Updates in the Management of Urothelial Carcinoma: Ensuring Optimal Management of Locally Advanced and Metastatic Disease

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Disclosures

• Dr. Galsky discloses receiving consulting fees from Bristol Myers Squibb, Merck, Genentech, AstraZeneca, Pfizer, EMD Serono, SeaGen Inc., Janssen, Numab Therapeutics, Dragonfly Therapeutics, GlaxoSmithKline, Basilea, UroGen Pharms, and Rappta Therapeutics.

• During the course of this lecture, the presenter may discuss the use of medications for both FDA-approved and non-approved indications.

• All relevant financial relationships have been mitigated

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Learning Objectives

• Explain the latest therapeutic developments in the management of locally advanced and metastatic urothelial carcinoma in consideration of patient specific factors

• Assess current clinical efficacy and safety data concerning the use of treatments in the management of urothelial carcinoma, both in frontline and later-line settings

• Relate current best practices in potential adverse event monitoring and management strategies in urothelial carcinoma

Bladder Cancer

United States

• An estimated 83,190 people will be diagnosed with urinary bladder cancer, and 16,840 people will die from this disease in 2024

Worldwide (2020 data)

• Bladder cancer is the 10th most common malignancy, with 600,000 new cases annually

• More than 200,000 people die each year from this disease
Evolution of Bladder Cancer Management

- Atezolizumab
- Durvalumab
- Nivolumab
- Pembrolizumab
- Avelumab
- Enfortumab-vedotin
- Sacituzumab-govitecan

BC = bladder cancer; BCG = Bacillus Calmette-Guerin; ICI = immune checkpoint inhibitor; MIBC = muscle-invasive BC; mUC = metastatic UC; NMIBC = nonmuscle-invasive BC; UC = urinary cancer.

- Granted accelerated approval (May)
  - Avelumab
  - Durvalumab
- 1st line mUC, platinum-ineligible and 2nd line mUC (May, accelerated approval)
  - Pembrolizumab
- Granted accelerated approval (May)
  - Durvalumab

Locally advanced UC ineligible for cisplatin (May)
- Atezolizumab
- Atezolizumab (April)
- 2nd line mUC (February)
- Pembrolizumab

Locally advanced or mUC with previous ICI and platinum or cisplatin-ineligible (July)
- Enfortumab-vedotin

A salvage for BCG-unresponsive, high-risk NMIBC (January)
- Pembrolizumab

Maintenance, mUC (June)
- Avelumab

Adjuvant, MIBC (August)
- Nivolumab

Locally advanced or mMUC who received prior platinum and either ICIs (April)
- Pembrolizumab
- Sacituzumab-govitecan

Core Structure of an Antibody-Drug Conjugate

- Recognition of target cancer cells
- Guidance system for cytotoxic drugs
- Bridge between antibody and drugs to control release of drugs inside cancer cells
- Warhead for killing cancer cells

Promise of ADCs: Improve Therapeutic Index of Systemic Chemotherapy

Most patients receive chemotherapy; however, significant toxicities remain

Optimized ADC technology and biology must align to build successful ADC

ADCs to replace chemotherapy
- Targeted delivery to cancer cell
- Improved efficacy
- Decreased toxicity
- Increased therapeutic index

ADC = antibody-drug conjugate; ADCC = antibody-dependent cell-mediated cytotoxicity.

Enfortumab Vedotin (EV): Structure and MOA

Nectin-4 transmembrane protein highly expressed in bladder cancer

- EV is an anti-nectin-4 ADC
- Nectin-4 is a tumor-associated transmembrane protein highly expressed in bladder cancer

- EV properties
  - Drug-to-antibody ratio of 4:1
  - Monomethyl auristatin E payload
  - May exert bystander effect (preclinical support)

IgG = immunoglobulin G; mAB = monoclonal antibody; MMAE = monomethyl auristatin E; MOA = mechanism of action.

Sacituzumab Govitecan (SG): Structure and MOA

SG is an anti-Trop-2 ADC with:
• High drug-to-antibody ratio (8:1)
• Topoisomerase inhibitor payload (SN-38)
• Ability to exert bystander effect

Linker for SN-38
• Hydrolyzable linker for payload release
• High drug-to-antibody ratio (7.6:1)

SN-38 payload
• SN-38 more potent than parent compound, irinotecan

Humanized anti-Trop-2 antibody
• Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

SG = trophoblast cell-surface antigen.

Humanized anti-Trop-2 antibody


NCCN Guidelines Version 4.2024
First-Line Systemic Therapy for Locally Advanced or Metastatic UC

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Cisplatin eligible (LOR)</th>
<th>Cisplatin ineligible (LOR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pembrolizumab + enfortumab vedotin (category 1)</td>
<td>Pembrolizumab + enfortumab vedotin (1)</td>
</tr>
<tr>
<td>Other recommended</td>
<td>Gemcitabine + cisplatin (1) → avelumab* (1)</td>
<td>Gemcitabine + carboplatin → avelumab* (1)</td>
</tr>
<tr>
<td>regimen</td>
<td>Nivolumab, gemcitabine, cisplatin (1) → nivolumab (1)</td>
<td></td>
</tr>
<tr>
<td>Useful in</td>
<td>DDMVC with GFS (1) → avelumab* (1)</td>
<td>Gemcitabine ± paclitaxel (2a)</td>
</tr>
<tr>
<td>certain</td>
<td></td>
<td>Ifosfamide + doxorubicin + gemcitabine* (2a)</td>
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<tr>
<td>circumstances</td>
<td></td>
<td>Pembrolizumab (2a)</td>
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<td>Atezolizumab‖ (2b)</td>
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</tbody>
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• Presence of both non-nodal metastases and ECOG PS ≥2 strongly predict poor outcome with CT; patients without these adverse prognostic factors have greatest benefit from CT; impact of these factors in relation to ICI is not fully defined, but they remain poor prognostic indicators in general
• For most patients, risks of adding paclitaxel to gemcitabine and cisplatin outweigh limited benefit seen in randomized trial
• Substantial proportion of patients cannot receive cisplatin-based CT due to renal impairment or other comorbidities; participation in clinical trials of new or more tolerable therapy is recommended

* Maintenance therapy with avelumab only if there is no progression on first-line platinum-containing CT; †Patients with good kidney function and good PS; ‡Patients not eligible for any platinum-containing CT; §Patients whose tumors express PD-L1 or who are not eligible for any platinum-containing CT regardless of PD-L1 expression; ‖Atezolizumab: SP142 assay, PD-L1–stained tumor-infiltrating immune cells covering ≥5% of the tumor area.

CT = chemotherapy; DDMVC = dose-dense methotrexate, vinblastine, doxorubicin, cisplatin; ECOG = Eastern Cooperative Oncology Group performance status; GFS = growth-factor support; LOR = level or recommendation; PD-L1 = programmed (cell) death 1 ligand; PS = performance status.

Patient-Centered Communication in Shared Decision-Making

Patient participation is key in medical decision-making to optimize treatment outcomes

Shared decision-making can facilitate:
- ↑ patient satisfaction
- ↑ productive conversations
- ↓ anxiety
- ↑ improve patient-clinician relationships
- ↑ patient-reported outcomes following treatment decisions
- ↑ Improved disease-related understanding

Exchanging information
- Responding to emotions
- Making decisions
- Managing uncertainty
- Enabling patient self-management
- Fostering healthy relationships

Patient Communication

We look forward to seeing you at our TeleECHO presentation to discuss Updates in the Management of Urothelial Carcinoma: Ensuring Optimal Management of Locally Advanced and Metastatic Disease!