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What Is the Future of Neoadjuvant ARI Intensification in Localized Prostate Cancer?

Announcer:
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Dr. McKay:
Hi, my name is Rana McKay and I'm a GU Medical Oncologist at the University of California in San Diego. Today we're going to be talking about the future of new adjuvant ARI intensification in localized prostate cancer.

The treatment paradigm for patients with high-risk prostate cancer has not changed over the past several decades, and includes either radical prostatectomy followed by adjuvant or salvage radiation and androgen deprivation therapy, or upfront definitive radiation with androgen deprivation therapy. Neoadjuvant therapy prior to radical prostatectomy is still under investigation. And neoadjuvant therapy is the standard for other tumors such as breast cancer, rectal cancer, bladder cancer, and given that it's been associated with improved long-term outcomes. Treatment results in local disease downstaging, which may facilitate surgical resection, may reduce or delay post-surgery treatment and provides an in vivo assessment of treatment response.

Historic neoadjuvant trials conducted in the early 1990s investigated LHRH agonists with or without first generation antiandrogens. And the intent of these initial studies was to evaluate the positive surgical margin rate at the time of radical prostatectomy. The majority of patients enrolled were low risk, and these trials didn't really systematically evaluate pathologic response, and long-term follow-up was limited. However, the advent of more potent antigen-targeting agents such as abiraterone, enzalutamide, apalutamide, which have demonstrated efficacy for patients with metastatic disease, provides an opportunity to investigate these agents in the neoadjuvant setting. And these more contemporary studies evaluated patients with high-risk disease, integrated systematic central pathology review to evaluate pathologic response post-treatment and embedded long-term follow-up.

So over the past 10 years, we've conducted a series of these neoadjuvant trials that have sequentially built on our understanding of disease biology. And acknowledging the limitations of phase 2 studies, these studies demonstrated that there was a signal that pathologic responses are observed with potent hormonal therapy in a subset of patients with high-risk disease.

One of the central tenants of neoadjuvant therapy is that pathologic response correlates with long-term outcomes, and a pooled analysis of three contemporary neoadjuvant studies was conducted. And with a median follow-up of around 3.4 years, there were no recurrences that were observed in patients who had a path CR or MRD at radical prostatectomy, and 88% of patients have testosterone recovery by 1 year post therapy completion.

There's been data that have been evaluating molecular features of exceptional responders. And this is data derived from multiregional pretreatment biopsies in exceptional responders and non-responders. And we demonstrated that SPOP alterations were exclusively observed in exceptional responders and PTEN, P53 alterations with increased TGF beta signaling was seen in non-responders.

So the critical paths for the future of neoadjuvant therapy really revolve around defining standardized pathologic endpoints, the

surrogacy of these pathologic endpoints with metastasis-free survival and overall survival, the integration of biomarkers to optimize therapy selection, and also the integration of imaging to assess response.

The PROTEUS trial is a large phase 3 trial looking at perioperative apalutamide in patients with high-risk localized disease who are candidates for radical prostatectomy that will certainly help with defining the landscape for patients with localized high-risk disease. Additionally, the ATLAS study is looking at apalutamide in combination with radiation therapy, given the neoadjuvant, concurrent and adjuvant to radiation therapy, compared to just ADT alone given with radiation treatment.

So in conclusion, currently, there are no phase 3 data to support neoadjuvant systemic therapy with radical prostatectomy. The phase 2 data shows promise for ADT with second generation ASRIs, and demonstrated favorable pathologic responses, minimal residual disease, and PSA relapse in salvage therapy rates. The phase 3 PROTEUS trial which has now completed accrual of over 2,000 patients had a co-primary endpoint of pathologic response MRD with MFS, and this will be a critical study. And future studies are going to integrate biomarkers which can help better help us with risk stratification of therapy for patients with localized disease.

Thank you so much for watching with us today.

Announcer:
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