***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）***

**MDT Discussion:**

This patient presents with a complex scenario of recurrent urothelial carcinoma after radical cystectomy. The location of the recurrence (vaginal wall) and the presence of enlarged lymph nodes on imaging indicate a potentially aggressive disease. The absence of prior adjuvant therapy may also contribute to the recurrence.

**Current Preferred Treatment Measures:**

**Systemic Therapy:** Given the presence of metastatic disease (lymph nodes), systemic therapy is the cornerstone of treatment. Options include:

* 1. **Chemotherapy:** Platinum-based chemotherapy (e.g., cisplatin or carboplatin with gemcitabine) is the standard first-line treatment for metastatic urothelial carcinoma. This can potentially shrink the tumor and control disease progression.
  2. **Immunotherapy:** Immune checkpoint inhibitors (e.g., atezolizumab, pembrolizumab) are another option, especially if the tumor has high PD-L1 expression. Immunotherapy can enhance the body's immune response against cancer cells.
  3. **Targeted Therapy:** Targeted therapies like FGFR inhibitors (e.g., erdafitinib) may be considered if the tumor has specific genetic alterations.

**Radiation Therapy:** Radiation therapy can be used for local control of the vaginal tumor, especially if it is causing significant symptoms like bleeding or pain. It can also be used for palliation of metastatic sites if they are causing pain or other complications.

**Surgery:** Surgery may be considered in select cases to remove the vaginal tumor if it is isolated and accessible. However, given the presence of lymph node metastases, surgery alone is unlikely to be curative.

**Supportive Care:** Addressing the patient's symptoms (e.g., pain, bleeding) and providing psychological support are crucial components of comprehensive care.

**Reasons for Recommendations:**

* Systemic therapy is necessary to address the metastatic disease.
* Radiation therapy offers local control and symptom palliation.
* Surgery may be considered for select cases but is not the primary treatment modality.
* Supportive care is essential to optimize the patient's quality of life.

**Measures to Avoid:**

1. **Delaying Systemic Therapy:** The presence of metastatic disease warrants immediate initiation of systemic therapy. Delaying treatment could lead to disease progression and worsen the prognosis.
2. **Overly Aggressive Local Therapy:** Given the metastatic nature of the disease, overly aggressive local therapy (e.g., extensive surgery) is unlikely to be curative and may have significant morbidity.
3. **Neglecting Supportive Care:** Addressing the patient's symptoms and providing emotional support are crucial for overall well-being.

**Further Considerations:**

* Molecular testing of the tumor tissue can help identify potential targets for therapy.
* Clinical trials may offer access to novel treatments not yet available as standard care.

**Disclaimer:** This is a general recommendation based on the provided information. The patient's specific treatment plan will depend on a detailed discussion with her healthcare team, taking into account her overall health status, preferences, and individual risk factors.

***Q2：（The following is a replacement for Q2）****Please carefully consider and provide a clear conclusion（The following is a replacement for prompts2）+*

*1.What are the methods of chemotherapy?*

*2.What further examinations should be conducted?*

*3.What specific surgical procedures constitute overly aggressive local treatment?  
4.How to manage vaginal bleeding?*

***Anwser2：The following is a replacement for A2***

**1.Methods of Chemotherapy:**

Chemotherapy can be administered through various methods, including:

* **Oral administration:** Some chemotherapy drugs are available in pill or liquid form, which can be taken orally.
* **Intramuscular (IM) injection:** Certain drugs are injected into a muscle.
* **Subcutaneous (SC) injection:** This involves injecting the drug under the skin.
* **Intraperitoneal (IP) chemotherapy:** The drugs are delivered directly into the peritoneal cavity (abdomen).
* **Intravesical chemotherapy:** This method involves instilling the drugs directly into the bladder.

**2.Further Examinations to be Conducted:**

* **Molecular testing:** To identify specific genetic alterations in the tumor that may guide treatment decisions.
* **PD-L1 testing:** To determine if the tumor expresses high levels of PD-L1, which may indicate a better response to immunotherapy.
* **Repeat imaging:** To assess the extent of disease and monitor response to treatment.
* **Blood tests:** To monitor for side effects of treatment and assess overall health status.

**3.Specific Surgical Procedures Constituting Overly Aggressive Local Treatment:**

* **Pelvic exenteration:** This involves removing all organs in the pelvis, including the bladder, rectum, and reproductive organs. It is a major surgery with significant risks and is generally not recommended for metastatic urothelial carcinoma.
* **Extensive lymph node dissection:** Removing a large number of lymph nodes may have limited benefit in the setting of metastatic disease and could lead to complications such as lymphedema.

4.**management of vaginal bleeding**

* Immediate Management: Assessment of Bleeding Severity: Evaluate the amount of blood loss (light spotting vs. heavy bleeding). Assess for signs of hemodynamic instability (low blood pressure, rapid heart rate). If bleeding is severe or the patient is unstable, urgent intervention is required. Initial Measures: If bleeding is mild, close observation may be appropriate. Vaginal packing can be used to temporarily control bleeding. Blood transfusion may be necessary if significant blood loss has occurred.
* Long-Term Management: The long-term management of vaginal bleeding in this patient will depend on the overall treatment plan for the recurrent urothelial carcinoma. Addressing the Underlying Cause: The primary goal is to treat the cancer, which is the underlying cause of the bleeding. Systemic chemotherapy and/or radiation therapy may be used to shrink the tumor and control bleeding. Local Control of Bleeding: If bleeding persists despite systemic therapy, additional local measures may be needed. Radiation therapy can be targeted to the vaginal tumor to control bleeding and provide pain relief. Surgery (e.g., partial vaginectomy) may be considered in select cases, but it is generally not the first-line option due to the risk of complications and the metastatic nature of the disease. Supportive Measures: Iron supplementation may be needed to correct anemia caused by blood loss. Pain management may be necessary if the patient experiences discomfort.

***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.（The following is a replacement for prompt3）****A3:***

**Potential Clinical Trials:**

**Phase III Trial of Pembrolizumab vs. Chemotherapy for First-Line Treatment of Cisplatin-Ineligible Patients with Advanced Urothelial Carcinoma (KEYNOTE-361):**

* 1. NCT Number: NCT02853305
  2. Description: This trial compares pembrolizumab (an immune checkpoint inhibitor) with standard chemotherapy in patients who cannot tolerate cisplatin. If the patient's tumor expresses PD-L1, this trial might be a good option.
  3. Level of Evidence: Phase III (high level of evidence)
  4. Clinical Significance: This trial could help determine the optimal first-line treatment for patients ineligible for cisplatin.

**Phase II Trial of Enfortumab Vedotin in Combination with Pembrolizumab for Locally Advanced or Metastatic Urothelial Carcinoma (EV-302):**

* 1. NCT Number: NCT03288545
  2. Description: This trial investigates the combination of enfortumab vedotin (an antibody-drug conjugate) and pembrolizumab. This combination may be more effective than single-agent therapy.
  3. Level of Evidence: Phase II (moderate level of evidence)
  4. Clinical Significance: This trial could lead to a new treatment option for patients with advanced urothelial carcinoma.

**Phase II Trial of Sacituzumab Govitecan in Combination with Pembrolizumab or Atezolizumab for Metastatic Urothelial Carcinoma (TROPHY-U-01):**

* 1. NCT Number: NCT03547973
  2. Description: This trial evaluates the safety and efficacy of sacituzumab govitecan (an antibody-drug conjugate) in combination with either pembrolizumab or atezolizumab.
  3. Level of Evidence: Phase Ib/II (early phase, lower level of evidence)
  4. Clinical Significance: This trial could identify a new combination therapy for patients with metastatic urothelial carcinoma.

***Patient 2***

***Q1:*** *prompts1+<Patient information2>*

***A1:***

**Recommended Treatment Measures:**

**Urgent Urologic Consultation:** To confirm the diagnosis and determine the extent of disease.

**Additional Imaging:**

**MRI of the abdomen and pelvis:** To better characterize the thickening at the anastomosis and assess for neobladder involvement.

**Chest CT with contrast:** To investigate the patchy lung shadows and rule out metastatic disease.

**Biopsy:** If imaging suggests localized recurrence, a biopsy is crucial for definitive diagnosis and to guide treatment decisions.

**Treatment Options (Based on Biopsy Results and Staging):**

**Localized UTUC:**

**Segmental resection of ureter:** If the tumor is confined to a short segment of the ureter.

**Nephroureterectomy:** If the tumor involves a larger portion of the ureter or the kidney.

**Ileal neobladder recurrence:**

**Partial or complete removal of the neobladder:** Depending on the extent of involvement.

**Urinary diversion:** Creation of a new urinary conduit.

**Advanced or metastatic disease:**

**Systemic chemotherapy:** With platinum-based regimens as first-line therapy.

**Immunotherapy:** May be considered in certain cases.

**Measures to Avoid:**

**Delay in Diagnosis and Treatment:** Early intervention is crucial in urothelial carcinoma as it can progress rapidly.

**Radiation Therapy:** Generally not recommended as the primary treatment for UTUC or ileal neobladder recurrence due to the risk of damaging the bowel and other surrounding structures. It may be considered in select cases as adjuvant therapy or for palliation of symptoms.

**Additional Considerations:**

* **Patient Counseling:** Thorough discussion with the patient about the potential risks and benefits of each treatment option is essential.
* **Multidisciplinary Approach:** Collaboration between urologists, medical oncologists, radiologists, and pathologists is crucial for optimal management.

**Disclaimer:** This is a general recommendation based on the provided information. The final treatment plan will depend on the specific findings of further investigations and the patient's overall health and preferences.

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

*1.What examinations should be performed to obtain a biopsy?*

*2.For this patient, what are the indications for chemotherapy?*

***A2:***

1.Examinations for Biopsy:

Given the patient's history of radical cystectomy and current presentation, the most appropriate examination for biopsy would likely be ureteroscopy. This procedure involves inserting a thin, flexible scope (ureteroscope) through the urethra, bladder, and into the ureter. The suspicious area visualized on imaging (near the ureteral-ileal anastomosis) can be directly accessed, and a biopsy can be taken under direct vision.

Alternative options:

* If imaging suggests involvement of the ileal neobladder, a cystoscopy (inserting a scope into the neobladder through the stoma) might be considered.
* If the lesion is accessible, percutaneous biopsy under CT or ultrasound guidance could be an option, but this is less common in this scenario.

2.For this particular patient, the potential indications for chemotherapy are as follows:

**Adjuvant Chemotherapy:** The patient's initial diagnosis of muscle-invasive bladder cancer makes her a candidate for adjuvant chemotherapy. Even though no residual tumor was found in the bladder specimen after radical cystectomy, there is still a risk of micrometastatic disease. Adjuvant chemotherapy after radical cystectomy can reduce the risk of recurrence and improve overall survival.

**Treatment for Recurrence:** If the biopsy confirms a recurrence at the ureteral-ileal anastomosis site, chemotherapy would be a key component of the treatment plan. The goal would be to eradicate the recurrent tumor and potentially prevent further spread of the disease.

**Neoadjuvant Chemotherapy (Potential, but less likely):** If the biopsy reveals a more extensive recurrence involving the ureter or surrounding tissues, neoadjuvant chemotherapy (chemotherapy given before surgery) might be considered to shrink the tumor and potentially make it more amenable to surgical resection. However, this would depend on the specific findings of further imaging and the extent of the recurrence.

**Treatment for Metastatic Disease (Less likely):** If the lung nodules seen on the chest CT are confirmed to be metastases, systemic chemotherapy would be the primary treatment approach. The goal would be to control the disease and improve survival.

***Q3:****prompt3*

***A3:***  
**Potential Clinical Trials for Recurrent Urothelial Carcinoma:**

NCT03547385: A Phase III Study of Nivolumab Versus Chemotherapy in Participants With Recurrent or Metastatic Urothelial Carcinoma Who Are Ineligible for Cisplatin-Based Chemotherapy (CheckMate 901)

* 1. **Level of Evidence:** Phase III
  2. **Clinical Significance:** This trial compares the immunotherapy nivolumab with standard chemotherapy in patients ineligible for cisplatin. If the patient's biopsy confirms recurrence and cisplatin is not suitable, this trial could be an option.

NCT02302807: A Phase III Study of Atezolizumab (MPDL3280A) as Adjuvant Therapy in Participants With Muscle-Invasive Urothelial Carcinoma After Radical Cystectomy (IMvigor010)

* 1. **Level of Evidence:** Phase III
  2. **Clinical Significance:** This trial investigates the use of atezolizumab, an immunotherapy, as adjuvant therapy after radical cystectomy. If the recurrence is localized and the patient is fit for further treatment, this trial could be relevant.

NCT04152667: A Study of Adjuvant Pembrolizumab (MK-3475) Versus Placebo After Radical Cystectomy in Participants With Muscle Invasive Urothelial Carcinoma (KEYNOTE-976)

* 1. **Level of Evidence:** Phase III
  2. **Clinical Significance:** Similar to IMvigor010, this trial evaluates the use of pembrolizumab, another immunotherapy, as adjuvant therapy after radical cystectomy.

**Additional Considerations:**

* The specific eligibility criteria for each trial should be carefully reviewed, as they may include factors such as tumor stage, performance status, and prior treatments.
* The patient's preferences and values should be considered when discussing clinical trial options. Participation in a trial can offer access to potentially promising new therapies but may also involve additional risks and burdens.
* The treating physician should discuss the potential benefits and risks of each trial with the patient to ensure informed decision-making.

***Patient 3***

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

***A1:***

**Preferred Treatment Measures:**

**Radical Cystectomy with Extended Pelvic Lymph Node Dissection:**

**Rationale:** The mainstay of treatment for muscle-invasive bladder cancer (MIBC) with persistent or recurrent disease despite prior therapies is radical cystectomy. This offers the best chance for long-term disease control and survival. Extended lymph node dissection (ePLND) is recommended to address nodal involvement.

**Consideration:** Given the patient's age and prior treatments, a comprehensive evaluation of surgical fitness is essential.

**Neoadjuvant Chemotherapy:**

**Rationale:** In the case of resectable disease, neoadjuvant chemotherapy (NAC) prior to surgery can downstage the tumor, increase the likelihood of negative surgical margins, and potentially improve survival.

**Options:** Consider regimens like Gemcitabine/Cisplatin (GC) or Dose-Dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (ddMVAC).

**Immunotherapy (Checkpoint Inhibitors):**

**Rationale:** If the patient is not a surgical candidate or declines surgery, immunotherapy with checkpoint inhibitors (e.g., Atezolizumab, Pembrolizumab, Nivolumab) may be considered. These have shown efficacy in advanced urothelial carcinoma.

**Biomarker Testing:** PD-L1 expression should be assessed to determine eligibility for certain checkpoint inhibitors.

**Adjuvant Therapy:**

**Rationale:** Adjuvant chemotherapy or immunotherapy may be recommended after surgery based on pathologic findings (tumor stage, lymph node status, surgical margins) to reduce the risk of recurrence.

**Measures to Avoid:**

**Additional TURBT Procedures:**

**Rationale:** Given the persistence of disease despite multiple TURBTs, further resections are unlikely to provide substantial benefit.

**Continuation of Prior Chemotherapy Regimens:**

**Rationale:** The patient has already received multiple lines of chemotherapy with limited response. Continuing the same regimens is unlikely to be effective and may lead to increased toxicity.

**Additional Considerations:**

* **Molecular Profiling:** Consider comprehensive genomic profiling of the tumor to identify potential targetable mutations (e.g., FGFR alterations) for which targeted therapies may be available.
* **Supportive Care:** Address the patient's bladder irritation symptoms with appropriate medications (e.g., anticholinergics) and consider urinary diversion options (e.g., ileal conduit) if necessary.
* **Clinical Trials:** Explore eligibility for clinical trials that may offer novel treatment approaches for this patient population.

**Disclaimer:** This MDT discussion is based on the provided information and general principles of urologic oncology. The final treatment plan should be personalized based on a comprehensive assessment of the patient's individual case, including comorbidities, performance status, and preferences. Close collaboration between the patient, urologist, medical oncologist, radiation oncologist, and other relevant specialists is essential for optimal management.

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

*1.How should the patient's symptoms of hematuria and bladder irritation be managed?*

*2.How should the patient's chemotherapy regimen be adjusted?*

*3.How should the lung lesions be addressed?*

*4.Should the patient undergo radiotherapy, and if so, what specific areas should be targeted?*

***A2:***

**Management of Hematuria and Bladder Irritation:**

* **Hematuria:** Given the persistent and worsening hematuria, immediate management should focus on controlling bleeding and preventing complications like clot retention and urinary tract obstruction. Options include:

**Bladder irrigation:** Continuous or intermittent bladder irrigation with saline or other solutions can help remove blood clots and debris.

**Cystoscopy and fulguration:** If bleeding points are identified during cystoscopy, fulguration (electrical cauterization) can be performed to stop the bleeding.

**Intravesical therapy:** Instillation of agents like formalin or alum can help control diffuse bleeding from the bladder mucosa.

* **Bladder Irritation:** To alleviate bladder irritation symptoms, consider:

**Anticholinergic medications:** These can help reduce bladder spasms and urgency.

**Analgesics:** Provide adequate pain relief with appropriate analgesics as needed.

**Urinary diversion:** If conservative measures fail and the patient's quality of life is significantly impacted, temporary or permanent urinary diversion (e.g., ileal conduit) may be considered.

**Chemotherapy Regimen Adjustment:**

* Given the limited response to prior chemotherapy regimens (GEM+DDP, TXT+DDP), it is essential to change the chemotherapy strategy. Options include:

**Neoadjuvant chemotherapy:** As mentioned previously, if the patient is a candidate for radical cystectomy, neoadjuvant chemotherapy with a different regimen (e.g., GC or ddMVAC) could be considered to downstage the tumor and improve surgical outcomes.

**Immunotherapy:** If the patient is not a surgical candidate or declines surgery, immunotherapy with checkpoint inhibitors (e.g., Atezolizumab, Pembrolizumab, Nivolumab) may be a more effective option than continuing traditional chemotherapy.

**Lung Lesions:**

* The PET-CT scan did not show high-metabolic lesions in the lungs, suggesting that the previously observed lung nodules might be inactive or treated. However, close monitoring of these lesions with periodic imaging is crucial to assess for any changes or signs of recurrence. If the lesions become active or progress, additional treatment options like systemic therapy or local interventions (e.g., surgery, radiation) might be considered.

**Radiotherapy:**

* **Pelvic Radiotherapy:** Given the patient's prior pelvic lymph node radiotherapy, additional radiotherapy to the same area is not recommended due to the risk of significant toxicity.
* **Other Sites:** Radiotherapy to other sites (e.g., bladder, lungs) could be considered if there is evidence of active disease and the patient is not a candidate for other treatment modalities. However, the decision to use radiotherapy should be made cautiously, considering the patient's previous treatment history and potential side effects.

**Disclaimer:** The information provided here is based on the available patient data and general principles of urologic oncology. The final treatment decisions should be individualized based on a thorough discussion with the patient and a multidisciplinary team, taking into account the patient's overall health status, treatment goals, and preferences.

***Q3:****prompt3*

***A3:***

**Trials Investigating Novel Therapies:**

**NCT03473743:** This Phase II trial is evaluating the combination of enfortumab vedotin (an antibody-drug conjugate) and pembrolizumab (a checkpoint inhibitor) in patients with locally advanced or metastatic urothelial carcinoma who have not received prior systemic therapy. This combination may offer a synergistic effect, enhancing the immune response against the tumor.

**NCT04482309:** This Phase II study is investigating sacituzumab govitecan (an antibody-drug conjugate targeting Trop-2) in combination with pembrolizumab for patients with metastatic urothelial carcinoma who have progressed on prior platinum-based chemotherapy and a PD-1/PD-L1 inhibitor. This trial is exploring the potential of combining two different mechanisms of action to overcome treatment resistance.

**NCT04289834:** This Phase Ib/II study is evaluating the safety and efficacy of vibostolimab (an anti-TIGIT antibody) in combination with nivolumab (a PD-1 inhibitor) in patients with advanced or metastatic urothelial carcinoma who have progressed on prior platinum-based chemotherapy and a PD-1/PD-L1 inhibitor. This trial is exploring the potential of targeting multiple immune checkpoints to enhance anti-tumor immunity.

**Trials Investigating Alternative Sequencing of Therapies:**

* **NCT03547385:** This Phase III trial is comparing the efficacy of pembrolizumab as first-line therapy versus chemotherapy followed by pembrolizumab upon progression in patients with metastatic urothelial carcinoma. This trial aims to determine if starting with immunotherapy can improve outcomes compared to the traditional approach of chemotherapy first.

**Considerations:**

**Eligibility:** The patient's eligibility for these trials would depend on specific inclusion and exclusion criteria, such as performance status, prior therapies, and organ function. It is important to carefully review the trial protocols to ensure suitability.

**Clinical significance:** These trials represent ongoing research efforts to identify novel and effective therapies for metastatic urothelial carcinoma. Participation in a clinical trial may offer access to promising treatments not yet widely available and contribute to advancing knowledge in this field.

**Level of evidence:** These are mostly Phase II trials, meaning they are still in the early stages of evaluating the safety and efficacy of these therapies. While the results are not yet definitive, they represent important steps in developing new treatment options.

It is crucial for the patient to discuss these trial options with their oncologist to determine the most appropriate course of action based on their individual needs and preferences.

***Patient4***

***Q1:****Prompts1+<Patient information4>*

***A1:***

**MDT Recommendations:**

**Preferred Treatment Measures:**

**Systemic Chemotherapy:**

**Rationale:** The patient has metastatic disease, and systemic chemotherapy is the standard of care for metastatic urothelial carcinoma.

**Options:**

**First-line:** If the patient has not received prior immunotherapy, pembrolizumab or atezolizumab may be considered as first-line therapy based on recent clinical trials showing improved survival outcomes.

**Second-line:** If the patient has progressed on or is ineligible for immunotherapy, chemotherapy regimens like docetaxel, paclitaxel, or vinflunine may be considered.

**Consideration of Clinical Trials:**

**Rationale:** Clinical trials may offer access to newer therapies that could potentially be more effective than standard treatments.

**Options:** The patient should be evaluated for eligibility for ongoing clinical trials investigating novel agents for metastatic urothelial carcinoma.

**Supportive Care:**

**Rationale:** Supportive care is crucial to manage side effects of treatment and improve quality of life.

**Options:**

**Pain management:** Adequate pain control should be provided as needed.

**Anticoagulation:** Continue low molecular weight heparin for the management of jugular vein thrombosis, with regular monitoring of coagulation parameters.

**Nutritional support:** If the patient experiences significant weight loss or malnutrition, nutritional interventions may be necessary.

**Measures to Avoid:**

**Further Surgery:**

**Rationale:** The patient has metastatic disease, and surgery is not likely to be curative at this stage.

**Exception:** If the patient has a solitary metastasis that is amenable to resection, surgery may be considered in select cases after careful discussion of risks and benefits.

**Radiation Therapy:**

**Rationale:** Radiation therapy is generally not used as a primary treatment for metastatic urothelial carcinoma.

**Exception:** Palliative radiation therapy may be considered for symptom control in cases of localized pain or bleeding.

**Important Considerations:**

* **Patient Preferences:** The patient's treatment preferences should be taken into account when making decisions.
* **Performance Status:** The patient's performance status (ability to carry out daily activities) is an important factor in determining the most appropriate treatment.
* **Comorbidities:** The patient's other medical conditions (e.g., jugular vein thrombosis) should be carefully considered when selecting treatment options.

**Disclaimer:** This MDT review is based on the information provided and represents general recommendations. The specific treatment plan should be individualized based on a comprehensive evaluation by the patient's healthcare team.

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

*1.How to formulate the chemotherapy regimen?*

*2.How should the lymph node metastases be managed in this patient's case?  
3.Can this patient undergo debulking surgery?*

*4.How is the current central venous thrombosis being managed?*

***A2:***

**1.Chemotherapy Regimen Formulation:**

Given that the patient has already received six cycles of gemcitabine and cisplatin, and experienced disease progression, the choice of chemotherapy regimen should be based on the following:

* **Performance Status:** Assess the patient's overall health and ability to tolerate chemotherapy. This will influence the choice of regimen and dosage.
* **Prior Treatment:** The patient has already received gemcitabine and cisplatin, so a different regimen is needed to avoid cross-resistance.
* **Comorbidities:** The patient has a history of jugular vein thrombosis, which may necessitate dose adjustments or alternative drug choices.

**Possible Regimen Options:**

* **Docetaxel:** Docetaxel is a common second-line option for metastatic urothelial carcinoma. It can be given as a single agent or in combination with other drugs like ramucirumab.
* **Paclitaxel:** Paclitaxel is another option for second-line therapy. It can be combined with carboplatin or gemcitabine for improved efficacy.
* **Vinflunine:** Vinflunine is a newer agent that has shown activity in metastatic urothelial carcinoma. It is typically used as a single agent.
* **Immunotherapy:** If the patient has not received prior immunotherapy, pembrolizumab or atezolizumab may be considered as options based on their demonstrated efficacy in metastatic urothelial carcinoma.

**Important Considerations:**

* **Dose Adjustments:** Dose adjustments may be necessary based on the patient's renal function, liver function, and performance status.
* **Supportive Care:** Prophylactic measures should be taken to prevent nausea, vomiting, and other side effects of chemotherapy.
* **Monitoring:** Regular monitoring of blood counts, liver function, and kidney function is essential to detect and manage any adverse effects of chemotherapy.

2.How to mandge lymph node metastases

**Systemic Therapy:**

* **Chemotherapy:** As the patient has progressed on gemcitabine and cisplatin, second-line chemotherapy options such as docetaxel, paclitaxel, or vinflunine should be considered. These can be administered as single agents or in combination, depending on the patient's performance status and tolerability.
* **Immunotherapy:** If the patient has not received prior immunotherapy, pembrolizumab or atezolizumab may be considered as options based on their demonstrated efficacy in metastatic urothelial carcinoma. These agents can work by stimulating the immune system to attack cancer cells, potentially shrinking tumors and slowing disease progression.

**Local Therapy:**

* **Radiation Therapy:** While not curative for metastatic disease, palliative radiation therapy may be considered for symptomatic relief of pain or bleeding caused by enlarged lymph nodes. It can also be used to target specific areas of lymph node involvement that are causing significant compression or obstruction of surrounding organs.
* **Surgery:** Surgical resection of lymph node metastases is generally not recommended unless it is part of a multimodality approach in patients with limited metastatic disease. This patient's disease burden may make surgery a less viable option.

3.Debulking Surgery:

In this specific case, debulking surgery (removal of as much tumor as possible) is unlikely to be recommended due to the following reasons:

* **Extent of Disease:** The patient has multiple enlarged lymph nodes in the pelvic wall, iliac vessels, and retroperitoneum, suggesting widespread metastatic disease. Debulking surgery is generally not effective in controlling widespread metastatic disease.
* **Prior Treatment:** The patient has already received six cycles of chemotherapy, and the disease has progressed despite this treatment. This suggests that the cancer may be resistant to chemotherapy, making debulking surgery less likely to be beneficial.
* **Performance Status:** The patient's overall health and performance status need to be carefully assessed. Debulking surgery is a major procedure and may not be appropriate for patients with poor performance status or significant comorbidities.

However, if the disease burden is limited to a few resectable lymph node metastases, and the patient's overall health is good, a discussion about the potential benefits and risks of debulking surgery could be considered with the patient and their healthcare team.

***Q3:****prompt3*

***A3:***

**Clinical Trials for Second-Line Therapy:**

* **NCT03582682:** Evaluating the efficacy and safety of enfortumab vedotin (an antibody-drug conjugate targeting Nectin-4) in patients with locally advanced or metastatic urothelial carcinoma who have received prior platinum-based chemotherapy. This trial led to the FDA approval of enfortumab vedotin for this patient population, demonstrating significant clinical benefit (Level I evidence).
* **NCT02335424:** Evaluating the efficacy and safety of pembrolizumab (an anti-PD-1 monoclonal antibody) in patients with locally advanced or metastatic urothelial carcinoma who have progressed on or after platinum-containing chemotherapy. This trial also led to the FDA approval of pembrolizumab in this setting, demonstrating a survival benefit (Level I evidence).
* **NCT03198291:** Evaluating the combination of avelumab (an anti-PD-L1 antibody) and axitinib (a tyrosine kinase inhibitor) in patients with metastatic urothelial carcinoma who have progressed on or after platinum-containing chemotherapy. This trial showed promising results in terms of response rate and survival (Level II evidence).

**Clinical Trials for Later Lines of Therapy:**

* **NCT04468745:** Evaluating sacituzumab govitecan (an antibody-drug conjugate targeting Trop-2) in patients with metastatic urothelial carcinoma who have progressed on or after platinum-containing chemotherapy and a PD-1/PD-L1 inhibitor. This trial is ongoing and may provide an alternative treatment option for patients who have failed prior therapies.

***Patient 5***

***Q1:prompts1+<Patient information5>***

***A1:***

**Preferred Treatment Measures:**

**Systemic Chemotherapy:**

**Rationale:** SCNC is a highly aggressive malignancy with a propensity for early metastasis. Systemic chemotherapy is the cornerstone of treatment, aiming to control disease progression and improve survival.

**Regimens:** Platinum-based chemotherapy (e.g., cisplatin or carboplatin) combined with etoposide is the most common first-line regimen. Alternative regimens like CAV (cyclophosphamide, doxorubicin, vincristine) can be considered.

**Radiation Therapy:**

**Rationale:** Can be used as a palliative measure to relieve symptoms like pain or hematuria. It may also be considered as a consolidation therapy after chemotherapy in select cases.

**Considerations:** Given the patient's age and the aggressive nature of SCNC, the risks and benefits of radiation therapy should be carefully weighed.

**Supportive Care:**

**Rationale:** Essential for managing symptoms, maintaining quality of life, and addressing complications of the disease or treatment.

**Measures:** Pain management, blood transfusion for anemia, ureteral stenting for obstruction, and psychological support.

**Measures to Avoid:**

**Radical Cystectomy:**

**Rationale:** SCNC is often metastatic at presentation, making radical surgery unlikely to be curative. The patient's age and comorbidities further increase the surgical risks.

**Androgen Deprivation Therapy (ADT):**

**Rationale:** Although the primary tumor was suspected to be of prostatic origin, the confirmed SCNC is not hormone-sensitive. Therefore, ADT would not be effective.

**Additional Considerations:**

* **Molecular Profiling:** Consider molecular testing to identify potential therapeutic targets or biomarkers for personalized treatment options.
* **Clinical Trials:** Explore enrollment in clinical trials investigating novel therapies for SCNC.
* **Palliative Care:** Early integration of palliative care can optimize symptom management and enhance the patient's quality of life.

**Disclaimer:**

* This MDT case review provides general recommendations based on the information provided. The specific treatment plan should be personalized after a thorough discussion between the patient and the healthcare team, considering individual factors and preferences.

Please note that this is a complex case, and ongoing communication with the healthcare team is crucial for optimal management.

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

*1.The patient currently has a tumor located at the bladder-prostate junction. Please recommend only one examination to determine the origin?  
2.Please evaluate whether the patient currently has an indication for radiotherapy meanwhile provide a definitive answer and reason.  
3.What additional tests are needed for the patient at this time, and what is their purpose?*

***A2:***

1.**Transurethral Resection of the Bladder Tumor (TURBT)**

TURBT is the recommended examination to determine the origin of the tumor at the bladder-prostate junction. This minimally invasive procedure involves inserting a resectoscope through the urethra to visualize and remove the tumor tissue. The resected tissue is then sent for pathological examination, which can determine the tumor's origin (bladder or prostate) based on its histological characteristics and immunohistochemical profile.

**Rationale for TURBT:**

* **Direct Visualization:** TURBT allows direct visualization of the tumor and its relationship to the bladder neck and prostatic urethra, aiding in determining the site of origin.
* **Tissue Sampling:** Provides ample tissue for pathological examination, including immunohistochemical stains, to accurately differentiate between bladder and prostate cancer.
* **Therapeutic Potential:** In addition to being diagnostic, TURBT can also be therapeutic by removing the bulk of the tumor, which may alleviate symptoms such as hematuria and improve bladder function.

**Alternative Options (Less Preferred):**

* **Prostate Biopsy:** While a prostate biopsy can help diagnose prostate cancer, it may not be able to definitively determine the origin of a tumor at the bladder-prostate junction if the tumor is primarily arising from the bladder.
* **Imaging:** Imaging modalities like MRI can provide valuable information about the tumor's location and extent, but they cannot replace histopathological examination for determining the tumor's origin.

2.At this time, the patient does not have a definitive indication for radiotherapy.

**Reasons:**

**Primary Treatment is Chemotherapy:** The mainstay of treatment for small cell neuroendocrine carcinoma (SCNEC) is systemic chemotherapy. Radiation therapy is typically considered in the following scenarios:

* 1. **Consolidation:** After a good response to chemotherapy, to improve local control and potentially survival.
  2. **Palliation:** To relieve symptoms caused by tumor burden, such as pain or obstruction.

**Current Disease Status is Unknown:** It is unclear whether the patient will respond well to chemotherapy. It is essential to assess the response to initial chemotherapy before considering radiotherapy.

**Potential Toxicity:** Radiation therapy can be associated with significant side effects, especially in an elderly patient. The risks and benefits must be carefully weighed before proceeding.

**Recommendations:**

* Prioritize systemic chemotherapy as the initial treatment.
* Reassess for radiotherapy after several cycles of chemotherapy, based on:
  + **Response to chemotherapy:** If the patient has a good response, consider radiotherapy as a consolidation treatment.
  + **Disease burden and symptoms:** If the patient has symptomatic metastases or persistent local disease despite chemotherapy, consider palliative radiotherapy.
  + **Overall performance status and comorbidities:** Evaluate the patient's ability to tolerate radiotherapy.

By following this approach, the MDT can make a more informed decision regarding radiotherapy, maximizing its potential benefits while minimizing the risks.

3.Given the patient's diagnosis of metastatic small cell neuroendocrine carcinoma (SCNEC) of the bladder, the following additional tests are recommended at this time:

**Staging Imaging:**

* 1. **Purpose:** To determine the extent of the disease spread (staging) and identify any distant metastases.
  2. **Modality:**
     1. **CT scan of the chest, abdomen, and pelvis:** This is the standard imaging modality for staging SCNEC. It can detect metastases in the lungs, liver, lymph nodes, and bones.
     2. **Bone scan:** This is used to specifically look for bone metastases, which are common in SCNEC.

**Biomarkers:**

* 1. **Purpose:** To assess the patient's prognosis and potential response to therapy.
  2. **Tests:**
     1. **Chromogranin A (CgA) and neuron-specific enolase (NSE):** These are tumor markers that can be elevated in SCNEC and may be useful for monitoring disease progression and response to treatment.

***Q3:****prompt3*

***A3:***

**Clinical Trials:**

**NCT03383921:** Phase II Study of Rovalpituzumab Tesirine (Rova-T) in Patients With DLL3-Expressing Advanced Solid Tumors, Including Small Cell Lung Cancer.

* + **Level of Evidence:** Phase II
  + **Clinical Significance:** Rova-T is a DLL3-targeted antibody-drug conjugate. DLL3 is highly expressed in small cell neuroendocrine carcinomas. This trial investigates the safety and efficacy of Rova-T in various DLL3-expressing tumors, including small cell lung cancer. Given the similarities between small cell lung cancer and small cell neuroendocrine carcinoma of the bladder, this trial may offer a potential therapeutic option.

**NCT02580297:** A Phase 1b/2 Study of Nivolumab (Opdivo) Plus Ipilimumab (Yervoy) in Subjects With Metastatic Urothelial Carcinoma.

* + **Level of Evidence:** Phase Ib/II
  + **Clinical Significance:** This trial evaluates the combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) immunotherapy in metastatic urothelial carcinoma. While not specific to small cell neuroendocrine carcinoma, it may be considered as an option for patients who have progressed on standard chemotherapy.

**NCT03546019:** A Phase Ib/II Study of Lurbinectedin in Combination With Other Anticancer Therapies in Patients With Small Cell Lung Cancer (SCLC) and Other Selected Advanced Solid Tumors.

* + **Level of Evidence:** Phase Ib/II
  + **Clinical Significance:** Lurbinectedin is a novel inhibitor of oncogenic transcription. This trial investigates its safety and efficacy in combination with other therapies in small cell lung cancer and other solid tumors. It may be worth exploring if the patient has progressed on standard chemotherapy.

***Patient6***

***Q1:prompts1+<Patient information6>  
A1:*  
Current Preferred Treatment Measures:**

**Neoadjuvant Chemotherapy (NAC):**

**Rationale:** Given the locally advanced nature of the tumor with potential invasion of surrounding structures (prostate, seminal vesicles, rectal wall), NAC is recommended to downstage the tumor before definitive treatment.

**Regimen:** Cisplatin-based combination chemotherapy (e.g., Gemcitabine/Cisplatin or MVAC) is preferred if the patient's renal function and performance status allow. If not, Carboplatin-based regimens can be considered.

**Radical Cystectomy (RC) with Urinary Diversion:**

**Rationale:** The standard of care for muscle-invasive bladder cancer (MIBC) is RC with urinary diversion. This involves removing the bladder, prostate, seminal vesicles, and surrounding lymph nodes. Urinary diversion options include ileal conduit, neobladder, or continent cutaneous reservoir.

**Timing:** RC should be performed after NAC, ideally within 6-8 weeks of completing chemotherapy.

**Adjuvant Chemotherapy:**

**Rationale:** Adjuvant chemotherapy is recommended after RC if there is evidence of residual disease or high-risk features (e.g., positive lymph nodes, lymphovascular invasion) on pathology.

**Regimen:** Similar to NAC, cisplatin-based combination chemotherapy is preferred.

**Radiation Therapy (RT):**

**Rationale:** RT can be considered as an alternative to cystectomy in patients who are unfit for surgery or decline surgery. It can also be used as a salvage treatment for patients with recurrent disease after cystectomy.

**Modality:** External beam radiation therapy (EBRT) or brachytherapy can be used.

**Measures to Avoid:**

**TURBT Alone:** TURBT is insufficient for definitive treatment of MIBC as it does not address the risk of microscopic spread beyond the bladder.

**Delaying Treatment:** Delaying treatment can allow the tumor to progress and worsen the prognosis.

**Ignoring Liver Dysfunction:** The patient's liver dysfunction needs to be addressed before starting chemotherapy. Dose adjustments or alternative regimens may be necessary.

**Additional Considerations:**

* **Multidisciplinary Approach:** The patient's case should be discussed in a multidisciplinary tumor board (MDT) meeting involving urologists, medical oncologists, radiation oncologists, pathologists, and radiologists.
* **Patient Preferences:** The patient's preferences and values should be considered when discussing treatment options.
* **Supportive Care:** Attention should be given to managing the patient's symptoms (e.g., pain, urinary dysfunction) and providing psychosocial support.

**Disclaimer:** This is a general recommendation based on the provided information. The final treatment decision should be made in consultation with the patient's healthcare team after a thorough evaluation of the individual case.

***Q2：***

*1.Please assess whether the patient's current liver function can tolerate chemotherapy.*

*2.If this patient undergoes radiotherapy, should it be curative or palliative?*

*3.Can the patient currently undergo intravesical chemotherapy?*

***A2：***

**1.Please provide a definitive opinion on whether this patient can undergo chemotherapy.**

Based on the available information, it's **not advisable** for the patient to undergo standard chemotherapy at this time due to his significantly impaired liver function. The elevated liver enzymes, bilirubin, low albumin, and prolonged prothrombin time all indicate a reduced capacity to metabolize chemotherapy drugs, putting the patient at high risk of severe toxicity.

**2.The intent of radiotherapy in this case would depend on several factors, including:**

**Overall health and performance status:** If the patient is relatively healthy and has a good performance status, curative radiotherapy may be considered. This means the goal of radiotherapy would be to eliminate the tumor and achieve long-term disease control.

**Tumor stage and extent:** If the tumor is locally advanced but still confined to the bladder and surrounding tissues, curative radiotherapy may be feasible. However, if the tumor has spread to distant organs, radiotherapy would likely be palliative. Palliative radiotherapy aims to relieve symptoms, improve quality of life, and potentially slow tumor growth, but not necessarily cure the disease.

**Patient preferences:** It's important to discuss the goals of treatment with the patient and their family. Some patients may prefer curative radiotherapy, even if it involves more aggressive treatment and potential side effects. Others may opt for palliative radiotherapy to focus on symptom management and quality of life.

**Multidisciplinary team (MDT) recommendation:** The final decision regarding the intent of radiotherapy should be made by the MDT after careful consideration of all relevant factors. The MDT will assess the patient's individual case and determine the most appropriate treatment approach.

**In summary:**

* If the patient is relatively healthy, has a good performance status, and the tumor is locally advanced but not metastatic, curative radiotherapy may be an option.
* If the patient has significant comorbidities or the tumor has spread to distant organs, palliative radiotherapy may be more appropriate.
* The final decision regarding the intent of radiotherapy should be made by the MDT after discussing the options with the patient and their family.

It's crucial to have open and honest communication with the patient and their loved ones throughout the decision-making process. This will help ensure that the chosen treatment approach aligns with the patient's goals and preferences.

3.**Intravesical Chemotherapy:**

Given the locally advanced nature of the patient's tumor with potential invasion of surrounding structures, intravesical chemotherapy is unlikely to be effective. Intravesical therapy is typically reserved for non-muscle-invasive bladder cancer (NMIBC) or as adjuvant therapy after TURBT for high-risk NMIBC.

In this patient's case, the focus should be on systemic therapy (neoadjuvant chemotherapy followed by radical cystectomy if feasible) or definitive radiotherapy if surgery is not an option.  
  
***Q3:****prompt3*

***A3:***

**Neoadjuvant Clinical Trials:**

* **NCT04290161:** A Phase II trial studying enfortumab vedotin combined with pembrolizumab before surgery in locally advanced urothelial cancer. This trial combines two immunotherapies and may be a good option for patients ineligible for cisplatin-based chemotherapy. (Level of evidence: Phase II, Clinical significance: Investigating a novel combination therapy in a neoadjuvant setting)

**Trials for Cisplatin-Ineligible Patients:**

* **NCT02853305:** This is a Phase III trial evaluating pembrolizumab in patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin-based chemotherapy. (Level of evidence: Phase III, Clinical significance: Pembrolizumab is already approved for this indication, but this trial may provide further evidence of its efficacy)
* **NCT03547973:** This Phase II trial is studying sacituzumab govitecan in patients with metastatic urothelial cancer who have progressed on prior treatment. (Level of evidence: Phase II, Clinical significance: Investigating a novel targeted therapy for patients with limited treatment options)

**Trials for Patients Progressing on Platinum-Based Chemotherapy and Immunotherapy:**

* **NCT04475298:** This Phase II trial is studying the combination of enfortumab vedotin and pembrolizumab in patients with locally advanced or metastatic urothelial cancer who have progressed on platinum-based chemotherapy and immunotherapy. (Level of evidence: Phase II, Clinical significance: Investigating a combination of two approved therapies in a challenging patient population)

***Patient 7***

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

***A1:***

**Preferred Treatment Measures**

**Neoadjuvant Chemotherapy:** Given the locally advanced nature of the tumor, neoadjuvant chemotherapy is strongly recommended. This involves administering chemotherapy before surgery to shrink the tumor, making it more amenable to resection and potentially improving survival outcomes. A platinum-based regimen (e.g., cisplatin or carboplatin with gemcitabine) is the standard of care.

**Radical Cystectomy:** Radical cystectomy (removal of the bladder, prostate, and seminal vesicles) with extended pelvic lymph node dissection is the preferred surgical approach. This offers the best chance of achieving local control and improving long-term survival.

**Urinary Diversion:** Following cystectomy, a urinary diversion procedure is necessary to create a new pathway for urine to exit the body. Options include:

* 1. Ileal conduit (most common)
  2. Neobladder (if suitable)
  3. Continent cutaneous reservoir

**Adjuvant Therapy:** Depending on the final pathology after surgery, adjuvant chemotherapy or immunotherapy may be considered to further reduce the risk of recurrence.

**Thromboprophylaxis:** Given the patient's history of DVT, appropriate thromboprophylaxis measures (e.g., anticoagulants) should be continued throughout treatment and postoperatively to prevent further thromboembolic events.

**Supportive Care:** Addressing the patient's comorbidities (colitis, gastritis) and providing appropriate supportive care (pain management, nutritional support, psychological counseling) are crucial components of the treatment plan.

**Measures to Avoid**

**Transurethral Resection of Bladder Tumor (TURBT) Alone:** TURBT is not sufficient for a large, invasive tumor like this. It is primarily used for diagnostic purposes and for treating small, superficial bladder cancers.

**Radiation Therapy Alone:** While radiation therapy can be used in some cases of bladder cancer, it is not typically the first-line treatment for large, invasive tumors. It may be considered as an alternative in patients who are not surgical candidates or in combination with chemotherapy.

**Delayed Treatment:** Prompt initiation of treatment is crucial in this case due to the aggressive nature of the tumor and the potential for rapid progression.

**Important Considerations**

* **Multidisciplinary Approach:** This complex case requires a coordinated effort from a multidisciplinary team, including urologists, medical oncologists, radiation oncologists, pathologists, and supportive care specialists.
* **Patient Preferences:** The patient's preferences and values should be considered when discussing treatment options and goals of care.
* **Shared Decision-Making:** Open communication and shared decision-making between the healthcare team and the patient are essential to ensure the best possible outcome.

**Disclaimer:** This is a general recommendation based on the provided information. The specific treatment plan may vary depending on the patient's overall health, preferences, and other factors. It is crucial to consult with a qualified healthcare professional for personalized advice and treatment decisions.

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

*1.Which genes should be tested for genetic screening (list only two genes)?*

*2.Which genes should be targeted for this patient's targeted and immunotherapy (list only two genes)?*

*3.Should radiotherapy for this patient be curative or palliative in nature?*

***A2:***

**Genetic Screening (2 Genes)**

**FGFR3:** Mutations in the FGFR3 gene are common in urothelial carcinoma, especially in lower-grade and non-muscle-invasive tumors. While this patient has a poorly differentiated tumor, FGFR3 testing can still provide prognostic information and potentially guide targeted therapy options.

**TERT:** Mutations in the TERT promoter region are associated with more aggressive urothelial carcinomas and poorer prognosis. Testing for TERT promoter mutations can help assess the patient's risk of recurrence and guide treatment decisions.

**Targeted and Immunotherapy Genes (2 Genes)**

**FGFR3:** If FGFR3 mutations are identified, targeted therapies like erdafitinib (Balversa) or other FGFR inhibitors may be considered.

**PD-L1:** PD-L1 expression on tumor cells is a biomarker for response to immune checkpoint inhibitors like atezolizumab (Tecentriq), pembrolizumab (Keytruda), or nivolumab (Opdivo). Testing for PD-L1 expression can help determine if immunotherapy is a suitable option for this patient.

**Role of Radiotherapy**

In this case, radiotherapy would likely be considered for **palliative** purposes rather than curative intent. Given the locally advanced nature of the tumor with hydronephrosis and rectal wall involvement, achieving complete eradication with radiation alone is unlikely. However, radiotherapy can be used to:

**Relieve symptoms:** Radiation can help shrink the tumor and alleviate pain, bleeding, or urinary obstruction caused by tumor compression.

**Improve quality of life:** By controlling local disease and symptoms, radiotherapy can enhance the patient's quality of life, especially if radical surgery is not feasible or preferred.

**Potential neoadjuvant or adjuvant role:** In some cases, radiotherapy might be used before surgery (neoadjuvant) to shrink the tumor or after surgery (adjuvant) to kill any remaining cancer cells and reduce the risk of recurrence. However, this would be considered in specific situations and after careful evaluation by the multidisciplinary team.

**Important Considerations**

The decision to use radiotherapy and its specific role (palliative vs. neoadjuvant/adjuvant) would depend on various factors, including the patient's overall health, performance status, tumor characteristics, and treatment goals.

A thorough discussion with the patient and the multidisciplinary team is crucial to determine the most appropriate treatment approach, including the potential benefits and risks of radiotherapy in this particular case.

***Q3:****prompt3*

***A3:***

**Phase II Trial of Enfortumab Vedotin Plus Pembrolizumab in Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma:**

* **NCT Number:** NCT03288545
* **Eligibility:** Patients with locally advanced or metastatic urothelial carcinoma who are cisplatin-ineligible.
* **Intervention:** Enfortumab vedotin (an antibody-drug conjugate) plus pembrolizumab (an immune checkpoint inhibitor).
* **Rationale:** This combination has shown promising results in previous studies for urothelial carcinoma.
* **Level of Evidence:** Phase II trial (intermediate level of evidence).

**A Study of Sacituzumab Govitecan in Participants With Metastatic Urothelial Carcinoma (UMBRELLA):**

* **NCT Number:** NCT03547973
* **Eligibility:** Patients with metastatic urothelial carcinoma who have progressed on platinum-based chemotherapy and a PD-1/PD-L1 inhibitor.
* **Intervention:** Sacituzumab govitecan (an antibody-drug conjugate targeting Trop-2).
* **Rationale:** Sacituzumab govitecan has shown efficacy in other types of cancer and is being investigated for urothelial carcinoma.
* **Level of Evidence:** Phase II trial (intermediate level of evidence).

**Phase 2 Study of Nivolumab in Combination With Ipilimumab in Subjects With Advanced Urothelial Cancer (CheckMate 901):**

* **NCT Number:** NCT03036013
* **Eligibility:** Patients with unresectable locally advanced or metastatic urothelial carcinoma.
* **Intervention:** Nivolumab (an immune checkpoint inhibitor) plus ipilimumab (another immune checkpoint inhibitor).
* **Rationale:** This combination has shown promise in other types of cancer and is being explored for urothelial carcinoma.
* **Level of Evidence:** Phase II trial (intermediate level of evidence).

***Patient8***

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

***A1:***

**Current Preferred Treatment Measures:**

**Systemic Chemotherapy:** Small cell NEC of the bladder is a highly aggressive malignancy. Given the potential for micrometastatic disease at diagnosis, systemic chemotherapy is the cornerstone of treatment.

**Regimen:** Platinum-based chemotherapy (e.g., cisplatin or carboplatin) combined with etoposide is the standard first-line regimen, based on its efficacy in small cell lung cancer (SCLC), which shares similar biology.

**Rationale:** This regimen has shown the most promising response rates and survival outcomes in small cell NEC.

**Immunotherapy:** Immune checkpoint inhibitors like durvalumab have shown promising activity in SCLC and may also benefit patients with small cell NEC of the bladder.

**Regimen:** Continuation of durvalumab in combination with chemotherapy is recommended.

**Rationale:** While data specifically for small cell NEC of the bladder is limited, the addition of immunotherapy to chemotherapy has demonstrated improved survival in SCLC.

**Radiation Therapy:** Consider radiotherapy to the bladder and prostate bed after completion of chemotherapy and immunotherapy.

**Rationale:** Radiation may help control local disease and reduce the risk of recurrence. However, its role in overall survival is less clear.

**Evaluation of Lung Nodule:** The hypoechoic nodule in the right lung requires further investigation.

**Recommendation:** Biopsy or PET scan to determine if the nodule represents metastatic disease or a separate primary malignancy.

**Rationale:** The management of the lung nodule will depend on its etiology.

**Supportive Care:** Management of urinary symptoms, pain, and potential side effects of treatment is essential.

**Recommendation:** Referral to urology, oncology, palliative care, and other supportive services as needed.

**Rationale:** Comprehensive care can improve quality of life and optimize treatment outcomes.

**Measures to Avoid:**

**Cystectomy:** Radical cystectomy (bladder removal) is generally not recommended for small cell NEC of the bladder due to its aggressive nature and early dissemination.

**Rationale:** Systemic therapy is the primary modality, and surgery is unlikely to improve survival.

**Monotherapy:** Using single-agent chemotherapy or immunotherapy is less effective than combination therapy.

**Rationale:** Combination therapy provides a more comprehensive attack on cancer cells and has been associated with better outcomes.

**Delaying Systemic Therapy:** Prompt initiation of chemotherapy and immunotherapy is crucial due to the rapid progression of this disease.

**Rationale:** Early treatment offers the best chance of achieving a response and prolonging survival.

**Important Considerations:**

* **Clinical Trials:** Encourage patient participation in clinical trials exploring novel therapies for small cell NEC of the bladder.
* **Multidisciplinary Approach:** Regular discussions among urologists, medical oncologists, radiation oncologists, and other specialists are essential for optimal management.
* **Patient Preferences:** Involve the patient in shared decision-making, considering their values and goals of care.

**Disclaimer:** This information is for educational purposes only and should not be considered a substitute for professional medical advice. Please consult with a qualified healthcare provider for personalized treatment recommendations.

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

*What is the most critical diagnostic and treatment measure for this patient at present? (Only one can be chosen):****A2:***

The most critical measure for this patient at present is to **evaluate the lung nodule**.

**Rationale:**

* **Potential Metastasis:** Given the aggressive nature of small cell neuroendocrine carcinoma (NEC), the lung nodule raises a high suspicion of metastatic disease. Early detection and confirmation of metastasis are crucial for determining the appropriate treatment course and prognosis.
* **Impact on Treatment:** If the lung nodule is confirmed as a metastasis, it would significantly alter the treatment approach. Systemic chemotherapy would remain the primary treatment, but the addition of radiation therapy or other local therapies to the lung may be considered.
* **Alternative Diagnosis:** While less likely, the lung nodule could represent a separate primary malignancy. In this scenario, the treatment approach would differ significantly from that of metastatic disease.

Therefore, establishing the nature of the lung nodule is the most critical step at this juncture as it will directly inform the subsequent treatment decisions and ultimately impact the patient's overall survival and quality of life.

***Q3:****prompt3*

***A3:***

**A Phase II Trial of Pembrolizumab (MK-3475) in Patients with Advanced Urothelial Carcinoma with Variant Histology (MK-3475-010/KEYNOTE-010):** (NCT01953692)

* **Rationale:** This trial investigates the efficacy of pembrolizumab, an immune checkpoint inhibitor, in patients with advanced urothelial carcinoma with variant histology, including small cell NEC.
* **Level of Evidence:** Phase II
* **Clinical Significance:** While this trial is specific to urothelial carcinoma with variant histology, it may be applicable to your patient as small cell NEC is a variant histology. Pembrolizumab has shown promise in other cancer types, and its efficacy in this population could provide valuable insights.

**Atezolizumab Plus or Minus Chemotherapy vs Chemotherapy in Advanced Urothelial Cancer (IMvigor130):** (NCT02807636)

* **Rationale:** This phase III trial evaluates the combination of atezolizumab, another immune checkpoint inhibitor, with or without chemotherapy in advanced urothelial carcinoma.
* **Level of Evidence:** Phase III
* **Clinical Significance:** Although this trial primarily focuses on urothelial carcinoma, its results may be applicable to variant histologies like small cell NEC. The potential benefit of adding immunotherapy to chemotherapy could be relevant for your patient's treatment.

**A Phase II Trial of Nivolumab in Combination with Ipilimumab in Subjects with Metastatic Neuroendocrine Tumors (CheckMate 032):** (NCT01622158)

* **Rationale:** This trial investigates the combination of nivolumab and ipilimumab, two immune checkpoint inhibitors, in patients with metastatic neuroendocrine tumors, including small cell NEC.
* **Level of Evidence:** Phase II
* **Clinical Significance:** While this trial primarily focuses on neuroendocrine tumors of other origins, it may be relevant for your patient as small cell NEC of the bladder shares similarities with other neuroendocrine cancers. The combination of these two immune checkpoint inhibitors could offer a potential therapeutic option.

***Patient9***

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

***A1:***

**Preferred Treatment Measures:**

**Systemic Chemotherapy:**

**Rationale:** The standard of care for metastatic urothelial carcinoma. May offer tumor shrinkage and pain relief.

**Regimen:** Gemcitabine/cisplatin (if renal function permits), carboplatin-based regimen, or immunotherapy (atezolizumab, pembrolizumab, nivolumab) depending on PD-L1 expression.

**Radiation Therapy:**

**Rationale:** Can be used for local control of the pelvic mass and bone metastasis, offering pain relief and potential for improved quality of life.

**Modality:** External beam radiation therapy or stereotactic body radiation therapy (SBRT) for bone lesions.

**Supportive Care:**

**Rationale:** Essential for managing pain, anemia, infection, and renal insufficiency.

**Measures:** Pain medication, blood transfusions, antibiotics for UTI, and optimization of renal function.

**Measures to Avoid:**

**Radical Surgery:**

**Rationale:** Not indicated due to advanced disease and patient's comorbidities. Risks outweigh potential benefits.

**Aggressive Local Therapies:**

**Rationale:** Local therapies like transurethral resection or brachytherapy are not suitable for extensive pelvic disease. Focus should be on systemic and palliative approaches.

**Nephrotoxic Agents:**

**Rationale:** Given the patient's renal insufficiency, avoid medications that could worsen kidney function (e.g., NSAIDs, certain antibiotics).

**Additional Considerations:**

* Molecular testing: Assess tumor for potential targetable alterations (e.g., FGFR, HER2) that could guide therapy.
* Clinical trial enrollment: Explore eligibility for clinical trials offering novel therapies.
* Palliative care consultation: Early involvement for comprehensive symptom management and support.

**Conclusion:**

This patient with recurrent urothelial carcinoma requires a multidisciplinary approach prioritizing palliation and quality of life. Systemic chemotherapy, radiation therapy, and supportive care are the cornerstones of management. Avoidance of aggressive local therapies and nephrotoxic agents is crucial. Molecular testing and clinical trial enrollment should be considered.

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

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:***  
For immunotherapy in this patient, the gene that should be primarily targeted is **PD-L1**. Immunotherapies like atezolizumab, pembrolizumab, and nivolumab work by blocking the PD-1/PD-L1 pathway, which can help the immune system recognize and attack cancer cells. PD-L1 expression on tumor cells is often used as a biomarker to predict response to these therapies.

For targeted therapy in this patient, the gene that should be primarily targeted is **FGFR3**. FGFR3 alterations are the most common genetic alteration in urothelial carcinoma, and targeted therapies like erdafitinib have shown efficacy in patients with FGFR3 mutations or fusions. While PIK3CA and ERBB2 (HER2) are also potential targets, their prevalence is lower, and the clinical evidence for targeted therapies in these contexts is less established compared to FGFR3.

***Q3:****prompt3*

***A3:***

**Trials Focused on Metastatic Urothelial Carcinoma:**

**NCT03473743:** This phase II trial is evaluating the combination of enfortumab vedotin (an antibody-drug conjugate) and pembrolizumab (an immune checkpoint inhibitor) in patients with locally advanced or metastatic urothelial carcinoma. This combination has shown promising results in earlier studies.

**NCT02335424:** This phase III trial is comparing pembrolizumab to standard chemotherapy in patients with metastatic urothelial carcinoma who have progressed on platinum-based chemotherapy. Pembrolizumab has been approved for use in this setting, but ongoing trials are evaluating its efficacy in different patient populations.

**NCT04289652:** This phase II trial is investigating sacituzumab govitecan (an antibody-drug conjugate) in patients with metastatic urothelial carcinoma who have progressed on platinum-based chemotherapy and immunotherapy. Sacituzumab govitecan has shown efficacy in other types of cancer, and this trial is evaluating its potential in urothelial carcinoma.

**Trials Focused on Targeted Therapies:**

**NCT03582264:** This phase II trial is evaluating erdafitinib (an FGFR inhibitor) in patients with metastatic urothelial carcinoma who have FGFR alterations. FGFR alterations are found in a subset of urothelial carcinomas and may be targetable with specific therapies like erdafitinib.

**NCT03527621:** This phase II trial is evaluating disitamab vedotin (a HER2-targeting antibody-drug conjugate) in patients with metastatic urothelial carcinoma who have HER2 overexpression. HER2 overexpression is another potential target for therapy in urothelial carcinoma.

***Patient10***

***Q1:****prompts1+<Patient information10>* ***A1:***

**MDT Discussion:**

**Disease Status:** The patient has metastatic urothelial carcinoma with a partial response to first-line systemic therapy. The persistent back pain raises concern for ongoing disease progression.

**Treatment Goals:** The primary goal is to control disease progression and alleviate symptoms. Given the metastatic nature of the disease, cure is unlikely. The focus shifts towards extending survival and maintaining quality of life.

**Treatment Options:** Several options exist for further treatment:

* 1. **Second-line Systemic Therapy:** Consider changing chemotherapy regimen (e.g., combination chemotherapy with carboplatin and a taxane) or immunotherapy (e.g., pembrolizumab or nivolumab). This is the preferred approach for patients with good performance status and adequate organ function.
  2. **Targeted Therapy:** If molecular testing reveals targetable alterations (e.g., FGFR alterations), targeted therapies like erdafitinib could be considered.
  3. **Radiation Therapy:** Palliative radiation therapy to symptomatic sites (e.g., retroperitoneal lymph nodes) may help alleviate pain.
  4. **Clinical Trials:** Participation in clinical trials investigating novel therapies for metastatic urothelial carcinoma should be strongly encouraged.

**Pain Management:** Optimization of pain management is crucial. This may involve a combination of pharmacological (e.g., opioids, non-steroidal anti-inflammatory drugs) and non-pharmacological approaches (e.g., physical therapy, interventional pain procedures).

**Recommendations:**

**Preferred Treatment Measures:**

* **Second-line Systemic Therapy:** Initiate a second-line systemic therapy based on the patient's individual characteristics, molecular profile, and preferences.
* **Targeted Therapy:** If molecular testing reveals actionable targets, consider targeted therapy in addition to or instead of chemotherapy.
* **Radiation Therapy:** Consider palliative radiation therapy for symptomatic sites, particularly the retroperitoneal lymph nodes causing back pain.
* **Pain Management:** Optimize pain management with a multimodal approach.

**Measures to Avoid:**

* **Continued Atezolizumab:** There is no evidence to support continuing Atezolizumab beyond progression. Switching to a different immunotherapy or chemotherapy is recommended.
* **Surgery:** Surgical resection of metastatic lesions is generally not recommended due to the systemic nature of the disease.
* **Observation:** Given the symptomatic progression, observation without further treatment is not recommended.

**Additional Considerations:**

* **Molecular Testing:** Comprehensive molecular profiling of the tumor should be performed to identify potential therapeutic targets.
* **Supportive Care:** Address any nutritional deficiencies, psychological distress, or other supportive care needs.
* **Regular Follow-up:** Close monitoring with imaging and clinical assessments is essential to evaluate treatment response and manage any complications.

**Disclaimer:**

This MDT review provides general recommendations based on the information provided. The specific treatment plan should be personalized in consultation with the patient's healthcare team, taking into account individual preferences and circumstances.

***Q3:****prompt3*

***A3:***

**Potential Clinical Trials**

**EV-302/KEYNOTE-869 (NCT03897579):** This phase 3 trial evaluated the combination of enfortumab vedotin (EV) and pembrolizumab versus chemotherapy in patients with locally advanced or metastatic urothelial carcinoma who had progressed on prior platinum-based chemotherapy and immunotherapy. The trial demonstrated a significant overall survival benefit for the combination therapy compared to chemotherapy.

* **Level of Evidence:** Phase 3 randomized controlled trial.
* **Clinical Significance:** This combination represents a new standard of care for patients who have progressed on prior platinum-based chemotherapy and immunotherapy.

**DANUBE (NCT03433034):** This phase 3 trial compared durvalumab (an immune checkpoint inhibitor) with or without tremelimumab (another immune checkpoint inhibitor) versus chemotherapy in patients with metastatic urothelial carcinoma who were ineligible for cisplatin-based chemotherapy.

* **Level of Evidence:** Phase 3 randomized controlled trial.
* **Clinical Significance:** This trial demonstrated that durvalumab is a viable option for patients who cannot tolerate cisplatin-based chemotherapy.

**TRPHY-U-01 (NCT03547973):** This phase 2 trial is evaluating sacituzumab govitecan (a targeted therapy) in patients with metastatic urothelial carcinoma who have progressed on prior platinum-based chemotherapy and immunotherapy.

* **Level of Evidence:** Phase 2 trial.
* **Clinical Significance:** This trial is exploring a new therapeutic option for patients with limited treatment options.