“Because this combination looks effective, we’re interested in whether it can prevent or delay the onset of resistance,” Goldberg said. Although patients generally do well with first-line therapies for EGFR-positive NSCLC, the U.S. Food and Drug Administration has approved no drugs for relapse in these cancers -- part of why the Janigian study is significant, she said.

“It is the first proof of concept and the first trial to look at this combination clinically,” Goldberg said. Only the duration of response proved somewhat disappointing. “We all hoped it would be longer,” she said. “But that’s why we’re hoping we’ll get more benefit if we start the therapy earlier.”

Martin Edelman, M.D., director of medical thoracic oncology at the University of Maryland’s Greenebaum Cancer Center in Baltimore, noted the regimen’s short-lived benefit as well, while calling the drug combination not especially tolerable. Two patients in the study died and several developed severe rashes covering much of the body. Despite these setbacks, he said, the study is important because it shows interesting aspects of biology, even though it might not work out as a clinical therapy.

“What this study tells you very clearly is the role of the EGFR,” Edelman said. “By completely blocking it, investigators showed a reversal of signal and a meaningful response in patients.”

Even though EGFR’s importance to lung cancer development has been known for a decade and demonstrated in the animal model, Edelman said, “in this paper, they’ve shown it in the only animal that’s important: humans.”

**On the Horizon**

Afatinib is a second-generation drug, whose ultimate role in treating acquired resistance in NSCLCs remains unknown.

“Events may have already overtaken it,” Edelman said, citing several third-generation designer drugs targeted to the EGFR-mutated receptor that appear less toxic and are entering late-stage clinical trials.

Fredric Kaye, M.D., medical director of the thoracic oncology program at the University of Florida’s Shands Cancer Center, in Gainesville, agreed.

He said these third-generation drugs seem promising, because they are highly specific to the T790→M mutation, whereas the afatinib–cetuximab combination works more generally.

Nevertheless, Kaye said, “this is an important first step in overcoming resistance,” especially with the regimen’s clinical benefit to patients whose tumors test negative for T790→M. “There’s little or nothing for these patients now,” he said, echoing his colleagues’ comments.

One remaining question, however, is where afatinib fits clinically, ever since its approval as another option for first-line therapy, Kaye said.

“There’s been uncertainty as to how to triage this drug relative to either erlotinib or gefitinib,” he said. “And this study provides no answers to that question.”

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**Promising Early Results for Immunotherapy–Antiangiogenesis Combination**

**By Ken Garber**

Although immune checkpoint blockade has become standard care in metastatic melanoma, angiogenesis inhibitors have had limited success. Now researchers have combined the two.

July’s *Cancer Immunology Research* reported a phase I study combining ipilimumab and bevacizumab (doi:10.1016/j.cvr.2014.06.012). Among 46 patients, the combined therapy yielded a 19.6% objective response rate and a median survival of 25.1 months—roughly twice expectations for ipilimumab alone in metastatic melanoma. And, at least by modern immunotherapy standards, patients tolerated the combination well.

“A 25-month survival in a pretreated population is pretty darned impressive,” said Jeffrey Weber, M.D., Ph.D., an oncologist at Moffitt Cancer Center in Tampa, Fla. “It looked awfully promising. And certainly it’s something that needs to be pursued in a proper phase II study.” This study is under way.

When Dana–Farber Cancer Institute oncologist F. Stephen Hodi Jr., M.D., conceived the phase I trial, he envisioned more than just combining two anticancer modalities—he sought synergy. Biopsy samples taken after treatment reveal a double paradox: Immunotherapy can be antiangiogenic, and antiangiogenesis can stimulate the immune system. So combining the treatments should enhance both antitumor effects. Several years ago, Hodi’s team examined posttreatment biopsy samples from patients taking ipilimumab following a cancer vaccine. The immune system specifically targeted tumor blood vessels, for still-unknown reasons.

“We actually saw the blood vessels feeding the tumor deposits being destroyed by lymphocytes,” Hodi said.

That observation suggested to Hodi that angiogenesis inhibitors could enhance antitumor effects, while removing a block on immunotherapy. Over the last 20 years, evidence has accumulated that vascular endothelial growth factor (VEGF), in addition to its angiogenic role, suppresses the immune system. In 1996, David Carbone, M.D., Ph.D., then at the University of Texas Southwestern Medical Center at Dallas, reported that VEGF secreted by mouse
tumor cells prevented dendritic cells from maturing, thus hampering the presentation of tumor antigen. VEGF thus blocked the antitumor immune response. Carbone’s group later showed that giving mice anti-VEGF antibodies yielded deeper and more durable immune response against the tumors, and prolonged tumor shrinkage.

“It’s simplistic to think of bevacizumab as only an angiogenesis inhibitor,” said Carbone, now at Ohio State University. Hypoxia causes tumor cells, stromal cells, and normal cells to produce VEGF, with immunosuppressive effects both locally and at distant sites, including the bone marrow. VEGF is one of many immunosuppressive mechanisms that tumors hijack, however. It’s not an on–off switch like the CTLA4 and PD-1 checkpoints, Carbone said, but “it’s a player, and it modulates multiple pathways. And it might be most important in exactly the situation described in this paper, as adjunct to some of these checkpoint inhibitors, like the ipilimumab, or anti–PD-1.

“It’s nice to see that [the bevacizumab–ipilimumab combination] was highly effective, a 67% disease control rate, and was not remarkably toxic,” Carbone added. Combining immunotherapy with other agents often is toxic. For example, a melanoma trial adding the U.S. Food and Drug Administration–approved targeted agent vemurafenib to ipilimumab shut down last year after five of the first seven patients showed signs of liver damage. Carbone’s trial, 13 of 46 patients experienced severe or life-threatening adverse events. Such a rate is typical for an immunotherapy trial—especially phase I, which probes for dose-limiting toxic effects. Fortunately, only two cases of high-grade colitis, the most feared of ipilimumab’s side effects, occurred. This is about the same number one would expect from ipilimumab alone.

“The one thing you worry about is intestinal perforation” from severe colitis, said David Minor, M.D., an oncologist at San Francisco’s California Pacific Center for Melanoma Research and Treatment. “If you get a perforation, then you have to remove the colon, almost always.” And since bevacizumab can cause hemorrhage, any surgery would be risky.

If the phase I efficacy results hold up in larger trials, will the improvement over ipilimumab alone be due to bevacizumab’s well-known antiangiogenic effects or to enhancing the immune response? In phase I, circumstantial evidence favored the latter. Posttreatment biopsies samples showed more infiltration of effector T cells and dendritic cells across the tumor vasculature, compared with archived tumors from an old ipilimumab monotherapy trial. And patients taking the combination had higher levels of circulating T cells. They also had more antibodies against galectins (proteins involved in tumor metastasis and invasion, angiogenesis, and immunosuppression) than ipilimumab-alone patients. But such immune correlates “have been historically very hard to interpret,” Carbone said, and inconsistently linked to clinical outcomes.

“A 25-month survival in a pretreated population is pretty darned impressive. It looked awfully promising. And certainly it’s something that needs to be pursued in a proper phase II study.”

The combination might have done better in phase I because of a higher dose of ipilimumab. All objective responses but one were in patients taking 10mg per kilogram of body weight. But because 3 mg/kg is the FDA-approved dose, that’s what investigators are using in phase II. Although 10mg was Hodis first choice, obtaining FDA approval for the combination at that dose would be harder.

Other investigators are using bevacizumab to enhance immunotherapy. Carbone is conducting a phase II lung cancer trial adding bevacizumab to a cancer vaccine. Genentech is combining its anti–PD-L1 antibody with bevacizumab in two trials, one in solid tumors and one in renal cancer. This approach is a “totally reasonable thing to do,” Weber said.

Carbone agreed: “What would excite me is adding bevacizumab to one of the PD-1 therapies.” On September 8, the FDA approved Merck’s pembrolizumab anti–PD-1 antibody for treating metastatic melanoma, and Hodis said he “would love to” combine it with bevacizumab in a melanoma trial.

Meanwhile, immunotherapy combinations are moving forward. The combination of ipilimumab and the anti–PD-1 antibody nivolumab is now in phase III, after promising phase I results reported in June at the American Society of Clinical Oncology annual meeting.

Minor would like to see bevacizumab added. “There’s no reason to think you would necessarily get prohibitive toxicities,” he said. Hodis is waiting for the ipilimumab–nivolumab combination, which already causes some severe autoimmune side effects, to prove itself in phase III before considering adding a third agent.

[Both bevacizumab (Avastin) and ipilimumab (Yervoy) are FDA-approved drugs. Should community oncologists give the combination now, assuming that patients can afford it?]

“If it were the greatest thing since canned beer, perhaps,” Weber said. “[But] I wouldn’t be using this off-label, off-protocol: A, insurers aren’t going to pay for it, almost never. And B, you shouldn’t rob the investigators of the chance to prove whether it works.”

Hodi agreed: “My preference would be to answer the question with a clinical trial first.” Adding bevacizumab is just one way to improve immunotherapy. An alphabet soup of other possible combinations exists.
“You’ll be looking at PD-1 and [ipilimumab] with things like anti-CD137, OX40, [and] other protein checkpoint inhibitors—like Vista, Tim-3, Lag-3, BTLA, CD160, CD244. There’s a rationale for all these things,” Weber said.

Cancer vaccines, kinase inhibitors, and other targeted drugs, and even chemotherapy are other possibilities.

“Obviously you’ve got to prioritize,” Weber said. “But people like me will be kept in business for a long time, testing all these combinations.”

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Overcoming Mantle Cell Lymphoma’s Ibrutinib Resistance

By Gunjan Sinha

Although ibrutinib can extend the lives of heavily treated, relapsed, or refractory patients with mantle cell lymphoma (MCL), many become resistant to the drug. A study in September’s Cancer Discovery (2014;4:1022–35) reveals one way that ibrutinib resistance develops and identifies two drugs that may help treat or even prevent it.

“It’s a significant advance,” said Nam Dang, M.D. Ph.D., deputy chief of the division of hematology and oncology at the University of Florida College of Medicine in Gainesville. “Ibrutinib is now becoming widely used,” he added. “By knowing a mechanism of resistance, we can come up with rational strategies to circumvent it.”

Ibrutinib is the first drug to target and inactivate Bruton tyrosine kinase (BTK), which mediates B-cell receptor signaling to enable B cells to survive and proliferate. In November 2013, the U.S. Food and Drug Administration (FDA) approved ibrutinib to treat MCL on the basis of an “unprecedented” response: 68% of patients went into partial or complete remission and the average duration of response was 13.5 months. But most patients eventually relapse.

Selina Chen-Kiang, Ph.D., professor of pathology and laboratory medicine at New York’s Weill Cornell Medical College, and colleagues compared DNA and RNA from normal and tumor cells of patients before, during, and after treatment. BTK genes in tumor cells of patients who developed ibrutinib resistance after responding for at least 14 months had a C481S mutation. Detectable only at relapse, this mutation hindered ibrutinib from binding to BTK.

This mechanism, however, did not explain why about 30% of patients failed to respond to ibrutinib or acquired resistance early. Tumor cells from these patients did not harbor the BTK mutation, suggesting other resistance mechanisms. Further study showed that although ibrutinib did bind to and inactivate BTK, cells expressed high levels of activated PI3K-AKT and cyclin-dependent kinase 4 (CDK4). (PI3K-AKT proteins promote survival; CDK4 drives MCL cells through the cell cycle.) These two mechanisms appeared to override ibrutinib’s inhibitory action in resistant cells, Chen-Kiang said.

“It’s a significant advance. Ibrutinib is now becoming widely used. By knowing a mechanism of resistance, we can come up with rational strategies to circumvent it.”

That discovery suggested two treatment strategies, which the researchers tested in lymphoma cells. In 2004 Chen-Kiang got an experimental selective CDK4/CDK6 inhibitor, now called palbociclib, from Pfizer to study the cell cycle. Her research suggested that the drug might treat blood cancers. In the present study, she and her colleagues killed lymphoma cells expressing the mutated BTKC481S protein. The team administered palbociclib first and then idelalisib—a PI3Kδ inhibitor that FDA approved in July to treat three B-cell blood cancers. The second strategy involved exposing lymphoma cells with normal BTK to palbociclib followed by ibrutinib, which killed the cells. This stepwise drug therapy might treat MCL patients who initially do not respond to ibrutinib, or the drugs given together might prevent resistance.

The team’s approach to understanding and overcoming resistance is laudable, Dang said. “Our approach to combination therapy is often only an educated guess. This paper points us towards a more rational approach.” This study, Chen-Kiang said, is the first to use longitudinal RNA and DNA exome sequencing to study a targeted cancer therapy.

Years ago, research showed that palbociclib might benefit MCL patients. Based on earlier work on lymphoma cell lines, Chen-Kiang persuaded Pfizer in 2007 to sponsor a phase I clinical trial in MCL. Of 17 patients, at least 3 saw their tumors shrink. Meanwhile, other researchers showed the drug to be much better at treating metastatic breast cancer. In August, Pfizer applied for FDA approval of palbociclib plus letrozole as a frontline treatment for postmenopausal women with estrogen receptor–positive, HER2-negative advanced breast cancer.