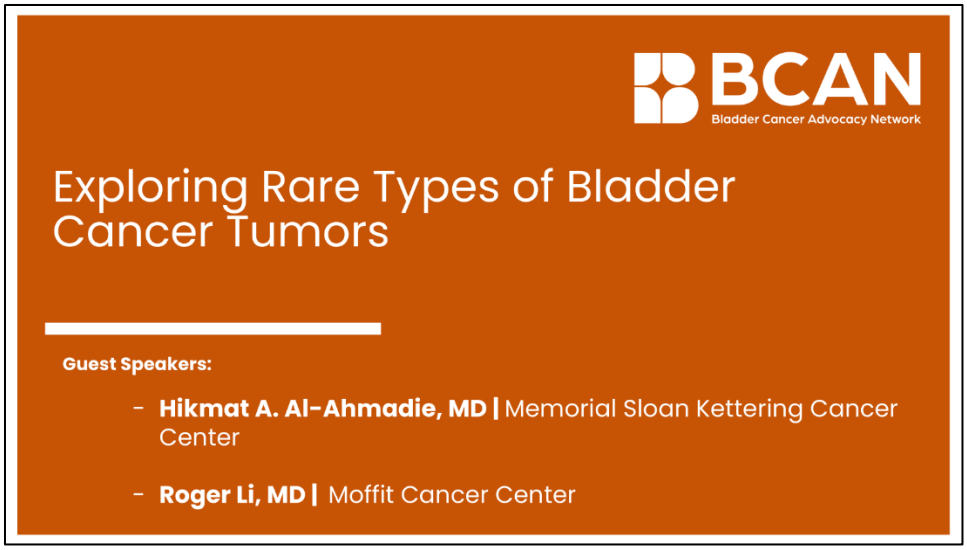


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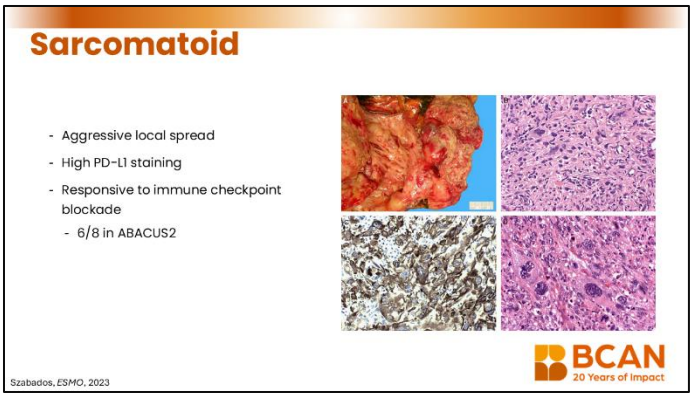
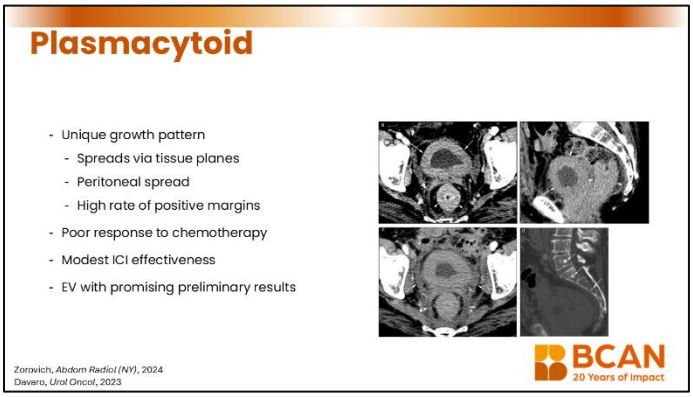
**Dr. Li:**




Moving on to another type of very rare disease, sarcomatoid bladder cancer. So, very much like the squamous cell type, this is also very aggressive locally and it's also known to have very high PD-L1 staining. What that means is that there are a lot of immune cells that will infiltrate into these tumors. And what that means from the clinical perspective is that because there are a lot of immune cells that are infiltrating into the tumor, it makes it oftentimes responsive to PD-1 inhibitors or immune checkpoint blockers such as Keytruda or Opdivo.

So, in the ABICUS trial, which is a clinical trial that was ran out of the UK, they enrolled a lot of patients with really rare subtype tumors, and eight of the patients actually did have sarcomatoid tumor in that trial that was treated with an immune checkpoint blocker, atezolizumab. And six out of the eight patients actually had a pathologic complete response. So, they were treated prior to them being taken to radical cystectomy, and at the time of radical cystectomy, after the bladder was removed, just by treating with atezolizumab, the patients' tumors were completely eliminated. So, very encouraging preliminary results from that study.

**Dr. Li:**




Dr. Al-Ahmadie also mentioned plasmacytoid disease. Clinically I would say this is one of the most challenging diseases that we treat as urologic surgeons, mainly because you could see here on the CT scan that the plasmacytoid tumors tend to spread along fascial planes. And what that means is that they will kind of circumscribe the organ, in this case the bladder, and that will almost act as a noose around where the bladder outlet is.

And so, that'll create this really tight noose so that the bladder has to work overtime in order to expel urine and causes thickening of the bladder walls. They can also cause the same sort of phenomenon around the rectum, too, which is very rare with any other type of bladder cancer. So, when we see that there is this sort of typical appearance of the bladder wall thickening along with rectal wall thickening, automatically we think plasmacytoid disease, even though it's very rare.

As we talked about, it has a high propensity for spreading via the tissue planes. Also it can spread into the peritoneum or the abdominal cavity. It'll spread alongside each of the different gut compartments. And as a result of it having this infiltrative growth pattern, you can imagine oftentimes when we go to do surgery for these folks, the surgery becomes very, very difficult because the infiltrative pattern makes it such that the bladder is completely adhesed to the surrounding pelvic organs, sometimes to the colon, to the point where we may have to take the colon along with the bladder. And the positive margin rate, so again, leaving cancer behind because we can't just really take out the entire tumor, that rate is also very high for these patients.

We typically will use chemotherapy upfront for these patients in order to downstage their tumor, and we often still do. As I mentioned, sometimes because the tumor actually grows around the colon, for instance, that'll actually choke off the passage of stool in your colon. And some patients may actually present with bowel obstruction.

So, I had a patient, again, that needed to have a colostomy done as the first surgical step in order to relieve the colonic obstruction, and then we put him on chemotherapy. That patient actually had a great response to the chemotherapy and we were able to remove the bladder as well as his rectum. And at the time, he still had T4 disease, but because he responded so well to the chemotherapy, he was actually able to live for a long time even after surgery.

The rule for these tumors, again, they're not only locally invasive, growing along these infiltrative patterns, but they also like to spawn off dista-metastases. So, oftentimes even if it's a success story locally when we are able to do these consolidative surgeries to more or less

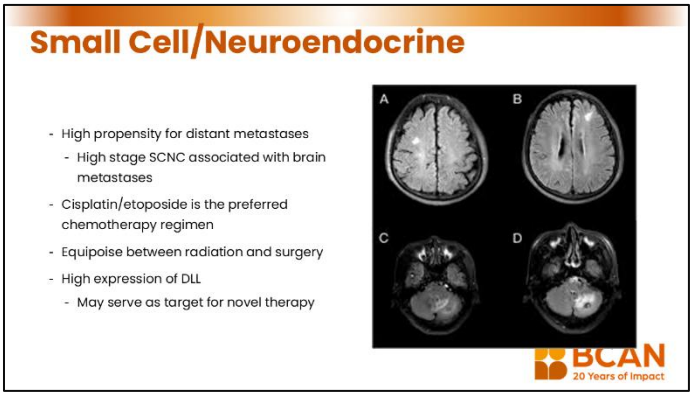
take out the vast majority of the tumor locally, oftentimes months, years afterwards the patients will develop a metastasis and they'll succumb to their disease.

So, over the years, because chemotherapy doesn't really work very well for these patients, we've looked to other types of therapy to treat these patients. So, immune checkpoint blockers have been used. Specifically at Memorial Stone Kettering, they had published a series on their patients being treated with immunotherapy. And unfortunately even with immunotherapy, there's very modest effectiveness.

But of course the new kid on the block, if you will, is enfortumab vedotin, which is another antibody drug conjugate that targets NECTIN4 and delivers an MMAE payload, which is kind of a chemotherapeutic agent. There have been very small numbers of patients who have been reported to be treated with EV. These patients obviously did have plasmacytoid disease, and they have demonstrated some very promising preliminary results.

So, the underlying theme that you see here is that a lot of these patients, because of the rarity of their tumors, they cannot be enrolled onto clinical trials to properly study the efficacy of various drugs to these tumors per se because of their rarity. And one of the missions that we have as part of the Global Society of Rare GU Tumors, which both myself and Dr. Al-Ahmadie are part of, is to think of ways so that we can be more encompassing for these patients to be enrolled onto clinical trials. So, even if they're just treated as a last-ditch effort, we're still going to be able to understand whether or not these novel therapies can be effectively used against these very rare but very aggressive tumors.

**Dr. Li:**

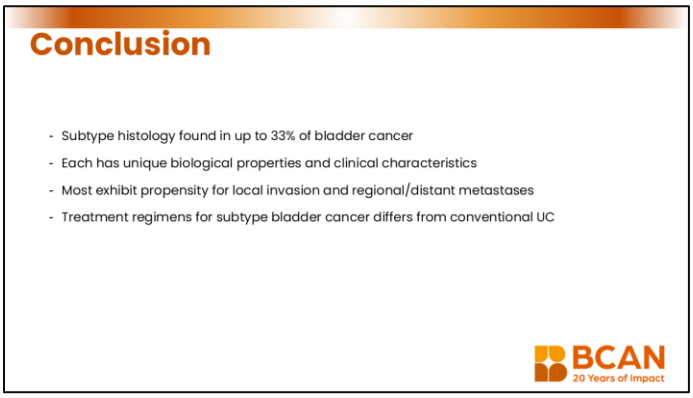



And finally, moving on to small cell or neuroendocrine tumor. These tumors I would say have the highest propensity for dista-metastasis. And you could tell here by this MRI of the brain, this is a very rare phenomenon in bladder cancer in general, but nevertheless, small cell cancer of the bladder tend to spread to the brain. And so, if a patient were to have small cell carcinoma and starts to have vision changes or headaches, certainly we need to get an MRI of the head to rule that out. In fact, in some places like MD Anderson, they actually just routinely get MRIs of the brain for small cell bladder cancer patients, especially for those patients with larger and higher-stage tumors.

So, the nice thing about small cell carcinoma is that we do have a very well-established chemotherapy regimen for it. And this is actually borrowed over from small cell lung cancer, which is still rare, but a lot more common than small cell bladder cancer. And fortunately, the regimen that works for small cell lung cancer also tends to work for small cell bladder cancer as well.

Beyond the treatment with systemic chemotherapy, as you know, we typically will consolidate the therapy by using local surgery or radical cystectomy or radiation. And there seems to be equipoise between the two modalities, particularly for small cell carcinoma. We know that small cell lung cancer or bladder cancer are exquisitely sensitive to radiation. And the final point about this tumor is that they are highly expressive of a target, again called DLL, and there are certain DLL-targeting antibody drug conjugates or bispecifics, T-cell engagers that may leverage the high expression of DLL that's found in these tumors for us to provide the effective treatments.

**Dr. Li:**




Finally, in conclusion, the subtype histologies altogether are found in up to a third of all bladder cancers. Each of the subtypes and the diversion differentiations have their unique biological properties, and I hope I convinced you that each of them behave a little bit differently than each other and have different clinical characteristics. Most will exhibit a high propensity either for local invasion or for distant or regional metastases. And of course, based on the molecular features of the different tumors, treatment regimens differ for these tumors.

But again, I want to just wrap up by saying that if you or one of your loved ones or one of your friends are unlucky enough to develop one of these rare subtype tumors, it's very, very important again to seek out help at an academic tertiary referral center where, because of the sheer volume of bladder cancer patients that we do see, we have relatively abundant experience compared to some of the community sites which may not have even seen a single case of these tumors.

**Dr. Li:**


So, I want to thank you for your attention, and we'll turn it over back to Patricia for some questions and answers. Thanks very much.

**Patricia Rios:**

One of the questions refers to nested subtypes, and Dr. Al-Ahmadie, I saw that on your slides. Could you explain what that is? And then Dr. Li, if you have any advice on treatments that are effective for that kind of subtype.

**Dr. Al-Ahmadie:**

Yeah. In this category of rare subtypes, it's one of the rarer ones. It has unique morphologic appearance. It has, I showed a picture of they look like a nest, and the pathologists who coined the term called it "nested" urothelial carcinoma.

It's challenging for us because most of the times it's very bland-looking. It doesn't look like an aggressive tumor. But at the same time it's deeply invasive. So, if you're dealing with a superficial biopsy, for example, where not all the layers of the bladder are represented, it may be dismissed as a reactive process or a benign process. And that's why I think being aware of this, and that's why to the point that Dr. Li mentioned, whenever there's doubt, it's important to have the material reviewed by people with experience. Because we're kind of attuned to these subtleties of these lesions, and once we see them, we recognize them, we alert.

So, if we're not definitive, at least we alert our clinical colleagues, the urologists. We're telling them, "Listen, this looks a little bit unusual. Maybe in the next visit to the patient, just maybe sample a little bit more, go deeper." Especially if the initial biopsy was very superficial, and that will give us ample material to examine. And then once you see it's deeply invasive, then it's an easier diagnosis to make despite that it has a very bland histology. So, that's how we deal with it on a diagnostic level. But the clinical, maybe I'll let Roger chime in.

**Dr. Li:**

Yeah. I think at least from everything that I've read, sometimes it may even resemble low-grade tumors, and it may actually be concomitantly present with low-grade tumors, which makes it even harder to diagnose.

I did actually have a patient who had nested variant. We gave him neoadjuvant chemotherapy, actually put him through a trimodality therapy regimen, and he was one of the very few patients who progressed right through the radiation. So, I don't know. This is a case of "N equals 1", but nevertheless, from this anecdote I can say that at least for this patient, he wasn't responsive at all to radiation.

And of course we really don't know what the reason for that is and we need to study more. But the recognition of these tumors I think is a first step, and we need to study better in a more robust cohort how to best treat these patients.

**Patricia Rios:**

Thank you. You both emphasize the importance of getting treated in a facility where there is expertise in these kind of subtypes in bladder cancer. And I'm wondering, what tips do you have for patients as they try to navigate that? Let's say if they're not close to either Moffit or

Memorial Sloan, what tips would you have for patients who may be recently diagnosed and are not sure how to navigate this?

**Dr. Li:**

I would say that at least you can get a consultation. In the very least what could be done is the pathology slides can be sent to a center like Memorial Sloan Kettering so that Dr. Al-Ahmadie can actually take a look at the slides and really make a diagnosis.

Because oftentimes, again these rare entities are not even recognized by the pathologists in the community. And you can imagine if you were to miss this diagnosis, your treatment's going to be completely altered and the efficacy of the treatment is also going to be off. So, in the very least I would recommend for that.

There are also some perks to what type of systemic agents we can give to patients, how we actually approach surgery versus radiation. Even once we've decided on doing surgery, for instance for the plasmacytoid patients, oftentimes we will not do an open surgery because we know that there is a danger for these infiltrative growth patterns. So, what we typically will do is actually laparoscopically look inside their belly to make sure that there's no metastatic disease first. So, in case if we were to find that, the patient doesn't have to recover from a large, open incision.

So, things like that, I just don't think that your average urologist or your average pathologist, medical oncologist will actually understand about these tumors. It really takes experts at tertiary referral centers to go through or see the number of bladder cancer patients that we see to really develop the experience to treat these well.