






















Bladder Cancer

	Signs and symptoms	
	Key risk factors	
	Key US & global statistics	
	Histology	

	US survival rate	
	Biology	
	Metastatic or locally advanced disease	
<ul style="list-style-type: none"> Epidemiology 1L treatment Treatment assessment and follow-up after 1L PBC Outcomes with 1L PBC treatment Patients not receiving 1L treatment Unmet need after 1L treatment 2L+ treatment options		





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



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 cancer¹
Genetic changes that affect the breakdown of toxins and mutations in known tumor suppressors¹



Chronic infections

Urinary infections, kidney and bladder stones, and schistosomiasis infections¹

ENVIRONMENTAL RISK FACTORS FOR BLADDER CANCER



Smoking

>3-fold increased risk¹



Chemicals

Exposure to specific chemicals in the workplace¹



Certain medicines or herbal supplements¹



Low fluid intake¹



Bladder Cancer: Key US and Global Statistics



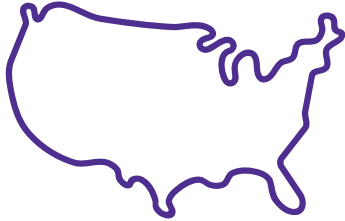
9th most common cancer globally¹

Estimated new cases in 2022¹

613,791

Estimated deaths in 2022¹

220,349



6th most common cancer in the US²

Estimated new cases in 2025²

84,870

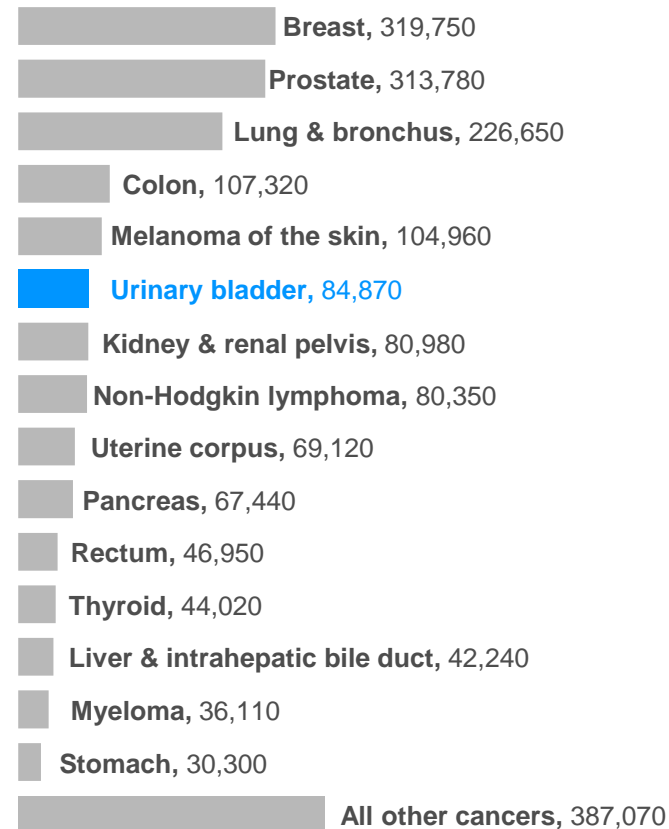
Estimated deaths in 2025²

17,420

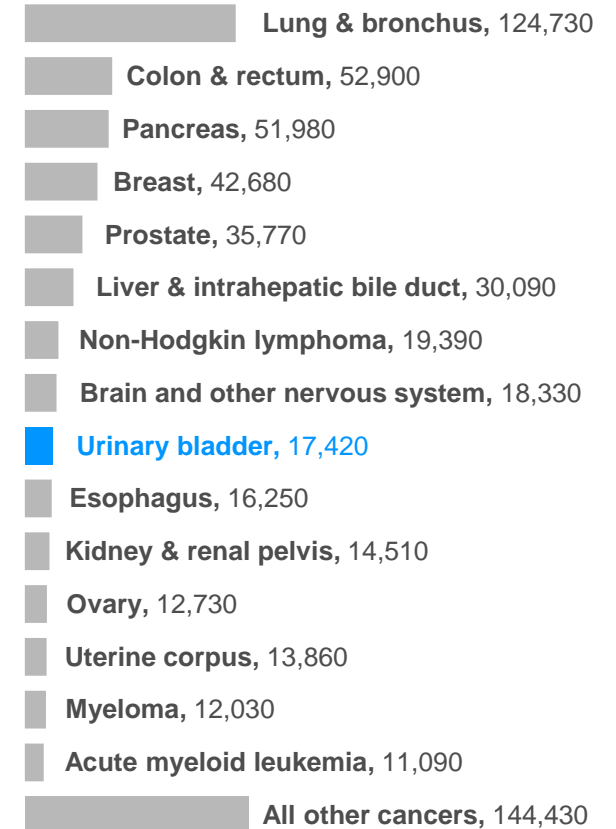
Median age at diagnosis²

73 yrs

ESTIMATED NEW CASES OF BLADDER CANCER IN THE US IN 2025³

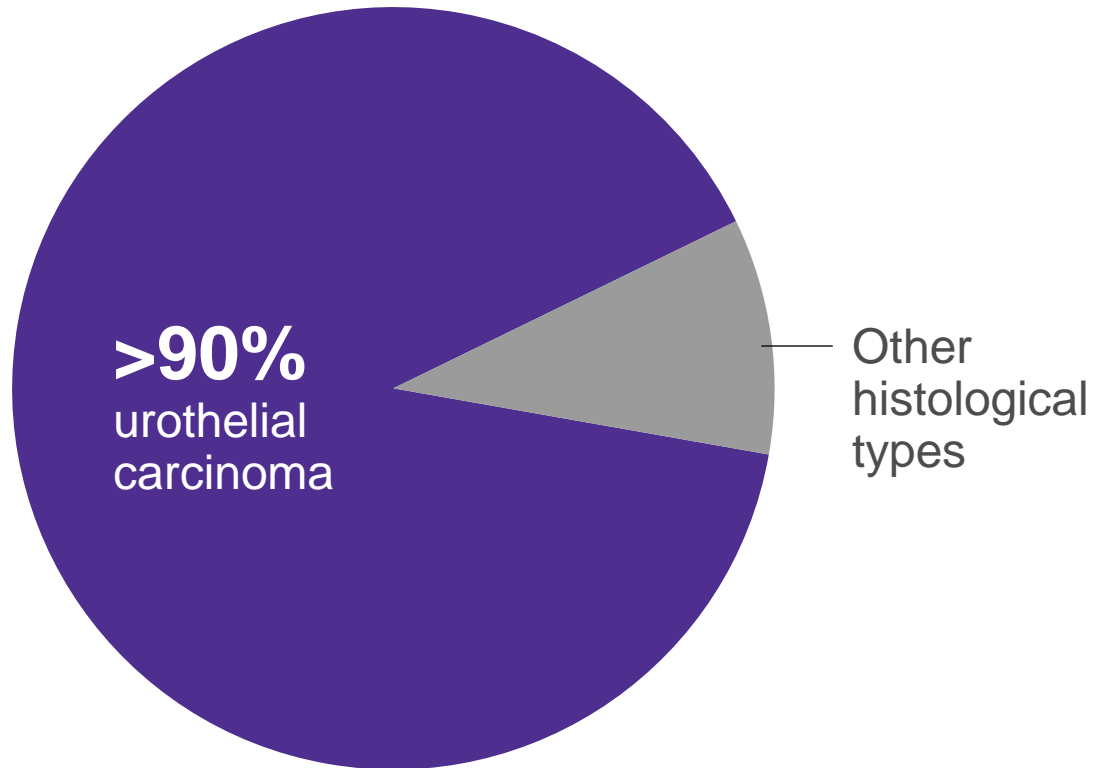


ESTIMATED DEATHS FROM BLADDER CANCER IN THE US IN 2025³





Bladder Cancer: Histology



ADDITIONAL INFORMATION ON DIFFERENT TYPES OF BLADDER CANCER¹⁻³

Urothelial carcinoma

- Also called transitional cell carcinoma
- 90% of UC originates in the urothelial cells that line the inside of the bladder⁴
- 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



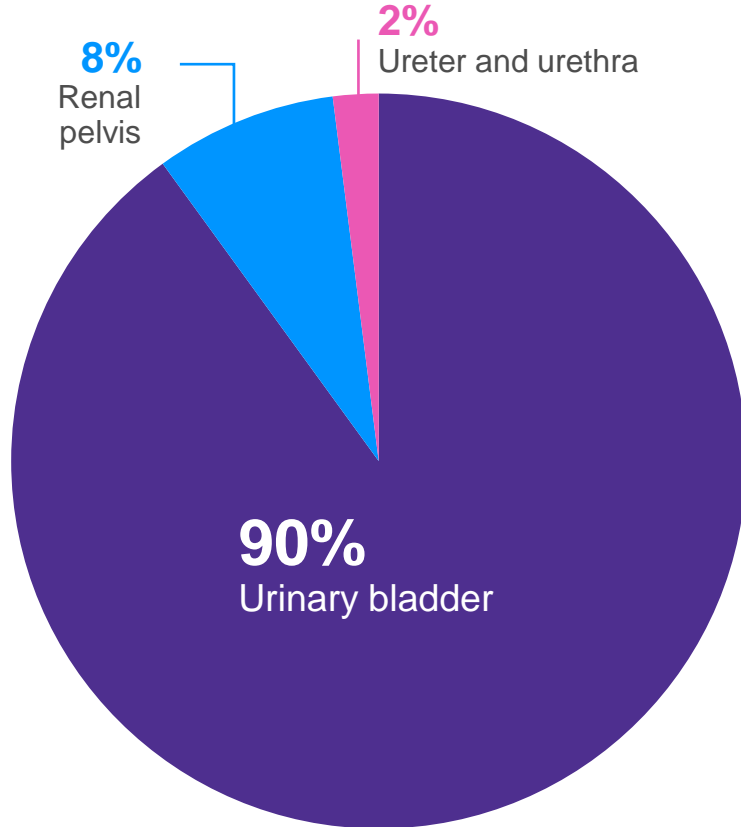
Small cell carcinoma

- 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 May 19, 2025. 2. American Cancer Society. About bladder cancer. <https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html>. Accessed May 19, 2025. 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.1.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed May 19, 2025. 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.

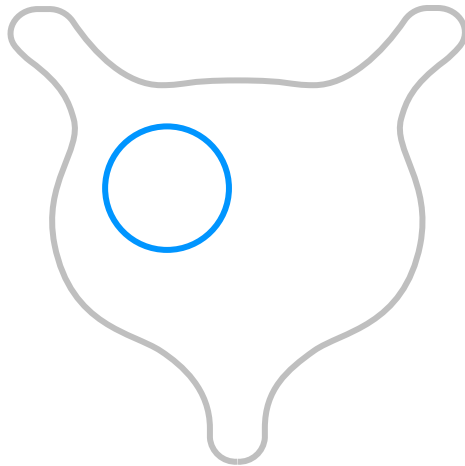
Urothelial Carcinoma



- 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



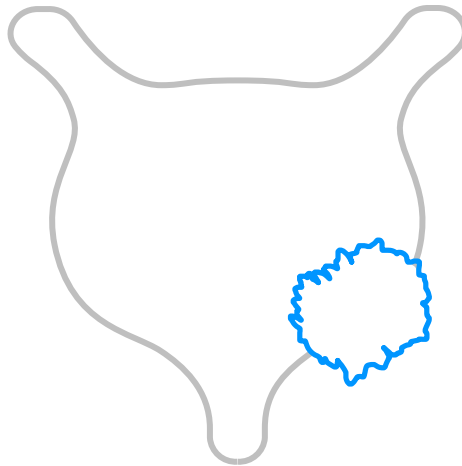
Squamous Cell Carcinoma



- 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

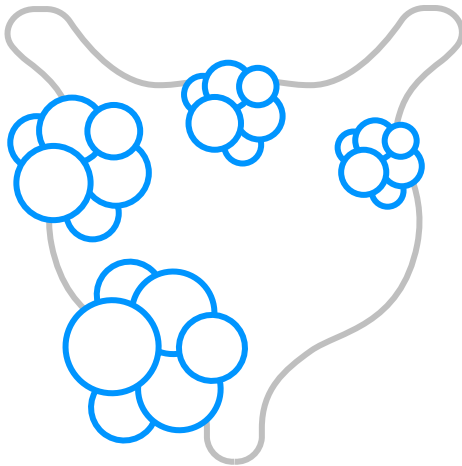


Adenocarcinoma



- Primary bladder adenocarcinoma is rare; it comprises only **0.5-2%** of all primary bladder malignancies¹
- Usually presents at an advanced stage with nodal involvement in **30-40%** of cases¹
- Morphologically heterogeneous, with enteric, mucinous, signet ring cell, and mixed subtypes¹
- Morphologic similarities with primary adenocarcinoma from other sites results in diagnostic challenges to confirm the urinary bladder origin¹
- 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}

Small Cell Carcinoma



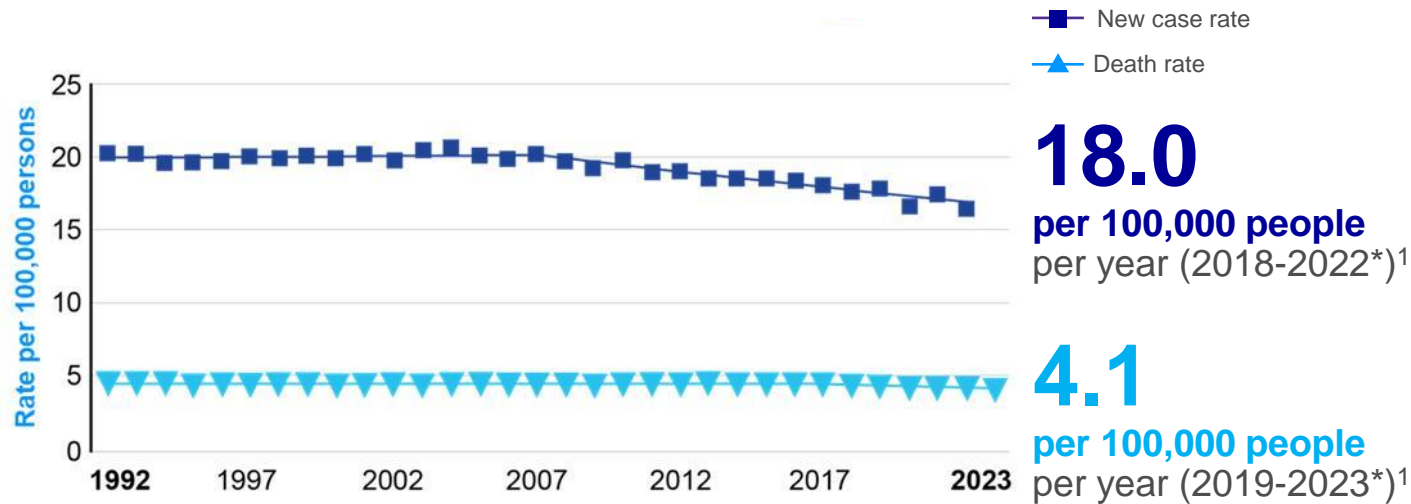
- Extremely rare, with a reported incidence of less than **1-9/1,000,000** people
- The pathogenesis of small cell carcinoma of the bladder is not well defined
- Histologically, it is identical to small cell lung carcinoma (SCLC), and the recommended treatment is also the same



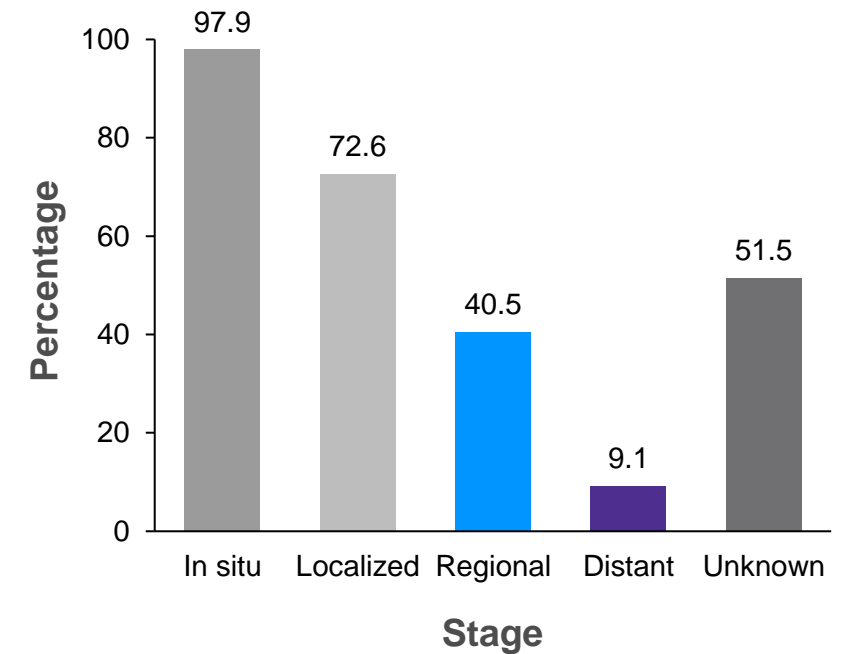
Bladder Cancer: US Survival

- In the last 20 years, the death rate from bladder cancer has remained relatively unchanged¹
- Metastatic disease has a 5-year relative survival rate[†] of **≈9.1%**

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



5-YEAR SURVIVAL BY BLADDER CANCER STAGE AT DIAGNOSIS¹

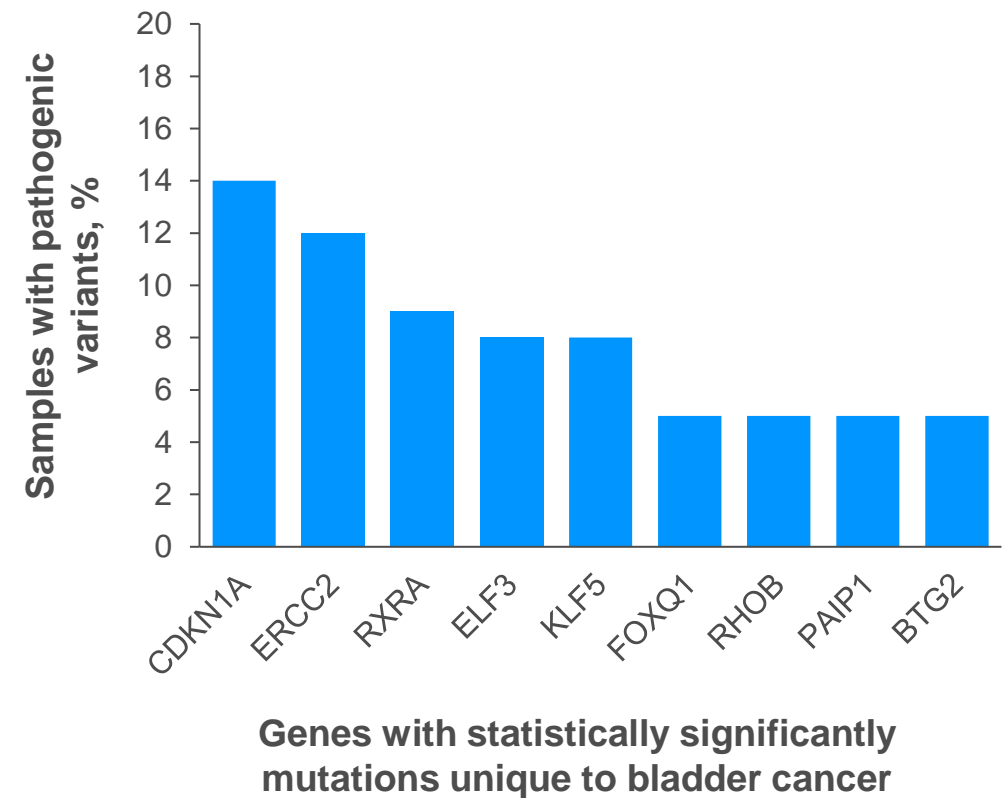




Urothelial Carcinoma: Biology

- Urothelial tumorigenesis is caused by clonal expansion and cellular acquisition of mutations in the urothelium¹
- **UC is characterized by high tumor mutational burden and genomic instability²**
- 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 cancer³
- The main pathways dysregulated in metastatic UC are involved in³:
 - Cell cycle regulation
 - Kinase and phosphatidylinositol-3-OH kinase (PI(3)K) signaling
 - Chromatin remodeling

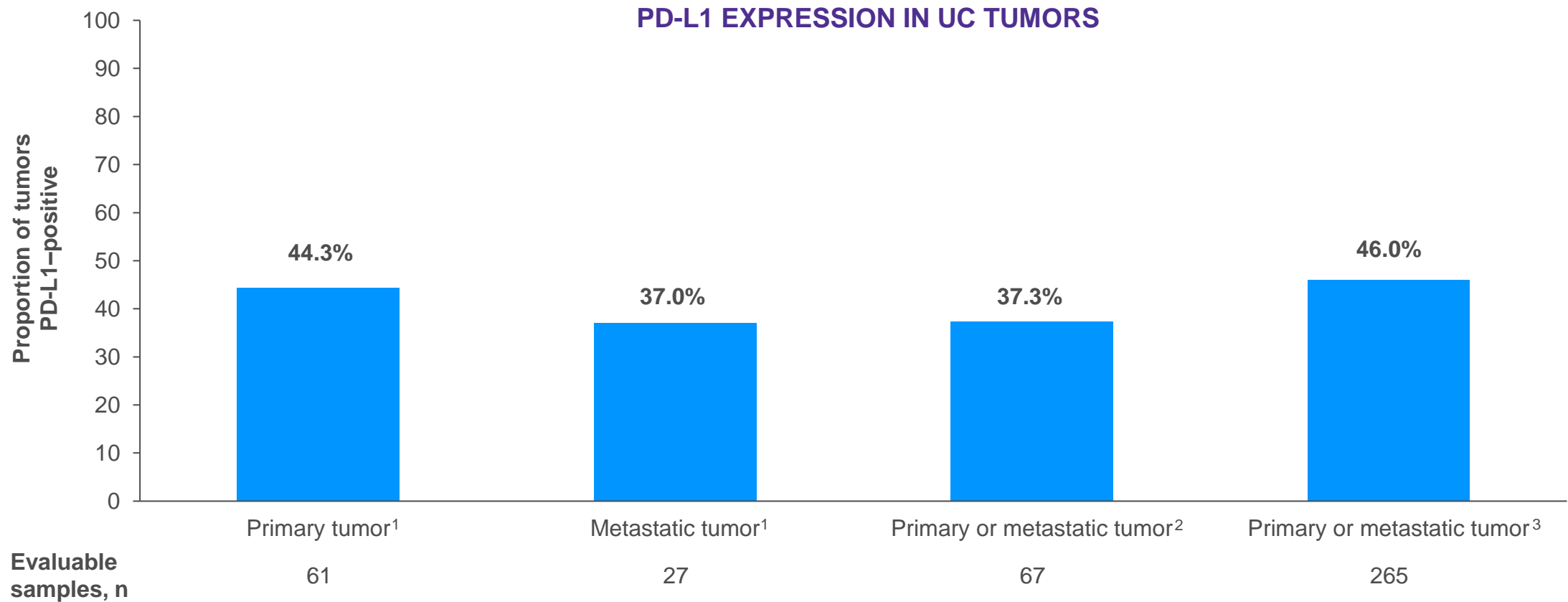
ALTERED GENES IN BLADDER CANCER NOT REPORTED IN ANY OTHER TCGA CANCER





Urothelial Carcinoma: Biology

UC tumors are characterized by PD-L1 expression ($\approx 35\text{-}45\%$ of tumors), which can downregulate antitumor immune responses by binding to PD-1 on T cells¹⁻⁶

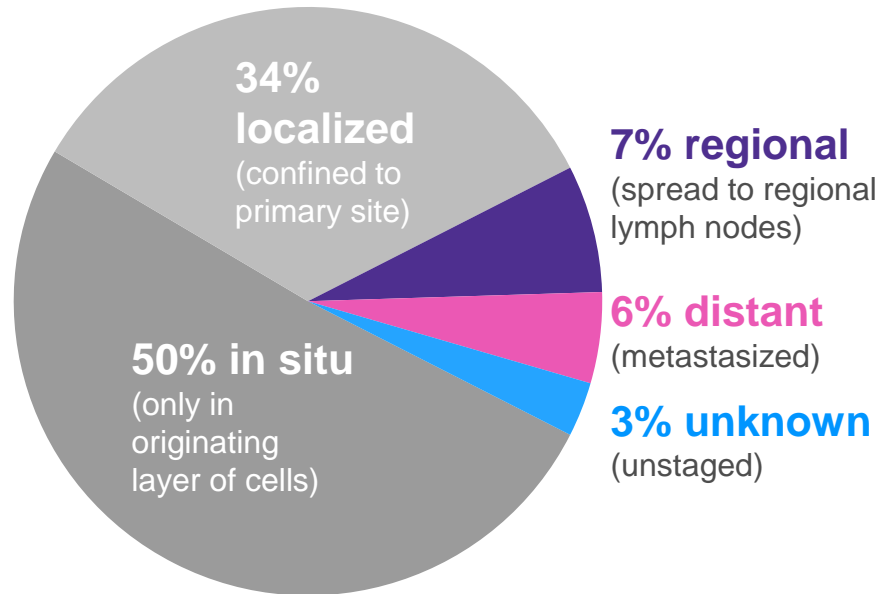




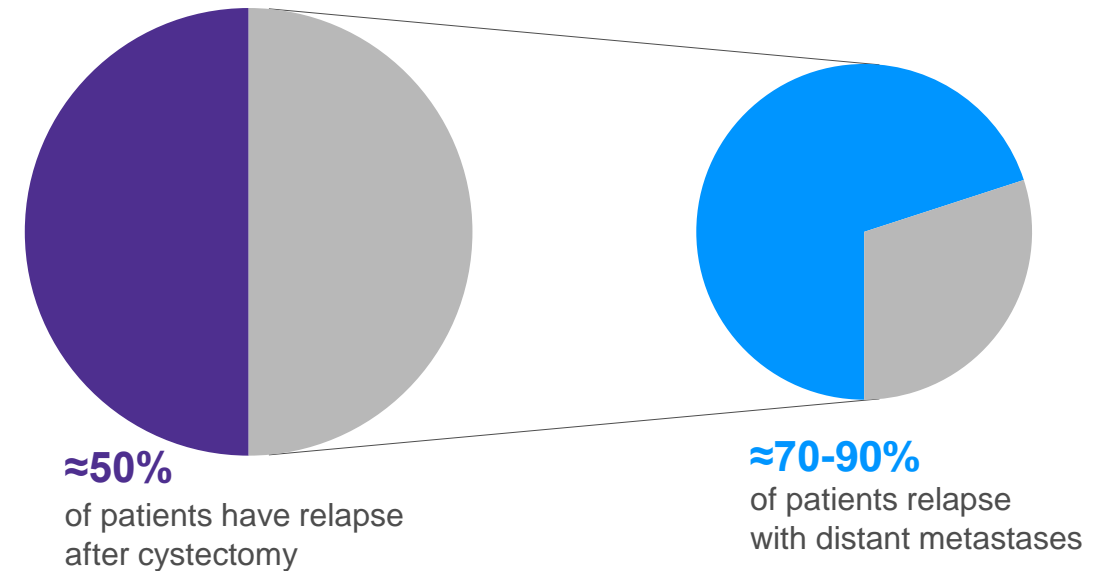
Bladder Cancer: Metastatic Disease

- Approximately **6%** of patients have metastatic bladder cancer at diagnosis¹
- Relapse occurs after cystectomy in approximately half of patients, with distant metastasis accounting for **70-90%** of relapses²

PERCENTAGE OF BLADDER CANCER CASES BY STAGE AT DIAGNOSIS¹



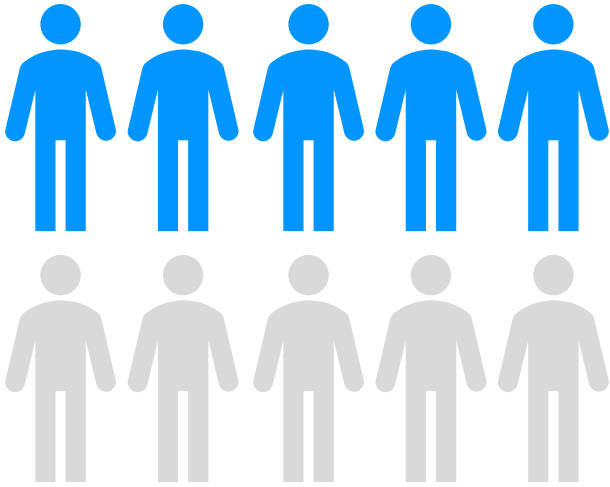
RELAPSE AFTER CYSTECTOMY IN BLADDER CANCER²



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 May 19, 2025.
2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V.1.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed April 19, 2025. 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.



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 maintenance¹

~50% of patients are eligible for cisplatin-based chemotherapy. For cisplatin-ineligible patients, carboplatin-based chemotherapy or immunotherapy might be an option²

Platinum eligibility for 1L treatment of metastatic UC in the United States



Platinum eligibility for 1L treatment of metastatic UC in Europe

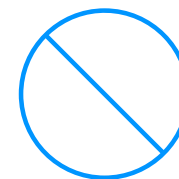


Platinum Eligibility for 1L Treatment of Metastatic UC (United States)



CISPLATIN INELIGIBLE IF ANY OF THE FOLLOWING CRITERIA ARE MET¹

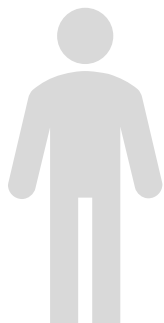
- ✓ ECOG PS ≥ 2
- ✓ Creatinine clearance **<60 mL/min**
- ✓ Grade ≥ 2 hearing loss
- ✓ Grade ≥ 2 neuropathy
- ✓ Heart failure NYHA class III



PLATINUM INELIGIBLE (CISPLATIN AND CARBOPLATIN INELIGIBLE) IF ANY OF THE FOLLOWING CRITERIA ARE MET²:

- ✗ 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**

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



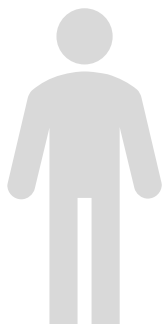
Platinum eligibility for 1L treatment of metastatic UC can be divided as follows¹:

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

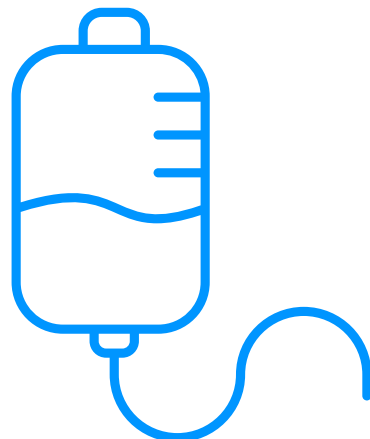


Patients are deemed unfit for any platinum-based chemotherapy if they meet any of the following criteria¹

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

Metastatic UC:

1L Platinum-Based Treatment Assessment & Follow-Up¹



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

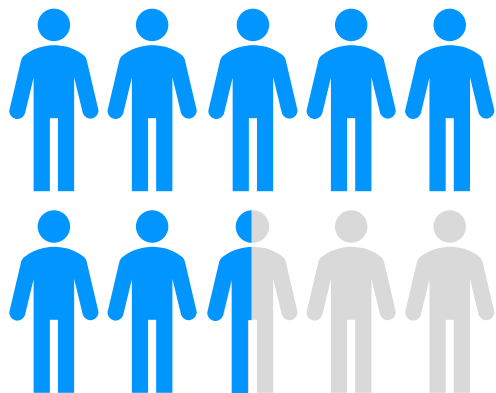
- Treatment is continued for 2 more cycles of chemotherapy in patients whose disease responds or remains stable
- Chemotherapy may be continued for up to 6 cycles, depending on response

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

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 control¹⁻³

Median OS

- Cisplatin-eligible patients: 12.7-15.8 months^{1,4}
- Carboplatin-eligible patients unfit for cisplatin regimens: 8.1-9.3 months²

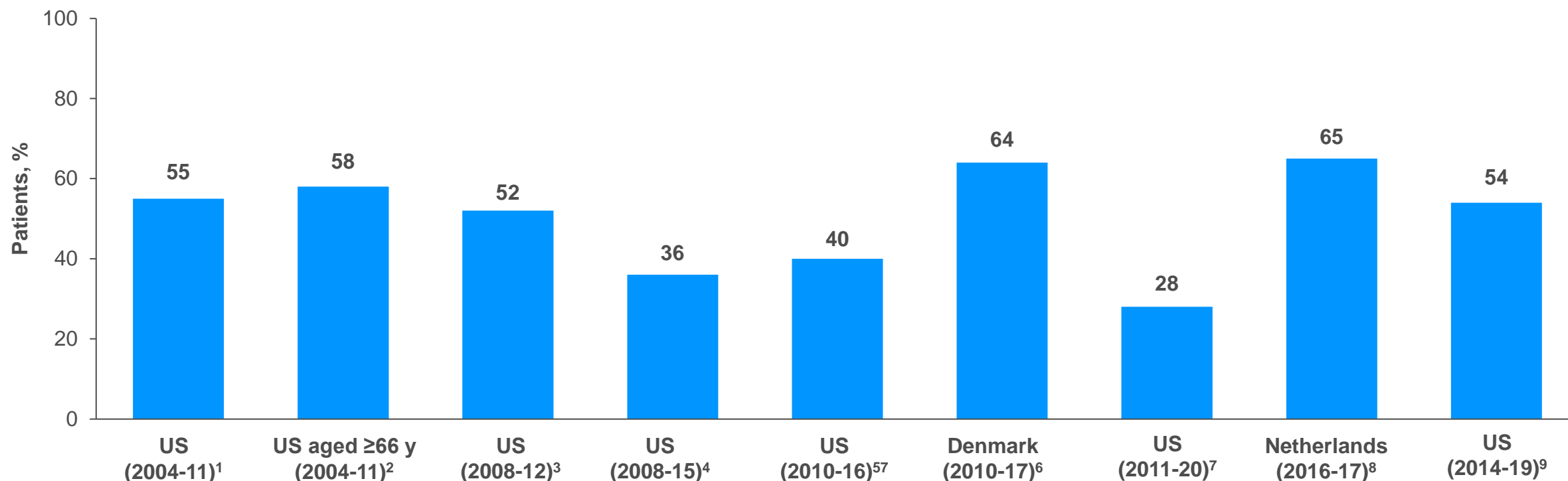
Median PFS

- Cisplatin-eligible patients: 7.6-8.3 months^{1,4}
- Carboplatin-eligible patients unfit for cisplatin regimens: 4.2-5.8 months²

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 therapy¹⁻⁹

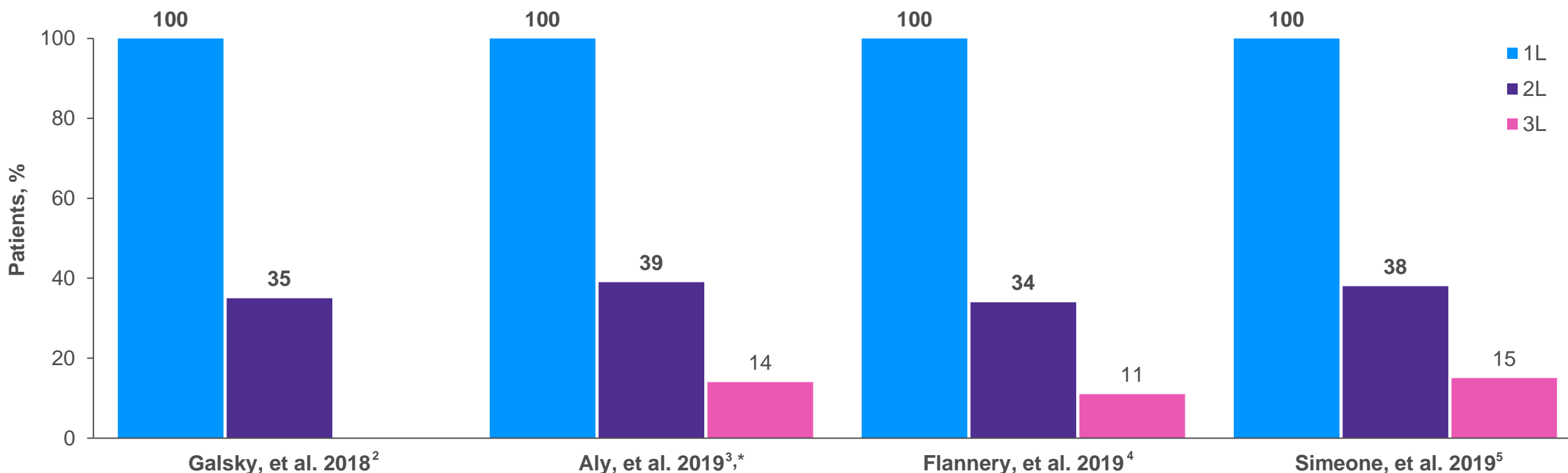


Urothelial Carcinoma:

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 treatment¹



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 Options¹



- **For patients who do receive 2L+ treatment, options depend on what was offered as 1L:**
 - Chemotherapy options (with or without platinum) are recommended for the treatment of locally advanced or metastatic urothelial cell carcinoma that has progressed during or after immunotherapy and antibody-drug conjugate combination therapy in the 1L setting
 - Immune checkpoint inhibitors and antibody-drug conjugates (as monotherapy or in combination) may be options for eligible patients who received a chemotherapy in the 1L setting
 - Antibody-drug conjugate (as monotherapy or in combination with immune checkpoint inhibitor) and chemotherapy are recommended for those progressed on previous immunotherapy
 - Biomarker-directed therapy (FGFR inhibitors and *HER2*-directed antibody–drug conjugates) is an option for patients with actionable mutations
 - Clinical trial enrollment is strongly recommended in the 2L+ setting for locally advanced or metastatic disease
 - Other chemotherapy or systemic therapy options as appropriate