Important Advances in the Treatment of Bladder Cancer

Integrating Targeted Strategies to Address Previously Unmet Clinical Needs
Faculty Information

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Assistant Professor of Pharmacy, Mayo Clinic
College of Medicine
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Educational Objectives for Pharmacists, Nurses, and Physicians

After completion of this activity, participants will be able to:

• Identify potential biomarkers to optimize selection of patients with bladder cancer eligible for immune checkpoint inhibitors or targeted agents

• Document the benefits and limitations of current guideline-based treatments for bladder cancer and their use in patients to appropriately incorporate agents

• Utilize recent and emerging data to select immune checkpoint inhibitor regimens appropriate for patients with bladder cancer
Educational Objectives for Pharmacy Technicians

After completion of this activity, participants will be able to:

• Discuss the rationale for use of biomarkers in the selection of therapy for patients with bladder cancer
• Recognize current guideline-based treatments for bladder cancer
• Review place in therapy for immune checkpoint inhibitors in bladder cancer
Urothelial Carcinoma (UC) Epidemiology

- 83,730 new cases and 17,200 deaths in 2021
  - Diagnosis median age: 73
  - Death median age: 79
  - Rare in <40 years
- 4th most common cancer in men, and men are 4 x more likely than women to be diagnosed with the disease
- Majority of cases in situ or localized at diagnosis, but prognosis is not good for those diagnosed with regional or metastatic disease

### Percent of Cases by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Situ</td>
<td>95.8%</td>
</tr>
<tr>
<td>Localized</td>
<td>69.2%</td>
</tr>
<tr>
<td>Regional</td>
<td>36.5%</td>
</tr>
<tr>
<td>Distant</td>
<td>5.5%</td>
</tr>
<tr>
<td>Unknown</td>
<td>47.9%</td>
</tr>
</tbody>
</table>

### 5-Year Relative Survival

- In Situ: 95.8%
- Localized: 69.2%
- Regional: 36.5%
- Distant: 5.5%
- Unknown: 47.9%

Urothelial Cancer Risk Factors and Presentation

• Risk Factors
  • Cigarette smoking
  • Workplace exposures
  • Bladder inflammation
  • Race
  • Sex
  • Diabetes and obesity
  • Family history

• Clinical Presentation
  • Microscopic or gross hematuria
  • Irritation while voiding
  • Advanced disease: pain or renal obstruction

• Clinical Spectrum of Disease
  • Non-muscle invasive disease
  • Muscle-invasive disease
  • Metastatic lesions

UC Staging and Management

TNM Staging System

Ta, T1, Tis: non-muscle invasive disease

T2: malignant extension into detrusor muscle

T3: perivesical tissue involvement

T4: Extravesical invasion into surrounding tissue

Goals for Therapy:

Non-muscle invasive disease (Ta, T1, Tis): Reduce recurrence and prevent progression

Muscle invasive (>T2): Determine if bladder should be removed and if primary lesion can be managed or if patient should be treated systemically

Metastatic (T4): Prolong quantity and maintain quality of life

UC Immunology

• Immunogenicity
  • High degree of mutational heterogeneity
  • High frequency of somatic mutations compared with other solid tumors
  • Pathways and driver genes:
    • Immune checkpoints
    • IDO
    • FGFR3
    • ERBB2
    • PI3KCA
    • TP53
    • STAG2
    • Tyrosine kinase
    • Histone deacetylase
    • CD30 expression

• Next generation of therapies likely to be based on patient-specific targetable mutations

Current Treatment Options for Bladder Cancer

Integrating Targeted Strategies to Address Previously Unmet Clinical Needs
Bladder Cancer: Treatment Overview

MIBC

Metastatic disease

Neoadjuvant cisplatin-based chemotherapy → cystectomy

ddMVAC, dose-dense methotrexate/vinblastine/doxorubicin/cisplatin.


1st line

Cisplatin eligible: Gem/cis, ddMVAC
Cisplatin ineligible: Gem/carbo; pembrolizumab or atezolizumab (if PD-L1+)

2nd line (post-platinum chemo)

IO: Pembrolizumab (category 1), nivolumab, avelumab
Targeted therapy: Erdafitinib (FGFR+)

Subsequent line (post-platinum CT and IO)

Enfortumab vedotin (category 1)
Sacituzumab govitecan
Erdafitinib (FGFR+)

Maintenance

Avelumab (post-platinum chemo only) (category 1)
Muscle Invasive UC (T2, T3, T4a, T4b)

- Goal: Cure, disease control, prevent metastasis
- TURBT (must include muscle sampling)
  - Generally diagnostic unless bladder sparing approach

### Initial therapy
- Cystectomy + PLND
- Bladder preservation
  - Neoadjuvant vs adjuvant chemotherapy
  - Chemoradiation

### Recurrent disease
- Checkpoint inhibitors
- Chemotherapy
- Chemoradiation

PLND, pelvic lymph node dissection.

Neoadjuvant Chemotherapy

• Cisplatin-based, generally 3 cycles
• Meta-analysis of 11 trials of 3005 patients who received cisplatin-based multiagent neoadjuvant therapy
  • OS = 5% absolute improvement
  • Disease-free survival (DFS) = 9% absolute improvement
• SWOG trial of 307 patients compared neoadjuvant MVAC followed by RC vs RC alone
  • Median survival 77 mo vs 46 mo ($P = 0.06$) and lowered rate of residual disease (15% vs 38%, $P <0.001$)
• ddMVAC (dose-dense methotrexate, vinblastine, doxorubicin, cisplatin)
  • 2 single-arm phase 2 studies comparing ddMVAC to historical results with MVAC
  • Median time to cystectomy: 9.7 weeks
  • Toxicity: grade 1-2, 82%, grade 3-4, equal
  • Pathologic downstaging, 49%
• CMV (cisplatin, methotrexate, vinblastine) followed by RC vs RC alone
  • CMV: 16% reduction in mortality risk (HR, 0.84; 95% CI, 0.72-0.99; $P = 0.037$)

Bladder Cancer: Treatment Overview

Bladder Cancer

- **MIBC**
- **Metastatic disease**

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- **Cisplatin eligible:** Gem/cis, ddMVAC
- **Cisplatin ineligible:** Gem/carbo; pembrolizumab or atezolizumab (*if PD-L1+*)

2nd line (post-platinum chemo)
- IO: Pembrolizumab (category 1), nivolumab, avelumab
- Targeted therapy: Erdafitinib (*FGFR+*)

Subsequent line (post-platinum CT and IO)
- Enfortumab vedotin (category 1)
- Sacituzumab govitecan
- Erdafitinib (*FGFR+*)

Maintenance
- Avelumab (post-platinum chemo only) (category 1)


#NCODAForum21
FDA Approval Is Not a “Home Run”

- May 18, 2016–May 18, 2017: 5 immuno-oncology options approved for advanced bladder cancer within 1 year
- June 19, 2018 – Keynote 361, IMvigor 130
  - FDA limits the use of atezolizumab and pembrolizumab for patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing therapy
- February 22, 2021 – DANUBE
  - AstraZeneca has voluntarily withdrawn the FDA indication for the PD-L1 inhibitor durvalumab for use in previously treated patients with locally advanced or metastatic bladder cancer
- March 8, 2021 – IMvigor211
  - Roche (Genentech) has voluntarily withdrawn the FDA indication for the PD-L1 inhibitor atezolizumab for use in patients with locally advanced or metastatic urothelial carcinoma previously treated with platinum-based chemotherapy

Initial Treatment Selection for mUC

Eligible for cisplatin-based chemotherapy

Yes
- Gemcitabine and cisplatin (category 1)
- ddMVAC + GCSF (category 1)

No
- Gemcitabine and carboplatin
- Gemcitabine
- Gemcitabine and paclitaxel
- Pembrolizumab*
- Atezolizumab*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Survival</th>
<th>Response Rates</th>
<th>Deaths (Toxicity)</th>
<th>Neutropenic Sepsis*</th>
<th>Mucositis (Grade 3/4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine/Cisplatin</td>
<td>13.8 months</td>
<td>49.4%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>MVAC</td>
<td>14.8 months</td>
<td>45.7%</td>
<td>3%</td>
<td>12%</td>
<td>22%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CR</th>
<th>Overall Response</th>
<th>Median Survival</th>
<th>TTP</th>
<th>FN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ddMVAC</td>
<td>21%</td>
<td>62%</td>
<td>15.5 months</td>
<td>11.1 months</td>
<td>10%</td>
</tr>
<tr>
<td>MVAC</td>
<td>9%</td>
<td>50%</td>
<td>14.1 months</td>
<td>9.6 months</td>
<td>26%</td>
</tr>
</tbody>
</table>

mUC: First-Line Maintenance Immunotherapy

- JAVELIN Bladder 100: Ph 3, open-label trial
- N = 700
- Maintenance avelumab/best supportive care vs best supportive care
  - CR/PR/SD to platinum/gemcitabine x 4-6 cycles
- Avelumab 10 mg/kg IV D1 and D15 q28 days until progression/unacceptable toxicity
  - Premeds for cycles 1-4: antihistamine + acetaminophen

<table>
<thead>
<tr>
<th></th>
<th>Avelumab vs BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (mo)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>21.4 vs 14.3</td>
</tr>
<tr>
<td>PD-L1+</td>
<td>NR vs 17.1</td>
</tr>
<tr>
<td>1-year OS rate (%)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>71.3 vs 58.4</td>
</tr>
<tr>
<td>PD-L1+</td>
<td>79.1 vs 60.4</td>
</tr>
<tr>
<td>PFS (mo)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>3.7 vs 2.0</td>
</tr>
<tr>
<td>PD-L1+</td>
<td>5.7 vs 2.1</td>
</tr>
</tbody>
</table>

mUC: First-Line Immunotherapy

- Keynote and IMvigor: 2 separate, single-arm phase 2 studies
- Non-cisplatin chemotherapy candidate

<table>
<thead>
<tr>
<th></th>
<th>KEYNOTE-052 Pembrolizumab (Ph 2; n=370)</th>
<th>IMvigor210 Atezolizumab (Ph 2; n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>28.6</td>
<td>23</td>
</tr>
<tr>
<td>PD-L1+</td>
<td>47.3</td>
<td>28</td>
</tr>
<tr>
<td>CR (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>8.9</td>
<td>9</td>
</tr>
<tr>
<td>PD-L1+</td>
<td>20.0</td>
<td>3</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>11.3</td>
<td>15.9</td>
</tr>
<tr>
<td>PD-L1+</td>
<td>18.5</td>
<td>12.3</td>
</tr>
<tr>
<td>Median DOR (mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>30.1</td>
<td>NR</td>
</tr>
<tr>
<td>PD-L1+</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Subsequent Therapy mUC: Enfortumab vedotin

- Binds to Nectin-4-expressing cells → internalization/release of MMAE → microtubule disruption → cell death

- Phase 3, open-label trial; enfortumab vs chemo
  - Patients: pretreated with platinum AND PD-1/L1, Eastern Cooperative Oncology Group 0-1
  - N = 608
  - Results
    - Median OS (mo): 12.88 vs 8.97
    - Median PFS (mo): 5.55 vs 3.71
    - ORR (%): 40.6 vs 17.9
      - CR (%): 4.9 vs 2.7
  - Adverse effects
    - Rash, fatigue, neutropenia, skin reactions, peripheral neuropathy

Locally advanced or mUC after IO therapy, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

MBC: Sacituzumab govitecan

- TROPHY-U-01: international, single-arm, open-label phase 2 trial
- Advanced or metastatic UC
- Progression after platinum-based chemo and PD-1/PD-L1
- MOA: antibody-drug conjugate; Trop-2 antibody coupled to cytotoxic agent SN-38 via hydrolyzable linker
- Sacituzumab govitecan 10 mg/kg on days 1 and 8 every 21 days

<table>
<thead>
<tr>
<th>Outcome, months</th>
<th>Cohort 1 (n = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up</td>
<td>6.3</td>
</tr>
<tr>
<td>Median PFS</td>
<td>5.4</td>
</tr>
<tr>
<td>Median OS</td>
<td>10.5</td>
</tr>
<tr>
<td>ORR, %</td>
<td>27.7</td>
</tr>
</tbody>
</table>

- 27 of 31 responders alive
- 8/31 patients have ongoing response and on treatment at data cutoff

Subsequent Therapy mUC: Erdafitinib

- FGFR alternations present in up to 20% of patients with advanced urothelial carcinoma
- Erdafitinib: potent tyrosine kinase inhibitor of FGFR1-4
- BCL2001: Phase 2, open-label study
  - Patients: progression after platinum chemo or non-cisplatin candidate, prior immunotherapy allowed; FGFR3 mutation or FGFR 2/3 fusion
  - N = 99
  - Results
    - CRR: 40% (CR 3%)
    - TTR: 1.4 mo
    - DOR: 5.6 mo
  - Adverse effects
    - Hyperphosphatemia, stomatitis, diarrhea, dry mouth, fatigue, dry skin, dry eye most common
    - Most common grade 3 or higher: hyponatremia, stomatitis, and asthenia
    - 13 patients discontinued treatment due to adverse effects

Adverse Effect Management for Bladder Cancer Therapies
Integrating Targeted Strategies to Address Previously Unmet Clinical Needs
Immune-Related AEs

- Immune checkpoint inhibitors (ICIs) introduce the potential for transformative, durable responses in multiple malignancies
- ICIs also introduce the potential for toxicity
- irAEs
  - Activation of immune system that can "target" host tissues/organs
  - Can mimic (or flare) preexisting autoimmune conditions
  - Pathophysiology is not well understood
  - Treatment involves immunosuppressive agents

Figure republished from Varricchi G, et al. ESMO Open 2017;2(4):e000247, under the terms of a Creative Commons Attribution Non Commercial (CC By-NC 4.0) license.
PD-1/PD-L1 Education Principles

Prior to start
- Document underlying conditions
- History of autoimmune diseases
- Medication history / allergies
- Performance status
- Reproductive status
- Breastfeeding status
- Provide wallet card or other identification

Patient Instructions
- Notify HCPs of new signs and symptoms
  - Fatigue, rash, cough, shortness of breath, muscle pain, weight loss, etc
- Symptoms should be monitored for a long time even after therapy completion
- Medication changes, vaccines, etc

Adverse Effect Management
- Review medications for DDIs
- Symptomatic management for mild to moderate irAEs
  - Best supportive care and work up
  - Steroids may be needed
  - Hormone substitution as needed
  - May delay Tx until recovery/ improvement
- Severe irAEs
  - Discontinue treatment
  - Steroids and other immuno-suppressants
  - Hospitalization may be required
  - Expert consultation

General Management of irAEs

- **Corticosteroids** remain cornerstone of care for immune-related adverse events
  - Resolved most irAEs among UC trials
  - Mild skin reactions can be treated with topical steroids
  - Higher grade/persistent toxicity requires systemic steroids
  - Oral preferred; IV may be used when absorption compromised (ie, colitis)
- **Moderate cases (grade II)**
  - Hold drug, re-dose if toxicity improves, consider low-dose steroids (prednisone 0.5-1 mg/kg/day)
- **Severe cases (grade III/IV)**
  - Start high-dose steroids (prednisone 1-2 mg/kg/day) with a slow taper (≥1 month)
  - Infliximab 5 mg/kg once every 2 weeks can be used
- **Endocrine adverse effects**
  - Hormonal replacement as needed

<table>
<thead>
<tr>
<th>CTCAE Grade</th>
<th>Corticosteroids</th>
<th>Other Adjunctive Therapies</th>
<th>Immunotherapy Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Not required</td>
<td>Not required</td>
<td>Continue</td>
</tr>
<tr>
<td>2</td>
<td>Topical or systemic</td>
<td>Not required</td>
<td>Hold temporarily</td>
</tr>
<tr>
<td></td>
<td>steroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Systemic steroids</td>
<td>If no response to steroids after 1-2 days</td>
<td>Discontinue and may consider resuming therapy* based on risk/benefit</td>
</tr>
<tr>
<td>4</td>
<td>Systemic steroids</td>
<td>If no response to steroids after 1-2 days</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

*Doses are either given or held. There are no dose reductions.

Erdafitinib Clinical Pearls

- Novel mechanism of action, first targeted therapy and orally available option in UC treatment
  - MOA: Pan-FGFR inhibitor (FGFR 1-4)
  - Approved for FGFR 2-3 mutations or fusions
- 8 mg PO daily (w/ or w/o food) with dose increase to 9 mg daily if criteria are met
  - Day 14 to 21 phosphorus <5.5 mg/dL
  - No ocular disorders
  - No grade ≥2 AEs
- Increase occurred in 41 patients
- Tablets: 3 mg, 4 mg, 5 mg

<table>
<thead>
<tr>
<th>Adverse Reaction (8 mg/day)</th>
<th>All Grade (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>100</td>
<td>67</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>92</td>
<td>24</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>90</td>
<td>16</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>69</td>
<td>13</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>75</td>
<td>16</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>62</td>
<td>11</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>57</td>
<td>5</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>56</td>
<td>20</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>40</td>
<td>7</td>
</tr>
<tr>
<td>Renal and urinary tract disorders</td>
<td>38</td>
<td>10</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>31</td>
<td>0</td>
</tr>
</tbody>
</table>

# Enfortumab vedotin Dose Modifications

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>Blood glucose &gt;250 mg/dL</td>
<td>Withhold until elevated blood glucose has improved to ≤250 mg/dL, then resume treatment at the same dose level</td>
</tr>
</tbody>
</table>
| Peripheral neuropathy            | Grade 2                   | Withhold until grade ≤1, then resume treatment at the same dose level (if first occurrence)  
                                            For recurrence, withhold until grade ≤1, then resume treatment reduced by one dose level |
|                                  | Grade ≥3                  | Permanently discontinue                                                          |
| Skin reactions                   | Grade 3 (severe)          | Withhold until grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level |
|                                  | Grade 4 or recurrent grade 3 | Permanently discontinue                                                         |
| Other nonhematologic toxicity    | Grade 3                   | Withhold until grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level |
|                                  | Grade 4                   | Permanently discontinue                                                          |

## Enfortumab vedotin Dose Modifications

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic toxicity</td>
<td>Grade 3 thrombocytopenia</td>
<td>Withhold until grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level</td>
</tr>
<tr>
<td></td>
<td>Grade 2 thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Withhold until grade ≤1, then resume treatment reduced by one dose level or permanently discontinue</td>
</tr>
</tbody>
</table>

### Starting Dose: 1.25 mg/kg, max dose 125 mg

- **First dose reduction → 1 mg/kg, max dose 100 mg**
- **Second dose reduction → 0.75 mg/kg, max dose 75 mg**
- **Third dose reduction → 0.5 mg/kg, max dose 50 mg**
Diarrhea

- Stop for grade 3-4 diarrhea at the time of scheduled treatment and resume when resolved to grade ≤1
- Presentation is similar as diarrhea from irinotecan
- Immediate-onset diarrhea or other cholinergic response (abdominal cramping, salivation)
  - Initiate atropine. Consider prophylactic use with subsequent infusions
- Late-onset diarrhea (>24 hours after infusion)
  - Initiate loperamide 4 mg x 1 followed by 2 mg with every episode of diarrhea (max = 16 mg/day). Discontinue 12 hours after diarrhea resolves
- Initiate nonpharmacologic supportive measures
  - Increase hydration, diet changes, closely monitor electrolytes

Highly emetogenic

- Premedication: Corticosteroid + 5-HT3-antagonist +/- NK1 antagonist +/- olanzapine

Hypersensitivity (all grades 37%; Grades 3/4, 1%)

- Premedication: Acetaminophen, H1, H2 antagonist, +/- corticosteroids (if prior infusion reaction)
- Administer first infusion over 3 hours and subsequent infusions over 1-2 hours
- Interrupt infusion and/or slow infusion rate for reaction

Black box warning for severe neutropenia and diarrhea
# Sacituzumab Govitecan Dose Modifications

<table>
<thead>
<tr>
<th>Hematologic toxicity</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 neutropenia (ANC &lt;500/mm3) lasting ≥7 days OR</td>
<td>Reduce sacituzumab govitecan dose by 25% and administer growth factor support.</td>
<td>Reduce sacituzumab govitecan dose by 50%.</td>
<td>Discontinue sacituzumab govitecan.</td>
</tr>
<tr>
<td>Grade 3 neutropenic fever (ANC &lt;1,000/mm3 and fever ≥38.5°C) OR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On day of scheduled sacituzumab govitecan dose, grade 3 or 4 neutropenia, which delays dosing by 2 or 3 weeks for recovery to ≤ grade 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On day of scheduled sacituzumab govitecan dose, grade 3 or 4 neutropenia, which delays dosing beyond 3 weeks for recovery to ≤ grade 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4 non-neutropenic hematologic toxicity, which does not recover to ≤ grade 1 within 3 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Trodelvy (sacituzumab govitecan) [prescribing information]. Morris Plains, NJ: Immunomedics Inc; April 2021.
#Sacituzumab Govitecan Dose Modifications

<table>
<thead>
<tr>
<th>Severe nonhematologic toxicity</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 nonhematologic toxicity of any duration OR</td>
<td>Reduce sacituzumab govitecan dose by 25%.</td>
<td>Reduce sacituzumab govitecan dose by 50%.</td>
<td>Discontinue sacituzumab govitecan.</td>
</tr>
<tr>
<td>Any grade 3 or 4 nausea, vomiting, or diarrhea due to sacituzumab govitecan that is not controlled with antiemetics and/or antidiarrheal treatment OR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other grade 3 or 4 nonhematologic toxicity lasting &gt;48 hours (despite optimal medical management) OR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On day of scheduled sacituzumab govitecan dose, grade 3 or 4 nonhematologic toxicity, which delays dosing by 2 or 3 weeks for recovery to ≤ grade 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4 nonhematologic toxicity, which does not recover to ≤ grade 1 within 3 weeks</td>
<td>First</td>
<td></td>
<td>Discontinue sacituzumab govitecan.</td>
</tr>
</tbody>
</table>

Trodelvy (sacituzumab govitecan) [prescribing information]. Morris Plains, NJ: Immunomedics Inc; April 2021.
Pipeline for Bladder Cancer

Integrating Targeted Strategies to Address Previously Unmet Clinical Needs
### Advanced Bladder Cancer

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Setting</th>
<th>Preferred Option</th>
<th>Standard Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic, no prior chemotherapy</td>
<td>Cisplatin-eligible</td>
<td>Cisplatin/gemcitabine f/b avelumab maintenance</td>
<td>Cisplatin-based combination chemotherapy f/b avelumab maintenance</td>
</tr>
<tr>
<td>Metastatic, no prior chemotherapy</td>
<td>Cisplatin-ineligible</td>
<td>Gemcitabine/carboplatin (PD-L1 low tumors in fit patients) f/b avelumab maintenance</td>
<td>Gemcitabine/carboplatin f/b avelumab maintenance Pembrolizumab</td>
</tr>
<tr>
<td>Metastatic, prior chemotherapy and immunotherapy</td>
<td></td>
<td>Enfortumab vedotin OR Erdafitinib (tumors with FGFR2/3 alterations)</td>
<td>Taxane (US) Vinflunine (EU)</td>
</tr>
</tbody>
</table>

Clinical trials are critical throughout disease spectrum and treatment settings!
## Adjuvant PD-1/PD-L1 Inhibitor Phase 3 Trials in UC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Control Arm</th>
<th>Experimental Arm</th>
<th>Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMvigor010</td>
<td>All-comers MIUC</td>
<td>No therapy</td>
<td>Atezolizumab</td>
<td>DFS</td>
</tr>
<tr>
<td></td>
<td>Prior NAC: ≥ pT2 No AC: ≥ pT3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CheckMate 274</td>
<td>All-comers MIUC</td>
<td>Placebo</td>
<td>Nivolumab</td>
<td>DFS</td>
</tr>
<tr>
<td></td>
<td>Prior NAC: ≥ pT2 No AC: ≥ pT3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMBASSADOR</td>
<td>All-comers MIUC</td>
<td>No therapy</td>
<td>Pembrolizumab</td>
<td>DFS/OS</td>
</tr>
<tr>
<td></td>
<td>Prior NAC: ≥ pT2 No AC: ≥ pT3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Phase 1b/2 EV-103 Trial: First-Line Pembrolizumab/Enfortumab vedotin**

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>All Patients (N = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, n (%) (95% CI)</td>
<td>33 (73.3) (58.1-85.4)</td>
</tr>
<tr>
<td>▪ CR, n (%)</td>
<td>7 (15.6)</td>
</tr>
<tr>
<td>▪ PR, n (%)</td>
<td>26 (57.8)</td>
</tr>
<tr>
<td>SD</td>
<td>9 (20.0)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>ORR in patients with liver metastasis, n/N (%)</td>
<td>8/15 (53.3)</td>
</tr>
<tr>
<td>ORR by PD-L1 status, n/N (%)</td>
<td>11/14 (78.6) 12/19 (63.2)</td>
</tr>
</tbody>
</table>

- Treatment-naïve patients with locally advanced/metastatic UC, not eligible for cisplatin-based therapy, regardless of PD-L1 expression levels
  - High RR regardless of PD-L1 expression (ORR, 73.3% with 88% of responses detected by week 10)
  - Median PFS: 12.3 months (95% CI, 7.98-NR)
  - 12-month OS rate: 81.6%
- Safety profile for combination therapy as expected with no new safety signal
  - Most common AEs (58%, 11% grade ≥3), alopecia (53%), and peripheral neuropathy (53%, 4% grade ≥3)

- Breakthrough Therapy Designation granted
- **Future: phase 3 EV-302**: enfortumab vedotin + pembrolizumab ± platinum-based chemotherapy vs platinum-based chemotherapy
- Trial is currently recruiting

CheckMate-032
Nivolumab vs Nivolumab/Ipilimumab

- Multicenter, international, open-label, randomized phase 1/2 trial
- Locally advanced or metastatic UC; PD within 1 year of ≥1 platinum agent or not chemotherapy candidate
- ECOG PS 0-1; brain metastases and autoimmune disease not allowed

<table>
<thead>
<tr>
<th></th>
<th>ORR Nivo 3 mg/kg</th>
<th>ORR Nivo 1 mg/kg + Ipi 3 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>20.5% (12.2 – 31.2)</td>
<td>37% (27.1 – 47.7)</td>
</tr>
<tr>
<td>PD-L1 &lt;1%</td>
<td>20.9% (10 – 36)</td>
<td>21.4% (10.3 – 36.8)</td>
</tr>
<tr>
<td>PD-L1 ≥1%</td>
<td>19.2% (6.6 – 39.4)</td>
<td>54.8% (36 – 72.7)</td>
</tr>
</tbody>
</table>

COSMIC-021: Atezolizumab and Cabozantinib

- Ongoing, multicenter, single-arm phase 1b study
- Locally advanced or metastatic UC with transitional cell histology, radiographic evidence of progression on/after platinum-containing chemotherapy
- ECOG PS 0/1, and no prior immune checkpoint inhibitors or cabozantinib
- Cabozantinib 40 mg PO once daily PO + atezolizumab 1200 mg IV q3wk
- Median PFS: 5.4 months (95% CI, 1.5-7.6)
- Reduction in target lesion size observed in 16 (53%) patients
- No association between PD-L1 expression and tumor response based on preliminary data

<table>
<thead>
<tr>
<th>Investigator-Assessed Tumor Response (RECIST v1.1 Criteria)</th>
<th>UC Cohort 2 (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (80% CI)</td>
<td>27 (16-40)</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
</tr>
<tr>
<td>▪ CR</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>▪ PR</td>
<td>6 (20)</td>
</tr>
<tr>
<td>▪ SD</td>
<td>11 (37)</td>
</tr>
<tr>
<td>▪ PD</td>
<td>7 (23)</td>
</tr>
<tr>
<td>▪ Missing</td>
<td>4 (13)</td>
</tr>
<tr>
<td>DCR (CR + PR + SD), n (%)</td>
<td>19 (63)</td>
</tr>
<tr>
<td>Median DOR, months (range)</td>
<td>NR (1.4+ to 15.6+)</td>
</tr>
<tr>
<td>Median time to objective response, months (range)</td>
<td>3 (1-6)</td>
</tr>
</tbody>
</table>

## Targeted Agents Combined With Durvalumab in Locally Advanced or Metastatic UC After PD on Platinum Chemo

<table>
<thead>
<tr>
<th></th>
<th>AZD4547 + Durvalumab</th>
<th>Vistusertib + Durvalumab</th>
<th>Olaparib + Durvalumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>FGFR inhibitor (1–3)</td>
<td>TORC 1 and 2 inhibitor</td>
<td>PARP inhibitor</td>
</tr>
<tr>
<td><strong>Data in urothelial cancer</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Biomarker hypothesis</strong></td>
<td>FGFR3 mutations and FGFR1–3 fusions</td>
<td>RICTOR amplification or TSC1/2 mutations</td>
<td>HRR gene panel</td>
</tr>
<tr>
<td><strong>Combination data with immune therapy</strong></td>
<td>None</td>
<td>None</td>
<td>Preliminary</td>
</tr>
<tr>
<td><strong>Other agents in class within urothelial cancer</strong></td>
<td>Erdfatinib: 40% RR in biomarker positive</td>
<td>Reported activity in case reports</td>
<td>Ongoing trials (eg, rucaparib)</td>
</tr>
</tbody>
</table>

BISCAY: Biomarker-Directed Randomized Trial

- Open-label, randomized, biomarker directed, multi-arm phase 1b trial

**DNA analysis**

**Biomarker**
- FGFR1, 2, 3 mutation or fusion: Prevalence: 21%
- ATM, BRCA1/2, HRR gene: Prevalence: 14%
- RICTOR, TSC1, TSC2 (partial selection): Prevalence: 15%
- No biomarker selection

**Treatment Regimen**
- AZD4547: FGFR inhibitors
- AZD4547 + durvalumab
- Olaparib + durvalumab: PARP inhibitors
- Vistusertib + durvalumab: TORC1/2 inhibitors
- Durvalumab

**Patients with metastatic UC and ≥1 previous line of platinum-based CT for mUC or PD <1 year of perioperative platinum-based CT; WHO PS 0/1; archived tissue for biomarker assessment (N = 108)**

- Primary end point: safety and tolerability
- Secondary end points: efficacy (ORR, DCR, PFS, DOR, OS) of durvalumab alone or in combination; immunogenicity of durvalumab; pharmacokinetics


#NCODAForum21
NKTR-214 Background: IL-2 Pathway

DOSE ESCALATION (multiple tumor types)

- Bempegaldesleukin 0.003 mg/kg q2wk
  Nivolumab 240 mg q2wk
- Bempegaldesleukin 0.006 mg/kg q2wk
  Nivolumab 240 mg q2wk
- Bempegaldesleukin 0.006 mg/kg q2wk
  Nivolumab 360 mg q2wk
- Bempegaldesleukin 0.006 mg/kg q2wk
  Nivolumab 240 mg q2wk
- Bempegaldesleukin 0.009 mg/kg q3wk
  Nivolumab 360 mg q3wk

DOSE EXPANSION

- Recommended phase 2 dose: Unresectable, locally advanced or metastatic UC; cisplatin ineligible or eligible and refused SoC; ECOG PS 0-1

Other tumor types being evaluated in separate expansion arms

Primary end points: safety/tolerability, ORR

- Secondary/exploratory end points: DOR, OS, PFS, CBR, PK, ORR by irRECIST
- Biomarker end points: ALC, blood immunophenotyping; biopsies at baseline and week 3 where feasible
- \( \geq 1 \) dose bempegaldesleukin in mUC cohort: \( n = 41 \)
  - Efficacy evaluable: \( n = 27 \)

Conclusion

• Immunotherapies and targeted therapies offer new modalities in treating bladder cancer
• Data maturation continues to impact therapy sequencing and enrollment in clinical trials across all disease settings
• Genetic composition and testing are likely to impact future treatment selection
• Oncology care teams face multiple challenges in the management of patients with locally advanced or metastatic urothelial carcinoma with respect to adverse effect management
## Additional Resources

<table>
<thead>
<tr>
<th>Resource</th>
<th>How to Access</th>
</tr>
</thead>
</table>