Title

Socioeconomic and Demographic Disparities in Immunotherapy Utilization for Advanced Kidney and Bladder Cancer

Journal

Urologic Oncology Seminars and Original Investigations, 42(11)

ISSN

1078-1439

Authors

Holland, Levi

Bhanvadia, Raj

Ibeziako, Nathanaelle

et al.

Publication Date

2024-11-01

DOI

10.1016/j.urolonc.2024.06.012

Urologic Oncology: Seminars and Original Investigations 42 (2024) 374.e11−374.e20

UROLOGIC ONCOLOGY

Clinical-Kidney cancer

Socioeconomic and Demographic Disparities in Immunotherapy Utilization for Advanced Kidney and Bladder Cancer

Levi Holland[a], Raj Bhanvadia[a], Nathanaelle Ibeziako[a], Jacob Taylor[a], Deitrich Gerlt[b], Iftach Chaplin[a], Aditya Bagrodia[c], Neil Desai[d], Kris Gaston[a], Yair Lotan[a], Vitaly Margulis[a], Tian Zhang[e], Suzanne Cole[e], Solomon Woldu[a,*]

[a] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX*
[b] *Texas College of Osteopathic Medicine, University of North Texas Health Science Center, Fort Worth, TX*
[c] *Department of Urology, University of California San Diego, San Diego, CA*
[d] *Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, TX*
[e] *Department of Internal Medicine, Division of Hematology and Oncology, University of Texas Southwestern Medical Center, Dallas, TX*

Received 17 January 2024; received in revised form 27 May 2024; accepted 10 June 2024

Abstract

Objectives: Immunotherapy (IO) drugs have been increasingly utilized in locally advanced or metastatic clear cell renal cell carcinoma (ccRCC) and urothelial carcinoma of the bladder (UC). Multiple trials have demonstrated clear survival benefit, however, there are often barriers to access for these advanced therapies which has been demonstrated in other non-urologic malignancies. The goal of this study was to assess socioeconomic and demographic factors associated with the receipt of IO for advanced ccRCC and UC.

Materials and methods: We queried the National Cancer Database (NCDB) for patients with stage IV ccRCC and UC. The study period was 2015 to 2020 for ccRCC (FDA approval date of IO) and 2017 to 2020 for UC (FDA approval date of broadened indication for IO, initial limited approval in 2016). The primary outcome of interest was receipt of IO therapy using multivariable logistic regression, adjusting for relevant socioeconomic and demographic variables.

Results: We identified 15,926 patients with stage IV ccRCC and 10,380 patients with stage IV UC of which 5,419 (34.0%) and 2,231 (21.5%) received IO therapy, respectively. IO utilization increased with each successive year. In both malignancies, treatment at a non-academic facility, education level, income, and insurance were independently associated with IO utilization. For ccRCC, black (OR = 0.77, 95% CI, 0.64−0.93, $P = 0.009$) and Hispanic race (OR = 0.73, 95% CI, 0.61−0.86, $P = 0.006$) were each associated with decreased IO utilization but there were no independent associations between race and receipt of IO in patients with UC.

Conclusions: In the era of FDA-approved IO therapy for advanced ccRCC and UC, this national cohort analysis suggests that IO utilization is increasing over time, but significant disparities exist based on income, education, and insurance status in both malignancies. Additionally, patients treated at non-academic facilities were less likely to receive IO therapy for these specific genitourinary malignancies. In ccRCC, additional disparities were seen black and Hispanic races which each were associated with lower odds of IO receipt. Identifying strategies to mitigate these differences and provide equitable access to IO therapy is of imperative need.

Keywords: Immunotherapy; Renal cell carcinoma; Kidney cancer; Bladder cancer; Healthcare disparities; Socioeconomic factors

1. Introduction

In 2023, there will be an estimated 81,800 new cases of kidney cancer and 82,290 of bladder cancer [1]. At diagnosis, over 30% of patients with renal cell carcinoma (RCC) have metastatic disease, and while survival rates have improved recently - historic long-term survival rates of stage IV RCC are low [2]. Similarly, a significant portion of patients with urothelial cancer (UC) present with or develop advanced disease [1,3]. Historically, long-term

*Corresponding author.
E-mail address: solomon.woldu@utsouthwestern.edu (S. Woldu).

https://doi.org/10.1016/j.urolonc.2024.06.012

survival of metastatic UC was exceedingly uncommon; however, some patients with stage IV UC are achieving long-term survival with the advent of novel therapies [3].

Improvement in survival for both metastatic RCC and UC has hinged upon the development and implementation of immunotherapy (IO) drugs, given as single agents and in combination therapy [4]. Since atezolizumab was Food and Drug Administration (FDA) approved in 2016 for metastatic or locally advanced UC, IO has been increasingly utilized in the first-line platinum-ineligible and second-line setting [5,6]. In less than a decade, multiple additional IO therapies have been approved to treat UC with improved survival outcomes. In metastatic clear cell renal cell carcinoma (ccRCC), the first IO drug granted approval by the FDA in 2015 was nivolumab [7]. The FDA granted approval for several combination IO therapies for metastatic ccRCC following the results of subsequent positive clinical trials [8−10].

Despite the evidence of benefit of these novel therapies, barriers to access exist. It is well known that racial/ethnic and socioeconomic factors are associated with disparities in cancer care [11,12]. Previous studies across various cancer subtypes have demonstrated racial and social disparities led to inequities in the administration of IO before and after FDA approval [13−16]. Analysis of IO administration in non-urologic malignancies have shed light on disparate utilization of IO associated with factors such as insurance status, education level, income, race, comorbidities, and treatment at academic vs. non-academic facilities [14−18].

In contrast, data evaluating potential disparities in IO use in urologic malignancies has been scarce despite rapid growth of IO utilization post FDA-approval. For example, in RCC, a study evaluating the National Cancer Database (NCDB) through 2018 demonstrated a correlation between lower IO utilization and Black race, Hispanic ethnicity, female sex, and lack of insurance [13]. Aside from this 1 study, which was conducted over a short window of time (2016−2018), the evaluation of post-FDA approval IO utilization in urologic malignancies is minimal.

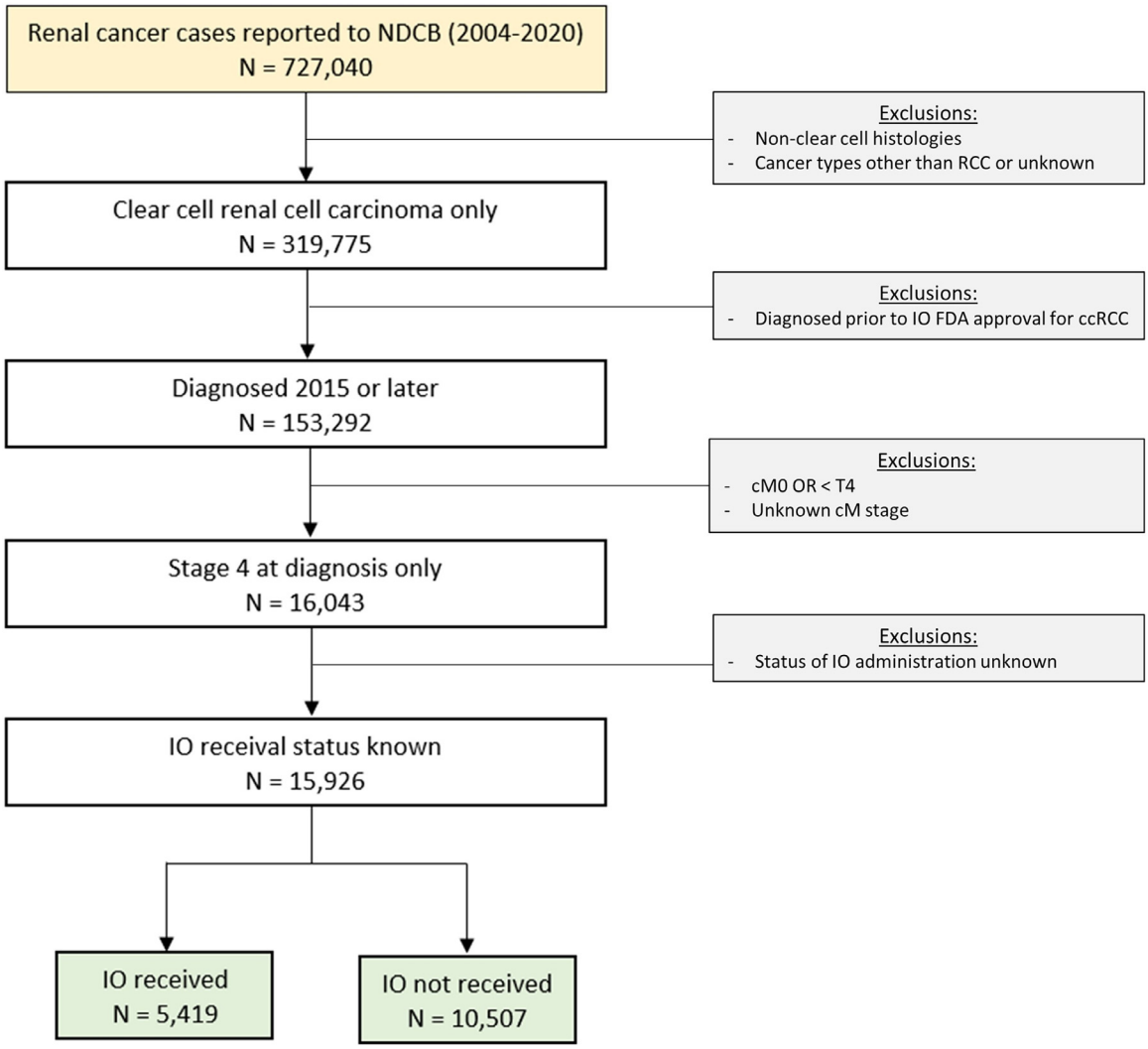

Fig. 1. Flow diagram of study sample selection for clear cell renal cell carcinoma.

Table 1
Baseline clinical, demographic, and facility characteristics of cohort, stratified by receipt of immunotherapy for ccRCC

	No Immunotherapy	Immunotherapy	*P*-value
N	10507	5419	
Year of diagnosis (%)			<0.001
2015	2127 (89.9)	239 (10.1)	
2016	2244 (88.5)	291 (11.5)	
2017	2241 (82.3)	483 (17.7)	
2018	1670 (59.2)	1153 (40.8)	
2019	1165 (42.0)	1608 (58.0)	
2020	1060 (39.2)	1645 (60.8)	
Age category (%), y			<0.001
≤55	1963 (61.1)	1252 (38.9)	
56−65	3427 (62.9)	2024 (37.1)	
66−75	3272 (68.3)	1518 (31.7)	
≥76	1845 (74.7)	645 (25.3)	
Sex (%)			<0.001
Male	7225 (64.8)	3925 (35.2)	
Female	3282 (68.7)	1494 (31.3)	
Race (%)			<0.001
White	8237 (65.3)	4372 (34.7)	
Hispanic	931 (70.3)	393 (29.7)	
Black	685 (70.9)	281 (29.1)	
Asian	215 (60.7)	139 (39.3)	
Other	209 (61.3)	132 (38.7)	
Charlson-Deyo score (%)			<0.001
0	6874 (64.5)	3776 (35.5)	
1	1973 (68.3)	914 (31.7)	
2	813 (67.1)	399 (32.9)	
≥3	847 (72.0)	330 (28.0)	
Income quartiles[a] (%)			<0.001
<$46.2K	1676 (69.6)	731 (30.4)	
$46.2K-57.8K	2183 (67.2)	1067 (32.8)	
$57.8K-74K	2230 (65.5)	1173 (34.5)	
>$74K	2780 (63.7)	1581 (36.3)	
Education level[b] (%)			<0.001
≥15.3%	2156 (68.4)	998 (31.6)	
9.1−15.2%	2565 (66.7)	1278 (33.3)	
5.0−9.0%	2592 (66.0)	1337 (34.0)	
<5.0%	1585 (62.5)	949 (37.5)	
Insurance status (%)			<0.001
Not insured	394 (74.5)	135 (25.5)	
Private insurance	3794 (61.2)	2405 (38.8)	
Medicaid	880 (65.7)	460 (34.3)	
Medicare	5100 (69.2)	2273 (30.8)	
Other government	187 (67.5)	90 (32.5)	
Facility type (%)			0.034
Academic	4466 (65.2)	2384 (34.8)	
Community/Other[c]	5935 (66.8)	2948 (33.2)	
Facility location (%)			0.129
New England	468 (63.6)	268 (36.4)	
Middle Atlantic	1332 (67.8)	633 (32.2)	
South Atlantic	1940 (66.4)	980 (33.6)	
East North Central	1823 (64.8)	989 (35.2)	
East South Central	726 (63.9)	410 (36.1)	
West North Central	1075 (67.4)	520 (32.6)	
West South Central	1237 (67.6)	592 (32.4)	
Mountain	510 (65.4)	270 (34.6)	
Pacific	1290 (65.8)	670 (34.2)	
Residential setting (%)			0.428
Metro	8089 (65.6)	4250 (34.4)	
Urban	1799 (66.9)	892 (33.1)	
Rural	221 (66.4)	112 (33.6)	
Travel distance category[d] (%), miles			0.019
≤20	5377 (66.6)	2700 (33.4)	
21−40	1497 (63.3)	867 (36.7)	
41−60	741 (67.1)	363 (32.9)	
>60	1359 (66.8)	675 (33.2)	
Medicaid Expansion State (%)			0.946
Yes	6250 (66.1)	3207 (33.9)	
No	4151 (66.1)	2125 (33.9)	

[a] Median annual household income in the patient's zip code.
[b] Percentage quartiles of individuals without a high school diploma in the patient's zip code.
[c] Community cancer programs, comprehensive community cancer programs, integrated network cancer programs, and other programs.
[d] Distance of patient's residence from hospital.

Given the clinical importance of IO and rapid adoption for metastatic UC and RCC, we sought to assess overall IO administration patterns for urologic malignancies further. Ultimately, this may allow targeting low utilization subgroups for improvements in advanced therapy health equity.

2. Materials and methods

2.1. Data source

The National Cancer Database (NCDB) is a joint venture of the American Cancer Society and American College of Surgeons, which collects clinical oncology data from more than 1,500 Commission on Cancer (CoC) accredited facilities. Approximately 70% of new malignancies diagnosed in the US are included. Various data are collected, including demographics, histopathology, treatments, outcomes, and follow-up information [19,20]. The data obtained from the NCDB is deidentified at both the facility and patient level; therefore, institutional review board approval was waived.

2.2. Study population

We queried the 2020 NCDB for all renal and bladder cancer cases diagnosed between 2004 and 2020. For the renal cancer cohort, those with stage IV disease and predominant clear cell histology at diagnosis were identified; excluding non-clear cell RCC and other primary renal malignancies. As the first Food and Drug Administration (FDA) approved IO in ccRCC was in 2015 (nivolumab) [21], patients diagnosed prior to this date were excluded.

For the UC cohort, patients with stage IV disease and predominant urothelial histology at diagnosis were identified; excluding non-urothelial predominant histology (pure squamous, pure adenocarcinoma, or small cell), neuroendocrine features, or unknown histology. Although IO

Table 2
Multivariable logistic regression analysis to identify predictors of immunotherapy receival for ccRCC

	OR (95% CI)[e]	*P*-value
Year of diagnosis		
2015	Ref	Ref
2016	1.27 (1.03−1.58)	0.027
2017	2.37 (1.94−2.88)	<0.001
2018	7.64 (6.35−9.18)	<0.001
2019	15.16 (12.59−18.25)	<0.001
2020	17.23 (14.31−20.75)	<0.001
Age (years)		
≤55	Ref	Ref
56−65	0.83 (0.74−0.94)	0.003
66−75	0.66 (0.56−0.77)	<0.001
≥76	0.46 (0.39−0.56)	<0.001
Sex		
Male	Ref	Ref
Female	0.92 (0.83-1.00)	0.063
Race		
White	Ref	Ref
Hispanic	0.73 (0.61−0.86)	<0.001
Black	0.77 (0.64−0.93)	0.006
Asian	1.24 (0.93−1.65)	0.141
Other	1.11 (0.84−1.48)	0.465
Charlson-Deyo score		
0	Ref	Ref
1	0.86 (0.77−0.96)	.008
2	0.88 (0.75−1.03)	.102
≥3	0.66 (0.56−0.78)	<.001
Income quartiles[a]		
<$46.2K	Ref	Ref
$46.2K−57.8K	1.14 (0.99−1.31)	0.068
$57.8K−74K	1.31(1.12−1.52)	<0.001
>$74K	1.26 (1.06−1.49)	0.009
Education level[b]		
≥15.3%	Ref	Ref
9.1−15.2%	1.03 (0.91−1.17)	0.677
5.0−9.0%	1.04 (0.90−1.19)	0.638
<5.0%	1.22 (1.03−1.45)	0.022
Insurance status		
Not insured	Ref	Ref
Private insurance	2.02 (1.57−2.60)	<0.001
Medicaid	1.54 (1.16−2.04)	0.003
Medicare	1.79 (1.37−2.32)	<0.001
Other government	1.63 (1.10−2.44)	0.016
Facility type		
Academic	Ref	Ref
Community/Other[c]	0.86 (0.78−0.95)	0.002
Facility location		
New England	Ref	Ref
Middle Atlantic	0.81 (0.64−1.02)	0.070
South Atlantic	0.87 (0.69−1.09)	0.228
East North Central	0.99 (0.80−1.24)	0.959
East South Central	1.11 (0.85−1.45)	0.429
West North Central	0.82 (0.64−1.04)	0.103
West South Central	0.81 (0.63−1.03)	0.085
Mountain	1.02 (0.77−1.35)	0.882
Pacific	0.95 (0.76−1.20)	0.683
Residential setting		
Metro	Ref	Ref
Urban	1.06 (0.93−1.21)	0.394
Rural	1.02 (0.75−1.39)	0.897
Travel distance category[d], miles		
≤20	Ref	Ref
21−40	1.11 (0.98−1.25)	0.089
41−60	0.91 (0.77−1.09)	0.300
>60	0.93 (0.79−1.08)	0.320
Medicaid Expansion State		
No	Ref	Ref
Yes	0.97 (0.85−1.09)	0.577

[a] Median annual household income in the patient's zip code.
[b] Percentage quartiles of individuals without a high school diploma in the patient's zip code.
[c] Community cancer programs, comprehensive community cancer programs, integrated network cancer programs, and other programs.
[d] Distance of patient's residence from hospital.
[e] Odds ratio (95% confidence interval) of receiving immunotherapy vs. not receiving immunotherapy.

(atezolizumab) was initially approved by the FDA in 2016 for stage IV UC, the indication was for a relatively smaller population, those with progression after platinum-based chemotherapy. In early 2017, the indication for atezolizumab was broadened to include cisplatin-ineligible patients, and pembrolizumab was also approved [22]. Thus, 2017 was chosen as the start date for the UC cohort to provide a more robust sample. In both groups, those with unknown cancer staging were excluded. Clinical stage IV disease was defined by the American Joint Commission on Cancer (AJCC) staging criteria.

2.3. Variables

Independent clinical and sociodemographic variables assessed included age, year of diagnosis, Charlson−Deyo comorbidity score (CD Score), sex, race/ethnicity, insurance status, residential setting, travel distance to reporting facility, surrogates for educational level, household income (at the level of individual's residential zip code), reporting facility location, facility type, and Medicaid expansion status.

2.4. Statistical analysis

The primary outcome of interest was the receipt of IO in both renal and bladder cohorts. Baseline sociodemographic and clinical characteristics between IO receivers and non-receivers were compared in each cohort using chi-square tests. Multivariable logistic regression was performed with the same variables to identify potential independently associated factors related to receipt of immunotherapy. Missing data was excluded from the analysis. Statistical analyses were conducted using SPSS version 29 (IBM, Armonk, NY). Two-sided statistical significance was defined as $P < 0.05$, with all confidence intervals reported as 95%.

3. Results

3.1. Renal cell carcinoma cohort characteristics

We identified 15,926 patients with stage IV RCC diagnosed between 2015 and 2020 who met the criteria for analysis (Figure 1). The mean age was 64.29 (SD 10.75) years with 49.4% aged 65 years or older. Of these, 5,419 (34.0%) received IO and there were notable differences in the overall characteristics of patients who received IO and those who did not (Table 1). Patients who received IO were younger, healthier (according to CD score), more likely to be male (35.2% vs. 31.3%, $P < 0.001$), and more likely to reside in more affluent and educated areas and have private insurance. The proportion of black and Hispanic IO recipients (29.1% and 29.7%, respectively) was also significantly lower than white (34.7%), Asian (39.3%), or other races (38.7%) ($P < 0.001$). Notably, there was a significant increase in IO utilization with each successive year after IO approval in 2015. In 2016, only 11.5% of patients received IO, compared to 40.8% in 2018 and 60.8% in 2020 ($P < 0.001$). Chemotherapy utilization simultaneously trended downward over the subsequent years in the analysis (Supplementary Figure 1). A slightly higher proportion of patients received IO at academic facilities compared to non-academic (34.8% vs. 33.3%, $P = 0.034$).

3.2. Factors associated with immunotherapy receipt for renal cell carcinoma

On adjusted analysis (Table 2), more recent year of diagnosis, younger age, and fewer comorbidities were independently associated with increased likelihood of IO receipt. Black (OR 0.77 [95% CI, 0.64−0.93], $P = 0.009$) and Hispanic (OR 0.73 [95% CI, 0.61−0.86] $P = 0.006$) races were associated with a lower likelihood of receiving IO. Those with any insurance, including private (OR 2.02 [95% CI, 1.57−2.60], $P < 0.001$), Medicaid (OR 1.54 [95% CI, 1.16−2.04], $P = 0.003$), Medicare (OR 1.79 [95% CI, 1.37−2.32], $P < 0.001$), and other government programs (OR 1.63 [95% CI, 1.10−2.44], $P = 0.016$), were more

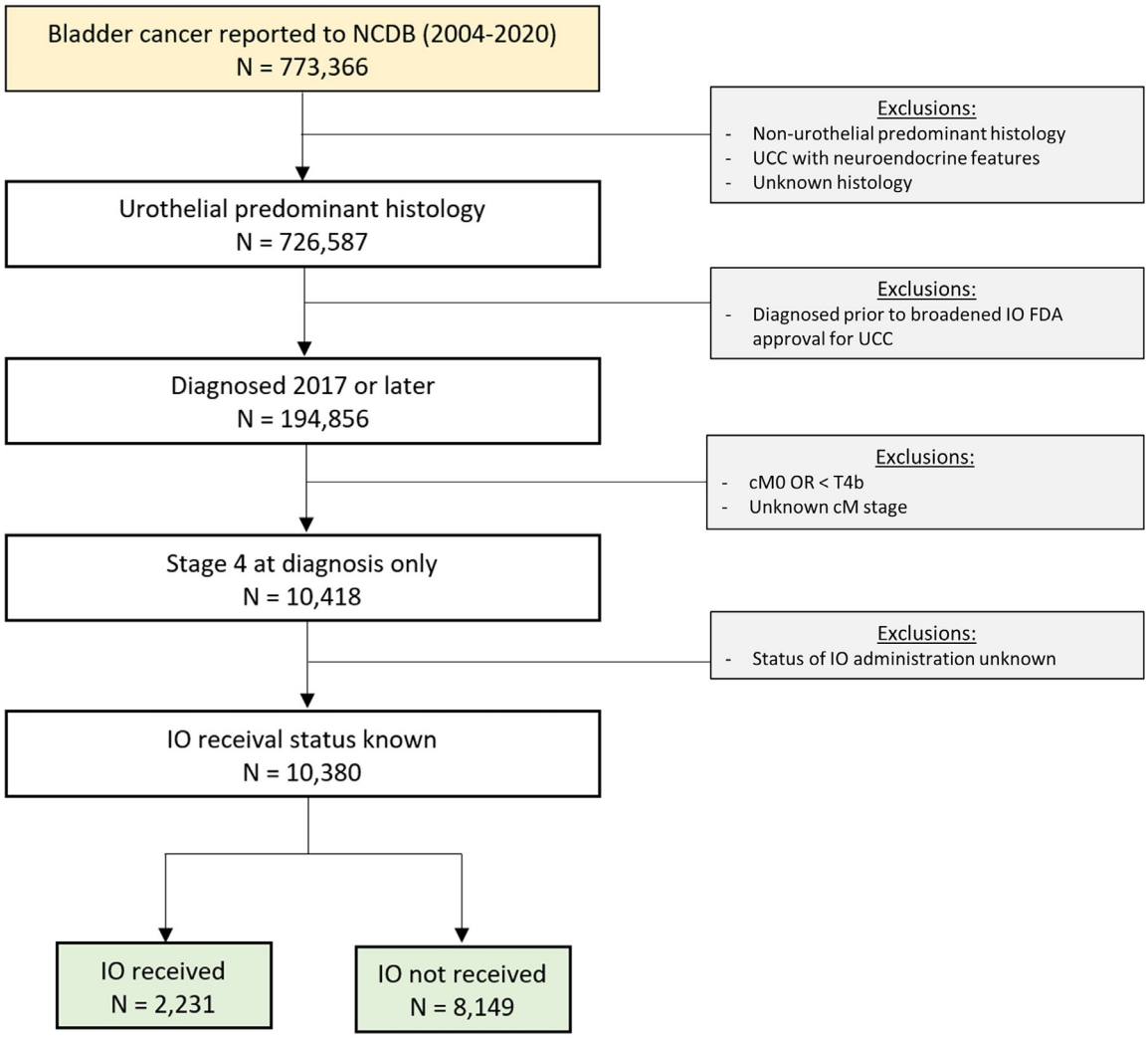

Fig. 2. Flow diagram of study sample selection for urothelial carcinoma of the bladder.

Table 3
Baseline clinical, demographic, and facility characteristics of cohort, stratified by receipt of immunotherapy for bladder UC

	No Immunotherapy	Immunotherapy	*P*-value
N	8,149	2,231	
Year of diagnosis (%)			<0.001
2017	3,190 (85.2)	554 (14.8)	
2018	1,735 (76.8)	524 (23.2)	
2019	1,748 (75.8)	558 (24.2)	
2020	1,476 (71.3)	595 (28.7)	
Age category (%), y			<0.001
≤55	718 (83.4)	143 (16.6)	
56−65	1,914 (80.4)	467 (19.6)	
66−75	2,697 (80.0)	675 (20.0)	
≥76	2,820 (74.9)	946 (25.1)	
Sex (%)			0.870
Male	5,826 (78.5)	1,599 (21.5)	
Female	2,323 (78.6)	632 (21.4)	
Race (%)			0.180
White	6,665 (78.2)	1,865 (21.8)	
Hispanic	402 (80.9)	95 (19.1)	
Black	757 (81.2)	175 (18.8)	
Asian	169 (76.5)	52 (23.5)	
Other	156 (78.0)	44 (22.0)	
Charlson-Deyo score (%)			0.100
0	5,326 (79.0)	1,418 (21.0)	
1	1,389 (78.7)	375 (21.3)	
2	718 (75.6)	232 (24.4)	
≥3	716 (77.7)	206 (22.3)	
Income quartiles[a] (%)			<0.001
<$46.2K	1,229 (82.0)	270 (19.0)	
$46.2K−57.8K	1,575 (78.6)	428 (21.4)	
$57.8K−74K	1,696 (78.8)	456 (21.2)	
>$74K	2,323 (75.9)	736 (24.1)	
Education level[b] (%)			<0.001
≥15.3%	1,430 (81.2)	332 (18.8)	
9.1−15.2%	2,015 (78.6)	548 (21.4)	
5.0−9.0%	2,034 (78.1)	571 (21.9)	
<5.0%	1,362 (75.3)	446 (24.7)	
Insurance status (%)			<0.001
Not insured	242 (85.2)	42 (14.8)	
Private insurance	1,744 (80.1)	433 (19.9)	
Medicaid	605 (81.0)	142 (19.0)	
Medicare	5,302 (77.3)	1,560 (22.7)	
Other government	148 (79.6)	38 (20.4)	
Facility type (%)			0.001
Academic	2,934 (76.8)	888 (23.2)	
Community/Other[c]	5,172 (79.5)	1,336 (20.5)	
Facility location (%)			0.370
New England	491 (76.0)	155 (24.0)	
Middle Atlantic	1,262 (78.2)	351 (21.8)	
South Atlantic	1,769 (79.4)	459 (20.6)	
East North Central	1,523 (78.6)	415 (21.4)	
East South Central	467 (77.8)	133 (22.2)	
West North Central	617 (79.7)	157 (20.3)	
West South Central	639 (77.3)	188 (22.7)	
Mountain	381 (81.6)	86 (18.4)	
Pacific	957 (77.4)	280 (22.6)	
Residential setting (%)			0.920
Metro	6,613 (78.6)	1,802 (21.4)	
Urban	1,155 (78.2)	322 (21.8)	
Rural	154 (77.8)	44 (22.2)	
Travel distance category[d] (%), miles			<0.001
≤20	4,732 (79.1)	1,250 (20.9)	
21−40	1,015 (74.0)	357 (26.0)	
41−60	432 (76.1)	136 (23.9)	
>60	1,970 (80.1)	488 (19.9)	
Medicaid Expansion State (%)			0.310
Yes	5,099 (78.2)	1,425 (21.8)	
No	3,007 (79.0)	799 (21.0)	

[a] Median annual household income in the patient's zip code.
[b] Percentage quartiles of individuals without a high school diploma in the patient's zip code.
[c] Community cancer programs, comprehensive community cancer programs, integrated network cancer programs, and other programs.
[d] Distance of patient's residence from hospital.

likely to receive IO than uninsured. Living in a community with higher educational and income levels was also associated with increased likelihood of IO receipt. Treatment at community or other non-academic cancer programs was associated with a lower likelihood of IO receipt compared to academic facilities (OR 0.86 (95% CI, 0.79−0.95], $P = 0.002$). With adjusted analysis, no significant difference in IO utilization was based on gender.

3.3. Urothelial carcinoma cohort characteristics

We identified 10,380 patients with stage IV UC between 2017 and 2020 who met the criteria for analysis (Figure 2). The average age was 70.90 (SD 10.89) years with 72.0% age 65 years or older. Of these, 2,231 patients (21.5%) received IO. IO utilization increased with each successive year after IO approval in 2017 (14.8%) to 28.7% in 2020. Simultaneously, chemotherapy utilization trended downward (Supplementary Figure 2).

On unadjusted analysis, there was proportionally more IO utilization each year after IO approval, like that seen in RCC (Table 3). In 2017, 14.8% of patients received IO, in contrast to 28.7% in 2020 ($P < 0.001$). There was a higher proportion of IO utilization at academic (23.2%) compared to non-academic facilities (20.5%, $P = 0.001$). There was no significant difference in the proportion of IO administration between each race/ethnicity or sex, in contrast to that seen in RCC.

3.4. Factors associated with immunotherapy receipt for urothelial carcinoma

On adjusted analysis (Table 4), a more recent diagnosis year was significantly associated with greater odds of IO receipt. Older age (Age >75, OR 1.48 [95% CI,

Table 4
Multivariable logistic regression analysis to identify predictors of immunotherapy receival for bladder UC

	OR (95% CI)[d]	*P*-value
Year of diagnosis		
2017	Ref	Ref
2018	1.66 (1.43−1.92)	<0.001
2019	1.85 (1.60−2.14)	<0.001
2020	2.26 (1.95−2.62)	<0.001
Age (years)		
≤55	Ref	Ref
56−65	1.17 (0.92−1.49)	0.187
66−75	1.13 (0.88−1.46)	0.343
≥76	1.48 (1.15−1.91)	0.002
Sex		
Male	Ref	Ref
Female	0.98 (0.87−1.10)	0.723
Race		
White	Ref	Ref
Hispanic	0.88 (0.67−1.15)	0.358
Black	0.94 (0.77−1.16)	0.577
Asian	0.86 (0.59−1.26)	0.445
Other	0.99 (0.67−1.48)	0.985
Charlson-Deyo score		
0	Ref	Ref
1	1.04 (0.90−1.20)	0.612
2	1.22 (1.02−1.46)	0.028
≥3	1.12 (0.93−1.35)	0.235
Income quartiles[a]		
<$46.2K	Ref	Ref
$46.2K−57.8K	1.20 (0.99−1.44)	0.059
$57.8K−74K	1.17 (0.96−1.42)	0.126
>$74K	1.34 (1.08−1.66)	0.008
Education level[b]		
≥15.3%	Ref	Ref
9.1−15.2%	1.15 (0.97−1.36)	0.105
5.0−9.0%	1.14 (0.95−1.38)	0.161
<5.0%	1.26 (1.01−1.55)	0.036
Insurance status		
Not insured	Ref	Ref
Private insurance	1.64 (1.09−2.45)	0.017
Medicaid	1.71 (1.10−2.64)	0.016
Medicare	1.82 (1.22−2.73)	0.004
Other government	1.59 (0.90−2.78)	0.108
Facility type		
Academic	Ref	Ref
Community/Other[c]	0.78 (0.70-0.88)	<0.001
Facility location		
New England	Ref	Ref
Middle Atlantic	0.85 (0.66−1.09)	0.193
South Atlantic	0.85 (0.65−1.11)	0.226
East North Central	0.89 (0.70−1.14)	0.348
East South Central	0.99 (0.71−1.38)	0.950
West North Central	0.77 (0.57−1.04)	0.086
West South Central	0.97 (0.71−1.32)	0.843
Mountain	0.73 (0.52−1.03)	0.077
Pacific	0.89 (0.69−1.15)	0.392
Residential setting		
Metro	Ref	Ref
Urban	1.04 (0.87−1.25)	0.637
Rural	1.30 (0.86−1.98)	0.211
Travel distance category[d], miles		
≤20	Ref	Ref
21−40	1.34 (1.15−1.56)	<0.001
41−60	1.23 (0.98−1.56)	0.080
>60	0.89 (0.71−1.12)	0.316
Medicaid Expansion State		
No	Ref	Ref
Yes	0.95 (0.80−1.12)	0.510

[a] Median annual household income in the patient's zip code.
[b] Percentage quartiles of individuals without a high school diploma in the patient's zip code.
[c] Community cancer programs, comprehensive community cancer programs, integrated network cancer programs, and other programs.
[d] Distance of patient's residence from hospital.
[e] Odds ratio (95% confidence interval) of receiving immunotherapy vs. not receiving immunotherapy.

1.15−1.91], $P = 0.002$) highest income quartile (OR 1.34 [1.08−1.66], $P = 0.008$), highest education quartile (OR 1.25[1.01−1.55], $P = 0.036$), and living within 21 to 40 miles of intervention facility (OR 1.34 [1.15−1.56], $P < 0.001$) were associated with greater odds of receipt of IO. Like that seen in RCC, IO utilization in UC was associated with the presence of any insurance type apart from other governmental insurance, which did not meet significance in the UC group. Treatment at a non-academic facility was associated with a lower likelihood of IO receipt (OR 0.78 [95% CI, 0.70−0.88] P <0.001), congruent with the association seen in RCC. Race, gender, co-morbidity status, and Medicaid expansion status did not impact the receipt of IO in UC in distinction to the differences seen in races and RCC.

4. Discussion

Disparities in healthcare have long been documented, particularly in patients with malignancy [12]. The rapid expansion of treatment options for malignancies is poised to improve survival in patients with advanced disease, access to these novel and costly therapeutics is not evenly distributed. A recent meta-analysis estimated that patients with lower socioeconomic status were approximately 17% less likely to receive novel therapeutics [23]. Our findings are consistent with the publications assessing IO utilization in non-urologic malignancies. For example, a SEER study in lung cancer found that black patients had 40% lower odds of receiving IO than white patients [24]. Hispanic ethnicity has also been associated with lower IO utilization in lung cancer, melanoma, and RCC [13]. Spanish-speaking-only Hispanics have additional barriers in the United States,

such as difficulty in obtaining cancer-related information spoken or written in the Spanish language and they may struggle with language barriers within their care team due to lack of access to translators. These language barriers make nuanced cancer treatment discussions challenging, even when interpretive services are available [25,26].

There has been limited analysis of potential disparities in IO utilization in urologic malignancies. One NCDB-based study analyzed both pre-FDA approval and early post-FDA approval trends in IO utilization in RCC, finding similar findings to ours regarding lower odds of IO received associated with black race, Hispanic ethnicity, and insurance status [13]. Aside from delineating trends in IO utilization in UC, our study adds important longer-term post-FDA approval data strengthening the current evidence for disparities in IO treatment for advanced ccRCC in addition to demonstrating persistence of these disparities. The delineation between pre-FDA approval and post-FDA approval is significant. Pre-FDA approval, a large avenue for IO utilization is via clinical trials which may not be representative of post-trial trends. While clinical trials may provide access to IO at a reduced cost, black and Hispanic individuals are consistently underrepresented in clinical trials [27]. Post-FDA approval, there was an expected increase in facilities offering IO, theoretically increasing access by decreasing travel burden [28,29]. However, we did not find equitable access across racial groups to these advanced therapies after FDA approval despite broader drug delivery among health systems. After FDA approval, cost plays an increasingly important role; thus, insurance status has increased relevance. Even those with insurance may have challenges receiving approved IO therapies given the large variability in private insurance plans and an average 17-month delay between FDA approval and Medicare coverage [30].

Interestingly, while we identified a racial disparity in IO utilization for RCC, we did not identify a similar association in UC. We postulate that this difference is due to disparate patient populations, as patients with UC are significantly older than patients with RCC. In the US healthcare system, patients older than 65 years are eligible for Medicare coverage. There are also differences in the systemic options for each disease. While options for RCC include IO and various targeted therapies in the first line and salvage settings, options for patients with advanced UC who are ineligible for chemotherapy or progressed after chemotherapy are much more limited. There was also a longer time during which IO was available for RCC allowing more time for adoption. For RCC, the utilization was only 18% 3 years after approval but more than doubled to 41% by year 4 and 58% by year 5. For UC, utilization 3 years after approval was 24%, with only a slight increase to 29% by year 4.

Understanding and acknowledging disparities in treatment is an important first step in addressing the differences in clinical outcomes noted in underrepresented minorities. The next step should be to better understand what is driving these disparities so that we might ameliorate the problem. As with most complex matters, the cause will undoubtably be multifactorial − and could involve language barriers, educational barriers, patient trust in provider, bias, financial and logistical support, and − as is commonly an issue in the United States − insurance coverage and out-of-pocket cost. Analyses such as these utilizing large scale data have strengths and weaknesses. While insurance coverage is noted and accounted for in the multivariable model, it lacks important nuance. While a patient may have Medicare or private insurance − this does not necessarily mean that this provides the patient with affordable coverage for expensive and novel therapies. Medicare recipients can opt to enroll in multiple and complex supplement plans, which are costly but without this coverage − out-of-pocket expenses for even "covered" treatments can be prohibitive. Similarly, private insurance has great heterogeneity, some of which might be inadequate for patients who might benefit from novel therapies such as IO for advanced malignancy. In UC in particular this will be an important consideration as the first line therapy for metastatic disease will likely shift to IO combination with enfortumab vedotin which will further increase the cost of first-line therapy for metastatic disease [31].

This study has several limitations aside from its retrospective, observational nature. The NCDB does not capture some data regarding contraindications to IO usage, such as autoimmune disease. While about 70% of cancer diagnoses are captured by the NCDB, these cases are only captured at CoC-accredited facilities which also has implications for potential differences in demographic case coverage which may not appropriately represent the entire population [20]. The NCDB does not specifically delineate the IO regimen, so there is potential that non-immune checkpoint inhibitor therapy (e.g. IL-2 or interferon) may result in over-categorization as IO utilization. However, contemporary therapy has moved away from this and the potential effect is minimal.

5. Conclusions

In the era of FDA-approved IO therapy for advanced ccRCC and UC, this national cohort analysis suggests that IO utilization is increasing over time, but significant disparities exist based on income, education, and insurance status in both malignancies. Patients treated at non-academic facilities were less likely to receive IO therapy for these specific genitourinary malignancies. In ccRCC, additional disparities were seen black and Hispanic races which were each associated with lower odds of IO receipt. Identifying strategies to mitigate these differences and provide equitable access to IO therapy is of imperative need.

Declaration of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Levi Holland: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Raj Bhanvadia:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Nathanaelle Ibeziako:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Jacob Taylor:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Deitrich Gerlt:** Writing – original draft, Resources, Project administration, Methodology, Investigation, Conceptualization. **Iftach Chaplin:** Writing – review & editing, Software, Resources, Project administration, Formal analysis, Data curation. **Aditya Bagrodia:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **Neil Desai:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **Kris Gaston:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **Yair Lotan:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **Vitaly Margulis:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **Tian Zhang:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Suzanne Cole:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Solomon Woldu:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Acknowledgements

N/A

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2024.06.012.

References

[1] SEER*Explorer. SEER Cancer Statistics. National Cancer Institute. Published April 19, 2023. Accessed October 30, 2023. https://seer.cancer.gov/statistics-network/explorer/.

[2] Chakiryan NH, Jiang DD, Gillis KA, et al. Real-world survival outcomes associated with first-line immunotherapy, targeted therapy, and combination therapy for metastatic clear cell renal cell carcinoma. JAMA Netw Open 2021;4(5):e2111329. https://doi.org/10.1001/jamanetworkopen.2021.11329.

[3] Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023;73(1):17–48. https://doi.org/10.3322/caac.21763.

[4] Jang A, Adler DM, Rauterkus GP, Bilen MA, Barata PC. Immunotherapies in genitourinary oncology: Where are we now? Where are we going? Cancers 2021;13(20):5065. https://doi.org/10.3390/cancers13205065.

[5] Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: A single-arm, multicentre, phase 2 trial. Lancet Lond Engl 2017;389(10064):67–76. https://doi.org/10.1016/S0140-6736(16)32455-2.

[6] Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: A single-arm, multicentre, phase 2 trial. Lancet North Am Ed 2016;387(10031):1909–20. https://doi.org/10.1016/S0140-6736(16)00561-4.

[7] Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal cell carcinoma. N Engl J Med 2015;373(19):1803–13. https://doi.org/10.1056/NEJMoa1510665.

[8] Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378(14):1277–90. https://doi.org/10.1056/NEJMoa1712126.

[9] Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380(12):1116–27. https://doi.org/10.1056/NEJMoa1816714.

[10] Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380(12):1103–15. https://doi.org/10.1056/NEJMoa1816047.

[11] Shavers VL, Brown ML. Racial and ethnic disparities in the receipt of cancer treatment. JNCI J Natl Cancer Inst 2002;94(5):334–57. https://doi.org/10.1093/jnci/94.5.334.

[12] Ward E, Jemal A, Cokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. CA Cancer J Clin 2004;54(2):78–93. https://doi.org/10.3322/canjclin.54.2.78.

[13] Ermer T, Canavan ME, Maduka RC, et al. Association between food and drug administration approval and disparities in immunotherapy use among patients with cancer in the US. JAMA Netw Open 2022;5(6):e2219535. https://doi.org/10.1001/jamanetworkopen.2022.19535.

[14] Haque W, Verma V, Butler EB, Teh BS. Racial and socioeconomic disparities in the delivery of immunotherapy for metastatic melanoma in the United States. J Immunother Hagerstown Md 1997 2019;42(6):228–35. https://doi.org/10.1097/CJI.0000000000000264.

[15] Sahara K, Farooq SA, Tsilimigras DI, et al. Immunotherapy utilization for hepatobiliary cancer in the United States: Disparities among patients with different socioeconomic status. Hepatobiliary Surg Nutr 2020;9(1):13–24. https://doi.org/10.21037/hbsn.2019.07.01.

[16] Verma V, Haque W, Cushman TR, et al. Racial and insurance-related disparities in delivery of immunotherapy-type compounds in the United States. J Immunother Hagerstown Md 1997 2019;42(2):55–64. https://doi.org/10.1097/CJI.0000000000000253.

[17] Al-Qurayshi Z, Crowther JE, Hamner JB, Ducoin C, Killackey MT, Kandil E. Disparities of immunotherapy utilization in patients with stage III cutaneous melanoma: A national perspective. Anticancer Res 2018;38(5):2897–901. https://doi.org/10.21873/anticanres.12536.

[18] Gupta A, Omeogu C, Islam JY, et al. Socioeconomic disparities in immunotherapy use among advanced-stage non-small cell lung cancer patients: Analysis of the national cancer database. Sci Rep 2023;13(1):8190. https://doi.org/10.1038/s41598-023-35216-2.

[19] National Cancer Database Participant User Files. ACS. Accessed October 18, 2023. https://www.facs.org/quality-programs/cancer-programs/national-cancer-database/puf/

[20] Boffa DJ, Rosen JE, Mallin K, et al. Using the national cancer database for outcomes research: A review. JAMA Oncol 2017;3(12):1722–8. https://doi.org/10.1001/jamaoncol.2016.6905.

[21] Xu JX, Maher VE, Zhang L, et al. FDA approval summary: Nivolumab in advanced renal cell carcinoma after anti-angiogenic therapy and exploratory predictive biomarker analysis. Oncologist 2017;22(3):311–7. https://doi.org/10.1634/theoncologist.2016-0476.

[22] Suzman DL, Agrawal S, Ning Y, et al. FDA approval summary: Atezolizumab or pembrolizumab for the treatment of patients with advanced urothelial carcinoma ineligible for cisplatin-containing chemotherapy. Oncologist 2019;24(4):563–9. https://doi.org/10.1634/theoncologist.2018-0084.

[23] Norris RP, Dew R, Sharp L, et al. Are there socio-economic inequalities in utilization of predictive biomarker tests and biological and precision therapies for cancer? A systematic review and meta-analysis. BMC Med 2020;18(1):282. https://doi.org/10.1186/s12916-020-01753-0.

[24] Chang A, Flores RM, Taioli E. Unequal racial distribution of immunotherapy for late-stage non-small cell lung cancer. J Natl Cancer Inst 2023;115(10):1224–6. https://doi.org/10.1093/jnci/djad132.

[25] Vanderpool RC, Kornfeld J, Rutten LF, Squiers L. Cancer information-seeking experiences: The implications of Hispanic ethnicity and Spanish language. J Cancer Educ 2009;24(2):141–7. https://doi.org/10.1080/08858190902854772.

[26] Howerton MW, Gibbons MC, Baffi CR, et al. Provider roles in the recruitment of underrepresented populations to cancer clinical trials. Cancer 2007;109(3):465–76. https://doi.org/10.1002/cncr.22436.

[27] Loree JM, Anand S, Dasari A, et al. Disparity of race reporting and representation in clinical trials leading to cancer drug approvals from 2008 to 2018. JAMA Oncol 2019;5(10):e191870. https://doi.org/10.1001/jamaoncol.2019.1870.

[28] O'Connor JM, Fessele KL, Steiner J, et al. Speed of adoption of immune checkpoint inhibitors of programmed cell death 1 protein and comparison of patient ages in clinical practice vs pivotal clinical trials. JAMA Oncol 2018;4(8):e180798. https://doi.org/10.1001/jamaoncol.2018.0798.

[29] Winzeler-Cotton A, Subramanian A, Kane K, et al. Rapid adoption of immunotherapy in community health systems, associated with changing treatment guidelines. J Clin Oncol 2022;40(16_suppl). https://doi.org/10.1200/JCO.2022.40.16_suppl.e18610:e18610-e18610.

[30] Roginiel AC, Dhruva SS, Ross JS. Evidence supporting FDA approval and CMS national coverage determinations for novel medical products, 2005 through 2016: A cross-sectional study. Medicine (Baltimore) 2018;97(40):e12715. https://doi.org/10.1097/MD.0000000000012715.

[31] Powles TB, Valderrama BP, Gupta S, et al. LBA6 EV-302/KEYNOTE-A39: Open-label, randomized phase III study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (Chemo) in previously untreated locally advanced metastatic urothelial carcinoma (la/mUC). Ann Oncol 2023;34:S1340. https://doi.org/10.1016/j.annonc.2023.10.106.