Assessing Current and Future Roles for Immuno-Oncology Strategies in Bladder Cancer

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Overview:
This activity is designed to inform physicians about the current availability and use of checkpoint inhibitors in advanced or metastatic bladder cancer.

Target Audience:
This activity is directed toward medical oncologists, primary care physicians, nurses, and nurse practitioners who treat and/or manage patients with advanced or metastatic bladder cancer. Surgical oncologists, radiation oncologists, pathologists, internists, fellows, physician assistants, and other healthcare providers are also invited to participate.

Learning Objectives:
After participating in this CME/CE activity, learners should be better prepared to:

- *Describe the biologic function of the PD-1/PD-L1 pathway and the rationale behind targeted inhibition in bladder cancer*
- *Explain the development history leading to the approval of immune checkpoint inhibitors in bladder cancer*
- *Discuss emerging treatment strategies and new indications in FDA-approved PD-1 or PD-L1 inhibitors*

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Introduction

Bladder cancer (BC) is the sixth most common form of cancer in the United States, responsible for 79,030 new cases of cancer annually, or 4.7% of all new cases.[1,2] In 2017, it is estimated that 16,870 people in the United States will die of BC, approximately 2.8% of all cancer deaths.[1,2] The 5-year survival rate in the United States is reported to be 77.3%.[2]

Approximately 51% of newly diagnosed cases are BC in situ. Localized disease accounts for 34% of new cases, whereas regional and distant disease accounts for 7% and 4%, of new cases, respectively. Five-year survival rates significantly decrease for advanced disease: in situ (95.7%), localized (70.1%), regional (35.2%), distant/metastatic (5.0%).[2]

Bladder cancer primarily occurs in older populations, with a median age of diagnosis of 73 years.[1,2] While men are 3 to 4 more times more likely than women to develop BC, and white individuals are diagnosed about twice as often as African American and Hispanic American individuals, the most important risk factor in developing BC is smoking history.[1] Smokers are 3 times more likely to develop BC than nonsmokers.[1]

The bladder wall consists of 4 layers: 1) the urothelium or transitional epithelium, lining the internal surface; 2) a layer of connective tissue consisting of blood vessels and nerves; 3) a thick muscle layer; and 4) an outer layer of fatty tissue that separates the bladder from other organs.[1] Bladder cancer staging is based on the American Joint Committee on Cancer TNM (tumor–nodes–metastases) staging system. The majority of BCs begin in the urothelium, with more-advanced BCs penetrating into the outer layers of the bladder wall.[1]

Stage 0 BC consists of noninvasive papillary carcinoma and carcinoma in situ in the urothelium.[1] Stage I BC involves the connective tissue found under the bladder lining, but that has not spread further. Stage II BC has spread to the muscle layer of the bladder wall. Stage III BC has spread to the fatty tissue that surrounds the bladder, or may have spread to the prostate, uterus, or vagina. Stage IV BC has spread to the pelvic or abdominal wall, or involves any growth past the urothelium that has also spread to the lymph nodes or metastasized to distant sites such as the bones, liver, or lungs.[1] Patients with metastatic BC (mBC) are traditionally treated with platinum-based chemotherapy in the frontline setting.[3] Until recently, few options have existed for these patients after they progress.

PD-1/PD-L1 Inhibition

Inhibition of checkpoint proteins, specifically PD-1 and its ligand, PD-L1, have been an increasing focus of immunotherapy strategies in BC specifically, and in oncology generally. The PD-1/PD-L1 axis works primarily to suppress an overresponse of effector T cells as a part of the immune system's defense against itself. PD-1, a transmembrane signaling protein, and the ligand limit autoimmune responses in order to prevent what can effectively be considered self-cannibalism.[4]

PD-1 is a type 1 transmembrane protein and a member of the immunoglobulin superfamily.[5] In healthy individuals, the PD-1 protein is minimally expressed in immune cells (ICs), including T cells, B cells, natural killer (NK) cells, NK T cells, and macrophages.[4,6] In the other tissues of individuals with an infection or other inflammatory event, PD-1 is actively transcribed to limit immune-mediated tissue destruction.[4]

PD-1 primarily binds 2 distinct ligands: PD-L1 and PD-L2. While PD-L2 expression is limited to ICs, PD-L1 is expressed on cells throughout the body, both hematopoietic and nonhematopoietic alike.[7] PD-L1 expression is induced by inflammatory cell signals, such as interferons and tumor necrosis factor–α, regardless of cell type. Interactions between PD-1 and its ligand promote the downstream inhibition of T cells as well as T-cell apoptosis.[4]

Cancer cells can utilize this checkpoint against self-cannibalism by expressing PD-L1, including in BC.[4] Paired with PD-1 expression on tumor-infiltrating lymphocytes, tumor cells (TCs) are able to activate the feedback-inhibition loop of the PD-1:PD-L1 axis that is typically observed in inflamed tissue. Added to this, multiple oncogenic signaling pathways exist to increase PD-L1 expression on malignant cells following a host immune response.[4] By interrupting this pathway, checkpoint inhibitors are able to restore the immune response against TCs. This inhibition is a stalwart area of ongoing oncology research.

PD-L1 is a particular area of interest in BC, high levels of PD-L1 expression have been linked to cancer severity and outcomes. Tumor cells that express higher levels of PD-L1 are more likely to be detected in the advanced stage, and they have higher frequencies of postoperative recurrence. Further, high PD-L1 expression results in poorer survival and increased resistance to certain types of treatment.[8–10]

Checkpoint Inhibitors in Bladder Cancer

Currently, 5 PD-1 or PD-L1 inhibitors are approved for the treatment of UC, across multiple indications and treatment settings. A summary of agents and their approved indications is presented in **Table 1**. A summary of key trial data leading to these approvals is summarized in **Table 2**. Data leading to these approvals are explored chronologically.

TABLE 1. Summary of PD-1 and PD-L1 Checkpoint Inhibitors, Targets, Dates of Approval, and Indications for Urothelial Carcinoma

Agent	Target	Approval	Indication Locally advanced or metastatic urothelial carcinoma…
Atezolizumab	PD-L1	May 18, 2016 (expanded approval Apr 17, 2017)	…following progression during or after first-line platinum-based chemotherapy …following progression within 12 months of neoadjuvant/adjuvant platinum-based chemotherapy …in cisplatin-ineligible patients
Nivolumab	PD-1	Feb 2, 2017	…following progression during or after first-line platinum-based chemotherapy …following progression within 12 months of neoadjuvant/adjuvant platinum-based chemotherapy
Durvalumab	PD-L1	May 1, 2017	…following progression during or after first-line platinum-based chemotherapy …following progression within 12 months of neoadjuvant/adjuvant platinum-based chemotherapy
Avelumab	PD-L1	May 9, 2017	…following progression during or after first-line platinum-based chemotherapy …following progression within 12 months of neoadjuvant/adjuvant platinum-based chemotherapy
Pembrolizumab	PD-1	May 18, 2017	…following progression during or after first-line platinum-based chemotherapy …following progression within 12 months of neoadjuvant/adjuvant platinum-based chemotherapy …in cisplatin-ineligible patients

Atezolizumab

Atezolizumab is an anti–PD-L1 antibody, and it was the first in this class of agents to be approved for the treatment of BC. Following positive results from a phase I trial (NCT01375842), which showed an objective response rate (ORR) of 43% for patients with metastatic disease and high PD-L1 expression, atezolizumab was granted breakthrough therapy designation by the FDA, the first step toward approval.[11]

In Cohort 2 of the follow-up phase II IMvigor 210 trial (NCT02108652), 310 patients with mBC who had progressed on or following platinum-based chemotherapy received atezolizumab at a dosage of 1200 mg every 3 weeks.[12] Across all patient populations, the ORR was 15% (95% CI, 11%-19%), with 84% of responders maintaining a response at 1 year. In all patients, the median overall survival (OS) was 7.9 months (95% CI, 6.6-9.3). In patients with PD-L1 expression in ≥5% of infiltrating ICs (IC 2/3), the reported ORR was higher at 26% (95% CI, 18%-36%) and median OS was 11.4 months. Further, a complete response (CR) was observed in 6% of all patients and in 11% of patients with high PD-L1 expression levels. Median progression-free survival (PFS) was 2.1 months in all patients (95% CI, 2.1-2.1) and 4.0 months (95% CI, 2.6-5.9) in patients with high PD-L1 expression (by investigator analysis). In total, 50 patients (16%) experienced a grade ≥3 adverse event (AE), including fatigue in 5 patients (2%), hypertension in 3 patients (1%), and anemia in 3 patients (1%).[12]we assessed treatment with atezolizumab, an engineered humanised immunoglobulin G1 monoclonal antibody that binds selectively to programmed death ligand 1 (PD-L1 This led to the approval of atezolizumab for patients with locally advanced or mBC following progression during or after first-line platinum-based chemotherapy or within 12 months of neoadjuvant/adjuvant platinum-based chemotherapy in May 2016.[13]

Cohort 1 of this trial investigated 123 platinum-ineligible, treatment-naïve patients. The ORR in this patient population was 23% (95% CI, 16%-31%), with a median OS of 15.9 months and CR rate of 9%. Median PFS was 2.7 months (95% CI, 2.1-4.2).[14] This led to the expanded approval of atezolizumab for the treatment of cisplatin-ineligible patients with locally advanced or mBC in April 2017.[15] The follow-up phase III IMvigor 211 (NCT02302807) trial failed to reach its primary endpoint of improved OS.[16]

Nivolumab

Nivolumab, a PD-1 inhibitor, was the second agent in this class to be approved, following results from the phase II CheckMate 275 trial (NCT02387996).[17] Here, 270 patients from 63 sites in 11 different countries received 3 mg/kg nivolumab every 2 weeks. The ORR across all patients was 19.6% (95% CI, 15.0%-24.9%), median PFS was 2.00 months (95% CI, 1.87-2.63), and median OS was 8.74 months. In PD-L1–expressing subgroups (≥5%), the ORR was raised to 28.4% (95% CI, 18.9%-39.5%) and median OS was raised to 11.30 months.[17]

Eight months after the initial approval of atezolizumab, another agent entered this space. In February 2017, nivolumab was approved for patients with locally advanced or mBC following progression during or after first-line platinum-based chemotherapy or within 12 months of neoadjuvant/adjuvant platinum-based chemotherapy in February 2017.[18]

Durvalumab

In May 2017, 3 additional agents in this class were approved, the first of which was durvalumab, another PD-L1 inhibitor. In the BC cohort of the phase I/II 1108 trial (NCT01693562), 182 patients with locally advanced or mUC who had progressed following platinum-based chemotherapy were treated with 10 mg/kg durvalumab every 2 weeks.[19]

Among 95 patients with high PD-L1 expression, the ORR was 17.0% (95% CI, 11.9%-23.3%) for all patients and 26.3% (95% CI, 17.8%-36.4%) for patients with high PD-L1 expression. At a median follow-up of 5.6 months, 31 patients achieved a response, including 5 CRs and 26 partial responses (PRs). Twenty-five of these patients were in the high-PD-L1–expression group, with 3 CRs and 22 PRs.[19]

High-grade AEs occurred in 46% of all patients. These AEs included acute kidney injuries (4.9%), urinary tract infections (4.4%), musculoskeletal pain (4.4%), liver injuries (3.3%), and general physical health deterioration (3.3%).[19]

Durvalumab was approved in May 2017 for patients with locally advanced or mBC following progression during or after first-line platinum-based chemotherapy or within 12 months of neoadjuvant/adjuvant platinum-based chemotherapy.[19]

Avelumab

A week after the approval of durvalumab, avelumab, a third PD-L1 inhibitor, was also approved based on results from the BC cohorts of the phase I JAVELIN Solid Tumor trial (NCT01772004).[20,21] In 242 patients who received 10 mg/kg avelumab every 2 weeks, the ORR was 13.3% (95% CI, 9.1%-18.4%) among patients who had been followed for at least 13 weeks, which increased to 16.1% (95% CI, 10.8%-22.8%) among patients who had been followed for at least 6 months.

In a multicenter, phase Ib study, 44 patients were followed for more than a year. In these patients, ORR was 18.2% (95% CI, 8.2%-32.7%), median PFS was 11.6 weeks (95% CI, 6.1-17.4), and median OS was 13.7 months (95% CI, 8.5-not estimable). The 12-month OS rate was 54.3% (95% CI, 37.9%-68.1%).[22]

Avelumab was approved in May 2017 for patients with locally advanced or mBC following progression during or after first-line platinum-based chemotherapy or within 12 months of neoadjuvant/adjuvant platinum-based chemotherapy.[20,21]

Pembrolizumab

Shortly after this approval, pembrolizumab, a second PD-1 inhibitor, was approved following the results of the phase II KEYNOTE-052 trial (NCT02335424) and the phase III KEYNOTE-045 trial (NCT02256436).[23,24] In the KEYNOTE-052 trial, 370 patients with locally advanced or mUC who were not eligible for cisplatin-containing chemotherapy regimens received 200 mg pembrolizumab every 3 weeks.[25] Initial reported ORR was 24% (95% CI, 20%-29%) for all patients and 38% (95% CI, 29%-48%) for patients with high levels of PD-L1 expression.[25] The ORR was listed as 28.6% (95% CI, 24%-34%) at time of approval.[23] Median PFS was 2 months (95% CI, 2-3), and 6-month OS rate was 67% (95% CI, 62%-73%).[25] The most common grade 3/4 AEs were fatigue (2%), alkaline phosphatase increase (1%), colitis (1%), and muscle weakness (1%).[25]

In the KEYNOTE-045 trial, 542 patients with advanced UC that recurred or progressed following treatment with platinum-based chemotherapy received pembrolizumab at a dosage of 200 mg every 3 weeks or investigator's choice of chemotherapy.[26] Reported ORR was significantly higher in the pembrolizumab arm at 21.1% (95% CI, 16.4%-26.5%) than in patients who received chemotherapy (ORR, 11.4% [95% CI, 7.9%-15.8%]). Median PFS was 2.1 months (95% CI, 2.0-2.2) in patients receiving pembrolizumab, which was not significantly different from median PFS, 3.3 months, in patients receiving chemotherapy, 3.3 months (95% CI, 2.3-3.5). Median OS was 10.3 months (95% CI, 8.0-11.8) in the pembrolizumab group compared with 7.4 months (95% CI, 6.1-8.3) in the chemotherapy group. This marked the first reported improvement in OS for a PD-1 or PD-L1 inhibitor for treatment of BC. Among patients with high PD-L1 expression, median OS was 8.0 months (95% CI, 5.0-12.3) in the pembrolizumab group compared with 5.2 months (95% CI, 4.0-7.4) in the chemotherapy group. Overall, patients receiving pembrolizumab had fewer high-grade AEs than patients receiving chemotherapy, 15.0% compared with 49.4%.[26]

A year to the day after the approval of durvalumab, pembrolizumab was approved for the same indication: for patients with locally advanced or mBC following progression during or after first-line platinum-based chemotherapy or within 12 months of neoadjuvant/adjuvant platinum-based chemotherapy, based on results from the phase III trial, as well as for the treatment of cisplatin-ineligible patients with locally advanced or mBC, based on results from the phase II trial.[23,24]

AJHO *spoke with Arjun V. Balar, MD, a medical oncologist and assistant professor in the Department of Medicine, and director of the Genitourinary Medical Oncology Program at the Perlmutter Cancer Center, New York University Langone, New York, New York, about the use of checkpoint inhibitors and future combination therapies in bladder cancer.*

AJHO®: Can you talk briefly about the PD-1/PD-L1 pathway and the role these proteins have in bladder cancer (BC)?

D. Balar: The PD-1/PD-L1 pathway has a critical immune regulatory function on effector T cells. And what we've realized is that BC is actually among the most mutated tumors

TABLE 2. Summary of Key Trials and Data on Checkpoint Inhibitors for Urothelial Carcinoma

Agent	Trial	NCT#	ORR (%)		Median PFS (mo)	Median OS (mo)
			All Patients	≥5% PD-L1		
Atezolizumab	IMvigor 210 (Cohort 2)[12]	NCT02108652	**15** (11-19)	**26** (18-36)	**2.1** (2.1-2.1)	**11.4**
	IMvigor 210 (Cohort 1)[14]		**23** (16-31)	-	**2.7** (2.1-4.2)	**15.9**
Nivolumab	CheckMate 275[17]	NCT02387996	**19.6** (15.0-24.9)	**28.4** (18.9-39.5)	**2.00** (1.87-2.63)	**8.74**
Durvalumab	Study 1108[19]	NCT01693562	**17.0** (11.9-23.3)	**26.3** (17.8-36.4)	-	-
Avelumab	JAVELIN Solid Tumor[22]	NCT01772004	**18.2** (8.2-32.7)	-	**11.6** (6.1-17.4)	13.7
Pembrolizumab	KEYNOTE-045[26]	NCT02256436	**21.1** (16.4-26.5)	-	**2.1** (2.0-2.2)	**10.3**
	KEYNOTE-052[25]	NCT02335424	**24** (20-29)	**38** (29-48)	**2** (2-3)	-

Parenthetical numbers objective indicate range of 95% CI.

ORR indicates overall response rate; OS, overall survival; PFS, progression-free survival.

among all human cancers, second really only to melanoma and on par with non–small-cell lung cancer. Cancers with high mutation levels tend to be more immunogenic and to stimulate the immune system to try to generate an antitumor immune response. The PD-1 pathway is activated on CD8-positive effector T cells to downregulate the immune system. Other immune populations and tumor cells will express PD-L1, which is the activating ligand for PD-1, and shut down effector T-cell responses. By targeting that pathway, by blocking that interaction between PD-1 and PD-L1, we are able to reinvigorate the immune system and allow the immune system to attack BC cells.

Going into specifics, can you talk about the approval of pembrolizumab as a second-line therapy?

The KEYNOTE-045 trial is a randomized phase III trial that tested pembrolizumab versus investigator's choice chemotherapy in the second-line setting in platinum-refractory or relapsed metastatic urothelial cancer (mUC). The high-level outcomes of the study were that pembrolizumab significantly improved survival versus chemotherapy. Twenty-one percent of patients achieved a response, responses were durable, and therapy was very well tolerated—and in fact, much better tolerated than chemotherapy. This was a multinational study, so patients were enrolled in the United States as well as in Western Europe and other parts of the world. This trial was really the definitive proof that in a second-line setting, immunotherapy improves survival.

Pembrolizumab is also approved as a first-line therapy. What is the impact of pembrolizumab as a treatment option in this setting?

The KEYNOTE-052 trial was a single-arm phase II trial that tested pembrolizumab in the first-line setting in patients with mUC who were ineligible for cisplatin. This is a unique group of patients, unique to BC. Given a patient's age, smoking or cardiovascular history, and a variety of comorbidities that accompany BC, they are often not able to tolerate cisplatin-based chemotherapy. Some studies suggest that up to 60% to 70% of patients with UC may be ineligible for cisplatin, due mainly to concerns related to toxicities for those patients. For those patients, there is no proven therapy to prolong survival. For years, we had been using carboplatin-based chemotherapy, which is better tolerated, but associated with worse outcomes and shorter survival. This is a group of patients who represents a significant proportion of patients with advanced BC.

The KEYNOTE-052 trial looked at pembrolizumab in this exact patient population. In a total of 370 patients treated on this trial, the response rate was around 29% based on the most recent analysis, including some patients with complete responses. Responses also appear to

be durable, and treatment is well tolerated. On the basis of these outcomes, the FDA granted accelerated approval for pembrolizumab in this patient population.

Nivolumab was granted accelerated approval for these patients based on results from the phase II CheckMate 275 trial. What impact does this approval have?

The CheckMate 275 trial tested nivolumab as a second-line therapy in a single-arm phase II trial. This trial was very similar in design to the IMvigor 210 trial, which tested atezolizumab, a PD-L1 antibody. The CheckMate 275 trial enrolled 270 patients with advanced BC who were previously treated with platinum-based chemotherapy. The trial showed that approximately 20% of patients achieved response to nivolumab. Further, the responses were durable, similar to other agents in this class. Therapy was well tolerated with similar severity and frequency of immune-related toxicities to other agents. It was the outcomes from this trial that led to accelerated approval of nivolumab. It's clear that based on this study and others, agents that target the PD-1/PD-L1 pathway clearly have activity in advanced BC in the second-line setting, and are safe, well tolerated, and represent a major advancement in the treatment of this disease.

You mentioned atezolizumab, a PD-L1 inhibitor. Can you discuss the pivotal IMvigor trials and how those results have affected your usage of atezolizumab?

Atezolizumab was the very first PD-1 pathway inhibitor to be tested in advanced UC. The phase II IMvigor 210 trial focused on 2 groups of patients. The main cohort of the trial was a second-line cohort that enrolled 310 patients who were previously treated with platinum-based chemotherapy. This cohort demonstrated an approximate 16% response rate, a tolerable safety profile, and durable responses—again, similar to what we see with other agents in this class.

The ancillary cohort in this trial ultimately enrolled 119 cisplatin-ineligible patients who were treated in the first-line setting. This cohort showed an approximate response rate of 23% as well as durable responses. Median survival was 15.9 months.

The key takeaways here are that therapy was active and well tolerated. The response rate in the first-line setting appears to be higher than that in the second-line setting, but obviously these are 2 separate groups of patients, so it's difficult to make inferences about the optimal sequence of treatment. Data from both cohorts ultimately led to accelerated approval in their respective indications. The second-line platinum refractory population was the very first approval of any immunotherapy targeting PD-1 in advanced BC, and the first-line cisplatin-ineligible population was approved earlier this year. Both represent a major advancement in this disease.

More recently, in June 2017, results from the phase III IMvigor 211 study were presented in June 2017. Notably, the primary endpoint of the study was not met, which may be attributed to factors related to the study design. This study compared atezolizumab with investigator's choice chemotherapy, including taxanes in the United States or the option of vinflunine in the European Union. The study was unique in design, in that the primary endpoint was to test survival in the PD-L1–overexpressing population, specifically the IC2/3 subgroup using the SP142 assay. Interestingly, we found that the SP142 assay for PD-L1 selected for better outcomes, in both the immunotherapy and chemotherapy groups, suggesting that the assay may be prognostic and not just predictive. This may have ultimately contributed to the study being a so-called "negative trial" and failing to meet its primary endpoint.

Interestingly, when the analysis was focused on the intent-to-treat group, which means the entire study population, there was a statistically significant benefit in survival. However, as this was not the primary endpoint of the trial, it was not included as a part of the primary efficacy analysis. Ultimately, the outcomes that we saw in the immunotherapy arm of the IMvigor 211 study were similar to what we saw in the IMvigor 210 trial. The 2 trials had similar safety profiles, as well, and tolerability was virtually identical. So, in summary, what we learned from IMvigor 211 is that the activity and the safety profile were virtually identical to what we saw in IMvigor 210, but issues related to the study design may have contributed to the study failing to meet its primary endpoint. Ultimately, I don't believe this trial significantly affects the use of atezolizumab despite the negative phase III trial. We know that agents targeting the PD-1 and PD-L1 pathway are active and well tolerated in advanced BC.

Avelumab and durvalumab are also PD-L1 inhibitors approved in this space. Can you talk about the development and use of these agents?

Avelumab and durvalumab are both PD-L1 antibodies that are, again, very similar in activity and safety to the other agents in this class. Two phase I studies tested these respective agents in mUC. Both were focused on the second-line setting in patients who had previously progressed on platinum-based chemotherapy.

Avelumab was tested in a small cohort of the JAVELIN study, which demonstrated a response rate of approximately 18% and a safety profile that was similar to other agents in its class. While the JAVELIN study focused on other solid tumors as well, for the patient population that included BC, the outcomes were promising enough to lead to accelerated approval for avelumab use in UC.

Durvalumab was approved on the basis of outcomes

from Study 1108, which is a very large phase I/II study that included approximately 1000 patients. A cohort of approximately 190 patients with advanced UC, the majority of whom had progressed on prior platinum-based chemotherapy, demonstrated a response rate of around 17% with durvalumab. Once again, responses were durable and had a tolerable safety profile.

The question we ask is, How do these agents differ and how are they similar? Avelumab is a unique agent, in that it has a fully humanized Fc [fragment crystallizable] region of the antibody that can trigger antibody-dependent cell-mediated cytotoxicity. It is believed, based on some very interesting preclinical work, that this may enhance antitumor activity based on some very interesting preclinical work. However, this will need to be demonstrated in patients to be sure. On the other hand, the humanized Fc region may contribute to some of the infusion reactions that have been observed with the agent.

Durvalumab is also being investigated in the first-line setting in combination with tremelimumab. What can we expect from immunotherapy combinations?

Durvalumab is being tested in the first-line setting in a 3-arm, randomized phase III trial that is testing durvalumab in combination with tremelimumab versus durvalumab alone versus chemotherapy. This trial is enrolling nearly 1000 patients. Ultimately, the question we're asking is whether combination immunotherapy, PD-1/PD-L1 with CTLA-4, improves response and survival compared with single-agent immunotherapy or chemotherapy, which up until now has been the standard of care.

Agents targeting PD-1 and CTLA-4 have been reported in the second-line setting, demonstrating numerically higher responses than what we would expect from a single agent alone. However, combination with CTLA-4 does lead to higher toxicity rates; anywhere between 25% to 35% of patients experience grade 3/4 adverse events [AEs]. So, while the outcomes may be better with combination immunotherapy, there may be a price to pay in terms of toxicity.

Can we expect all PD-1 and PD-L1 inhibitors to eventually be approved in multiple lines of treatment?

I think in the future, we can expect that agents targeting the PD-1 or PD-L1 pathway will eventually be approved in multiple lines of treatment. And, in fact, we are now seeing that these agents are quickly moving toward the frontline. Trials of novel combinations will also be tested in the frontline. So, over the next 3 to 5 years, I can easily envision that a substantial proportion of patients in the first-line setting will be treated with immunotherapy as a standard of care.

With such a wide field of checkpoint inhibitors now available, how do you decide among agents when treating your patients with BC?

This is a very challenging question. Now that we have 5 different agents approved in the second-line setting, as well as 2 agents approved in the first-line setting for cisplatin-ineligible patients, the question that is often asked is how do we choose among these agents. Ultimately, that answer is quite difficult. I think that the differences among these agents—if any—are quite subtle. As it stands, we don't have any direct evidence from direct comparisons in clinical trials to make any assumptions about which agents are better or worse or which agents are better tolerated.

The decision about which agent to choose becomes practical in nature. Which agent is on formulary for the health insurance company? For the institution where you're being treated? Frequency of dosing is also a factor. Some patients prefer dosing every 2 weeks, other patients prefer every 3 weeks. And now, some of these agents are being tested with dosing every 4 weeks to allow more flexibility. Practical issues like these will probably play a major role in determining which checkpoint inhibitor we might use, given that most of these agents are essentially quite similar.

Is there a role for sequencing checkpoint inhibitors for patients with BC?

In terms of sequencing, it's not clear that treating with one PD-1 pathway inhibitor followed by another has any clear role. It's not clear that patients who responded upfront and then progressed, or patients who progressed immediately on one agent, are destined to respond to another, given that these agents are all a part of the similar pathway. There is an issue where if patients in the first-line setting are treated with immunotherapy, and ultimately do not respond and progress, they will then need chemotherapy. We know that chemotherapy is still an important tool in treating patients with advanced BC, and certainly it will continue to be valuable in patients who do not respond to immunotherapy.

Where is the future of immunotherapy in BC heading? Is there a role for immunotherapy combinations or combinations with chemotherapies?

Of course. Immunotherapy in BC over the next 3 to 5 years is quickly going to move toward the first-line setting, earlier stages of disease, and is moving toward combinations. Those combinations might include other immune combinations versus combinations with traditional cancer therapy, such as radiation or chemo. It's not yet clear which is going to be the best partner and for what setting, but this is why trials are necessary. Still, I'm very optimistic.

In the coming years, a minority of patients will be treated with single-agent immunotherapy alone. Most will likely need a combination of some kind, be it immunotherapy combinations or possibly combinations with other standard therapies. Very few patients will just receive single-agent immunotherapy.

What role do CTLA-4 targeted therapies have in BC? What about therapies that target VEGFR?

The CTLA-4 pathway is among the first immune checkpoints that was discovered as a therapeutic target in cancer, going back to the earliest studies in melanoma. It's evident from early-phase studies that the combination of CTLA-4 and PD-1 pathways may lead to higher responses in BC. We've seen it in melanoma, we've seen it in non–small-cell lung cancer, and I believe we'll see it in advanced BC in larger studies soon. Ultimately, studies like the phase III DANUBE trial, which is testing durvalumab with or without tremelimumab, will answer that question. I do envision a future that combines PD-1 and CTLA-4 inhibitors in some patients with BC. The challenge is identifying who those patients are who warrant combination therapy, given the toxicity profile that we see. Certainly, strategies that include CTLA-4 lead to higher rates of immune-related AEs—up to 30% or more based on studies that have been presented so far. So that will clearly be an issue that needs to be resolved.

VEGF/VEGFR is also a very enticing target to look at. PD-1 combinations with VEGF/VEGFR-targeted therapies in advanced kidney cancer are leading to very high synergistic responses, up to 70%. We need to test whether these types of approaches lead to similar responses in BC, and those trials are currently ongoing. What is exciting about the combination of VEGF/VEGFR-targeted therapies with PD-1 pathway inhibitors is that therapy does appear to be well tolerated, and could then therefore be a very attractive option for these patients.

What about the combination with radiotherapy for these patients?

Spanning several decades now, investigators have noted that some patients who receive radiation for a solitary metastasis have an induced response in other metastatic sites that were never radiated. The concept that focused treatment of 1 site leads to responses in a distant site is called the *abscopal effect*. The idea here is that radiation can induce immunogenic cell death in the tumor that is radiated, which could then lead to a systemic antitumor immune response. Thus, checkpoint blockade could combine favorably with radiation to enhance the antitumor immune response.

Over the years, a number of studies have looked at radiation in combination with immunotherapy to test this idea more formally. In BC, I think that there are some clear opportunities to test this concept, particularly in patients who have localized muscle-invasive BC who are ineligible for or refuse radical cystectomy. Chemotherapy and radiation is standard of care for these patients, and has been shown to improve survival versus radiation on its own. It's very exciting to see trials that are testing radiation and chemotherapy in combination with immunotherapy in patients with localized disease, to see whether we can actually improve cure rates by inducing synergy between immunotherapy and radiation.

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