Meeting at the Communications Crossroads: Understanding Treatment Options for Advanced and Metastatic Bladder Cancer

Supplement: Terminology Definitions and References

Members of Your Care Team

- **Medical oncologists (or "med oncs"):** Physicians who specialize in using chemotherapy, targeted therapies, and immunotherapies to treat cancer
- **Oncologists:** Physicians who specialize in diagnosing and treating cancer
- **Oncology nurses:** Nurses with specialized training and expertise in cancer care
- **Oncology pharmacists:** Pharmacists with specialized training and expertise in the safe and effective use of drugs used to treat cancer
- **Oncology physician assistants:** Healthcare providers with specialized training in treating cancer
- **Pathologists:** Physicians trained in identifying and classifying tumor cells for accurate cancer diagnosis and staging
- **Patient navigators (or "patient advocate"):** Professionals trained in facilitating communication between patients and healthcare providers as well as helping with financial, legal, and social support
- **Radiation oncologists (or "rad oncs"):** Physicians who specialize in using various forms of radiation therapy to treat cancer
- **Surgical oncologists (or "surg oncs"):** Physicians trained in surgical techniques to diagnose, stage, and treat cancer by removing tumors or organs and tissues affected by cancer
- **Urologists:** Physicians who specialize in treating diseases of the urinary tract
- **Urologic oncologist:** Physicians who specialize in diagnosing and treating cancers of the urinary tract

Medical Terminologies You May Hear and What They Mean

Adverse events (AEs): Medical terminology for side effects caused by treatments. Most common side effects caused by cancer treatments include nausea, diarrhea, fatigue, itch, rash, sore muscles, mouth sores, hair loss, altered taste perception (called dysgeusia) and decreased appetite. It may also cause nerve damage (called neuropathy), marked by tingling and numbness in the hands and feet, and blood disorders such as high or low levels of red or white blood cells.

Adjuvant chemotherapy: Adjuvant means any treatment that is given after the primary intervention to enhance its effectiveness. In cancer, the primary intervention is usually surgery to remove a tumor or diseased organ. Any drug given after surgery is adjuvant and given for the purpose of killing cancer cells that may still be in the body. In the case of bladder cancer, adjuvant chemotherapy is a combination of 2 or more drugs, 1 of which ***must be*** a platinum-derived drug (ie, cisplatin or carboplatin). (Also see "Neoadjuvant chemotherapy")

Antibody drug conjugate (ADC): A laboratory-engineered antibody (an immune system component) designed to target a particular protein on cancer cells. This is linked with a cancer-killing drug that goes directly into cancer cells, bypassing healthy cells (also see "Monoclonal antibody"). The ADCs that are

approved by the Food and Drug Administration are Padcev (enfortumab vedotin, or EV), and Trodelvy (sacituzumab govitecan, or SG). (Also see “Third-line treatment”)

Best supportive care (BSC): Interventions intended to manage symptoms and provide relief of discomfort caused by the disease itself or by treatment side effects. This can include giving medications to control pain, nausea, and vomiting; managing infections and controlling fever; giving nutritional or hydration support; or using other measures that improve a patient’s comfort and quality of life. Although this is also sometimes referred to as “palliative care,” best supportive care can be used any time during cancer treatment and is ***not*** just for end-of-life care.

Cisplatin ineligible (or cis-ineligible): This indicates a person who for cannot take cisplatin (most often because of heart or kidney disease among other reasons) because they might not be able to tolerate the side effects. Cisplatin in combination with one or more other chemotherapy drugs is the preferred treatment for patients who are newly diagnosed with advanced or metastatic bladder cancer. Some cisplatin-ineligible patients can still safely take carboplatin because it has fewer side effects; others will need to receive immunotherapy with one of the checkpoint inhibitors instead. (Also see “Adjuvant chemotherapy,” “First-line treatment,” “Gem/Cis,” “Platinum-based chemotherapy,” and “Immune checkpoint inhibitors”)

Cycles: A repeated set number of days or weeks in which the patient receives cancer medications. A cycle may be 21 or 28 days long, and is used for chemotherapies and antibody drug conjugates (ADCs). Chemotherapies are usually given once a week for 2 weeks followed by one week off. In the next week, the process starts over again. This is a 21-day or 3-week cycle. ADCs are given on certain days (example: day 1 and day 8) in a 21-day or 28-day cycle. (Also see “Adjuvant chemotherapy,” “Antibody drug conjugate,” and “Platinum-based chemotherapy”)

FGFR: Stands for fibroblast growth factor receptor and consists of a family of 4 genes (FGFR1 to FGFR4). FGFR2 and FGFR3 are involved in cell division, cell maturity, formation of new blood vessels, and wound healing. Changes in these genes (referred to as “mutations,” “alterations,” or “fusions”) are the most commonly seen gene mutations in bladder cancer. People with bladder cancer and FGFR2/FGFR3 mutations are eligible for treatment with an FGFR inhibitor if the cancer comes back after completing chemotherapy. Called Balversa (erdafitinib), this is the only FGFR inhibitor that is approved by the Food and Drug Administration. (Also see “Second-line treatment”)

First-line treatment: Initial drug treatment after diagnosis and surgery. This is frequently also called “frontline” treatment. (Also see “Adjuvant chemotherapy,” “Gem/Cis,” and “Cisplatin-ineligible”)

Gem/Cis: Refers to the chemotherapy combination of gemcitabine + cisplatin. This is the most commonly prescribed and frequently recommended chemotherapy treatment for patients who are newly diagnosed with advanced or metastatic bladder cancer. (Also see “First-line treatment” and “Adjuvant chemotherapy”)

Immune checkpoint inhibitors (ICIs): Usually called just “checkpoint inhibitors,” these are 4 monoclonal antibody drugs that have been approved by the Food and Drug Administration to treat advanced or metastatic bladder cancer (also see “Immunotherapy”). The names of these drugs are Bavencio (avelumab), Keytruda (pembrolizumab), nivolumab (Opdivo), and Tecentriq (atezolizumab). (Also see “Immunotherapy” and “Maintenance Therapy”)

Immunotherapy: Treatment that unleashes the immune system's ability to recognize and destroy cancer cells. In advanced or metastatic bladder cancer, this is achieved with immune checkpoint inhibitors. (Also see "Immune checkpoint inhibitors")

Immune-related adverse events (irAEs): Side effects that can be caused by immune checkpoint inhibitors. Rash and itch (often called pruritis) are the most common irAEs. These side effects can occur at any time, even after treatment with the checkpoint inhibitor has been stopped. They can occur in any organ system and may be serious but are rarely life-threatening. Most irAEs are mild to moderate and can be controlled. (Also see "Immune checkpoint inhibitors" and "Immunotherapy")

Maintenance therapy: A drug that's started after the initial or first-line chemotherapy is finished. This is thought of as an extension of first-line treatment. The only drug approved by the Food and Drug Administration for maintenance therapy for advanced or metastatic bladder cancer is Bavencio (avelumab), which is a checkpoint inhibitor. (Also see "First-line treatment," "Adjuvant chemotherapy," and "Immune checkpoint inhibitors")

Monoclonal antibody (mAb): A laboratory-engineered protein derived by cloning a single B-cell (a type of white blood cell used by the immune system to fight disease) in large enough quantities to target many cancer cells simultaneously. These antibodies seek and bind to specific receptors on cancer cells. They can be used alone or to carry drugs or radioactive substances directly into cancer cells to kill them. (Also see "Immune checkpoint inhibitors" and "Antibody drug conjugate")

Neoadjuvant chemotherapy: Neoadjuvant means any treatment that is given before the primary intervention to enhance its effectiveness. In cancer, the primary intervention is usually surgery to remove a tumor or diseased organ. Neoadjuvant chemotherapy may be given before surgery to shrink the tumor and kill any circulating cancer cells. Neoadjuvant chemotherapy would not be given to patients with metastatic bladder cancer but may in some cases, be offered to patients with advanced bladder cancer. Neoadjuvant chemotherapy for bladder cancer is a combination of two or more drugs, one of which ***must be*** a platinum-derived drug (ie, cisplatin or carboplatin). (Also see "Adjuvant chemotherapy" and "Platinum-based chemotherapy")

PD-1/PD-L1: These stand for programmed death cell protein 1 and programmed death cell protein ligand 1. PD-1 is a protein on T-cells (a disease-fighting cell in the immune system). It is part of a checkpoint system that keeps the immune system from attacking the body's own cells. When PD-1 binds to PD-L1 (often found on the surface of cancer cells), the T-cell gets the message that it shouldn't attack that cell. Cancer cells often use PD-L1 to "trick" the immune system into believing it's just another harmless, normal cell. By blocking PD-1 or PD-L1, immunotherapy with immune checkpoint inhibitors releases the "brakes" on the immune system, increasing the ability of T-cells to recognize and kill cancer cells. (Also see "Immune checkpoint inhibitors" and "Immunotherapy")

Platinum-based chemotherapy: A combination of 2 or more chemotherapy drugs that contains either cisplatin or carboplatin. Both of these drugs are derived from platinum and are key to first-line or initial therapy after a diagnosis of advanced or metastatic bladder cancer. Cisplatin is the preferred drug because it is more effective against cancer. Carboplatin has fewer side effects than cisplatin but is not as effective. It is used for patients who might not be able to tolerate the side effects of cisplatin (mostly those with heart or kidney disease, among other conditions). (Also see "Adjuvant chemotherapy," "First-line treatment," and "Gem/Cis")

Second-line treatment: Drug therapies that can be used if the cancer comes back or gets worse after being on an initial or first-line treatment. (Also see “First-line treatment,” “Adjuvant chemotherapy,” and “Third-line treatment”)

Shared decision-making: The understanding that healthcare professionals in the cancer care team, including oncologists and other doctors, can work with and support the patient in making treatment decisions based on the patient’s desires and treatment goals, after having been given information about all possible treatment options.

Stage III: Cancer has grown past the bladder lining through the bladder muscle wall. It may have spread to 1 or more lymph nodes that are near the bladder.

Stage IV: Cancer has spread to lymph nodes or other body organs that are far from the bladder.

Systemic treatment: Any drug that can travel through the blood stream potentially affecting cells and organs throughout the body.

Third-line treatment: Drug therapies that can be used if the cancer comes back or gets worse after being on two previous kinds of treatments. This is sometimes called “later-line” treatment. (Also see “First-line treatment” and “Second-line treatment”)

TNM: A staging system used by oncologists for many different types of cancer. Staging is done as a part of diagnosis and is used to determine how advanced the cancer is, how far it may have spread, and what the best treatment options are. “T” stands for “tumor” and refers to the size of the main or primary tumor. “N” refers to the number of nearby lymph nodes that may have cancer. “M” stands for metastasis and refers to whether or not the cancer has spread to other parts of the body. Numbers and sometimes letters are placed next to the T, N, and M to more precisely indicate the tumor’s growth and cancer progression.

Urinary tract cancer (UTC): Umbrella term for cancers of the bladder and upper urinary tract. Bladder cancer is the most common UTC location, comprising 95% of all cases. Upper urinary tract cancer includes cancer in the renal pelvis (the part of the kidneys that collect urine) and in the ureters (tubes that carry urine from the kidneys to the bladder).

References

American Cancer Society (ACS). Bladder Cancer Risk Factors. Accessed August 23, 2021. https://www.cancer.org/cancer/bladder-cancer/causes-risks-prevention/risk-factors.html

American Cancer Society (ACS). Cancer Facts and Figures 2021. Accessed August 23, 2021. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2021.html

Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet.* 2017;389:67-76.

Balversa® [package insert]. Horsham, PA: Janssen Products, LP; April 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212018s001lbl.pdf

Bavencio® [package insert]. Rockland, MA: EMD Serono, Inc.; November 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761049s005lbl.pdf

Bellmunt J, de Wit R, Vaughn DJ, et al on behalf of the KEYNOTE-045 investigators. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med.* 2017;376:1015-1026.

Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. *J Clin Oncol.* 2012; 30:1107-1113.

Bladder Cancer Advocacy Network (BCAN). Bladder Cancer Basics Handbook. Accessed September 2, 2021. https://bcan.org/

Keytruda® [package insert]. White House Station, NJ: Merck & Co., Inc.; August 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s102lbl.pdf

Liu Y-H, Zang X-Y, Wang J-C, Huang S-S, Xu J, Zhang P. Diagnosis and management of immune related adverse events (irAEs) in cancer immunotherapy. *Biomed Pharmacother.* 2019;120:109437.

Loriot Y, Necchi A, Park SH, et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma. *N Engl J Med.* 2019;381:338-348.

Matulewicz RS, Sherman S, Bjurlin MA. Smoking cessation and cancer survivorship. *JAMA.* 2020;324:1475. Available at: https://jamanetwork.com/journals/jama/fullarticle/2771610.

National Cancer Institute (NCI). Visuals Online. Bladder Cancer. Accessed August 23, 2021. https://visualsonline.cancer.gov/searchaction.cfm?topicid=224

National Comprehensive Cancer Network (NCCN). Guidelines for Patients. Bladder Cancer. Version 2019. Accessed September 2, 2021. https://www.nccn.org/patients/guidelines/content/PDF/bladder-patient.pdf

National Comprehensive Cancer Network (NCCN). NCCN Guidelines. Bladder Cancer. Version 4.2021—July 27, 2021. Accessed August 23, 2021.

https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

Padcev® [package insert]. Northbrook, IL: Astellas Pharma US, Inc.; July 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf.

Patel MR, Ellerton J, Infante JR, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. *Lancet Oncol.* 2018;19:51-64.

Powles T, Park SH, Voog C, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med.* 2020;383:1218-1230.

Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. *N Engl J Med.* 2021;384:1125-1135.

Rosenberg JE, Galsky MD, Balar AV, et al. Atezolizumab monotherapy in cisplatin-ineligible patients with previously untreated metastatic urothelial carcinoma: 5-year response and survival analysis from the phase II IMvigor210 study (cohort 1). ESMO 2021 abstract 699P.

Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol.* 2017;18:312-322.

Surveillance, Epidemiology, and End Results Program (SEER). Cancer Stat Facts: Bladder Cancer. Accessed August 23, 2021. https://seer.cancer.gov/statfacts/html/urinb.html

Tagawa ST, Balar AV, Petrylak, et al. TROPHY-U-01: a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors. *J Clin Oncol.* 2021;39:2474-2485.

Tecentriq® [package insert]. South San Francisco, CA: Genentech, Inc.; April 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761034s041lbl.pdf

Trodelvy® [package insert]. Morris Plains, NJ: Immunomedics, Inc.; April 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761115s009lbl.pdf

Vuky J, Balar AV, Castellano D, et al. Long-term outcomes in KEYNOTE-052: phase II study investigating first-line pembrolizumab in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer. *J Clin Oncol.* 2020;38:2658-2666.

Yu EY, Petrylak DP, O'Donnell PH, et al. Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): a multicentre, single-arm, phase 2 trial. *Lancet Oncol.* 2021;22:872-882.