New Approaches Revolutionize the Treatment of Advanced Melanoma

By Sarah Bronson

Recent breakthroughs in immunotherapy and targeted therapy have improved outcomes for patients with advanced melanoma.

For decades, the median survival time for patients with advanced melanoma remained less than a year. But newly available treatments portend a better outlook for patients with this cancer.

Researchers have developed immunotherapies designed to prevent melanoma from deactivating T cells, targeted therapy combinations that block oncogenic pathways in the tumor cells, and multimodality approaches intended to both destroy the cancer and help prevent its recurrence. Patrick Hwu, M.D., a professor in and chair of the Department of Melanoma Medical Oncology at The University of Texas MD Anderson Cancer Center, said, “It’s an exciting time. Ten

A patient with ipilimumab-refractory melanoma is shown before (left), after one cycle, and after three cycles of treatment with the anti-PD-1 antibody MK-3475 (10 mg/kg every 3 weeks).
Ten years ago, we could cure about 5% of patients with advanced melanoma, and now we can achieve very good responses in 20%–25% of these patients because we have so many possible tools. And I believe we can drive response rates even higher and increase the durations of these responses over the next few years.”

Dr. Patrick Hwu

New Approaches for Melanoma Treatment

In the phase III trial that led to the approval of ipilimumab in 2011 by the U.S. Food and Drug Administration (FDA), patients with metastatic melanoma treated with 3 mg of ipilimumab per kilogram of body weight every 3 weeks for up to four treatments had an overall response rate of 10.9% after 55 months of follow-up, whereas those treated with a melanoma peptide vaccine had an overall response rate of 1.5%. And in an expanded access program at MD Anderson in which patients with advanced melanoma received induction therapy with 10 mg/kg of ipilimumab every 3 weeks for a total of four doses (and eligible patients received continued maintenance therapy every 3 months), 14% of patients had complete responses and another 2% had partial responses after induction therapy.

The initial response rates for ipilimumab were similar to those of the previous standard treatments for advanced melanoma, dacarbazine or interleukin-2 (IL-2); however, the responses to ipilimumab have been much more durable. In MD Anderson’s experience treating advanced melanoma with ipilimumab, patients whose disease responded to the drug have had a 5-year overall survival rate of 80%. “With chemotherapy, the tumor can grow back if some silent part of the cancer has been left alive. With immunotherapy, complete remission may mean a cure because the immune system is equipped to recognize any remainder of the cancer,” said Wen-Jen Hwu, M.D., Ph.D., a professor in the Department of Melanoma Medical Oncology.

A prominent difference between the PD-1 pathway blockers and ipilimumab is the extent of their toxicity. “Anti–PD-1 and anti–PD-L1 are much quieter than ipilimumab—their toxic effects are less severe,” said Srisuda Lecagoonporn, R.N., a research nurse in the Department of Melanoma Medical Oncology. “From the patient’s perspective, anti–PD-1 and anti–PD-L1 are a better experience.” The most common adverse effects of PD-1 blockade are increased liver enzyme levels and pneumonitis, which can cause shortness of breath and coughing.

Targeted therapy

Therapies targeted to specific gene mutations also show promise against...
BRAF mutations, for example, are present in nearly 50% of melanomas. Two inhibitors of the BRAF protein have been approved by the FDA for the treatment of melanoma: vemurafenib (formerly called PLX4032) was approved for metastatic melanoma in 2011, and dabrafenib (formerly called GSK2118436) was approved for BRAF-mutant melanoma in 2013. Both inhibitors have clinical response rates of about 50% in patients with metastatic melanoma and activating BRAF mutations.

Another targeted drug approved in 2013 for BRAF-mutant melanoma, trametinib, inhibits the MEK kinase that is downstream of and activated by BRAF in the MAP kinase pathway. In a head-to-head clinical trial, trametinib demonstrated a significant survival advantage over chemotherapy in patients who had advanced melanoma and activating BRAF mutations.

Unfortunately, although targeted therapies can have high response rates, these responses usually do not last. Melanomas treated with a BRAF inhibitor develop resistance after 5-6 months on average, and less than 10% of cases reach 12 months without developing drug resistance. The mechanisms of this resistance, and rational approaches to overcome it, are becoming clearer through the analysis of resistant tumor tissue.

Michael Davies, M.D., Ph.D., an associate professor in the Department of Melanoma Medical Oncology, said, “These findings are leading us to combinatorial approaches. You can’t just target one mutation—you need to block multiple targets simultaneously to achieve a maximum and durable clinical benefit. For example, many of the molecular changes that cause resistance to the BRAF inhibitors do so by reactivating the MAP kinase pathway. This finding provided the rationale to combine BRAF inhibitors with MEK inhibitors in order to block the MAP kinase pathway in two places.” Indeed, the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib demonstrated an impressive clinical response (25% decrease in tumor diameter) rate of 75% and an initial disease control rate of 100%. Furthermore, the combination almost doubled the average duration of the clinical responses. After 1 year of treatment, 40% of patients treated with the combination were alive and still responding to treatment—more than four times the rate seen in patients treated with a BRAF inhibitor only.

Usually, combining anticancer agents increases toxicities. But surprisingly, combined treatment with dabrafenib and trametinib was less toxic than treatment with either drug alone. Each agent alone frequently causes significant skin toxicities; dabrafenib and other BRAF inhibitors also cause squamous cell carcinomas of the skin in up to 25% of patients. Most of these squamous cell carcinomas have activating RAS mutations. “If your normal skin has RAS-mutant cells present, the BRAF inhibitor makes those cells grow faster through an effect called paradoxical activation of the MAP kinase pathway,” Dr. Davies said. “This effect causes the squamous cell cancers to grow and is also the reason that the BRAF inhibitors are used only in melanoma patients with activating BRAF mutations.”

But trametinib and other MEK inhibitors block the MAP kinase pathway in both the tumor cells and the paradoxically activated normal cells. As a result of this effect, the rate of the squamous cell carcinomas went from the 20% in patients treated with dabrafenib alone to less than 5% in patients treated with dabrafenib and trametinib together. Dr. Davies added, “This combination even reduces the incidence and severity of skin rashes.” Despite the beneficial effect on the cutaneous toxicities of the agents, the combination can have other side effects, including fever and vision problems.

Targeted therapies are also active in patients with brain metastases, who are often excluded from clinical trials and whose response rates to chemotherapy are usually very low. At MD Anderson, in the largest clinical trial ever conducted for melanoma patients with brain metastases, around 40% of patients treated with dabrafenib had clinical responses of their brain tumors. In
two more trials opening in the next few months, patients with BRAF-mutant melanoma and brain metastases will receive dabrafenib with or without trametinib. One trial will include only patients whose brain metastases are unresectable, while the other will include only patients for whom surgical resection of their brain metastases is planned.

Whether the responses to these new targeted drugs will be durable remains to be seen. Dr. Davies said, “It’s too early to tell whether there is a subpopulation of patients with metastatic melanoma who are being cured by dabrafenib combined with trametinib. We’re waiting to learn as we get longer follow-up data from these clinical trials.”

Combining approaches

The combination of targeted therapy and immunotherapy has been hypothesized to have better outcomes than either modality alone. This idea is based partly on the finding that BRAF inhibitors not only slow tumor growth and destroy tumor cells but also make melanoma more recognizable to the immune system. Also, these different modalities may complement each other. Dr. Patrick Hwu said, “We want to put the best qualities of targeted therapy and immunotherapy together and hopefully get high response rates that also last a long time.” These rationales have led to new clinical trials that combine BRAF inhibitors with immunotherapies such as high-dose bolus IL-2, ipilimumab, and anti–PD-L1.

In another approach, T cells are both stimulated and proliferated using IL-2 plus a procedure called adoptive T cell transfer. Dr. Patrick Hwu said, “We take the T cells that are in the tumor and are trying but failing to kill it, and we proliferate them to large numbers—billions—outside the body and then reinfuse them into the body in combination with IL-2. We’ve treated about 80 patients with metastatic melanoma now, and about half of them have responded well to it. And importantly, a lot of those responses are durable—for some of those patients, 5 years out, all of their disease is gone.” To qualify for adoptive T cell transfer plus IL-2, patients must have CD8-positive T cells that are highly reactive and tumor specific, a tumor that can be surgically accessed, and the ability to tolerate high-dose IL-2. Adoptive T cell transfer is also being tested in combination with T cell–boosting vaccines and with immune checkpoint blockades in ongoing trials.

“In the end, I think we need to put these treatment modalities together,” Dr. Hwu said. “But we have to do so in a way that’s not toxic, and we also need to make sure that they don’t negate each other—for example, some targeted therapies might hurt the immune system. We have to figure out how to combine and sequence these approaches in a way that will give patients the best opportunity for long-term survival.” Dr. Davies agreed that implementing these advances to the best possible effect will require further calculation. “It’s clear that we are in the middle of a transformative era in the development of treatments for patients with metastatic melanoma. While we have made a lot of progress, there is still a lot of work to do to meet the full potential of the advances that have been made over the past several years.”

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“[W]e are in the middle of a transformative era in the development of treatments for patients with metastatic melanoma.”

– Dr. Michael Davies

Comprehensive Help

By Kathryn L. Hale

Kicking a tobacco habit is a formidable task. Quitting tobacco after a diagnosis of cancer, a time of great stress, can be even more difficult.

An innovative program at The University of Texas MD Anderson Cancer Center offers cancer patients who use tobacco a variety of treatment strategies to quit once and for all.

“A small but growing body of evidence indicates that cancer patients who quit smoking after their diagnosis have better medical outcomes,” said Paul Cinciripini, Ph.D., a professor in the Department of Behavioral Science and the director of the Tobacco Treatment Program.

Based on the theory that cancer patients who smoke may benefit from quitting, MD Anderson’s Tobacco Treatment Program was created in 2006. The program—which is available at no cost to MD Anderson patients who use tobacco or who recently quit—takes a comprehensive approach that offers each participant a menu of counseling and pharmacological options that can be combined in various ways to best meet that individual’s needs.

Counseling and pharmacotherapy

Psychosocial interventions and counseling are the backbone of the Tobacco Treatment Program. Six full-time staff counselors and two clinical psychologists at the Tobacco Treatment Program provide the counseling. Vance Rabius, Ph.D., an instructor in the Department of Behavioral Science and part of the Tobacco Treatment Program leadership, said, “Counseling might include motivational interviewing for participants who have not yet decided
Tobacco Treatment Approach Quit on Their Terms

MD ANDERSON CANCER CENTER TOBACCO TREATMENT PROGRAM

Abstinence Rates in a Cohort of Patients

<table>
<thead>
<tr>
<th>ANALYSIS</th>
<th>3 MONTHS</th>
<th>6 MONTHS</th>
<th>9 MONTHS</th>
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<td></td>
<td>Number of Patients</td>
<td>Abstinence Rate</td>
<td>Number of Patients</td>
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<tr>
<td>Response only*</td>
<td>2,479</td>
<td>45%</td>
<td>2,282</td>
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<tr>
<td>Intent-to-treat†</td>
<td>2,779</td>
<td>40%</td>
<td>2,779</td>
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*The response-only analysis excludes participants with missing follow-up data.
†The intent-to-treat analysis assumes participants with missing follow-up data resumed smoking.

Source: The University of Texas MD Anderson Cancer Center Tobacco Treatment Program Annual Report, September 1, 2012 - August 31, 2013.

to quit or are struggling to attempt quitting, discussion of barriers to quitting, or development of strategies for quitting or maintaining abstinence.”

Dr. Rabius said that most patients undergo six to eight counseling sessions, but the number of sessions is flexible. Participants take the lead in deciding how much counseling is needed. While the ideal is on-site, face-to-face sessions, the program also offers counseling sessions via telephone or video conference.

Pharmacotherapy, the other major component of the Tobacco Treatment Program, approximately doubles a tobacco user’s chance of quitting successfully. Dr. Cinciripini said, “Pharmacotherapy often makes the difference between maintaining abstinence and relapsing.”

Pharmacotherapy in the Tobacco Treatment Program may include nicotine replacement therapy, bupropion, and/or varenicline. Because these drugs have different side effects, the therapy is tailored to each patient’s needs.

Current research

Now in its eighth year, the Tobacco Treatment Program is expanding its research and assessment activities. One area of investigation is how the quit rate of the Tobacco Treatment Program’s comprehensive approach stacks up against the quit rates for broader education-based programs.

The Tobacco Treatment Program is also studying the potential for its approach in the community. The program is now accruing participants in clinical trials looking at the efficacy of the comprehensive approach in individuals with psychiatric disorders and heavy alcohol users. Participants in these studies do not have to be MD Anderson patients.

Another area of investigation is the medical outcomes of cancer patients who participated in the Tobacco Treatment Program. “We’re mature enough as a program that we can go back and look carefully at the medical records of the patients we’ve treated in the past to see how those patients have fared,” Dr. Cinciripini said.

Researchers in the Tobacco Treatment Program will also soon begin a prospective study in patients with lung cancer to determine the effects of the Tobacco Treatment Program on cancer treatment efficacy, quality of life, and survival.

Dr. Cinciripini added that other cancer centers around the world will be watching to see whether the intensive and personalized Tobacco Treatment Program makes a material difference in cancer patients’ survival and quality of life. “What happens here has the potential to affect cancer patients and tobacco users everywhere,” he said.

“A small but growing body of evidence indicates that cancer patients who quit smoking after their diagnosis have better medical outcomes.”

– Dr. Paul Cinciripini

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Tobacco Treatment Program

To learn more about MD Anderson’s Tobacco Treatment Program, visit www.mdanderson.org/quitnow or call 713-792-QUIT (7849). For information about community studies, contact the program’s research manager, Jennifer Ferguson, at 713-563-7718.
Targeted Drug Shows Promise Against Advanced Breast Cancer

By Bryan Tutt

Adding the experimental kinase inhibitor palbociclib to standard hormonal therapy may delay disease progression in patients with advanced breast cancer that is estrogen receptor (ER) positive and human epidermal growth factor receptor 2 (HER2) negative.

Aromatase inhibitors such as anastrozole or letrozole inhibit the growth of ER-positive tumors by lowering serum levels of estrogen, whereas the experimental oral drug palbociclib (also called PD 0332991) inhibits cyclin-dependent kinases (CDK) 4 and 6.

“CDK 4 and 6 inhibitors arrest the cell cycle and do not allow the cancer cells to divide,” said Stacy Moulder, M.D., an associate professor in the Department of Breast Medical Oncology at The University of Texas MD Anderson Cancer Center. “There are multiple compounds that target this mechanism in cancer cells, but palbociclib is further along in its development than many of these.”

Clinical studies

The preliminary results of a phase II trial of letrozole with or without palbociclib in postmenopausal women with ER-positive, HER2-negative advanced breast cancer were presented at the 2012 San Antonio Breast Cancer Symposium. These results showed that the median progression-free survival duration of patients treated with letrozole and palbociclib (26.1 months) was significantly longer than that of patients treated with letrozole alone (7.5 months).

The phase II trial’s results have not been finalized or published, but the encouraging preliminary results led to a phase III trial, which is currently enrolling patients at MD Anderson and other institutions. Patients in the study are randomly selected to receive letrozole plus palbociclib or letrozole plus placebo. The patients will continue to receive the treatment until they have evidence of disease progression or withdraw from the study for other reasons.

Eligible patients are postmenopausal women who have ER-positive, HER2-negative metastatic or locoregionally recurrent adenocarcinoma of the breast that is not amenable to potentially curative surgery or radiation therapy and for whom chemotherapy is not clinically indicated. Excluded from the study are patients whose disease recurred during neoadjuvant or adjuvant treatment with anastrozole or letrozole or within 12 months of completing such treatment.

In the phase II trial, the most common side effect of palbociclib was myelosuppression. According to Dr. Moulder, the principal investigator for the phase III trial at MD Anderson, if palbociclib proves to be effective and becomes a part of standard care, patients taking it will need to be seen monthly to have their blood counts checked. In contrast, patients receiving hormonal therapy alone are typically seen every 2–3 months. Dr. Moulder added that the potential for myelosuppression with palbociclib requires other precautions, such as prompt evaluations for patients who have fever or other signs of illness.

Looking ahead

Dr. Moulder said that the next step in the development of palbociclib, if the drug continues to demonstrate safety and efficacy in patients with metastatic disease, is to use the drug in the adjuvant and neoadjuvant therapy settings. She hopes the drug will eventually improve the cure rate for all patients with ER-positive, HER2-negative breast cancer, including those with early-stage disease.

Other drugs that inhibit CDK 4 and 6 are being developed, as are drugs that inhibit CDK 2. “We’re very interested in developing this class of compounds,” Dr. Moulder said, “and we’ll be opening a number of trials in the near future.”

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To learn more about the ongoing clinical trial of palbociclib, visit www.clinicaltrials.org and select study No. 2013-0258.
Avoiding Food–Drug Interactions
Some foods and medicines don’t mix

Did you know that what you eat can affect the way your medicine works? Some foods, beverages, vitamins, and supplements can interact with your medicines. These interactions may limit the benefits of your medicines, cause side effects, or lead to a serious health condition. Here, we present some common food-drug interactions and provide tips to help you avoid them.

Foods that interact with medicine

Alcohol. If you take antihistamines or antidepressants—including mood-altering drugs called monoamine oxidase inhibitors, or MAOIs—avoid drinking alcohol because the combination can cause extreme drowsiness. Limit alcohol use when taking medicines that can cause liver damage, such as acetaminophen, aspirin, and ibuprofen. Some cancer medicines can also interact with alcohol, leading to liver damage or vomiting.

Caffeine. Some asthma medicines, such as albuterol and theophylline, can interact with caffeine, leading to excitability and a rapid heart rate.

Fruit. Grapefruit juice can increase the speed at which the body absorbs some medicines, and it may interfere with how the body processes other medicines. These interactions could lead to unwanted health effects. Speak with a pharmacist or doctor before eating grapefruit or drinking grapefruit juice when taking antidepressants or statins (a class of drugs used to treat high cholesterol). Some cancer medicines can also interact with grapefruit juice. Grapefruit, apple, or orange juice may reduce the effectiveness of fexofenadine (an antihistamine).

If you take blood thinners such as heparin and warfarin, ask your health care provider if you should avoid cranberry juice and cranberry supplements, which some reports indicate can reduce the benefits of these medicines or increase the risk of bleeding.

Vitamins and supplements. Garlic, ginseng, and ginkgo should also be avoided when taking blood thinners because these foods increase the chances of bleeding. Other vitamins and supplements can decrease the effectiveness of some medicines. For example, St. John’s wort is an herbal supplement that reduces the benefits of many prescription drugs, including digoxin (used to treat abnormal heart rhythms) and imatinib (used to treat leukemia).

Potassium. If you take medicines for high blood pressure, such as captopril and lisinopril, avoid eating large amounts of foods high in potassium, such as bananas and sweet potatoes. Excessive consumption of these foods when taking these medicines can cause a temporary increase in potassium levels, which may lead to heart palpitations and abnormal heart rhythms.

Tips for avoiding interactions

The list above includes only a few of the foods and supplements that interact with various medicines. So how can you avoid food-drug interactions with your specific medicines? Here are some tips that can help:

Stay organized. Use one pharmacy for all prescriptions so that your pharmacist can keep track of your medicines and warn you of possible interactions. Store all medicines, vitamins, and supplements in their original containers for easy identification. Throw out expired medicines, and do not take old medicines that are not currently prescribed by your physician.

You can also stay organized by using a spreadsheet to keep track of your medicines, vitamins, and supplements. Include information such as the size and shape of pills and tablets, possible side effects and interactions, and the dates when you began taking the drug, vitamin, or supplement. Bring this record with you to doctor’s appointments for easy reference.

Be informed. Read the drug information sheet that accompanies your medicine to find instructions about food-drug interactions, and contact your health care professional if you have any questions. Visit the Web sites below for more information about food-drug interactions.

• This comprehensive guide to food-drug interactions is published by the U.S. Food and Drug Administration: www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/GeneralUseofMedicineUCM229033.pdf.

• This medical record form can help you keep track of your medicines: www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM095018.pdf.

• Medline Plus has valuable information about specific drugs and supplements, including dosages, side effects, and precautions: www.nlm.nih.gov/medlineplus/druginformation.html.

• This privately owned Web site has a drug interaction checker: www.drugs.com.

Talk with your healthcare professional. Although the sources above may provide useful information, never stop taking your medicines or change the dose without consulting your doctor. Notify your doctor and pharmacist of all vitamins, prescription drugs, over-the-counter drugs, and supplements that you are taking. Also tell your doctor if you are on a special diet or considering a new diet.

Be sure to ask your doctor or pharmacist about potential interactions when taking a new medicine or when instructed to change the frequency or dose of a current medicine. Ask if your medicine can interact with foods, beverages, over-the-counter drugs, or other prescribed medicines.

—M. Yeoman

FOR MORE INFORMATION
• Talk to your physician
• Visit www.mdanderson.org
• Call askMDAnderson at 877-632-6789
PKM2 Identified as Potential Prognostic Marker for Glioblastoma

Pyruvate kinase M2 (PKM2), a protein kinase known to be overexpressed in solid tumors, has been identified as a critical component of cancer cell division and a possible prognostic marker and therapeutic target for glioblastoma.

In a study led by Zhimin Lu, Ph.D., a professor in the Department of Neuro-Oncology at The University of Texas MD Anderson Cancer Center, researchers found that PKM2 interacts directly with critical cell division machinery and is an essential regulator of glioblastoma cell reproduction. This finding clarified the role of PKM2 in glioblastoma tumorigenesis.

PKM2 had been identified as an oncogene owing to its role in tumor metabolism, especially in epidermal growth factor receptor-positive tumors. However, more recent research identified other functions of PKM2. Dr. Lu’s group sought to determine whether PKM2 played a role in mitosis.

“Cells go through several checkpoints during mitosis, and one of the most stringent of these is the spindle assembly checkpoint. Spindles are collections of microtubules that help segregate a single copy of each chromosome to each daughter cell by binding to chromosomes. A key component of this binding is the Bub3-Bub1-Blinkin protein complex.”

Dr. Lu’s group found that PKM2 phosphorylates Bub3; Bub3 phosphorylation is necessary for the Bub3-Bub1 complex to bind to Blinkin and participate in spindle assembly. The researchers also found that depletion of PKM2 led to defects in cell division and increased rates of apoptosis in multiple cancer cell lines. Dr. Lu said, “Depleting PKM2 led to an uneven distribution of DNA in the two new cells, triggering programmed cell death, or apoptosis, of those cells after division.”

When the researchers analyzed a library of glioblastoma tissue samples, they found that patients whose tumors had the lowest levels of Bub3 phosphorylation (indicating low PKM2 activity) had a significantly longer median survival duration than did patients with the highest levels of Bub3 phosphorylation. This finding indicates that PKM2 protein kinase activity may be a prognostic marker for glioblastoma.

“This new, additional role for PKM2 in cancer development and survival may provide a molecular basis for diagnosing and treating tumors with upregulated PKM2.”

— Dr. Zhimin Lu

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