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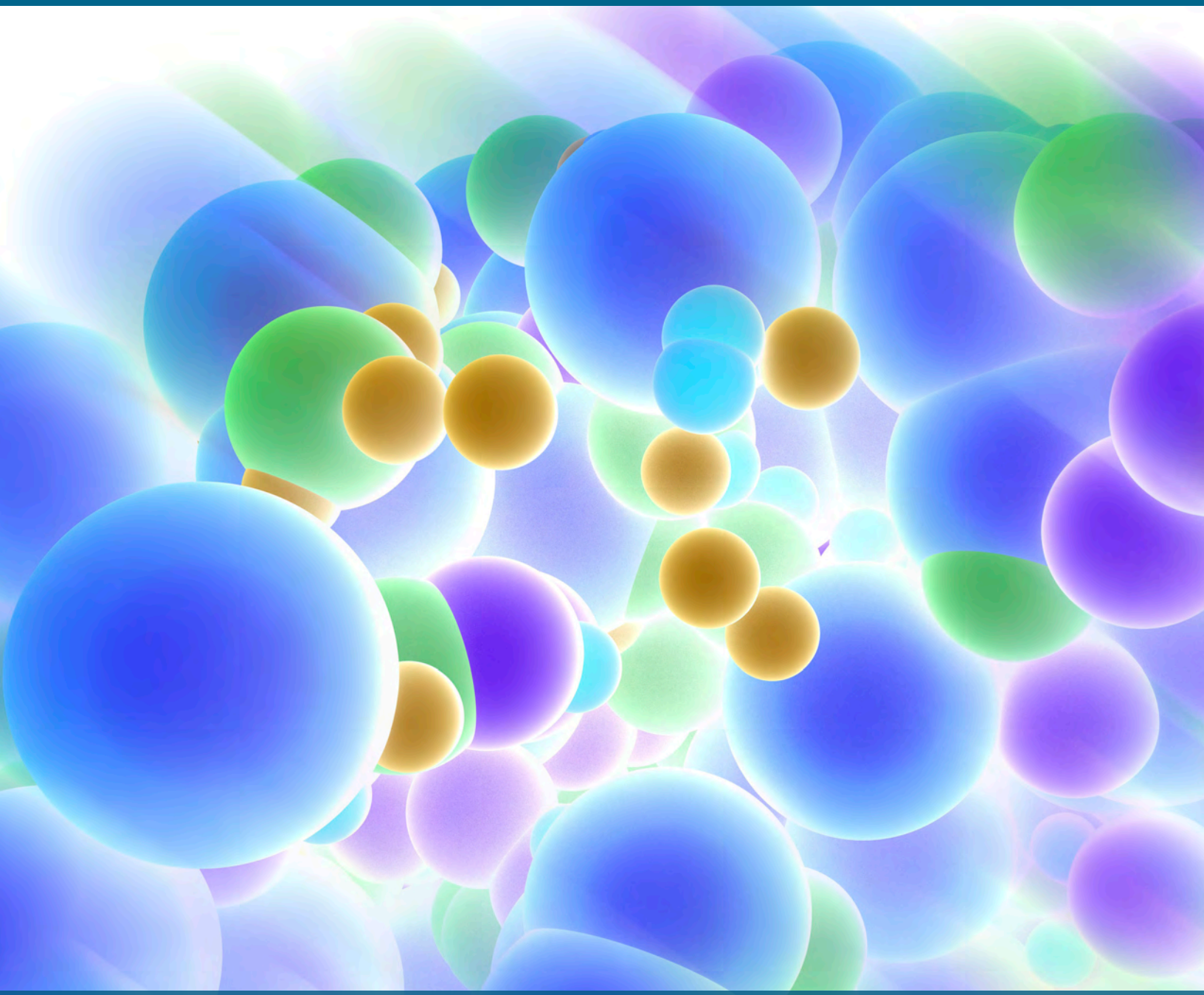
VOLUME 4, ISSUE 1



Optimizing TURBT and Optical Diagnostics in Bladder Cancer

By Ashish M. Kamat, MD, MBBS

Immuno-Oncology: The Urologist's Role

By Noah M. Hahn, MD

SPOTLIGHT

ASCO Genitourinary Cancers Symposium 2019

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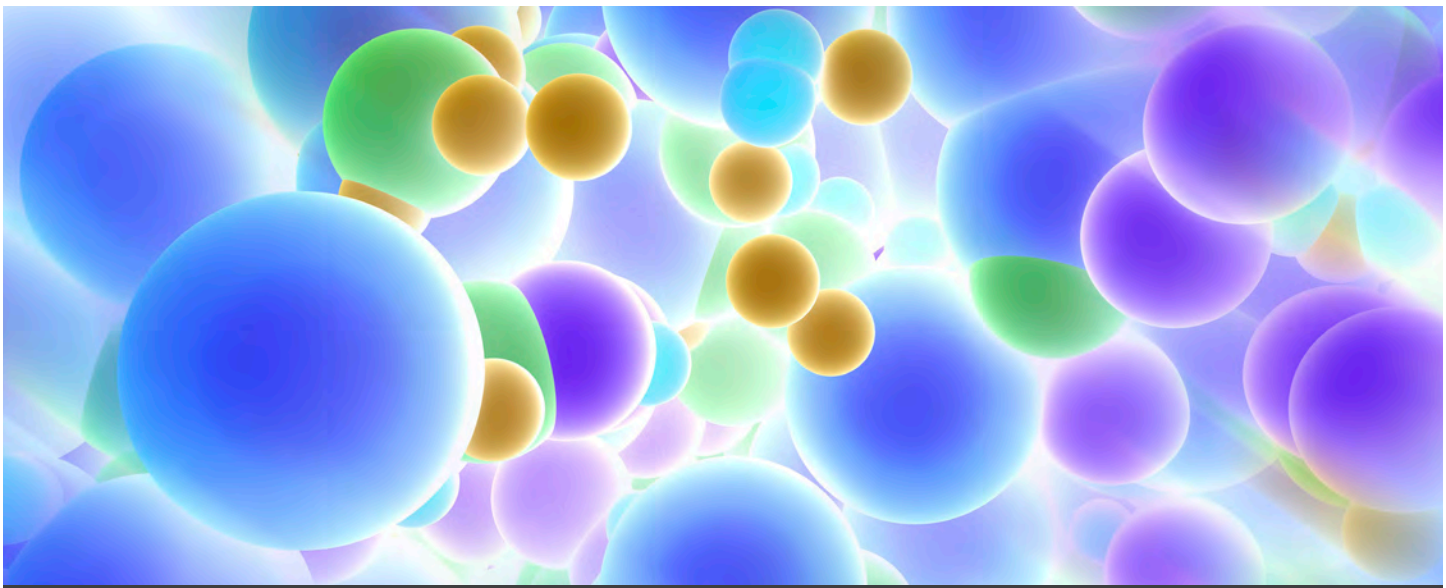

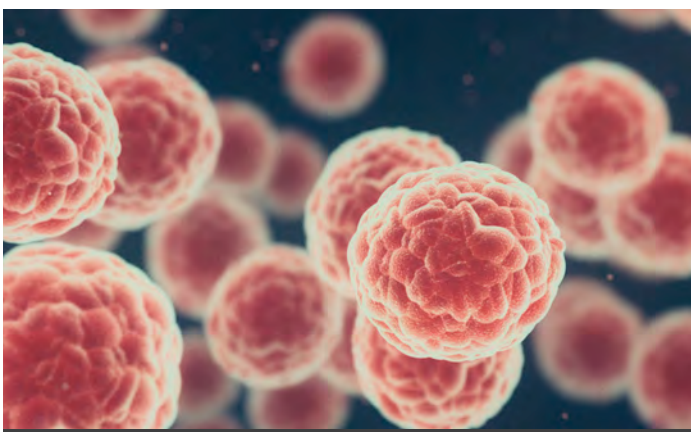

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Everyday Urology®- Oncology Insights (ISSN 2473-3784) is published four times a year by Digital Science Press, Inc., business office located at 548 Market St #41552, San Francisco, CA 94104-5401

POSTMASTER: Send address changes to *Everyday Urology®- Oncology Insights* Digital Science Press, Inc. Subscription Customer Service, 548 Market St #41552, San Francisco, CA 94104-5401

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FROM THE DESK OF THE EDITOR

Dear Colleagues:

Welcome to the current issue of *Everyday Urology – Oncology Insights*. We begin this issue with our cover story: "**Optimizing TURBT and Optical Diagnostics in Bladder Cancer**", authored by Ashish Kamat, MD. Dr. Kamat discusses the crucial importance of performing the optimal TURBT. This is the essential first step in managing newly diagnosed and recurrent bladder cancer, ultimately impacting potential multidisciplinary therapies, for both advanced disease and high risk NMIBC. While transurethral resection of the bladder tumor (TURBT) remains the gold standard 'first step' in bladder cancer management (both diagnosis and tumor removal), there can be a high rate of residual tumor left behind after TURBT. He details tips to optimize TURBT as well as a checklist of processes for consideration of prognostic factors. In addition, Dr. Kamat reviews state of the art methods for enhancing cystoscopic evaluation of malignant urothelium, the most recent AUA bladder management guidelines (2016) and reimbursement considerations. Our understanding of the complexity of bladder cancer management is expanding, and thus an optimally performed TURBT not only provides the accuracy for a correct diagnosis but may also prevent or delay recurrence as well as progression of bladder malignancy.

In this issue's **Expert Perspective**, Noah Hahn, MD, has authored: "**Immuno-Oncology: The Urologist's Role**" in which he reviews the efficacy of immuno-oncologic agents in advanced urothelial cancer with an assessment of the importance of urologic involvement. Dr. Hahn describes the trial landscape whereby the efficacy and administration of immuno-oncologic agents in advanced urothelial cancer may lead to their potential use in earlier-stage bladder cancer, which augurs the potential promise of the shift of immuno-oncologic therapy to earlier-stage use.

Practice changing studies evaluating the safety and efficacy apalutamide and enzalutamide in men with high-risk nonmetastatic castration-resistant prostate cancer have resulted in U.S. FDA approvals for both of these drugs for this indication. At the 2019 Genitourinary Cancers Symposium Karim Fizazi presented the first efficacy and safety results from the ARAMIS trial. **The Efficacy and Safety Study of Darolutamide (ODM-201) in Men With High-risk Nonmetastatic Castration-resistant Prostate Cancer (ARAMIS)** achieved its primary endpoint: improving metastasis-free survival (MFS) while offering a favorable safety and toxicity profile. Pending U.S. FDA regulatory approval, darolutamide will be the third drug to have an indication for the treatment of men with nmCRPC. A full summary of the ARAMIS presentation as well as a summary of the presentation results from **ARCHES - A Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Patients With Metastatic Hormone Sensitive Prostate Cancer (mHSPC)** and other highlights from presentations from this same meeting in bladder cancer, kidney cancer and others in men with prostate cancer can be found in this issue's **Spotlight**.

Thank you for reading these state-of-the-art discussions, as well as for your continued support.

Sincerely,
Neal Shore, MD, FACS

Neal Shore, MD, FACS, is an internationally recognized expert in systemic therapies for patients with advanced urologic cancers and innovative therapies to treat patients suffering from prostate enlargement symptoms. Dr. Shore was recently appointed President-Elect of the Large Urology Group Practice Association (LUGPA), which seeks to provide urologists with all the tools they need to effectively care for patients. Neal D. Shore, MD, FACS, is the Medical Director of the Carolina Urologic Research Center. He practices with Atlantic Urology Clinics in Myrtle Beach, South Carolina. Dr. Shore has conducted more than 100 clinical trials, focusing mainly on prostate and bladder disease.

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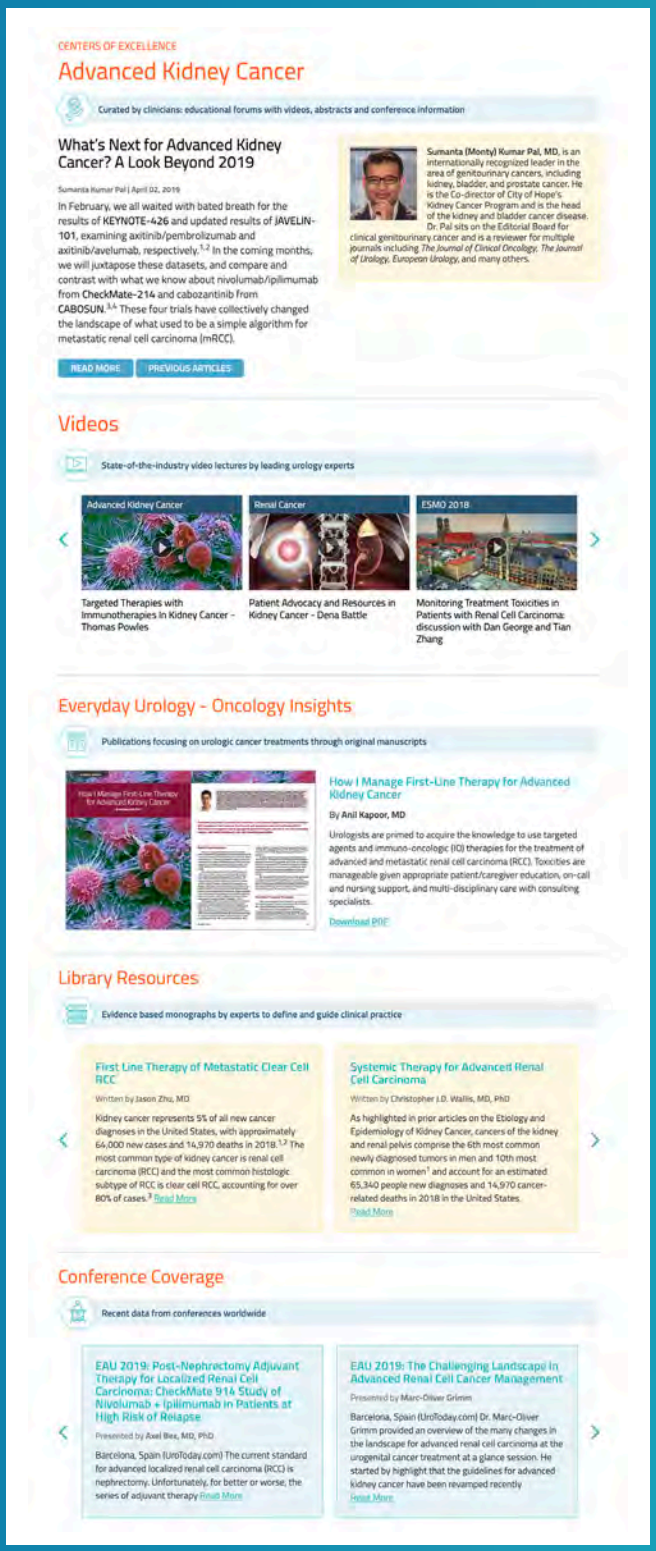

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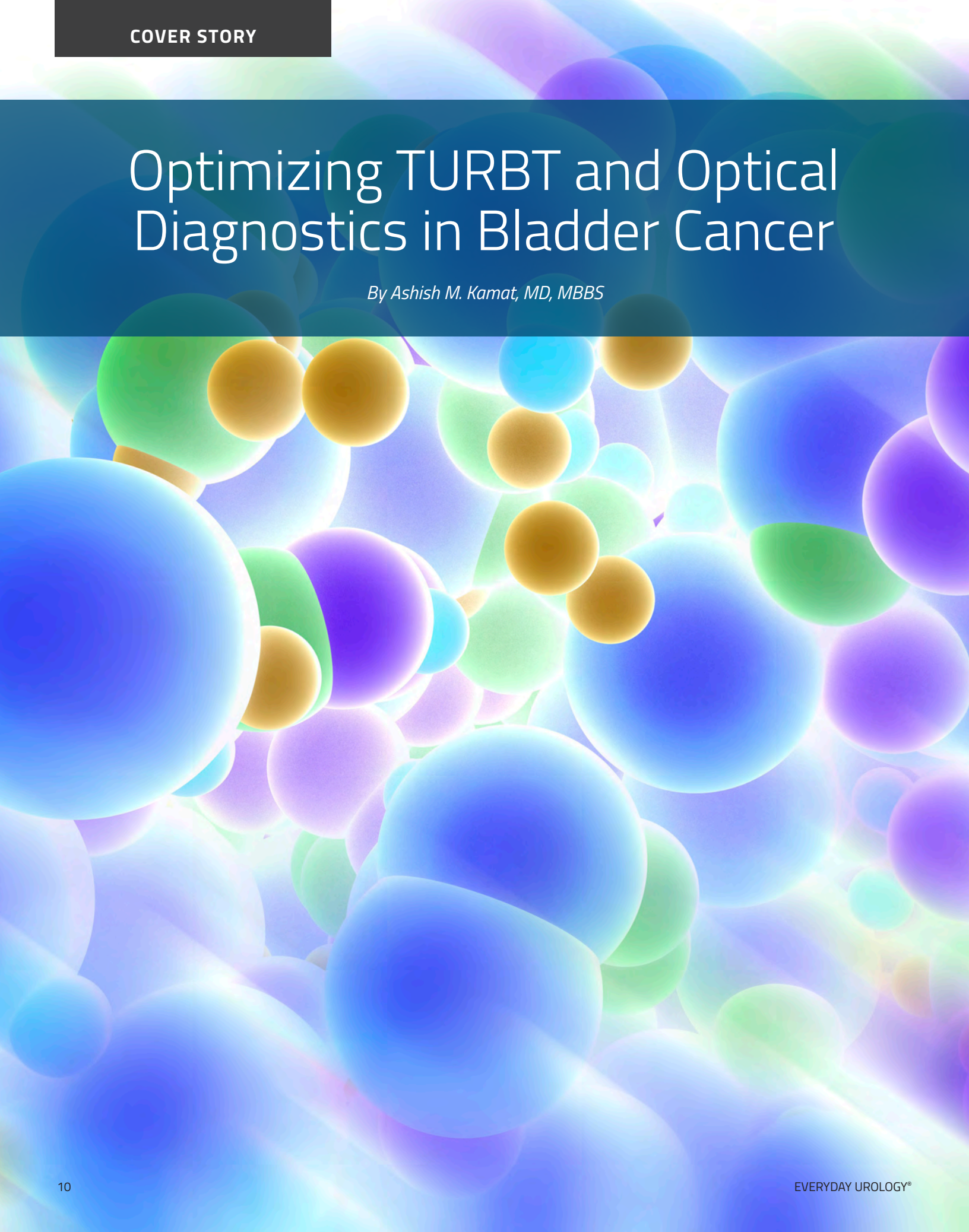
Optimizing TURBT and Optical Diagnostics in Bladder Cancer

By Ashish M. Kamat, MD, MBBS



Ashish M. Kamat, MD, MBBS, is a Professor (Tenure) of Urology and Director of Urologic Oncology Fellowship at M.D. Anderson Cancer Center, and a graduate of the AUA Leadership Program. Dr Kamat has authored over 200 publications, editorials & book chapters in prestigious journals; he is listed in 'Who's Who in Medicine' and 'Best Doctors in America' and has won the Compassionate Doctor Award from patient groups. He is an exceptional educator nominated twice for the Robert M. Chamberlain Distinguished Mentor Award and has been invited as a visiting professor to several universities across the world. Dr Kamat is Co President, International Bladder Cancer Network, Chair, Bladder Cancer Think Tank (2015), Chair, Bladder Cancer Task Force for SITC, actively participates in various global urologic efforts, and serves on the board of regional and national societies for Urology.

Bladder cancer is the ninth most common cancer worldwide, and its incidence and prevalence will significantly increase in future decades with global population aging.[1] Transurethral resection of bladder tumor (TURBT) is a first, crucial step in managing this complex disease. Not only is TURBT of high diagnostic, prognostic, and therapeutic value in itself, but it also is a vital part of multidisciplinary therapies.

The detection of recurrent tumor is a benchmark by which the success of intravesical agents is determined. Because the U.S. Food and Drug Administration (FDA) will now consider data from single-arm trials for patients with Bacillus Calmette-Guérin (BCG)-unresponsive bladder cancer, the complete response (CR) rates (i.e. absence of disease on biopsy) is a key factor that impacts the success of many registration studies.[2,3,4] In addition, several trials in the neoadjuvant setting focus on P0 rates, meaning that disease is not detected in the final pathologic specimen.[5] Since the extent of disease detected depends on the quality of the cystoscopy and an optimally performed TURBT can achieve P0 in up to 15% of patients even without enhanced cystoscopy,[5] – clearly this has the potential to impact results.

But performing high-quality TURBTs is not easy. Urologists must accurately assess tumor grade and stage during visual evaluation. She or he must then make an assessment of prognosis and proceed to appropriately resect tumors and suspicious lesions as completely (and deeply) as is required, safe and feasible, plus collect high-quality biopsies for pathologic review.[6] In this article, I share practical tips for doing this while minimizing the risk of adverse events. Because tumor detection is key to TURBT outcomes, I also review current data on enhanced cystoscopic imaging.

Tips for Optimizing TURBT

ANESTHESIA

Options for anesthesia should be discussed with patients during preoperative planning.[6] Complete paralysis is preferred to decrease movement, minimize motion from abdominal breathing, facilitate resection of the lateral, posterior, and anterior bladder walls, and decrease the likelihood of obturator reflex (obturator jerk).[7,8]

Until recently, TURBT patients often received epidural or general anesthesia along with either an obturator nerve block or succinylcholine, a short-acting depolarizing neuromuscular blocking agent (NMBA). Succinylcholine effectively prevents obturator reflex but can cause masseter muscle spasm, hyperkalemia, and rhabdomyolysis and it is short acting.[9,10,11] The use of longer acting agents such rocuronium, a non-depolarizing NMBA, was problematic since rocuronium has a longer duration of action and required patients to be under anesthesia for longer periods of time. Fortunately, anesthesiologists now have a safer option: rocuronium can be reversed rapidly by administering the selective relaxant binding agent sugammadex.[12,13]

CHECKLISTS

The use of a surgical safety checklist has been found to significantly reduce postoperative complications and 30-day mortality.[14,15] For patients with bladder cancer, however, a TURBT-specific checklist also supports procedural quality and the collection and reporting of key information, such as tumor stage and whether intravesical chemotherapy or bimanual examination under anesthesia (EUA) was performed.[6,7,16] Such observations and procedural details are vital for planning future cystoscopies.

Robust research supports the use of checklists during TURBT. In a recent large study, implementing a 10-item TURBT checklist markedly improved the documentation of both prognostic and procedural data.[6] In another large prospective multicenter study, the implementation of an eight-item TURBT checklist was associated with a significant reduction in the risk of bladder cancer recurrence (P=.02).[17]

I personally highly recommend using a checklist during every TURBT. An example of a checklist is shown in **Figure 1** and in addition, I would suggest adding two other fields, that of 'Blue Light used: yes/no' and 'NBI used: yes/no.'

PROGNOSTIC FACTORS	ACCEPTABLE RESPONSES						NOTES
Number of tumors	1	2-5	>5	diffuse			End of cutting loop is approximately 1 cm wide
Size of largest tumor (cm)	<1 cm	1-3 cm	>3 cm				
Characteristics of tumor	Sessile	Nodular	Papillary	Flat			
Recurrent or primary?	Recurrent		Primary				
Presence of carcinoma in situ	Yes	No	Suspicious				
American Joint Committee on Cancer (AJCC) clinical tumor stage	Ta	Tis	T1	T2	T3	T4	Based on 8th edition[AJCC]
INTRAOPERATIVE PROCESSES							
Bimanual exam under anesthesia	Yes						No
Visually complete resection	Yes						No
Visualization of detrusor muscle in base of resection	Yes						No
Visual evaluation for perforation	Yes						No

Figure 1. *TURBT Checklist according to Anderson et al.*[6]

PROCEDURE

Several more tips can help optimize TURBT. First, avoid placing the resectoscope sheath blindly since one can miss a urethral lesion.[6] Instead, visualization allows for urethroscopy and collection of non-traumatic urine for cytology at bladder entry. After entering the bladder, if needed, barbotage can increase cellular yield.

Once this is done, continue using all the lenses at your disposal: 30 and 70-degree lenses for mapping the bladder, and a 120-degree lens or a flexible cystoscope for the bladder neck.[6] This will prevent an unfortunate situation which I see not uncommonly: tumors at the bladder neck and anterior wall that have clearly been 'missed'.

It is important to correctly assess tumor grade and stage to guide decisions about whether to perform deep resection with musclularis propria removed (for high-grade [HG] tumors) or a less aggressive resection with cauterization of the tumor base (for low-grade tumors). In addition, one must often decide on whether to instill perioperative adjuvant therapy with gemcitabine or mitocycin C, which has the most impact in low-grade tumors. We are better at this than you might think. In one study, urologists correctly classified 85 of 86 (99%) LGTa tumors in patients with negative urinary cytology.[18] In another study, urologists misclassified only 7% of large HG tumors as LG, while correctly identifying 93% and 85% of non-muscle invasive and muscle-invasive bladder tumors, respectively.[19] Keep in mind that the great majority of bladder tumors are TaLG, and many of these patients experience successive tumor events. Thus, it is key to minimize trauma to the bladder by reserving deep resection for high-grade tumors.[6]

Of course, in the case of high-grade T1 tumors, a deep resection is required. Here, be kind to your pathologist: submit a separate biopsy of the base of large or T1HG tumors so that the depth of muscle invasion can more easily be assessed. Another option for improving pathologic staging of smaller (3 cm or less) tumors is en bloc resection.[20,21] This technique uses a needle to mark the tumor borders. The needle is then inserted through the marked borders into the bladder wall, the tumor tissue is pulled away, and the tumor is removed with blunt dissection. Point cautery is acceptable to detach the final fibers, but the tumor base is not cauterized, which conserves its 3-dimensional architecture.[21] Some experts posit that en bloc resection also decreases shedding and scattering of tumor cells, which might reduce the risk of early recurrence.[22]

Unlike monopolar electrocautery, bipolar electrocautery restricts electrical current between two polarized elements, enabling the current to bypass the patient. This allows less 'charring' of the tissue.[7] Isotonic saline also can be used during bipolar electrocautery, which decreases the risk of complications such as hypotonic (low sodium) syndromes.[7] Fortunately, such complications are so rare that the superiority of bipolar versus monopolar cautery is slight in absolute terms.[7] Nonetheless, a meta-analysis of six prospective trials and two observational studies comparing monopolar with bipolar electrocautery linked the latter with small but statistically significant reductions in operative and catheterization times, hospital length of stay, blood loss, and rates of obturator nerve reflex and bladder perforation.[23] Interestingly, bipolar cautery also was associated with a lower rate of recurrence at 2-year follow-up.

Enhanced Cystoscopy

BLUE LIGHT CYSTOSCOPY

Hexaminolevulinate (HAL; Cysview®), a hexyl derivative of aminolevulinic acid, was approved by the United States Food and Drug Administration (FDA) in 2010 as an adjunct to standard white light cystoscopy for detecting non-muscle invasive bladder cancer, particularly papillary tumors.[24] Currently, Cysview® is only approved for use with Karl Storz D-Light C Photodynamic Diagnostic (PDD) systems.

Hexaminolevulinate has been studied in five multicenter phase III trials of more than 1,800 patients with known or suspected bladder cancer.[25,26,27,28,29] Among these studies, the pivotal randomized trial leading to the FDA approval of Cysview® included 286 patients with biopsy-confirmed Ta or T1 tumors who underwent white light cystoscopy with or without HAL-assisted blue light cystoscopy.[25] In all, 16.4% of tumors were detected only by blue light cystoscopy (P=.001), including 46% of CIS lesions (P< .0001). The frequency of false positives was equal between groups (11%).

Blue light cystoscopy also was evaluated in a recent multicenter, prospective real-world registry study of 533 U.S. patients with known or suspected non-muscle-invasive bladder cancer.[30] White light cystoscopy detected 76% of malignant lesions, blue light alone detected 91%, and the two tools together detected 98.5%. Similar to the pivotal trial,[25] blue light cystoscopy increased the detection of CIS and papillary lesions by 43% and 12%, respectively.[30] Blue light cystoscopy also led to a change in the management of 14% of patients.

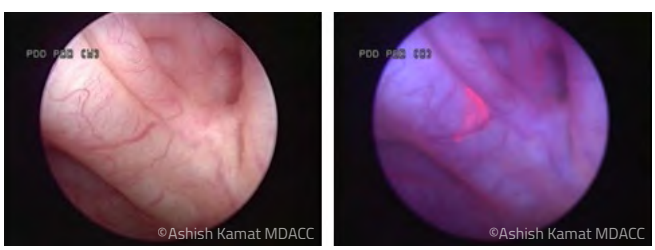


Figure 2: White light versus HAL-assisted blue light cystoscopy in a patient with non-muscle-invasive bladder cancer

Figure 2 illustrates white light versus HAL-assisted blue light cystoscopy in a patient with non-muscle-invasive bladder cancer. Not all tumors detected with blue light cystoscopy are life-threatening, but many are, and many cannot be detected by white light cystoscopy alone, even by highly experienced cystoscopists.

EFFECTS OF BLUE LIGHT CYSTOSCOPY ON RECURRENCE AND PROGRESSION

The use of blue light cystoscopy helps us teach, train, and perform better resections. But does it improve longer-term outcomes? In the pivotal trial of Cysview®, similar proportions of patients in each arm received intravesical therapy, but patients in the blue-light arm had a significantly decreased rate of recurrence at 9 months (47%, vs. 56% with white light only; P=.026).[31] This effect persisted at 54 months, when 38% and 31.8% of patients remained tumor-free, respectively, for a median recurrence-free survival of 16.4 months versus 9.6 months (P = .04).[32] Blue light cystoscopy also showed a trend toward a lower risk of cystectomy.[32]

Does blue light cystoscopy also prevent or postpone progression? Historically, this endpoint - of progression of NMIBC - was defined inconsistently, imprecisely, and often only applied to the state when NMIBC moved to MIBC or metastatic disease. To rectify this problem, the International Bladder Cancer Group (IBCG) recently defined progression of bladder cancer as any of the following: increase in T stage leading to invasion of the lamina propria (T1 disease), the development of muscle-invasive disease (stage T2 or greater), progression to lymph node (N+) or distant metastasis (M1), or an increase from low to high tumor grade.[33]

When this definition was subsequently applied to the pivotal trial of Cysview®,[32] adjunctive HAL-assisted blue light cystoscopy was found to reduce the risk of progression and the effect approached statistical significance (P = .085). Blue light cystoscopy also was associated with a longer median time to progression (P = .05) and a higher probability of progression-free survival (P=.05), possibly because bladder cancer was detected and resected earlier.[34]

Also noteworthy is a meta-analysis of five studies in which 1,301 patients with non-muscle-invasive bladder cancer underwent TURBT with white light with or without HAL-assisted blue light cystoscopy.[35] After approximately 28 months of follow-up, rates of progression were 10.7% and 6.8%, respectively, yielding a 64% greater odds of progression with white light cystoscopy only (odds ratio, 1.64, 95% confidence interval [CI], 1.10 to 2.45; P=.01).[35]

Based on these data, the addition of blue light to white light cystoscopy can be said to potentially have a favorable effect on risk of progression of bladder cancer. However, we need longer-term follow-up and more studies to draw definitive conclusions.

OUTPATIENT AVAILABILITY OF BLUE LIGHT CYSTOSCOPY

Until recently, blue light cystoscopy usually was not performed in outpatient settings because it was not available for use with an FDA-approved non-rigid cystoscope. While many of us remember performing rigid cystoscopies in clinical settings with local anesthesia, with the advent and use of flexible scopes, this practice is uncommon. In February 2018, the FDA approved a supplemental new drug application to extend the indication of Cysview® to include its use with the flexible version of the Karl Storz D-Light C Photodynamic Diagnostic system.[24] This effectively expanded the use of HAL-assisted blue light cystoscopy into outpatient settings.

In the randomized phase III clinical trial spurring this new approval, researchers at 17 U.S. sites compared white light flexible cystoscopy alone with adjunctive HAL-assisted blue light flexible cystoscopy for the office-based surveillance of patients with non-muscle invasive bladder cancer at high risk for recurrence.[36] Among 63 patients with histologically confirmed malignancies, 13 lesions (20.6%; 95% CI, 11.5% to 32.7%) were only detected by blue light cystoscopy (P<.0001), including one high-grade Ta tumor, six low-grade (LG) Ta tumors, one papillary urothelial neoplasm of low malignant potential (PUNLMP), and five CIS. None of the patients with CIS tumors had positive cytology and had no history of CIS. Furthermore, 34.6% of CIS lesions were only detected by blue light cystoscopy (95% CI, 17.2% to 55.7%).

Importantly, HAL-assisted blue light cystoscopy detected additional tumors in 46% of trial participants.[36] This implies that if we opt not to use blue light cystoscopy in patients with negative cytology, we might miss close to half of these additional recurrent bladder tumors. Therefore, I recommend against relying on cytology alone when deciding whether to perform blue light cystoscopy. Instead, one should take all known risk factors for recurrence into account.

NARROW BAND IMAGING

Narrow band imaging is an alternative method of advanced cystoscopic imaging that does not require the use of fluorescent dyes. Instead, optical filters are placed in the light source of the video endoscope system, narrowing the bandwidth of emitted light emitted to between 415 and 540 nm.[7] This increases the relative intensity of blue and green light while minimizing red light. Hemoglobin strongly absorbs green and blue light, increasing the contrast between mucosal tissue and surface capillaries and submucosal blood vessels.

In six separate cohort studies, narrow band imaging detected bladder tumors with a sensitivity of 93% to 100%, and with a specificity of 69% to 85%.[37,38,39,40,41,42] Notably, 12% to 27% of tumors were only detected with narrow band imaging.

Recently, the single-blind, randomized, multicenter trial Clinical Research Office of the Endourological Society (CROES) trial compared TURBT with either white light or narrow band imaging among 965 patients with non-muscle-invasive bladder cancer.[43] Narrow band imaging did not significantly reduce overall rates of recurrence (27.1% vs. 25.4%, respectively). However, among patients at low risk for recurrence (those without CIS and with solitary TaLG tumors measuring less than 30 mm), TURBT with narrow band imaging reduced the rate of recurrence by nearly five-fold (5.6%) compared with white light-assisted TURBT (27.3%; P=.002). Since these are the very patients who typically receive TURBT without additional adjuvant intravesical chemotherapy or BCG, narrow band imaging clearly helps these patients.

Finally, we should consider the multicenter DaBlaCa-7 study, which examined the clinical relevance of narrow band imaging when used with flexible cystoscopy.[44] The study included 955 Danish patients with either hematuria or known recurrence of non-muscle-invasive bladder cancer. Patients received white light cystoscopy, a clinical decision was made, and narrow band imaging cystoscopy was then performed. In all, 23% of patients had tumors identified by white light cystoscopy narrow band imaging and detected additional tumors in 7% of these patients and altered clinical decision-making in 1.9% of patients. Among patients with recurrent non-muscle-invasive bladder cancer, narrow band imaging also was significantly more sensitive than white light cystoscopy alone (100% vs. 83.2%; P<.05).[44]

Narrow band imaging did lead to a higher rate of false positives in this study (respective specificities, 86.5% vs. 92.1% with white light; P<.05). Blue light cystoscopy also has been tied to a small increase in false positives; in the prospective registry study, the rate was 30% versus 25% with white light cystoscopy alone. In my experience, false positives become less with common with experience and do not outweigh the advantages of either technique.

GUIDELINES FOR AND REIMBURSEMENT OF ENHANCED CYSTOSCOPY

Based on all the data available, joint guidelines from the American Urological Association (AUA) and the Society of Urologic Oncology (SUO) state that clinicians should offer blue light cystoscopy with Cysview®, if available, at the time of TURBT to patients with non-muscle invasive bladder cancer to improve rates of detection and recurrence.[45] The guideline authors classify this recommendation as moderate based on B-grade evidence.

These joint AUA/SUO guidelines also state that clinicians may consider the use of narrow band imaging to increase detection and decrease recurrence of non-muscle-invasive bladder cancer, based on C-grade evidence. The difference in strength between these recommendations reflects the more abundant and robust evidence supporting the clinical value of blue light cystoscopy over white light cystoscopy alone.

In addition to clinical benefits, cost and reimbursement are additional considerations. Studies indicate that HAL-assisted blue light cystoscopy ultimately is more cost-effective than standard white light cystoscopy alone. In a recent analysis of U.S. data, for example, initial TURBT performed with both blue and white light cystoscopy was projected to save more than $4,600 per patient over 5 years, compared with white light cystoscopy only.[46] By preventing or postponing the recurrence and progression of bladder cancer, blue light cystoscopy can avoid the cost, pain, and risk of additional operations.[47]

In keeping with these findings, the Centers for Medicare and Medicaid Services (CMS) has established a new permanent reimbursement code (A9589: ''instillation, hexaminolevulinate hydrochloride'') for HAL-assisted blue light cystoscopy performed with a flexible cystoscope.[48,49] The CMS also has increased its reimbursement of some (but not all) hospital-based procedures in which Cysview® is used.

Summary

Bladder cancer is a complex disease. The initial step in the diagnosis and management of all patients is a well-performed cystoscopy and tumor resection. When optimally performed, TURBT not only provides the correct diagnosis but also prevents or delays recurrence and progression and reduces the burden of management of successive tumor events. Achieving this standard requires not only technical skill but also due diligence and attention to details. During every TURBT, complete, accurate, and systematic recording of procedural decisions and clinical and prognostic data are paramount.

Multiple studies support the clinical and economic value of enhanced cystoscopy for both bladder cancer surveillance and TURBT. Blue light cystoscopy and narrow band imaging have distinct advantages. I use both techniques regularly in my practice personalizing the choice to the specific patient and situation. ■

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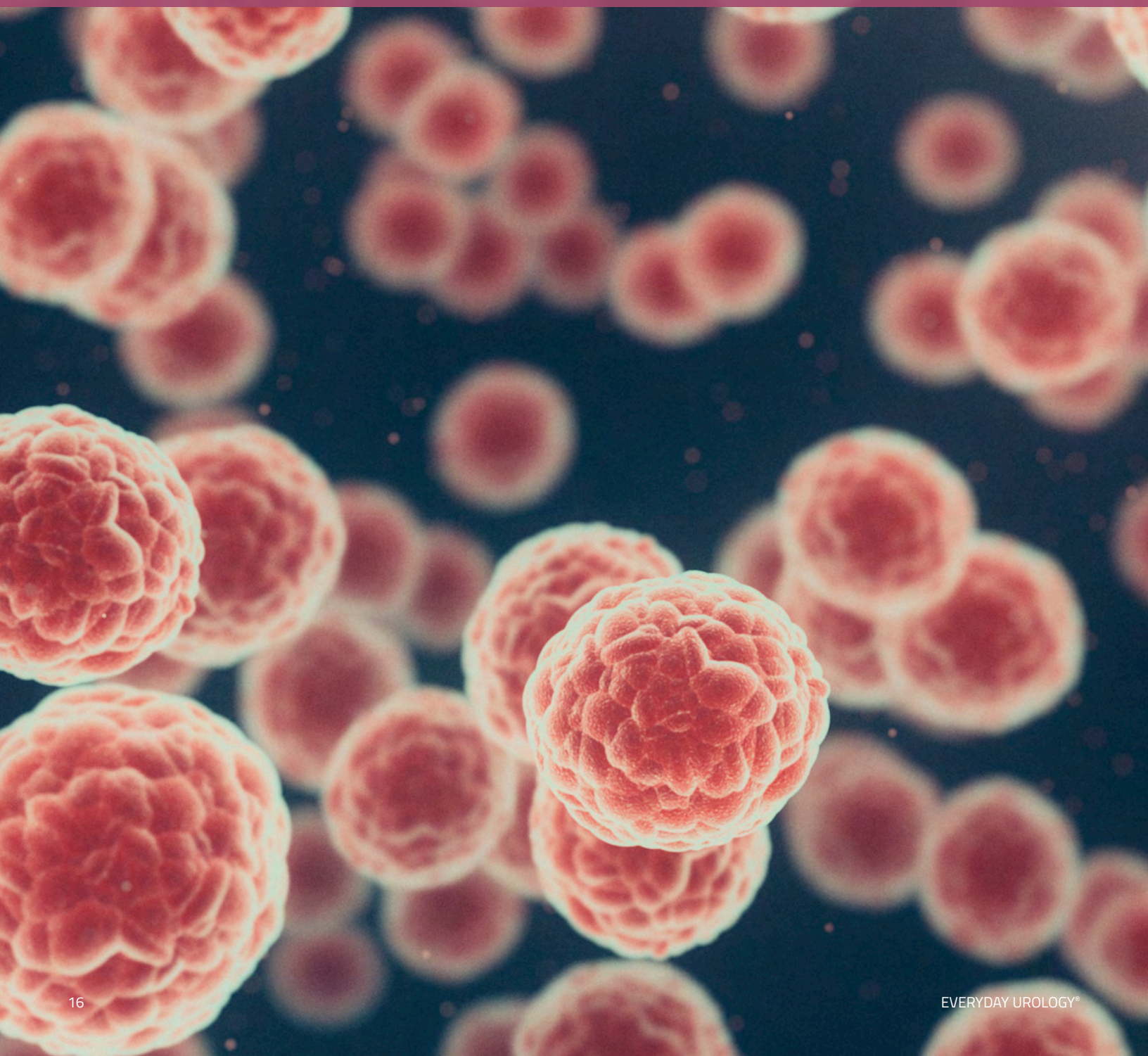
Immuno-Oncology: The Urologist's Role

By Noah M. Hahn, MD



Noah M. Hahn, MD, was born in Valparaiso, Indiana and attended the University of Notre Dame where he graduated in 1994 with a degree in mechanical engineering. He finished his medical school training at the Indiana University School of Medicine in 2000. He completed a transitional year internship at Emory University in 2001, his internal medicine residency at Duke University in 2003, and his hematology and oncology fellowship at the Indiana University Simon Cancer Center (IUSCC) in 2006. Upon completion of his fellowship training, he was appointed to the IUSCC oncology faculty and served as the leader of their prostate and bladder cancer programs. In addition, he served as the chief scientific officer of the Hoosier Cancer Research Group (formerly the Hoosier Oncology Group) and the executive officer of the Big Ten Cancer Research Consortium. In April 2014, Dr. Hahn joined the Johns Hopkins University School of Medicine faculty as the director of the medical oncology bladder cancer program with the academic rank of associate professor of oncology and urology.

This is an extraordinary time in urology. After decades of relative stagnation, patients with urothelial carcinoma are receiving approved immuno-oncologic drugs that significantly extend survival and are safer and more tolerable than chemotherapy.

The success of these treatments in metastatic bladder cancer has generated strong interest and promising early results for their use in localized disease. With this shift comes exciting opportunities for urologists and associated care teams to hone their immuno-oncologic expertise and partner with medical and radiation oncologists and other physician-specialists to create innovative new models for high-quality cross-disciplinary care.

Metastatic Disease

The initial phases of oncologic drug development often start in late-stage disease, where patients have scant treatment options. Bladder cancer is no exception. As recently as 2016, there were no approved therapies for metastatic urothelial carcinoma that had progressed during or after platinum-based treatment. Only approximately 10% of these patients responded to second-line chemotherapy with single-agent paclitaxel, docetaxel, or vinflunine (in Europe), and median overall survival (OS) typically was only 6 to 7 months.[1]

Clinician-researchers tried and failed for decades to improve outcomes for these patients. Then, in October 2016, the international, phase III KEYNOTE-045 trial confirmed the superior efficacy and safety of the programmed cell death 1 (PD-1) inhibitor pembrolizumab (200 mg IV every 3 weeks for up to 2 years) versus investigator's choice of chemotherapy with paclitaxel, docetaxel, or vinflunine.[1] In the intention-to-treat population of 542 post-platinum patients with advanced transitional cell-predominant urothelial carcinoma, objective rates of response were 21.1% with pembrolizumab versus 11.4% with chemotherapy. Furthermore, after a median follow-up of 14.1 months, median duration of response was not reached with pembrolizumab versus 4.3 months with chemotherapy, and 68% of patients continued to respond to pembrolizumab for at least 12 months compared with only about 35% of chemotherapy recipients.

However, the most striking result from KEYNOTE-045 was overall survival (OS), a median of 10.3 months (95% CI, 8.0 to 11.8 months) in the pembrolizumab arm versus 7.4 months (6.1 to 8.3 months) with chemotherapy. Estimated rates of OS at 12 months were 43.9% and 30.7%, respectively, for a statistically significant hazard ratio (HR) for death of 0.73 (95% CI, 0.59 to 0.91; P = .0022).[1]

Pembrolizumab also was more tolerable than chemotherapy. Despite a median of 2 months more treatment exposure, only 61% of patients who received pembrolizumab developed treatment-related adverse events versus 90% of chemotherapy recipients.[1] Pembrolizumab led to notably lower rates of grade 3 or higher toxicity (adverse events requiring intervention or changes in treatment) and serious adverse events.[1]

Pembrolizumab was the first agent to show an OS advantage over chemotherapy for the second-line treatment of metastatic urothelial carcinoma. This and its acceptable safety profile spurred its FDA approval for use in metastatic urothelial carcinoma that had progressed during or after platinum-based chemotherapy.[2]

Table 1 summarizes results from KEYNOTE-045 as well as other key trials of immuno-oncologic agents in patients with metastatic urothelial cancer.[1, 3, 4, 5, 6, 7, 8, 9, 10, 11,12] A birds-eye view shows that rates of grade 3-4 toxicity are approximately 15% in the single-agent setting. Approximately 15% of unselected patients respond to second-line immuno-oncologic monotherapy and this response increases to approximately 30% if we combine immuno-oncologics, such as PD-1 inhibitor and an anti-cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) agent. Used as first-line treatment, immuno-oncologic therapy induces responses in approximately 25% in unselected patients.

The results of these trials led to a flurry of approvals in the United States and Europe **(Figure 1)** that have revolutionized how we treat metastatic urothelial cancer. Since 2016, the FDA has approved five immune checkpoint inhibitors for use in post-platinum advanced or metastatic urothelial carcinoma. In addition to pembrolizumab (Keytruda), these include the PD-1 inhibitors atezolizumab (Tecentriq) and nivolumab (Opdivo) and the programmed death-ligand 1 (PD-L1) inhibitor durvalumab (Imfinzi), and avelumab (Bavencio).[1, 2, 8, 3, 12] Additionally, atezolizumab and pembrolizumab have received FDA approval for use in platinum-ineligible patients as well as cisplatin-ineligible patients with high tumor levels of PD-L1 expression.[6,7]

POPULATION	TARGET	DRUG	STUDY	RR (ALL)	RR (PD-L1+)	PD-L1 AB	MOS (ALL)	MOS (PD-L1+)	GR 3/4 TOXICITY
2L	PD-L1	atezolizumab	ImVigor 210	15%	27%	SP142	7.9 m	11.4 m	16%
		atezolizumab	ImVigor 211	13%	23%	SP142	8.6 m	11.1 m	<10%
		durvalumab	1108	18%	28%	SP263	18.2 m	20.0 m	7%
		avelumab	Javelin	17%	24%	73-10	6.5 m	8.2 m	8%
	PD-1	pembrolizumab	Keynote-045	21%	22%	22C3	10.3 m	8.0 m	15%
		nivolumab	Checkmate 275	20%	24%	28-8	8.7 m	11.3 m	18%
	PD-L1/ PD-1 + CTLA-4	nivolumab + ipilimumab	Checkmate 032	39%	NR	28-8	NR	NR	31%
		durvalumab + tremelimumab	4190	21%	29%	SP263	9.5 m	18.9 m	29%
1L	PD-L1	atezolizumab	ImVigor 2010	23%	28%	SP142	15.9 m	12.3 m	16%
	PD-1	pembrolizumab	Keynote 052	39%	47%	22C3	11.5 m	18.5 m	16%

Table 1: Key Trials of Immuno-Oncologics in Metastatic Urothelial Cancer [26,27,28,29,30,31,32,33,34,35]
RR, response rate; mOS, median overall survival; Gr, grade

Do Immuno-Oncologics Make Sense in Earlier-Stage Disease?

The efficacy of immuno-oncologic agents in advanced urothelial cancer has naturally raised questions about their potential use in earlier-stage disease. Could this approach achieve higher response rates and—most importantly—increase rates of cure for patients with muscle-invasive and non-muscle invasive bladder cancer?

To explore these questions, we first need to ask whether this approach makes sense biologically. Although urothelial cancer involves a host of potential targets for immunotherapy/immuno-oncology, I will focus on the PD-1/PD-L1 pathway because it is the target of currently approved agents in the metastatic setting. What role does this pathway play in localized disease?

Hints come from recent progress in understanding the mechanism of action of intravesical Bacillus Calmette-Guérin (BCG). For years, we have known that BCG incites an inflammatory response, but recent advances in bench research tools have enabled us to take a closer look. These studies confirm that BCG affects both innate and adaptive immunity **(Figure 2)**. With regard to the innate immune system, BCG molecules are phagocytosed, processed, and presented as antigens that trigger cell-mediated responses by natural killer (NK) cells and tumor-associated macrophages.[24] However, BCG also can lyse urothelial cells (apoptosis), thereby releasing urothelial proteins that are phagocytosed and presented as antigens to surrounding immune cells that function in adaptive immunity (what we think of as the "memory" response). It remains unclear which type of immunity underlies the majority of BCG-induced cures, but most experts now agree that both innate and adaptive immunity are important to responses to intravesical BCG.

A second piece of evidence lies in data linking the PD-1 pathway to BCG resistance. In one study, Mayo Clinic investigators used immunohistochemical staining to examine pathologic specimens from 280 patients with high-risk non-muscle-invasive or muscle-invasive urothelial carcinoma.[13] They found that stage progression correlated significantly with both high-grade tumor pathology and PD-L1 expression.[13] Furthermore, in a subset of paired tumor specimens, the proportion with high PD-L1 expression rose from 19% in the BCG-naïve setting to 69% in the BCG-relapsed setting.[13] This finding suggests that upregulation of the PD-1 pathway plays a role in BCG resistance, indicating that PD-1 blockers such as pembrolizumab might effectively treat these patients.

Animal studies also provide useful preclinical data. In one study at the National Cancer Institute, researchers compared peritoneal (systemic) injections of either saline or the anti-PD-L1 antibody avelumab in mice with non-muscle-invasive bladder tumors.[14] By day 21, avelumab produced superior tumor control based on both bladder weight and fluorescent imaging.

Together, these studies support the role of immunity and the PD-1 pathway in both BCG treatment response and relapse. They justify the study of checkpoint inhibition in patients with localized urothelial cancer.

Key Ongoing Trials in Localized Disease

Several dozen trials of immuno-oncologic trials in localized bladder cancer are underway. They are focusing on adjuvant or neoadjuvant therapy for muscle-invasive disease as well as the use of immunotherapy for patients with BCG-unresponsive non-muscle-invasive disease. Furthermore, some trials are focusing on single-agent immunotherapy while others are exploring adding an immuno-oncologic to BCG or gemcitabine, with or without cisplatin or external beam radiation (and at least one trial [NCT02845323] is examining combination immuno-oncologic therapy: nivolumab with or without the anti-CD137 antibody urelumab.).

This is a remarkable expansion of clinical trials in localized bladder cancer—in fact, a near-doubling of what we saw just a decade ago. We are witnessing intense drug development that I view as positive for patients and clinicians alike.

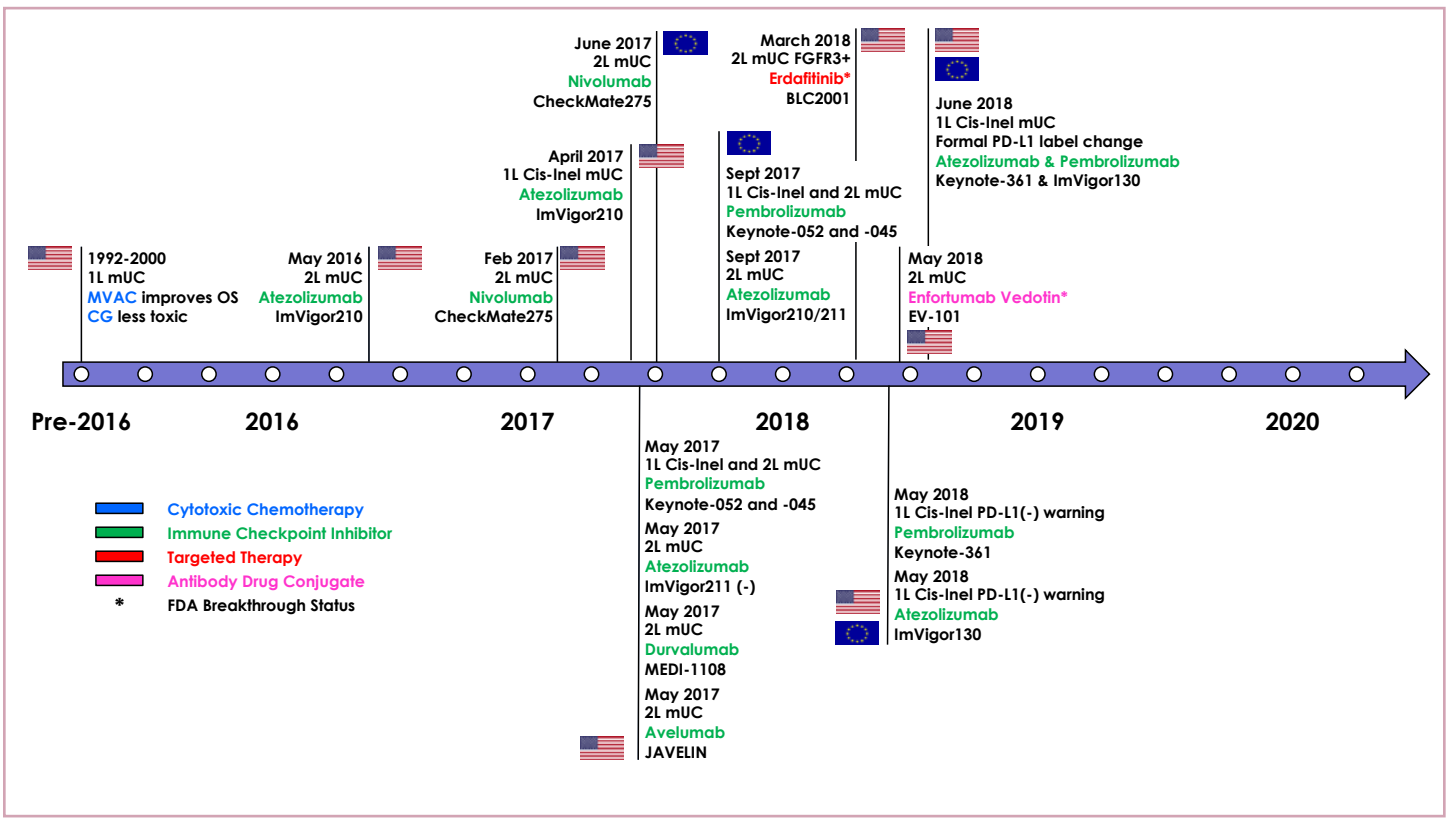


Figure 1: Regulatory Approval Timeline of Approvals in Advanced Bladder Cancer Therapies

Muscle-invasive disease

For patients with muscle-invasive bladder cancer, three large randomized phase 3 registration trials are underway. In the adjuvant setting, ImVigor 010 (NCT02450331) is randomly assigning approximately 800 post-operative patients with urothelial cancer at high risk for recurrence to receive the PD-L1 inhibitor atezolizumab (1200 mg every 3 weeks for 1 year) or to undergo observation only, which is the current standard of care for this population post-cystectomy.

ImVigor 010 investigators have defined high-risk disease as pathologic T2-T4 or node-positive (N+) margin-negative disease in patients who have received prior cisplatin-based neoadjuvant chemotherapy, ***or*** T3-4 or N+ margin-negative disease in patients who are ineligible for or decline cisplatin and have not received neoadjuvant therapy. The primary endpoint of this trial is disease-free survival (DFS). Although trials of adjuvants for bladder cancer take longer to read out than those in the metastatic setting, topline results are expected within the next one to two years. If immuno-oncologic treatment with atezolizumab shows a statistically significant and clinically meaningful benefit after cystectomy, this could be practice-changing.

In a parallel vein, the phase 3 Alliance A031501 (AMBASSADOR) trial (NCT03244384) has randomly assigned approximately 740 post-operative patients with high-risk, muscle-invasive bladder or upper urinary tract urothelial cancer to undergo observation only or to receive pembrolizumab (200 mg once every 3 weeks for 1 year).[17] Resembling ImVigor 010, high-risk disease is defined as pT2 or higher-grade or N+ disease in recipients of neoadjuvant chemotherapy ***or*** pT3 or higher-grade or N+ disease in those who refuse or are ineligible for cisplatin. This trial is being led in the United States by the Alliance for Clinical Trials in Oncology and in Europe by the European Organisation for Research and Treatment of Cancer (EORTC). Co-primary endpoints are DFS and OS.

Finally, the phase 3 CheckMate 274 trial (NCT02632409) is randomly assigning approximately 700 post-cystectomy patients with high-risk muscle-invasive bladder cancer to receive either

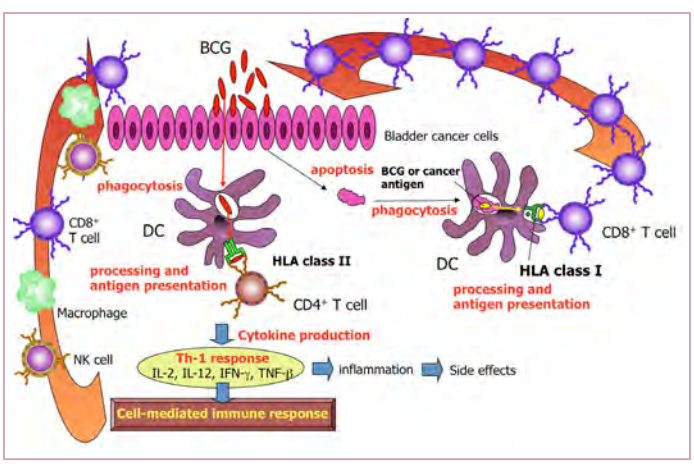


Figure 2: BCG Immunology Targets [25]

nivolumab (3 mg/kg) or placebo every 2 weeks for 1 year.[19] High-risk disease is defined similarly to the ImVigor 010 and AMBASSADOR trials. The primary endpoint is DFS.

Non-muscle-invasive disease

High-risk non-muscle-invasive bladder cancer (NMIBC) includes any carcinoma in situ (CIS), T1 tumors, or large high-grade Ta tumors. Currently, radical cystectomy is recommended for high-risk NMIBC patients that are refractory to or have relapsed after BCG therapy,[21] but perioperative risks and adverse implications for quality of life make this option infeasible or unacceptable for many of our patients. Consequently, high-risk NMIBC is an area of high unmet clinical need. For the past several years, the FDA has encouraged the use of single-arm clinical trials to hasten the development of effective and tolerable therapies for this population.[22]

Several such ongoing trials merit mention. First, the Southwest Oncology Group (SWOG) is leading a single-arm phase 2 study (NCT02844816) of atezolizumab (1200 mg every 3 weeks for up to 1 year) in BCG-unresponsive non-muscle-invasive bladder cancer.[18] This trial has enrolled approximately 130 patients to date. Coprimary endpoints are 6-month complete response (CR) and relapse-free survival.

Similarly, the single-arm, open-label, phase 2 KEYNOTE-057 study (NCT02625961) is evaluating monotherapy with pembrolizumab (200 mg every 3 weeks for up to 2 years) in cystectomy-ineligible or cystectomy-refusing patients with high-risk BCG-unresponsive non-muscle-invasive bladder cancer, defined as high-grade Ta, T1, or CIS. Primary endpoints are CR for patients with CIS, and DFS for patients without CIS. Approximately 260 patients are planned to enroll.

Interim KEYNOTE-057 results were reported at the 2018 meeting of the European Society for Medical Oncology (ESMO). Among 103 heavily pretreated patients with CIS, pembrolizumab therapy produced 3-month complete response rates (CRs) in 38.8% (95% CI, 29.4% to 48.9%). Median time to CR was 12.4 weeks, and 72.5% of CRs persisted at last follow up with a median follow-up of 14 months. In all, 80% CRs lasted at least 6 months and 54% lasted at least 9 months. Among the 25% of patients who experienced recurrence, none progressed to muscle-invasive or metastatic disease during follow-up. These are encouraging results because they point to some clearance of tumor at 3 months. However, data are not yet mature enough to support conclusions about duration of response.

When evaluating whether to shift systemic treatment to earlier-stage disease, we must consider not only rates and types of toxicities, but also whether these particular side effects are acceptable to a wider community of patients and physicians. Thus far, KEYNOTE-057 findings indicate that pembrolizumab has a similar toxicity profile in earlier-stage as in advanced bladder cancer. In all, 12.6% of patients developed grade 3-5 treatment-related adverse events. Treatment-related adverse events that were immune-mediated were uncommon but included type 1 diabetes mellitus as well as adrenal insufficiency, hypophysitis, pruritus, and generalized rash (1 patient each, or 1%). Additionally, one patient died from complications of grade 3 treatment-emergent immune-mediated colitis that was inadequately managed with corticosteroid therapy. This unfortunate result reflects what we see in the metastatic setting, where approximately 0.5% of patients who receive immuno-oncologic monotherapy develop a potentially fatal autoimmune toxicity. These are rare events, but they underline the need to carefully monitor patients for toxicities and implement systems ahead of time to ensure that adverse events are detected quickly and managed appropriately.

Based on the interim results of KEYNOTE-057, investigators in December 2018 opened the phase 3 KEYNOTE-676 trial (NCT03711032), which is assessing combination therapy with pembrolizumab and BCG for patients with non-muscle-invasive bladder cancer that is persistent or recurrent after BCG induction. There are three additional registrational trials underway of systemically administered PD-1/PD-L1 agents in NMIBC populations. The four-arm, randomized phase 2 CheckMate 9UT (NCT03519256) study is comparing nivolumab (480 mg every 4 weeks), with or without the investigative agent BMS-986205 (100 mg per day), with or without BCG in patients with BCG-unresponsive non-muscle-invasive bladder cancer.[23] BMS-986205 is an immunologic modulator that targets indoleamine 2,3-dioxygenase 1 (IDO1) to promote the proliferation and activation of dendritic cells, NK cells, and T lymphocytes.[22] Approximately 440 patients will be enrolled with primary endpoints of CR and RFS. In the BCG-naïve high-risk NMIBC population, the randomized phase 3 POTOMAC trial (NCT03528694) will enroll 975 patients to treatment with durvalumab (1500 mg every 4 weeks) with or without BCG with a disease-free survival (DFS) primary endpoint. Similarly, the randomized phase 3 ALBAN trial (NCT03799835) will enroll 614 patients to atezolizumab treatment (1200 mg every 3 weeks) with or without BCG also with a DFS primary endpoint. Collectively, the results of these studies should help answer questions about whether combining systemic and intravesical immunotherapies can improve the rate, depth, and duration of response in localized urothelial cancer.

Impact of Immuno-Oncologics on Urology Practice

Immuno-oncologic agents have so far produced durable responses in advanced urothelial cancer and initial responses in high-risk localized BCG-unresponsive patients. We are not yet at the point of discussing their potential for cure, but we are seeing patients live longer than ever before.

Translating these findings into real-world clinical practice requires careful planning and honest discussions with partners, care teams, and colleagues across disciplines. For urology practices, I recommend starting by exploring the group's philosophy on establishing an advanced practice in this area. A single physician champion might develop immuno-oncologic expertise and see patients, but who will cover at 4:30 p.m. on a Friday, when that person is on vacation and a patient calls about a possible toxicity? We need clear communication with partners regarding expectations to ensure reliable coverage and overall success.

Another early step is to establish dependable relationships with other specialties, such as medical and radiation oncology, pathology, and oncologic pharmacy. It is important that these are solid relationships to optimize the patient experience and outcomes.

On a related note, I suggest clarifying the infusion center infrastructure—will the urology practice provide this directly or refer patients to a hospital or outpatient center?

Another consideration is how to keep stakeholders current on available immuno-oncologic drugs and regimens and best practices for their use. Both the urology and oncology fields will require significant education—most oncologists are unfamiliar with treating non-muscle-invasive bladder cancer and most urologists have not previously administered systemic immunotherapies. This is a good opportunity for educational advances in both disciplines. Finally, patients with high-risk muscle invasive disease are at risk for metastasis, and we need a plan in place ahead of time to seamlessly transition patients to oncology or palliative care.

Summary

The use of immuno-oncologic agents leads to durable tumor responses in a minority of patients with metastatic urothelial carcinoma and is showing early promise for treating localized, high-risk BCG-nonresponsive or recurrent disease. Clinical trials are underway that should help clarify whether and how these drugs can be extended to earlier-stage settings, where the bar is higher with regard to both safety and successful clinical outcomes.[15] As this research continues, we anticipate a better understanding of which patient subgroups will significantly benefit from immuno-oncologics and when and how to use combination regimens.

The use of checkpoint inhibitors and other immuno-oncologic agents in earlier-stage patient populations will require urology group practices to hone their expertise, team education, cross-disciplinary relationships, and infrastructure for activities ranging from infusions to toxicity management to palliative care. This requires careful planning and communication but offers exciting chances to work across disciplines to significantly improve survival and quality of life for our patients. The shift of immuno-oncologic therapy to earlier-stage use is especially promising because this is where the possibility for cure is highest. ■

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ASCO Genitourinary Cancers Symposium 2019

The 2019 Genitourinary Cancers Symposium focused on translating evidence in multidisciplinary care. A multidisciplinary approach provides a rational and coordinated way to evaluate and treat patients with complex diseases by bringing health care providers in the surgical, medical, and radiation oncology disciplines together.

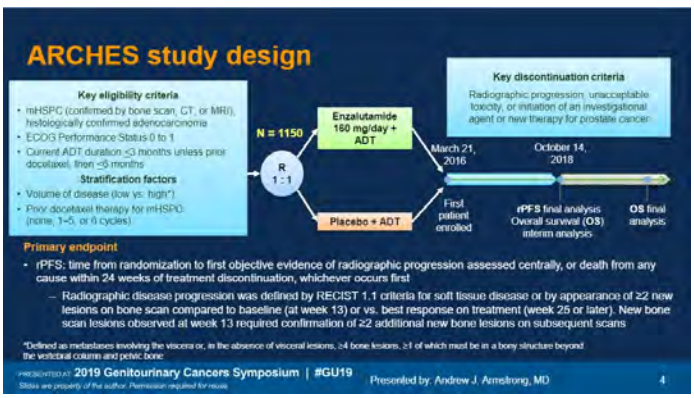
In this issue's Spotlight section, Jason Zhu, MD, fellow at the Division of Hematology and Oncology of Duke University, provides written coverage of selected ASCO GU presentations focused on optimizing diagnosis and treatment of clinically significant high-risk localized prostate cancer. Also, included is coverage in the areas of kidney and bladder cancer delivered by world renowned multidisciplinary providers.

Prostate Cancer

Phase 3 study of androgen deprivation therapy (ADT) with enzalutamide (ENZA) or placebo (PBO) in metastatic hormone-sensitive prostate cancer (mHSPC): The ARCHES trial

Dr. Andrew J. Armstrong

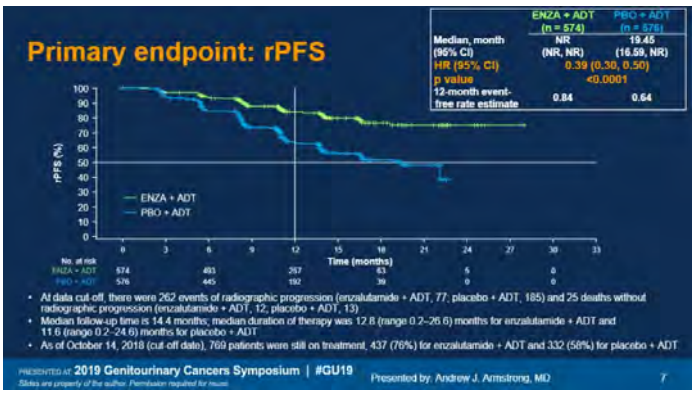
Enzalutamide is an androgen receptor signaling inhibitor which inhibits the androgen receptor signaling pathway by blocking the binding of androgen to the androgen receptor as well as inhibition of nuclear translocation of the androgen receptor.[1] Enzalutamide has been shown to be effective in improving overall survival in patients with metastatic castration resistant prostate cancer (mCRPC) both before and after chemotherapy.[2,3] First in 2012, AFFIRM showed in a population of post-chemotherapy mCRPC patients that enzalutamide improved overall survival compared with placebo (18.4 months vs 13.6 months, HR 0.63, p<0.001), which led to its first FDA approval in prostate cancer.[2] Next in 2014, PREVAIL showed that enzalutamide was able to decrease the risk of radiographic progression and death and delay chemotherapy which broadened its FDA approval to all patients with mCRPC.[3] Most recently, based on the results of PROSPER which showed that enzalutamide significantly reduced the risk of developing M1 CRPC by prolonging metastasis free survival (36.6 vs 14.7 months), enzalutamide gained an FDA indication in 2018 for use in men with non-metastatic CRPC with a PSA doubling time of less than 10 months.[4] This study aims to provide evidence for the only space left untouched by enzalutamide – metastatic castration sensitive prostate cancer.



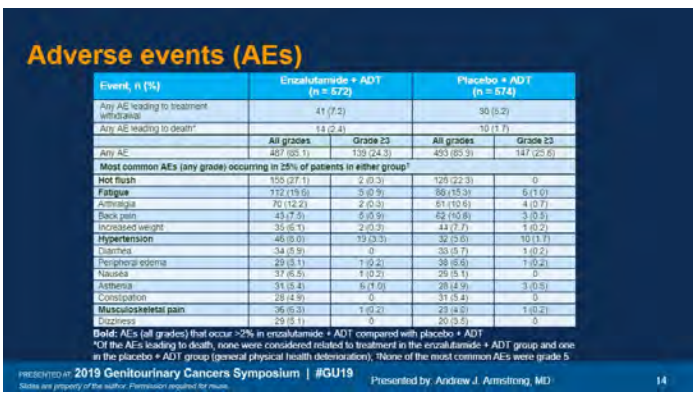
This was a phase III, international double-blind clinical trial which randomized patients to enzalutamide 160 mg/day plus ADT or placebo plus ADT. Patients were stratified by disease volume based on CHAARTED criteria as well as prior docetaxel therapy (high volume = presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis). The primary endpoint of the study was radiographic progression free survival or death within 24 weeks of stopping treatment.

A total of 1150 men were randomized to enzalutamide or placebo. Baseline characteristics were well balanced between the two cohorts. The majority of patients (63%) had metastatic prostate cancer at initial diagnosis. Most patients (63%) also had high volume disease. 18% of patients had prior docetaxel chemotherapy.

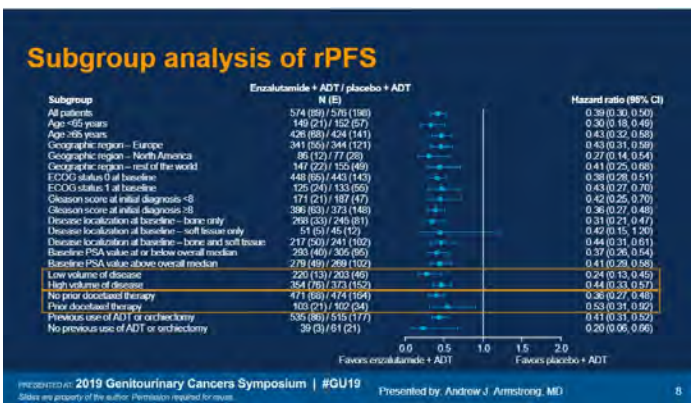
At a median follow up of 14.4 months, combination enzalutamide plus ADT significantly improved radiographic progression free survival in all pre-specified subgroups of disease including patients who had received prior docetaxel chemotherapy.



68.1% of patients on enzalutamide were able to reach a PSA<0.2, compared to 17.6% of patients on placebo. The objective response rate was 83.3% for enzalutamide arm and 17.6% for placebo + ADT arm.



In terms of safety, grade 3/4 adverse events were similar between the enzalutamide group and placebo patients (23.6% vs 24.7%). The most frequent AEs were hot flashes, fatigue, and arthralgia, which were all present >10% in both the placebo arm and enzalutamide arm (as both arms include ADT). Quality of life was not significantly different between the two arms, as defined by FACT-P (The Functional Assessment of Cancer Therapy-Prostate).



Prostate Cancer

Enzalutamide significantly increases radiographic progression free survival for patients with metastatic castration sensitive prostate cancer. Importantly, subgroup analysis shows that this improvement in rPFS holds in both high and low volume patients, as well as for patients who have had prior docetaxel chemotherapy. Analysis of overall survival is immature at this time due to a very low number of deaths in both arms. Enzalutamide was well tolerated and did not decrease the quality of life. Based on this preliminary data, I suspect enzalutamide will eventually be added to the growing armamentarium of therapies (abiraterone, docetaxel) for patients with mCSPC. Future studies should help answer sequencing questions as well as how to choose the best initial therapy.

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Presented by: Andrew J. Armstrong, MD

Written by: Jason Zhu, MD. Fellow, Division of Hematology and Oncology, Duke University; Twitter: @TheRealJasonZhu

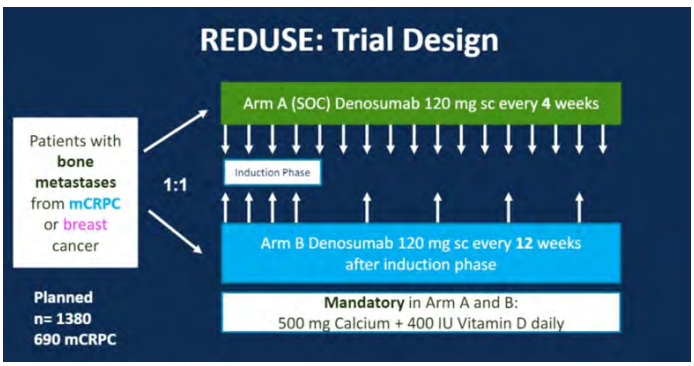
Incidence of hypocalcemia in patients with castration-resistant prostate cancer treated with denosumab: Data from a non-inferiority phase III trial assessing prevention of symptomatic skeletal events (SSE) with denosumab administered every four weeks (q4w) versus every 12 weeks (q12w)—SAKK 96/12 (REDUSE)

Dr. Silke Gillessen

Osteoblastic bone lesions are the most common site of metastasis in men with prostate cancer and may contribute significant comorbidities including pathologic fractures and epidural spinal cord compression. Quality of life is significantly impacted by bone metastasis and thus palliative treatment of bone metastases is one of the cornerstones of management for men with advanced prostate cancer. For the treatment of bone metastases as well as the prevention of complications, osteoclast inhibition may be helpful.

In patients with castration resistant prostate cancer and bone metastasis, a randomized, placebo-controlled trial in 2002 showed that zoledronic acid significantly reduced skeletal related events compared to those who received placebo and increased the median time to first skeletal related event.[1] Denosumab, a humanized monoclonal antibody which binds to RANK ligand, has also been shown to significantly delay the first skeletal related event, even more so than zoledronic acid in a randomized double blind study.[2] In a phase III study with 1904 patients (950 assigned to denosumab and 951 assigned to zoledronic acid), median time to first on-study skeletal-related event was 20.7 with denosumab compared with 17.1 months with zoledronic acid (hazard ratio 0.82, 95% CI 0.71-0.95; pp = 0.008). In that study, denosumab and zoledronic acid were given every four weeks. However, the optimal schedule of denosumab is unknown, and there does appear to be a dose dependent increase in osteonecrosis of the jaw.[3]

In this open label, randomized phase III non-inferiority study, the authors sought to determine what the time to first on trial symptomatic skeletal event was, defined as clinically significant pathologic fracture, radiation therapy to bone, or surgery to bone or spinal cord compression. The investigators also measured safety, time to first and subsequent on trial SSE, skeletal morbidity rate, quality of life, and health economic outcomes. The main hypothesis to be tested was whether or not denosumab efficacy is maintained at every 12 weeks compared with every 4 weeks.

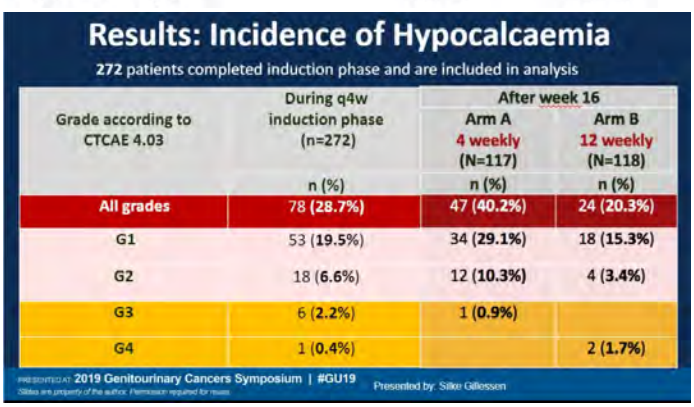


Eligibility criteria included patients with CRPC who had 3 more or bone metastases, a performance status of 0-2, corrected calcium of ≥2 mmol/L and ≤3 mmol/L with no history of osteonecrosis.

690 patients were randomly assigned to every 4 weeks vs every 12 weeks after a induction phase which included four doses given every 4 weeks. This interim analysis was completed after 3.5 years of trial accrual and all patients on study were placed on supplementation of calcium and vitamin D. Data from 282 patients is represented here.

During every four week induction phase, 28.7% of men experienced hypocalcemia. However, for patients who were switched to the every 12 week regimen, 52.3% of patients had improvement in hypocalcemia grade, compared with 26.3% of patients who rained on the every 4 week schedule.

	Arm A (N=57)	Arm B (N=44)
	n (%)	n (%)
Worsening of HC grade	23 (40.4%)	15 (34.1%)
HC grade unchanged	19 (33.3%)	6 (13.6%)
Improvement of HC grade	15 (26.3%)	23 (52.3%)



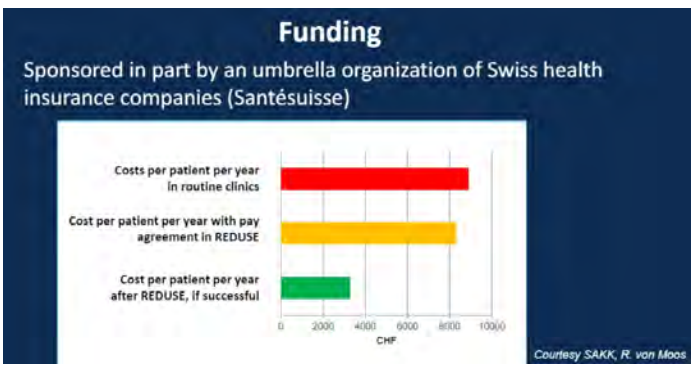
The incidence of all grade hypocalcemia was 40.2% for patients on q4 week treatment compared to 20.3% on q12 weekly treatment.

The rate of hypocalcemia shown in this trial was significantly higher than the initial denosumab vs zoledronic acid trial.

	REDUSE	Denosumab arm in initial trial vs zoledronic acid*
All grades	39.7%	13%
G 3/4	3.3%	5%

*Fizazi K et al, Lancet 2011

Lastly, and importantly, the author noted that this study was funded by an umbrella organization of Swiss health insurance companies and that this may be a promising source of funding for future drug de-escalation studies.



More patients (39%) experienced hypocalcemia than was previously reported in registration trials of denosumab (13%). The primary endpoint of this study has not been reported yet and Dr. Gillessen did not recommend making q12 week denosumab standard of care yet during the Q&A session. Clinicians should always be mindful of patients' vitamin D and calcium levels prior to treatments with denosumab and continue supplementation throughout treatment. Future drug de-escalation studies may be successfully funded by insurance companies.

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Presented by: Silke Gillessen, MD

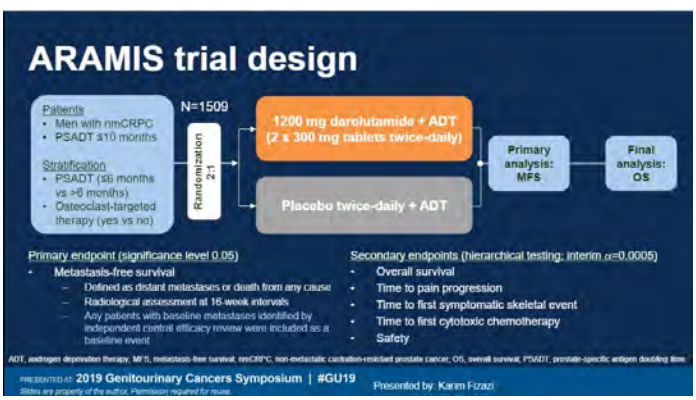
Written by: Jason Zhu, MD. Fellow, Division of Hematology and Oncology, Duke University; Twitter: @TheRealJasonZhu

ARAMIS: Efficacy and safety of darolutamide in nonmetastatic castration-resistant prostate cancer (nmCRPC)

Dr. Karim Fizazi

The treatment landscape for non-metastatic castration resistant prostate (nmCRPC) cancer is rapidly evolving. In 2018, Enzalutamide (July 2018) and Apalutamide (February 2018) became the first two drugs to obtain FDA approval for the treatment of nmCRPC. SPARTAN was a phase 3 double-blind, randomized study of apalutamide versus placebo in patients nmCRPC. Apalutamide significantly improved median metastasis free survival by 2 years in men with nmCRPC and also increased time to metastasis, progression free survival, symptomatic progression, and second progression free survival.[1] PROSPER was a double-blind, phase 3 trial, where patients with nmCRPC were randomly assigned to receive enzalutamide (at a dose of 160 mg) or placebo once daily. The median metastasis-free survival was 36.6 months for patients receiving enzalutamide compared with 14.7 months for patients receiving placebo (HR for metastasis or death, 0.29; 95% confidence interval, 0.24 to 0.35; P<0.001).[2] Both of these studies enrolled men who had a PSA doubling time of 10 months or less. This trial, ARAMIS, aims to study the efficacy of darolutamide in a similar population of patients with nmCRPC.

This is a placebo controlled, double blind study which randomized patients with non-metastatic castration resistant prostate cancer to darolutamide 600 mg twice daily or placebo. Patients were stratified by PSA doubling time of greater than 6 months and less than 6 months, as well as use of an osteoclast targeting agent. Metastasis free survival (MFS) was the primary endpoint and radiographic imaging was done every 16 weeks.

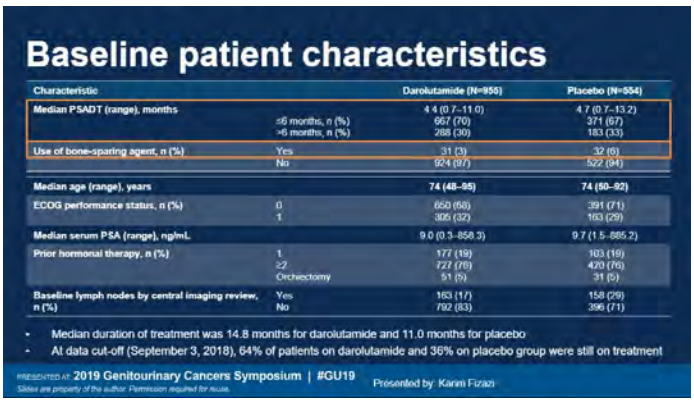


A total of 1509 patients were recruited and randomized, 955 to darolutamide and 554 to placebo. Baseline characteristics were balanced and median PSA doubling time was 4 months in both arms. The median age was 74 for all patients and the median PSA was 9.0 in the darolutamide arm and 9.7 in the placebo arm.

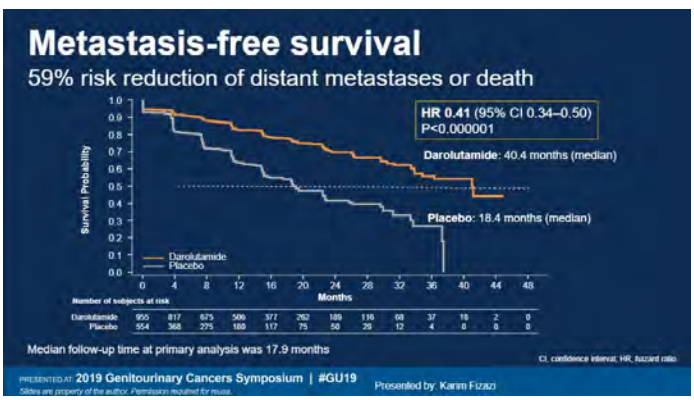
Median metastasis free survival was 40.4 months with darolutamide compared with 18.4 months with placebo (hazard ratio 0.41; 95% confidence interval [CI] 0.34–0.50; 2-sided p<0.0001) and overall survival trended towards improvement as well, with a hazard ratio of 0.71 (95% CI 0.50–0.99, 2-sided p=0.045). The MFS benefit was consistent across all pre-specified subgroup analyses (PSA doubling time above and below 6 months, patients

Prostate Cancer

on osteoclast targeted therapies, patients with high and low baseline PSA, and patients in all age groups.



In terms of safety, there was essentially no difference in discontinuation of darolutamide vs placebo (8.9% vs 8.7%) due to adverse events. There were no significant differences in grade 3-5 adverse events between placebo and darolutamide, and the only AE which occurred in more than 10% of patients was fatigue.



Based on the results of ARAMIS, darolutamide appears safe and effective for men with nmCRPC, increasing both metastasis free survival and overall survival at this interim analysis. Darolutamide will be the third drug to join the nmCRPC space, along with apalutamide and enzalutamide. Darolutamide is structurally unique compared with enzalutamide and apalutamide and does not cross the blood brain barrier – this may help patients avoid the fatigue that is sometimes seen with the other two therapies. The side effect profiles and final analysis of quality of life will be important for future studies to help clinicians decide which of these three drugs should be used for their patients with nmCRPC.

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Presented by: Karim Fizazi, MD, PhD

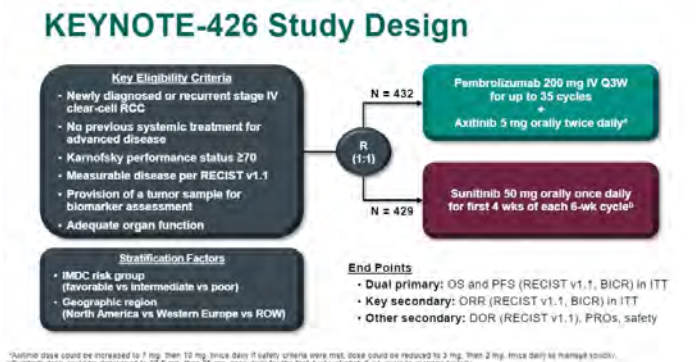
Written by: Jason Zhu, MD. Fellow, Division of Hematology and Oncology, Duke University; Twitter: @TheRealJasonZhu

Kidney Cancer

Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for locally advanced or metastatic renal cell carcinoma (mRCC): phase III KEYNOTE-426 study


Dr. Thomas Powles

Combination VEGF inhibition with immunotherapy has shown promising results in several phase I/II studies. During ASCO 2018, Dr. Lee et al presented a study of 30 patients with mRCC who were treated with Pembrolizumab and Levantinib, and this combination yielded an overall response rate of 66.7% by RECIST v1.1 and irRECIST with a median duration of response of 18.4 months.[1] 97% of patients experienced some tumor size reduction from baseline. A phase II study of Avelumab plus axitinib was presented at 2017 ASCO and this combination achieved an ORR of 58.20%.[2] Preliminary data regarding the combination of pembrolizumab and axitinib was initially presented at GU ASCO 2018, and out of 52 patients, 73.1% of patients had an objective response with a median PFS of 20.9 months.[3] This abstract provides the phase III update to that data.

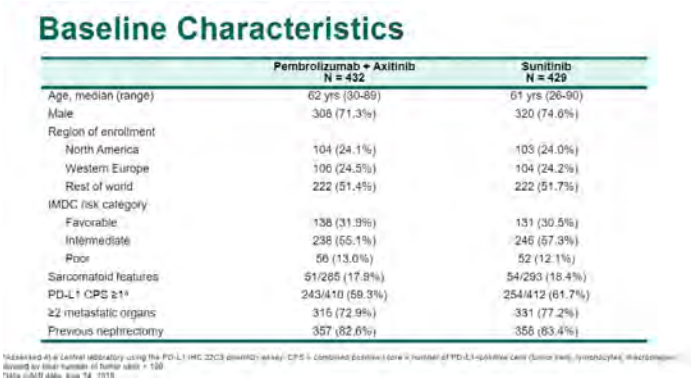


Summary

This global phase III study enrolled patients with untreated metastatic clear cell RCC and randomized patients to receive either pembrolizumab plus axitinib (PA) or sunitinib. Pembrolizumab was given in standard fashion at a dose of 200 mg every 3 weeks and axitinib was given at a dose of 5 mg twice a day. Sunitinib was dosed at 50 mg daily, 4 weeks on, 2 weeks off schedule.

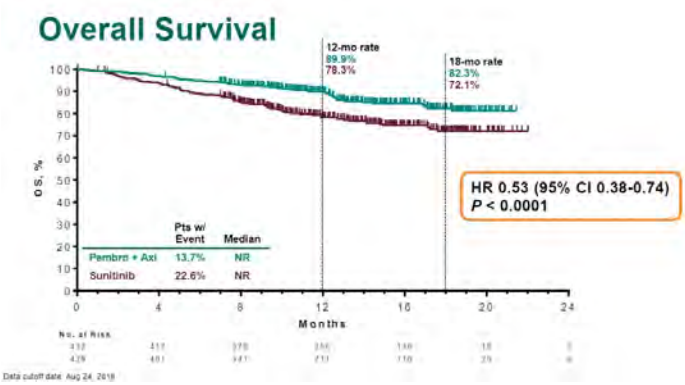
A total of 861 patients were enrolled in the study. The median age was 62 in the pembrolizumab arm and 61 in the sunitinib arm. The majority of patients were men (71%) and had intermediate or poor risk disease by IMDC criteria. This cohort also contained a high percentage of patients who were deemed PD-L1 positive, based on a CPS ≥1 (roughly 60% in both arms). Also, unlike many patients in the post-CARMENA era, the majority of patients had a previous nephrectomy (82%).

At the time of data cutoff, 59% of patients on pembro/axi remain on therapy, compared with 43% of patients on sunitinib. After a median follow up of 12.8 months, patients receiving PA had improved overall survival (HR 0.53 [95% CI 0.38-0.74]; P< 0.0001), progression free survival (HR 0.69 [95% CI 0.57-0.84]; P = 0.0001), and objective response rates (59.3% vs 35.7%; P< 0.0001).

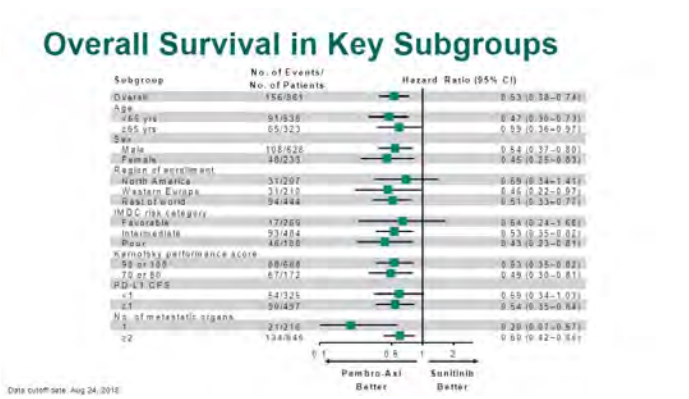


	Pembrolizumab + Axitinib N = 432	Sunitinib N = 429
Age, median (range)	62 yrs (30-89)	61 yrs (26-90)
Male	308 (71.3%)	320 (74.6%)
Region of enrollment		
North America	104 (24.1%)	103 (24.0%)
Western Europe	106 (24.5%)	104 (24.2%)
Rest of world	222 (51.4%)	222 (51.7%)
IMDC risk category		
Favorable	138 (31.9%)	131 (30.5%)
Intermediate	238 (55.1%)	246 (57.3%)
Poor	56 (13.0%)	52 (12.1%)
Sarcomatoid features	51/285 (17.9%)	54/293 (18.4%)
PD-L1 CPS ≥1[a]	243/410 (59.3%)	254/412 (61.7%)
≥2 metastatic organs	316 (72.9%)	331 (77.2%)
Previous nephrectomy	357 (82.6%)	356 (83.4%)

The median progression free survival was 15.1 months in the PA arm and 11. Month in the sunitinib arm.



The benefit of PA over sunitinib was observed in all IMDB risk groups and PD-L1 expression subgroups. In terms of patient safety, 62.9% of patients had grade 3-5 treatment related adverse events with PA compared to 58.1% with sunitinib. Patients receiving PA had a lower rate of discontinuation (6.3% vs 10.1%).



In terms of objective responses, ORR of PA was 59.3% compared with 35.7% on sunitinib. In terms of safety, 0.9% of patients on PA had a treatment related AE which led to death compared to 1.6% of patients on sunitinib. Overall, PA was well tolerated, but did have greater grade 3-5 adverse events

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of interest than sunitinib (10.7% vs 1.9%). Patients receiving PA did have more dysphonia, diarrhea, and hypertension.

Adverse Events of Interest: Incidence ≥1%

	Pembro + Axi (N = 429)		Sunitinib (N = 425)	
	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Any	51.3%	10.7%	36.2%	1.9%
Hypothyroidism	35.4%	0.2%	31.8%	0.2%
Hyperthyroidism	12.8%	1.2%	3.8%	0
Adrenal insufficiency	3.0%	0.7%	0.2%	0
Hepatitis	2.8%	2.3%	0.5%	0.2%
Pneumonitis	2.8%	0.5%	0.2%	0
Thyroiditis	2.8%	0.2%	0.5%	0
Colitis	2.6%	1.9%	0.7%	0
Severe skin reactions	1.9%	1.2%	1.4%	0.7%
Infusion reactions	1.6%	0.2%	0.9%*	0.2%*
Nephritis	1.4%	0.2%	0.2%	0
Hypophysitis	1.2%	0.9%	0	0

*Includes the preferred terms "anaphylactic reaction" and "hypersensitivity," which were experienced by patients in the sunitinib arm.
Events are listed in order of incidence in the pembro + axi arm and are included regardless of attribution to study treatment or immune relatedness by the investigator. The specific events listed are based on a list of terms specified by the sponsor. In addition to the specific terms listed, related terms were also summarized. Data cutoff date: Aug 24, 2018.

Pembrolizumab plus axitinib is effective and safe for patients with clear cell mRCC, with an impressive 59% objective response rate. This compares favorably to the Ipi/Nivo data (ORR 42%) from CheckMate 214, which truly established immunotherapy as a front-line option for patients with mRCC. As more and more combination trials began reporting out data, the choice for front line therapy becomes increasingly difficult. Future biomarker work may be important to define which patient populations best respond to immunotherapy, combination immunotherapy with TKI, or TKI alone. PD-L1 is not a reliable biomarker for response to immunotherapy for mRCC and gene signatures may be a better option in the future. An excellent review in the NEJM published at the same time as this oral presentation offers expert commentary comparing this combination therapy to avelumab/axi.[4]

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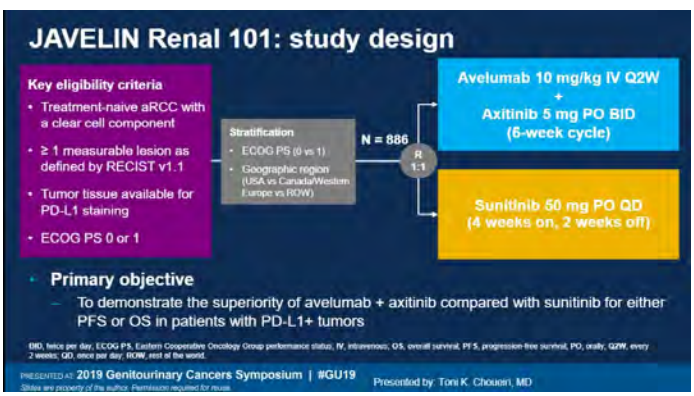
Presented by: Thomas Powles, MD, PhD, FCRP

Written by: Jason Zhu, MD. Fellow, Division of Hematology and Oncology, Duke University; Twitter: @TheRealJasonZhu

Subgroup analysis from JAVELIN Renal 101: Outcomes for avelumab plus axitinib (A + Ax) versus sunitinib (S) in advanced renal cell carcinoma (aRCC)

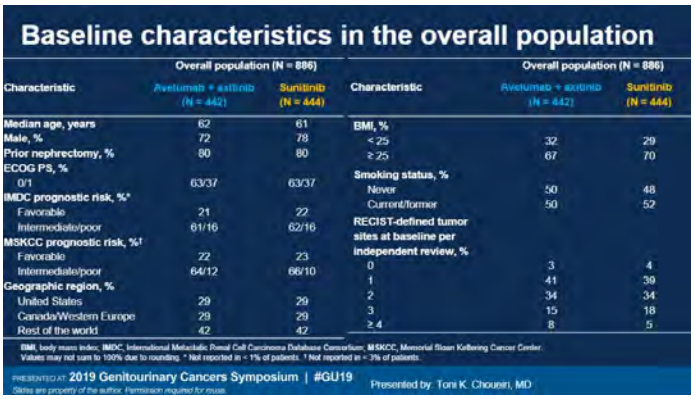
Dr. Toni K. Choueiri

While immunotherapy has entered both the first- and second-line treatment options for patients with metastatic renal cell carcinoma, the majority of patients do not have an objective response to single agent immunotherapy. Even with dual checkpoint inhibition as demonstrated in CheckMate 214, 58% of patients did not have an objective response.[1] Thus, several combination therapies are now being evaluated in this space, combining checkpoint inhibition with VEGF/VEGFR inhibition. JAVELIN Renal 101 is a global phase III study of avelumab plus axitinib versus sunitinib alone. During ASCO 2017, results from the avelumab + axitinib phase 1b study demonstrated that 58% of patients had an objective response (5% complete response, 53% partial response), and 45 out of 53 patients experienced tumor shrinkage.[2] This abstract provides the subgroup analysis of JAVELIN 101.

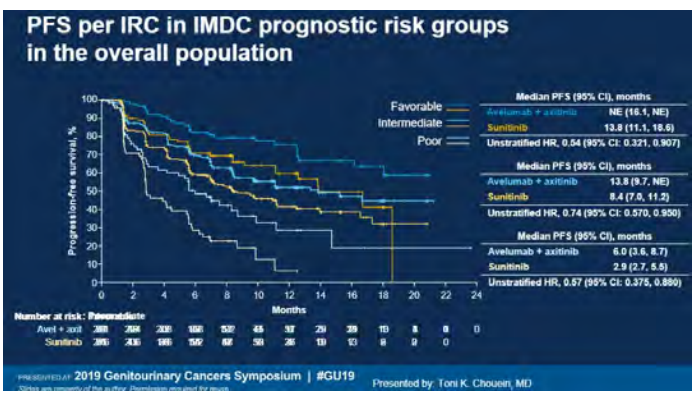


JAVELIN 3 is an going phase III study which evaluates avelumab + axitinib (AA) versus sunitinib for patients with previously untreated advanced renal cell carcinoma. Avelumab was given 10 mg/kg every 2 weeks and axitinib was given 5 mg twice daily. Sunitinib 50 mg was given on a 4 week on, 2 week off schedule. At the time of data cutoff in June 2018, the median follow up time was 12 months for the AA arm and 11.5 months for the sunitinib arm.

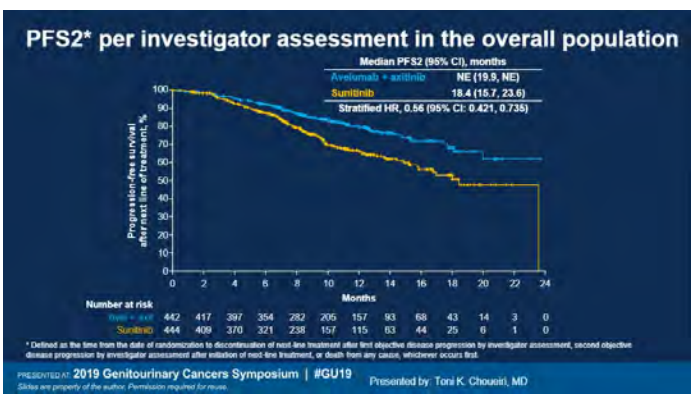
A total of 886 patients were randomized to AA or sunitinib. The baseline characteristics were well balanced. Patients were balanced by age, prior nephrectomy (80% in both arms), IMDC risk (~80% were poor/intermediate risk), and geographic region. Due to some data which had correlated BMI and smoking status with outcomes in RCC, patients were also balanced for BMI (~70% had a BMI≥25) and 50% were never smokers.[3,4]



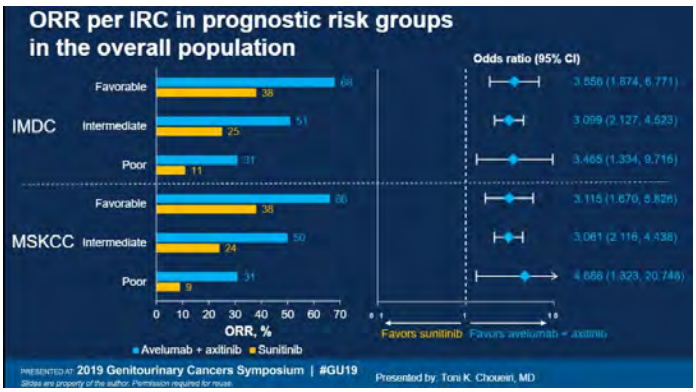
In terms of PFS per IMDBC risk groups, AA outperformed sunitinib for every risk group. For patients with MSKCC favorable risk disease, the median PFS has not yet been reached and was 13.8 months in the sunitinib arm (HR 0.54). For intermediate risk patients, mPFS was 13.8 months vs 8.4 months favoring AA, and for poor risk patients, mPFS was 6.0 vs 2.9 months also favoring AA.



Median PFS2, defined as the time from date of randomization to discontinuation of the next line of therapy, was not yet reached for AA and was 18.4 months for sunitinib. For patients who progressed on the sunitinib arm, 67% of patients were subsequently treated with a checkpoint inhibitor.



Objective response rate was 66% for favorable risk, 50% for intermediate risk, and 31% of poor risk. PD-L1 status did not consistently discriminate between responders and non-responders. Patients defined as PD-L1+ had an ORR of 55% compared to 47% of PD-L1 negative.



Avelumab plus axitinib joins the list of combination therapies which appear very promising for the front-line treatment of mRCC. Unlike combination ipilimumab/nivolumab which did not demonstrate benefit for patients with good risk disease, this is the space where AA thrives, with a 66% response rate. An excellent comparison by Dr. Escudier compares the this trial to the Pembrolizumab+axitinib study.[5] The study populations are fairly similar in terms of IMDC risk populations as well as patients with the percentage of patients with quantifiable PD-L1 expression ≥1%. However, at this time, pembrolizumab + axitinib has an OS benefit over sunitinib whereas this endpoint has not yet been reached for AA+sunitinib. However, this may change with longer follow up and future results may show an OS benefit for this combination, given the durability of responses of patients on immune checkpoint inhibitors as we have seen in numerous other trials.

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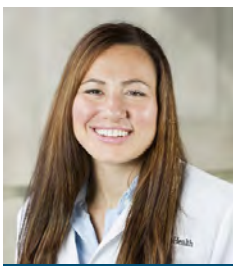
Presented by: Toni K. Choueiri, MD

Written by: Jason Zhu, MD. Fellow, Division of Hematology and Oncology, Duke University; Twitter: @TheRealJasonZhu

Kidney Cancer

Results of a phase II study of atezolizumab and bevacizumab in non-clear cell renal cell carcinoma (nccRCC) and clear cell renal cell carcinoma with sarcomatoid differentiation (sccRCC)



Dr. Rana R. McKay

There are five main types of non-clear cell RCC (nccRCC) – papillary, chromophobe, collecting duct, unclassified, and translocation carcinoma and represent 15-25% of all RCC cases1. Sarcomatoid differentiation can happen in both clear cell and non-clear cell RCC. While the treatment landscape has changed dramatically over the past few years for clear cell RCC, the data for changing management of non-clear RCC is less strong given the rarity of the disease. Papillary RCC is the most common sub-type of nccRCC and the largest randomized study evaluated sunitinib vs everolimus, and found that patients with sunitinib had a longer median progression free survival with sunitinib compared with everolimus (8.1 vs 5.5 months)2. However, there was a suggestion that patients with poor risk disease may do better with everolimus. MET inhibitors have also received some attention – Crizotinib was evaluated in 23 patients with type I papillary RCC and 2 patients in that study had an objective response3. This study evaluates the combination of an immune checkpoint inhibitor (atezolizumab) in combination with bevacizumab, a humanized monoclonal antibody which inhibits vascular endothelial growth factor A.

This abstract describes a phase II clinical trial which enrolled 65 patients with non-clear cell RCC (ncRCC) or clear cell RCC with ≥ 20% sarcomatoid differentiation (sRCC).

Patients may have received prior therapy but prior immune checkpoint inhibitor treatment was not permitted. Patients received atezolizumab 120 mg and bevacizumab 15 mg/kg intravenously every 3 weeks. 65 patients have been enrolled and 60 patients have one or more response assessments.

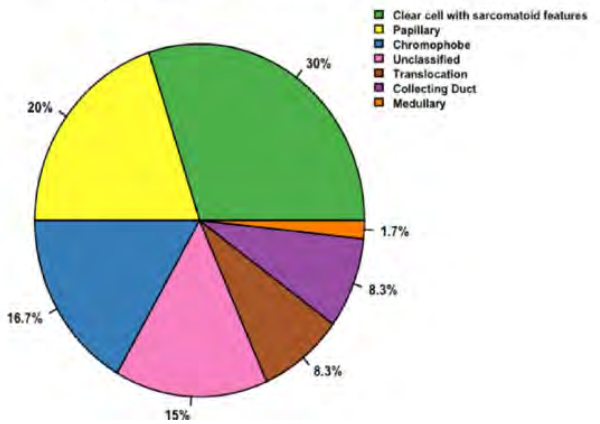
Table 1. Patient characteristics

Factor	ccRCCsd (N=18)		ncRCC (N=42)		Total (N=60)	
Age, years (range)	52 (36-75)		62 (22-82)		61 (22-82)	
	N	%	N	%	N	%
Gender						
Male	13	72.2%	34	81%	47	78%
Female	5	37.8%	8	19%	12	22%
M stage at diagnosis						
M0	3	17%	5	12%	8	13%
M1	7	39%	9	21%	16	27%
Unknown	8	44%	28	67%	36	60%
ECOG PS						
0	9	50%	20	48%	29	48%
1	9	60%	21	50%	30	50%
2	0	0%	1	2%	1	2%
Nephrectomy	17	94%	35	83%	52	87%
Prior systemic therapy	1	6%	20	48%	21	35%
Bone/Liver Metastases	3	17%	9	21%	12	20%
IMDC risk group						
Favorable	2	11%	7	17%	9	15%
Intermediate	8	44%	25	60%	33	55%
Poor	8	44%	10	24%	18	30%
PD-L1 positivity*						
Negative	6/12	50%	8/22	36%	14	41%
Positive	6/12	50%	14/22	64%	20	59%

*PD-L1 positivity ≥ 1% PDL1+ Tumor cells/Total Tumor Cells
ECOG= Eastern Cooperative Oncology Group
IMDC = International Metastatic Database Consortium

Median age was 62 for patients with ncRCC and 52 for patients with sRCC. The majority of patients were men, and almost all patients had prior nephrectomy. PD-L1 positivity was defined as ≥1% PDL1+ tumor cells/total tumor cells and the majority of patients were PD-L1 positive. The distribution of histologic subtypes is shown below.

Figure 1: Distribution of Subtypes



The ORR for patients with sRCC was 53%, and 26% for patients with nccRCC. The ORR for the overall cohort was 34% and interestingly, there was a higher response rate for those who were previously treated (37%) compared with those who were treatment naïve (14%). Patients with IMDC favorable risk and intermediate risk had greater response rates (33%, 42%) than poor risk (14%). At a median follow up of 9.7 months, the median progression free survival was 8.4 months and estimated median overall survival was 21.2 months.

In terms of safety, the most frequent grade 3 adverse events were colitis (10%), diarrhea (5%), elevated AST (3.3%), and elevated ALT (3.3%). 7% of patients required steroids for treatment of immune related adverse events.

This study shows that the combination of atezolizumab/bevacizumab is safe for patients with nccRCC and sRCC, and very effective in sRCC with an objective rate of 53%. Only 7% of patients required high dose steroid treatment for immune related adverse events. Checkpoint inhibitors are effective in non-clear cell RCC and further biomarker work is necessary to select for patients who will have the best response.

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Presented by: Rana R. McKay, MD

Written by: Jason Zhu, MD. Fellow, Division of Hematology and Oncology, Duke University; Twitter: @TheRealJasonZhu

Figure 2. Maximum tumor response

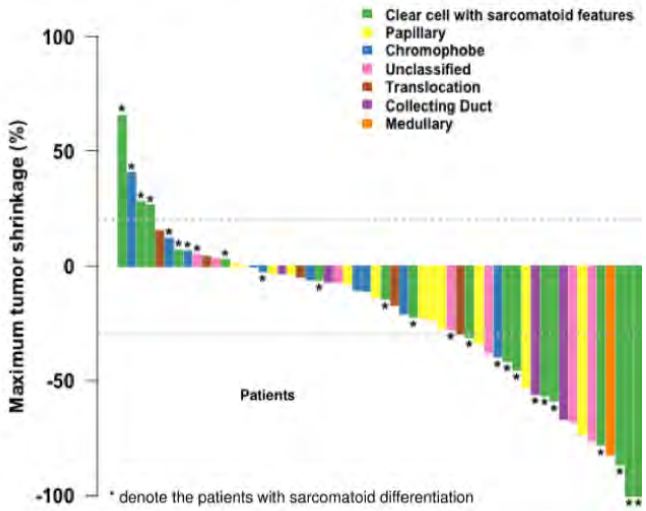
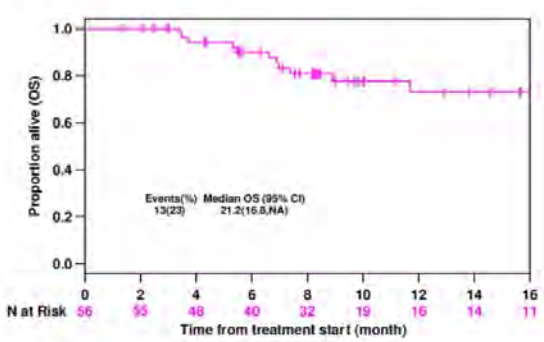


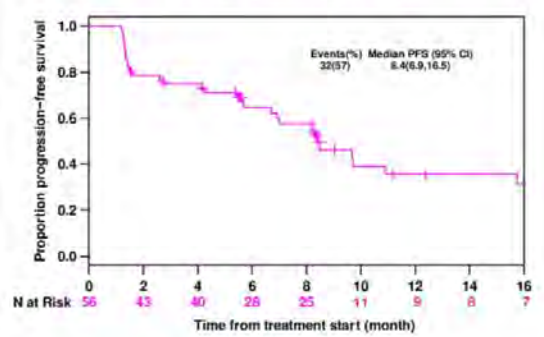
Table 2: Breakdown of ORR

	ORR
Overall	34% (n=19/60)
Prior Treatment	
Treatment Naive	14% (n=1/7)
Previously Treated	37% (n=18/49)
IMDC Risk Group	
IMDC Favorable Risk	33% (n=3/9)
IMDC Intermediate Risk	42% (n=14/33)

	ORR
ccRCCsd	53% (n=9/17)
ncRCC	26% (n=10/39
Papillary	25% (n=3/12)
Chromophobe	10% (n=1/10)
Translocation	20% (n=1/5)
Unclassified	29% (n=2/7)
Collecting Duct	50% (n=2/4)

Figure 4: Kaplan Meier Curves for PFS, OS





The median follow-up time is 9.7 months