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Real-world effectiveness of pembrolizumab as first-line therapy for cisplatin-ineligible patients with advanced Urothelial Carcinoma: the ARON-2 study

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Abstract

To be completed according to Journal Instructions.

Keywords: ARON-2 study; Immunotherapy; NCT05290038; Pembrolizumab; Real-world data; Survival; Tumor Response; Urothelial Cancer.

Introduction

The American Cancer Society has estimated 164,190 new cancer cases of the urinary system only in the United States in 2022 [1]. Approximately the 50% of these cases consist in tumors of the urinary bladder, which represents the 6% of all cancer diagnoses and the 4% of cancer-related deaths in men [1].

Urothelial cancer (UC) is the most prevalent histologic subtype of tumors of the upper and lower urinary tracts, accounting for approximately 90% of all cases [2]. About 25% of patients with UC present with metastatic disease, reporting a 5-year survival rate of only 7.7% [3].

In the past three decades, the management of first-line advanced UC has consisted in the administration of platinum-based chemotherapy [4]. The advent of immune-checkpoint inhibitors (ICIs) have challenged previous treatment paradigms of advanced UC in the post-platinum setting as well as in the first-line setting for cisplatin-ineligible patients [5,6], defined by the presence of at least one of the criteria published by Galsky *et al.* in 2011 [7]: (1) Eastern Cooperative Oncology Group (ECOG)-Performance Status (PS) of 2, (2) Creatinine clearance of less than 60 mL/minute, (3) Common Terminology Criteria for Adverse Events (CTCAE) of at least grade 2 hearing loss, (4) CTCAE of at least grade 2 neuropathy and (5) New York Heart Association Class III heart failure.

The approval of pembrolizumab by the Food and Drugs Administration (FDA) in cisplatin-unfit patients followed the results of the Keynote-052 phase 2 trial [8]. In this study, patients previously treated with prior systemic chemotherapy for unresectable or metastatic UC were excluded, while patients receiving platinum-based chemotherapy for tumor recurrence >12 months since completion of

adjuvant or neoadjuvant therapy were eligible. The primary endpoint was objective response; 374 patients were enrolled; at a median follow-up of 5 months, Overall Response Rate (ORR) was 24%. In 2020, Vuky *et al.* [9] published the results of the long-term outcomes of patients included in the Keynote-052 study, with a minimum follow-up of 2 years. The ORR was 28.6%, with 8.9% of complete remissions, with median overall survival (OS) and duration of response of 11.3 months (95% CI, 9.7 to 13.1 months) and 30.1 months (95% CI, 18.1 months to not reached [NR]), respectively.

The ARON project was designed to globally share and analyze real-world data from patients with genitourinary tumors treated by immunotherapy. In particular, the ARON-2 study included UC patients receiving pembrolizumab as first or subsequent line therapy. In this study, we investigated the effectiveness of pembrolizumab as first-line treatment for cisplatin-ineligible patients affected by advanced UC.

Patients and Methods

Study population

The ARON-2 study retrospectively collected data from patients aged ≥ 18 years having a cytological and/or histological confirmed diagnosis of cisplatin-ineligible UC receiving first-line pembrolizumab (200 mg i.v. flat dose, every three weeks until clear radiological or clinical progression of disease) from January 1st 2017 to September 1st 2022. Cisplatin ineligibility was defined according to the Galsky criteria [7]. Thirty-three Institutions from 18 countries were involved in the ARON-2 study.

The ARON-2 dataset included clinical and laboratory data extracted from patients'

paper and electronic charts on age, gender, ECOG-PS, tumor histology, surgery, sites of metastases, and response to therapy were retrospectively collected. Patients with insufficient data on tumor response to therapy were not included in the ARON-2 study.

Computed tomography (CT) or magnetic resonance imaging (MRI) scans were performed following standard local procedures every 8–12 weeks. Physical and laboratory tests were usually carried out every 4–6 weeks during patients' follow-up.

Study endpoints

The primary endpoint of the study was the effectiveness, assessed as ORR, duration of response (DoR), progression-free survival (PFS) and OS. Objective Response Rate (ORR) was calculated as the proportion of patients who achieved a complete (CR) or partial response (PR) defined by RECIST 1.1 criteria [10]. DoR was defined as the time from CR or PR to progression. Overall Survival (OS) was the time from treatment initiation to death from any cause. Progression-Free Survival (PFS) was calculated from the start of first-line pembrolizumab to progression or death from any cause, whichever occurred first. Patients without disease progression or death or lost at follow-up at the time of the analysis were censored at the last follow-up visit.

Statistical Analysis

The Kaplan-Meier statistical methods with Rothman's 95% confidence intervals (CI) were used to estimate median OS, PFS and DoR. Cox proportional hazards models were used to compare the multivariable effects on patients' survival and to calculate hazard ratios (HRs) and 95% CIs. Receiver operating characteristic (ROC)

analysis was also used to understand the sensitivity and specificity profile and to identify potential cut-offs that better stratify patients in risk groups. The chi-square test was used to compare each group for categorical variables. Statistical differences were considered significant when the p -value was <0.05 , and all p values were two-sided.

The upper tract was defined as the renal pelvis or ureter, and the lower tract as the bladder or urethra. Bajorin prognostic classification (including both the presence of visceral/bone metastases and Eastern Cooperative Oncology Group-Performance Status, ECOG-PS), was used to stratify patients according the number of risk factors [11].

MedCalc version 19.6.4 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium) was used for the statistical analyses.) for all analyses. This study is registered with ClinicalTrials.gov, number NCT05290038.

Results

Baseline characteristics

Our analysis included 162 patients. The median follow-up time was 18.9 months (95%CI 15.3–76.9); 117 patients (74%) were males. Median age was 71y (range 43–94). ECOG-PS was ≥ 2 in 27 patients (17%). Tumors of the upper urinary tract accounted for the 16% of all cases. Tumor histology was pure UC in 142 patients (88%), squamous in 8 (5%), micropapillary in 3 (2%), glandular in 2 (1%), nested in 2 (1%), sarcomatoid in 2 (1%), undifferentiated in 2 (1%), and clear cell in 1 (1%). The 27% of patients presented metastatic disease at UC diagnosis. Lymph node and visceral metastases were identified in 112 (69%) and 90 (56%) patients, respectively.

Stratifying by Bajorin prognostic classification [11], 63 patients (39%) presented 0 factors, 81 patients (50%) 1 factor and 18 patients (11%) both factors.

Seventy-three patients (45%) had died at time of the analysis. Treatment with pembrolizumab was ongoing in 74 patients (46%). Twenty-nine (33%) of the 88 patients progressed during first-line pembrolizumab were treated with second-line therapies. Patients' baseline characteristics are summarized in Table 1.

Overall Survival and Progression-Free Survival analyses

In the overall study population, the median OS was 15.8 months (95%CI 11.3–32.4, Figure 1). The median OS was significantly longer in males vs females (21.2 months, 95%CI 12.3–45.9, vs 11.7 months, 95%CI 5.9–16.8, $p=0.031$, Figure 2). Otherwise, no statistically significant differences were observed between patients aged <65y vs ≥ 65 y (16.8 months, 95%CI 10.5–45.9 vs 15.8 months, 95%CI 10.5–32.4, $p=0.614$) and between smokers and non-smokers (16.8 months, 95%CI 11.1–45.9, vs 13.4 months, 95%CI 8.8–29.4, $p=0.594$).

Patients with ECOG-PS ≥ 2 showed worst median OS compared to ECOG-PS 0-1 (7.4 months, 95%CI 6.1–14.3, vs 19.4 months, 95%CI 11.7–45.9, $p=0.044$, Figure 2).

Patients with pure UC histology showed a median OS of 16.8 months (95%CI 11.2–45.9), while in patients with mixed histology was 12.5 months (95%CI 3.3–32.4, $p=0.438$). Analogously, no statistically significant differences were found between patients with tumors of the upper tract (29.4 months, 95%CI 10.5–29.4) vs lower tract (14.3 months, 95%CI 11.1–33.4, $p=0.160$).

Metachronous metastatic disease was associated with longer median OS (19.4 months, 95%CI 11.3–45.9, vs 11.7 months, 95%CI 4.3–32.4, $p=0.038$, Figure 3). Patients

with lymph node metastases only showed longer median OS compared to those with visceral metastases (29.4 months, 95%CI 13.4–45.9, vs 11.1 months, 95%CI 7.7–17.0, $p=0.026$, Figure 3). By stratifying patients according to sites of metastasis, a statistically significant difference was observed between patients with or without bone metastases (7.6 months, 95%CI 3.6–16.8, vs 21.2 months, 95%CI 12.5–45.9, $p=0.016$, Figure 3).

According to Bajorin risk factors [11], the median OS resulted 32.4 months (95%CI 15.8–45.9) in patients with 0 risk factors, 12.3 months (95%CI 7.7–17.0) in patients with 1 risk factor and 11.1 months (95%CI 1.7–14.3) in patients with 2 risk factors ($p=0.019$, Figure 3).

Furthermore, no significant differences were found between patients treated with first-line pembrolizumab who had received or not previous adjuvant or neoadjuvant chemotherapy (14.2 months, 95%CI 10.5–32.4, vs 17.0 months, 10.5–45.9, $p=0.791$).

In the overall study population, the median PFS was 10.2 months (95%CI 6.2–17.6, Figure 1). The median PFS was longer in males vs females, but the difference was not statistically significant (11.4 months, 95%CI 8.2–28.6, vs 5.1 months, 95%CI 2.7–26.3, $p=0.155$). Analogously, no statistically significant differences were observed between patients aged <65y vs $\geq 65y$ (9.0 months, 95%CI 6.2–36.7 vs 11.3 months, 95%CI 4.8–26.3, $p=0.688$), smokers vs non-smokers (9.1 months, 95%CI 6.2–17.0, vs 12.2 months, 95%CI 4.3–28.6, $p=0.734$), ECOG-PS ≥ 2 vs <2 (9.3 months, 95%CI 1.9–15.2, vs 10.2 months, 95%CI 6.2–24.2, $p=0.585$), pure vs mixed UC histology (11.4 months, 95%CI 6.2–24.2, vs 4.8 months, 95%CI 2.0–13.4, $p=0.111$), upper vs lower urinary tract (18.6 months, 95%CI 2.2–28.6, vs 10.2 months, 95%CI 6.2–17.6, $p=0.790$), and previous adjuvant or neoadjuvant chemotherapy vs no previous treatments (7.5 months,

95%CI 4.8–11.3, vs 15.2 months, 6.6–28.6, $p=0.120$).

Synchronous metastatic disease was associated with shorter median PFS (5.3 months, 95%CI 2.3–11.7, vs 11.7 months, 95%CI 7.5–28.6, $p=0.017$, Figure 4). Patients with lymph node metastases only showed longer median PFS compared to those with visceral metastases (26.3 months, 95%CI 11.3–33.7, vs 5.5 months, 95%CI 3.8–9.1, $p=0.002$, Figure 4). By stratifying patients according to sites of metastasis, patients with bone metastases showed a significantly shorter median PFS (3.4 months, 95%CI 1.9–5.5, vs 17.0 months, 95%CI 9.4–28.6, $p<0.001$, Figure 4).

Finally, according to Bajorin risk classification, the median PFS resulted 26.3 months (95%CI 9.4–33.7) in patients with 0 risk factors, 8.6 months (95%CI 5.1–17.0) in patients with 1 risk factor and 4.8 months (95%CI 1.2–13.4) in patients with 2 risk factors ($p=0.022$, Figure 4).

Response to therapy

According to Recist 1.1 criteria, 26 patients (16%) experienced CR, 32 (20%) PR, 39 (24%) SD and 55 (34%) PD. Patients with 0, 1 or 2 Bajorin risk factors showed an ORR of 43%, 33%, and 22%, respectively ($p=0.007$).

The median OS resulted significantly different according to the type of response, being NR (95%CI NR–NR), 45.9 months (95%CI 17.0–45.9), 13.4 months (95%CI 7.4–19.4) and 6.4 months (95%CI 2.9–21.2) in patients with CR, PR, SD, and PD, respectively ($p<0.001$, Figure 5). In the 58 patients who presented CR or PR, 44 were still ongoing at time of the analysis. The median DoR was NR (95%CI NR–NR).

Role of prognostic factors

At univariate analysis, gender, synchronous metastatic disease and Bajorin risk classification were significant predictors of OS, and their prognostic role was confirmed at multivariate analysis (Table 2).

Furthermore, IMDC group, synchronous metastatic disease and Bajorin risk classification significantly correlated with PFS at univariate analysis, although only Bajorin risk factors proved to be associated with PFS at multivariate analysis (Table 2).

Discussion

Cisplatin-unfit patients represent at least 30–40% of patients with metastatic UC [12]. Owing to a median age at diagnosis of 70 years, and being smoking an associated risk factor, many patients have pulmonary and/or cardiovascular diseases that lead to an accelerated deterioration of renal function. Age-related decrease in glomerular filtration rate impairs the patients' possibility to receive cisplatin, as well as impaired ECOG-PS.

A randomized EORTC study [13] comparing M-CAVI and gemcitabine plus carboplatin in patients cisplatin-unfit not only proved acceptable Response Rate of the gemcitabine plus carboplatin arm (38%), but also supported the importance of stratification parameters and Bajorin risk groups on RR. Indeed, patients with 0, 1 or 2 Bajorin risk factors showed a RR of 47%, 39% and 20%, respectively.

More recently, Martini *et al.* [14] led a meta-analysis to compare chemotherapy and immunotherapy in the first-line setting of advanced UC. They observed no OS benefit for patients treated with first-line immune checkpoint inhibition compared to

chemotherapy among the overall population, cisplatin-ineligible patients, and PD-L1-high patients.

The ARON-2 study was designed to assess the effectiveness of pembrolizumab as first or successive line therapy in patients with advanced UC and the presence of factors influencing the prognosis of these patients. In this sub-analysis, we focused on the efficacy of pembrolizumab in the first-line setting of patients unable to receive cisplatin. We showed that median OS and PFS were 15.8 and 10.2 months, respectively. The presence of synchronous metastatic disease, visceral or bone metastases and a higher number of Bajorin risk factors were significantly associated with worst OS and PFS. The ORR was 36% with 16% of CR and type of tumor response according to RECIST 1.1 criteria was a significant predictor of OS.

Our results in terms of both OS and PFS are more favorable than those previously published in the Keynote-052 study investigating pembrolizumab in the same context. This difference can be explained by the presence of a lower percentage of patients with ECOG-PS \geq 2 (17% vs 42%) and visceral metastases (56% vs 85%) included in the ARON-2 study population. This means that in our population we have 83% of patients considered cisplatin unfit due to reasons other than PS (i.e. renal failure, hearing loss, neuropathy and heart failure), probably reflecting better the population in real life who need first-line treatment in this setting. Of note, the recent presentation of novel cisplatin-unfit criteria at ASCO 2022 [15] may influence the selection of patients candidate to receive first-line pembrolizumab and should be prospectively investigated.

Our study presents several limitations, mainly due to its retrospective nature. We had no available data neither on the criteria of eligibility of cisplatin-unfit patients nor on

concomitant medication or other comorbidities that could affect the efficacy of first-line therapy. As a consequence, our results should be interpreted with caution and are in need of a larger prospective validation.

Despite a centralized review of radiological imaging was not performed, the strong correlation between response and OS suggest a reliable assessment of RECIST 1.1 in the present study.

Nevertheless, our data show that pembrolizumab was effective as first-line therapy for cisplatin-unfit patients. Further studies investigating the biological and immunological characteristics of UC patients are warranted in order to optimize the outcome of patients receiving immunotherapy in this setting.

Conflicts of Interest

Matteo Santoni has received research support and honoraria from Janssen, Bristol Myers Squibb, Ipsen, MSD, Astellas and Bayer, all unrelated to the present paper.

R. Kanavarar has received fees for speaker bureau and advisory board activities from the following companies; Pfizer, MSD, BMS, Eisai, Ipsen, Johnson and Johnson, Merck, Amgen, Astellas and Bayer.

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Camillo Porta has received honoraria from Angelini Pharma, AstraZeneca, BMS, Eisai, General Electric, Ipsen and MSD and acted as a Protocol Steering Committee Member for BMS, Eisai and MSD.

Sebastiano Buti received honoraria as speaker at scientific events and advisory role by BMS, Pfizer, MSD, Ipsen, AstraZeneca, Merck.

The other authors declare to have no conflicts of interest.

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None to declare.

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Table Legends

Table 1. Patients' characteristics.

| | Patients (n=162) |
|---|---------------------|
| Sex | |
| Male | 117 (72) |
| Female | 45 (28) |
| Age, years (y) | |
| Median | 71 |
| Range | 43–94 |
| ECOG Performance Status | |
| 0 | 53 (33) |
| 1 | 81 (50) |
| 2 | 25 (16) |
| 3 | 2 (1) |
| Current or former smokers | 114 (70) |
| Primary tumour location | |
| Upper urinary tract | 26 (16) |
| Lower urinary tract | 136 (84) |
| Tumor histology | |
| Pure urothelial carcinoma | 142 (88) |
| Variants | 20 (12) |
| Metastatic disease | |
| Synchronous | 44 (27) |
| Metachronous | 119 (73) |
| Common sites of metastasis | |
| Lymph nodes | 112 (69) |
| Lung | 40 (25) |
| Liver | 21 (13) |
| Bone | 40 (25) |
| Brain | 3 (2) |
| Visceral metastases | |
| Yes | 90 (56) |
| No | 72 (44) |
| Previous adjuvant or neoadjuvant platinum based chemotherapy | 62 (38) |
| Second-line therapy | |
| Carboplatin + Gemcitabine | 10 (6) |
| Vinflunine | 5 (3) |
| Paclitaxel | 5 (3) |
| Gemcitabine | 2 (1) |
| Enfortumab vedotin | 2 (1) |
| Clinical trials | 5 (3) |

Table 2. Univariate and Multivariate analyses of predictors of Progression-Free Survival and Overall Survival in cisplatin-unfit UC patients treated with first-line pembrolizumab. Statistically significant values were reported in bold.

| Overall Survival | Univariate Cox Regression | | Multivariable Cox regression | |
|---|---------------------------|--------------|------------------------------|--------------|
| | HR (95%CI) | p-value | HR (95%CI) | p-value |
| Gender (females vs males) | 1.68 (1.04–2.72) | 0.033 | 1.71 (1.05–2.77) | 0.031 |
| Age (≥65y vs <65y) | 1.14 (0.69–1.86) | 0.614 | | |
| Smokers vs no-smokers | 0.88 (0.54–1.43) | 0.876 | | |
| Histology (mixed vs pure UC) | 1.30 (0.67–2.54) | 0.440 | | |
| Upper vs Lower urinary tract | 0.59 (0.28–1.24) | 0.165 | | |
| Synchronous metastatic disease (yes vs no) | 1.94 (1.20–3.15) | 0.007 | 1.61 (0.97–2.66) | 0.048 |
| Bajorin risk factors | 1.66 (1.16–2.37) | 0.005 | 1.57 (1.09–2.24) | 0.014 |
| Previous neoadjuvant or adjuvant chemotherapy | 1.07 (0.66–1.71) | 0.791 | | |

| Progression-Free Survival | Univariate Cox Regression | | Multivariable Cox regression | |
|---|---------------------------|--------------|------------------------------|--------------|
| | HR (95%CI) | p-value | HR (95%CI) | p-value |
| Gender (females vs males) | 1.38 (0.88–2.18) | 0.161 | | |
| Age (≥65y vs <65y) | 1.10 (0.70–1.73) | 0.691 | | |
| Smokers vs no-smokers | 1.09 (0.68–1.74) | 0.725 | | |
| Histology (mixed vs pure UC) | 1.56 (0.90–2.73) | 0.115 | | |
| Upper vs Lower urinary tract | 0.92 (0.51–1.66) | 0.790 | | |
| Synchronous metastatic disease (yes vs no) | 1.71 (1.09–2.67) | 0.019 | 1.49 (0.93–2.37) | 0.094 |
| Bajorin risk factors | 1.55 (1.12–2.13) | 0.007 | 1.43 (1.03–1.98) | 0.033 |
| Previous neoadjuvant or adjuvant chemotherapy | 1.40 (0.91–2.14) | 0.122 | | |

ECOG-PS = Eastern Cooperative Oncology Group-Performance Status; UC = Urothelial Carcinoma

Figure Legends

Figure 1. Median Overall Survival and Progression-Free Survival in cisplatin-unfit UC patients treated with first-line pembrolizumab.

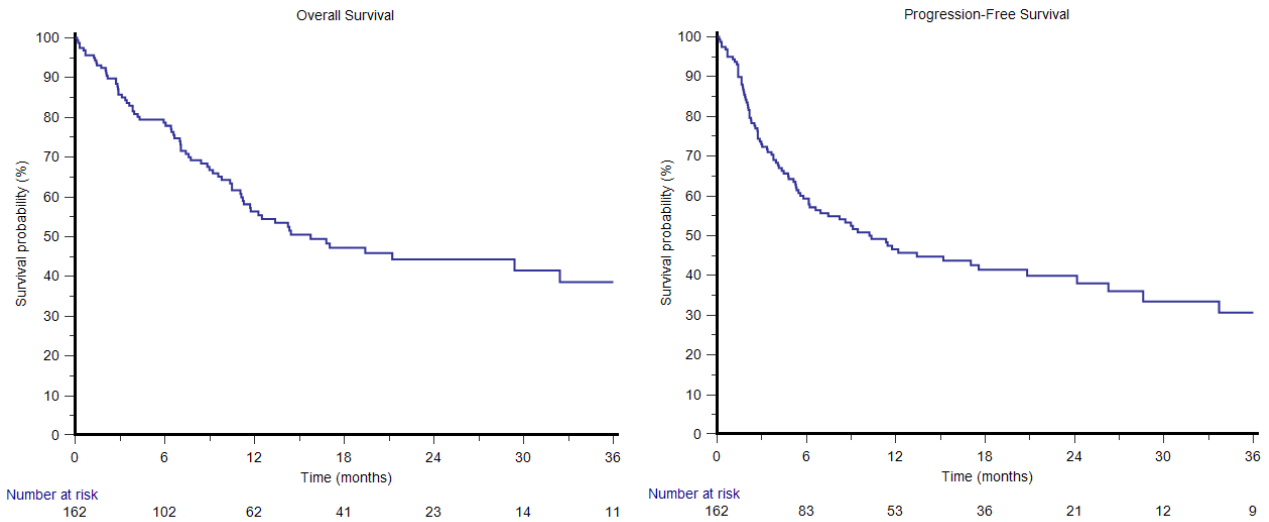


Figure 2. Median Overall Survival in cisplatin-unfit UC patients treated with first-line pembrolizumab stratified by sex and ECOG-PS.

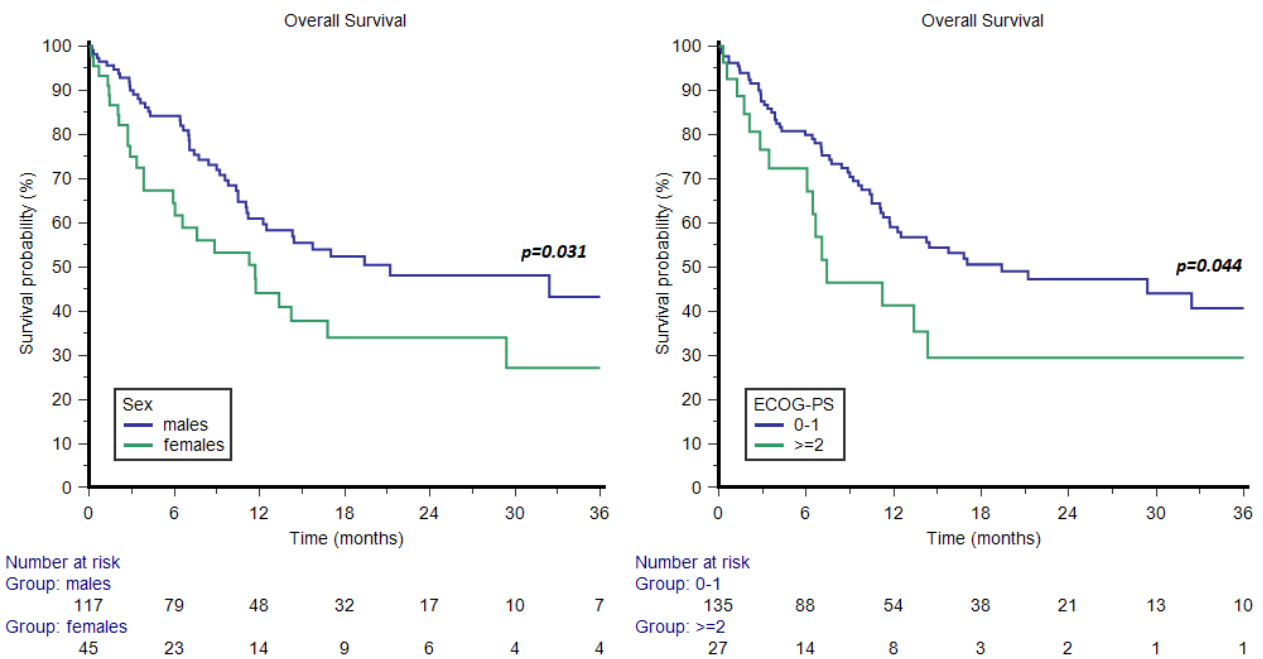


Figure 3. Median Overall Survival in cisplatin-unfit UC patients treated with first-line pembrolizumab stratified by synchronous or metachronous metastatic disease, visceral metastases, bone metastases and Bajorin risk classification.

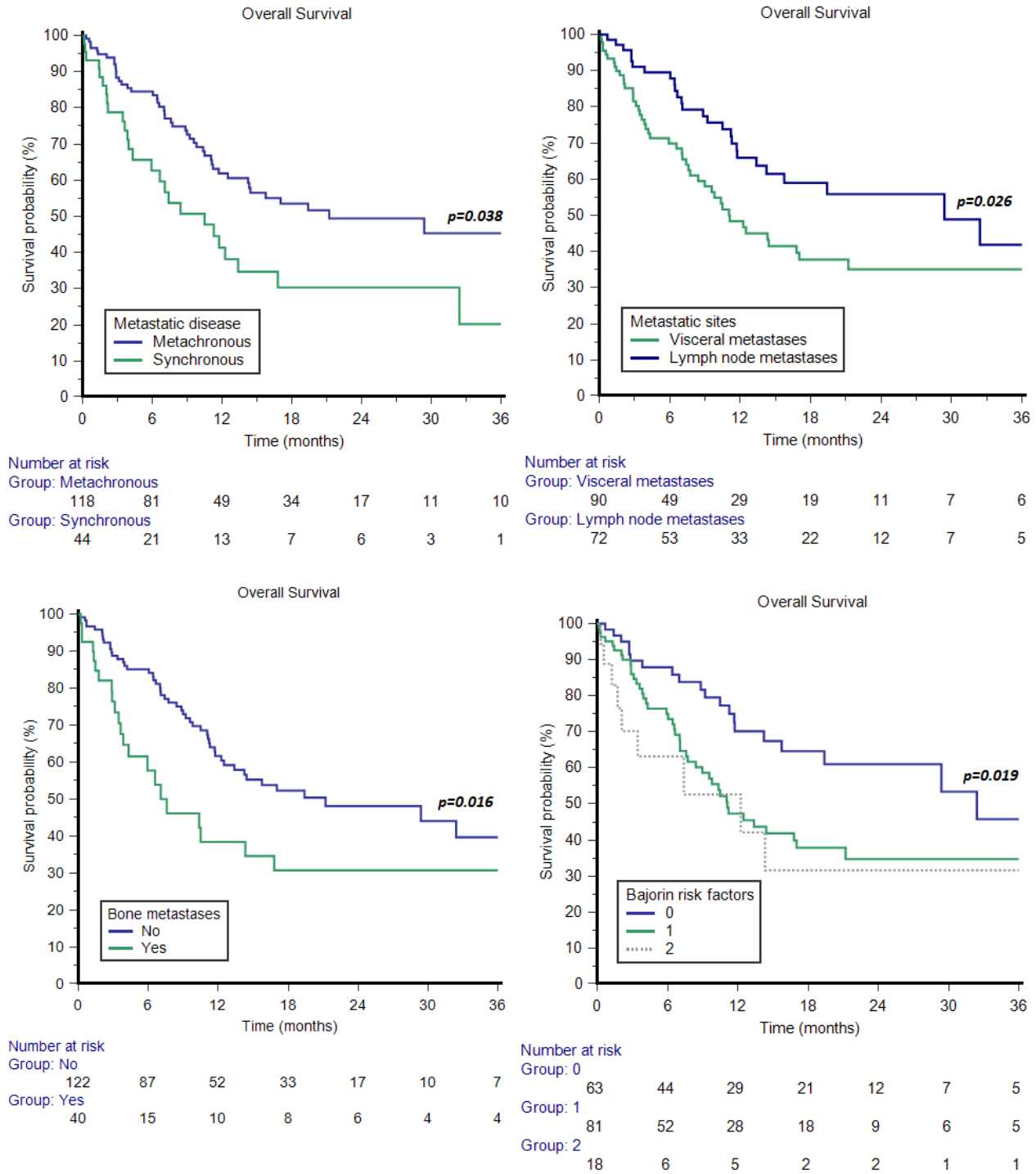


Figure 4. Median Progression-Free Survival in cisplatin-unfit UC patients treated with first-line pembrolizumab stratified by synchronous or metachronous metastatic disease, visceral metastases, bone metastases and Bajorin risk classification.

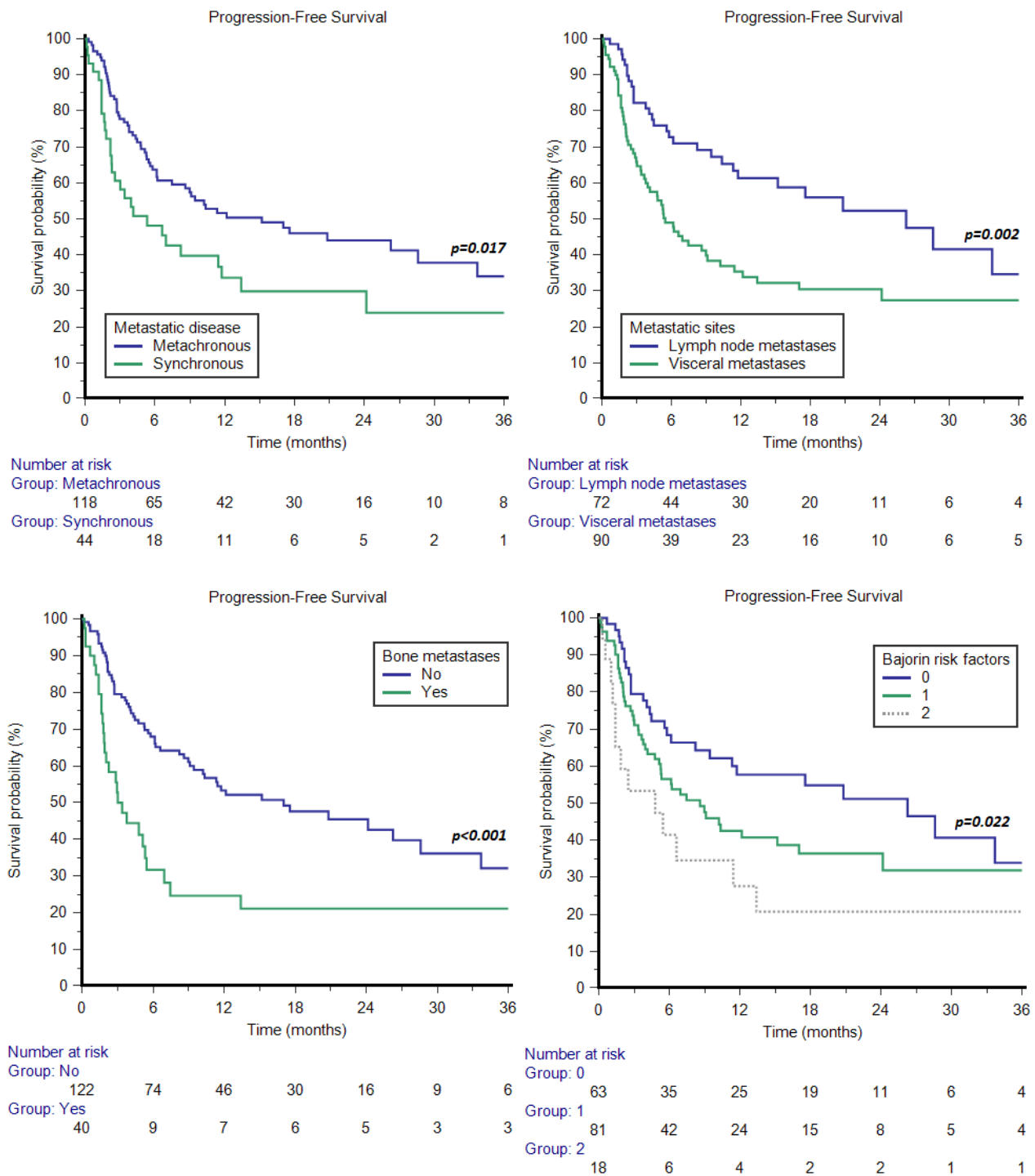
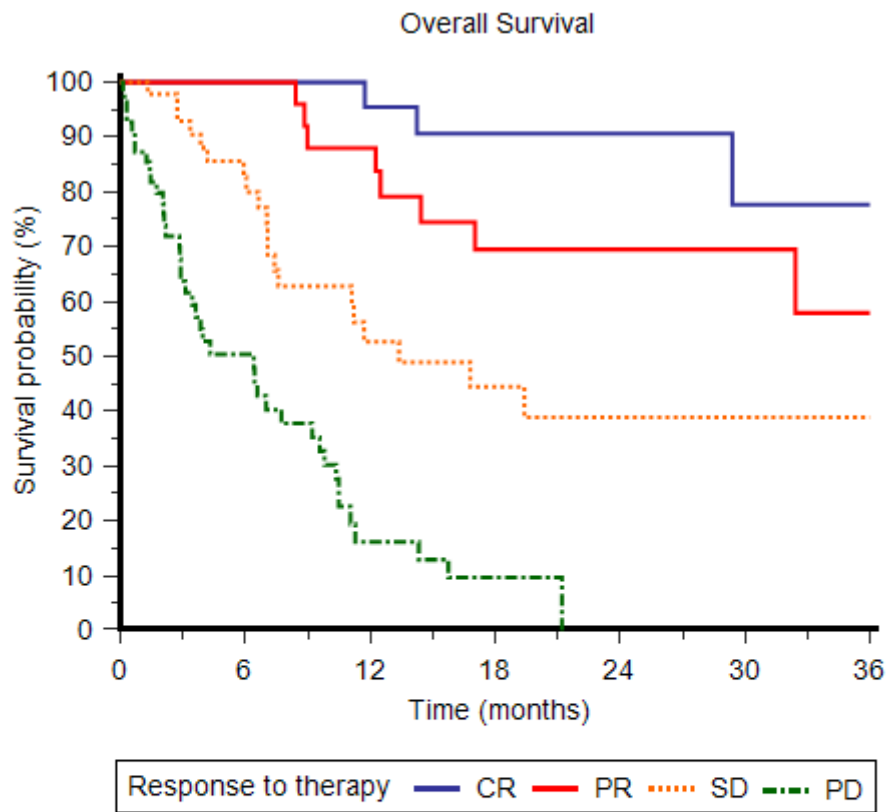


Figure 5. Overall Survival by tumor response to therapy (RECIST 1.1).



| Number at risk | | | | | | | |
|----------------|----|----|----|----|----|----|----|
| Group: | 0 | 6 | 12 | 18 | 24 | 30 | 36 |
| Group: CR | 26 | 26 | 21 | 15 | 10 | 5 | 5 |
| Group: PR | 32 | 27 | 21 | 14 | 9 | 6 | 4 |
| Group: SD | 49 | 29 | 15 | 10 | 4 | 3 | 2 |
| Group: PD | 55 | 20 | 5 | 2 | 0 | 0 | 0 |