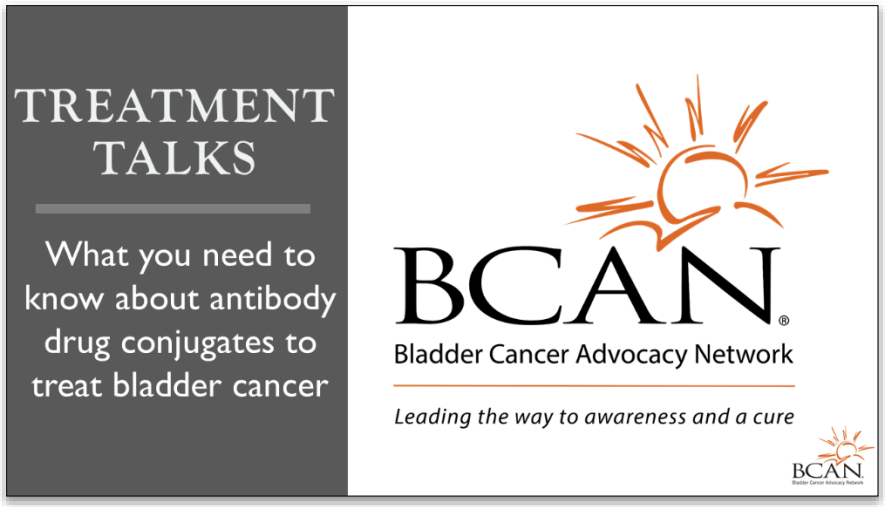


Introduction

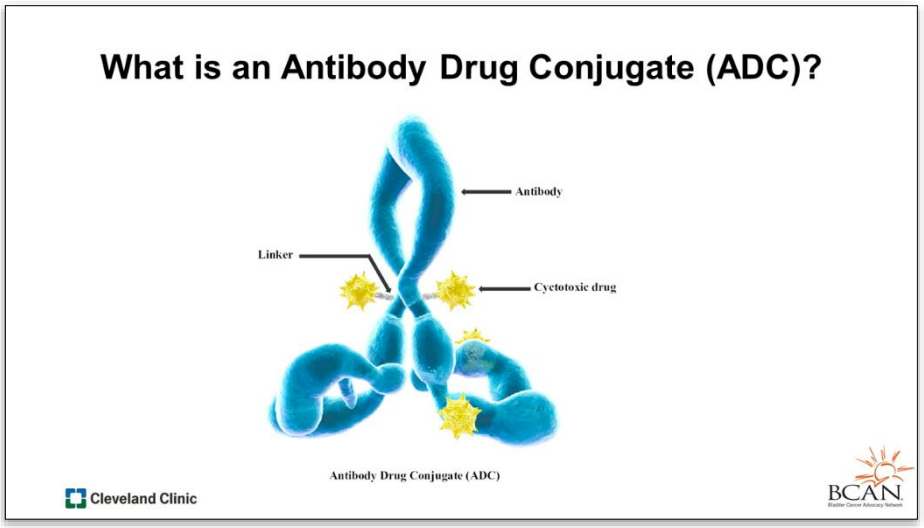
Stephanie Chisolm: I'd like to welcome everyone. Today our physician expert is Dr. Shilpa Gupta. She's a medical oncologist at the Cleveland Clinic, and we are delighted to have Dr. Gupta join us today to explain how a relatively new bladder cancer treatment known as Antibody-Drug Conjugates are being used, and then we're going to have a patient who's going to share his experience with the treatment. The goals are basically to help you understand all of the treatment options that are out there, to give you some questions that you might ask to empower you to be part of that active communication with your healthcare team, and to highlight current treatments that are available for bladder cancer.

Dr. Shilpa Gupta's research interests include novel drug development, and she really works to understand the biomarkers of response and resistance to therapies for bladder cancer. She's led many early and late phase clinical trials in bladder cancer. So we're delighted to have her here. We're also going to be joined a little while later by patient advocate, Guy Riegling, and you'll meet him after her presentation. So Dr. Gupta, I'm going to turn it over to you so you can explain how we're using Antibody-Drug Conjugates to treat bladder cancer these days.

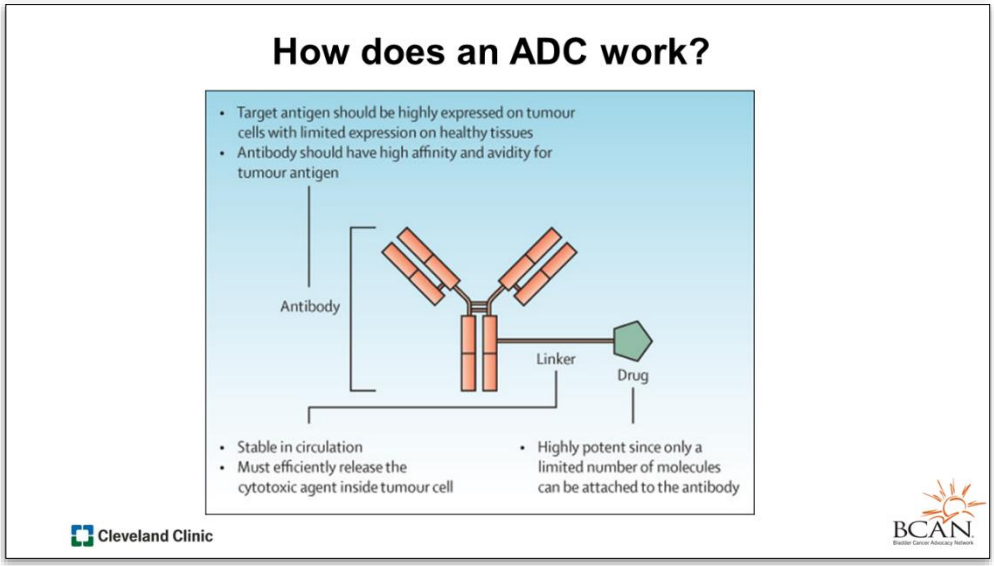
Dr. Gupta: Thank you Stephanie, and I would like to thank the Bladder Cancer Advocacy Network to arrange these treatment talks and a special thanks to our patient Mr. Guy Riegling who's graciously offered to share his experience. We are at a very exciting point in our treatment advances in bladder cancer with new drugs being approved and Antibody-Drug Conjugates are one such a class of drugs which have really moved the field forward.

What Are Antibody Drug Conjugates?

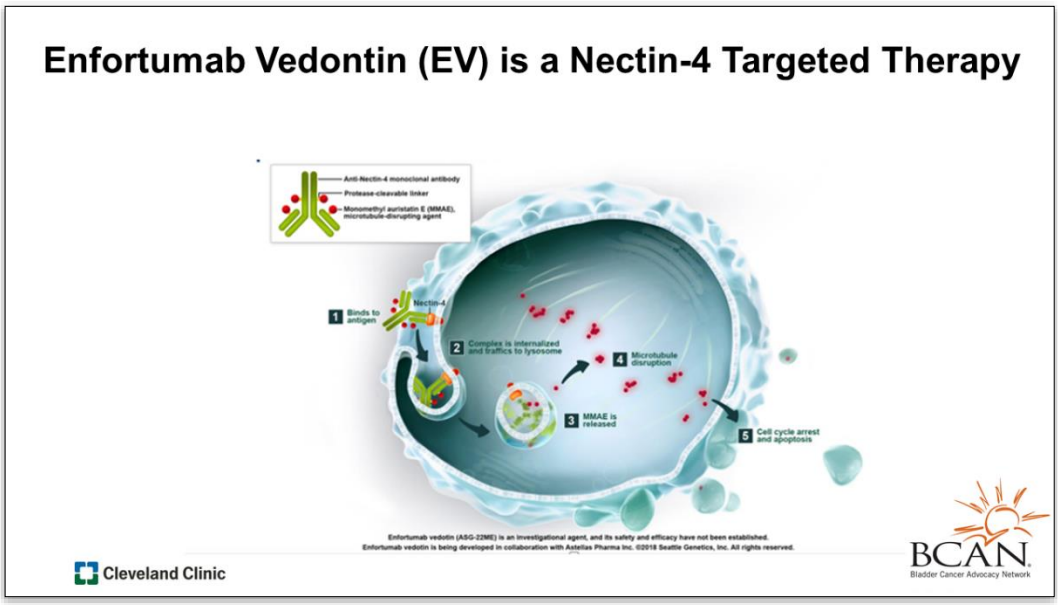
Dr. Gupta: So we'll start with the basics. What is an Antibody-Drug Conjugate? This is a diagram depicting what it really means. You know traditionally cytotoxic drugs are what we call chemotherapy, and as we know that besides killing cancer cells they also kill normal cells, and these Antibody-Drug Conjugates are a new class of drugs which is primarily an antibody against an antigen which is expressed on cancer cells, which is linked to the cytotoxic drug using a linker.



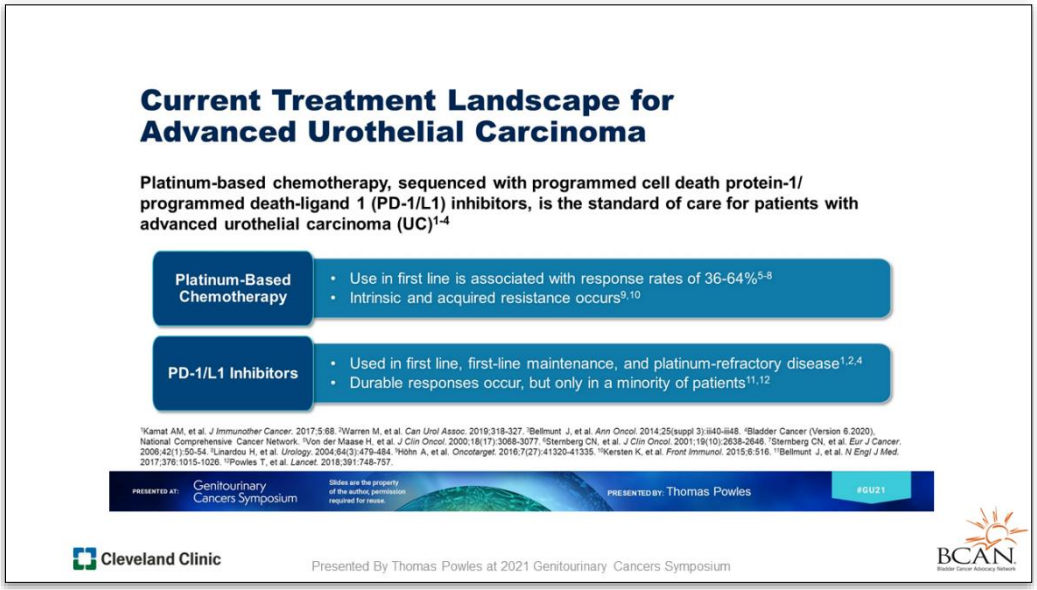
So really there are three parts of this drug and how does it work? It targets the antigen which ideally should be highly expressed on tumor cells with limited expression on healthy tissues to avoid toxicity, and the antibody should have a high affinity and avidity for the tumor antigen. It should be stable in circulation. The linker must also efficiently release the cytotoxic agent inside the tumor cell so that it provides that targeted focused effect, and the drug obviously should be highly potent since only a limited number of molecules can be attached to the antibody.



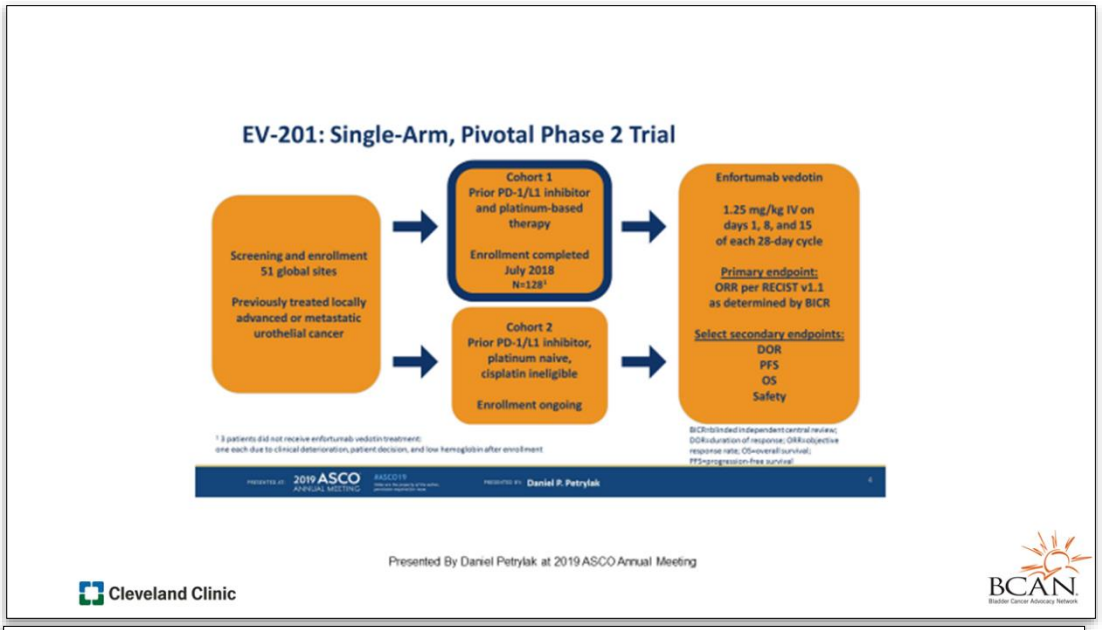
Dr. Gupta: So it's really a lot of science and chemical engineering that goes into the development of a proper Antibody-Drug Conjugate, and Enfortumab Vedontin is the major Antibody-Drug Conjugate that we saw being advanced recently, and it's a Nectin-4-targeted therapy. This diagram shows the structure. So the antibody is against the Nectin-4, which is ubiquitously expressed on bladder cancer cells hence we don't need to really test for the biomarker. It has a protease-cleavable linker and the cytotoxic agent here is the monomethyl auristatin E or MMAE, which is a microtubule disrupting agent. So what happens is that once this drug is given as an infusion, the antibody bind to the antigen on the bladder cancer cells and is internalized in the cell and the complex, then traffics to the lysosomes where the MMAE or the key microtubule disrupting agent is released, microtubules are disrupted and it causes cell cycle arrest and apoptosis thus resulting in killing of the cancer cells. So it's a very unique mechanism of action as you can see.

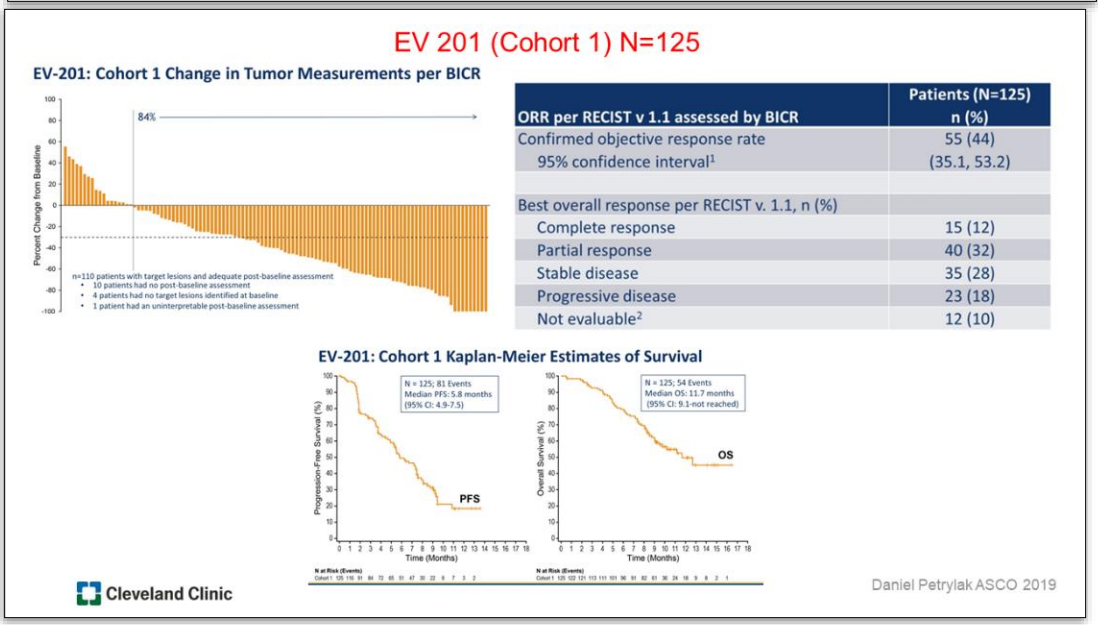


Just want to highlight the current treatment landscape for advanced urothelial cancer. As we have seen over the last many decades, platinum based chemo therapies are all that we had, and this is used in first-line. Results in a response rates of up to 60% or so. However, the responses are not very durable and only in 2015 and '16 did we start seeing the advent of immunotherapy, which really provided a beacon of hope for our patients, but immunotherapy only works in about 20 to 25% patients. So right now the landscape consists of the platinum based chemotherapy and checkpoint inhibitors or immunotherapy, and that's where the development of newer agents was needed for patients who do not respond to



chemotherapy and immunotherapy, and then Enfortumab Vedontin pivotal trial was the EV-201, which was the initial phase two trial, and this was a global study.

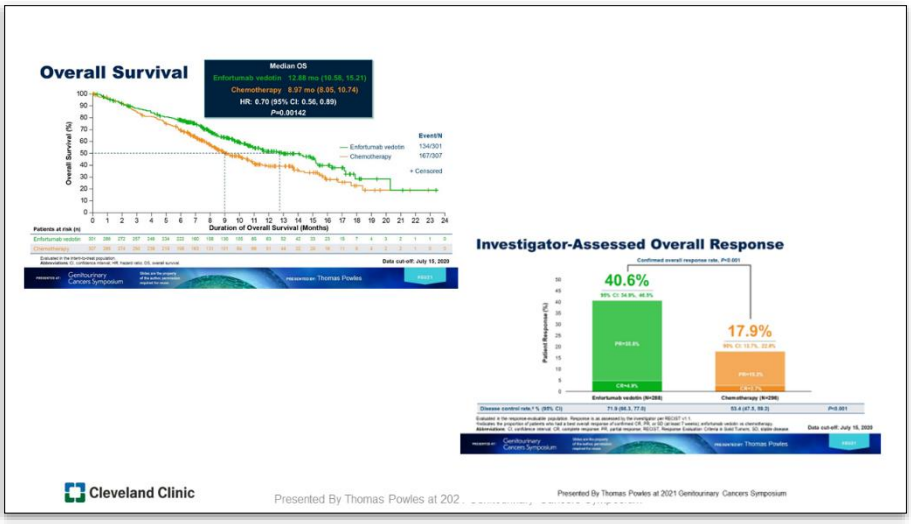




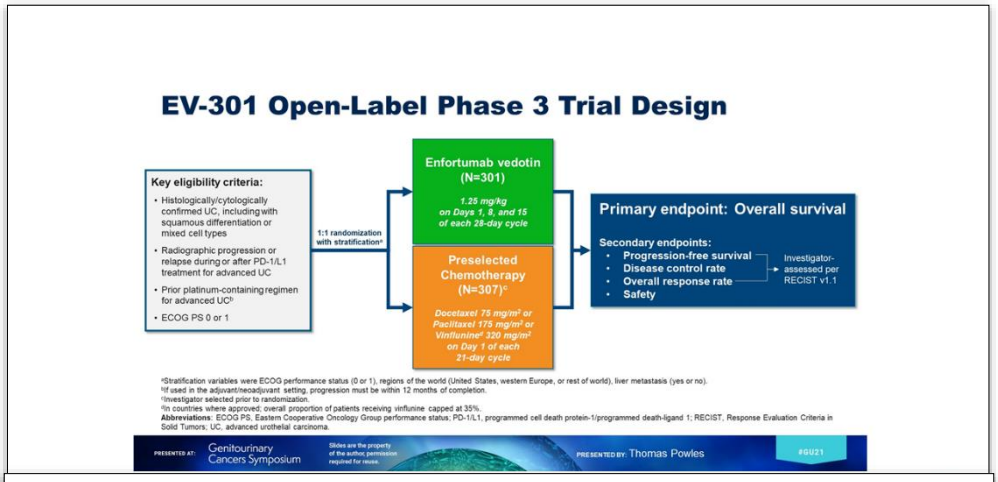
Dr. Gupta: It had two cohorts, one cohort was for patients who had received prior chemotherapy and immunotherapy, and the second cohort for patients who had only received immunotherapy, and who were not eligible for chemotherapy and who had received only immunotherapy. Patients received Enfortumab vedontin at a dose of 1.25 mcg per kilograms on days one, eight and 15 every month, and primary endpoint was objective response rates. As you can see here the first plot here demonstrates remarkable responses in these patients who were heavily pretreated. So 44% patients had responses, and the overall survival was around 12 months in these heavily pretreated patients which was quite remarkable. This was initially granted accelerated approval for patients with prior platinum and immunotherapy use and EV-301 is the phase three trial, which was the open label phase three trial which was the confirmatory study for the results seen with the initial study.

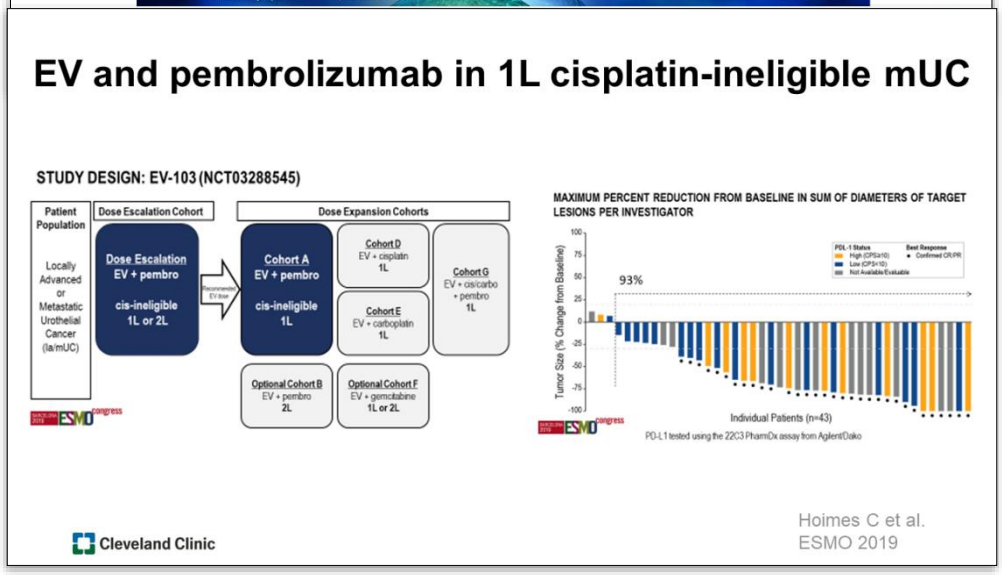
So patients who had locally advanced or metastatic urothelial cancer who had progressed after a checkpoint inhibitor and had received prior platinum chemotherapy were randomized to receive Enfortumab Vedontin, or the chemotherapy of choice which could be docetaxel, paclitaxel, vinflunine which is used in Europe. Primary endpoint was overall survival and secondary end point was progression

free survival disease control rate, and overall response rate, and of course safety. The results were recently presented at the GU ASCO meeting, and this study showed that compared to chemotherapy Enfortumab Vedontin resulted in significant improvement in survival, and the median overall survival was around 13 months compared to nine months seen with chemotherapy, and overall response rates were around 41% compared to 18% seen with chemotherapy. The most common side effects related to EV are rash and other subcutaneous reactions, peripheral neuropathy, hyperglycemia, fatigue, but these are the key reactions that we observe in our patients.

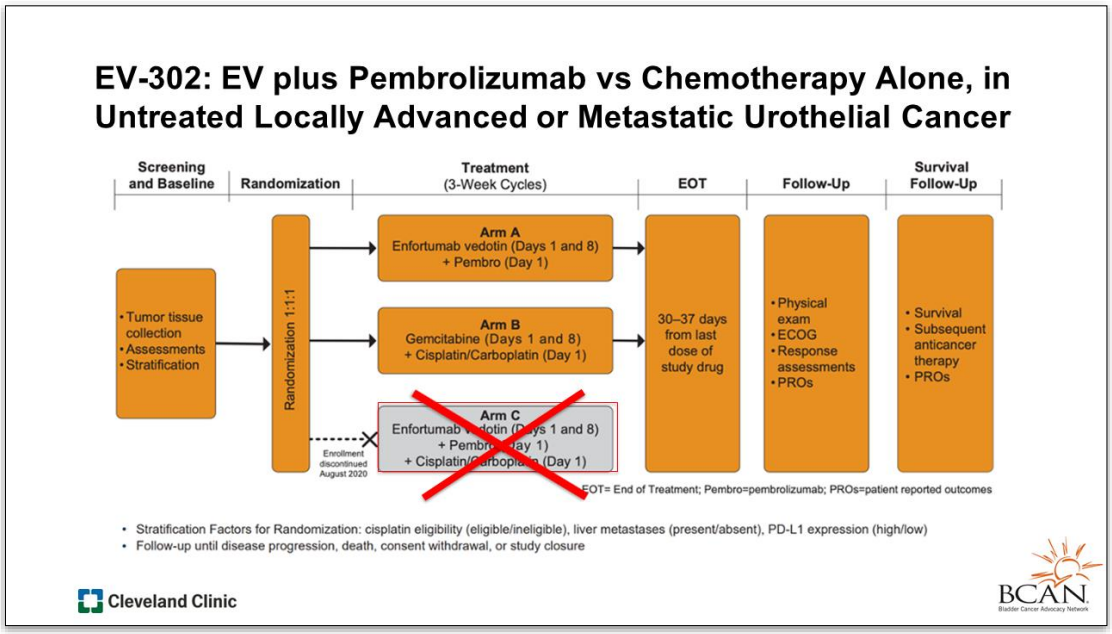


Dr. Gupta: I want to also highlight here that Enfortumab Vedontin and Pembrolizumab was tested in first line cisplatin ineligible metastatic, or locally advanced urothelial cancer patients as a part of those expansion cohort in EV-301 study, and as you can see here, majority of patients demonstrated some response, and this was really very promising data that we saw with this combination, and this prompted a larger study called EV-302, which is a phase three study where we are comparing EV and Pembrolizumab versus chemotherapy, platinum based chemotherapy as a first line treatment in patients with advanced or metastatic urothelial cancer. So I want to highlight here

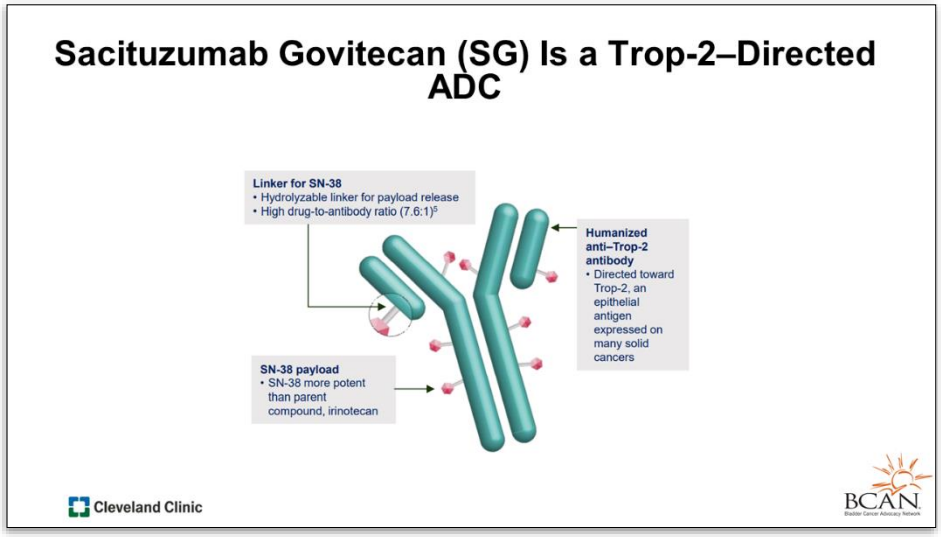




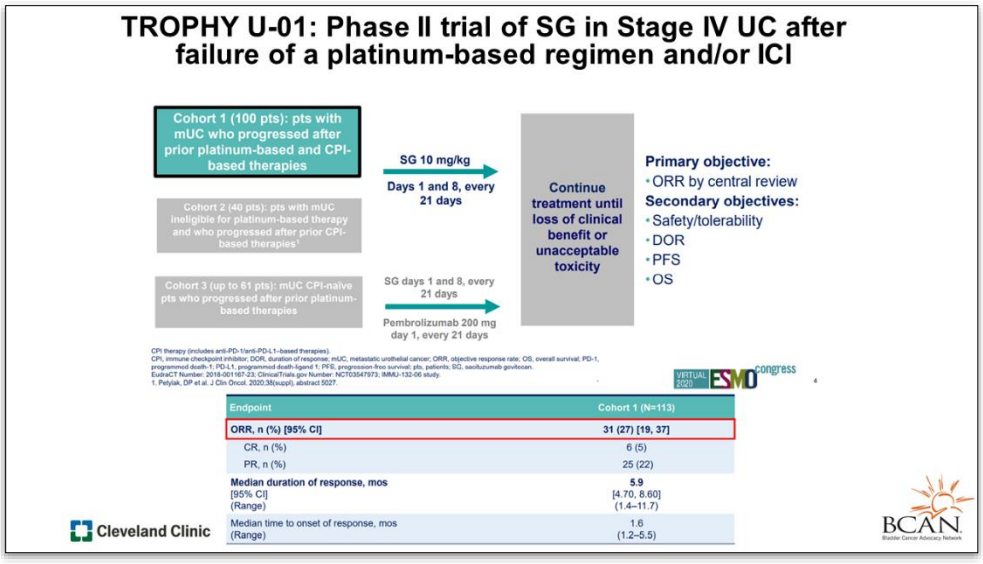
that the initial study designed had three arms. Arm A was Enfortumab Vedontin and Pembrolizumab, arm B was standard of care platinum based chemotherapy, and in arm C initially there was Enfortumab Vedontin, Pembrolizumab and Cisplatin or carboplatin, but based on the promising data seen with EV and pembrolizumab as first-line, the arms C was removed because there is now expectation that just Enfortumab and Pembro would be better than chemotherapy, and that is the reason this trial is being done to see how it compares to chemo. This is the general study schema for this trial, and this is currently ongoing.



Dr. Gupta: Now I want to highlight that besides Enfortumab Vedontin which has been around for or approved for over a year now, Sacituzumab Govitecan or SG is another novel Antibody-Drug Conjugate, and this is directed against Trop-2. So here we can see that the payload is of SN-38, which is more potent than the traditional chemotherapy called irinotecan. There's a linker and the antibody is the humanized anti-Trop-2 antibody, which is directed towards Trop-2. Again, a ubiquitously expressed antigen on a lot of cancers including urothelial cancer. This was the study that was done called Trophy-U-1 in patients with locally advanced or metastatic urothelial cancer after failure of a platinum based chemo and, or immunotherapy, and in cohort one, patients who had received platinum and immunotherapy were studied, they were treated with the SG on day one and eight, every 21 days.



Dr. Gupta: Primary objective was objective response rates and secondary objectives were safety, tolerability, duration of response, progression-free survival and overall survival, and here again, we saw very promising response rates of almost 27% in these patients of around 113. In cohort one there were 5% complete responses, 22% partial responses and median duration of response was around six months. So this again provides an additional option for patients who've had prior chemo and immunotherapy and just the most common SG related adverse events are neutropenia, anemia, hypophosphatemia, diarrhea and fatigue.



The talk wouldn't be complete without including the breaking news from last night, FDA granted this drug accelerated approval for advanced urothelial cancer based on the Trophy-U-1 study and the confirmatory phase three trials are ongoing comparing this against the savage chemotherapy regimen. So these two antibody drug conjugates are now FDA approved both EV and SG for urothelial cancer patients. Each drug can be used in sequence because the toxicity is not overlapping. While with EV the key toxicity is better for neuropathy and rash, with SG, it is mainly myelosuppression and with proper dose adjustments and schedule adjustments these drugs can be offered safely to our patients in their journey for treatments, and lastly, I would like to thank all the patients and families who have over the years participated in these trials paving the way for new therapies in bladder cancer, and don't forget to join us for our virtual Walk to End Bladder Cancer. Thank you.

Stephanie Chisolm: Thank you so much Dr. Gupta.