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Bladder Cancer

Effectiveness of First-line Immune Checkpoint Blockade Versus Carboplatin-based Chemotherapy for Metastatic Urothelial Cancer

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Abstract

Background: Limited data compare first-line carboplatin-based chemotherapy and immune checkpoint blockade in cisplatin-ineligible metastatic urothelial carcinoma (mUC) patients. The primary evidence guiding treatment decisions was a recent Food and Drug Administration/European Medicines Agency safety alert based on emerging data from two ongoing phase III trials, reporting shorter survival in programmed death-ligand 1 (PD-L1)-negative patients receiving immunotherapy. Final results from these trials are unknown.
Objective: To compare survival in cisplatin-ineligible mUC patients receiving first-line immunotherapy versus those receiving carboplatin-based chemotherapy.
Design, setting, and participants: We conducted a retrospective cohort study of 2017 mUC patients receiving first-line carboplatin-based chemotherapy ($n = 1530$) or immunotherapy ($n = 487$) from January 1, 2011 to May 18, 2018 using the Flatiron Health electronic health record–derived database.
Outcome measurements and statistical analysis: The primary outcomes were overall survival (OS), comparing 12- and 36-mo OS, and hazard ratios before and after 12 mo. Propensity score–based inverse probability of treatment weighting (IPTW) was used to address confounding in Kaplan-Meier and Cox regression model estimates of comparative effectiveness.
Results and limitations: IPTW-adjusted OS rates in the immunotherapy group were lower at 12 mo (39.6% [95% confidence interval {CI} 34.0–45.3%] vs 46.1% [95% CI 43.4–48.8%]) but higher at 36 mo (28.3% [95% CI 21.8–34.7%] vs 13.3% [95% CI 11.1–15.5%]) relative to the chemotherapy group. Immunotherapy treatment demonstrated inferior OS during the first 12 mo relative to carboplatin-based chemotherapy (IPTW-adjusted hazard ratio [HR] 1.37, 95% CI 1.15–1.62), but superior OS beyond 12 mo (IPTW-adjusted HR 0.50, 95% CI 0.30–0.85). Limitations include retrospective design and potential unmeasured confounding.
Conclusions: In the setting of mUC, clinicians and patients should carefully consider how to balance the short-term benefit of chemotherapy against the long-term benefit of immunotherapy.
Patient summary: To determine the optimal first-line therapy for metastatic bladder cancer patients who are unfit for cisplatin, we compared carboplatin-based chemotherapy versus immunotherapy using real-world data. Survival in the 1st year of treatment was lower with immunotherapy relative to chemotherapy, but for patients surviving beyond the 1st year, immunotherapy was superior.

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1. Introduction

Metastatic urothelial carcinoma (mUC) primarily affects older individuals. As a result, age-related comorbidity precludes over 50% of patients from receiving standard cisplatin-based chemotherapy—the only first-line treatment shown to improve survival [1]. For cisplatin-ineligible patients, outcomes are poor and there is no universally accepted treatment standard. Historically, carboplatin-based regimens have been used in this setting [2–4].

Recently, two immune checkpoint inhibitors, pembrolizumab and atezolizumab, received accelerated approval for front-line use in cisplatin-ineligible patients, providing an alternative to carboplatin-based chemotherapy. However, no data directly comparing these first-line treatment strategies are available. Expedited approval of immunotherapy was based on surrogate endpoints (eg, response rates) from two phase II single-arm trials: KEYNOTE-052 and IMVigor-210 [5,6]. Response rates from these uncontrolled immunotherapy trials (24–29%) were lower than those seen in trials of carboplatin-based chemotherapy (40–45%) [1,3,4]. Without comparative data using patient-centered endpoints (eg, survival), important effectiveness information may be missed, preventing informed decision making. Further complicating treatment selection, recently, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) issued a safety alert reporting decreased survival in programmed death-ligand 1 (PD-L1)-negative mUC patients treated with immunotherapy relative to platinum-based chemotherapy [7,8]. As a result, immunotherapy use was restricted to cisplatin-ineligible mUC patients who are PD-L1 positive or who are ineligible for any platinum-containing chemotherapy [9]. Since the EMA and FDA reports were based on early review of two ongoing phase III trials of platinum-eligible patients, KEYNOTE-361 and IMVigor-130, the full results are unknown and applicability to routine clinical practice is uncertain.

While randomized clinical trial data represent the gold standard for therapeutic approvals, there is growing interest by patients, physicians, and regulators in leveraging real-world evidence to better inform practice, as emphasized in the 21st Century Cures Act [10]. In this retrospective cohort study, we compared the effectiveness of immunotherapy versus carboplatin-based chemotherapy as first-line therapy for cisplatin-ineligible mUC patients in routine clinical practice.

2. Patients and methods

Reporting follows recommendations from the International Society for Pharmacoeconomics and Outcomes Research and the International Society for Pharmacoepidemiology Special Task Force on Real World Evidence in Health Care Decision Making [11]. The study protocol was approved by the University of Pennsylvania institutional review board with waiver of informed consent.

2.1. Data source

Data were obtained from the Flatiron Health electronic health record (EHR)-derived database, a geographically diverse US database comprising patient-level structured and unstructured data, curated via technology-enabled abstraction. All data from unstructured EHR-derived digital documents were manually reviewed by centrally managed and trained medical record abstractors, using explicit abstraction protocols for each data element [12]. Quality control during the abstraction process consists of duplicate chart abstraction, logic checks, and formal adjudication based on the complexity of select variables, as has been described in previous analyses [13–15]. The database includes deidentified data from over 280 academic and community oncology practices (800 sites of care) representing more than 2.1 million US cancer patients available for analysis. The data were cut by Flatiron Health on September 30, 2018, with recency from January 1, 2011 through August 31, 2018. The cohort is similar in age, race, and gender to the US population with advanced urothelial carcinoma based on Surveillance, Epidemiology, and End Results (SEER) data from 2004 to 2013 [16].

2.2. Study population

The study sample included patients diagnosed with stage IV urothelial carcinoma (bladder, renal pelvis, ureter, or urethra), and those diagnosed with early-stage urothelial carcinoma who subsequently developed metastatic disease and initiated first-line therapy (Supplementary Fig. 1). Each patient had an ICD code for urothelial cancer, at least two documented clinical visits on or after January 1, 2011, pathology consistent with urothelial cell carcinoma, and confirmation of node-positive or metastatic disease between January 1, 2011 and May 18, 2018. The study excluded patients who did not receive systemic therapy for advanced bladder cancer, received first-line agents as part of a clinical trial, had a >90-d gap between diagnosis and first structured EHR activity, or received first-line agents that were not listed in the National Comprehensive Cancer Network (NCCN) guidelines for systemic therapy of mUC. Patients were excluded if they initiated first-line treatment after May 18, 2018, the time of the FDA safety alert and subsequent label revision for mUC immunotherapy, to reduce confounding from choice of first-line therapy by PD-L1 status.

2.3. Exposure

Carboplatin-based chemotherapy was defined as an NCCN guideline–recommended carboplatin-containing doublet or other evidence-based carboplatin-containing regimen. Immunotherapy treatment was defined as single-agent nivolumab, pembrolizumab, atezolizumab, durvalumab, or avelumab.

2.4. Outcome measures

The primary outcome was overall survival (OS), defined as the time from the start of the first-line treatment of interest to the date of death. Follow-up was terminated at the earliest of death, data extraction date of August 31, 2018, or last activity in the EHR. The secondary outcome was second-line therapy-free survival, defined as the time from the start of first-line therapy to the earliest of the start date of second-line therapy or death.

Mortality information in the Flatiron Health database is derived from structured and unstructured documents within the EHR, as well as the Social Security Death Index and a commercial death data set that mines data from obituaries and funeral homes. When compared with the National Death Index, Flatiron Health's mortality data showed high sensitivity (85–90%), specificity (97%), positive predictive value (>96%), and exact date agreement (>90%) [17].

2.5. Covariates

Eleven covariates thought likely to influence the choice of first-line therapy were measured in the 62 d prior to treatment start. These included patient

factors such as age, sex, race/ethnicity, smoking status, body mass index, primary site of disease, Eastern Cooperative Oncology Group (ECOG) performance status (using the most proximate value to first treatment episode), comorbidity score (using ICD-9/10 diagnosis codes as outlined by Elixhauser et al; see the work of van Walraven et al [18]), and use of opioid pain medication or corticosteroids as a surrogate of symptomatic or high-volume disease, as well as practice factors including academic or community practice and immunotherapy prescribing rate by practice.

2.6. Statistical analysis

Cohort characteristics in chemotherapy and immunotherapy groups were compared using standard descriptive statistics. Multiple imputation via chained equations was used to address missing data that were assumed to be missing at random [19]. Ten imputed data sets were created, including all covariates listed above in the imputation model. Rubin's [20] rules were used to generate pooled effect estimates and variances across imputed data sets [21].

To address systematic differences between chemotherapy and immunotherapy initiators (ie, confounding by indication), we used inverse probability of treatment weighting (IPTW) analyses. IPTW, a form of propensity score analysis, uses weighting by the inverse of the propensity score to reduce imbalance in measured confounders between treatment groups [22]. The propensity score model included all baseline characteristics listed above.

Propensity scores were estimated using Super Learner, an ensemble machine-learning algorithm [23]. The algorithm combined weighted estimates across several parametric and nonparametric prediction modeling approaches based on the accuracy of predictions from the models to create an overall propensity score estimate, which increased the robustness of the analysis. These estimated propensity scores were used to calculate each patient's inverse probability of being treated with carboplatin-based chemotherapy or immunotherapy. Postweighting balance in covariates between treatment groups was evaluated using the standardized difference approach. Imbalance was defined as a standardized difference of >10%. Overlap of propensity score distributions between treatment groups was assessed graphically using density plots (Supplementary Fig. 2).

IPTW-adjusted Kaplan-Meier curves compared OS (median OS, 12-mo OS, and 36-mo OS) between treatment groups. Multivariable Cox proportional hazard regression analysis estimated IPTW-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for immunotherapy compared with carboplatin-based chemotherapy. The proportional hazard assumption was evaluated by testing the correlation of the scaled Schoenfeld residuals and time. After observing deviations from proportionality for the immunotherapy effect, we incorporated a time-varying coefficient for immunotherapy, allowing for a single change point in the immunotherapy effect at 12 mo. In a sensitivity analysis to assess the degree of unmeasured confounding, we calculated E-values based on point estimates before and after 12 mo, to quantify the minimum strength of association between an unmeasured confounder, and both the treatment and the outcome needed to nullify the observed treatment-outcome association [24]. In an exploratory analysis, we repeated the primary analysis, stratified by PD-L1 test status. PD-L1 was primarily assessed by immunohistochemistry using the Dako 22C3 or 28-8 assay (positive if combined positive score of ≥10%) or Ventana assay SP142 or SP263 (positive if tumor-infiltrating immune cells ≥5%). All statistical tests were two sided, conducted at the 5% significance level using R version 3.5.1.

3. Results

3.1. Unweighted and weighted baseline characteristics

Of 2017 patients, 487 received immunotherapy and 1530 received carboplatin-based chemotherapy (Table 1). The median age was 78 yr, and the majority of patients were male (73%), were white (74%), had a history of smoking (72%), and received treatment at a community practice (97%). Notably, PD-L1 was tested in only 7% of patients, consistent with the original label indication for immunotherapy, which did not mandate PD-L1 testing for cisplatin-ineligible patients.

Unweighted baseline characteristics were generally similar between treatment groups, with two exceptions: immunotherapy initiators had higher ECOG performance status (ECOG ≥2: 33% vs 24%) and higher Elixhauser comorbidity score (>5, 14% vs 5.8%; Table 1). All weighted baseline characteristics included in the propensity score model were well balanced between treatment groups (Table 1 and Supplementary Fig. 2). The median time from diagnosis to first-line treatment initiation was 31 d for patients receiving immunotherapy and 35 d for patients receiving carboplatin-based chemotherapy.

3.2. Overall survival

Median follow-up time was 7.2 mo (interquartile range [IQR] 3.2–14 mo), defined as the time from the start of treatment to the earliest of death, data extraction, or last EHR activity. The follow-up time among individuals who remained alive was 11 mo (IQR 5–22 mo). During follow-up, there were 1219 deaths (n = 939 among carboplatin-chemotherapy initiators and n = 280 among immunotherapy initiators). IPTW-adjusted Kaplan-Meier curves are displayed in Fig. 1. Adjusted and unadjusted Kaplan-Meier curves were similar (Supplementary Fig. 3). The median OS was 9 mo in the immunotherapy group and 11 mo in the carboplatin-based chemotherapy group. Relative to the carboplatin-based chemotherapy group, the estimated OS rate in the immunotherapy group was lower at 12 mo (40% [95% CI 34–45%] vs 46% [95% CI 43–49%], p = 0.05) but higher at 36 mo (28% [95% CI 22–35%] vs 13% [95% CI 11–16%], p < 0.001; Table 2). In the first 12 mo, treatment with immunotherapy was associated with an increased hazard of death compared with chemotherapy (HR 1.37, 95% CI 1.15–1.62, p < 0.001). Among patients who survived 1 yr after the initiation of treatment, subsequent survival was improved for immunotherapy compared with chemotherapy (HR 0.50, 95% CI 0.30–0.85, p = 0.01). The difference in the immunotherapy effect before and after 12 mo was statistically significant (p < 0.001). The E-values (relative risk) for the point estimates for death were 1.79 (≤12 mo) and 2.59 (>12 mo).

3.3. Second-line therapy–free survival

A total of 818 patients (41%) received second-line therapy. For immunotherapy initiators, 22% of patients received second-line treatment, whereas for carboplatin-based chemotherapy initiators, 47% received second-line treatment. In the immunotherapy group, 39% (41/106) received a platinum-based regimen as second-line therapy; in the carboplatin-based chemotherapy group, 39% (279/712) received immunotherapy as second-line therapy (Table 3). The follow-up time among patients who remained alive and

Table 1 – Baseline characteristics of patients ($n = 2017$) who received first-line immunotherapy or carboplatin-based chemotherapy.

	Unweighted population			Inverse probability of imputed treatment weighted population		
	Immunotherapy ($n = 487$)	Carboplatin-based chemotherapy($n = 1530$)	SMD	Immunotherapy ($n = 487$)	Carboplatin-based chemotherapy($n = 1530$)	SMD
Median age	77	78	0.038	77	78	0.059
Sex						
Male	360 (74)	1115 (73%)	0.024	75%	74%	0.031
Female	127 (26)	415 (27%)		25%	26%	
Race/ethnicity						
White	358 (74%)	1137 (74%)	0.111	74%	74%	0.076
Black	18 (3.7%)	75 (4.9%)		4.5%	4.9%	
Other	53 (11%)	180 (12%)		11%	12%	
Unknown	58 (12%)	138 (9.0%)		11%	9.2%	
Year of diagnosis						
2011	0 (0%)	109 (7%)	2.081	0%	6.7%	1.923
2012	0 (0%)	166 (11%)		0%	10%	
2013	0 (0%)	219 (14%)		0%	14%	
2014	0 (0%)	226 (15%)		0%	14%	
2015	8 (1.6%)	277 (18%)		2.4%	18%	
2016	93 (19%)	296 (19%)		21%	20%	
2017	265 (54%)	184 (12%)		55%	13%	
2018	121 (25%)	53 (3.5%)		22%	3.8%	
Site of disease						
Bladder	367 (75%)	1131 (74%)	0.160	76%	74%	0.087
Renal pelvis	63 (13%)	256 (17%)		13%	16%	
Ureter	56 (12%)	131 (8.6%)		10%	9.0%	
Urethra	1 (0.21%)	12 (0.78%)		0.47%	0.71%	
Smoking history						
Current/former smoker	362 (74%)	1093 (71%)	0.115	76%	72%	0.123
Never smoker	120 (25%)	400 (26%)		23%	26%	
Unknown	5 (1.0%)	37 (2.4%)		0.91%	2.2%	
Mean BMI	26	27	0.109	27	27	0.032
ECOG performance status[a]						
0	88 (26%)	238 (30%)	0.429	44%	45%	0.073
1	143 (42%)	367 (46%)		6.1%	5.6%	
2	92 (27%)	149 (19%)		23%	21%	
≥3	21 (6.1%)	37 (4.7%)		27%	28%	
Missing	143 (29%)	739 (48%)		0.00%	0.00%	
Immunotherapy prescribing rate (%)[b]						
<25	219 (45%)	1063 (69%)	0.591	63%	64%	0.036
25–50	194 (40%)	421 (28%)		31%	30%	
50–75	52 (11%)	43 (2.8%)		4.9%	4.9%	
>75	22 (4.5%)	3 (0.20%)		1.3%	0.98%	
PD-L1 tested	41 (8.4%)	93 (6.1%)	0.090	8.9%	6.2%	0.099
PL-L1 result, among tested						
Positive	9 (22%)	16 (17%)	0.311	22%	16%	0.285
Negative	18 (44%)	55 (59%)		47%	61%	
Unknown	14 (34%)	22 (24%)		31%	22%	
Mean comorbidity score[c]	2.5	1.1	0.355	1.5	1.5	0.017
Prescription medication use at treatment initiation[d]						
Any opioids	133 (27%)	308 (20%)	0.169	72%	71%	0.034
Any steroids	39 (8.0%)	210 (14%)	0.184	44%	45%	0.016

BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; PD-L1 = programmed death-ligand 1; SMD = standardized mean difference.
[a] Proportions computed among nonmissing patients.
[b] Immunotherapy prescribing rate at the clinic where patients received treatment.
[c] By Elixhauser et al, see the work of van Walraven et al [18].
[d] Defined as 60 d prior to 7 d after starting the therapy.

did not receive second-line treatment was 8 mo (IQR 4–17 mo). During follow-up, there were 1643 deaths or progression to second-line treatment ($n = 1304$ among carboplatin-chemotherapy initiators and $n = 339$ among immunotherapy initiators). At 12 mo, the estimated second-line therapy–free survival in the immunotherapy group was similar to that in the carboplatin-based chemotherapy group (26% [95% CI 21–31%] vs 24% [95% CI 43–49%], $p = 0.5$). At 36 mo, second-line therapy–free survival was higher in the immunotherapy group (28% [95% CI 22–35%] vs 13% [95% CI 11–16%], $p < 0.001$). Similar to observed associations with OS, treatment with immunotherapy was associated with decreased second-line therapy–free survival in the first 12 mo (HR 1.18, 95% CI 1.03–1.36, $p = 0.02$) and increased second-line therapy–free survival

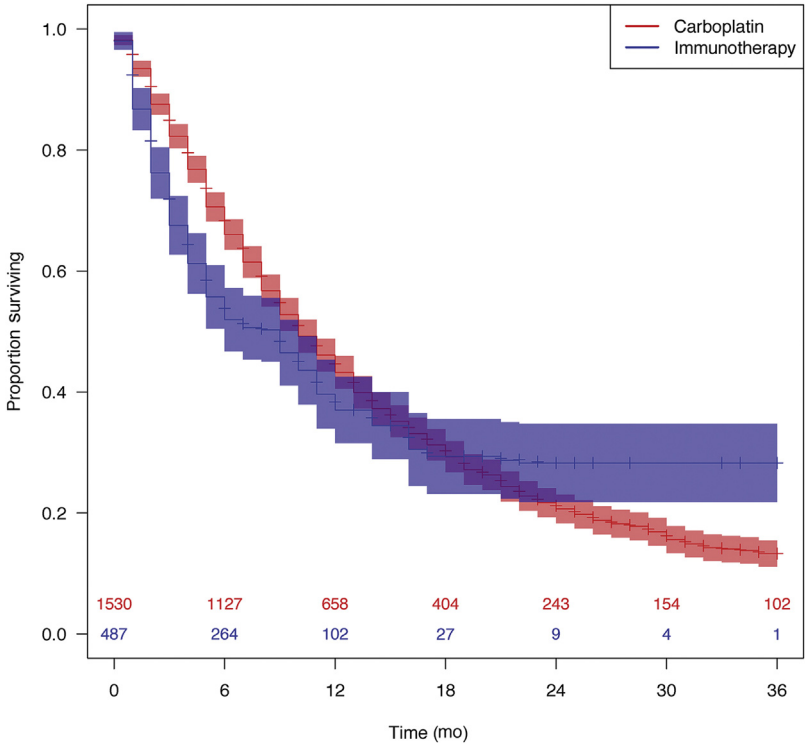

Fig. 1 – IPTW-adjusted Kaplan-Meier estimates for overall survival. Numbers along *x* axis are the numbers of patients remaining in the risk set at each time point. IPTW = inverse probability of treatment weighting.

beyond 12 mo (HR 0.38, 95% CI 0.20–0.71, $p = 0.003$), compared with chemotherapy (Table 2). The E-values for the point estimates for second-line therapy–free survival were 1.50 (≤12 mo) and 3.33 (>12 mo).

3.4. *Exploratory subgroup analysis*

At 6 mo, survival was highest for PD-L1–positive patients treated with immunotherapy and lowest for PD-L1–negative patients treated with immunotherapy, relative to patients treated with chemotherapy (Fig. 2).

4. Discussion

For mUC patients who are ineligible for standard cisplatin-based chemotherapy, no prior studies have directly compared first-line immunotherapy with carboplatin-based chemotherapy. Most of the evidence comes from

Table 2 – Inverse probability of treatment weighting–adjusted survival outcomes.

	First-line immunotherapy (*N* = 487) Estimate, 95% CI	First-line carboplatin-based chemotherapy (*N* = 1530) Estimate, 95% CI
Overall survival (OS)[a]		
Median OS	9 mo	11 mo
12-mo OS	40% (34–45%)	46% (43–49%)
36-month OS	28% (22–35%)	13% (11–16%)
Hazard ratio ≤12 mo	1.37 (1.15–1.62)	1.00 (reference)
Hazard ratio >12 mo	0.50 (0.30–0.85)	1.00 (reference)
Second-line therapy-free survival (TFS)[b]		
Median TFS	6 mo	7 mo
12-mo TFS	26% (21–31%)	24% (21–26%)
36-mo TFS	16% (11–22%)	5.9% (4.5–7.4%)
Hazard ratio ≤12 mo	1.18 (1.03–1.36)	1.00 (reference)
Hazard ratio >12 mo	0.38 (0.20–0.71)	1.00 (reference)

CI = confidence interval.
[a] Defined as the time from the start of first-line therapy to the date of death.
[b] Defined as the time from the start of first-line therapy to the earliest of the start date of second-line therapy or death.

Table 3 – Second-line treatment.

	First-line immunotherapy ($N = 487$)	First-line carboplatin-based chemotherapy ($N = 1530$)
Second-line treatment received, n (%)		
Yes	106 (22)	712 (47)
No	381 (78)	818 (53)
Second-line regimen, among patients receiving second-line therapy, n (%)		
Immunotherapy	30 (28)	279 (39)
Carboplatin-based chemotherapy	31 (29)	153 (21)
Cisplatin-based chemotherapy	10 (9.4)	37 (5.2)
Other non-NCCN guideline or non–evidence-based therapy[a]	48 (45)	259 (36)

NCCN = National Comprehensive Cancer Network.
[a] Therapies include the following: (1) immunotherapy and carboplatin-based chemotherapy, (2) immunotherapy and non–carboplatin/non–cisplatin-based chemotherapy, (3) immunotherapy and nonchemotherapy, (4) carboplatin- and cisplatin-based chemotherapy, (5) carboplatin-based chemotherapy and nonchemotherapy, (6) cisplatin-based chemotherapy and nonchemotherapy, (7) single-agent non–carboplatin/non–cisplatin-based chemotherapy, and (8) non–carboplatin/non–cisplatin-based chemotherapy and nonchemotherapy.

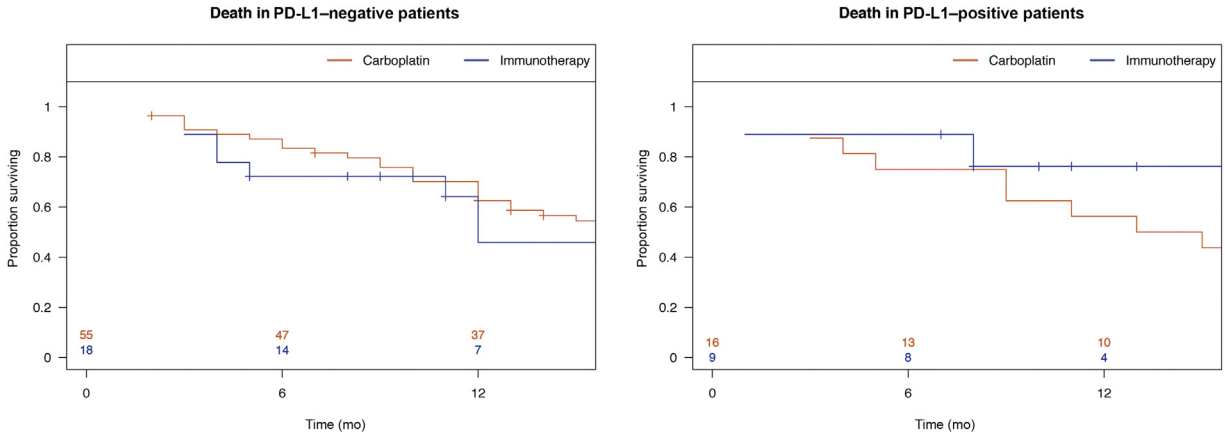

Fig. 2 – Kaplan-Meier estimates for overall survival stratified by PD-L1. Numbers along *x* axis are the numbers of patients remaining in the risk set at each time point. PD-L1 = programmed death-ligand 1.

cross-trial comparisons of response rates rather than from comparisons with real-world OS. In the absence of comparative data, providers and patients face a difficult choice regarding first-line treatment selection in clinical practice. In this study, we demonstrate that patients treated with immunotherapy had a 37% increase in the hazard of death in the first 12 mo after the initiation of therapy, but among those who survived 1 yr, there was a 50% lower hazard of death beyond 12 mo after the initiation of therapy. These results suggest that clinicians and patients should carefully balance the short-term benefit of chemotherapy against the long-term benefit of immunotherapy.

Our observation of decreased short-term survival with immunotherapy is consistent with the preliminary results from data monitoring committees' early review of two ongoing first-line immunotherapy trials, which showed decreased survival in patients treated with immunotherapy monotherapy relative to the chemotherapy arms. Although exploratory in nature, our PD-L1–stratified analysis also suggests that PD-L1–negative patients have inferior survival with immunotherapy relative to chemotherapy, supporting the EMA and FDA label revision restricting immunotherapy use to mUC patients whose tumors are PD-L1 positive (approximately 30% of all tumors). Future studies should compare patient outcomes associated with a biomarker-guided versus an unguided treatment strategy. While more granular data from the ongoing phase III trials are pending, our results provide critical insight into this label change, suggesting that the risk-benefit profile with immunotherapy is not favorable for all mUC patients. Early decreased survival with immunotherapy relative to chemotherapy may reflect the subset of patients who do not respond to immunotherapy (65% in KEYNOTE-052) or, less commonly, who exhibit a phenomenon of hyperprogression [5,25,26]. Therefore, some populations (eg, those with symptomatic or high-volume disease) may instead benefit from chemotherapy as initial therapy. However, our data also suggest a long-term benefit of immunotherapy. The long-term benefit may not have been captured in the early review of the phase III trials upon which the EMA and FDA's label restriction was based. Our findings of improved short-term survival with carboplatin-based chemotherapy but superior long-term survival with immunotherapy provide a rationale for considering first-line combination

of chemotherapy and immunotherapy in an effort to achieve maximal survival for all patients. This is currently being explored in the ongoing trials KEYNOTE-361 and IMVigor-130.

Our reported 40% 12-mo OS rate for first-line immunotherapy is modestly lower than that observed in the two phase II trials that led to accelerated approval for immunotherapy, which showed 12-mo OS rates of 48% (pembrolizumab) and 57% (atezolizumab) [6,27]. The higher 12-mo OS rate in these studies is likely reflective of the narrow eligibility criteria of the clinical trials, which often exclude patients with multiple comorbid illnesses and the elderly [28]. Notably, the long survival tail for patients receiving immunotherapy in our study mirrors findings across disease groups for patients treated with checkpoint inhibitors. In contrast, few patients receiving carboplatin-based chemotherapy survived beyond 3 yr in our study, similar to the results from clinical trials of carboplatin-containing chemotherapy [3].

This study had several unique strengths. The large sample size of over 2000 patients and recency of data allowed us to study long-term effectiveness of immunotherapy as first-line therapy for mUC, a relatively new indication compared with the historical standard of carboplatin-based chemotherapy. In the absence of randomized data, our observations have real-world treatment implications. The analyses were conducted with IPTW models to account for confounding by factors associated with treatment selection and the outcome of interest, an approach with improved power relative to propensity score matching and improved confounding control relative to propensity score adjustment [29].

There are several limitations to this study. First, despite including a large range of covariates in our propensity score models, there is a risk of residual confounding. Although advanced propensity score–based methods are efficient for reducing bias from imbalance in observed confounders, such a methodology does not address unmeasured confounders. For example, we were unable to assess the presence of visceral metastases, which are associated with poor outcome in mUC patients, as data on metastatic sites of disease were unavailable in the database. However, for the outcome of OS, the sensitivity analysis using the E-value methods suggests that our observed associations could be explained only by an unmeasured confounder that was associated with both receipt of immunotherapy and risk of death by a risk ratio of $>$1.79 ($\leq$12 mo) or 2.59 ($>$12 mo) beyond that of the covariates measured in our study. Furthermore, residual confounding would be expected to explain only the observed treatment effects if the unmeasured confounder was associated with receipt of immunotherapy and with both increased early mortality and decreased late mortality. As the direction of the association reverses, an unmeasured confounder would either need to be time varying, with a distribution within treatment groups that changes partway through follow-up, or need to have a time-dependent effect that switched direction partway through follow-up. Therefore, while possible, it is unlikely that such an unmeasured confounder exists. Additionally, ECOG performance status, an important predictor of outcomes in cancer patients, required imputation for a large percentage of patients. Multiple imputation has been shown to be effective in EHR research under many missingness patterns as long as the fraction of missing information is not too large [30]. Across 10 imputed data sets, we observed minimal variation in parameter estimates, suggesting that information lost due to missing data was small (Supplementary Fig. 4). Further, we relied on ICD-9/10 codes to identify comorbidity, which may be imperfect as comorbidity may not be documented in an oncology-specific EHR unless it affects treatment selection. Second, because PD-L1 testing was not mandated until June 2018, analyses stratified by PD-L1 status had reduced statistical power—over 90% of patients did not have PD-L1 testing performed. Third, within the confines of the Flatiron Health database, specific criteria were not used to define cisplatin ineligibility. Rather, patients were assumed cisplatin ineligible if they received carboplatin or immunotherapy in the first line, consistent with commonly accepted treatment guidelines for cisplatin-ineligible patients. However, only 5.7% of patients received cisplatin in the second line, suggesting that the majority of patients were likely to be ineligible for front-line cisplatin. Fourth, treatment-related toxicity is not yet available in the Flatiron Health database. Indeed, optimal first-line treatment selection involves consideration of both efficacy and safety. For example, in a prospective clinical trial, high-grade toxicity, including death, was reported in 15% of cisplatin-ineligible mUC patients treated with carboplatin-based chemotherapy [3]. Although immunotherapy is often considered a well-tolerated option, it is also associated with severe and fatal immune-mediated adverse events [31].

5. Conclusions

In summary, this observational cohort study demonstrated inferior short-term but superior long-term survival with first-line immunotherapy relative to carboplatin-based chemotherapy among patients with mUC treated in routine clinical practice. We cannot exclude the possibility that an unmeasured confounder contributed to this association. Choosing between these options will require the identification of patient subgroups that may derive benefit or harm from first-line immunotherapy or chemotherapy. Likewise, understanding patient preference for short- versus long-term benefit with systemic therapy is important, particularly in the setting of metastatic disease. Until the currently pending trial results become available, these results provide important information to facilitate decision making between physicians and patients.

Author contributions: Emily Feld had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Feld, Mamtani.
Acquisition of data: Meropol, Adamson, Cohen.
Analysis and interpretation of data: Feld, Mamtani, Harton, Hubbard.
Drafting of the manuscript: Feld, Mamtani, Harton, Hubbard.

Critical revision of the manuscript for important intellectual content: Feld, Harton, Meropol, Adamson, Cohen, Parikh, Galsky, Narayan, Christodouleas, Vaughn, Hubbard, Mamtani.
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Appendix A. Supplementary data

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