Assessment of treatment patterns and real-world outcomes following changes in the treatment paradigm for locally advanced/ metastatic urothelial carcinoma (Ia/mUC) in the US

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SCOPE

- This study aims to understand treatment patterns and real-world outcomes in patients with Ia/mUC in the US, including the early implementation of avelumab first-line maintenance (1LM) since its US Food and Drug Administration approval in June 2020

CONCLUSIONS

- In this real-world cohort, most treated patients received standard-of-care platinum-based chemotherapy (PBC) in the 1L (64.3%), with those receiving 1L cisplatin-based therapy demonstrating the best outcomes
- Of patients who received 1L therapy, half (50.6%) received second-line (2L) therapy during the study period, highlighting the need to use the most effective and tolerated treatment regimen upfront
- Early uptake of avelumab 1LM was observed in accordance with treatment guidelines
- As longer follow-up becomes available, future analyses should examine clinical outcomes of patients who received avelumab 1LM following 1L PBC

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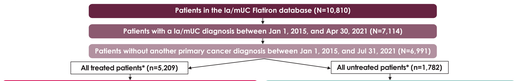
BACKGROUND

- Bladder cancer is the sixth most common cancer in the US and is 4 times more prevalent in men than in women[1]
- Patients with unresectable Ia/mUC have especially poor survival outcomes[2]
- The current standard-of-care 1L treatment for Ia/mUC is PBC followed by avelumab 1LM in those with disease that has not progressed following 1L PBC[3]
- Most real-world studies explored the treatment landscape prior to the approval of avelumab 1LM in 2020, and data in the post-switch maintenance setting are limited

METHODS

- This is a noninterventional, retrospective cohort study of patients with Ia/mUC in the US using data from the Flatiron Health database. Flatiron Health is a longitudinal, demographically and geographically diverse database with data originating from approximately 280 cancer clinics[4]
- The study design and patient attrition is summarized in **Figure 1**
  - Study period: January 1, 2015, to July 31, 2021
  - Identification period: January 1, 2015, to April 30, 2021 (to ensure ≥3-month follow-up unless the patient died)
  - Index date: Ia/mUC diagnosis date in the identification period
- Patients aged ≥18 years diagnosed with Ia/mUC during the study period were split into 2 cohorts, treated vs untreated (no evidence of systemic treatment). This analysis focused on the treated cohort
- Treatment cohorts were assigned based on 1L treatment, defined as the first treatment regimen following Ia/mUC diagnosis
- Patient characteristics at baseline and clinical outcomes were described by the 1L treatment received. Treatment sequences for each patient were assessed from 1L to 2L and reported as the frequency of patients with each sequence of treatments. Kaplan-Meier curves were used to describe overall survival (OS) and progression-free survival (PFS) from start of 1L treatment
- Patients were classified as being treated with avelumab in 1LM if they received PBC in 1L, initiated avelumab within 180 days of 1L PBC discontinuation (per clinical suggestion), and had no documented progression before initiation of avelumab

Figure 1. Patient attrition diagram

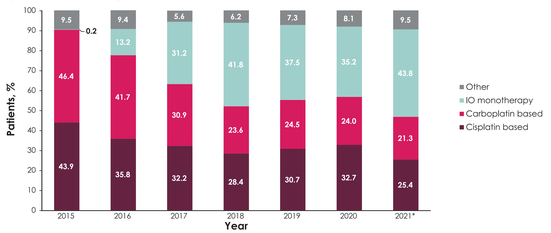


*All patients were aged ≥18 years; †Unless in the case of death; ‡To reach this patient number, additional eligibility criteria were met: (1) no systemic treatment for Ia/mUC in the baseline period (n=5,118); (2) <180 days between Ia/mUC diagnosis date and administration of 1L treatment (n=4,634); (3) no clinical study drug during the study period (n=4,532).
1L, first line; **Ia/mUC**, locally advanced/metastatic urothelial carcinoma.

RESULTS

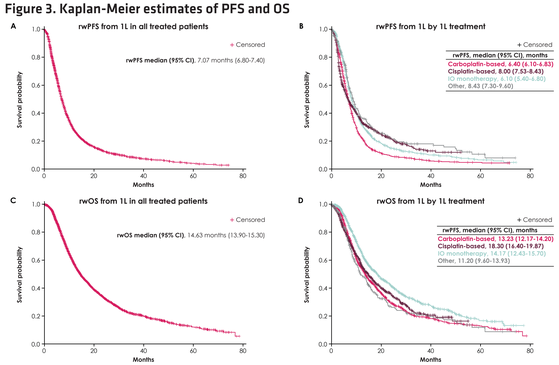
- Of 4,387 patients included in this study, 3,706 (84.5%) received systemic anticancer treatments (**Table 1**)
- Cisplatin-based therapy was the most common 1L therapy (33.3%), followed by carboplatin-based therapy (30.9%), then immuno-oncology (IO) therapies (28.0%) (**Table 1**)
- Bladder was the most common site of disease (76.2%), with most patients having a high disease grade at Ia/mUC diagnosis (grade ≥2 in 85.9%) (**Table 2**)
- Mean follow-up from Ia/mUC diagnosis was similar for treated vs untreated patients (16.7 vs 16.8 months, respectively)
- Due to the recent approval of IO therapies in the 1L, there was a decrease in the proportion of patients receiving 1L PBC and an increase in those receiving 1L IO from 2015 to 2021 (**Figure 2**)
- Median PFS was longest in patients treated with 1L cisplatin-based therapies (8.0 months [95% CI, 7.5-8.4]), followed by 1L carboplatin-based therapies (6.4 months [95% CI, 6.1-6.8]), then IO therapies (6.1 months [95% CI, 5.4-6.8]) (**Figure 3B**)
- Median OS in the treated cohort was 14.6 months (95% CI,13.9-15.3) from the initiation of 1L therapy (**Figure 3C**)
- Median OS was longest in patients treated with 1L cisplatin-based therapies (18.3 months [95% CI, 16.4-19.9]), followed by 1L IO therapies (14.2 months [95% CI, 12.4-15.7]), then 1L carboplatin-based therapies (13.2 months [95% CI, 12.2-14.2]) (**Figure 3D**)
- Of 1L-treated patients, 50.6% moved on to 2L therapy during the study period
- Since July 2020, 89 patients received avelumab 1LM (**Table 1**); median follow-up from the start of avelumab 1LM was 6.0 months, and clinical outcomes data were immature

Figure 2. Treatment patterns by index year



*Only the first 6 months of 2021 were included in study. The study period ended prior to recent changes in the FDA approvals of pembrolizumab and atezolizumab.[5,6]
Other = other platinum-based therapies (eg, cisplatin/) and any other treatments not falling into any previous drug class.
IO, immuno-oncology.

Figure 3. Kaplan-Meier estimates of PFS and OS



1L, first-line; **IO**, immuno-oncology; **rwOS**, real-world overall survival; **rwPFS**, real-world PFS.

Table 1. Patient demographics

Characteristic	All treated, n (%)	Cisplatin-based, n (%)	Carboplatin-based, n (%)	IO monotherapy, n (%)	Other, n (%)	Avelumab 1LM, n (%)
	3,706 (100.0)	1,235 (33.3)	1,147 (30.9)	1,038 (28.0)	286 (7.7)	89 (2.4)
Age at Ia/mUC diagnosis, mean (SD), years	71.0 (9.0)	67.0 (8.9)	72.1 (8.0)	74.6 (8.2)	71.6 (8.9)	69.2 (10.1)
Sex						
Female	984 (26.6)	335 (27.1)	284 (24.8)	290 (27.9)	75 (26.2)	20 (22.5)
Male	2,721 (73.4)	899 (72.8)	863 (75.2)	748 (72.1)	211 (73.8)	69 (77.5)
Unknown	1 (<0.1)	1 (0.1)	0	0	0	0
Race						
Asian	48 (1.3)	22 (1.8)	13 (1.1)	11 (1.1)	2 (0.7)	0
Black or African American	168 (4.5)	57 (4.6)	53 (4.6)	39 (3.8)	19 (6.6)	2 (2.3)
Hispanic or Latino	5 (0.1)	1 (0.1)	4 (0.3)	0	0	0
Other race	596 (16.1)	192 (15.5)	183 (16.0)	185 (17.8)	36 (12.6)	23 (25.8)
White	2,585 (69.8)	867 (70.2)	796 (69.4)	716 (69.0)	206 (72.0)	54 (60.7)
Unknown	304 (8.2)	96 (7.8)	98 (8.5)	87 (8.4)	23 (8.0)	10 (11.2)
Region of residence						
Northeast	492 (13.3)	172 (13.9)	136 (11.9)	144 (13.9)	40 (14.0)	14 (15.7)
Midwest	464 (12.5)	157 (12.7)	147 (12.8)	123 (11.8)	37 (12.9)	14 (15.7)
South	1,723 (46.5)	552 (44.7)	554 (48.3)	489 (47.1)	128 (44.8)	41 (46.1)
West	511 (13.8)	174 (14.1)	164 (14.3)	144 (13.9)	29 (10.1)	13 (14.6)
Other territories	41 (1.1)	10 (0.8)	13 (1.1)	14 (1.3)	4 (1.4)	0
Unknown	475 (12.8)	170 (13.8)	133 (11.6)	124 (11.9)	48 (16.8)	7 (7.9)

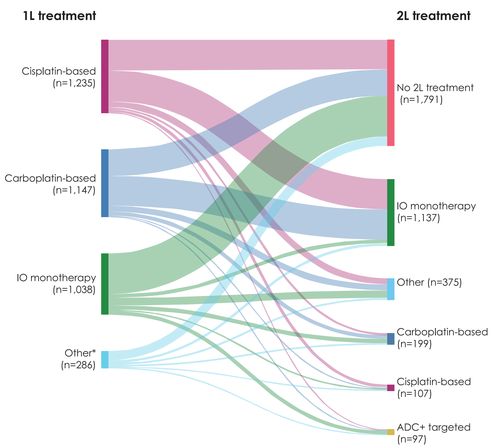
1LM, first-line maintenance; **Ia/mUC**, locally advanced/metastatic urothelial carcinoma; **IO**, immuno-oncology; **SD**, standard deviation.

Table 2. Clinical characteristics

Characteristic	All treated, n (%)	Cisplatin-based, n (%)	Carboplatin-based, n (%)	IO monotherapy, n (%)	Other, n (%)	Avelumab 1LM, n (%)
	3,706 (100.0)	1,235 (33.3)	1,147 (30.9)	1,038 (28.0)	286 (7.7)	89 (2.4)
Site of disease						
Bladder	2,825 (76.2)	990 (80.2)	832 (72.5)	794 (76.5)	209 (73.1)	73 (82.0)
Renal pelvis	485 (13.1)	141 (11.4)	175 (15.3)	127 (12.2)	42 (14.7)	9 (10.1)
Ureter	366 (9.9)	91 (7.4)	128 (11.2)	116 (11.2)	31 (10.8)	7 (7.9)
Urethra	30 (0.8)	13 (1.1)	12 (1.0)	1 (0.1)	4 (1.4)	0
Disease grade						
High grade (grades 2-4)	3,185 (85.9)	1,093 (88.5)	951 (82.9)	890 (85.7)	251 (87.8)	70 (78.7)
Low grade (grade 1)	174 (4.7)	50 (4.0)	58 (5.1)	52 (5.0)	14 (4.9)	4 (4.5)
Unknown/not documented	347 (9.4)	92 (7.4)	138 (12.0)	96 (9.2)	21 (7.3)	15 (16.9)
Stage at initial diagnosis						
0	13 (0.4)	5 (0.4)	4 (0.3)	4 (0.4)	0	1 (1.1)
I	66 (1.8)	20 (1.6)	22 (1.9)	20 (1.9)	4 (1.4)	3 (3.4)
II	286 (7.7)	52 (4.2)	54 (4.7)	149 (14.4)	31 (10.8)	6 (6.7)
III	335 (9.0)	139 (11.3)	68 (5.9)	103 (9.9)	25 (8.7)	3 (3.4)
IV	1,415 (38.2)	593 (48.0)	480 (41.8)	246 (23.7)	96 (33.6)	40 (44.9)
Unknown/not documented	1,591 (42.9)	426 (34.5)	519 (45.2)	516 (49.7)	130 (45.5)	36 (40.5)
Smoking status						
History of smoking	2,717 (73.3)	908 (73.5)	850 (74.1)	747 (72.0)	212 (74.1)	59 (66.3)
No history of smoking	975 (26.3)	322 (26.1)	292 (25.5)	287 (27.6)	74 (25.9)	29 (32.6)
Unknown/not documented	14 (0.4)	5 (0.4)	5 (0.4)	4 (0.4)	0	1 (1.1)
PD-L1 testing status						
Yes						
Negative	342 (9.2)	107 (8.7)	115 (10.0)	94 (9.1)	26 (9.1)	15 (16.9)
Positive	393 (10.6)	117 (9.5)	107 (9.3)	144 (13.9)	25 (8.7)	20 (22.5)
Unknown	365 (9.8)	106 (8.6)	97 (8.5)	127 (12.2)	35 (12.2)	15 (16.9)
No	2,606 (70.3)	905 (73.3)	828 (72.2)	673 (64.8)	200 (69.9)	39 (43.8)
GFR (mL/min/1.73m²) at Ia/mUC diagnosis date (±30 days)						
30-60	128 (3.5)	6 (0.5)	53 (4.6)	57 (5.5)	12 (4.2)	20 (22.5)
<30	845 (22.8)	171 (13.8)	319 (27.8)	279 (26.9)	76 (26.6)	0
>60	800 (21.6)	363 (29.4)	221 (19.3)	163 (15.7)	53 (18.5)	30 (33.7)
Unknown	1,933 (52.2)	695 (56.3)	554 (48.3)	539 (51.9)	145 (50.7)	39 (43.8)

1LM, first-line maintenance; **Ia/mUC**, locally advanced/metastatic urothelial carcinoma; **GFR**, glomerular filtration rate; **IO**, immuno-oncology.

Figure 4. Treatment sequences from 1L to 2L



Proportion of patients with treatment sequence from 1L to 2L

		2L treatment					
	Patients, n (%)	Cisplatin-based	Carboplatin-based	IO monotherapy	ADC+ targeted	Other	No 2L treatment†
1L treatment	Cisplatin-based	50 (4.0)	35 (2.8)	522 (42.3)	18 (1.5)	110 (8.9)	500 (40.5)
	Carboplatin-based	17 (1.5)	66 (5.8)	508 (44.3)	10 (0.9)	103 (9.0)	443 (38.6)
	IO monotherapy	22 (2.1)	69 (6.6)	63 (6.1)	65 (6.3)	128 (12.3)	691 (66.6)
	Other*	18 (6.3)	29 (10.1)	44 (15.4)	4 (1.4)	34 (11.9)	157 (54.9)

Of patients treated with 1L therapy, 4.1% of those treated with cisplatin-based therapy and 3.3% of those treated with carboplatin-based therapy received avelumab 1LM treatment; 58.4% were still receiving avelumab 1LM at the end of follow-up. *Other* includes other platinum-based therapies (eg, cisplatin/) and any other treatments not falling into any previous drug class. Treatment groups are mutually exclusive. Patients were placed into each group regardless of cross-treatment group combination with this hierarchy: IO, targeted, ADC, cisplatin, carboplatin, any other. Percentages may not add to 100 due to rounding.
*Inclusive of ADC+ targeted. †Inclusive of patients still receiving 1L at end of follow-up: cisplatin-based therapy (46.8%); carboplatin-based therapy (62.3%); IO monotherapy (79.9%); other (61.1%).
1L, first-line; **2L**, second-line; **ADC**, antibody-drug conjugates; **IO**, immuno-oncology.

LIMITATIONS

- The Flatiron Health data are not fully generalizable to the wider US population, electronic health record data are often incomplete, and data on visits to non–Flatiron Health clinics were unavailable

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