

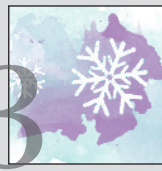
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Martin Luther King Jr.
on Jan. 17

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At 16, Zuzana Tothova came to the United States as an exchange student – an experience that led to her career at Dana-Farber.

Mentors created ‘life-changing’ opportunities for Tothova

In recounting her odyssey from Slovakian high school exchange student to Dana-Farber principal investigator, Zuzana Tothova, MD, PhD, often says modestly, “I was very lucky.”

Perhaps. But it’s also true that, at pivotal points in her journey, Tothova was recognized as a person of exceptional promise, with mentors encouraging her and taking extra steps to open opportunities.

“[Mentors] can empower and inspire you to strive for goals you didn’t know existed, or succeed at things you didn’t know you were capable of,” she says. “Now that I’m running my own team, it’s important to me to encourage them the same way.”

Tothova heads a lab, sees patients, and advises students in the Harvard/MIT MD-PhD program of which she is a product. Her research focuses

on the biology, genetics, epigenetics, and treatment of blood cancers, especially myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML).

Tothova employs cutting-edge techniques such as CRISPR gene-editing to create new types of animal models for studying cancer. She investigates structures called cohesins – which act as epigenetic modulators – that help organize the genetic material in cells’ nuclei, and which often are mutated in cancer. An experimental drug that targets mutated cohesins will soon be tested in a clinical trial, involving blood cancer patients who are not candidates for chemotherapy.

“For the first time in my life, I have been involved in a project all the way from basic

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Immunotherapy shows benefit in hard-to-treat breast cancer

While immunotherapy has brought an impressive new treatment option to several types of cancer, drugs that harness the immune system haven’t shown a significant benefit in treating breast cancer – until now.

According to a new clinical trial report, published in *The New England Journal of Medicine*, a combination of chemotherapy and immunotherapy achieved better outcomes than chemotherapy alone in women with advanced triple-negative breast cancer – a particularly hard-to-treat form of the disease. The combination that included the immunotherapy drug improved both progression-free survival and overall survival rates for women with a subtype of previously untreated triple-negative metastatic disease.

Triple-negative breast cancer – which doesn’t respond to drugs that block estrogen, progesterone, or over-expression of the *HER2* gene – accounts for about 15 percent of breast cancer cases and generally has a poor prognosis.

The researchers conducting the Impassion130 trial say that the combination should become a new treatment option for some women with metastatic breast cancer. The specific group of patients who benefited in this trial had PD-L1 positive triple-negative disease, meaning their tumor-infiltrating immune cells were being restrained by the PD-L1 “checkpoint” molecular brake.

The phase 3 clinical trial, results of which were also discussed at the recent meeting of the

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Reduced-intensity transplant keeps grandfather active

Alan Dynner was diagnosed with acute myeloid leukemia (AML) in 2016 at age 76. Treatment for the cancer would require a life-saving stem cell transplant, a procedure that most hospitals deemed too grueling for someone Dynner’s age.

But thanks in large part to treatment options at Dana-Farber/Brigham and Women’s Cancer Center (DF/BWCC) – which is just a short drive from his Boston home – Dynner qualified for a reduced-intensity transplant. Now, with effectively a new immune system, the former attorney and business executive is back to his regular routine of exercise, travel, charity work, and enjoying museums and concerts with his wife, Lisa.

“Before my doctors told me I was a candidate for a stem cell transplant, I thought my life was about to end and put my affairs in order,” Dynner says. “Suddenly Lisa and I were excited and energized, and we were full of hope because a transplant would give me the chance to live.”

He had planned on writing his memoir for his grandchildren after he retired, but these plans were postponed by his travel and other activities. Now, suddenly, he had to begin chemotherapy under the care of David Steensma, MD, in preparation for a reduced-intensity transplant, geared toward older patients and those with certain medical conditions and infections.

Grandfather, page 3



Alan Dynner (right) and his wife, Lisa, are back to their active and social lifestyle thanks to a life-saving stem cell treatment Alan received in 2017 at Dana-Farber/Brigham and Women’s Cancer Center.



Pasi Jänne

Jänne receives prestigious award from NCI

Pasi Jänne, MD, PhD, director of the Lowe Center for Thoracic Oncology recently received an Outstanding Investigator Award from the National Cancer Institute's (NCI).

Established in 2014, the prestigious award provides investigators with substantial time to break new ground, or extend previous discoveries to advance biomedical, behavioral, or clinical cancer research. Up to \$600,000 in direct costs per year for seven years is provided to investigators to work on projects of unusual potential.

Award recipients are cancer researchers who have been nominated by their institutions, served as a principal investigator on an NCI grant for the last five years, and have demonstrated outstanding research.

"The NCI Outstanding Investigator Award addresses a problem that many cancer researchers experience: finding a balance between focusing on their science while ensuring that they will have funds to continue their research in the future," says Dinah Singer, PhD, director of NCI's division of Cancer Biology. "With seven years of uninterrupted funding, the NCI is providing investigators the opportunity to fully develop exceptional and ambitious cancer research programs." [1]



Rosalind Segal

Segal honored for advancing women's careers

Rosalind Segal, MD, PhD, has earned the 2018 Edward J. Benz Jr. Award for Advancing the Careers of Women Faculty. Presented by the Office for Faculty Development and Committee for Women Faculty, the award is named after Dana-Farber's President Emeritus Edward J. Benz Jr., MD. It honors a faculty member who has gone above and beyond to advance women's careers.

Segal is cited for her commitment to mentoring and being a consummate role model. "The mentoring I received from [Dr. Segal] was critical and transformative," reads one nomination. "She leads by example and offers tangible, practical, and effective advice."

"She's an exceptional advocate and role model for young people," says another.

Segal holds a professor appointment in Neurobiology at Harvard Medical School, and serves as the Edward J. Benz Jr., MD, Chair at Dana-Farber. She is also the director of Harvard's PhD Program in Neuroscience. Since joining the Institute in 1998, she's been principally involved in laboratory research on nervous system development. She was previously awarded the Casty Family Award for Achievement in Mentoring, and the Harold Amos Award Faculty Diversity Award. [1]



Margaret Shipp

Shipp appointed to Douglas S. Miller Chair

Margaret A. Shipp, MD, is the first incumbent of the Douglas S. Miller chair in Hodgkin Lymphoma at Dana-Farber. Marlin Miller Jr. and the Marlin Miller Jr. Family Foundation established the chair in memory of his son, Douglas. The generous gift will reinforce the Institute's leadership in the hematologic malignancies.

Shipp is chief of Hematologic Neoplasia in medical oncology, the director of both the Dana-Farber/Harvard Cancer Center's Lymphoma and Myeloma Program

and the Dana-Farber Lymphoma Program and Research Center, and a professor of medicine at Harvard Medical School. Shipp earned her medical degree from Washington University School of Medicine where she completed an internship and residency in internal medicine at Barnes Hospital. She completed a fellowship in medical oncology at Dana-Farber before joining the faculty.

Her research focuses on the molecular heterogeneity of aggressive B-cell lymphomas – including Hodgkin lymphoma and large B-cell lymphomas (LBCLs) – and the identification of lymphoma subtypes amenable to more targeted therapy. She coordinated the development of the International Prognostic Index, which is used worldwide to individualize treatment approaches. She has led efforts to characterize the genetic and molecular signatures of Hodgkin lymphomas and LBCLs, identify biologically distinct subsets of these diseases, and elucidate mechanisms behind immune system evasion in Hodgkin lymphoma. These studies are leading to more specific and effective treatment approaches.

Philanthropic support from the Douglas S. Miller Chair in Hodgkin Lymphoma will enable Shipp and her team to more rapidly apply their findings to clinical practice. [1]



Eric P. Winer

Winer receives Brinker Award

Eric P. Winer, MD, chief clinical strategy officer, and Thompson Chair in Breast Cancer Research at Dana-Farber, has received the Susan G. Komen Foundation's 2018 Brinker Award for Clinical Distinction in Clinical Research.

Winer was honored for his seminal contributions in improving breast cancer treatments, which have helped shape the standard of care for breast cancer patients globally. Winer has devoted his career to applying the advances

from clinical trials to daily practice to improve survival and quality of life for individuals with breast cancer. His accomplishments in breast cancer research and in the clinic have influenced treatment for all stages and all the major biologic subtypes of the disease and led to lasting changes on patient outcomes.

The Brinker Awards for Scientific Distinction were established in 1992 to recognize the efforts of pioneers in clinical research and basic science for breast cancer. [1]

Spread joy, help Dana-Farber patients and families

More than 500 Dana-Farber adult and pediatric patients and their families are in significant financial need this holiday season, which makes this year's program the largest to-date. You can help alleviate this stress and spread cheer.

Consider a donation to support the Holiday Patient Assistance program by **Friday, Dec. 14**. The funds raised will be used to purchase gift cards for patients to buy presents for loved ones, put a holiday meal on the table, or afford gas to visit family and friends.

To make your gift, or to learn more, visit [DFCI Online](https://dfci.harvard.edu/holiday_assistance) or contact Hannah McCoy at holiday_assistance@dfci.harvard.edu or **617-632-6247**.

Thank you for your ongoing support this season.



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Story ideas are welcome. Please email Naomi Funkhouser at Naomi_Funkhouser@dfci.harvard.edu, or Jessica Cassidy at JessicaL_Cassidy@dfci.harvard.edu.

Missed a story or want to read more? Visit the Dana-Farber website at dana-farber.org or the intranet at dfcionline.org.

Senior Vice President for Communications
Steven R. Singer

Director, Content and Creative Services
Michael Buller

Associate Director, Content and Creative Services
Gillian Buckley

Manager, Content and Creative Services
Naomi Funkhouser

Editor
Jessica L. Cassidy

Designer
Lee Whale

Staff Photographer
Sam Ogden

Editorial Contributors
Austin Fontanella, Robert Levy,
Megan Riesz, Richard Saltus, Saul Wisnia

Photo and Design Contributors
John DiGianni, Deanna Finlayson,
Francisco Marty, Elisabeth Vaughan

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biology to conducting a clinical trial with a drug that modifies that biology, and that, having a drug that, luckily for us, is already approved for another cancer indication and therefore can be administered to MDS and AML patients in a phase 1 trial, she says.

A surprise pre-college road trip

Born in Slovakia in Central Europe, the child of academic physicists, Tothova came to the United States at age 16 as an exchange student at a New Jersey high school. Speaking more German than English upon arriving, she quickly assimilated the language and culture of America. At the end of the year, before she returned home, two teachers stunned her with a surprise farewell gift.

“They signed me up for American college entrance exams, without my knowing,” says Tothova. The teachers also traveled with her to visit top Eastern colleges and universities. “If it wasn’t for these two women I wouldn’t have come to America for college,” she says. “I remember this when I think about young people I teach or work with in my lab, and how the experiences I create for them can change their lives.”

After finishing high school in Slovakia, she received a full scholarship to Williams College, entering as a freshman in 1997.

Tothova was always interested in human biology and health, and this deepened when, early in her college years, her mother, a nonsmoker, was diagnosed with advanced lung cancer. Her death was devastating, but the Williams community “felt like a family and was incredibly generous,” during that difficult time, she reflects. Named valedictorian in her senior year, Tothova used her class speech to read a letter to her mother about her experiences at Williams.

After college, Tothova undertook the MD-PhD program at Harvard and MIT. Again, mentors were influential. Her advisor, Gary Gilliland, MD, PhD, then at Brigham and Women’s Hospital (BWH), and now president of the Fred Hutchinson Cancer Center, specialized in hematological malignancies, “which became my life passion,” says Tothova.

She completed a residency at BWH and for her postdoctoral training joined the laboratory of Benjamin Ebert, MD, PhD, – another Williams alumnus – who is now chair of Medical Oncology at Dana-Farber.

“Zuzana is an extraordinary physician-scientist who does innovative, rigorous, and ambitious basic research that applies directly to the development of new therapies for leukemia,” says Ebert. “I am thrilled that she decided to start her independent laboratory at the Dana-Farber.”

Even now, she maintains close ties with the many influential figures who helped her – including the family she lived with while an exchange student in New Jersey.

As for her native country, Tothova says she returns to Slovakia at least twice a year, visiting her father and one of her two brothers. “One of my brothers is a mathematician and the other is an economist. They think my choice, medicine, is the ‘soft science,’” she says, with a laugh. ^[RS]

Luncheon focuses on extending excellence

“Excellence for all” was the theme of this year’s 10th annual Beyond Boston Luncheon, hosted by the Susan F. Smith Center for Women’s Cancers Executive Council. The interactive forum and fundraising event offered nearly 250 attendees the opportunity to learn how Dana-Farber is extending its reach to communities throughout New England, nationally, and internationally. Currently, the Institute oversees four satellite locations as well as Pathways – an online tool available to in-network providers that offers real-time recommendations on cancer treatments, protocols, and clinical trial opportunities.

“You should have the same treatment regardless of where you live,” said Susan Campos, MD. Campos was part of a four-member panel moderated by Eric P. Winer, MD, chief clinical strategy officer and Thompson Chair in Breast Cancer research. Campos was joined by Carole Tremonti, RN, MBA, director of Pathways Operations; Huma Rana, MD, clinical director of the Center for Cancer Genetics and Prevention; and Sara Toloney, MD, MPH, associate director of the Susan F. Smith Center.

Following the panel presentation, Lisa Kane shared her story with the audience from a patient’s perspective. The 36-year-old was diagnosed with ovarian cancer in 2011 and is still in treatment today. Recently, Kane was able to transfer her care from Longwood to one of the Institute’s satellite locations – Dana-Farber/Brigham and Women’s Cancer Center in clinical affiliation with South Shore Hospital. For the Rockland, Mass., resident, this switch made a tremendous difference.

“I feel I have a little more control over my day, and my life. Control: That’s something that goes out the window with a cancer diagnosis, so having some really does have a positive impact,” said Kane.

The luncheon is expected to raise \$250,000, bringing the Executive Council’s fundraising total to more than \$18 million in support of research at the Susan F. Smith Center. ^[AF]

At left: Lisa Kane (middle) shared her experience navigating through an ovarian cancer diagnosis. She is shown here with husband Patrick (right) and Susan Campos (left), an institute physician at Dana-Farber.

Employee Resource Groups volunteer for Pie in the Sky

Members of the Young Professionals and Mosaic Employee Resource Groups packaged donated pies during the 26th annual Pie in the Sky event. It was hosted by Community Servings – a Massachusetts organization providing food and nutrition programs to individuals and families living with critical and chronic illnesses. ^[TI]



Grandfather, continued from page 1

He underwent the procedure in April 2017, under the care of oncologist Robert Soiffer, MD, and physician assistant Amy Joyce, PA. After a long period at home to avoid infection and allow the transplant to take hold, Dynner completed writing and illustrating his memoir.

Reduced-intensity transplants, which use lower doses of chemotherapy than standard transplants, are making stem cell transplants possible for a growing number of older patients. At DF/BWCC, 1,650 patients age 55 and older had transplants from 2013 to 2017, a number that has been growing steadily in recent years.

“Our transplant colleagues have been able to guide older patients through the rigors of transplant successfully,” says Steensma. “When I was in training in the 1990s, no one older than 60 was considered a good transplant candidate. But now it is routine at DF/BWCC to transplant otherwise healthy patients who are 70, and the upper bound continues to increase.”

Dynner’s wife, Lisa, credits the caring, calming way that Soiffer, Steensma, Joyce, and the rest of their care team walked them through the process beforehand. That helped them prepare for it logistically and emotionally.

“A social worker at Dana-Farber gave us wonderful advice on how to explain

his diagnosis and upcoming transplant to our grandchildren, factually and sensitively,” explains Lisa Dynner. “It wasn’t easy, but it helped prepare the family for the journey ahead.”

A year after his treatment began, when his family gathered for Thanksgiving, Alan was already well into his recovery period – making for a happy holiday. There have been hurdles for him along the way, including gout and graft-versus-host disease, a condition that impacts many transplant recipients. Still, Soiffer says Alan’s optimism for the future is well-founded.

The Dynners are enjoying and appreciative of every healthy day, and are taking steps so that other families can experience the same good fortune. To that end, they have made a generous philanthropic gift to Dana-Farber to fund efforts by Soiffer and his team to advance transplant strategies for patients with AML and other hematologic disorders.

“The support Alan and Lisa are providing will help us discover new ways to reduce relapse rates after transplantation and reduce long-term complications,” says Soiffer, co-chief of Stem Cell Transplantation and chief of Hematologic Malignancies at Dana-Farber. ^[SW]



Alan (far left) enjoys traveling with his three children and six grandchildren, is involved with charity work, and enjoys visiting museums and concerts with his wife, Lisa (second from left).

Save the date:

17th Annual Martin Luther King Jr. Celebration

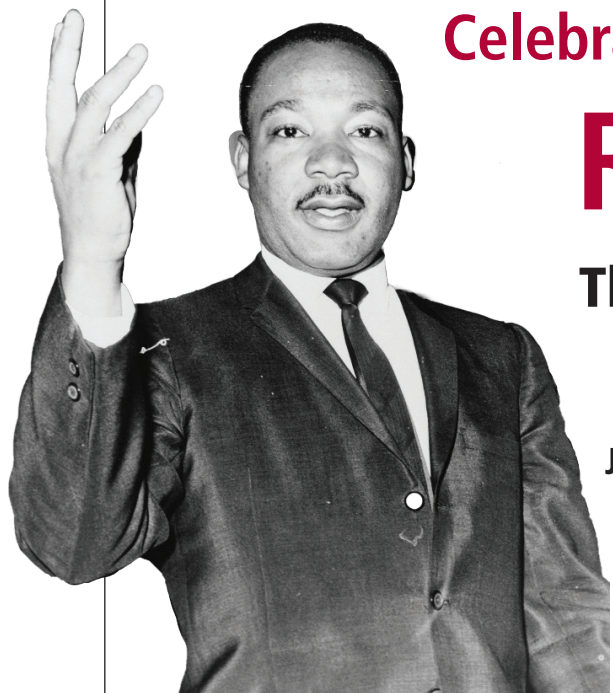
Rise Up

Thursday, Jan. 17

3 – 4:30 p.m.

Boston Red Sox

Jimmy Fund Auditorium



Program focuses on skin side effects of therapy

Think of the most common side effects of cancer treatment, and skin problems may not top the list – but for patients, they can be all too prominent. One study, in fact, found that patients often rank skin problems above nausea, fatigue, and nerve pain as the side effect most detrimental to their well-being.

Which explains why Dana-Farber and the Dermatology Associates at Brigham and Women's Hospital established the Program in Skin Toxicities from Anticancer Therapies, or STAT, in 2014, and why its team of physicians, nurses, and support staff has grown to nearly 25 members. The team holds several clinics weekly, at Dana-Farber and at Brigham Dermatology Associates, and is available as needed for patients experiencing urgent dermatologic issues. Staff members are also involved in research projects to better understand why certain therapies often produce skin problems and how they can be prevented.

“Cancer treatments are associated with a wide variety of skin changes, such as rashes, dryness, itching or burning sensations, cracked or lifted nails, autoimmune diseases, and sun sensitivity,” says the STAT program's director, Nicole LeBoeuf, MD, MPH. “The range of problems linked to individual drugs is so great that it's not realistic to expect oncologists to be experts in all of them. That's where we can be of assistance.”

Skin problems can result from many types of cancer therapy. (One of the best-known side effects of chemotherapy – hair loss – is in fact a dermatologic issue.) But targeted therapies and immunotherapies have proven especially prone to such toxicities.

Roughly 80 percent of patients receiving targeted therapies known as EGFR inhibitors, for example, develop rashes, LeBoeuf notes. More than half of patients treated with some targeted therapies develop skin reactions on their hands and feet; in 20 percent of those patients, the reactions are severe, limiting patients' abilities to carry out their daily tasks. With immunotherapy, skin problems are the most common, and often the earliest, side effects, affecting 30 to 50 percent of patients. In many of those patients, the problem is itch, which can range from “mild to maddening,” LeBoeuf remarks.

Tracking the variety and severity of dermatologic side effects of the

ever-growing arsenal of cancer therapies is a daunting task. When such drugs are used in combination – and when the combinations involve different types of drugs, such as chemotherapy and targeted agents – the complexity multiplies.

It was the surge in cases of skin toxicity from targeted and immunotherapies that led to the STAT program's creation. LeBoeuf was a clinical fellow in cutaneous (dermatologic) oncology at Dana-Farber in the mid-2000s, when clinical trials of targeted and immunotherapies for melanoma were underway. Many of the trial participants developed rashes – and some were unfamiliar to oncologists leading the studies. “It was clear there was a knowledge gap with respect to the specific skin side-effect patterns produced by these drugs,” LeBoeuf states. “The STAT program was an opportunity to provide expert consultations to our colleagues and for our patients.”

Within three weeks of the STAT clinic's opening, patient volume had exceeded the capacity of the initial staff. Now, four years later, Dana-Farber and Brigham and Women's remain the only major U.S. cancer center with such a robust program focused on the skin-related side effects of treatment.

Making a link

STAT clinicians are often able to make connections between skin problems and cancer medications that aren't readily apparent to patients' primary oncologists. One priority is to select treatments that target the skin condition itself, without interfering with other therapies a patient may be receiving.

Treating large numbers of patients has enabled STAT dermatologists to identify patterns that might have otherwise gone unnoticed. They found, for example, that targeted therapies known as BTK inhibitors may produce the same acne-like rash as EGFR inhibitors – a discovery soon to be reported in a research journal.

Research is central to the STAT program's mission. Investigators continue to build a database of the skin toxicities associated with different cancer therapies, alone and in combination, and study the biological mechanisms that give rise to these toxicities, so they can help patients live as well as possible while undergoing treatment. ^{RL}

Immunotherapy, continued from page 1

European Society for Medical Oncology in Munich, included 902 women with this diagnosis. Half were randomly assigned to receive an immunotherapy drug, atezolizumab (Tecentriq), plus a chemotherapy agent, nab-paclitaxel. The other group received only nab-paclitaxel plus a placebo.

Atezolizumab is a checkpoint inhibitor antibody drug that releases a molecular brake on immune cells. This brake suppresses the immune response against cancer. Atezolizumab specifically targets the PD-L1 molecular brake present on immune cells that have infiltrated the breast tumor. In the clinical study patients, about 41 percent were found to have high levels of PD-L1.

Women whose tumors tested positive for PD-1 and received the immunotherapy-chemotherapy combination experienced a median overall survival of 25 months, versus 15.5 months for the chemo-only group.

The immunotherapy-chemotherapy combination also improved progression-free survival (PFS) – the length of time before the cancer worsened. Median PFS in the combination group was 7.3 months versus 5.5 months in the chemo-only patients.

A similar proportion of patients in each treatment group had adverse events. The type and severity of those adverse events were similar in the groups.

The trial was supported by F. Hoffman-La Roche. ^{RS}

Immunotherapy combination steps up

First diagnosed in December 2013, Rita McGuire O'Brien's triple-negative inflammatory breast cancer recurred soon after receiving preoperative chemotherapy and undergoing a mastectomy and six weeks of radiation treatments. The disease then progressed despite receiving two different regimens of chemotherapy.

O'Brien, who lives in Fall River, Mass., says that after the cancer recurred, she felt “depressed and not hopeful.” Then, while being treated at Dana-Farber, she met Sara Tolaney, MD, MPH, a breast oncologist and associate director of the Susan F. Smith Center for Women's Cancers.

Tolaney told her about a new clinical trial for patients like her. The phase 1 study was testing a combination of immunotherapy and chemotherapy for triple-negative breast cancer. The rationale was that immunotherapy – which hadn't yet shown effectiveness in breast cancer – might be spurred to greater potency by the addition of chemotherapy.

O'Brien began the combination trial in April of 2015 and is still in treatment. She comes to Dana-Farber once a week for three weeks, receiving nab-paclitaxel (chemotherapy) and atezolizumab, the immunotherapy antibody, and takes one week off.

More than three years later, the only remnant of her cancer is a small lymph node in her armpit that shows on scans, “and it's not clear if this has active cancer in it or not at this time,” says Tolaney.

“I'm very grateful, and will never again give up hope,” says O'Brien. “In December it will be five years” since her initial diagnosis – a very good outcome for patients with triple-negative breast cancer.

Not everyone in the phase 1 trial she participated in has done as well, but even in this group of patients, with recurrent breast cancer, 39 percent of patients responded, and the median survival rate was nearly 15 months.

Those encouraging results led to the phase 3 Impassion130 clinical trial of nab-paclitaxel and atezolizumab as an upfront, initial therapy in triple-negative breast cancer. The results, recently reported in *The New England Journal of Medicine*, are being hailed as the first demonstration of immunotherapy improving progression-free survival, and also improved overall survival in patients with tumors that have the PD-L1 receptor.

“This regimen will likely receive Food and Drug Administration approval as first-line therapy for some patients with triple-negative breast cancer,” says Tolaney. ^{RS}

Healthful holidays

Join the Zakim Center for Integrative Therapies and Healthy Living in December for **Zakim's Kitchen: Healthier Spins on Holiday Favorites**, sponsored by the Friends of Dana-Farber. The program will offer suggestions and samples of traditional seasonal dishes with healthy makeovers to optimize nutrition. The demonstration is open to patients and caregivers. Registration is required. For more information or to register, call 617-632-3322 or email Zakim_Center@dfci.harvard.edu.

