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Impact of performance status on treatment outcomes: A real-world study of advanced urothelial cancer treated with checkpoint inhibitors

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Abstract

Background: Immune checkpoint inhibitors (ICI) represent an appealing treatment for patients with advanced urothelial cancer (aUC) and poor performance status (PS). However, ICI benefit for poor PS patients remains unknown. We hypothesized that poor PS (ECOG ≥2 vs 0–1) correlates with shorter overall survival (OS) in patients receiving ICI.

Methods: We performed a retrospective cohort study and collected clinicopathologic, treatment and outcomes data on patients with aUC treated with ICI at 18 institutions (2013–2019). We compared overall response rate (ORR) and OS in patients with ECOG PS 0–1 versus ≥2 at ICI initiation. We also tested the association between new ICI in last 30 and 90 days of life (DOL) and death location.

Results: Of 519 patients treated with ICI, 395 and 384 were included in OS and ORR analysis with 26% and 24% with PS≥2. OS was higher in those with PS 0–1 versus ≥2 treated in first line (median 15.2 vs 7.2 months; HR 0.62, p=0.01), but not in subsequent lines (median 9.8 vs 8.2 months; HR 0.78, p=0.27). ORR was similar between PS 0–1 and ≥2 in both lines. Of 288 patients who died, 10% and 32% started ICI in last 30 and 90 DOL. ICI initiation in last 30 DOL was associated with increased odds of death in hospital (OR 2.89, p=0.04).

Conclusions: Despite comparable ORR, ICI may not overcome the negative prognostic role of poor PS, particularly in 1L setting, and initiation of ICI in the last 30 DOL was associated with hospital death location.

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Multi-institution retrospective cohort study showed that patients with ECOG PS ≥2 (compared to ECOG PS 0–1) had comparable overall response rate but worse overall survival with treatment with immune checkpoint inhibitor as first line therapy, while treatment initiation in the last 30 days of life was associated with increased odds of hospital death.

Keywords

Bladder Cancer; Urothelial Carcinoma; Immunotherapy; Outcomes Research; Performance Status

Introduction:

Bladder cancer is the sixth most common malignancy in the United States (US) with an estimated 80,470 new cases and 17,670 deaths in 2019.[1] Immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of advanced urothelial cancer (aUC). Pembrolizumab, an anti-PD-1 ICI, improved overall survival (OS) after platinum-based chemotherapy as a primary endpoint in the Keynote 045 phase III trial.[2] Four other anti-PD-(L)1 ICIs are FDA-approved for treatment of platinum-refractory aUC, while atezolizumab and pembrolizumab are FDA approved in first line (1L) setting for cisplatin-unfit patients whose tumors express high PD-L1 or for platinum (cisplatin and carboplatin)-unfit patients.[3–8]

Eastern Cooperative Oncology Group (ECOG)[9] performance status (PS) has been used as a tool to guide clinicians regarding fitness for systemic therapy. It has been shown to be independently prognostic at estimating OS for patients with advanced cancer, including aUC.[10–12] The perceived favorable toxicity profile of ICIs has led to the selection of these agents in patients otherwise unfit for systemic chemotherapy. Real-world utilization patterns have shown an increase in ICI use in aUC within 60 days of death from 1% in the final quarter of 2015 to 23% in the final quarter of 2017 with at least 38% of those treated having a recorded ECOG performance status (PS) of ≥2 at the start of treatment.[13]

However, there is a paucity of data supporting the use of ICIs in patients with poor PS, who were not very well represented in the clinical trials that led to their approval with no trial enrolling patients with ECOG PS ≥3 and only three trials including patients with ECOG PS 2.[2,7,8] In addition, ECOG PS ≥3 has been associated with an imbalance in circulating CD8+ and CD4+ T-lymphocytes in patients with gastric cancer, thus raising the concern that ICI may be less effective in these patients.[14]

Based on the above, we hypothesized that clinical outcomes with ICIs are worse in patients with poor PS. Therefore, we compared overall response rate (ORR) and OS in patients with aUC and ECOG PS ≥2 vs 0–1 treated with an ICI using a newly assembled multi-institution cohort of over 500 patients. We also investigated the proportion of patients in the cohort with

new ICI initiation in last 30 and 90 days of life (DOL) and describe their site (location) of death (hospital vs other).

Methods:

Patient Selection

Patients were included if they had aUC (locally advanced / unresectable or metastatic) and received an ICI for this indication. Patients were excluded if they had pure non-UC (patients with mixed histology were included), and if an ICI was given for an alternate diagnosis or setting (e.g. (neo)adjuvant therapy). Additional exclusions were applied related to a specific analysis and are stated in detail in Figure 1. Each collaborating institution independently identified consecutive patients and collected data based on a pre-defined collection data instrument. A combination of provider-driven and electronic health record search algorithms was used to identify patients. This study was approved by institutional review board and followed the ethics from the Declaration of Helsinki.[15]

Data collection

De-identified data was collected by review of the electronic health record using secure, web-based, standardized REDCap electronic data capture tools hosted at the Institute of Translational Health Sciences.[16] Data collected using alternate methods were uploaded into REDCap for secure storage and standardization of variables. Demographic, clinicopathologic, laboratory and clinical outcomes data were collected. Given the retrospective study design, treatment response was determined by data collector based on radiographic studies and clinic notes and did not include central evaluation by a blinded radiologist per RECIST 1.1 criteria.

ORR was calculated as the sum of patients with reported complete and partial response among all patients with available information. OS was defined as time from ICI initiation until date of death or censored at date of last follow-up visit. ORR and OS data were analyzed separately for patients treated with ICI in the 1L and the subsequent setting (second line and beyond; 2+L).

Statistical Analysis

Demographic information and clinical variables were summarized using descriptive statistics. Categorical and continuous variables were compared with chi-squared and t-test, respectively. OS was estimated using Kaplan-Meier curves. Univariate and multivariable Cox proportional-hazards models were used to evaluate the association between ECOG PS (0–1 vs ≥2) and OS. The covariates chosen for analysis included age at ICI initiation, sex, race (white vs other), smoking history, history of extirpative surgery, pure UC histology, hemoglobin (Hgb) <10 g/dL at ICI initiation and liver metastases at ICI initiation. Each covariate was tested with univariate analysis and those with $p<0.1$ were included in final multivariate model. Univariate logistic regression was used to compare ORR for patients with ECOG PS 0–1 vs ≥2 and to evaluate whether new ICI initiation in the final 30 and 90 DOL was associated with death in the hospital (vs elsewhere). Analyses were performed by STATA 15.1 (StataCorp, College Station, TX).

Results:

Baseline patient and clinicopathologic characteristics

Data on 519 patients across 18 institutions were collected. After exclusions (Figure 1), 395 patients were included in the OS analysis, 206 (52%) were treated with an ICI in 1L and 189 (48%) in the 2+L setting, with 30% and 21% of patients with ECOG PS ≥2, respectively. Table 1 shows the baseline characteristics of patients stratified by treatment line and ECOG PS. Mean age was 70 for both ECOG PS 0–1 and ≥2 in 1L, and 68 for both 0–1 and ≥2 in 2+L. The proportion of patients with hemoglobin (Hgb) <10 g/dL at ICI initiation was 19% vs 36% among patients with ECOG PS 0–1 vs ≥2 in 1L (p=0.01) and 22% vs 38% for ECOG PS 0–1 vs ≥2 in 2+L (p=0.05). However, the proportion of patients with liver metastases with ECOG PS 0–1 vs ≥2 in 1L and 2+L did not differ significantly (p=0.55 and p=0.71, respectively). Altogether, the proportion with Bellmunt[12] risk factors of zero, one, two and three in the 1L and 2+L are shown in Table 1.

Overall survival

Kaplan-Meier curves for OS in the 1L and 2+L are shown in Figure 2 (A and B, respectively) and median OS in Table 2A. Among the 206 patients treated with an ICI in 1L, the median OS was 15.2 months (95% confidence interval [CI] 11.5–21.9) vs 7.2 months (95% CI 3.4–12.8) for those with ECOG PS 0–1 vs ≥2 (HR 0.62, 95% CI 0.42–0.91, p=0.01). This association remained significant with multivariate Cox analysis after adjusting for significant covariates hemoglobin<10g/dL and presence of liver metastases, both at time of ICI initiation (Table 2A). Among the 189 patients treated with an ICI in the 2+L, the median OS was 9.8 months (95% CI 7.7–14.0) and 8.2 months (95% CI 3.5–11.9) for those with ECOG PS 0–1 vs ≥2 (HR 0.78, 95% CI 0.51–1.21, p=0.27). Among 12 patients (five in 1L and seven in 2+L) with ECOG PS 3, the median OS was 3.5 months (95% CI 0.2 months-not reached [NR]) for all patients; and 3.4 months (95% CI 0.16-NR) in 1L and 3.7 months (95% CI 0.20-NR) in 2+L.

Overall response rate

Table 2B shows ORR for patients with ECOG PS 0–1 and ≥2 treated with an ICI in 1L and 2+L. A total of 384 patients were included in this analysis (196 1L, 188 2+L). Baseline characteristics (not shown) were comparable to those shown for OS analysis cohort in Table 1. In the 1L setting, patients with ECOG PS 0–1 vs ≥2 had ORR of 31% vs 33% (p=0.75); in the 2+L setting, patients with ECOG PS 0–1 vs ≥2 had ORR of 27% vs 23% (p=0.56). However, among 11 patients (four in 1L and seven in 2+L) with ECOG PS 3, no patient had response, two died within a week of treatment, two had stable disease as best response (remaining on treatment for five months and 12 months), six had progressive disease on first restaging CT, and one patient did not have detailed data regarding time of progression. Median number of ICI doses for patients with ECOG PS 3 was three.

Site of death in patients receiving ICI near end of life (EOL)

Overall, 288 patients were deceased at the time of data collection. Among the deceased patients, 29 (10%) had started an ICI in the last 30 DOL and 93 (32%) started an ICI in last

90 DOL. Of the 288 patients, 187 had recorded site of death, including 18 (10%) who started an ICI in the final 30 DOL and 62 (33%) in the final 90 DOL. Ten of the 18 (56%) who started with ICI initiation in the last 30 DOL died in the hospital (90% due to aUC and 10% from unrelated comorbidity) though only 40% (four of ten) had ECOG PS 2 at ICI initiation. Conversely, only 51 of the 169 patients (30%) who had not started an ICI in the last 30 DOL died in the hospital. ICI initiation in the last 30 DOL was associated with increased odds of death in the hospital vs elsewhere (OR 2.89, 95% CI 1.07–7.75, p=0.04). The same association between ICI initiation and hospital site of death was not observed for those started on an ICI in the last 90 DOL (OR 1.35, CI 0.71–2.56, p=0.36). Only five patients out of 187 deceased patients (2%) had initiated other systemic therapy in the last 30 DOL and 20 (7%) in the last 90 DOL; considering the small sample size there was no significant association of non-ICI treatment initiation with site of death in final 30 DOL (OR 3.21 [95% CI 0.52–19.72], p=0.21) or for final 90 DOL (OR 1.96 [95% CI 0.72–5.37], p=0.19).

Discussion:

PS has been incorporated into multiple prognostic tools in oncology, including both Bajorin[11] and Bellmunt[12] for aUC. However, since initial approval of atezolizumab in 2016, ICIs have changed the treatment landscape in aUC. Given ICIs are generally better tolerated than chemotherapy, much higher use has been reported near the EOL and among those with poor PS[13] despite limited data from clinical trials regarding benefit in this population. Recent accelerated FDA-approval of erdafitinib for tumors harboring FGFR2/3 alterations and promising results in phase II trials with other targeted therapies and antibody drug conjugates, such enfortumab-vedotin, sacituzumab govitecan (IMMU-132) and anti-HER2 compounds, can further increase non-chemotherapy treatment options for aUC.[17,18] In our study, patients with ECOG PS ≥2 treated with ICI had significantly shorter OS vs those with ECOG PS 0–1 treated in the 1L, and ICI use near the EOL was associated with increased odds of dying in the hospital. In addition, the few patients in the study with ECOG PS 3 had 0% ORR with median OS of 3.5 months, suggesting limited benefit for this population.

Our study provides valuable information about the real-world practice and outcomes for patients with ECOG PS ≥2 treated with ICI. Most prior studies with real-world data investigated utilization practices, efficacy (measured by ORR) and safety. In addition to reporting general clinical use patterns and efficacy, our study also extends to report specific outcomes for patients with ECOG PS 2–3 and information on site of death in patients who started ICI near EOL.

Mhatre et al. noted 27% of patients treated with atezolizumab in 1L and 17% as salvage had ECOG PS ≥2, which is comparable to our data with 31% and 21%, respectively.[19] Conversely, other real-world studies generally reported worse outcomes compared to our study. The SAUL study,[20] investigating worldwide safety and efficacy of atezolizumab, enrolled 101 patients with ECOG PS 2 and noted ORR 5% and mOS 2.3 months. Barata et al.[21] reported a single institution series of 79 patients with aUC patients treated with atezolizumab, including 24% with ECOG PS ≥2, and reported ORR for the entire cohort (including ECOG PS 0–1) of 18%. Pal et al. reported outcomes from an expanded access program with atezolizumab, which included 20 patients with ECOG PS ≥2 and noted ORR

of 17% among all patients with evaluable disease (including ECOG PS 0–1). All three studies reported lower ORR than the 33% we observed for patients with ECOG PS ≥2 in 1L and 23% in 2+L. This discrepancy may be due to several factors, such as different populations and other confounders. Also, the other studies used RECIST v.1.1[22] criteria to determine response, while in our study response was determined based on review of radiology reports and clinical notes (interpreted by treating provider) as use of RECIST v.1.1 was not feasible with our retrospective multi-site study design.

However, the ORR in our study is comparable to that reported in clinical trials among patients with aUC and ECOG PS ≥2.[2,7,8] ORR for patients with ECOG PS ≥2 enrolled in these trials ranged from 25% in the cisplatin-ineligible 1L cohort 1 of the IMvigor210 trial[7] to 27% in the cisplatin-ineligible 1L population in KEYNOTE-052 trial[8]. KEYNOTE-045, the phase 3 trial that showed OS advantage of pembrolizumab over salvage chemotherapy for platinum-refractory aUC, also enrolled patients with ECOG PS 2 but only six were enrolled and only two received pembrolizumab (four randomized to chemotherapy control), thus no ORR was reported for this cohort.[2] Similar data regarding ORR and OS is not widely available for chemotherapy as chemotherapy trials for aUC have mostly enrolled patients with ECOG PS 0–1. Among patients with ECOG PS 0–1 in clinical trials, ORR with 1L platinum doublet chemotherapy[23–25] is 33–73% which is higher than the ORR of 23–29% for 1L ICIs in cisplatin-ineligible patients[7,8], but with comparable median OS (14–15 months with 1L platinum doublet vs 11–16 months with ICI). Likewise, 2+L outcomes are comparable with ORR of 11–28% vs 13–21% and median OS of 7–11 months vs 7–18 months between chemotherapy[2,26–29] and ICI[2–6,29], respectively. However, with the exception of randomized phase III clinical trials (e.g. KEYNOTE-045, IMvigor211), it is very hard to compare chemotherapy and ICI (among different studies).Despite the comparable ORR between ECOG PS 0–1 and ≥2 in our study, we still noted shorter OS for those with ECOG PS ≥2 treated with ICI in 1L setting. A recent meta-analysis from Bersanelli et al. evaluated ICI outcomes of clinical trial participants (across multiple tumor types) with ECOG PS 1–2 compared to 0.[30] In this study, stratified hazard ratios for death reported by ECOG PS were extracted from 15 phase 2 and 3 randomized controlled ICI clinical trials (including two aUC trials[2,29]) and patients with ECOG PS 1–2 had similar HR to those with ECOG PS 0 with HR 0.78 (95% CI 0.71–0.86) and 0.78 (95% CI 0.69–0.89), respectively. However, only 11 patients with ECOG PS 2 were included in the meta-analysis. Overall, data suggests that ICI may not circumvent the robust negative prognostic role of ECOG PS ≥2 in aUC.

Minimization of chemotherapy utilization near EOL has been identified as a metric of high quality (value-based) cancer care.[31] The same metric has not necessarily been carried over to ICI utilization. A study of ICI utilization practices using the Flatiron Health dataset showed that 23% of patients with UC were treated with ICI in the final 30 DOL and at least 38% of those patients had ECOG PS≥2 at the start of ICI treatment.[13] In addition, a single-institution retrospective cohort study by Glisch et al.[32] investigated ICI use (across tumor types) near the EOL and identified 27% of patients in their cohort of 157 who were treated with ICI in the last 30 DOL; ICI use in the last 30 DOL was associated with lower hospice enrollment and higher chance of dying in the hospital. In our study, only 10% had ICI initiation in the last 30 DOL, however ICI initiation near EOL was associated with higher

odds of dying in the hospital. It is notable that 60% of the patients who were treated with an ICI in the last 30 DOL and died in the hospital had ECOG PS 0–1 at ICI initiation so death may not have appeared imminent at the time of ICI initiation. Further, given the retrospective study nature, we cannot prove a causal relationship between ICI initiation near EOL and hospital death, but we noted a similar association as was reported by Glisch et al.[32]

While a meaningful number of patients with ECOG PS ≥2 appeared to benefit, at least based on ORR, 0 out of 11 patients with ECOG PS 3 had response to ICI and only two (18%) had stable disease, whereas two of 12 (17%) died within a week of receiving ICI. Overall, our data suggests that the decision of ICI initiation near EOL, akin to the practice for chemotherapy, should be considered carefully and accompanied by a detailed discussion of data, rationale, risks and benefits to minimize unnecessary potential adverse events, cost and intensity of EOL care. Furthermore, while our sample size is limited, it suggests that those with ECOG PS 3 are unlikely to benefit from ICI.

Our study underscores the importance in developing prospectively validated predictive biomarkers to aid in identifying patients most and least likely to benefit from ICI. Although, prognostic nomograms have been developed, composite predictive biomarkers (which can aid in decision making) need to demonstrate clinical utility via interrogation in clinical trials.[33,34] Numerous putative biomarkers are under exploration, including PD-L1 protein expression, tumor mutational burden, T-effector, TGF-β, EMT and other gene signatures, DNA damage response gene and FGFR3 alterations, molecular subtypes, T cell clonality / diversity, etc., but more work needs to be done to further validate clinically useful predictive biomarkers.[35–38] Without identification of such reliable and granular predictive tools, clinicians are left to utilize more blunt prognostic tools, like ECOG PS, to guide practice.

The strengths of this study include utilization of “real-world” data, multi-institution representation and the reasonable cohort size. Limitations include the retrospective nature, lack of randomized comparisons or external validation, heterogeneity in clinical practice and data collection across institutions, lack of adjustment for other selection and confounding biases at the time of ICI initiation, and missing data. In addition, the assembled cohort only includes patients treated with an ICI, so conclusions are limited in comparison to those not treated with ICI. We also did not report toxicity, robust cost-effectiveness models or evaluation of molecular biomarkers, and there was no central radiology or pathology review. There was no objective standardization of response measurements (e.g. RECIST 1.1 criteria) and subjective investigator assessment was instead utilized. This subjective nature of response assessment may potentially be susceptible to an over-estimation of ORR. Despite these inherent limitations, our study may contribute to the ongoing discussions regarding the optimal use of ICIs in aUC and other tumor types and generate hypotheses to be tested in larger cohorts and prospective studies.

In conclusion, our data show that patients with ECOG PS ≥2 have similar ORR to ICIs as those with ECOG PS 0–1, but this may not overcome the negative prognostic role of poor PS, and ICIs started near the end of life are associated with increased odds of death in the hospital.

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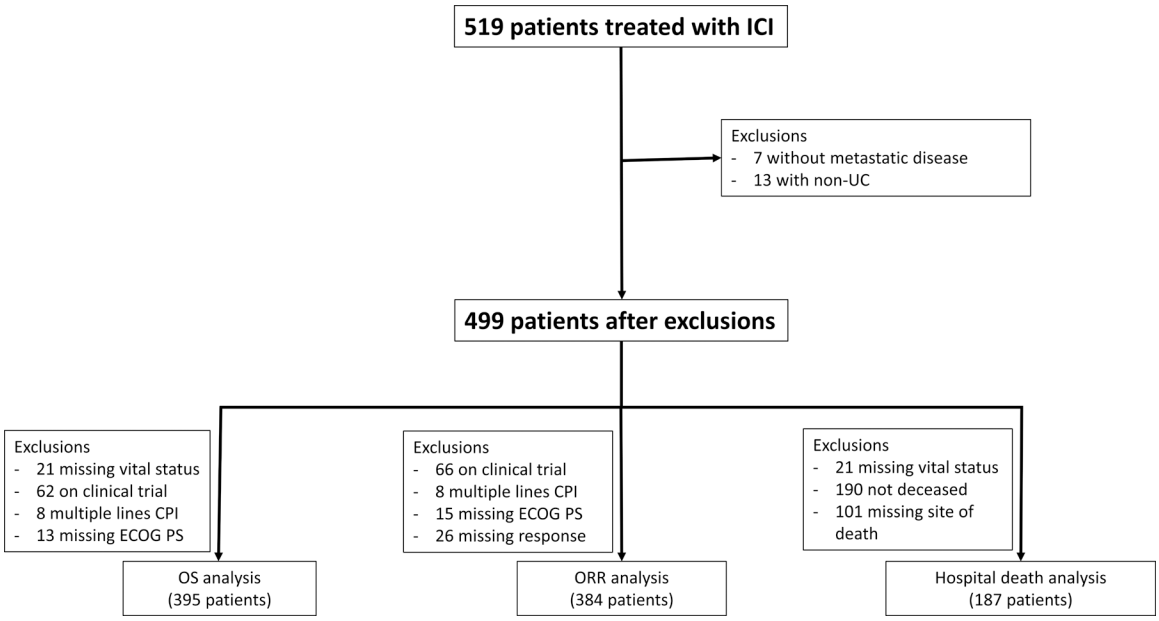
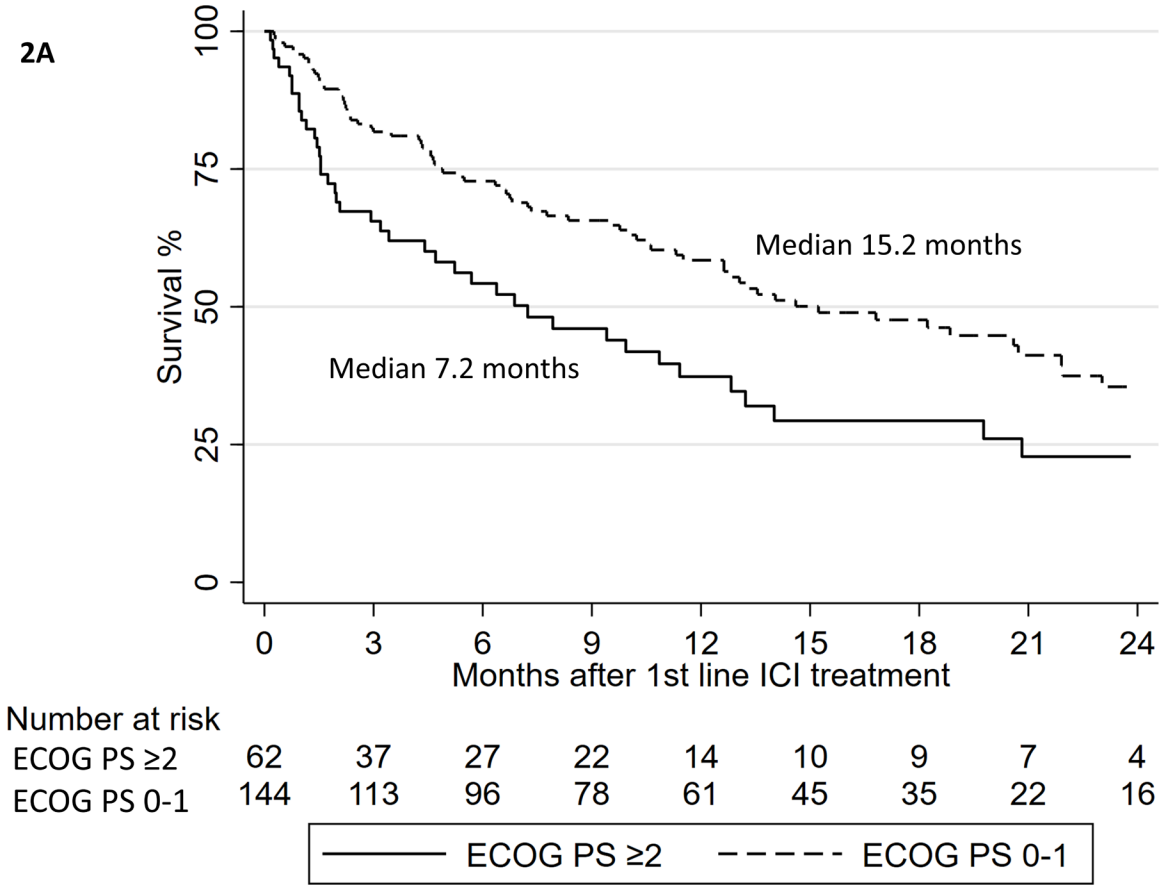


Figure 1.
Consort diagram of patients for multi-institution cohort

2A



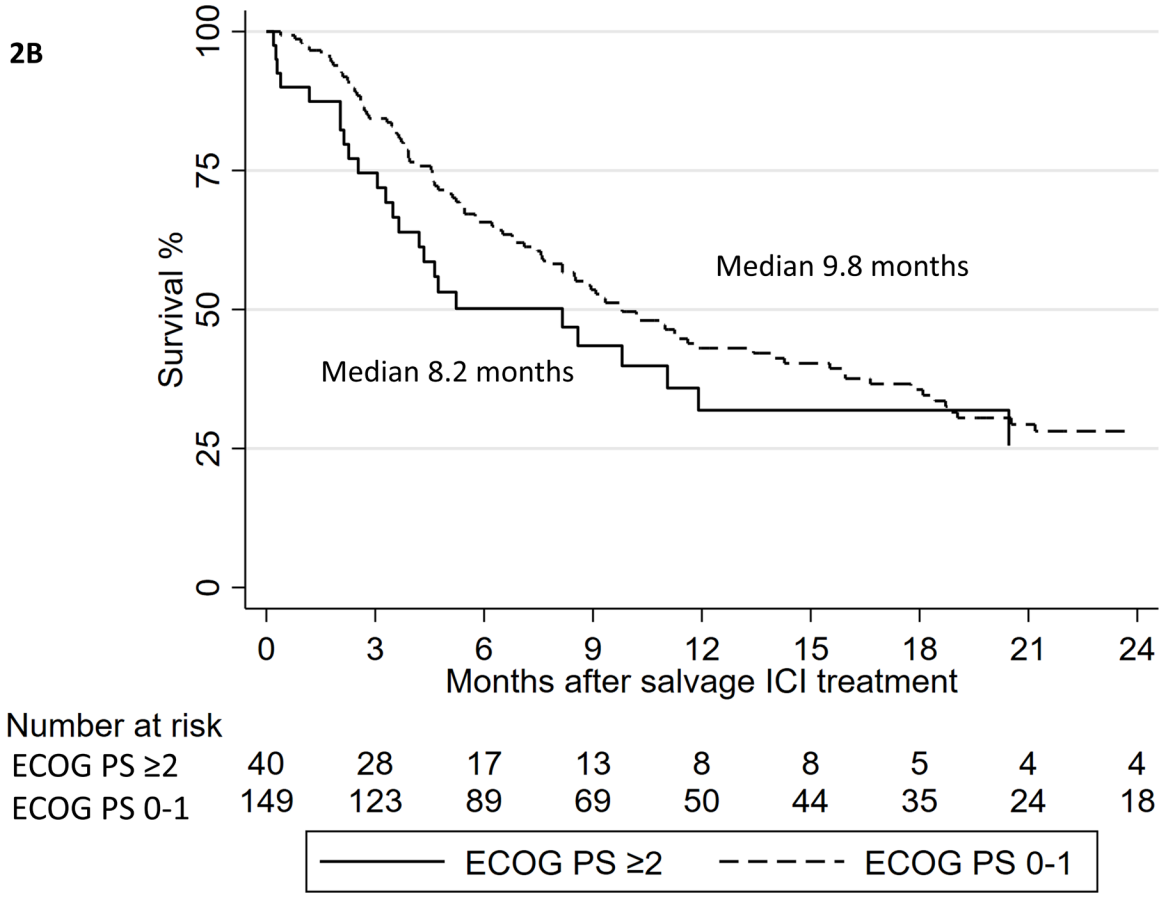


Figure 2.
Kaplan-Meier curves for overall survival by ECOG PS (0–1 vs ≥2) in first line (2A) and second or later line (2B) ICI

Table 1.

Baseline characteristics of patients for overall survival analysis cohort.

	First line ICI			Second or later line ICI			Total Cohort
ECOG PS	**0–1**	**≥2**	**P**	**0–1**	**≥2**	**P**	**395**
Number of Patients	144	62		149	40		
Age at ICI initiation (mean ± SD)	70 ± 11	70 ± 13	0.71	68 ± 9	68 ± 10	0.92	69 ± 10
Male	108	40	0.13	118	29	0.37	295 (75%)
Ever Smoker	92 (64%)	41	0.81	105	27	0.72	265 (67%)
White race	118	48	0.45	123	28	0.08	317 (80%)
Pure UC	93 (65%)	45	0.26	108	31	0.38	277 (70%)
Cystectomy or (Nephro)ureterectomy	74 (60%)	28 (48%)	0.13	65 (53%)	15 (41%)	0.19	182 (53%)
Hgb<10 g/dL [number (%)] at ICI initiation	27 (19%)	21 (36%)	0.01	32 (22%)	15 (38%)	0.05	95 (25%)
Albumin<4 g/dL [number (%)] at ICI initiation	80 (58%)	49 (83%)	0.001	91 (63%)	29 (73%)	0.25	249 (65%)
Liver Metastasis (%) at ICI initiation	23 (16%)	12 (19%)	0.55	26 (17%)	8 (20%)	0.71	69 (17%)
ECOG [number (%)]							
0	45 (31%)	n/a	n/a	48 (32%)	n/a	n/a	93 (24%)
1	99 (69%)	n/a		101	n/a		200 (51%)
2	n/a	57		n/a	33		90 (23%)
3	n/a	5 (8%)		n/a	7 (18%)		12 (3%)
Bellmunt Risk Factors [number (%)]							
0	32 (22%)	0 (0%)	<0.001	36 (24%)	0 (0%)	<0.001	68 (17%)
1	79 (55%)	33		72 (48%)	18		202 (51%)
2	29 (20%)	25		36 (24%)	21		111 (28%)
3	4 (3%)	4 (6%)		5 (3%)	1 (3%)		14 (4%)

Table 2.

Overall survival (A) and observed response rate (B) by ECOG PS in first line and second or later line. Odds ratio for ORR was determined by univariate logistic regression and hazard ratio for OS by univariate and multivariate Cox regression.

2A. Overall Survival		
ECOG PS	**First Line ICI**	**Second or later line ICI**
0–1	Median 15.2 months (11.5–21.9)	Median 9.8 months (7.7–14.0)
≥2	Median 7.2 months (3.4–12.8)	Median 8.2 months (3.5–11.9)
HR (95% CI) *	0.62 (0.42–0.91)	0.78 (0.51–1.21)
HR (95% CI)) **	0.66 (0.44–0.98)	0.83 (0.53–1.28)
2B. Observed response rate		
ECOG PS	**First Line ICI**	**Second or later line ICI**
0–1	31%	27%
≥2	33%	23%
OR (95% CI)	0.90 (0.46–1.75)	1.28 (0.56–2.91)

* Univariate Cox Regression Model

** Multivariate Cox regression model including hgb<10g/dL and liver metastases at ICI initiation