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https://reachmd.com/programs/cme/advancements-in-gu-cancers-key-data-from-aua-2024/24417/

Released: 07/18/2024
Valid until: 07/18/2025
Time needed to complete: 30 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Advancements in GU Cancers: Key Data from AUA 2024

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Chapter 1: Prostate Cancer

Dr. Chu:
Welcome to this educational series on key data in prostate and bladder cancer that were presented at AUA 2024 in San Antonio, TX. This is CME on ReachMD and I'm Dr. Carissa Chu, an Assistant Professor at the University of California, San Francisco.

Dr. Hafron:
I'm Dr. Jason Hefron, Chief Medical Officer of the Michigan Institute of Urology. So happy to be here.

Dr. Chu:
OK, let's get started. so, there were some interesting abstracts on testing for prostate cancer. Jason, can you review some of these studies for us?

Dr. Hafron:
Thanks, Carissa. Yeah, there was, a lot of great material. one of the abstracts that stood out was Germline Genetic Testing for Prostate Cancer; Ordering Trends in the Era of Expanded Hereditary Cancer Screening Recommendations. this was an interesting, study because we all know that urologists on the front lines of prostate cancer and, germline testing is indicated for men with metastatic prostate cancer, for men with high-risk, and very high-risk localized disease, as well as men with family history.

I think as urologists, the data what this shows is that we are on the front lines of prostate cancer. It's important that you have a plan, on how to order these tests. If you need to refer to a genetic counselor or if you're going to do the pre-testing, that we need to be the ones advocating for our patients to make sure that they get the germline testing that they need.

Dr. Chu:
Completely agree.

Dr. Hafron:
I think another one that stood out was the PSMA PET-guided metastasis directed therapy for oligometastatic prostate cancer. And we all know that oligometastatic prostate cancer is a prostate cancer that has less than, five metastatic lesions. And this was data from a single center, that looked at, using PSMA PET, their management of these patients with oligometastatic disease.

I think one item that really stands out in this study is that patients who receive adjuvant ADT with their metastasis-directed therapy did better than those that did not receive the ADT.

I think key here is that MDT appearing early studies and small series to be a viable option to increase progression-free survival, and based on the data presented, as well as some other of the published literature it probably should be used in conjunction with ADT and possibly even a novel hormone therapy.

And then, I think there is another one that really loved, and I think is really timely, is the PSMA PET findings in patients with high-risk biochemical recurrence, after local treatment of prostate cancer. So, think we're all familiar with the EMBARK trial, and we've started this new category of high-risk, biochemical recurrent disease, which is defined as a PSA doubling-time less than 9 months, a PSA, greater than 1, after surgery. And I think it's a greater than 2 after radiation.

What this single site, did was they looked at all those patients that met this criteria, or this high-risk BCR criteria, and did PET scans on them. And what's shocking about this – and I think important to understand this – is the EMBARK trial was based on conventional imaging. So, I think as, you know, EMBARK was a great trial, but when you apply modern technique or modern evaluation with the PET scan, as most of these patients, 80%, are metastatic. And 20% of them, actually, in this trial had salvageable, disease, that may benefit from additional radiation therapy. So, I think that the bottom line here our audience is that, the value of the PET scan in a BCR is critical, and that when these patients are obtained, most of these patients are actually metastatic CSBC patients that may benefit from radiation, but definitely will benefit from oral novel hormone or ARPI's and management of their disease.

Dr. Chu:
That was an amazing summary, and I think this highlights a really interesting space, in prostate cancer right now where, you know, we operate on high-risk disease and, you know, with, PSMA PET we've also seen a stage migration of cases that we used to think were local are now likely, you know, metastatic radiographically metastatic. And so, understanding, one, where surgery fits in that treatment spectrum, but also, you know, how we're now treating sites of visible disease and how we think about intensification of treatments kind of, you know, earlier, and how this benefits patients. It's not just progression-free survival, but overall survival.

Dr. Chu:
There were also some, interesting data on, treatment sequence and survival in locally advanced prostate cancer. Jason, can you review this study for us?

Dr. Hafron:
This was a real-world treatment sequence in survival and localized, or locally advanced, prostate cancer and post-progression disease states. this used US Optum Claims and Electronic Health Records and looked at over 60,000 patients from 2008 to 2020. And basically, they followed patients with locally advanced or localized prostate cancer and looked at them over decade to see what really happened to them, and compared their outcomes. I think the bottom line here is that 11 to 12% of patients with localized or locally advanced progressed over this decade, and those that progressed, most progressed within 3 years, and then all progressed almost within 5 years.

This was kind of the theme the AUA, is that the first treatment with these locally, patients, the first thing that we offer them is really critical, and the patients that fail that first line of therapy never really catch up, don't do as well, and even after, multiples, therapies, they never reach that first patient who never recurs.

Some kind of obvious concepts, but it's it's shown out in over this decade study of over 60,000 patients, kind of highlights where we got to focus as a specialty on making sure that the first line treatment is the best treatment because afterwards those patients never catch up.

Dr. Chu:
Yeah, completely agree. And there was some additional, data in the metastatic setting. there was a study that you presented, maybe you can go into that with us a little bit.

Dr. Hafron:
So, what this trial was, was a Phase 2 trial, looking at apalutamide for high risk or very high risk 12 months after surgery. They could qualify, for the high-risk based on their biopsy or based on their, pathology specimen.

And what we found in this trial is very exciting, is that there were no failures, the 2-year period. There were two unconfirmed failures, patients that did not have documented two successive rises, but did have a slight rise in their PSA after treatment.

A lot of people will say, oh, you know, they received intense ADT. They received apalutamide, a very strong androgen receptor inhibitor, but what happened is 76% of those patients regained testosterone greater than or equal to 150. And what's even more impressive is that, based compared to what the previous standard of what the previous literature says, is that in the same patient population with high risk/very high risk, the biochemical free survival rate is 76%. So, what we planned when we planned this study was that, for this study to be positive, it had to show a 10% improvement. And we actually saw over a 10% improvement and had 100%, biochemical free survival

rate.

This important study, it's a Phase 2 study, but this is just kind of entry or the entree, the appetizer to the major study that's going on right now, which is the PROTEUS trial. the PROTEUS trial is a worldwide 2,500-patient, study that's looking at apalutamide plus ADT for 6 months prior to surgery, and 6 months after surgery, to see if that affects, metastasis free survival. I'm very excited to see, obviously based on the Phase 2 results, it looks promising. But we have to obviously wait until the results PROTEUS trial, which hopefully will be coming out shortly.

Dr. Chu:
Yeah, it's an incredible, response rate. Very, very encouraging for our patients. how did you find that patients tolerated the therapy, and how many of them were able to complete the full course?

Dr. Hafron:
All of them were able to complete it. tolerated it very well. I think ADT plus apalutamide is well tolerated. Obviously, there were some, treatment-related events,but nothing significant. There were no new safety signals compared to, the previous trials with apalutamide compared to titan. Overall, you know, very well tolerated.

Dr. Chu:
That's great. I like the idea of, you know, having the pathology in hand, so you know who's at the highest risk for recurring, you know, in a post prostatectomy setting.

Dr. Hafron:
Right. And this was kind of, if PROTEUS positive, you know, you can apply, Apa-RP, that's what we called it, the apalutamide, after prostatectomy based on that. So, sometimes, you know, we were doing both trials at the same. Some patients would want to just get their prostate out, they didn't want to do six months of apalutamide and ADT prior to the prostatectomy. Now, based on the results of this finding, is that you can consider, apalutamide plus ADT after prostatectomy based on the prostatectomy specimen.

Dr. Chu:
There were some other real-world data on treatment patterns and outcomes of patients now with metastatic castrate-resistant prostate cancer. Jason, can you summarize some of these findings for us?

Dr. Hafron:
Another real-world study, looking at claims data was about, 4,600 patients that claims studied, and from the Flatiron Group. And it's kind of interesting. I think there's a couple key points that they basically looked at the pretreatment prior to these patients becoming mCRPC. And what they found was that, I think 50% of the mCRPC patients, were never treated before. They never received a novel hormone, and they never received a taxane, which is kind of interesting. Also, what was interesting is that there's some suggestion that, treatment sequence impactful, or maybe, a factor because when they also looked at the overall survival based on how the patients were treated in the, prior to mCRPC and the patients that did the best in the mCRPC, or had improved overall survival in the mCRPC, was the patients that only were exposed to a taxane, and they weren't exposed to a hormone. So, I don't know if we can make any significant judgments. I think the bottom line is we've got to, you know, make sure that the mCSPC patients are treated combination therapy, oral plus, a novel hormone plus or minus docetaxel, and that, you know, the sequencing, I think, you know, just requires further study to understand.

Dr. Chu:
Yeah. Yeah, I think, you know, these real-world data sets it's nice because it kind of holds the mirror up to, you know, how well the evidence and the clinical trials are actually being implemented. And there's always a gap there. And there's actually been a lot of interest in improving that execution. You know, the implementation science around it, but it's also hypothesis-generating.

Dr. Chu:
Any data on androgen receptor signaling and, what we notice about side effects, and any other trials?

Dr. Hafron:
There was an interesting abstract, I thought, that addressed side effects associated with novel hormone therapy, and that was the evaluation of cardiovascular events among men with prostate cancer treated with androgen receptor and signal inhibitors. And what they found was that there was an increased risk of cardiac disorder, relative risk was 1.4, hypertension risk, and then based on some of their further analysis, abiraterone/enzalutamide increased the risk of hypertension compared to standard of care. And, abiraterone, demonstrated significant increase in cardiac disorder.

I think this is, you know, important for urologists to be aware of this. That many of these therapies increase the cardiac risk. Many of these therapies can increase hypertension, heart failure, coronary artery disease. I think as you use these agents as a urologist, that

they maximize their cardiac health. You involve the appropriate specialist, the primary care cardiologist, to make sure that their blood pressure is being adequately managed, their heart disease is being adequately managed, and that if they should develop any of these side effects, that you work closely with your specialists, the cardiologists and the primary care, because these agents will cause potentially increased risk of cardiac disease.

Dr. Chu:
There was another study on apalutamide, the ARNEO trial. I was wondering if you would talk about that as well.

Dr. Hafron:
ARNEO's a culled investigator-initiated trial that was done in Europe. The original ARNEO trial was to look at Degarelix plus apalutamide versus Degarelix alone 3-months prior to prostatectomy, again, in high-risk state. But what abstract that was shown at the AUA was a little bit different. They took the ARNEO Degarelix plus apalutamide and then compared it to their standard of care, And it's kind of interesting what they found, it was a matched analysis and at 3-year follow up, there was no, significant differences in biochemical recurrence, but they did see an improvement in metastasis free survival.

So, there is, again, a signal. I don't want to sound like a broken record, but, you know, we got to wait to see what the PROTEUS trial shows, because that will be the definitive, trial to show that, tumor intensification with surgical therapy will benefit our patients with the highest risk disease.

Dr. Chu:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Carissa Chu, and here with me today is Dr. Jason Hafron. We're reviewing updates in genitourinary cancers from 2024 AUA Conference in San Antonio, Texas.

Chapter 2: Bladder Cancer

Dr. Hafron:
Carissa, let's now look at abstracts on bladder cancer. Two abstracts that I liked and I'm curious what your thoughts are, were Bladder, Epicheck and Uromonitor. can you summarize these abstracts? What did you think of them?

Dr. Chu:
Yeah. So, there are similar studies, looking at, kind of important disease surveillance space for patients with non-muscle invasive bladder cancer.

So, the first study was podium presented, a study led by Dr. Lotan, is a pivotal study evaluating the performance of Bladder EpiCheck, which is, FDA-cleared, for non-muscle invasive bladder cancer. it's sort of an epigenetic EpiCheck. sort of looking at, methylated genes that are shed in the urine and 15 loci. the main take away from the study was that the negative predictive value was quite high, was 95%, and that's kind of what you want. You know, you want a test that will tell you, OK, I can avoid this next cystoscopy, or maybe I can just do, you know, keep doing this test. and a very low false-positive rate.

There was another podium, on UroMonitor and, that was looking at a very similar, urine-based test. this one's focused on three specific, oncogenes that we know to be pervasive in non-muscle invasive disease. So, that's the TERT promotor mutation, TERT promoter mutation, FGFR3, and KRAS. So, the three together, kind of, you get this sort of aggregate signature that can be used also in lieu of cystoscopy for non-muscle invasive disease.

You can't really compare across studies,, but you know, they're designed a little bit differently. but this study had a really high negative predictive value of, you know, 99%, positive predictive value of 93%, sensitivity of 87 compared to 64, and EpiCheck. so, you know, you want something that's got really high fidelity to what you might expect to find.

So I think this is a really exciting space. I think that, you know, many, many patients would be interested in doing home urine testing, especially those where, you know, they've already reached a certain number of years, without recurrence, or maybe they've got other goals of care, to consider where they may not want to be coming in for that. I think this is a really nice option, to offer them.

Dr. Hafron:
Yeah, Carissa, I agree. I mean, the NPV of both of these is very high, false-positive rate is very low, and I think it, you know, it's thought provoking in the sense that, Can we use these very powerful urine markers to avoid cystoscopy, lessen the therapeutic burden, in especially the low- and intermediate-risk patients.

There also was a couple of interesting abstracts on BCG at the AUA. I think, overall, bladder cancer was very exciting. probably it was the year of the bladder, I think, for the AUA 2024.

Dr. Chu:

There were a couple of great studies on BCG, The first one was real-world experience, It's a Komodo claims database, which is inclusive of over 300-million patients, with, Medicare or Medicaid, claim data looking at, you know, just sort of really, really 30,000-foot perspective. essentially, there were 7,000 patients with non-muscle invasive bladder cancer who received BCG. more than half of them, so 65% of them, underwent adequate BCG induction described as, you know, at least 5 out of 6 cycles.

Of these, 50% underwent additional BCG of any sort, but only about a quarter had any evidence of maintenance.

About 14% of patients proceeded to cystectomy, which I think is an important number, and sort of in keeping with current literature. and then, less frequently, radiotherapy and, sort of, combination BCG interferon-alpha.

What I was surprised by, and I was wondering if you might want to comment on this, is that, you know, the use of immunotherapy was only about 5%, 5.5%, and this is a, sort of, an FDA-approved, you know, second-line therapy for BCG unresponsive disease. And I'm curious why, you think that number might be so low, since it sounds like it's something that, use in your practice.

Dr. Hafron:
We use, pembrolizumab in our practice for CIS refractory disease based on the, indication. But it's just systemic therapy. I mean, I think there's not huge appetite within the urology community for systemic therapies. I think, and what we'll highlight is, there's a lot of development going on in localized therapy for CIS refractory or BCG experienced, so I think there are significant systemic side effects, that potentially, can be avoided with localized disease.

Dr. Chu:
The last study that I wanted to highlight, is a podium that was presented by a group from the Memorial Sloan Kettering led by Eugene Pietzak, looking specifically at ERCC2, which is a DNA damage/repair gene. and it seems that these alterations are pretty prevalent.

So, the mutations present in 20% of non-muscle invasive, bladder tumors, and also associated with increased tumor mutational burden, or TMB. And we know high tumors are, more sensitive to BCG. They may be more immunogenic. And so, the recurrence free survival of these TMB high tumors, was improved with a hazard ratio of 0.55 compared to those with low TMB. And this effect was even more pronounced in the ERCC2 alteration recorded with a hazard ratio of 0.29.

This is retrospective data, but I do think it's very thought provoking to think that, you know, some of these alterations and these DNA damage/repair genes can make these tumors more sensitive to BCG. and in a world where we have constant shortages, we're trying to, at one point, you know – someday we will be stratifying patients to these different therapies. And so, sort of understanding some of the molecular underpinnings, which may render a tumor more sensitive to BCG, is an important, you know, piece of data. so, I thought that was nice, a kind of early biomarker study.

Dr. Hafron:
I think the concept of what's coming in the future is, you know, tissue typing, you know, bladder tumors and based on their gene or their genomic expression, will dictate how we treat it, which is, you know, true precision medicine. So, very exciting.

Dr. Hafron:
Let's shift gears a little bit and talk about TAR-200, a novel therapy that's under investigation in bladder. Before we get into some of the abstracts, Carissa, could you describe, you know, TAR-200? I call it pretzel therapy, but, you know, can you explain how it works?

Dr. Chu:
Yeah, so, TAR-200 does look like a little pretzel. it's about the size of a quarter. It's sort of a thin, tube that coils into a pretzel, and it floats around the bladder. and the idea is alludes over time. right now, single-agent, gemcitabine is what TAR-200 is. It's a drug that we know and love. We use it all the time, you know, after TURBT, in the post BCG setting, and it's well tolerated by patients. And I think that's the key. and, we know from, you know, just single intravascular gemcitabine that drug is washed out right away as soon as the patient urinates, more or less, but this allows for a much, much, longer duration therapy, in the bladder. And, so, there have been, a couple of studies of TAR-200, in some of these, you know, high demand groups of, you know, patient groups where we've really needed something after BCG, before cystectomy. and so, a couple of exciting trials were presented at AUA, this year.

So, the first one, is the SUNRISE-1 trial. That one's probably, along, quite a bit. And it's for BCG unresponsive, high-risk, non-muscle invasive bladder cancer with, CIS. all of these patients had CIS and there was a large percentage with CIS-only disease. and, TAR-200 was instilled into the bladder. So, how you do it is, in the office. Patient comes in for a cystoscopy, and the device is, sort of, just pushed into the bladder, at the time of cystoscopy and then exchanged, every 3 months.

And so, there was an 84% complete response rate without any retreatment allowed, and that's a pretty jaw-dropping number.

The one-year durability response was about 75%. and the complete response rate at data cutoff. And 4 out of 5 patients, you know, free

of recurrence, who had reached a 2-year follow-up

It was also quite, well-tolerated. there's SUNRISE-5. and so, this one was, TAR-200 versus chemotherapy, high-risk BCG experienced. A little bit more, inclusive with the prior BCG exposure. Papillary-only disease. and, the BCG experienced included any adequate induction. No maintenance was needed. Recurrence within 12 months. and, the sites for this study are, only just opening. Now there's also SUNRISE-3, and that's in BCG-naive patients, And this is TAR-200 plus or minus cetrelimab, which is a PD-1 inhibitor, versus BCG. So, now we're moving it, you know, earlier and we're seeing how well it does, against BCG in high-risk, non-muscle invasive, groups, so high-rate TA, T1 and CIS.

Dr. Hafron:
Yeah, it's just amazing, you know, all the SUNRISE trials going on. Also, what's interesting, too, is there's, other trials with TAR-200 looking at muscle invasive bladder cancer.

Dr. Chu:
This one is, a bladder-sparing trial, for muscle invasive disease. so, SUNRISE-2. believe it's a Phase 3 study, comparing, TAR-200 cetrelimab versus trimodal therapy. this study, is, looking at an endpoint of bladder intact event-free survival. So, is, muscle-invasive disease, nodal metathesis, radical cystectomy or death. So, pretty, inclusive event rate.

Dr. Hafron:
Clearly significant investment going on with TAR-200. we've been involved in many of these trials. I think what you see is that it's an easy application, it's very well tolerated, and that induction is typically 24 weeks, you know, 3 weeks of pretzel stays in for 3 weeks, usually for 24 weeks or 8 exchanges. And then typically, the patients will stay on some sort of maintenance regimen, which is quarterly, for one pretzel insertion for 3 weeks.

And I think what's cool is they've taken it to another level and they, were starting trials called MOONRISE. So, we've gone from SUNRISE to MOONRISE, and, investigating TAR-210, in non-muscle-invasive bladder cancer. And I think what's interesting is TAR-210, or the MOONRISE series, we only have one right now, is that erdafitinib, which is a different drug than the gemcitabine.

Dr. Chu:
So MOONRISE-1, so, this is TAR-210 now, so, the next iteration of the pretzel, comparing TAR-210 versus, intravesical chemotherapy in intermediate risk, non-muscle invasive bladder cancer with an FGFR3 alteration. a Phase 1 early study showed a really, 87% complete response in intermediate risk disease and 82 recurrence free in BCG exposed patients

Dr. Hafron:
Great points, great comments, Carissa. Thank you so much.

Unfortunately, that's all the time we have today. So, I want to thank our audience for listening in and thank you, Carissa, for your insightful discussion. Great speaking with you today.

Dr. Chu:
Jason, to you as well. Really enjoyed our conversation.

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