

## Multidrug approach fights resistance

COMBINATION DRUG therapies targeting at least two different pathways may be the key to making several types of cancer more manageable in the future, according to the findings of a recent analysis.

“This will be the main avenue for research into cancer treatment, I think, for the next decade and beyond,” predicted investigator Martin Nowak, a professor of mathematics and of biology at Harvard University, Boston, Massachusetts. As the director of the school’s Program for Evolutionary Dynamics, Nowak studies the evolution of drug resistance in cancer. His comments appeared in a statement issued by Harvard University to describe his group’s latest research findings.

As Nowak and coauthors wrote in a letter published in the journal *Nature* (2012;486:537–540), previous studies of targeted therapeutic agents for cancer have shown that most lesions recur at approximately the same time following treatment. Now, the research team’s own results suggest that of the billions of cancer cells that exist in a patient, only about one in a million is resistant to drugs using targeted therapy. Nonresistant cells are destroyed when treatment starts, but the few resistant cells quickly repopulate,

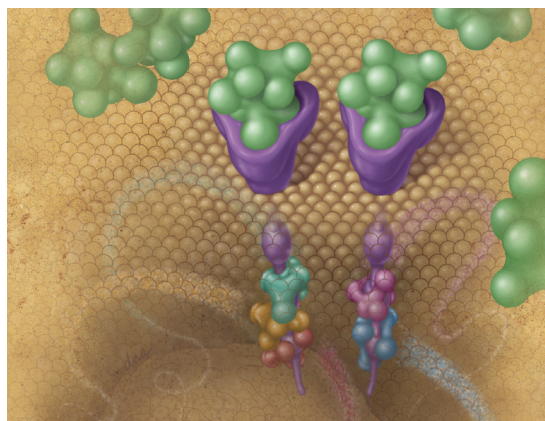


Illustration of the EGFR dimer on the surface of a cell and the various pathways it triggers

and treatment eventually fails, usually within a few months.

Specifically, Nowak and colleagues analyzed data from patients with chemorefractory metastatic colorectal carcinoma who had been involved in one of two studies of the targeted agent panitumumab (Vectibix). Panitumumab is an inhibitor of epidermal growth factor receptor (EGFR), a protein that can facilitate the growth and division of cancer cells. Twenty-four of the patients had tumors that were initially *KRAS* wild type; colorectal tumors that are wild type for *KRAS* are often sensitive to EGFR blockade.

Nine of the patients (38%) whose tumors were initially *KRAS* wild type developed detectable mutations to the gene, generally within 5 to 6 months

following panitumumab monotherapy. Mathematical models indicated that the mutations were present before therapy was initiated, suggesting that the emergence of *KRAS* mutations is a mediator of acquired resistance to EGFR blockade, and that these mutations can be detected in a noninvasive manner. “They explain why solid tumors develop resistance to targeted therapies in a highly reproducible fashion,” concluded the study authors.

The good news, say Nowak and associates, is that only a small number of genes can confer resistance in colorectal cancer, giving scientists hope that combining panitumumab with other drugs might circumvent resistance. Although the investigators see drug resistance as inevitable in a large metastatic colorectal lesion, remissions can be made to last longer than 5 to 6 months if combination therapies targeting at least two different pathways are used.

Nowak likens the situation to the rapid evolution of drug resistance in human immunodeficiency virus (HIV), and the subsequent development of the multidrug “cocktail” many HIV-positive patients use to manage their disease. The challenge in the near term, explains Nowak, is to develop the hundreds of drugs that could be needed to address all the possible treatment variations. Once available, however, the multidrug approach not only offers a new avenue for cancer treatment, but may revolutionize such treatment altogether. ■

Research results suggest that of the billions of cancer cells that exist in a patient, only about one in a million is resistant to drugs using targeted therapy.

# ACS applauds Supreme Court health care ruling

AFTER DECADES of being denied health coverage, charged far more than they can afford for life-saving care, and forced to spend their life savings on necessary treatment simply because they have a pre-existing condition, people with cancer and their families will benefit from the Supreme Court's recent decision in favor of the Affordable Care Act, said John R. Seffrin, PhD, chief executive officer of the American Cancer Society (ACS) and the ACS's non-profit and nonpartisan advocacy affiliate, the ACS Cancer Action Network (CAN).

Seffrin made his strong remarks in a statement issued by ACS CAN on the same day that the Supreme Court of the United States (SCOTUS) issued a 5-to-4 ruling that President Barack Obama's Affordable Care Act is, in fact, constitutional. Largely at issue was whether Congress has the power to authorize that most Americans obtain insurance or pay a penalty. In the majority opinion, Chief Justice John Roberts likened the penalty to a tax, the levying of which is constitutional.



The ruling preserves vital provisions that are already improving the ability of people with cancer to access needed care.

The ruling preserves "vital" provisions that are already improving the ability of people with cancer, as well as their families, to access needed care. For example, preventive services as are now offered for free, arbitrary dollar limits on coverage that can suddenly terminate care have been eliminated, and insurance companies are prohibited from unfairly revoking coverage when a person gets sick.

But in addition, commented Seffrin, the SCOTUS decision ensures that critical protections will be implemented for cancer patients and survivors, such as those that

- Prohibit insurance companies from denying coverage to people with a pre-existing condition
- Require health plans for individuals to offer essential benefits for prevention and treatment of cancer and other conditions
- Require insurers to provide consumers with easy-to-understand summaries about their coverage.

More information on the Affordable Care Act can be found at [www.healthcare.gov](http://www.healthcare.gov). ■

## FDA Update

The FDA has approved **per-tuzumab** injection (**Perjeta**) for use in combination with trastuzumab (Herceptin) and docetaxel (Taxotere) for the treatment of patients with HER2-positive metastatic breast cancer who have not yet received anti-HER2 therapy or chemotherapy for metastatic disease. Pertuzumab works by blocking HER2-related processes.

GlaxoSmithKline is changing the label of **Zofran (ondansetron)**, a drug used to suppress chemotherapy- and radiotherapy-induced nausea and vomiting, to remove the 32-mg single IV dose, and to state that no single IV dose of the drug should exceed 16 mg. Preliminary study results suggest that the 32-mg dose may affect the electrical activity of the heart, possibly leading to the development of the potentially fatal heart arrhythmia Torsades de Pointes.

Persons with multiple myeloma who have received at least two prior therapies, including bortezomib (Velcade) and an immunomodulatory therapy, are now eligible for treatment with **carfilzomib** injection (**Kyprolis**). The FDA granted accelerated approval; however, it advises that patients be monitored closely and taken off the therapy if heart failure or shortness of breath occur.

## MELANOMA 5-YEAR SURVIVAL BY STAGE\*

98%

Localized

62%

Regional

15%

Distant

\*Percentages are for survival by stage at diagnosis.

Source: 5-year relative survival data from 2002 to 2008. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review. [http://seer.cancer.gov/csr/1975\\_2009\\_pops09/browse\\_csr.php?section=16&page=sect\\_16\\_table.08.html](http://seer.cancer.gov/csr/1975_2009_pops09/browse_csr.php?section=16&page=sect_16_table.08.html). Accessed July 19, 2012.

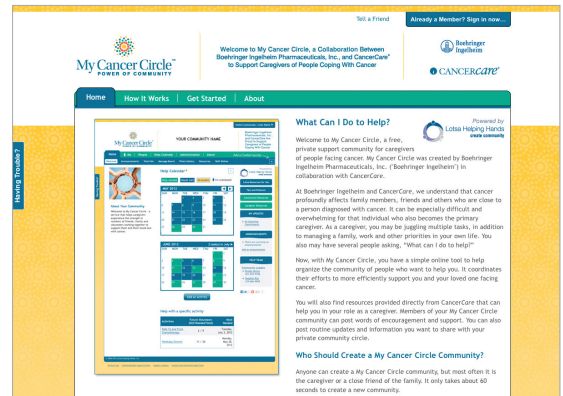
# MyCancerCircle creates a community of caregivers

PEOPLE with cancer and their caregivers can turn to a new Web site to help answer the question from concerned relatives and friends, “What can I do to help?”

A collaboration between Boehringer Ingelheim Pharmaceuticals Inc and the national nonprofit organization CancerCare, www.MyCancerCircle.net is a free, private, customizable online tool designed to help caregivers or the patients themselves organize and coordinate the practical and emotional help offered by friends and family members. The Web site enables the caregiver, patient, or designated coordinator to create an online community that allows people to easily and efficiently offer

their assistance with daily tasks such as cooking meals, doing household chores, or driving the patient to a medical appointment. In addition, www.MyCancerCircle.net is set up to encourage message and photo sharing among members of the private online community the caregiver or patient created, which also provides access to resources available through CancerCare, such as counseling services, support groups, and educational workshops.

The simple process for creating a MyCancerCircle community and community page is explained in step-by-step instructions on the Web site. Potential members of a particular person’s community have to be invited to join the



A cancer patient’s community page on MyCancerCircle

person’s circle or have to request membership.

The patient or caregiver can develop a list of tasks that need to be done, and community members can sign up for a specific assignment. Members are notified by e-mail when new needs are posted, and those who volunteered their services receive reminders of their commitments. The patient or caregiver is free to shut down their community page at any time. ■

# Oncology clinicians work to cope with patient deaths

IN INTERVIEWS with 20 oncologists addressing the nature and impact of grief related to the loss of a patient, the single most consistent and recurrent finding was the description of the concept of compartmentalization. The participants described their ability to separate feelings of grief from other aspects of their jobs and lives after the death of a patient, characterizing it as a coping strategy and a result of continual patient loss.

The study by Leeat Granek, PhD, of the Hospital for Sick Children in Toronto, Ontario, Canada, and colleagues also revealed that oncologists employed the strategy of distancing themselves from a

**The grief experienced by the oncologists had unique elements beyond sadness, crying, and sleep loss.**

patient and the patient’s family as death drew closer by making fewer hospital and bedside visits and by expending less energy overall on the patient.

The oncologists, who were interviewed in three groups, were men and women from three different adult oncology centers in Ontario. They represented different subspecialties, ethnicities, and career stages.

As the investigators described in a research letter published in *Archives of Internal Medicine* (2012;172[12]:964-966), the grief experienced by the interviewees had unique elements beyond sadness, crying, and sleep loss. These

elements related to the providers’ sense of responsibility for their patients’ lives, and included feelings of powerlessness, self-doubt, guilt, and failure.

Most of the participants reported feeling that they could not strike the proper balance between growing close enough to care about a patient while remaining distant enough to avoid feeling pain when the patient died. The oncologists discussed having difficulty separating their work lives from their personal lives by bringing their grief home with them, but many also talked about having a better perspective on life as a result of frequent exposure to patient loss. ■



FDA Update

The first genetic test to help determine whether the drug cetuximab (Erbix) would be effective in certain people with colorectal cancer has received FDA approval. The **Therascreen KRAS RGQ PCR Kit** can provide information about the *KRAS* gene mutation in persons whose cancer has metastasized; cetuximab has been shown to be ineffective in patients with this mutation.

The FDA has granted premarket approval to the **Prostate Health Index (phi)**, manufactured by Beckman Coulter Inc. The manufacturer describes *phi* as a simple, noninvasive blood test that is 2.5 times more specific in detecting prostate cancer than measuring prostate-specific antigen (PSA) in men with elevated PSA values (4-10 ng/mL). According to a statement from the manufacturer, the *phi* test reduced the number of unnecessary prostate biopsies by 31%.

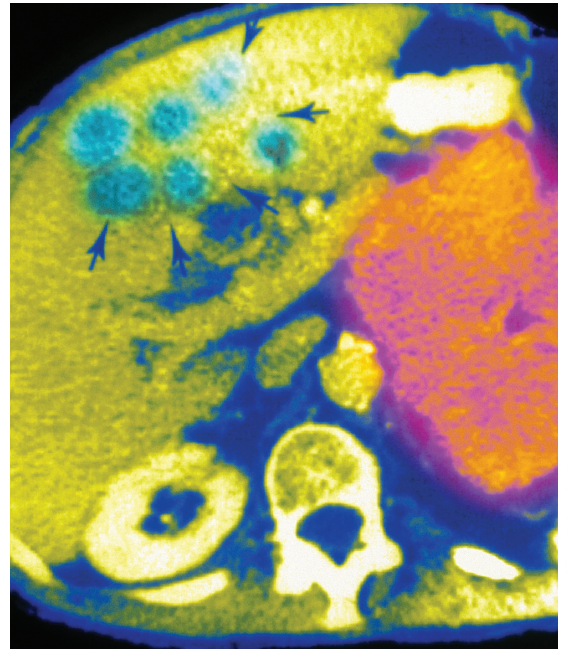
Another option for colonoscopy preparation has reached the market in the form of **Prepopik** (sodium picosulfate, magnesium oxide, and citric acid). The FDA has approved the colon-cleansing powder, which consists of two packets of powder. Patients must mix the packets with cold water and drink them in two separate doses.

# “Inoperable” pancreatic cancer may be treatable after all

FOLLOWING radiographic restaging, the majority of pancreatic ductal adenocarcinomas in persons who had previously undergone unsuccessful resection attempts were reclassified as resectable or borderline resectable.

Surgical oncologist Jason B. Fleming, MD, and fellow medical, surgical, and radiation oncologists from the University of Texas M.D. Anderson Cancer Center in Houston, Texas, evaluated 88 patients with pancreatic cancer to determine whether accurate radiographic restaging, multimodality treatment, and advanced surgical technique could offer persons previously deemed unresectable the possibility for curative salvage pancreatectomy. In a statement announcing the group’s findings, which were published in *Journal of the American College of Surgeons* (2012;215[1]:41-51), Fleming commented that the key to screening patients for treatment and staging of their cancer lies in the interpretation of preoperative computed tomography (CT) scans by both radiologist and surgeon to give the surgeon a clear idea of tumor location and vessel involvement before beginning the surgery.

All study participants originally received diagnoses of operable, localized cancer at outside institutions, but attempts at tumor removal were aborted when the initial surgery revealed more extensive disease than originally detected. Through radiographic restaging, Fleming’s



Scan showing pancreatic adenocarcinoma (pink) and hepatic metastases (blue).

team confirmed that only seven (8%) tumors were actually locally advanced and unresectable. Nearly all the others (92%) were found to be resectable (n=61) or borderline resectable (n=20).

A total of 66 patients (81%) subsequently underwent successful reoperative pancreatectomy using surgery first (9%) or preoperative chemoradiation (91%). Median overall survival was 29.6 months for the successfully resected patients, compared with 10.6 months for those with locally advanced unresectable disease at initial referral and 5.1 months for those patients who developed metastatic disease before resection.

The major complication rate was 20%, with three patients (4.5%) dying perioperatively. ■

© VEM / PHOTO RESEARCHERS, INC.