Real-world treatment patterns and sequencing in patients with locally advanced or metastatic urothelial cancer (la/mUC) in the US

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SCOPE

- **This study aimed to describe baseline demographic and clinical characteristics, real-world treatment patterns, and treatment sequencing in patients with la/mUC in the US**
- **Characterizing the patient population to determine how avelumab's approval has impacted treatment sequencing was a key objective of this analysis**

CONCLUSIONS

- **The treatment patterns observed are consistent with known and evolving treatment paradigms in la/mUC[1]**
  - **77% of patients received systemic anticancer treatment following la/mUC diagnosis; among them, most patients (62%) received guideline-recommended first-line (1L) platinum-based chemotherapy (PBC)**
- **The use of PBC has increased and the use of immuno-oncology (IO) therapy and non-PBC has decreased in the 1L setting from 2020 through February 2022 following updated clinical guidelines and FDA label changes for IO monotherapy**
- **Post-avelumab approval, in patients receiving IO therapy as subsequent treatment to PBC, 80% received IO therapy as first-line maintenance (1LM), of which 84% received avelumab 1LM**
- **High attrition rates beyond 1L were observed with only 33.1% of patients receiving second-line (2L) therapy, indicating the persistence of high unmet treatment needs**
- **Enfortumab vedotin was the most commonly used 2L agent in patients who received 1LM therapy**
- **Future real-world studies could provide further insight into the optimal sequencing of targeted therapies in this disease**

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BACKGROUND

- PBC is the preferred 1L treatment for patients with la/mUC followed by 1LM with avelumab, a programmed cell death ligand 1 ~~ligand 1~~ (PD-L1)–blocking antibody and immune checkpoint inhibitor (ICI), in those whose disease does not progress on 1L PBC[2]
- Avelumab was approved as 1LM treatment for la/mUC by the FDA in June 2020, based on the seminal data from the JAVELIN Bladder 100 study[3,4]
  - Avelumab 1LM with best supportive care (BSC) significantly prolonged overall survival (OS) vs BSC alone in patients with la/mUC that had not progressed with 1L PBC (median OS, 21.4 vs 14.3 months; hazard ratio, 0.69 [95% CI, 0.56-0.86]; p=0.001)[3,5]
- The treatment options for la/mUC have rapidly evolved over recent years with the approval of fibroblast growth factor receptor (FGFR) inhibitors, various ICIs, and antibody-drug conjugates (ADCs)[6] enfortumab vedotin and sacituzumab govitecan and updates to clinical guidelines[1,2,7,8]

METHODS

Data sources

- This retrospective observational study used the Tempus database, ~~a nationwide longitudinal electronic health records (EHR) database,~~ comprising de-identified patient-level structured and unstructured data; curated by Tempus[9]

Patient population

- Patients aged ≥18 years and diagnosed with la/mUC (T4b, N2/3, and/or M1 or overall cancer stage 3/4) (index date) between January 1, 2016, and February 23, 2022, were included
- Patients who completed 1L PBC and then received an IO therapy were categorized as 1LM or 2L, according to the algorithm in **Figure 1**
- These patients were further split into pre- and post-groups based on when they completed their 1L PBC treatment in relation to avelumab's 1LM US approval[4] on June 30, 2020

Statistical analysis

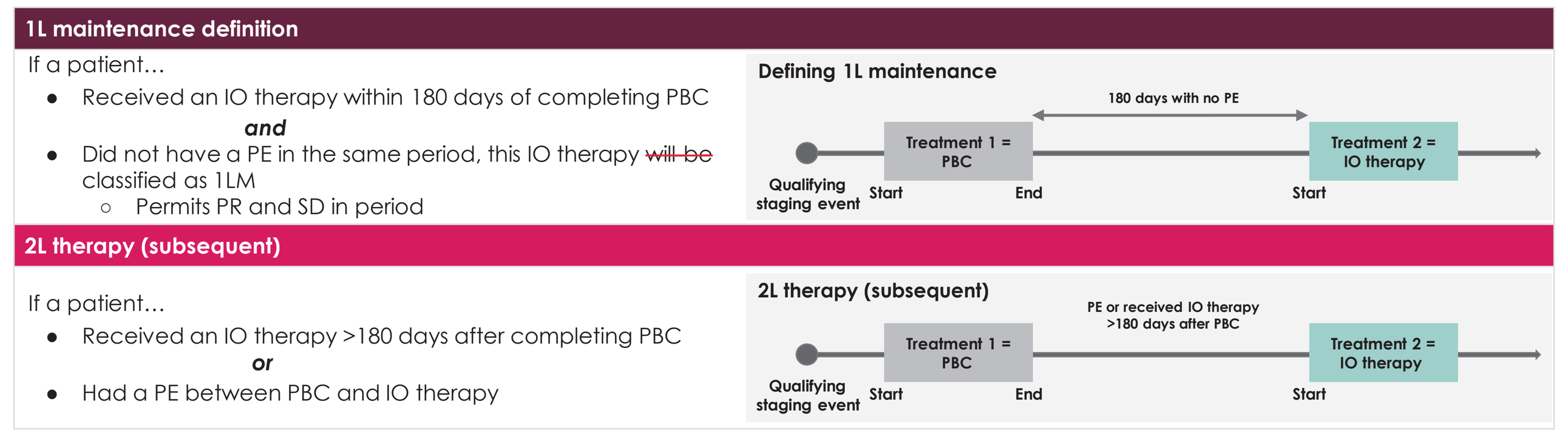
- Demographic and clinical characteristics were summarized by descriptive statistics

Ethics approval

- As the study used de-identified patient records, it was exempt from review and approval by ethics committees and the need for patient informed consent

Figure 1. Algorithm to define 1LM and 2L IO therapy

- 1LM was differentiated from 2L treatment based on a stated clinical intent of 1LM or initiation of IO therapy within 180 days of 1L PBC completion without disease progression in the Tempus data



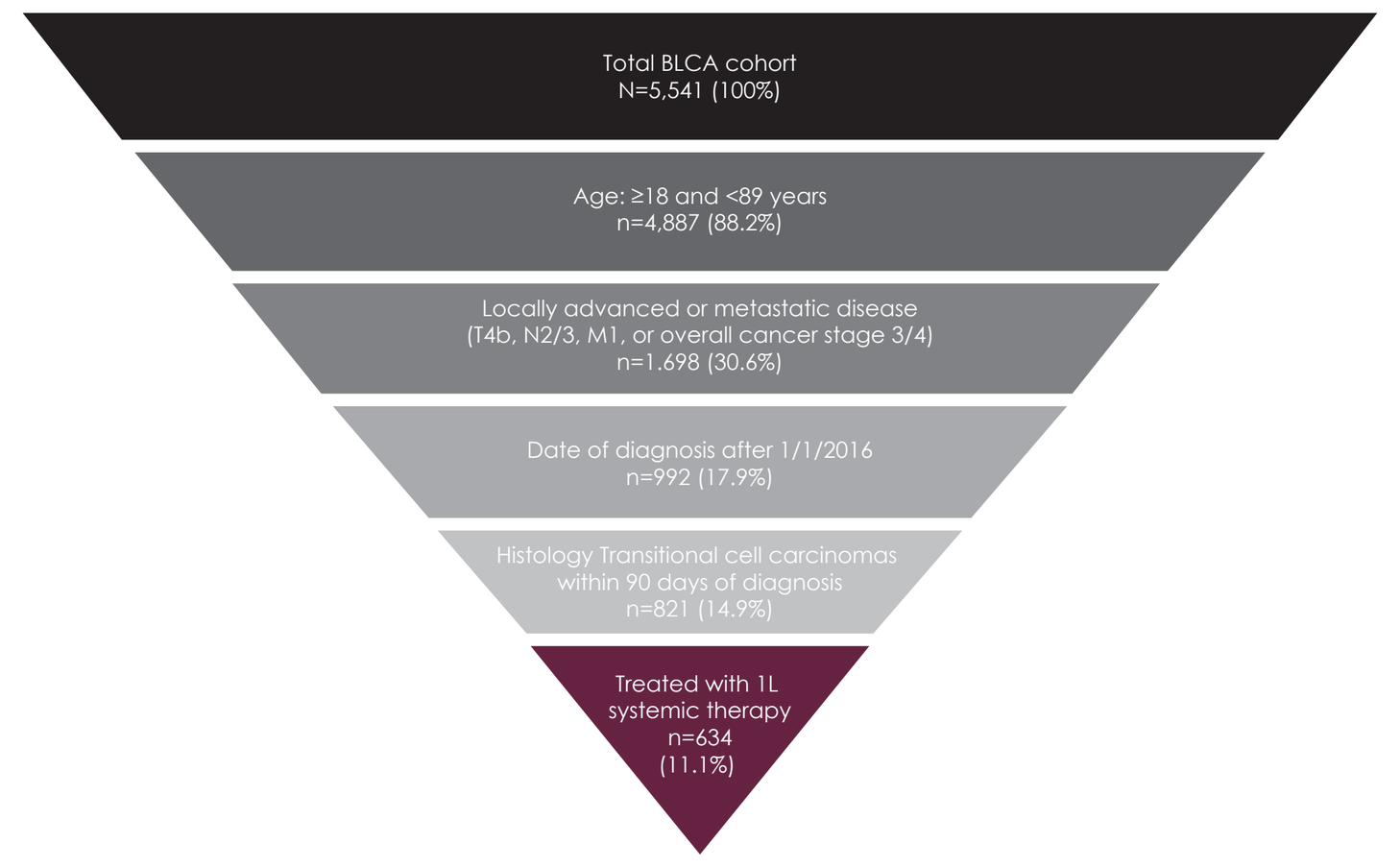
1LM, first-line maintenance; **2L,** second-line; **IO,** immuno-oncology; **PBC,** platinum-based chemotherapy; **PE,** progression event; **PR,** partial response; **SD,** stable disease.

RESULTS

Patient population

- A total of 821 patients were included (**Figure 2**) from community centers (21%), academic centers (27%), and ASCO CancerLinQ network sites (52%)
- Baseline demographic and clinical characteristics in the final la/mUC cohort are reported in **Table 1**
- The median age at diagnosis was 69 years (interquartile range, 62-76 years), 73% of patients were male, 63% were White, 80% had transitional cell carcinoma, and 44% had a documented smoking history (**Table 1**)

Figure 2. Study population



1L, first line; **BLCA,** bladder cancer.

Treatment patterns

- A total of 634 patients (77%) received 1L systemic treatment; of those, 62% (395/634) received PBC, 24% (155/634) received IO monotherapy, 7% (45/634) received non-PBC, and 6% (39/634) received other regimens* (**Table 2**)
- Among all patients who received 1L PBC, the majority received cisplatin (63.8%; 252/395), and most of the remaining patients received carboplatin (35.7%; 141/395). Only 0.5% (2/395) received oxaliplatin
- Among all patients who received 1L treatment, 33.1% (210/634) had evidence of receiving a 2L treatment. The most common 2L therapies included pembrolizumab (27.1%), enfortumab vedotin (16.7%), and carboplatin plus gemcitabine (9.0%)
- Among all patients who received 2L treatment, 31.0% (65/210) had evidence of receiving a third-line (3L) treatment. The most common 3L therapies included enfortumab vedotin (21.5%), pembrolizumab (20.0%), and atezolizumab† (10.8%) (**Table 2**)
- The distribution of systemic 1L therapy initiated according to treatment class is summarized by year in **Figure 3**
- In the 1L setting, the use of PBC has increased and the use of IO monotherapy and non-PBC has decreased since 2020

*Other regimens included: ADCs, ADC combinations with IO therapy, chemotherapy or IO therapy + chemotherapy, IO therapy combinations, hormone + targeted therapy, tyrosine kinase inhibitors, and unlabeled investigational new drugs. †Atezolizumab is no longer approved in the US to treat patients with la/mUC following the manufacturer's decision to withdraw its indication after consulting with the FDA. The withdrawal was made in accordance with the FDA's Accelerated Approval Program after results from the phase 3 IMvigor130 trial (NCT02807636) failed to meet the postmarketing requirement necessary to convert the accelerated approval for atezolizumab into regular approval.[10]

Table 1. Baseline demographic and clinical characteristics in patients in the overall la/mUC cohort (N=821)

Characteristic	N=821
Systemic treatment, n (%)	
Treated, curated	634 (77)
Untreated	187 (23)
Follow-up from la/mUC diagnosis, median, months	9.20 (3.71-18.80)
Age at la/mUC diagnosis, median (IQR), years	69 (62, 76)
Year of la/mUC diagnosis, n (%)	
2016	90 (11)
2017	95 (12)
2018	110 (13)
2019	182 (22)
2020	207 (25)
2021	129 (16)
2022	8 (1)
Sex, n (%)	
Female	221 (27)
Male	600 (73)
Race, n (%)	
American Indian or Alaska Native	1 (0.1)
Black or African American	53 (6.5)
Other	48 (5.8)
Unknown	200 (24)
White	519 (63)
Region, n (%)	
Midwest	214 (46)
Northeast	33 (7)
South	108 (23)
West	115 (24)
Unknown	351
Data source, n (%)	
Academic	221 (27)
Community	169 (21)
Other	426 (52)
Unknown	5

Characteristic (cont)	N=821 (cont)
Smoking status, n (%)	
History of smoking	361 (63)
Never	212 (37)
Unknown	248
Histology type, n (%)	
Ambiguous carcinoma	131 (16)
Other	30 (3.7)
Squamous	2 (0.2)
Transitional	658 (80)
Histopathology grade, n (%)	
Grade 2 (moderately differentiated)	8 (1.6)
Grade 3 (poorly differentiated)	67 (14)
Grade 4 (undifferentiated)	1 (0.2)
High	416 (84)
Low	1 (0.2)
Unknown	328
Comorbidities, n (%)	
1	147 (37)
2	86 (22)
3	54 (14)
4+	106 (27)
Unknown	428
Death records, n (%)	305 (37)
PD-L1 status, n (%)	
Negative	123 (64)
Positive	70 (36)
Unknown	628

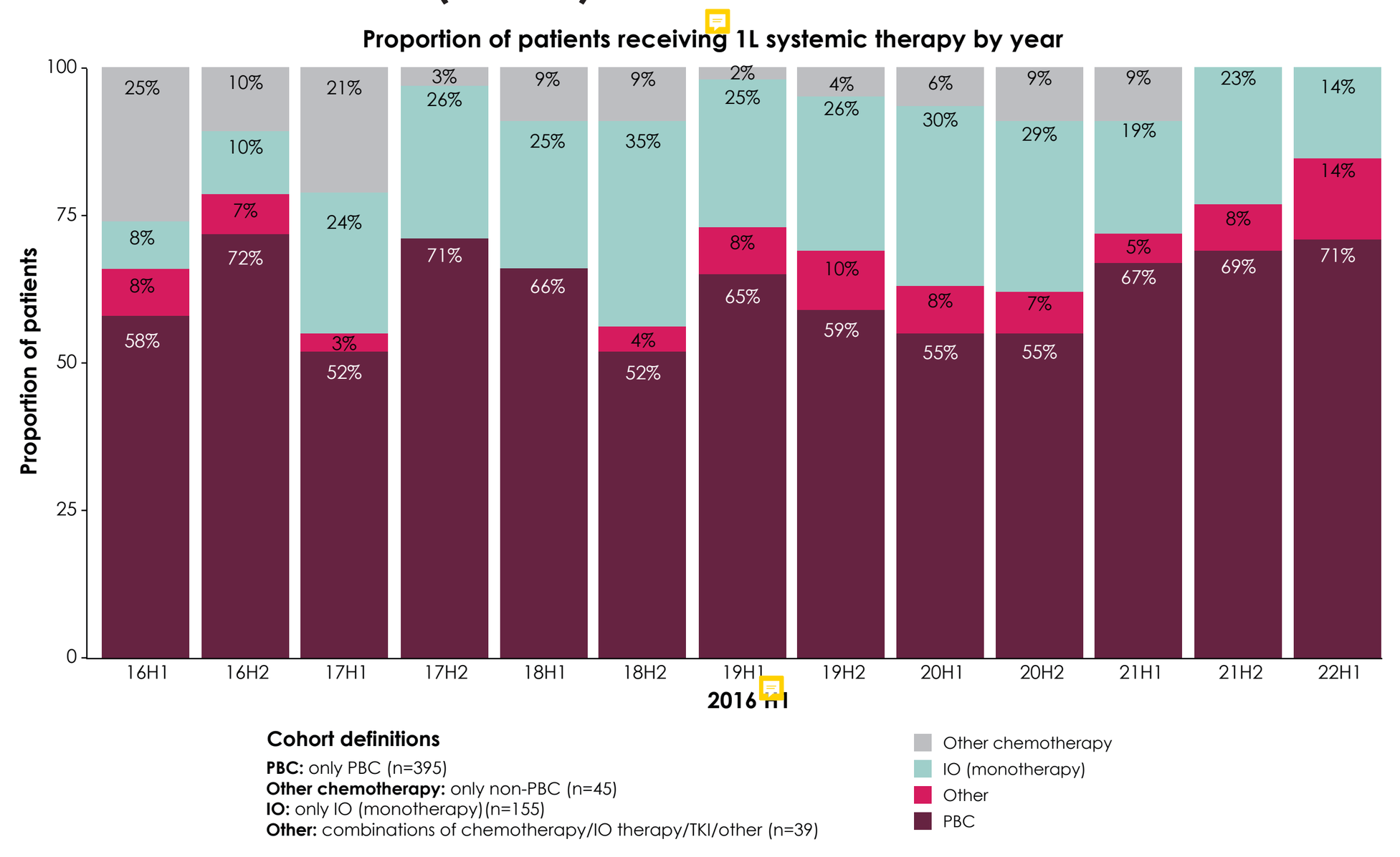
IQR, interquartile range; **la/mUC,** locally advance metastatic urothelial carcinoma.

Table 2. Treatment patterns across lines of treatment

	All patients (N=821)	Most common tx
Untreated	187 (22.8%)	N/A
Treated		
1L tx	**634 (77.2%)**	**Cisplatin + gemcitabine:** 175 (27.6%) **Carboplatin + gemcitabine:** 124 (19.6%) **Pembrolizumab:** 108 (17.0%) **Cisplatin + doxorubicin + methotrexate + vinblastine:** 45 (7.1%) **Atezolizumab*:** 35 (5.5%) **Other†:** 147 (23.2%)
1LM tx	**97 (15.3%)**	**Avelumab:** 63 (64.9%) **Other IO therapy‡:** 34 (35.1%)
2L tx	**210 (33.1%)**	**Pembrolizumab:** 57 (27.1%) **Enfortumab vedotin:** 35 (16.7%) **Carboplatin + gemcitabine:** 19 (9.0%) **Atezolizumab*:** 12 (5.7%) **Avelumab:** 14 (6.7%) **Other§:** 73 (34.8%)
3L tx	**65 (10.3%)**	**Enfortumab vedotin:** 14 (21.5%) **Pembrolizumab:** 13 (20.0%) **Avelumab:** 8 (12.3%) **Atezolizumab*:** 7 (10.8%) **Carboplatin + gemcitabine:** 4 (6.2%) **Other‖:** 19 (29.2%)

1L, first-line; **1LM,** first-line maintenance; **2L,** second-line; **3L,** third-line; **IO,** immuno-oncology; **N/A,** not applicable; **tx,** treatment.
*Atezolizumab is no longer approved in the US to treat patients with locally advanced or metastatic urothelial carcinoma following the manufacturer's decision to withdraw its indication after consulting with the FDA. The withdrawal was made in accordance with the FDA's Accelerated Approval Program after results from the phase 3 IMvigor130 trial (NCT02807636) failed to meet the postmarketing requirement necessary to convert the accelerated approval for atezolizumab into regular approval.[10] †Other regimens include: gemcitabine, carboplatin + cisplatin + gemcitabine, avelumab, carboplatin +paclitaxel, enfortumab, mitomycin, cisplatin, carboplatin, nivolumab, carboplatin + etoposide, atezolizumab + carboplatin + etoposide, carboplatin + gemcitabine + pembrolizumab, cisplatin + paclitaxel, fluorouracil, fluorouracil + mitomycin, carboplatin + enfortumab, cisplatin + doxorubicin + methotrexate + vincristine, cisplatin + fluorouracil, cyclophosphamide + doxorubicin + methotrexate + vinblastine, doxorubicin + gemcitabine + paclitaxel, durvalumab + investigational new drug, erdafitinib, gemcitabine + paclitaxel, investigational new drug + nivolumab, ipilimumab + nivolumab, paclitaxel, abemaciclib + letrozole, atezolizumab + cabozantinib, atezolizumab + gemcitabine, bevacizumab + fluorouracil + leucovorin + oxaliplatin, brentuximab vedotin + cisplatin + pembrolizumab, capecitabine, capecitabine + paclitaxel, carboplatin + doxorubicin + methotrexate + vinblastine, carboplatin + durvalumab + gemcitabine, celecoxib + cisplatin + gemcitabine, cisplatin + doxorubicin + durvalumab + methotrexate + vinblastine, cisplatin + doxorubicin + vinblastine, cisplatin + enfortumab, cisplatin + enfortumab + pembrolizumab, cisplatin + etoposide, cisplatin + fluorouracil + mitomycin, cisplatin + gemcitabine + investigational new drug, cisplatin + gemcitabine + nivolumab, cisplatin + gemcitabine + pembrolizumab, cisplatin + ifosfamide + paclitaxel, denosumab + pemetrexed, enfortumab + pembrolizumab, eribulin + gemcitabine, fluorouracil + leucovorin + oxaliplatin, fluorouracil + oxaliplatin, gemcitabine + nivolumab + oxaliplatin, investigational new drug, pemetrexed, and topotecan. ‡Other regimens include: pembrolizumab, atezolizumab, nivolumab, atezolizumab + pembrolizumab, avelumab + bevacizumab, investigational new drug + pembrolizumab, and paclitaxel + pembrolizumab. §Other regimens include: cisplatin + gemcitabine, nivolumab, docetaxel, erdafitinib, gemcitabine, carboplatin + paclitaxel, paclitaxel, capecitabine, carboplatin, cisplatin, aflibercept + fluorouracil + irinotecan + leucovorin + ramucirumab, atezolizumab + carboplatin + etoposide, atezolizumab + gemcitabine, avelumab + pemetrexed, capecitabine + mitomycin, carboplatin + cisplatin, carboplatin + etoposide, carboplatin + gemcitabine + paclitaxel, cisplatin + doxorubicin + methotrexate + vinblastine, cisplatin + etoposide, cisplatin + gemcitabine + pembrolizumab, cisplatin + investigational new drug, cisplatin + paclitaxel, denosumab, doxorubicin + gemcitabine + ifosfamide, durvalumab, enfortumab + pembrolizumab, fluorouracil + mitomycin, ibrutinib + pembrolizumab, investigational new drug + nivolumab, ipilimumab + nivolumab, olaparib, pazopanib, pemetrexed, and pemigatinib. ‖Other regimens include: cisplatin + gemcitabine, carboplatin + paclitaxel, nivolumab, olaparib, docetaxel, doxorubicin liposome, erdafitinib, gemcitabine, investigational new drug, lurbinectedin, paclitaxel, pemetrexed, and ramucirumab.

Figure 3. Trends in 1L therapy over the study period (2016-2022) for the 1L-treated cohort (n=634)



1L, first-line; **IO,** immuno-oncology; **PBC,** platinum-based chemotherapy; **TKI,** tyrosine kinase inhibitor.

Treatment sequencing patterns

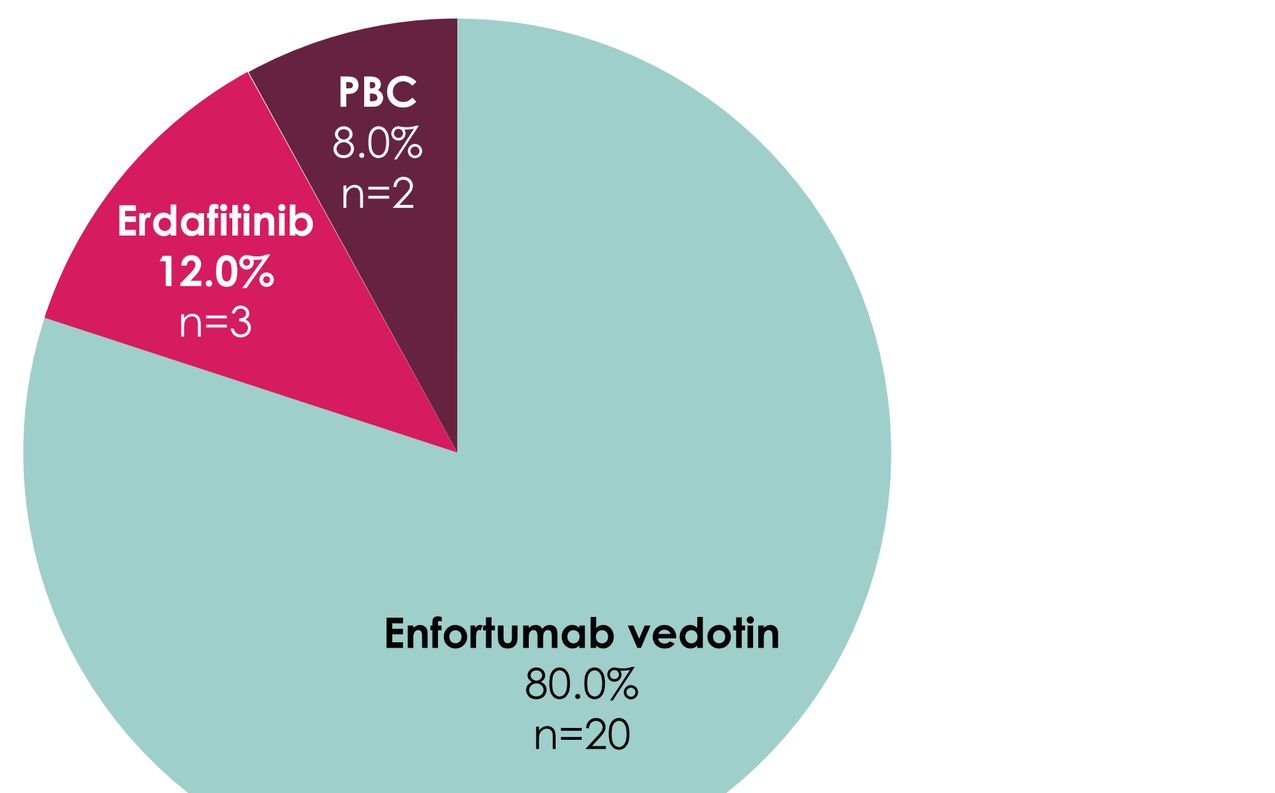
- Treatment sequencing for a group of patients who discontinued 1L PBC pre- and post-avelumab 1LM approval is shown in **Table 3**
- Of those receiving IO therapy (n=84) as subsequent treatment post-avelumab approval, 80% (67/84) received an IO therapy as 1LM, of which 84% (56/67) received avelumab 1LM
- Of the 25 patients who received 2L treatment after progression on IO therapy 1LM post-avelumab approval, enfortumab vedotin was the most commonly used 2L agent (80%; 20/25) (**Figure 4**)

Table 3. Treatment sequencing

	1L PBC end date pre-avelumab 1LM approval (n=243) n/N (%)	1L PBC end date post-avelumab 1LM approval (n=152) n/N (%)
Received IO therapy as 2L or 1LM following 1L PBC	87/243 (36)	84/152 (55)
Received IO therapy as 2L	59/87 (68)	17/84 (20)
Received IO therapy as 1LM	28/87 (32)	67/84 (80) **Avelumab:** 56/67 (84) **Other:** 11/67 (16)
Received 2L tx after progression on IO 1LM	9/28 (32) **Enfortumab vedotin:** 4/9 (44) **PBC:** 5/9 (56)	25/67 (37) **Enfortumab vedotin:** 20/25 (80) **Erdafitinib:** 3/25 (12) **PBC:** 2/25 (8)
Did not receive IO therapy after 1L PBC but received 2L or later tx	110/243 (45)	34/152 (22)

1L, first-line; **1LM,** first-line maintenance; **2L,** second-line; **PBC,** platinum-based chemotherapy; **IO,** immuno-oncology; **tx,** treatment.

Figure 4. Breakdown of 2L treatments after progression on IO 1LM post-avelumab approval



1LM, first-line maintenance; **2L,** second-line; **PBC,** platinum-based chemotherapy; **IO,** immuno-oncology.

Strength and limitations

Strengths

- ~~Data from the Tempus real-world database came from the~~ ASCO CancerLinQ network, which includes >300 community health systems, 2,500 oncologists, and >2 million patients across the US
- This study is one of the first real-world studies showing the integration of 1LM therapy in patients with mUC in the US

Limitations

- Data were collected primarily in the oncology clinical practice setting through routine clinical care and not for research purposes; therefore, nonrandom missingness may be present for several variables of interest, and data on healthcare received outside of the Tempus network of practices are not available
- Complete medical history outside of the oncology EHR was not captured, which may lead to underreporting of treatments received
- Algorithms used to identify 1LM and 2L agents may not reflect the definitions used in clinical practice
- Patients who initiated 1L systemic therapy later in the study period may not have had enough follow-up time to observe 2L and subsequent treatment rates, which may have led to underestimates in these lines of treatment
- Similarly, the study was limited in its ability to comprehensively understand the use of avelumab in 1LM as it was approved by the FDA[3] on June 30, 2020

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DISCLOSURES M. Kearney is an employee of the healthcare business of Merck KGaA, Darmstadt, Germany, and owns stock and other ownership interests in Merck KGaA, Darmstadt, Germany, Novartis, and UCB. **S. H. Mahmoudpour** is an employee of the healthcare business of Merck KGaA, Darmstadt, Germany. **C. Ike** is an employee of EMD Serono, Rockland, MA, USA, and owns stock and other ownership interests in Merck KGaA, Darmstadt, Germany. **A. Modh, S. Monzon,** and **S. Fragkogianni** are employees of Tempus. **K. Carson** was employed by Tempus at the time of the study; owns stock and other ownership interests in Tempus; has received research funding from Tempus; has provided expert testimony for Bayer; and has received travel and accommodations expenses from Curio Science. **ACKNOWLEDGMENTS** This trial was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945) as part of an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany and Pfizer. Medical writing support was provided by Eleanor Bishop of Clinical Thinking and was funded by the healthcare business of Merck KGaA, Darmstadt, Germany and Pfizer.

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