OncoLog
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Innovative Trial Investigates Molecular Drivers of Triple-Negative Breast Cancer

By Brandon C. Strubberg

A new clinical trial focusing on molecular biomarkers of triple-negative breast cancer (TNBC) is attempting to advance targeted therapy against the deadly disease.

Fifteen to twenty percent of breast cancers are TNBC (i.e., negative for estrogen receptor, progesterone receptor, and human epidermal growth factor type 2 receptor)—among the most difficult breast cancers to treat. Typically, only 50% of patients with TNBC respond to neoadjuvant treatment with standard chemotherapy regimens. Until recently, clinicians have had no method to determine which patients will respond well to chemotherapy.

An innovative clinical trial called ARTEMIS seeks to determine if molecular testing of tumors can improve response to neoadjuvant treatment by guiding patients with chemosensitive tumors to standard chemotherapy (anthracy-

Ultrasound images from a patient with triple-negative breast cancer who participated in the ARTEMIS trial show no reduction in tumor size after initial treatment with doxorubicin (left) but substantial reduction after treatment with a targeted immunotherapy agent (right). The patient had only minimal residual cancer at the time of resection. Images courtesy of Dr. Stacy Moulder.

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cline followed by a taxane) and those with chemo-insensitive tumors (i.e., tumors with biomarkers that predict a poor response to standard chemotherapy) to clinical trials of agents that target their tumors' specific molecular drivers. "We want to try to home in on groups of patients for which targeted drugs may have the greatest effects," said Stacy Moulder, M.D., an associate professor in the Department of Breast Medical Oncology at The University of Texas MD Anderson Cancer Center and the principal investigator of ARTEMIS. "This would be a way to show that targeted drugs can be effective if the correct patient population is identified."

ARTEMIS

ARTEMIS is open to patients with previously untreated stage I–III TNBC who have primary tumors at least 1.5 cm in diameter. All patients enrolled in ARTEMIS undergo a biopsy of the primary tumor and molecular testing prior to treatment. To determine if the molecular testing improves outcomes, patients are randomly assigned to one of two study arms; each patient has a 2 in 3 chance of being assigned to arm B, the experimental arm. Patients in arm A do not receive the results of the molecular testing; those in arm B do receive the results.

It takes a few weeks to receive the molecular testing results, so all patients are given neoadjuvant anthracycline-based chemotherapy without delay. After four cycles of standard chemotherapy, patients in both arms work with their oncologists to determine whether the best course of action is to continue standard chemotherapy with a taxane or to enroll in a clinical trial of a targeted agent. However, patients in arm B are given the additional molecular profiling information to guide their treatment decisions.

After the completion of neoadjuvant therapy, patients undergo planned surgical resection. The amount of residual cancer in the surgical specimen is used to determine the efficacy of neoadjuvant therapy for each patient.

"I think this will be one of the first clinical trials to show that precision medicine benefits patients [with TNBC]."

– Dr. Stacy Moulder

Molecular profiling

The initial molecular profiling of the tumors includes a test for chemosensitivity developed by W. Fraser Symmans, M.D., a professor in the Department of Pathology. To develop the test, Dr. Symmans examined TNBC specimens resected after patients had received neoadjuvant chemotherapy. The tumors were categorized by chemotherapy response and the presence of specific molecular biomarkers, and Dr. Symmans developed a gene signature profile based on the observed patterns to predict which tumors were chemosensitive and which were chemo-insensitive.

In addition to guiding treatment for patients, the knowledge gained in the ARTEMIS trial will help pharmaceutical companies decide which experimental treatments to pursue in large clinical trials. When particular agents selected on the basis of molecular profiling show promise in ARTEMIS, larger trials of those agents can be conducted in other patients who have chemo-insensitive TNBC with similar profiles.

Patient enthusiasm

Enthusiasm from patients has been impressive, according to Dr. Moulder. "About 80% of patients who are approached about this trial ultimately participate—much higher than any other neoadjuvant therapy trial we've run. We feel like that is because the trial gives patients the option of a backup plan. The ARTEMIS trial does not mandate the treatment for patients; it simply advises treatment based on new information collected," Dr. Moulder said. "Patients really develop a relationship with their oncologist because they go through chemotherapy together and then sit down with the molecular testing results and together make decisions about the next steps in the treatment. We've had really positive comments made by patients in the study." This response may reflect the fact that ARTEMIS was designed with input from MD Anderson's breast cancer patient advocates.

Dr. Moulder is optimistic about the impact ARTEMIS could have for patients and clinicians. "I think this will be one of the first clinical trials to show that precision medicine benefits patients and that targeted therapy has an impact on pathological complete response rates for TNBC," she said. ■

FOR MORE INFORMATION

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To learn more about ARTEMIS, visit www.clinicaltrials.org and select study No. 2014-0185.

FURTHER READING

Hatzis C, Symmans WF, Zhang Y, et al. Relationship between complete pathologic response to neoadjuvant chemotherapy and survival in triple-negative breast cancer. *Clin Cancer Res.* 2016;22:26–33.

Smac Mimetics Show Activity against Myelofibrosis

By Sarah Bronson

Not all cases of myelofibrosis respond well to ruxolitinib, the only drug approved for this disease. However, early studies indicate that a new class of drugs, Smac mimetics, can achieve a response in some patients with myelofibrosis.

These drugs imitate an endogenous protein called second mitochondria-derived activator of caspases (Smac), which induces cell death. A clinical trial of one such drug is now enrolling patients who cannot receive or whose disease is resistant to standard treatment for myelofibrosis.

Many patients with myelofibrosis are in their 60s or 70s, have abnormal blood counts, or have other comorbid health conditions—all of which can preclude the use of ruxolitinib and other drugs. "There is an urgent, unmet clinical need for treatment options for these patients," said Naveen Pemmaraju, M.D., an assistant professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center. Clinical trials, if available, are often the best and sometimes the only option for this group of patients.

Smac mimetics

One potential treatment for these patients is Smac mimetics. These drugs target a natural mechanism that inhibits programmed cell death, or apoptosis, by mimicking a protein that cells normally release to promote apoptosis in a stressful environment. "Smac mimetics take away the apoptosis-blocking mechanism to promote cell death," Dr. Pemmaraju said. "Because this blocking of apoptosis is upregulated in cancer cells, we hypothesize that this class of drugs should preferentially hit the cancer cells over the healthy cells."

There is a strong rationale for pursuing the use of Smac mimetics in hematological cancers specifically. Researchers have observed that blood and tissue samples from patients with myeloproliferative neoplasms, including myelofibrosis (see "Myeloproliferative Neoplasms," right), have elevated levels of pro-inflammatory cytokines, particularly tumor necrosis factor α. Additionally, Bing Carter, Ph.D., a professor in the Department of Leukemia, has found that tumor necrosis factor α or related cytokines are required for the activity of Smac mimetics in acute myelogenous leukemia cells. These findings, along with the results of a recent dose-escalation trial that showed activity of the Smac mimetic LCL-161 in patients with various advanced solid tumors, gave MD Anderson investigators the impetus needed to undertake trials of Smac mimetics in myelofibrosis and other hematological cancers.

LCL-161

Dr. Pemmaraju, Dr. Carter, and Srdan Verstovsek, M.D., a professor in the Department of Leukemia, are performing a single-institution phase II trial (No. 2013-0612) at MD Anderson

Myeloproliferative Neoplasms

Primary myelofibrosis, the most aggressive myeloproliferative neoplasm, is characterized by uncontrolled growth of bone marrow cells, reactive bone marrow fibrosis, and a subsequent lack of red blood cells. Symptoms of myelofibrosis include anemia and enlargement of the spleen or liver.

Polycythemia vera and *essential thrombocythemia* typically are not life threatening, although both disorders carry an increased risk of thrombosis. Polycythemia vera is characterized by uncontrolled growth of bone marrow cells that increases the total blood volume and essential thrombocythemia by an overproduction of platelets.

Primary myelofibrosis, polycythemia vera, and essential thrombocythemia are considered the three classic myeloproliferative neoplasms. Although some myeloproliferative neoplasms were once considered clinically benign, all are now classified as cancers by the World Health Organization. ■

"Of the 13 patients analyzed so far [in the phase II trial of LCL-161], eight have had reductions in cIAP1 protein levels."

– Dr. Bing Carter

Smac Mimetics Show Activity against Myelofibrosis

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"There is an urgent, unmet clinical need for treatment options for these patients."

– Dr. Naveen Pemmaraju

to test LCL-161 for adult patients with intermediate- to high-risk myeloproliferative neoplasms, including myelofibrosis, who are ineligible for or intolerant to ruxolitinib or other JAK inhibitors. An unusual aspect of the trial is its inclusion of patients with characteristics that often disqualify patients from other trials or treatments. Specifically, there are no limits on spleen size, platelet count, or prior therapies such as stem cell transplants.

"Our thinking was to offer a different mechanism of action from that of the approved drugs that are available," said Dr. Pemmaraju. "LCL-161 targets a completely different pathway, and this is the first LCL-161 study in patients with a myeloproliferative neoplasm."

The trial follows a Simon optimal two-stage design, which means that LCL-161 must meet predefined efficacy and safety requirements in the first 13 patients before the trial can be expanded to include the planned 40 patients. The drug is given orally once per week in 4-week cycles. The patients undergo blood tests and physical examinations after every three cycles and bone marrow biopsies after the third cycle and then every six cycles. Objective responses are stringently defined: they must last more than 12 weeks and consist of a change in hemoglobin level, in symptoms as scored by a validated survey done over time, or in spleen size.

The patients enrolled so far are a heavily pretreated group with a median age in the 70s, with mostly high-risk myelofibrosis, and with a median platelet count of around 50,000/μL, whereas the normal range is 140,000–440,000/μL. Four of the first 13 patients had objective responses: two had increased hemoglobin levels, two had decreased symptoms, and one had a decreased spleen size (one patient responded according to two measures).

Importantly, none of the patients has experienced cytokine release syndrome, a dysregulation of the immune system that harms healthy cells. The investigators were on the lookout for cytokine release syndrome in these patients because Smac mimetics have the potential to intolerably increase cytokine levels, which are already elevated in myelofibrosis patients. To avoid this effect, patients received a conservative dose at first and did not at any point exceed the dose recommended by the investigators who carried out the dose-escalation trial of LCL-161 in patients with solid tumors. A small dose of steroids also may have helped prevent cytokine release syndrome in the current study. The most common side effects in the myelofibrosis patients have been fatigue, nausea, and vomiting. No major hematological toxic effects have been seen.

Analyses of blood samples collected before, during, and at the end of treatment from the patients who responded to LCL-161 supported the hypothesized mechanism of the drug. "We measured whether cIAP1, the anti-apoptotic protein targeted by the drug, was indeed inhibited after treatment. The lab results reflected the clinical results," Dr. Carter said. "Of the 13 patients analyzed so far, eight have had reductions in cIAP1 protein levels. Four of these patients had minor reductions, and their disease did

Birinapant

Another Smac mimetic that has been tested against hematological cancers is birinapant, which is bivalent, whereas LCL-161 is monovalent. (Monovalent and bivalent Smac mimetics may have different advantages and disadvantages, but these are not known yet.) Preclinical work from Dr. Carter showed that birinapant combined with azacitidine, a commonly used hypomethylating agent, was more effective than azacitidine alone in acute myelogenous leukemia cell lines and patient primary tumor samples and in mouse xenograft models of human acute myelogenous leukemia.

On the basis of these preclinical studies, Gautam Borthakur, M.B.B.S., an associate professor in the Department of Leukemia, has led two clinical trials of birinapant combined with azacitidine in patients with myelodysplastic syndrome. In the phase I trial of this combination, he said, "We established the right dose, and we did see that the combination had activity against myelodysplastic syndrome." However, the phase II trial, comparing the combination with azacitidine alone, did not meet its predefined endpoints for efficacy and safety, so the trial was stopped. The data from that trial are still being examined.

No further trials of birinapant are planned as far as Dr. Borthakur knows, but there remains potential for the drug. He said, "We do have a strong data-based rationale to combine Smac mimetics such as birinapant with more standard drugs in acute leukemias." ■

not respond to the drug. The other four had strong reductions, and their disease responded clinically."

Dr. Pemmaraju remarked that this type of correlative analysis, done in real time, extends the insights to be gained from a trial. "Whether the trial has positive, negative, or in-between results, this type of multifaceted collaboration between our patients, doctors, investigators, and scientists creates a loop of information that benefits the entire patient community."

On the whole, the first stage of the trial demonstrated that LCL-161 can feasibly be administered to patients with myelofibrosis who are ineligible for or intolerant of the approved JAK inhibitor therapy. Over the next year, the trial will continue enrolling patients.

Next steps

If LCL-161 continues to show activity in patients with myelofibrosis, the next steps would include testing the drug in combination with other agents, both novel and standard. LCL-161 also could potentially be tested in other hematological cancers, including acute myelogenous leukemia, myelodysplastic syndrome, and chronic myelomonocytic leukemia. Like myelofibrosis, these three cancers have few standard therapies.

Through clinical trials of Smac mimetics and other therapies, Dr. Pemmaraju said that MD Anderson researchers hope to increase the treatment options for patients with hematological cancers. "It's not just about the latest therapy, it's the availability of a personalized clinical trial that may be right for a particular patient at a particular time in their disease course," he said. "Furthermore, if patients can participate in clinical trials with correlative laboratory studies, that helps not only the patients but potentially every other patient with that disease to come." ■

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Urothelial Cancer Subtypes Predict Treatment Response

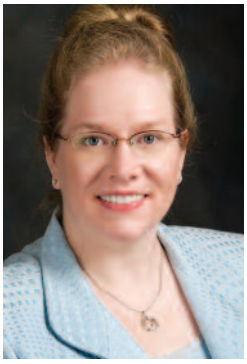
By Stephanie Deming

Subtypes of urothelial cancer identified through gene expression profiling predict which patients are most likely to respond to neoadjuvant cisplatin-based chemotherapy, according to research from The University of Texas MD Anderson Cancer Center. These findings will pave the way for a more personalized approach to treatment for urothelial cancers, including difficult-to-treat muscle-invasive bladder cancer.

The work was led by Arlene Siefker-Radtke, M.D., an associate professor in the Department of Genitourinary Medical Oncology. She said, "For decades, we've been treating bladder cancer as if it's all one disease. And until recently, we didn't have the techniques available to try to predict responders to specific therapies. Using gene expression profiling, we can start to understand the biology of different bladder cancers and predict which tumors will respond to specific therapies."

Bladder cancer subtypes

In recent years, researchers from The Cancer Genome Atlas, MD Anderson, and other groups have shown through gene expression profiling that urothelial cancers can be divided into three subtypes: basal, regular luminal, and p53-like, which is a distinct subset of the luminal subtype. Basal tumors have a stem cell–like appearance and proliferate rapidly. Regular luminal tumors share features with the umbrella cells of the bladder, tend to have enrichment for mutations in the gene encoding fibroblast growth factor receptor 3 (FGFR3) on gene set enrichment analysis, and have an intermediate rate of proliferation. p53-like tumors, which account for approximately half of luminal tumors, are characterized by a gene expression signature resembling that of wild-type p53, infiltration with stromal fibro-



"We're heading toward a more personalized approach to the treatment of our bladder cancer patients."

– Dr. Arlene Siefker-Radtke

Urothelial Cancer Subtypes Predict Treatment Response

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*In a clinical trial, patients with high-risk urothelial cancers received neoadjuvant chemotherapy plus bevacizumab followed by cystectomy. A survival analysis showed a distinct advantage for patients whose tumors were the basal subtype compared with patients with tumors of other subtypes (*P = .015*). Adapted with permission from* Eur Urol. *2016;69:855–862.*

blasts, and a slow proliferation rate.

Dr. Siefker-Radtke and her colleagues Woonyoung Choi, Ph.D., an assistant professor in the Department of Urology, and David McConkey, Ph.D., formerly a professor in the Department of Urology at MD Anderson and now director of the Johns Hopkins Greenberg Bladder Cancer Institute, decided to test whether these three subtypes predicted survival after neoadjuvant chemotherapy. Specifically, the researchers looked at tumor specimens from patients with muscle-invasive or other high-risk urothelial cancers who were treated at MD Anderson in a phase II trial of neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) plus bevacizumab followed by cystectomy. Cisplatin-based neoadjuvant chemotherapy is offered to many patients with muscle-invasive urothelial cancer but proves beneficial in only 30%–40% of treated patients; the ability to predict up front which patients are likely to respond to such therapy would help oncologists tailor treatment.

Thirty-eight patients in the phase II trial had bladder specimens available for gene expression profiling. Of these, 16 patients had basal, 11 had regular luminal, and 16 had p53-like tumors. Despite the small sample size, the results clearly showed that patients with basal tumors had a higher 5-year overall survival rate (91%) than did patients with regular luminal tumors (73%) or p53-like tumors (36%; P = .015). The survival advantage of patients with basal tumors remained significant in a multivariable analysis that included age at clinical trial registration and the presence of lymphovascular invasion. An additional finding of interest was that bone metastases within 2 years were observed in nine of the 16 patients with p53-like tumors but in no patients with the other subtypes.

These findings suggest that information about urothelial cancer subtypes could be used to guide treatment decisions. Basal tumors, despite their aggressive features, were responsive to MVAC; therefore, patients with basal tumors could be good candidates for neoadjuvant cisplatin-based chemotherapy. In contrast, the observation of bone metastases in more than half of the patients with p53-like tumors suggests that patients with p53-like tumors should be treated with surgery first and might be good candidates for adjuvant treatment with agents targeting stroma or bone.

The predictive power of the urothelial cancer subtypes was then confirmed through gene expression analysis and survival analysis in a separate group of 49 patients who had been treated with MVAC in an earlier clinical trial. Results from these analyses confirmed the survival advantage of patients with basal tumors: the 5-year overall survival rates were 77%, 56%, and 56% for patients with basal, regular luminal, and p53-like tumors, respectively (P = .02).

Ongoing clinical trials

Researchers are now trying to learn whether urothelial cancer subtypes predict responses to targeted anticancer drugs. Dr. Siefker-Radtke is currently leading two trials that address this question. Both are open to patients with metastatic or surgically unresectable urothelial cancers already treated with chemotherapy and/or immunotherapy.

One trial (No. 2015-0112) is testing the safety and efficacy of two different doses of a pan-FGFR tyrosine kinase inhibitor in patients who have urothelial tumors with genomic alterations in FGFR3. This is one of several trials worldwide testing FGFR3 inhibitors in urothelial cancer. A significant

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How Smoking Affects Appearance

Tobacco smoke causes premature aging, other cosmetic problems

You've probably heard that cigarette smoking causes lung cancer as well as cancers of the mouth, throat, liver, kidney, pancreas, colon, and many more. You may also know that smoking can cause heart disease, reproductive health issues, breathing disorders such as bronchitis and emphysema, and other health problems. But did you know that cigarette smoking affects the way you look?

Premature aging

Smokers are two to three times more likely to develop premature facial wrinkles than are nonsmokers. Smoking causes skin to lose its elasticity and moisture, take on a gray appearance, and form lines and grooves. While this is caused largely by the tightening of blood vessels and the drying effects of tobacco smoke, the motion of smoking itself—squinting of the eyes and tightening of the mouth—is thought to contribute to wrinkling around the eyes and upper lip. Because smokers repeatedly suck on cigarettes, they may also develop hollow cheeks, leading to a gaunt appearance.

These premature aging effects of cigarette smoking are even more dramatic than those resulting from sun exposure. The aging effects of smoking can become noticeable when a smoker is as young as 20–30 years old. By the time a smoker is 40 years old, he or she could have as many wrinkles as a 60-year-old nonsmoker.

Poor oral health

Smoking can wreak havoc on a person's mouth. Cigarette smoke is well known to cause bad breath as well as stained teeth and gums. The darkening of the gums by tobacco smoke is called "smoker's melanosis." Another cosmetic effect of smoking, "smoker's tongue," is characterized by white spots or patches on the tongue. A similar effect is "smoker's palate," also called nicotine stomatitis, a gray-white patch with red bumps on the roof of the mouth.

Because cigarette smoke weakens the ability of gum tissue to fight infection, smokers have an increased risk of periodontitis (an inflammation of the tissues surrounding the teeth), which can cause swollen gums and loss of teeth. Not only are smokers more likely to develop periodontitis in the first place, they also tend to respond more poorly to treatment than do nonsmokers.

Smokers who require dental implants are more likely than nonsmokers to have complications. And the more someone smokes, the more likely it is that dental implants will fail.

Not only do dental problems affect appearance, they can affect a person's ability to speak and eat. Even when the problems can be repaired, they can require many trips to the dentist.

Other consequences

In addition to premature aging and dental problems, cigarette smoking is linked to several conditions that affect your appearance.

Psoriasis. Compared with nonsmokers, smokers are about twice as likely to develop psoriasis, a chronic skin condition characterized by an uncomfortable and unsightly scaly rash. Also, psoriasis tends to be more severe in smokers than in nonsmokers.

Belly fat. The chemicals in cigarette smoke cause the body to store fat around the waist and upper torso instead of the hips. As a result, smokers often have a higher waist-to-hip ratio than nonsmokers. This not only causes belly flab but also increases the risk of diabetes and heart disease.

Acne. Compared with nonsmokers, smokers have more frequent and severe acne breakouts, which then take longer to heal.

Damaged hair. Cigarette smoke affects the hair by decreasing blood circulation and changing the DNA of hair follicles. The result can be a lackluster appearance, discoloration, thinning, and premature graying of the hair.

Stained fingers. Smokers tend to have yellowing of the fingers and fingernails on the hand used to hold cigarettes.

For many smokers, the effect of smoking on their appearance plays an important role in their decision to quit. Quitting smoking reduces their likelihood of developing life-threatening conditions like cancer and stops accumulating damage to their appearance. ■

– E. Nielsen

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- *Visit www.mdanderson.org*
- *Call MD Anderson's Tobacco Treatment Program at 713-792-QUIT or 866-245-0862*
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Urothelial Cancer Subtypes Predict Treatment Response

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proportion of both regular and p53-like luminal bladder cancers have *FGFR3* mutations.

In another trial (No. 2014-0661), patients with metastatic, unresectable urothelial cancer receive the proteasome inhibitor ixazomib in combination with gemcitabine and doxorubicin. In preclinical studies, ixazomib increased the sensitivity of bladder cancer cells to chemotherapy. Dr. Siefker-Radtke and her colleagues plan to perform gene expression profiling of the patients enrolled in this study to find out if certain subtypes of urothelial cancer are more sensitive than others are to ixazomib. Some data suggest that ixazomib inhibits angiogenesis; thus, this drug may be more effective against basal urothelial cancer, which is highly proliferative, than against other subtypes.

Future directions

At present, gene expression profiling is not the standard of care for patients with urothelial cancer. However, Drs. Siefker-Radtke, McConkey, and Choi are working with several private companies to further investigate the ability to predict response to chemotherapy and targeted agents. The researchers also hope to perform gene expression profiling on more patients with urothelial cancer who are enrolled in clinical trials. The resulting knowledge of the underlying tumor biology would allow rational development of therapies and combinations of therapies to target specific types of tumors.

> **"Using gene expression profiling, we can start to understand the biology of different bladder cancers and predict which tumors will respond to specific therapies."**
>
> **– Dr. Arlene Siefker-Radtke**

"Bladder cancer is not just one disease," Dr. Siefker-Radtke said. "We're heading toward a more personalized approach to the treatment of our bladder cancer patients." ■

FOR MORE INFORMATION

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FURTHER READING

McConkey DJ, Choi W, Shen Y, et al. A prognostic gene expression signature in the molecular classification of chemotherapy-naïve urothelial cancer is predictive of clinical outcomes from neoadjuvant chemotherapy: a phase 2 trial of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with bevacizumab in urothelial cancer. *Eur Urol.* 2016;69: 855–862.

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