Dr. Fred Saad, Professor and Chief of Urology, Director of Urologic Oncology, Centre hospitalier de l’Université de Montréal, traced recent progress in the treatment of metastatic prostate cancer.

SUMMARY: Dr. Saad contrasted the current landscape to the situation even 5 years ago, when a patient with metastatic castration resistant prostate cancer (mCRPC) would have had only docetaxel as an option in terms of life-prolonging therapy, along with supportive care from zoledronic acid or denosumab. Today, as seen in Figure 2, there are options in the post-docetaxel and pre-docetaxel spaces: he emphasized the importance of having things to offer patients for whom docetaxel is not an option. “The M0 prostate cancer space is one we basically created,” said Dr. Saad, “and in some countries it is still not recognized, and hormone therapies are reserved for metastatic patients.” He considers, however, that there is enough data to support starting androgen deprivation therapy (ADT) to delay metastatic state and improve survival. While it appears clear that targeting the androgen receptors will delay disease, clinical trials are needed to show whether it will delay symptoms and death.

HAVE WE MADE A SIGNIFICANT DIFFERENCE?
The 2004 docetaxel study showed a median survival of 18.9 months; in the recent PREVAIL study with enzalutamide, survival reached 35.3 months, and many centres are seeing mCRPC patients survive beyond 3 years. There is no indication that the patients today are different from those in the early docetaxel studies, half of whom were asymptomatic upon entry. “We can tell patients who come in today with mCRPC,” said Dr. Saad, “that if they are in reasonable condition, are able to and accept to go on to multiple lines of therapy, that we can hope to go beyond 3 years median survival. We now have patients living more than 5 years.”

In managing these patients, androgen receptor pathways are targeted either by reducing production of androgen synthesis or attacking the androgen receptor itself. “Even though we call this hormone-refractory,” stated Dr. Saad, “we now understand that they are still hormone-sensitive to a certain extent and probably much more sensitive to minute amounts of androgens.”

The post-docetaxel studies with abiraterone and enzalutamide showed a significant improvement in OS with abiraterone (4.6 month improvement) and with enzalutamide (4.8 month improvement). However, half the patients in Canada were prevented from getting enzalutamide or abiraterone when it was limited to the post-docetaxel space. Dr. Saad stressed the fact that, in many Canadian provinces, where you live determines whether or not you receive chemotherapy. “In our centre, among patients who come in and are well, probably 80% are getting docetaxel at some point, whereas in other centres it’s as low as 20% of patients getting docetaxel before dying of the disease.” The COU-AAA-302 and PREVAIL studies randomized chemotherapy-naive patients to placebo or abiraterone or enzalutamide, respectively, and both drugs clearly delayed the progression of metastatic lesions. Data published in a subgroup analyses in Lancet Oncology showed that patients with no pain, and prostate-specific antigen (PSA) and alkaline phosphatase below the median, gained greater overall survival (OS) benefit from starting these new agents early.
Dr. Saad considers that bone-targeted therapies remain relevant to prevent morbidity and lower the cost of complications that come mainly from the bone. Earlier studies of zoledronic acid showed decreases in all skeletal-related events (SRE), and reduced need for radiation therapy for pain relief and spinal cord compression. A study of denosumab showed even greater improvement in time to first SRE, and a trial of radium-223 showed not only delays to SREs but also OS improvements. It also helped to understand when these drugs are best used. “Patients with higher alkaline phosphatase seem to get a little more benefit,” said Dr. Saad, “showing that you need to have at least a minimal amount of bone turnover for the drug to be picked up.” Further analyses of the COU-AAA-302 abiraterone study found that the 40% of patients who were on bone-targeted therapy during the study saw a delay in the appearance of pain, better Eastern Cooperative Oncology Group (ECOG) performance status and possibly even an OS benefit. A UK study of docetaxel likewise found that patients who were also on zoledronic acid had a 5-month improvement in the appearance of SREs. In the radium-223 study as well, patients who continued on bisphosphonates saw an over 9-month improvement in time to first symptomatic SRE.

GUIDELINES FOR NEW AGENTS
Dr. Saad presented guidelines established by a consensus group chaired by himself and Dr. Kim Chi, based on an analysis of all available literature on new agents to attempt to answer questions around sequencing and cross-resistance. Figure 3 on page 22 presents the algorithm.

Dr. Saad concluded by providing practical recommendations for managing mCRPC:
• Wait at least 3 months before deciding if hormonal agents are effective or not, as PSA often goes up before it comes down. Clinical trials did not conduct measurement before 3 months, so there are no data available on these mechanisms.
• If PSA declines and then rises in an asymptomatic patient, reimaging should be done. If patients have not previously seen a medical oncologist, this is a good time for the treating urologist to get them involved, because these patients are going toward a next line of therapy where a real multidisciplinary approach needs to be taken.
• If on imaging no new metastases are seen and patients are asymptomatic, they can either be monitored or started on chemotherapy.
• If patients are clearly progressing, chemotherapy should be started as early as possible. Waiting too long risks shortchanging patients.
• Upfront chemotherapy can be considered if there is significant discordance between PSA levels and burden of metastatic disease; in patients with visceral metastases; in patients who are short responders to ADT; and in moderately or severely symptomatic patients.

Dr. Saad anticipates progress coming from a multimodal approach to mCRPC rather than a sequential approach, which is less and less used in other solid tumour models. “The first glimpse of that as a successful approach is in the hormone-sensitive setting, where upfront hormones and

FIGURE 2. Treatment landscape of mCRPC

mCRPC=metastatic castration-resistant prostate cancer. Courtesy: Dr. Fred Saad.
chemotherapy have really led to the most spectacular improvement in OS we have seen in prostate cancer so far.” Finally, Dr. Saad emphasized the need to balance quality of life and living longer, and to see both as reasons for treating patients.

References:

NEXT STEPS
- Early findings of an improvement in OS with the combination of radium-223 and abiraterone are now being validated in a prospective phase 3 study where both arms are getting abiraterone, and half the patients will get radium in a setting of asymptomatic mCRPC.