Controversies in Prostate Cancer Treatment

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In this segment of the ONCONVO oncology conversations, esteemed experts deliberated on the efficacy and safety outcomes presented by the SPARTAN trial for non-metastatic castration-resistant prostate cancer (nmCRPC), as well as its impact on shaping healthcare practitioners' approach to managing the condition.

Q1. What were the key findings and significant treatment effects observed in the SPARTAN trial for nmCRPC, particularly in terms of efficacy and safety outcomes?

Dr Matthew Smith

The data surprised not only me but also others involved in designing the trial, due to the robustness of the efficacy and safety results. The SPARTAN trial focused on nmCRPC, which involved patients experiencing rising prostate-specific antigen (PSA) levels despite androgen-deprivation the rapy, without detectable metastasis using conventional imaging, and included those with a higher risk of progression based on a PSA doubling time of under 10 months.[1]

The efficacy data covers secondary endpoints such as time to metastasis, progression-free survival, time to symptomatic progression, and most notably, overall survival. The treatment effect observed was striking, with a substantial hazard ratio of 0.284 for distant metastasis or death, translating to a remarkable 72% reduction in the risk of metastasis or death. Over an extended follow-up period, the SPARTAN trial reported a striking improvement in overall survival by over a year, favouring the addition of Apalutamide. In addition, the benefits in terms of metastasis-free survival were consistently observed across all predefined subgroups, encompassing PSA doubling time, previous use of bone-sparing agents and locoregional disease.[1]

> "The most surprising revelation was the improvement in overall survival by over a year, favouring the addition of Apalutamide."
>
> – Dr Matthew Smith

Q2. What led to your positive surprise regarding the data surpassing your expectations, and in your opinion, what is the primary factor contributing to the notable success of this trial?

Dr Matthew Smith

Positive studies like this one, as well as numerous others, may seem straightforward in hindsight; however, during the design phase and forward-looking perspective, it presents a distinctly different narrative. Consequently, misconceptions about this disease state were prevalent, with many assuming that these patients likely succumb to other causes—an assumption that contradicts reality. Most patients with nmCRPC indeed die from prostate cancer itself. While there was an initial belief in the potential of early Apalutamide introduction to enhance metastasis-free survival, the magnitude of improvement achieved was unexpected.

> **"The magnitude of improvement achieved [by early introduction of Apalutamide] was unexpected."**
> **– Dr Matthew Smith**

Additionally, the prospect of demonstrating an overall survival improvement in this disease context was almost universally regarded as implausible. Remarkably, all these assumptions have been substantiated by the data, not solely in this study but also in two other investigations* involving nmCRPC, yielding analogous observations. The collective evidence strongly bolsters the credibility of these pivotal findings.

Q3. How will the results of the SPARTAN trial change HCP's practice in managing nmCRPC?

Dr Loh Chit Sin

The patient cohort represents a small subset within the spectrum of individuals diagnosed with prostate cancer and their numbers are relatively limited. Malaysia, for instance, falls within this category. The significance of the SPARTAN trial lies in its capacity to shed light on the efficacy of agents in specific disease stages. Our prior conversation delved into prostate-specific membrane antigen positron emission tomography scans, and M0 CRPC likely encompasses micrometastatic CRPC, which I believe comprises most of such cases. Essentially, the utilisation of drugs like this across different disease stages appears to yield positive outcomes. While the COU-AA trial data focuses on later-stage CRPC, this pertains to what conventional imaging identifies as M0, essentially signifying micrometastatic CRPC.

> **"The significance of the SPARTAN trial lies in its capacity to shed light on the efficacy of agents in specific disease stages."**
> **– Dr Loh Chit Sin**

The intriguing aspect is that intervention during this disease phase produced an impact that is notably and conspicuously pronounced, suggesting the possibility of initiating treatment at even earlier stages. In fact, it appears that the most remarkable outcomes arise from studies where intervention occurs at the disease's earlier stages.

COU-AA, Chemotherapy-Naïve Men with mCRPC receiving Abiraterone Acetate plus Prednisone; **SPARTAN**, Selective Prostate Androgen Receptor Targeting with ARN-509

Reference:
1. Smith MR, et al. *New Engl J Med* 2018;378:1408-1418.

*Apart from the SPARTAN (apalutamide) trial, the PROSPER (enzalutamide) and ARAMIS (darolutamide) trials have demonstrated an improved overall survival for men with nmCRPC.

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