Bladder Cancer

- Signs and symptoms
- Key risk factors
- Key US & global statistics
- Histology
- US survival rate
- Biology
- Metastatic disease
  - Epidemiology
  - 1L treatment
  - Outcomes with 1L platinum-based chemotherapy
  - Patients not receiving 1L treatment
  - Unmet need after 1L treatment
  - 2L+ treatment

US-NONO-00565 05/24

Bladder Cancer: Signs and Symptoms

COMMON SIGNS AND SYMPTOMS OF BLADDER CANCER

Hematuria; changes in urination may occur, such as:

- Frequent urination
- Painful urination
- Urinary urgency even if the bladder is not full
- Trouble urinating or weak urine stream
- Having to urinate multiple times during the night

SYMPTOMS OF ADVANCED BLADDER CANCER

Large cancers or those that have spread to other parts of the body can sometimes cause other symptoms:

- Being unable to urinate
- Lower back pain on one side
- Loss of appetite, weight loss
- Tiredness or weakness
- Swelling in the feet
- Bone pain

1. American Cancer Society. Bladder cancer signs and symptoms. https://www.cancer.org/cancer/types/bladder-cancer/detection-diagnosis-staging/signs-and-symptoms.html. Accessed April 19, 2024.

Bladder Cancer: Key Risk Factors

INTRINSIC RISK FACTORS FOR BLADDER CANCER

Age
>90% of cases occur in individuals aged **≥55 years**[1]

Sex
≈75% of cases occur in **men**[2]

Race/ethnicity
Occurrence is **twice as likely in White** than in African-American and Hispanic **individuals**[1]

Genetics
Family history of bladder cancer[1]
Genetic changes that affect the breakdown of toxins and mutations in known tumor suppressors[1]

Chronic infections
Urinary infections, kidney and bladder stones, and schistosomiasis infections[1]

ENVIRONMENTAL RISK FACTORS FOR BLADDER CANCER

Smoking
>3-fold increased **risk**[1]

Chemicals
Exposure to specific chemicals in the workplace[1]

Certain medicines or herbal supplements[1]

Low fluid intake[1]

1. American Cancer Society. Bladder cancer risk factors. https://www.cancer.org/cancer/bladder-cancer/causes-risks-prevention/risk-factors.html. Accessed April 19, 2024. 2. Richters A, et al. World J Urol 2020;38:1895-904.

Bladder Cancer: Key US and Global Statistics

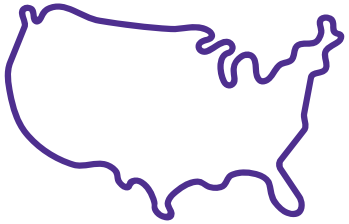
10th most common cancer globally[1]

Estimated new cases in 2020[1]

573,278

Estimated deaths in 2020[1]

212,536



6th most common cancer in the US[2]

Estimated new cases in 2023[2]

82,290

Estimated deaths in 2023[2]

16,710

Median age at diagnosis[2]

73 yrs

ESTIMATED NEW CASES OF BLADDER CANCER IN THE US IN 2023[3]

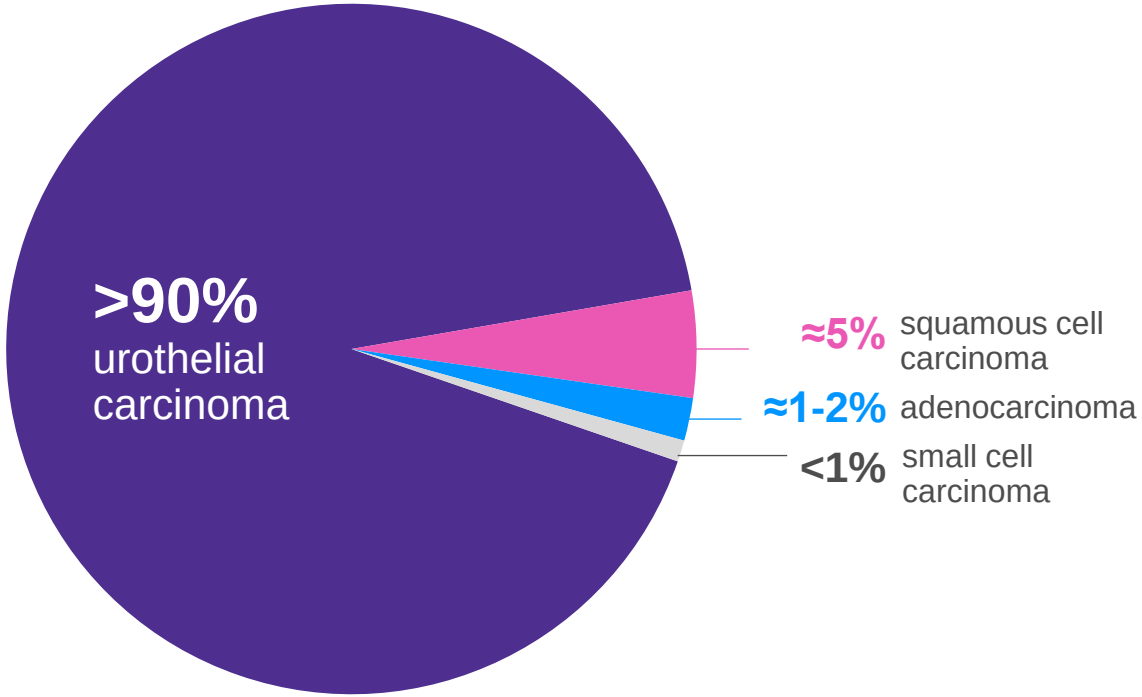
- **Breast,** 300,590
- **Prostate,** 288,300
- **Lung & bronchus,** 238,340
- **Colon,** 106,970
- **Melanoma of the skin,** 97,610
- **Urinary bladder,** 82,290
- **Kidney & renal pelvis,** 81,800
- **Non-Hodgkin lymphoma,** 80,550
- **Uterine corpus,** 66,200
- **Pancreas,** 64,050
- **Rectum,** 46,050
- **Thyroid,** 43,720
- **Liver & intrahepatic bile duct,** 41,210
- **Myeloma,** 35,730
- **Stomach,** 26,500
- **All other cancers,** 358,400

ESTIMATED DEATHS FROM BLADDER CANCER IN THE US IN 2023[3]

- **Lung & bronchus,** 127,070
- **Colon & rectum,** 52,550
- **Pancreas,** 50,550
- **Breast,** 43,700
- **Prostate,** 34,700
- **Liver & intrahepatic bile duct,** 29,380
- **Non-Hodgkin lymphoma,** 20,180
- **Brain and other nervous system,** 18,990
- **Urinary bladder,** 16,710
- **Esophagus,** 16,120
- **Kidney & renal pelvis,** 14,890
- **Ovary,** 13,270
- **Uterine corpus,** 13,030
- **Myeloma,** 12,590
- **Acute myeloid leukemia,** 11,310
- **All other cancers,** 134,780

1. Sung H, et al. CA Cancer J Clin 2021;71:209-49. 2. Cancer stat facts: bladder cancer [Internet]. Surveillance, Epidemiology, and Ends Result Program, National Cancer Institute. Available from https://seer.cancer.gov/statfacts/html/urinb.html. Accessed April 19, 2024. 3. Siegel RL, et al. CA Cancer J Clin 2023;73:17-48.

Bladder Cancer: Histology

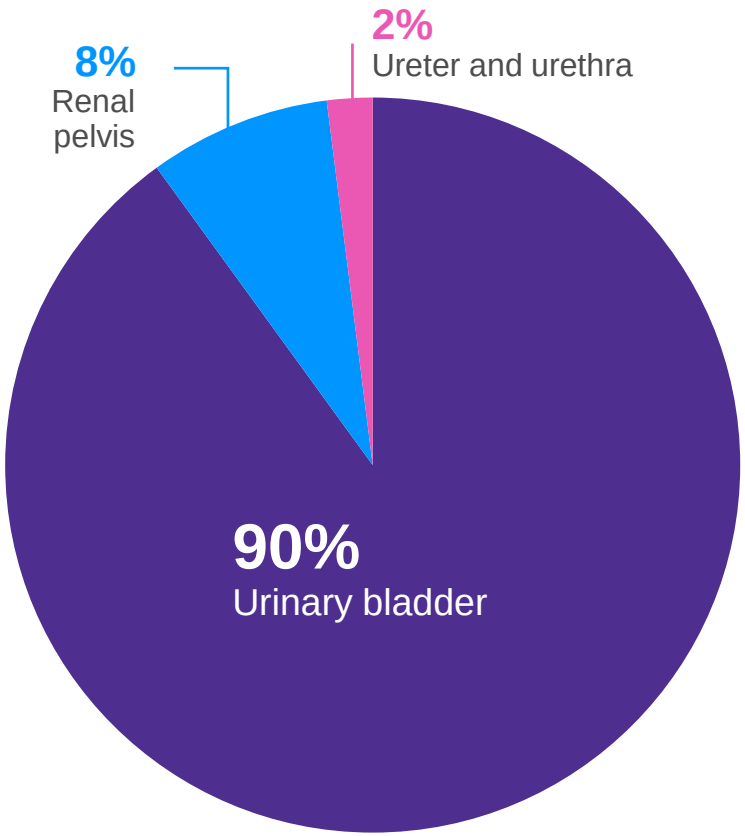


ADDITIONAL INFORMATION ON DIFFERENT TYPES OF BLADDER CANCER[1-3]

Urothelial carcinoma	• Also called transitional cell carcinoma • 90% of UC originates in the urothelial cells that line the inside of the bladder[4] • May also originate in the renal pelvis, ureters, or urethra
Squamous cell carcinoma	• More common in developing countries • Most cases are invasive
Adenocarcinoma	• Develops from mucus-producing cells • Usually invasive
Small cell carcinoma	• Originates in neuroendocrine cells • Standard treatment is similar to small cell carcinoma of the lung

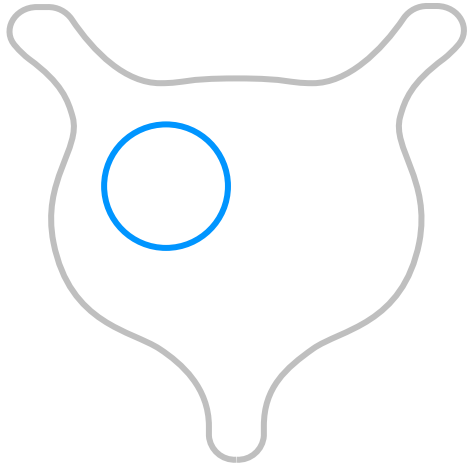
1. Cancer Research UK. Bladder cancer. https://www.cancerresearchuk.org/about-cancer/bladder-cancer/types-stages-grades/types. Accessed April 19, 2024. 2. American Cancer Society. About bladder cancer. https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html. Accessed April 19, 2024. 3. Yousef PG, Gabril MY. *Pathol Res Pract* 2018;214:1-6. 4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V.3.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed April 19, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Urothelial Carcinoma



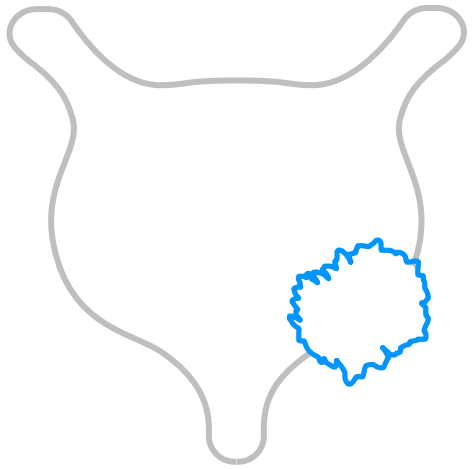
- Classified as low or high grade, depending on the extent of cytologic and architectural atypia
- Most common histologic subtype in the US and Europe
- Urothelial (transitional cell) carcinomas may develop anywhere urothelium is present

Squamous Cell Carcinoma



- Squamous cell carcinoma constitutes **3%** of the urinary tumors diagnosed in the US. However, in regions where *Schistosoma* is endemic, it may account for up to **75%** of bladder cancer cases
- Diagnosed by the presence of keratinization in the pathologic specimen
- Morphologically indistinguishable from squamous cell carcinoma of other locations
- Commonly presents at an advanced stage
- Can be defined into three variants:
  - Pure squamous cell carcinoma
  - Verrucous carcinoma
  - Squamous cell papilloma

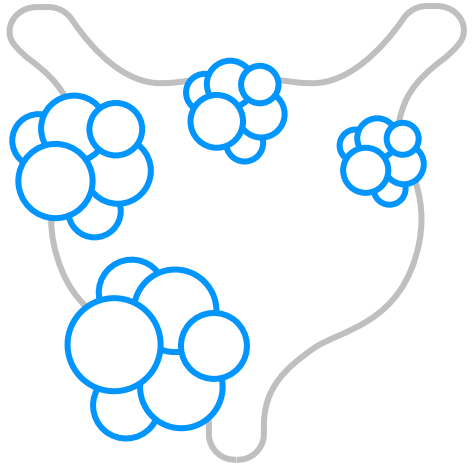
Adenocarcinoma



- Primary bladder adenocarcinoma is rare; it comprises only **0.5-2%** of all primary bladder malignancies[1]
- Usually presents at an advanced stage with nodal involvement in **30-40%** of cases[1]
- Morphologically heterogeneous, with enteric, mucinous, signet ring cell, and mixed subtypes[1]
- Morphologic similarities with primary adenocarcinoma from other sites results in diagnostic challenges to confirm the urinary bladder origin[1]
- Treatment typically consists of radical cystectomy and bilateral pelvic lymph node dissection[1,2]
- There is no proven role for neoadjuvant or adjuvant chemotherapy[1,2]

1. Roy S, Pradhan D, Ernst WL, et al. *Mod Pathol*. 2017;30(8):1133-1143. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V.3.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed April 19, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Small Cell Carcinoma



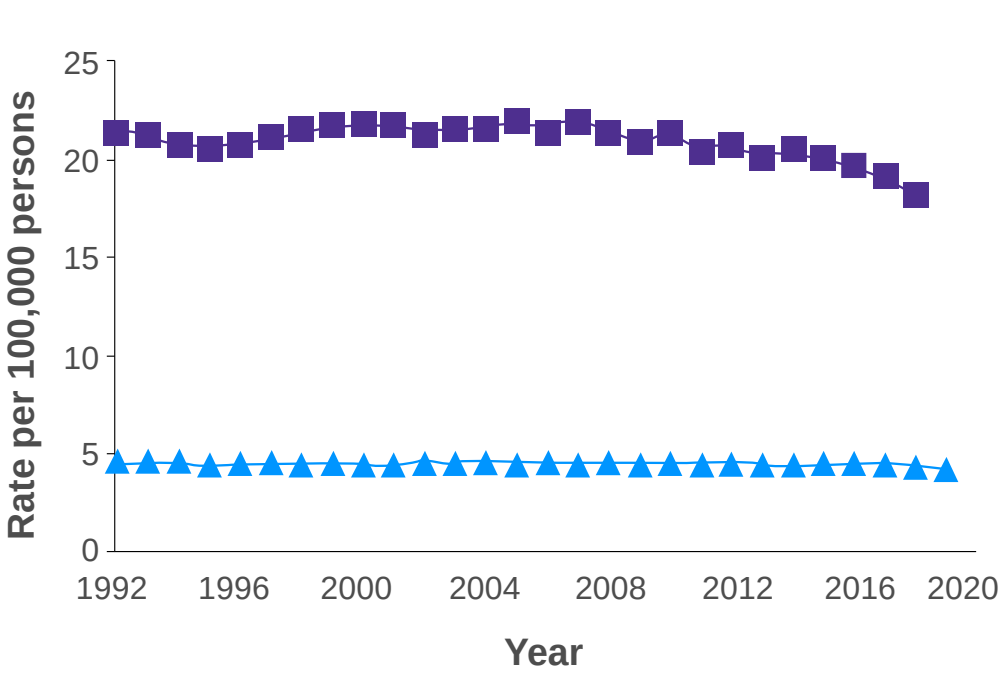
- Extremely rare, with a reported incidence of less than **1-9/1,000,000** people
- The pathogenesis of small cell carcinoma of the bladder is not well defined
- Histologically, it is identical to small cell lung carcinoma (SCLC), and the recommended treatment is also the same

Ismaili N. *Orphanet J Rare Dis*. 2011;6:75.

Bladder Cancer: US Survival

- In the last 20 years, the death rate from bladder cancer has remained relatively unchanged[1]
- Metastatic disease has a 5-year relative survival rate† of **≈8.3%**

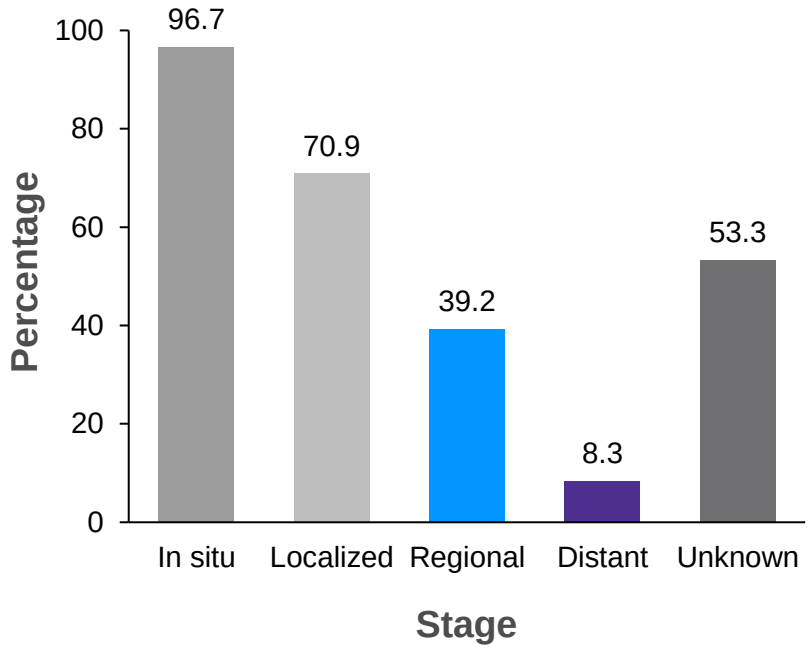
NEW CASES OF BLADDER CANCER AND DEATHS PER 100,000 PEOPLE IN THE US*[1]



18.2
per 100,000 people
per year (2016-2020*)[1]

4.2
per 100,000 people
per year (2016-2020*)[1]

5-YEAR SURVIVAL BY BLADDER CANCER STAGE AT DIAGNOSIS[1]

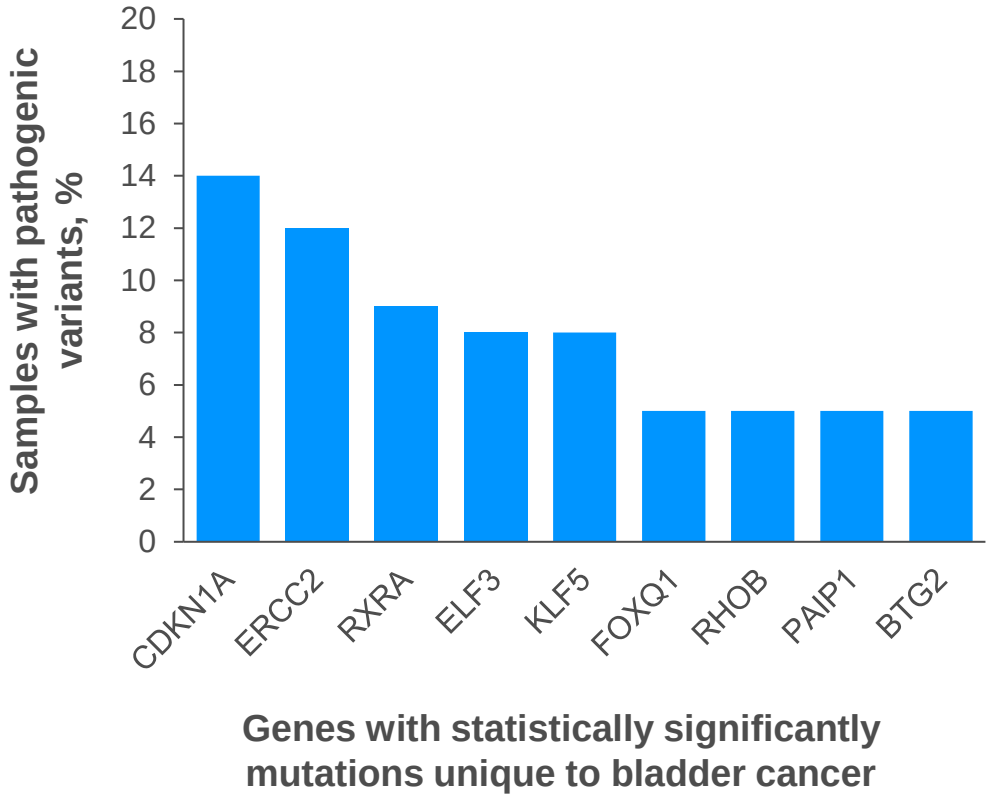


*Age-adjusted observed data.
1. Cancer stat facts: bladder cancer [Internet]. Surveillance, Epidemiology, and Ends Result Program, National Cancer Institute. Available from https://seer.cancer.gov/statfacts/html/urinb.html. Accessed April 19. 2024.

Urothelial Carcinoma: Biology

- Urothelial tumorigenesis is caused by clonal expansion and cellular acquisition of mutations in the urothelium[1]
- **UC is characterized by high tumor mutational burden and genomic instability[2]**
- Common alterations include *FGFR3*, *TP53*, *PIK3CA*, *RB1*, *CDKN2A*, and *E2F3*[1,3]
- The Cancer Genome Atlas (TCGA) found 9 urothelial cancer-specific genes not previously reported as significantly mutated in any cancer[3]
- The main pathways dysregulated in metastatic UC are involved in[3]:
  - Cell cycle regulation
  - Kinase and phosphatidylinositol-3-OH kinase (PI(3)K) signaling
  - Chromatin remodeling

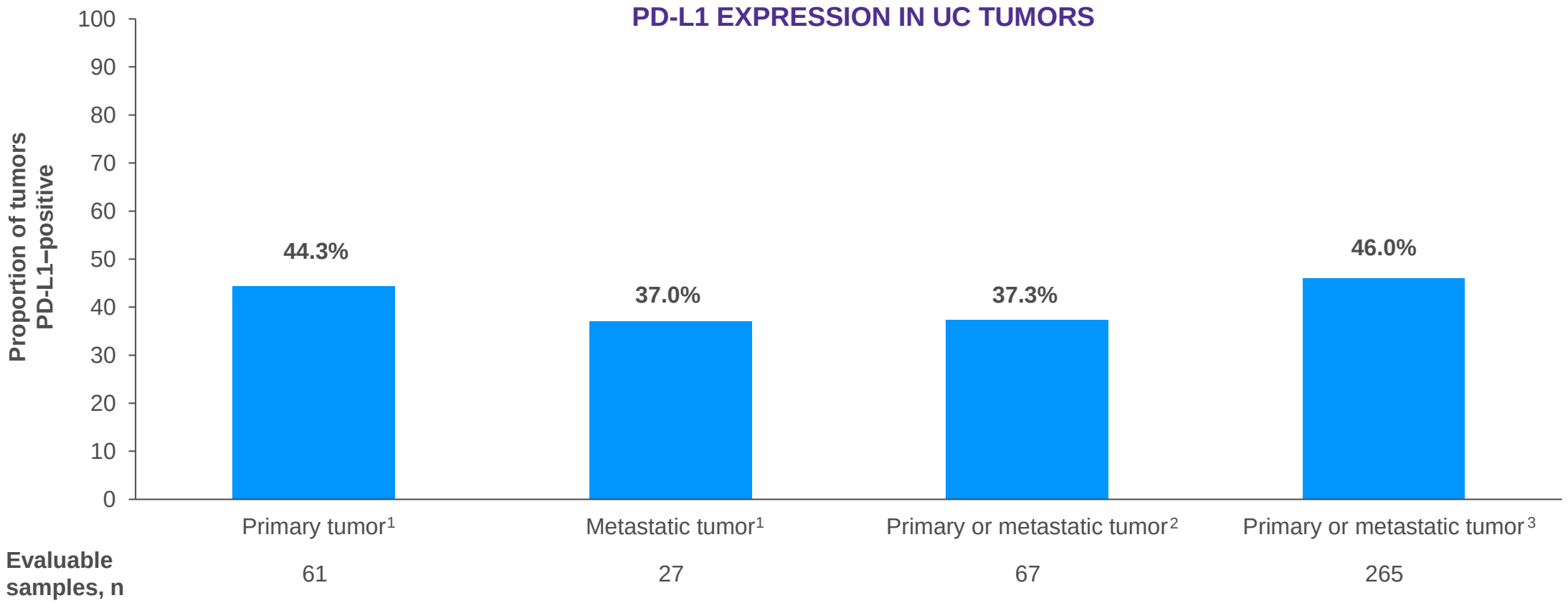
ALTERED GENES IN BLADDER CANCER NOT REPORTED IN ANY OTHER TCGA CANCER



1. Lopez-Beltran A, Cimadamore A, Montironi R, Cheng L. *Hum Pathol*. 2021;113:67-83. 2. Alexandrov LB, et al. *Nature* 2013;500:415-21. 3. Cancer Genome Atlas Research Network. *Nature* 2014;507(7492):315-22

Urothelial Carcinoma: Biology

UC tumors are characterized by PD-L1 expression (≈35-45% of tumors), which can downregulate antitumor immune responses by binding to PD-1 on T cells[1-6]

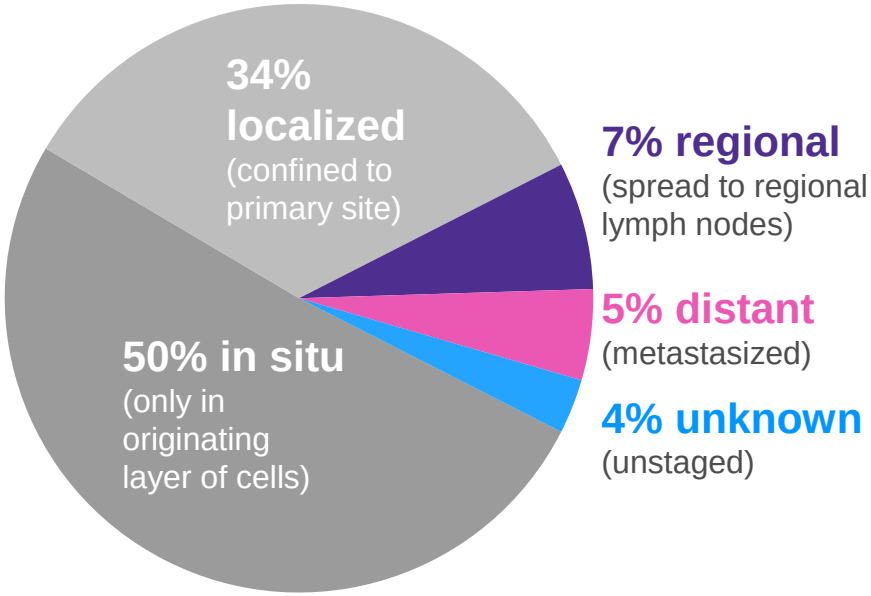


1. Pichler R, et al. Oncotarget 2017;8:66849-64. 2. Sharma P, et al. Lancet Oncol 2016;17:1590-8. 3. Sharma P, et al. Lancet Oncol 2017;18:312-22. 4. Cheng W, et al. Oncogenesis 2018;7:2. 5. Kim JW, et al. Curr Opin Oncol 2015;27:191-200. 6. Dudley JC, et al. Clin Cancer Res 2016;22:813-20.

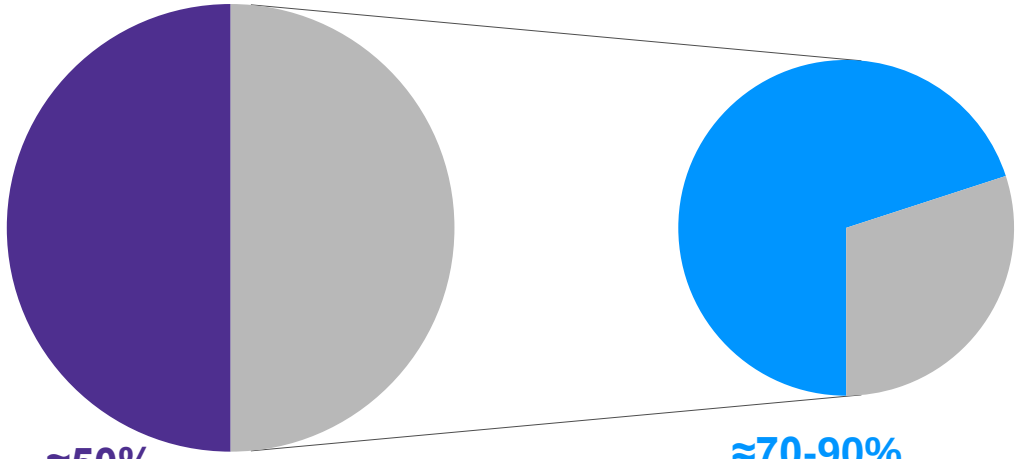
Bladder Cancer: Metastatic Disease

- Approximately **5%** of patients have metastatic bladder cancer at diagnosis[1]
- Relapse occurs after cystectomy in approximately half of patients, with distant metastasis accounting for **70-90%** of relapses[2]

PERCENTAGE OF BLADDER CANCER CASES BY STAGE AT DIAGNOSIS[1]



RELAPSE AFTER CYSTECTOMY IN BLADDER CANCER[2]



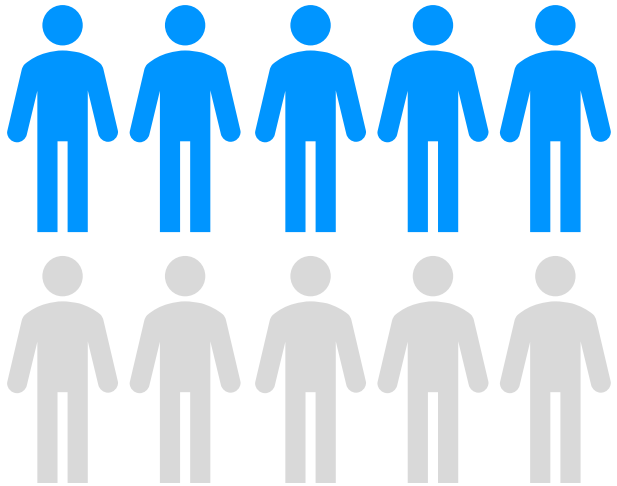
≈50%
of patients have relapse after cystectomy

≈70-90%
of patients relapse with distant metastases

1. Cancer stat facts: bladder cancer [Internet]. Surveillance, Epidemiology, and Ends Result Program, National Cancer Institute. Available from https://seer.cancer.gov/statfacts/html/urinb.html. Accessed April 19, 2024.
2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V.3.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed April 19, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

EMD SERONO

Metastatic or Locally Advanced UC: 1L Treatment



- Immune checkpoint inhibitor with antibody-drug conjugate is the preferred 1L treatment option, regardless of cisplatin eligibility.[1]
- Other recommended regimens in the 1L setting include platinum-based chemotherapy followed by immunotherapy maintenance or in combination with immunotherapy followed by immunotherapy maintenance[1]

~50% of patients are eligible for cisplatin-based chemotherapy. For cisplatin-ineligible patients, carboplatin-based chemotherapy might be an option[2]

Platinum eligibility for 1L treatment of metastatic UC (United States)

1L platinum-based treatment for metastatic UC: eligibility assessment & follow-up (EU)

Platinum Eligibility for 1L Treatment of Metastatic UC (United States)

CISPLATIN INELIGIBLE IF ANY OF THE FOLLOWING CRITERIA ARE MET[1]

- ✓ ECOG PS ≥2
- ✓ Creatinine clearance **<60 mL/min**
- ✓ Grade ≥2 hearing loss
- ✓ Grade ≥2 neuropathy
- ✓ Heart failure NYHA class III

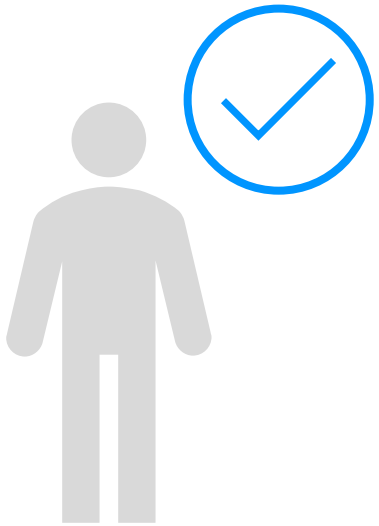
PLATINUM INELIGIBLE (CISPLATIN AND CARBOPLATIN INELIGIBLE) IF ANY OF THE FOLLOWING CRITERIA ARE MET[2]:

- ✗ ECOG PS ≥3
- ✗ Creatinine clearance **<30 mL/min**
- ✗ Peripheral neuropathy grade ≥2
- ✗ Heart failure NYHA class >III
- ✗ ECOG PS 2 and creatinine clearance **<30 mL/min**

CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; NYHA, New York Heart Association; PS, performance status; UC, urothelial cancer.

1. Galsky MD, Hahn NM, Rosenberg J, et al. *J Clin Oncol*. 2011;29(17):2432-2438. 2. Gupta S, Sonpavde G, Grivas P, et al. *J Clin Oncol*. 2022;40(suppl 16):4577.

Platinum Eligibility for 1L Treatment of Metastatic UC (EU)



Platinum eligibility for 1L treatment of metastatic UC can be divided as follows[1]:

Cisplatin eligible

- ECOG PS 0-1
- GFR >50-60 mL/min
- Audiometric hearing loss grade <2
- Peripheral neuropathy grade <2
- Cardiac insufficiency NYHA class <III

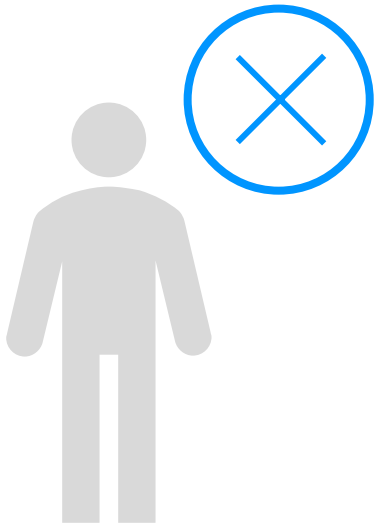
Carboplatin eligible

- ECOG PS 2 or GFR between 30-60 mL/min
- Not fulfilling other cisplatin-eligibility criteria

ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; GFR, glomerular filtration rate; NYHA, New York heart association.

1. Cathomas R, Lorch A, Bruins HM, et al. *Eur Urol*. 2022;81(1):95-103.

Platinum Eligibility for 1L Treatment of Metastatic UC (EU)



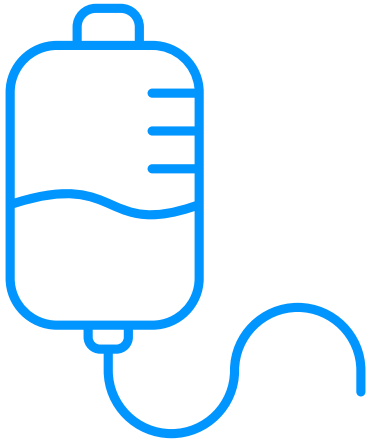
Patients are deemed unfit for any platinum-based chemotherapy if they meet any of the following criteria[1]

- GFR <30 mL/min
- ECOG PS >2
- ECOG PS 2 and GFR <60 mL/min
- Comorbidities grade >2

ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; GFR, glomerular filtration rate.

1. Cathomas R, Lorch A, Bruins HM, et al. *Eur Urol*. 2022;81(1):95-103.

Metastatic UC:
1L Platinum-Based Treatment Assessment & Follow-Up[1]



Regardless of the specific regimen used, patients with metastatic UC are re-evaluated after 2-3 cycles of chemotherapy

- Treatment is continued for 2 more cycles of chemotherapy in patients whose disease responds or remains stable
- Chemotherapy may be continued for up to 6 cycles, depending on response

If no response is noted after 2 cycles, or if significant morbidities are encountered, a change in therapy is advised

- For patients who show response or stable disease through a full course of platinum-based chemotherapy, maintenance therapy with an immune checkpoint inhibitor is a recommended option
- Platinum-based chemotherapy may also be combined with immunotherapy followed by immunotherapy maintenance

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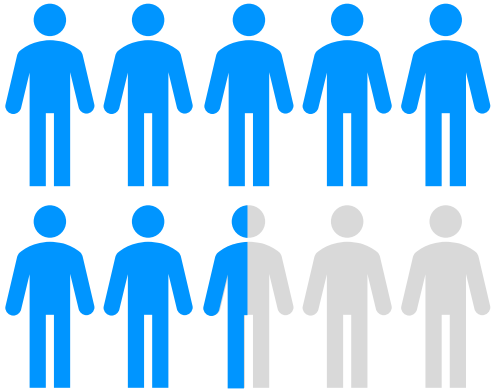
Metastatic or Locally Advanced UC:
Outcomes With 1L Platinum-Based Chemotherapy (Without Maintenance Immunotherapy)



~75% of patients who received 1L platinum-based chemotherapy in randomized clinical trials achieved disease control[1-3]

Median OS

- Cisplatin-eligible patients: 12.7-15.8 months[1,4]
- Carboplatin-eligible patients unfit for cisplatin regimens: 8.1-9.3 months[2]

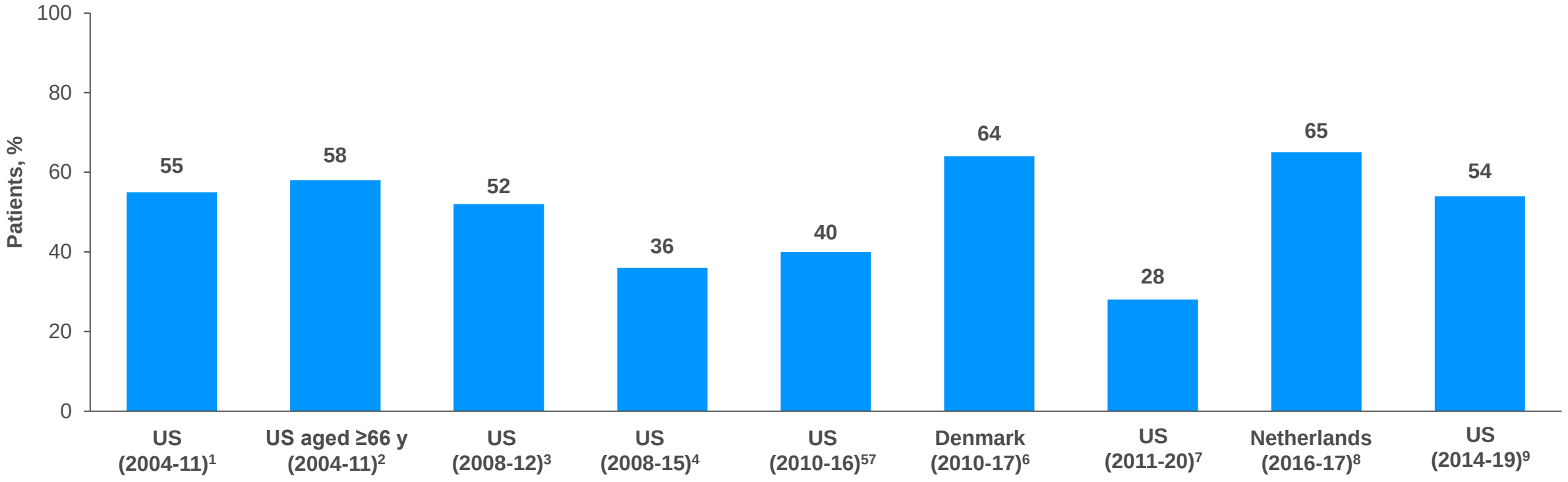
Median PFS

- Cisplatin-eligible patients: 7.6-8.3 months[1,4]
- Carboplatin-eligible patients unfit for cisplatin regimens: 4.2-5.8 months[2]

1. Bellmunt J, von der Maase H, Mead GM, et al. *J Clin Oncol*. 2012;30(10):1107-1113. 2. De Santis M, Bellmunt J, Mead G, et al. *J Clin Oncol*. 2012;30(2):191-199. 3. von der Maase H, Hansen SW, Roberts JT, et al. *J Clin Oncol*. 2000;18(17):3068-3077. 4. von der Maase H, Sengelov L, Roberts JT, et al. *J Clin Oncol*. 2005;23(21):4602-4608.

Metastatic or Locally Advanced UC:
Patients Not Receiving Treatment

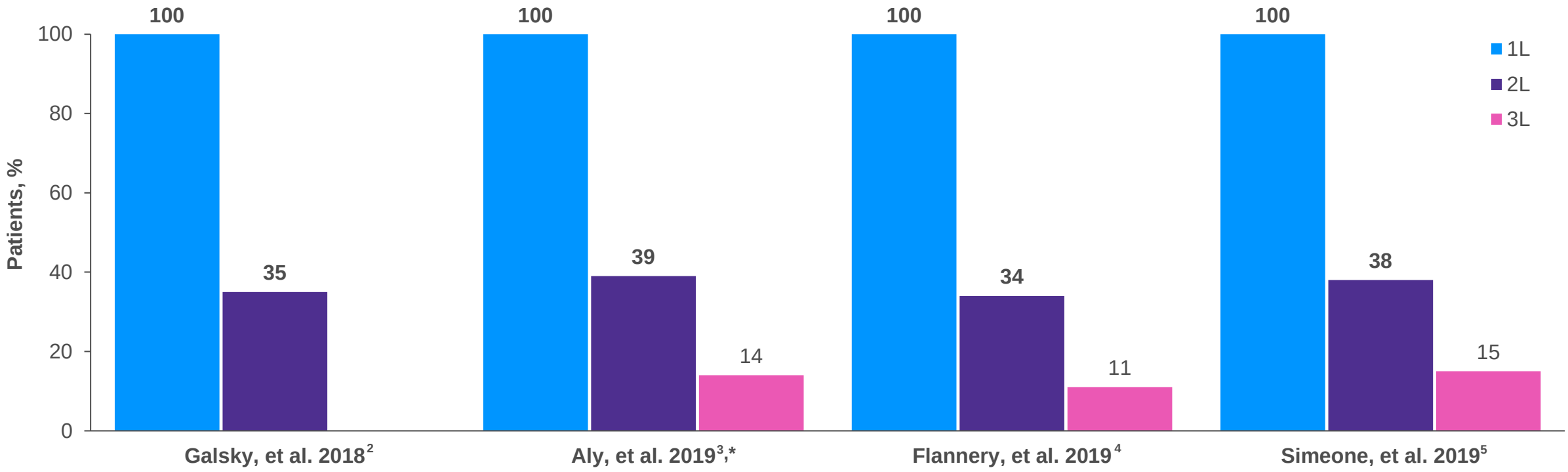
Across several real-world studies, **≈40-60%** of patients presenting with locally advanced or metastatic UC did not receive any 1L drug therapy[1-9]



1. Aly A, et al. J Med Econ 2019;22:662-70. 2. Galsky MD, et al. Bladder Cancer 2018;4:227-38. 3. Dinan MA, et al. J Geriatr Oncol 2021;12:298-304. 4. Fisher MD, et al. Clin Genitourin Cancer 2018; 16:e1171-9. 5. Flannery K, et al. Future Oncol 2019;15:1323-34. 6. Jensen JB, et al. Ann Oncol 2021. Abstract 707P (poster presentation). 7. Geynisman DM, et al. J Clin Oncol. 2021;39:(suppl 15): Abstract 4538 (poster presentation). 8. Richters A, et al. Cancer Treat Res Commun 2020;25:100266. 9. Bilen M, et al. Ann Oncol 2021. Abstract 701P (poster presentation).

Urothelial Carcinoma:
Unmet Need After 1L Treatment for Metastatic or Locally Advanced Disease

Data from real-world studies show that **34-39%** of patients who received 1L chemotherapy for metastatic or locally advanced UC received 2L treatment[1]



1L, first line; 2L, second line; UC, urothelial cancer.
* Included patients with staging of T4b/N0/M0, any T/N1-3/M0, or any T/any N/M1.[3]

1. Grivas P, et al. Cancer Treat Rev. 2021;97. doi:10.1016/j.ctrv.2021.102187. 2. Galsky MC, et al. Bladder Cancer. 2018;4:227-38. doi:10.3233/blc-170149. 3. Aly A, et al. J Med Econ. 2019;22:662-70. doi:10.1080/13696998.2019.1591424. 4. Flannery K, et al. Future Oncol. 2019;15:1323-34. doi:10.2217/fon-2018-0564. 5. Simeon JC, et al. Cancer Epidemiol. 2019;60:121-7. doi:10.1016/j.canep.2019.03.013.

Metastatic or Locally Advanced UC:
2L+ Treatment Options[1]

- **For patients who do receive 2L+ treatment, options depend on what was offered as 1L:**
  - Immune checkpoint inhibitors are approved for the treatment of locally advanced or metastatic urothelial cell carcinoma that has progressed during or after platinum-based chemotherapy or that has progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy, regardless of PD-L1 expression levels
  - Antibody-drug conjugates may also be options for eligible patients who received a platinum-based chemotherapy in the 1L setting or after treatment with a platinum-based chemotherapy and an immune checkpoint inhibitor
  - FGFR inhibitors are an option for patients who have a susceptible *FGFR3* genetic alteration* who have received a chemotherapy (with or without platinum) or a checkpoint inhibitor
  - Clinical trial enrollment is strongly recommended in the 2L+ setting for locally advanced or metastatic disease
  - Other chemotherapy or systemic therapy options as appropriate

* The NCCN Bladder Cancer Panel recommends that molecular/genomic testing be performed for stages IVA/B bladder cancer and may be considered for stage IIIB.

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