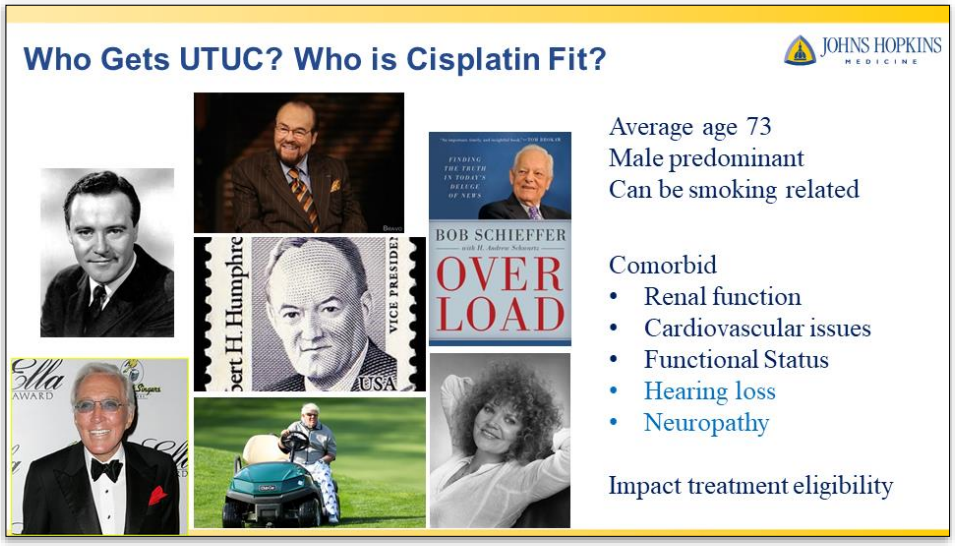
Dr. Hoffman-Censits:

Thanks so much Dr. Singla. And I just wanted to again thank the BCAN team for allowing us to come in and talk to y'all today about upper tract urothelial cancer. We know that this is an uncommon presentation of urothelial cancer, and we're just thrilled that BCAN is a safe place on the internet that our patients can go to get information about the disease and that you really raise awareness of the disease. I'm a medical oncologist and you're hearing from a medical oncologist, I give intravenous and oral therapies for urothelial cancer, as well as a surgeon, a urologist, Dr. Singla today, because we really do have a partnership in how we treat this disease. And our decision about how we're giving the presentation today is no accident. Dr. Singla is oftentimes the point person when patients present with urothelial cancer, whether or not it be in the bladder, the upper tract or both, and the main person who would treat a low grade tumor.

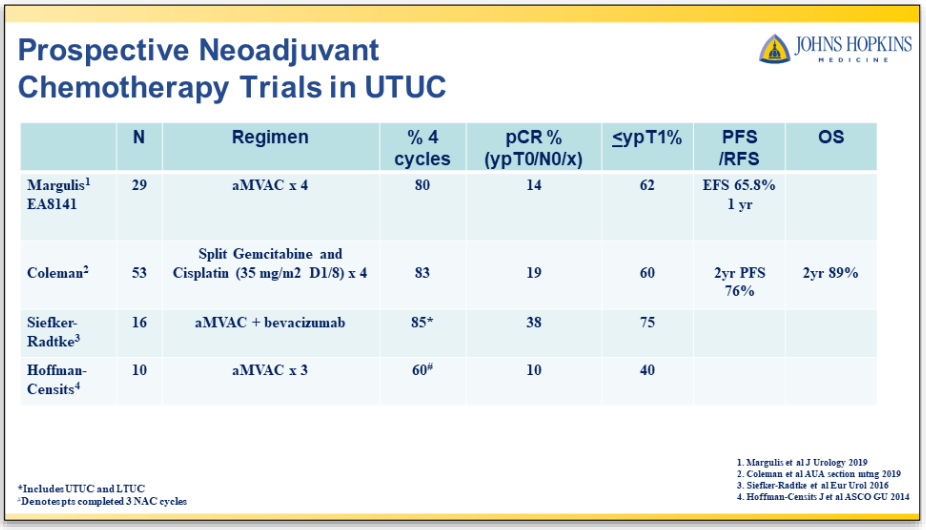
Tumors that are low grade under the microscope, they do not, as far as we know, respond to systemic treatments, IV or oral treatments that we would give, at least at this point in time. That may change in the future, we'll see with research, and so really we don't tend to see those patients with low grade upper tract disease. As you mentioned, it's topical therapy. For high grade disease just becomes more of a multi-modality discussion with at least urology, medical oncology discussion, and then of course our other colleagues that help us take care of our patients. Pathology, radiology, nephrology, and others. Next slide.

I'm going to talk about that neoadjuvant or preoperative as well as post-operative chemotherapy. What do we know about the use of chemotherapy in upper tract disease? I know Dr. Singla had alluded to this level one evidence, or large populations of patients that have been treated in clinical trials over the course of decades with muscle-invasive bladder cancer, and the design of those trials have lead us to better understand what a current standard of care is for an invasive bladder cancer, which is to give a cisplatin-based chemotherapy prior to surgery that provides best outcomes for patients with muscle-invasive bladder cancer, because patients with upper tract urothelial cancer that's high grade are a less common population, and because more of them are not great candidates for platinum-based chemotherapy, and that's because of the drug is metabolized by the kidneys, also potentially toxic to the kidneys.



Dr. Hoffman-Censits:

We have very few prospective, meaning moving forward in time, clinical trials, and those designs are what best inform and help us change or alter and update standard of care. This is just a summary of some clinical trials that are out there. These are prospective studies. One that we did through what's called a cooperative group, bringing a lot of different cancer centers together. The second one Dr. Coleman did, and this was just recently updated at a recent national meeting, looking at a regimen of cisplatin-based chemotherapy, and then two other historic ones, just providing some evidence for the use of preoperative cisplatin-based chemotherapy. Next slide.

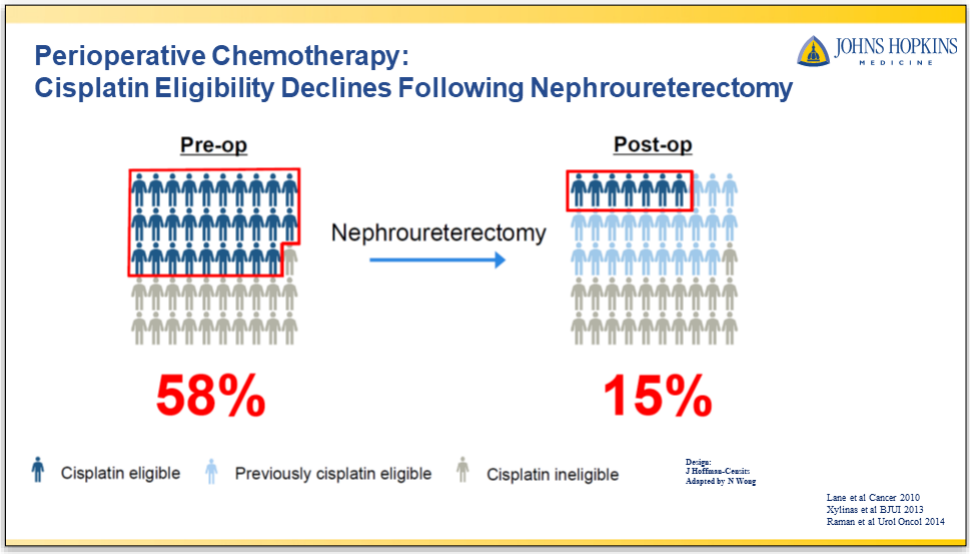


	N	Regimen	% 4 cycles	pCR % (ypT0/N0/x)	≤ypT1%	PFS /RFS	OS
Margulis[1] EA8141	29	aMVAC x 4	80	14	62	EFS 65.8% 1 yr	
Coleman[2]	53	Split Gemcitabine and Cisplatin (35 mg/m2 D1/8) x 4	83	19	60	2yr PFS 76%	2yr 89%
Siefker-Radtke[3]	16	aMVAC + bevacizumab	85*	38	75		
Hoffman-Censits[4]	10	aMVAC x 3	60#	10	40		

*Includes UTUC and LTUC
#Denotes pts completed 3 NAC cycles

1. Margulis et al J Urology 2019
2. Coleman et al AUA section mtng 2019
3. Siefker-Radtke et al Eur Urol 2016
4. Hoffman-Censits J et al ASCO GU 2014

Dr. Hoffman-Censits:

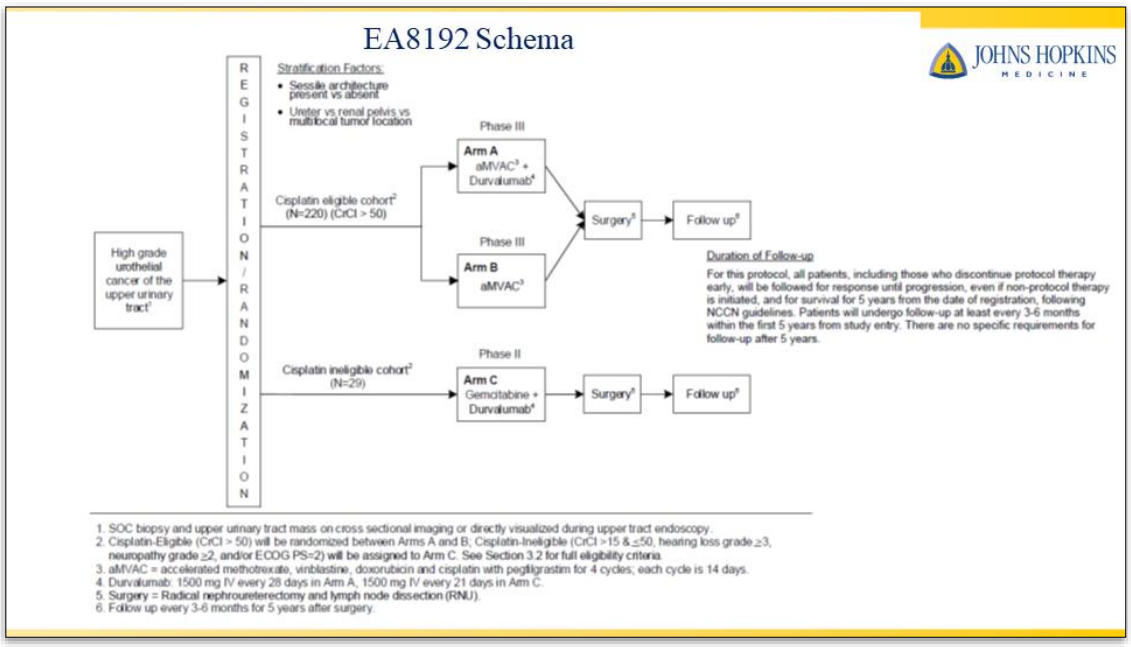


The issue is that, as Dr. Singla alluded to, the trying to stage upper tract urothelial cancer, trying to understand whether or not this is a tumor that's invasive is really challenging, and so the rules of who may get preoperative chemotherapy, who may qualify for preoperative chemotherapy, aren't exactly the same as those with bladder cancer. For bladder cancer, the rules are pretty clear. You have to have a specimen that has muscle in the specimen, and then tumor has to be invading into muscle. For upper tract tumor, that's not usually possible. It's just the way that the ureter, which is like this long straw, is designed and the way that the tumor's going to grow off. And the equipment that's used, you're not often getting a ton of information, so we're using both radiographic information, as well as the pathology to decide who is and is not an optimal candidate to get preoperative chemotherapy.

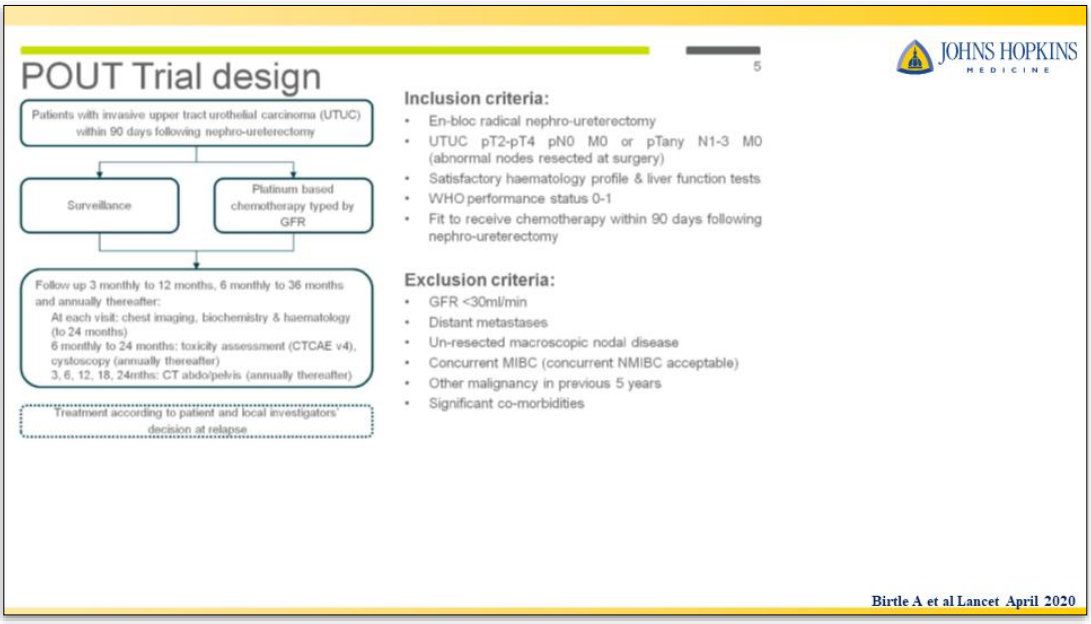
Once patients have the curative surgery and having nephroureterectomy, even our population where most... A lot of patients aren't always good candidates to get platinum-based chemotherapy. Have to be very fit, very robust, have pretty good kidney function, pretty good cardiac function, because we give a lot of fluids. You're going to pump those fluids through the system. No evidence of significant hearing loss, because platinum can impact that, as well as numbness tingling in the fingers and toes. As you can imagine in a population of patients with an average age in the mid-70s, there's not a lot of optimal candidates for that treatment, so the number of candidates go down significantly in the post-op setting.

It's a decision about whether or not to give chemotherapy with incomplete information in the pre-op setting, and someone has two kidneys and maybe a better candidate for chemotherapy, versus thinking about doing it in the post-operative setting when you have more clinical information, complete staging because the kidney and the ureter are out, and we understand what the stage of the cancer is, but maybe not an optimal time to give the treatment. We're always living in this balance and trying to interpret all this information when we meet patients in clinic. Next slide.

This is what's called a design of a clinical trial. This is a clinical trial that's up and running now, actually across the country. And the design of this study is put together with teams of physicians, so medical oncologists, surgeons, other advocates and statisticians to try and influence or update the standard of care. This is just an example of what we're doing in what's called the cooperative group through multiple different cancer centers across the country, trying to decide whether or not standard chemotherapy with a four-drug regimen called MVAC would remain a standard that we can give pre-surgery, or should we add an immunotherapy drug called durvalumab? That's a main part of the study. We're looking to enroll about 220 patients. And another arm in this study, that'll be much smaller, more what we call hypothesis-generating, is to see what are the outcomes for patients who are not great candidates for that platinum-based chemotherapy, using a non-platinum regimen with immunotherapy.



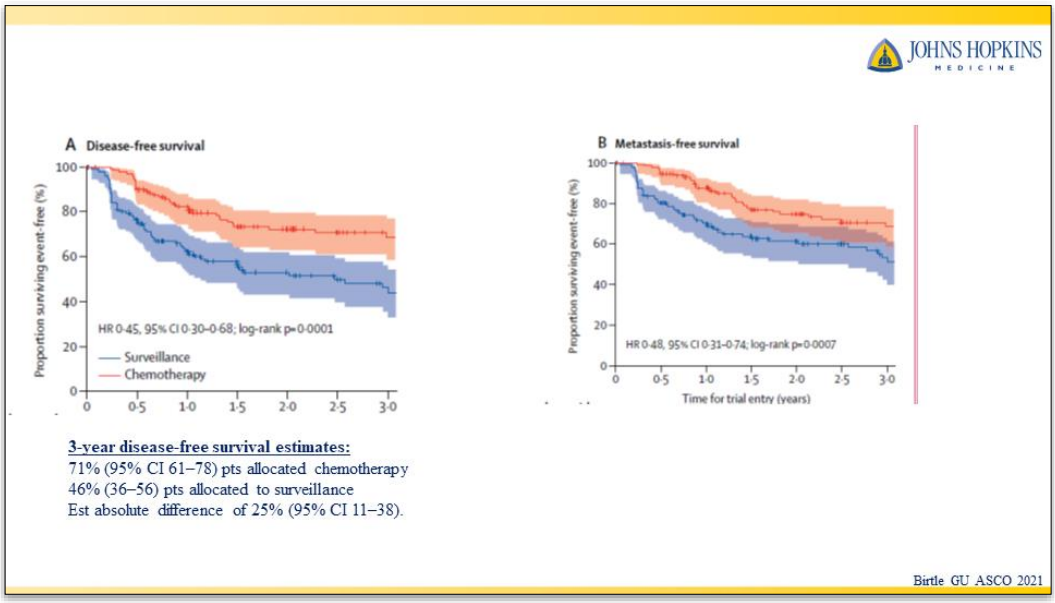
As we were talking about clinical trials and when to just present with a current example is of a large clinical trial going on in upper tract disease as we speak. What about postoperative chemotherapy? A lot of our patients have heard about the POUT trial, and kudos to our European colleagues, Dr. Alison Birtle and her colleagues that have done this trial, because it's really the first large scale clinical trial that's been done solely in upper tract disease. As we've said, because upper tract urothelial cancer is a subset of all patients with urothelial



cancer, depending on the clinical trial, you can have sometimes up to 10%, 20%, even 30% of patients in a clinical trial that may have upper tract disease, depending on the study. Some are just bladder cancer, but others incorporate everybody, but this is the first really big trial that was completed in upper tract disease, and so this is important because I think this communicates to physicians, to patients, to advocates, to industry that this is a space that really is its own entity, and that clinical trials can be done, and that we'll learn more by doing this kind of research.

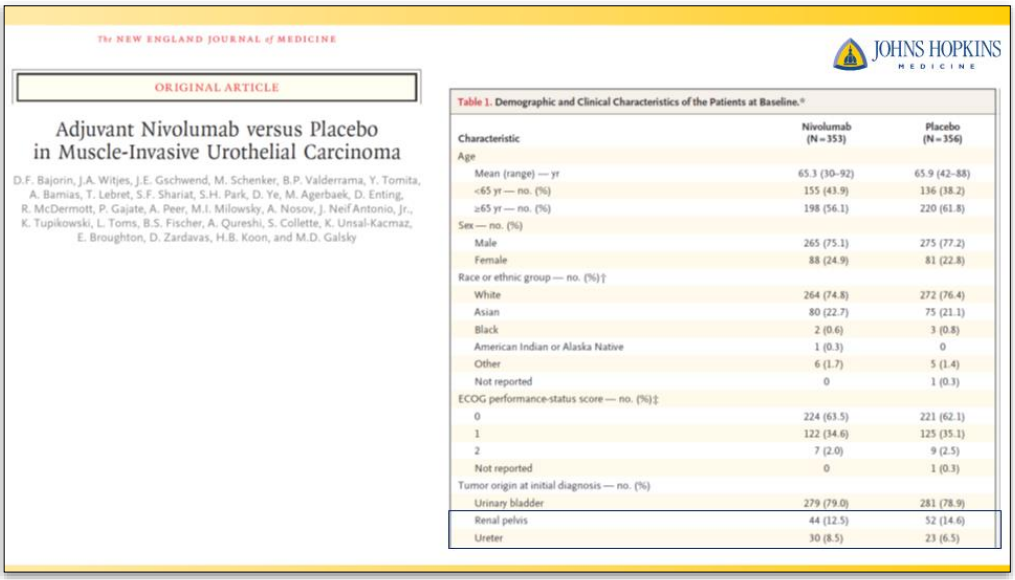
Dr. Hoffman-Censits:

Essentially in this clinical trial, patients with upper tract disease, they weren't referred for chemotherapy before surgery, they were referred only after surgery. And part of the reason that this trial worked in Europe is because that is their kind of European standard. And everyone felt comfortable with that standard, so patients with a locally advanced tumor invading into muscle or lymph node-positive were randomized. Half just were observed with surveillance, follow-up scans and cystoscopies, and the other half got chemotherapy, and that chemotherapy was predicated on their kidney function. Next slide. And what these, what's called Kaplan-Meier plots (learn more about how to understand survival curves) have shown is that the three-year disease-free survival of the time where someone did not have recurrence of metastatic disease was significantly influenced by whether or not they received this postoperative chemotherapy, whether or not that was cisplatin or another drug called carboplatin.



And it was an estimated absolute difference of about 25%, which is really important. Same as metastasis-free survival. These were the curves that showed a statistical benefit in terms of getting that chemotherapy, and this was what changed standard of care, where really the push for more chemotherapy in the postoperative setting came about. The statistics didn't work out exactly for what's called overall survival. There may be different reasons for that. One of them that everyone hypothesizes is that there were the patients who were given carboplatin and cisplatin were looked at in the same way, and sometimes that can affect the statistics. We don't know, but despite that I think Herculean effort and a huge congratulations to this team, because I think they really changed the face of what we understand about this disease. Next slide.

Another standard that has come about in the last year or so is using a standard of care immunotherapy drug, FDA approved for urothelial cancer, as well as many other kinds of cancers, but using it in the post-op setting. In this clinical trial, the drug called nivolumab was given to, again, a randomized design, where half the patients were just followed and half the patients were followed and given nivolumab. And in this study, patients could have gotten preoperative chemotherapy or potentially they were in that category where they really weren't great candidates to get chemotherapy. And I'm just pointing out that about 20% of this population of all comers with urothelial cancer had upper tract disease, so a substantial amount, but again, this study wasn't designed just to look at upper tract disease. And what this study showed, next slide, was just like in the POUT study, that there was an improvement in what's called the intent to treat population, meaning all comers, in terms of the disease-free survival at both six months and 12 months.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma

D.F. Bajorin, J.A. Witjes, J.E. Gschwend, M. Schenker, B.P. Valderrama, Y. Tomita, A. Bamias, T. Lebret, S.F. Shariat, S.H. Park, D. Ye, M. Agerbaek, D. Enting, R. McDermott, P. Gajate, A. Peer, M.I. Milowsky, A. Nosov, J. Neif Antonio, Jr., K. Tupikowski, L. Toms, B.S. Fischer, A. Qureshi, S. Collette, K. Unsal-Kacmaz, E. Broughton, D. Zardavas, H.B. Koon, and M.D. Galsky

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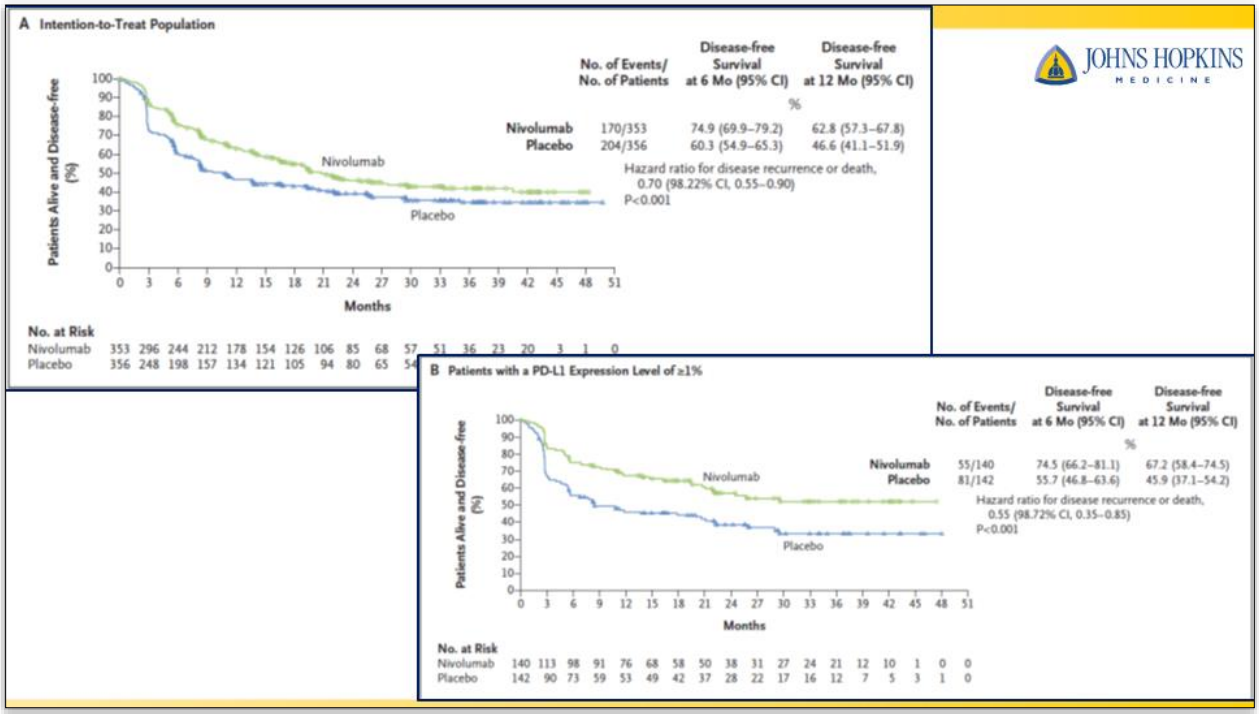
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Nivolumab (N=353)	Placebo (N=356)
Age		
Mean (range) — yr	65.3 (30–92)	65.9 (42–88)
<65 yr — no. (%)	155 (43.9)	136 (38.2)
≥65 yr — no. (%)	198 (56.1)	220 (61.8)
Sex — no. (%)		
Male	265 (75.1)	275 (77.2)
Female	88 (24.9)	81 (22.8)
Race or ethnic group — no. (%)†		
White	264 (74.8)	272 (76.4)
Asian	80 (22.7)	75 (21.1)
Black	2 (0.6)	3 (0.8)
American Indian or Alaska Native	1 (0.3)	0
Other	6 (1.7)	5 (1.4)
Not reported	0	1 (0.3)
ECOG performance-status score — no. (%)‡		
0	224 (63.5)	221 (62.1)
1	122 (34.6)	125 (35.1)
2	7 (2.0)	9 (2.5)
Not reported	0	1 (0.3)
Tumor origin at initial diagnosis — no. (%)		
Urinary bladder	279 (79.0)	281 (78.9)
Renal pelvis	44 (12.5)	52 (14.6)
Ureter	30 (8.5)	23 (6.5)



A Intention-to-Treat Population

	No. of Events/ No. of Patients	Disease-free Survival at 6 Mo (95% CI)	Disease-free Survival at 12 Mo (95% CI)
		%	
Nivolumab	170/353	74.9 (69.9–79.2)	62.8 (57.3–67.8)
Placebo	204/356	60.3 (54.9–65.3)	46.6 (41.1–51.9)

Hazard ratio for disease recurrence or death, 0.70 (98.22% CI, 0.55–0.90)
P<0.001

Patients Alive and Disease-free (%)

Nivolumab

Placebo

Months

No. at Risk

Nivolumab	353	296	244	212	178	154	126	106	85	68	57	51	36	23	20	3	1	0
Placebo	356	248	198	157	134	121	105	94	80	65	54							

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B Patients with a PD-L1 Expression Level of ≥1%

	No. of Events/ No. of Patients	Disease-free Survival at 6 Mo (95% CI)	Disease-free Survival at 12 Mo (95% CI)
		%	
Nivolumab	55/140	74.5 (66.2–81.1)	67.2 (58.4–74.5)
Placebo	81/142	55.7 (46.8–63.6)	45.9 (37.1–54.2)

Hazard ratio for disease recurrence or death, 0.55 (98.72% CI, 0.35–0.85)
P<0.001

Patients Alive and Disease-free (%)

Nivolumab

Placebo

Months

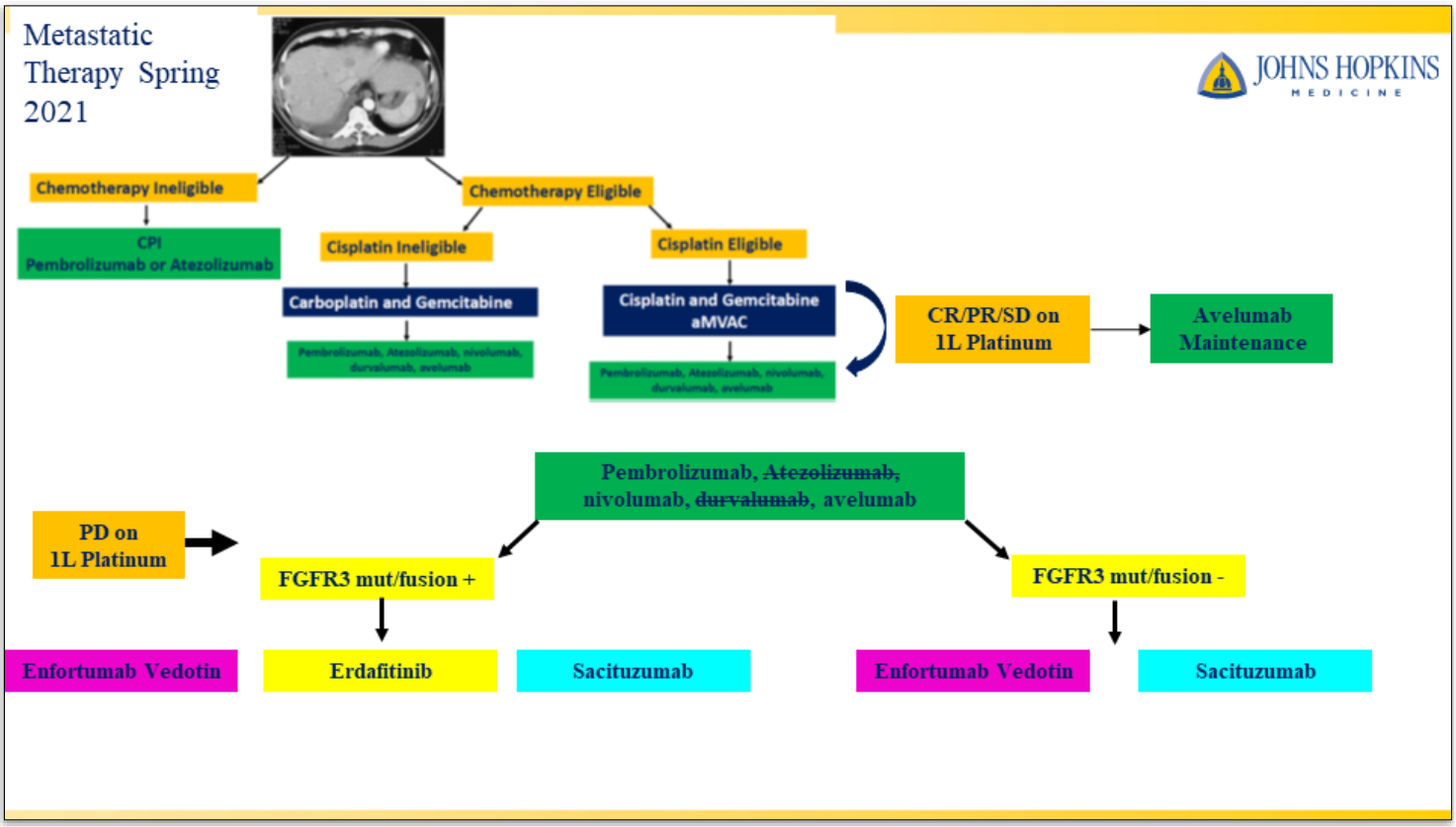
No. at Risk

Nivolumab	140	113	98	91	76	68	58	50	38	31	27	24	21	12	10	1	0	0
Placebo	142	90	73	59	53	49	42	37	28	22	17	16	12	7	5	3	1	0

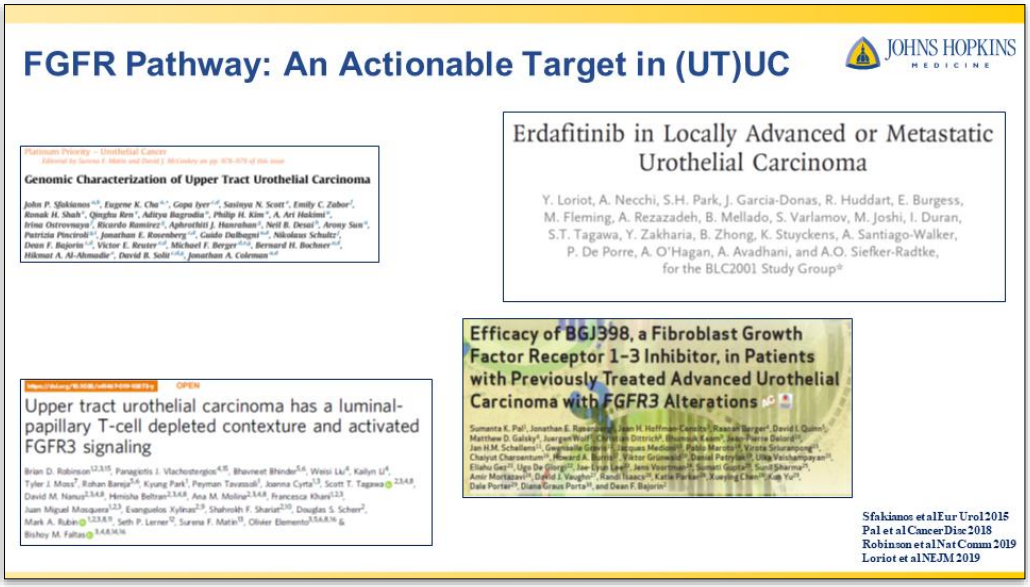
It was pretty significant, so the nivolumab-treated patients were in green and the patients who were treated with placebo are in yellow, the patients alive and disease-free are on the top, and the separation

of the curves is the difference between getting a treatment and not getting a treatment. This is something that we look at a lot in medicine. The biomarker called PD-L1 was also looked at on the tissue of these patients, and that may have some influence on the outcomes, but despite that, this is an option for some patients that we will talk about that have urothelial cancer, upper tract disease. Next slide. I just wanted to give a landscape of treatment in the advanced setting, just to get a sense of where maybe a treatment you may have received may be on a landscape.

Looking at where we are currently in terms of the tools available to treat advanced urothelial cancer, and whether or not that's upper tract, urothelial cancer or bladder cancer, if someone presents with a metastatic disease, meaning tumor that's moved outside of the organ into other areas, then we'll treat with a frontline or first step platinum-based chemotherapy, carboplatin or cisplatin. For patients that have what's called a clinical benefit, meaning that they have disease control, there's now this option to extend that disease control with immunotherapy, and we can use a drug called avalumab, FDA approved for urothelial cancer.

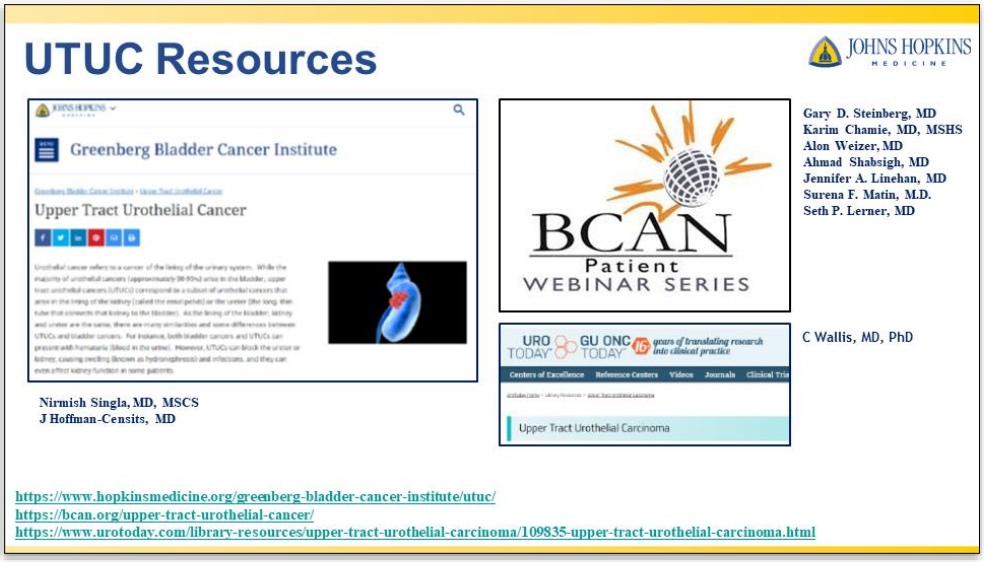


Dr. Hoffman-Censits:



For patients who have disease progression, or the cancer gets worse on platinum-based chemotherapy, or for patients that are not great candidates to get chemotherapy at all, we could start with one of the immunotherapy agents, and that's noted in green. We do next generation sequencing, looking for mutations or changes in the tumor. And the reason that we do that is because we want to know, can our toolkit be expanded to include an oral-targeted drug that works on this change or mutation called the FGFR3 mutation, fibroblast growth factor three, that's present on really a minority of high grade urothelial cancers. More commonly seen in low grade tumors, but can we use that drug? If a cancer tells us it's dependent on that pathway, then that's a drug that we can potentially use. If it's not, then we, of course, would spare patient cost and toxicity and use alternate agents. That Erdafitinib drug, that oral-targeted drug is in yellow.

And then finally we have two antibody drug conjugates, so these are encapsulated chemotherapy agents that are attached to an antibody. And I think of those like a heat-seeking missile of chemotherapy, an updated version of chemotherapy, compared to platinum-based chemotherapy, which was designed decades ago. This is a more modernized kind of chemotherapy with the goal of killing the cancer and sparing patient of toxicity. Both of these antibody drug conjugates are approved. There is more drugs in pipelines, and so potentially this slide might look different and we're invited to give a follow-up a year from now, but this is the current treatment landscape for advanced urothelial cancer, bladder and upper tract.



In terms of resources, I think one of the things that Dr. Singla and I are often doing is providing patients and families with information about their disease. It is not

uncommon that patients will maybe meet me in clinic that are maybe referred from elsewhere, who hear about where their tumor is and aren't quite clear, do they have a kidney tumor? Do they have a renal pelvis tumor? Where exactly is this? I think it is important to have resources like the Bladder Cancer Advocacy Network, as well as our own internal resources to refer back to, to have again, safe places on the internet to look up information, to read more about it, because I think it it's challenging to find, I think, accurate information about upper tract urothelial cancer out there. And it's one of the reasons that we felt it's really important as a program to develop a specific medical home for upper tract urothelial cancer, where we really think about this disease a lot, we treat it and really think about accelerating the standard of care. And that's just our Hopkins team here. Thank you so much.