available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

European Association of Urology

Comparative Effectiveness of Non-cisplatin First-line Therapies for Metastatic Urothelial Carcinoma: Phase 2 IMvigor210 Study Versus US Patients Treated in the Veterans Health Administration

Nancy Vander Velde [a,b,*], *Annie Guerin* [c], *Raluca Ionescu-Ittu* [c], *Sherry Shi* [c], *Eric Q. Wu* [d], *Shih-Wen Lin* [e], *Ling-I Hsu* [e], *Kai-Uwe Saum* [f], *Sabine de Ducla* [g], *Jingjing Wang* [e], *Shi Li* [e], *AnnChristine Thåström* [e], *Shuqian Liu* [a,b], *Lizheng Shi* [a,b], *John T. Leppert* [h,i]

[a] *Southeast Louisiana Veterans Health Care System, New Orleans, LA, USA;* [b] *Tulane University, New Orleans, LA, USA;* [c] *Groupe d'Analyse, Montréal, QC, Canada;* [d] *Analysis Group, Boston, MA, USA;* [e] *Genentech, South San Francisco, CA, USA;* [f] *Roche Pharma AG, Grenzach-Wyhlen, Germany;* [g] *F. Hoffmann-La Roche, Basel, Switzerland;* [h] *Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA;* [i] *Stanford University School of Medicine, Stanford, CA, USA*

Article info

Article history:
Accepted July 10, 2018

Associate Editor:
Ashish Kamat

Keywords:
Atezolizumab
Chemotherapy
Comparative effectiveness
Entropy balancing
First-line treatment
Immunotherapy
Metastatic urothelial carcinoma
Real-world data

Abstract

Background: First-line treatments for cisplatin-ineligible patients with metastatic urothelial carcinoma (mUC) include carboplatin-based chemotherapy and checkpoint inhibitors such as atezolizumab (anti–PD-L1).
Objective: To compare overall survival (OS) among patients with mUC treated in the first-line setting with atezolizumab versus carboplatin-based chemotherapies (any carboplatin-based regimens or carboplatin-gemcitabine).
Design, setting, and participants: Cisplatin-ineligible patients with mUC from the phase 2 trial IMvigor210 (ClinicalTrials.gov NCT02951767) treated with atezolizumab and patients from the Veterans Health Administration (VHA) health care system (2006–2017, with IMvigor210 eligibility criteria applied using proxy measurements) treated according to normal clinical practice.
Interventions: IMvigor210 cohort 1 patients were treated with atezolizumab, and real-world VHA cohorts were treated with carboplatin-based regimens.
Outcome measurements and statistical analysis: Entropy-balance weighting was applied to balance prespecified baseline patient characteristics. OS was analyzed using weighted Kaplan-Meier and Cox methods.
Results and limitations: The median OS was 15.0 mo with atezolizumab (n = 110), 12.1 mo with any carboplatin-based chemotherapy (n = 282), and 8.7 mo with carboplatin-gemcitabine (n = 120). An OS benefit occurred with atezolizumab versus carboplatin-based regimens after 9 mo (hazard ratio [HR] 0.43; p = 0.004) and with atezolizumab versus carboplatin-gemcitabine after 5 mo (HR 0.52; p = 0.005). Study limitations include a predominantly male VHA cohort and ≤24-mo follow-up. Adjustment for confounding, a potential limitation of nonrandomized studies, was limited by the availability of clinical measurements in the VHA data, which allowed for replication of IMvigor210 exclusions in the VHA cohorts.
Conclusions: First-line atezolizumab for cisplatin-ineligible mUC may provide an OS benefit over carboplatin-based treatments after 5–9 mo, depending on the regimen.
Patient summary: Many patients with metastatic urothelial carcinoma are ineligible for cisplatin-based chemotherapy. This study compared patients from a clinical trial receiving the immunotherapeutic agent atezolizumab with those in Veterans Health Administration clinical practice receiving carboplatin-based chemotherapy. Atezolizumab provided a survival benefit over chemotherapy after 5–9 mo.

* Corresponding author. Southeast Louisiana Veterans Healthcare System, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, LA 70112, USA. Tel.: +1 504 9885482; Fax: +1 504 9885483.
E-mail address: nvanderv@tulane.edu (N. Vander Velde).

https://doi.org/10.1016/j.euo.2018.07.003
2588-9311/Published by Elsevier B.V. on behalf of European Association of Urology.

1. Introduction

Cisplatin-based combination chemotherapy is the first-line (1L) standard of care for patients with metastatic urothelial carcinoma (mUC) and can confer a median overall survival (OS) in excess of 15 mo [1]. However, approximately half of patients are cisplatin-ineligible owing to comorbidities or impaired functional status [2]. Treatment alternatives for cisplatin-ineligible patients include carboplatin-based, non–platinum-based, and single-agent chemotherapy regimens, with carboplatin-gemcitabine being the most common regimen [3,4]. However, these therapies can result in poorer outcomes over cisplatin, although randomized phase 3 data are unavailable and real-world data are limited [5].

Recent immunotherapy advances, including immune checkpoint inhibitors, appear promising for cisplatin-ineligible mUC patients [6]. Atezolizumab is an engineered humanized monoclonal antibody that binds to PD-L1 to prevent interactions with its receptors PD-1 and B7.1, thereby restoring and enhancing anticancer immunity [7] without affecting the PD-L2/PD-1 interaction. Efficacy and safety results from the phase 2 IMvigor210 trial [8] led to US and European approvals of atezolizumab for 1L treatment of cisplatin-ineligible patients with advanced UC. Atezolizumab is also approved for previously treated mUC and non–small-cell lung cancer [9,10]. The anti–PD-1 agent pembrolizumab is approved in the USA and Europe in the 1L cisplatin-ineligible setting [6,11], and other anti–PD-L1/PD-1 inhibitors are in development.

No randomized comparisons of checkpoint inhibitor therapy and chemotherapy for mUC in the 1L setting are available, so alternative approaches are required to estimate the comparative effectiveness of these agents. The objective of this study was to compare OS between mUC patients from IMvigor210 treated with 1L atezolizumab and those treated in clinical practice at the Veterans Health Administration (VHA) with 1L carboplatin-based chemotherapy.

2. Patients and methods

2.1. Data sources

IMvigor210 was a single-arm phase 2 clinical trial conducted in North America and Europe (ClinicalTrials.gov NCT02108652 and NCT02951767); cohort 1 comprised cisplatin-ineligible patients with locally advanced UC (n = 9) or mUC (n = 110) [8]. Population-based cohorts included patients treated according to routine clinical practice in the US VHA from January 1, 2006 to May 31, 2017. The largest national integrated US health care system, the VHA, has more than 1500 sites serving approximately 8.76 million veterans annually. Its Corporate Data Warehouse (CDW) includes all medical encounter information in the VHA system. UC is the sixth most common cancer diagnosis in the VHA [12]. Deidentified patient-level data from these sources was used in the analyses summarized here.

2.2. Study design and objectives

This study, which uses a retrospective cohort design, was designed to compare OS between VHA cohorts that received non-cisplatin carboplatin-based agents for mUC and IMvigor210 patients treated with atezolizumab. Here, carboplatin-based chemotherapy included carboplatin as a single agent or combined with other agents listed (even if the combination itself was not listed) in the 2015 National Comprehensive Care Network (NCCN) guidelines for mUC, except cisplatin.

2.3. Cohort identification and patient characteristics

VHA patients with de novo or recurrent mUC were identified using International Classification of Diseases, Ninth Revision and Tenth Revision (ICD-9/10) diagnosis codes (mUC diagnosis between January 1, 2006 and August 30, 2017). Cohort attrition is presented in Figure 1. Drug prescription and administration information was used to identify 1L regimens as antineoplastic agents administered or dispensed within 28 d of the index date, defined as the date of initiation of 1L therapy for mUC (for atezolizumab and VHA cohorts). Eligible VHA patients included in this analysis were those treated with 1L carboplatin-based regimens, which defined the preferred treatment approaches for patients ineligible for cisplatin-based chemotherapy. Two cohorts were further evaluated: patients treated with any carboplatin-based regimen and the subgroup treated with carboplatin-gemcitabine (the most common regimen, further described in the Results section).

IMvigor210 eligibility and patient characteristics were previously described [8]. Because locally advanced UC cannot be identified using CDW data, only IMvigor210 patients with mUC were included. To ensure comparability between the atezolizumab and VHA cohorts, the IMvigor210 exclusion criteria were replicated and applied to the VHA cohort of eligible patients (Fig. 1). Further details are provided in the Supplementary material. Confounding control methods were used to account for remaining differences in patient characteristics between the atezolizumab and VHA cohorts [13]. We prespecificed patient characteristics to control for in the analysis on the basis of literature reports (liver metastases, hemoglobin $<$10 g/dl, Eastern Cooperative Oncology Group performance status [14], and additional clinical characteristics including the Quan-Charlson comorbidity index (QCCI) [15]. All characteristics controlled for are indicated in Table 1. Sex and C-reactive protein were not controlled for owing to a male predominance in the VHA cohorts and nonroutine testing in clinical practice. Entropy-balance weighting (EBW) was used to balance the distribution of patient characteristics between cohorts [13], with VHA patients reweighted to have the same distribution of covariates (mean and variance) as IMvigor210 patients. Standardized differences were used to assess the balancing of patient characteristics (atezolizumab vs VHA cohorts) before and after weighting [16]. A standardized difference $>|0.2|$, indicating a $<$15% overlap in covariate distribution in the two cohorts, was the cutoff used to indicate covariate balance. Sensitivity analyses including statistical confounder adjustment, inverse probability weighting (IPW), and analyses restricted to males are described in the Supplementary material.

2.4. Outcomes and statistical analyses

For the atezolizumab and VHA cohorts, OS was defined from the index date to death from any cause during the study, up to 24 mo of postindex follow-up (truncated for VHA cohorts to align with IMvigor210 follow-up). OS was compared between cohorts using weighted Kaplan-Meier analyses and weighted Cox proportional hazards models. Patient-level weights were derived using EBW methods described above and subsequently normalized to preserve the unweighted size of the atezolizumab and VHA cohorts. To mitigate violation of proportional hazards assumptions, Cox analyses were stratified according to the study periods before (early effect) and after (latent effect) crossing of Kaplan-Meier curves (further described in the Supplementary material).

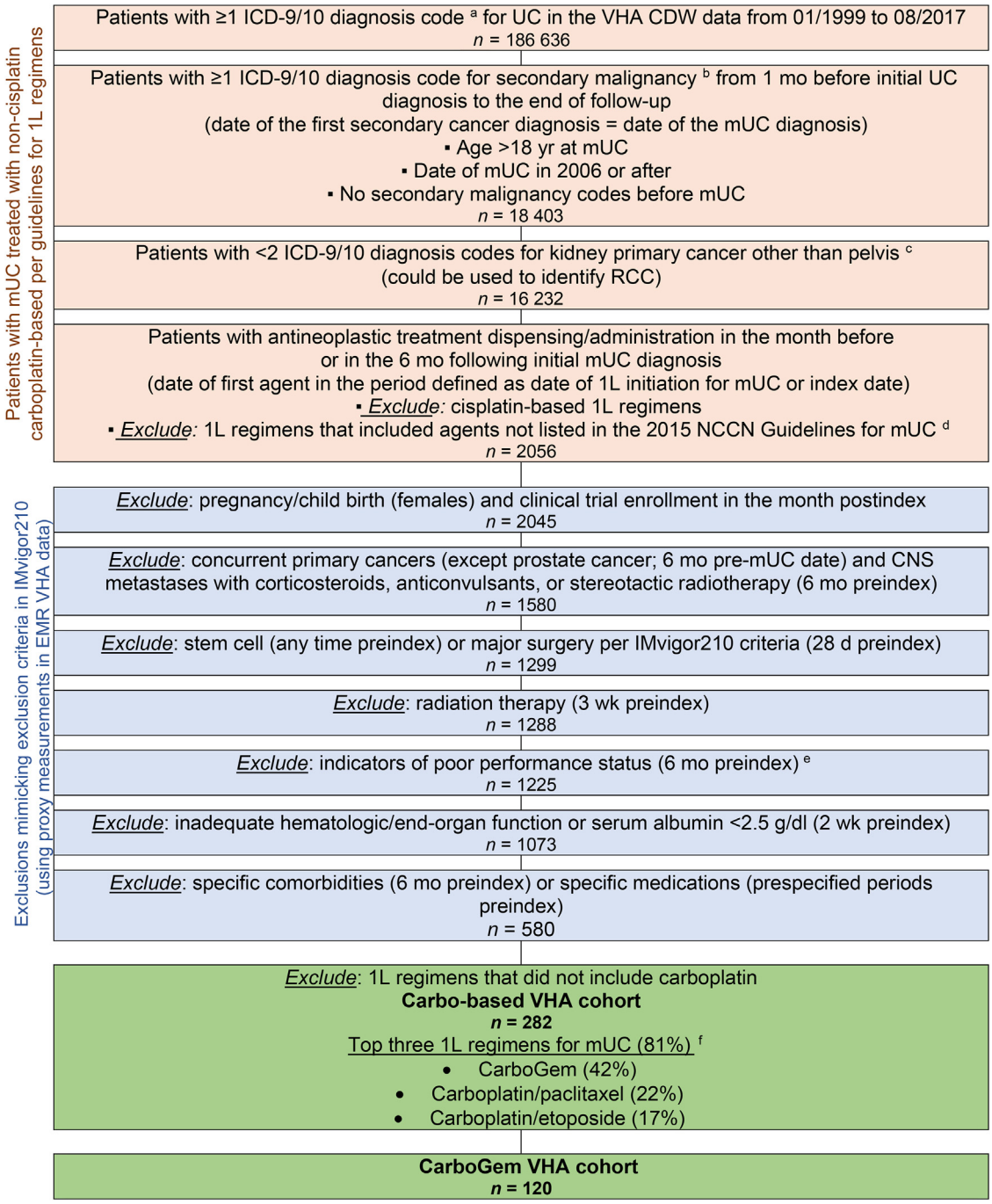


Fig. 1 – Veterans Health Administration (VHA) cohort attrition. Selection of patients with metastatic urothelial carcinoma (mUC) treated with non-cisplatin first line (1L) regimens according to National Comprehensive Cancer Network (NCCN) guidelines. Carbo = carboplatin; CarboGem = Carbo-gemcitabine; CDW = Corporate Data Warehouse; CNS = central nervous system; EMR = electronic medical records; ICD-9/10 = International Classification of Diseases, ninth and tenth revisions; RCC = renal cell carcinoma.

[a] ICD9: 188.xx, 189.1x, 189.2x, 189.3x; ICD-10: C67.xx, C65.xx, C66.xx, C68.0.

[b] ICD-9: 196.xx–199.xx; ICD-10: C7B, C77–C79.

[c] ICD-9: 189.0; ICD-10: C64.

[d] Treatment for mUC that was consistent with the NCCN guidelines V2.2015 for 1L treatment in a metastatic setting and that did not include cisplatin. Regimens that included any combination of agents recommended for mUC treatment without any agent not recommended in mUC were considered to be in accordance with the guidelines, while regimens that included at least one agent not recommended in mUC were not considered in accordance with the guidelines. 1L regimens were identified on the basis of the antineoplastic agents used in the 28 d following the index date.

[e] As a proxy for Eastern Cooperative Oncology Group performance status of ≤2, four indicators of poor performance status were identified on the basis of procedure codes in the CDW data: oxygen and related respiratory therapy supplies; wheelchair and supplies; home health agency services; and skilled nursing facility services [31].

[f] Other treatment regimens included: Carbo monotherapy (*n* = 17), Carbo + pemetrexed (*n* = 11), Carbo + cytarabine + gemcitabine (*n* = 1), CarboGem + doxorubicin (*n* = 1), Carbo + fluorouracil (*n* = 1), Carbo + fluorouracil + paclitaxel + pemetrexed (*n* = 1), Carbo + docetaxel + paclitaxel (*n* = 2), Carbo + docetaxel (*n* = 9), CarboGem + etoposide (*n* = 1), CarboGem + fluorouracil (*n* = 1), CarboGem + paclitaxel (*n* = 5), Carbo + irinotecan (*n* = 1), and Carbo + paclitaxel + pemetrexed (*n* = 1).

Table 1 – Distribution of baseline characteristics in atezolizumab and VHA cohorts

Characteristic	Atezolizumab cohort	VHA cohorts before e-balance weighting		VHA cohorts after e-balance weighting [a,b]	
		Carbo-based	CarboGem	Carbo-based	CarboGem
Patients (*n*)	110	282	120	282	120
Age at index date (yr)					
Mean ± SD [Diff [c]]	71.4 ± 8.9	71.6 ± 8.2 [−0.02]	71.3 ± 8.1 [+0.01]	71.4 ± 8.8 [0.00]	71.4 ± 8.8 [0.00]
Median (interquartile range)	72 (66–79)	71 (65–78)	71 (65–78)	71 (65–78)	69 (66–79)
Males, *n* (%) [Diff [c]]	90 (81.8)	281 (99.6) [−0.65]	120 (100.0) [−0.67]	281 (99.6) [−0.64]	120 (100.0) [−0.67]
Race, *n* (%) [Diff [c]]					
White	99 (90.0)	247 (87.6) [+0.08]	106 (88.3) [+0.05]	254 (90.0) [0.00]	108 (90.0) [0.00]
Non-white	11 (10.0)	35 (12.4) [−0.08]	14 (11.7) [−0.05]	28 (10.0) [0.00]	12 (10.0) [0.00]
Black	3 (2.7)	20 (7.1)	9 (7.5)	–	–
Asian	2 (1.8)	0 (0.0)	0 (0.0)	–	–
Other	5 (4.5)	7 (2.5)	2 (1.7)	–	–
Unknown	1 (0.9)	8 (2.8)	3 (2.5)	–	–
Metastasis site, *n* (%) [Diff [c]]					
Visceral [d]	78 (70.9)	157 (55.7) [+0.32]	61 (50.8) [+0.42]	200 (70.9) [0.00]	85 (70.9) [0.00]
Other	32 (29.1)	125 (44.3) [−0.32]	59 (49.2) [−0.42]	82 (29.1) [0.00]	35 (29.1) [0.00]
Lymph node only	32 (29.1)	89 (31.6)	45 (37.5)	–	–
Site not known [e]	–	36 (12.8)	14 (11.7)	–	–
Previous CTx use, *n* (%) [f] [Diff [c]]	25 (22.7)	56 (19.9) [+0.07]	23 (19.2) [+0.09]	64 (22.7) [0.00]	27 (22.7) [0.00]
Body mass index (kg/m^2)					
Mean ± SD [Diff [c]]	27.1 ± 5.3	26.8 ± 5.2 [+0.05]	26.8 ± 5.4 [+0.05]	27.1 ± 5.2 [0.00]	27.1 ± 5.2 [0.00]
Median (interquartile range)	27 (23–30.0)	26 (23–30)	26 (23–29)	27 (23–31)	26 (24–30)
Quan-Charlson comorbidity index					
Mean ± SD [Diff [c]]	7.1 ± 1.1	6.7 ± 0.9 [+0.36]	6.6 ± 0.8 [+0.46]	7.1 ± 1.1 [0.00]	7.1 ± 1.1 [0.00]
Median (interquartile range)	7 (6–7)	7 (6–7)	6 (6–7)	7 (6–7)	7 (6–8)
Anemia, *n* (%) [Diff [c]]	20 (18.2)	93 (33.0) [−0.34]	51 (42.5) [−0.55]	51 (18.2) [0.00]	22 (18.2) [0.00]
Hemoglobin, *n* (%) [Diff [c]]					
<10 g/dl	16 (14.5)	57 (20.2) [−0.15]	32 (26.7) [−0.30]	41 (14.5) [0.00]	17 (14.5) [0.00]
Other	94 (85.5)	225 (79.8) [+0.15]	88 (73.3) [+0.30]	241 (85.5) [0.00]	103 (85.5) [0.00]
≥10 g/dl	94 (85.5)	198 (70.2)	75 (62.5)	–	–
Test not performed	–	27 (9.6)	13 (10.8)	–	–
Serum albumin, *n* (%) [Diff [c]]					
Abnormal values	21 (19.1)	116 (41.1) [−0.49]	55 (45.8) [−0.60]	54 (19.1) [0.00]	23 (19.1) [0.00]
Other	89 (80.9)	166 (58.9) [+0.49]	65 (54.2) [+0.60]	228 (80.9) [0.00]	97 (80.9) [0.00]
Normal values	–	152 (53.9)	57 (47.5)	–	–
Test not performed	–	14 (5.0)	8 (6.7)	–	–

Carbo = carboplatin; CarboGem = Carbo-gemcitabine; CTx = chemotherapy; e-balance = entropy balance; SD = standard deviation; VHA = Veterans Health Administration.

[a] To improve the efficiency of the model for e-balance weighting, some categories were collapsed. Only the entries shown were included in e-balance models.

[b] The e-balance weights were not normalized for this analysis, so the sum of weights in the VHA cohorts adds up to the size of the unweighted VHA cohorts. Weighted *n* values reported in this column were obtained by multiplying the original value by the patient weight; as nonintegers, values were rounded.

[c] Standardized difference between VHA (unweighted or weighted) and atezolizumab cohort. A cutoff of >|0.2| was used to indicate covariate balance.

[d] At least one metastatic site other than lymph node.

[e] International Classification of Diseases, Ninth Revision and Tenth Revision codes were not specific enough to infer the metastatic site.

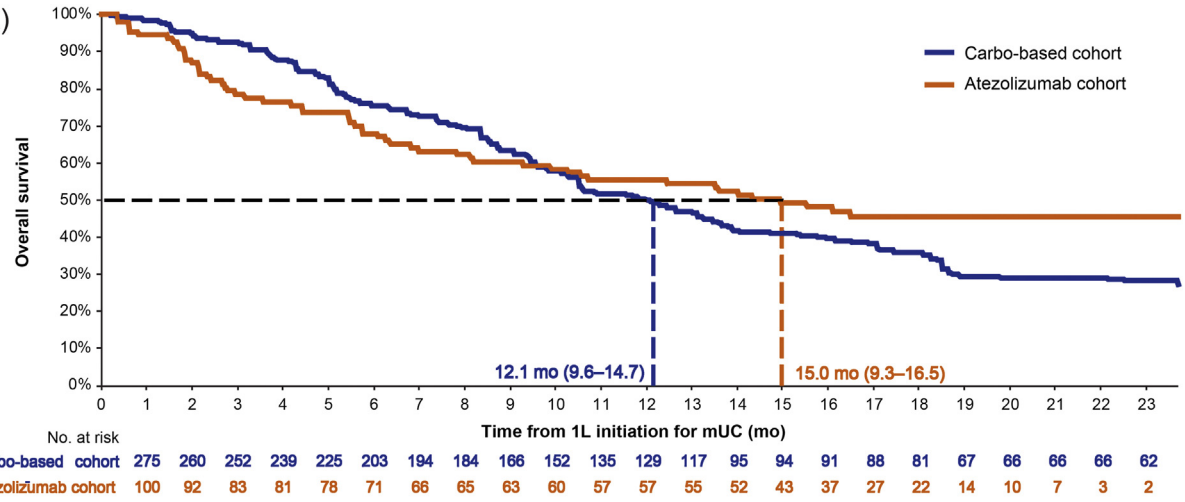
[f] According to the exclusion criteria, no patients received chemotherapy in the year before the index date.

3. Results

3.1. Patient characteristics

Overall, 110 patients were included in the IMvigor210 atezolizumab cohort, 282 patients in the VHA cohort that received any carboplatin-based treatment, and 120 patients in the VHA cohort that received carboplatin-gemcitabine (Table 1 and Fig. 1). Overall median follow-up in the atezolizumab, carboplatin-based, and carboplatin-gemcitabine cohorts was 13.0, 10.3, and 9.4 mo (mean duration 11.0, 12.2, and 11.6 mo), respectively. For patients not known to have died, the median follow-up was 17.0 mo for the atezolizumab cohort and 24.4 mo for both VHA cohorts. Sixteen distinct 1L carboplatin-based regimens were observed in the VHA cohort, and the top three regimens (carboplatin-gemcitabine, carboplatin-paclitaxel, and carboplatin-etoposide) collectively accounted for 81% of all 1L regimens (Fig. 1). Before weighting, the cohorts were generally similar (standardized differences <|0.2| between cohorts) with respect to mean age, body mass index, proportion of white patients, and previous chemotherapy use (Table 1). However, relative to the VHA cohorts, more patients in the atezolizumab cohort had visceral metastases, patients had a slightly higher comorbidity burden (according to QCCI), and fewer patients had anemia, hemoglobin <10 g/dl, or abnormal serum albumin values at baseline (Table 1). After applying EBW, all the observed differences in patient characteristics between the atezolizumab and VHA cohorts were effectively eliminated (Table 1).

(A)



(B)

	Postindex events and milestone OS rates						
	3 mo	6 mo	9 mo	12 mo	15 mo	18 mo	24 mo
Atezolizumab, IMvigor210							
Patients with events, *n*	23	34	42	47	53	56	56
OS rate, %	78.4	68.0	60.3	55.5	49.3	45.4	45.4
95% CI	69.3–85.1	58.2–76.0	50.3–68.9	45.5–64.4	39.4–58.5	35.3–54.9	35.3–54.9
Carbo-based, VHA							
Patients with events, *n*	26	78	110	143	163	176	193
OS rate, %	92.4	75.4	63.3	49.5	41.2	36.0	27.0
95% CI	86.8–95.7	67.4–81.7	54.7–70.8	40.7–57.6	32.6–49.5	27.7–44.3	19.4–35.2

Fig. 2 – Overall survival (OS) for atezolizumab versus all carboplatin (Carbo)-based regimens. (A) Kaplan-Meier curves, with median OS indicated by dashed lines and 95% confidence interval (CI) in parentheses. (B) Number of death events and milestone OS rates. 1L = first line; mUC = metastatic urothelial cancer; VHA = Veterans Health Administration.

3.2. *Overall survival comparative effectiveness*

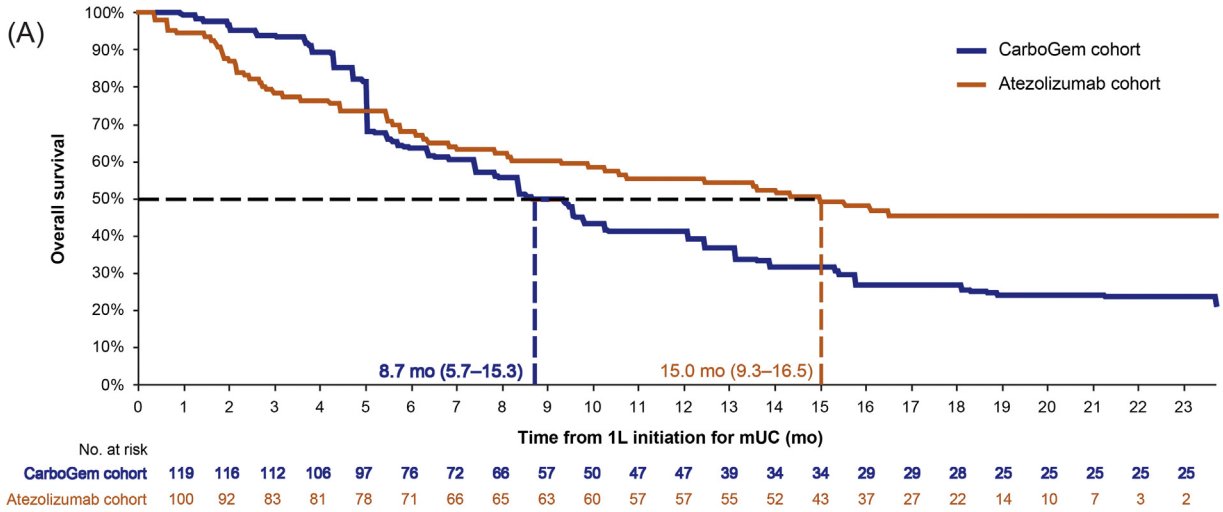
Weighted Kaplan-Meier analyses (Figs. 2 and 3) revealed median OS of 15.0 mo for the IMvigor210 atezolizumab cohort, compared with 12.1 mo for the carboplatin-based cohort and 8.7 mo for the carboplatin-gemcitabine cohort. OS rates at 12 mo were 56% for atezolizumab-treated patients, 50% for patients treated with any carboplatin-based chemotherapy, and 39% for patients treated with carboplatin-gemcitabine. Additional milestone OS rates are included in Figures 2B and 3B. An OS benefit was observed with atezolizumab treatment over chemotherapy after 9 mo for carboplatin-based chemotherapy and after 5 mo for carboplatin-gemcitabine (Figs. 2 and 3). Weighted Cox regression analyses showed a latent OS benefit in favor of atezolizumab versus carboplatin-based therapy that became significant after 9 mo of treatment (overall hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.62–1.12; p = 0.2; latent HR 0.43, 95% CI 0.24–0.76; p = 0.004; Table 2). OS HRs also favored atezolizumab over carboplatin-gemcitabine, both overall (HR 0.67, 95% CI 0.48–0.94; p = 0.02) and after 5 mo of treatment (latent effect HR 0.52, 95% CI 0.33–0.82; p = 0.005; Table 2). Differences between the atezolizumab and VHA cohorts in the first months of treatment were not statistically significant (Table 2).

Sensitivity analyses using alternative confounding control methods were consistent with OS HR results with EBW (Supplementary Table 1). Specifically, with statistical confounder adjustment and IPW methods, latent-effect (after crossing of the Kaplan-Meier curves) OS HRs were 0.41 (p = 0.003) and 0.39 (p = 0.002) for atezolizumab versus carboplatin-based regimens, and 0.44 (p = 0.002) and 0.38 ($p < 0.001$) for atezolizumab versus carboplatin-gemcitabine, respectively. Sensitivity analyses conducted using EBW Cox models in which study cohorts were restricted to male patients also yielded similar results. For example, EBW Cox regression models after crossing of Kaplan-Meier curves gave HRs of 0.42 (p = 0.009) for atezolizumab versus any carboplatin-based chemotherapy and 0.56 (p = 0.019) for atezolizumab versus carboplatin-gemcitabine.

4. Discussion

Many patients with mUC receive no 1L cisplatin-based chemotherapy because of comorbidities or impaired functional status [5]. Until recently, carboplatin-gemcitabine chemotherapy was a preferred treatment alternative for cisplatin-ineligible patients. As part of the phase 2 IMvigor210 study, atezolizumab monotherapy, investigated in cisplatin-ineligible patients with mUC, was well tolerated and resulted in durable responses and favorable OS [8]. Here, we performed a comparative effectiveness analysis to determine the relative OS benefit for IMvigor210 patients with mUC treated with atezolizumab versus real-

(A)



(B)

	Postindex events and milestone OS rates						
	3 mo	6 mo	9 mo	12 mo	15 mo	18 mo	24 mo
Atezolizumab, IMvigor210							
Patients with events, *n*	23	34	42	47	53	56	56
OS rate, %	78.4	68.0	60.3	55.5	49.3	45.4	45.4
95% CI	69.3–85.1	58.2–76.0	50.3–68.9	45.5–64.4	39.4–58.5	35.3–54.9	35.3–54.9
CarboGem, VHA							
Patients with events, *n*	12	37	53	69	75	78	85
OS rate, %	94.1	63.7	49.9	39.1	31.6	26.8	21.8
95% CI	77.4–98.6	44.9–77.6	33.8–64.0	25.0–52.9	18.9–45.0	15.2–39.8	11.4–34.3

Fig. 3 – Overall survival (OS) for atezolizumab versus carboplatin-gemcitabine regimens (CarboGem). (A) Kaplan-Meier curves, with median OS indicated by dashed lines and 95% confidence interval (CI) in parentheses. (B) Number of death events and milestone OS rates. 1L = first line; mUC = metastatic urothelial cancer; VHA = Veterans Health Administration.

world patients from the VHA health care system treated with carboplatin-based regimens. We found an OS benefit with atezolizumab over carboplatin-based regimens after 9 mo of treatment and over carboplatin-gemcitabine after 5 mo of treatment. These results were robust in sensitivity analyses that used alternative confounding control methods or restricted the analysis to male patients.

Results from IMvigor210 and from trials investigating other checkpoint inhibitors are changing the treatment landscape for both previously treated and treatment-naive mUC. Notably, given the inherent toxicities associated with chemotherapy and the prevalence of mUC patients with renal insufficiency, these well-tolerated agents have the potential to treat a wider patient population. Large randomized studies in the 1L setting—comparing single-agent or combination immunotherapies versus historic standards (eg, IMvigor130, NCT02807636; KEYNOTE-361, NCT02853305)—will provide data to validate these results. Currently, randomized data are limited to the postplatinum setting [17,18], so comparisons between real-world data and single-arm clinical trial data represent a valuable approach that has attracted greater interest in recent years [19]. However, this approach requires careful patient selection and statistical reweighting for comparison to patients treated in a clinical trial [20]. In this study, to appropriately compare OS outcomes between atezolizumab and carboplatin-based regimens, we first controlled for inherent population differences by restricting the VHA cohorts to patients who met the IMvigor210 inclusion and exclusion criteria (with several measurements for IMvigor210 proxied from VHA electronic medical record [EMR] data), and then balanced residual differences in patient characteristics using EBW, an approach applied in other observational studies [21,22]. OS outcomes in the VHA carboplatin-based cohort compared well with previous clinical trials in this setting; the OS observed with carboplatin-based regimens (weighted median OS 12.1 mo, unweighted median OS 11.6 mo; data not shown) is consistent with the range previously reported in patients treated with 1L non-cisplatin carboplatin-based regimens (median OS 7–15 mo, depending on the regimen) [2,23]. Likewise, the median OS for carboplatin-gemcitabine in the present study (weighted median OS 8.7 mo, unweighted median OS 9.6 mo; data not shown) is also consistent with that in previous clinical trials, ranging from 7 to 10 mo, depending on the population [24–26]. It should be noted, however, that direct OS comparisons between the two VHA cohorts in our study is not advisable because one of the two confounding control methods used (mimicking the IMvigor210 exclusions in the VHA cohorts) was specifically designed to address a comparison between a clinical trial–based cohort and a real-world cohort. Given that the treatment selection

Table 2 – Cox proportional hazards regression for overall survival: comparison of the atezolizumab and VHA cohorts

Comparison	HR (95% CI)	*p* value
Atezolizumab vs Carbo-based cohort		
Unweighted (no control of confounders)		
Overall effect [a]	0.79 (0.59–1.07)	0.12
First 9 mo following 1L initiation [a]	1.06 (0.74–1.51)	0.70
After 9 mo of 1L treatment [a]	0.44 (0.25–0.78)	0.005 [d]
After weighting [c]		
Overall effect [a]	0.83 (0.62–1.12)	0.2
First 9 mo following 1L initiation [a]	1.20 (0.84–1.72)	0.30
After 9 mo of 1L treatment [a,b]	0.43 (0.24–0.76)	0.004 [d]
Atezolizumab vs CarboGem cohort		
Unweighted (no control of confounders)		
Overall effect [a]	0.72 (0.52–1.02)	0.06
First 5 mo following 1L initiation [a]	1.30 (0.76–2.21)	0.30
After 5 mo of 1L treatment [a]	0.49 (0.31–0.77)	0.002 [d]
After weighting [c]		
Overall effect [a]	0.67 (0.48–0.94)	0.02 [d]
First 5 mo following 1L initiation [a]	1.60 (0.91–2.79)	0.10
After 5 mo of 1L treatment [a,b]	0.52 (0.33–0.82)	0.005 [d]

1L = first line; Carbo = carboplatin; CarboGem = Carbo-gemcitabine; HR = hazard ratio; CI = confidence interval.
[a] Overall effect refers to the complete 24-mo follow-up period. Owing to violation of the proportionality of hazards assumption, stratified analyses evaluated overall survival before or after a follow-up duration of 9 mo for the Carbo-based cohort and 5 mo for the CarboGem cohort, corresponding to crossing of Kaplan-Meier curves.
[b] Weights were derived from patients in the study cohorts who were still alive and followed as of the 5- or 9-mo periods corresponding to crossing of Kaplan-Meier curves.
[c] The entropy-balance weighting (control of confounders) was applied for age (continuous), race (white vs other), visceral metastases (vs other), previous use of chemotherapy (yes vs no), body mass index (continuous), Quan-Charlson comorbidity index (continuous), anemia at baseline (yes vs no), hemoglobin <10 g/dl (yes vs no), and abnormal serum albumin levels.
[d] $p < 0.05$.

mechanisms in IMvigor210 were prespecified and well documented, it was appropriate to mimic these exclusions in the VHA cohorts and apply weighting using a short list of OS predictors selected a priori to control for residual confounding. This confounding control approach may not be sufficient for a comparison of two real-world cohorts, in which treatment decisions are more complex and multifactorial.

Responses to immunotherapies can manifest as delayed or nonclassical responses [27], and different mechanisms of action and pharmacokinetics between immune checkpoint inhibitors and chemotherapy can also result in nonproportional hazards in OS analyses [17,18]. An important future challenge will be to evaluate the drivers (eg, clinical biomarkers) underlying this phenomenon. When considering the 24-mo follow-up period, weighted Cox regression demonstrated a significant overall OS benefit with atezolizumab compared to carboplatin-gemcitabine, the regimen most commonly used in this setting; a similar but nonsignificant trend was observed versus all carboplatin-based regimens. In both comparisons, a significant latent OS benefit was observed. However, the OS benefit with atezolizumab versus carboplatin-gemcitabine manifested earlier and was more pronounced compared with the effect of atezolizumab versus carboplatin-based regimens. Indeed, VHA patients in the carboplatin-based cohort received a variety of different combinations of agents (according to the NCCN guidelines v2.2015), reflecting the spectrum of clinical practice treatment decisions and potentially introducing heterogeneity into the models.

This study had several strengths and limitations. In particular, VHA data are well suited for external comparisons, as they represent the largest integrated US health care system and provide a broad spectrum of care settings (>1400 outpatient clinics, veteran centers, and domiciliaries as of 2011) and rich EMR data. However, while the VHA CDW provides detailed information on cancer diagnoses and treatment, these data may be subject to possible coding errors or misclassification in clinical practice. Although VHA patients may have differences in physical and mental health compared with the general population (eg, lower performance status, higher rates of severe comorbidity) [28,29], after adjusting for these factors, VHA patients do not have inferior cancer-specific survival relative to those treated in the Medicare system [30]. Likewise, the median time from mUC diagnosis (using ICD9/10 diagnosis codes) to 1L treatment for the carboplatin- and CarboGem-treated VHA cohorts was only 28 and 27 d, respectively, with patients who had delayed treatment (>6 mo) excluded. The median time from mUC diagnosis to first dose administered for the atezolizumab cohort was 2.6 mo (data not shown). Owing to the predominantly male VHA population, sex could not be controlled for in the main analyses; however, sensitivity results restricted to males confirmed our primary findings. Characteristics measured in a clinical trial setting cannot be exactly replicated in real-world populations, and a few IMvigor210 eligibility criteria could not be replicated from the VHA data (Supplementary material); however, most patients with unmeasured exclusion factors were probably already excluded because

of other criteria. Likewise, performance status, which was measured for IMvigor210 patients, was retrospectively proxied from evaluable procedure codes for the VHA patients [31]. QCCI (a measure of the overall disease burden and a strong predictor of the risk of death) [15] was also included in the model to mitigate these limitations. Restriction (to patients who satisfied the IMvigor210 eligibility criteria) and the EBW method were used to control for observed confounders, but residual confounding related to unmeasured characteristics (eg, C-reactive protein, biomarkers) is not accounted for. Moreover, the maximum follow-up duration was truncated at 24 mo to align the VHA and IMvigor210 data, precluding analyses for longer-term trends. Furthermore, OS was evaluated as the primary clinical endpoint owing to its high validity, while disease progression and safety outcomes were not reported here. Lastly, patient exclusions based on IMvigor210 eligibility criteria may limit the generalizability of our findings to broader populations; however, these exclusions were needed to increase the validity of comparisons between atezolizumab and carboplatin-based regimens. Nevertheless, since many patients with mUC are ineligible for chemotherapy, these results have OS implications.

5. Conclusions

We performed the first comparative analysis of non-cisplatin 1L treatments for mUC. We compared outcomes in patients treated with atezolizumab (in IMvigor210) and patients receiving carboplatin-based regimens (in VHA clinical practice). Our results show that atezolizumab conferred an OS benefit in cisplatin-ineligible patients compared with carboplatin-based chemotherapies at 5–9 mo after treatment initiation, depending on the regimen. Future randomized studies in the 1L setting are needed to validate these results and further delineate appropriate 1L treatment regimens and sequencing in mUC.

Author contributions: Nancy Vander Velde had full access to all of 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: Guerin, Ionescu-Ittu, S. Shi, Wu, Lin, Hsu, Li, Leppert.

Acquisition of data: Wu, Li, Liu, L. Shi.

Analysis and interpretation of data: Vander Velde, Ionescu-Ittu, S. Shi, Lin, Hsu, Saum, de Ducla, Wang, Li, Thåström, Liu, L. Shi, Leppert.

Drafting of the manuscript: Guerin, Ionescu-Ittu, Li, Thåström, Leppert.

Critical revision of the manuscript for important intellectual content: Vander Velde, Guerin, Ionescu-Ittu, S. Shi, Wu, Hsu, Saum, de Ducla, Thåström, Liu, L. Shi, Leppert.

Statistical analysis: Guerin, Ionescu-Ittu, S. Shi, Wu, Wang, Li, Liu.

Obtaining funding: Wu, Lin, Hsu.

Administrative, technical, or material support: Lin, Hsu.

Supervision: Guerin, Ionescu-Ittu, Hsu, L. Shi.

Other: None.

Financial disclosures: Nancy Vander Velde certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Nancy Vander Velde, Shuqian Liu, Lizheng Shi, and John Leppert have nothing to disclose, Annie Guerin, Raluca Ionescu-Ittu, Sherry Shi, and Eric Wu are employees of Analysis Group, which received research funding from Genentech-Roche for this study. Shih-Wen Lin, Ling-I Hsu, Shi Li, and AnnChristine Thåström are employees of Genentech-Roche and own Roche stock. Shih-Wen Lin has received travel expenses from Genentech-Roche. Jingjing Wang is a consultant for Genentech-Roche. Kai-Uwe Saum is an employee of Roche Pharma AG. Sabine de Ducla and an immediate family member are employees of F. Hoffmann-La Roche and own Roche stock.

Funding/support and role of the sponsor: F. Hoffmann-La Roche supported this study and was involved in the study design and conduct, data interpretation, and review and approval of the manuscript.

Acknowledgments: We thank the patients and their families and the investigators and staff of the clinical study sites. We also thank Christina Derleth for her contributions to the study. Medical writing assistance for this manuscript was provided by Wendy See-Zepeda and Ashley J. Pratt of Health Interactions and was funded by F. Hoffmann-La Roche.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.euo.2018.07.003.

References

[1] von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23:4602–8.

[2] Galsky MD, Hahn NM, Rosenberg J, et al. Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. J Clin Oncol 2011;29:2432–8.

[3] Bellmunt J, Orsola A, Leow JJ, et al. Bladder cancer: ESMO practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(Suppl 3), iii40-8.

[4] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: bladder cancer. V5.2017. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.

[5] Galsky MD, Pal SK, Lin SW, et al. The effectiveness of chemotherapy in "real world" patients with metastatic bladder cancer. Eur J Cancer 2015;51(Suppl 3):S520–1.

[6] Gartrell BA, He T, Sharma J, Sonpavde G. Update of systemic immunotherapy for advanced urothelial carcinoma. Urol Oncol 2017;35:678–86.

[7] Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563–7.
[8] 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 2017;389:67–76.
[9] Genentech. Tecentriq (atezolizumab). Package insert. www.accessdata.fda.gov/drugsatfda_docs/label/2016/761034s000lbl.pdf.
[10] Roche Registration. Tecentriq (atezolizumab). Summary of product characteristics. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004143/WC500235778.pdf.
[11] Merck Sharp & Dohme. Keytruda (pembrolizumab). Summary of product characteristics. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003820/WC500190990.pdf.
[12] Zullig LL, Sims KJ, McNeil R, et al. Cancer incidence among patients of the U.S. Veterans Affairs health care system: 2010 update. Mil Med 2017;182:e1883–91.
[13] Hainmueller J. Entropy balancing for causal effects: a multivariate reweighting method to produce balanced samples in observational studies. Political Anal 2011;20:25–46.
[14] Taguchi S, Nakagawa T, Uemura Y, et al. Validation of major prognostic models for metastatic urothelial carcinoma using a multi-institutional cohort of the real world. World J Urol 2016;34:163–71.
[15] Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–9.
[16] Yang D, Dalton JE. A unified approach to measuring the effect size between two groups using SAS®. In: Proceedings of the SAS Global Forum 2012. http://support.sas.com/resources/papers/proceedings12/335-2012.pdf.
[17] Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015–26.
[18] Powles T, Loriot Y, Durán I, et al. IMvigor211: a phase III randomized study examining atezolizumab versus chemotherapy for platinum-treated advanced urothelial carcinoma. Special lecture presented at: EACR-AACR-SIC Special Conference, June 24-27. 2017.
[19] Mack C, Pavesio A, Kelly K, et al. Breaking news: novel design methodology combining a registry with claims data to study fracture non-union. Pharmacoepidemiol Drug Saf 2017;26(Suppl 2):161.
[20] Viele K, Berry S, Neuenschwander B, et al. Use of historical control data for assessing treatment effects in clinical trials. Pharm Stat 2014;13:41–54.
[21] Adhikary SD, Liu WM, Memtsoudis SG, Davis III CM, Liu J. Body mass index more than 45 kg/m^2 as a cutoff point is associated with dramatically increased postoperative complications in total knee arthroplasty and total hip arthroplasty. J Arthroplasty 2016;31:749–53.
[22] Bahler C, Schoepfer AM, Vavricka SR, Brungger B, Reich O. Chronic comorbidities associated with inflammatory bowel disease: prevalence and impact on healthcare costs in Switzerland. Eur J Gastroenterol Hepatol 2017;29:916–25.
[23] De Santis M, Wiechno PJ, Bellmunt J, et al. Vinflunine-gemcitabine versus vinflunine-carboplatin as first-line chemotherapy in cisplatin-unfit patients with advanced urothelial carcinoma: results of an international randomized phase II trial (JASINT1). Ann Oncol 2016;27:449–54.
[24] Bamias A, Lainakis G, Kastritis E, et al. Biweekly carboplatin/gemcitabine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: report of efficacy, quality of life and geriatric assessment. Oncology 2007;73:290–7.
[25] De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 2012;30:191–9.
[26] Linardou H, Aravantinos G, Efstathiou E, et al. Gemcitabine and carboplatin combination as first-line treatment in elderly patients and those unfit for cisplatin-based chemotherapy with advanced bladder carcinoma: phase II study of the Hellenic Co-operative Oncology Group. Urology 2004;64:479–84.
[27] Mazieres J, Fehrenbacher L, Rittmeyer A, et al. Non-classical response measured by immune-modified RECIST and post-progression treatment effects of atezolizumab in 2L/3L NSCLC: results from the randomized phase II study POPLAR. J Clin Oncol 2016;34 (15 Suppl):9032.
[28] Agha Z, Lofgren RP, VanRuiswyk JV, Layde PM. Are patients at Veterans Affairs medical centers sicker?. A comparative analysis of health status and medical resource use. Arch Intern Med 2000;160:3252–7.
[29] Rogers WH, Kazis LE, Miller DR, et al. Comparing the health status of VA and non-VA ambulatory patients: the Veterans' Health and Medical Outcomes studies. J Ambul Care Manage 2004;27:249–62.
[30] Landrum MB, Keating NL, Lamont EB, et al. Survival of older patients with cancer in the Veterans Health Administration versus fee-for-service Medicare. J Clin Oncol 2012;30:1072–9.
[31] Davidoff AJ, Tang M, Seal B, Edelman MJ. Chemotherapy and survival benefit in elderly patients with advanced non–small-cell lung cancer. J Clin Oncol 2010;28:2191–7.