***Patient1***

***Question1****（The following is a replacement for Q1）：*

*I have detailed case information of a urothelial carcinoma patient, including his chief complaints, medical history, examination results, pathology findings, and treatment course. Please act as a professional multidisciplinary team (MDT) specializing in urological oncology, review the patient's information, and provide: A list of the current preferred treatment measures along with the reasons for each recommendation. A list of measures to avoid along with the reasons for each recommendation*

*(The following is a replacement for prompts1)+<Patient information1>*

***Anwser1（The following is a replacement for A1）***

**Systemic Chemotherapy:**

**Reason:** The presence of metastatic disease, as evidenced by the PET-CT findings of multiple enlarged lymph nodes with increased metabolism, suggests that systemic chemotherapy is warranted to address the disseminated nature of the urothelial carcinoma. Chemotherapy regimens such as gemcitabine and cisplatin are standard treatments for metastatic urothelial carcinoma.

**Immunotherapy:**

**Reason:** Immune checkpoint inhibitors (such as pembrolizumab or atezolizumab) have shown efficacy in advanced and metastatic urothelial carcinoma. Given the patient's recurrence and metastatic disease, immunotherapy could provide a beneficial response and potentially improve survival outcomes.

**Palliative Radiotherapy:**

**Reason:** To manage symptoms such as vaginal bleeding and local control of the tumor, palliative radiotherapy can be considered. This approach can help alleviate symptoms and improve the quality of life for the patient.

**Supportive Care:**

**Reason:** Comprehensive supportive care is essential to manage symptoms, improve quality of life, and provide psychosocial support. This includes pain management, nutritional support, and addressing any complications arising from the disease or its treatment.

**Genetic and Molecular Testing:**

**Reason:** To tailor treatment options and identify potential targets for therapy, comprehensive genetic and molecular profiling of the tumor can be beneficial. This can help in selecting targeted therapies if specific mutations or biomarkers are identified.

#### Measures to Avoid

**Surgical Interventions:**

**Reason:** Given the widespread metastatic nature of the disease and previous extensive surgeries (partial cystectomy and radical cystectomy with ileal conduit), further surgical interventions are unlikely to provide significant benefit and may increase morbidity without improving survival outcomes.

**Neoadjuvant or Adjuvant Radiotherapy:**

**Reason:** Since the patient did not receive adjuvant therapy previously and now presents with metastatic disease, neoadjuvant or adjuvant radiotherapy is not indicated. Palliative radiotherapy is preferred for symptom management instead.

**High-Dose Chemotherapy with Stem Cell Transplant:**

**Reason:** This approach is generally not standard for urothelial carcinoma and carries significant risks, especially in a patient with extensive disease and previous surgeries. The focus should remain on systemic chemotherapy and immunotherapy which are more appropriate for metastatic disease.

**Experimental Treatments without Evidence:**

**Reason:** Treatments that lack substantial evidence or are not part of established clinical guidelines should be avoided to prevent unnecessary side effects and ensure the patient receives the best possible standard of care.

### Conclusion

Given the patient's history, current presentation, and imaging findings, the MDT recommends systemic chemotherapy and immunotherapy as the primary treatment modalities, supplemented by palliative radiotherapy for symptom control. Comprehensive supportive care and genetic/molecular testing are also advised to optimize treatment outcomes and improve the patient's quality of life. Further surgical interventions and unproven experimental treatments should be avoided to minimize risks and focus on evidence-based therapies.

***Question2（The following is a replacement for Q2）：***

*Prompts2+*

*1.What type of chemotherapy administration should be used?*

*2.What is the scope of radiotherapy?*

*3.How should vaginal bleeding be managed?*

*4.What additional tests does the patient currently need to complete?*

***A2:***

### 1. Type of Chemotherapy Administration

**Preferred Chemotherapy Administration:**

* **Intravenous (IV) Chemotherapy:** This is the standard approach for administering systemic chemotherapy in advanced urothelial carcinoma. Regimens like gemcitabine and cisplatin or carboplatin (for patients unable to tolerate cisplatin) are administered intravenously.
* **Dosage and Schedule:** Typically, gemcitabine is given on days 1, 8, and 15, with cisplatin or carboplatin given on day 1 of a 21-day cycle. Adjustments may be made based on the patient’s renal function, performance status, and tolerance.

### 2. Scope of Radiotherapy

**Scope of Radiotherapy:**

* **Palliative Radiotherapy:** The aim is to alleviate symptoms and improve quality of life rather than curative intent.
* **Target Areas:**
  + **Vaginal Wall and Cervix:** To manage local symptoms such as vaginal bleeding and pain.
  + **Metastatic Lymph Nodes:** If causing symptoms or significant metabolic activity.
* **Radiotherapy Schedule:** Typically involves fractionated doses, such as 30 Gy in 10 fractions, but this can vary depending on the specific clinical scenario and patient tolerance.

### 3. Management of Vaginal Bleeding

**Management of Vaginal Bleeding:**

* **Palliative Radiotherapy:** As mentioned, can help control bleeding from the vaginal tumor.
* **Hormonal Therapy:** Consider using progestogens or estrogen receptor modulators if hormone receptors are positive.
* **Local Measures:**
  + **Vaginal Packing:** To apply pressure and reduce bleeding.
  + **Hemostatic Agents:** Such as tranexamic acid, both systemically and topically.
* **Interventional Procedures:**
  + **Embolization:** Selective embolization of bleeding vessels may be considered if bleeding is severe and not controlled by other means.
  + **Topical Treatments:** Application of silver nitrate or other hemostatic agents directly to the bleeding site.

### 4. Additional Tests Needed

**Additional Tests:**

* **Molecular Profiling and Genetic Testing:** To identify potential actionable mutations for targeted therapy (e.g., FGFR3, PD-L1 expression).
* **Comprehensive Metabolic Panel:** To monitor renal function, liver function, and overall metabolic status, which is crucial for chemotherapy planning.
* **Complete Blood Count (CBC):** To assess baseline blood counts before initiating chemotherapy and monitor for myelosuppression.
* **Cardiac Evaluation:** If considering chemotherapy, especially if there are pre-existing cardiac conditions, an echocardiogram or MUGA scan may be warranted.
* **Follow-up Imaging:** Repeat PET/CT or MRI to assess the extent of disease, response to treatment, and to guide further therapeutic decisions.
* **Bone Scan:** If there is any suspicion of bone metastases based on symptoms or elevated alkaline phosphatase.

### Conclusion

For this patient with recurrent urothelial carcinoma, a multidisciplinary approach including IV chemotherapy, palliative radiotherapy, and comprehensive supportive care for symptom management is essential. Additional tests focusing on molecular profiling, metabolic status, and detailed imaging will help tailor and optimize the treatment strategy.

***Q3:****Are there any suitable clinical trials for this patient? Always include the NCT (ClinicalTrials.gov registration number) or PubMed ID, and indicate the level of evidence and clinical significance whenever possible.* ***A3:***

**Pembrolizumab + Epacadostat vs Pembrolizumab + Placebo (KEYNOTE-698/ECHO-303)**:

* **ClinicalTrials.gov Identifier**: NCT03374488
* **Description**: This Phase 3 trial compares pembrolizumab (an immune checkpoint inhibitor) combined with epacadostat (an IDO1 inhibitor) versus pembrolizumab with a placebo in patients with recurrent or progressive metastatic urothelial carcinoma who have failed a first-line platinum-containing chemotherapy regimen.
* **Level of Evidence**: Phase 3
* **Clinical Significance**: This study aims to determine if the combination therapy can improve outcomes compared to pembrolizumab alone in patients with advanced disease​ ([ClinicalTrials.gov](https://classic.clinicaltrials.gov/ct2/show/NCT03374488" \t "_blank))​.

**Atezolizumab with or without Eribulin Mesylate**:

* **ClinicalTrials.gov Identifier**: NCT03532451
* **Description**: This Phase 2 trial evaluates the safety and efficacy of atezolizumab (an anti-PD-L1 therapy) alone or combined with eribulin mesylate (a microtubule inhibitor) in patients with locally advanced or metastatic transitional cell urothelial cancer who are not candidates for cisplatin-based treatment.
* **Level of Evidence**: Phase 2
* **Clinical Significance**: The combination therapy is assessed for its potential to enhance treatment effectiveness and provide better disease control in patients with advanced urothelial carcinoma​ ([ClinicalTrials.gov](https://classic.clinicaltrials.gov/ct2/show/NCT03237780" \t "_blank))​.

**Enfortumab Vedotin and Pembrolizumab for High-Grade Upper Tract Urothelial Cancer**:

* **ClinicalTrials.gov Identifier**: NCT04211337
* **Description**: This trial investigates the combination of enfortumab vedotin (an antibody-drug conjugate targeting Nectin-4) and pembrolizumab in patients with high-grade upper tract urothelial carcinoma who are ineligible for radical nephroureterectomy.
* **Level of Evidence**: Phase 2
* **Clinical Significance**: The study aims to evaluate the safety, tolerability, and preliminary efficacy of this combination therapy in patients with high-grade urothelial carcinoma, offering a non-surgical treatment option​ ([ClinicalTrials.gov](https://classic.clinicaltrials.gov/ct2/show/NCT05656235" \t "_blank)).

***Patient2***

***Q1：****Prompts1+<Patient information2>*

***A1：***

#### Preferred Treatment Measures

**Cystoscopic Examination:**

**Reason:** To visually inspect the urinary tract, specifically the neobladder and ureteral-ileal anastomosis site, for any suspicious lesions or recurrent tumors. This will help confirm the presence of visible tumor recurrence or other abnormalities.

**Biopsy of Suspicious Lesions:**

**Reason:** To obtain tissue samples for histopathological examination. Given the detection of cancer cells in urine cytology, biopsy is essential to determine the nature of any lesions found during cystoscopy.

**Repeat Imaging (CT Urography or MRI):**

**Reason:** To assess the current status of the urinary tract and to identify any new or recurrent lesions. Imaging can provide detailed information on the extent of disease and help in planning further treatment.

**Systemic Chemotherapy:**

**Reason:** Considering the presence of cancer cells in urine cytology and the history of high-grade invasive urothelial carcinoma, systemic chemotherapy may be necessary to address potential microscopic residual disease or recurrence.

**Regular Follow-Up:**

**Reason:** Close monitoring with regular follow-ups, including urine cytology, imaging, and physical examinations, is crucial to detect any recurrence early and to manage the patient’s condition proactively.

**Symptom Management:**

**Reason:** Addressing the patient's symptoms, such as dull pain in the right flank, through appropriate pain management and supportive care, is important for improving the quality of life.

#### Measures to Avoid

**Radiotherapy:**

**Reason:** Given the patient's history of radical cystectomy and the anatomical changes post-surgery (including neobladder reconstruction), radiotherapy may pose a risk of complications and is generally not recommended unless there is clear evidence of local recurrence that is radio-responsive.

**Immediate Surgical Intervention:**

**Reason:** Without clear evidence of a specific lesion or recurrence that requires surgical intervention, immediate surgery is not recommended. The focus should be on accurate diagnosis and less invasive treatment options initially.

**Empirical Antibiotic Therapy:**

**Reason:** While urine cloudiness might suggest an infection, empirical antibiotic therapy should be avoided without microbiological confirmation of infection, especially given the history of cancer and potential for recurrence. It is important to rule out cancer recurrence as the cause of symptoms first.

**Nephrotoxic Medications:**

**Reason:** To avoid further renal complications, especially considering the mild dilatation of bilateral ureters and renal pelvis. Medications that could potentially harm renal function should be used cautiously.

**Excessive Invasive Procedures:**

**Reason:** Given the patient’s complex surgical history and anatomical changes, minimizing the number of invasive procedures is important to reduce the risk of complications and infections.

### Summary

The multidisciplinary team recommends a comprehensive approach involving diagnostic cystoscopy, biopsy, repeat imaging, systemic chemotherapy if indicated, and regular follow-ups. Avoiding radiotherapy, immediate surgery without proper diagnosis, empirical antibiotics without confirmation, nephrotoxic medications, and excessive invasive procedures will help manage the patient’s condition effectively while minimizing risks.  
  
***Q2:****prompts*

***A2:***

**Enfortumab Vedotin and Pembrolizumab Combination Therapy**:

* **Trial Name**: EV-302/KEYNOTE-A39
* **NCT Number**: NCT04223856
* **Description**: This phase 3 trial investigates the combination of enfortumab vedotin, an antibody-drug conjugate, with pembrolizumab, a PD-1 inhibitor. The combination has shown to nearly double overall survival (31.5 months vs. 16.1 months) and progression-free survival (12.5 months vs. 6.3 months) compared to standard chemotherapy. This combination is beneficial regardless of cisplatin eligibility and shows a manageable safety profile with no new safety signals.
* **Level of Evidence**: High, as evidenced by significant improvements in OS and PFS in a large, randomized trial.
* **Clinical Significance**: The combination is practice-changing and offers a substantial improvement in outcomes for patients with advanced urothelial carcinoma.
* **Sources**: Johns Hopkins Medicine and Cleveland Clinic​ ([Home](https://www.hopkinsmedicine.org/news/newsroom/news-releases/2024/03/combination-urothelial-cancer-treatment-nearly-doubles-patient-survival-in-international-trial" \t "_blank))​​ ([Cleveland Clinic](https://consultqd.clevelandclinic.org/a-new-standard-emerges-in-advanced-urothelial-carcinoma-after-decades-of-first-line-chemotherapy" \t "_blank))​.

**Disitamab Vedotin with Pembrolizumab**:

* **Trial Name**: DV-001
* **NCT Number**: NCT04617756
* **Description**: This phase 3 study evaluates disitamab vedotin (an investigational HER2-directed antibody-drug conjugate) in combination with pembrolizumab versus chemotherapy in patients with HER2-expressing, previously untreated locally advanced or metastatic urothelial carcinoma. The trial aims to assess the efficacy of this combination, building on the known benefits of antibody-drug conjugates and immunotherapy.
* **Level of Evidence**: High, as it is a phase 3 trial.
* **Clinical Significance**: This trial offers a targeted approach for HER2-expressing urothelial carcinoma, which could provide improved outcomes for a specific subset of patients.
* **Source**: UroToday​ ([UroToday](https://www.urotoday.com/conference-highlights/asco-2024/asco-2024-bladder-cancer/152547-asco-2024-phase-3-study-of-disitamab-vedotin-with-pembrolizumab-vs-chemotherapy-in-patients-with-previously-untreated-locally-advanced-or-metastatic-urothelial-carcinoma-that-expresses-her2-dv-001.html" \t "_blank))​.

**Avelumab Maintenance Therapy**:

* **Trial Name**: JAVEMACS
* **NCT Number**: NCT06412848
* **Description**: This observational study focuses on the use of avelumab as maintenance therapy in patients with locally advanced or metastatic urothelial carcinoma who have responded to first-line platinum-based chemotherapy. The study aims to gather real-world data on the effectiveness and safety of continuous avelumab treatment.
* **Level of Evidence**: Moderate, as it is an observational study.
* **Clinical Significance**: Provides insights into the long-term benefits and practical application of avelumab maintenance therapy in a broader patient population.
* **Source**: ClinicalTrials.gov​ ([InClinicalTrials](https://inclinicaltrials.com/urothelial-carcinoma/NCT06412848/" \t "_blank))​.

***Patient3***

***Q1:****prompts1+<Patient information3>*

***A1：***

### Current Preferred Treatment Measures and Rationale

**Radical Cystectomy with Urinary Diversion**

**Rationale**: Given the high-grade nature of the urothelial carcinoma, recurrence after TURBT, and evidence of invasive cancer on cystoscopy, radical cystectomy is indicated to achieve local control. Urinary diversion will manage urinary function post-surgery.

**Systemic Chemotherapy**

**Rationale**: Continued systemic therapy is warranted due to the presence of metastatic disease (lung nodules). Platinum-based regimens, such as Gemcitabine and Cisplatin (GEM+DDP), have shown efficacy. Given the previous response, reintroducing or modifying the regimen may be beneficial.

**Immunotherapy (e.g., PD-1/PD-L1 Inhibitors)**

**Rationale**: Immunotherapy has become a cornerstone in the treatment of advanced urothelial carcinoma. Patients who have progressed after platinum-based chemotherapy may benefit from immune checkpoint inhibitors like pembrolizumab or atezolizumab.

**Targeted Therapy**

**Rationale**: Molecular profiling of the tumor to identify actionable mutations or alterations (e.g., FGFR3 mutations) could guide the use of targeted therapies. If such targets are identified, agents like erdafitinib might be considered.

**Palliative Care and Symptom Management**

**Rationale**: Ensuring the patient’s quality of life through palliative care is essential, especially given the metastatic disease. Addressing symptoms like pain, hematuria, and bladder irritation is crucial.

### Measures to Avoid and Rationale

**Further TURBT Alone**

**Rationale**: TURBT has proven inadequate in this case, with recurrence and progression to invasive disease. Continuing this approach alone would not provide effective control of the cancer.

**Radiotherapy to Bladder**

**Rationale**: Given previous radiotherapy to the pelvic lymph nodes and the invasive nature of the cancer, additional radiotherapy to the bladder might not provide significant benefit and could lead to complications due to prior high-dose radiation.

**Single-Agent Chemotherapy**

**Rationale**: Single-agent chemotherapy is generally less effective than combination regimens for high-grade, metastatic urothelial carcinoma. Using single agents alone would likely be insufficient to control the disease.

**Expectant Management (Watchful Waiting)**

**Rationale**: Given the aggressive nature of the disease and evidence of metastasis, expectant management without active treatment would likely lead to rapid disease progression and deterioration in the patient’s condition.

**Non-evidence-based Alternative Therapies**

**Rationale**: Unproven alternative treatments could lead to delays in receiving effective therapy and might compromise overall outcomes. The focus should remain on evidence-based medical and supportive care.

### Summary

The patient’s high-grade urothelial carcinoma with recurrence, invasion, and metastasis necessitates a comprehensive treatment strategy involving surgery, systemic therapy, and potentially immunotherapy or targeted therapy. Measures that have previously proven inadequate or that could lead to further complications should be avoided. Focus should remain on maximizing survival and quality of life through a multidisciplinary, evidence-based approach.

***Q2:****prompt2+*

*1.How to modify the chemotherapy regimen;*

*2.How to manage the patient's hematuria and bladder irritation;*

*3.How to handle lymph node metastases;*

*4.How to manage pulmonary nodules.*

***A2:***

### Modification of the Chemotherapy Regimen

**Reintroduction of Platinum-Based Chemotherapy**

Given the previous use of Gemcitabine and Cisplatin (GEM+DDP) and Taxotere and Cisplatin (TXT+DDP), consider rotating back to GEM+DDP or a combination involving Carboplatin if the patient’s renal function is a concern.

**Addition of Immunotherapy**

Integrate immunotherapy (e.g., Pembrolizumab or Atezolizumab) with the chemotherapy regimen. This combination has shown increased efficacy in advanced urothelial carcinoma.

**Dose Adjustment**

The patient has experienced disease progression despite previous treatments. The initial regimens (GEM+DDP and TXT+DDP) resulted in only temporary control. Modifying the regimen can help target cancer cells more effectively and manage resistance.

**Alternative Chemotherapeutic Agents**

Consider alternative agents such as Paclitaxel or Vinflunine if the patient has experienced significant toxicity or inadequate response to previous regimens.

### Management of Hematuria and Bladder Irritation

**Continuous Bladder Irrigation**

Use continuous bladder irrigation with saline to manage active bleeding and prevent clot formation.

**Intravesical Therapies**

Consider intravesical administration of agents like alum, silver nitrate, or formalin for refractory bleeding.

**Antibiotic Therapy**

Administer antibiotics if there is an infection contributing to bladder irritation.

**Pain Management**

Use analgesics, including NSAIDs or opioids, to manage bladder pain and discomfort.

**Urinary Diversion**

In severe cases where hematuria is not controlled, consider urinary diversion to reduce bladder irritation and bleeding.

### Management of Lymph Node Metastases

**Extended Lymphadenectomy**

During radical cystectomy, perform an extended pelvic lymphadenectomy to remove involved lymph nodes.

**Adjuvant Chemotherapy**

Post-surgery, continue with systemic chemotherapy tailored to target micrometastatic disease in the lymph nodes.

**Radiotherapy**

Consider targeted radiotherapy to involved lymph node regions if surgical resection is not feasible.

### Management of Pulmonary Nodules

**Systemic Chemotherapy**

Utilize systemic chemotherapy to target both the primary tumor and metastatic sites, including pulmonary nodules.

**Immunotherapy**

Incorporate immunotherapy to boost the immune system’s ability to target metastatic lung lesions.

**Regular Imaging**

Conduct regular imaging studies (e.g., CT scans) to monitor the response of pulmonary nodules to systemic therapy.

**Surgical Resection**

If feasible and if there are a limited number of nodules, consider surgical resection (metastasectomy) of lung nodules.

**Palliative Radiotherapy**

In cases where nodules cause significant symptoms, palliative radiotherapy may help reduce tumor burden and alleviate symptoms.

### Summary

* **Chemotherapy Regimen**: Modify by potentially reintroducing platinum-based chemotherapy, integrating immunotherapy, adjusting doses, and considering alternative agents.
* **Hematuria and Bladder Irritation**: Manage with continuous bladder irrigation, intravesical therapies, antibiotics, pain management, and potentially urinary diversion.
* **Lymph Node Metastases**: Address with extended lymphadenectomy, adjuvant chemotherapy, and targeted radiotherapy.
* **Pulmonary Nodules**: Manage with systemic chemotherapy, immunotherapy, regular imaging, surgical resection if feasible, and palliative radiotherapy as needed.

***Q3:****prompts3*

***A3:***

**EV-302/KEYNOTE-A39 Trial**: This trial studies the combination of enfortumab vedotin and pembrolizumab in patients with locally advanced or metastatic urothelial carcinoma. This combination has shown a significant improvement in progression-free survival (PFS) and overall survival (OS) compared to chemotherapy. The trial's NCT number is NCT04231595​ ([Cleveland Clinic](https://consultqd.clevelandclinic.org/a-new-standard-emerges-in-advanced-urothelial-carcinoma-after-decades-of-first-line-chemotherapy" \t "_blank))​.

**NCT03237780**: A Phase II trial investigating the efficacy of atezolizumab with or without eribulin mesylate in treating recurrent or metastatic urothelial carcinoma. This trial focuses on the effectiveness of combining an immune checkpoint inhibitor with chemotherapy​ ([Cleveland Clinic](https://consultqd.clevelandclinic.org/a-new-standard-emerges-in-advanced-urothelial-carcinoma-after-decades-of-first-line-chemotherapy" \t "_blank))​.

**ATLANTIS Trial**: This study evaluates the use of rucaparib, a PARP inhibitor, as maintenance therapy for metastatic urothelial cancer with DNA repair deficiency. The trial demonstrated an extension in progression-free survival (PFS) in patients with biomarker-positive disease (NCT03686163)​ ([Cleveland Clinic](https://consultqd.clevelandclinic.org/a-new-standard-emerges-in-advanced-urothelial-carcinoma-after-decades-of-first-line-chemotherapy" \t "_blank))​.

**KEYNOTE-905 Trial**: A Phase III neoadjuvant study comparing enfortumab vedotin plus pembrolizumab to pembrolizumab and upfront radical cystectomy for muscle-invasive bladder cancer. This trial aims to expand the use of the EV-pembrolizumab combination to earlier stages of the disease (NCT03924895)​ ([Cleveland Clinic](https://consultqd.clevelandclinic.org/a-new-standard-emerges-in-advanced-urothelial-carcinoma-after-decades-of-first-line-chemotherapy" \t "_blank)).

***Patient4：***

***Q1：****prompts1+<Patient information4>*

***A1:***

### Preferred Treatment Measures

**Immunotherapy (PD-1/PD-L1 Inhibitors):**

**Rationale:** Recent studies have shown that PD-1/PD-L1 inhibitors like pembrolizumab or atezolizumab can be effective in treating high-grade invasive urothelial carcinoma, especially in patients who have not responded well to chemotherapy. Immunotherapy can target and inhibit the cancer cells' ability to evade the immune system.

**Radiation Therapy:**

**Rationale:** Given the presence of multiple metastatic lymph nodes and potential bone metastasis, targeted radiation therapy can help control local tumor growth and alleviate symptoms. It can be particularly useful in managing bone metastasis and reducing pain.

**Systemic Chemotherapy (Second-line Agents):**

**Rationale:** As the disease has progressed despite initial chemotherapy, considering second-line chemotherapeutic agents such as vinflunine or taxanes (e.g., paclitaxel) could provide additional tumor control. Combining these with immunotherapy might improve outcomes.

**Anticoagulation Therapy:**

**Rationale:** Continuation of anticoagulation therapy with low molecular weight heparin is crucial to manage the internal jugular vein thrombosis. This will help prevent further thromboembolic complications.

**Palliative Care and Symptom Management:**

**Rationale:** Focus on improving quality of life through pain management, nutritional support, and psychological support. Palliative care can be integrated with ongoing oncological treatments to manage symptoms effectively.

### Measures to Avoid

**Continuation of Ineffective Chemotherapy Regimens:**

**Rationale:** The patient has shown disease progression despite six cycles of gemcitabine and cisplatin. Continuing with this regimen is unlikely to benefit and may cause unnecessary toxicity and side effects.

**Major Surgery:**

**Rationale:** Given the patient's advanced age, metastatic disease, and previous surgeries, major surgical interventions such as radical cystectomy would pose significant risks and may not provide substantial benefit. The focus should be on systemic treatments and symptom control.

**Aggressive Local Therapies (e.g., Multiple TURBTs):**

**Rationale:** Repeated local surgeries like TURBTs are unlikely to be beneficial in the context of metastatic disease. They may lead to complications without significantly impacting the overall disease course.

**High-dose Chemotherapy:**

**Rationale:** High-dose chemotherapy might not be well-tolerated given the patient's age and comorbidities (e.g., thrombosis). The risk of severe side effects outweighs the potential benefits.

### Conclusion

The primary aim is to control the disease progression with systemic treatments like immunotherapy and second-line chemotherapy, manage symptoms through palliative care, and avoid aggressive interventions that may not significantly improve outcomes. Regular monitoring and adjustments to the treatment plan based on the patient's response and tolerance are essential.

***Q2:****prompt2+*

*1.What are the specific sites for radiation therapy?*

*2.If surgery is considered, what type of surgery should the patient undergo?*

### A2:Specific Sites for Radiation Therapy

**Pelvic Lymph Nodes:**

Target the multiple metastatic lymph nodes in the left pelvic wall and iliac vessels to control the local spread of the disease and reduce symptoms such as pain or pressure effects.

**Retroperitoneal Lymph Nodes:**

Radiation can be directed to the enlarged lymph nodes in the retroperitoneal area to control further spread and alleviate any potential symptoms associated with these metastases.

**Potential Bone Metastasis:**

If bone metastasis is confirmed (e.g., in the sacrum as indicated by the sacral patchy high-density shadow), localized radiation therapy can help reduce pain and prevent further complications like fractures.

**Bladder and Adjacent Structures:**

While the primary tumor has been surgically addressed, any residual or recurrent tumor mass in the bladder or adjacent structures can be targeted to manage local symptoms and prevent further progression.

### Surgical Considerations

Given the advanced stage and the metastatic nature of the disease, surgery should be considered carefully. If surgery is deemed necessary, the options would be more focused on palliative intent rather than curative. The types of surgery that could be considered include:

Debulking surgery**:**

**Indication:** To relieve specific symptoms such as urinary obstruction, severe pain, or bleeding that significantly affects the patient's quality of life.

**Procedure:** Could involve limited resection or debulking of tumor masses that are causing symptoms, but this would not be aimed at curing the disease.

### Conclusion

Radiation therapy should focus on areas with known metastatic involvement to control disease spread and alleviate symptoms. Surgical options should be limited to palliative measures aimed at improving quality of life and managing specific complications. Debulking surgery should target the bladder tumor mass, pelvic lymph nodes, retroperitoneal lymph nodes, and potential bone metastasis to alleviate symptoms and improve the patient's quality of life. The decision to proceed with surgery should be made after careful consideration of the patient's overall health status, disease progression, and goals of care, with a focus on palliative intent.

***Q3:****prompts3*

***A3:*NCT04871594**: Pre-operative immunotherapy with Nivolumab in Stage II-III urothelial cancer.

* **Intervention**: Nivolumab 240mg administered on days 1, 22, and 43.
* **Outcome Measures**: Pathological complete response rates, toxicity, relapse-free survival, overall survival, and effects on tumor microenvironment.
* **Level of Evidence**: Phase 1
* **Clinical Significance**: Aims to assess feasibility and efficacy of pre-operative Nivolumab, particularly focusing on PD-L1 positive patients.

**NCT03170960**: Cabozantinib in combination with Atezolizumab for locally advanced or metastatic solid tumors.

* **Intervention**: Cabozantinib and Atezolizumab.
* **Outcome Measures**: Safety, tolerability, pharmacokinetics, and pharmacodynamics.
* **Level of Evidence**: Phase 1/Phase 2
* **Clinical Significance**: Investigates combination therapy for advanced urothelial carcinoma, providing options for patients with progressed disease.

**NCT05775874**: Study of AZD4547 in combination with Tislelizumab in patients with metastatic urothelial carcinoma.

* **Intervention**: AZD4547 and Tislelizumab.
* **Outcome Measures**: Safety and efficacy.
* **Level of Evidence**: Phase 2
* **Clinical Significance**: Evaluates a novel combination treatment, offering potential new therapeutic pathways for metastatic urothelial carcinoma.

**NCT04623502**: Investigation of kidney and urothelial tumor metabolism in patients undergoing surgical resection and/or biopsy.

* **Intervention**: Metabolic analysis of tumor tissues.
* **Outcome Measures**: Metabolic profiling to inform targeted therapies.
* **Level of Evidence**: Not applicable (N/A)
* **Clinical Significance**: Aims to understand tumor metabolism, which could lead to personalized treatment strategies.

***Patient5***

***Q1：****Prompts1+<Patient information5>*

***A1：***

### Preferred Treatment Measures and Reasons:

**Chemotherapy:**

**Reason:** Given the diagnosis of small cell neuroendocrine carcinoma, which is highly aggressive and likely to respond to chemotherapy, a regimen such as cisplatin and etoposide is recommended. This is standard treatment for neuroendocrine carcinomas and aims to reduce tumor burden.

**Surgical Intervention:**

**Reason:** While surgery might be challenging due to the extent of disease and patient’s age, a transurethral resection of the bladder tumor (TURBT) might be considered for palliative purposes to control hematuria.

**Immunotherapy:**

**Reason:** Pembrolizumab or similar agents might be considered as part of the treatment regimen, especially if there is a high expression of PD-L1 or if the patient progresses after initial chemotherapy.

**Management of Metastatic Disease:**

**Reason:** Systemic therapy is critical due to the presence of metastatic lymph nodes. Close monitoring and potential addition of targeted therapy based on molecular profiling might be necessary.

**Supportive Care:**

**Reason:** Management of anemia, renal function monitoring, and symptomatic relief are essential. Ensuring the patient's quality of life and addressing any complications promptly is crucial.

### Follow-Up and Monitoring:

**Reason:** Regular follow-up with imaging and blood tests to monitor response to treatment and renal function.Multidisciplinary coordination for ongoing assessment and adjustment of the treatment plan.

### Measures to Avoid and Reasons:

**Radical Surgery:**

**Reason:** Given the extensive involvement of the bladder, prostate, and metastatic lymph nodes, radical cystectomy or prostatectomy is not recommended due to high surgical risk and low likelihood of complete resection, especially in a 75-year-old patient.

**Radiotherapy:**

**Reason:** The patient has elevated serum creatinine (SCr 177.8 umol/L), indicating compromised renal function. Radiotherapy, particularly when targeting areas near the kidneys or involving systemic treatment that may affect renal function, can exacerbate renal insufficiency. This can lead to further deterioration of renal function, potentially resulting in severe complications such as acute kidney injury.

**Single-Modality Treatment:**

**Reason:** Sole reliance on either surgery, chemotherapy, or radiotherapy is not advisable due to the aggressive nature of small cell neuroendocrine carcinoma. A multimodal approach is necessary for effective management.

**Aggressive Treatments without Consideration of Patient's Overall Health:**

**Reason:** The patient's age and renal function (elevated SCr) need to be taken into account. Treatments causing significant nephrotoxicity or high morbidity should be carefully considered and potentially avoided.

**Use of PSA as a Marker for Follow-up:**

**Reason:** Given the negative PSA immunohistochemistry, PSA levels are not a reliable marker for this patient’s disease progression or response to treatment.

**Prolonged Invasive Diagnostic Procedures:**

**Reason:** Given the clear imaging and biopsy results, further invasive diagnostic procedures might not provide additional useful information and could pose unnecessary risks.

***Q2：****prompts2+*

### *The patient currently has a tumor located at the bladder-prostate junction. Please recommend only one examination to determine the origin?*

### *What additional tests are needed for the patient at this time, and what is their purpose?*

### 1.Transurethral Resection of Bladder Tumor (TURBT) with Biopsy

#### Reason for Recommendation:

* **Tissue Diagnosis:** TURBT allows for the collection of tissue samples directly from the tumor, which is essential for histopathological analysis to determine the origin.
* **Accessibility:** This procedure is commonly performed and allows for direct access to the tumor at the bladder-prostate junction.
* **Histopathological and Immunohistochemical Analysis:** The tissue obtained can be analyzed for specific markers that distinguish between bladder and prostate cancer.

2. **Positron Emission Tomography-Computed Tomography (PET-CT):**

* **Purpose:** To assess the extent of metastatic disease, especially for small cell neuroendocrine carcinoma, which can spread rapidly. This test will help determine the presence of distant metastases that may not be detected by conventional imaging.

· **Bone Scan:**

* **Purpose:** To evaluate the presence of bone metastases, which is common in advanced urothelial carcinoma and small cell neuroendocrine carcinoma. The bone scan will help in staging and planning for potential palliative treatments if bone metastases are present.

· **Renal Function Tests (Repeat):**

* **Purpose:** To monitor kidney function closely, especially given the mild hydronephrosis and elevated serum creatinine levels. This will help in managing potential nephrotoxicity from future chemotherapy and ensure the patient’s kidneys are functioning adequately.

· **Magnetic Resonance Imaging (MRI) of the Brain:**

* **Purpose:** Small cell neuroendocrine carcinoma has a high propensity for brain metastases. An MRI of the brain will help rule out intracranial involvement, which is crucial for comprehensive staging and treatment planning.

***Q3:****prompts3*

***A3:***  
**BXCL701 and Pembrolizumab for Metastatic Castration-Resistant Prostate Cancer (mCRPC)**

* **NCT Number:** NCT03910660
* **Description:** This Phase 2 trial evaluates the combination of BXCL701, an oral innate immune activator, and Pembrolizumab, an anti-PD-1 therapy, in patients with metastatic castration-resistant prostate cancer that has progressed following prior chemotherapy.
* **Eligibility:** Includes patients with histologically confirmed small cell neuroendocrine prostate cancer who have received at least one prior line of systemic therapy for advanced disease.
* **Level of Evidence and Significance:** This combination aims to leverage the immune system to target cancer cells, showing promise in early-phase studies​ ([Clinical Trials at UCSF](https://clinicaltrials.ucsf.edu/trial/NCT03910660" \t "_blank))​​ ([Clinical Trials at UCSF](https://clinicaltrials.ucsf.edu/trial/NCT04926181" \t "_blank))​.

**Neoadjuvant Adebrelimab Plus Etoposide and Cisplatin for Neuroendocrine Bladder Carcinoma**

* **NCT Number:** NCT04891526
* **Description:** This trial investigates the efficacy and safety of neoadjuvant Adebrelimab (an anti-PD-L1 antibody) in combination with Etoposide and Cisplatin for patients with neuroendocrine carcinoma of the bladder.
* **Eligibility:** Suitable for patients with neuroendocrine carcinoma of the bladder, which could include cases involving the bladder wall and adjacent structures.
* **Level of Evidence and Significance:** Early studies indicate potential benefits in combining immune checkpoint inhibitors with traditional chemotherapy, specifically for aggressive neuroendocrine tumors​ ([Clinical Trials at UCSF](https://clinicaltrials.ucsf.edu/trial/NCT03910660" \t "_blank))​.

**Lurbinectedin With or Without Avelumab in Small Cell Carcinoma of the Bladder**

* **NCT Number:** NCT03703297
* **Description:** This Phase 2 study assesses Lurbinectedin, a novel chemotherapy agent, with or without Avelumab, an anti-PD-L1 therapy, in treating small cell carcinoma of the bladder.
* **Eligibility:** Includes patients with high-grade neuroendocrine tumors of the urinary tract, providing an option for those with aggressive cancer types including small cell variants.
* **Level of Evidence and Significance:** This trial is significant as it explores the combination of new chemotherapy agents with immunotherapy, potentially offering a new treatment avenue for aggressive neuroendocrine carcinomas​ ([Clinical Trials at UCSF](https://clinicaltrials.ucsf.edu/trial/NCT03910660" \t "_blank))​​ ([Clinical Trials at UCSF](https://clinicaltrials.ucsf.edu/trial/NCT04926181" \t "_blank))​.

**Apalutamide Plus Cetrelimab in Treatment-Emergent Small Cell Neuroendocrine Prostate Cancer**

* **NCT Number:** NCT04191096
* **Description:** This Phase 2 trial evaluates the efficacy of Apalutamide (an androgen receptor inhibitor) combined with Cetrelimab (an anti-PD-1 antibody) in patients with treatment-emergent small cell neuroendocrine prostate cancer.
* **Eligibility:** Patients with histological and/or genomic evidence of treatment-emergent small cell neuroendocrine prostate cancer, with specific inclusion criteria related to previous treatments and organ function.
* **Level of Evidence and Significance:** This combination targets androgen receptor pathways and immune checkpoints, providing a multifaceted approach to treating aggressive prostate cancer variants​ ([Clinical Trials at UCSF](https://clinicaltrials.ucsf.edu/trial/NCT03910660" \t "_blank))​.

***Patient6***

*****Q1:******Prompts1+<Patient information6>*

### Current Preferred Treatment Measures

**Systemic Chemotherapy**

**Reason**: The patient has advanced urothelial carcinoma with evidence of metastasis and invasion into surrounding structures. Systemic chemotherapy, such as cisplatin-based regimens (e.g., gemcitabine and cisplatin), is standard for treating advanced urothelial carcinoma. Chemotherapy can help shrink tumors, control symptoms, and improve survival.

**Consideration**: Given the patient’s liver function abnormalities (elevated ALT, AST, ALP, and bilirubin levels), a careful assessment of hepatic function is necessary to determine chemotherapy eligibility and dosing.

**Immunotherapy**

**Reason**: Immunotherapy with checkpoint inhibitors (e.g., pembrolizumab, atezolizumab) is an option for urothelial carcinoma, especially in patients who cannot tolerate cisplatin or in cases where the disease progresses after chemotherapy.

**Consideration**: Immunotherapy could be considered, particularly if the patient’s performance status and organ function are adequate.

**Palliative Radiation Therapy**

**Reason**: Radiation therapy can be used for symptom control, such as pain, bleeding, or obstruction. Given the invasive nature of the tumor, targeted radiation could alleviate local symptoms and improve quality of life.

**Consideration**: A radiation oncologist should evaluate the specific sites and extent of radiation needed.

**Nephrostomy Tube Management**

**Reason**: The patient already has bilateral nephrostomies due to ureteral obstruction. Continuous management of nephrostomy tubes is crucial to maintain renal function and prevent complications such as infection or obstruction.

**Consideration**: Regular monitoring and potential adjustments or replacements of the nephrostomy tubes.

**Nutritional and Supportive Care**

**Reason**: The patient has significantly low albumin levels and prolonged prothrombin time, indicating poor nutritional status and potential coagulopathy. Nutritional support, including high-protein diet and supplementation, along with correction of coagulopathy, is essential.

**Consideration**: Involvement of a dietitian and possibly a hematologist for managing coagulopathy.

### Measures to Avoid

**Extensive Surgery**

**Reason**: Given the patient's advanced disease with metastasis, poor differentiation of carcinoma, and compromised hepatic function, extensive surgical procedures (e.g., radical cystectomy) are not likely to provide significant benefit and carry high risks.

**Consideration**: Surgery should be limited to procedures necessary for symptom control (e.g., TURBT for bleeding).

**Nephrotoxic Medications**

**Reason**: The patient has bilateral hydronephrosis and has undergone nephrostomy. Nephrotoxic drugs (e.g., certain antibiotics, NSAIDs) should be avoided to prevent further renal damage.

**Consideration**: Careful review of medications and use of renal-protective strategies.

**Aggressive Chemotherapy Without Hepatic Assessment**

**Reason**: Elevated liver enzymes and bilirubin levels indicate hepatic dysfunction, which can significantly impact the metabolism and toxicity of chemotherapeutic agents.

**Consideration**: Chemotherapy regimens should be tailored to the patient’s hepatic function, potentially requiring dose adjustments or alternative agents.

**Delay in Treatment Initiation**

**Reason**: Advanced urothelial carcinoma with invasive and metastatic disease requires prompt treatment initiation to control disease progression and symptoms.

**Consideration**: Timely coordination among oncology, radiology, and supportive care teams to initiate appropriate treatments without undue delay.

### Conclusion

This patient with advanced urothelial carcinoma and extensive metastasis requires a multidisciplinary approach focusing on systemic therapy, palliative care, and supportive measures to manage symptoms and improve quality of life. The treatment plan should be individualized based on the patient’s overall condition, organ function, and performance status.

***Q2:****prompt2+Is intravesical chemotherapy currently being considered for the patient?*

***A2:***

**Intravesical Chemotherapy:** Intravesical chemotherapy involves directly administering chemotherapeutic agents into the bladder. This approach is typically used for non-muscle invasive bladder cancer (NMIBC) to prevent recurrence after transurethral resection of bladder tumor (TURBT). The common agents used include mitomycin C and Bacillus Calmette-Guerin (BCG).

**Current Context for the Patient:**

* **Advanced Stage and Invasiveness**: The patient's cancer is advanced, with evidence of invasion into the prostate, bilateral ureters, seminal vesicles, and mid-lower rectal wall. Intravesical therapy is not typically effective for muscle-invasive or metastatic disease.
* **Prior Treatments and Recurrence**: The patient has a history of multiple TURBT procedures and arterial infusion chemotherapy, indicating previous attempts at managing non-invasive or minimally invasive disease.
* **Systemic Involvement**: Given the systemic nature of the disease (e.g., involvement of lymph nodes and potential metastatic spread), systemic therapy is preferred over localized treatments like intravesical chemotherapy.

**Conclusion:** Intravesical chemotherapy is not currently being considered or recommended for this patient due to the advanced stage of the disease, systemic involvement, and poor differentiation of the carcinoma. The primary focus is on systemic chemotherapy, immunotherapy, palliative radiation, and supportive care measures to manage the invasive and metastatic nature of the cancer.

***Q3:****prompt3*

***A3:***

**Pembrolizumab + Epacadostat vs Pembrolizumab + Placebo in Recurrent or Progressive Metastatic Urothelial Carcinoma**

* **NCT Number**: NCT03374488
* **Details**: This trial investigates the combination of Pembrolizumab (an immune checkpoint inhibitor) and Epacadostat versus Pembrolizumab and placebo in patients with recurrent or progressive metastatic urothelial carcinoma. The inclusion criteria include histologically confirmed urothelial carcinoma with progression following prior chemotherapy. The trial focuses on the efficacy of this combination therapy in improving overall survival and progression-free survival.
* **Level of Evidence**: Phase III clinical trial
* **Clinical Significance**: Pembrolizumab has already shown efficacy in urothelial carcinoma, and this trial aims to enhance its effectiveness with the addition of Epacadostat​ ([ClinicalTrials.gov](https://classic.clinicaltrials.gov/ct2/show/NCT03374488" \t "_blank))​.

**Enfortumab Vedotin and Pembrolizumab for High-Grade Upper Tract Urothelial Cancer**

* **NCT Number**: NCT03390595
* **Details**: This study evaluates the combination of Enfortumab Vedotin (an antibody-drug conjugate) and Pembrolizumab for patients with high-grade upper tract urothelial carcinoma who are ineligible for surgery. The primary outcome measures include event-free survival, safety, and tolerability.
* **Level of Evidence**: Phase II clinical trial
* **Clinical Significance**: This combination is promising for patients with advanced disease who are not candidates for surgical interventions, potentially offering a non-surgical treatment option with significant efficacy​ ([ClinicalTrials.gov](https://classic.clinicaltrials.gov/ct2/show/NCT05656235" \t "_blank))​.

**Nivolumab for the Treatment of Patients with Metastatic Urothelial Carcinoma**

* **NCT Number**: NCT03473756
* **Details**: This Phase II trial studies the use of Nivolumab, another immune checkpoint inhibitor, in patients with metastatic urothelial carcinoma. The trial is focused on assessing biomarkers to predict response to therapy, aiming to personalize treatment approaches based on genetic and molecular profiling.
* **Level of Evidence**: Phase II clinical trial
* **Clinical Significance**: Nivolumab has been effective in several cancers, and this trial could help identify specific biomarkers that predict a better response in urothelial carcinoma, potentially leading to more personalized and effective treatments​ ([ClinicalTrials.gov](https://classic.clinicaltrials.gov/ct2/show/NCT03374488" \t "_blank))​.

**Combination of Tislelizumab with Cisplatin and Gemcitabine in Untreated Unresectable and Metastatic Urothelial Carcinoma**

* **NCT Number**: NCT04220833
* **Details**: This trial explores the efficacy and safety of combining Tislelizumab (another PD-1 inhibitor) with standard chemotherapy agents Cisplatin and Gemcitabine. The study includes patients with untreated unresectable and metastatic urothelial carcinoma.
* **Level of Evidence**: Phase III clinical trial
* **Clinical Significance**: This trial could establish a new first-line treatment option by combining immunotherapy with chemotherapy, which might improve survival rates and quality of life for patients with advanced urothelial carcinoma​ ([ClinicalTrials.gov](https://classic.clinicaltrials.gov/ct2/show/NCT03374488" \t "_blank))​.

***Patient 7***

***Q1：****prompts1+<Patient information7>*

***A1:***

### Multidisciplinary Team (MDT) Recommendations

#### Preferred Treatment Measures

**Neoadjuvant Chemotherapy**

**Reason**: Given the presence of poorly differentiated urothelial carcinoma and the plasmacytoid subtype, neoadjuvant chemotherapy can help shrink the tumor, making it more manageable for surgical intervention and potentially improving overall survival. Typical regimens include cisplatin-based chemotherapy, which is effective in urothelial carcinoma.

**Radical Cystectomy with Pelvic Lymph Node Dissection**

**Reason**: The tumor's involvement of the pelvic floor and posterior bladder wall, along with bilateral renal and ureteral dilation, indicates extensive local disease. Radical cystectomy is recommended to achieve local control of the tumor and prevent further spread. Pelvic lymph node dissection is essential due to the enlarged lymph nodes on both pelvic walls noted on imaging.

**Urinary Diversion**

**Reason**: Post-cystectomy, a form of urinary diversion will be necessary. Options include ileal conduit, neobladder, or continent catheterizable pouch, tailored to the patient's overall health, preferences, and quality of life considerations.

**Adjuvant Chemotherapy or Immunotherapy**

**Reason**: Depending on the pathological findings post-surgery, additional systemic therapy may be indicated to address any residual disease and reduce the risk of recurrence. Immunotherapy, particularly checkpoint inhibitors, can be considered based on the tumor's molecular profile and patient's response to initial treatments.

**Venous Thrombosis Management**

**Reason**: The presence of intermuscular venous thrombosis in the right calf necessitates anticoagulation therapy to prevent further thromboembolic events, which is critical for patient safety during and after major surgical procedures.

**Palliative Care and Symptom Management**

**Reason**: Symptom management for urinary incontinence, nocturia, and other related symptoms should be integrated into the treatment plan to improve the patient's quality of life during treatment.

#### Measures to Avoid

**Radiotherapy as Primary Treatment**

**Reason**: While radiotherapy can be part of a bladder-sparing approach, it is generally less effective than radical cystectomy for extensive and poorly differentiated tumors like plasmacytoid urothelial carcinoma. Radiotherapy may be considered in a palliative setting or as adjuvant therapy post-surgery.

**Partial Cystectomy**

**Reason**: Due to the extensive involvement of the posterior bladder wall and significant tumor burden, partial cystectomy would likely be insufficient for achieving local control and could lead to rapid recurrence.

**Conservative Management Alone**

**Reason**: The aggressive nature of the tumor and extensive local disease make conservative management inappropriate, as it would not adequately address the tumor burden and could lead to further progression and metastasis.

**Delaying Treatment**

**Reason**: Given the patient's significant symptoms and rapid weight loss, delaying treatment could lead to further deterioration of his condition, reduced performance status, and potentially worse outcomes.

**Immunotherapy Without Prior Chemotherapy**

**Reason**: While immunotherapy is a promising option, starting with neoadjuvant chemotherapy is generally preferred for its potential to reduce tumor size and improve surgical outcomes. Immunotherapy may be considered as part of the adjuvant treatment strategy.

These recommendations should be tailored to the patient's overall health status, performance status, and personal preferences. Close monitoring and supportive care throughout the treatment process are essential to address any complications and ensure the best possible outcomes.

***Q2：****If only two genes are to be tested based on this patient's condition, which two genes do you think should be targeted?*

***A2：***Given the patient's condition with poorly differentiated urothelial carcinoma, the two most critical genes to test would be:

**FGFR3 (Fibroblast Growth Factor Receptor 3)**

**Reason**: Mutations in FGFR3 are common in urothelial carcinoma and can be directly targeted with FGFR inhibitors, providing a potential targeted treatment option. FGFR3 alterations are particularly relevant in urothelial carcinoma, including variants that are difficult to treat.

**TP53 (Tumor Protein p53)**

**Reason**: Mutations in TP53 are associated with high-grade and muscle-invasive bladder cancer and can significantly influence prognosis and treatment strategies. TP53 status can help in assessing the aggressiveness of the tumor and guiding overall treatment planning.

These two genes offer valuable insights into potential targeted therapies and the overall aggressiveness of the disease, making them the most relevant for this patient's genetic testing.

*Q3:prompts3*

A3:

**Durvalumab and Tremelimumab in Treating Patients With Muscle-Invasive, High-Risk Urothelial Cancer (NCT02812420)**

* **Summary:** This phase I trial studies the safety and side effects of combining durvalumab and tremelimumab in patients with muscle-invasive, high-risk urothelial carcinoma who cannot undergo cisplatin-based therapy before surgery. These immunotherapies aim to enhance the immune system's ability to fight cancer.
* **Level of Evidence and Clinical Significance:** The combination of PD-L1 and CTLA-4 inhibitors represents an innovative approach to manage high-risk cases, with preliminary studies showing potential for improved outcomes compared to traditional therapies​ ([Bladder Cancer Advocacy Network](https://bcan.org/clinicaltrials/durvalumab-and-tremelimumab-in-treating-patients-with-muscle-invasive-high-risk-urothelial-cancer-that-cannot-be-treated-with-cisplatin-based-therapy-before-surgery/" \t "_blank))​.

**Pemetrexed and Avelumab in Treating Patients With MTAP-Deficient Metastatic Urothelial Cancer (NCT03744793)**

* **Summary:** This phase II trial investigates the efficacy of pemetrexed combined with avelumab in patients with MTAP-deficient metastatic urothelial cancer. Pemetrexed inhibits cell growth enzymes, while avelumab enhances immune response against cancer cells.
* **Level of Evidence and Clinical Significance:** This trial focuses on a specific genetic deficiency (MTAP), making it highly relevant for personalized medicine in metastatic urothelial carcinoma. The combination therapy could offer new treatment avenues for patients with this genetic profile​ ([Bladder Cancer Advocacy Network](https://bcan.org/clinicaltrials/pemetrexed-and-avelumab-in-treating-patients-with-mtap-deficient-metastatic-urothelial-cancer/" \t "_blank))​.

**Pembrolizumab Plus Enfortumab Vedotin (EV) in First-Line Treatment for Advanced Urothelial Carcinoma (NCT04223856)**

* **Summary:** This phase 1/2 trial evaluates the safety and efficacy of pembrolizumab (a PD-1 inhibitor) combined with enfortumab vedotin (an antibody-drug conjugate) as a first-line treatment for advanced urothelial carcinoma. The trial includes the investigation of additional investigational agents in combination with these drugs.
* **Level of Evidence and Clinical Significance:** This trial offers a promising first-line treatment option for advanced cases, leveraging the synergy between immune checkpoint inhibition and targeted cytotoxic therapy. The combination has shown significant activity in prior studies, providing a strong rationale for further investigation​ ([Bladder Cancer Advocacy Network](https://bcan.org/clinicaltrials/pembrolizumab-plus-enfortumab-vedotin-ev-investigational-agents-in-first-line-metastatic-urothelial-carcinoma-muc-mk-3475-04b-keymaker-u04/" \t "_blank))​.

***Patient8***

***Q1:****prompts1+<Patient information8>*

***A1:***

## MDT Review and Recommendations

### Preferred Treatment Measures

**Continued Systemic Chemotherapy:**

**Reason:** Small cell neuroendocrine carcinoma (NEC) of the bladder is aggressive and systemic chemotherapy can help control metastatic disease. The current regimen (etoposide and cisplatin) is standard for NEC, showing some effectiveness in this patient.

**Immunotherapy (Durvalumab):**

**Reason:** Ongoing immunotherapy with durvalumab should be continued as it has been well tolerated and can help in prolonging disease control, particularly in cases where the disease shows a response to initial treatment.

**Thoracic Oncology Consultation:**

**Reason:** Given the presence of a hypoechoic nodule in the right lung, it is critical to assess for potential metastasis or a primary lung malignancy. This could significantly impact the treatment plan.

**Surgical Intervention (Cystectomy):**

**Reason:** Given the location and the nature of the bladder tumor, radical cystectomy might be considered if the patient is a suitable surgical candidate. This could provide local control of the disease.

**Radiotherapy:**

**Reason:** Radiotherapy may be considered for local control, especially if surgery is not an option. It can be effective in treating local symptoms and managing residual disease post-TURBT.

**Regular Follow-Up and Monitoring:**

**Reason:** Frequent monitoring through imaging (CT scans) and cystoscopy is essential to evaluate the effectiveness of the treatment and adjust the strategy as needed.

### Measures to Avoid

**Aggressive Surgical Intervention without Thorough Assessment:**

**Reason:** Given the patient's complex medical history and presence of multiple comorbidities, aggressive surgery without comprehensive assessment could pose significant risks. Evaluating the overall health and surgical risks is crucial.

**Single-Modality Treatment:**

**Reason:** Given the aggressive nature of small cell NEC, relying on a single treatment modality (e.g., only chemotherapy or only radiotherapy) is unlikely to be effective. A multimodal approach is necessary.

**Neglecting Potential Metastases:**

**Reason:** Ignoring the nodule in the lung and possible metastatic disease could lead to a lack of comprehensive treatment, potentially allowing the disease to progress unchecked.

**Overlooking Palliative Care Needs:**

**Reason:** Focusing solely on curative treatment without considering the patient’s quality of life and palliative care needs can lead to unnecessary suffering. Pain management and supportive care should be integral parts of the treatment plan.

### Conclusion

The patient's treatment should continue with a multimodal approach, involving systemic chemotherapy, immunotherapy, possible surgical intervention, and radiotherapy, along with comprehensive follow-up and monitoring. A holistic view that includes potential metastases and palliative care needs is crucial for optimal management.

***Q2:****prompts2+The reason why radiotherapy is not currently recommended as the primary treatment for the patient is:*

***A2:***Radiotherapy is not currently recommended as the primary treatment for the patient for the following reasons:

**Aggressiveness of Small Cell Neuroendocrine Carcinoma (NEC):**

Small cell NEC is highly aggressive and often requires a systemic approach due to the high likelihood of metastasis. Chemotherapy and immunotherapy are more effective in targeting both the primary tumor and potential micrometastases.

**Systemic Nature of Disease:**

Given the presence of a hypoechoic nodule in the right lung, there is a strong suspicion of metastatic disease. Radiotherapy primarily offers local control and is less effective in treating systemic disease compared to chemotherapy and immunotherapy.

**Need for Multimodal Treatment:**

The optimal management of small cell NEC typically involves a combination of systemic therapy (chemotherapy and immunotherapy) and local control measures. Radiotherapy might be considered as an adjunct to systemic therapy but not as the primary treatment modality.

**Current Treatment Response:**

The patient has already received three cycles of chemotherapy and immunotherapy, which are standard initial treatments for small cell NEC. Evaluating the response to this treatment is crucial before considering additional modalities like radiotherapy.

**Focus on Comprehensive Management:**

A comprehensive approach that includes systemic therapy addresses both local and distant disease. Radiotherapy might be included later in the treatment plan for local control if necessary, but the primary focus should remain on systemic management at this stage.

In summary, while radiotherapy can be valuable for local control in some cases, the primary treatment for small cell neuroendocrine carcinoma of the bladder should focus on systemic therapy due to the aggressive and potentially metastatic nature of the disease.

Q3:***prompts3***

A3:

### Suitable Clinical Trials

**NCT03898180**: **A Study of Enfortumab Vedotin for Patients With Locally Advanced or Metastatic Urothelial Cancer**

* 1. **Level of Evidence**: Phase 3
  2. **Clinical Significance**: This trial evaluates Enfortumab Vedotin, an antibody-drug conjugate targeting Nectin-4, in patients with advanced urothelial carcinoma. Previous studies have shown promising results, particularly in patients who have progressed on chemotherapy and immunotherapy​ ([BioMed Central](https://surgexppathol.biomedcentral.com/articles/10.1186/s42047-020-0056-5" \t "_blank))​​ ([UroToday](https://www.urotoday.com/recent-abstracts/urologic-oncology/bladder-cancer/149154-outcomes-following-radical-cystectomy-for-plasmacytoid-urothelial-carcinoma-defining-the-need-for-improved-local-cancer-control.html" \t "_blank))​.

**NCT03473743**: **A Study of Pembrolizumab (MK-3475) in Combination With Other Treatments in Participants With Metastatic Bladder Cancer (KEYNOTE-921)**

* 1. **Level of Evidence**: Phase 3
  2. **Clinical Significance**: Pembrolizumab, an immune checkpoint inhibitor, is being tested in combination with chemotherapy. This combination aims to enhance anti-tumor activity and improve outcomes in patients with advanced disease​ ([BioMed Central](https://bmccancer.biomedcentral.com/articles/10.1186/1471-2407-13-71" \t "_blank))​.

**NCT03390504**: **Study of Erdafitinib in Subjects With Advanced Urothelial Cancer and FGFR Gene Aberrations**

* 1. **Level of Evidence**: Phase 2
  2. **Clinical Significance**: Erdafitinib targets FGFR genetic alterations, which are present in a subset of urothelial carcinomas. This study is particularly relevant if molecular testing reveals FGFR mutations or fusions in the patient’s tumor​ ([BioMed Central](https://surgexppathol.biomedcentral.com/articles/10.1186/s42047-020-0056-5" \t "_blank))​.

**NCT03661320**: **A Study of Enfortumab Vedotin Plus Pembrolizumab for Locally Advanced or Metastatic Urothelial Cancer (KEYNOTE-869/EV-103)**

* 1. **Level of Evidence**: Phase 1/2
  2. **Clinical Significance**: This study combines Enfortumab Vedotin with Pembrolizumab to explore the synergistic effects of these agents in advanced urothelial cancer. Early results have shown encouraging response rates and manageable safety profiles​ ([UroToday](https://www.urotoday.com/recent-abstracts/urologic-oncology/bladder-cancer/149154-outcomes-following-radical-cystectomy-for-plasmacytoid-urothelial-carcinoma-defining-the-need-for-improved-local-cancer-control.html" \t "_blank))​.

***Patient9：***

***Q1:****prompts1+<Patient information9>*

***A1：***

#### Preferred Treatment Measures

**Systemic Chemotherapy**

**Reason**: Given the recurrent and invasive nature of the carcinoma, systemic chemotherapy can help control the spread of cancer. The patient has a history of moderately to highly differentiated invasive urothelial carcinoma and invasive urothelial carcinoma in the pelvic mass.

**Specific Regimen**: Cisplatin-based chemotherapy (e.g., MVAC - Methotrexate, Vinblastine, Adriamycin, and Cisplatin) or alternative regimens like Gemcitabine and Cisplatin may be considered if the patient’s renal function permits.

**Immunotherapy**

**Reason**: For advanced or metastatic urothelial carcinoma, immune checkpoint inhibitors (e.g., Pembrolizumab, Atezolizumab) have shown efficacy in patients who are cisplatin-ineligible or have progressed after chemotherapy.

**Eligibility**: The patient’s renal function and performance status should be considered when deciding on immunotherapy.

**Palliative Radiation Therapy**

**Reason**: To alleviate pain and control local tumor growth, especially given the patient's complaint of pain around the anus and the presence of a fixed mass as per the digital rectal exam.

**Target Areas**: Pelvic mass and any bone metastases, particularly the first lumbar vertebra with increased radiotracer uptake.

**Management of Urinary Tract Infections**

**Reason**: The patient has ESBL(+) Escherichia coli positive urine culture, indicating an ongoing infection that needs to be managed to prevent further complications.

**Antibiotic Therapy**: Utilize antibiotics based on sensitivity to ESBL-producing organisms.

**Supportive Care**

**Reason**: Comprehensive supportive care to manage symptoms, improve quality of life, and address anemia (Hemoglobin 113 g/L) and renal insufficiency (Creatinine 152.8 µmol/L).

**Measures**: Blood transfusions, erythropoiesis-stimulating agents, hydration, and renal function monitoring.

**Close Monitoring and Follow-up**

**Reason**: Continuous assessment of the patient's response to treatment, adjustment of therapy as needed, and early detection of any new metastases or complications.

**Tools**: Regular imaging studies, blood tests, and clinical evaluations.

#### Measures to Avoid

**Nephrotoxic Chemotherapy Regimens**

**Reason**: The patient has impaired renal function (Creatinine 152.8 µmol/L), which can be further exacerbated by nephrotoxic agents.

**Alternatives**: Use non-nephrotoxic agents or adjust dosages to minimize renal toxicity.

**Aggressive Surgical Interventions**

**Reason**: Considering the patient's age (78 years), comorbidities, and advanced disease with a fixed pelvic mass, aggressive surgery may not be beneficial and could pose significant risks.

**Focus**: Non-surgical management to maintain quality of life.

**High-dose Radiation Therapy**

**Reason**: High-dose radiation may lead to significant side effects, particularly in an elderly patient with a fixed mass near the rectum.

**Approach**: Palliative doses aimed at symptom relief rather than curative intent.

**Delay in Infection Management**

**Reason**: Untreated or inadequately treated urinary tract infections can lead to sepsis and further complicate the patient's condition.

**Action**: Prompt and appropriate antibiotic therapy based on culture sensitivities.

**Non-individualized Treatment Plans**

**Reason**: Standardized treatments without considering the patient’s specific medical history, current health status, and personal preferences may lead to suboptimal outcomes.

**Strategy**: Tailor the treatment plan to the patient’s unique clinical scenario and engage in shared decision-making.

***Q2：***

1. *For this patient, if immunotherapy is performed, which gene should it primarily target (select only one)*
2. *For this patient, if targeted therapy is performed, which gene should it primarily target (select only one).*

### ***A2：*** 1. Immunotherapy Target Gene

**PD-L1 (Programmed Death-Ligand 1):**

* **Reason for Targeting:** PD-L1 expression on tumor cells and tumor-infiltrating immune cells is a key biomarker for predicting response to immunotherapy with immune checkpoint inhibitors such as Pembrolizumab and Atezolizumab.
* **Targeted Therapy:** Pembrolizumab (anti-PD-1), Atezolizumab (anti-PD-L1)

### 2. Targeted Therapy Gene

**FGFR3 (Fibroblast Growth Factor Receptor 3):**

* **Reason for Targeting:** FGFR3 mutations and fusions are present in a significant subset of urothelial carcinoma cases. These genetic alterations can drive tumor growth, and specific FGFR inhibitors have shown efficacy in treating tumors with these alterations.
* **Targeted Therapy:** Erdafitinib (FGFR inhibitor)

These selections ensure that the treatment is focused on the most relevant and potentially actionable genetic targets for this patient's urothelial carcinoma.

***Q3:****prompts3*

***A3:***

### ****EV-302/KEYNOTE-A39 Trial****

* **NCT Number:** NCT04223856
* **Description:** This phase 3 trial evaluates the combination of enfortumab vedotin (EV) and pembrolizumab (P) versus chemotherapy in patients with advanced urothelial carcinoma. The study has shown significant improvements in overall survival (OS) and progression-free survival (PFS) compared to standard chemotherapy.
* **Clinical Significance:** The combination therapy nearly doubled the median OS (31.5 months vs. 16.1 months) and PFS (12.5 months vs. 6.3 months)​ ([Home](https://www.hopkinsmedicine.org/news/newsroom/news-releases/2024/03/combination-urothelial-cancer-treatment-nearly-doubles-patient-survival-in-international-trial" \t "_blank))​​ ([Med Xpress](https://medicalxpress.com/news/2024-01-clinical-trial-dual-therapy-revolutionize.html" \t "_blank))​.

### 2. ****AMBASSADOR Alliance A031501 Trial****

* **NCT Number:** NCT03244384
* **Description:** A phase 3 randomized study of pembrolizumab as an adjuvant therapy in patients with muscle-invasive and locally advanced urothelial carcinoma who have undergone surgery. This trial is assessing disease-free survival (DFS) and overall survival (OS).
* **Clinical Significance:** This trial is crucial for patients with high-risk muscle-invasive urothelial carcinoma, showing promising interim results in improving DFS​ ([UroToday](https://www.urotoday.com/conference-highlights/asco-gu-2024/asco-gu-2024-bladder-cancer/149425-asco-gu-2024-ambassador-alliance-a031501-phase-iii-randomized-adjuvant-study-of-pembrolizumab-in-muscle-invasive-and-locally-advanced-urothelial-carcinoma-versus-observation-late-breaking-abstract.html" \t "_blank))​​ ([Targeted Oncology](https://www.targetedonc.com/view/pembrolizumab-improves-dfs-in-muscle-invasive-urothelial-carcinoma" \t "_blank))​.

### 3. ****THOR Study for Erdafitinib****

* **NCT Number:** NCT03390504
* **Description:** A phase 3 study evaluating the efficacy of erdafitinib, an FGFR inhibitor, versus chemotherapy in patients with advanced urothelial carcinoma with specific FGFR genetic alterations.
* **Clinical Significance:** Erdafitinib has shown substantial benefits in patients with FGFR alterations, offering an effective targeted therapy option with manageable side effects​ ([Urology Times](https://www.urologytimes.com/view/fda-grants-full-approval-to-erdafitinib-for-fgfr3-positive-urothelial-carcinoma" \t "_blank))​.

### 4. ****LASER Trial****

* **NCT Number:** NCT06228066
* **Description:** This trial investigates the use of Lurbinectedin with or without Avelumab in patients with small cell carcinoma of the bladder.
* **Clinical Significance:** This trial focuses on a rare and aggressive subtype of urothelial carcinoma, providing potential new treatment avenues​ ([UroToday](https://www.urotoday.com/conference-highlights/asco-2024/asco-2024-bladder-cancer/152654-asco-2024-what-is-variant-histology-urothelial-cancer-and-what-are-the-available-treatment-options.html" \t "_blank))​.

***Patient10***

***Q1:****prompts1+<Patient information10>*

***A1：***

### MDT Recommendations

#### Preferred Treatment Measures

**Systemic Therapy:**

**Reason:** Given the presence of multiple lymph node metastases and the persistence of lesions despite initial chemotherapy and immunotherapy, systemic therapy with a combination of chemotherapy, immunotherapy, and targeted therapy may be beneficial. Possible regimens could include:

**Pembrolizumab** or **Nivolumab** (PD-1 inhibitors) due to their efficacy in urothelial carcinoma.

**Enfortumab vedotin**, an antibody-drug conjugate targeting Nectin-4, approved for metastatic urothelial carcinoma post-immunotherapy and chemotherapy.

**Rationale:** These therapies have shown promising results in controlling disease progression and potentially improving survival rates.

**Radiotherapy:**

**Reason:** Radiotherapy can be considered for symptomatic relief, especially for the retroperitoneal mass causing back pain.

**Rationale:** Targeted radiotherapy can help reduce tumor burden and alleviate pain, improving quality of life.

**Palliative Care:**

**Reason:** Given the patient's persistent symptoms and metastatic disease, incorporating palliative care early is crucial for managing symptoms and improving quality of life.

**Rationale:** Palliative care can help address pain management, nutritional support, and psychological support, enhancing the overall treatment experience.

#### Measures to Avoid

**Further Extensive Surgery:**

**Reason:** Given the metastatic nature of the disease and the multiple lymph node involvements, further extensive surgery is unlikely to be curative and may lead to unnecessary morbidity.

**Rationale:** The risks and recovery time associated with major surgery in the context of widespread metastatic disease outweigh potential benefits.

**Monotherapy with Cisplatin:**

**Reason:** The patient has already received six cycles of GC (Gemcitabine and Cisplatin), and the disease persists.

**Rationale:** Monotherapy with Cisplatin is unlikely to provide additional benefits given the prior treatment history and the resistance observed.

**Non-specific Systemic Therapy:**

**Reason:** Non-specific systemic therapies without targeting the specific molecular and immunological characteristics of the tumor are less likely to be effective.

**Rationale:** Precision medicine approaches, including targeted therapy and immunotherapy, offer a more tailored and potentially effective treatment strategy.

### Summary

The multidisciplinary team recommends a combination of advanced systemic therapies (including immunotherapy and targeted therapy) and radiotherapy for symptomatic relief. Palliative care should be integrated early to manage symptoms and improve the patient's quality of life. Further extensive surgery and non-specific systemic therapies should be avoided due to their limited efficacy in the context of metastatic disease.  
  
***Q2:****prompts3* ***A2:***

**Nivolumab Plus Ipilimumab (TITAN-TCC Study)**

* **NCT Number:** NCT03036098
* **Summary:** This phase II study evaluated the combination of nivolumab and ipilimumab in patients with metastatic urothelial carcinoma. The results showed promising objective response rates and progression-free survival, especially in patients receiving high-dose ipilimumab.
* **Level of Evidence and Clinical Significance:** The study provided strong evidence for using combination immunotherapy as a potential treatment option, particularly for patients with advanced disease refractory to standard treatments​ ([The ASCO Post](https://ascopost.com/news/may-2024/nivolumabipilimumab-boost-in-metastatic-urothelial-carcinoma/" \t "_blank))​.

**Sacituzumab Govitecan Plus Enfortumab Vedotin (DAD Phase I Trial)**

* **NCT Number:** NCT04724018
* **Summary:** This phase I trial investigates the safety and efficacy of combining sacituzumab govitecan and enfortumab vedotin in patients with metastatic urothelial carcinoma who have progressed on platinum-based chemotherapy and PD1/L1 inhibitors. The trial aims to establish the appropriate dose for further studies and evaluate the combination's effectiveness in controlling cancer progression.
* **Level of Evidence and Clinical Significance:** Preliminary results indicate that this combination could offer a novel therapeutic option for patients with advanced metastatic disease who have exhausted other treatment options​ ([Bladder Cancer Advocacy Network](https://bcan.org/clinicaltrials/sacituzumab-govitecan-plus-ev-in-metastatic-uc/" \t "_blank))​.

**Enfortumab Vedotin and Pembrolizumab Combination Therapy**

* **NCT Number:** NCT04223856
* **Summary:** This phase II trial at Memorial Sloan Kettering Cancer Center is evaluating the combination of enfortumab vedotin, an antibody-drug conjugate, with pembrolizumab, a checkpoint inhibitor, in patients with metastatic urothelial carcinoma who are ineligible for cisplatin-based chemotherapy. Early results showed significant tumor shrinkage and a high response rate.
* **Level of Evidence and Clinical Significance:** This combination has shown remarkable efficacy, potentially offering a first-line treatment alternative for patients who cannot undergo standard cisplatin-based chemotherapy​ ([Memorial Sloan Kettering Cancer Center](https://www.mskcc.org/news/who-can-be-helped-new-bladder-cancer-drugs-immunotherapy-and-antibody-drug-conjugates" \t "_blank))​.

**Disitamab Vedotin for HER2+ Metastatic Urothelial Carcinoma**

* **NCT Number:** NCT04879329
* **Summary:** This phase II study focuses on patients with HER2-positive metastatic urothelial carcinoma, testing the efficacy and safety of disitamab vedotin. The trial includes patients who have progressed on at least one prior line of systemic chemotherapy.
* **Level of Evidence and Clinical Significance:** Results demonstrate a significant overall response rate and durable clinical benefit, indicating that disitamab vedotin could be a valuable option for patients with HER2-positive tumors​ ([Urology Times](https://www.urologytimes.com/view/disitamab-vedotin-shows-promise-in-her2-metastatic-urothelial-carcinoma" \t "_blank))​.