Real-World Outcomes With Taxane Monotherapy Following Platinum and Anti-Programmed Death 1/Death-Ligand 1 Therapy in Locally Advanced or Metastatic Urothelial Carcinoma

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Background

- Locally advanced or metastatic urothelial carcinoma is an incurable disease with a poor long-term prognosis.[1,2]
- Novel therapies have recently emerged, including enfortumab vedotin-ejfv, which received FDA approval in December 2019 for adults with la/mUC previously treated with anti-PD-1/L1 therapy, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, la/mUC setting. This indication was approved under accelerated approval based on tumor response rate. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.[3]
  - Enfortumab vedotin is now recommended in NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) as a preferred regimen (category 2A) for subsequent-line systemic therapy in patients with la/mUC who have already received platinum and anti-PD-1/L1 therapy.[4]
- Prior to the availability of enfortumab vedotin, data suggest that single-agent taxanes have been commonly used following anti-PD-1/L1 therapy[5]; however, there are very limited data on clinical outcomes in this setting.[6]
- Although a response rate of 10.5% (n=2 of 19) was observed among a subset of patients in the RANGE trial who received docetaxel following progression on platinum and anti-PD-1/L1 therapy,[7] and of 21% (n=3 of 14) among patients who received chemotherapy after failure of platinum and anti-PD-1/L1 therapy in a real-world setting,[8] data from larger clinical trials and real-world populations are lacking.
- Further, no studies have examined PFS or OS in this patient population.

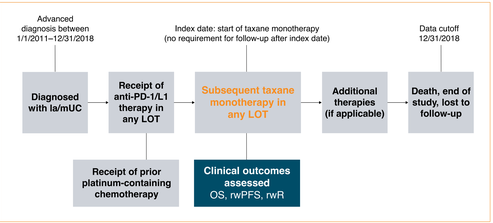
Objective

- To describe real-world outcomes in patients with la/mUC treated with taxane monotherapy following progression on anti-PD-1/L1 therapy and who had received platinum chemotherapy.

Methods

- The study included patients aged ≥18 years treated in the United States with a histologically confirmed diagnosis of la/mUC from January 1, 2011–December 31, 2018, ≥2 clinical visits, and sufficient relevant unstructured data were included from the de-identified nationwide Flatiron Health EHR-derived oncology database.
  - Flatiron Health uses a proprietary technology-enabled chart abstraction methodology to extract research-grade data points from the EHR.
  - PFS and OS are validated endpoints using Flatiron Health EHR data and may provide additional context into real-world outcomes measures than ORR alone.[9]
- The study cohort included patients treated with taxane monotherapy (docetaxel, paclitaxel, or nab-paclitaxel) following anti-PD-1/L1 therapy and who had received platinum-containing chemotherapy (**Figure 1**).

Figure 1. Study design



- Baseline characteristics, OS, rwPFS based on clinician documentation of disease status, and rwR (CR or PR followed by a CR, PR, or stable disease) based on clinician-confirmed radiologic assessments were reported (**Table 1**).
- Patients were followed until death, data cutoff, or loss to follow-up.

Table 1. Definitions for real-world outcomes

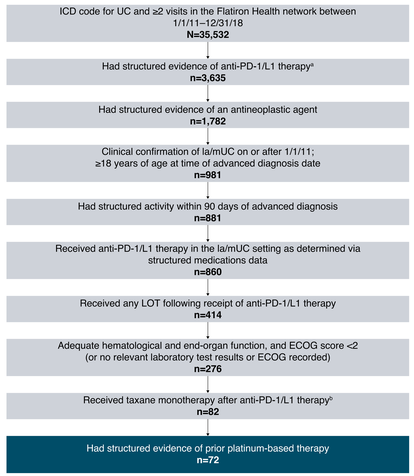
	rwPFS	rwR
Definition	Progression event is a distinct episode in which the treating clinician concludes that there has been growth or worsening in the disease of interest	Change in tumor burden based on clinician's interpretation of radiology (and other) data
Main source of evidence	Clinician assessment	Clinician assessment (anchored to radiology)
Confirmatory documentation	Radiology, laboratory, and pathology	Clinical assessments, radiology reports

Results

Patient population

- Among 276 patients treated following anti-PD-1/L1 therapy and who met all of the inclusion/exclusion criteria, 72 were treated with taxane monotherapy following documented evidence of prior platinum chemotherapy (**Figure 2**).
- Other therapies used post-PD-1/L1 therapy included carboplatin-containing regimens (n=48, 17.4%), cisplatin-containing regimens (n=15, 5.4%), and other single-agent chemotherapies (n=42, 15.2%); 28.6% of patients received a subsequent anti-PD-1/L1 therapy regimen (n=79) and 2.9% (n=8) received a clinical study drug.

Figure 2. Summary of cohort selection



[a]Atezolizumab, pembrolizumab, durvalumab, avelumab, or nivolumab.
[b]Docetaxel, paclitaxel, or nab-paclitaxel.

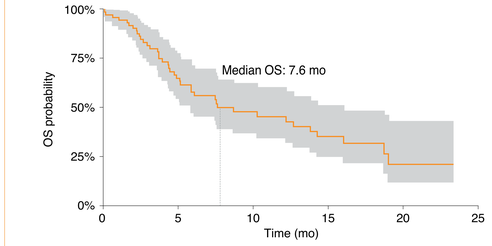
Baseline demographics

- Patients were mostly male (75.0%) and Caucasian (73.6%), with a mean age of 73 years (**Table 2**).
- 65.3% (n=47) had ≥2 sites of metastasis at index.
- 81.9% (n=59) received anti-PD-1/L1 therapy immediately prior to taxane monotherapy.
- Only 12.5% (9 of 72) of patients were tested for PD-L1 status because testing was not required until 2018[10]; of these 9 patients, 3 (33.3%) were PD-L1 positive.

Outcomes

- The median OS for the study cohort was 7.6 months (95% CI: 5.2–14.4), and the 6-month survival probability was 56% (95% CI: 45–70%; **Figure 3**).

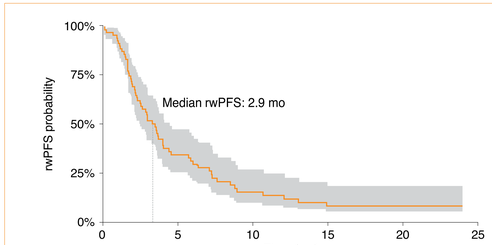
Figure 3. OS following initiation of taxane monotherapy[a]



[a]The median OS for the study cohort was 7.6 months (95% CI: 5.2–14.4), and the 6-month survival probability was 56% (95% CI: 45–70%).

- The median rwPFS for the study cohort was 2.9 months (95% CI: 2.4–4.0), and the 6-month rwPFS probability was 26% (95% CI: 17–40%; **Figure 4**).

Figure 4. rwPFS following initiation of taxane monotherapy[a]



[a]The median rwPFS for the study cohort was 2.9 months (95% CI: 2.4–4.0), and the 6-month rwPFS probability was 26% (95% CI: 17–40%).

- Among the 50 patients in the study cohort with ≥1 rwR assessment, confirmed rwR was approximately 18–19%.

Table 2. Demographic, clinical, and treatment characteristics in study cohort

Characteristic	N=72
Gender, n (%)	
Female	18 (25.0)
Male	54 (75.0)
Age, y, mean (SD)	73.0 (8.7)
Race/Ethnicity, n (%)	
Caucasian	53 (73.6)
African American	7 (9.7)
Asian	2 (2.8)
Other	3 (4.2)
Unknown/Not documented	7 (9.7)
Primary tumor location, n (%)	
Bladder	53 (73.6)
Renal pelvis	13 (18.1)
Ureter	6 (8.3)
ECOG status at index[a], n (%)	
0	20 (27.8)
1	27 (37.5)
Unknown/Not documented	25 (34.7)
Number of metastasis sites, n (%)	
0	4 (5.6)
1	21 (29.2)
2+	47 (65.3)
Location of metastasis[b], n (%)	
Lymph node	42 (58.3)
Lung	29 (40.3)
Bone	22 (30.6)
Liver	21 (29.2)
Renal function at index[c,d], n (%)	
Normal: ≥90 mL/min	7 (9.7)
Mild decrease: ≥60 and <90 mL/min	16 (22.2)
Mild/Moderate decrease: ≥45 and <60 mL/min	17 (23.6)
Moderate decrease: ≥30 and <45 mL/min	15 (20.8)
Unknown/Not documented	17 (23.6)
Hepatic function at index[d], n (%)	
Normal: total bilirubin ≤ULN and AST ≤ULN	56 (77.8)
Mild: either [total bilirubin >1 and ≤1.5x ULN] or [total bilirubin ≤ULN and AST >ULN]	2 (2.8)
Unknown/Not documented	14 (19.4)
Hemoglobin at index[d], n (%)	
<10 g/dL	8 (11.1)
≥10 g/dL	55 (76.4)
Unknown/Not documented	9 (12.5)
Number of prior lines of therapy, n (%)	
1	11 (15.3)
2+	61 (84.7)
Received anti-PD-1/L1 therapy immediately prior to index, n (%)	59 (81.9)
Time from advanced diagnosis to index date, mo, median [IQR]	26.0 [16.1–44.8]
Time from last platinum-containing therapy[e] to index date, mo, median [IQR]	8.3 [4.8–15.5]

[a]Although ECOG is collected in clinical trials, it is not routinely assessed in real-world clinical settings; hence approximately one-third of patients have missing ECOG scores. [b]A patient may have metastatic disease in >1 site. [c]Calculated based on estimated creatinine clearance using the Cockcroft-Gault equation. [d]Laboratory values may have been recorded on or up to 28 days prior to the index date. When multiple records were available, the result closest to the index date was used. When there were multiple results on the same day, the highest result was used. [e]Platinum-based therapy was based on non-cancelled or administrative orders from structured data, and was not specifically abstracted for this project.

Limitations and Discussion

- The analyses are descriptive in nature and the abstraction of several potential key variables was unavailable (eg, comorbidities, presence of multiple primary tumors); further, safety data were not collected, precluding analysis of safety outcomes.
- Real-world outcomes data are potentially different to those captured in clinical trials as they are subject to clinician decisions on treatment selection and disease progression.
  - Although OS and PFS outcomes have been validated using Flatiron Health EHR data,[9] caution should be taken when interpreting rwR as it differs conceptually from the prospective collection of response data within the context of a traditional clinical trial, which is primarily based on RECIST criteria at set time points.
  - Due to differences in data capture between rwR and RECIST, rwR cannot be used as a direct comparator to RECIST; there is ongoing work to validate the appropriateness of using rwR for response-based outcomes.
- Although this is the largest real-world study in this population to date, the sample size is still small, which is likely due to the recent approval of anti-PD-1/L1 therapy and the limited number of patients who receive late-line therapy.
- Despite these limitations, this study represents the first robust analysis of PFS and OS outcomes using real-world evidence in patients with la/mUC who were treated with chemotherapy following progression on anti-PD-1/L1 therapy.

Conclusions

Real-world outcomes in patients with la/mUC treated with taxane monotherapy following platinum and anti-PD-1/L1 therapy, as determined by rwPFS and OS, are poor, highlighting a significant unmet need in this population.

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Glossary

AST, aspartate aminotransferase; CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; EHR, electronic health record; FDA, Food and Drug Administration; ICD, International Classification of Disease; index date, start of taxane monotherapy; IQR, interquartile range; la/mUC, locally advanced or metastatic urothelial carcinoma; LOT, line of therapy; ORR, objective response rate; OS, overall survival; PD-1/L1, programmed death 1/death-ligand 1; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; rwPFS, real-world progression-free survival; rwR, real-world response; SD, standard deviation; UC, urothelial carcinoma; ULN, upper limit of normal.

DISCLOSURES

Zsolt Hepp is an employee of Seattle Genetics and holds stock/stock options in Seattle Genetics. Sonali N. Shah is a contractor for Astellas Pharma. Shreya Balakrishna and Katherine Tan are employees of Flatiron Health, INC., which is an independent subsidiary of the Roche Group, and paid consultants to Seattle Genetics in connection with this research. Shreya Balakrishna holds stock at Flatiron Health. Katherine Tan holds stock at Roche.

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