

# ADVANCES IN ONCOLOGY



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**INSIDE THIS ISSUE**

**5** Ongoing Research in Early-Stage Invasive Breast Cancer Treatment



## Targeting Early Breast Cancers with Ablation Therapies

Surgeons at NewYork-Presbyterian/Columbia University Medical Center are turning up the heat (or cold as the case may be) on early-stage breast cancer tumors with the use of ablation therapies.

“Surgery is the oldest oncologic discipline and, in fact, it is still the most effective therapy for cancer,” says **Margaret Chen, MD**, a breast surgeon and Director of Clinical Operations in the Clinical Breast Cancer Program in Columbia’s Department of Surgery. “However, surgery is also associated

with pain and scarring, which has led us to look for other ways to treat breast tumors. Laser ablation treatment provides a minimally invasive alternative to lumpectomy, while still preserving options for additional procedures or adjuvant therapies.”

Traditionally, early-stage breast cancer nodules have been removed by lumpectomy, which can have an unfavorable cosmetic effect on the breast, says Dr. Chen, whose primary clinical interest is minimally invasive breast surgery. “Moreover, during a lumpectomy, it is not possible to perfectly define the extent of the cancer or know precisely which tissue to excise. As a result, 20 to 30 percent of women require a second lumpectomy to remove remaining cancerous tissue. Even after a second lumpectomy, microscopic remnants may persist, leading to mastectomies in 8 percent of patients.”

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**“Laser ablation treatment provides a minimally invasive alternative to lumpectomy, while still preserving options for additional procedures or adjuvant therapies.”**  
— Dr. Margaret Chen

## Neoadjuvant Therapy in Breast Cancer: A New Raison D’être

“Human breast tumors are diverse in their natural history and in their responsiveness to therapy,” says **Eleni Andreopoulou, MD**. A medical oncologist and Director of the Breast Cancer Research Program at NewYork-Presbyterian/Weill Cornell Medical Center, Dr. Andreopoulou specializes in breast cancers and is an integral collaborator with clinicians and scientists who study the development of cancer cells from their initial, more simple existence to discretely defined breast cancer cell types. “The dynamic status of tumor biology diversity influences the phenotype and sensitivity to treatment, and ever-growing knowledge of the early stages of the disease provides fertile ground for the development of novel therapies.”



*Dr. Eleni Andreopoulou*

The past 50 years have seen an evolution in the use of neoadjuvant chemotherapy for breast cancer. In its early days, neoadjuvant therapy was indicated for patients with inoperable, locally advanced disease. It later evolved as a preoperative treatment to downstage the disease

in order to facilitate breast conservation surgery. Today, neoadjuvant therapy offers a valuable research platform to tackle residual tumor – the most intrinsically hard-wired to invade, migrate, and metastasize. “This is a really meaningful component that has to be addressed if we’re

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## Targeting Early Breast Cancers with Ablation Therapies *(continued from page 1)*

### A Closer Look at Ablation Therapies

Laser ablation breast therapy is performed in an outpatient setting under direct ultrasound visualization so that surgeons can see the cancer in real time as they ablate it. “Under local anesthesia, we make two tiny incisions in the breast through which we insert two probes – one into the center of the tumor and one alongside the edge of the tumor.” The second thermal probe contains multiple temperature sensors and is positioned parallel to the laser probe at the periphery of the tumor within the ablation zone in order to monitor treatment progress in real time.

“The laser is then activated using thermal energy to destroy the cancerous cells,” says Dr. Chen. The procedure is typically completed in 30 to 60 minutes, and the incisions are sealed with small bandages instead of sutures. The laser treatment is less painful than lumpectomy, and causes little or no scarring while preserving the breast’s natural shape and feel. Patients also benefit from a short recovery and can generally return to normal activities within a day.

Dr. Chen served as the principal investigator at Columbia for the Ablate and Resect feasibility study of Novilase® interstitial laser therapy for the ablation of small breast cancers conducted at 11 sites in the United States and Europe. She was the first surgeon to introduce this approach to potentially treat small breast cancers without surgery. The Novilase device had already been FDA approved for the treatment of benign breast tumors, such as fibroadenomas. The Ablate and Resect study enrolled 61 patients to examine the effectiveness of laser therapy for the treatment of unifocal invasive ductal carcinoma of 2 centimeters or less.

“The tumor also had to be in an ideal position in the breast – not too close to the skin and not too close to the chest wall – so that we could treat it safely and effectively,” says Dr. Chen. “There are two challenges with ablation therapies. One is certainly the ability to determine the margin, and the other is the ability to assess any residual tumors. In the Ablate and Resect study, not only did we have pathologic exam correlation in terms of whether the tumor had been completely killed, but we also had imaging correlations. Our patients had a set of images – mammograms, ultrasound, MRI – taken before the ablation, as well as one month after the ablation. We then performed a



*Dr. Margaret Chen*

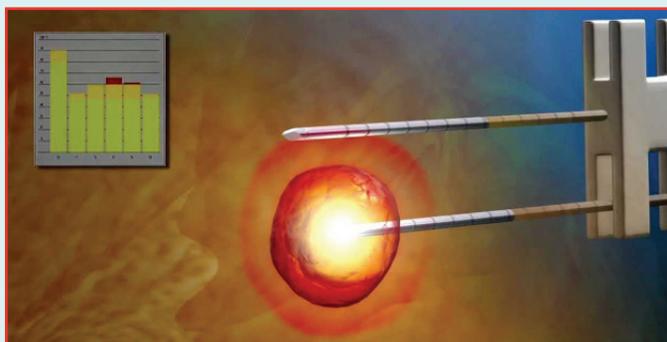
lumpectomy and compared the results of the imaging to see if there was any residual tumor after the ablation, with the pathology results, which are more definitive as to any residual tumor.”

Following surgery, patients proceeded with any recommended adjuvant or systemic therapy, such as radiation and/or chemotherapy, and were asked to return for follow-up visits with their surgeon.

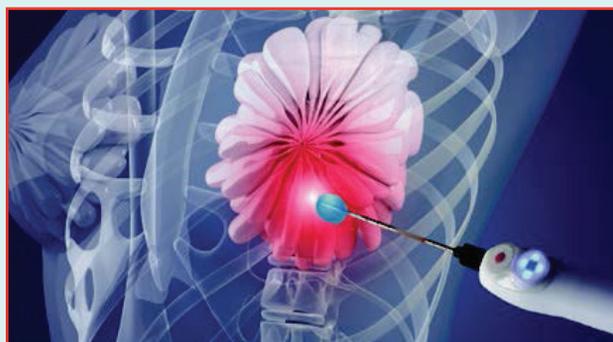
“Analysis of the results of 61 patients showed that overall, complete tumor ablation was achieved in 84 percent of the patients. Among a subset of patients whose tumors were 1.5cm or smaller, 98 percent of the tumors were completely ablated,” says Dr. Chen. “The study also found that there is a high correlation between MRI and the pathology and that the false-negative rate – that is the residual tumor missed by the MRI – was very low at 7 percent. In four patients, the MRI did not detect post-ablation residual tumor, which was discovered in the pathology once we excised it. However, in all four patients the amount of tumor that remained was very small, less than 2 millimeters. It was determined that MRI is very good and very accurate in determining any remaining tumor.”

Laser ablation appears to be a promising alternative to lumpectomy to treat early-stage breast cancer. A multicenter pivotal trial examining the use of laser ablation eliminating surgery is underway.

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*With laser ablation two probes are inserted – one into the center of the tumor and one alongside the edge of the tumor. The second thermal probe is positioned at the periphery of the tumor within the ablation zone in order to monitor treatment progress.*



*In cryotherapy, a thin, hollow needle is inserted through the skin, pumping liquid nitrogen into the tumor site and freezing the tumor.*

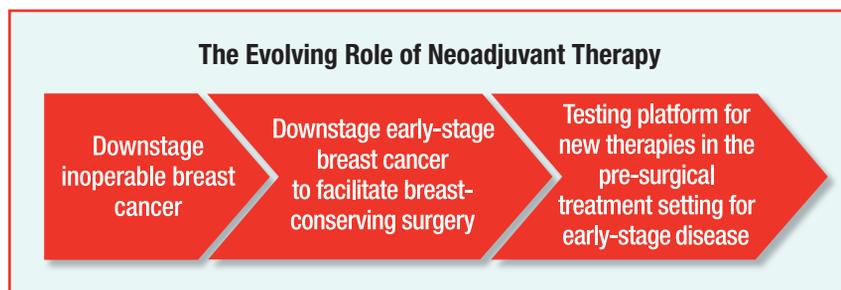
## Neoadjuvant Therapy in Breast Cancer: A New Raison D'être (continued from page 1)

talking about curing breast cancer,” says Dr. Andreopoulou, “and our final test to accomplish this is in the adjuvant setting.”

“Individuals with the same stage disease and similar pathological diagnosis can experience very different clinical courses,” adds Dr. Andreopoulou.

Drug development in the adjuvant setting for breast cancer typically has a very protracted timeline, and approvals for new drugs or regimens can take more than 10 years. According to Dr. Andreopoulou, the neoadjuvant therapy platform has the potential to accelerate the testing of new treatments, regimens, and agents. “This setting is gaining traction because it provides the opportunity to integrate biomarkers and surrogate endpoints into the process of care, allow rapid assessment of targeted therapeutics, and accelerate the development of effective therapy.”

Dr. Andreopoulou further notes that the approach offers the ability to obtain biospecimens that can serve as a baseline during the course of disease evolution. “This provides an opportunity for monitoring treatment response with serial biopsies up to and including the point of surgical excision if residual disease is present,” says Dr. Andreopoulou. “The clinical management in these recalcitrant tumors requires the focus of innovative research coupled with a commitment to translate findings into effective clinical practice, and this is what I am set to do as an academic oncologist. I work together with clinicians from all disciplines and scientists in the lab to address these problems.”



Dr. Andreopoulou notes that the biospecimen acquisition process is so important. “By assessing the status of cell fate at multiple points of treatment and tracking the disease through its evolutionary lineage, we can interrogate the impact of cancer therapies – standard or novel, targeted, or investigational. Importantly, it supports the development of a library of personalized *in vitro* and *in vivo* models other than cancer cell lines that mimic the ecosystem of aggressive breast tumors. These models retain the principal characteristics of their donor tumor and are used for high throughput drug testing with the ultimate goal to fast-track the development of effective treatment broadening our curative reach. This model has been shown to be predictive of clinical outcomes.”

“This is important,” continues Dr. Andreopoulou. “This approach can also help our understanding as to why some patients respond poorly to chemotherapy; develop novel strategies to identify and select these patients in the clinic; and finally enroll patients in clinical trials to develop alternate precision medicine treatments which can afford us better survival results.”

Modern technology platforms, such as genomics, proteomics, circulating tumor cells, and minimally invasive functional and

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— Dr. Eleni Andreopoulou

molecular imaging each has a potential role in accelerating the innovative direction taking place within the neoadjuvant setting on three fronts:

- improving the success rate and speed of drug development
- interrogating the consequences of therapeutic intervention
- providing unique insight into human disease biology

“Because of the strong relationship of response, especially pathologic complete response, to patient outcomes, neoadjuvant chemotherapy offers a valuable research platform to test new treatment agents and increase our understanding of breast cancer biology,” says Dr. Andreopoulou. “This, in turn, will lead to truly individualized therapy based on biologic and molecular parameters. Incorporating a biomarker-based selection process

in the early phase clinical trials and integrating surrogate markers of outcome as pathologic complete response rate has the potential to accelerate anticancer drug development for the care of patients with high-risk biology such as triple-negative breast cancer.”

“The administration of the same chemotherapy before surgery in the neoadjuvant setting for newly diagnosed patients with early-stage disease is as safe and as effective as the administration of these therapies postoperatively,” adds Dr. Andreopoulou.

“However, the patients with hormone receptor negative disease who will experience this pathologic complete response – eradication of the disease and all viable, invasive cancer cells from the breast and the lymph nodes – have more favorable outcomes in terms of survival. This is why this is considered to be one of the most reliable and early surrogates for a cure. In the pre-treatment setting, you can embrace different, innovative clinical trial designs as ‘adaptive’ with backbone standard chemotherapy and ‘window of opportunity’ with experimental treatment.”

Dr. Andreopoulou suggests that the greatest challenge faced by the oncology community is acceptance and commitment to changing current clinical practice. “Standard neoadjuvant chemotherapy has served a proportion of breast cancer patients with aggressive biology well; however, the time is upon us to move toward implementation of molecular testing at diagnosis to define the genetic ‘fingerprint’ and accompanying molecular dependencies of the tumors we seek to eliminate,” she says. “The presurgical and neoadjuvant setting is the testing platform for the next generation of oncology trials.”

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## Targeting Early Breast Cancers with Ablation Therapies (continued from page 2)

Dr. Chen also serves as a principal investigator for ABLATE (American Breast Laser Ablation Therapy Evaluation), a multicenter trial that tracks and evaluates long-term clinical outcomes of patients undergoing laser ablation therapy for fibroadenoma. The data captured by the ABLATE Registry will be used to assess the potential advantages and disadvantages of the procedure, as well as help establish uniform and standardized imaging, pathological assessment, and ablation timing protocols.

In addition, Dr. Chen, at Columbia, and **Rache M. Simmons, MD**, Chief of Breast Surgery at NewYork-Presbyterian/Weill Cornell Medical Center, are leading a clinical trial at their respective sites to evaluate the efficacy of cryoablation without lumpectomy and its impact on local and distant recurrence of early-stage breast cancer. The trial will monitor patient outcomes up to five years from the date of the cryoablation therapy. The trial is being offered to patients 60 and older diagnosed with early, low-risk breast cancer. Since cancer found

at this stage tends to be less advanced, older patients may need less aggressive therapy.

Therapeutic ultrasound is the third technique in Dr. Chen's ablation armamentarium, and she is now conducting a clinical trial using high-intensity focused ultrasound to destroy fibroadenomas. "We are very fortunate to care for patients in an academic medical center, where there is so much expertise in breast disease, so many advances in diagnostic and treatment approaches, and so many resources for patients and families," says Dr. Chen.

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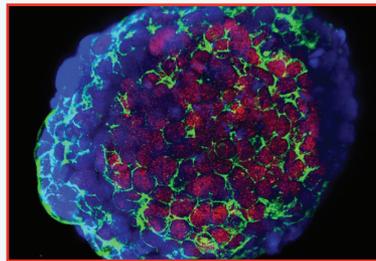
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## Weill Cornell Medicine Awarded SPORE Grant in Prostate Cancer

Weill Cornell Medicine has been awarded a five-year, \$11.3 million Specialized Programs of Research Excellence (SPORE) grant from the National Cancer Institute to improve the detection, diagnosis, and treatment of prostate cancer. Established in 1992, SPORE grants serve as the cornerstone of the NCI's efforts to promote collaborative, interdisciplinary translational cancer research. This SPORE grant is the first ever awarded to Weill Cornell Medicine and will expand an already vibrant prostate cancer basic and translational research program at the institution's Sandra and Edward Meyer Cancer Center and the



Neuroendocrine prostate cancer cells from a patient biopsy. Courtesy of Dr. Loredana Puca.

Caryl and Israel Englander Institute for Precision Medicine.

"This prestigious grant will enable us to enhance our innovative, translational research into prostate cancer and inspire new collaborations as we work together to find a cure for this disease," says **Augustine M.K. Choi, MD**, the Stephen and Suzanne Weiss Dean of Weill Cornell Medicine. "The team of SPORE investigators is exceptional and its groundbreaking work will undoubtedly advance our mission of scientific discovery and patient care, reinforcing Weill Cornell Medicine's reputation as a leader in research."

## Neoadjuvant Therapy in Breast Cancer: A New Raison D'être (continued from page 3)

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## Ongoing Research in Early-Stage Invasive Breast Cancer Treatment

“One of the unresolved areas for those of us in the field of breast cancer is to better understand who is responding to treatment early and who is not,” says **Dawn L. Hershman, MD, MS**, Leader of the Breast Cancer Program in the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian/Columbia University Medical Center. “Traditionally, we have done this by administering chemotherapy prior to surgery to see when the tumor shrinks. However, some patients have breast cancers that respond poorly to chemotherapy. If significant cancer remains at the time of surgery, risk of recurrence may be higher. If we know who is not going to respond, we can then offer those patients experimental therapies with the opportunity to have a better outcome.”

Searching for approaches to address this ongoing challenge, Dr. Hershman, along with **Kevin Kalinsky, MD, MS**, a Columbia oncologist specializing in breast cancer, have undertaken a number of studies, including clinical trials evaluating new approaches for neoadjuvant therapies and early phase clinical trials to assess novel therapeutic agents based on tumor genomics.

### Genetically Targeting Tumor Growth

Unlike other genetic studies that focus on mutations, a pilot study is underway by Dr. Kalinsky and **Andrea Califano, PhD**, Chairman, Department of Systems Biology, and Director of the JP Sulzberger Columbia Genome Center, to investigate genetic factors that are important for growth of the tumor. “Our goal is to reduce the risk of breast cancer recurrence after surgery by targeting treatment of tumors according to their molecular dependencies,” explains Dr. Kalinsky. “The study includes patients scheduled to undergo surgery for breast cancer after receiving chemotherapy treatment and who continued to have evidence of residual breast cancer.”

The investigators are using the N-of-1 clinical trial model, which does not begin with a predefined treatment in mind, but rather assesses the best treatment on an individual patient basis. Conducted in one patient at a time, N-of-1 clinical trials seek to identify the tumor vulnerabilities that represent the Achilles’ heel of the tumor growth in that patient from the analysis of its RNA rather than DNA. “Our initial results suggest that the type of N-of-1 studies performed at Columbia and NewYork-Presbyterian can enable a more precise therapeutic selection compared to other standard-of-care methods, and may identify treatments that are more universal than mutation-based personalized therapy,” says Dr. Califano.

“In this study, we remove tumor tissue from the patients for whole genome DNA sequencing and RNA expression analysis,” adds Dr. Kalinsky. Researchers in Dr. Califano’s lab then grow these tumors in mice, analyzing the information within the context of models of gene regulation that are specific to that tumor type. This enables them to identify the distinctive master regulators representing critical tumor vulnerabilities necessary to its growth and stability in a specific patient. They then use drug-perturbation experiments



*Dr. Dawn L. Hershman*



*Dr. Kevin Kalinsky*



*Dr. Andrea Califano*

to assess which ones of the existing FDA-approved or investigational drugs currently in an advanced stage of clinical testing is best suited to target these master regulators and evaluate these drugs on the patient’s tumor sample. The latter is performed either in cell culture or in a mouse transplant to determine if the agent can stop the tumor growth.

In collaboration with researchers at the Texas MD Anderson Cancer Center, the study, which is funded by SWOG, has accrued two dozen patients. “The goal of this study is to see if the approach is feasible,” says Dr. Kalinsky.

### Facilitating Drug Studies as an I-SPY 2 Trial Site

NewYork-Presbyterian/Columbia recently has been named a clinical study site for the I-SPY Trial Program, one of only 16 sites in the U.S. and Canada and the only site in New York State. I-SPY is a partnership of private and public organizations, including the National Cancer Institute and the Food and Drug Administration. Its approach to clinical trials is accelerating the pace of development, approval, and market availability of new agents for patients with all types of breast cancer.

I-SPY 2, in which NewYork-Presbyterian/Columbia is participating led by Dr. Kalinsky, is a multicenter trial for women with newly diagnosed, locally triple-negative breast cancer or hormone receptor-positive/HER2-negative breast cancer. The study is designed to screen promising new treatments and identify which therapies are most effective in specific patient subgroups based on biomarker signatures.

“The arms of the study that are currently open include new immune therapies, as well as new antibody drug conjugates that can deliver high doses of chemotherapy directly to the cancer,” says Dr. Kalinsky. “These studies focus on patients with stage two and stage three breast cancer at the time of primary diagnosis and therefore are at the highest risk of progression.” Unlike other phase two trials, however, the I-SPY 2 trial has adapted the study design to compare the combination of biologically targeted investigational drugs with standard chemotherapy in the neoadjuvant setting to standard chemotherapy alone.

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