FGFR Inhibition for Bladder Cancer

Erdafitinib has favorable response rate in advanced bladder cancers, including those that do not respond to immunotherapy

By Sarah Bronson

For patients with advanced or metastatic bladder cancer whose disease does not respond to standard cisplatin-based chemotherapy, immunotherapy is an attractive treatment option. However, only 15%–20% of bladder cancers respond to immune checkpoint inhibitors, and patients whose disease does not respond to chemotherapy or immunotherapy have few treatment options. Fortunately, some such patients may achieve a response to new agents that target FGFR (fibroblast growth factor receptor). FGFR genes are mutated in 20%–60% of urothelial carcinomas, the most common bladder cancers. In particular, FGFR3, which appears to be involved in the development of bladder cancer, is mutated in about 15% of patients with metastatic urothelial carcinoma. FGFR3 mutations are believed to contribute to higher rates of cancer cell proliferation in the urothelial lining, allowing the cells to acquire more mutations and transition to higher-grade, more invasive disease.

Bladder tumors with these mutations seem uniquely resistant to immunotherapy, “FGFR3-mutant bladder tumors appear to be associated with the luminal 1 subtype, which is immunologically cold, with low expression of immune markers,” said Arlene Siefker-Radtke, M.D., a professor in the Department of Genitourinary Medical Oncology at The University of Texas MD Anderson Cancer Center. “As we were treating bladder cancer patients...
with immune checkpoint inhibitors, I started noticing that the FGFR3-mutant tumors were not responding well, and these patients were stopping treatment relatively quickly."

To address the unmet need of patients whose advanced or metastatic bladder cancer does not respond to chemotherapy or immune checkpoint inhibitors, Dr. Siefker-Radtke is leading clinical trials of the pan-FGFR inhibitor erdafitinib and the FGFR3 inhibitor B-701.

Erdafitinib

Potential of erdafitinib

Because erdafitinib inhibits all four FGFR isotypes at low concentrations of the drug, this agent may work better than previously studied FGFR-inhibiting compounds in tumors with FGFR mutations. After erdafitinib showed early evidence of activity against FGFR-mutant bladder cancer in a small phase I trial, a phase II trial (No. 2015-0112) was performed to test the tolerability and effectiveness of various dose regimens of the drug in patients with previously treated metastatic or unresectable FGFR2- or FGFR3-mutant urothelial carcinoma of the bladder. The drug was well tolerated at a continuous dose of up to 8 mg orally daily, and the dose could be titrated up to 9 mg daily in patients who did not experience toxic effects or high phosphorus levels.

Better yet, among the 59 patients treated, “The overall response rate at the optimal daily dose of 8–9 mg, depending on the patient, was 42%, and we are seeing evidence of durable responses, with some responses lasting more than 1 year with continued treatment,” Dr. Siefker-Radtke said. These responses have included partial remissions of urothelial carcinoma liver metastases, which typically have a poor prognosis, even with treatment. Liver metastases from bladder cancers typically do not respond well to treatments that target the immune system, Dr. Siefker-Radtke said. However, some patients in the erdafitinib trial saw their liver metastases shrink dramatically, including one patient who had previously tried immunotherapy and had not had any benefit from it.

The experiences of the patients in the trial supported the theory that FGFR3-mutant tumors are less responsive to immunotherapy. “Twenty-two of the patients had prior immunotherapy, and only one of them had responded to an immune checkpoint inhibitor,” Dr. Siefker-Radtke said. “And that response was not durable.”

Because of these results, presented at the American Society of Clinical Oncology meeting this June, the U.S. Food and Drug Administration has granted erdafitinib a breakthrough therapy designation for the treatment of metastatic urothelial carcinoma.

Current erdafitinib trials

An upcoming phase III trial (No. 2018-0027) will more clearly define the role of both erdafitinib and immune checkpoint inhibitors in the treatment of FGFR-mutant bladder cancers. The trial will enroll patients who have FGFR-mutant metastatic or unresectable urothelial carcinoma of the bladder and have undergone prior systemic therapy. Patients who have previously been treated with a PD-I

“[W]e are seeing evidence of durable responses [to erdafitinib], with some responses lasting more than 1 year with continued treatment.”
— Dr. Arlene Siefker-Radtke

Progression-free (left) and overall (right) survival curves are shown for patients with metastatic or unresectable urothelial carcinoma treated with the optimal dose of erdafitinib in a phase II trial. The median progression-free and overall survival durations were 5.5 and 13.8 months, respectively. Images courtesy of Dr. Arlene Siefker-Radtke.
therapy (n = 596) given alone or com-
ginated therapy (n = 711) or nonm atched therapy, their cancer and received m atched tar-
lar analysis of 3,743 patients w ho have been referred to phase I clini-
als undergoing treatment, either erdafitinib or chem o-
spond better to erdafitinib or immuno-
be random ly assigned to receive either erdafitinib or the PD-1 inhibitor pembrolizumab.
“T his trial will help us determine whether FGFR3-m utant tumors re-
therapy w ith taxanes (the standard of care). And patients w ho have not
inhibitors in combination therapy, possibly by allowing more immune cells to
tumor. Patients in the phase II portion of the trial will receive erda-
tinib alone or combined with the PD-
strategy in patients with FGFR3-m utant bladder cancer because
toxic effects may increase as more FGFR
isotypes are inhibited. To illuminate the potential of a more selective inhibitor,
an ongoing phase IB/II trial (No. 2017-
will determine the safety and effi-
cients are inhibited. To illum inate the
m atched targeted therapy group and
survival rate w as 15%  in the m atched
durations (4.0  and 9.3 m onths) than for those
were associated w ith shorter
ably by doing these trials will we gain an
m ated trials, is led by Dr. Siefker-Radtke. “On-
many of the trials. In addition to treat-
durations.
T he B -70 1 trial, like the erdafitinib
m ore aggressive
tumor. Patients in the phase
m ated therapy group, and
m ated therapy at M D  Anderson undergo
or in combination with pembrolizumab
also analyzed the interaction w ith im mune
inhibitors, possibly by allowing more immune cells to
tumor environment to one that’s more sensitive to im mune
checkpoint inhibition and perhaps have
synergistic effects,” said Dr. Siefker-
Rad tke, who will be the principal inves-
gators of both trials.
B-701
It is not clear whether a pan-FGFR inhibitor such as erdafitinib or a spe-
cific inhibitor of FGFR3 will provide a more effective strategy in patients with
m utant bladder cancer because toxic effects may increase as more FGFR
isotypes are inhibited. To illum inate the potential of a more selective inhibitor,
an ongoing phase IB/II trial (No. 2017-
will determine the safety and effi-
cacy of an agent that selectively targets
FGFR3. The drug, B-701, is given alone
or in combination with pembrolizumab
patients who have locally advanced
metastatic urothelial carcinoma with
or without FGFR3 mutations.

The B-701 trial, like the erdafitinib
trials, is led by Dr. Siefker-Radtke. “On-
ly by doing these trials will we gain an
understanding of whether pan-FGFR
hibition or FGFR3 inhibition is required
for a treatment that is both safe and ef-
eficient,” she said.

Future possibilities
Although pan-FGFR inhibitors such
as erdafitinib and more specific FGFR3
inhibitors such as B-701 have been
developed with advanced bladder can-
cer in mind, their uses could eventually
extend to earlier-stage disease. Dr.
Siefker-Radtke said that either drug,
it continues to demonstrate activity
against bladder cancer, could present
new option for patients whose early-
stage disease may require cystectomy.
She added, “M aybe erdafitinib or B-701
will allow patients to keep their blad-
dors longer or keep their tumors from
transforming into a more aggressive
disease.”

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To learn more about clinical trials
at MD Anderson, visit www.clinical
trials.org and search by cancer type,
treatment, physician, or trial number.

IN BRIEF
Targeted Therapies Matched
to Tumor-Specific Mutations
Prolong Survival

Targeted therapies matched to
specific gene mutations in patients’
tumors yielded longer progression-free
and overall survival durations than did
nonmatched therapies in an analysis
of long-term data from a study at The
University of Texas M D  Anderson
Cancer Center.
In the ongoing “umbrella” study
(IM PACT, No. 2007-0885), patients
with advanced, refractory solid cancers
who have been referred to phase I clini-
cal trials at M D  Anderson undergo
molecular testing of their tumors. In
a recent analysis of 3,743 patients who
had undergone such testing, 1,307 had
at least one molecular alteration in
their cancer and received matched tar-
ged therapy (n = 711) or nonm atched
therapy (n = 596) given alone or com-
bined with other anticancer drugs, de-
pending on the trials.
“We hypothesized that genetic and
molecular analysis of solid tumors could
enable the selection of optimal ther-
apy,” said Apostolia Tsim beridou, M. D.,
Ph.D., a professor in the Department
of Investigational Cancer Therapeutics
and the study’s principal investigator.
In the analysis, the median progres-
sion-free and overall survival durations
were significantly longer for patients
who received matched targeted therapy
(4.0  and 9.3 months) than for those
who received nonmatched therapy (2.8
and 7.3 months). The 3-year overall
survival rate was 15%  in the matched
targeted therapy group and 7%  in the
nonmatched therapy group. And the
10-year overall survival rate was 6%  in
the matched targeted therapy group
and 1%  in the nonmatched therapy
group. Alterations in the PI3K/AKT/mTOR
pathway were associated with shorter
progression-free and overall survival
durations.
The analysis also revealed several
prognostic factors. In addition to treat-
m ent with matched targeted therapy,
independent predictors of longer over-
all survival included normal lactate
dehydrogenase levels, functional status,
albumin levels, and platelet counts
and the absence of liver metastases
or PI3K/AKT/mTOR alterations.

Dr. Tsimberidou and colleagues
presented their findings at the Ameri-
can Society of Clinical Oncology an-
nual meeting in June (abstract No.
LBA2553). The researchers are now
conducting a randomized phase II trial
(IM PACT2, No. NCT02152254) to
confirm the benefits of matched tar-
ged therapy. “I deally, in the future,
tumor testing and cell-free DNA analy-
sis at the time of patients’ diagnosis
will become the standard of care,” Dr.
T simberidou said.
Managing High-Risk Breast Lesions

Strong provider recommendation for preventive therapy increases its use in women with lobular carcinoma in situ, atypical hyperplasia

By Bryan Tutt

Although preventive therapy can reduce breast cancer risk in patients with lobular carcinoma in situ (LCIS) or atypical hyperplasia, most patients choose not to undergo such therapy. Clinicians at The University of Texas MD Anderson Cancer Center have developed a program to educate patients with LCIS or atypical hyperplasia about the importance of preventive therapy and encourage them to take this critical step to reduce their breast cancer risk.

Without intervention, women with LCIS or atypical hyperplasia are at least four times as likely as women without the conditions to develop breast cancer in their lifetimes. Hormonal therapy with tamoxifen or raloxifene can reduce this risk by 75%.

“Primary care physicians can prescribe these medications and follow up women in their clinic,” said Abenaa Brewster, M.D., M.H.S., a professor in the Department of Clinical Cancer Prevention and medical director of the Nellie B. Connally Breast Center. “Or physicians who do not feel comfortable prescribing these medications can refer their patients to a high-risk clinic.”

One such high-risk clinic is MD Anderson's Cancer Prevention Center. But even here, Dr. Brewster, along with colleagues including Therese Bevers, M.D., a professor in the Department of Clinical Cancer Prevention and medical director of the Cancer Prevention Center, found that less than half of patients with LCIS or atypical hyperplasia were opting for preventive therapy. The clinicians developed a program to increase the use of preventive therapy by making sure patients understand the benefits of preventive therapy and ensuring that physicians strongly recommend such therapy.

Preventive therapy

When used for breast cancer prevention in women at high risk of the disease, tamoxifen or raloxifene is typically given for 5 years. Tamoxifen is approved for use in both pre- and postmenopausal women, whereas raloxifene is approved for use only in postmenopausal women.

Most women who receive tamoxifen or raloxifene experience no adverse effects. However, both drugs can cause menopausal symptoms, such as hot flashes, and the rare but more serious side effect of blood clots—specifically, deep venous thrombosis or pulmonary embolism. Tamoxifen, but not raloxifene, also increases the risk of uterine cancer.

“Patients and physicians need to think about the pros and cons of taking these drugs and decide whether they are favorably balanced,” Dr. Bevers said. “Some patients and physicians worry about the increased risk of uterine cancer with tamoxifen, but it’s a numbers game. We’re going to cause only a handful of uterine cancers while we prevent many more breast cancers. In women with LCIS or atypical hyperplasia, absent an absolute contraindication like a previous blood clot, the risk reduction is so large that it far outweighs the potential harms of the drug.”

Making a strong recommendation

The benefits of preventive hormonal therapy so outweigh its risks that the National Comprehensive Cancer Network guidelines call for physicians to strongly recommend such therapy for women with LCIS or atypical hyperplasia. However, despite these guidelines, only 20%–30% of women with LCIS or atypical hyperplasia in high-risk clinics receive preventive therapy.

“Physicians have been explaining the risks and benefits and then leaving the decision up to the patient,” Dr. Brewster said. “Of course, the patient makes the final decision about any...”
Clinic Diagnoses

Breast Lesions

The sole focus of the Undiagnosed Breast Clinic in MD Anderson’s Cancer Prevention Center is to detect and accurately diagnose breast cancer. The clinic provides consultations and second opinions for patients with breast symptoms such as lumps, swelling, redness, nipple discharge, or abnormal findings on mammography or other imaging studies.

Patients seen in the clinic undergo a thorough examination with a review of their medical history. In addition, any outside pathology specimens and imaging studies are reviewed by a multidisciplinary team of cancer detection specialists, pathologists, and/or radiologists.

“If the lesion has previously been biopsied, we review the pathology to see if we concur with the diagnosis,” Dr. Bevers said. “For LCIS and atypical hyperplasia, we typically talk about how extensive the proliferation is on the pathology slides—does it only involve one or two terminal ductal lobular units, which we consider a limited amount, or is it more extensive? An additional consideration in a high-risk lesion is whether the neoplasia was associated with the targeted lesion or was an incidental background finding in the pathological specimen. We also want to make sure that more than 50% of the lesion has been sampled, so a review of the pre- and postbiopsy mammograms with our breast imaging team is critical.”

Needle or excisional biopsies may be ordered for patients whose lesions have not been biopsied or for whom an additional biopsy is required. In some centers, women with abnormal lesions such as LCIS or atypical hyperplasia routinely undergo excisional biopsy to rule out ductal carcinoma in situ or invasive breast cancer; however, only certain patients at MD Anderson undergo excisional biopsy. “If the lesion has been well sampled and the LCIS or atypical hyperplasia is limited or incidental, excision is commonly not recommended. This decision is made in our weekly multidisciplinary conference for the management of benign breast lesions.” Dr. Bevers said. However, she added, if less than half of the lesion was sampled or the proliferative lesion was extensive (i.e., more than three terminal ductal lobular units), an excisional biopsy would be recommended to make sure no cancer was missed owing to sampling error.

Additional biopsies and imaging studies, when needed, typically are done the day of the patient’s initial visit. Dr. Bevers said that every effort is made to get information to the patient as soon as possible. “We’re often able to give an indication of our level of concern based on our workup the same day,” she said. “It’s reassuring for women when we’re able to answer some of their questions at the end of the day. There’s less fear of the unknown, so they can start to formulate a plan and know what the next steps in cancer treatment, screening, or preventive therapy will be.”

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Aerosolized Gemcitabine for Pulmonary Metastases

Clinical trial tests novel chemotherapy delivery system for patients with lung metastases from osteosarcoma or other solid tumors

By Bryan Tutt

Pulmonary metastases are the leading cause of death in patients with osteosarcoma. Resection of the lung metastases is potentially curative, but surgery is not feasible for some patients. Many patients with lung metastases therefore receive systemic chemotherapy, which has significant side effects and, in this population, limited survival benefits. To reduce side effects and improve outcomes for patients with lung metastases from osteosarcoma and other cancers, researchers have developed a novel approach that delivers aerosolized chemotherapy directly to the lungs.

The potential benefit of aerosolized chemotherapy was established in preclinical studies by researchers including Eugenie Kleinerman, M.D., and Nancy Gordon, M.D., a professor and assistant professor, respectively, in the Division of Pediatrics at The University of Texas MD Anderson Cancer Center. “We found that we can administer a much lower dose by aerosol than what is usually given systemically and achieve greater benefit, thus decreasing the systemic toxic effects of the treatment,” Dr. Gordon said.

In the preclinical studies, the aerosolized cytotoxic agent that was most effective against lung metastases from osteosarcoma was gemcitabine. Normally given intravenously, gemcitabine is approved by the U.S. Food and Drug Administration for the treatment of several cancers and has shown activity against various types of sarcoma in clinical trials. On the basis of the preclinical findings, a clinical trial of aerosolized gemcitabine for children and adults with solid tumors and lung metastases is now enrolling patients at MD Anderson.

Clinical trial

The phase I trial (No. 2015-0720) is open to patients 12–50 years old who have lung metastases from osteosarcoma or other solid tumors and no proven survival-extending treatment options. “Because we’re studying the feasibility, safety, and toxicity of this treatment strategy rather than efficacy, we’re including patients with all types of solid tumors who have lung metastases,” said Najat Daw Bitar, M.D., a professor in the Division of Pediatrics and the trial’s principal investigator. She added that patients who have asthma or poor lung function for other reasons are excluded from the trial.

Patients in the trial receive aerosolized gemcitabine twice weekly for up to 12 28-day cycles. The primary outcome measures are the maximum tolerated dose and toxic effects. The researchers will also study the drug’s pharmacokinetics and tumor response according to Response Evaluation Criteria In Solid Tumors, version 1.1.

Once the maximum tolerated dose is established, the trial will enroll only

“"We found that we can administer a much lower dose by aerosol than what is usually given systemically and achieve greater benefit."”

– Dr. Nancy Gordon
What the National Cancer Institute Does

Resources for cancer patients, caregivers, physicians, researchers

If you’re a cancer patient or caregiver, you’ve no doubt heard of the U.S. National Cancer Institute (NCI). You may have visited their Web site to learn about a cancer-related topic. But you probably don’t know everything the NCI does to fight cancer.

As part of the National Institutes of Health (NIH), the NCI is charged with the mission to conduct and support cancer research and help people live longer, healthier lives. The NCI also helps educate cancer professionals, patients, and caregivers. Through these efforts, the NCI benefits cancer patients directly and indirectly.

Research

NCI-supported research helps cancer patients in many ways. Cutting-edge treatments are available to some patients through clinical trials, and many established cancer treatments are the result of previous NCI-funded research.

The NCI funds more cancer research than any organization in the world. Some of this research takes place in the NCI’s own laboratories at the Center for Cancer Research in Maryland. The NCI supports other research projects through grants to universities, hospitals, private industry, and research foundations.

A key feature of the NCI’s research initiatives is collaboration between institutions, especially in conducting clinical trials. For a trial to prove that a new treatment is safe and effective against a particular type of cancer, the treatment must be tested in hundreds or even thousands of patients. It’s often impossible for a single cancer center to recruit this many patients. The NCI recognized this problem in the 1950s and established the Cooperative Group program, now called the National Clinical Trials Network (NCTN), to provide funding and infrastructure to support large, multi-institutional clinical trials. As many as 25,000 cancer patients participate in NCTN treatment or imaging trials at more than 3,100 centers each year.

The NCI also supports designated cancer centers, which conduct laboratory, clinical, and population-based research. The NCI sets the standards for these centers, which receive funds from the NIH in the form of Cancer Center Support Grants. Some of these NCI-designated cancer centers, including The University of Texas MD Anderson Cancer Center, earn the additional designation of comprehensive cancer center by providing community outreach and education programs.

Education

Education is an important part of the NCI’s mission, and the agency’s efforts in this area are broad in scope. Some of these efforts are geared toward professionals (cancer researchers and physicians), while others are focused on patients and caregivers.

For professionals, the NCI provides fellowships, training grants, and career development awards. Fellowships help people who have recently finished their advanced degrees to gain hands-on clinical or research experience under the guidance of expert mentors. Training grants help institutions set up fellowship and other training programs, and career development awards fund research by fellows and other junior researchers.

For both professionals and patients, the NCI offers Physician Data Query (PDQ, www.cancer.gov/publications/pdq), an online source of information about a multitude of cancer-related topics. PDQ summaries give information about screening, treatment, and supportive care for various cancers in children and adults. There are two summaries for each topic: a detailed, technical version for professionals and a patient-focused version. PDQ also provides information about genetics, cancer drugs, alternative/complementary medicine, and cancer prevention as well as dictionaries of cancer terms, genetic terms, and cancer drugs.

The NCI provides a wealth of online resources specifically for patients at www.cancer.gov/resources-for/patients, including basic information about cancer, diagnosis and staging, treatment, treatment side effects, clinical trials, coping, managing care, and other cancer-related topics. More detailed fact sheets are available about individual types of cancer and specific treatments.

The NCI’s online resources for caregivers (www.cancer.gov/resources-for/caregivers) include much of the same information that is available for patients. But additional information is available on topics such as support for caregivers and advice for parents of children with cancer.

Finally, the NCI Contact Center (www.cancer.gov/contact), also called the Cancer Information Service, is available to answer questions from patients, caregivers, health care providers, and researchers. The toll-free phone line (800-4-CANCER, or 800-422-6237) and live online chat are available Monday through Friday from 9:00 AM to 9:00 PM Eastern Time. And questions can be submitted at any time by an online submission form.

By funding cancer research and providing education for patients, caregivers, physicians, and researchers, the NCI supports cancer prevention, treatment, and survivorship throughout the United States.

FOR MORE INFORMATION
- Visit the NCI at www.cancer.gov
- Call askMDAnderson at 877-632-6789
- Email The Learning Center at MD Anderson at asktlcstaff@mdanderson.org
- Visit www.mdanderson.org
- To learn more about clinical trials, visit www.clinicaltrials.org

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Aerosolized Gemcitabine
(Continued from page 6)

patients with osteosarcoma. “We want to get preliminary information to see if we should pursue a bigger study in patients with osteosarcoma,” Dr. Daw Bitar said. “But this novel therapeutic strategy doesn’t necessarily only apply to lung metastases from osteosarcoma. It can potentially be used in lung metastases from any solid tumors that respond to gemcitabine.”

Ensuring safety
“We monitor patients’ pulmonary function throughout the trial,” Dr. Gordon said. To facilitate this monitoring, patients are provided with a spirometer and a tablet. Before coming to the clinic on the day of each treatment, patients answer a questionnaire about their current health using the tablet and blow into the spirometer. The data from the questionnaire and spirometer are transferred to the patients’ physicians via a Web portal. A 10% or greater decline in pulmonary function is immediately investigated and, if the decline persists, could result in treatment cessation.

Several precautions are taken to ensure that hospital staff and patients’ family members are not exposed to the aerosolized cytotoxic agent during treatment. Treatment is given on an outpatient basis at MD Anderson with the patient under a plastic canopy in a negative pressure room. The patient receives gemcitabine via a nebulizer that delivers treatment only when the patient inhales. Furthermore, the nurses administering the treatment wear filtration masks and protective gloves and garments.

“If we can prove that the treatment is safe and does not pose a risk to caregivers, our ultimate goal is for the patients to get their therapy at home,” Dr. Daw Bitar said.

ERRATUM