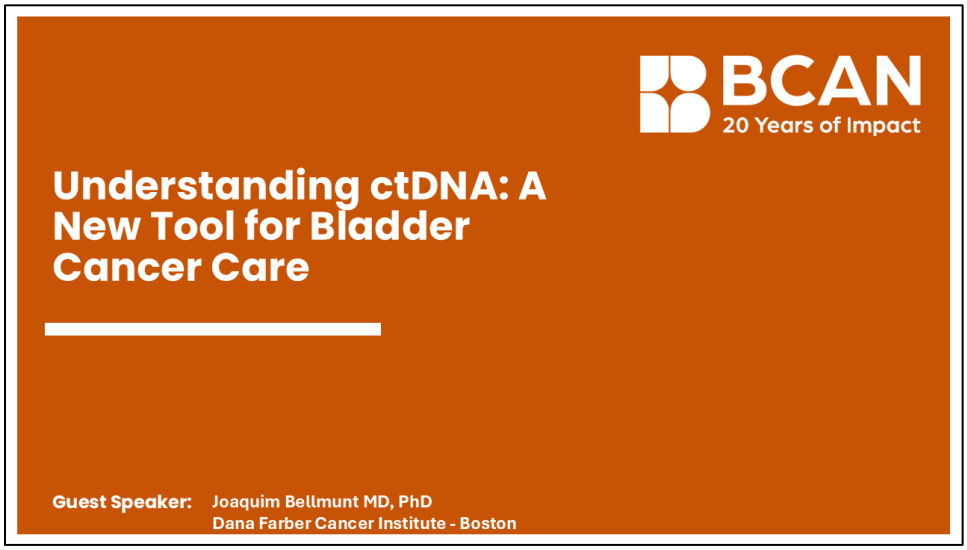
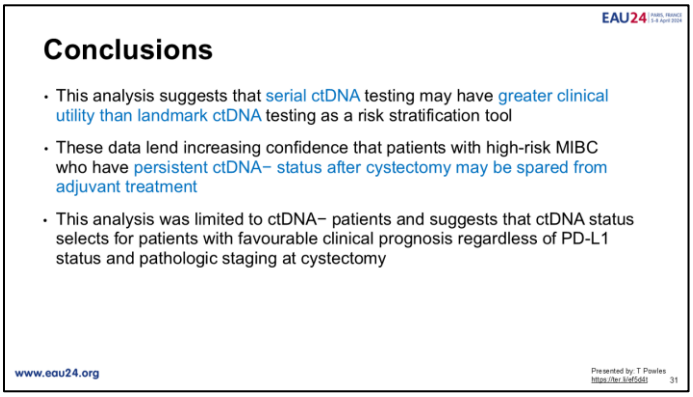


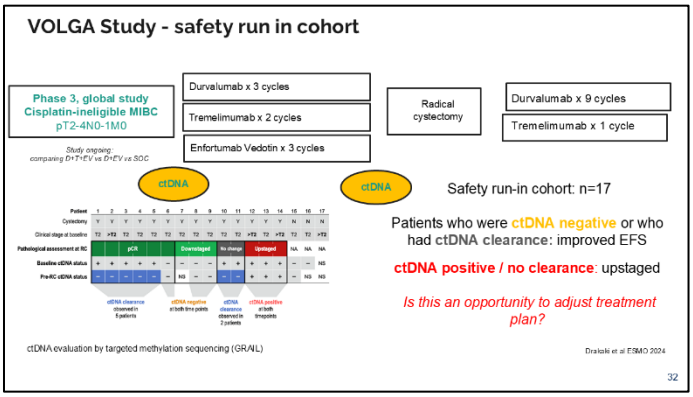
Dr. Joaquim Bellmunt:

So this data lend increasing confidence that patients with high-risk muscle invasive who have persistent ctDNA negative status after cystectomy, maybe even thinking maybe spared from adjuvant treatment. So that's something that we will see after analyzing the results of this trial.



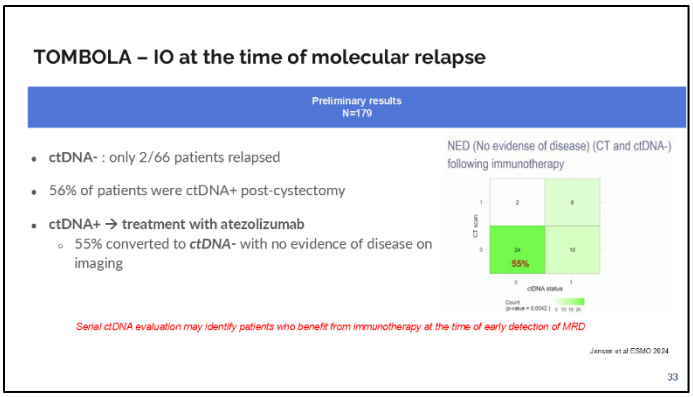
Dr. Joaquim Bellmunt:

So that's not the only trial, there has been other trials presented. So the VOLGA study is a study that is exploring combination of immunotherapy and ADCs, enfortumab vedotin. This was presented at ESMO 2024. And here again it was confirmed that patients who were ctDNA negative or who had ctDNA clearance, they had improved eventful survival, but patients having ctDNA positive with no clearance, those patients were abstained.



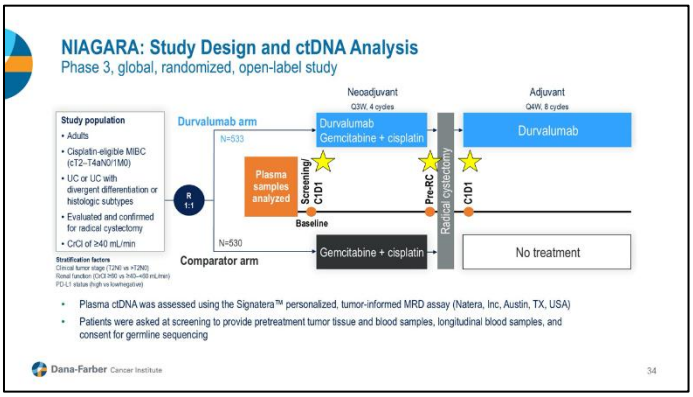
Obviously this trial is ongoing, still we don't have the results, but in this trial they use a different platform. That's something. The Natera Signatera was not used. They use a, a different way to identify DNA in blood, that is the methylation sequencing. So the methylation of DNA, the pattern of methylation can help us also to monitor cancer. It's a different way. As mentioned there are different tests, the Natera Signatera, there are the Guardant, there are the GRAILs or so many different platforms.

Dr. Joaquim Bellmunt:



Another, another, trial that was reported, this was a single-arm trial, this was reported by the Danish. So patients with ctDNA positivity after surgery, they receive Atezolizumab and they report that 55% of patients converted to ctDNA negative meaning these patients that you didn't know what to do, do I need to give adjuvant immunotherapies? The ctDNA help on deciding, "Okay, you need to receive immunotherapy." And when receiving Atezolizumab immunotherapy being ctDNA positive, those patients became negative. So helping to identify patients that might, might benefit.

Dr. Joaquim Bellmunt:

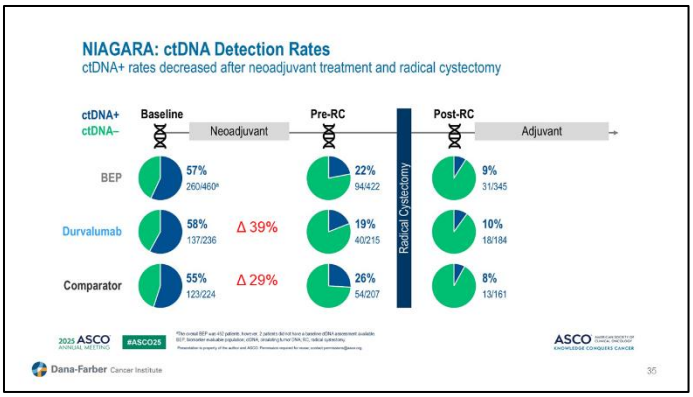


And then the last news on the ctDNA has been being able to go back, rescue samples from the NIAGARA trial. And as you know, the NIAGARA trial is a trial that has been done and also not in high risk. It has been done in muscle-invasive bladder cancer. This trial was comparing the combination of chemotherapies, cisplatin, gemcitabine, plus durvalumab that is a PD-L1 inhibitor before surgery. Here you can see the radical cystectomy, patients receiving four cycles before the surgery. This was compared with the standard of care that is giving neoadjuvant chemotherapy only. These patients randomized to each one of these arms, then they had the surgery, they receive some receive adjuvant durvalumab here or the others, sorry, the others didn't receive anything. This trial was designed in 2016 where there was no role for adjuvant chemotherapy immunotherapy. There was role for nothing.

So this trial that you know now it is the, is the, has level one evidence. That's the way that we need to treat patients with muscle-invasive bladder cancer. They need to receive chemotherapy and immunotherapy. Patients need to have an adequate renal function. There

is also an option to give a split-dose platinum if they have more than 40 mLs per minimum. And this trial lead to a survival improvement in patients receiving chemoimmunotherapy followed by adjuvant immunotherapy after surgery. So what was presented at ASCO this year, and this was done by Tom Powles, is that the this plasma, they were able to collect plasma, sorry, this trial they were able to collect plasma before starting the treatment during the neoadjuvant period, plasma before cystectomy, and then plasma after cystectomy.

Dr. Joaquim Bellmunt:

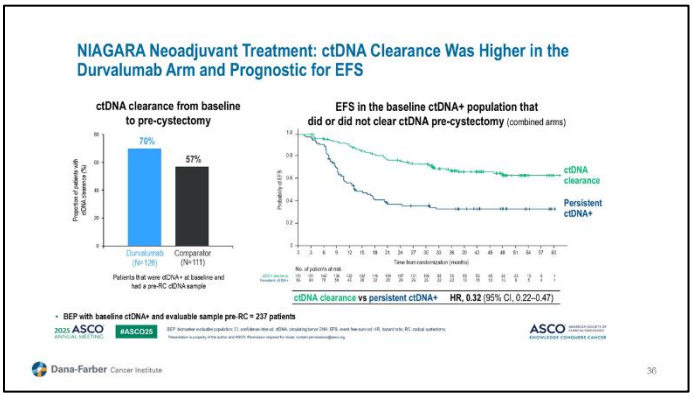


And then what the this trial did show, as you can see here, the blue is the percentage of patients having ctDNA positive. This is baseline. Here is when they receive neoadjuvant chemotherapy. This is before radical cystectomy, the time of cystectomy, and then in the follow-up, post-radical cystectomy when they some of them they were receiving adjuvant. But as seen here is that we see that the percentage of ctDNA positivity, sorry, is going down. So going down to 22% after neoadjuvant treatment, and then after surgery it's going down to 9%. An interesting observation is telling here that patients that receive neoadjuvant chemotherapy plus durvalumab, the rate of decrease in the ctDNA from baseline to pre-surgery was higher, 39%, compared to patients receiving chemotherapy. Confirming also the value of adding immunotherapy in the neoadjuvant setting.

So this was a something to support that ctDNA is helpful to identify benefit of drugs when this is in clinical trials.

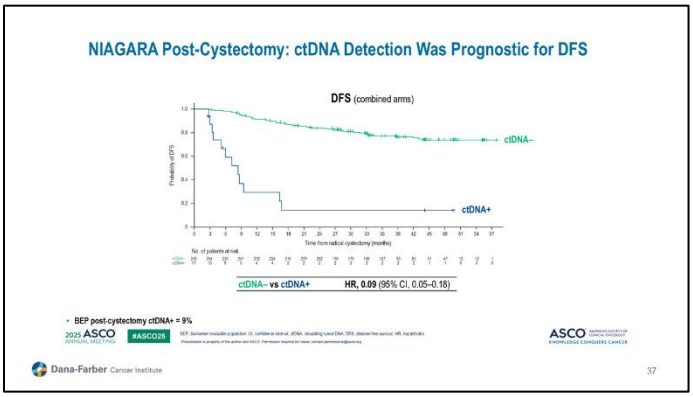
Dr. Joaquim Bellmunt:

So also, the clearance did show a higher benefit patients that the ctDNA disappear while being on this neoadjuvant trials.



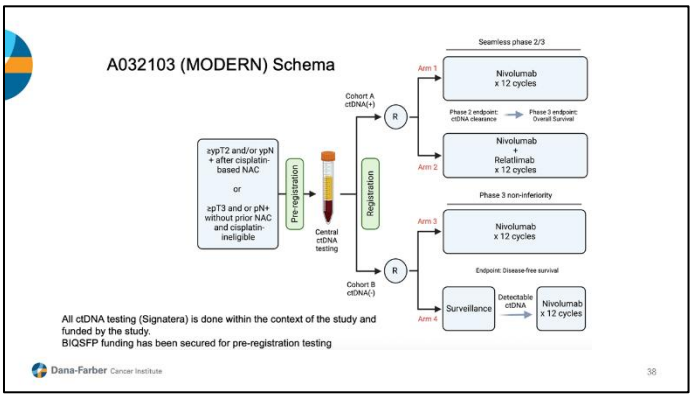
Dr. Joaquim Bellmunt:

And we see here in the post-cystectomy, the ctDNA detection was prognostic. So the same that we have seen before. So ctDNA is helpful in terms of prognosis, helpful on... The rate of decline is telling us that the patients are going to do much better than those that you don't see a decline. And obviously now the ctDNA is built in several different trials.



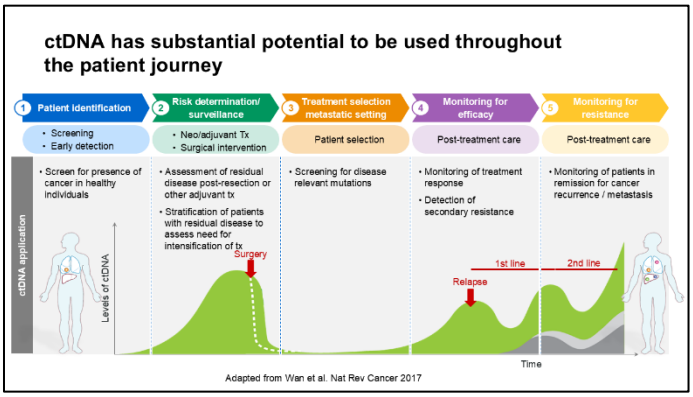
Dr. Joaquim Bellmunt:

So here is the Alliance adjuvant trial. So trying to improve outcome in our patients having massive invasive bladder cancer. And as you can see here, the ctDNA is implemented before deciding to give adjuvant. You can see here that patients that have ctDNA positive here are randomized to the standard that is Nivolumab or an intensified adjuvant therapy that is Nivolumab plus Relatlimab. And also patients that are negative, this obviously these patients are high risk, are randomized to immediate treatment Nivolumab or surveillance, monitoring the ctDNA, and in case the ctDNA becomes positive, receive Nivolumab.



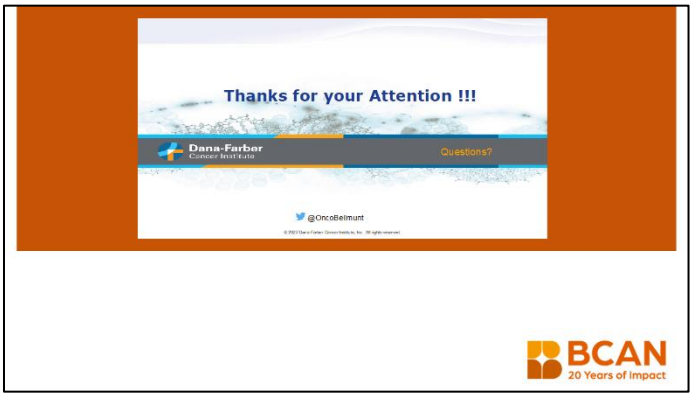
I know that is a complicated trial the first time that you see that, but this trial will further confirm the value of using ctDNA on deciding, for example, if you need to intensify the adjuvant therapy or if you need just to only monitor patients and treat at the time that the ctDNA is coming positive. So saying that we can like save treatment options for patients, you don't need to treat these patients that are maybe continuously negative, or maybe you need to treat anyhow patients with ctDNA with Nivolumab. So it's exploring trying to answer several questions. This trial is accruing and hopefully it's going to provide some, some new inputs on the way to use the ctDNA.

Dr. Joaquim Bellmunt:



So I think that we are on time. So that's my last slide. This is summarizing everything that I have been presenting. So those are the different settings where the ctDNA could be used. So yeah, you could see here the setting where now all these tools are being used for early detection for screening. I have not discussed, but also the urine ctDNA can be used to monitor recurrence in patients with non-muscle-invasive bladder cancer. So urine is also a place where we can check the DNA. And here we have said we can like follow the ctDNA to see the kinetics under treatment, follow after surgery if the ctDNA is coming negative. And in when patients unfortunately they develop metastatic disease, we can detect relapse even before that is evident by imaging. We can monitor if there are like changes on the, on the genomics and implement or changing therapy based on the findings that we see on ctDNA with... As mentioned, there are different platforms just to do all these things. So with that

Dr. Joaquim Bellmunt:



I would like to thanks Stephanie and BCAN for the opportunity to invite me to share all these data and I'm open to questions if I am able to answer because, as mentioned, this is an emerging area in bladder cancer and other tumors. So thank you very much for your attention.

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