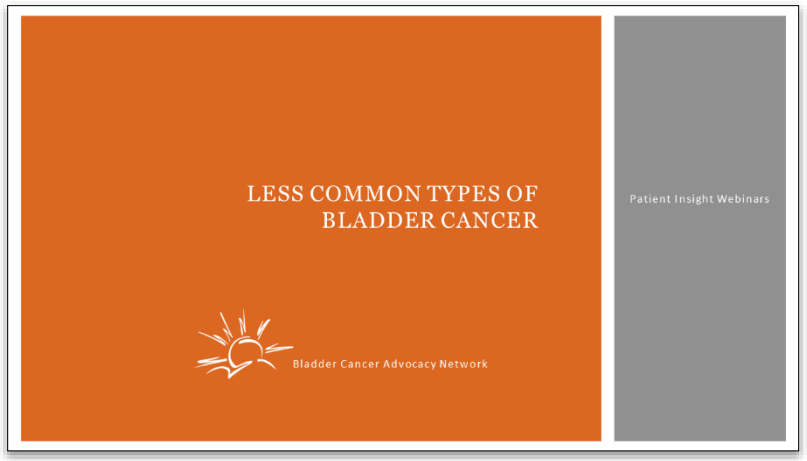
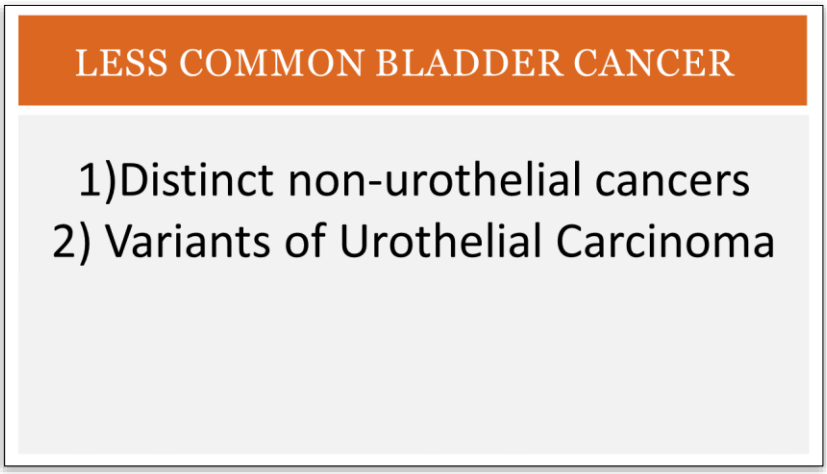


Morgan Stout:

Welcome to Less Common Types of Bladder Cancer. As the sixth most common type of cancer in the US, bladder cancer is not a rare disease, but within the scope of bladder cancer, there are rare variations that are more challenging to diagnose and treat known as tumors with variant histology. They include any bladder malignancy other than pure urothelial carcinoma. Advances in medicine and genomic testing are helping to identify more of these uncommon types of bladder cancer. Beacon is delighted to welcome urologist Dr. Max Kates from the Greenberg Bladder Cancer Institute at Johns Hopkins. Working at a large institution like Johns Hopkins, Dr. Kates sees quite a few of these rare varieties of bladder cancer. He's a clinician researcher working to better understand and treat these rare variants. Welcome, Dr. Kates.

Dr. Max Kates:

Thank you, Morgan and thank you to BCAN for having me. When you're asked to give a webinar on less common types of bladder cancer to a group of patients and patient advocates, what you worry about is, "Oh, goodness, there's a hundred types of less common bladder cancers. I'm not going to be able to cover everything." So what we decided to do is I'm going to go through a few of what I would call more common varieties or variant histologies of this sort of less common group, knowing that some of you may have a bladder cancer, may have a loved one with bladder cancer that I'm not going to cover here.

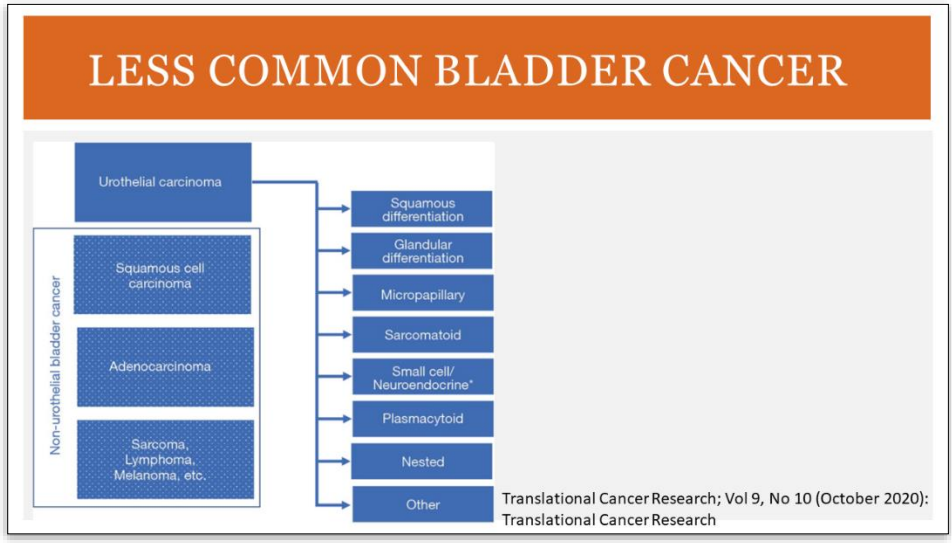


So I'm going to spend just about 20 minutes talking about these two distinct... I mean, these two distinct types of less common bladder cancer. And then we're really going to spend the rest of the time in a Q&A because I have a feeling I'm not going to be covering everything that you may have questions about.

Dr. Max Kates:

I really do want to make this as interactive and cover as much as we possibly can together in this next hour. So the way I think about less common bladder cancers is there are distinct non-urothelial cancers. When I say non-urothelial cancers, I think of the lining, the main cells, these urothelial cells that line the urinary system. Some types of bladder cancers are different cells altogether. And then there are variants of urothelial carcinoma in which it will have a lot of similarities and components of the traditional conventional bladder cancer that urothelial carcinoma.

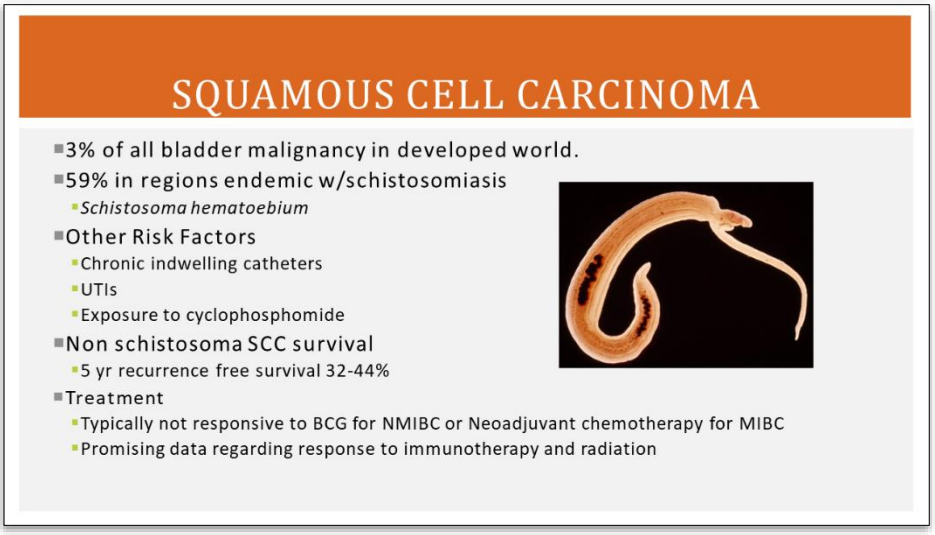
But 10% of it or 20% of it may have this different type of cell that sporadically appears. And those are the two different broad groupings of these less common bladder cancers. I'll take you through a couple of each of these groupings just as a starting point, a framework for us to discuss and then we can sort of take it from there.



I don't even have to say anything. The slides are just appearing. I love it. So broadly grouped, the non-urothelial cancers and the ones I'll discuss today are going to be squamous cell carcinoma of the bladder, and adenocarcinoma of the bladder. And there are many others that I won't discuss today. Lymphoma, sarcoma, paraganglioma, melanoma. Each is a little unique and distinct and I'll tell you that last group, the sarcomas, lymphomas, melanomas, paragangliomas, many of them are treated like you would treat other types of, say, sarcomas or lymphomas in other parts of the bodies.

They're treated the exact same way. They just happen to be in the bladder and they're going to be maybe subtle differences of them being in the bladder that would make you sort of add something or take something away. But broadly speaking, they're going to be treated very similarly to if it was in a different part of the body, whereas squamous cell carcinoma of the bladder and adenocarcinoma of the bladder, I'll discuss a little bit in detail because they may be particularly unique by being in the bladder.

And then the urothelial carcinoma that conventional histology or what the cell looks like under a microscope can be further differentiated, can be further divided into different subtypes. I'll be discussing a couple of these variant histologies, specifically micropapillary sarcomatoid, small cell and plasmacytoid. But there are also others that I will not be discussing in this slide deck I have, but we can also discuss afterwards.



Dr. Max Kates:

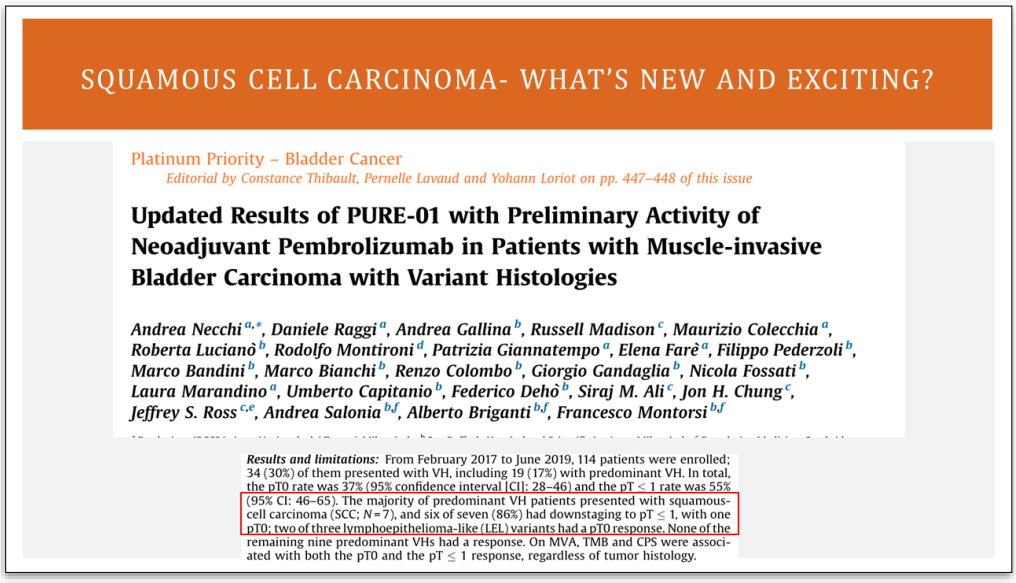
So squamous cell carcinoma. So this is a pure type of bladder cancer that's distinct from urothelial carcinoma. If you look at the world, it's about 3% of

all bladder malignancies, but there are certain areas of the world in which a parasite called schistosoma is very prevalent, specifically the Nile River Valley and specifically Egypt. So the rates of pure squamous cell carcinoma there are going to be exceptionally higher, but it may be a little bit different from the squamous cell carcinomas that we see in the United States.

Dr. Max Kates:

The ones we see in the United States are often associated with chronic use of indwelling catheters, recurrent urinary tract infections, and then exposures to carcinogens like cyclophosphamide. And the treatment is going to be a little different from conventional urothelial carcinoma and that it's not particularly sensitive to BCG when it's in the non-muscle invasive setting.

It's not sensitive from to chemotherapy when it's muscle invasive. So that's going to certainly impact how we manage it. There is some data I'll discuss about its potential response to radiation and immunotherapy. So this is pretty interesting to me. I'm going to try to show you a couple things of what we know and then some kind of exciting things that maybe what we as scientists would call more hypothesis driving or things that are exciting on the horizon that we can't yet prove but are exciting enough to be something that we're actively thinking about and potentially working on.


SQUAMOUS CELL CARCINOMA- WHAT'S NEW AND EXCITING?

Platinum Priority – Bladder Cancer

Editorial by Constance Thibault, Pernelle Lavaud and Yohann Loriot on pp. 447–448 of this issue

Updated Results of PURE-01 with Preliminary Activity of Neoadjuvant Pembrolizumab in Patients with Muscle-invasive Bladder Carcinoma with Variant Histologies

Andrea Necchi[a,], Daniele Raggi[a], Andrea Gallina[b], Russell Madison[c], Maurizio Colecchia[a], Roberta Lucianò[b], Rodolfo Montironi[d], Patrizia Giannatempo[a], Elena Farè[a], Filippo Pederzoli[b], Marco Bandini[b], Marco Bianchi[b], Renzo Colombo[b], Giorgio Gandaglia[b], Nicola Fossati[b], Laura Marandino[a], Umberto Capitanio[b], Federico Dehò[b], Siraj M. Ali[c], Jon H. Chung[c], Jeffrey S. Ross[c,e], Andrea Salonia[b,f], Alberto Briganti[b,f], Francesco Montorsi[b,f]*

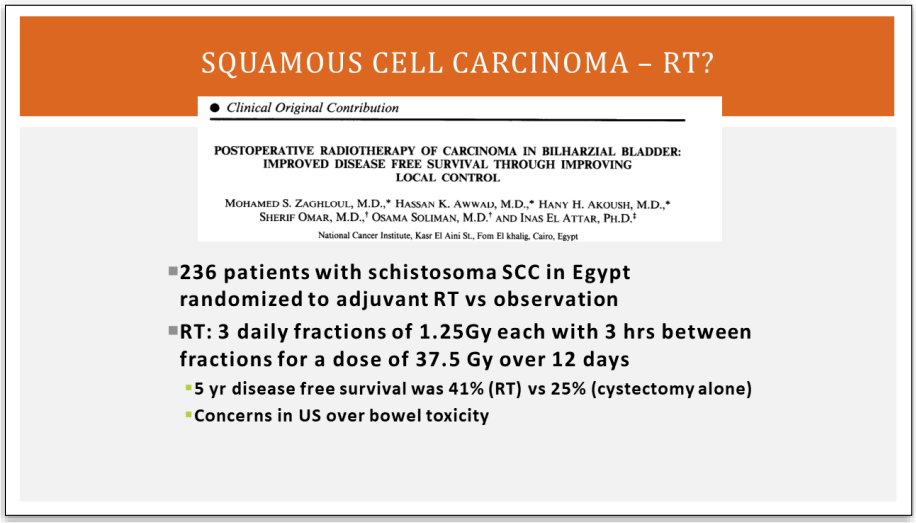
Results and limitations: From February 2017 to June 2019, 114 patients were enrolled; 34 (30%) of them presented with VH, including 19 (17%) with predominant VH. In total, the pT0 rate was 37% (95% confidence interval [CI]: 28–46) and the pT ≤ 1 rate was 55% (95% CI: 46–65). The majority of predominant VH patients presented with squamous-cell carcinoma (SCC; *N* = 7), and six of seven (86%) had downstaging to pT ≤ 1, with one pT0; two of three lymphoepithelioma-like (LEL) variants had a pT0 response. None of the remaining nine predominant VHs had a response. On MVA, TMB and CPS were associated with both the pT0 and the pT ≤ 1 response, regardless of tumor histology.

So this is a clinical trial of neoadjuvant pembrolizumab. Pembrolizumab is an immune checkpoint inhibitor. It's an immunotherapy that was given in this trial for patients with muscle invasive bladder cancer. And this specific article looked at the patients who were on this trial with these variant histologies and found that actually among the majority of these patients were patients that presented with squamous cell carcinoma.

So seven of the, I think 19 patients that had variant histology on the trial were these pure squamous cell carcinoma patients. Six out of seven of them that started with muscle invasive bladder cancer, by the time they had their cystectomy when their bladder was removed, they were downstage to at least T1 or lower. So that would be considered a fantastic success.

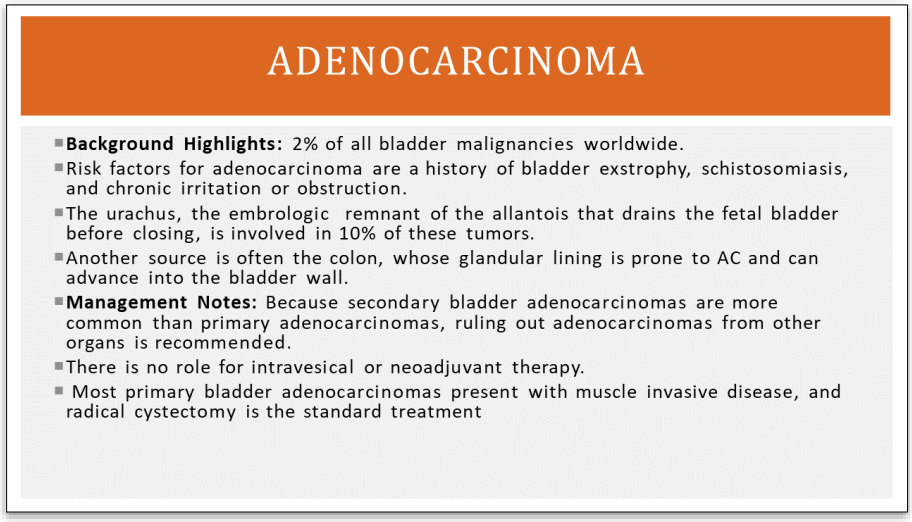
Now, it is only seven patients. So that's when I say it's hypothesis generating. I mean to say, I wouldn't recommend to a patient, "Hey, you need this drug if you have pure squamous cell carcinoma. But it's enough of a signal that I think it's something that many of us are thinking about very seriously for these patients. So this is something new and exciting on the horizon that these pure squamous cell carcinomas could be more responsive to immunotherapy and is something that we need to actively be investigating, and we are.

Dr. Max Kates:



This is over 200 patients with the schistosoma, that parasite induced squamous cell carcinoma in Egypt that were randomized to receiving radiation therapy versus observation and was found that radiation therapy after bladder removal had a disease free survival that was way better than without 41% versus 25%.

So this speaks to the potential radio sensitivity of squamous cell carcinoma. Now, as I said, this was a very different group of patients in Egypt with a different squamous cell carcinoma that we see in the United States, but nevertheless, it suggests there may be some patients with this pure squamous cell carcinoma that may be sensitive to radiation therapy.



. So let's talk a little bit about adenocarcinoma. So this is another pure... When I say pure, I mean different altogether from conventional urothelial carcinoma. Adenocarcinomas are about 2% of all bladder malignancies. The risk factors are an entity called bladder exstrophy, which is a congenital anomaly that needs to get fixed in infancy. Also, schistosoma or chronic irritation or obstruction. There is a specific entity of adenocarcinoma that originates from a structure called the urachus. The urachus is in most adults, actually a ligament that connects the belly button to the bladder.

Dr. Max Kates:

When you're a fetus that is how urine is eliminated from the bladder into the placental cavity through the umbilicus or the belly button. And when it closes, it becomes the urachus and it's what we call a potential structure, which means it's not really supposed to be anything, but in some people it doesn't close completely. And in some people they can get cancer and the cancer is an adenocarcinoma.

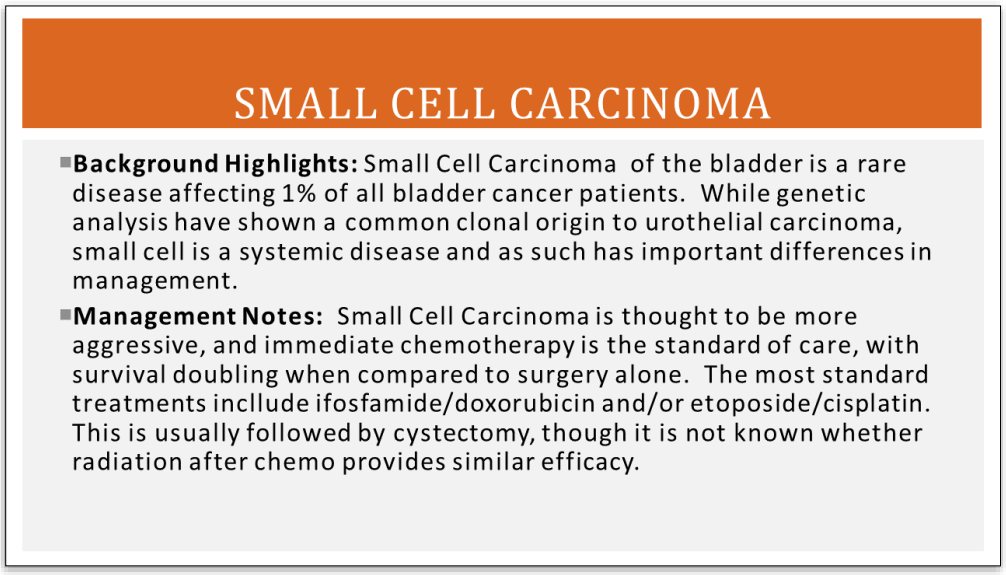
So with an adenocarcinoma, these are very rare. So the most important thing and I saw actually two patients with this in clinic today, and the first thing you want to do is make sure it is not an adenocarcinoma coming from somewhere where adenocarcinomas are very common. And that would be namely the colon and the rectum. Colorectal cancer is one of the top five cancer in the United States, and it's most common cell type is this adenocarcinoma.

So all my patients who come in this will get a colonoscopy to make sure that it's not a tumor growing from their rectum into their bladder or coming from their large intestine into their bladder. And the thing that we know about these adenocarcinomas is that similar to the pure squamous cells, there really is no role we think for intravesical BCG or intravesical therapy for non-muscle invasive disease or neoadjuvant chemotherapy.

Dr. Max Kates:

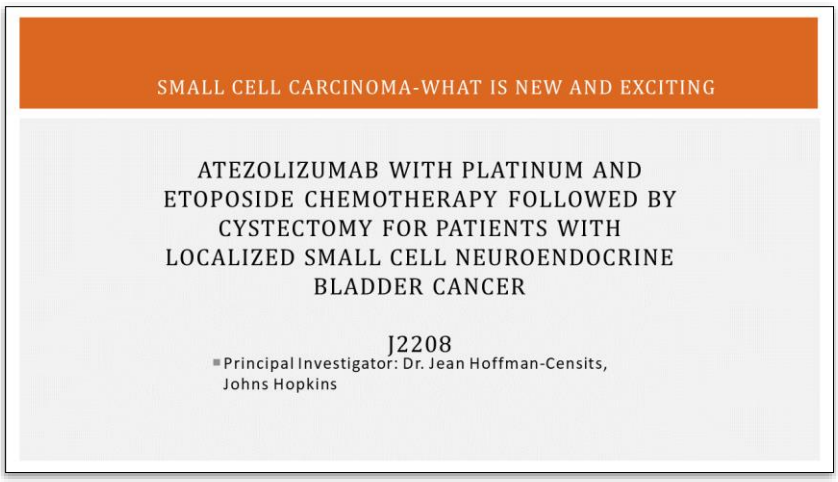
Now, there could be two reasons for that. Number one, we haven't identified the correct intravesical therapies or systemic therapies or number two, they're surgical diseases and there is no correct therapy. But at least for the time being, these are typically managed with aggressive surgical treatment. So for muscle invasive bladder cancer, that would be a radical mastectomy.

So this is small cell carcinoma of the bladder. It is a rare disease that it affects about 1% of patients. And there are different types of small cell carcinomas throughout the body. They can occur in different organs. Typically though the small cell carcinoma when it occurs in the bladder is thought to be a systemic disease.



So what do I mean by that? What I mean by that is when it's in the bladder, it's thought to by definition likely be in other parts of the body. And because of that, the traditional thinking is that it's best managed with initial systemic therapy. In this day and age that would be initial chemotherapy. And then when the patient receives chemotherapy, oftentimes, afterwards we will do what's called consolidation on the bladder, which means that's removal of the bladder, potentially radiation to the bladder.

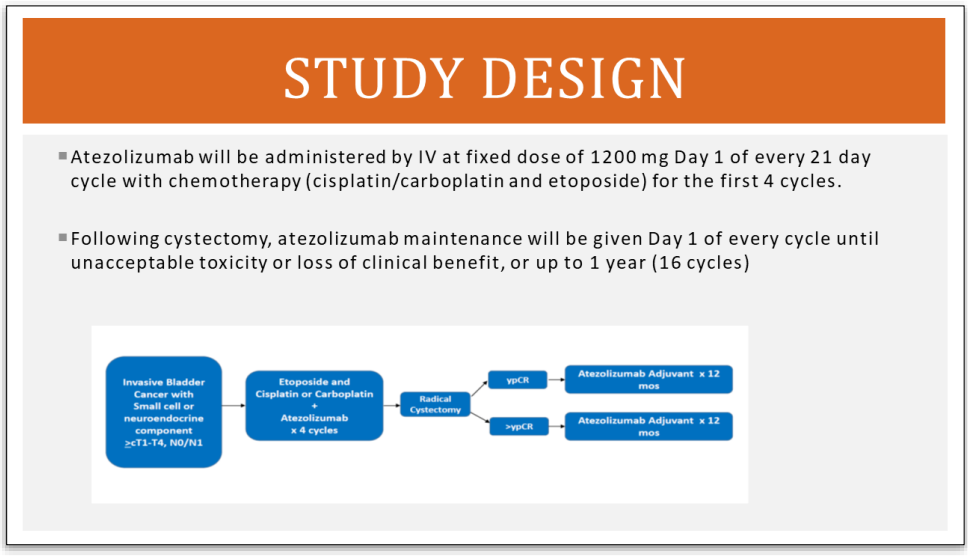
But the idea here is that the first thing a patient will benefit from is systemic chemotherapy. Although, now in terms of what's exciting, let's go to the next slide... So this is really exciting and I want to highlight it. It's happening at Hopkins, but it's one of the first trials to be a clinical trial that is wholly focused on a variant histology of bladder cancer.



It was an immense undertaking to get this trial off the ground by my colleague at Hopkins, Dr. Jean Hoffman-Censits. And it's evaluating the traditional chemotherapy, which is typically cisplatin and atopic side for small cell bladder cancer patients and looking at whether adding

immunotherapy with atezolizumab benefits these patients.

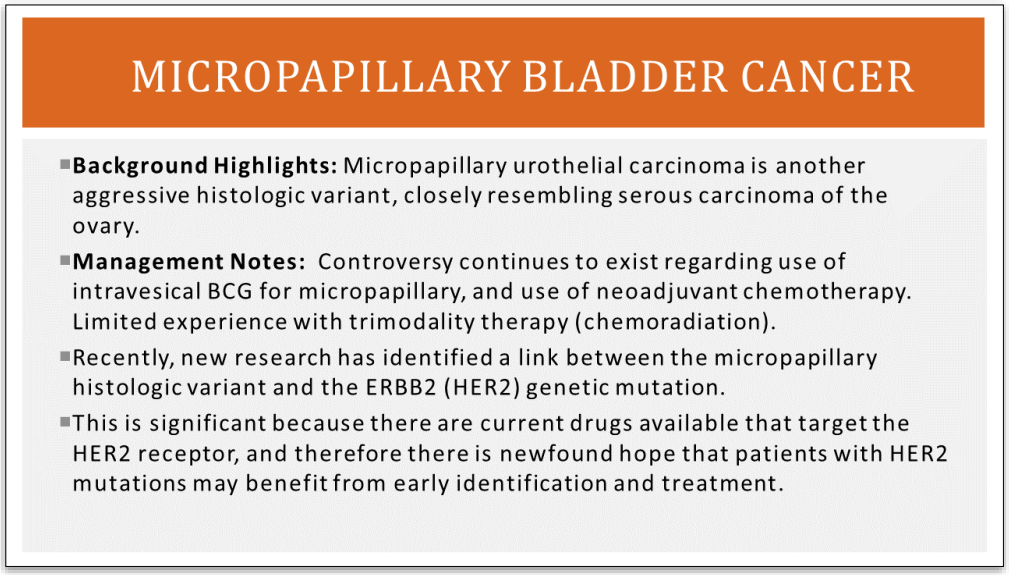
And so what this trial is doing is it is really evaluating all of these patients by giving them this combination treatment of cisplatin and etoposide chemotherapy with this immunotherapy. Then they go on to have a radical cystectomy and then based on... And then we'll go on to have maintenance immunotherapy with atezolizumab.



Dr. Max Kates:

So I'm once again really excited by... I want to see more of these trials. We're trying to get more off the ground where a lot of times they'll need to be fully nationally cohesive, meaning multiple centers working together because these are rare diseases, but we still need to have clinical trials that address them. And this highlights that. Next slide.

So micropapillary bladder cancer is another histologic variant. It's considered to be more aggressive than traditional sort of conventional urothelial. So the reason that becomes a little bit controversial is when it's non-muscle invasive bladder cancer. There are two schools of thought. Some will immediately suggest that the patient should have their bladder removed because it is this more aggressive type and some will be comfortable with an aggressive transurethral resection of the bladder followed by BCG.



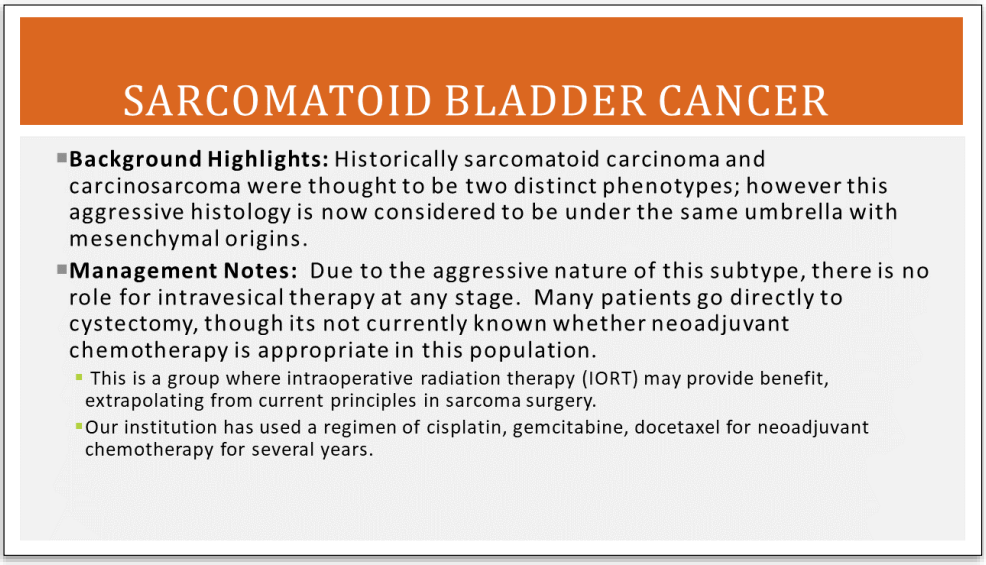
The controversy also exists, I'll tell you with regard to whether patients should undergo neoadjuvant chemotherapy followed by bladder removal or avoid chemotherapy upfront and just have their bladder removed and then consider chemotherapy afterwards.

I'll tell you right now, I don't have a... It's not all or nothing in terms of the way I manage micropapillary bladder cancer. Many of these patients are presented to our tumor board. I think there's a lot of thought that goes into it and I think there's nuances in making the decisions for each patient. So I'm not one to have a defined school of thought of one versus the other in all patients.

There's been some really interesting research here. So new research has identified a link between micropapillary histology variant and a gene called ERBB2 or HER2 genetic mutation. Why is this significant? Well, this is really significant because there are several drugs currently available that actually target the HER2 receptor. And so there's a lot of hope here and there's a lot of people trying to get trials off the ground and try to evaluate whether some of these patients with micropapillary bladder cancer may benefit from these newer agents. And that's something that we're working on here at Hopkins. Other people are working on nationally to try to get a trial like this off the ground.

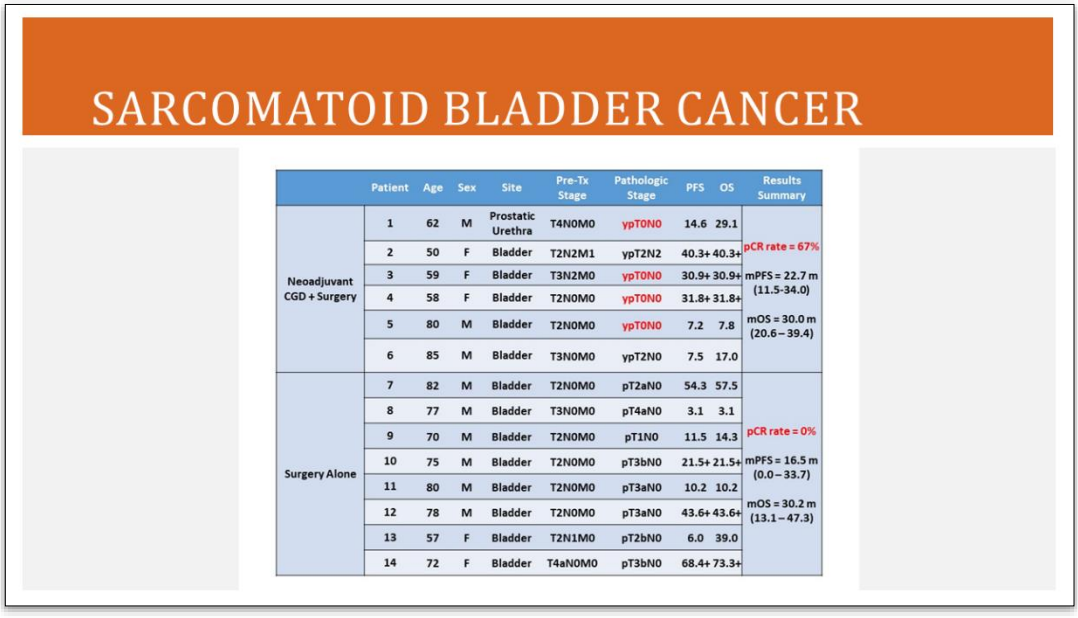
Dr. Max Kates:

Sarcomatoid bladder cancer. So sarcomatoid bladder cancer is another histology that is a variant of urothelial cancer. Sometimes it's just 5% of the urothelial bladder cancer. Sometimes it's more. I think that by and large with a few exceptions, when it presents in the bladder, even if it's non-muscle invasive, most patients are benefited by having their bladder removed.



I don't tend to treat a lot of these patients with intravesical therapy, but there are exceptions to that. Once again, it's not an all or nothing approach. It's definitely going to be nuanced. We have a series about some of these patients responding well to what's called IORT or intraoperative radiation therapy, particularly the types that are more locally advanced where they may be growing outside the bladder.

Our institution has a unique regimen of cisplatin, gemcitabine and docetaxel for neoadjuvant chemotherapy. I think the point here is that it helps for some of these more rare forms of bladder cancer to be the center that sort of has a philosophy or has a unique treatment modality for how they're treating these cancers. The way we treat sarcomatoid bladder cancer would be an example of we use this triplet chemotherapy regimen.

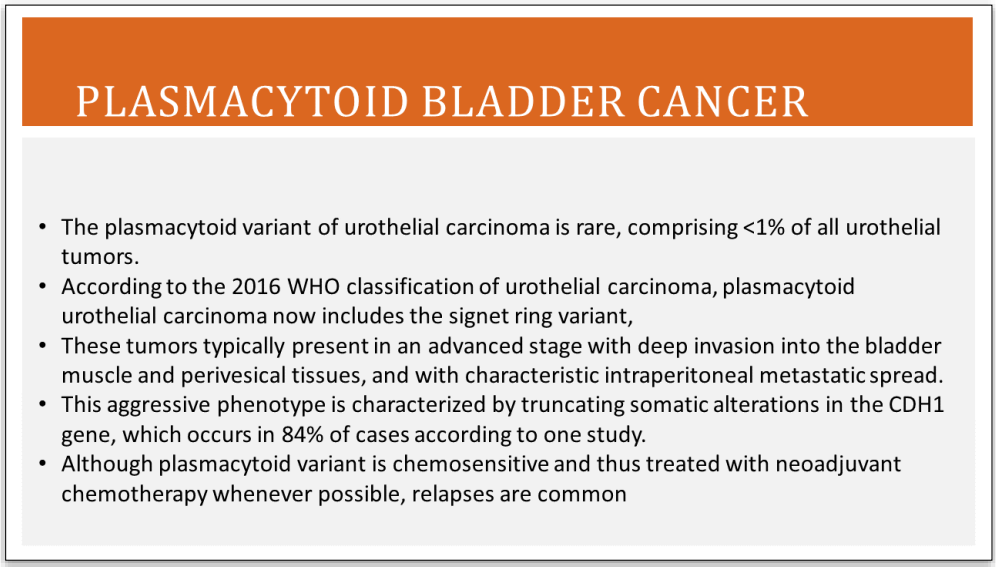


And this was led by my colleague Dr. Noah Hahn this triplet therapy. We've seen a number of complete responses with this new adjuvant

therapy.

Dr. Max Kates:

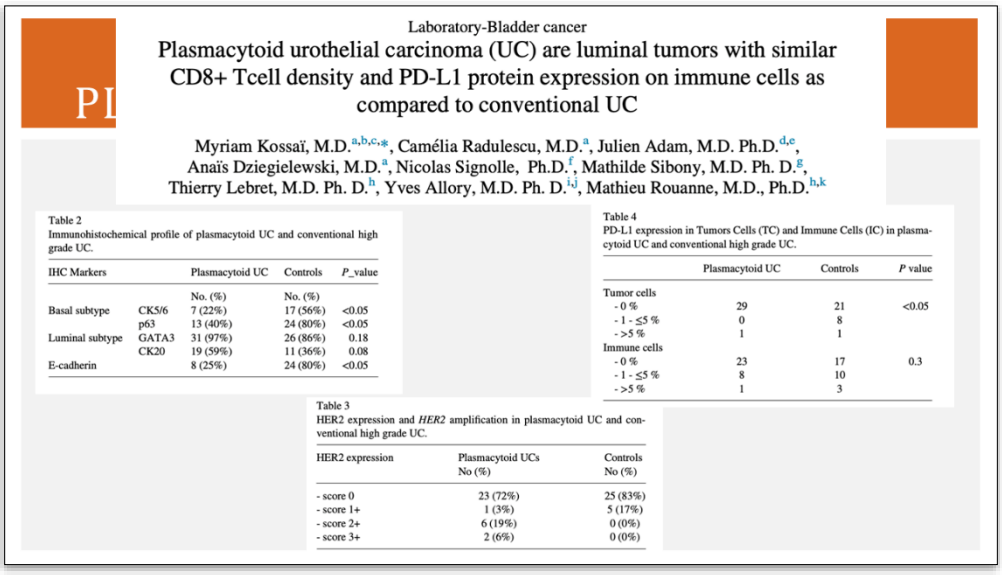
So now I'll talk about plasmacytoid. I realize I'm going fast, but I do want to make most of this at Q&A.



So plasmacytoid bladder cancer is also exceptionally rare, although we're seeing it a little bit more and more we think. It includes something called signet ring variant. Many of these tumors are very difficult to stage because they may look like they're not very advanced on CT imaging or MRI, but at the time of surgery they may be more advanced than is initially thought. They tend to travel up the lining of the peritoneum, which is the body that encases the intestines.

They are also we're making new advances in finding out that they're associated with alterations in the CDH1 gene. And that is significant that we're finding out that some of these variant histologies have common mutations is obviously encouraging because the hope is then, "Okay, can we address that mutation through a therapeutic intervention?"

I want to show you some other exciting things about plasmacytoid. So some recent laboratory work has shown that these are more typically luminal tumors. They're higher in CD8 T cells. So this type of immune T cells and they express PDL1. Well, why is that? More than conventional urothelial cancers? Why is that important? That's important because the main immunotherapy that I've been talking about that we have available is an immune checkpoint inhibitor that addresses PDL1.



Laboratory-Bladder cancer

Plasmacytoid urothelial carcinoma (UC) are luminal tumors with similar CD8+ Tcell density and PD-L1 protein expression on immune cells as compared to conventional UC

Myriam Kossaï, M.D.[a,b,c,*], Camélia Radulescu, M.D.[a], Julien Adam, M.D. Ph.D.[d,e], Anaïs Dziegielewski, M.D.[a], Nicolas Signolle, Ph.D.[f], Mathilde Sibony, M.D. Ph. D.[g], Thierry Lebret, M.D. Ph. D.[h], Yves Allory, M.D. Ph. D.[i,j], Mathieu Rouanne, M.D., Ph.D.[h,k]

Table 2
Immunohistochemical profile of plasmacytoid UC and conventional high grade UC.

IHC Markers		Plasmacytoid UC	Controls	*P*_value
		No. (%)	No. (%)	
Basal subtype	CK5/6	7 (22%)	17 (56%)	<0.05
	p63	13 (40%)	24 (80%)	<0.05
Luminal subtype	GATA3	31 (97%)	26 (86%)	0.18
	CK20	19 (59%)	11 (36%)	0.08
E-cadherin		8 (25%)	24 (80%)	<0.05

Table 4
PD-L1 expression in Tumors Cells (TC) and Immune Cells (IC) in plasmacytoid UC and conventional high grade UC.

	Plasmacytoid UC	Controls	*P* value
Tumor cells			
- 0 %	29	21	<0.05
- 1 - ≤5 %	0	8	
- >5 %	1	1	
Immune cells			
- 0 %	23	17	0.3
- 1 - ≤5 %	8	10	
- >5 %	1	3	

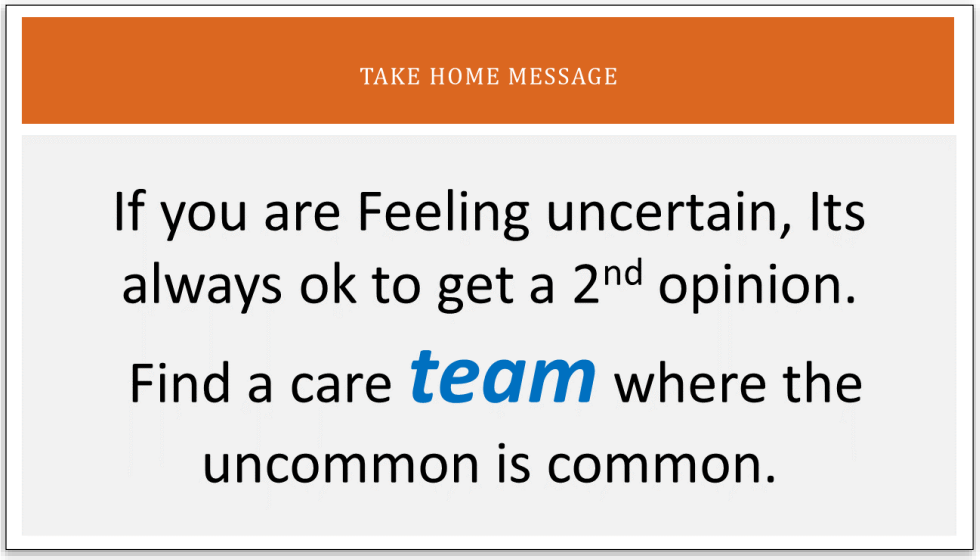
Table 3
HER2 expression and *HER2* amplification in plasmacytoid UC and conventional high grade UC.

HER2 expression	Plasmacytoid UCs No (%)	Controls No (%)
- score 0	23 (72%)	25 (83%)
- score 1+	1 (3%)	5 (17%)
- score 2+	6 (19%)	0 (0%)
- score 3+	2 (6%)	0 (0%)

So the thought is, "Well, these variant tumors may be amenable to this immunotherapy." So that also needs to get tested out in trials and in further studies, but it's encouraging.

Dr. Max Kates:

So I wanted to briefly cover some of these and then I would love to get into some more Q&A and interactions, but I really believe strongly that if you're feeling... This is true regardless of whether you have a variant histology or a loved one does, but for all types of bladder cancer, but in particular, these more rare subtle forms of bladder cancer where the treatment strategies may seem subtle, but they really are very important. If you're feeling uncertain, it's always okay to get a second opinion and finding a care team where the uncommon is common is also very important.



I'll end there. I do want to just talk broadly about something that came up that I didn't discuss in the slides, but that is... "Well, are these responsive to bladder preservation or to radiation these uncommon cancers?" And the truth is we think that the largest series looking at chemotherapy and radiation or trimodality therapy, non-cystectomy therapy comes out of MGH.

And they did look at variant histology in one of their series. It's just not that many patients that they were able to look at. So the number of patients that they actually looked at from the tumor types that I discussed with you today was I believe around 20 patients or close to that. And really it's hard to draw conclusions. Thankfully, there is a randomized control trial called SWOG 1806 that is randomizing patients to the traditional trimodality therapy of chemotherapy and radiation versus chemotherapy and radiation plus immunotherapy.

And the reason that that is going to be really exciting is because they're allowing almost all histologic variants, I believe, with the exception of small cell cancer. And so we're going to learn... Hopefully there'll be a number of patients that sign on to that trial who have these more rare types of bladder cancer and we're going to learn a lot about how they respond to radiation, excuse me, by being on that trial. So with that, I'll turn it over to questions.