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ORIGINAL ARTICLE

Does the administration of preoperative pembrolizumab lead to sustained remission post-cystectomy? First survival outcomes from the PURE-01 study☆

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Background: Initial studies of preoperative checkpoint inhibition before radical cystectomy (RC) have shown promising pathologic complete responses. We aimed to analyze the survival outcomes of patients enrolled in the PURE-01 study (NCT02736266).

Patients and methods: We report the results of the secondary end points of PURE-01 in the final population of 143 patients. In particular, we report the event-free survival (EFS) outcomes, defined as the time from the first cycle of pembrolizumab to radiographic disease progression precluding RC, initiation of neoadjuvant chemotherapy (NAC), recurrence after RC, or death from any cause. Other end points were recurrence-free survival (RFS) and overall survival (OS). Subgroup analyses were carried out, including pathological response category, clinical complete responses (CR) assessed via multiparametric magnetic resonance imaging (mpMRI), and molecular subtyping. Cox regression analyses for EFS were also carried out.

Results: After a median [interquartile range (IQR)] follow-up of 23 (15-29) months, 12- and 24-month EFS were 84.5% [95% confidence interval (CI): 78.5-90.9] and 71.7% (62.7-82). The prognosis was favorable across all the different pathological response subgroups, with the exception of ypN+ ($N = 21$), showing a 24-month RFS (95% CI) of 39.3% (19.2% to 80.5%). A statistically significant EFS benefit was observed in patients with a clinical CR ($P = 0.002$). Programmed cell-death-ligand-1 combined positive score was significantly associated with longer EFS in multivariable analyses. Four patients refused RC after clinical evidence of CR, and none of them have recurred after a median follow-up of 10 months (IQR: 11-15). The claudin-low subtype displayed a numerically longer EFS after pembrolizumab and RC compared with the other subtypes.

Conclusions: The EFS results from PURE-01 revealed that the immunotherapy effect was maintained post-RC in most patients. Pembrolizumab compared favorably with neoadjuvant chemotherapy, irrespective of the biomarker status. Molecular subtyping may be a useful tool to select the patients who are predicted to benefit the most from neoadjuvant pembrolizumab.

Key words: pembrolizumab, event-free survival, muscle-invasive bladder cancer, radical cystectomy, pathological response

INTRODUCTION

During the past 2 years, several studies have provided a proof-of-concept for the activity of preoperative checkpoint inhibition in patients with muscle-invasive urothelial bladder cancer (MIBC). These studies followed the successful use of immune-checkpoint inhibitors in locally-advanced or metastatic stages[1] and were accompanied by the results of pembrolizumab in non-MIBC, tested in the landmark Keynote-057 trial.[2-4]

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Initial reports of unprecedented, yet preliminary, activity of single-agent checkpoint inhibitors, documented as pathologic complete (ypT0ypN0) or near-complete response (CR) at radical cystectomy (RC) have been initially provided by two academic studies conducted in Europe, the PURE-01 (supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2020.09.011) and the ABACUS study.[5-7] Subsequently, several other phase 2 trials have pursued the strategy of delivering courses of preoperative immunotherapy in patients with MIBC who were eligible for RC, either using immunotherapy alone or in combination with chemotherapy according to patients' eligibility to cisplatin. With the exception of the NABUCCO trial (NCT03387761), which tested the sequential and combination use of ipilimumab and nivolumab and allowed the inclusion of patients with clinically enlarged regional lymph nodes,[8] the remaining studies have focused on patients with organ-confined disease, defined as clinical T2-4N0M0 at standard cross-sectional imaging. All these phase 2 studies had the pathologic CR as primary end point.

Initial results of PURE-01 revealed a ypT0ypN0 of 42% in the first 50 treated patients and a downstaging to $\leq$ypT$_{1/a/is}$ypN0 was achieved in 54% of cases.[5,6] The updated pathologic response data confirmed the initial activity and showed a ypT0ypN0 in 42 out of 114 patients (37%). Noteworthy, the proof of activity was extended to the population of patients with predominant squamous-cell or lymphoepithelioma-like variant histology.[6] Surgical safety data from PURE-01 have also been reported using a standardized methodology and revealed high-grade complications (defined as Clavien–Dindo $\geq$IIIa) in only 34% of patients with no perioperative mortality at 90 days.[9] At present, the only study that reported preliminary survival outcomes is ABACUS, in which the recurrence-free survival (RFS) at 12 months was 79%, after a median follow-up of 13.1 months.[7] Retrospective data (from SWOG-8710 trial) and the RAZOR trial have reported the pathological response as a potential surrogate for survival in patients that received neoadjuvant chemotherapy.[10-12] Whether this relationship applies to neoadjuvant immunotherapy is unsettled. Herein, we present the first survival analysis of the PURE-01 study.

MATERIALS AND METHODS

PURE-01 study oversight

The study design and inclusion and exclusion criteria have been previously described, as well as the end points and the remaining trial procedures. An extra cohort not exceeding 10% was allowed to be included in addition to the amended sample size of 136 patients. After RC, the administration of adjuvant chemotherapy was discussed in patients with pathological high-risk disease. During the follow-up period, thoracoabdominal contrast-enhanced computed tomography (CT)-scan was carried out every 4 months for the first year and every 6 months for the second year. The intention-to-treat (ITT) study population of 143 patients, enrolled between February 2017 and December 2019, had available response and outcome data and these were used for the present analyses.

Study outcomes

The primary outcome of interest was event-free survival (EFS), which represented a secondary end point of the clinical trial. EFS was defined as the time from first pembrolizumab dose to either: (i) radiographic disease progression precluding a curative intent surgery per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 before RC, (ii) initiation of neoadjuvant chemotherapy preceding RC as per investigator decision, (iii) inability to undergo RC due to the onset of treatment-related side-effects, (iv) inability to complete a curative intent surgery determined by the urologist at the time of RC (e.g. unresectable tumor, metastases discovered at RC), (v) local or distant recurrence assessed by cross-sectional imaging and/or biopsy after RC, and (vi) death from any cause. In this study, patient refusal to undergo RC after the evidence of CR assessed with multiparametric magnetic resonance imaging (mpMRI) of the bladder (as previously described)[13,14] was not considered an event. These patients were censored at the date of last follow-up if no events occurred. These patients underwent out-of-protocol procedures and were offered a redo-transurethral resection of the bladder tumor (TURBT) followed by close follow-up if the final pathological examination confirmed a ypT$<$2 response; otherwise they were offered a chemoradiation with curative intent.

The secondary outcomes were RFS (in patients who had received pembrolizumab and RC), defined as the time from RC to local or distant recurrence, second urothelial cancer or death, and overall survival (OS). The inverse Kaplan–Meier method was used to calculate the follow-up duration.

Biomarker analyses

Procedures for programmed cell-death-ligand-1 (PD-L1) combined positive score (CPS) assessment (Dako 22c3 antibody), tumor mutational burden (TMB) assessment (via FoundationOne® CDx assay), RNA extraction, and microarray-based transcriptome profiling (by Decipher Biosciences Inc.) have been previously described.[5,6,15] For the biomarker analyses, data were now available for a larger sample size ($N = 102$ passing quality control metrics) with longer follow-up compared with the original publication of the data.[15] Molecular subtypes were assigned to the patient tumors using the Consensus Classification and The Cancer Genome Atlas (TCGA) molecular subtypes as described.[16,17] The Decipher subtypes were assigned by first identifying neuroendocrine (NE)-like patients[18] and then classifying the remaining tumors using the Seiler 2017 model.[19]

Statistical analyses

The Kaplan–Meier method was used to estimate EFS, RFS, and OS within the total population. Analyses were further stratified according to the use of adjuvant chemotherapy after RC, pathological response subgroups (ypT0ypN0, ypT$_{1/a/is}$ypN0, ypT2-4ypN0, and ypT$_{any}$ypN+), and clinical

response assessed via mpMRI. For the analyses investigating the prognostic value of clinical response, the EFS was calculated from the date of post-pembrolizumab mpMRI. Additional analyses tested EFS according to the different molecular subtypes, across classifications.

Twelve- and 24-month EFS were tested in different patient and disease subgroups. Univariable Cox regression analyses for EFS were run, including known response predictors. For the multivariable model, due to the limited number of events, pre-specified factors were included (CPS, TMB, and clinical T-stage) according to clinical judgment. All statistical tests were two-sided with a level of significance set at $P < 0.05$. Analyses were carried out using the R software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study cohort and updated activity data

At the time of data cut-off (12 March 2020), 143 patients had completed neoadjuvant therapy and had available follow-up information. The median follow-up was 23 months [interquartile range (IQR): 15-29]. A total of 135 patients underwent RC; 8 did not receive RC because of systemic progression or patient refusal, and none of them did not receive RC because of pembrolizumab-related side-effects (supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2020.09.011). Overall, 13 patients received additional systemic therapy post-pembrolizumab, including cisplatin-based chemotherapy ($n = 11$) and the pan-fibroblast growth-factor receptor inhibitor pemigatinib in a clinical trial ($n = 2$). Nine of 13 patients subsequently underwent RC. In total, nine patients received adjuvant cisplatin-based chemotherapy after RC.

At the time of data cut-off, 55 patients (38.5%, 95% CI: 30.5% to 46.5%) underwent pembrolizumab and RC and achieved a ypT0ypN0 and 80 patients (55.9%, 95% CI: 47.4% to 64.2%) achieved a pathologic downstaging to $\leq ypT_{1/a/is}$ ypN0. The remaining cohort characteristics are reported in Table 1.

Efficacy analyses

Median EFS (95% CI) was not reached (NR) in the ITT cohort. The 12- and 24-month EFS were 84.5% (78.5-90.9) and 71.7% (62.7-82; Figure 1A), respectively. Within the cohort of patients who did not receive adjuvant chemotherapy ($n = 125$), 12- and 24-month EFS were 87.3% (81.4-93.6) and 77.9% (69.3-87.6; Figure 1B), respectively. Subgroup analyses showing the 12-month EFS rates according to different baseline patient characteristics are reported in supplementary Figure S3A, available at https://doi.org/10.1016/j.annonc.2020.09.011 (and corresponding 24-month EFS rates are presented in supplementary Figure S3B, available at https://doi.org/10.1016/j.annonc.2020.09.011).

RFS outcomes, in the population of patients treated with three cycles of pembrolizumab and RC without preoperative chemotherapy and by pathological response subgroups, are presented in Figure 2. In particular, 24-month RFS (95% CI) was 95.9% (90.5-100) for ypT0ypN0, 74.9% (50.8-100) for $ypT_{1/a/is}$ ypN0, 78.8% (61.2-100) for ypT2-4ypN0, and 39.3% (19.2-80.5) for $ypT_{any}ypN+$. In total, nine patients died, seven due to disease progression (PD), one for surgical-related complications, and one due to co-morbidities. The 24-month OS in the ITT population was 91% (95% CI: 85.4-97.1) as presented in supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2020.09.011.

Results of the Cox regression analyses for EFS

Univariable Cox regression analyses on EFS in the overall cohort ($N = 143$) showed that higher CPS score [hazard ratio (HR): 0.98, 95% CI: 0.96-0.99; $P = 0.01$] was associated with lower rates of events, while cT3-4 (HR: 2.71, 95% CI: 1.24-5.93; $P = 0.01$) was associated with higher rates of events. At multivariable Cox regression analyses, CPS and cT3-4 remained statistically significantly associated with EFS ($P = 0.02$ and $P = 0.03$; Table 2).

Updated molecular subtyping results for EFS end point in PURE-01

Molecular subtyping was used to stratify the cohort (for cases in which transcriptome data were available; $n = 102$) into basal ($n = 38$), claudin-low ($n = 14$), luminal ($n = 25$),

Table 1. Baseline patient and disease characteristics ($N = 143$)

Characteristics	N (%)
Age in years, median (IQR)	68 (62-73)
Female sex	18 (12.6)
Smoking status	
Non-smoker	38 (26.6)
Current smoker	34 (23.8)
Former smoker	71 (49.6)
Histology:	
Pure UC	102 (71.3)
Predominant VH	26 (18.2)
Non-predominant VH	15 (10.5)
Concomitant CIS	24 (16.8)
Previous history of NMIBC	28 (19.6)
Previous BCG instillations	18 (12.6)
Clinical T-stage[a]	
cT2N0M0	70 (49)
cT3-4N0M0	73 (51)
TMB (Mut/Mb), median (IQR)	10.5 (6-15)
CPS (%), median (IQR)	10 (3-46.5)
Pathologic response:	
ypT0ypN0 (95% CI)	55 (38.5; 30.5-46.5)
$\leq ypT_{1/is/a}$ ypN0 (95% CI)	80 (55.9; 47.4-64.2)
$ypT_{1/is/a}$ ypN0	25 (17.5)
ypT2-4ypN0	28 (19.6)
$ypT_{any}ypN+$	18 (12.6)
Sequential neoadjuvant therapy	13 (9.1)
RC not carried out	8 (5.6)
Adjuvant CT post-RC	9 (6.3)

BCG, Bacillus Calmette—Guérin; CI: confidence interval; CIS: carcinoma-in-situ; CPS: combined positive score; CT: chemotherapy; IQR: interquartile range; NMIBC, non-muscle-invasive bladder cancer; RC: radical cystectomy; TMB: tumor mutational burden; UC: urothelial carcinoma; VH: variant histology.

[a] Determined with transurethral resection of the bladder tumor (TURBT), bladder multiparametric resonance imaging (mpMRI), contrast-enhanced thorax-abdomen computed tomography (CT), fluorodeoxyglucose positron-emission tomography (PET)/CT.

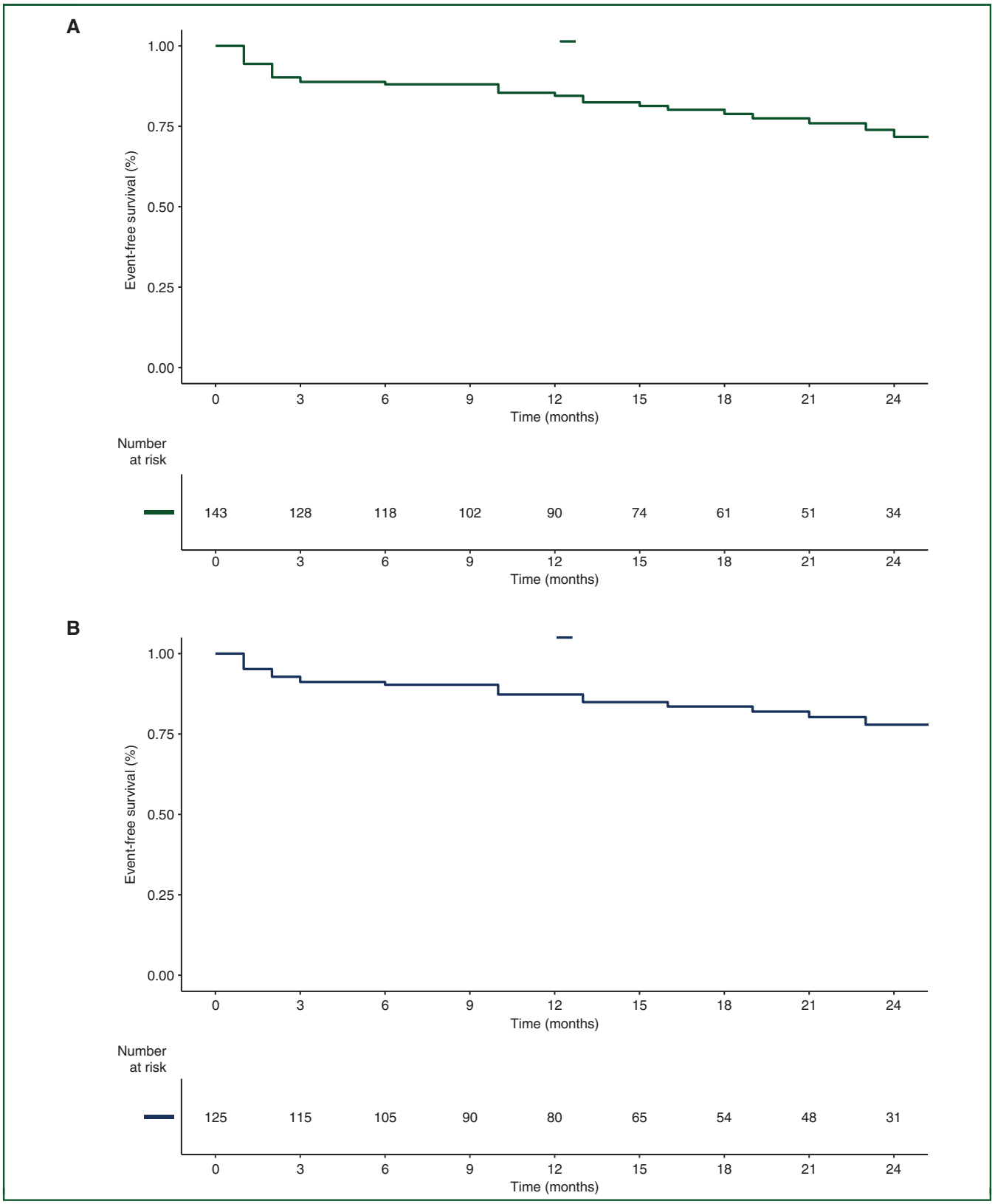

Figure 1. Kaplan–Meier curves of event-free survival in (A) the overall cohort ($N = 143$), and only in (B) patients who did not receive adjuvant chemotherapy ($n = 125$).

In the overall population of 143 patients the type of events and corresponding time of occurrence were the following:

- 30 events in total.
- 13 patients received chemotherapy after pembrolizumab, before radical cystectomy (median time from first dose of pembrolizumab to salvage chemotherapy): 1 month (IQR: 1-2).
- 12 patients developed a recurrence after a median of 12.5 months (IQR: 9-18.3).
- 5 patients died for other causes after a median of 13 months (IQR: 10-15).

IQR, interquartile range.

luminal infiltrated ($n = 22$), and neuroendocrine-like ($n = 3$) subtypes according to the Decipher classifier.[18,19] Similar patterns were observed for both the consensus and TCGA models (supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.09.011).[16,17] For each subtyping model, we explored the composite EFS end point as shown in Figure 3A-C. With longer follow-up, the claudin-low subtypes counted only one event, exhibiting the best outcomes after pembrolizumab and RC.[15]

Outcomes of patients who achieved a radiological CR and of those who refused RC

EFS was significantly longer in patients who achieved a CR at mpMRI, versus non-CR patients. In CR patients, the 24-month EFS was 96.1% (95% CI: 90-100) whereas in non-CR patients the 24-month EFS was 59.6% (95% CI: 44.9-79.2, supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2020.09.011).

The characteristics of the four patients who refused RC and who received three cycles of neoadjuvant pembrolizumab followed by re-TURBT are shown in supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2020.09.011. Of these patients, three were ypT0 and one achieved a ypT_a response at pathologic report of TURBT. After a median follow-up of 10 months (IQR: 11-15), none of these patients had recurred or progressed. Of note, all but one of these patients presented with at least one favorable biomarker (CPS or TMB) pre-pembrolizumab.

DISCUSSION

Single-agent immunotherapy trials, with the PURE-01 at the forefront, have provided provocative results that challenged the role of standard-of-care chemotherapy in the preoperative space, although the data are preliminary. The initial data on the activity of immune-checkpoint inhibition in MIBC, quantified as pathologic complete or major responses, provided a proof-of-concept for a potential shift in the therapeutic paradigm towards simpler, quicker, and more tolerable systemic therapies. Consequently, at our center, the number of preoperative therapies delivered to MIBC patients substantially increased compared with the past years, which were characterized by several difficulties in delivering multimodal therapy, at our center and in several referral centers alike.[20] In general, the explosion of clinical trials that are being increasingly offered to patients in the neoadjuvant landscape of MIBC represents another indicator that we are close to significant changes in clinical practice.

Our major concerns, however, were relative to the reliability of what we were obtaining in the short term, that is, the survival impact of the pathologic responses seen at RC. As of today, uncertainties persist with regards to the likelihood of a sustained effect of short courses of neoadjuvant immunotherapy in tumors at high risk of relapse and progression post-RC. In this manuscript, we present the first survival outcomes of the PURE-01 study, primarily as EFS outcome analyses. The primary findings are related to two arguments of vivid debate: the definition and prognostic impact of pathologic CR as an end point of neoadjuvant immunotherapy trials and the EFS as another suitable end point for these trials. The pathological CR has been correlated with improved survival in patients treated with neoadjuvant chemotherapy, raising the possibility of its use as an intermediate end point to accelerate the development of novel neoadjuvant regimens.[10,21-24] However, the potential role of ypT0ypN0 as an individual- and trial-level surrogate end point in this disease is poorly defined. Furthermore, there is heterogeneity in the definition of pathologic CR.[25] In particular, a few authors allowed the inclusion of residual 'carcinoma-in-situ' together with ypT0ypN0.[26,27] The associations between the type of pathologic response and outcome reported here seem to differ from those observed with neoadjuvant chemotherapy: despite the ypT0ypN0 response confirmed to be associated with exceptionally good survival, the residual $ypT_{1/a/is}$ ypN0 had worse RFS, similar to ypT2-4ypN0 responses which were instead endowed with a better prognosis compared with the literature.[28] Indeed, the lack of a randomized design does not allow the stating of definitive conclusions regarding the surrogacy effect of pathological response on outcome. Generally, we could hypothesize that neoadjuvant immunotherapy could result in a better control of the nodal micrometastases, compared with neoadjuvant chemotherapy, also in patients with residual high-risk disease due to the primary tumor extent, and that the prognosis is quite dismal in the proportion of immunorefractory patients showing locoregional (nodal) disease spread. Conversely, there could be a suboptimal control of carcinoma-in-situ with only three cycles of pembrolizumab.

EFS fits quite well with the design of the PURE-01 study. In particular, EFS was able to count as events the few patients who did not experience a disease progression according to RECIST but who received sequential standard chemotherapy per investigator decision, based on the radiologically-ascertained potential lack of response to pembrolizumab.[13,14] The definition that we adopted, in the study as well as in this analysis, is a modified version of the one proposed by the United States Food and Drug Administration (US-FDA; accessible at https://fda1.webex.com/webappng/sites/fda1/recording/ef2209fadb7c4add90483d716977d32c). The main difference includes the aforementioned cases receiving sequential chemotherapy as further events. Most noteworthy, in line with FDA guidance, we did not include patients' refusal to undergo RC as an event, but indeed there is an ongoing debate on this issue and the definitions may vary over time. Regarding both the EFS and RFS outcomes, the results obtained in the population treated with three cycles of pembrolizumab plus RC without preoperative chemotherapy outperformed what has been reported in the literature of RC trials.[28] As an example, the overall 2-year RFS of 78.3% is numerically higher than the 2-year RFS (about 72%) reported in the RAZOR trial, a randomized study of open versus robot-assisted RC.[11] Moreover, at a 36-month follow-up, the RAZOR trial reported an RFS rate

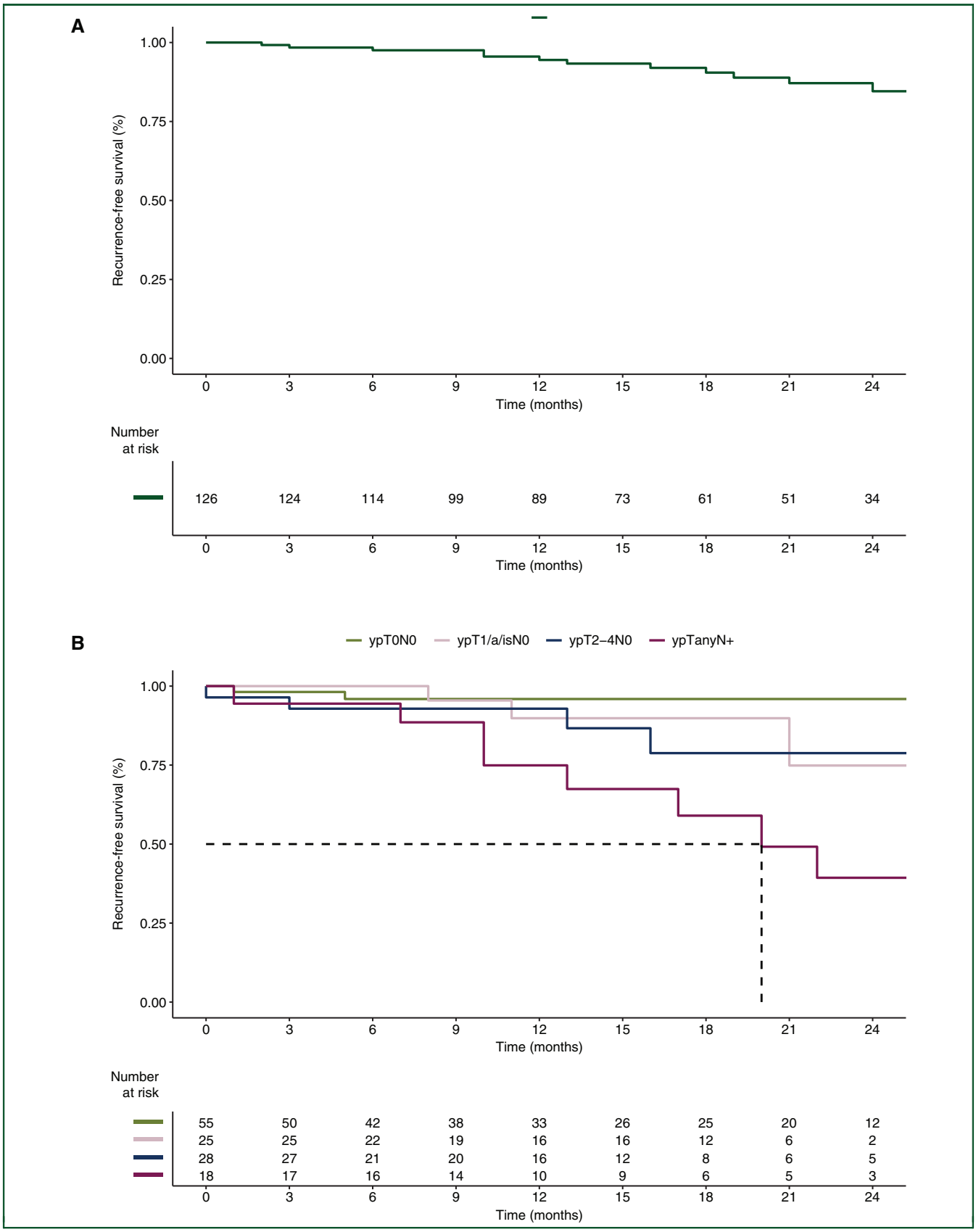

Figure 2. Kaplan–Meier curves of recurrence-free survival in patients (n = 126) treated with radical cystectomy without preoperative chemotherapy (A).
The type of events and corresponding time of occurrence were the following:
- 17 events in total.
- 12 patients developed a relapse after a median of 10 months (IQR: 6-16.3).
- 5 patients died for other causes after a median of 11 months (IQR: 5-13).
(B) recurrence-free survival (RFS) according to the ypTypN-stage category. The 12- and 24-month RFS (95% CI) in the total population was 90.5% (84.9-96.4) and 78.3% (68.9-89). The 12- and 24-month RFS (95% CI) according to the pathological response subgroups were the following: 95.9% (90.5-100) and 95.9% (90.5-100) for ypT0ypN0; 89.8%

Table 2. Univariable and multivariable Cox regression models predicting events

Factors	Univariable analyses				Multivariable analyses			
	HR	5%	95%	*P*-value[a]	HR	5%	95%	*P*-value[a]
Age (continuous)	1.03	0.98	1.07	0.2				
Sex (male versus female)	2.27	0.54	9.54	0.3				
Previous BCG	0.72	0.22	2.36	0.6				
Histology:								
Non-predominant VH (Ref.)								
Predominant VH	0.94	0.25	3.51	0.9				
Pure UC	0.88	0.30	2.56	0.8				
Smoking status:								
Non-smoker (Ref.)								
Former smoker	1.22	0.51	2.93	0.7				
Non-smoker	0.61	0.19	1.91	0.4				
Previous history of NMIBC	0.80	0.31	2.08	0.6				
Clinical T-stage:								
cT2N0 (Ref.)								
cT3-4N0	2.71	1.24	5.93	0.01	2.43	1.07	5.50	0.03
TMB (Mut/Mb; continuous)	0.96	0.91	1.01	0.1	0.96	0.91	1.02	0.2
CPS (%; continuous)	0.98	0.96	0.99	0.01	0.98	0.96	0.99	0.02

BCG, Bacillus Calmette—Guérin; CPS, combined positive score; HR, hazard ratio; NMIBC, non-muscle-invasive bladder cancer; Ref., reference group; TMB, tumor mutational burden; UC, urothelial carcinoma; VH, variant histology.
[a] Two-sided Wald test *P*-value.

approximating 65%-68%,[12] which is a bit lower than the estimate from the PURE-01 (around 75%). The OS results, representing the ultimate end point of any perioperative trial, are also promising although still immature. Another key aspect that was addressed in this study was the outcome of patients according to the clinical response, either assessed radiologically with mpMRI or radiologically and with a re-TURBT, the latter carried out in patients who refused to undergo RC. EFS of CR patients exceeded 95% at 24 months, and this result is very promising in this clinical setting, further supporting the role of a noninvasive assessment of tumor response in MIBC after neoadjuvant immunotherapy. In addition, in those patients who refused to undergo RC and received a re-TURBT, the pathological response at re-TURBT resulted in a major response in all cases, and all of them are currently disease-free under active surveillance.

From these results, by looking at baseline biomarkers in the total population as well as in the latter subgroup, the role of biomarker selection to identify the most suited candidates for neoadjuvant immunotherapy emerges as potentially significant, deserving validation studies. Patients

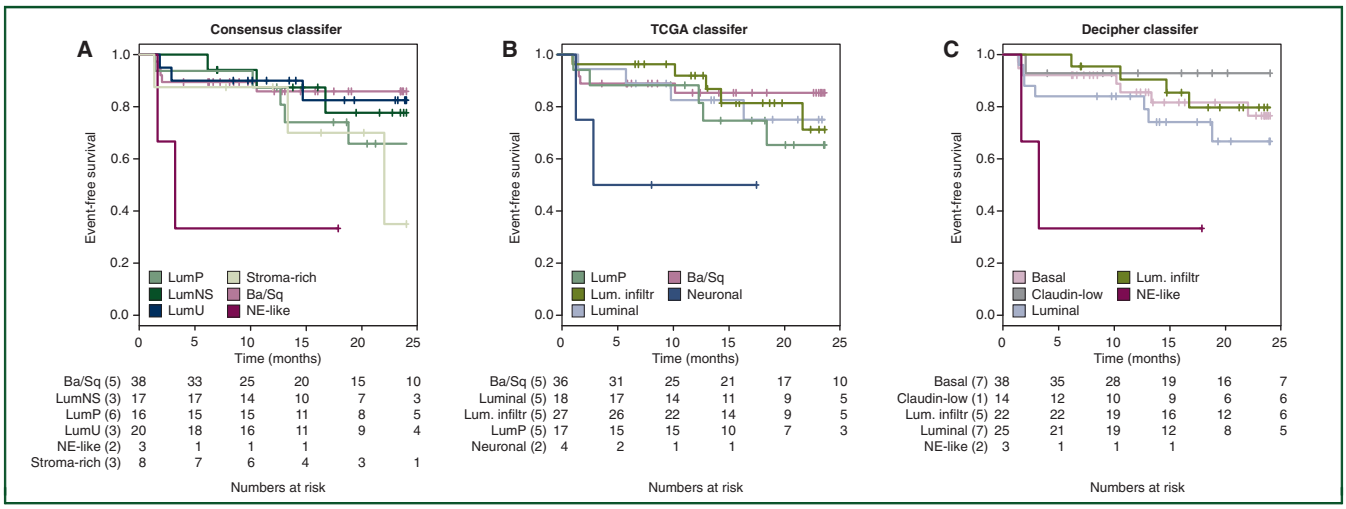

Figure 3. Kaplan—Meier curves of event-free survival by molecular subtype.
(A) Consensus classifier, (B) TCGA, and (C) GSC-Decipher classifier. The number of patients at risk is indicated, as well as the number of events for each subtype (in brackets).
Ba/Sq, basal/squamous; Lum. infiltr, luminal infiltrated; LumNS, luminal not specified; LumP, luminal papillary; LumU, luminal unstable; NE, neuroendocrine; TCGA, The Cancer Genome Atlas.

(77.3-100) and 74.9% (50.8-100) for ypT$_{1/a/is}$ ypN0; 92.9% (83.8-100) and 78.8% (61.2-100) for ypT2-4 ypN0; and 74.9% (56.2-99.8) and 39.3% (19.2-80.5) for patients with pathologically lymph node-involvement (ypN+).
CI, confidence interval; IQR, interquartile range.

with PD-L1-expressing tumors or, even better, claudin-low tumors had more favorable EFS compared with the remainder. These data were consistent with the results obtained from the molecular subtyping where we found patients with tumors of the claudin-low subtype had very favorable EFS compared with the other subtypes using the Decipher model. Importantly, claudin-low tumors have higher levels of immune infiltration and higher expression of immune suppressor markers, including *CD274/PD-L1*,[19,29] which may explain, at least in part, the sensitivity of these tumors to pembrolizumab.

If we look at patients who refused RC, the impact of baseline PD-L1 expression, possibly coupled with high-TMB values in the way we have previously described,[30] may become highly relevant in identifying the population with the best bladder-intact EFS. All four patients were free from recurrence at a median follow-up of 10 months. These hypothesis-generating results could be prospectively tested in trials in which patients with clinical T2N0 stage or with the newly-defined early bladder cancer,[31] and with tumors showing high CPS values, could be assigned to receive three cycles of pembrolizumab followed by re-TURBT. In case of centrally-reviewed ypT0 response, these patients could be offered a maintenance pembrolizumab therapy instead of any other local treatment to the primary tumor. Inherent limitations of the present analyses are certainly related to the single-arm design of PURE-01 and the fact that the analyses on biomarker-selected cohorts, as well as the entire survival analyses, were not pre-specified, therefore were largely underpowered.

CONCLUSIONS

In summary, in spite of compelling overall EFS and RFS in the PURE-01 study, we have shown that the RFS curves according to the pathologic response have some peculiarities compared with the literature. Although the design of the study did not allow a definitive evaluation of surrogacy, our results suggested that the population of patients currently defined as having a high risk of relapse after neoadjuvant chemotherapy and RC could be different in the context of preoperative immunotherapy. Our results also provided a first proof-of-concept that ypT0ypN0 response may be a good surrogate of EFS within immunotherapy trials and will be used in clinical trials to orient bladder-sparing strategies, possibly including pembrolizumab and re-TURBT alone in biomarker-selected patients.

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DISCLOSURE

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