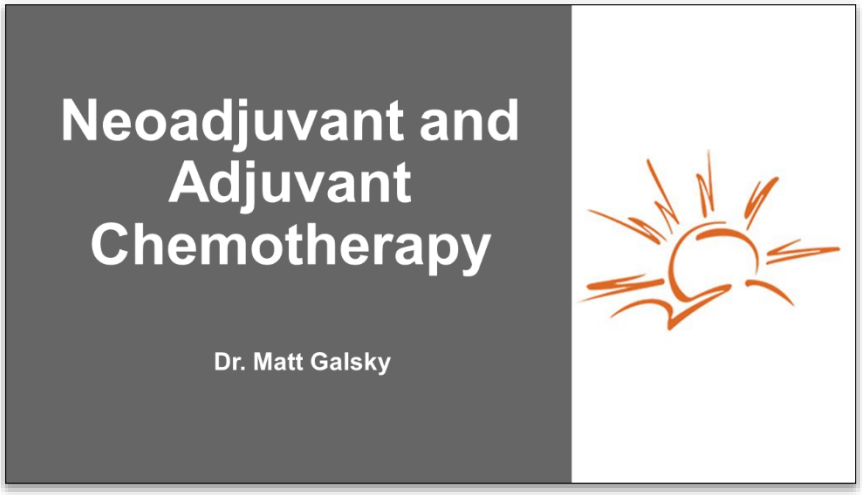


Dr. Matthew Galsky:

And I already described the relative pros and cons of treatment in the adjuvant setting versus the neoadjuvant setting. So, what did the data look like? It might be obvious to you, but in case it's not, we're giving treatment in the perioperative setting with medication and we're giving it based on the possibility that cancer cells have spread, but not being able to determine that definitively in each individual, that also makes understanding how well the treatment has conferred a benefit in an individual patient, very complicated.

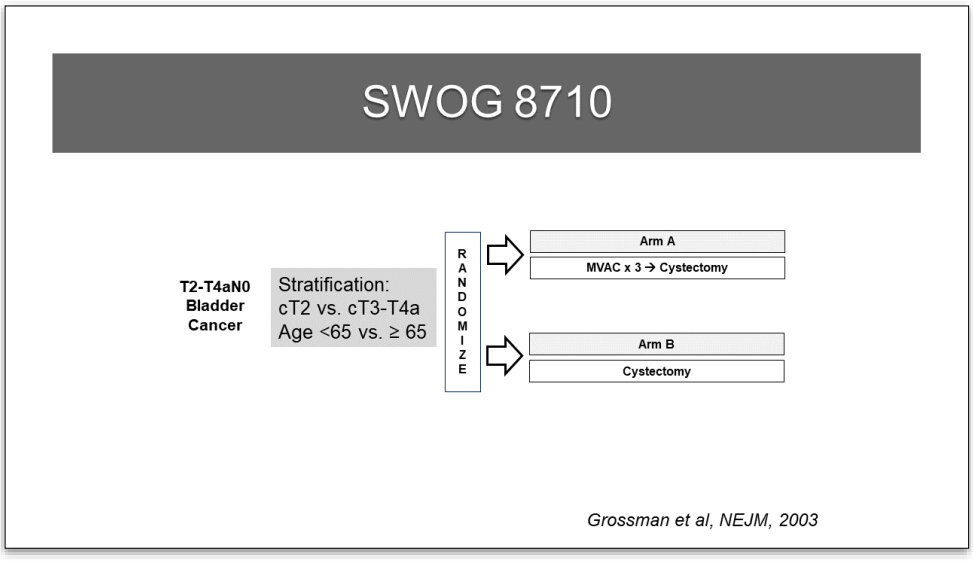
And in reality, it's really virtually impossible in an individual patient to know for certain the contribution of the chemotherapy. So, what am I talking about? Well, if you give 100 individuals chemotherapy prior to surgery and the cancer doesn't come back in any of those patients, was that because there had been no microscopic spread of cancer at all prior to surgery.

Or, was it because the chemotherapy eradicated those microscopic cells. In an individual patient, we don't know that for sure. There are some indirect measures of benefit in the neoadjuvant setting, the setting prior to surgery, as I mentioned, measuring what happens in the primary tumor, but that's really somewhat an indirect measure of what might be happening in the microscopic metastatic setting.

And even if we see a regression of that primary tumor, that still doesn't tell us 100% percent that there had been microscopic spread of the cancer in the first place. So, that's my long-winded way of saying that to really determine the benefit of approaches like this, we need randomized studies.

We need patients randomly assigned to one treatment versus another, and then ultimately determine which treatment effect is more... which treatment strategy is more beneficial in the majority of patients treated. And so, randomized clinical trials have been conducted exploring neoadjuvant chemotherapy and exploring adjuvant chemotherapy.

These trials date back a few decades now. There were a few decades really spent on serial clinical trials trying to answer this question, and it's actually been a more challenging question to answer than you might think. In many clinical trials failed, they couldn't enroll enough patients, there was some methodological flaws.

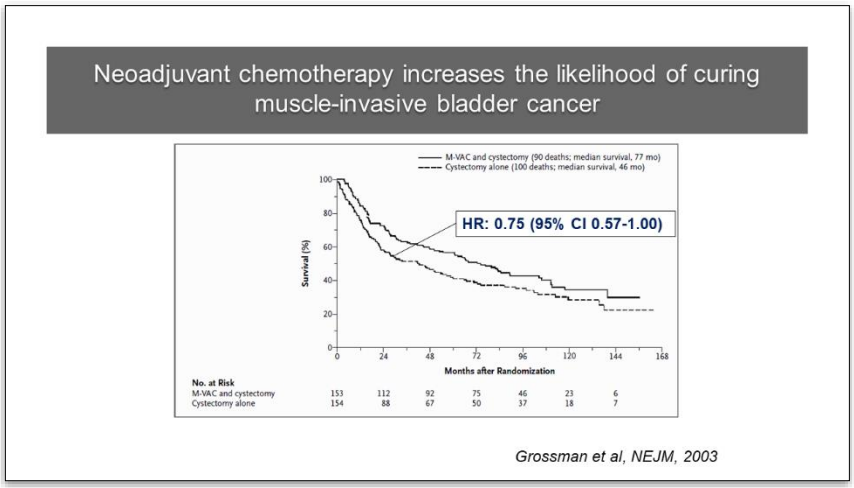


But we have a few studies that we really hang our hats on, and one of those studies is called SWOG 8710, it's a study that was conducted by SWOG, which is a National Cancer Institute supported clinical trials network across the United States.

In this study, enrolled patients with muscle invasive bladder cancer and they were randomized to receive three cycles of chemotherapy prior to surgery for bladder cancer versus going directly to surgery, directly to cystectomy. And what this study showed was that there was an improvement in longevity and improvement in survival in individuals who had chemotherapy prior to surgery versus those who had surgery alone.

Dr. Matthew Galsky:

And what I'm showing you here is the primary result of this study, and this is called a Kaplan Meier curve, if you haven't looked at these before. And really these curves represent over time the proportion of patients who are alive on each arm.



And really showing this separation of the curves with the curve... at the higher curve indicating patients who had chemotherapy prior to surgery demonstrating a higher proportion of patients alive at each time point during follow up compared to patients who had surgery alone.

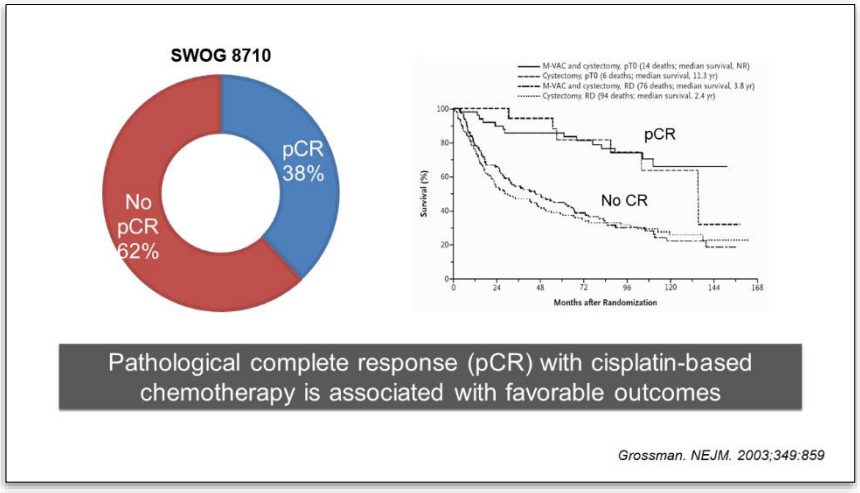
And there are a few different ways to represent the benefit of chemotherapy in a situation like this. There's relative risk reduction, there's absolute risk reduction. Absolute risk reduction is probably a little bit easier to wrap one in its head around.

So, there's probably between a 5% to 10% absolute reduction in the risk of death from bladder cancer by getting chemotherapy prior to surgery, roughly translating into if 100 patients were treated with chemo-

So, that's the description of the benefit of chemotherapy prior to surgery and not all patients benefit. But for those who do benefit, of course, there's much to gain.

I already mentioned this, but one of the potential surrogate measures of whether or not treatment is beneficial in an individual patient is what happens to that primary tumor from chemotherapy when it's removed and analyzed under the microscope.

And there's a phenomenon referred to as a pathological complete response, which essentially means that when the pathologist analyzes the bladder under the microscope, they can't find any evidence of cancer. When that occurs in the setting of chemotherapy prior to surgery, that's associated with a much lower likelihood of metastatic recurrence versus when that doesn't occur.



And that might seem straightforward, but it's actually very important to document that as that reinforces the potential benefit of chemotherapy. There are side effects of chemotherapy, and so that potential benefit of chemotherapy needs to be weighed against those side effects.

And the side effect profile of chemotherapy has changed somewhat over time, so this is with an older way of administering chemotherapy and without some of the supportive measures that we have available today. But the side effect profile, the likelihood of having side effects is less than described here, but the side effect profile is pretty similar.

Dr. Matthew Galsky:

And this describes some side effects that are chemotherapy like side effects. There can be suppression of the bone marrow, the organ that makes our blood cells in one of those blood cells are the white blood cells and white blood cells help fight against infection.

Side effects…

Adverse Event	Grade 3	Grade 4
Neutropenia	23%	30%
Thrombocytopenia	6%	0
Nausea or vomiting	6%	0
Mucositis	10%	0
Renal failure	<1%	0
Neuropathy	2%	0
Fatigue	3%	0
Any	**35%**	**37%**

Grossman et al, NEJM, 2003

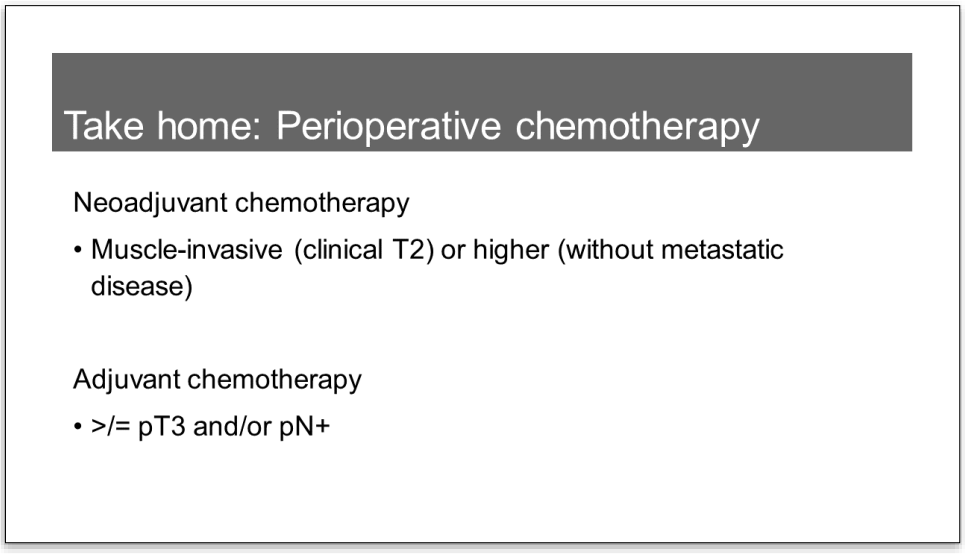
So, after chemotherapy, those cells in the blood will be lower for a period of time and there can be an increased risk for infection. There can be nausea and vomiting. With cisplatin, one of the key drugs that we use, there can be some effect on the kidneys.

And so, we watch kidney function very closely when patients are receiving this medicine, there can be fatigue, which is probably one of the more common side effects from chemotherapy. So, what about giving the chemotherapy after surgery and basing the decision on that more precise pathological staging that I referred to.

And certainly, there's a rationale for this approach and multiple clinical trials have been performed, and this is... it's a little bit of a practical issue that the clinical trials that have been done in the adjuvant setting in the post-surgery setting just are a bit less compelling.

And whether or not that relates to this issue that is harder to receive chemotherapy after surgery as individuals are recovering or it's just a function of how the studies were

conducted, that's hard to say for sure. But based on a culmination of the evidence, really getting chemotherapy prior to surgery is the preferable approach.



Dr. Matthew Galsky:

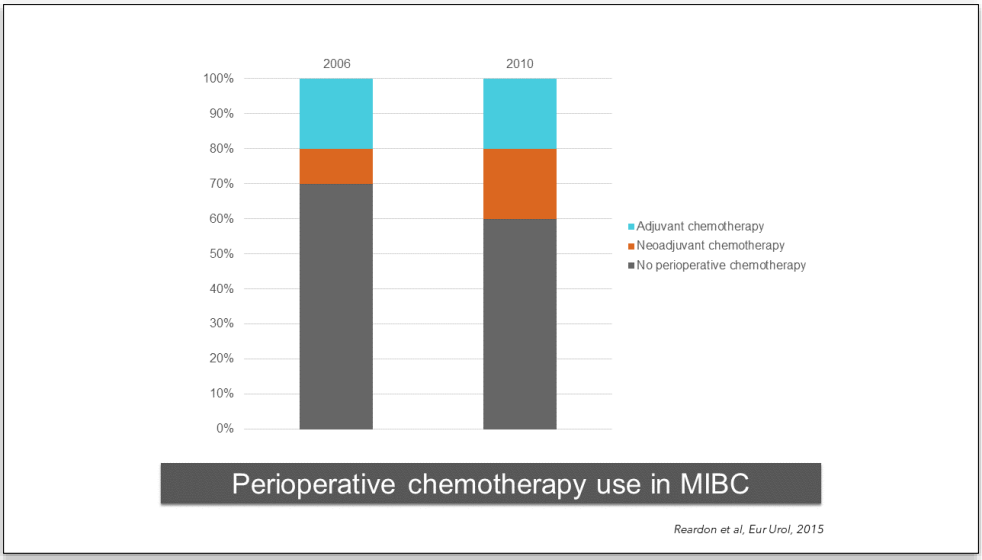
But in individuals who haven't received chemotherapy prior to surgery, we still do recommend chemotherapy after surgery in the right context. And that context really has to do with the stage of the cancer that I was referring to. So, neoadjuvant chemotherapy, we generally recommend in patients without contraindications to chemotherapy when there's a muscle invasive bladder cancer.

And if chemotherapy wasn't before surgery, then after surgery, if there's a pathological stage T3 or higher cancer, again, referring to the depth of invasion of cancer into the bladder wall, or if the lymph nodes are microscopically involved and that's noted when the surgical specimen is analyzed.

Despite the evidence to support perioperative chemotherapy either in the neoadjuvant or adjuvant setting. There's been multiple analyses published over the past 20 years looking to see how often this treatment strategy is employed. And in most of the analyses really do suggest that this is a strategy that's underemployed, and it's probably underemployed for many, many reasons.

One reason is based on what I was mentioning before, because we recommend this treatment in patients without contraindications to cisplatin-based chemotherapy. And it turns out that there are several, at least relative contraindications to that treatment, and sometimes the risk does outweigh the benefit.

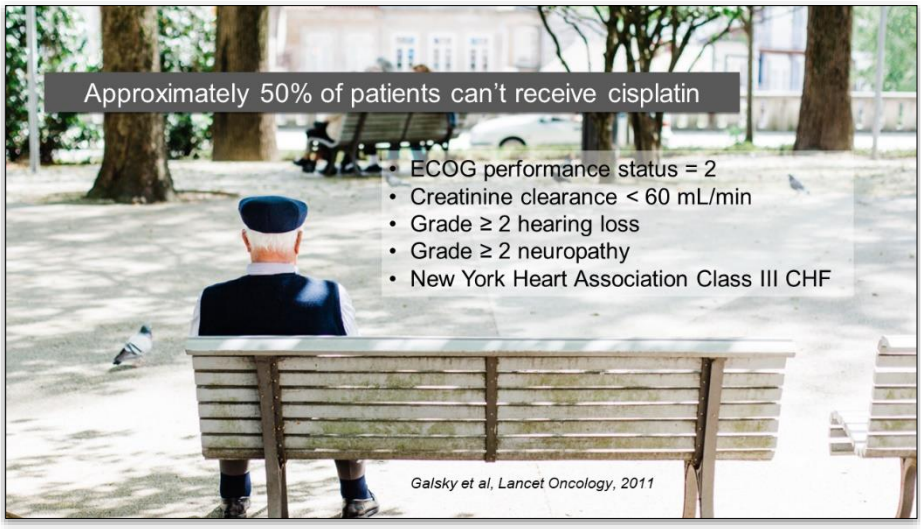
But there are other reasons as well, of course, individual preference, practice patterns, et cetera. So, you can see here that over time the uptake of these treatment strategies shown in the turquoise in the orange increased from 2060 2010, but really not markedly so.



And still many patients with muscle invasive bladder cancer don't receive perioperative chemotherapy. In this, I already mentioned one of the key reasons is this issue of having contraindications to receiving cisplatin. So, that really represented an unmet need historically in bladder cancer and still represents an unmet need.

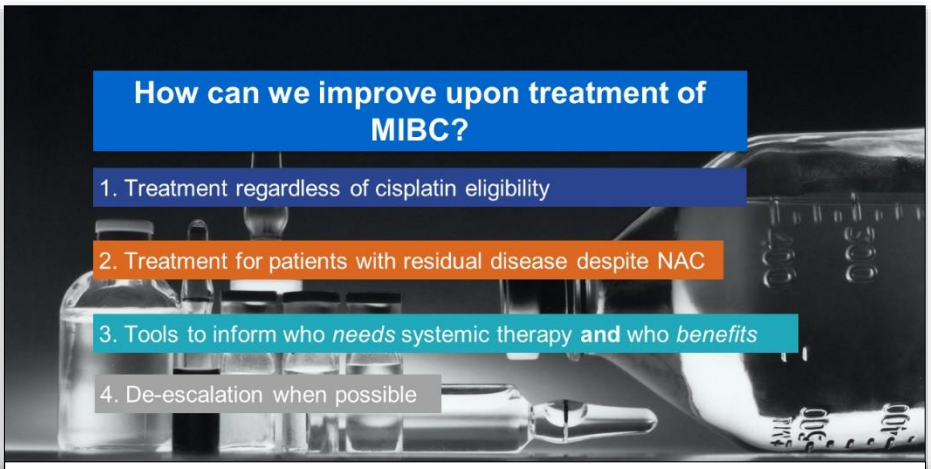
Dr. Matthew Galsky:

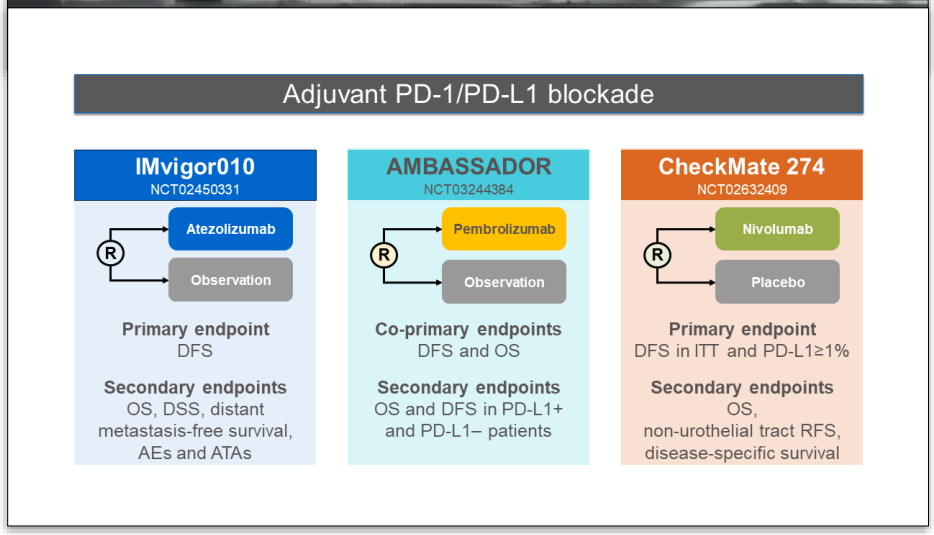
How do we improve outcomes for individuals with muscle invasive bladder cancer who can't receive cisplatin. And how can we improve outcomes for patients who did receive neoadjuvant chemotherapy, but on surgical removal of the bladder, there is still evidence of cancer deeply invading the wall of the bladder or lymph nodes that are microscopically involved.



And historically, we haven't had a strategy to employ that had been shown to be potentially beneficial in this setting. And this has changed recently with the advent of another class of medications to treat bladder cancer, which are called immune checkpoint inhibitors or immunotherapy as the more general term that's used.

And these drugs inhibit either the PD1 or PDL1 protein. And by doing that, that allows the immune system to recognize cancer as foreign and try and attack it. So, these treatments work in a very different way than chemotherapy works, and based on demonstrating that those types of treatments can be effective in patients whose bladder cancer has already spread.





And even in patients whose bladder cancer has spread and chemotherapy didn't work or stopped working, a logical question was, should we give these treatments around the time of surgery to try and increase the likelihood of eradicating bladder cancer?

And so, there have been three clinical trials designed in a similar fashion to try and address this question. And these trials included either a PD1 inhibitor or a PDL1

inhibitor, so the drugs are quite similar.

Dr. Matthew Galsky:

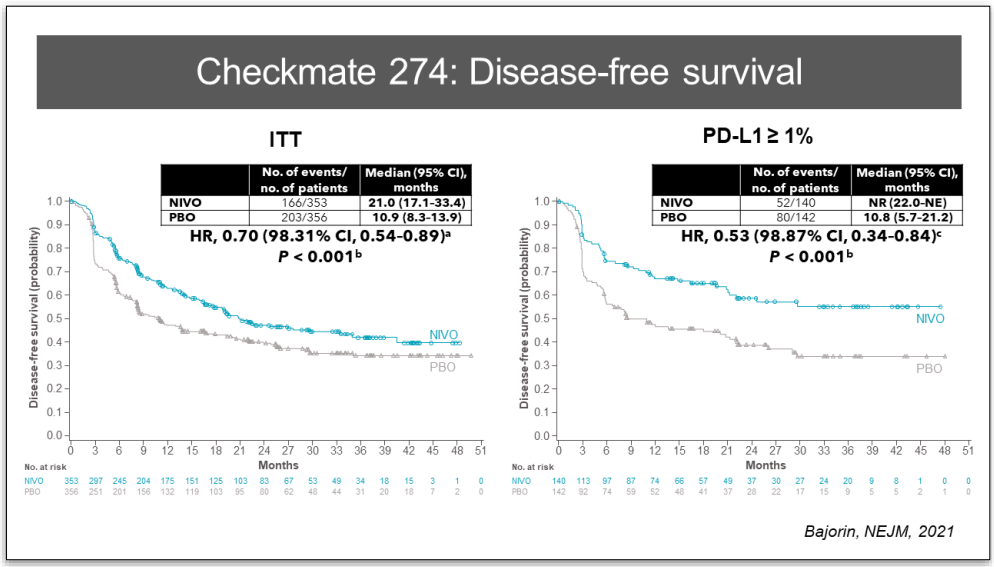
The way that the trials were designed was really quite similar as well, randomizing individuals to receive one of these drugs or to just be observed as that was really the standard treatment in this setting.

Individuals enrolled on these studies had muscle invasive bladder cancer with features that suggested a high risk of recurrence, and that really fell into two buckets.

One group included those who had received neoadjuvant chemotherapy, but on surgical removal of the bladder has mentioned or has described had residual cancer invading through the wall of the bladder or having the lymph nodes involved.

Or, patients who hadn't received any chemotherapy prior to surgery but weren't felt to be ideal candidates for chemotherapy based on weighing the risks versus benefits of chemotherapy. So, both of those groups of patients could enroll on this study and again, randomizing to one of these immunotherapy drugs versus a placebo or observation.

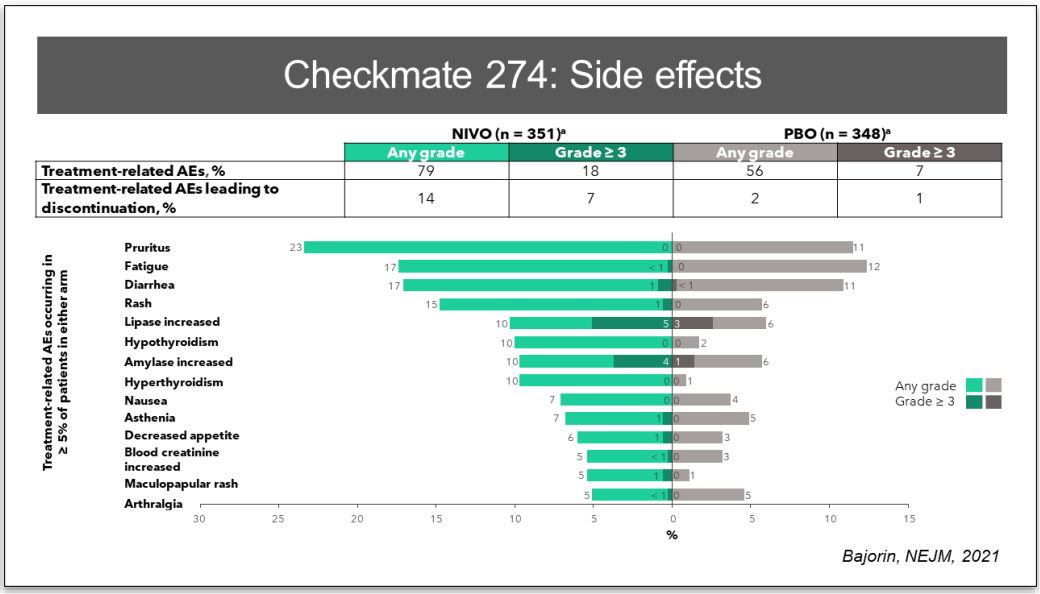
And these are the results from one of those studies, CheckMate 274 showing that inpatients who received immunotherapy after surgery versus a placebo, there was a significant decrease in the likelihood of cancer recurrence with the immunotherapy versus patients receiving placebo.



And the effect or the degree of benefit seemed to be even higher in individuals who had a specific protein expressed on their tumor specimen. And so, this approach was approved by the FDA and has now been integrated into our standard treatment algorithms as well.

The side effects of immunotherapy are quite different than the side effects of chemotherapy, and they have to do with modulation of the immune system. So, instead of seeing things like lowering of the

white blood cells, nausea, more chemotherapy related side effects with immunotherapy, there can be side effects related to inflammation, which is described with the suffix.



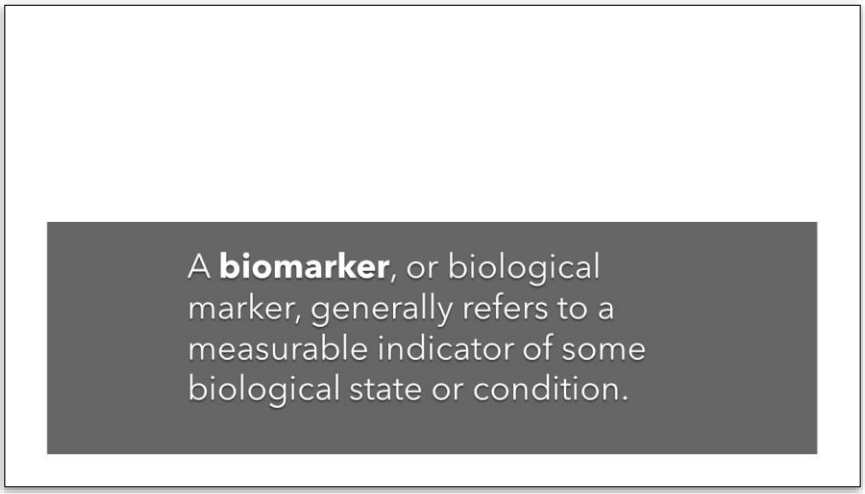
Dr. Matthew Galsky:

So, there can be colitis, inflammation of the bowel, which manifest as diarrhea, there can be pneumonitis, inflammation of the lungs, which manifests coughing or shortness of breath, dermatitis, inflammation of the skin, which manifests rash or itching.

All these “itises”, these different organ systems can be involved. Unlike chemotherapy though, a large subset of patients treated with immunotherapy actually don't have any side effects.

And when the side effects occur, unlike chemotherapy where there tends to be a constellation of side effects that differ in their severity from one individual to another. With immunotherapy, most commonly it's one side effect might occur in one patient, another side effect might occur in another patient, et cetera.

So, those are the treatment strategies that we employ commonly in the presurgical setting or the post-surgical setting. But we really do take the same approach in everyone. And of course, there's an interest in precision medicine or personalized medicine.

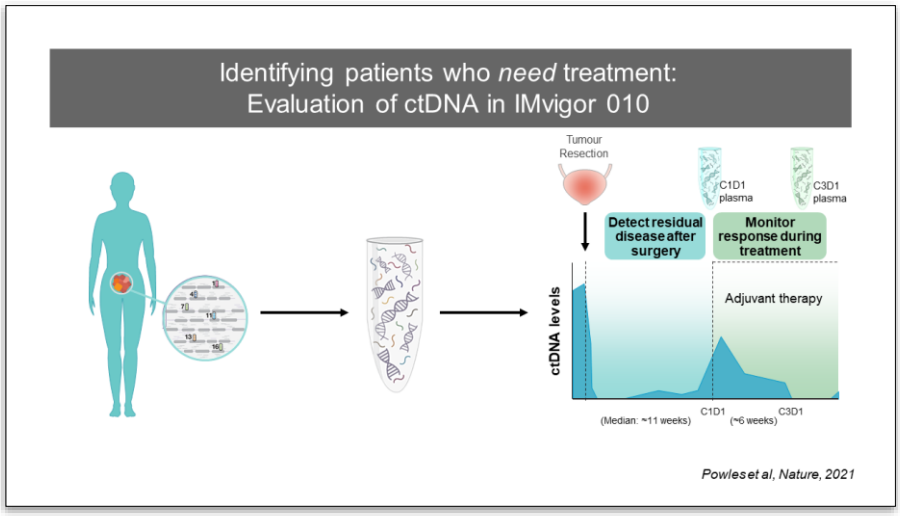


How can we know what the right approach is for the individual that is needing to make a decision about integrating these treatment strategies? And the way that we try and do that is with biomarkers. And biomarkers just determine that refers to a measurable indicator of some biological state or condition.

Something that one could measure in a tumor specimen in blood, in urine, et cetera, that might tell us that that individual might be best suited for treatment A and another individual might be best suited for treatment B. And so, I generally put biomarkers in this setting into two main buckets.

There are biomarkers to indicate who needs treatment and there are biomarkers to indicate who might benefit from treatment. And that might sound confusing and they might sound like the same things, but they're actually quite different.

Dr. Matthew Galsky:



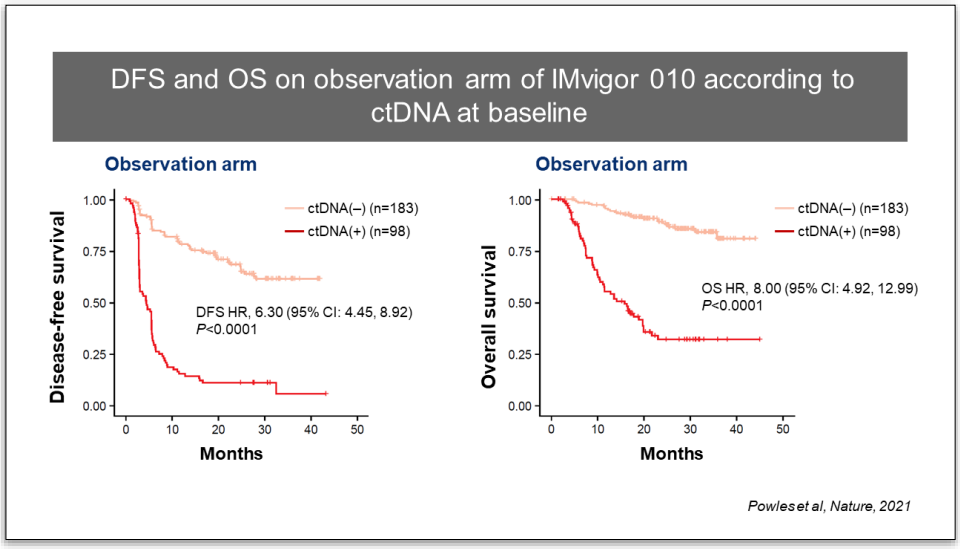
So, one can think about in the perioperative setting, in an individual with muscle invasive bladder cancer, knowing if an individual has microscopic spread of cancer, that would be a biomarker that would tell you who needs treatment. But that cancer might not necessarily be sensitive to the treatment that's being employed, which would be a biomarker of benefit.

So, in an ideal situation, we have both biomarkers to tell us who needs treatment and biomarkers to tell us who benefits from treatment. Biomarkers to determine who benefits have been a bit more elusive. And I showed you the PDL one protein data for immunotherapy delivered after chemotherapy, and that's promising.

But even in the absence of that information in all patients who were enrolled in that study, there was a benefit from treatment. And so, it's hard to employ that strategy necessarily to make a treatment decision about immunotherapy in the postoperative setting.

Biomarkers to determine who needs treatment. I think we're getting closer to. And what I'm referring to specifically are measures of what's called molecular residual disease or circulating tumor DNA. One could measure DNA in the blood and one can actually determine whether or not that DNA might have been shed from cancer cells as an indicator of microscopic spread of cancer.

And so, this was done in a large clinical trial, in a clinical trial similar to the one that I just showed you with immunotherapy given after surgery. And here, you see based on this blood test to try and measure tumor DNA in the blood.

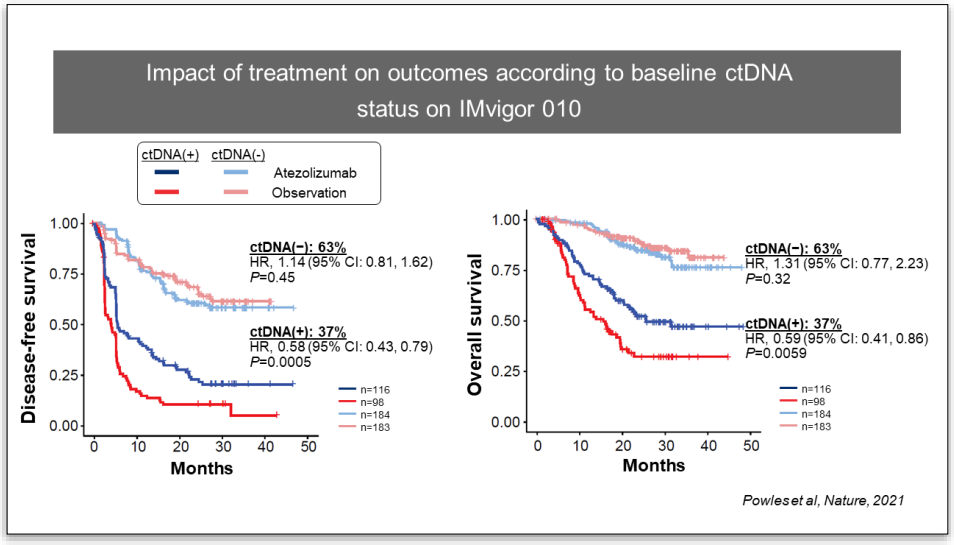


If there was tumor DNA in the blood, you can see from these curves a much higher likelihood of cancer coming back, cancer metastasizing versus if you can't measure tumor DNA in the blood, that might seem obvious. This is arguably a measure of microscopic metastatic cancer, an indirect one though, of course.

And so, the investigators from this clinical trial then looked to see if there was a benefit to giving immunotherapy after

surgery that was restricted to those individuals who had the detectable tumor DNA in the blood versus those who didn't.

Dr. Matthew Galsky:



And they showed that most of the benefit from immunotherapy was indeed in the patients who had circulating tumor DNA in the blood. I have to provide the caveat that this is what's called a retrospective study, and it's an exploratory study.

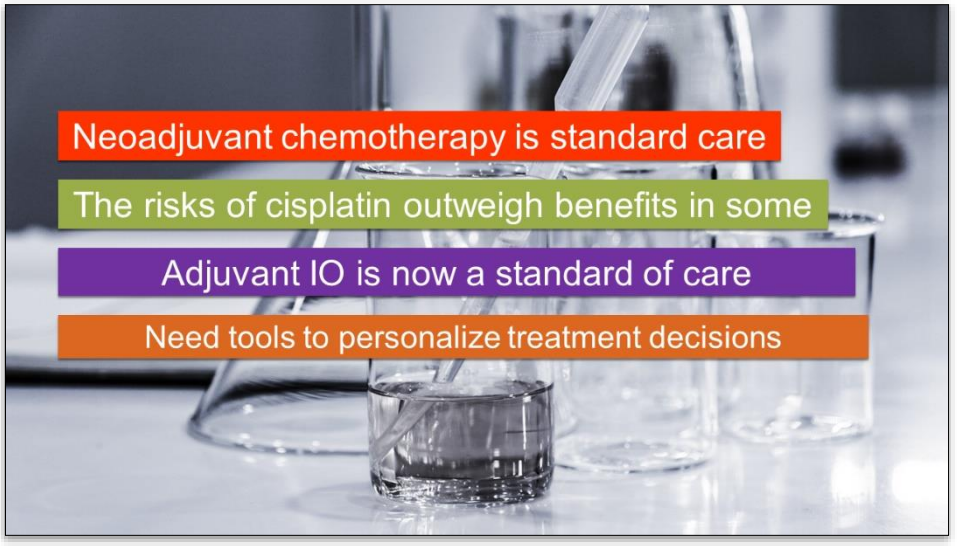
Retrospective meaning that this was done after the completion of this clinical trial, all the specimens were run in a batch fashion after the trial was done, the results were already known. And it wasn't a pre-planned analysis from the standpoint that it was adequately, that the experiment was adequately designed to test this concept definitively.

So, this is very intriguing data, but it's not quite ready for primetime. One might ask, "Well, what about in the neoadjuvant setting where chemotherapy is standard? Are we doing this testing in the neoadjuvant setting to see who should get chemotherapy and who shouldn't?"

And it's a very interesting concept. And one of the limitations to doing that to date is really more of a technical issue, which is that it takes a lot of time to do this test. It could take weeks to do it because many of the approaches are bespoke based on an individual patient's tumor.

And so, the timing of those results coming back has not been quick enough to really develop studies to test this concept in the clinic yet, but the tests are getting better and better.

And so, we'll be seeing some studies seeking to determine whether or not we should be using testing like this to decide who might be best suited for neoadjuvant chemotherapy in the not-too-distant future. So, neoadjuvant chemotherapy, as I mentioned, is a standard of care. In some patients, the risks of cisplatin outweigh, the benefits, and of course, it's very personal decision to employ this treatment.



Adjuvant immune checkpoint blockade is now a standard of care, but we really still need tools to personalize these treatment decisions in the research community, I can assure you is

working very hard to try and develop such strategies. So, thank you for your attention and I'm going to stop there and happy to answer questions if there are questions.