Optimizing immunotherapy in locoregional and metastatic urothelial cancer

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Survival after neoadjuvant/induction combination immunotherapy versus platinum-based chemotherapy for stage III urothelial cancer

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ABSTRACT

Despite treatment with cisplatin-based chemotherapy and surgical resection, clinical outcomes of patients with locally advanced urothelial carcinoma (UC) remain poor. We compared neoadjuvant/induction platinum-based combination chemotherapy (NAIC) with combination immune checkpoint inhibition (cICI). We identified 602 patients who attended our outpatient bladder cancer clinic in 2018-2019. Patients were included if they received NAIC or cICI for cT3-4aN0M0 or cT1-4aN1-3M0 UC. NAIC consisted of cisplatin-based chemotherapy or gemcitabine-carboplatin in case of cisplatin-ineligibility. A subset of patients (cisplatin-ineligibility or refusal of NAIC) received ipilimumab plus nivolumab in the NABUCCO-trial (NCT03387761). Treatments were compared using the log-rank test and propensity score-weighted Cox regression models. We included 107 stage III UC patients treated with NAIC (n=83) or cICI (n=24). NAIC was discontinued in 11 patients due to progression (n=6;7%) or toxicity (n=5;6%), while cICI was discontinued in 6 patients (25%) after 2 cycles due to toxicity (p=0.205). After NAIC, patients had surgical resection (n=50;60%), chemoradiation (n=26;30%), or no consolidating treatment due to progression (n=5;6%) or toxicity (n=2;2%). After cICI, all patients underwent resection. After resection (n=74), complete pathological response (ypT0N0) was achieved in 11 (22%) NAIC-patients and 11 (46%) cICI-patients (p=0.056). Median (IQR) follow-up was 26 (20-32) months. cICI was associated with superior progression-free survival (p=0.003) and overall survival (p=0.003) compared to NAIC. Our study showed superior survival in stage III UC patients pretreated with cICI if compared to NAIC. Our findings provide a strong rationale for validation of cICI for locally advanced UC in a comparative phase-3 trial.

INTRODUCTION

Locally advanced urothelial carcinoma (UC) is an aggressive disease characterized by poor prognosis and frequent distant recurrence (1). Cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy (RC) is strongly recommended for patients with non-metastatic muscle-invasive bladder cancer (2), while induction chemotherapy is encouraged in node-positive disease (3). However, survival benefit gained from neoadjuvant or induction chemotherapy (NAIC) is modest and generally limited to patients without residual (muscle-invasive) disease (1,2). Moreover, up to 50% of patients are cisplatin-ineligible due to comorbidities (2). Recently, several single-arm trials showed promising pathological response rates (31-46%) to neoadjuvant immune checkpoint inhibition (ICI) (4-7). In the NABUCCO study (NCT03387761), feasibility of preoperative combination ICI (cICI) with ipilimumab (anti-CTLA4) plus nivolumab (anti-PD1) combination treatment was determined (7). Efficacy of cICI compared to NAIC is yet to be assessed. In this study, we compared clinical outcome of the NABUCCO-patients to a cohort of stage-matched patients, who attended our bladder cancer clinic during the same time period and received pretreatment with platinum-based combination NAIC.

METHODS

Patients

We identified 602 patients who attended our outpatient bladder cancer clinic in 2018-2019 **(Figure1)**. Patients were included if they received NAIC or cICI for locally advanced UC (i.e. cT3-4aN0M0 or cT1-4aN1-3M0). We excluded patients with stage I, II or IV UC (n=313), patients with another or no malignancy (n=74 and n=23, respectively) as well as patients with pure variant histology (n=12). Of the patients with stage III UC, we excluded those who only visited our center for a second opinion (n=33), those who did not undergo systemic pretreatment due to refusal or poor performance status (n=27), and those who received pretreatment other than NAIC or cICI (n=13) **(Figure1)**. NAIC was cisplatin-based. In case of cisplatin-ineligibility, gemcitabine-carboplatin was offered in the induction setting. Some referral centers had started gemcitabine-carboplatin in the neoadjuvant setting. Patients were offered ipilimumab plus nivolumab in the NABUCCO-trial in case of cisplatin-ineligibility or refusal of NAIC in the time period when this trial was enrolling (February 2018 – February 2019). Pre-treatment staging in our bladder cancer clinic was similar for all patients and included urethro-cystoscopy, trans-urethral resection, and imaging with contrast-enhanced CT of the chest/abdomen/pelvis and full-body FDG-PET/CT. Clinical TNM-stage was determined at multidisciplinary rounds according to the American Joint Committee on Cancer guidelines. After NAIC, con-

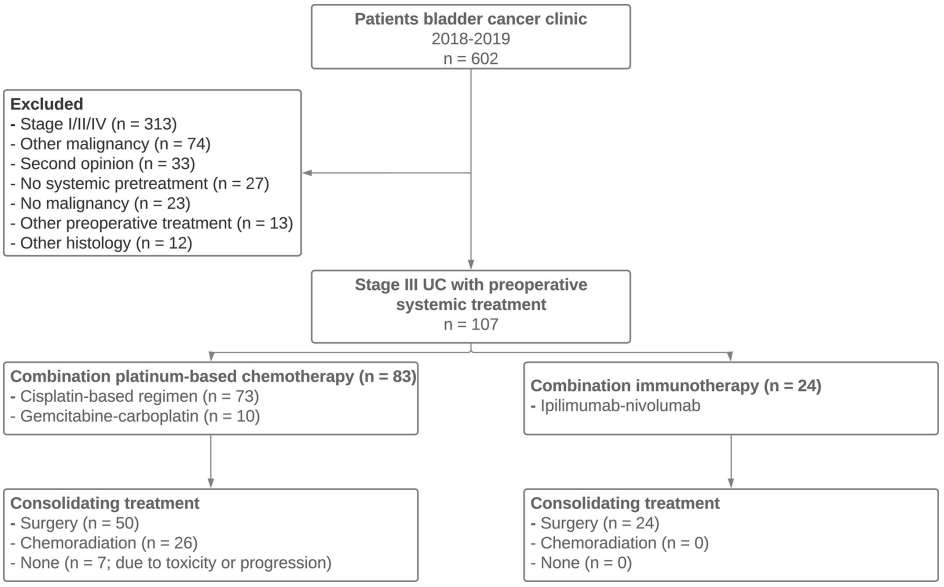


Figure 1. This figure depicts patient selection for the analyses. Patients were included if they had stage III urothelial cancer for which they had received systemic pre-treatment. Other histology included pure sarcoma (n=1), pure adenocarcinoma (n=1), pure squamous cell carcinoma (n=5), pure large cell neuroendocrine carcinoma (n=1), pure small cell carcinoma (n=4). Other pre-treatment included mono-immune checkpoint inhibition in the ABACUS (NCT02662309; n=3) or NIAGARA (NCT03732677; n=7) clinical trials, or radiation (n=3). Abbreviations: UC = urothelial cancer

solidating treatment involved surgery, or chemoradiation in case of response during on-treatment evaluation. Consolidating treatment after cICI consisted of surgery. Surgery consisted of RC or nephro-ureterectomy, both with lymph-node dissection (LND).

Combination chemotherapy

Cisplatin-eligible patients were treated with either 4-6 cycles of gemcitabine (day 1 and 8; 1000mg/m^2) and cisplatin (day 1; 70mg/m^2) in a 21-day cycle, or with 4 cycles of dose-dense methotrexate (day 1; 30mg/m^2), vinblastine (day 2; 3mg/m^2), doxorubicin (day 2; 30mg/m^2) and cisplatin (day 2; 70mg/m^2) (MVAC) in a 14-day cycle. Patients were deemed cisplatin-ineligible in case of poor renal function (GFR <50-60 ml/min), poor performance status (ECOG-PS ≥2), severe (grade ≥2) neuropathy or hearing loss, or heart failure (NYHA-class-III/IV) (8). Cisplatin-ineligible patients were treated with 4-6 cycles of gemcitabine (day 1 and 8; 1000mg/m^2) and carboplatin (gem/carbo) (day 1; 5AUC) in a 21-day cycle.

Combination immune checkpoint inhibition

Patient were offered treatment within the NABUCCO study if considered cisplatin-ineligible or if chemotherapy was refused. Treatment involved combination immunotherapy

with anti-CTLA4 (ipilimumab 3mg/kg on day 1 and 22) and anti-PD1 (nivolumab 1mg/kg and 3mg/kg on day 22 and 43, respectively) followed by surgical resection (7). The recruitment period of the NABUCCO study was between February 2018 and February 2019.

Templates for lymph node dissection

At RC, bilateral pelvic LND was performed according to a standardized template, which included the region between the genitofemoral nerve, the obturator fossa, along the internal iliac artery, including the triangle of Marcille, and along the common iliac artery, up to the crossing of the ureter. Nephro-ureterectomy with unilateral pelvic LND was performed if the primary tumor was located caudal to the crossing of the ureter with the common iliac artery or a left/right template retro-peritoneal LND including the inter aorto-caval nodes was performed if the primary tumor was located cranially to the crossing of the ureter with the common iliac artery.

Treatment regimen for chemoradiation

Chemoradiation consisted of 60Gy administered in 25 fractions of 2.4Gy in a 5-week schedule using volumetric modulated arc therapy (VMAT) or intensity modulated radiotherapy (IMRT). On day 1, mitomycin-C (12 mg/m^2, max 20mg) was administered intravenously. Capecitabine (825 mg/m^2) was administered orally twice per day during the course of radiotherapeutic treatment, excluding weekends (9).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) and R version 1.4.1103 (R Foundation for Statistical Computing, Vienna, Austria). Patients were analyzed in the treatment group they were assigned to in multidisciplinary rounds. Depending on sample size, categorical variables were compared with Chi-square or the Fisher's exact test. Continuous variables with a non-normal distribution were presented as median (interquartile range) and compared with the Kruskal Wallis test. Survival analyses were performed using the Kaplan-Meier method and treatments were compared using the log-rank test. A propensity score-weighted analysis was performed to account for potential selection bias. Specifically, inverse probability of treatment weighting (IPTW)-adjusted Cox proportional hazards analyses were performed. The logistic regression model to determine the predicted probability of receiving either chemo- or immunotherapy included cisplatin-ineligibility and the Charlson Comorbidity Score. A two-tailed value of $p < 0.05$ was considered statistically significant.

RESULTS

In total, 107 patients met the inclusion criteria **(Figure 1)**. Of these, 73 patients received cisplatin-based NAIC and 10 patients received gemcitabine-carboplatin. Gemcitabine-carboplatin was administered to cisplatin-ineligible patients in the induction setting (stage IIIb; n=5) or in the neoadjuvant setting (stage IIIa; n=5; 4 had already started before referral). Patients in the NABUCCO-trial (n=24) were either cisplatin-ineligible (n=13) or refused NAIC (n=11). Patient and tumor characteristics are listed in **Table 1**. Cisplatin-ineligibility was more frequent in cICI than NAIC patients (46% vs 12%, p=0.001). Charlson comorbidity index and ASA score were not statistically significantly different between patients treated with NAIC and cICI (p=0.304 and p=0.325, respectively).

Moreover, clinical tumor and nodal stage were comparable between the groups (p=0.821 and p=0.378, respectively). cICI was discontinued in 6 patients (25%) after 2 cycles due to immune-related adverse events, whereas NAIC was discontinued in 16 patients (19%) due to progression (n=6;7%) and/or toxicity (n=11;13%) (p=0.571). After NAIC, 50 (60%) and 26 patients (31%) underwent surgery and chemoradiation, respectively. In total, 7 NAIC-patients (8%) did not undergo consolidating treatment due to either progression (n=5;6%) or toxicity (n=2;2%), whereas all cICI-patients underwent consolidating surgical treatment (p=0.345). Surgical characteristics including approach and urinary diversion were not statistically significantly different between groups **(Table 1)**. Within the NAIC cohort, type of consolidating treatment (surgery or chemoradiation) did not significantly impact on survival (p=0.091) as chemoradiation was generally offered to patients having a response to NAIC.

After surgery (n=74), complete pathological response (pCR; ypT0N0) was achieved by 11 (22%) NAIC-patients and 11 (46%) cICI-patients (p=0.056). Complete pathological downstaging (pCD; ≤ypT1N0) was achieved by 17 (35%) NAIC-patients and 14 (58%) cICI-patients (p=0.077). Median (IQR) follow-up from start of neoadjuvant treatment was 26 (20-32) months. Median (IQR) follow-up of the NAIC- and cICI-cohorts were 25 (19-33) months and 28 (24-32) months, respectively. The cut-off data for follow-up was January 31st 2021.

UC progressed in 37 (45%) NAIC-patients and 2 (8%) cICI-patients (p=0.001). Cause of death was UC in all but two NAIC-patients (out-of-hospital cardiac-arrest and cerebral-vascular accident). **Figure 2a-b** shows the Kaplan-Meier curves for overall survival (OS) and progression-free survival (on-treatment progression or recurrence; PFS) stratified by type of neoadjuvant treatment. Both PFS and OS were significantly longer in patients pretreated with cICI (both log rank tests p=0.003). Both PFS and OS remained significantly

Table 1. Patient, tumor and treatment characteristics of patients with stage III urothelial cancer included in this present study (n=107).

	Platinum-based Chemotherapy (NAIC) (n=83)	**Immune Checkpoint Inhibition (ICI) (n=24)**	**p-value**	**95% Confidence Interval**
Age (median, IQR)	66 (58-71)	67 (63-73)	0.145	
Sex, male (n, %)	56 (68)	18 (75)	0.618	
Cisplatin-ineligible (n, %)	10 (12)	13 (54)	<0.001	
Charlson Comorbidity Index (n, %)			0.304	
0-2	42 (51)	10 (42)		
3-5	39 (47)	12 (50)		
≥6	2 (2)	2 (8)		
ASA score (n, %)			0.325	
1	17 (28)	4 (17)		
2	25 (56)	18 (75)		
3	10 (16)	2 (8)		
Renal function				
eGFR, MDRD, ml/min/1.73m2 (median, IQR)	75 (62-85)	74 (50-90)	0.466	
Creatinine, µmol/l (median, IQR)	85 (69-101)	86 (72-122)	0.505	
Hydronephrosis (n, %)	21 (25)	10 (42)	0.132	
Setting (n, %)			1	
Neoadjuvant (T3-4aN0M0)	49 (59)	14 (58)		
Induction (T1-4aN+M0)	34 (41)	10 (42)		
cT-stage (n, %)			0.821	
1	3 (4)	0 (0)		
2	8 (10)	1 (4)		
3	58 (70)	18 (75)		
4	14 (17)	5 (21)		
cN -stage (n, %)			0.378	
0	49 (59)	14 (58)		
1	22 (27)	4 (17)		
2	12 (15)	6 (25)		
Location			0.537	
Bladder	81 (98)	23 (96)		
Upper tract	2 (2)	1 (4)		
Histology (n, %)			0.68	
UC	75 (90)	23 (96)		
UC with variants	8 (10)	1 (4)		
Concomitant CIS (n, %)	7 (8)	5 (21)	0.135	

Table 1. Patient, tumor and treatment characteristics of patients with stage III urothelial cancer included in this present study (n=107). *Continued*

	Platinum-based Chemotherapy (NAIC) (n=83)	Immune Checkpoint Inhibition (ICI) (n=24)	p-value	95% Confidence Interval
Type of systemic pre-treatment (n, %)				
Gemcitabine-Cisplatin	61 (73)	n.a.		
ddMVAC	12 (14)	n.a.		
Gemcitabine-Carboplatin	10 (12)	n.a.		
Ipilimumab-Nivolumab	n.a.	24 (100)		
Treatment cycles (n, %)				
2	3 (4)	6 (25)		
3	6 (7)	18 (75)		
4	61 (74)	n.a.		
5	1 (1)	n.a.		
6	12 (15)	n.a.		
Switch to another regimen (yes)[b]	8 (10)	0 (0)	0.194	
Discontinuation (any reason) (n, %)[c]	16 (19)	6 (25)	0.571	
Toxicity (n, %)	11 (13)	6 (25)	0.205	
On-treatment progression (n, %)	6 (7)	0 (0)	0.334	
Consolidating treatment (n, %)			0.345	
No (progression/toxicity)	7 (8)	0 (0)		
Surgery	50 (60)	24 (100)		
Chemoradiation	26 (31)	0 (0)		
Surgery (n, %)[d]			0.858	
Not done	1 (2)	0 (0)		
Radical cystectomy	46 (92)	22 (92)		
Total exenteration	1 (2)	1 (4)		
Nephro-ureterectomy	2 (4)	1 (4)		
Surgical approach			0.469	
Open	25 (50)	12 (50)		
Robotic	25 (50)	11 (46)		
Laparoscopic	0 (0)	1 (4)		
Urinary Diversion (n, %)[d]			1	
Not done	1 (2)	0 (0)		
Orthotopic neobladder (Studer)	6 (13)	3 (13)		
Ileal conduit (Bricker)	39 (81)	20 (87)		
Continent pouch (Indiana)	1 (2)	0 (0)		
Ureterocutaneostomy	1 (2)	0 (0)		
Nodes removed (median, IQR)[e]	22 (15-28)	27 (15-33)	0.184	
Positive Surgical Margins (n, %)[e]	6 (12)	1 (4)	0.416	

Table 1. Patient, tumor and treatment characteristics of patients with stage III urothelial cancer included in this present study (n=107). *Continued*

	Platinum-based Chemotherapy (NAIC) (n=83)	Immune Checkpoint Inhibition (ICI) (n=24)	p-value	95% Confidence Interval
ypT-stage (n, %)[e]			0.311	
0	13 (26)	13 (54)		
cis	5 (10)	2 (8)		
a	0 (0)	1 (4)		
1	2 (4)	0 (0)		
2a	0 (0)	0 (0)		
2b	8 (16)	2 (8)		
3a	6 (12)	2 (8)		
3b	7 (14)	3 (13)		
4a	8 (16)	1 (4)		
X	1 (2)	0 (0)		
ypN-stage (n, %)[e]			0.172	
0	36 (66)	16 (67)		
1	7 (13)	5 (21)		
2	12 (21)	2 (8)		
3	0 (0)	1 (4)		
Pathological outcome (n, %)[e]				
pCR (ypT0N0)	11 (22)	11 (46)	0.056	0.10-1.08
pCD (≤ypT1/is/aN0)	17 (35)	14 (58)	0.077	0.12-1.12
Progression (n, %)	37 (45)	2 (8)	0.001	0.015-0.62

NOTE: Except for cisplatin-ineligibility, there were no statistically significant differences in patient, tumor and treatment characteristics between neoadjuvant/induction platinum-based combination chemotherapy and pre-treatment with immune checkpoint inhibition. Pathological outcomes for tended to be in favor of pre-treatment with immune checkpoint inhibition. Recurrence after consolidating treatment was more frequent in patients pre-treated with neoadjuvant/induction chemotherapy.

a. For NAIC: urothelial cancer with ≤5% small cell differentiation (2), plasmacytoid differentiation (1), sarcomatoid differentiation (2), squamous differentiation (1), poorly differentiated (1), lymphoepithelioma-like variant (1). *For ICI*: urothelial cancer with squamous differentiation (1)

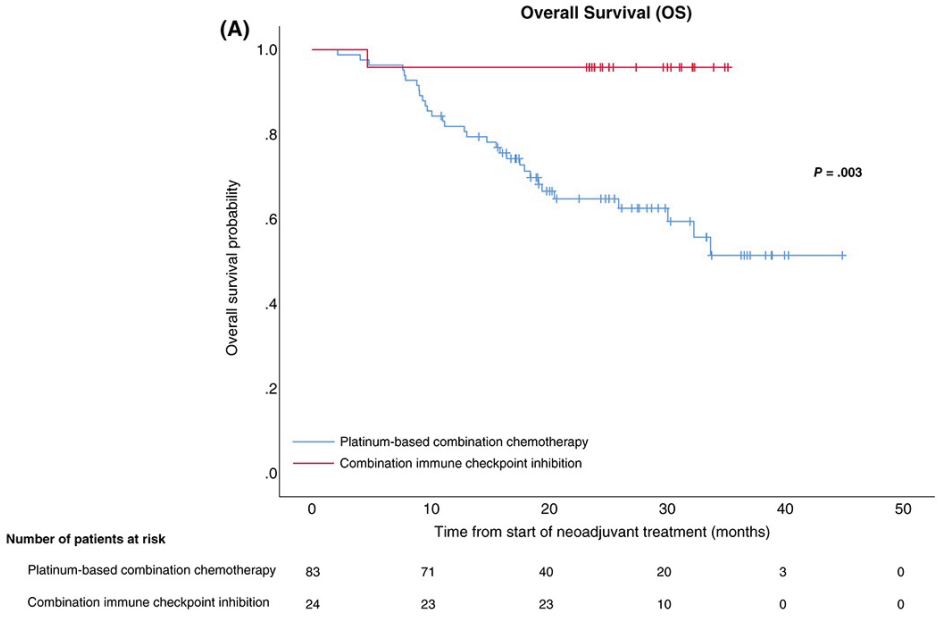
b. Switch from a cisplatin-based regimen to gemcitabine-carboplatin (n=6) and vice versa (n=2) due to decreased or improved renal function, respectively

c. Please note that the numbers for discontinuation of NAIC do not add up because NAIC was discontinued in one patient due to both progression and toxicity

d. Peroperative inoperable tumor, only lymph node dissection

e. Analysis of all patients who underwent surgery

Abbreviations: ASA = American Society of Anesthesiologists; CIS = carcinoma in situ; cN-stage = clinical nodal stage; cT-stage = clinical tumor stage; ddMVAC = dose dense methotrexate, vinblastine, doxorubicine, cisplatin; eGFR = estimated glomerular filtration rate; IQR = interquartile range; n.a. = not applicable; pCD = complete pathological downstaging; pCR = complete pathological response; ypN-stage = pathological nodal stage; ypT-stage = pathological tumor stage; UC = urothelial carcinoma



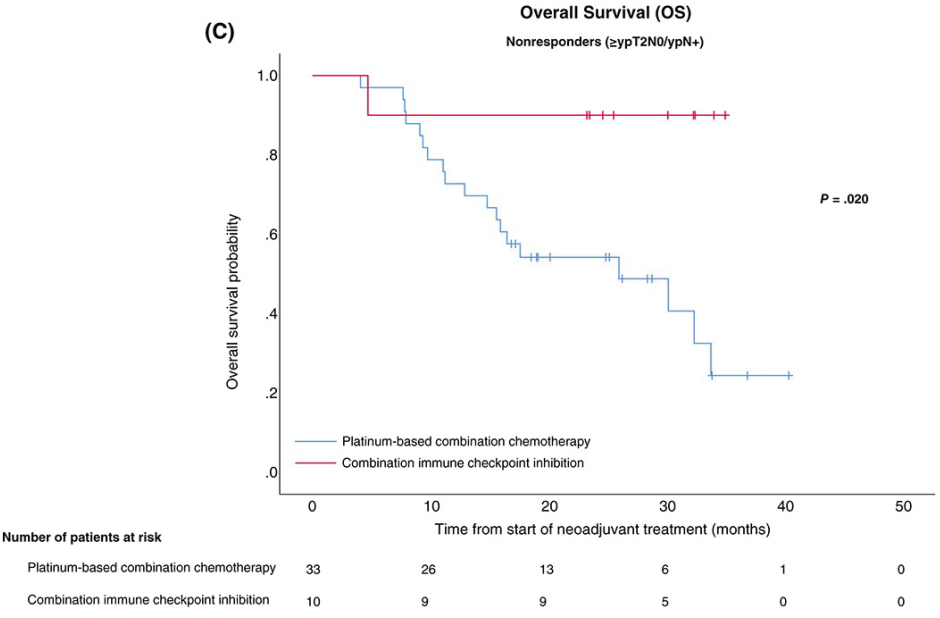
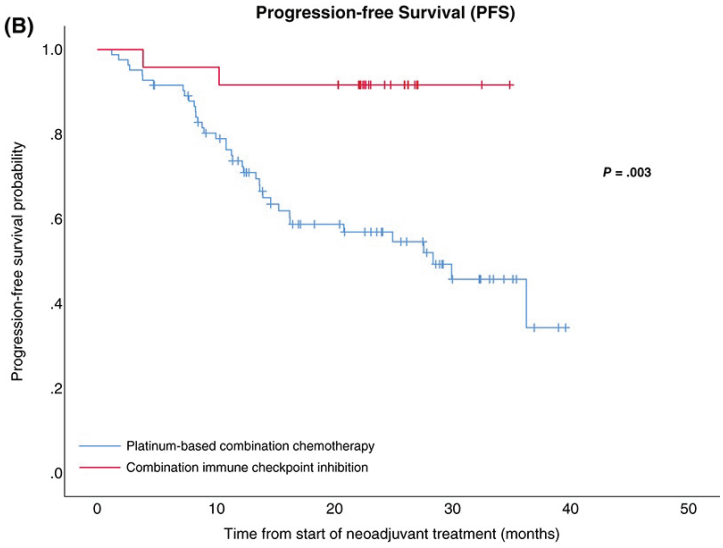
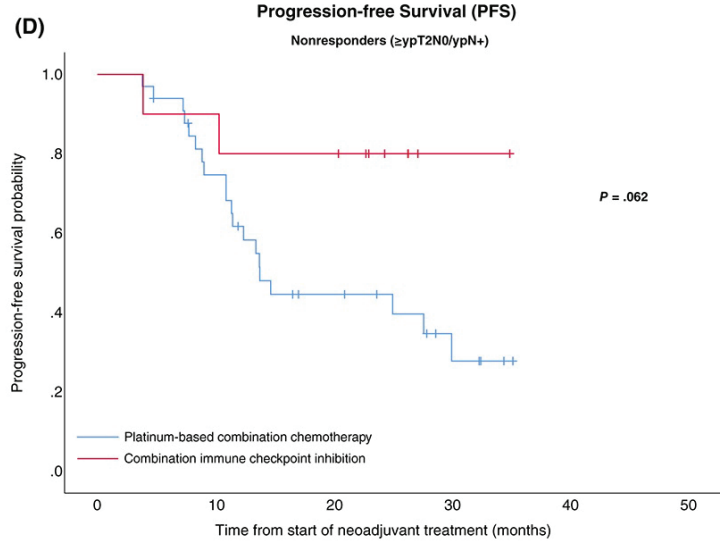


Figure 2. Progression-free survival (2A) and overall survival (2B) in the entire population were statistically significantly in favor of patients who received neoadjuvant/induction combination immune checkpoint inhibition compared to platinum-based chemotherapy (both p-log-rank=0.003). In a subanalysis of non-responders (≥ypT2N0 or ypTanyN+), progression-free survival (2C) showed a borderline statistically significant difference in favor of patients treated with neoadjuvant/induction combination immune checkpoint inhibition (p-log-rank=0.062). Overall survival of non-responders (2D) was statistically significantly in favor of patients who received neoadjuvant/induction immune checkpoint inhibition (p-log-rank=0.020).



Number of patients at risk

Platinum-based combination chemotherapy	83	62	33	14	0	0
Combination immune checkpoint inhibition	24	23	22	2	0	0



Number of patients at risk

Platinum-based comination chemotherapy	33	23	11	5	0	0
Combination immune checkpoint inhibition	10	9	8	1	0	0

longer for patients pretreated with cICI using IPTW-adjusted Cox proportional hazards models (Hazard Ratio (HR): 0.08; 95% CI 0.018-0.36; p=0.001 and HR: 0.05; 95% CI 0.007-0.41; p=0.005, respectively; **Suppl. Table 1**). Of note, OS and PFS were also significantly longer in patients treated with cICI compared to patients treated with cisplatin-based NAIC (log rank test p=0.004 and log rank test p=0.006, respectively; **Suppl. Figure 1A-B**).

In a sub-analysis of only RC-patients, PFS and OS were significantly longer in patients treated with cICI compared to patients treated with cisplatin-based NAIC (log rank test p=0.002 and log rank test p=0.001, respectively; **Suppl. Figure 2A-B**). Finally, a sub-analysis of cystectomy-patients who have finished the complete treatment regimen showed that PFS and OS were significantly longer in patients treated with cICI compared to NAIC (log rank test p=0.006 and log rank test p=0.005, respectively; **Suppl. Figure 3A-B**). All patients with pCR at surgery were alive and progression-free. All patients with pCD were alive, while recurrence occurred in 2 NAIC-patients with pCD vs. 0 cICI-patients with pCD. In the non-responders (i.e. ≥ypT2N0 and/or ypN+) at surgery, OS was (log rank test p=0.02) and PFS was borderline statistically significantly (log rank test p=0.062) longer in patients treated with cICI **(Figure 2c-d)**.

DISCUSSION

Despite maximum treatment with cisplatinum-based chemotherapy and surgical resection, clinical outcomes of patients with stage III UC remains poor. Hence, there is an unmet need for novel systemic treatment strategies. Our study showed superior survival of patients with stage III UC pretreated with cICI compared to NAIC. Importantly, subanalyses in which the NAIC-group was limited to patients with a cisplatin-based regime and/or only RC-patients showed that both PFS and OS were superior in patients pretreated with cICI.

High rates of (36-46%) of micro-metastatic spread in patients with locally advanced disease suggests that local treatment alone provides insufficient clinical benefit[10]. Due to lack of data for carboplatin-based regimens, upfront RC is currently recommended in cisplatin-ineligible patients with stage IIIa UC (11). For stage IIIb UC, there is a lack of solid data to guide treatment. A response to systemic pretreatment with a carboplatin-based regimen is considered necessary to proceed to consolidating treatment. Although generally considered less effective than cisplatin-based regimens, carboplatin-based therapy in cisplatin-ineligible patients with stage IIIb UC is acceptable and incorporated in guidelines (11). Despite not being standard practice, carboplatin-based NAIC was given to 5 stage IIIa patients; most of these treatments were initiated in referral centers.

Given the results of the present comparative study on NAIC and cICI, we believe that immunotherapy, and especially cICI, represents a promising alternative systemic pre-treatment for cisplatin-(in)eligible patients.

Pathological response rates after surgery tended to be in favor of cICI pretreatment although statistical significance was not reached in these relatively small cohorts. All patients with pCR or pCD were alive irrespective of pretreatment group. Interestingly, we found a relatively favorable survival of cICI compared to NAIC for patients with residual muscle invasive and/or node positive disease after consolidating treatment. Consequently, our results suggest that survival benefit from cICI is not restricted to the (complete) responders. Previous reports on cisplatin-based NAIC have shown that 5-year OS of patients with pCR was high (80-90%) and only approximately 45% for patients with residual muscle invasive disease (12,13).

Our findings have to be interpreted within the limitations of the study design, which did not include a randomization procedure. However, propensity score-weighted analyses were performed to account for potential selection bias and results on favorable PFS and OS after cICI remained comparable to the survival analyses with the log rank test. Moreover, the patients were recruited from the same institutional bladder cancer clinic within the same timeframe and underwent uniform staging. More patients in the NABUCCO-trial were cisplatin-ineligible and other important prognostic factors such as comorbidities and tumor characteristics were not different between treatment groups. Although consolidating treatment after NAIC and cICI differed, this factor was not associated with survival as chemoradiation was generally offered to responding patients. The heterogeneous cohort of patients with UC in the bladder as well as the upper tract represents another limitation, although these patients were evenly distributed between treatment groups. Finally, cisplatin-ineligible patients were included in the NAIC-cohort and treated with gemcitabine-carboplatin. This may not be guideline-treatment in the pre-operative setting but represents real-world practice and results on survival were still in favor of cICI if we only considered cisplatin-treated patients who underwent RC.

In conclusion, this study represents the first to compare clinical outcomes of NAIC and cICI. Pathological response rates were higher in patients treated with cICI, although this difference did not reach statistical significance. Moreover, our data suggested superior survival of cICI in non-responders compared to NAIC. Although the retrospective nature of this study only allows for tentative conclusions, our results suggest that cICI is associated with improved survival compared to NAIC. Our findings provide a compelling rationale for validation of preoperative cICI for stage III UC in a comparative phase-3 study.

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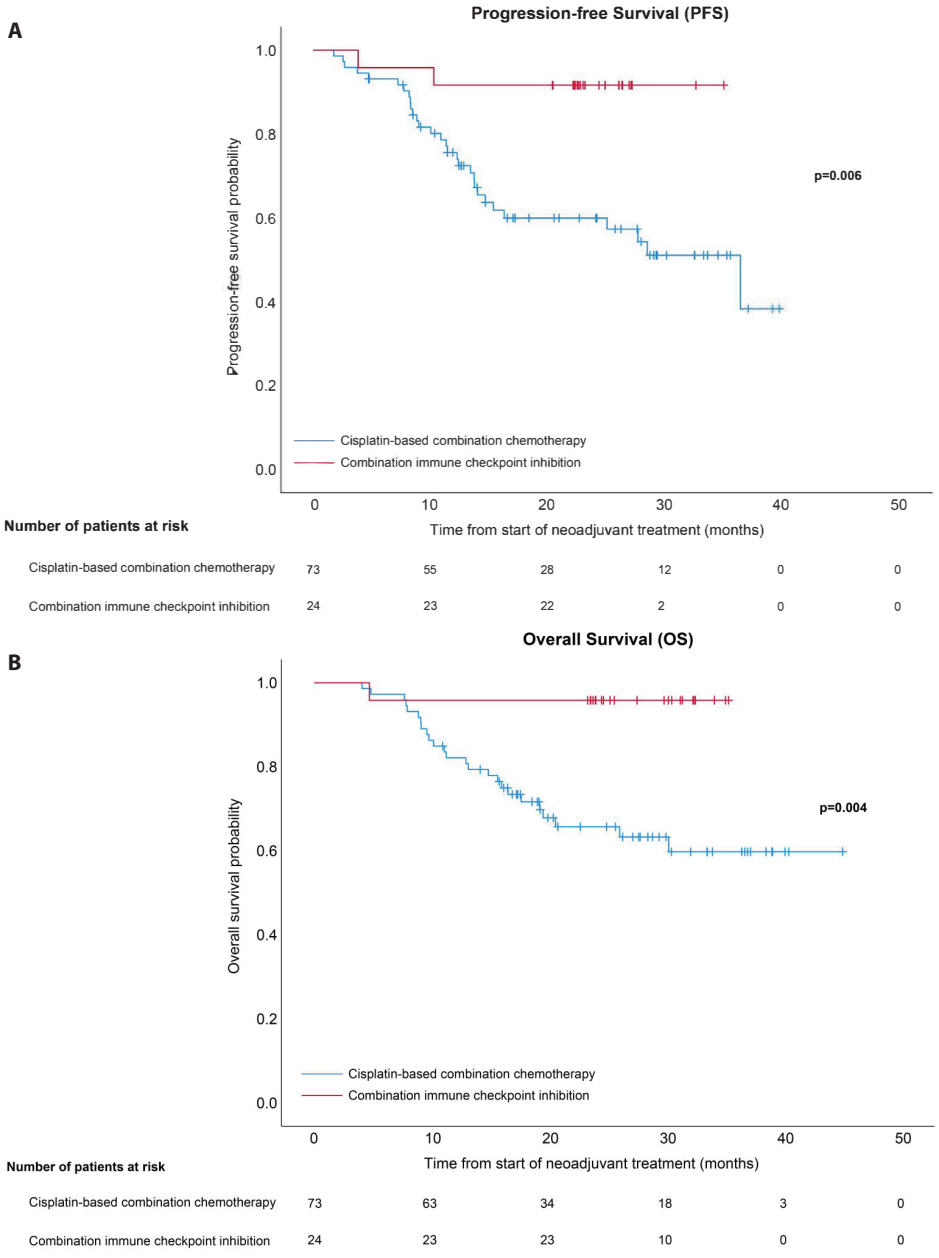
SUPPLEMENTARY MATERIAL

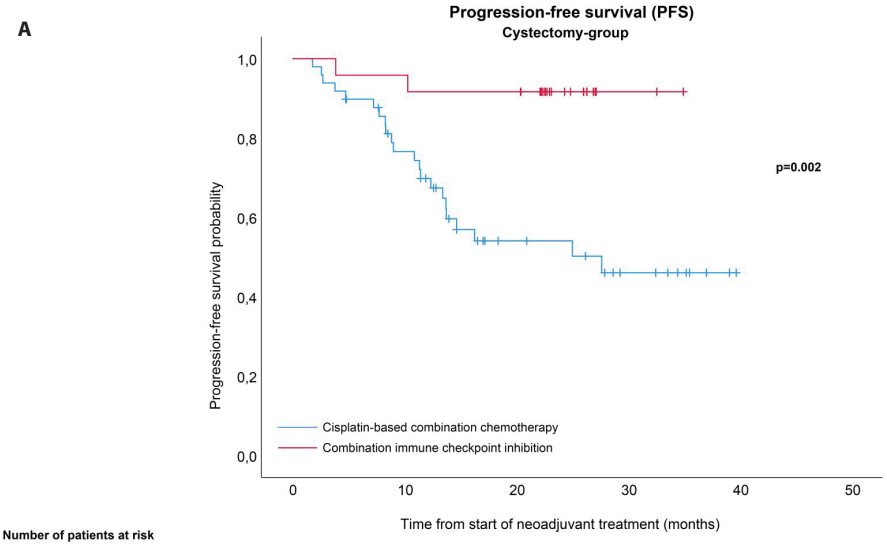
Table S1. Propensity-weighted cox regression model for overall and progression-free survival.

Variable	Cox regression analysis	
	Hazard Ratio (95% CI)	**p-value**
Progression-free Survival		
Neoadjuvant treatment		
Platinum-based chemotherapy	1	
Combination immunotherapy	0.08 (0.018-0.36)	0.001
Overall Survival		
Neoadjuvant treatment		
Platinum-based chemotherapy	1	
Combination immunotherapy	0.05 (0.007-0.41)	0.005

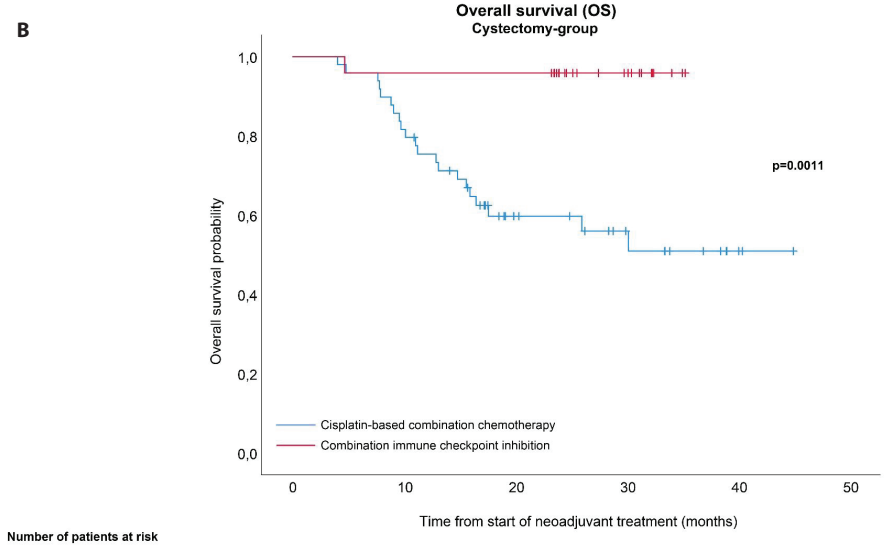
The logistic regression models to determine the predicted probability of receiving either chemo- or immunotherapy included cisplatin-ineligibility and the Charlson Comorbidity Index as important prognostic factors. This table shows that survival remains superior in patients treated with combination immunotherapy after accounting for lack of randomization and possible imbalance between the treatment groups.



Supplementary Figure 1 – Survival for cisplatin-based regimen versus immune checkpoint inhibition. Progression-free and overall survival of patients pretreated with neoadjuvant/induction cisplatin based chemotherapy versus combination immune checkpoint inhibition. **A.** Progression-free survival was statistically significant in favor of patients treated with combination immune checkpoint inhibition compared to patients treated with a cisplatin-based neoadjuvant regime (p-log-rank=0.006). **B.** Overall survival was statistically significant in favor of patients treated with combination immune checkpoint inhibition compared to patients treated with a cisplatin-based neoadjuvant regime (P-log-rank=0.004).

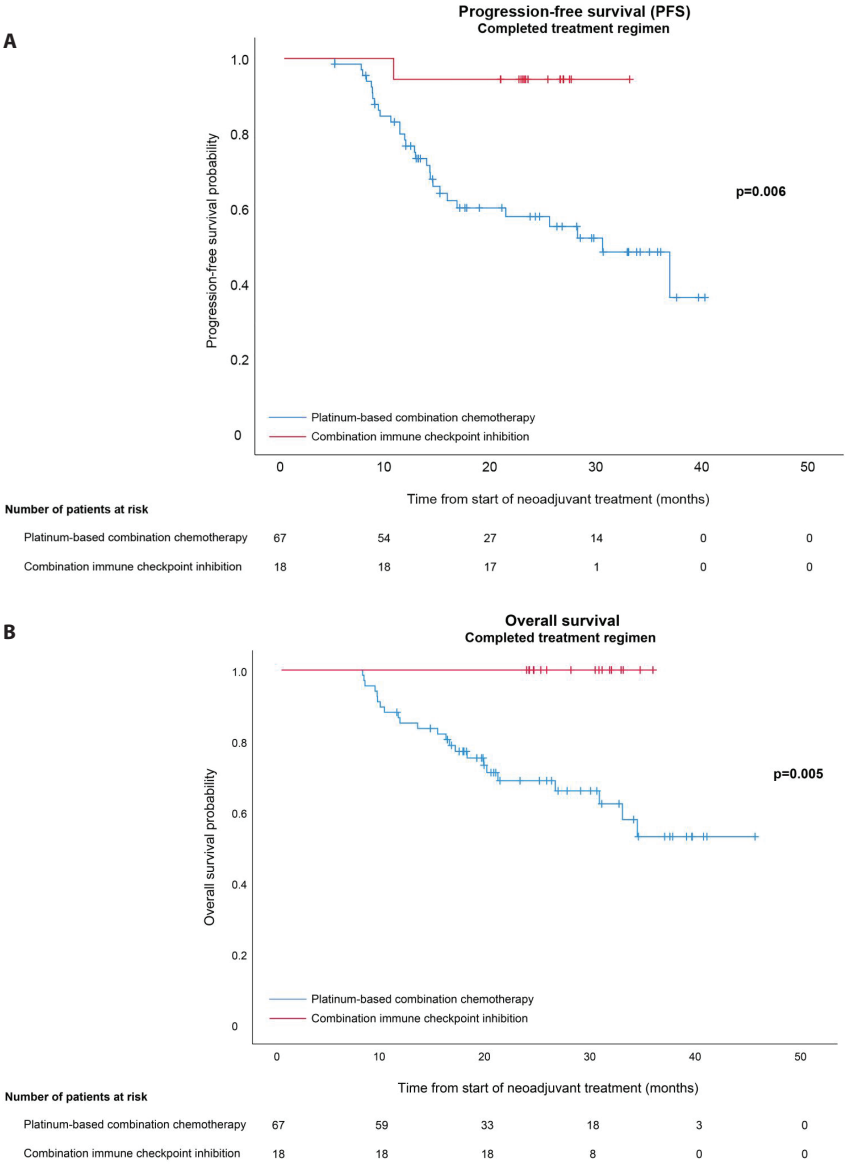


Number of patients at risk						
Cisplatin-based combination chemotherapy	49	34	15	8	0	0
Combination immune checkpoint inhibition	24	23	22	2	0	0



Number of patients at risk						
Cisplatin-based combination chemotherapy	49	40	18	11	3	0
Combination immune checkpoint inhibition	24	23	22	2	0	0

Supplementary Figure 2 - Survival cisplatin-based NAIC vs cICI in patients undergoing cystectomy. Progression-free and overall survival of patients pretreated with neoadjuvant/induction cisplatin based chemotherapy versus combination immune checkpoint inhibition followed by RC. **A.** Progression-free survival was statistically significant in favor of cystectomy-patients treated with combination immune checkpoint inhibition compared to patients treated with a cisplatin-based neoadjuvant regime (p-log-rank=0.002). **B.** Overall survival was statistically significant in favor of cystectomy-patients treated with combination immune checkpoint inhibition compared to patients treated with a cisplatin-based neoadjuvant regime (P-log-rank=0.0011).



Supplementary Figure 3 - Survival cisplatin-based NAIC vs cICI in patients with completed treatment. Progression-free and overall survival of patients who completed the pre-treatment regimen with neoadjuvant/induction cisplatin-based chemotherapy versus combination immune checkpoint inhibition. Patients who discontinued treatment were excluded from this analysis. **A.** Progression-free survival was statistically significant in favor of patients treated with a completed regimen of combination immune checkpoint inhibition compared to patients treated with a completed regimen of neoadjuvant or induction chemotherapy (P-log-rank=0.006). **B.** Overall survival was statistically significant in favor of patients treated with a completed regimen of combination immune checkpoint inhibition compared to patients treated with a completed regimen of neoadjuvant or induction chemotherapy (P-log-rank=0.005).