Immune Checkpoint Inhibitors Show Promise Against Metastatic Renal Cell Carcinoma, Other Difficult-to-Treat Cancers

By Kathryn L. Hale

A decade ago, oncologists had little to offer most patients with metastatic renal cell carcinoma (RCC). However, a breakthrough discovery that has already changed the treatment of metastatic melanoma is showing promise against other metastatic cancers—including metastatic RCC—and giving patients new hope for long-term survival.

The breakthrough was the discovery of cytotoxic T lymphocyte antigen 4 (CTLA-4), a receptor on the surface of T cells that blocks the immune response by inhibiting T cell activation. James Allison, Ph.D., then a professor at the University of California, Berkeley, and now a professor in and chair of the Department of Immunology at The University of Texas MD Anderson Cancer Center, developed an antibody, anti–CTLA-4, that blocks this “immune checkpoint” protein, freeing the immune system to attack and inactivate tumors. Dr. Allison and his team discovered that blocking the CTLA-4 pathway caused tumor regression.

In clinical trials, anti–CTLA-4 (now known as ipilimumab) significantly extended survival in patients with advanced melanoma, and the approval of ipilimumab by the U.S. Food and Drug
Immune Checkpoint Inhibitors Show Promise

(Continued from page 1)

Administration (FDA) in 2011 for the treatment of metastatic melanoma was a game-changing development. Many oncologists have now turned their attention to the use of immune checkpoint inhibitors against other types of cancer.

**Immunotherapy in advanced RCC**

One cancer in which the new immunotherapy approach is generating excitement is metastatic RCC. Conventional therapies typically have little effect on survival in patients with metastatic RCC. While this began to change in the past decade with the introduction of targeted agents such as vascular endothelial growth factor pathway or mammalian target of rapamycin inhibitors, these agents are effective only in subsets of patients. An alternative is needed for patients who do not benefit from these therapies.

“Immunotherapy has been around a very long time,” said Padmanee Sharma, M.D., an associate professor in the Department of Genitourinary Medical Oncology. “Cancer researchers have grappled for decades with how to harness the body’s innate immune system to fight tumors. The early studies focused on how to turn the immune system on.” She said these studies led to the treatment of advanced RCC with high doses of cytokines such as interleukin-2 and interferon, which promote T cell proliferation. Although the high-dose cytokine treatment has been available for more than 20 years, only a small portion of patients with metastatic RCC are candidates.

“For years, many permutations of this ‘on switch’ approach have been tried without major success because the complexity of the immune system was not well understood,” Dr. Sharma said. “Dr. Allison’s work showed that turning the immune system on isn’t enough because once turned on, the immune system is programmed to turn itself off. Only by overriding the ‘off switch’ can we get an antitumor effect, and that’s what the checkpoint inhibitors do.”

Nizar Tannir, M.D., an associate professor in and deputy chair of the Department of Genitourinary Medical Oncology, likened the effect of the checkpoint inhibitors to “releasing the brakes” on the immune system, allowing the T cells to attack cancer cells.

After the discovery of CTLA-4 and its inhibitor, Dr. Tannir said “the whole field just broke open” as substantial efforts were made to develop inhibitors of other checkpoint proteins. Nivolumab—an inhibitor of another checkpoint protein, programmed cell death protein 1 (PD-1)—is now in phase III clinical trials at MD Anderson and elsewhere for the treatment of metastatic RCC and other cancers. Dr. Tannir said, “We now have a whole new class of drugs targeting these checkpoint proteins, and the excitement is building. We’re seeing remarkable responses.” (See “Checkpoint Inhibitor Success Story,” page 3.)

The success of checkpoint inhibitors has generated a great deal of public interest. “Patients are very much aware of the effectiveness of these agents and are eager to enroll in an immunotherapy trial,” Dr. Sharma said. “They don’t want to wait for FDA approval; the earlier they can get the treatment, the better.”

Drs. Sharma and Tannir said that they expect new trials of checkpoint inhibitors for treating RCC and other cancers to be opening soon and that they anticipate FDA approval of nivolumab for the treatment of advanced RCC in the near future.

**High expectations for combination regimens**

While the checkpoint inhibitors tested thus far have yielded some remarkable results, the drugs are not effective in all patients. Attempts at improving response rates led naturally to combinations of more than one checkpoint inhibitor. Various combinations of CTLA-4 and PD-1 inhibitors are now in phase I and II clinical trials for treating various cancers.

Although study results of combinations of checkpoint inhibitors for the treatment of metastatic RCC are not yet available, an early trial of one such combination for the treatment of advanced melanoma yielded a 1-year overall survival rate near 80%, which was previously unheard of for agents used to treat advanced melanoma. Drs. Tannir and Sharma anticipate equally outstanding results in patients with RCC.

Checkpoint inhibitors are also being combined with targeted agents such as sorafenib and sunitinib for treating metastatic RCC. While the results of these trials are not yet available, the combination approach is expected to have a big impact on the survival of patients with advanced cancer.

**Checkpoint inhibitors unlike conventional therapies**

One of the most exciting aspects of checkpoint inhibition in cancer therapy is that, unlike conventional cytotoxic drugs and targeted agents, it has the potential to work universally in all cancers. Checkpoint inhibitors, alone or in combination, have yielded promising results not only in advanced melanoma and RCC but also in triple-negative breast cancer and cancers of the prostate, bladder, lung, and head and neck.

Dr. Sharma said, “Checkpoint inhibition works in many different tumor types because it doesn’t target specific tumor cells, which can vary dramatically from patient to patient. Rather it targets the immune system, which is essentially the same in everyone. We all have T cells, and all T cells have CTLA-4 and other checkpoint proteins—and that’s why blocking the checkpoints can work in so many different kinds of cancer.”

The checkpoint inhibitors also differ from conventional therapies in their side effects. Dr. Sharma explained, “We

“We now have a whole new class of drugs targeting these checkpoint proteins, and the excitement is building. We’re seeing remarkable responses.”

– Dr. Nizar Tannir
see inflammatory effects—uveitis, dermatitis, colitis, hepatitis, pancreatitis—all due to the continued activation of the immune response. These immune-related adverse events can be controlled very well with corticosteroids as long as they are caught early and treated promptly. Most of these effects are readily reversible.”

One side effect of checkpoint inhibitors that is not reversible is hypophysitis, affecting the pituitary gland. The few patients who develop this adverse effect require long-term treatment with a low-dose oral steroid.

Surprisingly, steroid treatments for immune-related adverse events do not seem to substantially reduce the checkpoint inhibitors’ antitumor effects. Dr. Sharma said, “We don’t fully understand this yet. We believe it’s because the patient has had the chance to build a considerable immune response before starting the steroid treatment. The patient has enough intact memory B and T cells to mount the antitumor response while the steroid suppresses the newer, developing immune cells. We’re still learning about the pathways regulating these responses.”

Duration of therapy is another way checkpoint inhibitors differ from other systemic therapies. In the early clinical trials of ipilimumab, investigators noticed that patients who stopped treatment early, sometimes after only a few doses, still had dramatically prolonged survival. Eventually the researchers determined that only four treatments over 12 weeks would confer the therapy’s survival benefit, and this is now the standard, approved regimen. While it is too early yet to tell whether nivolumab and other checkpoint inhibitors will show similar survival benefits with such a brief treatment period, Drs. Sharma and Tannir believe the new drugs will follow the same pattern as ipilimumab.

A final way that checkpoint inhibition differs from other therapeutic approaches is in how success is defined. While responses to conventional therapies are measured by imaging studies or laboratory tests, response to checkpoint inhibitors is typically measured by survival benefit. “We have patients with metastatic melanoma who have survived for nearly 10 years since starting checkpoint inhibition therapy in a phase 1 clinical trial,” Dr. Tannir said. “And patients with advanced RCC have survived 2 or 3 years—or even longer—since beginning treatment with a checkpoint inhibitor. They’re alive and they’re doing well, but we can’t call their responses complete. Many of these patients have abnormalities on computed tomography that may be residual tumor. We’ll never know for sure because the disease has been stable so long, and the patient has been living so long, that it doesn’t really matter. These are patients who a decade ago wouldn’t have been expected to live 1 year.”

Future looks bright

Following the success of checkpoint inhibitors in patients for whom other therapies had failed, some current trials are looking at the drugs’ efficacy in treatment-naïve patients with metastatic RCC or other cancers. Dr. Tannir said, “There is enough confidence and excitement about the efficacy of these drugs to say yes, we can put them up front: we don’t necessarily have to try a targeted agent, such as a tyrosine kinase inhibitor, as a first-line therapy. We can go right to the checkpoint inhibitor.”

Drs. Tannir and Sharma anticipate that checkpoint inhibition will be one of the dominant paradigms in cancer research over the next several years, as
Clinical Study Offers Definitive Local Treatment of Bone Metastases from Breast Cancer

By Bryan Tutt

Metastatic breast cancer carries a poor prognosis, and most systemic treatments for metastatic disease aim to slow its progression rather than to cure it. In a select group of patients, however, systemic treatment combined with definitive local treatment of the metastatic tumors can offer long-term progression-free survival—and perhaps a cure.

“For several years, we’ve been prescribing aggressive treatment for a select group of patients—those with breast cancer and 1–3 bone metastases,” said Eric A. Strom, M.D., a professor in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center.

Dr. Strom said some of his patients have no evidence of disease more than 15 years after such treatment. Although he and many colleagues at MD Anderson were convinced that aggressive treatment of bone metastases was effective, no prospective study had been done to confirm this belief.

Clinical study

Six years ago, MD Anderson physicians opened a phase I clinical trial in which women with breast cancer and skeletal metastases at 1–3 sites receive standard systemic treatment plus definitive treatment of their bone metastases with surgery or radiation. Patients with more than 3 metastases or with metastases to distant organs are excluded from the study.

Dr. Strom, the study’s principal investigator, said patients enrolled in the study receive initial systemic therapy—which may include chemotherapy, targeted therapy, and/or hormonal therapy, depending on the characteristics of the tumors. After 3–9 months of systemic treatment, patients are reassessed.

Patients whose disease has progressed are removed from the study, and their treatment plan is reassessed by their physicians; patients whose disease does not progress will receive definitive local therapy to each metastasis.

The metastases are treated with radiation therapy or surgical excision depending on the site. For example, Dr. Strom said, lesions on the spine are difficult to remove surgically but can be effectively treated with radiation. Other sites, such as a rib or the skull, are very amenable to surgery. Dr. Strom said it is not uncommon for a patient to have one metastasis removed surgically and another treated with radiation.

The radiation modality most often used in the study is intensity-modulated radiation therapy, which allows the delivery of high doses of radiation to the tumor with much lower doses to the surrounding tissue. “The dose to the metastatic tumor is 66–72 Gy, which is high enough to kill the tumor,” Dr. Strom said.

The study’s primary endpoint is 3-year progression-free survival. Each patient has follow-up visits every 3 months for the first year after the completion of treatment and every 6 months for the next 2 years.

Interim results

Dr. Strom and his colleagues conducted an interim analysis of the study in August 2013. At a median follow-up of 2.25 years, 13 of 24 patients had no evidence of disease, 10 patients had metastatic disease in sites other than those treated in the study, and 1 patient had died of a cause unrelated to her cancer. No patient has had recurrent disease at a site where a metastasis was removed surgically or treated with radiation.

“Metastatic breast cancer is usually not curable. The fact that we have a number of patients with no evidence of disease is very compelling,” Dr. Strom said. “At the very least, local treatment of the metastases is good palliation. Even if these patients later develop metastases in other sites, they have a period where they’re free from symptoms and free from detectable cancer. Their quality of life is very high.”

Dr. Strom added that there have been no adverse events of grade 3 or

“Metastatic breast cancer is usually not curable. The fact that we have a number of patients with no evidence of disease is very compelling.”

– Dr. Eric Strom
higher from any treatments given in
the study. “The radiation is incredibly
well tolerated,” he said.

**Patient-specific treatment**
Most of the patients enrolled in the
study had metastases arise 1 or more
years after their breast cancer was ini-
tially treated. However, some patients
take the study while receiving treat-
ment for their primary tumors, and
their treatment in the study is tailored
accordingly.

“When a patient is diagnosed with
metastatic disease at the same time as
her primary tumor, we watch how the
metastases respond to her initial che-
motherapy and then we develop a com-
prehensive plan that includes the breast
tumor and regional lymph nodes as well
as the metastatic sites,” Dr. Strom said.
In one patient, Dr. Strom delivered
postoperative radiation therapy to the
chest wall and regional lymph nodes
and the metastatic sites concurrently.

Dr. Strom acknowledged that it is
rare to find patients with the precise
disease characteristics required by the
study’s protocol. He added that this
study is the only one of its kind for
patients with those characteristics.

“Selected patients with metastatic
breast cancer may in fact be curable,”
Dr. Strom said. “We have an open
study where we’re treating patients
with 1–3 bone metastases, and we’d
really like to see these patients.”

**FOR MORE INFORMATION**

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To learn more about the ongoing clin-
ical trial of definitive local treatment of
bone metastases from breast cancer,
visit www.clinicaltrials.org and select
study No. 2008-0319.

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**New Scoring System for Hepatic Reserve Could Help in Planning Treatment for Hepatocellular Carcinoma**

By Sunita Patterson

**An innovative test for evaluating hepatic reserve may improve clinicians’ ability to predict prognosis and select appropriate therapy for patients with hepatocellular carcinoma (HCC).**

A standard step in HCC staging is
the assessment of hepatic reserve, or
how much of the liver is functional.
Since the 1970s, hepatic reserve has
been assessed using the Child-Turcotte-
Pugh (CTP) score. Five factors make
up this score: serum bilirubin level,
serum albumin level, prothrombin
time, severity of ascites, and severity
of encephalopathy.

The CTP score has a major draw-
back, however, said Ahmed Kaseb,
M.D., an associate professor in the
Department of Gastrointestinal Medical
Oncology at The University of Texas
MD Anderson Cancer Center. Ascites
and encephalopathy, which are evaluat-
ed through imaging and clinical signs
and symptoms, can be affected by a
number of variables. “Those two param-
eters are very subjective,” Dr. Kaseb
said. “They can also change day to day
based on treatment, such as a diuretic.
It can be tough to score them.”

**Developing a new system**

In hopes of improving prognostic
accuracy, Dr. Kaseb, who heads the De-
partment of Gastrointestinal Medical
Oncology’s HCC program, and his
group have been looking for a more
objective measure to replace the CTP
score’s two subjective parameters. Re-
ognizing that insulin-like growth fac-
tor 1 (IGF-1) is synthesized by healthy
liver cells, Dr. Kaseb and his colleagues
hypothesized that the IGF-1 level,
which can be measured in a routine
blood test, would work as a substitute
for the subjective measures. Plasma
IGF-1 levels have been shown to be
lower in patients with cirrhosis and/or
HCC than in people without liver
disease. Dr. Kaseb’s group has now
developed a new scoring system, IGF-CTP.

In the standard CTP scoring system,
the five parameters are each assigned
a score of 1–3, and the total number
of points determines the CTP “class.”
CTP class A has the best prognosis;
CTP class C, the worst. Usually, only
patients with CTP class A are consid-
ered candidates for active HCC treat-
ment with surgery or tumor ablation.
In the new scoring system, four objec-
tive parameters—serum bilirubin level,
serum albumin level, prothrombin time,
and plasma IGF-1 level—are each
scored as 1–3, and the total number
of points determines the IGF-CTP
class.

**Testing the new system**

Funded by a grant from the National
Cancer Institute, Dr. Kaseb’s group
compared the score assignments and
prognoses between CTP class and IGF-
CTP class in two sets of patients. The
researchers evaluated clinical data and
plasma samples for an initial set of 310
HCC patients and determined effective
IGF-1 level cutoffs for stratifying pa-
tients. These levels were then tested
in another set of 155 HCC patients.

The investigators found that pa-
tients whose hepatic reserve was scored
as CTP class A but IGF-CTP class B
had a shorter median overall survival
than did patients whose hepatic reserve
was scored as class A by both systems.

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**FOR MORE INFORMATION**

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To learn more about the ongoing clin-
ical trial of definitive local treatment of
bone metastases from breast cancer,
visit www.clinicaltrials.org and select
study No. 2008-0319.
Needle Biopsy Underused in Breast Cancer Diagnosis

Needle biopsy—the standard of care for diagnosing breast cancer—is underused, and too many patients instead undergo the more invasive excisional biopsy, according to a recent study.

The study also corroborated previous studies that showed needle biopsy reduced the need for multiple breast cancer surgeries.

One advantage of needle biopsy, according to Benjamin Smith, M.D., an associate professor in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center and the corresponding author of the study's report, is that an excisional biopsy can increase the risk for false-negative findings on the sentinel lymph node biopsy, which is used to guide adjuvant treatment.

“Often, the excisional biopsy negatively affects other aspects of breast cancer treatment.”

– Dr. Benjamin Smith

Of the patients, 68.4% underwent a needle biopsy; this rate increased from 60.8% in 2003 to 76.5% in 2007. Nearly a third of all patients went a needle biopsy (usually performed by a radiologist) before consulting with a surgeon. Of the patients who consulted a surgeon before their biopsy, 53.7% underwent a needle biopsy.

New Scoring System for Hepatic Reserve

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(see table). These results suggest that the new system can better select patients with a good prognosis. “These patients might be more likely to benefit from active treatment; they might have fewer adverse effects and longer survival,” Dr. Kaseb said.

The next step is to evaluate the new scoring system in a group of patients who have unresectable HCC with CTP class A hepatic reserve and receive the standard-of-care systemic therapy, sorafenib. After the patients’ times to disease progression and overall survival times have been determined, Dr. Kaseb will calculate patients’ IGF-CTP scores from the blood samples that were used for CTP scoring. Time to disease progression, overall survival time, and rate of adverse events will be compared among IGF-CTP class A, B, and C patients. These data will confirm whether the IGF-CTP score identifies patients who end up doing well and those who end up doing poorly. The same strategy will also be tested in patients undergoing local therapy, such as chemoembolization or radiation, for small HCCs as part of a collaborative study between the departments of Gastrointestinal Medical Oncology and Interventional Radiology.

If further independent and international validation testing confirms the IGF-CTP score’s utility, approval of IGF-1 testing to assess liver function will be sought from the U.S. Food and Drug Administration. (IGF-1 testing is already approved for diagnosing growth hormone deficiency.) “We have to prove that the new score is more valuable than the old one before we recommend it as a standard and use it to prospectively guide therapy decisions,” Dr. Kaseb said.

Overall Survival by IGF-CTP Class Among Two Cohorts of Patients With HCC and Hepatic Reserve Scored as CTP Class A

<table>
<thead>
<tr>
<th>IGF-CTP class</th>
<th>Number of patients</th>
<th>Median overall survival, mo*</th>
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<td>Initial cohort</td>
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<tr>
<td>A</td>
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</tbody>
</table>


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FURTHER READING
Managing Stress After Cancer Treatment

Communication helps cancer survivors cope with stress

When cancer survivors finish treatment, they have completed a trying journey—they no longer have to cope with hair loss, nausea, pain, and other side effects. But as survivors prepare to move on with their lives, they may need help managing the stress that comes after treatment.

Common stressors

One of the most common stressors for cancer survivors who finish treatment is the fear of recurrence or of new cancers. The most important aspect of the fear of recurrence is its domino effect. In addition to stress, the fear of recurrence triggers anxiety, sleep disturbance, and fatigue—which can negatively affect health, lifestyle, and relationships with others.

Other common stressors for cancer survivors include beginning a new chapter in life (many survivors worry about how friends, family, or coworkers might perceive them), lacking energy to complete daily activities, and facing the financial aftermath of treatment. Young survivors may also struggle with infertility resulting from cancer treatment.

Managing stress

The first step in coping with stress after cancer treatment is communicating openly with caregivers and health care providers. Survivors and caregivers must be able to recognize and understand stress and be ready to start the conversation about stress even if health care providers do not bring it up. For example, lack of sleep, anxiety, and low mood are symptoms of stress that should be reported to physicians or social workers.

Guadalupe Palos, Dr.P.H., R.N., a manager in the Office of Cancer Survivorship and coordinator of the survivorship research program at The University of Texas MD Anderson Cancer Center, has seen firsthand how stress affects the emotional and spiritual health of cancer survivors. She advises survivors undergoing stress to talk about it and seek help right away. “Without help, managing stress is very difficult,” she said.

Dr. Palos said it is important to be open and communicate stress symptoms so that they can be treated properly. Ignoring stress or not seeking help from others can limit survivors’ quality of life after finishing cancer treatment. Dr. Palos added that some cancer survivors might be reluctant to discuss their stress. In those cases, she said, caregivers can help by turning to health care providers for alternative options.

Finding resources

Several resources are available to help cancer survivors cope with stress. Support groups, online services, phone help lines, social workers, and friends and family are social platforms where stress can be discussed.

Social workers are a valuable resource. They can perform psychological assessments and locate resources that can help to reduce stress. Many hospitals have social workers on staff, or cancer survivors can find social workers in their area with the help of the National Association of Social Workers.

Numerous resources are available through the American Cancer Society, including support communities and networks, tips for a healthy life after treatment, online live chats, and phone help lines that are open around the clock.

Looking ahead

According to Dr. Palos, cancer survivors can improve their quality of life by addressing stress early. “Clinicians and oncologists do a fantastic job in taking care of the physical side effects, but we also need to focus on the spiritual and emotional health,” she said. “We encourage survivors to be proactive to prevent a crisis rather than reactive when they are in a really bad one.”

– R. Molar-Candanaso

FOR MORE INFORMATION

• Ask your physician
• Visit www.mdanderson.org/survivorship
• Call askMDAnderson at 877-632-6789
• Visit the American Cancer Society at www.cancer.org/treatment
• Find a social worker through the National Association of Social Workers at www.helpstartshere.org/find-a-social-worker
Immune Checkpoint Inhibitors Show Promise

[Continued from page 3]

investigators try various combinations and regimens to determine the optimal treatment for specific patient populations.

In this era of genomic medicine, predicting which patients will respond to a specific agent or combination of agents or modalities has become feasible. “But, given the complexity of the immune system,” Dr. Sharma said, “a single predictive biomarker is probably not going to determine patient response. Rather than selecting a subgroup of patients who are the ideal candidates for immunotherapy, we will think about how each and every patient could benefit from immunotherapy. Our objective will be to modulate each patient’s immune response with an appropriate agent or combination to optimize the antitumor effect. The point is not to exclude patients, but to get each patient’s immune system to function the way the immune systems of responders are functioning.”

The clinical trials now under way should set the direction for future treatment refinements. “The combination regimens are so promising—they offer endless opportunities to alter dose and schedule and synergistic effects to invoke a powerful antitumor immune response in every patient,” Dr. Sharma said. “Immunotherapy is different than other therapies. It’s a paradigm shift, a culture change. We are beginning to elicit its true potential.”

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IN BRIEF

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The researchers studied the characteristics of patients who consulted surgeons before their biopsy and of the surgeons who were consulted. Patients who lived more than 8.1 miles from a radiologic facility that performs needle biopsies were more likely to consult a surgeon before undergoing a biopsy than were patients who lived closer to such facilities. Among the surgeon characteristics associated with patients’ undergoing excisional biopsy rather than needle biopsy were lack of board certification and low case volume.

“While there are access issues that should be addressed, it’s clear that the surgeon’s role is very important for the patients’ care,” Dr. Smith said.

An important aspect of care, the number of breast cancer surgeries performed per patient, was also studied. Multiple breast cancer surgeries were performed in 69.6% of patients who underwent excisional biopsy but in only 33.7% of those who underwent needle biopsy.

The study’s report was published in July in the Journal of Clinical Oncology.