Cleveland Clinic

Cancer Consult

Taussig Cancer Institute | Summer 2015

Breast Cancer Research Update:

Targeted Therapy, Fertility Preservation, Chemotherapy Timing, Intraoperative Radiation Therapy

Also Inside:

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ON THE COVER: A Cleveland Clinic team prepares to deliver intraoperative radiation therapy during breast conservation surgery.

Dear Colleagues,

Welcome to the latest issue of *Cancer Consult*.

Treatment value rather than patient volume is now the driving force in American healthcare. At Cleveland Clinic, we are initially focusing on two areas where we believe value-based medicine will have the greatest impact on lowering costs and improving quality: population health management and cancer care coordination.

Coordinated, value-based cancer care depends on rigorously analyzing what treatments work best and adopting those as the standard of care. As you will read in my question-and-answer session on P. 16, we are leading an unprecedented project during the next two years to develop and deploy 100 cancer care paths — evidence-based algorithms that guide the most effective and economical treatment for our cancer patients in a wide variety of clinical situations.

Value-based cancer care also depends on cutting-edge research; multidisciplinary teams for expert, streamlined treatment; and strong patient support services. Our Comprehensive Breast Cancer Program is at the forefront of those areas, as evidenced by articles in this issue highlighting the results of four significant breast cancer research projects and the launch of our Young Women's Breast Cancer Clinic.

Cancer Consult also recounts encouraging developments from Cleveland Clinic research in genetically targeted lung cancer therapies; noncytotoxic differentiation treatment for disseminated cancers; and the first-ever validation of regression scores as a prognostic tool for rectal cancers.

I welcome the opportunity to collaborate, to discuss new ideas and to answer your questions. If we can help you with a patient's care or a clinical issue, please let me know. Our Cancer Answer Line staff at 866.223.8100 is ready to assist with appointment referrals and other information.

Sincerely,

Brian J. Bolwell, MD, FACP
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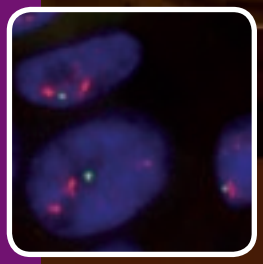
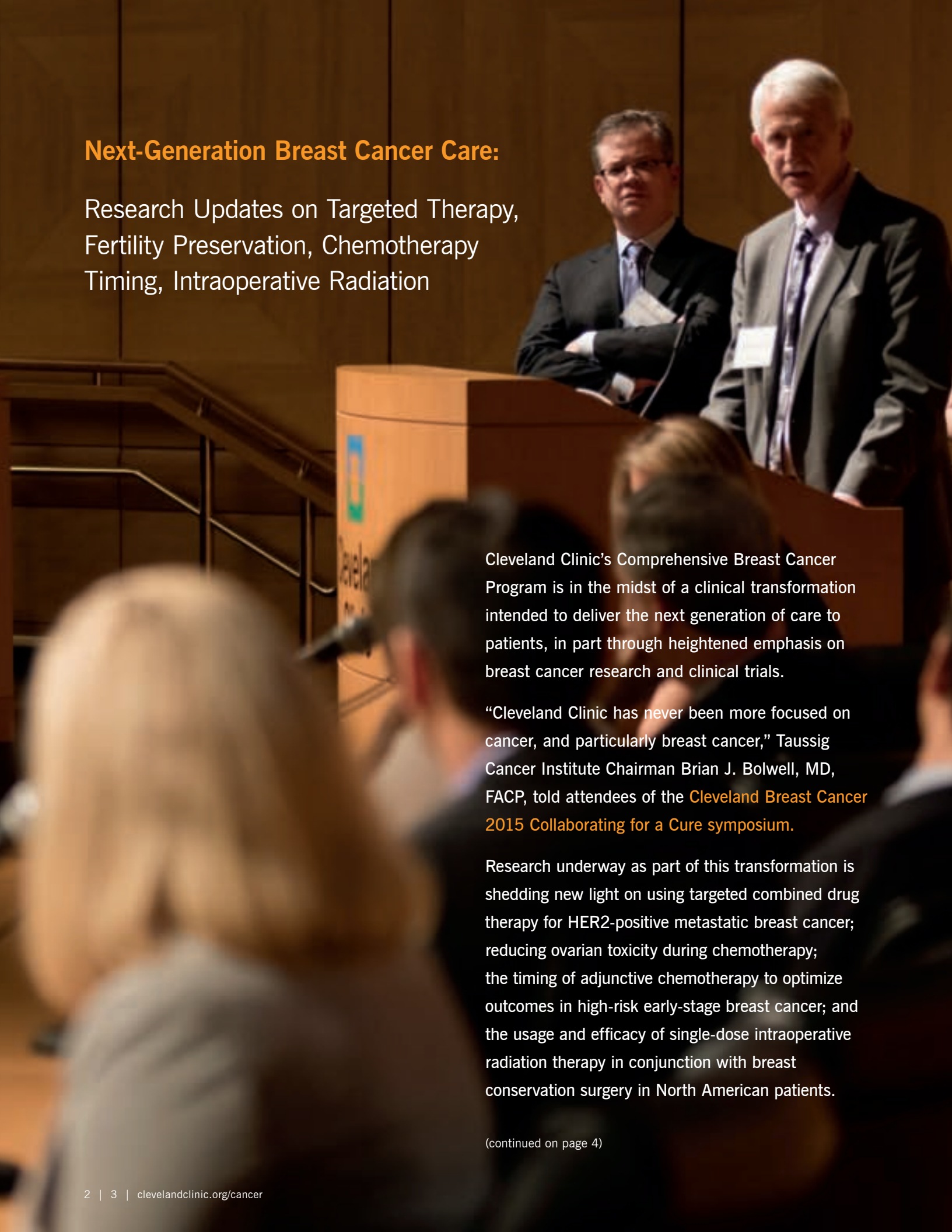


Next-Generation Breast Cancer Care:

Research Updates on Targeted Therapy, Fertility Preservation, Chemotherapy Timing, Intraoperative Radiation



Cleveland Clinic's Comprehensive Breast Cancer Program is in the midst of a clinical transformation intended to deliver the next generation of care to patients, in part through heightened emphasis on breast cancer research and clinical trials.

"Cleveland Clinic has never been more focused on cancer, and particularly breast cancer," Taussig Cancer Institute Chairman Brian J. Bolwell, MD, FACP, told attendees of the Cleveland Breast Cancer 2015 Collaborating for a Cure symposium.

Research underway as part of this transformation is shedding new light on using targeted combined drug therapy for HER2-positive metastatic breast cancer; reducing ovarian toxicity during chemotherapy; the timing of adjunctive chemotherapy to optimize outcomes in high-risk early-stage breast cancer; and the usage and efficacy of single-dose intraoperative radiation therapy in conjunction with breast conservation surgery in North American patients.

(continued on page 4)

BREAST CANCER RESEARCH UPDATE

Unique HER2 Trial Uses New Targeted Drug Therapy

In a first-of-its-kind clinical trial led by Cleveland Clinic researchers, women with HER2-positive metastatic breast cancer will receive a treatment regimen of two powerful targeted drugs — one investigational and highly promising, designed to shrink tumors and stabilize the often fatal disease.

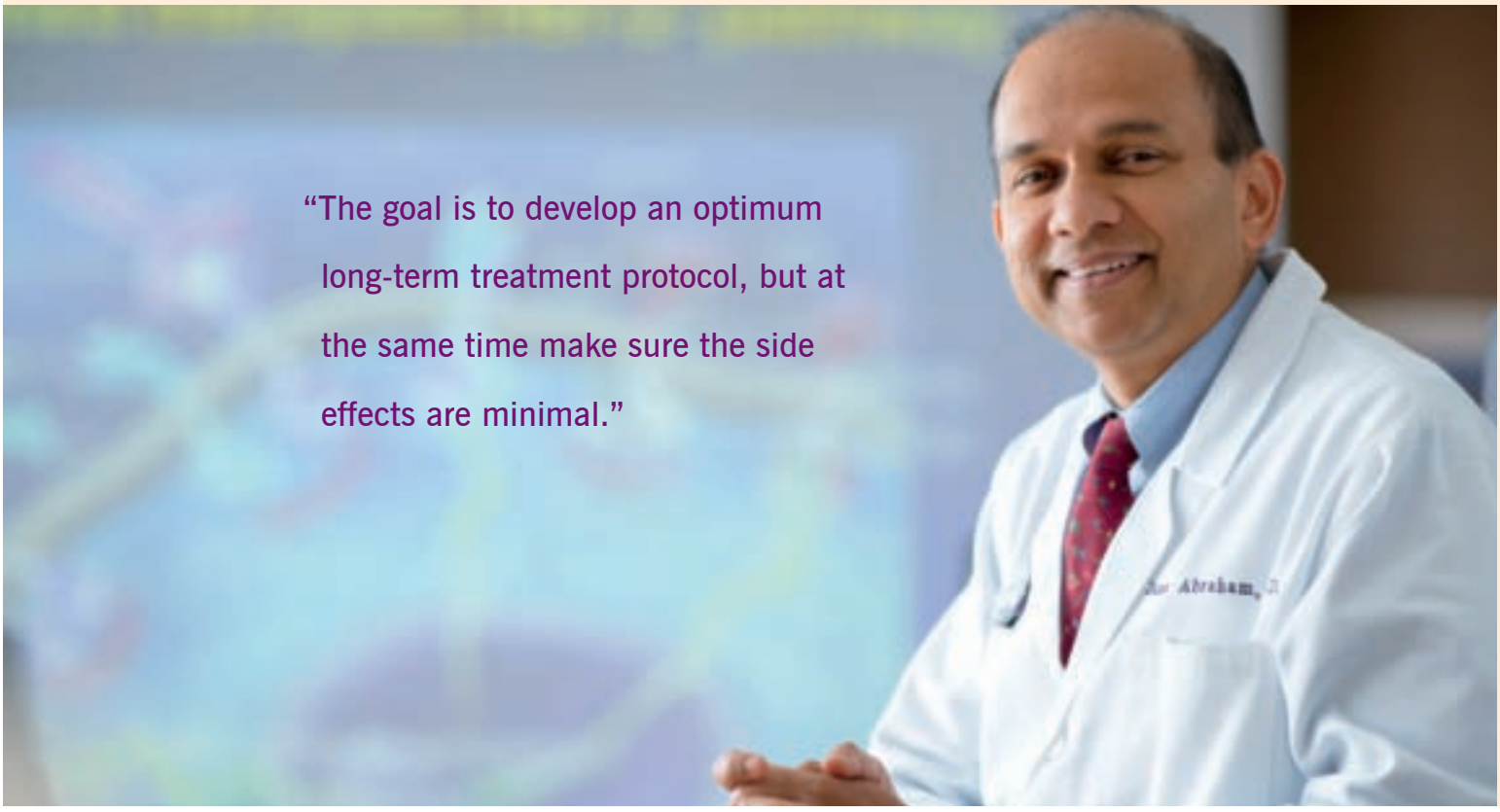
Dr. Abraham can be reached at abrahaj5@ccf.org or 216.445.0150. On Twitter:@jamecancerdr.

The national trial, "A Phase Ib/II Dose-Escalation Study Evaluating the Combination of Trastuzumab Emtansine (T-DM1) with Neratinib in Women with Metastatic HER2-Positive Breast Cancer," is sponsored by the National Surgical Adjuvant Breast and Bowel Project Foundation.

The trial is currently recruiting patients at multiple sites. The sample size will be about 50 patients.

Lead researcher Jame Abraham, MD, Director of Medical Breast Oncology and Co-Director of Cleveland Clinic's Comprehensive Breast Cancer Program, says the trial will test the feasibility of very specific dose levels of T-DM1 and neratinib, agents that have different mechanisms of action and different toxicity profiles. As monotherapy, both agents have been shown to overcome resistance to trastuzumab alone in HER2-positive breast cancer patients.

"These are probably the most exciting drugs to date in targeted therapy, and we want to test their synergy," Dr. Abraham says. Based on the proven effectiveness of the drugs when used separately, he expects that combining the two will yield even better results. "We're hoping this can translate



into a virtually nonchemotherapeutic approach — a targeted treatment with fewer side effects and less toxicity.

"Since this is long-term therapy (in stage IV breast cancer), it's almost like treating a chronic disease. So the goal is to develop an optimum long-term treatment protocol, but at the same time make sure the side effects are minimal."

Testing a Combined Approach

The trial's phase Ib will focus on the safety and tolerability of the combined drug regimen as doses are increased, while phase II will determine the overall response rate among the patients with measurable disease.

The investigational breast cancer drug neratinib has been shown in a phase III trial to have a statistically significant benefit in women with early-stage HER2-positive breast cancer when used as an adjuvant treatment after the use of trastuzumab.

Recent research also shows that T-DM1 promotes tumor cell death, and early results regarding overall patient survival have been promising. T-DM1 also has been shown to work even in heavily pretreated HER2-positive breast cancer patients, and some leading researchers have labeled it as the preferred treatment for progressive HER2-positive breast cancer.

The response rate to T-DM1 and neratinib individually in patients has ranged from 32 to 60 percent, Dr. Abraham says, "so it makes sense to combine these two highly effective treatments. We're hoping their combination will result in a much higher response rate."

BREAST CANCER RESEARCH UPDATE

Study Suggests Approach to Reduce Ovarian Toxicity While Fighting Breast Cancer

Ovarian toxicity is a significant concern for women undergoing chemotherapy treatment for breast cancer — especially those of child-bearing age who wish to preserve their fertility.

Damage from such toxicity can include premature ovarian failure, marked by amenorrhea, sexual dysfunction and infertility. But a recent study in the *New England Journal of Medicine* suggests that ovarian failure may be preventable in some patients, potentially altering the ways in which clinicians care for these women.

Improved Fertility Prospects

The Prevention of Early Menopause Study (POEMS) was a phase III clinical trial developed to assess whether ovarian failure could be prevented by temporarily suppressing ovarian functioning by including goserelin, a luteinizing hormone-releasing hormone agonist, with standard chemotherapy.

Previous investigations of this approach have yielded mixed results and typically only used return of menstruation as an indicator of ovarian functioning. But this can be misleading, says Cleveland Clinic oncologist Halle Moore, MD — chair of the Taussig Cancer Institute Survivorship Program and the study's lead author — because menstrual bleeding can occur even in the presence of infertility.

POEMS used a rigorous definition for ovarian failure that included absence of menses at two years and menopausal hormone levels. Furthermore, previous studies did not comprehensively track future pregnancies as an outcome — a clear benchmark for fertility. POEMS sought to resolve these limitations.

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STUDY SUGGESTS APPROACH TO REDUCE OVARIAN TOXICITY

(CONTINUED)

Dr. Moore can be reached at mooreh1@ccf.org or 216.445.4624.

The study randomized 218 eligible estrogen receptor-negative/progesterone receptor-negative female breast cancer patients to receive either cyclophosphamide-containing chemotherapy or the same chemotherapy with goserelin. Researchers found that among 135 participants for whom ovarian function was assessable at two years, only 8 percent of those receiving the goserelin-supplemented treatment experienced ovarian failure, compared with 22 percent of the women who did not (odds ratio [OR] = 0.30, $p = 0.03$).

Furthermore, among all 218 eligible participants, almost twice as many women in the treatment group were able to achieve pregnancy compared with those in the control group (21 percent versus 11 percent of women, respectively; OR = 2.45, $p = 0.03$).

"Disease-free survival and overall survival also were higher among the women receiving goserelin," Dr. Moore adds. She notes that the study's findings offer the first demonstration of improved fertility prospects using goserelin with chemotherapy — as well as demonstration of the safety of the approach.

Spreading the Word

Dr. Moore and her colleagues will follow up on these novel findings by participating in a meta-analysis examining all randomized controlled trials in both hormone receptor-negative and hormone receptor-positive breast cancer patients. The goal: to increase the overall sample size and better determine the impact of this ovarian protection strategy.

Even with larger-scale data yet to come, results from the current study are expected to significantly affect breast cancer treatment approaches. They also may affect other types of malignancies treated with similar chemotherapy, including non-Hodgkin lymphoma.

For some young women with breast cancer, the prospect of treatment with chemotherapeutic agents that could prolong survival at the potential cost of fertility is a heartbreaking decision — and one that sometimes leads patients to turn down the therapy. Outcomes from POEMS may help diminish these fears and help women preserve their lives and their reproductive abilities.

"I believe many clinicians have already started implementing this strategy to protect ovarian functioning for young women being treated for breast cancer," Dr. Moore says.

In addition to the study's publication in the *New England Journal of Medicine,* the American Society of Clinical Oncology (ASCO) has selected it for inclusion in the recently published report *Clinical Cancer Advances 2015: ASCO's Annual Report on Progress Against Cancer*.

"This information needs to be available to patients, primary care physicians, gynecologists, surgeons and other people helping women make decisions early on in the breast cancer diagnosis process," says Dr. Moore. "This is an important long-term survivorship issue, and hopefully publication in a high-impact journal and citation by ASCO as a significant clinical advancement will help to inform a broader base of people providing for these women."

BREAST CANCER RESEARCH UPDATE

For Breast Cancer Treatment, Chemotherapy Comparison Suggests that Timing May Be Everything

Findings from a recent phase 3 clinical trial comparing chemotherapy schedules in high-risk early-stage breast cancer are shedding light on the best way to administer treatments. These findings have the potential to change the way oncologists use adjunctive chemotherapy.

The use of chemotherapy following primary treatment for breast cancer has significant potential to extend lives. For patients with early-stage breast cancer, adjuvant intervention is particularly important for halting illness progression and preventing recurrence. However, oncologists have yet to determine the dose and schedule of chemotherapy that will yield optimal mortality outcomes. The new trial offers first steps toward changing that.

Fine-Tuning Frequencies

Oncology researchers from the North American Breast Intergroup, which includes Cleveland Clinic and other medical centers in the United States and Canada, recently collaborated on a novel study to better determine the optimal dose and frequency of commonly administered chemotherapies for breast cancer. Findings from the trial, which was supported by the National Cancer Institute, were published in the *Journal of Clinical Oncology*.

The study did not consider new drugs; rather, it assessed the best way of administering medications that oncologists have given for some time to patients with breast cancer.

"Previous studies had shown that it appeared to be better to give some chemotherapies every two weeks as opposed to every three weeks, and in the case of Taxol®, to give it weekly as opposed to every three weeks," explains Cleveland Clinic oncologist George Thomas Budd, MD, the study's lead author. "This study looked at giving all chemotherapies weekly or every two weeks."

In most of the 3,000-plus patients enrolled, the schedule of chemotherapies tested — doxorubicin (Adriamycin®), cyclophosphamide (Cytoxan®) and paclitaxel (Taxol) — had no significant effect on survival outcomes and time to recurrence. For instance, Taxol given on a weekly basis had no effect on mortality; it resulted in more doctors' visits but fewer side effects. But in a small subset of patients with triple-negative disease (that is, individuals whose tumors tested negative for the presence of estrogen, progesterone and HER2 hormone receptors), results supported giving chemotherapies every two weeks.

"From a practical point of view, that means that most patients can be treated with Adriamycin and Cytoxan every two weeks and Taxol weekly, but for patients with triple-negative breast cancer, it might be better to give all the treatments every two weeks," says Dr. Budd, adding that because the findings in the triple-negative group came from

(continued on page 8)

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CHEMOTHERAPY COMPARISONS SUGGEST THAT TIMING MAY BE EVERYTHING (CONTINUED)

unplanned statistical analyses, they should be interpreted with caution.

Implications for Patients

The study's results suggest that, in the future, it may be beneficial to tailor chemotherapy to an individual's type of breast cancer, particularly for whether the tumor is hormone-receptor positive or negative. Further studies will need to determine if different cancers should be treated with different doses and schedules of chemotherapies.

Dr. Budd warns against making assumptions about survival. One unusual finding from the study indicated an improvement in overall survival for patients on the "every two weeks" schedule but no improvement in disease-free survival, meaning time from diagnosis to recurrence.

However, this might reflect differential effects from triple-negative breast cancer, which has a worse prognosis after recurrence. It also may be due to random differences between the study groups that have nothing to do with the treatment, he notes.

Additional trials are needed to more definitively inform potential changes in treatment approaches.

"The next steps will include genetic studies looking at the side effects experienced by patients enrolled in this trial, and also molecular studies of the tumors of these patients, in order to gain insight into how best to treat breast cancer," Dr. Budd says.

BREAST CANCER RESEARCH UPDATE

Encouraging Results From a Snapshot of Intraoperative Radiation Therapy Use in North American Breast Cancer Patients

The use of single-dose intraoperative radiation therapy (IORT) in conjunction with breast conservation surgery, as an alternative to traditional postsurgical external beam whole-breast irradiation, is increasing.

Partial breast radiation's goal is to limit exposure in selected early-stage patients whose tumors are less aggressive and confined to a single breast segment. TARGIT-A, an international randomized trial comparing a single IORT dose given at the time of lumpectomy to standard radiation therapy given over several weeks after lumpectomy, found that five-year local breast cancer recurrence rates and breast cancer mortality rates were similar for the two modalities. Mortality from other causes was significantly lower with IORT, due to fewer deaths from cardiovascular causes and other cancers.

Need for North American Data

While TARGIT-A's cohort of 3,451 patients represented 11 countries, less than 10 percent were from North America. Little is currently known about IORT's frequency of use in North America, the types of patients who receive it and, most important, the therapy's outcome. While the Targeted Intraoperative Radiotherapy United States (TARGIT-US) Registry Trial is currently being conducted to address questions of long-term efficacy and toxicity, the results of this prospective study will not be available for years.

Cleveland Clinic researchers organized the retrospective TARGIT-R trial to provide an interim snapshot of IORT usage and outcomes, using data from patients treated at selected North American institutions prior to July 2013. Stephanie Valente, DO, a breast surgeon with Cleveland Clinic's Comprehensive Breast Cancer Program, presented results of the initial TARGIT-R analysis at the 2015 Society for Surgical Oncology meeting. This is the first large-scale evaluation of IORT for breast cancer treatment in North America.

Nineteen institutions, representing academic and community practices, submitted data involving 1,086 women treated with lumpectomy and IORT between 2007 and 2013. The analysis included 1,050 of those patients who had at least six months of follow-up. Their median age was 67. Most of the women had estrogen receptor-positive (91 percent), invasive ductal carcinoma (69 percent), with tumor less than 2 cm in size (86 percent), and were lymph node negative (89 percent).

Most patients (80 percent) received primary IORT (performed at initial lumpectomy); 7 percent received IORT as a secondary procedure and 13 percent as a planned boost. Almost 19 percent of patients who had primary IORT went on to receive external beam radiation. Complications included seroma requiring aspiration (8 percent), hematoma (1 percent) and infection requiring intravenous antibiotics (2.6 percent).

Median follow-up time was 12 months. The crude local in-breast recurrence rate was 1.6 percent, and regional nodal recurrence was 0.2 percent.

Confirming Value in Appropriate Patients

"Our early results from the TARGIT-R registry basically mirror TARGIT-A's results and confirm that recurrence rates are low in properly selected patients," says study co-author Stephen Grobmyer, MD, Director of Surgical Breast Oncology and Co-Director of Cleveland Clinic's Comprehensive Breast Cancer Program.

With the preliminary findings, "we now have a portrait of who's being treated with IORT in North

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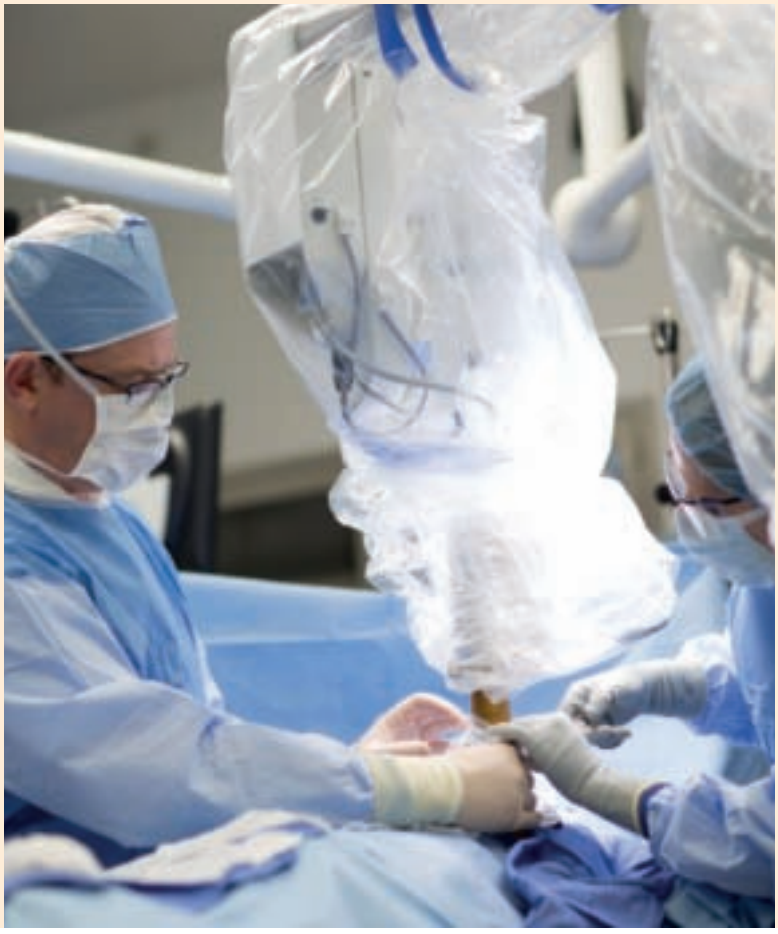
ENCOURAGING RESULTS FROM A SNAPSHOT OF INTRAOPERATIVE RADIATION THERAPY USE (CONTINUED)

America," says Dr. Grobmyer, who is a member of the TARGIT-US steering committee. "Physicians are being very conservative. They're treating hormone-positive patients with smaller tumors and patients whose average age is 67 — not the younger patients who tend to have more aggressive disease.

"Selecting less aggressive treatments for less aggressive disease is appropriate, and better for patients," Dr. Grobmyer says. "Patients like IORT because treatment duration is shorter, side effects are less and they're able to quickly return to normal functioning. We present it as an option for properly selected patients."



Young Women's Breast Cancer Clinic

SERVICES

Genetic counseling to review screening options, and genetic testing to detect alterations in *BRCA1*, *BRCA2* or other genes associated with increased breast cancer risk, which may enable management targeted to specific mutations

A thrice-weekly clinic with coordinated medical, surgical, radiology and **related consultation appointments**, to accelerate treatment time and reduce return visits

Dedicated pathology and **imaging specialists** who deal exclusively with breast diagnostic issues

Access to the latest strategies for fertility preservation and **assisted reproduction**, including ovarian cycling suppression during chemotherapy; oocyte, embryo and ovarian tissue harvesting and cryopreservation; and in vitro fertilization

Advanced surgical options for breast conservation, reconstruction and **lymphedema reduction**, including nipple-sparing mastectomy; single-stage mastectomy and breast implant insertion; and vascularized lymph node flap transfer

Single-dose intraoperative radiation therapy for appropriate patients

Access to a wide array of clinical trials, including areas of research with particular impact on young breast cancer patients

Support groups and other psychological and lifestyle counseling and therapy intended for young breast cancer patients

BREAST CANCER RESEARCH UPDATE

New Young Women's Breast Cancer Clinic Addresses Special Needs

Breast cancer is relatively uncommon in younger women. Of the more than 230,000 new cases of breast cancer expected to be diagnosed in the United States in 2015, only about 11 percent will involve women younger than 45.

Young breast cancer patients have special concerns. Their cancers tend to be more advanced, more aggressive, more likely to be caused by an inherited defective gene, and may respond differently to treatment compared with breast tumors in older women. Issues of infertility, body image, and the disease's impact on family life, relationships, career and finances also are different for younger women.

Cleveland Clinic has launched the Young Women's Breast Cancer Clinic to coordinate care and address the specific needs of newly diagnosed patients younger than 50.

"These women have a lot going on in their lives," says oncologist Halle Moore, MD, the clinic's director and a national authority on breast cancer. "They're juggling jobs, parenting and educational demands. They have complex diagnostic, therapeutic and support issues. We have more and more options to discuss with them. We want to offer these patients everything they need as soon as possible."

"When breast cancer happens to women in their 20s, 30s and 40s, it poses some different challenges," adds Jame Abraham, MD, Director of Medical Oncology and Co-Director of Cleveland Clinic's Comprehensive Breast Cancer Program. "From diagnosis to treatment and survivorship, it requires a coordinated, comprehensive approach."

"Along with advanced medical and surgical care, having a support system of mental health professionals, social workers and peers who understand and can help with what young breast cancer patients are going through is extremely important," says Stephen Grobmyer, MD, Director of Surgical Oncology and Co-Director of the Comprehensive Breast Cancer Program.

KEY POINTS

Breast cancer is uncommon in younger women but poses unique challenges due to differences in cancer behavior, genetic components and lifestyle impact in these patients.

Cleveland Clinic has begun a Young Women's Breast Cancer Clinic to coordinate care and address the specific needs of newly diagnosed patients younger than 50.

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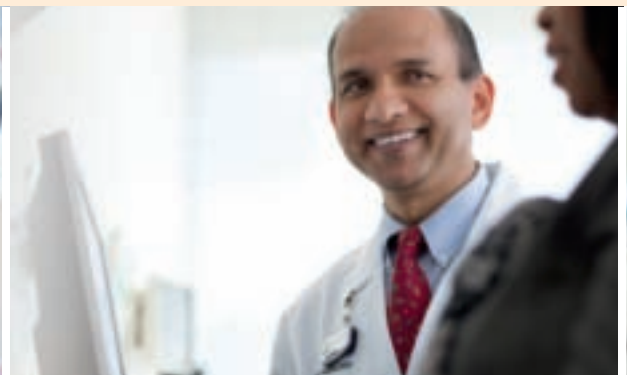
Dr. Abraham can be reached at abrahaj5@ccf.org or 216.445.0150. On Twitter:@ jamecancerdr.

Dr. Grobmyer can be reached at grobmys@ccf.org or 216.636.2843.



Using **Genetic Targeting** to Exploit Lung Cancer's Vulnerabilities

KEY POINTS

Genetic and genomic sequencing of lung cancers is identifying numerous promising gene variations that may be targetable using existing drugs

Umbrella clinical trials enable the simultaneous testing of multiple targets, accelerating the development process for new lung cancer treatments

Cleveland Clinic is involved in various clinical trials evaluating potential targeted therapies

By Nathan Pennell, MD, PhD

Dr. Pennell is Director of Medical Oncology for Cleveland Clinic's Lung and Thoracic Cancer Program. He can be reached at pennelN@ccf.org or 216.445.9282. On Twitter:@n8pennell.

Cancer is fundamentally a disease of genes gone awry, diverting normal cellular functions into abnormal growth, invasion and metastasis. Nowhere is that more true than in lung cancer, which has spurred efforts by researchers in the field of cancer genomics to determine how a cancer behaves and to identify its Achilles' heel.

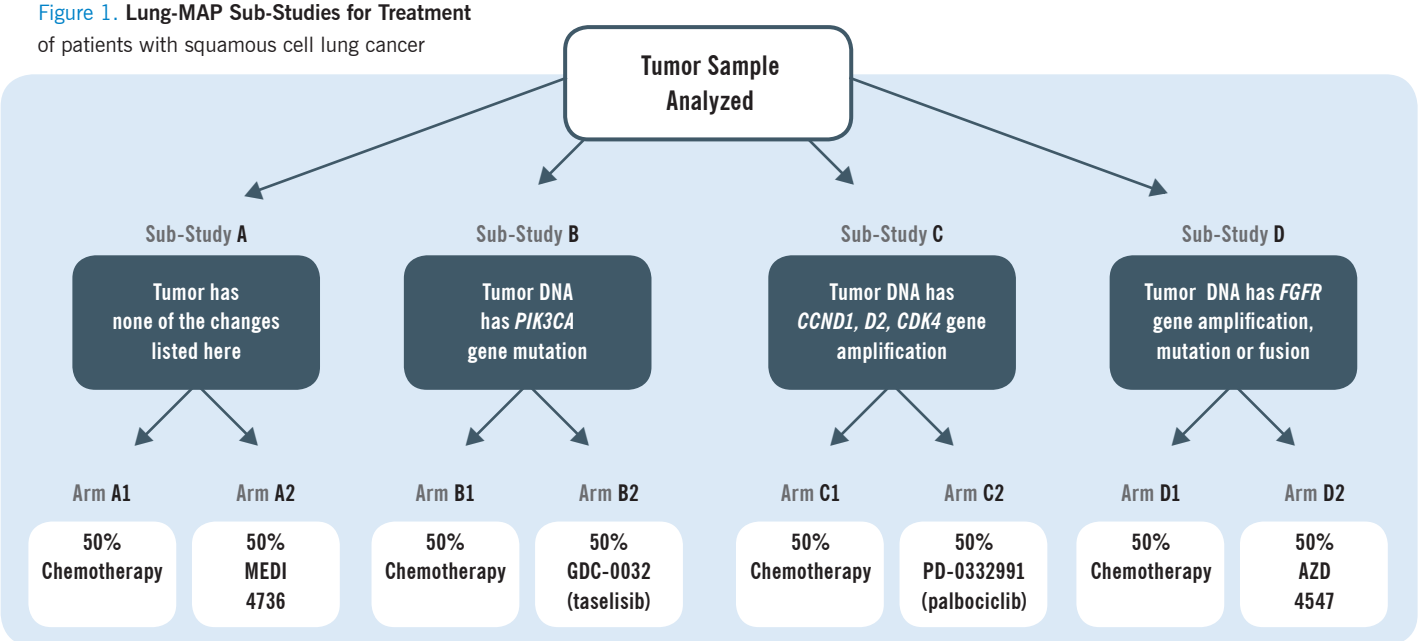
Through large-scale efforts to sequence the entire genomes of hundreds of non-small cell lung cancers (NSCLC), we now understand that lung cancer is not one disease or even several different diseases, but instead is made up of dozens of different types of cancer, all of which just happen to originate in the lungs.

Cleveland Clinic partnered with the National Cancer Institute (NCI) on The Cancer Genome Atlas (TCGA) Program, whose goal is to understand the complete genetic makeup of 1,000 NSCLC cases to find targets for new treatments. As a result of this and similar efforts, many unique and exploitable targets have been identified, and a number of revolutionary clinical trials are available that aim to bring active treatments to lung cancer patients in a few years rather than decades.

Master Protocol for Squamous Cell Lung Cancer

Squamous cell carcinoma (SCC) of the lung is a formidable disease, with a median survival of about 10 months in its advanced stage, and is treated in

Figure 1. **Lung-MAP Sub-Studies for Treatment** of patients with squamous cell lung cancer



2015 very much like it was 20 years ago. As a result of the TCGA project, several promising genetic targets were identified in SCC for which potential drugs were available.

Instead of testing each drug individually in hundreds of SCC patients in hopes of achieving efficacy in a select few, the NCI designed a new trial in which Cleveland Clinic is participating called the Master Protocol, or Lung-MAP, to test many different targets simultaneously. Patients with previously treated, advanced SCC of the lung have their tumor tissue sent for broad genomic analysis. Using the so-called umbrella trial design, patients are then entered into one of four different arms of the trial based on the genomic analysis results. Each of the arms — targeting PI-3 kinase *(PIK3CA)* mutations, cyclin dependent kinase *(CDK)* abnormalities, fibroblast growth factor receptor *(FGFR)* amplifications or, in the final group, using immunotherapy — will be compared in a randomized fashion to the FDA-approved second-line chemotherapy agent docetaxel.

The trial, aside from assigning patients to arms based on tumor genetics, is also unique in that if any of these drugs shows promise in the phase 2 portion, the investigation will immediately expand into a registration phase 3 trial, cutting the time to possible drug approval by years. As new targets in NSCLC are discovered, they can be seamlessly added to the design, essentially creating a pipeline for targeted drug approvals in SCC.

Can ALCHEMIST Turn Genes Into Gold?

Another important trial open at Cleveland Clinic is the NCI-sponsored ALCHEMIST trial, which is testing the idea that giving targeted drugs as adjuvant therapy in early-stage lung cancer will lead to higher cure rates. In an earlier pivotal phase 2 trial presented at the American Society of Clinical Oncology's 2014 annual meeting, Cleveland Clinic investigators led an adjuvant trial of erlotinib in epidermal growth factor receptor (*EGFR*) mutant early-stage NSCLC, which resulted in a significant increase in disease-free survival in these patients.

In ALCHEMIST, patients with stage IB-IIIA non-squamous NSCLC who undergo surgery will have their tumors sequenced for either *EGFR* mutations or anaplastic lymphoma receptor tyrosine kinase *(ALK)* gene translocations, which are common genetic alterations with approved targeted treatments in advanced disease. *EGFR* mutant or *ALK*+ patients will then randomly be assigned to two years of adjuvant erlotinib *(EGFR)* or crizotinib *(ALK)* or placebo, with a primary goal of improving overall survival. As both of these targeted drugs are significantly superior to chemotherapy in these molecular subtypes of NSCLC when the disease is incurable, there are high hopes that they will make a similar impact in curable patients.

RET Targeted Agents Aren't Just for Thyroid Cancer Anymore

Aside from the umbrella trials that test multiple genes and drugs in a single study, Cleveland Clinic's Lung Cancer Program also has a large panel of clinical trials testing single drugs in molecular subtypes of NSCLC.

In one exciting trial recently highlighted at the Santa Monica Targeted Therapies of Lung Cancer meeting, patients with NSCLC harboring activating *RET* gene fusions are being treated with the oral *RET* inhibitor lenvatinib. *RET* fusions are common in thyroid cancer, but are now also recognized to be present in about 2 percent of NSCLC cases, and may benefit from the same type of therapy. My Cleveland Clinic colleague Vamsidhar Velcheti, MD, is one of the lead investigators on this phase 2 trial, which screens patients for the presence of *RET* fusions to identify 20 patients for treatment with once-daily lenvatinib, with a primary endpoint of objective response rate.

Together, these trials will try to prove that genetic alterations in cancer are more important than the site of origin. With that information, we may one day force lung cancer to relinquish its position as the No. 1 cause of cancer-related mortality worldwide.

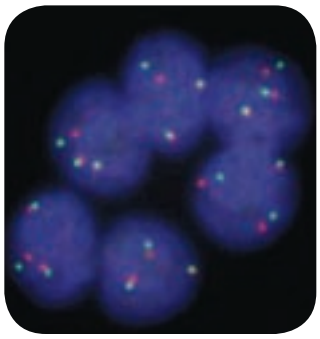


Figure 2. **Break-apart fluorescent in situ hybridization** (FISH) in a patient with anaplastic lymphoma kinase (*ALK*) gene translocation-positive NSCLC. The gene translocation is present when the red and green probes are distinctly separated, while normal *ALK* (negative) would be represented by fused probes in yellow. All of the *ALK* signals are positive for translocation in this patient's tissue sample.

Rectal Cancer Update

Study Validates Prognostic Significance of AJCC/CAP Regression Grading

Dr. Kalady is a member of Cleveland Clinic's departments of Colorectal Surgery, Cancer Biology, and Stem Cell Biology and Regenerative Medicine. He also is an Associate Professor of Surgery at Cleveland Clinic Lerner College of Medicine. He can be reached at kaladym@ccf.org or 216.445.2655.

When patients receive neoadjuvant chemoradiation (CRT) followed by proctectomy for locally advanced rectal cancer, variability in treatment response ranges from complete histologic regression to progression of disease. Most patients have a partial response, the implications of which are unclear.

As a step toward standardizing reporting and treatment response information, the American Joint Committee on Cancer (AJCC) and the College of American Pathologists (CAP) published guidelines in 2010 for grading rectal cancer response to neoadjuvant CRT. The four-grade scoring system was designed to include two partial response grades, on the premise that incremental improvement in response serves as a surrogate for better outcomes.

While these guidelines were established based on expert consensus, the clinical relevance of the grading system as related to oncologic outcomes had not been validated and remained unknown until recently.

KEY POINTS

Patients with locally advanced rectal cancer vary in their response to neoadjuvant chemoradiation (CRT) followed by proctectomy, from complete regression to progression.

The American Joint Committee on Cancer (AJCC) and the College of American Pathologists (CAP) published guidelines in 2010 for grading rectal cancer response to neoadjuvant CRT, but the prognostic value and clinical relevance of the four AJCC/CAP grades were not established.

A Cleveland Clinic retrospective study sought to determine the prognostic significance of the AJCC/CAP regression grading system.

Analysis revealed that the AJCC/CAP grades were independent predictors of overall survival, disease-free survival and cumulative recurrence.

First-Ever Validation Study

A retrospective cohort study of more than 500 patients conducted at Cleveland Clinic and published in *Diseases of the Colon & Rectum* is the first study to delineate the AJCC/CAP regression grade as an independent prognostic factor. Primary outcome measures were overall disease-free survival, cancer-specific mortality and cumulative recurrence rate.

"We looked at the AJCC/CAP grading, which ranges from 0 to 3, in relation to survival and determined that each of the categories has a sequential survival advantage," says Matthew Kalady, MD, a surgeon in Cleveland Clinic's Department of Colorectal Surgery and the paper's senior author. "This validation allows us to talk to patients about what their prognosis is in a more concrete way and could influence wider adoption of the AJCC/CAP scoring system."

As Dr. Kalady and colleagues state in their study, "These findings highlight the importance of reporting tumor regression according to these criteria so that this important prognostic information is widely available to clinicians who treat rectal cancer."

Grading as a Predictor of Survival and Recurrence

The retrospective cohort study was based on data from Cleveland Clinic's prospectively maintained colorectal cancer database of patients with primary rectal adenocarcinoma who underwent neoadjuvant therapy between 1992 and 2012. Researchers defined the cohorts based on the AJCC/CAP tumor regression grading system.

Of the 538 patients included in the study, the AJCC/CAP grading was:

Grade 0	105 patients (19.5 percent)
Grade 1	153 patients (28.4 percent)
Grade 2	181 patients (33.6 percent)
Grade 3	99 patients (18.4 percent)

The researchers determined using Kaplan-Meier analysis that AJCC/CAP grade was associated with significant differences in overall survival, disease-free survival and cumulative recurrence ($p < 0.001$ for all). Patients assigned a grade 0 did not experience any local recurrence; 7 percent of those patients developed distant recurrence.

Five-year overall survival rates ($p < 0.001$) were:

Grade 0	89 percent
Grade 1	74 percent
Grade 2	63 percent
Grade 3	40 percent

Five-year disease-free survival rates ($p < 0.001$) were:

Grade 0	85 percent
Grade 1	64 percent
Grade 2	54 percent
Grade 3	33 percent

Five-year overall recurrence rates ($p < 0.001$) were:

Grade 1	7 percent
Grade 2	18 percent
Grade 3	25 percent
Grade 4	33 percent

After using Cox regression analyses to adjust for significant covariates, including pathologic stage, AJCC/CAP grading remained an independent predictor of overall survival, disease-free survival and cumulative recurrence ($p < 0.001$ for all).

"Even though the AJCC/CAP grading system has been in existence since 2010, no one had put numbers on it to say what the outcomes were," Dr. Kalady says. "The idea has always been the better the grade, the better the survival — but we had no data to say what that meant specifically. Now we have specific numbers that can be attached to the scoring."

Clinical Significance and Future Research

Dr. Kalady's team first reported the research results at the American Society of Colon and Rectal Surgeons (ASCRS) meeting in 2014. The presentation won an award from the Canadian Society of Colon and Rectal Surgeons, and "our colleagues were excited about it and said it was something they plan to use with their patients," Dr. Kalady says.

At Cleveland Clinic, the clinical validation of the AJCC/CAP grading system means additional evidence-based prognostic information that can be considered at multidisciplinary tumor board meetings where oncologists, surgeons, radiation oncologists and other specialists review rectal cancer cases before and after surgery.

"Patients appreciate knowing what the expectations may be, and now we have more concrete information to share with them," Dr. Kalady says. "I also tell them every patient is a bit different, but if we treated 100 people, this is what we would expect across the board."

Looking forward, Dr. Kalady and colleagues are continuing to analyze their patient databases to look for "subsets of nuances" within the grading system that may trigger future research efforts.

CHAIRMAN'S **Q&A**

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

Dr. Bolwell is Chairman of Taussig Cancer Institute. He can be reached at bolwelb@ccf.org or 216.444.6922. On Twitter: @clebmt.

What is Cleveland Clinic's rationale for developing cancer care paths?

It is a way to standardize various parts of clinical treatment for a given cancer. It is also a way to extract important data such as quality metrics associated with cancer treatments, so that we can continually monitor what we do and try to improve our care. The three major areas we focus on when constructing care paths are identifying the best way to treat the patient, minimizing treatment toxicity to preserve functionality and quality of life, and identifying the most economical, most efficient treatment. The primary driver is to come up with algorithms that generate the best clinical outcomes, the best way to make patients get better. But with the direction of healthcare reform, we also have to continually think about value. We have generated a value equation in which cost over outcomes equals value. If we have the same outcomes using many different treatment options, we want to be as cost-efficient as we can.

How many care paths do you have?

Approximately 20, with 30 to 40 more in development. Our goal is to deploy about 100 in the next 18 to 24 months.

How are they developed?

It is a lot of work. The people who are experts in the disease have to put their heads together and come up with common strategies. And because a cancer may start at a very early stage, care paths for diagnosis and surgery are going to involve different caregivers than those for more advanced disease, which primarily involves medical oncology and radiation therapy. Our team develops decision-making trees for every treatment step, realizing that these evolve rapidly. They have to be updated at least quarterly. Next, we make sure that all treating physicians have an opportunity to provide input. We have a large regional network and we take a fair amount of time socializing care paths as they are being developed with our regional colleagues, because we want to make sure they make sense outside the main campus, with different mixes of patients and different sorts of support.

What about implementation?

Ideally, the entirety of a care path would be fully embedded in an electronic medical record. It turns out that that is difficult to execute as an initial step. So we have started by simply making the entire treatment algorithm available to every clinician, so they can at least follow the recommendations without leaving their workstation. Then you need to track progress, with embedded metrics that can be extracted to look at quality, outcomes, toxicity and cost. We are trying to start this relatively simply. We think it can be much more robust, but we are very pleased with the initial phase because our physicians have embraced it, and the number of patients enrolled on care paths is increasing monthly.

Were you concerned that physicians might be reluctant to accept something that reduces their clinical decision-making capacity?

We were actually quite worried that the care paths would be too prescriptive. And in all honesty, it took me a while to get on board with the concept, because there will always be exceptions and clinical parameters that make following a care path a bit of a challenge. But we think for most patients there is an opportunity. And it turns out that, somewhat surprisingly, our physicians have embraced them in a big way — especially our regional colleagues who, if anything, wanted us to be

more prescriptive than we were. Cancer care is complex. Genomics and immunological therapy are making it very different today than it was 10 years ago. I think care paths provide a certain sense of buy-in, in that clinicians know they are following something that is the right thing to do today and is not dated, because we update these all the time.

Genomics continues to reinforce that cancer is a highly individualized disease. Does that pose a challenge to developing care paths that are effective for, and applicable to, every patient?

We must build that sort of variation into care paths, certainly with genomic testing. If there are known actionable genomic alterations for which there are specific drugs that might be of benefit, they have to be embedded into the care path. As we have more and more genomic knowledge and more drugs that are known to be useful in this space, I think that actually makes care paths even more important. Having a treatment algorithm that is continuously updated and is a guide for a clinician seeing a wide variety of patients with different cancers is incredibly useful.

How do care paths take into account therapeutic value and cost?

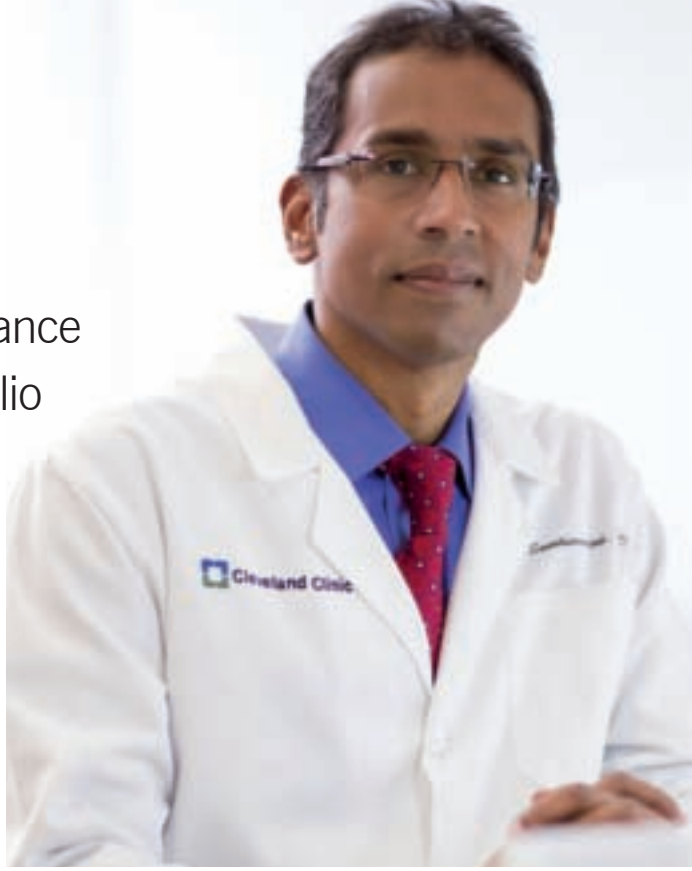
The value equation is a major part of a care path. So as our cancer programs are developing their care paths, it forces them to look at the available treatment options and ask what makes sense — not just from an outcome perspective, but also a cost perspective. Without question, when there is a new medical advance, it is incorporated into a care path, because our goal is to try to cure cancer. But many new, expensive, precision-based medicines are similar to each other. If there is not much difference in outcomes, and if the toxicities are relatively similar, it simply makes sense to pick the least expensive option. In our advanced lung cancer care path, for example, our experts decided that one form of therapy, which did not seem to add significant clinical value compared with more traditional therapies, did not make sense to include. We looked at the first 20 or so patients on the care path, and by not including that drug and by following the care path, the savings were about $80,000 per patient. So imagine if that were adopted for the thousands of patients with advanced lung cancer. It shows the potential that care paths have in the whole value equation and making cancer care more affordable. The data showing the cost savings of care paths at present are relatively sparse. I think there will be significantly more literature in the next five years or so about how care paths can make care more affordable.

What about cancer patient outcomes data on care paths?

We want patient care to be optimal. We do not want care paths to in any way make things worse; we want them to make things better. So it is something that we track all the time. Given that we have really only started in the past year or so, it is a little early to have enough numbers to talk about outcomes. But we are hopeful there will be significant improvements.

What is ahead for cancer care paths?

The field is changing very quickly. Medicare officials recently announced that half of all traditional fee-for-service reimbursements will be tied to quality metrics by 2018. Because care paths are a vehicle to define quality in cancer treatment — which has historically been very challenging to do — I think there will be a marriage between care path development and reimbursement strategies. At Cleveland Clinic, we think our cancer care paths are a form of currency we can use to enhance our affiliations with healthcare systems around the United States and internationally. There are a lot of generalized treatment guidelines produced by national healthcare and cancer organizations. But our care paths are extremely specific and logical. I think they will soon be a model for other academic medical centers. It is likely that people will start to ask us how we did it. We are certainly glad to share the techniques. We would like to have a fairly free exchange of information with our affiliates. And we have already started to publish our results.



Noncytotoxic Differentiation Treatment:

Correcting an Irrational Imbalance in the Oncotherapeutic Portfolio

By Yogen Saunthararajah, MD

Dr. Saunthararajah is a staff member of Cleveland Clinic's Department of Hematology and Medical Oncology and a Professor of Medicine at Cleveland Clinic Lerner College of Medicine. He can be reached at saunthy@ccf.org or 216.444.8170.

Today, only five types of nonresectable cancers are routinely cured: certain lymphomas and myeloid leukemias, and testicular cancer. Although there has been exciting progress, most recently with immune-checkpoint inhibitors, most patients with disseminated cancer still face a difficult and uncertain future, with financial distress adding to the burdens of the diagnosis.

This situation prompts several important questions:

- **Why can we cure some disseminated cancers but not others?**
- **Why are treatments so arduous?**
- **Why does oncology drug development have a 95 percent failure rate, with consequent high costs that are shifted to patients?**

The answers ultimately lie in biology. Thus, it is worth reflecting on results of recent large-scale cancer genomic studies.

Confronting a Paradox

First, the single most commonly inactivated gene in all cancer types is that for p53, the master transcription factor regulator of apoptosis. This is very significant, since radiation and hundreds of drugs, including agents in development, intend apoptosis (cytotoxicity). That p53-system alterations subvert cytotoxic oncotherapeutic intent has been shown by several in vitro studies, but perhaps it is most vividly illustrated by the near absence of *TP53* mutations in the few disseminated cancers that are routinely cured (e.g., testicular cancer). Conversely, refractory/relapsed testicular cancer, and incurable subsets of the few other usually curable disseminated malignancies, are characterized by *TP53* mutation/deletion and/or homozygous *CDKN2A* (p16) loss. And of course the cancers that are most notoriously difficult to treat are characterized by the highest rates of p53 loss.

A second revelation has been essentially universal inactivating events in coactivator genes (e.g., *PBRM1, ARID1A*) — that is, deletion of cofactors needed by master transcription factors to activate target genes. These findings explain a striking paradox of cancer cells, including cancer stem cells: Cancer stem cells express high levels of the master transcription factors that usually drive terminal differentiation, yet the target genes of these transcription factors are epigenetically repressed rather than being activated.

Coactivator disruption causes unbalanced recruitment of corepressor counterparts (e.g., DNA methyltransferase 1 [DNMT1]) to the transcription factors, repressing instead of activating proliferation-terminating differentiation target genes. Importantly, inhibiting these specific corepressors (e.g., DNMT1) renews differentiation and restores physiologic, p53/p16-independent cell cycle exits. Wonderfully, the same treatments increase self-renewal of normal stem cells, which express high levels of master stem cell transcription factors, not differentiation-driving transcription factors.

Dealing with Decitabine Inactivation

The deoxycytidine analog decitabine depletes DNMT1 and can potentially translate this science into a therapeutic strategy. (Decitabine and 5-azacytidine are the only FDA-approved drugs that

KEY POINTS

Most disseminated cancers are difficult to treat, with few cures and high therapeutic failure rates.

Radiation and many drugs are intended to be cytotoxic (apoptotic), but the single most commonly inactivated gene in all cancer types — *p53* — subverts cytotoxic oncotherapeutic intent.

Differentiation, not apoptosis, is the main physiologic control on cell growth and division in metazoa.

Noncytotoxic differentiation treatment via inhibition of specific corepressors can be broadly effective, sparing normal stem cells and circumventing mutational apoptosis defects in cancer cells.

can be repositioned for noncytotoxic corepressor inhibition). With NIH support, we demonstrated that repositioning decitabine to avoid cytotoxicity and increase DNMT1 depletion was remarkably safe and effective in treating myelodysplastic syndromes, including in elderly subjects with multiple comorbidities.

Historically, however, use of decitabine to deplete DNMT1 in solid tissue cancers has been unsuccessful in the clinic, most likely because of the enzyme cytidine deaminase (CDA), which rapidly inactivates decitabine, severely curtailing solid tissue distribution and oral bioavailability and drastically abbreviating in vivo half-life to ~10 minutes compared with ~12 hours in vitro.

To address this severe pharmacokinetic problem, we have combined decitabine with an inhibitor of CDA — tetrahydrouridine (THU) — and proved in mice, baboons and humans (phase 1 clinical trial) that the combination produces ~ tenfold improvement in oral bioavailability, as well as the low Cmax and multihour Tmax needed for noncytotoxic DNMT1-depletion by decitabine in multiple tissues.

Building on the previous clinical trial, the National Cancer Institute's Myeloproliferative Disorders (MPD) Research Consortium will conduct a multicenter trial of oral THU-decitabine in transfusion-dependent MPDs. This has been an academic drug development effort at Cleveland Clinic, but we have managed to raise the funds to also initiate clinical trials of this approach to treat p53-mutated/deleted solid tumor malignancies, and will begin clinical trials in 2015. We hope to demonstrate that oral THU-decitabine administration can actualize DNMT1's potential as a clinically relevant molecular target, with a distinctive p53/p16 pathway of action that can meaningfully salvage (without toxicity) refractory/resistant metastatic solid tumors and liquid malignancies.

A Way Forward

Differentiation, not apoptosis, is the main physiologic control on cell growth and division in metazoa. Yet in contrast to hundreds of treatments whose intent is cytotoxicity — an essentially futile goal in the face of p53/p16-inactivation — there are only two oncotherapeutics used in the clinic with explicit noncytotoxic differentiation intent: all-trans retinoic acid (ATRA) and arsenic. Unfortunately, for mechanistic reasons, ATRA and arsenic activity is restricted to the rare myeloid cancer acute promyelocytic leukemia.

Science indicates that noncytotoxic differentiation treatment via inhibition of specific corepressors can be broadly effective, sparing normal stem cells and circumventing mutational apoptosis defects in cancer cells. Addressing these most common genetic alterations in cancer in this rational way hopefully will decrease drug failures in phase 2 and 3 trials, thereby reducing the overall cost of cancer drug development that currently is shifted to patients and the public. We plan to determine whether oral THU-decitabine can be the first of many agents to translate this science and begin to correct an irrational imbalance in the oncotherapeutic portfolio.

New Director of Cleveland Clinic's Melanoma Program Sees Rapid Advances in Targeted Therapies

A strong research enterprise and a tradition of pioneering diagnostic and therapeutic approaches strategically position Cleveland Clinic's Melanoma Program to improve patient outcomes, the program's recently appointed leader says.

Dr. Ernstoff can be reached at ernstom@ccf.org or 216.444.0888.

"The opportunity to lead an outstanding team of colleagues in our work to advance the health of patients with melanoma is a privilege and honor," says Marc Ernstoff, MD, who was named Director of the Melanoma Program in mid-2014.

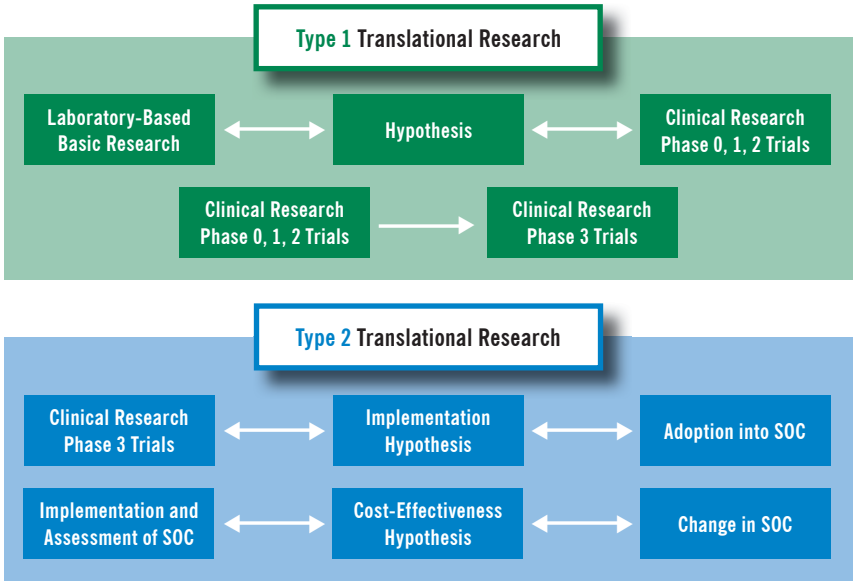
The burgeoning understanding of the nature of melanoma at the molecular level is spurring the rapid development of new tools to improve therapy.

"We have entered an era where technology and knowledge have converged to provide unprecedented benefit for melanoma patients," Dr. Ernstoff says. "These exciting scientific developments, along with Cleveland Clinic's success at assembling a multidisciplinary group of scientists and physicians, provide a strong foundation for us to contribute to improving melanoma diagnosis, refining risk assessment and prognosis, and advancing new therapies."

A Two-Way Flow for Translational Melanoma Research

The Melanoma Program utilizes a two-step, bidirectional model of translational research as the underpinning for cancer care (see Figure 1). The first step moves basic science and biological concepts developed in the laboratory through preclinical testing and into clinical care. This aspect of the plan provides melanoma patients with access to leading-edge diagnostic and therapeutic approaches through the opportunity to participate in proof-of-principle and first-in-human research protocols.

Figure 1. **Bidirectional model of translational research.**



SOC = Standard of Care

KEY POINTS

Marc Ernstoff, MD, the new Director of Cleveland Clinic's Melanoma Program, is a veteran researcher whose career has been devoted to expanding understanding of the immunobiology of human cancer and the development of new immune therapies for renal cell carcinoma, melanoma and glioblastoma multiforme.

Under Dr. Ernstoff's direction, the Melanoma Program will utilize a two-step, bidirectional model of translational research as the underpinning for cancer care.

Conversely, observations from patients' participation in early-phase clinical trials allow laboratory scientists to enhance the relevance of their research on human disease. Positive results from early clinical trials are expanded in phase 2 and 3 studies to confirm the findings and determine whether they should be the basis for practice changes.

New Targeted Therapeutic Options

"The geometric growth of our understanding of oncogenesis has led to rapid changes in the therapeutic landscape, with an explosion of new agents that have a high likelihood of success," Dr. Ernstoff says. "Our greater understanding of the molecular basis of melanoma carcinogenesis, tumor progression and metastasis — and the increasing knowledge of immune networks and regulation — has provided us with new targeted tools to interrogate melanoma biology and improve therapy."

Since 2011, the Food and Drug Administration has approved five new agents for metastatic melanoma, including three targeted agents (vemurafenib, dabrafenib and trametinib) and two new immune therapies (ipilimumab and pembrolizumab). Many more targeted agents and immune therapies are poised for emergence into clinical care in the next few years.

Exchanging Ideas, Advancing Discoveries

"My vision for Cleveland Clinic's Melanoma Program is an integrated, systemwide management approach to melanoma patients based on hypothesis-driven and evidence-based care," says Dr. Ernstoff. "This team approach will permit the free interchange of ideas between laboratory and clinical scientists. It will also provide a mechanism to advance the discoveries from our clinical trials into the broader Cleveland Clinic network and beyond in a cost-effective and compassionate manner, improving the health outcomes of the melanoma population and those at risk for getting this cancer."

A Career Steeped in Research

During his 30-year career, Dr. Ernstoff has focused his clinical research on expanding understanding of the immunobiology of human cancer and the development of new immune therapies for renal cell carcinoma, melanoma and glioblastoma multiforme. He has participated in National Cancer Institute-funded clinical trials with a goal of minimizing regulatory and suppressive pathways and enhancing existent tumor-specific immune function.

Dr. Ernstoff has published more than 200 original research manuscripts in the areas of renal cell cancer, melanoma and immune therapy strategies, including cytokine therapies, dendritic cell vaccines, immune checkpoint inhibition, targeted therapies and ex vivo expanded effector cells for adoptive transfer.

Dr. Bolwell is Chairman of Taussig Cancer Institute. He can be reached at bolwelb@ccf.org or 216.444.6922. On Twitter: @clebmt.

Patient Support Is Paramount in New Cancer Facility

The psychological impact of a cancer diagnosis is profound.

"When someone hears that they have cancer, it is a life-changing two or three seconds," says Cleveland Clinic Taussig Cancer Institute Chairman Brian J. Bolwell, MD, FACP.

"They are filled immediately with anxiety and fear. A cancer diagnosis may not always be a medical emergency, but it is always a psychological emergency."

(continued on page 24)

NEW CANCER FACILITY
(CONTINUED)

Cleveland Clinic's new cancer care building, opening in 2017, is designed for easy access to the array of patient support services intended to reduce cancer's psychological stress. Those services will occupy most of the first floor of the $276 million, 377,000-square-foot outpatient tower currently under construction.

Conserving Resources, Aiding Well-Being

"We strongly believe in the benefits of such programs, which range from reiki to relaxation therapy to mentoring," Dr. Bolwell says. "They are not always easy to quantify scientifically. But what we do know is that patients with cancer and a psychiatric diagnosis consume six times more healthcare resources than those without a psychiatric diagnosis. If you manage anxiety and other stress-related issues, you can significantly reduce resource utilization. It is also the right thing to do for the well-being of patients and their families."

Dr. Bolwell and other Cleveland Clinic officials toured numerous cancer facilities around the country to compile best-practice ideas for the new building's design. Patient comfort and convenience were paramount on their lists.

"In almost every cancer facility, the thing that I really did not like were the lines in which patients had to wait to get their blood drawn," Dr. Bolwell says. "A quote from a cancer patient that sticks with me is, 'If I have six months to live, waiting four hours to get chemotherapy is a big deal to me.' We have dedicated a lot of space in the new building to try to make sure that does not happen." That includes a sizable blood-testing laboratory on the first floor.

Light and Space for Patients

The open-plan first level — suffused with natural light from floor-to-ceiling windows — also will contain an outpatient pharmacy; a retail store stocked with items to meet cancer patients' needs, such as skin care lotion for dry hands; and a cafeteria with food offerings to accommodate special dietary needs and medical conditions.

The first floor will be home to:

- A resource center where patients and families can access printed and online cancer information.
- Art and music therapy spaces.
- A boutique where patients with chemotherapy-associated hair loss can receive free wigs, caps and scarves.
- A wellness center for reiki, reflexology, guided imagery, facials and other aesthetic services.
- A private prosthetics fitting area.
- The 4th Angel Mentoring Program, an initiative begun by figure skating champion and Cleveland Clinic cancer patient Scott Hamilton to provide patients with free, confidential, one-on-one advice and support from a trained volunteer and cancer survivor.
- A spiritual area where patients and families can go for prayer or meditation.

"There is a reason for having all these services on the first floor of our new cancer center," Dr. Bolwell says. "We want to show patients as they first walk in that this is a warm and inviting atmosphere, and that we understand what they are going through. We understand that they are scared, and we have a lot of caregivers and programs right in front of them to help."

Renderings courtesy of William Rawn Associates, Architects, Inc. and Stantec Inc.

HIGHLIGHTS from the

ASCO

ANNUAL MEETING

Cleveland Clinic physicians and investigators made major contributions to the 2015 American Society of Clinical Oncology Annual Meeting in Chicago, reporting results from a number of significant studies. Here are abstracts from six of those research projects. (Cleveland Clinic authors are listed in bold.)

For a complete listing of ASCO abstracts, go to **http://abstracts.asco.org**

Impact of BRAF Mutation in Patients with Brain Metastasis from Melanoma

Vyshak Alva Venur, MD; Rupesh Kotecha, MD; Zhijian Chen, MD, PhD; Samuel T. Chao, MD; Paul Elson, ScD; John H. Suh, MD; Manmeet Singh Ahluwalia, MD

Background: Melanoma patients with brain metastasis (MBM) have a dismal prognosis. BRAF mutation occurs in approximately 50% of patients with metastatic melanoma; however, its impact on MBM outcomes is unknown. We evaluated the prognostic significance of BRAF mutation in MBM at our institution.

Methods: With Institutional Review Board approval, the Cleveland Clinic Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center's database was used to identify MBM patients. Overall survival (OS) from the diagnosis of MBM was the primary end point. OS was summarized using the Kaplan-Meier method and analyzed using the logrank test.

Results: 256 patients with MBM were treated between 2000 and 2013. BRAF status was available for 76 MBM. BRAF mutation was present in 35 patients; 41 had wild type BRAF. V600 mutations were present in 28 patients (21V600E mutations, 4 V600K). The median interval from melanoma diagnosis to BM was 22.2 months (m). Median age at diagnosis was 63 years (26-85), 65% were male, and 67% were symptomatic at presentation. KPS was 90-100 in 45%, 80 in 28% and < 80 in 27% of MBM. Stereotactic radiation (SRS) ± surgery was the initial modality of treatment in 33 (43%) and whole-brain radiation therapy (WBRT) ± surgery in 28 (37%) patients. 18 patients received vemurafenib (VEM) after BM. Median OS for the 76 patients was 6.2 m OS in BRAF (+) patients was 8.8 m while in BRAF (-) it was 5.4 m. In patients treated with WBRT ± other modalities, the BRAF (+) and BRAF (-) patients had OS of 4.6 m and 5.4 m respectively. In patients treated with SRS ± other modalities, BRAF (+) had OS of 18.6 m while BRAF (-) had 5.5 m.

Conclusions: In this small cohort of MBM, SRS ± other modalities improved survival in BRAF (+) patients compared with BRAF (-). A prospective trial to validate this finding is planned.

Impact of a Stage IV NSCLC Care Pathway on Front-line (FL) and Maintenance (M) Chemotherapy Use at Cleveland Clinic Taussig Cancer Institute (TCI)

Marc Shapiro, MD; James Stevenson, MD; Emily Van Wagoner; Kate Glass, MPH, MS; Chad Cummings; Nathan Pennell, MD, PhD; Patrick Ma, MD; **Vamsidhar Velcheti, MD; Bruno Bastos, MD; Abdo Haddad, MD; Brian Bolwell, MD, FACP**

Background: Care pathways can reduce cancer care costs and variability in non-small cell lung carcinoma (NSCLC). Effective implementation requires measurable outcomes and available data in near real-time.

Methods: Between 10/1/13 and 7/7/14, TCI developed an evidence- and value-based stage IV NSCLC pathway. For patients with non-squamous EGFR WT/ALK negative NSCLC, ECOG PS 0-2 and sufficient renal function, FL carboplatin/pemetrexed (pem) followed by M pem is recommended standard care, while bevacizumab (bev) is not. The pathway recommends best supportive care for pts with ECOG PS ≥ 3. To test feasibility, 4 academic thoracic and 12 community oncologists implemented the pathway into their practices starting 7/7/14. This analysis studies pathway impact on FL and M treatment decisions and charges in patients with metastatic non-squamous EGFR WT/ALK negative NSCLC. 57 pts meeting pathway criteria initiated care with these oncologists from 7/7/14 to 12/31/14 (Cohort A). A retrospective cohort (Cohort B) of 181 pts meeting similar criteria initiated care from 1/1/12 to 7/1/13. Care patterns were defined by manual chart review through 1/8/15. As only 1 Cohort A pt has progressed on M therapy, charge results assume pts who have initiated M pem will receive the same average of 5.11 doses seen in Cohort B. For Cohort B, actual FL and M therapy charges are reported. 3 Cohort B pts remain on M therapy.

Results: Care patterns in Cohorts A and B were compared. 53 (93%) vs 128 (71%) ($p = 0.0003$) pts received pathway recommended FL care respectively. 42 (74%) vs 110 (61%) received chemotherapy ($p = 0.0839$). In pts receiving FL platinum-based regimens, 2 (6%) vs 35 (39%) received bev ($p < 0.0001$) outside of pathway recommendations. In Cohort A, 6 (32%) completing FL therapy initiated M therapy vs 36 (40%) in Cohort B. In pts completing FL therapy, FL and M drug charges per pt were an estimated $107,258 vs $205,431 (48% decrease).

Conclusions: Implementation and measurement of adherence to a stage IV NSCLC pathway is feasible at an academic oncology practice with a regional network. This implementation led to a significant improvement in care variation and a nearly 50% reduction in chemotherapy charges primarily through decreased bev use.

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ASCO (CONTINUED)

Prospective Clinical Study of Precision Oncology in Solid Tumors

Davendra P.S. Sohal, MD, MPH; Brian I. Rini, MD; Alok A. Khorana, MD; Robert Dreicer, MD; **Jame Abraham, MD; Gary W. Procop, MD; Yogen Saunthararajah, MD; Nathan A. Pennell, MD, PhD; James P. Stevenson, MD; Robert Pelley, MD; Bassam Estfan, MD; Dale Shepard, MD, PhD; Pauline Funchain, MD; David J. Adelstein, MD; Brian J. Bolwell, MD, FACP**

Background: Advances in tumor genomic profiling offer the promise of precision oncology, but a systematic prospective evaluation is lacking. We conducted a prospective cohort study of tumor genomic testing to identify prevalence of actionable alterations and their impact on management decisions.

Patients and Methods: Patients provided written informed consent for this prospective cohort study approved by Cleveland Clinic's Institutional Review Board. Eligibility requirements included pathologic diagnosis of select solid tumor malignancies without a known curative option, age ≥ 18 years and ECOG PS 0-2. Tumor samples were sequenced for as many as 315 candidate genes using FoundationOne® (Cambridge, MA). Results were reviewed by Cleveland Clinic's Genomics Tumor Board (GTB) for biologically actionable alterations, defined as those linked to an approved therapy in the solid tumor under study or another solid tumor, a clinical trial, or a contraindication to a targeted therapy. Sample size was 250 patients. Outcomes were feasibility and clinical impact of tumor sequencing.

Results: From Aug 2013 to Oct 2014, all 250 patients were enrolled. Median age was 60 years; 128 (51%) were female; 220 (88%) were white. Colorectal (25%), breast (18%), lung (13%), pancreatobiliary (12%), and head and neck (10%) cancers were common diagnoses. Median time from consent to genomic test result was 25 days (range, 3-140), with 27 (11%) samples having insufficient tissue for analysis. Of 223 resulted samples, an alteration was found in 96% (n = 214), with a median of 4 (0-20) alterations per sample. At GTB review, a biologically actionable alteration was declared in 63% (n = 141) of cases. However, only 10% (n = 22) of patients received tumor genomics-driven targeted therapies: 12 went on clinical trials, 3 received on-label drugs, and 7 received off-label drugs. Lack of clinical trial access was the most common reason for non-recommendation/receipt of genomics-driven therapy.

Conclusions: This prospective study shows that routine tumor genomic profiling is feasible, with almost two-thirds of resulted samples having a biologically actionable alteration, but a paucity of genomics-driven clinical trials of targeted therapies is a barrier to the success of precision oncology.

Can Oncology Readmissions Be Reduced? The Cleveland Clinic Experience

Alberto J. Montero, MD; James Stevenson, MD; Amy E. Guthrie; Carolyn Best, NM; Lindsey Martin Goodman, MD; Armida Parala, MD; Ruth Lagman, MD; Brian J. Bolwell, MD, FACP; Matt E. Kalaycio, MD; Alok A. Khorana, MD

Background: Reducing 30-day readmissions is a national policy priority. Readmissions in medical oncology patients have not been extensively evaluated and may not be reasonably preventable. We examined the impact of interventions focused on reducing oncology readmissions in the palliative medicine (PM) and general medical oncology (GMO) units.

Methods: Baseline rates of readmissions were gathered in the period January 2013 to March 2014. Interventions were initiated in the period leading to April 1, 2014, including: (i) provider education, (ii) within 48 hours post-discharge, nursing phone calls, and (iii) within 5-day post-discharge, provider follow-up appointments. Calling nurses performed symptom management, provided education and encouraged prescription/appointment compliance.

Results: There were a total of 3,729 combined admissions and 1,003 readmissions in the baseline period, for a readmission rate of 26% for PM and 27% for GMO units. In the 8-month intervention period (May-Dec 2014), there were 1,694 admissions and 396 readmissions. Callbacks and 5-day appointments were monitored with a mean compliance of 77% and 70%, respectively, improving during the study period. PM readmission rates declined by 5% to 21% ($p = 0.01$, relative risk reduction 19%). GMO readmissions also decreased by 3% to 24% ($p = 0.02$, relative risk reduction 11%). The mean total cost of one readmission was $18,365, suggesting an annual potential cost savings of $2.91 million with the observed reduction in readmissions.

Conclusions: Readmission reductions in both units were achieved through better systematic transitions to outpatient care, including follow-up calls and early provider visits, thereby leading to a reduction in utilization of inpatient resources. These data suggest that efforts focused on improving outpatient care transition are effective in reducing oncology readmissions. This is particularly relevant in the transition toward novel bundled payment models in oncology. The observed feasibility and patient/provider acceptance of these interventions suggests sustainability, which will be validated over longer time periods.

Clinical Predictors of Recurrent Venous Thromboembolism (VTE) in Cancer Patients from a Randomized Trial of Long-term Tinzaparin Versus Warfarin for Treatment — the CATCH Study

Alok A. Khorana, MD; Rupert Bauersachs, MD; Pieter W. Kamphuisen, MD, PhD; Guy Meyer, MD; Mette S. Janas, MD, PhD; Mikala F. Jarner, MSc; Agnes Y.Y. Lee, MD; on behalf of the CATCH Investigators

Background: Cancer patients with VTE continue to remain at high risk for recurrent VTE even with adequate anticoagulation. We determined baseline clinical predictors of recurrent VTE, including the previously developed Ottawa Score, in a pre-specified analysis of the CATCH study.

Methods: The CATCH study was a randomized, open-label, multicenter Phase III trial (NCT01130025) comparing tinzaparin 175 IU/kg once daily for 6 months with initial tinzaparin transitioning to dose-adjusted warfarin (target INR 2-3) for 6 months in patients with active cancer and acute, symptomatic proximal deep vein thrombosis and/or pulmonary embolism. Clinical predictors of recurrent events were identified using Fisher's exact test; competing risk regression analysis was then conducted accounting for multiple variables.

Results: We evaluated multiple clinical variables present at or prior to randomization. Of 900 randomized patients, 492 (54.7%) had metastatic disease, 288 (32.0%) were on chemotherapy, 286 (31.8%) had recent hospitalization, 209 (23.2%) had ECOG performance status 2, 129 (14.3%) had venous compression from mass or adenopathy and 92 (10.2%) had recent radiation therapy; VTE occurred in 6.9% of the tinzaparin arm versus 10.0% of the warfarin arm (HR 0.65; 95% CI 0.41-1.03), as reported. In multivariate analysis, risk factors associated with recurrent VTE included venous compression (HR 2.96; 95% CI 1.8-4.86; $p < 0.001$) and diagnosis of hepatobiliary cancer (HR 2.91; 95% CI 1.2-7.02; $p = 0.018$). Ottawa score did not predict for recurrence risk, with recurrent VTE rates of 3.4, 9.7 and 8.2% in low-, intermediate- and high-risk groups, respectively.

Conclusions: Cancer patients with acute VTE are at significant risk for recurrent events, despite anticoagulation. Major clinical predictors of recurrence include tumor venous compression and a diagnosis of hepatobiliary cancer. More intense treatment strategies for higher-risk patients should be considered.

Expanded Cohort Results from CheckMate 016: a Phase I Study of Nivolumab in Combination with Ipilimumab in Metastatic Renal Cell Carcinoma (mRCC)

Hans J. Hammers; Elizabeth R. Plimack; Jeffrey R. Infante; **Brian I. Rini;** David F. McDermott; **Marc S. Ernstoff;** Martin H. Voss; Padmanee Sharma; Sumanta K. Pal; Albiruni Razak; Christian Kollmannsberger; Daniel Y.C. Heng; Jennifer Spratlin; Yun Shen; Paul Gagnier; Asim Amin

Background: Nivolumab (N), a fully human IgG4 immune checkpoint inhibitor antibody, has shown durable response and encouraging overall survival (OS) in mRCC. Previously in CheckMate 016, N + ipilimumab (I) demonstrated manageable safety and promising antitumor activity in mRCC. Here, we report results from expansion cohorts in this study (NCT01472081).

Methods: Patients (pts) with mRCC were randomized to N 3 mg/kg + I 1 mg/kg (N3 + I1), N 1 mg/kg + I 3 mg/kg (N1 + I3) or N 3 mg/kg + I 3 mg/kg (N3 + I3) IV Q3W for 4 doses, then N 3 mg/kg IV Q2W until progression or toxicity. Primary end point: safety. Other end points: objective response rate (ORR), duration of response (DOR), OS. DOR and OS were assessed by Kaplan-Meier method.

Results: Pts randomized to N3 + I1 and N1 + I3 cohorts were expanded to 47 pts per arm; N3 + I3 (n = 6) arm showed early toxicity and did not proceed to expansion. 53% and 47% of pts were treatment-naive and previously treated in N3 + I1; 45% and 55% were in N1 + I3. Median (range) follow-up was 34.3 (15.4-80.1) wks in N3 + I1 and 31.3 (4.6-79.9) wks in N1 + I3. Treatment-related adverse events (AEs) were seen in 88% of pts. Discontinuations for any grade AE occurred in 16% of pts. Grade 3-4 treatment-related AEs occurred in 34% and 64% of pts in N3 + I1 and N1 + I3, respectively; most common: ↑ lipase (13% and 26%), ↑ ALT (4% and 19%), diarrhea (2% and 15%), colitis (0 and 13%), ↑ AST (4% and 9%), and ↑ amylase (4% and 9%). Most common grade 3-4 select AEs were GI and hepatic (N3 + I1, N1 + I3); GI: 2%, 23%; hepatic: 4%, 21%.

Conclusions: Updated results from expanded cohorts in CheckMate 016 confirm initial safety findings and promising antitumor activity for N + I in pts with mRCC. OS results for N + I in mRCC appear encouraging and support further development of this combination in the first-line setting.

New Staff

Hematologist Anne Neff, MD, a highly regarded clinician and researcher with expertise in hemostasis and thrombosis as well as red cell and platelet disorders, has joined Cleveland Clinic's Department of Hematology and Medical Oncology.

Previously, Dr. Neff was Professor of Medicine and Pathology, Microbiology and Immunology at Vanderbilt University School of Medicine, and Director of the Vanderbilt Hemostasis and Thrombosis Clinic at Vanderbilt University Medical Center.

"We are excited to welcome Dr. Neff to our staff," says Matt Kalaycio, MD, Chairman of the Department of Hematology and Medical Oncology. "She is a nationally recognized expert in bleeding disorders, with extensive experience in blood banking and hematopoietic stem cell apheresis. In addition to conducting a clinical practice in benign hematology, Dr. Neff will contribute to the academic mission of our department by helping with the fellowship program and directing research efforts involving bleeding disorders."

Dr. Neff has held leadership and/or advisory positions in the American Association of Blood Banks, the American Society of Hematology, the Tennessee Association of Blood Banks and the local chapters of the National Hemophilia Foundation and the American Red Cross Blood Center. She is the recipient of the Tennessee Association of Blood Banks' 2004-2005 President's Award and its 2008 Lemuel W. Diggs Award for significant and lasting contributions to blood banking in Tennessee.

Dr. Neff conducts clinical research in hemophilia and other bleeding and blood disorders, and has authored numerous research publications, abstracts and book chapters.

She is board-certified in internal medicine, hematology and blood banking/transfusion medicine.

Dr. Neff received her medical degree from the University of Missouri. She completed her medical internship at Indiana University Hospitals, her medical residency at the University of Missouri and her hematology training at Vanderbilt University Medical School.

Dr. Neff can be reached at neffa@ccf.org or 216.444.6833.

Nima Sharifi, MD, Earns Prostate Cancer Foundation Grants for Game-Changing Castration-Resistance Research

Cleveland Clinic medical oncologist and prostate cancer researcher Nima Sharifi, MD, is a recipient of two of the six 2015 Challenge Awards presented by the Prostate Cancer Foundation (PCF).

The peer-reviewed, highly competitive grants are intended to support innovative research that has the potential to make near-term, "game-changing" impacts on prostate cancer diagnosis and treatment.

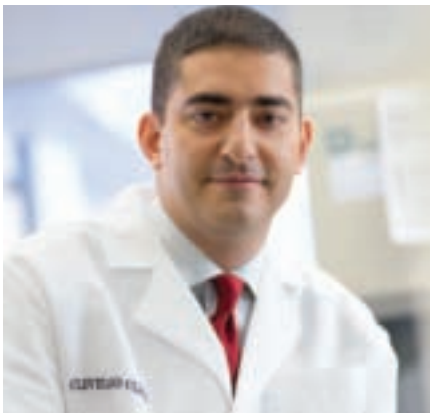
Dr. Sharifi is the principal investigator on one of the 2015 Challenge Award-winning projects and a co-investigator on the second, each of which provides the research team $1 million over two years. His research focuses on metabolic and molecular mechanisms of resistance to hormonal therapy in prostate cancer.

"These awards recognize the outstanding prostate cancer research at Cleveland Clinic and continue to build on our tradition of team science that has substantive benefits for patient care," said Eric A. Klein, MD, Chairman of Cleveland Clinic's Glickman Urological & Kidney Institute.

Probing Treatment Resistance

When patients with late-stage or aggressive prostate cancers undergo chemical or surgical castration, their tumors shrink due to testosterone deprivation. However, tumors often recur, forming ultimately lethal castration-resistant prostate cancer (CRPC).

CRPC tumors gain their resistance to androgen-deprivation therapy by reactivating the androgen receptor. Tumors accomplish this primarily by acquiring the ability to synthesize their own 5α-dihydrotestosterone (DHT) from adrenal precursor steroids. Dr. Sharifi's research has demonstrated the involvement of a previously underappreciated intermediate steroid metabolite — 5α-androstanedione — in prostate tumors' synthesis of DHT. In 2013, Dr. Sharifi's lab identified the first example of a mutation



that increases DHT synthesis to promote hormone therapy resistance. This mutation can also be inherited as a variant of the enzyme 3β-hydroxysteroid dehydrogenase-1 (3βHSD1), which boosts the conversion of precursor steroids to DHT, thus enabling tumors to grow in the absence of gonadal testosterone.

Seeking a CRPC Biomarker

The PCF Challenge Award-winning project for which Dr. Sharifi is the principal investigator aims to develop a diagnostic test to identify patients with the variant of 3βHSD1 that predisposes them to CRPC. This actionable biomarker could inform therapeutic decision-making and lead the way to tailored treatment, such as more intensive upfront hormonal therapy along with castration therapy, potentially increasing symptom-free and overall survival. Dr. Sharifi will lead a multidisciplinary team of basic scientists and clinicians at Cleveland Clinic and Mayo Clinic on the project.

"This grant provides the potential to change the standard of care in treatment-resistant prostate cancer," Dr. Sharifi said. "This kind of strategy of personalized medicine will help us further our understanding of this deadly disease."

Dr. Sharifi is a co-investigator on a second PCF Challenge Award-winning project that seeks to identify early biomarkers of anti-androgen treatment resistance. He will work with investigators from the University of Michigan and Washington University, using next-generation sequencing of prostatectomy specimens banked from a large clinical trial of radiation plus hormonal therapy to look for intrinsic resistance biomarkers and to define the clinical impact of the genetic alterations.

"Cleveland Clinic has one of the finest academic and clinical prostate cancer programs in the world," said Taussig Cancer Institute Chairman Brian J. Bolwell, MD, FACP. "Dr. Sharifi's brilliant research has a very real opportunity to improve patient care worldwide."

Supporting High-Risk, High-Impact Science

The PCF Challenge Awards go to high-risk, first-in-field and currently unfunded cross-disciplinary research projects that don't fit conventional funding organizations' requirements. Submissions undergo two rounds of peer review and are assessed for clinical relevancy and their potential to have near-term impact on standard of care. Fifty-five applicants representing 48 institutions in 13 countries competed for the 2015 awards.

Dr. Sharifi received a PCF Young Investigator Award in 2008 and was a co-investigator on a previous Challenge Award. He won the 2014 American Association for Cancer Research Award for Outstanding Achievement in Cancer Research, and previously received the Howard Hughes Medical Institute Physician-Scientist Early Career Award and the American Cancer Society Research Scholar Award.

Dr. Sharifi holds the Kendrick Family Endowed Chair for Prostate Cancer Research in Cleveland Clinic Lerner Research Institute's Department of Cancer Biology. He is an associate staff member of the Glickman Urological & Kidney Institute's Department of Urology and the Taussig Cancer Institute's Department of Hematology and Medical Oncology. He received his medical degree from the University of Pittsburgh School of Medicine. He completed his internal medicine residency at Yale-New Haven Hospital and his medical oncology fellowship at the National Cancer Institute.

Dr. Sharifi can be reached at sharifn@ccf.org or 216.445.9750.

CME Opportunities

The first segment of **Cleveland Clinic's Tumor Board Series**, a free continuing medical education webcast, is available for viewing at ccfcme.org/tumorboards.

The segment, **"Management of Locally Advanced HER2-Positive Breast Cancer,"** has been approved for AMA PRA Category 1 Credit.™

This webcast provides expert insight on optimizing treatment of patients with HER2-positive early-stage/locally advanced breast cancer. It consists of a case presentation. Cleveland Clinic and University of Florida Health Cancer Center faculty present various aspects of the case, including radiologic imaging, pathologic findings (particularly HER2 testing) and options for neoadjuvant therapy with HER2-targeted agents. Suggested treatment options based on best practices, current treatment guidelines, and data from relevant recent clinical trials are discussed. Recommendations regarding surgical resection, options for adjuvant therapy with chemotherapy and targeted agents, and postsurgical radiation therapy also are addressed.

This CME activity is designed for practitioners including medical oncologists, surgical oncologists and general surgeons, radiation oncologists, radiologists, pathologists, and other healthcare professionals who manage patients with breast cancer.

The 18th International Symposium on
Palliative Medicine and Supportive Oncology

Cleveland, July 23-25, 2015
Cleveland Marriott Downtown at Key Center

The symposium will provide an intensive multidisciplinary review of a wide variety of topics in the rapidly developing field of palliative medicine and supportive oncology. Speakers will explore potential solutions to improve the quality of care of patients with chronic illnesses through palliative and supportive oncology therapies. Parallel workshops will focus on falls prevention and starting a home-based palliative medicine program.

The CME symposium is intended for healthcare professionals including hematologists/oncologists, family practice physicians, internal medicine physicians, physician assistants, advanced practice nurses, nurses, social workers, pharmacists and hospice care providers.

Deadline for registration is July 21, 2015. For more information and to register, visit ccfcme.org/pallmed15.

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Stay up to date on Cleveland Clinic's more than 100 active clinical trials for cancer patients. Our free Cancer Clinical Trials app — available for iPhone®, iPad®, Android™ phone and Android tablet — makes it easy.

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Connect to our Cancer Answer Line for more information about a trial or to enroll patients.

"Making clinical trials accessible offers patients important treatment options," says Brian I. Rini, MD, FACP, of the Department of Hematology and Medical Oncology. "This app is one more way for doctors to know what trials are available, in real time."

To download, go to clevelandclinic.org/cancerclinicaltrials

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

Please direct correspondence to:

Taussig Cancer Institute/R35
Cleveland Clinic
9500 Euclid Ave.
Cleveland, OH 44195

Cleveland Clinic Taussig Cancer Institute annually serves more than 20,000 cancer patients. More than 250 cancer specialists are committed to researching and applying the latest, most effective techniques for diagnosis and treatment to achieve long-term survival and improved quality of life for all cancer patients. Taussig Cancer Institute is part of Cleveland Clinic, an independent, nonprofit, multispecialty academic medical center.

Cleveland Clinic

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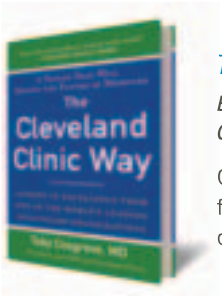

The Cleveland Clinic Way

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

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

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Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,200 physicians and scientists represent 120 medical specialties and subspecialties. We are a main campus, 18 family health centers, eight community hospitals, more than 75 northern Ohio outpatient locations (including 16 full-service family health centers), Cleveland Clinic Florida, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City and Cleveland Clinic Abu Dhabi.

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

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