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Original research

Final clinical analysis of pre-operative ipilimumab and nivolumab in locally advanced urothelial cancer and exploration of tumor-draining lymph node composition: The NABUCCO trial

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ABSTRACT

Background: Pre-operative immune checkpoint blockade (ICB) with ipilimumab and nivolumab has shown encouraging pathological complete response (pCR) rates in stage III urothelial cancer (UC). A previous analysis of NABUCCO suggested that ipilimumab 3 mg/kg is more effective than ipilimumab 1 mg/kg. However, long-term progression-free and overall survival (PFS, OS) following pre-operative combination ICB are unknown.

Methods: In NABUCCO, 54 patients received pre-operative ipilimumab plus nivolumab in different dosing regimens. PFS and OS were determined for the entire NABUCCO population and various clinically relevant subgroups. We explored ICB effects on the cellular composition of tumor-draining lymph nodes (tdLN) from ICB-treated patients (n = 5) and untreated or chemotherapy-treated patients (n = 5) using multiplex immunofluorescence for the PhenoCycler Fusion (Akoya).

Results: With a median follow-up of 70 months, PFS and OS at 60 months were 67 % and 70 %, respectively, for the entire study. PFS and OS at 60 months were similar for patients with residual non-muscle invasive UC (NMIBC) and patients with a pCR. The presence of a nodal micrometastasis (<2 mm) after ICB, the development of grade ≥ 3 immune-related adverse events (irAE) and corticosteroids or antibiotics did not negatively impact survival. We observed smaller distances from $CD20^+$ cells to $CD14^+$ cells in tdLN following ICB compared to tdLN from untreated or chemotherapy-treated patients.

Conclusions: Our data demonstrate a 5-year PFS of 67 % and OS of 70 % after pre-operative ICB in stage III UC. Survival was not impaired for patients with residual NMIBC, a nodal micrometastasis at resection, grade ≥ 3 irAE or corticosteroid use.

Clinical trial registration number: NCT03387761

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1. Introduction

The standard of care for muscle-invasive urothelial cancer (UC) is pre-operative platinum-based chemotherapy, which results in an overall survival (OS) benefit of only 5–8 % [1]. Given that more than 50 % of patients are ineligible for platinum-based chemotherapy due to comorbidities [2], there is an unmet need to improve systemic treatment in patients with locally advanced UC.

The inhibition of immune checkpoints such as PD-(L)1 and CTLA-4 has shown anti-tumor activity in advanced UC [3–6]. In the pre-operative setting, immune checkpoint blockade (ICB) showed encouraging response rates with anti-PD-(L)1 as monotherapy [7, 8] or combined with CTLA-4 blockade [9]. In the NABUCCO trial, 54 locally advanced UC patients were treated with pre-operative ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) [10, 11]. In the first NABUCCO cohort [10], a single-arm study with 24 patients, we established the feasibility of three sequential cycles of pre-operative nivolumab plus ipilimumab [10]. Based on a pathological complete response (pCR; ypT0N0) rate of 46 % and the development of grade ≥ 3 immune-related adverse events (irAE) in 55 % of the patients [10], two different ipilimumab dosing regimens (3 mg/kg (arm 2A) and 1 mg/kg (arm 2B)) were evaluated in an extension cohort to identify the most optimal dosing [11]. Although grade ≥ 3 toxicity was observed less frequently following ipilimumab 1 mg/kg, efficacy diminished as reflected by a pCR rate of 7 % following ipilimumab 1 mg/kg versus 45 % following ipilimumab 3 mg/kg [11].

In contrast to previous reports, which mainly focused on pCR, we here describe long-term clinical outcome following pre-operative ipilimumab and nivolumab in NABUCCO and explore various clinically relevant subgroups.

2. Methods

2.1. Study treatment

The NABUCCO trial is an investigator-initiated phase 1b trial (NCT03387761) evaluating pre-operative ipilimumab and nivolumab in different dosing schedules (Supplementary Figure 1)[10, 11]. In- and exclusion criteria were identical for both cohorts and were reported previously [10]. NABUCCO was executed following the Code of Ethics of the World Medical Association (Declaration of Helsinki). All included patients provided written informed consent before any study procedures. All procedures complied with relevant laws and institutional guidelines and have been approved by the appropriate institutional committee (NL62511.031.17; Irbm20–339 2–6–2023; CFMPB664 25–11–2021).

2.2. Subgroup analyses

2.2.1. PD-L1 positivity, toxicity and concomitant medication

Baseline tumor tissue was stained for PD-L1 (22C3) and the combined positivity score (CPS) and tumor proportion score (TPS) were determined by an experienced uro-pathologist (MLvM) according to standard methods [12, 13]. IrAE were graded using the Common Terminology Criteria for Adverse Events v4. For the survival analysis for patients treated with and without corticosteroids and antibiotics, we chose a window from 14 and 30 days before ICB initiation (respectively) until resection [14, 15].

2.3. Lymph node analysis

To explore the potential effects of ICB on tumor-draining lymph nodes (tdLN), we used lymph nodes with a nodal micrometastasis (< 2 mm) obtained at resection from five patients who received pre-operative ICB. As a comparison, we identified five patients with a nodal micrometastasis who were naïve for systemic treatment or treated with neoadjuvant platinum-based chemotherapy. None of these patients received systemic corticosteroids. We made a tissue microarray (TMA) with 1 mm cores containing the micrometastatic area of the various tdLN. Subsequently, the TMA was stained with a 26-plex customized immune panel using conjugated antibodies (Akoya) for the PhenoCycler Fusion (Akoya). Next, we performed cell segmentation and classification to retrieve cell fractions and distances between cells. A more detailed description of our lymph node analysis is depicted in Supplementary Table 1.

2.4. Statistical considerations

The clinical cut-off date was January 10, 2025. Median follow-up was calculated using the reverse Kaplan-Meier method. Progression-free survival (PFS) and OS were determined using the Kaplan-Meier method. PFS was defined as the time from the first ICB infusion until disease progression - determined based on radiological or pathological assessment - or death, whichever came first. Patients without disease progression were censored at their last clinical visit or telephone consultation. In an additional PFS analysis of the entire cohort, patients who received adjuvant therapy were censored at the start of adjuvant treatment. OS was defined as the time from the first ICB infusion until death from any cause. Patients who were still alive at the cut-off date were censored at the date of their last clinical visit or telephone consultation. The log-rank test was applied to compare independent survival curves. We applied the Holm-Bonferroni correction for multiple testing when we had multiple comparisons for the same endpoint. R version 4.4.0 was used for the statistical analyses.

3. Results

From 2018–2021, 54 patients with locally advanced UC were treated with pre-operative ipilimumab and nivolumab in NABUCCO (Supplementary Figure 1). The median follow-up time was 70 months (95 % confidence interval 63.7 – 78.3). By the end of the study, 19 out of 54 evaluable patients (35 %) had a PFS event: 12 patients developed progressive disease, and seven patients without disease progression died. 17 out of 54 patients (32 %) had an OS event. Median PFS and OS were not reached. At 60 months, PFS and OS were 67 % and 70 % respectively (Figure 1a-b). Five patients received adjuvant platinum-based chemotherapy. PFS at 60 months was 68 % when these patients were censored (Supplementary Figure 2).

Among the three patients who refused surgical resection and were without radiological evidence of progression following pre-operative ICB, one patient experienced disease progression during the follow-up period. There was one patient among those who achieved a pCR at resection who developed progressive disease during follow-up, and two patients with a pCR died without recurrent disease during the follow-up period.

As the risk of progressive disease for patients with high-grade non-muscle invasive bladder cancer (NMIBC) is low [16], we hypothesized that NABUCCO patients with residual NMIBC at resection might achieve similar long-term survival rates as NABUCCO patients with a pCR. PFS was not the same across pathological stage groups (Figure 1c; $p = 0.004$). When comparing between pathological stage groups directly (adjusted for multiple testing), we observed similar PFS-rates for patients with a pCR (ypT0N0) vs. node-negative NMIBC (p-adjusted = 0.31), whereas patients with residual MIBC or node-positive disease (ypT2–4aNx or ypTxN1–3) had worse PFS (pCR vs. MIBC/node-positive p-adjusted = 0.04 and NMIBC vs. MIBC/node-positive p-adjusted = 0.04). Similarly, for OS we also observed survival curves for pCR, NMIBC and MIBC/node-positive to be significantly different (Figure 1d, $p = 0.02$). However, when making individual comparisons (adjusted for multiple testing), OS was not significantly better in patients with a pCR or residual NMIBC than in patients with residual MIBC/node-positive disease (pCR vs.

MIBC/node-positive; p-adjusted = 0.08 and NMIBC vs. MIBC/node-positive; p-adjusted = 0.07).

3.1. Clinical outcome in subgroups based on ipilimumab-dosing and PD-L1 positivity

In NABUCCO, three dosing regimens of ipilimumab and nivolumab were studied to find the optimal balance between efficacy and toxicity. In a previous analysis, we observed that pCR rates were superior in the ipilimumab 3 mg/kg arms (arm 1: 46 %; arm 2A: 43 %) compared to ipilimumab 1 mg/kg (arm 2B: 7 %)[11]. Here, we examined long-term survival for the different treatment arms. Although the treatment regimens in arm 1 and arm 2A were similar, PFS and OS appeared more favorable in arm 1 (PFS arm 1 vs. 2A p-adjusted = 0.09; OS arm 1 vs. 2A p-adjusted = 0.04; Figure 2a-b). Clinical outcome in arm 2B (ipilimumab 1 mg/kg) was similar to arm 2A (ipilimumab 3 mg/kg; PFS arm 2A vs. 2B p-adjusted = 0.91; OS arm 2A vs. 2B p-adjusted = 0.8).

PD-L1 has been extensively studied as a potential biomarker for ICB response [7, 13]. In a prior analysis of NABUCCO cohort 1, we observed numerically higher response rates in PD-L1 + tumors according to CPS, but this result was not statistically significant, probably due to the low sample size [10]. We now assessed long-term survival in PD-L1 CPS and TPS subgroups for the entire NABUCCO population. Similar to the results from our previous analysis in cohort 1, we did not observe a statistically significant difference in PFS and OS for PD-L1 subgroups in the entire NABUCCO population (p = 0.17 (CPS) and p = 0.21 (TPS) for PFS; p = 0.23 (CPS) and p = 0.12 (TPS) for OS; Figure 2c-f).

3.2. The effect of severe immune-related toxicity and concomitant medication on long-term survival

In NABUCCO, the incidence of grade ≥ 3 irAE was substantial, especially in the ipilimumab 3 mg/kg cohorts (55 % (arm 1) and 33 % (arm 2A)) versus the ipilimumab 1 mg/kg cohort (20 % (arm 2B)) [11]. The majority of patients had grade 3 irAE, and six patients developed grade 4 irAE. No grade 5 irAE were observed. The most common grade ≥ 3 irAE in all arms were laboratory abnormalities and diarrhea [11]. In previous studies, high-grade irAE were reported to correlate with tumor regression [17]. We evaluated the effect of severe irAE on long-term survival in NABUCCO and observed a trend towards better PFS (p = 0.08) and OS (p = 0.06) for patients who developed grade ≥ 3 irAE (Figure 3a-b). No difference in PFS and OS was observed comparing patients with < grade 3, grade 3 and grade 4 irAE (Supplementary Figure 3). Most high-grade irAE in NABUCCO were treated with corticosteroids. Given that corticosteroids could dampen the anti-cancer immune response because of their immunosuppressive effects [18], we assessed if the use of corticosteroids (prednisone > 10 mg equivalent) between 14 days prior to ICB initiation and resection affected long-term clinical outcome by comparing PFS and OS for patients who did and did not use corticosteroids during this time frame. We observed similar PFS (p = 0.6) and OS (p = 0.92) for patients who did and did not receive corticosteroids in the neo-adjuvant period Figure 3c-d).

There is increasing evidence for crosstalk between the intestinal microbiome and the anti-cancer immune response [19]. As antibiotics cause a disbalance of the gut microbiome, they are suggested to impair

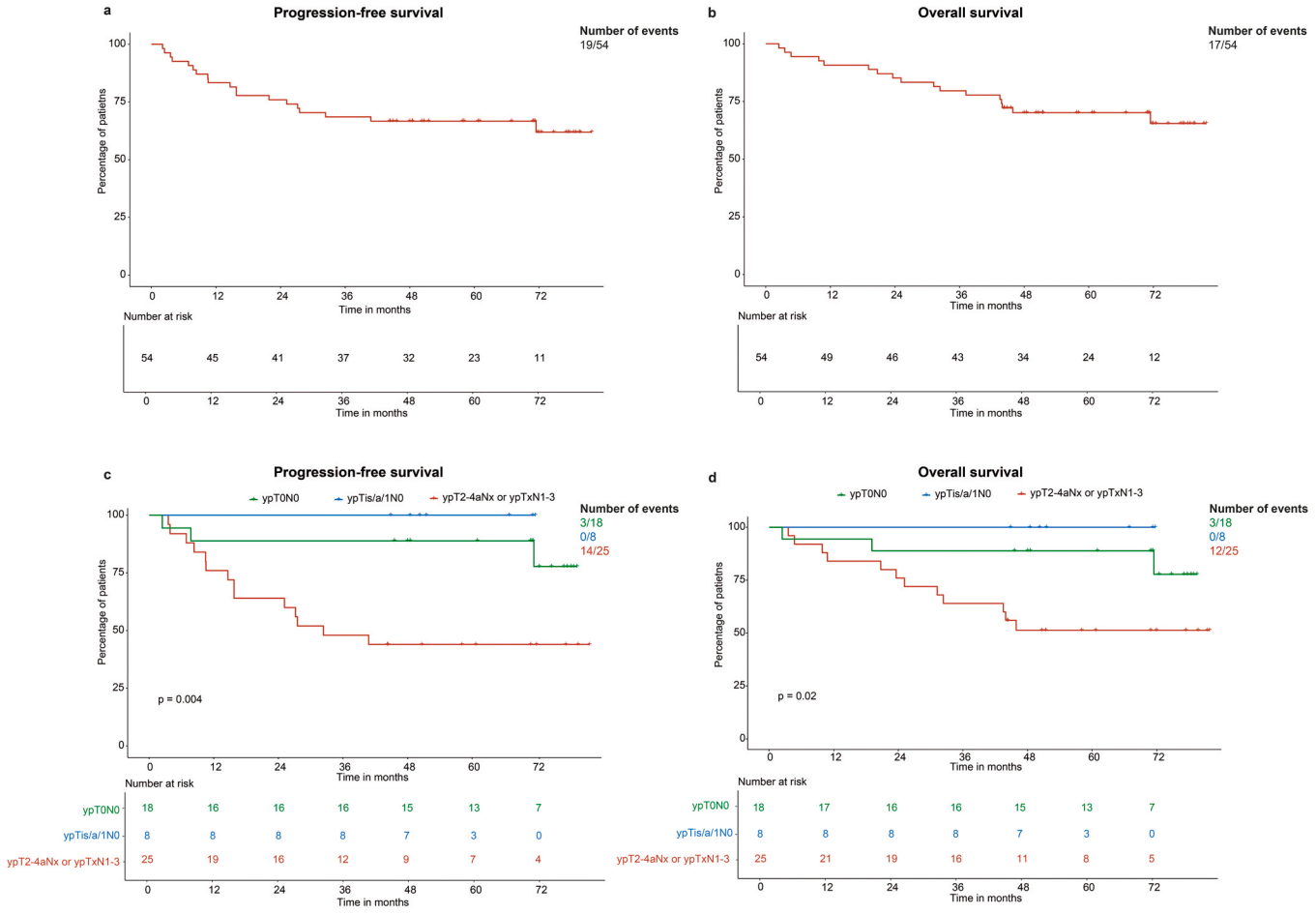

Fig. 1. Long-term survival for the entire NABUCCO cohort and for various pathological response groups. **a.** PFS of the entire cohort; **b.** OS of the entire cohort; **c.** PFS of patients with ypT0N0, ypTis/a/1N0 and ypT2–4aNx or ypTxN1–3; **d.** OS of patients with pT0N0, ypTis/a/1N0 and ypT2–4aNx or ypTxN1–3. P-values in c-d are based on a comparison of all curves using a log-rank test.

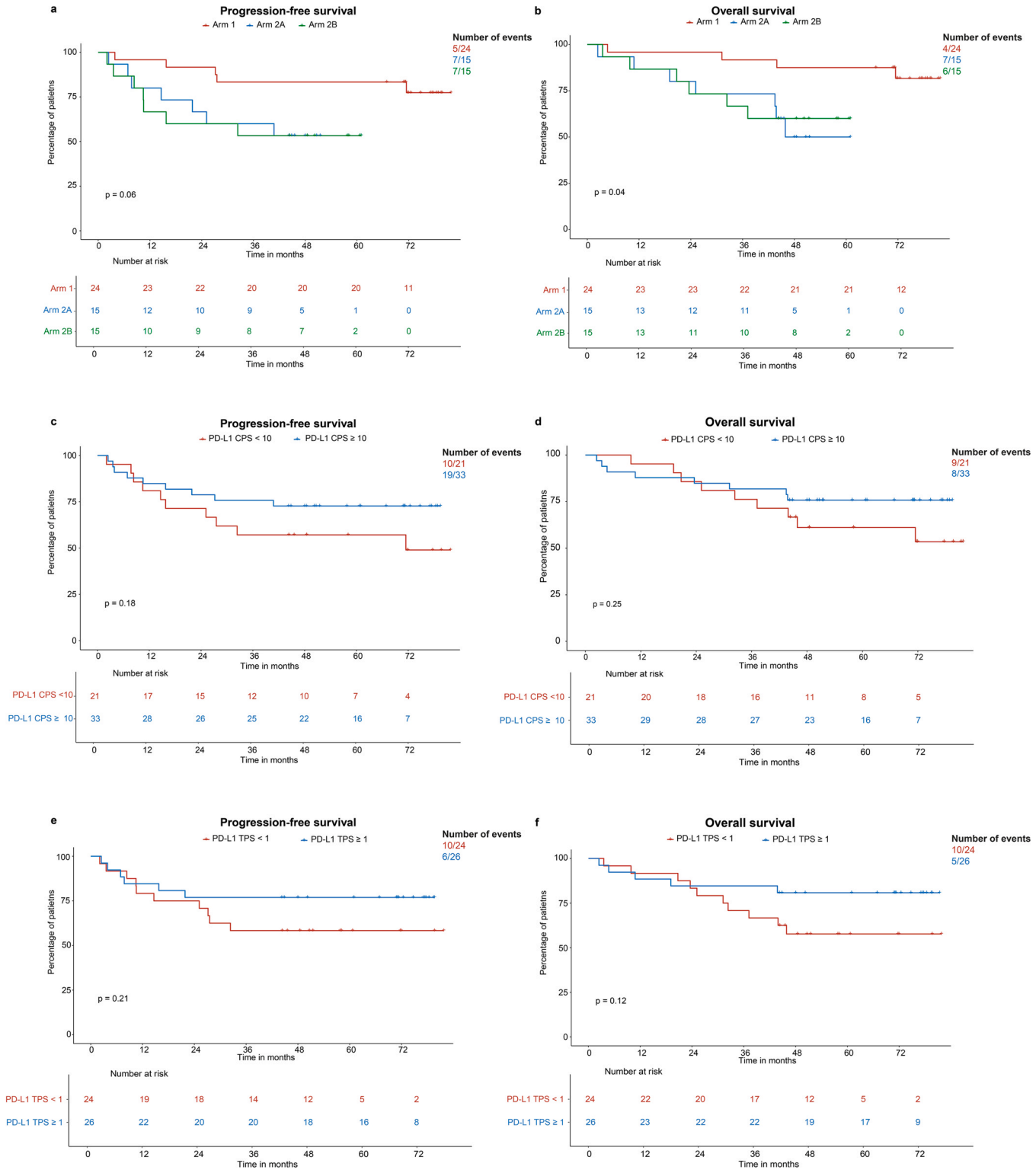

Fig. 2. Subgroup survival analyses based on treatment arm and PD-L1 positivity by CPS and TPS. **a.** PFS of the different treatment arms; **b.** OS of the different treatment arms; **c.** PFS of patients with PD-L1 + and PD-L1- tumors according to CPS; **d.** OS of patients with PD-L1 + and PD-L1- tumors according to CPS; **e.** PFS of patients with PD-L1 + and PD-L1- tumors according to TPS; **f.** OS of patients with PD-L1 + and PD-L1- tumors according to TPS. P-values in a-b are based on a comparison of all curves using a log-rank test. **Abbreviations:** PD-L1 = protein cell death ligand 1; CPS = combined positivity score; TPS = tumor proportion score.

ICB efficacy [20]. We compared long-term survival in NABUCCO patients who did and did not use antibiotics and observed comparable PFS ($p = 0.75$) and OS ($p = 0.82$) for these subgroups (Figure 3e-f).

3.3. Lymph node involvement and long-term clinical outcome

Patients with clinically suspected lymph node-positive disease (≥ 1 node of ≥ 10 mm) at baseline CT-imaging are at high risk of developing distant metastases. We assessed the long-term survival of NABUCCO

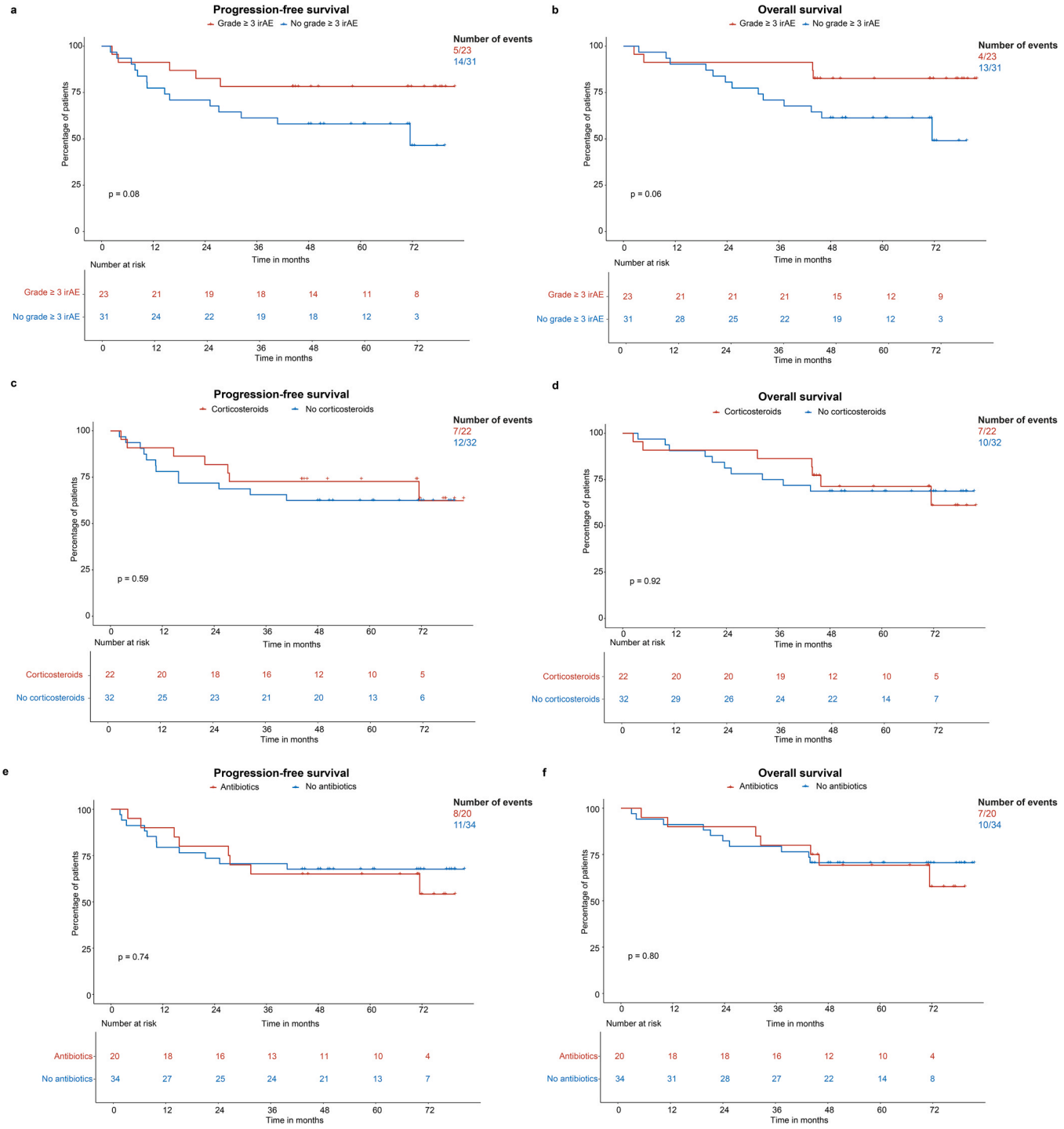

Fig. 3. Long-term survival in patients with high-grade treatment-related toxicity and patients with concomitant medication. **a.** PFS of patients with and without grade ≥ 3 irAE; **b.** OS of patients with and without grade ≥ 3 irAE; **c.** PFS of patients with and without corticosteroids; **d.** OS of patients with and without corticosteroids; **e.** PFS of patients with and without antibiotics; **f.** OS of patients with and without antibiotics. **Abbreviations:** irAE = immune-related adverse events

patients with and without nodal involvement at baseline and did not observe a statistically significant difference for both PFS and OS (PFS p = 0.27; OS p = 0.33; Figure 4a-b).

During pathological assessment following resection, 18 patients were staged as node-positive. In 6 out of these 18 patients, a nodal micrometastasis (< 2 mm) was observed. The clinical significance of micrometastases in ICB-treated patients has not been established before and has remained largely unexplored in urothelial bladder cancer. We evaluated PFS and OS for patients with node-negative disease and those with nodal micro- or macrometastasis. Interestingly, PFS and OS were similar in patients with node-negative disease and a nodal micrometastasis (PFS pN0 vs. pNmi p-adjusted = 0.69; OS pN0 vs. pNmi p-adjusted = 0.96). In contrast, patients with nodal macrometastases showed a worse PFS (pNma vs. pN0 p-adjusted = 0.007; pNma vs. pNmi p-adjusted=0.08) and OS (pNma vs. pN0 p-adjusted = 0.001; pNma vs. pNmi p-adjusted = 0.09; Figure 4c-d).

Our clinical results indicate that an anti-cancer immune response may still be ongoing in resected lymph nodes containing a micrometastasis. We used the PhenoCycler Fusion (Akoya) with a customized 26-plex immune antibody panel to explore potential ICB effects on the

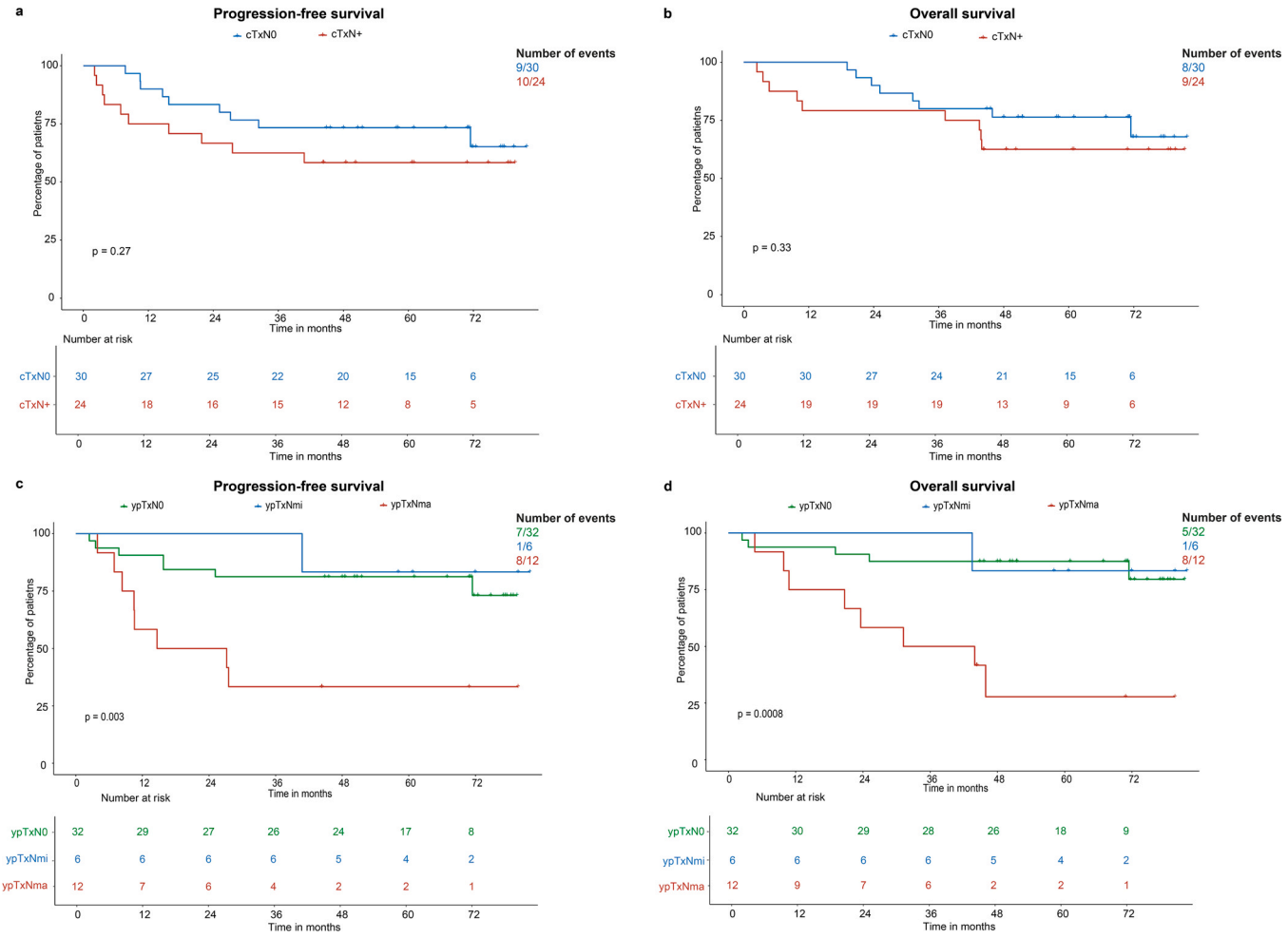

Fig. 4. Long-term survival and nodal involvement. **a.** PFS of patients with clinical node-negative and node-positive disease at baseline; **b.** OS of patients with clinical node-negative and node-positive disease at baseline; **c.** PFS of patients with pathological node-negative disease and micro- or macrometastasis in lymph nodes; **d.** OS of patients with pathological node-negative disease and micro- or macrometastasis in lymph nodes. P-values in c-d are the result of comparing all curves. **Abbreviations:** ypTxNmi = nodal micrometastasis; ypTxNma = nodal macrometastasis

local immune microenvironment in micrometastasis-containing tumor-draining lymph nodes (tdLN; Supplementary Table 1). We compared ICB-treated patients (n = 5) to untreated or chemotherapy-treated patients (n = 5) with micrometastasis-containing lymph nodes (dLN) and evaluated the fraction of several important immune cells, including activated and proliferating T-cell subsets. Whereas some T-cell fractions in tdLN from ICB-treated patients were numerically higher than those in chemotherapy-treated and untreated patients, none of these differences were statistically significant (Supplementary Figure 4a). Additionally, we explored distances between immune cells for ICB-treated patients and untreated and chemotherapy-treated patients. With a false discovery rate of 10 %, we observed that $CD20^+$ cells (B-cells) were closer to $CD14^+$ cells (dendritic cells) in tdLN from ICB-treated patients compared to untreated and chemotherapy-treated patients (Supplementary Figure 4b-**c**). Based on this exploratory analysis, we hypothesize that the close proximity of $CD20^+$ B-cells and $CD14^+$ cells following ICB could hint at priming of B-cell responses.

4. Discussion

The outlook for stage III UC patients is poor. Upon upfront radical cystectomy, patients with pT3b-4aN0M0 UC have a five-year recurrence-free survival (RFS) of 50–62 % [21]. Patients with node-positive disease have a worse outlook, with an RFS of 35 % at five years [21]. In NABUCCO, 54 stage III UC patients were treated with combination ICB followed by surgery. In this long-term survival analysis, with a median follow-up of 70 months, pre-operative ipilimumab plus nivolumab resulted in a PFS of 67 % and an OS of 70 % at five years.

We observed the most favorable clinical outcome in patients treated in cohort 1 (ipilimumab 3 mg/kg). Given that patients in cohorts 1 and 2A received a similar ipilimumab dose and based on comparable pCR rates between both cohorts, we expected a comparable long-term clinical outcome. Surprisingly, PFS and OS appeared less favorable in cohort 2A than cohort 1. The incidence of irAEs was also higher in cohort 1. One could speculate that the specific dosing schedule - starting with only ipilimumab in the first cycle - leads to increased immune induction. Alternatively, a difference in patient selection may have occurred between cohorts 1 and 2, as these cohorts were separated in time and additional centers were added for cohort 2. Given the limited statistical power to compare survival between treatment arms, these comparisons should be interpreted cautiously and are mainly hypothesis-generating.

An ongoing debate is whether the development of irAE is associated with ICB efficacy. Data in irresectable and metastatic UC suggest that irAE following anti-PD-(L)1 are correlated with favorable OS [22]. The pathophysiological development of irAE is not entirely understood. We established the long-term clinical outcome of patients with severe toxicity and observed a positive trend for PFS and OS in patients who developed grade $\geq$ 3 irAE, which suggests that the clinical outcome is not affected by the development of severe toxicity. Whether an actual causal relation between toxicity and ICB efficacy exists remains to be

elucidated.

Most NABUCCO patients with grade ≥ 3 irAE required treatment with corticosteroids. Given that corticosteroids have immunosuppressive effects, they might counteract ICB efficacy and therefore impair survival in ICB-treated patients [23]. Our data suggest that using corticosteroids in the period from 14 days before ICB initiation until resection does not negatively impact long-term survival. However, this outcome could differ for subgroups based on corticosteroid (peak) dose and the duration of steroid tapering. These parameters were not explored due to limited patient numbers.

When correlating the pathological stage with clinical outcomes, we observed that outcome was not compromised in patients with a nodal micrometastasis at surgical resection compared to node-negative patients. Nodal micrometastases are mainly known from the breast cancer field, where a similar outcome was observed in patients with a nodal micrometastasis and node-negative patients [24]. However, the effect of a nodal micrometastasis on long-term outcome in UC, specifically in the context of ICB, is unknown. In NABUCCO, two of the six patients with a nodal micrometastasis at resection were node-negative according to baseline CT-imaging and clinical staging, which can be inprecise. Therefore, it was unclear if a nodal micrometastasis at resection was an unresponsive small lymph node metastasis or whether it represents an ongoing anti-cancer immune response. The favorable outcome of these patients and the (largely) unknown effect of combination ICB on tdLN prompted us to study the immune landscape of the micrometastatic niche to explore potential immune-priming effects. As opposed to micrometastasis-containing tdLN from chemotherapy-treated and untreated patients, we observed that the distance between $CD20^+$ cells and $CD14^+$ cells in tdLN from ICB-treated patients was smaller. Although this analysis was highly exploratory, this result may illustrate priming of B-cell responses in ICB-treated patients [25].

Although valuable insights were obtained from the NABUCCO trial, we acknowledge that the patient number is limited, particularly in the ipilimumab-low arm and the exploratory work on nodal micrometastases. Additionally, the heterogeneity in patient populations across pre-operative ICB trials in UC precludes a cross-trial comparison. For future trials, larger cohorts should be assessed in a randomized study design.

In conclusion, the final survival data from the NABUCCO trial highlight the long-term efficacy of pre-operative combination ICB in patients with stage III UC, a patient population with a high risk of recurrence and death. Our data additionally suggest that survival is not impaired in patients with residual NMIBC or a nodal micrometastasis following ICB and that the development of grade ≥ 3 irAE and corticosteroid use do not negatively impact survival.

Bladder cancer treatment in the peri-operative period is rapidly evolving, with adjuvant pembrolizumab [26] and nivolumab [13] demonstrating disease-free survival benefit, and peri-operative cisplatin/gemcitabine plus durvalumab [27] showing event-free and overall survival benefit. Highly active systemic induction treatment could potentially enable bladder preservation in larger subsets of MIBC patients. Given the encouraging results of pre-operative combination ICB, the NABUCCO regimen from cohort 1 is studied in a phase 2 bladder-sparing trial (INDIBLADE trial; NCT05200988)[28].

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CRediT authorship contribution statement

Antoine G. van der Heijden: Writing – review & editing, Resources. **Nick van Dijk:** Writing – review & editing, Resources, Project administration. **Antonios Daletzakis:** Writing – review & editing, Methodology, Formal analysis. **Jeroen van Dorp:** Writing – review & editing, Resources, Project administration. **Maurits L. van Montfoort:** Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. **Chantal F. Stockem:** Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jeantine M. de Feijter:** Writing – review & editing, Resources. **Maartje Alkemade:** Writing – review & editing, Methodology. **Lodewyk F.A. Wessels:** Writing – review & editing, Methodology. **Bram van den Broek:** Writing – review & editing, Software, Methodology. **Niven Mehra:** Writing – review & editing, Resources. **Rolf Harkes:** Writing – review & editing, Software, Methodology. **Richard P. Meijer:** Writing – review & editing, Resources. **Daniel J. Vis:** Writing – review & editing, Methodology, Formal analysis. **Thierry N. Boellaard:** Writing – review & editing, Resources, Data curation. **Michiel S. van der Heijden:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Kees Hendricksen:** Writing – review & editing, Resources. **Britt B. M. Suelmann:** Writing – review & editing, Resources. **Annegien Broeks:** Writing – review & editing, Methodology. **Bas W.G. van Rhijn:** Writing – review & editing, Supervision, Resources.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors did not use generative AI.

Declaration of Competing Interest

Thierry N. Boellaard receives research funding from Pfizer paid to the institution, free-to-use server and software for research purposes from Siemens and speakers fees from Pfizer and MSD.J.M. de Feijter has an advisory role for Janssen- Cilag B.V. (paid to institute).Antoine G. Van der Heijden reports speaker fees from Merck Sharp & Dohme and Merck, research grants from Astellas, AstraZeneca, Merck, Johnson & Johnson, and Bristol Myers Squibb (BMS). Richard P. Meijer has an advisory role (institutional) for Merck B.V., MSD, Janssen–Cilag B.V. and BMS. Richard P. Meijer received research support (institutional) from Merck B.V., Janssen–Cilag B.V., Astellas Pharma Europe and Gilead Sciences Netherlands B.V. Niven Mehra reports grants from Janssen-Cilag, Astellas Pharma, AstraZeneca, BS Foundation, MSD Oncology and personal fees for his consulting or advisory role from Janssen-Cilag, Astellas Pharma, AstraZeneca, MSD Oncology, Bayer and Pfizer.Lodewyk F.A. Wessels received research funding from BMS.Bas W.G. van Rhijn participated in Advisory Boards for QED Therapeutics and Incyte International Biosciences.Britt B.M. Suelmann has an advisory role (institutional) for MSD, Astellas Pharma Europe, Janssen–Cilag B.V. and BMS. Britt B.M. Suelmann received research support (institutional) from Merck B.V. and Astellas Pharma Europe. Michiel S. van der Heijden declares the following competing interests: consultation (paid to institute) for AstraZeneca, BMS, Astellas, SeaGen, Pfizer, MSD Daiichi Sankyo and Janssen and grant support (to institute) from BMS, AstraZeneca, Roche, MSD and 4SC. Chantal F. Stockem, Jeroen van Dorp, Nick van Dijk, Daniel J. Vis, Rolf Harkes, Bram van den Broek, Maartje Alkemade, Annegien Broeks, Kees Hendricksen, Maurits L. van Montfoort and Antonios Daletzakis have nothing to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115731.

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