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Proceedings from the SIU B2B Uro-Oncology: GU Cancers Triad Virtual Meeting
November 7–8, 2020
Bladder Cancer

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#B2BGUCancerTriad
Dr. Wes Kassouf (Canada) presented practice-changing advances on the horizon for BCa. One of these advances is immunotherapy optimization for bacillus Calmette-Guérin (BCG)-unresponsive NMIBC, with an ultimate goal of avoiding or postponing radical cystectomy (RC). This is important because RC is associated with significant mortality, especially in frail and elderly patients[1].

The novel gene therapy nadofaragene firadenovec, a replication-deficient recombinant adenovirus that delivers human interferon alfa-2b complementary DNA (cDNA) into the bladder epithelium, was investigated in a recent study[2] in this context. Complete response (CR) among patients with carcinoma in situ (CIS) was 53.4%, and all CRs occurred within 3 months of first treatment. At 12 months, the rate of high-grade recurrence-free survival was 30.5%, including a rate of 24.3% among patients with CIS and 43.8% among those with papillary disease. Progression to muscle-invasive disease remained low at 4.8% in the CIS patient population and 6.2% in the papillary disease population. This treatment was quite tolerable, with a grade 3 adverse event rate of 3.8%.

In the MIBC space, RC is the traditional approach, offering a 5-year overall survival (OS) of about 60%[3], but more than 80% of patients have no effective perioperative systemic therapy option. Recently, several studies exploring various combinations of immunotherapy, sometimes with the addition of chemotherapy, in the neoadjuvant setting demonstrated impressive CRs of approximately 40%[4–10]. There are three trials in the adjuvant setting: AMBASSADOR[11], IMvigor010[12], and CheckMate 274. The latter trial randomized patients to nivolumab versus placebo at cystectomy. A recent press release reported that the trial met its primary endpoint of improvement in disease-free survival (DFS) in the nivolumab arm in the entire population as well as in those with high programmed death-ligand 1 (PD-L1) tumour expression.

Immunotherapy can also be integrated with trimodal therapy (TMT), in both the adjuvant and neoadjuvant setting. Dr. Kassouf’s preclinical work combining immune checkpoint inhibition with radiation showed anti-tumour activity in situ, where the tumour was radiated, as well as an abscopal effect[13]. There are currently several clinical trials looking at this approach, which will answer lingering questions, not least of which is whether the sequence of treatment will affect efficacy or toxicity.

In the metastatic disease setting, results of the JAVELIN Bladder 100 trial[14] have led to approval by the United States Food and Drugs Administration (FDA) of avelumab for first-line maintenance therapy in patients with advanced disease, independent of PD-L1 expression. These are practice-changing findings.

Next, Dr. Tilman Todenhöfer (Germany) discussed recent developments in NMIBC that address three important challenges: 1) lack of adequate models to sufficiently predict progression risk and long-term response to BCG; 2) worldwide BCG shortage; and 3) lack of options for patients with recurrence after BCG.
One important step in understanding of NIMBC was the comprehensive profiling of 460 tumors in the UROMOL project[15]. The study identified three distinct classes that differ by gene expression and prognosis, and 81% of tumors that progress to muscle-invasive disease belonged to class two. Transcriptome analysis may help improve risk stratification of T1 tumors treated with BCG-induction and maintenance therapy[16]. There remains significant interest in identifying risk factors that can be assessed with standard pathology lab equipment, such as lymphovascular invasion. A meta-analysis of more than 1,000 patients confirmed the relevance of lymphatic and blood vessel invasion for predicting progression[17], which can be detected via immunohistochemistry[18].

Dr. Todenhöfer discussed the potential to reduce the number of BCG installations or lower the doses per installation, to help address worldwide shortages, particularly in the developing world. The NIMBUS trial[19] demonstrated that reducing the number of installations leads to a significant increase in recurrence, but a European Organisation for Research and Treatment of Cancer (EORTC) trial[20] revealed that lowering the dose of BCG may be safe. One study suggested mitomycin may be a reasonable substitute[21], but access to this drug is limited in many countries, as are options to enhance mitomycin efficacy.

When no other reasonable treatment option is available, RC should be discussed with the patient. No randomized trials have compared early versus deferred RC, but a retrospective study comparing immediate RC in 175 BCG-naïve patients versus delayed RC after BCG failure in 99 patients revealed a greater than 10-year OS with the immediate approach[22].

In the setting of BCG-unresponsive disease, most guidelines recommend RC. However, new developments in this field are likely to increase use of bladder-sparing approaches, such as intravesical drug administration. A retrospective series of patients treated with a combination of intravesical docetaxel and gemcitabine revealed high-grade recurrence-free survival rate of 50% in patients with CIS and 58% in patients with papillary disease after 2 years[23].

There is continued effort to improve intravesical drug efficacy and delivery. Hyperthermia-induced mitomycin, frequently used in Europe, has shown promise[24–25], as has use of the TAR-200 (GemRIS™), which is inserted into the bladder using a transurethral catheter to allow slow, continuous release of chemotherapy[26]. The TAR-200 device will be used in a prospective randomized trial comparing this method with standard of care and intravesical chemotherapy.

In a recent phase 3 study of patients with BCG-unresponsive disease, installations of the protein fusion drug oportuzumab monatox resulted in a 3-month CR of 40% in patients with CIS[27]. In addition, two single-arm trials have assessed the use of systemic immunotherapy in patients with BCG-unresponsive CIS. Pembrolizumab[28] and atezolizumab[29] showed similar efficacy, with 6-month CR rates of 31% and 27%, respectively. Pembrolizumab has been approved in this setting, based on the Keynote 057 trial, which showed that systemic immunotherapy has a relatively moderate risk of progression to muscle-invasive disease from delay of RC[28].

In BCG-naïve patients, three trials are investigating the use of combined BCG and immunotherapy. The POTOMAC trial combines BCG with durvalumab. ALBAN combines it with atezolizumab, and CREST combines it with sasanlimab.

Ongoing trials are investigating the use of targeted systemic therapies in patients with BCG-unresponsive disease. In the THOR 2 trial, patients with fibroblast growth factor receptor (FGFR) alterations are treated either with the FGFR inhibitor erdafitinib or with standard care intravesical therapy. The proportion of patients with FGFR mutations in the NMIBC setting has shown to be higher than in the metastatic setting.

Next, Dr. Arjun Balar (United States) focused on MIBC. He noted that neoadjuvant chemotherapy has been the standard of care for years. Nevertheless, pathologic response to treatment cannot be assessed unless a cystectomy is performed.
Recent clinical trials, notably ABACUS[5] and PURE-01[4], suggest a role for neoadjuvant checkpoint inhibition among patients who are not eligible for cisplatin-based therapy or who decline it. When compared with chemotherapy, checkpoint inhibitors provide a pathologic CR rate of roughly 30% to 35%. The NABUCCO[6] study, which used ipilimumab and nivolumab, also demonstrated promising CR rates. However, this is a small study of only 24 patients. Studies in which checkpoint inhibitors are combined with chemotherapy include HOG GU14-1887 and BLASST[8]. The DUTRENO[9] and MDACC[10] studies combined immunotherapy with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)-based therapy. In these studies, pathologic CR was comparable, at 30% to 40%. An important unanswered question is whether neoadjuvant therapy can prevent or delay the need for RC.

Ongoing phase 3 trials of neoadjuvant immunotherapy in patients with MIBC include NIAGARA, comparing durvalumab plus chemotherapy with chemotherapy alone, as well as ENERGIZE, comparing chemotherapy + nivolumab versus chemotherapy alone versus nivolumab + chemotherapy + BMS 986205 (an IDO1 inhibitor that is administered orally along with nivolumab). KEYNOTE 866 is comparing chemotherapy + pembrolizumab with chemotherapy alone in cisplatin-eligible patients. KEYNOTE 905 is looking at pembrolizumab followed by RC versus RC alone in cisplatin-ineligible patients. An additional trial is comparing neoadjuvant and adjuvant nivolumab + NKTR-214 (a CD122-preferential IL2 pathway agonist) with nivolumab alone or standard of care. Primary endpoints include pathologic CR, but ultimately it will be necessary to determine the rate at which patients develop recurrence and whether pathologic CR predicts recurrence risk.

In the adjuvant setting, IMvigor 010[12] results sounded a cautionary note about DFS with adjuvant atezolizumab. This study involved patients with high-risk bladder cancer and upper tract urothelial cancer. Atezolizumab, at least in this setting, appears to delay recurrences very little, and the trial did not meet its primary endpoint of DFS. Subgroup analyses revealed no major differences in outcomes based on PD-L1 expression. Ongoing trials in the adjuvant setting include CheckMate-274 and AMBASSADOR[11].

The second half of Dr. Balar’s talk was focused on bladder preservation via immunotherapy and other strategies. TMT focused on bladder preservation comprises maximal transurethral resection of the bladder tumour (TURBT), followed by a combination of radiation therapy and concurrent chemotherapy. Depending on the choice of agent, it could also have some effect on micrometastases. The optimal chemoradiation regimen is yet to be identified, but weekly cisplatin is a reasonable choice. TURBT has better outcomes when the tumour is resected completely[30–31]. When it comes to radiation versus cystectomy, a retrospective risk-matched matched analysis demonstrated that tumour biology drives outcomes[32].

Another potential bladder-sparing approach is to incorporate immunotherapy into the treatment of early-stage disease. Several trials are investigating how best to do this, but the threshold for effective therapy is high in MIBC. Data from the PACIFIC trial[33] demonstrated a survival benefit with the addition of immunotherapy to standard chemoradiation for stage III lung cancer, suggesting a potential for the addition of immunotherapy to TMT.

A phase 2 multicentre study is investigating outcomes of a single dose of immunotherapy, maximal TURBT, followed by a combination of radiation, chemotherapy, and immunotherapy concurrently. The patients then receive transurethral resection of the tumour bed 12 weeks later. They are targeting enrolment of 54 patients, and a primary outcome is bladder-intact-disease-free survival (BIDFS). Hopefully, the addition of immunotherapy will expand tumour resident T-cell clones, which could then be used as a predictive biomarker. The potential to use this biomarker to differentiate responders from non-responders has been investigated in patients receiving systemic immunotherapy for advanced bladder cancer. In responders, T-cell clone expansion, T-cell diversity, and improved T-cell clonality was observed[34].

Dr. Balar discussed how this knowledge can be applied in the real world. Patients with small tumors located in the bladder dome would be ideal for bladder preservation approaches, while those with large tumors and extravesical extension are ideal candidates for cystectomy. For an “in between” case, such as patient with
a multifocal tumour, no hydronephrosis, and some CIS. Ongoing clinical trials will help elucidate whether bladder preservation is feasible.

Several trials are examining the impact of combining immunotherapy with chemoradiation. The phase 3 SWOG 1806 trial is looking at bladder preservation in the form of chemoradiation with or without atezolizumab in patients with MIBC who refuse or are not candidates for cystectomy[35]. KEYNOTE 992, a multinational trial led by Merck, is similar, except pembrolizumab is being used in place of atezolizumab and patients also undergo maximal TURBT[36]. In both of these trials, BIDFS or event-free survival are primary endpoints. In the CCTG BL 13 study, patients with MIBC undergo TMT, followed by treatment with durvalumab or surveillance. The primary endpoint is DFS.

The fourth talk was by Dr. Srikala Sridhar (Canada), who provided an update on systemic therapy for advanced disease, with a focus on the metastatic setting. In the first-line setting, the JAVELIN 100 study demonstrated excellent outcomes of avelumab maintenance therapy for patients with advanced metastatic urothelial cancer[37]. OS in the arm that received avelumab was 21.4 months, compared with 14.3 months in the best supportive care arm, with a hazard ratio of 0.69. All subgroups benefited regardless of whether they received gemcitabine-cisplatin or gemcitabine-carboplatin as frontline chemotherapy. They also benefited regardless of whether they had stable disease, a partial response (PR), or a CR to frontline chemotherapy. No established biomarkers clearly predicted outcomes, including PD-L1 expression, tumour cell expression, immune cell expression, tumour mutational burden, and gene signatures.

This study raises some key questions: How many cycles of upfront chemotherapy are ideal? What happens with second-line immunotherapy? What about the subset of patients who do not respond to first-line chemotherapy?

IMvigor 130[38] and KEYNOTE 361[39] looked at combination therapies in similar populations of patients with advanced BCa, although use of carboplatin was greater in IMvigor 130. IMvigor 130’s treatment arms included atezolizumab versus atezolizumab + chemotherapy versus chemotherapy alone. The KEYNOTE 361 study compared pembrolizumab alone, pembrolizumab + chemotherapy, and chemotherapy alone. The mono-therapy arms in both of these studies were halted by the FDA because patients with low PD-L1 expression had decreased survival.

In both trials, improvement in PFS was modest, at 1 to 2 months. In terms of OS, an interim analysis of IMvigor 130 showed that it did not meet the prespecified threshold. The key learning from these trials is that the combined approach does not yield hoped-for outcomes, nor is a synergistic effect likely. In fact, there is some question as to whether immune checkpoint inhibitors and chemotherapy may be antagonistic. It is unclear how much benefit was achieved from simply maintaining immunotherapy and whether older, frailer patients would be able to tolerate these regimens. The financial impact must also be considered. Finally, it is unclear whether biomarkers can be used to guide therapy.

DANUBE[40] was another study looking at combination therapy, this time comparing durvalumab + the CTLA-4 inhibitor tremelimumab with chemotherapy. The OS with durvalumab versus chemotherapy in the PD-L1 high group, and the OS with durvalumab + tremelimumab in the intent-to-treat group did not meet the prespecified thresholds. However, the secondary endpoint of OS in the durvalumab + tremelimumab in the PD-L1-high population did show a benefit. Similarly, the objective response rate (ORR) in the PD-L1-high population treated with durvalumab + tremelimumab approached the response rates observed with chemotherapy.

Key learnings from DANUBE are that standard chemotherapy is quite effective in the frontline setting, but the response to durvalumab + tremelimumab in the PD-L1-high group was encouraging and warrants further study. The findings have renewed interest in CTLA-4 inhibitors and raises the question of how ipilimumab + nivolumab might perform.

Pooling together data from DANUBE, IMvigor 130, and KEYNOTE 361 reveals that immune checkpoint inhibitor monotherapy and chemotherapy produce similar outcomes in the overall intent-to-treat population.
When looking specifically at the PD-L1-high group, however, there is a significant amount of variability, indicating a need for further research.

One exciting novel approach in advanced BCa is use of the antibody-drug conjugates (ADCs). Enfortumab vedotin, an ADC, targets nectin-4, which is highly expressed in metastatic urothelial cancers. The chemotherapy component is monomethyl auristatin E (MMAE), a microtubule-targeting agent. Another ADC, sacituzumab govitecan, uses TROP2 as an antibody, and the chemotherapy is SN38, which is a prodrug to irinotecan.

Enfortumab vedotin was evaluated in the EV-201 study[41], which comprised patients with disease that progressed on platinum and immunotherapy. In this study, ORR was 44%, PFS was 5.8 months, and OS was 11.7 months. Benefits were observed across all subgroups, including patients with prior exposure to immune checkpoint inhibitors and taxanes and in those with liver metastases. There were a few discontinuations, but peripheral sensory neuropathy was identified as a potentially problematic toxicity. The EV-301 phase 3 study compared enfortumab with chemotherapy. A recent press release reported that this is a positive trial, with an improvement in OS.

Also in the third-line setting, studies are underway on the combination of enfortumab vedotin and pembrolizumab. EV-103[42] enrolled 45 patients and showed an ORR of 71%, which rivals what is seen with chemotherapy. Further larger studies are needed to confirm these results.

The phase 2 TROPHY study[43] evaluated sacituzumab govitpecan in the third-line setting, reporting an ORR of 31%, PFS of 6.4 months, and immediate OS of 10.5 months. Treatment-related adverse events were similar to chemotherapy. Three patients discontinued due to neuropsychiatric complications, and 30% required granulocyte colony-stimulating factor support. A phase 3 trial is planned.

Another rapidly evolving area is in the use of FGFR inhibitors. These target specific FGFR mutations or translocations, which occur in about 15% to 20% of BCa patients. The BLC 2001 study[44] led to the accelerated approval of the FGFR inhibitor erdafitinib. This study had an ORR of 40%, a PFS of 5.5 months, and a median OS of 11.3 months in a subset of patients who have FGFR2/3 alterations. Key toxicities with erdafitinib were hyperphosphatemia, eye changes, and nail changes. Erdafitinib is being tested both in the post-platinum and the post-immunotherapy setting among patients with FGFR2/3 alterations.

Following the four presentations, attendees were given the opportunity to ask questions. This discussion led to some key learnings. Notably, a role for systemic therapy is continuing to be investigated for MIBC, with efforts focused on biomarkers, such as deleterious mutations in DNA damage repair proteins, to help identify patients who may respond to cisplatin-based chemotherapy. Secondly, it remains unclear whether squamous cell carcinoma of the bladder could be optimally treated with an approach different from that used for standard BCa. Studies of immunotherapy of squamous cell carcinoma at other organ sites show promising results. Thirdly, the faculty asserted that there should not be an age cut-off for BCG therapy. Rather, patient condition, such as the ability to keep the drug in the bladder for two hours, should be taken into account. In terms of combining therapy with BCG, the preferred choice is currently docetaxel-gemcitabine, although this is based on retrospective data only. Combining BCG with pembrolizumab should be considered in regions where it is available for this indication.

The session wound up with a case-based discussion on management of immune-related adverse events and toxicities. This was led by Dr. Kilian Gust (Austria). He started with recommendations on management of diarrhea, which is not uncommon with use of some of the new checkpoint inhibitors. It usually starts around cycle 2 or 3. When it occurs, other causes must be ruled out, so stool should be sent for culture. Treatment involves early initiation of steroids, with increased doses if symptoms persist. Start a slow taper to avoid flares or steroid-induced side effects, such as fatigue. Therapy involves early initiation of steroids, with increased doses if symptoms persist. Start a slow taper to avoid flares or steroid-induced side effects, such as fatigue. Therapy should continue for 1 to 2 months. Diarrhea may recur at a later date, requiring another steroid treatment. These patients require close follow-up. Consider a colonoscopy and have a low threshold for stopping immunotherapy to let symptoms resolve, then potentially re-initiate if feasible.
Other immune-related toxicities that can be quite problematic include skin manifestations and arthralgia. These can have a significant impact on patients’ quality of life. Thus, it may be wise to consider other treatment options. In these patients, chemotherapy maybe doubly beneficial because of its immune suppression.

Some patients may need to discontinue immunotherapy all together. Consider this approach when side effects are severe and difficult to control, particularly if the patient does not appear to be experiencing major benefits from the therapy. Conversely, if the benefits appear high, it may be worthwhile to continue immunotherapy, with the addition of a low dose of prednisone.

Immune-related nephritis and pancreatitis are additional problems that might be encountered. However, amylase and lipase elevation are common in patients who receive treatment with immune checkpoint inhibitors, and this must be differentiated from clinically evident pancreatitis and nephritis. When nephritis is suspected, consult with a nephrologist. There may be a need for kidney biopsy, often preceded by steroid therapy.

Finally, immune-related pneumonitis may be encountered. Dr. Gust discussed a patient with this side effect who responded well to long-term prednisone, but ultimately landed in the intensive care unit with secondary adrenal insufficiency. While such cases are rare, it is important to recognize the possibility that they will arise.

Abbreviations Used in the Text

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ADC</td>
<td>antibody-drug conjugates</td>
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<tr>
<td>BCa</td>
<td>bladder cancer</td>
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<tr>
<td>BCG</td>
<td>bacillus Calmette-Guérin</td>
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<tr>
<td>BIDFS</td>
<td>bladder-intact-disease-free survival</td>
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<tr>
<td>cDNA</td>
<td>complementary DNA</td>
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<td>CIS</td>
<td>carcinoma in situ</td>
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<td>CR</td>
<td>complete response</td>
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<td>CTLA-4</td>
<td>cytotoxic T-lymphocyte-associated protein 4</td>
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<tr>
<td>DFS</td>
<td>disease-free survival</td>
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<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
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<td>FDA</td>
<td>United States Food and Drug Administration</td>
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<td>FGFR</td>
<td>fibroblast growth factor receptor</td>
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<td>GU</td>
<td>genitourinary</td>
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<td>MIBC</td>
<td>muscle-invasive disease</td>
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<td>MMAE</td>
<td>monomethyl auristatin E</td>
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<td>NMIBC</td>
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<tr>
<td>ORR</td>
<td>objective response rate</td>
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<td>overall survival</td>
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<td>programmed death-ligand 1</td>
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<td>progression-free response</td>
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<td>PR</td>
<td>partial response</td>
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<td>RC</td>
<td>radical cystectomy</td>
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<tr>
<td>TMT</td>
<td>trimodal therapy</td>
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<tr>
<td>TURBT</td>
<td>transurethral resection of the bladder tumour</td>
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</table>
References


40. Powles T, van der Heijden MS, Castellano D, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. The Lancet Oncology. 2020;21(12):1574-1588. doi:10.1016/S1470-2045(20)30541-6


43. Loriot Y, Balar AV, Petrylak DP, et al. LBA24 TROPHY-U-01 cohort 1 final results: a phase II study of sacituzumab govitecan (SG) in metastatic urothelial cancer (mUC) that has progressed after platinum (PLT) and checkpoint inhibitors (CPI), Annals of Oncology. 2020;31:S1156. doi:10.1016/j.annonc.2020.08.2253

Proceedings from the SIU B2B Uro-Oncology: GU Cancers Triad Virtual Meeting

November 7–8, 2020

Kidney Cancer
The Bench-to-Bedside Uro-Oncology GU Cancer Triad Meeting was organized by the Société Internationale d’Urologie and was held online on November 7th and 8th. The session on kidney cancer took place on the morning of Saturday, November 7th. It was chaired by Dr. Simon Tanguay (Canada). This session covered topics on selecting appropriate treatment for renal cell carcinoma (RCC), upcoming practice-changing advancements, how to adapt RCC care to changing times, and how to address immune-related adverse events. In addition, there was a case-based discussion and question-and-answer session.

The first session was led by Dr. Christian Kollmannsberger (Canada). He discussed the selection of vascular endothelial growth factor (VEGF)-tyrosine kinase inhibitor (TKI)-targeted therapy or immunotherapy, which has become a major clinical focus in the wake of many recent clinical trials that have influenced the standard of care. With regard to combination immunotherapy, CheckMate 214[1] compared nivolumab + ipilimumab with sunitinib for treatment-naïve metastatic RCC and found a significant and maintained survival benefit in favour of nivolumab + ipilimumab in intermediate- and high-risk patients. With regard to the combination of immunotherapy and TKIs, KEYNOTE 426[2] compared pembrolizumab + axitinib with sunitinib in a similar group of patients and also found survival improvements with immunotherapy + a TKI. JAVELIN Renal 101[3] compared avelumab + axitinib with sunitinib as a first-line therapy for metastatic RCC and found an improvement in progression-free survival (PFS) with immunotherapy + a TKI, but the overall survival (OS) data are not yet mature. Finally, CheckMate-9ER[4] compared nivolumab + cabozantinib with sunitinib, also as a first-line treatment for metastatic RCC, which again revealed improved OS with the immunotherapy + TKI combination.

When selecting among the available treatment options, Dr. Kollmannsberger first described who should not receive certain therapies. Patients with a pre-existing autoimmune disease, particularly if this condition requires active therapy, should typically not receive combination immunotherapy. For patients with an autoimmune condition in remission, the likelihood that combination immunotherapy will reactivate the disease varies from condition to condition, and so should be used with caution. Combination immunotherapy should also be avoided in patients in whom high-dose steroid therapy is contraindicated or when high-level resources are not available to manage a severe immune-mediated side effect. On the other hand, TKIs should be avoided in patients with uncontrolled hypertension, posterior reversible encephalopathy syndrome, recent stroke or myocardial infarction (MI), poor renal function, or a recent hemorrhagic episode.

Another differentiating factor among these regimens is the rapidity and duration of action. VEGF TKI-based therapies appear to have a more rapid onset of action as well as better response and primary progressive disease rates than the combination immunotherapy regimens[2–4]. Thus, this may be the best option for patients who are very symptomatic and will not be able to tolerate a period of progression before a clinical response is observed. On the other hand, combination immunotherapy appears to offer a benefit in terms of late progression[1,5,6]. Longer follow-up is needed to confirm this, but for now, Dr. Kollmannsberger recommends choosing combination immunotherapy when the primary goal is complete response and long-term survival.

Next, Dr. Tanguay summarized five practice-changing advances on the horizon. The first of these is the shift in first-line therapy, which was largely driven by the clinical trials discussed in Dr. Kollmannsberger’s talk. Soon to be added to these data are the results of ongoing trials, notably COSMIC 313[7], comparing nivolumab + ipilimumab with and without cabozantinib in advanced RCC,
as well as CLEAR[8], comparing lenvatinib + everolimus or pembrolizumab with sunitinib in advanced clear-cell RCC. The expectation is that, within a few years, first-line options will expand significantly, and the challenge will be to choose the best option for individual patients.

Secondly, HIF-2 alpha inhibition with investigational MK-6482 is a promising avenue for novel therapy. It originally demonstrated benefit in Von Hippel-Lindau disease-associated RCC, where almost all patients responded with stable disease or reduction in tumour size[9]. It also had a positive impact on pancreatic lesions and hemangioblastomas of the central nervous system[9]. This well-tolerated drug is currently being investigated for clear-cell RCC[10].

Thirdly, predictors of response are becoming an increasingly urgent need as more and more effective therapies become available for RCC. Programmed cell death-ligand 1 (PD-L1) staining has not proven to be as helpful as once hoped. Other predictors currently being investigated include PBMR1 mutations as well as the gut microbiome and impact on response to immune checkpoint inhibitors[11,12]. In addition, genomic profile predictors of response to TKIs are being investigated[13,14], and liquid biopsy technology may aid in diagnosis as well as in profiling of patients likely to respond better to specific interventions[15].

Fourthly, adjuvant therapy has been a discouraging area in RCC, with multiple regimens failing to show benefit[16]. The long-lasting benefits of immunotherapy suggest it may be useful in the adjuvant setting, however. A number of studies are investigating this, and reports of their results should be available in the coming years.

Finally, recent research has helped shed light on when cytoreductive nephrectomy might prove useful. For instance, the CARMENA study demonstrated that cytoreductive nephrectomy with sunitinib did not provide benefits over sunitinib alone among intermediate-to-high-risk patients[17]. However, SURTIME suggested that deferring nephrectomy until after TKI therapy may be beneficial[18]. International Metastatic RCC Database Consortium (IMDC) risk factors can help clinicians determine who might benefit from cytoreductive nephrectomy. The role of this approach in the era of immunotherapy will become clearer as new data emerge.

Next, Thomas Powles (United Kingdom) discussed personalizing treatment in RCC and adapting to the changing times. He summarized the current European Society of Medical Oncology (ESMO) guidelines on the treatment of metastatic RCC, with first-line therapies being axitinib + pembrolizumab among unselected patients and ipilimumab + nivolumab for intermediate-to-poor-risk disease patients[19]. Results of CheckMate 9ER will likely lead to approval of nivolumab + cabozantinib first-line, which represents an exciting new option[4].

Biomarkers, other than IMDC criteria, are not currently used for treatment selection in RCC, largely because this cancer expresses very little tumour mutational burden and has high immune signatures[20]. Angiogenesis and immune-associated genetic biomarkers[21,22,23,24] as well as PD-L1 status[25,26] are being investigated for their ability to predict response to therapy.

Dr. Powles then shifted to speak specifically about how the coronavirus disease of 2019 (COVID-19) pandemic has influenced care for patients with RCC. Initially, in the face of poor and inconsistent data, services for diagnosis of cancer patients were largely closed down in some parts of the United Kingdom, but most existing cancer patients did not experience a pause in their treatment. VEGF TKI therapy was favored over combination immunotherapy, most nephrectomies were delayed, and oral therapy was used preferentially over intravenous therapy. The number of patients undergoing evaluation and treatment for cancer is not back up to pre-pandemic levels, and patients are presenting with more advanced disease. With more information, the approach has shifted, and there is confidence that another wave of COVID-19 will be managed more effectively.

There is no clear evidence that any treatment for RCC places patients at higher risk for COVID-19.27 In addition, there is no longer concern that hospitals will be unable to manage patients requiring hospitalization. Surgery and treatment are back to pre-pandemic protocols, with additional safety measures in place to minimize risk of spreading the virus. Patient education about how to minimize risk is essential, and follow-up is being conducted via telemedicine, when feasible.
Next, there was a case-based discussion on the management of oligometastatic RCC, which was moderated by Dr. E. Jason Abel (United States) and included input from a panel of experts comprising Dr. Kollmannsberger, as well as Dr. Jose Karam (United States) and Dr. Hirotsugu Uemura (Japan).

Some of the highlights that emerged during this discussion were difficulty in estimating the likelihood that a 77-year-old RCC patient with a large primary tumour and chronic kidney disease would require dialysis following cytoreductive nephrectomy. The recommendation from the panel was that the patient undergo the surgery, with continued monitoring of a slow-growing lung metastasis.

For a 50-year-old woman with an 18-cm renal mass with possible metastasis into the pancreas and psoas muscle and a level 3 inferior vena cava (IVC) thrombus, the panelists discussed upfront nephrectomy followed by reassessment or a combination of immunotherapy and a TKI, followed by surgery. This patient did undergo surgery and was found to have M1 grade 4 clear cell RCC. In the absence of clinical trial data to guide treatment in this patient, the panelists recommended close observation. After 12 months, she was found to have an enhancing right renal mass, which the panelists recommended treating locally.

In a third case, a 54-year-old male was found to have clear cell RCC with metastasis into the lungs, adrenals, and liver, during workup following discovery of a scalp nodule. The panelists recommended bone imaging and biopsy of the renal mass, as well as systemic therapy with combination immunotherapy with or without a TKI. The patient was treated with nivolumab + ipilimumab and was found to have an enlarging spleen and adrenal nodules. The panelists recommended aggressive surgery and continuation of systemic therapy or a switch of systemic therapy to address the growing masses. The patient underwent aggressive surgery, restarted nivolumab, and had stable disease for 12 months, but the primary tumour began to enlarge, with a small anterior nodule. A final recommendation by the panelists was additional surgery to remove the tumors. As there are little data to guide continued use of nivolumab, the decision is based on discussion of risks and benefits with the patient.

The final case was a 57-year-old male with fevers, night sweats, weight loss, cough, microscopic hematuria, and recent travel in Asia. Workup revealed pulmonary nodules, right renal mass, lymphadenopathy, and a left pelvic mass as well as multiple small pulmonary embolisms. The panelists recommended biopsy, which revealed grade 4 clear cell RCC from kidney biopsy and evidence of Castleman disease from biopsy of the pelvic mass. The panelists recommended a TKI with or without a programmed cell death protein 1 (PD-1) inhibitor. The patient developed gross hematuria with anticoagulation and was still having night sweats and fevers. The panelists recommended anticoagulation and/or combination immunotherapy. This patient underwent surgery, followed by nivolumab + ipilimumab, followed by nivolumab. Symptoms improved, but he developed brain metastases after 13 months. The panelists recommended continuing nivolumab, if the patient tolerates it well.

The final talk was by Dr. Brian Rini (United States), who discussed minimizing immune-related adverse events and maximizing efficacy in RCC. He explained that toxicity from immunotherapy arises as a result of inflammation within healthy cells. While any organ can be affected, the skin, gut, and liver are the most common targets. Most toxicity from immunotherapy occurs early in treatment, usually in the first 2 weeks to 2 months, although it can occur many months or even years later. Time to resolution is usually 18 to 24 weeks, but hypothyroidism and hypopituitarism may require lifelong replacement therapy. Immune-related adverse events can be a sign of anti-tumour activity, but it is important to consider how these toxicities, and their management, affect patients’ quality of life, said Dr. Rini. Data from CheckMate 214 suggest a major negative impact early on, which improves over time.

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Long-term, the goal is to treat patients with the minimum amount of therapy needed to manage the disease. Studies demonstrating durable response in some patients who discontinue therapy early suggests...
the potential inherent in this approach[1]. A number of trials are investigating the risks and benefits of stopping therapy among patients with an adequate response.

Immunosuppression with steroids is the mainstay of treatment for immune-related adverse events. Early evidence suggests this approach will not affect the efficacy of treatment[29,30]. Dr. Rini also addressed whether it is safe to give immunotherapy to patients with pre-existing autoimmune disease. To date, data on this to date are inconsistent, with outcomes depending on autoimmune disease type and severity, as well as the intensity of the immunotherapy[31]. Risks are lower with single agents than with combination immunotherapy.

With regard to specific immunotherapies, the risk of immune-related adverse events is higher with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors than PD-1/PD-L1 inhibitors and higher still when both types of agents are used in combination. With CTLA-4 antibodies, the risk is dose-dependent.

Common adverse events associated with TKIs, such as fatigue, hand-foot syndrome, and hypertension, must be kept in mind, as these drugs are frequently combined with immunotherapy. In general, adding immunotherapy to TKI therapy does not substantially increase risk of adverse events[3,32,33]. It remains unclear how long TKI therapy must be continued and at what dose, when balancing risk and benefit, in the context of both monotherapy and combination therapy. The anti-VEGF properties of TKIs are dose- and duration-dependent, but the immunomodulatory properties may not be. It is unknown if depth of response correlates with long-term outcomes[34,35,36]. Thus, how to balance the intensity and duration of anti-VEGF treatment in an immunotherapy + TKI regimen for maximal benefit/risk is unknown.

The session on kidney cancer closed with questions from the audience. One participant asked whether a patient with a very large tumour, such as that presented in the first case, might be preoperatively embolized. Dr. Abel replied that they do not take this approach, as embolization if often incomplete. Another question related to how to choose a systemic therapy regimen among patients with an IVC thrombus in whom cytoreductive nephrectomy is not considered a good option. Dr. Kollmannsberger said that IVC thrombi do not typically respond well to systemic therapy, so he would not base treatment selection on this clinical feature. A third question related to treatment selection among patients who are not overtly symptomatic. Dr. Kollmannsberger replied that the decision would be based on patient long-term goals, with combination immunotherapy selected for those aiming for long-term remission and immunotherapy + TKI selected for those primarily interested in minimizing side effects.

To a question about the role of positron emission tomography (PET) scanning in RCC, Dr. Uemura replied that it was not usually used but could be helpful for identifying metastatic disease, depending on the metastatic site. Finally, there was a question on when to consider use of cytoreductive nephrectomy among patients with stable disease on systemic therapy. To this, Dr. Tanguay replied that the data are not clear, but he would lean toward surgery in younger, healthier patients with clear-cut deep responses.
B2B: Kidney Cancer Summary

Abbreviations Used in the Text

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>CTLA-4</td>
<td>cytotoxic T-lymphocyte-associated protein 4</td>
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<tr>
<td>COVID-19</td>
<td>coronavirus disease of 2019</td>
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<td>ESMO</td>
<td>European Society of Medical Oncology</td>
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<tr>
<td>FGFR</td>
<td>fibroblast growth factor receptor</td>
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<td>genitourinary</td>
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<td>IMDC</td>
<td>International Metastatic RCC Database Consortium</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<td>overall survival</td>
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<td>programmed cell death protein 1</td>
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<td>PD-L1</td>
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<td>PET</td>
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<td>VEGF</td>
<td>vascular endothelial growth factor</td>
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References


15. Riazalhosseini Y et al., unpublished


B2B: Kidney Cancer Summary


Proceedings from the SIU B2B Uro-Oncology: GU Cancers Triad Virtual Meeting
November 7–8, 2020

Prostate Cancer
The Bench-to-Bedside Uro-Oncology GU Cancer Triad Meeting was organized by the Société Internationale d’Urologie and was held online on November 7th and 8th. The session on prostate cancer (PCa) took place on the morning of Sunday, November 8th. Dr. Christopher Evans (United States) and Dr. Peter Hammerer (Germany) co-chaired the session, which covered research topics and the identification of innovative treatments for localized PCa, locally advanced PCa, and metastatic PCa. In addition, there were three case-based discussions and a question-and-answer session.

The first talk, the state-of-the-art presentation, was led by Dr. Todd Morgan (United States). He discussed the decision-making involved in selecting PCa patients for germline testing of DNA repair mutations, as well as recent United States Food and Drug Administration (FDA) approvals of drugs for treating metastatic PCa linked to germline mutations. One in ten men with metastatic PCa have such mutations, the most common of which are breast cancer susceptibility gene 1/2 (BRCA1/2) and ataxia-telangiectasia mutated (ATM) mutations[1]. BRCA1/2 germline mutations are also linked to some breast, ovarian, and pancreatic cancer[2]. BRCA1/2 mutations in localized PCa increase the odds of metastasis three-fold over the odds of metastasis in PCa patients who do not carry these mutations, and median survival times are significantly reduced in these more aggressive cases[3]. Moreover, BRCA1/2 and ATM germline mutations are associated with with Gleason Score (Gs) upgrading in men on active surveillance (AS) and these germline mutations are much more common in lethal than in nonlethal localized PCa. However, the inherited susceptibility to PCa is complex and still poorly understood. To gain insight into genetic susceptibility, the National Comprehensive Cancer Network (NCCN) [4] has developed guidelines for assessment of familial risk for localized PCa, which include a determination of blood relatives with ovarian, breast, or pancreatic cancer. PCa patients at highest risk have both a strong family history of these cancers and intraductal/crribiform histology[5]. Following counselling, education, and informed consent, screening recommendations are made; multigene panel testing is recommended if genetic testing indicates pathogenic or likely pathogenic variants, or variants of unknown significance. This panel testing should be limited and targeted in its approach. AS is recommended for patients having localized PCa who are considered at low risk[6]. In contrast, multimodality treatment is recommended for patients at high risk; this would include those with metastatic castration-resistant PCa (mCRPC), 23% of whom have homologous DNA (HR DNA) repair pathway alterations (including BRCA1/2) and 8% of whom have germline findings[7].

Four clinical trials using poly(ADP-ribose) polymerase (PARP) inhibitors have shown promise for treatment of mCRPC. For those mCRPC patients with HR DNA repair defects, treatment with olaparib resulted in an 88% response in the small TOPARP-A trial[8]. A larger phase 2 trial with olaparib indicated a composite overall response of 83% in patients with BRCA1/2 mutations, and a 37% response in those with the ATM germline mutation[9]. Another PARP inhibitor, rucaparib, was tested in a phase 2 trial, TRITON2, and was shown to produce durable responses in patients with mCRPC and BRCA1/2 mutations. In this trial, PSA was assessed and found to decrease more than 50% from the baseline[10]. The FDA granted accelerated approval to rucaparib for treatment of BRCA1/2 mutated mCRPC in May 2020. Olaparib was approved by the FDA in May 2020 on the basis of a large clinical trial, PROfound, in which a cohort that included men with BRCA1/2 or ATM mutations treated with olaparib demonstrated a nearly 50% longer survival time than men treated with abiraterone or enzalutamide[11].
The next presentation was a case-based panel discussion of treatment for localized PCAs and was moderated by Dr. Dan Lin (United States). The panelists included Dr. Morgan Roupret (France), Dr. Marc Dall’Era (United States), and Dr. Peter Mulders (Netherlands). Dr. Lin presented an index case to introduce the specific panel topic: Can imaging and biomarkers replace surveillance biopsies for localized PCAs? The index case was a 63-year-old man with a PSA of 6.2 ng/mL in 2020 and a normal digital rectal exam (DRE) who had recently undergone biopsy which indicated Grade Group isoechoc 1 (GG1) cancers. His PSA levels had risen gradually from 1.5 ng/mL in 2007. The NCCN has specific recommendations for such clinically localized PCAs and for patients who are considering AS; the follow-up should include initial multiparametric prostate MRI (mpMRI) or biopsy to confirm candidacy for AS, PSA assessments should be no more often than every 6 months, and repeat biopsy and DRE should be no more often than every 12 months.[4]. 

Germline testing for such cases is recommended only if there is an indication of family history or intraductal/crinoform histology. The American Urological Association (AUS) 2017 Guidelines[12] and the European Urological Association (EUA) 2020 Guidelines generally concur with these recommendations for AS[13].

The first panelist, Dr. Mulders, posed the question: If biomarkers replace surveillance biopsy, which biomarkers should be used? The four categories of biomarkers are germline susceptibility biomarkers, which were described by Dr. Morgan in the previous presentation; biomarkers of disease risk; risk stratification markers; and biomarkers for prediction of treatment response[14]. Biomarkers with negative predictive value (NPV) are the most valuable[15], and biomarker kits with high selectivity detect the biomarkers PCA3, PHI, 4k, MiPS, PHI, DLX1, HOXC6, and KLK3. These biomarker panel kits can help with the decision model for initial biopsy, as well as later risk stratifications in cases of positive biopsy. A proprietary kit that detects the biomarkers DLX1, HOXC6, and KLK3 has been shown to have the highest NPV and area under the curve (AUC) and a combination of multiparametric magnetic resonance imaging (mpMRI) with this panel kit yields a NPV of over 99%. In the surveillance setting, individual biomarkers such as PCA3 or TNPRSS2-ERG have a lower but discernible ability to stratify the risk of having aggressive cancer, but the increase of power over PSA alone to predict high grade disease is not significant. Dr. Mulders concluded that biomarkers have additional value in PCA detection and stratification, but the additional value in the surveillance setting still needs level 1 evidence.

Dr. Dall’Era, the second panelist, addressed the questions: Can imaging alone be used to forgo biopsy, and can a change in imaging results be used to justify treatment? Prostate ultrasound (US) has several limitations. Standard grey scale imaging (5-10 MHz) poorly discriminates cancer, and detected cancers are often small and less likely to be hypoechoic; many are isoechoc. Moreover, a mixed echo pattern combined with calcification can obscure anterior tumors. High-resolution US using 29 MHz micro-US (MUS) can be used to determine the prostate risk identification score, and this risk score correlates with the lesion size and GS[16]. Moreover, MUS outperformed a magnetic resonance imaging / ultrasound(MRI/US) fusion transperineal approach for detection of target lesions. Another study concluded that MRI alone is insufficient to detect grade reclassification and found that for men with low prostate specific antigen density (PSAD) NPV on surveillance biopsy is 92%. In the surveillance setting, the PCa AS Study (PASS) found that the NPV (83%) for MRI used to detect Gleason grade (GG) greater than 2 did not improve upon clinical variables used in prediction models, while the Memorial Sloan Kettering (MSK) study found that 31% of men with a ‘stable’ MRI finding had disease progression on 3-year biopsy. A 2020 study (MRIAS)[17] found that men with persistently positive MRIs had highest rate of grade progression, and a 2017 study found that MRI and PSAD can predict outcome of targeted biopsy on AS[18].

Dr. Dall’Era drew several conclusions from these combined studies: MRI technique, quality, and interpretation are highly variable[18], and not all cancers are visible on MRI, including low-volume GS 3 + 3 and 3 + 4, as well as aggressive histological variants such as ductal and small cell. Thus, imaging should not replace biopsy, although a well-performed MRI can be used to tailor surveillance biopsy frequency. Improved US may have a future role. Changes in imaging results should prompt early biopsy, not just intervention.
The final panelist, Dr. Roupret, presented studies supporting his contention that the use of biomarkers and imaging are not sufficient for AS of PCa, and of the mandatory need for biopsy. He noted the change in national and international guidelines for the use of MRI. First-line multiparametric MRI (mpMRI) is currently indicated for any clinical suspicion of PCa. This change was in part the result of a prospective multicentre randomized control trial of the use of targeted biopsy combined with mpMRI for PCa detection in men with elevated PSA levels who had not undergone biopsy. The study found that the use of mpMRI combined with MRI-targeted biopsy was superior to standard US-guided biopsy for the diagnosis of clinically insignificant cancer. Other benefits include increased detection of significant PCa, improved volume evaluation and detection of aggressive PCa, and the need for fewer biopsy cores to detect significant PCa[19]. mpMRI combined with MRI-combined therapy represent a new standard for PCa and has led to a diagnostic strategy supported by the French Committee of Urologic Cancer Guidelines[20]. The 2020 EAU Guidelines recommend repeat biopsy at a minimum interval of 3 to 5 years and state that mpMRI cannot be used as a stand-alone tool to trigger follow-up biopsies[21]. The limitations in using mpMRI alone in the AS population are its inadequate NPV, as well as poor inter-observer variability in MRI interpretation even among experts, its low reproducibility, and its lack of sufficient quantitative measures to allow assessment of change over time (PRECISE)[22]. However, the MRIAS trial determined that the use of baseline mpMRI imaging combined with saturation biopsy reduces the frequency of surveillance prostate biopsies[23]. Dr. Roupret drew several conclusions: To reduce the frequency of biopsy, mpMRI requires improvement in performance and interpretation reproducibility, a suspicion scale trained upon a surveillance population (AS-specific Prostate Imaging Reporting and Imaging System [PI-RADS]), better measures of MRI change over time, and improved quantitative metrics.

In summary, mpMRI has a clear role in the PCa diagnosis algorithm, but its role in surveillance is still evolving. However, biomarkers have not yet been proven to replace surveillance biopsy. Both biomarkers and mpMRI should be studied as adjuncts to biopsy.

The next three presentations addressed the management of locally advanced PCa.

Dr. Martin Gleave (Canada) discussed the topic of neoadjuvant therapy in high-risk PCa to improve the more aggressive surgical outcomes now employed for localized high-risk PCa. Similar trials in bladder and breast cancer have resulted in significantly improved survivals with pCR rates > 30%[24-26]. In the 1990’s, 0 vs. 3-month neoadjuvant trials in PCa using ADT showed a 50% reduction in positive margin rates but no improvement in PSA relapse rates. A larger CUOG trial of 3 vs. 8-month NHT indicated improved pathologic surrogates, but also no difference in PSA recurrence rates. However, these trials did not select for high-risk PCa. A RCT of neoadjuvant LHRHa + abiraterone in localized high-risk PCa showed a reduction in intraprostatic androgens, but a low incidence of pCR and MRD at 3 and 5 years[28,29].

The AR signalling pathway was targeted in more recent studies. A 2017 trial compared enzalutamide monotherapy to combined enzalutamide + dutasteride + LHRHa but found pCR and MRD rates were not improved relative to historical controls. From these findings, clinical trials were developed to more effectively suppress AR activity[30]. A 2019 Dana Farber trial analyzed neoadjuvant LHRHa + enzalutamide +/- abiraterone and found pCR and MRD were 30% and 16% with and without abiraterone. On the basis of these findings, a much larger phase 3 RCT, PROTEUS, is now underway, comparing 6-month neoadjuvant therapy plus 6-month adjuvantLHRHa +/- apalutamide in men with high-risk localized PCa. pCR and metastasis-free status (MFS) analyses are currently in progress.

Another strategy involves neoadjuvant ADT + chemotherapy. In the CUOG P01b trial, NHT + docetaxel showed improved pCR over NHT alone[31]. In the CALGB 90203 study, neoadjuvant NHT + docetaxel was given before radical prostatectomy (RP) and compared to RP alone; however, 40% of the patients had received early treatment with salvage radiation treatment (RT), ADT, or both and there were no differences in the 3-year biochemical PFS (bPFS) rates between treatments, although the overall bPFS was improved. This trial provided the biological materials to examine treatment-induced
genomic and transcriptome changes and the possible mechanisms of resistance in patients treated with neoadjuvant docetaxel + ADT. Fifty-nine percent of post-RP tissues had mutations versus 85% of pre-treatment biopsies, suggesting the possibility of reduced tumour clone diversity after neoadjuvant docetaxel + ADT treatment. There was significant down-regulation of AR-target genes such as KLK3, and higher gene expression of a subset of plasticity and neuroendocrine genes\[32\]. In the current ACDC-RP trial, neoadjuvant leuprolide + abiraterone +/- cabazitaxel are being studied with a primary endpoint of pCR; there will be a read-out in 2021.

Biomarker-driven neoadjuvant strategies in high-risk PCa include genomic sequencing to enable the matching of molecularly targeted agents to distinct genomic and molecular aberrations within individual cancers. The genomic umbrella neoadjuvant study (GUNS) is currently evaluating targeted therapeutics in biomarker pre-selected patients with high-risk localized PCa\[33\]. The hope is to pathologically define the conditional lethality of targeted therapies. Four genomic groups have been assigned to receive treatment: LHRHa + apalutimide (APA) +/- abiraterone acetate (AAP) for the ‘no targetable aberrations’ group; LHRHa + APA +/- docetaxel for the ‘loss of tumour suppressor’ group; LHRH + AAP +/- niraparib (a PARP inhibitor) for the ‘DNA damage response alterations’ group; and LHRHa + APA +/- atezolizumab for the ‘immunogenic’ group. This adaptive design allows early closure or the addition of new combinations. A pCR of ≥ 20% would be of interest for further clinical evaluation.

Dr. Gleave summarized neoadjuvant strategies for the treatment of localized, high-risk PCa. Neoadjuvant ADT-based combination therapies result in pCR rates of < 10% and no reduced recurrence rates. Neoadjuvant ADT + docetaxel produce signs of clinical improvement, but a longer follow-up is needed. There is a new opportunity to evaluate biomarker-driven therapies in neoadjuvant trials to identify conditional lethality of targeted therapies.

Dr. Alberto Bossi (France), the next speaker, compared adjuvant to salvage RT for the treatment of high-risk PCa. For the purpose of adjuvant and salvage RT after RP, the EAU and American Urological Association/American Society for Radiation Oncology (AUA/ASTRO) Guidelines have agreed that recurrent cancer after RP is defined as two PSA values of > 0.2 ng/mL and rising. Salvage RT is used only when post-operative PSA levels are rising from undetectable levels and represents a “wait and see” approach, which may avoid unnecessary treatment. In contrast, adjuvant RT is used immediately after RP in cases of extraprostatic extension, positive margins, seminal vesicle infiltration, high GS, positive lymph nodes (pN+), and persistently elevated PSA levels. In these patients, earlier rather than delayed adjuvant RT is more effective. In the Briganti study of a group of surgically-treated high-risk PCa patients, the overall 5-year biochemical relapse-free survival (bRFS) rate was 55%, indicating rising PSA levels in almost half of these patients\[34\]. However, not all of the remaining 45% have similar risks of dying; earlier relapse after RP results in mortality of 10%, whereas later relapse results in lower mortality. Higher survival rates are also associated with lower PSA levels (≤ 20 ng/mL), fewer prognostic features, as well as lower cT. The Karnes study looked at the impact of time from surgery to recurrence in assessing the long-term risk of clinical progression after biochemical recurrence and found a significant survival association of the adjuvant timing with the reduced length of time between RP and treatment. Fossati et al. assessed the optimal time for salvage RT in patients with rising PSA levels higher than 0.5 ng/mL after RP and found a decrease in bRFS in patients with a greater number of pathologic risk factors\[35\]. Stephenson et al. found significantly reduced progression-free survival (PFS) in patients undergoing salvage RT but with very high pre-treatment PSA levels; if salvage RT is undertaken, it should start when PSA levels are very low. Similarly, low pre-salvage radiation treatment (SRT) PSA levels (less than 0.5 ng/mL) are associated with lower rates of metastasis\[36\].

Using these combined findings, the EAU has defined characteristics of low-risk biochemically-recurrent PCa (BCR) following RP, which include a PSA doubling time (DT) of greater than 1 year for low-risk, and a PSA-DT of ≤ 1 year and a GS > 8 for high-risk\[37\]. For those patients with low-risk features at relapse, EU Guidelines recommend AS and possibly delayed SRT. However, SRT for high-risk patients should occur as quickly as possible. The TROG 08.03/ANZUP RAVES trial compared adjuvant...
RT (ART) to early SRT (after AS and a PSA ≥ 0.2 ng/mL) following RP[38]. There were no differences in either freedom from biochemical failure or freedom from local or distant failures, but the prevalence of grade 2 genito-urinary (GU) toxicities was significantly higher for the adjuvant group. Thus, SRT may offer greater benefit. The RADICALS-RT trial examined the timing of RT following gRP in both the ART and SRT settings. No differences were found for bPFS. However, ART was associated with significantly higher GU toxicities, a finding similar to the RAVES trial. The ARTISTIC mega-analysis has summarized these combined findings for the RAVES, GETUG-AFU 17, and RADICALS trials and found no differences in event-free survival between ART and SRT approaches. However, in a significant subset (75%) of patients with node-positive PCa, there may be a survival advantage if immediate SRT is administered[39]. The association of ART with or without anti-androgen therapy (AAT) in the RTOG trial indicated a small survival benefit with the use of AAT, as well as an increased time to death from PCa. However, the GETUP-AFU trial indicated a significantly longer PFS comparing SRT to SRT+ AAT[40].

Dr. Bossi’s conclusions are that increasing PSA levels after RP are not uncommon and may not always impact prostate cancer specific mortality (PCSM). A PSA cut-off value of 0.2 ng/mL may be quite arbitrary in determining the need for SRT, and a more personalized approach should be used. Finally, a non-negligible group of patients may benefit from ART following RP; this would include those with node-positive PCa.

The final presentation on the management of locally advanced PCa was a case-based panel moderated by Dr. Evans. Biochemically recurring (BRC) PCa is defined differently by the AUA (remission after RP = PSA < 0.2 ng/mL) and NCCN (4-8 weeks after RP, the failure of PSA levels to become undetectable, > 0.1 ng/mL [persistence] or the rise of PSA levels from undetectable to detectable on 2 determinations [recurrence]). The topic of PSA persistence versus biological recurrence and oncological outcomes was addressed with evaluations of three salvage therapies: SRT, salvage RP, and salvage lymph-node dissection.

Persistence may result from persistent local disease, pre-existing metastases, or, far less commonly, residual benign prostate tissue. It generally results in worse outcomes. Dr. Derya Tilki (Germany) conducted a large-scale study of 11,604 RP cases and found persistent PSA levels in 9% of these patients[41]. At 15 years after RP, MFS was 53% and CSS was 76% in this group, versus 90% + for the undetectable group. Patients with persistent PSA treated with SRT vs. no SRT were compared 10 years after RP, looking at cause-specific survival (CSS). The CSS for the CSS group was 94% vs. 82% for the entire cohort. Dr. Tilki presented results showing that BCR should be characterized using the recent low- and high-risk group categories defined by the EAU, evidence supported by the ability to predict metastasis and mortality 10 years after RP using these categories[41].

Dr. Bossi noted that SRT results in better PFS after RP if six months of ADT is also provided, but ADT may not be needed in cases of lower PSA levels. He cited three landmark trials, GETUG-AFU-17, RAVES, and RADICALS, that had compared ART to early SRT but had found little difference between these treatments[42]. In a study of 3,400 intermediate-risk patients 4 years after RP, 30% with favourable clinical signs required SRT, salvage ADT, or both; Dr. Bossi emphasized the need to follow this group carefully[43]. A 24-gene predictor has been developed that helps in the decision to use SRT or ART post-RP[44].

BCR patients scheduled for SRT and who have PSA levels < 0.5 ng/mL have the best long-term prognosis. In such cases of low PSA levels, it would also be beneficial to use imaging to detect prostate-specific membrane antigen (PSMA); if PSMA is detected, tumour aggressiveness and metastasis often occurs. Dr. Shin Egawa (Japan) said that PSMA Postitron Emission Tomography/Computed Tomography (PET/CT) has a high detection rate of positive lesions, in one study showing adetection rate of 38% in patients with PSA levels < 0.5 ng/mL. Moreover, PSMA-PET imaging is also helpful in localizing recurrent PCa and has shown that lower PSA values (<0.5 ng/mL) correlate to low (38%) extrapelvic spread, while higher PSA levels (>1.0 ng/mL) correlate with high (>80%) extrapelvic spread. Imaging is also used for SRT planning for post-RP patients with PSA levels < 1.0 ng/mL using radiological PCa volume determination by PSMA or PET/CT[44]. Recent EAU guidelines specify even lower PSA levels, 0.2 ng/mL. BCR patients scheduled for SRT and
who have PSA levels < 0.5 ng/mL have the best long-term prognosis. In such cases of low PSA levels, it would also be beneficial to use imaging to detect PSMA; if PSMA is detected, tumour aggressiveness and metastasis often occurs. Dr. Shin Egawa (Japan) said that PSMA PET/CT has a high detection rate of positive lesions, in one study showing a detection rate of 38% in patients with PSA levels < 0.5 ng/mL. Moreover, PSMA-PET imaging is also helpful in localizing recurrent PCa and has shown that lower PSA values (<0.5 ng/mL) correlate to low (38%) extrapelvic spread, while higher PSA levels (>1.0 ng/mL) correlate with high (>80%) extrapelvic spread. Imaging is also used for SRT planning for post-RP patients with PSA levels < 1.0 ng/mL using radiological PCa volume determination by PSMA or PET/CT[44]. Recent EAU guidelines specify even lower PSA levels, 0.2 ng/mL. Dr. Egawa said that PSMA-PET imaging can be useful, but it has its limitations in SRT planning.

Dr. Tilki emphasized that salvage prostatectomy requires careful patient selection, and the side effects are not trivial. In a study of 1,500 patients, the 5-year BCR free survival estimates ranged from 47-82% but resulted in high percentages of urinary and erectile dysfunction[45,46]. In general, SRP should be considered only for patients with low comorbidity and a life expectancy of ≥ 10 years, as well as a pre-SRP PSA < 10 ng/mL, a GS ≤ 7, no lymph node involvement, and initial clinical stage of T1 or T2[45].

PET imaging prior to salvage lymph-node dissection can correctly predict the presence of lymph node metastasis. However, Dr. Evans concluded that salvage lymphadenectomy (sLND) is still unproven as a standard of care, as biochemical recurrence after sLND still occurs in the majority of cases.

The last three presentations addressed the management of metastatic PCa.

Dr. Kim Chi (Canada) presented some updates on androgen receptor axis targeted therapies (ARAT) strategies. He compared previous ARAT strategies to PARP inhibition and taxane-based sequencing therapies. In earlier studies, PCa that progressed after ARAT given with ADT for treatment of metastatic castrate sensitive prostate cancer (mCSPC) was clinically similar to PCa progression after the same treatment for metastatic castrate resistant prostate cancer (mCRPC) [47–50]. Moreover, switching treatment to another ARAT, such as following enzalutamide with abiraterone or vice versa, had only modestly improved efficacy[48,51–53]. In chemo-naïve patients, there was minimal activity of abiraterone after enzalutamide, and only modest activity of enzalutamide after abiraterone: The PSA response was 34% and the median time to PSA progression was 3.5 months. For this reason, different classes of sequenced treatments with different mechanisms of action have been investigated for treatment of mCRPC. A 2019 study indicated that cabazitaxel and abiraterone/enzalutamide are active in sequence, with a clinical benefit rate of 88% if cabazitaxel is given as a first-line therapy, and 63% if given as second-line therapy[54]. In studies of taxane chemotherapy as second or third-line therapy, taxanes retain activity and survival benefits in mCRPC after ARAT therapy. Dr. Chi feels that patients who are chemotherapy-eligible should be offered taxane chemotherapy. Most recently, promising results have been shown with the use of a PARP inhibitor, olaparib, followed by taxane chemotherapies such as docetaxel and cabazitaxel, as shown in the recent trial PROfound[55]. The greatest survival benefit occurs for mCRPCs that contain mutations in BRCA1/2 and are chemo-naïve[11]. More analysis is required to understand optimal selection and sequencing of olaparib.

Next, Dr. Fred Saad (Canada) led a case-based panel discussion on practical adoption of systemic therapy for treatment of metastatic prostate cancer (mPCa). The distinguished panelists (Drs. Alexandre de la Taille [France], Daniel Lin [United States], and Axel Merseburger [Germany]) have been active in producing guidelines and at the forefront of clinical practice for treating PCa. The panelists compared treatment strategies for three scenarios: a healthy mPCa patient presenting with low-risk, low-volume disease and two bone mets, a patient diagnosed with cT3NxMO but bone scan negative, and a high-risk, high-volume case with multifocal Gleason 4 + 4 and multiple bone mets.

A healthy, low-volume, low-risk 63-year-old patient presented with the following: PSA 43, DRE cT3, Gleason 4 + 4, 2 bone mets in the spine and left hip, a 2 cm retroperitoneal node seen on the abdominal CT, a negative chest CT, Eastern Cooperative Oncology Group (ECOG) 0, and no pain. All three panelists agreed that
ADT standard of care (SOC) would not be enough for treating this patient. Dr. Lin noted that patients in the United States tend to avoid IV treatments, if at all possible, which would exclude chemotherapeutics. He would advocate for observation and no imaging of this patient. Dr. de la Taille said that PSMA imaging would likely reveal more sites. Dr. Merseburger discussed this patient in the context of the CHAARTED, LATITUDE, and STAMPEDE trials. Imaging might move this patient into the high-risk, high-volume category. The CHAARTED study indicated much-improved OS with high-volume tumours treated with ADT + docetaxel versus ADT alone. Similarly, the LATITUDE trial indicated improved OS in treatment with abiraterone + ADT versus ADT alone, in high-risk mCNPC. In the STAMPEDE study of ADT + AAP versus ADT alone, both low-risk/low-volume and high-risk/high-volume groups showed major OS benefits. The TITAN all-comer study, using apalutamide, is expected to produce similar results in a long-term analysis in 2021 to the ENZAMET all-comer study which used enzalutamide for mCSPC. Docetaxel has demonstrated effectiveness following AR targeting. Dr. Merseburger’s recommendations for this patient would be to follow the sequencing described by Dr. Chi. He would start with ADT, use frequent imaging, and move to docetaxel upon rising PSA levels. Some ongoing trials for mPCa were described. Dr. Lin would also recommend treating the prostate, noting that RP in M1 disease has proven safe and effective.

The next case was of a 69-year-old retired dentist diagnosed with cT3NxMO PCa, GS 4 + 5, a 1 cm right iliac lymph node (LN), and bone scan negative. His treatment plan had included electron beam radiation therapy (EBRT) + 3 years of ADT. After 3 years, the CT and bone scans were negative on novel imaging, but the PSA DT had increased to 4.5 months, to 10.5 ng/mL. Dr. Merseburger would consider this non-metastatic CRPC to be high risk. He would treat this patient with three approved drugs: apalutamide, enzalutamide, and darolutamide, followed by PSMA imaging. If the imaging indicated no mets, he would narrow the treatment to enzalutamide alone but would not continue imaging. Dr. de la Taille summarized the findings of the three trials, SPARTAN, PROSPER, and ARAMIS, comparing the effectiveness of these three drugs to placebo alone. All indicated a reduction in the risk of death and improved OS, with the time to resistance three-fold longer than in patients with true mPCa. Dr. Saad noted that any rise in PSA levels, however small, following AR-targeted therapies should be cause for concern for metastasis. The patient did receive one of the AR-targeted therapies and his PSA declined to 0.4 ng/mL, with improved quality of life (QOL).

The final case was of a 67-year-old with mPCa. He presented with a PSA of 180, biopsy multifocal GS 4 + 4, multiple bone mets in the spine, hip, and femur, 4 retroperitoneal nodes 2 to 3 cm in size, and discomfort. He received ADT + 6 cycles of docetaxel and at 6 months the PSA was 1.1. The imaging showed a reduction in bone mets, and the disappearance of the lymph node mets. At 8 months, the PSA had risen to 6, with imaging indicating increases in bone and LN mets. Dr. Merseburger and Dr. Saad felt that genomic testing may benefit this post-docetaxel high-volume, high-risk case, and if BRCA1/2 or ATM mutations are found, ARAT therapy involving a PARP inhibitor would be especially recommended, following the AUA guidelines that in sequencing agents, clinicians should avoid treatments that use a similar mechanism of action as previous treatments.

In the final session of the day, Dr. Karim Fizazi (France) discussed recent treatment targets for mCRPC treatment, each representing a different proliferative pathway. These include the Akt/PI3K and AR pathways, as well as DNA repair mechanisms. AR mutations occur in about 25% of mCRPC, producing constitutively-active AR. Germline mutations occur in 12% of men with M1 PCa, and somatic DNA repair mutations occur in 10% of men with mCRPC.

Treatment alternatives to AR pathway inhibitors are under active investigation. PSMA theranostics using 177Lu-PSMA-617 demonstrated a > 50% PSA response at 12 weeks. Immunotherapy approaches targeting PD-1/PD-L1 with pembrolizumab + continuous enzalutamide in enzalutamide-progressing CRPC have shown promising results compared with cabazitaxel. In the phase 3 IPATential150 trial, abiraterone + ipatasertib have demonstrated extended PFS in the presence of phosphatase and tensin homology (PTEN) loss. A number of other biomarkers associated with mCRPC...
have been identified, including those linked to homologous recombination deficiencies. Dr. Fizazi summarized the biomarkers whose loss or mutation have defined roles in mCRPC, and treatments that have demonstrated efficacy:

- DNA-damage repair mutations and PARP inhibitors[64].
- Microsatellite instability and PD-1 inhibitors.
- PTEN loss and Akt inhibitors[65].
- AR mutations and ligand inhibitors.
- Cdk12 -/- (a tumour suppressor) and PD-1 inhibitors.
- PSMA and $^{177}$Lu-PSMA-617[66,67].

The therapeutic targeting of these biomarkers opens promising and novel avenues of treatment for metastatic prostate cancer.

Dr. Hammerer thanked all panelists and attendees for taking part in the prostate cancer session. He then led a 15-minute Q&A session with the entire panel which addressed key issues on the treatment of prostate cancer, with a particular focus on recent research of germline mutations. To the question of what kind of sample would be appropriate for testing of BRCA1/2 mutations, Dr. Morgan said that blood tests are best for sampling all germline mutations. Dr. Fizazi confirmed the efficacy of the use of PARP inhibitors at early timepoints for treatment of advanced PCa. He said that the recent PROfound clinical trial supports this, although the long-term effects of PARP inhibitors are unknown. Because of this, he would recommend their use only in the context of a clinical trial. Dr. Fizazi noted that the United States has broader approval standards for the use of PARP inhibitors that goes beyond treating patients with BRCA1/2 mutations; patients with other germline mutations would also be considered for this treatment.

Dr. Black thanked the SIU and all panelists and attendees of the 2-day meeting and said that this global virtual meeting had met the SIU mission of providing a means for attendees around the world to update their knowledge on the latest research and changing treatment paradigms of these uro-oncological cancers.
## Abbreviations Used in the Text

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADT</td>
<td>androgen deprivation therapy</td>
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<tr>
<td>ARAT</td>
<td>androgen axis-targeted therapies</td>
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<tr>
<td>ATM</td>
<td>ataxia-telangiectasia mutated</td>
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<td>AUC</td>
<td>area under the curve</td>
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<tr>
<td>BCR</td>
<td>biochemical recurrence</td>
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<td>BRCA1/2</td>
<td>breast cancer susceptibility gene 1/2</td>
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<td>CSS</td>
<td>cancer-specific survival</td>
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<td>CUOG</td>
<td>Canadian Urological Oncology Group</td>
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<tr>
<td>DRE</td>
<td>digital rectal examination</td>
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<tr>
<td>EBRT</td>
<td>external beam radiation therapy; brachytherapy</td>
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<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
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<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
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<tr>
<td>GG</td>
<td>Gleason grade</td>
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<td>Grade Group 1</td>
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<tr>
<td>Gs</td>
<td>Gleason score</td>
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<tr>
<td>GU</td>
<td>Genitourinary</td>
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<tr>
<td>LN</td>
<td>Lymph node</td>
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<tr>
<td>mCRPC</td>
<td>metastatic castration-resistant prostate cancer</td>
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<tr>
<td>mCSPC</td>
<td>metastatic castration-sensitive prostate cancer</td>
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<tr>
<td>MFS</td>
<td>metastasis-free status</td>
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<tr>
<td>mpMRI</td>
<td>multiparametric magnetic resonance imaging</td>
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<tr>
<td>MRI/US</td>
<td>magnetic resonance imaging /ultrasound</td>
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<td>MRD</td>
<td>minimal residual disease</td>
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<td>MSK</td>
<td>Memorial Sloan Kettering</td>
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<td>NHT</td>
<td>neoadjuvant hormonal treatment</td>
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<td>PARP</td>
<td>poly (ADP-ribose) polymerase</td>
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<td>PCSM</td>
<td>prostate cancer-specific mortality</td>
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<td>PET/CT</td>
<td>positron emission tomography / computed tomography</td>
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<tr>
<td>PFS</td>
<td>progression-free survival</td>
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<tr>
<td>PSMA</td>
<td>prostate-specific membrane antigen</td>
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<td>PTEN</td>
<td>phosphatase and tensin homologue</td>
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<td>RCT</td>
<td>randomized control trial</td>
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<td>RP</td>
<td>radical prostatectomy</td>
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<td>SOC</td>
<td>standard of care</td>
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<tr>
<td>SRT</td>
<td>salvage radiation therapy</td>
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</tbody>
</table>
References


50. Fizazi K, Drake C, Beer T. Overall survival (OS) results of phase III ARAMIS study of darolutamide (DARO) added to androgen deprivation therapy (ADT) for nonmetastatic castration-resistant prostate cancer (nmCRPC). *Eur Urol*. 2020;78(6).


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