. Maciejewski. Below is an overview of four drugs in development, all presented at the 2018 American Society of Hematology Annual Meeting.

### Targeting *TET2* mutations in myeloid neoplasia

One study led to the development of a novel class of *TET*-specific inhibitors for *TET2* mutant-associated diseases. *TET2* encodes a methylcytosine $Fe^{2+}$-dependent DNA-dioxygenase that catalyzes the conversion of 5-methylcytosine-DNA (5mC) to 5-hydroxymethylcytosine-DNA (5hmC) and is involved in active DNA methylation. Loss-of-function *TET2* mutations are the most common mutations found in myeloid neoplasia and some lymphomas.

"*TET2* mutations are good targets for drug discovery because they are common, occur early in the disease process and affect fundamental processes of leukemogenesis; we learned a lot about the consequences of these mutations through study of the disease," explains Dr. Maciejewski. "Our goal was to develop a *TET*-specific inhibitor capable of inducing synthetic lethality in diseases with *TET2* mutations."

Using a structure-guided, targeted discovery approach, Dr. Maciejewski and his collaborators designed and synthesized a novel class of *TET*-specific inhibitors, which demonstrated dose-dependent inhibition of dioxygenase activity, as well as promising results in vitro and in preclinical murine disease models. An agent from this class, designated as TETi76, was shown to selectively induce cell death in *TET2* mutation cells with minimal toxicity to residual healthy bystander cells.

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*Cover image: Russell Lee*

*"Our results point to a promising novel therapeutic strategy expansion."*

(continued)

*Dr. Maciejewski is the Chair of the Department of Translational Hematology and Oncology Research. He is a Professor of Medicine at Cleveland Clinic Lerner College of Medicine.*

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Another unexpected biological activity of this agent included its positive effects on healthy stem cells, which point to potential application of this class of drugs in bone marrow failure syndromes. *TET* DNA dioxygenase inhibitors are a completely new class of drugs not previously used in oncology.

### Inhibiting FABP5-mediated retinoic acid signaling in AML

In a separate study, cancer center investigators reported on a novel therapeutic strategy for acute myeloid leukemia (AML) based on a highly specific fatty-acid-binding protein 5 (FABP5) inhibitor.

"ATRA [all-trans retinoic acid] has been a miracle drug for acute promyelocytic leukemia [APL], but other more common forms of AML have been resistant," explains Dr. Maciejewski.

Similar to the cellular retinoid-binding protein II (CRABP-II), FABP5 serves as a retinoic acid (RA) transporter. In leukemia cells with high levels of CRABP-II and low levels of FABP5 (e.g., APL), RA actives the retinoic acid receptor (RAR), which leads to cell growth arrest and apoptosis. However, in leukemia cells with high FABP5 expression, RA activates the peroxisome proliferator-activated receptor β/δ (PPAR β/δ) instead of RAR, which leads to cell (tumor) growth and proliferation. Thus, inhibiting FABP5 constitutes a potential novel therapeutic approach for types of AML previously resistant to ATRA.

"There is great need for improvement of outcomes of these AML patients, and the combination of FABP5 with ATRA may constitute a novel mutation-agnostic therapy approach," he says.

### Improving the function of HSCs in aging and bone marrow failure

Nicotinamide adenine dinucleotide ($NAD^+$) related to vitamin B3 is an essential cofactor implicated in the regulation of cellular processes, oxidative stress and bone marrow function. $NAD^+$ levels decline with age, and preventing this process has been shown to prolong the life span. Research suggests that some of these effects may be attributed to the effects of $NAD^+$ on stem cells including HSCs.

"The levels of $NAD^+$ in bone marrow are regulated by CD38, an $NAD^+$ degrading enzyme," says Dr. Maciejewski. "We have identified an agent that selectively inhibits enzymatic activity of CD38. This agent has been further modified to improve its biologic activity in terms of optimization of HSC function."

This is a unique property because, to date, only a few agents have been shown to prevent relentless HSC attrition in vitro.

"We have observed that CD38 inhibitor allows for the preservation of the stem cell pool in vitro even if the proliferation and inherent differentiation have been induced by hematopoietic growth factors," he says. "Of importance is that the positive effects of the lead compound ccf1172 on normal HSCs were not associated with proleukemogenic properties. Leukemic cells were not stimulated by this drug — indeed, they were inhibited. Our results point to a promising novel therapeutic strategy expansion of HSCs involving CD38 in vivo in inherited or acquired bone marrow failure states and ex vivo in generating better bone marrow grafts for transplantation."

### Efficacy of a first-in-class SMARCA5/CHD4 inhibitor

Investigators from Cleveland Clinic Cancer Center also presented data demonstrating the efficacy of a


*"We are optimistic that these molecular scaffolds hold within them the promise for an alternative, rational, effective and nontoxic paradigm of leukemia and cancer therapy."*

first-in-class inhibitor (ED2-AD101) of SMARCA5/CHD4 (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 5/chromodomain helicase DNA binding protein 4) in cell-based assays of AML.

"This is the first agent from a new class of drugs that exerts its effect not through direct cell death but through terminal differentiation of AML cells, turning them into nondividing granulocytes," says Yogen Saunthararajah, MD, staff in the departments of Hematologic Oncology and Blood Disorders and THOR. "We discovered this scaffold by screening a small molecule library of compounds that induce terminal differentiation of leukemia cells. We then executed a gamut of assays to identify the specific molecular targets of this family of potent differentiation-inducing compounds."

*Focusing on the pathway, not just the molecular target*

Dr. Saunthararajah explains that in drug discovery, it is important not only to think about the molecular target, but also to consider the downstream pathway by which the drug is proposed to act on diseased cells.

"It is important to think about the pathway because if a pathway downstream of the target is inactivated in cancer cells, then the cancer cells readily resist multiple different drugs that depend on that same pathway," he explains. "For example, most of our drugs to treat leukemias and other cancers use apoptosis as their pathway of action, but most leukemias and cancers attenuate the apoptosis program, conferring resistance to multiple drugs and radiation. Meanwhile, normal dividing cells, with intact apoptosis programs, are destroyed."

This new drug class is significant because it utilizes a different mechanism of action. Because hundreds of monocyte and granulocyte terminal-differentiation genes are epigenetically suppressed in AML cells, they can escape terminal granulomonocytic fates.

"The important aspect is that these proliferation-termination genes are physically intact and poised for activation by the master transcription factors that are highly expressed in AML cells," says Dr. Saunthararajah. "This new class of drugs exploits this biology of AML to terminate the proliferation of malignant cells without harming normal, dividing hematopoietic cells."

*ED2-AD101 selectively inhibits the growth of leukemia cells*

In their search for new drug candidates, Dr. Saunthararajah and colleagues specifically focused on compounds that only cause differentiation of leukemia cells. The ED2-AD101 class of compounds that they identified causes selective differentiation of leukemia cells by inhibiting a class of epigenetic enzymes called the ISWI (Imitation SWItch) family — members of this enzyme family include SMARCA5 and CHD4.

At concentrations ranging from less than 1 to 10 μM, ED2-AD101 effectively suppressed the growth of AML cells containing a spectrum of genetic alterations, including genetic inactivation of apoptosis. AML cell proliferation was terminated by activation of the terminal granulocytic differentiation program. The growth of normal, healthy hematopoietic cells was spared.

Dr. Saunthararajah cautions that there is still much work to do before these molecules can be used in the clinic.

"We are continuing to work on refining the molecules and have to conduct extensive, preclinical in vivo proof-of-principle experiments using patient-derived xenotransplant models of leukemia," he says. "We are optimistic, however, that these molecular scaffolds hold within them the promise for an alternative, rational, effective and nontoxic paradigm of leukemia and cancer therapy."

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## KEYNOTE-426:

# Pembrolizumab + Axitinib or Sunitinib Alone for Advanced Renal Cell Carcinoma?

### Combo therapy shows longer OS and PFS and higher ORR

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Since 2005, the advanced renal cell carcinoma (RCC) treatment landscape has undergone a major evolution — moving from cytokine-based immunotherapy, which achieved little clinical benefit, to targeted therapy against vascular endothelial growth factor (VEGF) and today to novel immunotherapy agents. As a cancer with immunogenic properties, RCC has responded well to immunotherapy. It has also proved susceptible to anti-angiogenic treatment.

Enter KEYNOTE-426, a phase 3 trial comparing standard first-line anti-VEGF therapy sunitinib with a combination of two agents that have shown antitumor activity in previously untreated, advanced RCC: VEGF receptor tyrosine kinase inhibitor axitinib and anti-programmed death 1 (PD-1) monoclonal antibody pembrolizumab.

"These results mark another transition in the RCC treatment landscape. This is the first time a regimen has improved OS, PFS and ORR in an unselected front-line metastatic RCC population," says Brian Rini, MD, Director, Genitourinary Cancer Program, Cleveland Clinic Cancer Center, and principal investigator of the global trial. "Capitalizing on both an antiangiogenic and immunotherapeutic approach, benefit was seen across prognostic groups and regardless of PD-L1 expression."

## Staggering improvement in OS and PFS

The results of this open-label, randomized trial were staggering: The combination treatment resulted in a 47 percent lower risk of death and a 31 percent lower risk of disease progression or death compared with sunitinib treatment alone. The objective response rate in the pembrolizumab-axitinib arm was 59.3 percent (95% CI, 54.5-63.9) versus 35.7 percent in the sunitinib arm (95% CI, 31.1-40.4). Median progression-free survival was 15.1 months for the combination therapy and 11.1 months for sunitinib alone (HR for disease progression or death, 0.69; 95% CI, 0.57-0.84; $P < 0.001$).

Patients received either pembrolizumab (200 mg) intravenously once every three weeks plus oral axitinib (5 mg) twice daily (N = 432) or oral sunitinib (50 mg) once daily for the first four weeks of each six-week cycle (N = 429). Patients all had previously untreated advanced clear-cell RCC. Imaging was performed at week 12 and then every six weeks for the first year and every 12 weeks thereafter. Bone scans were performed at baseline and, when positive, repeated at weeks 18, 30, 42 and 54 and every 24 weeks thereafter. Adverse events were monitored throughout and graded per National Cancer Institute Common Terminology Criteria for Adverse Events.

Eligible patients were treatment naïve with histologically confirmed metastatic RCC with a clear-cell component (with or without sarcomatoid features), measurable disease (RECIST v1.1, investigator review), no prior systematic therapy for advanced disease and a Karnofsky Performance Scale status greater than 70 percent.

## Combination therapy the way of the future in RCC

As multiple front-line trials of checkpoint immunotherapy in combination with either targeted therapies or other checkpoint inhibitors are demonstrating promising results, there is newfound hope for patients with advanced RCC. "We're seeing positive results in many trials, including KEYNOTE," says Dr. Rini. "We are also finally starting to get larger numbers of advanced kidney cancer patients into remission. Clinical research will continue, however, until all metastatic kidney cancer patients can be cured."

# **Oral Anticoagulants** Show Benefit for Cancer Patients at High Risk of Venous Thromboembolism

## CASSINI results favor use of rivaroxaban

Venous thromboembolism (VTE) is the second leading cause of death for cancer patients after cancer itself. To prevent it, the American Society of Clinical Oncology (ASCO) guidelines recommend prescribing low-molecular-weight heparin (LMWH).

Using LMWH to prevent VTE in cancer patients, however, is complicated. LMWH clinical trials were not risk-adapted, so physicians don't know how well they work in high-risk patients. In addition, because most cancer patients today are not hospitalized while receiving treatment, cancer patients who are prescribed LMWH must inject themselves at home.

"Daily self-injection is a barrier to patient compliance," says Alok Khorana, MD, Sondra and Stephen Hardis Chair in Oncology Research and Director of the Gastrointestinal Malignancies Program at Cleveland Clinic Cancer Center. "In addition, physicians don't know how well LMWH works in high-risk VTE cancer patients, which is who you want to focus on because taking blood thinners also carries a risk of bleeding."

Now a new multicenter trial — that was risk-adapted — shows oral anticoagulants might be a better way to treat high-risk VTE cancer patients. Results of the CASSINI trial show that the oral anticoagulant rivaroxaban significantly reduced VTE and VTE-related deaths for outpatient, at-risk cancer patients.

"This could potentially signal a change in the prevention approaches to cancer-associated VTE," says Dr. Khorana, who was co-chair of the steering committee for the trial and presented the results as a late-breaking abstract at the 2018 American Society of Hematology meeting. The results were also published in the *New England Journal of Medicin*e in February 2019.

### Fewer blood clots

CASSINI included 841 patients, of which 274 (32.6 percent) had pancreatic cancer; 698 (83 percent) were white and 428 (50.9 percent) were male. Patients were randomized 1-to-1 to rivaroxaban 10 mg once daily or a placebo for 180 days.

Each patient's risk of blood clots was identified at the time of chemotherapy initiation by the Khorana score, previously designed by Dr. Khorana and colleagues. The score predicts blood clots based on simple variables: cancer type, body mass index and complete blood count (platelet, leukocyte, hemoglobin). Patients with a Khorana score of 2 or greater are considered at higher risk for developing blood clots, and were included in the trial.

Only 2.62 percent of patients who took rivaroxaban developed blood clots compared with 6.41 percent of the placebo group. In addition, those taking rivaroxaban were less likely to die — 23.1 percent, compared with 29.5 percent in the placebo group. Less than 2 percent of patients suffered major bleeding, a side effect of

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(continued)

anticoagulants — on par with what would be expected with prophylactic anticoagulation in cancer patients.

**Procoagulant state persists**

After the patients stopped taking rivaroxaban, trial investigators continued to observe them for an additional 180 days. The gap between the two groups narrowed, with 5.95 percent of the previous rivaroxaban patients developing blood clots during this period compared with 8.79 percent of the placebo patients. This led to the primary analysis period of 180 days not being statistically significant.

"It shows that the procoagulant state in cancer is persistent," says Dr. Khorana. "If you get a knee or hip replacement, the clotting state lasts for a few weeks after surgery, and then it goes away. But in patients with advanced cancer, it's pretty clear based on this trial that the risk of getting a blood clot doesn't go away."

**Screen prior to cancer treatment**

Eighteen months ago, Dr. Khorana and colleagues began a study in which they created an electronic health record alert that identified high-risk VTE cancer patients based on their Khorana score (score of 3 or higher for this project). The alert also prompted physicians to screen those patients' lower extremities for blood clots before initiating cancer treatment.

The study had an initial silent phase — from August 2016 through January 2017 — that involved 194 patients. Fourteen (7.2 percent) developed subsequent deep vein thrombosis (DVT) or pulmonary embolism (PE) over 90-day follow-up, with a median of 27 days.

During the active phase — from June 2017 through December 2017 — an alert occurred when a physician opened a high-risk patient's electronic record and suggested a bilateral, lower-extremity screening ultrasound. It fired only once per provider for each patient, with the option to accept, to ignore or to repeat at a later time.

During this phase, 197 alerts met the inclusion criteria, and 40 patients (20.3 percent) received a screening ultrasound. Five (12.5 percent) had a DVT and were started on therapeutic anticoagulation. Of patients with alerts who had screening deferred, 13 (8.3 percent) were later diagnosed with DVT (median 50.5 days) and seven (4.5 percent) with PE.

"This prescreening for blood clots in high-risk cancer patients is something we're doing at Cleveland Clinic that's unique," Dr. Khorana says. "And we're seeing a lot of potential benefits for patients."


## Statistics Expert Leads National Clinical Trials Task Force for Seamless Trial Design

In addition to leading national clinical trials, Cleveland Clinic staff are leading the national conversation on clinical trial design. Recent innovations in clinical trials include statistical designs devised to consolidate traditional phases of oncologic drug development as well as facilitate inclusive eligibility and evaluations of multiple indications. These so-called seamless trial designs have many potential benefits but have not yet been objectively studied.

The National Cancer Institute (NCI) has recognized the need for more careful consideration of seamless trial design. A special working group was formed as a subcommittee of NCI's Clinical Trials Design Task Force with the goal of providing national consensus recommendations for first-in-human cancer drug trials. NCI selected Brian Hobbs, PhD, associate staff in Lerner Research Institute's Department of Quantitative Health Sciences, to lead the group. Dr. Hobbs is an expert in statistical methods for clinical trial design.

Dr. Hobbs and his group identified 1,786 first-in-human, early-phase trials conducted from 2010 to 2017. They selected high-impact studies playing an important role in oncologic drug development. They examined several factors in each study, including infrastructure, statistical design and inference, oversight, reporting, selection of dose and schedule, and late-stage toxicities. They also considered the design's potential impact on regulatory policy and drug developers if widely adopted for multiple-indication drug development strategies. Dr. Hobbs and his colleagues published their findings and recommendations in the *Journal of the National Cancer Institute*. They compare seamless versus conventional discrete-phase trials and provide recommendations for future study planning. "With targeted and immune-oncology agents demonstrating both successes and treatment benefit heterogeneity in early-phase trials, trialists require design methodology that is more appropriate for precision medicine contexts and better suited to overcoming assumptions that were established for the development of cytotoxic agents," Dr. Hobbs says. "Accelerating the pace of human experimental inquiry, however, elevates the need for oversight and sufficient scientific rigor to ensure that established standards are being followed."

The task force hopes that the published recommendations will help guide drug developers to plan ethical, scientifically sound trials that are better suited to elucidating heterogeneities in treatment benefit for targeted agents and immunotherapies across multiple treatment indications.

Dr. Hobbs is Section Head of Cancer Biostatistics in the Lerner Research Institute. He holds a joint appointment in Cleveland Clinic's Taussig Cancer Institute. He also serves as Co-Director of the Biostatistics and Bioinformatics Core for the Case Comprehensive Cancer Center. His methodological expertise comprises Bayesian inference, subtyping, prediction and trial design as well as cancer radiomics.

# **Molecular Profiling** Improves Progression-Free Survival in Patients with Pancreatic Cancer

## Know Your Tumor initiative matches treatments with patients

Next-generation sequencing (NGS) offers oncologists the ability to identify actionable targets and select appropriate therapies for some patients. Most patients with metastatic pancreatic ductal adenocarcinoma don't respond to standard-of-care therapies, so researchers turned to molecular profiling in an effort to optimize therapy by grouping these patients into therapeutically actionable subgroups. Results from this Know Your Tumor initiative, published in *Clinical Cancer Research*, demonstrate the feasibility and utility of a comprehensive precision medicine program to both discover actionable findings and improve progression-free survival (PFS) in patients who receive targeted therapy.

"One of the hallmarks of this program is that it was not limited to academic medical centers," says Davendra Sohal, MD, MPH, Director of Cleveland Clinic Cancer Center's Clinical Genomics Program. "This study tested the real-world relevance of this approach, to make it accessible to as many patients as possible."

### Targeted therapy increases survival

The Pancreatic Cancer Action Network's Know Your Tumor initiative, in partnership with Perthera Inc., included tumor samples from 640 patients from 287 academic and community practices in 44 states. A cloud-based tumor board reviewed the results of each patient's NGS and immunohistochemistry testing and found actionable targets in 50 percent (with 27 percent highly actionable) of patients tested. Commonly altered pathways discovered by testing included AKT/mTOR (19 percent), DNA repair (15 percent) and cell cycle (11 percent). Patients who received targeted therapy based on these results (N = 17) experienced significantly longer PFS, 4.1 months, than patients receiving unmatched therapy (N = 18, PFS 1.9 months; HR, 0.47; 95% CI, 0.24-0.94; $P_{adj} = 0.03$).

"These results, albeit not in a randomized trial, add to the growing evidence that treating patients with biomarker-matched agents increases survival when compared with historical data on standard therapies," says Dr. Sohal. "We also showed that it's possible to increase clinical trial enrollment in a population of patients that historically has enrolled at very low rates." Features of the program designed to engage patients more actively in their results contributed to a 21 percent enrollment rate in applicable clinical trials, versus a 5 percent average across all patients with metastatic pancreatic cancer.

### Challenges and future studies

Not all patients in the program chose the targeted treatments suggested in their individual reports. Overall, 63 percent of patients were still placed on standard-of-care regimens. "This could be due to issues with insurance coverage, access to clinical trial sites or reluctance from physicians to try regimens that, while not without evidence of benefit, are not as well-tested as standard therapies," says Dr. Sohal.

Efforts to inform patients and physicians about the potential benefits of molecular profiling continue, and the initiative continues to expand. "We know that pancreatic cancer should be treated based on an individual patient's tumor biology," says Dr. Sohal. "This initiative aims to make that possible."

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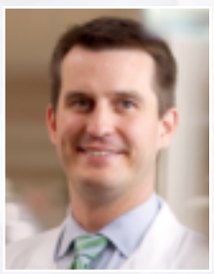
# **More Evidence that CAR T-Cell Therapy Works** for Many Patients with Large B-Cell Lymphoma



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The ZUMA-1 trial studied the use of axicabtagene ciloleucel (axi-cel, Yescarta®) as a CD19-targeted chimeric antigen receptor (CAR) T-cell therapy in relapsed and refractory aggressive B-cell lymphomas. It reported impressive results: an overall response rate (ORR) of 82 percent and a complete response (CR) rate of 58 percent.

Now investigators have longer-term follow-up data from high-risk patients involved in the ZUMA-1 trial as well as from real-world patients — many of whom would not have met the criteria to join the clinical trial — who received the drug after the FDA approved it in October 2017.

"With the relatively small number of patients who have been treated with CAR T-cell therapy, it's important to follow their long-term outcomes," says Brian T. Hill, MD, PhD, Director of the Lymphoid Malignancies Program at Cleveland Clinic Cancer Center.

"These studies report on those outcomes, give more detail on the response rates and the outcomes of patients with high-risk features to their lymphoma, and also document the real-world clinical experience of patients taking the drug after FDA approval."

Dr. Hill, who was an investigator with ZUMA-1, is a member of the consortium of investigators that presented data from both of these follow-up studies at the 2018 American Society of Hematology meeting.

### High-risk patients' equivalent response rate

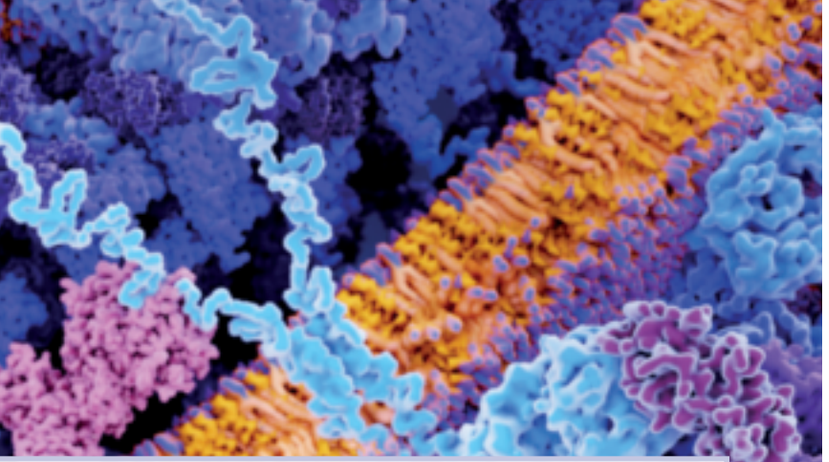
For the study examining ZUMA-1 patients with double-expresser B-cell lymphoma, the investigators found the CR rate was 53 percent (29/55) in patients with disease refractory to two or more consecutive prior lines of therapy and 72 percent (18/25) in patients who had relapsed within 12 months after autologous stem-cell transplantation.

They also assessed the genetics of the high-risk patients using 47 evaluable pretreatment tumor samples: 37 patients (79 percent) had high-grade B-cell lymphoma or double-expresser B-cell lymphoma and had an ORR of 89 percent (33/37), including a CR rate of 68 percent (25/37). Forty-two percent of patients overall had ongoing responses with a median follow-up of 15.4 months, including 49 percent (18/37) of patients with high-risk genetics.

"These data suggest that high-risk patients with large B-cell lymphomas seem to have equivalent response rates as other patients who are treated with CAR T-cell therapy," says Dr. Hill. "In addition, if these high-risk patients achieve a complete remission, they're likely to have durable remissions with the follow-up that's available."

### Detectable B cells

To investigate the relationship between B-cell recovery and ongoing response, the researchers assessed B-cell levels over time. Overall, of the 87 evaluable patients, 47 percent had no detectable B cells at baseline, and the remainder had levels close to or below the lower level of quantification of the assay. In patients with ongoing responses at 12 months post-treatment, 19 of the 35 (54 percent) patients with evaluable samples had detectable B cells.



"These data suggest that persistence of CAR T cells is not required in order for a patient to maintain their remission," says Dr. Hill. "In other words, the CAR T cells can get in, do their job, then get out, and the patient will remain in remission, as opposed to the CAR T cells having to stay in forever to eliminate any new cancer cells that may develop."

### Real-world patients also respond

The second study, a multicenter investigation that involved 163 patients, examined how well CAR T-cell therapy worked in regular patients after FDA approval in 2017.

"What was noteworthy about this study is these patients had more comorbidities, poorer performance status and other issues than the patients enrolled in ZUMA-1," says Dr. Hill. "In fact, about half would not have been eligible for that clinical trial."

Despite the differences in patient populations, he says, the real-world patients responded similarly to the drug as those in the trial, with an ORR of 79 percent and CR of 50 percent.

What's more, he says, the drug's toxicities, such as cytokine release syndrome and neurologic events, were not disproportionately higher for these patients as compared with the ZUMA-1 patients.

"I think these are potentially practice-informing preliminary data," he says, "in justifying the use of axi-cel in patients who are less fit than those originally studied."

# SAVE THE DATE

## CONTINUING MEDICAL EDUCATION

For a full list of CME events, please visit ccfcme.org.

**October 18-19, 2019**

**6th Annual Multidisciplinary Colorectal Oncology Course**
Naples Beach Hotel & Golf Club
Naples, FL

**November 13, 2019**

**Breast Cancer Update: From Detection Through Treatment to Survivorship**
Embassy Suites Hotel
Independence, OH

## SPEAKERS BUREAU

Cleveland Clinic Cancer Center Speakers Bureau offers presentations by leading experts on a full range of oncology topics. Educational sessions are available to physicians, nurses and other healthcare professionals. Experts in hematology, medical oncology, radiation oncology, blood and marrow transplant, palliative medicine, and translational hematology and oncology research are available. Recent topics have included management of late effects of cancer treatment, circulating tumor cells and renal cell carcinoma advancements. To customize a speaker's program for your organization's specific needs or to learn more, contact Sheryl Krall at kralls2@ccf.org or 216.444.7924.

# Hyperfractionated Radiotherapy, Intrabiliary Brachytherapy and Liver Transplant for **Localized Perihilar Cholangiocarcinoma**

Three-step treatment improves outcomes in difficult-to-treat liver cancer

Perihilar cholangiocarcinoma (PC) is a rare form of liver cancer that originates in the epithelial cells of the bile duct. It is associated with poor outcomes and a high morbidity rate because most patients present with advanced-stage disease. Treatment of PC is further complicated by involvement of both bile ducts, which makes the tumor unamenable to surgical resection. Outcomes of liver transplant alone are likewise poor unless the tumor is first treated properly. A multimodal approach of highly specialized radiation and chemotherapy followed by liver transplant can result in extremely promising outcomes in this difficult-to-manage disease.

Kevin Stephans, MD, Department of Radiation Oncology, shares his experiences with treating localized PC with a three-step approach that involves hyperfractionated radiotherapy, intrabiliary brachytherapy and liver transplant.

*Dr. Stephans is staff in the Department of Radiation Oncology and Associate Professor of Medicine at Cleveland Clinic Lerner College of Medicine.*

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## What is hyperfractionated radiotherapy, and why is it useful in the treatment of PC?

Hyperfractionated radiotherapy refers to the delivery of very small radiation treatments (1.5 Gy per fraction) in two separate daily doses. This approach allows the normal tissue that surrounds PC to heal after an initial radiation dose. We then deliver a second dose of radiation before the tumor has the opportunity to fully recover.

For distinction, a standard radiation dose is approximately 2 Gy per fraction. For liver metastases, intrahepatic cholangiocarcinoma or hepatocellular carcinoma that arises in the liver, we use hypofractionated radiation, which delivers focused, large doses of radiation (about 7 to 15 Gy per fraction) to the tumor. But for pretransplant patients with cholangiocarcinoma that affects both bile ducts, this is not an option because high doses of radiation would likely cause damage or scarring of the bile ducts and other adjacent sensitive tissue. Hyperfractionated radiation allows an aggressive dose to be delivered to the tumor while remaining gentle to the surrounding normal tissue.

*A multimodal approach of highly specialized radiation and chemotherapy followed by liver transplant can result in extremely promising outcomes in this difficult-to-manage disease.*

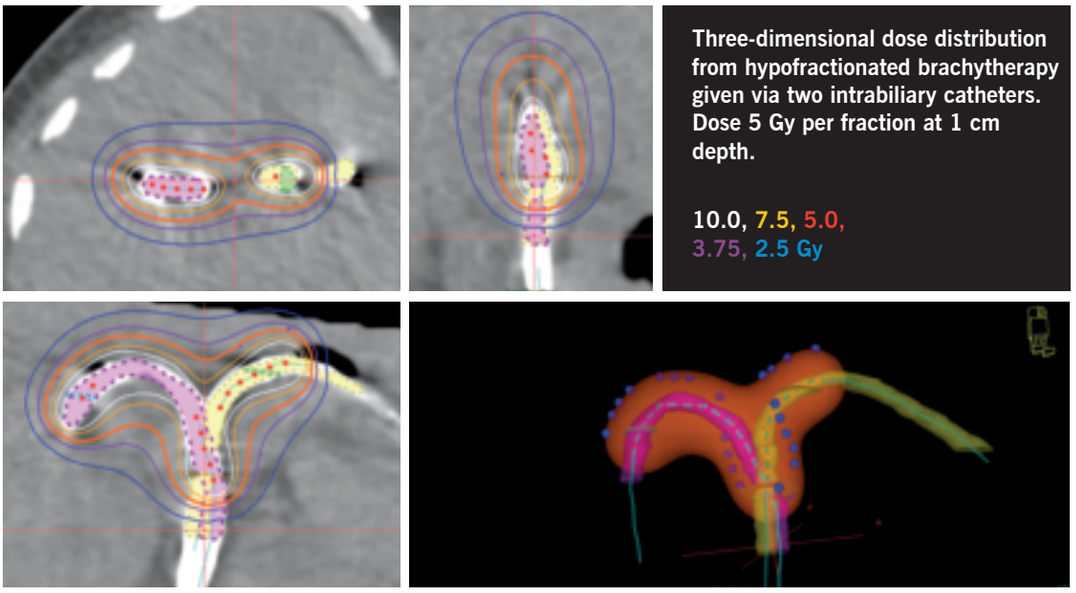
## How is hyperfractionated radiotherapy delivered?

We typically use intensity-modulated radiation therapy (IMRT) as the delivery method because it allows us to focus the radiation beam on the tumor and reduce the intensity of radiation to the surrounding healthy tissues. IMRT also delivers radiation at the most geometrically and anatomically favorable angles. The use of multiple beams creates a stronger focal point of radiation, sparing the surrounding normal tissues.

## What are some of the advantages of hyperfractionated radiotherapy compared with other radiation treatment modalities?

In clinical trials conducted in patients with small cell lung cancer, twice-per-day hyperfractionated radiotherapy resulted in better short-term tumor control and less long-term side effects due to dose splitting. Side effects typically associated with standard radiotherapy of the liver include fatigue, nausea, vomiting and appetite suppression. However, in our clinical experience with hyperfractionated radiotherapy to date, we found it to be exceptionally tolerable. The patients typically report minimal side effects during the first few days of treatment, and often even continue to work throughout its duration, which is truly amazing.

Furthermore, our patient outcomes have shown that, when combined with intrabiliary brachytherapy, radiation is able to completely ablate the cholangiocarcinoma about 70 to 80 percent of the time, leaving no residual tumor in most patients. However, a liver transplant is still required after radiotherapy because radiation can cause stricture of the bile ducts over the long term.



**Three-dimensional dose distribution from hypofractionated brachytherapy given via two intrabiliary catheters. Dose 5 Gy per fraction at 1 cm depth.**

**10.0, 7.5, 5.0, 3.75, 2.5 Gy**

## Can you outline the steps involved in treating PC?

Perihilar cholangiocarcinoma treatment is a three-step process. External hyperfractionated radiotherapy is delivered twice per day, Monday through Friday, for three weeks. Approximately one week after completing external radiation, the patients are admitted for three days and given high-dose brachytherapy, which is delivered internally from within the bile ducts.

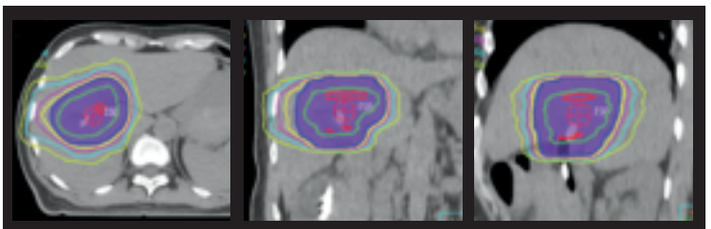
In this step, one access catheter is placed in the right bile duct and another in the left bile duct, and a source of radiation is placed inside both catheters. The source delivers radiation at 10 to 15 different positions inside the tumor, and the tumor ultimately receives a very large cumulative dose of radiation.

With the initial 30 external treatments, we are treating the edges of the tumor and the surrounding lymph nodes, while the final three high-precision, high-dose treatments are delivered to the tumor internally.

Throughout the three-week external radiation treatment, the patients are given radiation-sensitizing chemotherapy. Chemotherapy is not given during brachytherapy but is then reintroduced while the patient awaits liver transplant, which is the final treatment step.

## Is hyperfractionated radiotherapy currently incorporated in the standard of care for localized cholangiocarcinoma?

Given the rarity of PC, the standard of care is always evolving; however, this approach of hyperfractionated radiation, intrabiliary brachytherapy and liver transplant is associated with excellent survival and is the preferred approach for patients with PC who are candidates for aggressive treatment.



**Three-dimensional dose distribution from hyperfractionated image-guided external beam radiotherapy. Dose is 45 Gy in 30 fractions of 1.5 Gy given twice daily, planned hot spot to > 50 Gy in center of tumor.**

**52.50, 50.0, 45.0, 40.0, 35.0, 30.0, 25.0 Gy**

Although this question is difficult to answer, what we can say from our clinical experience at Cleveland Clinic is that hyperfractionated radiotherapy, combined with brachytherapy and liver transplant, results in improved survival and outcomes for patients with PC.

## How do you ensure the best possible outcomes with this approach?

This multidisciplinary approach requires coordination between five medical teams including hepatobiliary surgery, hepatology, medical oncology, radiation oncology and interventional radiology, and can best be delivered in a large medical center. Given the high degree of coordination of specialized care that is required, referring patients to a high-volume transplant center that has experience with all aspects of care for PC is the best option.

# Taking on Glioblastoma Through Translational Research

**By Manmeet S. Ahluwalia, MD**

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Glioblastoma (GBM), the most common and lethal primary malignant brain tumor, still has limited effective treatment options. Current standard therapies — including surgery, radiation and conventional chemotherapies — have not been able to extend survival much beyond 15 to 18 months.

Physicians and basic scientists from Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center and Lerner Research Institute are closely collaborating on efforts across multiple fronts to find a breakthrough to combat this daunting disease. Their multidisciplinary partnership has contributed to Cleveland Clinic's status as home to one of the largest and most active brain tumor clinical trial programs in the U.S. (Figure).

Our institution's large, international patient population and deep, broad scientific and clinical resources promote the rapid translation of promising basic research findings to clinical trials. Below are four representative examples of ongoing GBM clinical trials that stem from translational research projects and highlight the bench-to-bedside efforts of our multidisciplinary teams.

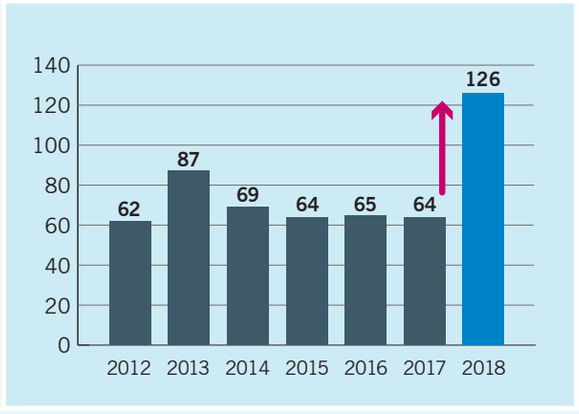


**Figure. Cleveland Clinic's brain tumor clinical trials program is one of the nation's largest, with expected enrollment of 126 patients in 2018.**

## 1. Combating tumor-mediated immunosuppression

GBM confounds conventional therapies by suppressing the host immune system and bouncing back from the guns fired at it. Medical oncologist David Peereboom, MD, and stem cell biologist Justin Lathia, PhD, both with the Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, are leading efforts to understand the mechanism of immunosuppression and develop innovative therapies to address it. Rather than targeting tumor cells — the usual focus of GBM therapeutics — their strategy is to reverse the immunosuppressed microenvironment of GBM to reduce tumor growth.

Their research is focused on human myeloid-derived suppressor cells (MDSCs), which have potent immunosuppressive qualities. The work is built on our findings that MDSCs are elevated in the blood of patients with GBM and also present close to self-renewing cancer stem cells in the tumors themselves. It is believed that the tumor secretes factors that promote migration of host MDSCs to the brain, where they are activated by cancer stem cells, resulting in blocking of beneficial host antitumor immune responses. The result: promotion of GBM growth and metastasis.

Enter capecitabine — an oral analogue of 5-fluorouracil (5-FU) — which is cytotoxic to MDSCs. Currently used to treat colorectal cancer, metastatic breast cancer and (off-label) several other cancers, capecitabine offers a possible novel approach to treating GBM.

In the current phase 0/1 clinical trial for which Dr. Peereboom is principal investigator, patients with recurrent GBM and planned tumor resection are treated with a seven-day cycle of capecitabine, then surgery, then capecitabine again, combined with bevacizumab. Bevacizumab is a standard therapy for GBM; although it blocks angiogenesis and slows tumor growth, it does not extend survival.

This proof-of-concept study will help determine whether MDSC suppression is feasible by evaluating the change in concentration of circulating MDSCs following treatment. The concentration of MDSCs in the resected

# Four promising bench-to-bedside initiatives

tumor and blood will also be evaluated, as will the concentration of T-regulatory cells, using new technology such as mass cytometry time of flight, which allows simultaneous assessment of more than 30 parameters. This approach, just reported in a large-scale analysis of brain tumor patients, will allow the team to further pinpoint key changes in the immune system associated with favorable response.[1] Progression-free survival and adverse effects will be assessed as well.

Dr. Peereboom presented preliminary results of this trial at the Society for NeuroOncology's annual meeting in November 2018. Early evidence is encouraging, and his team expects to further advance this strategy.

### 2. Inactivating glioma stem cells — a key to resistance

Ibrutinib, a small-molecule compound recently approved by the FDA to treat various forms of lymphoma and leukemia, is being evaluated by Shideng Bao, PhD, Department of Stem Cell Biology and Regenerative Medicine, in a phase 1 study for its application to GBM.

A major challenge in GBM treatment has been the inability to effectively target the glioma stem cell (GSC) population that gives rise to tumor recurrence. Earlier work by Dr. Bao's group found that GSCs have high levels of BMX (bone marrow and X-linked nonreceptor tyrosine kinase). BMX activates signal transducers and promoters of transcription 3 (STAT3), which resist radiation therapy and enable GSCs to replicate, spread and promote tumor growth. Ibrutinib specifically disrupts the BMX-mediated STAT3 activity.[2]

In a preclinical mouse model of GBM and cultured human GBM cells, Dr. Bao's team found that ibrutinib suppressed GSC-driven tumor growth and potently induced GSC death. It was significantly more effective in slowing tumor growth than temozolomide, the current standard-of-care chemotherapy for GBM. Average survival increased significantly in preclinical models. His team's work has also demonstrated that ibrutinib has excellent blood-brain barrier penetration.

The current phase 1 clinical trial is testing various ibrutinib dosages for safety and efficacy in patients with newly diagnosed methylated or unmethylated MGMT GBM. The study is combining ibrutinib with radiation in the patients with unmethylated MGMT promoter. Patients with methylated MGMT GBM will have temozolomide added to their treatment regimen.

Patient accrual is ongoing and expected to be completed in the summer of 2019.

### 3. Interfering with the JAK-STAT signaling pathway

Another investigation targeting GSCs uses ruxolitinib, a drug currently used to treat myelofibrosis and polycythemia vera. A Janus kinase (JAK) inhibitor (specifically of JAK1 and JAK2), ruxolitinib targets the JAK-STAT pathway, which has been implicated in GBM as a promoter of tumor cell survival, growth and invasion. Levels of JAK 1/2 and STAT3 are increased in GBM tissues.

Our group and others have found that inhibiting JAK2 reduces survival and proliferation of glioma cells in vitro and that JAK2/STAT3 inhibition slows disease progression in animal models of GBM. We have since initiated a phase 1 trial testing efficacy, safety and tolerability of ruxolitinib combined with radiation and temozolomide for newly diagnosed grade 3 gliomas and GBM. The study's combination of ruxolitinib and radiation is anticipated to facilitate breakdown of the blood-brain barrier and delivery of ruxolitinib to the tumor in the unmethylated MGMT promoter arm. Patients with methylated MGMT promoter will receive various doses of ruxolitinib, temozolomide and radiation.

### 4. Enhancing immune response with laser thermal therapy

Delivering hyperthermia shortly before radiation therapy is likely to sensitize cancer stem cells to radiation. That's the premise of an ongoing phase 0 clinical trial being led by Jennifer Yu, MD, PhD, of Cleveland Clinic's Department of Radiation Oncology and Department of Stem Cell Biology and Regenerative Medicine.

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The study builds on a publication by Dr. Yu's team showing that hyperthermia sensitizes glioma stem-like cells to radiation by inhibiting AKT signaling in a preclinical orthotopic model of human GBM.[3] The team then confirmed these findings in a mouse model of GBM, showing that animals that received both hyperthermia and radiation survived longer than those receiving radiation alone.

The present phase 0 trial is evaluating the effect of shortening the time between laser interstitial thermal therapy (LITT) and subsequent adjuvant chemotherapy and radiation in patients with GBM. The hope is that a shortened interval will allow radiation oncologists to take advantage of the biological properties of LITT, such as sensitizing cancer stem cells to radiation, priming the immune system and opening up the blood-brain barrier.

### New strategies offer new hope

These four innovative translational studies are the direct result of basic research that yielded greater understanding of cellular mechanisms of GBM. Our hope is that targeted cellular and immunotherapy approaches will soon make headway against this disease that has so far confounded conventional therapeutic approaches.

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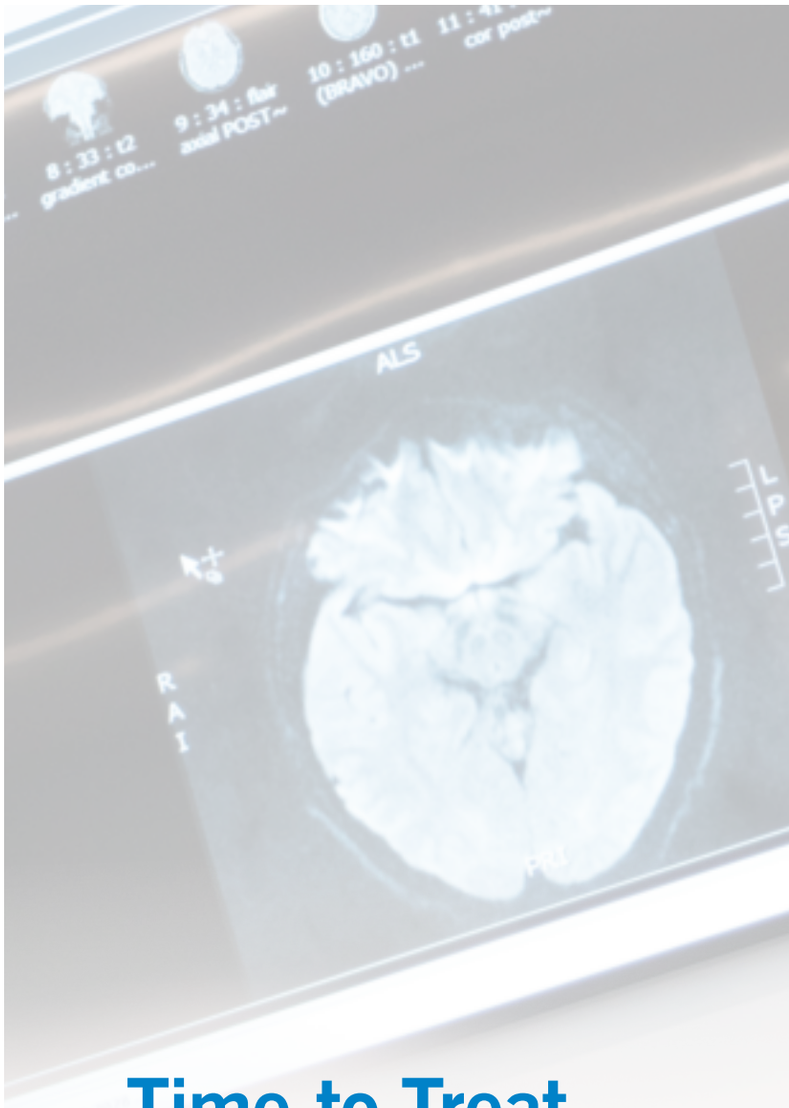


# Time-to-Treat, Two Years Later

**By Brian J. Bolwell, MD, FACP**

Two years ago, *Cancer Advances* featured an interview with me in which I discussed our efforts in reducing the time patients with cancer wait from diagnosis to treatment. I was pretty proud of the progress we'd made in 2017, but as I wrote then, "The work isn't done."

We haven't slowed down our efforts; at that time, we were only beginning to understand the significance of time-to-treat (TTT) on patient outcomes. We were just beginning to see the benefits of our programs. Much has changed in two years.

What hasn't changed is our core belief that reducing delays in TTT is the right thing to do. Cancer is associated with more fear than any other diagnosis, and that fear gets magnified the longer a patient and their family wait to begin treatment. We now have even more evidence that prolonged TTT may be associated with


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deleterious outcomes in certain cancers, including our most recent publication in *PLoS One* showing that the absolute risk of mortality increases weekly for cancers like early-stage breast, lung, renal and pancreatic cancers.

And despite our significant progress, we still consider TTT a top priority for our cancer center. 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. Time-to-treat is now simply part of our patient-oriented culture, and it's embedded into our cancer programming model that brings together clinicians by disease, not by department.

What has changed — and changed significantly — is our patients' time-to-treatment. In 2017, we were proud to share that we'd cut about 10 days from our initial TTT average of 39 days. In a recent article in *NEJM Catalyst,* we reported a 33 percent reduction since the program began.

I wrote in 2017 that our challenge wasn't achieving the result, but maintaining it. It's been two more years of hard work, but we've maintained our focus, which has resulted in this additional decrease in TTT.

We've also continued to eliminate outliers. When we started the process, about 30 percent of our patients had a TTT of more than 45 days, which is way too long. We want that number to be zero. We've reduced the proportion of all outliers from 30 to 14 percent, a 53 percent drop.

Another area of focus is patients who come to us from other institutions. We've done quite well reducing TTT for patients from within our own system, but sometimes weeks have gone by since a patient's diagnosis before we are even notified that they need us. So one of our next big goals is to enhance our education to referring physicians, to emphasize the importance of getting their patients to us quickly, and to have the tools in place to see them right away.

The most significant change in the past two years has been in the national conversation on this issue. TTT is not a Cleveland Clinic issue; it's a healthcare issue, and that's becoming clear as we publish more data and show the benefits of getting cancer patients in faster. In fact, some national organizations are incorporating TTT as one of their quality metrics. That kind of widespread cultural change is something we couldn't have achieved two years ago.

Finally, I don't believe the only way to go from here is down in terms of number of days from diagnosis to treatment. We can't just go on autopilot now that we've identified and addressed all the hurdles. The initial part of this process can be especially difficult, particularly in academic cancer centers, but this isn't a problem that will go away anytime soon, as healthcare systems trend toward complexity and fragmentation. We'll always need to pay close attention to TTT. It's part of our culture, and it's the right thing to do for our patients.

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# **Hyperthermic Intraperitoneal Chemotherapy** in Newly Diagnosed Advanced Ovarian Cancer

HIPEC extends overall survival by approximately 12 months

**By Robert DeBernardo, MD**

*Dr. DeBernardo leads the Ob/Gyn & Women's Health Institute's HIPEC program and is Director of Minimally Invasive Surgery for the institute. He is Associate Professor of Surgery at Cleveland Clinic Lerner College of Medicine.*

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Although rare, ovarian cancer remains one of the leading causes of cancer-related death in the United States. The American Cancer Society anticipated that in 2018 more than 22,000 women would be diagnosed and 14,000 would die from ovarian cancer. Despite recent advances in medical and surgical techniques used to treat ovarian cancer, mortality remains high because the majority of women are identified at an advanced stage.

Because of ongoing treatment challenges, we are particularly encouraged by a recent trial that demonstrates extended overall survival for patients with newly diagnosed advanced ovarian cancer with the use of hyperthermic intraperitoneal chemotherapy (HIPEC).

### Current treatment

Ideal treatment for advanced ovarian cancer includes complete or optimal cytoreductive surgery and platinum/taxane-based chemotherapy. Progression-free survival (PFS) and overall survival (OS) are directly linked to the amount of residual disease following surgery, with optimal surgery defined as < 1 cm residual tumor. Outcomes improve when patients have no gross residual disease following surgery.

There has been and continues to be a debate in gynecologic oncology regarding surgical timing — whether it should take place at presentation or after three cycles of neoadjuvant chemotherapy.

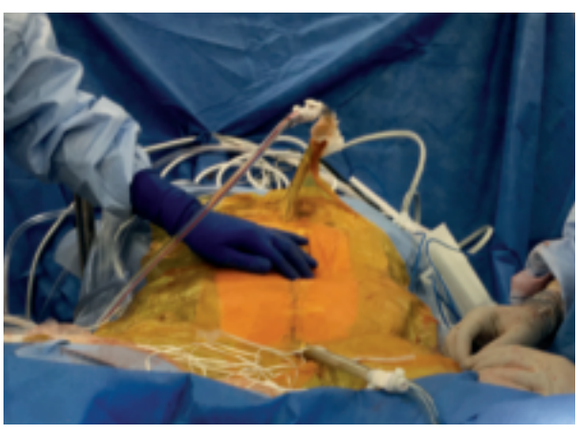

**Figure. HIPEC perfusion:** Following surgical removal of all gross cancer, tubing is placed in the abdomen and the patient is closed. An assistant at the bedside gently shakes the abdomen, and the heated chemotherapy circulates for the prescribed time period.

A randomized trial conducted in Europe showed that cancer-related outcomes were equivalent.[1] However, surgical morbidity was substantially higher in women undergoing upfront surgery. The trial has been criticized for a number of reasons, leaving many experts still favoring upfront surgery. Nonetheless, we are seeing an increase in the use of neoadjuvant chemotherapy.

### HIPEC at time of surgery

Using HIPEC to treat ovarian cancer has been explored at a number of centers around the world. Initially developed to treat rare chemoresistant gastrointestinal malignancies, HIPEC takes place at the time of surgery, once resection is complete. Tubing is placed in the abdomen, and chemotherapy is circulated at 42°C (Figure). After 45 to 90 minutes, the tubing is removed and the incision closed.

### What the data show for newly diagnosed cancer

Much retrospective data, and more recently randomized data, suggest there is a benefit in using HIPEC to treat women with recurrent ovarian cancer. A group from the Netherlands reported on a phase 3 randomized trial in which women with newly diagnosed stage III ovarian cancer received HIPEC at interval surgery following neoadjuvant chemotherapy.[2]

Their results demonstrate a significant advantage for women receiving HIPEC, with a hazard ratio of recurrence or death of 0.66 ($P = 0.003$), PFS of 10.7 versus 14.2 months, and OS of 33.9 versus 45.7 months. Adverse events in the two groups were equivalent.

These data are significant because this is the first time since Gynecologic Oncology Group (GOG)-172, a randomized trial showing the benefit of intraperitoneal chemotherapy over conventional intravenous chemotherapy, that both PFS and OS were improved in women with newly diagnosed ovarian cancer.

### HIPEC now on the rise

We are witnessing a number of HIPEC programs opening across the country. Our hope is that these programs offer the clinical expertise required to successfully perform cytoreductive surgery and safely administer HIPEC.

HIPEC is only effective in patients who have minimal or no residual disease after surgery. The radical surgery necessary to achieve these results is generally more successful at high-volume centers with a well-established program and proven track record.

### Cleveland Clinic experience

The Cleveland Clinic Ob/Gyn & Women's Health Institute team managed 144 ovarian cancer surgical cases in 2017, with outcomes better than the national average. In addition, we have offered HIPEC for four years to selected women with advanced and recurrent ovarian cancer. With well over 100 patients treated, ours is one of the largest programs in the country. We have recently seen a surge in referrals specifically for HIPEC as a result of these new and promising data.

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## Sarcoma Fusion Next Generation Sequencing Assay Available

Benign and malignant mesenchymal tumors (sarcomas and their mimics) are difficult to diagnose, with many that differ in their clinical behavior and response to therapy. Many of these tumors harbor gene fusions that are crucial to establishing a definitive diagnosis.

The Sarcoma Fusion next generation sequencing (NGS) panel is a custom-designed, 34-gene panel, high-complexity, laboratory-developed test (LDT) designed for targeted sequencing of benign and malignant soft tissue neoplasms. This assay identifies fusion transcripts in targeted regions of RNA from total nucleic acid (TNA) isolated from FFPE tissue specimens.

The test will identify the vast majority of known fusions in benign and malignant mesenchymal tumors but also has the ability to identify a limitless number of as-yet-undiscovered gene fusions. This is because the technology only "primes" from one partner of the gene fusion, allowing for discovery of new gene fusion partners.

The assay is part of the CC-SIGN initiative (Sequencing, Informatics and GeNomics) of the Molecular Pathology Section within the Robert J. Tomsich Pathology & Laboratory Medicine Institute, led by Daniel Farkas, PhD, HCLD, Section Head of Molecular Pathology. "CC-SIGN will take molecular diagnostics at Cleveland Clinic to new heights by adding important precision medicine tests to help our patients," says Dr. Farkas. "It will also modernize how we manage genomic information." For more information, contact molecularpathology@ccf.org.

## FDA Recognizes *PTEN* Variant Criteria

For the first time, the FDA has formally recognized the process that led to curation of a public database containing information about genes, gene variants and their relationship to disease as a source of valid scientific evidence that can be used to support clinical validity in pre-market submissions. Among the gene variants listed in this database are variants of *PTEN*, a highly penetrant cancer susceptibility gene.

Known as ClinVar, the NIH-funded database was curated by teams of more than 700 genetics experts who make up the Clinical Genome Resource (ClinGen) consortium. The ClinGen consortium's work encourages sharing expertly curated and interpreted data on genetic variants, permitting developers to point to the genetic information available in the database to support the clinical validity of their tests rather than gathering their own data, thus saving time and money.

Prior to this advancement, data about genetic variants were not always accessible, or were widely accessible but without uniform curation. Genetic database information can be useful to researchers and developers, reducing regulatory hurdles in test development and spurring advancements in precision medicine. ClinVar differs from other databases because it is curated by experts from multiple institutions using systematic review procedures and is open to the public, and the FDA considers it a source of scientific evidence. This curation process is the first that is FDA approved.

### Developing *PTEN*-specific criteria for the ClinVar database

A ClinGen *PTEN* Expert Panel was formed in order to develop specifications meeting the Sequence Variant Interpretations Guidelines set forth in 2015 by the American College of Medical Genetics and the Association for Molecular Pathology for *PTEN* variants. Charis Eng, MD, PhD, founding Chair of Cleveland Clinic's Genomic Medicine Institute and Professor of Molecular Medicine at Cleveland Clinic Lerner College of Medicine, co-chaired the panel.

In a recent article in *Human Mutation*, the ClinGen *PTEN* Expert Panel described the finalized criteria for *PTEN*-specific variant classification and the outcomes of applying the criteria to a pilot group of 42 variants with benign/likely benign (BEN/LBEN), pathogenic/likely pathogenic (PATH/LPATH), uncertain significance (VUS) and conflicting (CONF) ClinGen assertions. Applying the *PTEN* Expert Panel criteria to the BEN/LBEN and PATH/LPATH variants led to an overall concordance of 96.8 percent. When applying these rules to six VUS and two CONF variants, with some additional data from a shared internal library, one VUS was reclassified as LBEN and two CONF variants were reclassified as PATH and LPATH.

One of *PTEN*'s roles in the body is as a tumor suppressor gene. Receiving a result of VUS or CONF can present clinical challenges, as genetic findings are often used in surgical decision-making and to determine a patient's cancer surveillance protocol.

"FDA recognition of the *PTEN* Expert Panel's assertions means that cancers may be found earlier, and perhaps even prevented, in some patients," says Dr. Eng.

## New Multi-Institution Lobular Breast Cancer Registry Will Shed Light on Rare Disease

Lobular breast cancer is the second most common type of breast cancer from a histological perspective, but it represents only about 10 to 15 percent of breast cancer cases. Because it is so rare, oncologists have tended to view lobular breast cancer and treat it in the same way as they do the more common ductal breast cancer.

But as more research is performed on lobular cancers, investigators are starting to recognize that it has some distinct features from ductal cancer, especially with respect to how it metastasizes and its decreased sensitivity to chemotherapy.

With this in mind, scientists from Cleveland Clinic, University of Pittsburgh Medical Center, The Ohio State University and University Hospitals Cleveland Medical Center are creating a lobular breast cancer registry that will include cases from 1990 to the present.

"Many of us in the community feel like these cancers need some special attention," says Megan Kruse, MD, Hematology and Medical Oncology, Cleveland Clinic. "That maybe it's not best that we treat lobular breast cancer the same as ductal breast cancer. But the challenge in doing so is that lobular breast cancer cases are pretty rare, and so in order to get a comprehensive look at its characteristics and treatment patterns, you really have to do it across multiple institutions."

### CDK4/6 inhibitors and genetic changes

In addition to the new registry, Dr. Kruse says she plans to soon start a genomics project around CDK4/6 inhibitors, a relatively new class of breast cancer drug, to see how the medication affects the DNA of both metastatic lobular breast cancer and metastatic ductal breast cancer.

"There is not that much information out there about what types of patients have the best response to these medications," she says, "and how treatment with CDK4/6 inhibitors may alter genetic expressions in the cancer after treatment.

"So we'll be looking to answer several questions: Can we identify any genomic predictors of which patients will respond best to therapy? How do we characterize the genomic changes we see after treatment? And will that give us an idea of how the cancers become resistant to treatment?"

Dr. Kruse said she and other researchers at Cleveland Clinic are already gathering data on their lobular breast cancer patients for the registry — which she expects to contain data on 4,000 to 5,000 patients once it's finished.

"The registry will allow us to look in the aggregate at the characteristics of lobular breast cancer, like size and hormone sensitivity," she says. "It will also show us the type of treatments patients received: who got chemotherapy, who didn't and how they responded. Finally, we'll also look at the genomics of these breast cancer cases to see whether there's a difference between what we expect and what we find."

## New Grant Boosts Hereditary Breast and Ovarian Cancer Research

Zihua Gong, MD, PhD, was recently awarded a new grant from the National Cancer Institute to continue his research related to *BRCA1*- and *BRCA2*-associated breast and ovarian cancers.

PARP inhibitors (PARPi) induce cell death in *BRCA1*- and *BRCA2*-deficient cancer cells through a phenomenon called synthetic lethality. Unfortunately, PARPi have only about a 40 percent response rate in *BRCA*-mutated breast and ovarian cancers. With his new, five-year, $1.8 million award, Dr. Gong hopes to improve PARPi therapy by better understanding the mechanisms of resistance.

In papers published in *Nature Communications* (2018) and the *Journal of Biological Chemistry* (2017), Dr. Gong and his collaborators identified a previously unrecognized DNA repair pathway that confers PARPi resistance. They showed that the protein 53BP1 (P53-binding protein 1) together with another protein called TIRR (Tudor-interacting repair regulator) mediates cancer cells' PARPi sensitivity. TIRR regulates the expression of and binds with a specific region of 53BP1 to form a protein complex. Both proteins are crucial for the stability of the complex. Without one or the other, therapeutic resistance in *BRCA*-mutated breast and ovarian cancer cells may result.

Dr. Gong and his team will further investigate the TIRR-53BP1 pathway, looking specifically at how these proteins are up- and downregulated. Proteins that inhibit or turn off TIRR and/or 53BP1 may be targets for future therapy.

Dr. Gong's research is also funded by the Ovarian Cancer Research Alliance. He was recently awarded a renewal of his Liz Tilberis Early Career Award, which he originally received in 2016. The grant renewal will allow Dr. Gong to further define DNA mismatch repair deficiency, which is the most common cause of hereditary ovarian cancer after *BRCA1* and *BRCA2* mutations.


# VeloSano Goes **100% to the Cure**

In its five-year history, VeloSano has raised over $17 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 10 to more than 200 miles over two days. One hundred percent of the funds collected are applied to cancer research projects across Cleveland Clinic health system.

The inaugural VeloSano ride in 2014 raised nearly $2 million, with another $3 million in 2015. VeloSano 2016 raised $3.37 million, and VeloSano 4 in 2017 raised $4.17 million. VeloSano 5 weekend was held July 20-22, 2018, and raised over $4.5 million. VeloSano Kids was introduced in 2018 and specifically raises funds to support pediatric cancer research. Funds are also allocated to selected projects at Case Comprehensive Cancer Center.

Beyond the $17 million allocated by VeloSano, over $14.4 million in additional, external grants has been received due to the promise shown by VeloSano-funded projects.

**Proceeds from the event are distributed primarily in two ways:**

**VeloSano Pilot Awards** provide seed funding for cancer research activities across the Cleveland Clinic enterprise. 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 and transition recent advancements in cancer genetics, epigenetics, and basic and translational tumor immunology.

**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.

**Nineteen Pilot Awards and nine Impact Awards were allocated using 2018 VeloSano funds:**

**Pilot Awards**

Extracellular noncoding RNA biomarkers in glioblastoma **Manmeet Ahluwalia, MD**

Translational investigation into the cellular mechanisms of hyperthermic intraperitoneal chemotherapy (HIPEC) in advanced ovarian cancer **Robert DeBernardo, MD**

Interplay and perturbations of the microbiome and host immune system in breast cancer **Charis Eng, MD, PhD**

Molecular mechanisms of platinum resistance in MMR-mutant ovarian cancer **Zihua Gong, MD**

Leukemogenic actions of mutated *NPM1* and *FLT3* and their reversal **Xiaorong Gu, PhD**

Novel cellular immunotherapeutics against T-cell lymphomas **Neetu Gupta, PhD**

Targeting AR-dependent prostate cancer cell division using clinically tested small kinase inhibitors **Hannelore Heemers, PhD**

New ATRA-based therapeutic strategy for acute myelogenous leukemia **Babal Jha, PhD**

Photoacoustic immunotherapy of glioblastoma **Vijay Krishna, PhD**

A randomized, double-blind, placebo-controlled trial to investigate the effect of a perioperative analgesia protocol on opioid usage and postsurgical pain in patients undergoing major head and neck cancer surgery requiring microvascular free-flap reconstruction **Jamie Ku, MD**

Development of a cancer stem cell-specific targeting strategy for triple-negative breast cancer **Justin Lathia, PhD**

Neoadjuvant immunotherapy in rectal cancer: a pilot study examining the safety and feasibility of PD-1 blockade in the treatment of rectal cancer **David Liska, MD**

Single-cell sequencing to identify mechanisms and biomarkers of cancer-associated thrombosis **Keith McCrae, MD**

Gut microbiome modulation of platinum chemotherapy response and efficacy in ovarian cancer **Chad Michener, MD**

Understanding the mechanisms of resistance to azacitidine in myelodysplastic syndromes using multiplex CRISPR/Case9-based genome editing **Aziz Nazha, MD**

Development of ILK-targeted therapy to treat triple-negative breast cancer **Jun Qin, PhD**

Breath, blood and saliva: noninvasive metabolite-based detection of hepatocellular carcinoma **Daniel Rotroff, PhD**

Noncytotoxic, p53/p16-independent treatment for metastatic pancreatic adenocarcinoma **Davendra Sohal, MD**

A design-of-experiment approach toward novel therapeutics targeting renal cell carcinoma **Oliver Wessely, PhD**

**Impact Awards**

*New recipients:*

Joshua Arbesman, MD
Aaron Gerds, MD
Sudipto Mukherjee, MD, PhD
Jennifer Yu, MD, PhD

*Ongoing awards:*

Mohamed Abazeed, MD, PhD
Manmeet Ahluwalia, MD
Seth Corey, MD, MPH
Brian Hill, MD, PhD
Yogen Saunthararajah, MD

# **New** Staff

**Bhukima Patel, MD**, is a new staff member in Cleveland Clinic's Department of Hematology and Medical Oncology. Before joining the staff, Dr. Patel was a fellow in Cleveland Clinic's Hematology and Medical Oncology fellowship program. She is part of the Leukemia Program.

## **Search** Our Cancer Clinical Trials Database

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Cleveland Clinic Cancer Center provides complete cancer care enhanced by innovative basic, genetic and translational research. It offers the most effective techniques to achieve long-term survival and improve patients' quality of life.

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 Cleveland Clinic Florida. Cleveland Clinic is a nonprofit academic medical center ranked as a top 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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