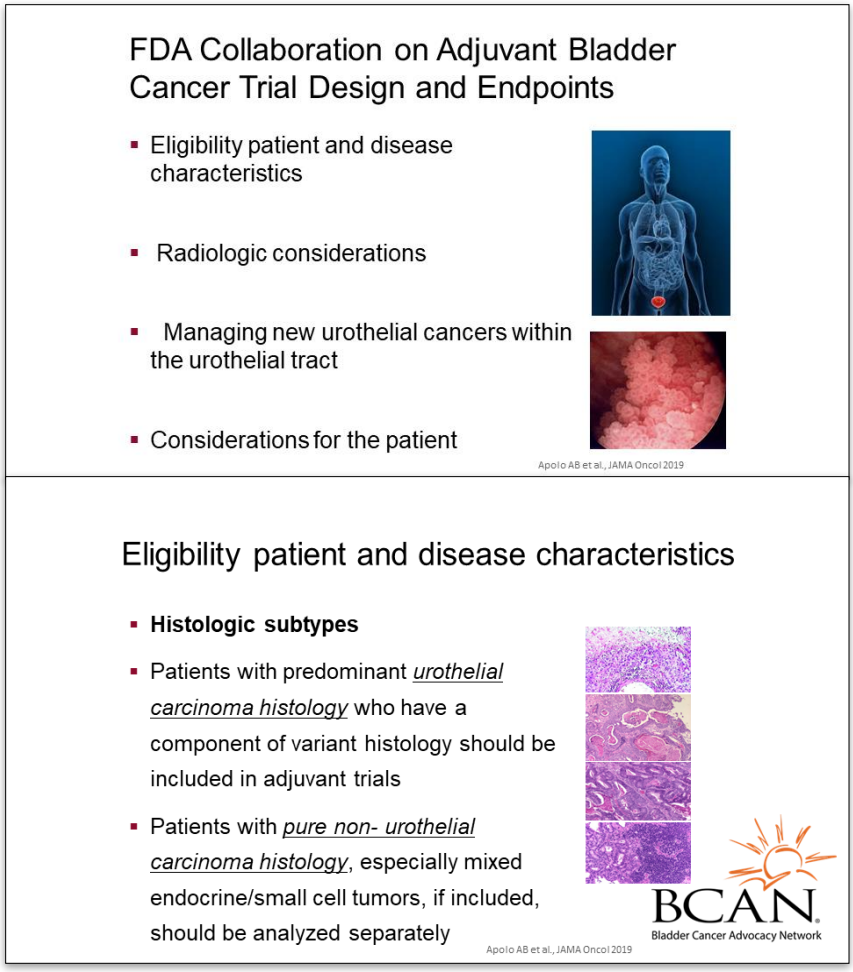
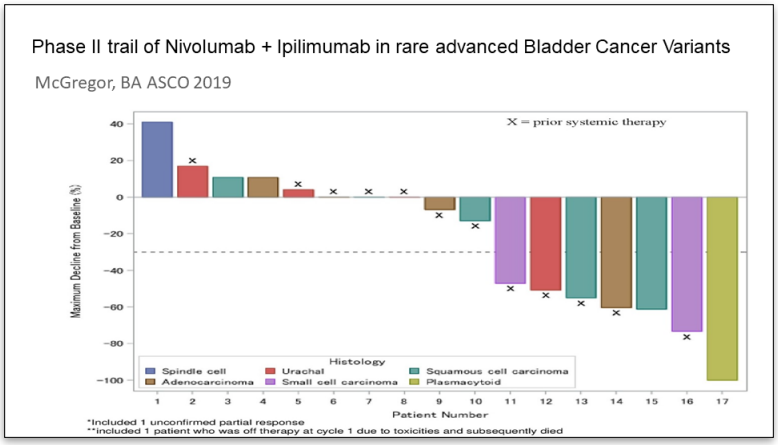
Rare Forms of Bladder Cancer: Clinical Trials for Rare Bladder Cancers



Dr. Apolo: So, we had a meeting with the FDA, many investigators, patient advocates, urologists, medical oncologists, radiologists, to discuss the development of clinical trials for patients with bladder cancers. We specifically met to discuss adjuvant trials. So this is after surgery for local tumors. And one of the things that we discussed is the eligibility of the patients, and we discussed histology.

In terms of allowing patients to enroll when they have a variant histology, was really important. So, most of the investigators... I mean, there was a consensus that patients with variant histologies should be included in clinical trials. And the investigators felt that this was really important that although the responses may vary, it's important for us to understand what the response is for the variant histologies, and how effective novel therapies are for these variant histologies as compared to urothelial carcinoma. In terms of the pure non-urothelial carcinomas, like the pure squamous, the pure

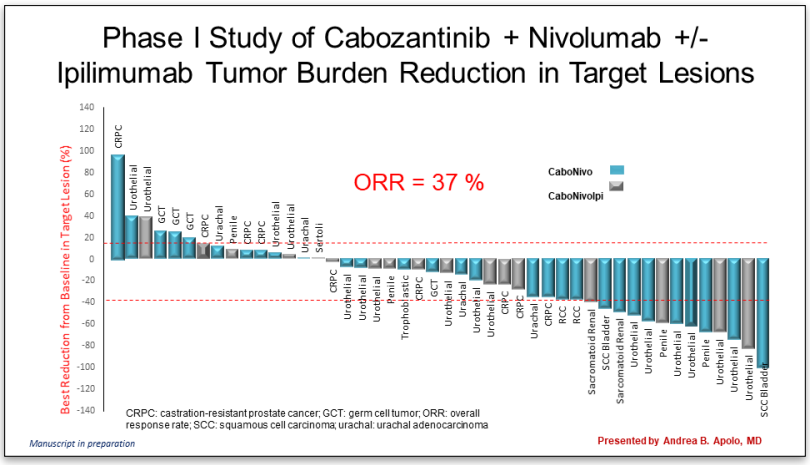
adenocarcinoma, the urachal, or the small cell. The consensus was that yes, you can include these also in clinical trials, but if they are included, they should be counted as an exploratory cohort with a separate statistical arm because we know that the responses are going to be very different than urothelial carcinoma. And we wouldn't want the trial to fail by including too many mixed tumors. So, the trial could still include them, but they should be counted separately as an exploratory cohort. And this was the consensus. Next slide.



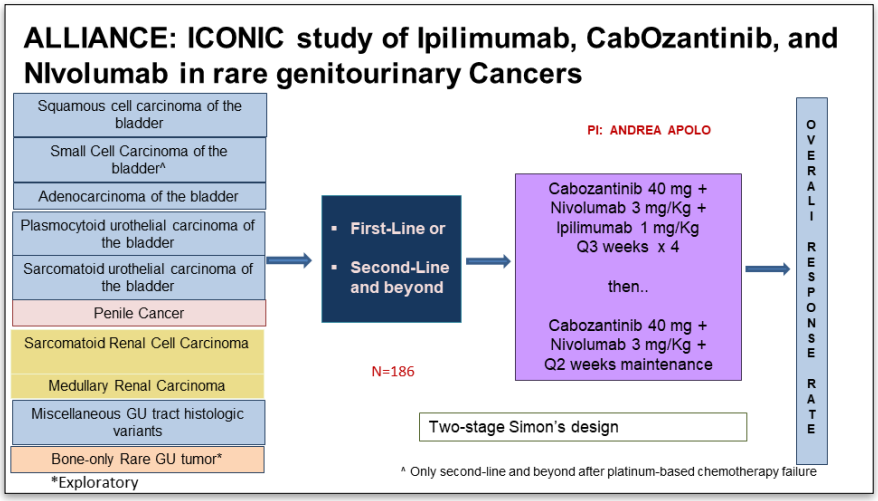
And there are several trials that have looked at novel agents, such as nivolumab and ipilimumab. These are the immune checkpoint inhibitors, an old generation and a new generation, kind of combined for patients with bladder cancer variants. And this study was reported at ASCO. This was a small study, but it tested these two immunotherapy combinations, given together to patients with adenocarcinoma of the bladder, urachal, small cell carcinoma, squamous cell carcinoma, and plasmacytoid. And each bar represents one patient. The color, that represents what kind of tumor they had. So for example, this green one is the plasmacytoid. And this line right here, the dotted line is a 30% shrinkage of the tumor. So, the doctor measures the tumor from one end to the other. And then if it shrinks more than 30%, that's the 30% line. So, that reaches a partial response. If it goes down to 100, than that's a complete response. But if it goes at least 30%, that's a partial response.

So, here we see very nice responses to immunotherapy. And most of these patients had gotten already chemotherapy. If they had an X, that means they got chemotherapy before, and they had very nice responses to immunotherapy. So that's really exciting because immunotherapy could be potentially a combination or a treatment option for patients with rare tumor. But of course, this is a really, really small study. But I think from these small studies, we learn a lot.

And I've conducted a clinical trial also with the same agents, the nivolumab and ipilimumab, these two immunotherapy agents. I did it in combination with a drug called cabozantinib, which is a pill. It's a targeted therapy. And I did a double combination, the cabozantinib plus nivolumab. And then I did a triple, cabozantinib, nivolumab, plus ipilimumab. So, all the blue bars are patients that received the double. And the gray bars are patients that received the triple combination. And we included regular urothelial carcinoma, regular prostate, regular kidney, regular testicular. But we also included rare tumors such as here all the way at



the end, the last patient is a squamous cell carcinoma of the bladder. We also included patients with urachal adenocarcinoma. And we saw nice responses, so that was really exciting to us.



And based on that, now I opened national trials, called ICONIC. And it's the combination of ipillimumab, nivolumab, and cabozantinib for rare GU tumors. And it includes squamous cell carcinoma of the bladder, small cell carcinoma of the bladder, adenocarcinoma of the bladder, plasmacytoid, sarcomatoid urothelial carcinoma. It includes some kidney cancers that are rare too, penile cancer, which is really, really rare. And a miscellaneous cohort for other more rare, rare tumors. And in this trial, patients are given the triple combination to see the efficacy of these drugs as measured. So, there are a lot of clinical trials. Maybe I shouldn't say a lot, but there are clinical trials now that are incorporating rare tumors, either on their own or as an exploratory arm in addition. So they have a regular urothelial bladder cancer arm, and then they have a rare variant or rare non-urothelial cancer arm. So we can learn about the effectiveness of some of these drugs. It's hard to do these studies in a small center where you don't see as many of the rare ones. So, it's important to do these either in collaboration with multiple centers or through a cooperative group where you're going to have a lot of different sites, including academic oncologists and community oncologists enrolling patients within a clinical trial because some people may see one within two years. But if you put 500 centers together, then you have a lot more chances of getting these rare tumors to be incorporated into clinical trials. And really, it's going to be through clinical trials and through our understanding, and collecting samples, collecting blood samples, saliva samples, tumor samples, that we're really going to understand how to manage these patients. And even though we're seeing some early responses with immunotherapy and some responses with targeted therapy, these really are stepping stones that we can use to build on these activities, and improve the activity that we're seeing now because although we're seeing responses, they're just not good enough. I think we can do a lot better. And the way that we're going to do that is through testing novel drugs in patients with rare tumors.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