YALE CANCER ANSWERS

Advances in Bladder Cancer Treatment

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February 24, 2019
Bladder cancer, I guess everyone is kind of always afraid about blood in the urine, right? Is that usually what happens that gets somebody to your attention?

And is bladder cancer equally common in men and women?

No. Actually, it is a male-predominant disease. It is about 3:1 in favor of men.

Wow, in favor? Lucky us.

It is bad enough we have got prostate glands to worry about.

The interesting thing is that the androgen receptor is present in the epithelium of the bladder, so the question is, does that have any bearing on the incidence, we are really not sure yet.

That’s the receptor that responds to testosterone or male hormones?
Petrylak  Correct.

Gore  Gotcha. And that has something to do with the development of prostate cancer as well, right?

Petrylak  It is not really clear what exactly is involved. We know it is involved in proliferation, but whether it really truly is involved in risk for prostate cancer is not really known.

Gore  But are you suggesting that perhaps it is involved in the development of bladder cancer or that is also not clear?

Petrylak  It is not clear. We have actually gone back and looked at some of the sealed databases to see if patients who go on hormone therapy and receive radiation therapy for prostate cancer are at an increased risk for bladder, and we really did not see anything. There are other groups who are looking at that question in terms of therapy and reusing some of the more novel anti-androgens that are being used for prostate cancer to treat bladder cancer.

Gore  Interesting. And women actually have some testosterone as well right, and some kind of androgen?

Petrylak  We all have testosterone regardless of whether we are male or female. In fact, there is a conversion of estrogen to testosterone, usually it occurs in the peripheral fat. So, everybody does have some testosterone in them.

Gore  But from the way you responded to my first question, it sounds like blood is not the only way in which patients may come to attention for bladder cancer. You mentioned infections?

Petrylak  That's right. Yes. Infections, any sort of urinary tract abnormality.

Gore  I think many of us, particularly guys of a certain age, which I will put myself in that category, come to expect the frequency of urination, the force of the stream decreases over time just due to
ageing of the prostate and so on, and so when should people be concerned that their urinary issues are more than age related run of the mill?

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Petrylak I think that blood clearly has to be investigated.

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Gore Blood is always bad right?

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Petrylak Blood is always bad. Infections, urinary tract infections in men are very, very uncommon. So, that is usually an indication of some abnormality in the urinary tract and that needs to be investigated or a crescendo of the symptoms. If somebody is having worsening frequency, worsening issues in terms of burning or other symptoms, that also needs to be investigated as well. So, I think you really have got to listen to your patient's history to see how that has been evolving.

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Gore Right, but I think it is important for our listeners to understand that not all blood will mean cancer, right?

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Petrylak Right. It could be BPH in a male. So, it could be related to that.

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Gore It could just be the prostate getting too big?

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Petrylak Exactly.

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Gore And not all infections similarly will mean cancer.

0:04:17.6 --&gt; 0:04:18.3
Petrylak That's correct.

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Gore So, people should not be afraid to go to their doctors?

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Petrylak No. They should investigate it because to let it go, it is just not going to get any better.

0:04:24.8 --&gt; 0:04:29.1
Gore Right, and if it does turn out to be cancer, you do not want to delay right?
What is the general approach to bladder cancer? As I recall back in the day when I used to know something about the stuff, early stage tended to be treated locally, is that still the case?

There are really two different types of bladder cancer. There is the muscle invasive, which can be lethal if it is not taken care of. And then, there is the non-muscle invasive, which in the most benign scenario, you basically do repeat TURBTs or scraping through the bladder and remove the tumors. And if it becomes more aggressive, you can instill some forms of immune therapy or chemotherapy into the bladder. So, they are two different kinds.

And is that done going through the abdomen or do you put a catheter into the bladder?

Right through the urethra into the bladder and a cystoscope is done the same way. That is just basically a way to look inside and then potentially grab any tissue that may look abnormal.

I was going to make a comment about grabbing, but I think in the interest of a family show, probably not a good idea. But that is to say that I think men are uncomfortable talking and thinking about having their privates manipulated. It sounds very uncomfortable, that is why I was thinking about the grabbing. So, are people sedated or is it something you do while awake?

General cystoscopy, you can do while awake.

Really? And it is not a big deal?

You can have local lidocaine injected into the urethra and it is fairly painless, it is not comfortable but it can be done. The more invasive types or the TURBTs, you do need anesthesia for that and you can do an examination under anesthesia to see how mobile a bladder lesion is or how fixed it is to the pelvis or to the bladder wall. So, there are different degrees of it.

And these are urologic surgeons who do these kind of procedures for the most part is that right?
Petrylak  That is correct.

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Gore  Which you are not?

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Petrylak  No. I am not.

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Gore  So, when do you get to see the patient?

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Petrylak  I get to see the patient when they are muscle invasive. We may be starting to see patients earlier in the course of the disease as well, and we can go into that a little bit later. But, if a patient has muscle-invasive disease, the blood vessels, the lymphatics, those can carry the tumor to distant sites.

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Gore  And just to be clear we are talking about the muscle of the bladder and we are not talking about the muscle of the pelvis or leg muscles or something like that? Because the bladder is a muscle right?

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Petrylak  No, we are talking about the muscle of the bladder. The way the urinary tract is set up, is we have the inner lining which is the urothelium and that lines the bladder, the urethra, the ureters as well as the renal pelvis. So, sometimes we slip and say bladder cancer, but it is actually in the ureter or in the renal pelvis. In fact, we are becoming more and more aware of the fact that even though they may have the same histology, there may be some biological differences in how they respond to treatment and their mutational loads. But it is the entire urinary tract. And in fact, if you think about it, bladder cancer is much more frequent than tumors of the upper urinary tract and that is because carcinogens will sit in the bladder for longer periods of time, there is longer exposure. The carcinogens we are talking about is tobacco smoke as well as chemicals. So, when the patient comes in, they are often flabbergasted to hear about the fact that their bladder cancer was caused by smoking and they say, oh I thought lung cancer was caused by smoking and it is like, no the carcinogens that you are ingesting by smoking have to be excreted somewhere and they go through the bladder and they can expose the bladder and the urothelium to these chemicals which can cause cancer.

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Gore  Wow. And so, most of the cancers that arise in the bladder come from this inner lining?

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Petrylak  They come from this inner lining. When I see the patient, if they have locally advanced or localized disease and it invades into the muscle of the bladder, we talk to them about chemotherapy
as a neo-adjuvant chemotherapy which means before they have their surgery or the definitive therapy. And the thought is that you can clean up the local tumor, or make it go away completely. It happens in about a third of patients or if there is micro-metastatic disease that we can see on a CT scan, then the chemotherapy will help to take care of that. And it has been demonstrated that patients who get what is called cisplatin-based chemotherapy, they have an improved survival with surgery than those patients who just simply receive the surgery alone.

Gore And does surgery mean removing the bladder?

Petrylak Surgery means removing the bladder, yes.

Gore Which I think people are very worried about.

Petrylak They are worried about that. In some cases, a new bladder can be reconstructed from intestine, and in the best scenarios, somebody can urinate normally and not have to have a stoma or a bag that is outside of their bodies. So, that can be done in certain select cases.

Gore So, it is actually connected to the urethra?

Petrylak Exactly. It is called a neobladder.

Gore Wow, a neobladder. But that is not always possible?

Petrylak It is not always possible.

Gore And some people will have to wear a collection bag.

Petrylak Some people will, some people will have an internal reservoir that they have to catheterize. It all depends upon their disease and where it is located with the ability of the surgeon as to remove tumor.

Gore If you give one of these chemotherapies before surgery and the tumor goes away as far as you can tell, do the patients still need to have their bladder removed?
Petrylak: That's a really controversial question.

Gore: That's why I asked.

Petrylak: You are absolutely right. Often, we will have patients come in as there is a 1 in 3 chance; now, if the bladder is removed in these patients, they have an 85% chance of being disease free at 5 years. So, it really selects for a very, very good prognostic improvement. The question you are asking is, do we need to take their bladders out. The answer is we really do not know. There are some patients who harbor occult metastasis within a lymph node, there are some patients who will recur locally within the bladder, and some very, very select studies in patients who are treated with that approach, neoadjuvant chemotherapy, followed by repeat cystoscopies and resections of tumors, about half of patients will be able to retain their bladder. So, that is possible in that situation.

Gore: I guess you need to have a patient who is very compliant; how often will they need cystoscopies?

Petrylak: Initially every 3 months.

Gore: That's pretty often.

Petrylak: It is interesting, when you look at the data from those patients who do not have a complete response to chemotherapy, in the first studies it is almost superimposable over surgery without the chemotherapy. So, you are selecting for a less resistant clone, perhaps an even less aggressive clone with the patients who respond. But, right now, if you have had chemotherapy before surgery, there is no standard treatment to give after surgery. We watch these patients every 3 months to be sure that they are not relapsing, and then you administer the appropriate therapy at that point. We are looking at clinical trials right now to evaluate some of these new immune checkpoint inhibitors in the
postoperative setting, so the thought is that by giving immune therapy early, we may have more of an effect with a low residual volume of disease than giving it later on when they have more bulky disease and they may have less of a chance to respond.

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Gore Interesting. I certainly want to come back to that in a few minutes, but I am just wondering again as a layperson here or pseudo-layperson here in my case, taking the bladder out, where is the tumor going to recur? I do not get that, there is no more bladder!

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Petrylak Well, it can recur anywhere. Because, remember we talked about before the channels still in the muscle, the lymphatics and the blood vessels, that can carry tumor cells anywhere in the body -- to the lymph nodes, to the bone, to the liver.

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Gore You mean before the bladder came out?

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Petrylak It could be there before the bladder came out, yeah - could be microscopic. And the thought is that by giving the chemotherapy when it is microscopic and small, you potentially can have more of an effect with your treatment. So, again, the numbers and the statistics from the studies have shown that that is the best approach to take.

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Gore Gotcha. I think we are going to want to come back to this for sure, particularly this interesting immune aspect after the break, but Dan right now, I have to take a short break for a medical minute. Please stay tuned to learn more about bladder cancer with Dr. Daniel Petrylak.

Medical Minute
Support for Yale Cancer Answers comes from AstraZeneca, dedicated to providing innovative treatment options for people living with bladder cancer. Learn more at astrazeneca-us.com.

0:14:03.6 --> 0:14:58.0
This is a medical minute about breast cancer, the most common cancer in women. In Connecticut alone, approximately 3000 women will be diagnosed with breast cancer this year, but thanks to earlier detection, non-invasive treatments and novel therapies, there are more options for patients to fight breast cancer than ever before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with breast cancer. Digital breast tomosynthesis or 3D mammography is transforming breast screening by significantly reducing unnecessary procedures while picking up more cancers and eliminating some of the fear and anxiety many women experience. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio.
Welcome back to Yale Cancer Answers. This is Dr. Steven Gore, and I am joined tonight by my guest, Dr. Dan Petrylak. We have been discussing advances in bladder cancer treatment. Dan, just before the break, you started telling me about some really interesting ideas about these immune drugs and how to use them better. You are really involved with developing the first immune drug in bladder cancer.

Atezolizumab. Actually, the first patient that was treated with atezolizumab was treated at Yale.

What is atezolizumab? I love that saying all those Zs together.

Cancer cells have a unique ability to basically make themselves invisible to immune surveillance. It is almost like the cloaking device from Stark Trek.

Now, these are like the immune cells that you get activated when you have the flu kind of thing?

These are more specific for cancer cells. T-cells. And so, these immune cells are circulating and their signals, there is a PD-1, PDL-1 access, which is a way for the immune cell to recognize the tumor cells, and the tumor cells can block that particular pathway. We have developed ways of unmasking the tumors, shutting the cloaking device off. And so, these tumor cells now can be visible to the immune system, they can be killed by the immune system. And bladder cancer has a long history with immune therapy, so that was one of the reasons why we went after that about 5 years ago.

This is like the cancer cells have Harry Potter's invisibility cloak on as far as the immune system is concerned and you give this drug and it takes away the invisibility cloak, something like that?

Exactly. We first started looking at this in patients who were refractory to chemotherapy, and some of these patients had multiple treatments beforehand, and so, our first patient had failed 3 chemotherapies, he had literally a golf ball that was sitting in his neck, a large tumor mass in his neck. And was probably a borderline performance status, he was not doing well, he used to be active and out shoveling the snow in his backyard. We had him out shoveling snow within 6 weeks.

You gave him the atezolizumab, taking away the invisibility cloak.
Petrylak And 6 weeks later, he was shoveling snow again.

Gore But what happened to the thing in his neck?

Petrylak It disappeared.

Gore Disappeared?

Petrylak Went away.

Gore And did all of his tumors go away or just some of them?

Petrylak About 90% of his tumors went away, and he remained in a very good response for about 4 years. So, in the past, historically, a patient like that basically had 6 months to live.

Gore Yeah, I know.

Petrylak They did very, very poorly. And he got 4 years. And Dr. Paul Eder and Dr. Joseph Kim were part of this as well, looking at this in a large phase-1 trial and this eventually was published, and we actually published our data, long-term data, with this drug, and we found that some of these responses were very, very durable.

Gore Oftentimes I know in a phase-1 study it is first time drugs being brought to humans, doctors might treat many patients with different kinds of cancer just because they are looking at the doses and stuff, right? So, did you do a study then just with bladder cancer?

Petrylak This was part of a larger phase-1 trial and the results were compelling, so compelling that the FDA granted breakthrough status, which means that rather than doing a large randomized trial, you can get FDA approval based upon a small or a phase-2 trial was not as large as the phase-1 trial.
Gore: But you certainly need to treat more than one person with bladder cancer to say that it is really working right?

Petrylak: Right. So, on this phase-1 trial, we had about 80 patients.

Gore: 80 bladder cancer patients?

Petrylak: 80 bladder cancer patients.

Gore: Wow.

Petrylak: And this was an international study. We then went to a much larger phase-2 trial where the patients were more uniform. I believe that was somewhere around 150 patients internationally.

Gore: All with bladder cancer that had recurred?

Petrylak: Right, all with bladder cancer that had recurred. The FDA took a look at that data. They were impressed with the response rate and they granted accelerated approval.

Gore: Wow. What percent of those patients actually had a good response?

Petrylak: Generally, it is about 1 in 4.

Gore: Okay, it is still not perfect.

Petrylak: Still not perfect, but what is really driving the survival with these particular drugs is the durability of the response. Because if you respond, you have got a good chance of staying in a good response for a while.

Gore: So, if you are in that lucky 25%, you really can stay in remission?
Petrylak: You can stay in remission. Some people come out of it, but a lot of people stay in remission for a long period of time.

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Gore: Wow, and is there any way to select ahead of time which are the patients who are likely to be in that good group?

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Petrylak: There is a lot of conflicting data about that. And when we stain for the marker, the PDL-1 marker that we talked about before.

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Gore: The invisibility cloak marker.

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Petrylak: The invisibility marker, there are differences in the technique and there are some drugs that look like they correlate, in some states of disease, they look like they correlate with PDL-1 expression, others do not. The problem with looking at this is that PDL-1 can predict response to atezolizumab or pembrolizumab or any of those drugs. But it is also prognostic; so, if you just look at bladder cancer patients not treated with PDL-1, PDL-1 expression portends for poorer outcome if it is on the tumor cell. It portends for better outcome if it is on the immune cell. So, it depends upon the assay. There is a lot of different subtleties to this. The other thing we are looking at in terms of prediction is something called mutational load. We know that these tumors that are responsive to immune therapy tend to have a lot of mutations.

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Gore: In their DNA?

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Petrylak: In their DNA, and these mutations translate into abnormal proteins, which sit on the cancer cells and make them -- for lack of a better word, like a steak juicier to the immune system. And the immune system sees that and says hey! this is something abnormal, let's get rid of it.

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Gore: That's for you non-vegetarian immune systems.

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Petrylak: Right. And vegetarian immune systems perhaps we put more tofu.

0:21:28.6 --> 0:21:31.6
Gore: It looks like a tofu right?

0:21:28.9 --> 0:21:50.3
Petrylak  It looks like a tofu or something like that. But it makes it more visible to the immune system. So, we have been looking at not only PDL-1 status, but mutational load and perhaps the way of looking at a predictor for response to immune therapy is a combination of both. So, there are ways of trying to refine this particular test.

Gore  Now, I know that atezolizumab is one of several of these invisibility unmasker immune drugs, have others also been tried in bladder cancer?

Petrylak  Yes. There are 5 that are approved by the FDA. Pembrolizumab and atezolizumab were the first to be approved, nivolumab is approved, durvalumab is approved and avelumab. So, all 5 of those are FDA approved for second-line therapy.

Gore  And I am guessing that the drug companies are not going to want to put theirs against another one to see which one is better?

Petrylak  No. There has never been a head-to-head comparison with any of these.

Gore  So, you just pick the one you like or?

Petrylak  Well, you also look at the different clinical states. So, those 5 are all approved for second-line therapy. A patient who has had prior chemo. There are only two that are approved for frontline therapy and only in a group of patients who are not eligible to receive cisplatin.

Gore  Which is the chemotherapy.

Petrylak  That's about 30% of the metastatic bladder cancer patients.

Gore  Why couldn’t you give the platinum to everybody?

Petrylak  Well, cisplatin, which is a more active drug than carboplatin, needs good kidney function to be administered and not all bladder cancer patients have kidney function or they may have peripheral neuropathy which is numbness of the fingers and toes, they may have hearing loss; all these are relative contraindications to giving cisplatin.
Gore: I see, and you cannot switch to the other, the carboplatin?

Petrylak: A lot of us feel the carboplatin is not as active a drug as cisplatin. So, the one thing that came out over the summertime was there are randomized trials going on right now comparing immune therapy to chemotherapy upfront in patients who never received treatment. And it seems that those patients who do not have PDL-1 do not have as good a survival as those patients who are treated with chemotherapy.

Gore: Let us think about this. So, these are the patients whose cancer cells are not expressing the PDL-1, am I right?

Petrylak: Correct.

Gore: They are benefiting from atezolizumab?

Petrylak: It looks like they are not benefiting in the upfront setting. Their survival is not as good as receiving chemotherapy upfront. So, the FDA put out a warning this summer, basically saying that if you have a patient who is not eligible for cisplatin, they should be tested for PDL-1 status because if they’re PDL-1 negative, they should get chemotherapy upfront. If they are PDL-1 positive, they should get immune therapy.

Gore: So, presumably the research trial was stopped?

Petrylak: The research trial is still going on, but that particular arm was shut for that reason.

Gore: I see, so the hope is, I am guessing from what you are telling me, that at least in the patients who are the right candidates that the immune therapy will be as good or better. So, you are doing this before the surgery then?

Petrylak: This is when they are metastatic. We are looking at other trials with doing it before surgery or as an adjuvant after surgery. Those are still in clinical trials.
Gore: It sounds like patients have a lot of choices they have got to consider even very early on when their disease presents? How do people walk through that experience? I mean, most people do not know a lot about cancer except they are afraid of it and probably even if they have experiences with a relative who had breast cancer or something, it is going to be different than bladder cancer and now you are going to say, well you know usually we do this for this, but you know we can give you atezolizumab and I think my head will be swimming.

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Petrylak: What we try to do is we try to make it as simple as we can. We try to come up with a roadmap. If you go up this road, then you are going to go down this pathway. If you go down this road, you will go down this pathway. We try to make it as visually understandable to the patient by drawing flowsheets or showing how it is going to go after that.

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Gore: You really need to take some time with the patient, it is not a 15-minute consultation.

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Petrylak: No, 5 years ago, it was a 15-minute consultation because we did not have anything to offer and now we do.

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Gore: I see, and if a patient is being treated somewhere and they are not offered these research trials, of course they may not know about them, but are these trials generally available in most places or certain centers?

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Petrylak: It is branching out. The trials with immune therapy initially started out at a few centers and then they went to larger trials. Some of the other studies that we are doing at Yale are open at Yale and are open at our care centers as well throughout Connecticut. So, we have a lot of our studies open and accessible to patients either locally or nationally or internationally for that matter.

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Gore: I guess that it is fair for any cancer really and particularly for patients with bladder cancer if their doctor presents a plan, it is always reasonable to say well are there any clinical trials I should be considering?

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Petrylak: Absolutely.

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Gore: And if the doctor says, I don't of any, is that a good answer?

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Petrylak: That is not a good answer.
Gore: So, that's a sign that the patient either needs to do some research or get another opinion maybe?

Petrylak: Absolutely. I think that is very, very reasonable.

Gore: Are there resources where patients can get online and look for these trials themselves? I know that is not so easy?

Petrylak: There is a bladder cancer organization called BCAN, Bladder Cancer Advisory Network. Basically they have a list of clinical trials and some of the centers that have their trials open.

Gore: But how urgent are these initiations of treatment? You have got a new diagnosis of cancer, you want to get that thing taken care of.

Petrylak: They are pretty urgent. In bladder cancer, if it fails primary chemotherapy and then if you fail immune therapy, you have to really move quickly because these patients can have very, very aggressive disease and by the time you start thinking about a new trial at that point, it may be too late. You've got to come with a game plan right at the beginning.

Gore: Do patients have the time when they are first diagnosed to do a little bit of research, to get a second opinion, or do they need to hop into the hospital and get that bladder wiped out?

Petrylak: They have a little time to get another opinion, but when they are refractory or resistant to their primary treatments, then it is going to move.

Gore: And this organization that you mentioned, the Bladder Cancer Advocacy Group, I imagine they may know centers of excellence.

Petrylak: Absolutely, yes.

Gore: I would assume that most people in the United States are probably somewhere close to a place like that?
Most people are.

And certainly in Connecticut, given Boston to Baltimore, we’ve got a lot of very good cancer centers. This is really interesting and so it sounds to me just in the last minute that we have got left that you are pretty excited that these immune therapies are making a big difference.

Right. But what I am also excited about is one in four patients respond to immune therapy. We have been working with a targeted smart bomb, something called enfortumab vedotin, which is a drug that delivers chemotherapy directly to the cancer cell. There is an adhesion molecule or sticky molecule that helps the cancer cells stick to each other that we target and by using a monoclonal antibody which is a smart bomb, we can deliver an anti-cancer agent directly to the cancer cells. We are seeing a 40% response rate in our preliminary studies in patients who failed immune therapy.

The people who have recurrent cancer?

Exactly. And we are seeing a 30% response rate in patients with spread to the liver, which is unheard of.