

Avelumab First-Line Maintenance Treatment in Advanced Bladder Cancer: Practical Implementation Steps for Infusion Nurses

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ABSTRACT

Immune checkpoint inhibitors, such as programmed cell death ligand 1 inhibitors pembrolizumab, nivolumab, atezolizumab, and avelumab, are used to treat patients with advanced urothelial carcinoma (UC). Based on data from the phase 3 JAVELIN Bladder 100 trial, avelumab first-line (1L) maintenance is now considered the standard-of-care treatment for patients with locally advanced or metastatic UC who responded or experienced disease stabilization after 1L platinum-containing chemotherapy, and it is the only category 1 preferred checkpoint inhibitor maintenance option in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for patients with cisplatin-eligible and cisplatin-ineligible locally advanced or metastatic UC. This article reviews key considerations related to avelumab 1L maintenance therapy that infusion nurses should be familiar with, including dosing, administration, and immune-related adverse event recognition and management, to ensure safe and appropriate use of this important and impactful therapy.

Key words: adverse event management, avelumab, bladder cancer, immune checkpoint inhibitor, infusion nurse, infusion reactions, maintenance therapy, oncology, toxicity management, urothelial cancer

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Disclosures and Conflicts of Interest.

Ms Wood has received honoraria for speaker bureau participation and is on the advisory board for EMD Serono. Ms Conway and Ms Lapuente have received honoraria from EMD Serono for an advisory board. Mr Salvador and Ms Fernandez Gomez declare no competing interests. Ms Carroll Bullock is an employee of EMD Serono. Dr Devgan is an employee of Pfizer. Ms Burns has received honoraria for speaker bureau participation for Merck & Co, Astellas, Pfizer, Aveo Oncology, and Exelixis and has participated in an advisory board for EMD Serono, Pfizer, and Aveo Oncology.

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As one of the most common cancers worldwide, bladder cancer is estimated to be responsible for more than 500 000 new cases and approximately 200 000 deaths globally every year.¹ Risk factors for bladder cancer include older age, family history of bladder cancer, being male, history of smoking, and/or chronic urinary infections.^{2,3} Approximately 5.0% of patients have metastatic bladder cancer at diagnosis, which is associated with a 5-year survival rate of 5.5%.⁴ Urothelial carcinoma (UC) is the most common type of bladder cancer, with >90% of UC tumors originating in the bladder.^{5,6} Patients with UC tend to be a frail and older population with multiple comorbidities.⁷

Based on real-world analyses conducted in the United States, United Kingdom, Germany, Netherlands, and Denmark, a large proportion of patients with metastatic bladder cancer do not receive first-line (1L) chemotherapy.⁸⁻¹¹ Platinum-containing combination chemotherapy is the 1L standard-of-care treatment for platinum-eligible patients with locally advanced or metastatic UC.^{6,12,13} Although UC is an aggressive disease,¹⁴ UC tumors are sensitive to chemotherapy. However, some patients are cisplatin-ineligible, as defined by meeting at least 1 of the following criteria: Eastern Cooperative Oncology Group performance status equal to 2, creatinine clearance <60 mL/min, grade 2 hearing loss, grade \geq 2 neuropathy, and/or New York Heart Association Class III heart failure.¹⁵ Among patients who receive 1L chemotherapy, approximately 27% to 35% of patients receive second-line treatment.^{8,9,11,16} However, because one limitation of chemotherapy is the short durability of response,^{17,18} there is a need for further maintenance treatment to extend overall survival, as patients treated with only 1L platinum-containing chemotherapy may eventually develop disease progression.

Avelumab, a programmed cell death ligand 1 (PD-L1)-blocking antibody, is an immune checkpoint inhibitor (ICI).

ICIs are immunotherapy drugs that block immune checkpoint proteins from binding with their partner proteins, thereby allowing T cells to kill cancer cells.¹⁹ This immunotherapy is the only treatment approved for use as 1L maintenance treatment in advanced UC in multiple countries, including the United States, Canada, Japan, and the European Union.²⁰⁻²⁴ Unlike other ICIs used to treat UC, avelumab 1L maintenance treatment has a category 1 recommendation from the National Comprehensive Cancer Network (NCCN) bladder cancer treatment guidelines for use in patients who are cisplatin-eligible or cisplatin-ineligible with locally advanced or metastatic UC.⁶ The European Society for Medical Oncology and European Association of Urology guidelines similarly recommend avelumab as the only ICI for 1L maintenance in this patient population.^{13,25} The approval and guideline recommendations are based on paradigm-changing results from the JAVELIN Bladder 100 trial, in which patients received a new sequencing approach of initial chemotherapy followed by avelumab.^{6,13,25-27} Avelumab maintenance is considered an extension of 1L treatment, administered after induction chemotherapy in patients who have achieved disease control, and is associated with an overall survival benefit.^{26,27} Avelumab should be administered as 1L maintenance treatment until the patient experiences disease progression.²⁰

Infusion nurses play a key role in administering avelumab. Thus, an understanding of the mechanism of action, clinical profile, and safety profile will be useful in clinical practice. This article provides an overview of the evidence supporting the use of avelumab in the 1L maintenance setting in UC and discusses the key practical considerations for infusion nurses when implementing avelumab 1L maintenance therapy in patients, with a focus on administration, as well as recognition and management of infusion-related reactions and immune-related adverse events (irAEs).

OVERVIEW OF IMMUNE CHECKPOINT INHIBITORS

Platinum-containing chemotherapy agents (eg, cisplatin and carboplatin) act directly on tumor cells through DNA binding, which disrupts DNA replication and transcription, resulting in a cytotoxic effect that leads to cell death. However, these agents do not discriminate between tumor and healthy cells and are associated with an array of side effects.^{28,29} Agents targeting the immune system exert their anticancer effect by recruiting the cells of the immune system, including T cells, to specifically target and eliminate tumor cells.³⁰ One of the ways in which tumor cells evade recognition and destruction by the immune system is by downregulating antitumor immune responses via expression of PD-L1³⁰; up to 50% of UC tumors express high levels of PD-L1.²⁷ This ligand binds to the programmed cell death receptor 1 (PD-1) on the surface of T cells as part of an immune checkpoint pathway.^{30,31} The interaction between PD-1 and PD-L1

can suppress the activity of T cells and prevent potential antitumor immune responses.^{32,33} Blocking the activity of PD-1 and/or PD-L1 removes the inhibition of immune cells, thereby restoring the antitumor responses.^{30,34}

A number of ICIs are now used in the United States for treating patients with locally advanced or metastatic UC (Table 1).^{20,35-37} Avelumab is a monoclonal antibody, a type of targeted binding protein that acts by binding to PD-L1, preventing it from binding to PD-1 on the surface of T cells (Figure 1). These T cells remain active and available to target and destroy tumor cells.²⁰ Avelumab binding to PD-L1 on tumor cells may also activate natural killer cells to mount anticancer effects via antibody-dependent cell-mediated cytotoxicity.^{38,39} Other PD-1 inhibitors include pembrolizumab and nivolumab, which act in a slightly different way than avelumab and atezolizumab, by binding to PD-1 and inhibiting the interaction between PD-1 and PD-L1.^{35,36}

First-line platinum-containing chemotherapy, in addition to direct cytotoxic activity, has a range of immunogenic

TABLE 1

Immune Checkpoint Inhibitors Approved for Use in Patients With Locally Advanced or Metastatic Urothelial Carcinoma in the United States^a

	First-Line	Second-Line
PD-L1 inhibitors		
Avelumab	Indicated as maintenance treatment for patients with locally advanced or metastatic UC that has not progressed with 1L platinum-containing chemotherapy	Indicated for patients with locally advanced or metastatic UC who: <ul style="list-style-type: none"> • Have disease progression during or after platinum-containing chemotherapy • Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
Atezolizumab ^b	Indicated for adults with locally advanced or metastatic UC who: <ul style="list-style-type: none"> • Are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells \geq5% of the tumor area)^c • Are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status 	Not approved
PD-1 inhibitors		
Pembrolizumab	Indicated for patients with locally advanced or metastatic UC who are not eligible for platinum-containing chemotherapy	Indicated for patients with locally advanced or metastatic UC who: <ul style="list-style-type: none"> • Have disease progression during or following platinum-containing chemotherapy or • Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
Nivolumab	Not approved	Indicated for patients with locally advanced or metastatic UC who: <ul style="list-style-type: none"> • Have disease progression during or after platinum-containing chemotherapy • Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

^aData from References 20, 35-37.

^bThis indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent on verification and description of clinical benefit in a confirmatory trial(s).³⁷

^cAs determined by an FDA-approved test.^{35,37}

Abbreviations: 1L, first-line; FDA, US Food and Drug Administration; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death ligand 1; UC, urothelial carcinoma.

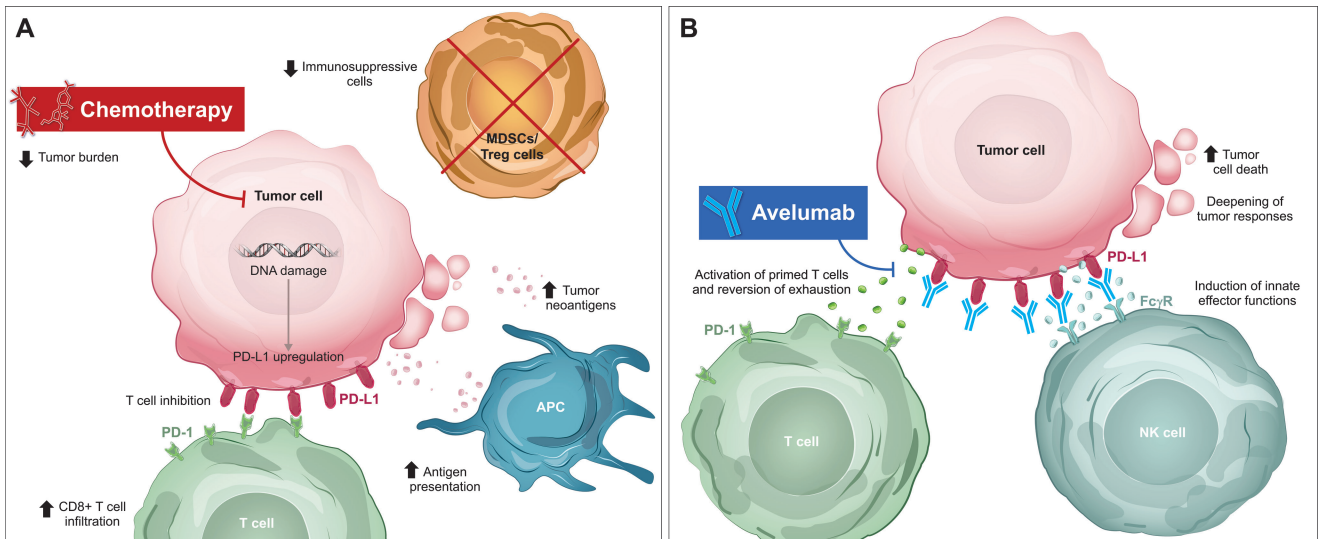


Figure 1 Avelumab mechanism of action. A, Chemotherapy can have potentially immunogenic effects, in addition to its direct cytotoxicity. B, Avelumab is an anti-PD-L1 monoclonal antibody that binds PD-L1 on tumor cells and prevents PD-L1 from binding PD-1 receptors on activated T cells. Blockade of this PD-1/PD-L1 immune checkpoint pathway prevents T-cell inactivation and restores active antitumor T-cell responses. Avelumab binding to PD-L1 on tumors may also activate natural killer cells to mount anticancer effects via antibody-dependent cell-mediated cytotoxicity. Abbreviations: APC, antigen-presenting cell; CD8, cluster of differentiation 8; FcγR, Fc-gamma receptor; MDSC, myeloid-derived suppressor cell; NK, natural killer; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death ligand 1. Copyright © 2021 Grivas et al, reprinted with permission.³⁴

effects that may enhance the antitumor effects of an ICI (Figure 1).^{26,29,34,40,41} Using a sequential approach with an ICI after 1L platinum-containing chemotherapy can potentially maintain and extend the benefits of the chemotherapy.²⁶

AVELUMAB AS 1L MAINTENANCE TREATMENT IN ADVANCED UC

Avelumab approval as a 1L maintenance treatment for advanced UC was based on the seminal data from the JAVELIN Bladder 100 study.^{20,34} This was a phase 3 clinical trial comparing avelumab 1L maintenance and best supportive care (BSC; 350 patients) versus BSC alone (350 patients) in patients with locally advanced or metastatic UC who did not have disease progression after 4 to 6 cycles of 1L platinum-containing chemotherapy (Figure 2).²⁷ Fifty-one percent of patients had PD-L1-positive tumors, 39% had PD-L1-negative tumors, and 10% had unknown PD-L1 tumor status.²⁰ Avelumab 1L maintenance plus BSC improved outcomes, resulting in significantly prolonged overall survival (Figure 3) and progression-free survival compared with BSC alone.²⁷ Overall survival was significantly longer in the avelumab arm despite more patients in the BSC arm receiving ICI treatment after discontinuing BSC, with a median overall survival of 21.4 months (95% CI, 18.9-26.1 months) in the avelumab plus BSC arm versus 14.3 months (95% CI, 12.9-17.9 months) in the BSC arm (hazard ratio = 0.69 [95% CI, 0.56-0.86]; $P = .001$).²⁷

The study also showed that avelumab maintenance treatment did not negatively affect clinically relevant patient-reported outcomes, where the median time to

deterioration was not reached for avelumab plus BSC (95% CI, 13.9 months to not estimable) versus BSC alone (95% CI, 12.9 months to not estimable) at 13.8 months.⁴² Treatment-related adverse events (AEs), of which the most common ($\geq 10\%$ of patients) included pruritus, hypothyroidism, diarrhea, and infusion-related reaction, occurred more frequently in the avelumab arm (active treatment) than in the BSC arm (no active treatment; Figure 4).²⁷ Discontinuation rates due to AEs were low with avelumab, and the toxicity profile seems to be consistent with that reported in other trials of ICIs, with the most common (67% of patients) AEs of any cause being fatigue, nausea, diarrhea, and increased serum biomarkers.^{27,43}

These data show the clear benefit of administering avelumab maintenance therapy directly after 1L chemotherapy for patients with initial complete response, partial response, and stable disease after 4 to 6 cycles of platinum-containing chemotherapy rather than delaying until disease progression has occurred.²⁷ Data suggest that the schema of a platinum-containing chemotherapy agent followed by avelumab 1L maintenance may provide the best responses to 1L therapy, because maintenance therapy with an ICI after 1L chemotherapy may result in enhanced antitumor activity while avoiding potential interactions, including cross-resistance and cumulative toxicity.²⁷

PATIENT PROFILES: CANDIDATES FOR AVELUMAB 1L MAINTENANCE

To be considered for avelumab maintenance treatment, patients should have had a partial response, a complete

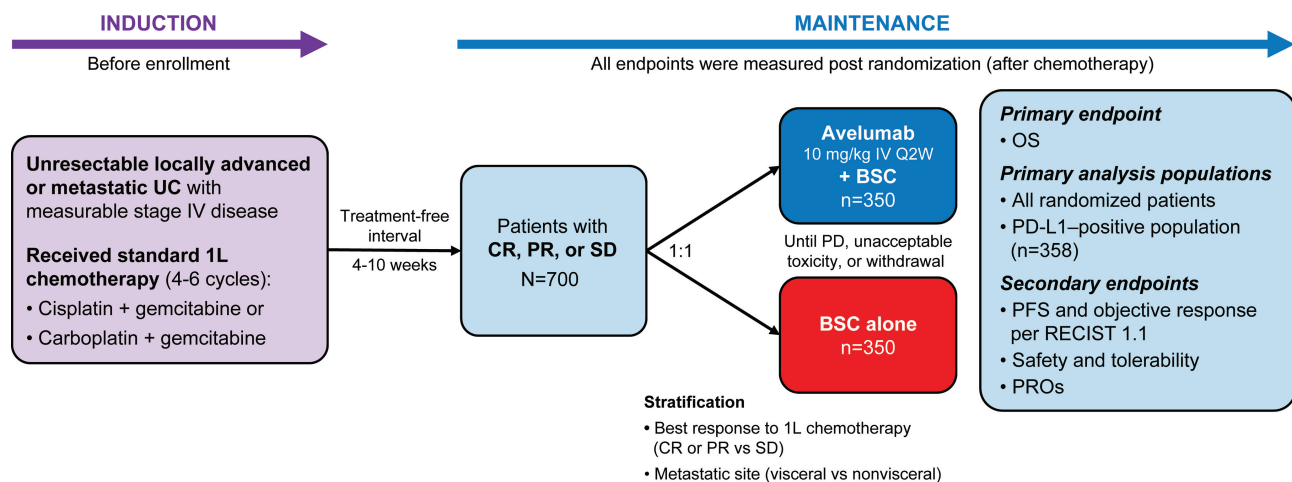


Figure 2 Study design of JAVELIN Bladder 100 trial. In the JAVELIN Bladder 100 trial, patients with locally advanced or metastatic UC without disease progression (in CR, PR, or SD) after 4 to 6 cycles of 1L platinum-containing chemotherapy were randomized to receive either avelumab (10 mg/kg Q2W) plus BSC or BSC alone until disease progression, unacceptable toxicity, or withdrawal.²⁷ Abbreviations: 1L, first-line; BSC, best supportive care; CR, complete response; IV, intravenous; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PD, progressive disease; PR, partial response; PRO, patient-reported outcome; Q2W, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; UC, urothelial carcinoma. Copyright © 2021 Grivas et al, reprinted with permission.³⁴

response, or stable disease in response to 1L platinum-containing chemotherapy.²⁷ Therefore, monitoring a patient's response to 1L platinum-containing chemotherapy is needed to determine whether they may be a candidate for avelumab as 1L maintenance and when treatment can be initiated. In the JAVELIN Bladder 100 trial, patients had a treatment-free interval of 4 to 10 weeks (since the last dose of chemotherapy) before proceeding with avelumab 1L maintenance therapy.²⁷ Therefore, patients had time to recover from the effects of 1L chemotherapy and could have a brief treatment break, if desired, before initiating 1L maintenance treatment.

Data from the JAVELIN Bladder 100 study showed that avelumab is suitable for patients with a range of demographic, clinical, and disease characteristics.^{27,44}

Survival benefits compared with BSC were observed in patients identified as high risk (eg, older patients or those with renal impairment) and among patients with PD-L1-

positive and PD-L1-negative tumors.^{20,27,44} Prolonged overall survival was observed in patients who received either 1L cisplatin-based or carboplatin-based chemotherapy, regardless of best response to 1L chemotherapy, including in patients with stable disease, a partial response, or a complete response.⁴⁴ It should be noted that a complete response as determined by imaging may not mean that a patient has a pathologic complete response and is cured, as even patients who appear to be "disease free" may progress quickly without maintenance treatment. Prolonged overall survival was also observed with the JAVELIN Bladder regimen irrespective of the number of cycles of platinum-containing chemotherapy patients received (4 to 6 cycles) or the total duration of chemotherapy (<15.0 to >20.1 weeks).⁴⁵

Initiation of avelumab 1L maintenance treatment at 4 to 10 weeks after the last dose of chemotherapy in the JAVELIN

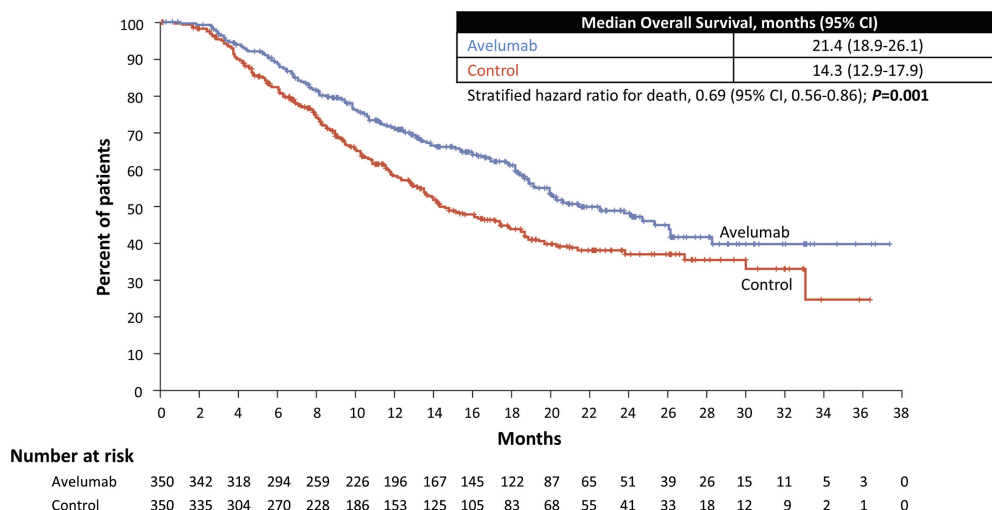


Figure 3 Overall survival benefit with avelumab 1L maintenance treatment in the overall study population from the JAVELIN Bladder 100 trial. Control = best supportive care. Abbreviation: 1L, first line. Copyright © 2020, Massachusetts Medical Society. Reprinted with permission.²⁷

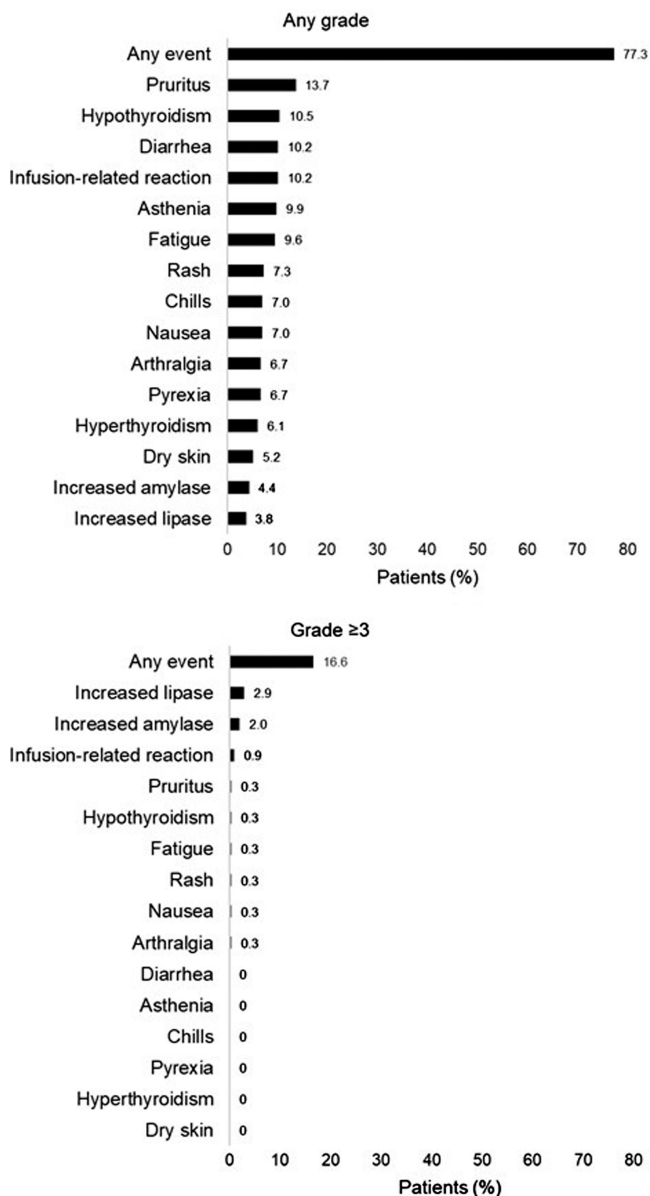


Figure 4 Treatment-related AEs reported for the avelumab + BSC group (N = 344) in the JAVELIN Bladder 100 trial. Safety was assessed in all patients who received at least 1 dose of avelumab in the avelumab + BSC arm or who completed the cycle 1 day 1 visit in the BSC arm (N = 689; safety population). In JAVELIN Bladder 100, 77.3% and 16.6% of patients in the avelumab + BSC group (N = 344) reported any grade and grade 3 or higher treatment-related AEs, respectively, and 1.2% and 0% of patients in the BSC-alone group (N = 345) reported any grade and grade ≥ 3 treatment-related AEs, respectively. Data shown are for treatment-related AEs of any grade occurring in $\geq 5\%$ or grade ≥ 3 or higher events occurring in $\geq 2\%$ of the safety population.²⁷ Abbreviations: AE, adverse event; BSC, best supportive care.

Bladder 100 trial²⁷ allowed for imaging to confirm response to chemotherapy. It also provided time for resolution of treatment-related toxicities. Avelumab plus BSC resulted in prolonged overall survival regardless of the treatment-free interval of 4 to 6 weeks, 6 to 8 weeks, or 8 to 10 weeks after the last dose of chemotherapy.^{27,46} The timing of the initiation of avelumab 1L maintenance therapy after completion of 1L platinum-based chemotherapy will be influenced

by clinical judgment and individual patient considerations (eg, patient preference, resolution of chemotherapy-related toxicity, logistics related to scheduling).^{34,46} It is not known whether a treatment-free interval longer than 10 weeks would be associated with a positive benefit–risk ratio. Oncology providers and patients must be aware that there may be an increased risk of disease progression with treatment-free interval durations longer than 10 weeks.³⁴

ROLE OF INFUSION NURSES IN THE TREATMENT OF PATIENTS WITH ADVANCED UC

Infusion nurses trained in the administration of chemotherapy will likely begin interacting with patients with advanced UC when 1L platinum-containing chemotherapy is initiated and may maintain a relationship throughout treatment with avelumab. In addition to administering therapy, infusion nurses proactively assess the patient's tolerance of therapy, monitor and assess for AEs, answer questions, provide educational materials and resources, and support treatment adherence. Conversations about treatment expectations can support treatment adherence.⁴⁷ At some institutions, a nurse navigator, rather than an infusion nurse, will work closely with the oncologists and initiate conversations with patients. Advanced UC should be treated as a chronic, aggressive disease; thus, patients should be educated on the need for continued avelumab maintenance treatment in accordance with their treating physician. There is no fixed duration, but avelumab 1L maintenance treatment should be administered until disease progression or unacceptable toxicity, consistent with the JAVELIN Bladder 100 clinical trial and as indicated in the prescribing information.^{20,27}

Avelumab Preparation

While pharmacists will generally be responsible for avelumab preparation, infusion nurses at some institutions may be required to prepare immunotherapy agents. It should be noted that, because avelumab is not classified as chemotherapy, traditional chemotherapy certification is not required for nursing administration; however, requirements may vary by country and institution. Furthermore, the drug preparation does not require the same preparation as traditional chemotherapy. Avelumab is supplied as a single-dose vial containing 200 mg/10 mL as a solution that is clear and colorless or slightly yellow in color.²⁰ To prepare avelumab for infusion, the vial should be examined carefully; if any particulate matter, discoloration, or cloudiness is observed, the vial should be discarded.²⁰ Avelumab withdrawn from the vial should be injected into a 250-mL infusion bag of 0.9% or 0.45% sodium chloride injection fluid. After gently inverting the bag to mix (avoiding foaming or excessive shearing), it should be inspected to ensure that the solution is clear and colorless, without any visible particles.²⁰ One technique that some hospitals use to prepare avelumab

and other immunotherapies is the “lock-in system,” or closed system device.⁴⁸

Dosing and Administration

Avelumab is approved to be administered at a dose of 800 mg as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.^{20,49} The flat dose of 800 mg every 2 weeks, rather than a weight-based 10 mg/kg every 2 weeks dose, is supported by population pharmacokinetics modeling data, where simulations suggested that exposure to avelumab was similar between the 2 dosing strategies. The approximate 6-day half-life provides the rationale for a dosage interval of every 2 weeks.^{20,50} This also explains why the dosing schedule for avelumab differs from that of other ICIs, which have much longer half-lives (ie, >3 weeks).³⁵⁻³⁷ The infusion set should include a sterile, nonpyrogenic, low-protein-binding in-line filter (pore size 0.2 μm) and should not be used to administer any other drugs.⁴⁹ Avelumab can be administered in any vein, using catheters of any type (peripheral or central) and relatively small (20- to 24-gauge) needles.

Health Care Provider Safety With Avelumab Infusions

If accidental spillage occurs, consultation of site-specific institutional guidelines on spill management is recommended.

Infusion-Related Reactions and Premedication

Avelumab has adverse effects consistent with those of other ICIs.⁴³ Avelumab can potentially cause severe or life-threatening infusion-related reactions.²⁰ In the JAVELIN Bladder 100 trial, 10% of patients experienced an infusion-related reaction, with 0.9% having a grade 3 reaction.^{20,27} Infusion-related reactions resulted in permanent discontinuation of avelumab in 1.2% of patients in JAVELIN Bladder 100.²⁰ In data from across the avelumab clinical development program (based on 1738 patients treated with avelumab 10 mg/kg across multiple tumor types), infusion-related reactions (all grades) occurred in 25% of patients, and the vast majority of events were mild: 9 patients (0.5%) experienced a grade 3 reaction, and 3 (0.2%) experienced a grade 4 reaction.²⁰

In a pooled analysis of several avelumab trials across different tumor types, 80% of infusion-related reactions occurred at the time of the first infusion, and 99% occurred within the first 4 infusions.⁴³ The risk of infusion-related reactions diminished with subsequent infusions, as 20%, 5%, <2%, and <1% of patients had an infusion-related reaction with the first, second, third, and fourth infusion, respectively, in this analysis.⁴³ Patients should receive premedication with an antihistamine and acetaminophen before the first 4 avelumab infusions.²⁰ Premedication may also be needed for subsequent infusions, depending on clinical judgment and the presence and severity of prior infusion-related reactions.²⁰ In the JAVELIN Bladder 100 trial, premedication was administered approximately 30 to 60 minutes before

the avelumab infusion was initiated.²⁷ Nurses should instruct patients to have someone accompany them for the first infusion visit (and potentially for subsequent infusion visits) as a precautionary measure, because some may experience an infusion reaction or drowsiness from certain types of premedication (eg, antihistamines such as diphenhydramine).

Patients should be monitored throughout the infusion process for signs and symptoms of infusion-related reactions. These may include pyrexia, chills, flushing, dyspnea, wheezing, hypotension, back or abdominal pain, and urticaria.²⁰ Infusion-related reactions may occur up to 2 days after infusion,⁴³ so it is important to educate patients and their caregivers to immediately alert a health care provider if they have any unusual symptoms after leaving the infusion center. At some institutions, a nurse will call the patient on the following day to determine whether any infusion-related reactions or irAEs have occurred. The nurse needs to communicate effectively with other members of the oncology team regarding identification and management of AEs that might occur with avelumab. All symptoms and AEs should be documented in the patient’s electronic medical record.

One useful tool is the Common Terminology Criteria for Adverse Events (CTCAE) grading system, which was developed to standardize AE reporting across different specialties.^{51,52} A good understanding of CTCAE criteria can help infusion nurses effectively respond and communicate with a patient’s primary oncology team. Grade 1 typically refers to AEs that are mild and require no intervention. Grade 2 refers to moderate AEs that may require minimal, local, or noninvasive intervention. Grade 3 refers to severe or medically significant but not immediately life-threatening AEs, where hospitalization or prolongation of hospitalization may be needed; these AEs are considered to be disabling. Grade 4 refers to AEs with life-threatening consequences, where urgent intervention is needed. Grade 5 refers to death related to an AE.⁵³

RECOGNITION AND MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS IN PATIENTS RECEIVING AVELUMAB 1L MAINTENANCE TREATMENT

Treatment with ICIs such as avelumab may lead to severe and fatal irAEs, which can occur in any organ system or tissue.^{20,51}

Monitoring and Recognition of irAEs

These irAEs may occur at any time after treatment with avelumab, including after treatment has been discontinued.²⁰ irAEs are AEs with an immune-mediated etiology and have a distinct pathology and treatment approach. irAEs are also dissimilar from AEs caused by chemotherapy or other non-immunotherapy agents.⁴³ irAEs include immune-mediated pneumonitis, immune-mediated colitis, hepatotoxicity and immune-mediated hepatitis, immune-mediated adrenal

insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, immune-mediated type I diabetes mellitus, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, myocarditis, and neurological toxicities.²⁰

In the JAVELIN Bladder 100 trial, the frequency of irAEs of any grade occurring in patients treated with avelumab plus BSC was 29.4%; the most common irAEs are listed in Figure 5.²⁷ Grade 3 irAEs were reported for 7% of patients; no patients experienced a grade 4 or fatal irAE.²⁷ In 9% of patients who received avelumab, high-dose glucocorticoids (≥ 40 mg total daily dose of prednisone or equivalent) were administered after an irAE.²⁷

Infusion nurses should monitor patients closely for signs and symptoms of potential irAEs, because early recognition and management is critical.²⁰ Patient monitoring should include evaluations of liver enzymes, creatinine, and thyroid function conducted at initial consultation and throughout treatment.²⁰ An appropriate workup to exclude alternative etiologies, such as infections, should be initiated if an irAE is suspected.²⁰ Medical management, which may include consultation with specialists, should be enacted quickly.

Avelumab Dose Interruption and Treatment Modification

In case a moderate or severe irAE occurs, avelumab should be withheld or permanently discontinued depending on the severity and type of irAE (see the Supplemental Digital

Content at <http://links.lww.com/JIN/A102> for additional details on management strategies for specific irAEs).²⁰ Dose reduction of avelumab is not recommended, and there are no evidence-based data to support this strategy. Avelumab should be withheld for severe irAEs (grade 3) and permanently discontinued for life-threatening irAEs (grade 4), recurrent severe irAEs (grade 3) that require systemic immunosuppressive treatment, or in cases where corticosteroid dose cannot be reduced to 10 mg or less of prednisone or equivalent per day within 12 weeks of corticosteroid initiation.²⁰

In cases where avelumab treatment requires interruption or discontinuation, systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) should be administered until improvement to grade 1 or lower is observed.²⁰ Once improvement to grade 1 or lower occurs, corticosteroid tapering can be initiated and continued for 1 month or longer.²⁰ Use of other systemic immunosuppressants can be considered for patients with irAEs that cannot be controlled by corticosteroids.²⁰ If warranted, rechallenge with avelumab should be considered.

For infusion-related reactions, grade 1 or 2 events may be managed by interrupting or slowing the rate of infusion. For grade 3 or 4 infusion-related reactions, permanent discontinuation of avelumab is recommended.²⁰ The management of infusion-related reactions from the JAVELIN Bladder 100 trial protocol is shown in Figure 6.²⁷ For patients who undergo long treatment delays due to unforeseen circumstances, the

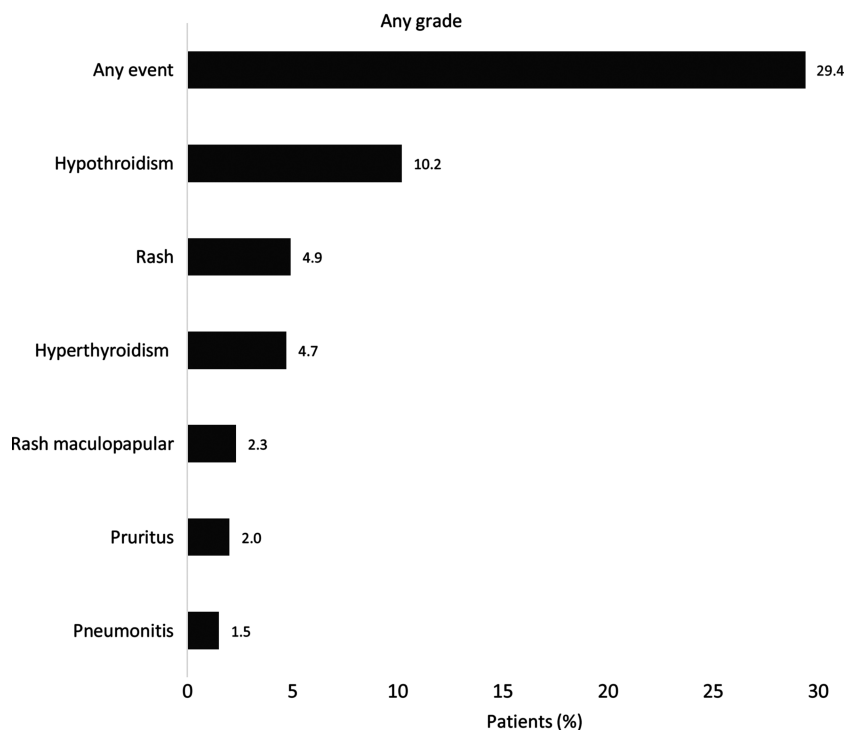


Figure 5 Immune-related AEs reported for the avelumab + BSC group (N = 344) in the JAVELIN Bladder 100 trial. Safety was assessed in all patients who received at least 1 dose of avelumab in the avelumab + BSC arm or who completed the cycle 1 day 1 visit in the BSC arm (N = 689; safety population). In JAVELIN Bladder 100, 29.4% of patients in the avelumab plus BSC group (N = 344) reported any grade immune-related AEs. Data shown are for immune-related AE events of any grade occurring in $\geq 1\%$ of the safety population.²⁷ Abbreviations: AE, adverse event; BSC, best supportive care.

oncology team should consider retreatment of premedication to prevent any infusion-related reaction. Some patients may require treatment delay or interruption after an infusion-related reaction or irAE or for other reasons associated with comorbidities, vacations, or unexpected events.

Management of infusion-related reactions depends on each patient's response to the medications given. Infusion-related reactions may resolve after 1 dose of antihistamine, whereas others may require a corticosteroid (eg, hydrocortisone). For patients who develop a fever, consider treatment with acetaminophen. These medications should be preprescribed in case they are required.

SAFETY PROFILES OF 1L PLATINUM-CONTAINING CHEMOTHERAPY AND AVELUMAB MAINTENANCE THERAPY

Chemotherapy and immunotherapy are associated with differing safety profiles as a result of their unique modes of anticancer effects.^{18,27,54,55} Thus, AEs related to each therapy typically require different approaches to their management. Patients will first be treated with platinum-containing chemotherapy, which may lead to AEs affecting the gastrointestinal system (eg, nausea, vomiting, diarrhea), blood cell production (eg, pancytopenia), and renal impairment.^{18,54,55} However, these AEs are typically recognizable and can be managed. Patients should be allowed time to recover from any chemotherapy-related AEs before initiating avelumab.

When patients initiate treatment with avelumab, they may experience different AEs from those associated with platinum-containing chemotherapy. The most commonly reported treatment-related AEs in the JAVELIN Bladder 100 trial included pruritus, hypothyroidism, diarrhea, and infusion-related reactions, which occurred in 10% to 14% of

patients.²⁷ The kinetics of AEs also differ for platinum-containing chemotherapy and ICIs such as avelumab. Although AEs associated with platinum-containing chemotherapy generally occur during treatment, most often within days or weeks of starting treatment,^{56,57} the timing of irAEs associated with ICIs is less predictable, and they may emerge a few days, or weeks to months, after treatment has started.^{20,21} Nurses must also be aware that irAEs can develop or worsen after completion of therapy and may occur after initiation of subsequent therapy. Patients and caregivers should be educated regarding this possibility, and infusion nurses should be vigilant of the development of AEs that are not consistent with the adverse event profile of drugs being used as subsequent treatment. Thus, active surveillance for irAEs throughout treatment with avelumab by both patients and infusion nurses is essential to ensure appropriate management so that patients can continue treatment. Because irAEs can often resolve with prompt treatment, it is essential that patients communicate any new symptoms to their health care team as soon as possible and do not wait for their next clinic visit.

COVID-19-RELATED CONSIDERATIONS

The COVID-19 pandemic has led to additional issues that may complicate the management of patients with advanced UC. In the authors' experiences, patients have had questions about the compatibility of avelumab treatment with COVID-19 vaccinations. The NCCN COVID-19 Vaccination Advisory Committee endorses COVID-19 vaccination for all eligible persons based on US Food and Drug Administration–approved indications or emergency use authorization. The committee reiterates the need for patients with cancer to be fully immunized, including receiving third doses and boosters.⁵⁸ The NCCN recommends that

Infusion-Related Reactions With Avelumab: CTCAE Grade and Treatment Modification

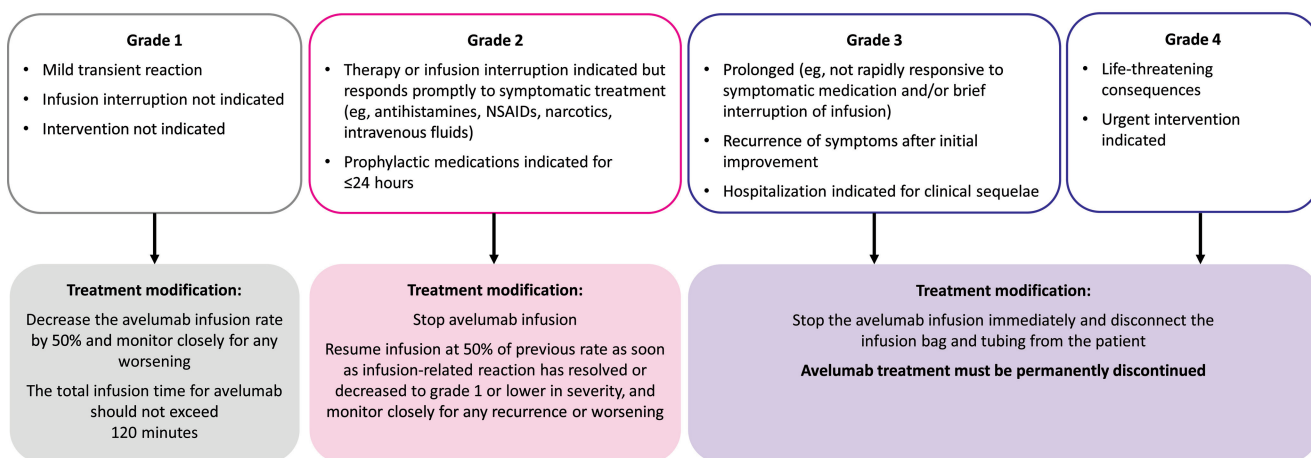


Figure 6 Management of infusion-related reactions: protocol from the JAVELIN Bladder 100 trial. Once the avelumab infusion rate has been decreased by 50% due to an infusion-related reaction, it must remain so for all subsequent infusions.²⁷ Based on NCI CTCAE version 4.03. Definitions of CTCAE grades can be accessed at the following link: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm. Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; NSAID, nonsteroidal anti-inflammatory drug.

patients with solid-tumor malignancies receiving cytotoxic chemotherapy or ICIs also receive a COVID-19 vaccine as soon as possible, although they also state that there is a theoretical risk of exacerbated irAEs in patients receiving ICIs.⁵⁸ Based on the authors' experiences, infusion nurses may want to be aware of vaccination timing to help prevent confusion between COVID-19 vaccine-related toxicities and chemotherapy- or avelumab-related toxicities. There are no data available on the timing of vaccine administration with respect to immunotherapy, so they may be considered for the same day for convenience and to reduce office visits.⁵⁸ However, institution-specific recommendations may exist, as, in the authors' experiences, some centers advise patients to receive their vaccine at least 7 days after an infusion.

The COVID-19 pandemic may also affect treatment adherence, as avelumab 1L maintenance treatment requires an infusion every 2 weeks²⁰; patients and their caregivers might express concern about frequent treatment center visits and how treatment delays due to the pandemic could potentially affect their treatment outcomes and prognosis. In these cases, it would be important for nurses to emphasize the rationale for staying on the JAVELIN Bladder regimen to maximize the benefits of anti-cancer therapy.

ADDITIONAL WAYS INFUSION NURSES SUPPORT PATIENTS WITH UC

In addition to administration, in-person patient monitoring, and irAE management, there are ways the infusion nurse can provide support for patients with advanced UC receiving avelumab 1L treatment (Figure 7). Before beginning treatment, infusion nurses in some practices may hold a consultation with patients and their caregivers to discuss the time commitment required and to provide

detailed instructions and educational materials related to recognizing and reporting potential side effects. Although a patient's primary oncology team may have already provided some patient and caregiver education, this preavelumab consultation provides an opportunity for reinforcement of this critical information.

As discussed previously, infusion nurses play an important role in recognizing symptoms and/or complications that arise during infusions. Some infusion nurses may also conduct postinfusion checkups on patients. Frequent communication with the patient's primary oncology team is essential, during which the infusion nurse can provide feedback on a patient's progress or express any concerns. Additionally, infusion nurses can serve as an important support partner for patients with UC. Many patients may feel anxiety and uncertainty about receiving a new treatment; infusion nurses can help patients feel as comfortable as possible while they are in the clinic, which may also encourage treatment adherence.

CONCLUSIONS

Infusion nurses are at the front line of patient care and play a vital role throughout the treatment journey of patients with advanced UC. Key responsibilities include administration of platinum-containing chemotherapy and avelumab 1L maintenance, as well as patient monitoring, coordination with other members of the patient's oncology team, and patient and caregiver education and support. Infusion nurses may serve as both valuable educational resources and important champions for patients' needs. A thorough understanding of the rationale and benefit of avelumab 1L maintenance, as well as the recognition and management of infusion-related reactions and irAEs, will enable infusion nurses to ensure that patients with advanced UC receive optimal cancer care. As a result, treatment with avelumab

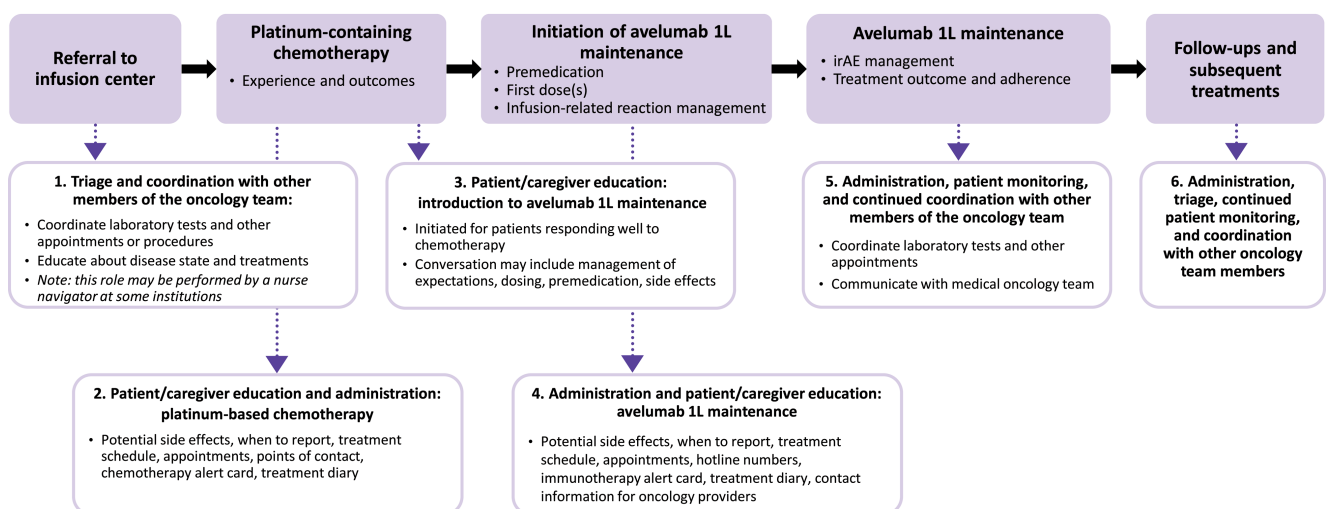


Figure 7 Patient treatment pathway with avelumab 1L maintenance in UC: role of infusion nurses. Abbreviations: 1L, first-line; irAE, immune-related adverse event; UC, urothelial carcinoma.

1L maintenance has the potential to extend the eligible patient response to therapy and thereby their overall survival.

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