Original Study

Treatment Patterns and Efficacy of Chemotherapy After Pembrolizumab in Advanced Urothelial Cancer-a Real-World Study in the pre-Antibody-Drug Conjugate Era

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Abstract

This retrospective real-world study shows that vinflunine and platinum-combinations were the most common regimens after previous pembrolizumab in patients with metastatic urothelial cancer (mUC). The median progression-free and overall survival were 3.3 and 7.7 months respectively. Conventional chemotherapy after immunotherapy may remain to be a late-stage treatment option for selected patients in the era of targeted precision medicine of mUC.

Background: Immune checkpoint inhibitors (ICIs) have been established as a routine treatment in patients with metastatic urothelial cancer (mUC). However, there has been no standard of care after progression on ICIs. We investigated real-world treatment patterns and efficacy of chemotherapy (CHT) after pembrolizumab, in the era before introduction of maintenance avelumab and antibody-drug conjugates (ADC). **Patients and Methods:** An observational, retrospective study was conducted at twelve Nordic centers. Patients with mUC were treated according to investigatorś choice of CHT after pembrolizumab. Primary endpoint was overall response (ORR) and disease control rate (DCR); secondary endpoints were progression-free (PFS) and overall survival (OS). **Results:** In total, 102 patients were included whereof 23 patients received CHT after pembrolizumab as second line treatment (subcohort A) and 79 patients in third line (subcohort B). Platinum-gemcitabine combinations were the most common regimens in subcohort A, and vinflunine in subcohort B. The ORR and DCR were 36% and 47%, respectively. Presence of liver metastases was independently associated with lower ORR and DCR. The PFS and OS were 3.3 months and 7.7 months, respectively. Eastern Cooperative Oncology Group Performance Status (ECOG PS) and number of previous cycles of pembrolizumab were found to be independent prognostic factors associated with OS. **Conclusion:** In a real-world setting, CHT showed clinically

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meaningful response rates and survival in mUC patients after progression with pembrolizumab. Clinical benefit may primarily be achieved in patients with favorable ECOG PS, in patients treated with > 6 cycles pembrolizumab as well as in patients without presence of liver metastases.

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Introduction

Metastatic urothelial carcinoma (mUC) is a lethal disease with poor prognosis and median survival limited to 21 months with best available treatment.[1] Platinum-based combination chemotherapy (PCT) has been the first line standard of care for decades with response-rates up to 49% to 62%.[2,3] However, the duration of response following PCT is generally short, and at progression patients often experience disease-related morbidity. The introduction of immune checkpoint inhibitors (ICIs) has significantly changed the treatment landscape for mUC and ICIs are today incorporated as a standard first line treatment option for cisplatin-ineligible PDL1 positive patients and as second line treatment for patients progressing after PCT, irrespective of PDL1 status.[4-6] Although atezolizumab and nivolumab are approved as well, pembrolizumab has been the preferred ICI in PCT-refractory patients in the Nordic countries because of level I evidence demonstrating an overall survival (OS) benefit as compared to investigators choice of chemotherapy (CHT).[4] Furthermore, avelumab was recently approved in first line switch maintenance treatment for patients achieving disease control after first line PCT.[1] Consequently, a large proportion of mUC patients are likely to receive therapy with ICIs at some stage of their disease. Even though ICIs induce long-lasting durable responses for a subset of patients, the overall response rates (ORR) are rather low.[4-6] Clarifying the underlying causes of differences in response to treatment and identifying predictive biomarkers remains an unmet need.

Until recently, there has been no uniform standard of care in the PCT and ICIs refractory space. Nonetheless, several novel treatments have newly been approved or are in late-stage development, i.e. inhibitors of the fibroblast growth factor receptor (FGFRi) and the antibody-drug conjugates (ADCs) enfortumab-vedotin (EV), which targets nectin-4 utilizing the microtubule inhibitor disrupting agent monomethyl auristatin E (MMAE) as payload, and sacituzumab-govitecan, targeting TROP-2 with SN-38, which is the active metabolite of irinotecan.[7-9] In the pivotal phase III trial EV-301, EV demonstrated a median OS benefit (12.9 months) as compared to investigators choice of CHT ie, vinflunine, paclitaxel or docetaxel (9.0 months) in mUC progressing after PCT and ICIs.[7] Even though ADCs are conceptually very promising, compound-specific side effects must be considered, and conventional CHT will likely remain a treatment option for subgroups of patients also in the future.

Additionally, the optimal sequencing of today's available compounds is an area attending increasing interest.[10-13] Unexpectedly high responses to single- and combination-CHT after previous treatment with PCT and ICIs have been described, indicating a possible lack of cross-resistance and resensitization between ICIs and CHT, but the underlying biological mechanisms are unclear. This phenomenon may however be similar to underlying promising effects observed of ADCs after ICIs.[10,13-19]

Given the variable efficacy of different ICIs, which is observed across various stages of mUC, i.e. treatment in first line,[5,20,21] maintenance,[1,22] and second line[4,23-25] we believe that efficacy of post-ICIs CHT should be addressed in the context of the specific previous ICI compound. In the present retrospective study, we aimed to investigate real-world treatment patterns and efficacy outcomes of investigators choice of conventional chemotherapy in a cohort of mUC patients strictly defined by being treated with CHT after the specific anti-PD1 antibody pembrolizumab in first- or in second line, in the pre-ADC era.

Patients and Methods

Study Design and Patient Population

This trial was conducted as an observational, multicenter, retrospective clinical study at twelve centers associated to the Nordic Urothelial Cancer Oncology Group (NUCOG) and Swedish Society for Urological Oncology (SFUO) Bladder Cancer group. The trial was approved by the Swedish Ethical Review Authority (Dnr 2017/2501-31, 2019-00969, 2020-04905, 2021-01336) and the Danish Patient Safety Authority (3-3013-3272/1).

Patients with locally advanced or metastatic lower or upper tract urothelial cancer who had completed treatment with pembrolizumab and were further treated with routine systemic chemotherapy were included. All patients were to be treated outside prospective clinical trials, as per standard practice and before the introduction of maintenance avelumab and ADC therapies.

The patients were divided into two sub-cohorts: cisplatin-ineligible patients treated with pembrolizumab in first line following diagnosis with mUC (subcohort A) or if pembrolizumab was given in second line after previous first line PCT for mUC (subcohort B). Cisplatin-ineligible patients in subcohort A were treated according to the Swedish, Danish and EAU guidelines, recommending pembrolizumab to PDL1 positive patients only. The choice of CHT post-pembrolizumab was made according to best clinical practice at investigator's discretion. Data on all systemic treatments (ie, type of regimen, number of cycles, dose reductions, dose delays, reason for stopping treatment and efficacy parameters) were collected from medical records using a study specific questionnaire and captured into the electronic Case Report Form (eCRF) system PheedIt at the

department of Clinical Cancer Studies, Karolinska Hospital Solna, Sweden.

Outcome Measures

Outcomes of CHT post-pembrolizumab and relation to clinical variables were analyzed in the complete cohort and in the 2 subcohorts, defined above. Response evaluation was based on radiological assessments using computerized tomography (CT) according to clinical routine. The primary outcome measures were ORR comprising the rate of complete (CR) and partial responses (PR), and disease-control rate (DCR) comprising the rate of CRs, PRs and stable disease (SD) patients. Secondary outcome measures included progression-free survival (PFS) defined as time from start of CHT post-pembrolizumab to progression or death, whichever occurred first, and OS defined as time from the start of CHT post-pembrolizumab until death from any cause or until last follow-up. Explorative analyses were performed to evaluate the possible associations between type of regimen, clinical prognostic factors (initial curative surgery, presence of liver, bone, or visceral metastases), renal function (estimated GFR), treatment length and response to the CHT regimen, as well as the impact of the previous pembrolizumab treatment length on outcome of the post-pembrolizumab CHT.

Statistical Analysis

Differences in nominal data were assessed by the Pearson $\chi 2$ test with a significance level of $p < 0.05$. Continuous variables were categorized into nominal data. Descriptive statistics were applied to present baseline characteristics and treatment patterns. Odds ratios (OR) were estimated with 95% confidence intervals (CIs) using uni- and multivariable logistic regression analyses to quantify differences in response (ORR and DCR). Uni- and multivariable analyses of time to event data (PFS and OS) were performed using the log-rank (Mantel-Cox) model and survival curves were estimated using the Kaplan-Meier method. Hazard ratios (HR) were estimated with 95% CI using uni- and multivariable Cox-proportional hazards (CoxPH) regression. Data were analyzed using SPSS statistics software for Windows (version 26; IBM SPSS, Armonk, NY, USA).

Results

Baseline Characteristics at Start of CHT Post-pembrolizumab

In total, 102 patients were included in the study from January 2018 to January 2022, whereof 23 patients were treated in subcohort A (ie, CHT post-pembrolizumab as second line treatment for mUC) and 79 patients in sub-cohort B (ie, CHT post-pembrolizumab as third line treatment for mUC). Baseline characteristics at start of CHT post-pembrolizumab are summarised in Table 1. Baseline characteristics were generally similar in the two sub-cohorts; however, males were strongly overrepresented (91%, $P = .010$) amongst patients that received CHT post-pembrolizumab in second line for mUC (subcohort A).

Treatment Patterns

The most common post-pembrolizumab CHT regimens were carboplatin-gemcitabine and vinflunine, with different treatment patterns in subcohorts A and B (Figure 1A-C and Table 2). In subcohort A, the most commonly used CHT post-pembrolizumab was platinum-gemcitabine (61%) whereas in subcohort B, vinflunine was the most common regimen, given to 49 of 79 (62%) patients (Figure 1A-C). Notably, only five patients received cisplatin-based CHT after pembrolizumab whereas the majority received carboplatin-gemcitabine. Fifteen percent of the patients received "other CHT regimens," mainly referring to taxane-based combination regimens. Forty-three patients (42%) received a second line CHT after their initial CHT post-pembrolizumab and further eight patients (8%) received a third line CHT post-pembrolizumab. Fifteen patients died (15%) within 28 days after CHT-treatment, due to progressive disease and clinical deterioration. There were no treatment related deaths. The median number of cycles of previous pembrolizumab was 5, and 39% of the complete cohort received > 6 cycles (Supplemental Data Table 1). In subcohort B, ie, among patients that received CHT before pembrolizumab, 94% received platinum-based CHT as the upfront regimen for mUC.

Response to CHT Post-pembrolizumab and Prognostic Factors

The ORR and DCR for CHT given post-pembrolizumab of the complete cohort were 36% and 47%, respectively. There were no significant ORR differences among the 2 subcohorts; in subcohort A the ORR was 44% (9% CR, 35% PR) and in sub-cohort B the ORR was 34% (1% CR, 33 % PR) (Figure 1A-C). The ORR in second- and third line CHT after post-pembrolizumab CHT was 14% and 13% respectively in the complete cohort (Supplemental Data Figure 1 and Supplemental Data Table 2). The ORR and DCR for pembrolizumab in the complete cohort were 18% and 43%, respectively, no differences in ORR or DCR were observed among the two sub-cohorts ($P = .634$).

Potential clinical prognostic factors were analyzed by univariable logistic regression for association to ORR and DCR (Supplemental Data Table 3). Presence of liver metastases and treatment with "other" CHT post-pembrolizumab were independently associated with lower ORR and presence of liver metastases was independently associated with lower DCR in multivariable analyses (Table 3).

Survival

The PFS and OS in the complete cohort were 3.3 and 7.7 months respectively, with no significant differences between the two subcohorts (Figure 2A and B). When analyzing OS from start of the very first systemic treatment for mUC to death or last follow-up, survival was 20.6 months for the complete cohort. Further, patients in subcohort B were found to have a longer survival of 21.0 months compared 16.1 months for patients in sub-cohort A, $P = .007$ (Figure 2C), well in line with previously established survival differences between cisplatin-eligible and cisplatin-ineligible patients in mUC.

When analyzing potential clinical prognostic factors and their association to OS (Supplemental Data Table 4), Eastern Cooperative Oncology Group Performance Status (ECOG PS) and number of previous cycles of pembrolizumab, were independently associated with OS in multivariable analyses (Table 4). ECOG PS 0 patients demonstrated an OS of 14.4 months, ECOG PS 1 patients an OS

Table 1 Baseline Characteristics at Start of Chemotherapy Post-pembrolizumab

Characteristics	All Patients (n = 102)	Cohort A (n = 23)	Cohort B (n = 79)	*P*-Value
Age (years)				
Median	71	73	71	
Range	43-83	43-83	52-82	
Age interval (years)				.718
43-64	28 (28)	7 (30)	21 (27)	
65-75	42 (41)	8 (35)	34 (43)	
76-83	30 (29)	8 (35)	22 (28)	
Missing	2 (2)	0	2 (3)	
Sex				.010
Male	71 (70)	21 (91)	50 (63)	
Female	31 (30)	2 (9)	29 (37)	
ECOG PS				.286
0	31 (30)	8 (35)	23 (29)	
1	43 (42)	8 (35)	35 (44)	
2	21 (21)	5 (22)	16 (20)	
3	3 (3)	2 (9)	1 (1)	
Missing	4 (4)	0	4 (5)	
Hb < 10 g/dL	8 (8)	2 (9)	6 (8)	.863
GRF < 60 ml/min[a]	62 (61)	15 (65)	47 (60)	.688
Primary tumor location[b]				.137
Lower tract	67 (66)	16 (70)	51 (65)	
Upper tract	34 (33)	6 (26)	28 (35)	
Primary curative or metastatic disease				.234
Primary metastatic disease	42 (42)	7 (30)	35 (44)	
Prior curative treatment[c]	60 (59)	16 (70)	44 (56)	
Perioperative chemotherapy				
Neoadjuvant	19 (19)	9 (39)	10 (13)	.004
Adjuvant	6 (6)	3 (13)	3 (4)	.097
Metastatic site[b]				
Local recurrence	21 (21)	9 (39)	12 (15)	.009
Lymph nodes	77 (76)	18 (78)	59 (75)	.487
Liver	30 (29)	6 (26)	24 (30)	.778
Lung	51 (50)	13 (57)	38 (48)	.362
Bone	37 (36)	10 (44)	27 (34)	.332
Other	27 (26)	4 (17)	23 (29)	.306
Visceral metastases[b]				.734
No (only lymph nodes)	16 (16)	4 (17)	12 (15)	
Yes	85 (83)	18 (78)	67 (85)	

Data are *n* (%), expect where indicated.
Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performancestatus; Hb, haemoglobin; GFR, glomerular filtration rate.
[a] n = 96, missing data in 6 patients.
[b] n = 101, missing data in 1 patient.
[c] Cystectomy, nephroureterectomy or radiotherapy.

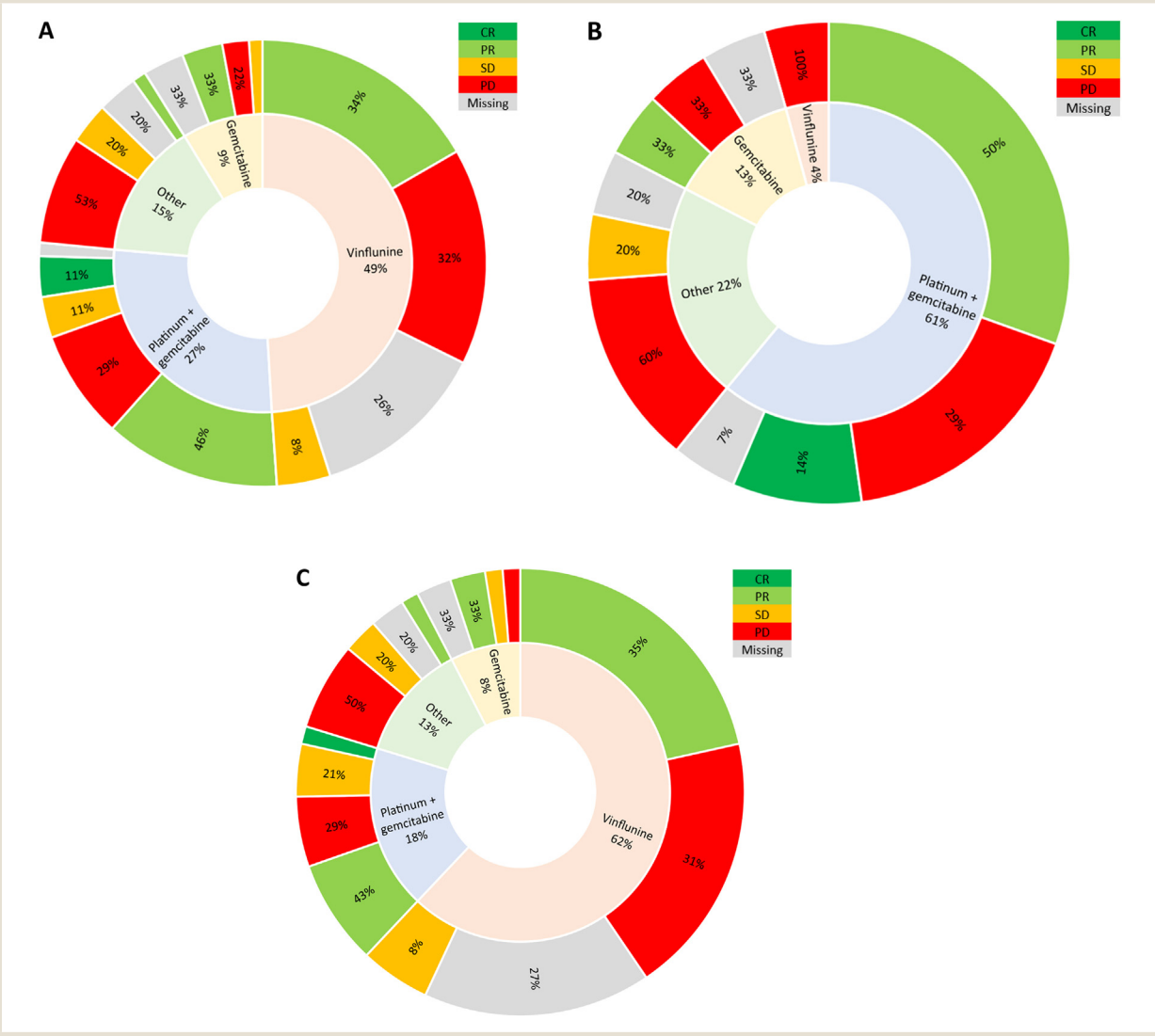
of 9.7 months and ECOG PS > 2 an OS limited to 3.2 months ($P < .005$). Patients having received ≥ 7 cycles of pembrolizumab had significantly longer OS, 9.7 months, as compared to patients who received 4 to 6 cycles, 5.8 months, and 1 to 3 cycles, 4.5 months, $P = .020$ (Figure 3 and Table 4).

Discussion

After pembrolizumab in a real-world setting of mUC patients, vinflunine was the most commonly used CHT whereas in patients treated with pembrolizumab upfront, platinum-gemcitabine combinations were the preferred regimens. Clinical meaningful CHT response rates and survival in mUC patients after progression with pembrolizumab were observed, especially in patients with favorable ECOG PS, in patients treated with > 6 cycles pembrolizumab as well as in patients without presence of liver metastases.

The optimal systemic treatment for mUC is a moving target and ICIs have become part of the standard treatment options in mUC.[26] Even though some patients achieve long-term durable responses, the

Figure 1 Treatment pattern and response in first line chemotherapy post-pembrolizumab in (A) the overall cohort (n = 102), (B) subcohort A (ie, chemotherapy post-pembrolizumab in second line treatment for mUC, n = 23) and (C) subcohort B (ie, chemotherapy post-pembrolizumab in third line treatment for mUC, n = 79)



ORR of ICIs is low and resistance to therapy is eventually expected in most patients.[11,12] Until recently, there was no approved third line treatment for mUC and treatment options have been different CHT regimens based on physician's choice. Although novel therapies such as ADCs and FGFRi represent a significant step forward to reach disease control and prolong OS, these drugs are newly approved, available in only a few countries, and will not be tolerable for all patients.[1,7,9,27] Therefore, understanding treatment landscape and outcome of subsequent CHT after ICIs are of utmost importance.

This observational, multicenter real-world study investigated efficacy and treatment patterns of CHT after pembrolizumab in Nordic patients with mUC, in the era before the introduction of maintenance avelumab, ADCs and FGFRi. The selected CHT after pembrolizumab was based on investigators-choice and none of our patients were included in controlled interventional prospective clinical trials.

In the complete cohort, the most common post-pembrolizumab CHT regimens were vinflunine (49%) and PCT (27%). Most patients (77%) received CHT in third line (after PCT and pembrolizumab; subcohort B), whereas 23% of patients received CHT in second line (after upfront treatment with pembrolizumab; subcohort A). The CHT of choice in subcohort A was PCT (61%), whereas vinflunine single drug was the first choice in majority of patients (62%) in subcohort B. These differences may be attributed to differences in previous perioperative treatment, ie, in subcohort A more patients had received cisplatin based neoadjuvant CHT prior to cystectomy, as compared to subcohort B (39% vs. 13%). The lack of data on reasons for being deemed cisplatin-ineligible is a

Table 2 Treatment Patterns

Treatment	All Patients (n = 102)	Cohort A (n = 23)	Cohort B (n = 79)	*P*-value
Type of chemotherapy first line post-pembrolizumab (n = 102)				<.005
Cisplatin + gemcitabine	4 (4)	1 (4)	3 (4)	
Carboplatin + gemcitabine	24 (24)	13 (57)	11 (14)	
Vinflunine	50 (49)	1 (4)	49 (62)	
Gemcitabine	9 (9)	3 (13)	6 (8)	
Other[a]	15 (15)	5 (22)	10 (13)	
Cycles first line postpembro (no)				
Median	4	4	4	
Range	1-17	1-13	1-17	
Reason to stop chemotherapy first line postpembro				.450
Progressive disease	52 (51)	13 (57)	39 (49)	
Toxicity	12 (12)	1 (4)	11 (14)	
Other[b]	38 (37)	9 (39)	29 (37)	
No of patients who died within 1 month after last chemotherapy-treatment[c]	15 (15)	2 (9)	13 (16)	
Type of chemotherapy second line post-pembrolizumab (n = 43)				-
Cisplatin + gemcitabine	1 (2)	0	1 (3)	
Carboplatin + gemcitabine	10 (23)	2 (22)	8 (24)	
Vinflunine	13 (30)	5 (56)	8 (24)	
Gemcitabine	2 (5)	0	2 (6)	
Other[d]	17 (40)	2 (22)	15 (44)	
Type of chemotherapy third line post-pembrolizumab (n = 8)				-
Cisplatin + gemcitabine	0	0	0	
Carboplatin + gemcitabine	1 (13)	0	1 (20)	
Vinflunine	2 (25)	1 (33)	1 (20)	
Other[e]	5 (63)	2 (67)	3 (60)	
Pembrolizumab (n = 102)				
Cycles (no)				
Median	5	5	5	
Range	1-33	1-33	1-30	
Reason to stop pembrolizumab				.860
Progressive disease	91 (89)	21 (91)	70 (89)	
Toxicity	7 (7)	1 (4)	6 (8)	
Other[f]	4 (4)	1 (4)	3 (4)	

[a] Docetaxel (n = 6), gemcitabine + paclitaxel (n = 4), paclitaxel (n = 2), carboplatin + paclitaxel (n = 1), carboplatin (n = 1), docetaxel + trastuzumab (n = 1).
[b] According to plan (n = 12), clinical deterioration (n = 10), death (n = 8), unknown (n = 3), covid-19 (n = 2), complete response (n = 2), drug not available (n = 1).
[c] Due to progressive disease/clinical deterioration (n = 15).
[d] Paclitaxel (n = 7), gemcitabine + paclitaxel (n = 4), docetaxel (n = 3), vinflunine + sorafenib (n = 1), ifosfamid + docetaxel + gemcitabine (n = 1), pembrolizumab rechallenge (n = 1).
[e] Paclitaxel (n = 4), Erdafitinib (n = 1).
[f] Unknown (n = 3), clinical deterioration (n = 1).

limitation in this study. Interestingly, while a multicenter retrospective European study showed similar distribution of mUC patients receiving ICIs versus PCT in first line, an American multicenter study showed an opposite trend[15,28]; in the American study, two-thirds of patients were treated with ICIs upfront and one third with PCT,[28] which may indicate that treatment patterns post-ICIs varies considerably between Europe and U.S.

The ORR and DCR of the complete cohort for first line CHT post-pembrolizumab were 36% and 47%, respectively. In comparison with previous real-world data (RWD) studies investigating efficacy of CHT after ICI, the present study which evaluated a homogenous cohort treated with the ICI pembrolizumab, demonstrated a similar or superior response-rate.[10,14,18,19] Vinflunine was the most common CHT after ICIs and demonstrated an unexpectedly high ORR of 34%. This compares favorably to the pivotal randomized study investigating vinflunine (ORR 8.6%) in PCT refractory patients by Bellmunt et al.[29] Similar observations were recently reported by Riedel et al.[18] The mechanism behind the

Table 3 Multivariable Analysis of Response in First Line Chemotherapy Post-pembrolizumab

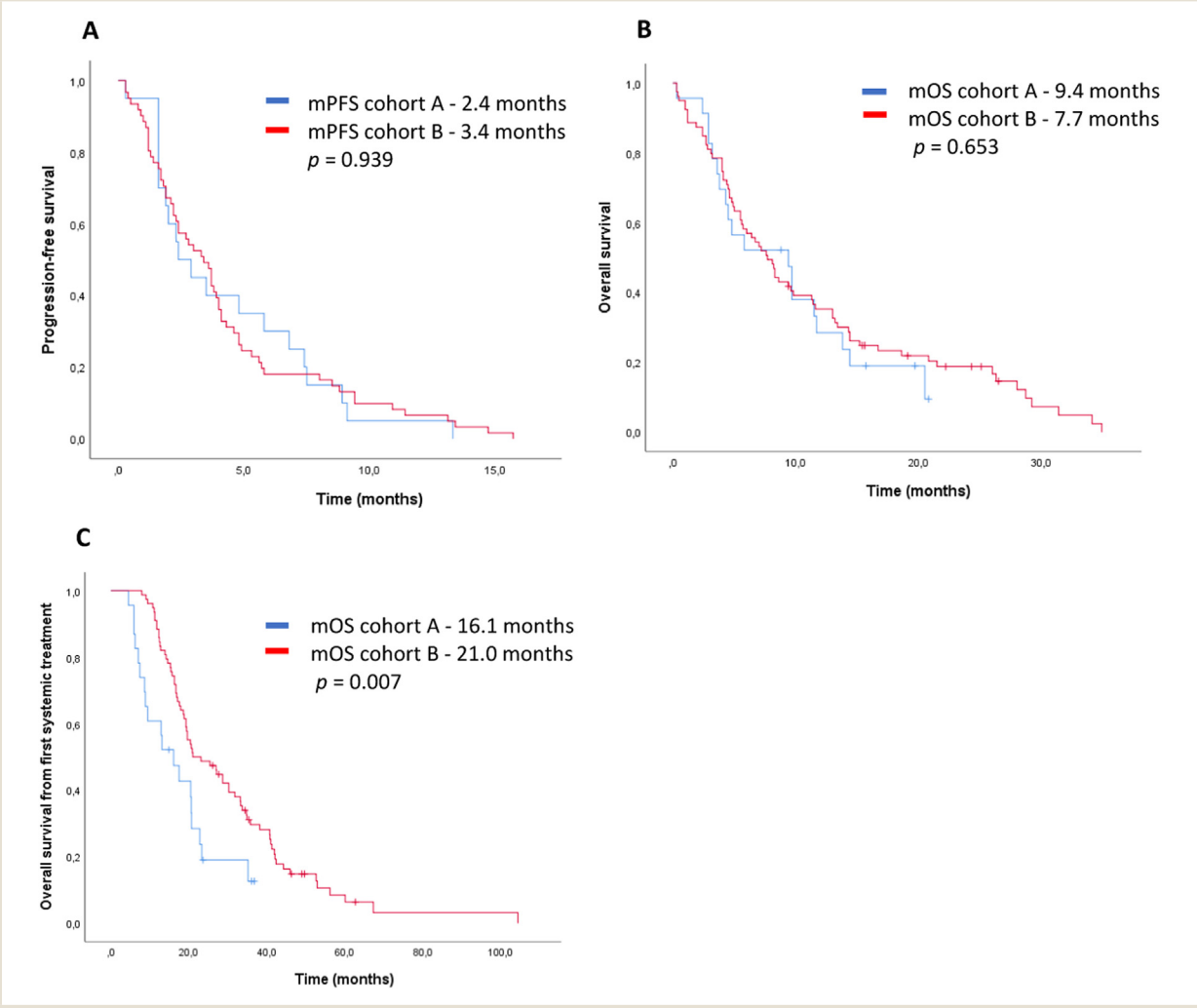
Variable at Baseline[a]	ORR	
	OR (95% CI)	*P*-Value
Type of chemotherapy post-pembrolizumab		
Platinum + gemcitabine	1	
Vinflunine	0.57 (0.17-1.90)	.358
Gemcitabine	0.44 (0.06-3.51)	.437
Other	0.06 (0.01-0.59)	.016
Initial curative surgery[b]		
Yes	1	
No	0.38 (0.13-1.12)	.079
Liver metastases		
No	1	
Yes	0.22 (0.06-0.78)	.019
Bone metastases		
No	1	
Yes	0.49 (0.15-1.56)	.228
Visceral metastases		
No	1	
Yes	0.76 (0.24-2.37)	.636
Variable at baseline[c]	**DCR**	
	OR (95% CI)	***p*-value**
Type of chemotherapy post-pembrolizumab		
Platinum + gemcitabine	1	
Vinflunine	0.85 (0.21-3.36)	.816
Gemcitabine	0.36 (0.03-4.17)	.414
Other	0.61 (0.10-43.88)	.598
No of cycles of pembrolizumab		
1-3 cycles	1	
4-6 cycles	2.04 (0.48-8.57)	.332
≥ 7 cycles	3.55 (0.77-16.36)	.104
ECOG PS		
0	1	
1	0.91 (0.26-3.21)	.882
≥ 2	0.49 (0.09-2.69)	.410
GFR interval		
> 60 mL/min	1	
< 60 mL/min	3.27 (0.94-11.31)	.062
Liver		
No	1	
Yes	0.21 (0.05-0.78)	.020

Abbreviation: ORR, overall response rate; OR, odds ratio; CI, confidence interval; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate.
[a] Variables significantly associated with ORR in univariable logistic regression analysis were included (Supplementary Data Table 3).
[b] Cystectomy or nephroureterectomy.
[c] Variables significantly associated with DCR in univariable logistic regression analysis were included (Supplementary Data Table 3).

observed unexpected efficacy after ICIs is not known; while CHT has been suggested to potentially induce immunogenic cell death through multiple mechanisms, to synergize with the post-ICIs immunological status of the patients, and to enhance the activation and functional rescue of exhausted CD8+ T-cells following previous treatment with ICIs,[11,14] ICIs may possibly resensitize tumors to subsequent CHT.[10,14,16] Similar observations have been done in other malignancies where ICIs are standard treatment including malignant melanoma and non–small cell lung-cancer.[30,31]

A significant number of patients (42%) received subsequent chemotherapy after the initial chemotherapy post-pembrolizumab and further eight patients (8%) a third line, with taxanes, vinflu-

Figure 2 KM survival curves for chemotherapy post-pembrolizumab per cohort A (blue = chemotherapy post-pembrolizumab in second line mUC) and B (red = chemotherapy post-pembrolizumab in third line mUC) (A) progression-free survival, (B) overall survival and (C) overall survival from start of first systemic treatment of mUC to death or last follow up



nine, and platinum-gemcitabine being the most commonly used regimens. Surprisingly, the ORR with these late regimens was almost 15%. These data suggest that selected chemotherapy eligible patients may have benefit of several lines of chemotherapy after pembrolizumab, at least in terms of response. However, toxicity and quality of life must be considered but these data were not collected as a part of this study, which is a study limitation.

PFS and OS for the complete cohort were 3.3 and 7.7 months, respectively. Similar PFS and OS have been reported in recent RWD studies exploring outcome after a mix of various PD1 and PDL1 ICIs[15,17,19,28] as well as in the CHT control arm of the EV-301 study.[7] We found OS from start of first systemic treatment for mUC to be significantly shorter in sub-cohort A compared to sub-cohort B (16.1 months versus 21 months, $P = .007$), in line with established survival differences in cisplatin-eligible and -ineligible patients. However, these survival differences may also corroborate the importance of upfront PCT to achieve disease control in mUC before treatment with ICIs, which is in line with the demonstrated benefits of the switch maintenance approach of avelumab after PCT.[1] Favorable ECOG PS and longer duration of treatment with previous pembrolizumab (ie, more than 6 cycles of therapy) were independently and significantly correlated to longer OS in our study, confirming findings by Gomez de Liano Lista et al, who investigated CHT after various ICIs.[15] Similarly, and in line with our findings, Riedel et al.[18] showed that OS following treatment vinflunine after progression on ICIs was significantly associated with ECOG PS.

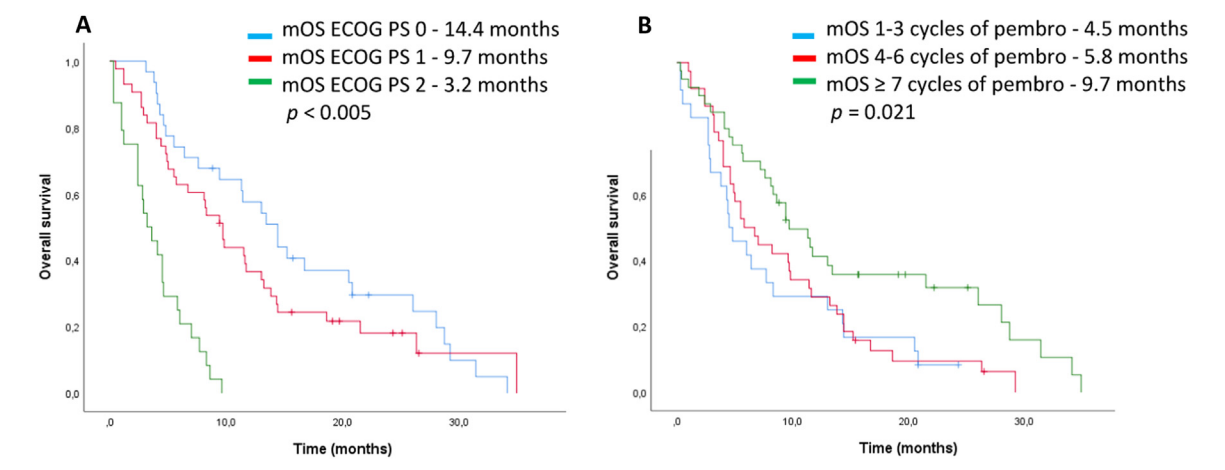
The study was performed in a Nordic multicenter real-world data context applying the same guidelines and the post-pembrolizumab CHT was unsupervised and according to investigator's choice. To the best of our knowledge, this is the first study reporting treatment patterns and outcome of CHT in a homogenous cohort of patients

Table 4 Multivariable CoxPH Analysis of Survival for Chemotherapy in First Line Post-pembrolizumab

	OS	
Variable at baseline[a]	**HR (95% CI)**	***P*-Value**[b]
Type of chemotherapy post-pembrolizumab		
Platinum + gemcitabine	1	
Vinflunine	1.02 (0.58-1.80)	.939
Gemcitabine	1.37 (0.54-3.47)	.512
Other	1.62 (0.74-3.56)	.225
No of cycles of pembrolizumab		
1-3 cycles	1	
4-6 cycles	0.63 (0.34-1.16)	.140
≥ 7 cycles	0.48 (0.26-0.88)	.018
ECOG PS		
0	1	
1	1.08 (0.63-1.86)	.783
≥ 2	3.26 (1.60-6.66)	<.005
Liver		
No	1	
Yes	1.58 (0.88-2.82)	.124
Bone		
No		
Yes	1.23 (0.73-2.06)	.439
Visceral metastases		
No	1	
Yes	1.74 (0.83-3.65)	.140

Abbreviation: CoxPH, Cox-proportional hazards regression; OS, overall survival; HR, Hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status.
[a] Variables significantly associated with OS in univariable CoxPH analysis were included (Supplementary Data Table 4).
[b] Log-rank (Mantel-Cox).

Figure 3 KM survival curves for chemotherapy post-pembrolizumab for variables independently associated with overall survival, (A) ECOG PS and (B) number of cycles of previous pembrolizumab



treated with the same ICI, pembrolizumab, before the introduction of ADCs, FGFRi or avelumab as maintenance therapy. Still, the known caveats of a nonrandomized observational study with limited number of patients must be taken into consideration and the results should therefore be interpretated with caution. Nevertheless, our study adds to the body of evidence that conventional chemotherapy post-ICI therapy with pembrolizumab may continue to be an important treatment option for selected patients, also in the evolving era of targeted precision medicine of mUC.

Conclusions

We demonstrate that mUC patients in a real-world setting mainly were selected for vinflunine or PCT after progression on pembrolizumab. High ORR and OS were observed, indicating clinically meaningful benefits of this treatment strategy. The presence of liver metastases and type of CHT regimen were factors independently associated with ORR, while ECOG PS and duration of treatment with pembrolizumab were independently associated with OS. Treatment with CHT after PCT and pembrolizumab may remain to be a relevant treatment option for selected eligible patients also in the evolving era of targeted precision medicine of mUC.

Clinical Practice Points

- Systemic chemotherapy after previous ICIs in the pre-ADC era has been investigated in several RWD studies with disparate results and sometimes unexpected efficacy. To our knowledge, the present retrospective RWD study is the first one addressing treatment patterns and efficacy of chemotherapy in mUC patients previously treated specifically with the ICI pembrolizumab.
- We found vinflunine and platinum-combinations with gemcitabine to be the most commonly used regimens in routine care. The overall response rate was 36% and median progression-free and overall survival were 3.3 and 7.7 months respectively.
- Clinical benefit may primarily be achieved in patients with favorable Eastern Cooperative Oncology Group Performance Status, in patients treated with > 6 cycles of previous pembrolizumab and in patients without presence of liver metastases.
- This study adds to the body of evidence supporting that treatment with chemotherapy after immunotherapy may remain a treatment option for selected patients in the era of targeted precision medicine of mUC.

Disclosure

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Author Contribution

Conceptualization K.H., H.P., A.U.; methodology A.U., J.E., K.H.; data collection J.E., K.H., E.Ö., P.D., F.J., A.L., I.V., E.J., J.S., E.W.-D., I.L., K.S., F.C-S., F.L., M.B., LH-O., H.P., A.U.; data analysis K.H., J.E., A.U.; funding resources A.U.; writing-original draft preparation K.H., A.U., J.E.; writing, review and editing, all authors; project administration A.U.; supervision A.U., K.H. All authors have read and agreed to the published version of the manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2023.05.008.

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