UC San Diego
UC San Diego Previously Published Works

Title
A New Prognostic Model in Patients with Advanced Urothelial Carcinoma Treated with First-line Immune Checkpoint Inhibitors

Permalink
https://escholarship.org/uc/item/6ft7s89c

Journal
European Urology Oncology, 4(3)

ISSN
2588-9311

Authors
Khaki, Ali Raza
Li, Ang
Diamantopoulos, Leonidas N
et al.

Publication Date
2021-06-01

DOI
10.1016/j.euo.2020.12.006

Peer reviewed

A New Prognostic Model in Patients with Advanced Urothelial Carcinoma Treated with First-line Immune Checkpoint Inhibitors

Ali Raza Khaki[a], **Ang Li**[b], **Leonidas N. Diamantopoulos**[a], **Natalie J. Miller**[a], **Lucia Carril-Ajuria**[c], **Daniel Castellano**[c], **Ivan De Kouchkovsky**[d], **Vadim Koshkin**[d], **Joseph Park**[e], **Ajjai Alva**[e], **Mehmet A. Bilen**[f], **Tyler Stewart**[g], **Victor Santos**[h], **Neeraj Agarwal**[h], **Jayanshu Jain**[i], **Yousef Zakharia**[j], **Rafael Morales-Barrera**[k], **Michael Devitt**[l], **Ariel Nelson**[m,n], **Christopher J. Hoimes**[m,o], **Evan Shreck**[p], **Benjamin A. Gartrell**[p], **Alex Sankin**[p], **Abhishek Tripathi**[q], **Roubini Zakopoulou**[r], **Aristotelis Bamias**[s], **Alejo Rodriguez-Vida**[t], **Alexandra Drakaki**[u], **Sandy Liu**[u], **Vivek Kumar**[v], **Mark P. Lythgoe**[w], **David J. Pinato**[w], **Jure Murgic**[x], **Ana Fröbe**[x], **Monika Joshi**[y], **Pedro Isaacsson Velho**[z], **Noah Hahn**[z], **Lucia Alonso Buznego**[aa], **Ignacio Duran**[aa], **Marcus Moses**[bb], **Pedro Barata**[bb], **Matthew D. Galsky**[cc], **Guru Sonpavde**[dd], **Evan Y. Yu**[a], **Veena Shankaran**[a], **Gary H. Lyman**[a], **Petros Grivas**[a,*]

[a]Division of Oncology, Department of Medicine, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, University of Washington, Seattle, WA, USA

[b]Section of Hematology/Oncology, Department of Medicine, Baylor College of Medicine, Houston, TX, USA

[c]Hospital Universitario 12 de Octubre, Madrid, Spain

[d]Division of Oncology, Department of Medicine, University of California, San Francisco, San Francisco, CA, USA

[e]Division of Oncology, Department of Medicine, University of Michigan, Ann Arbor, MI, USA

[f]Winship Cancer Institute of Emory University, Atlanta, GA, USA

[g]Division of Oncology, Department of Medicine, University of California, San Diego, La Jolla, CA, USA

[h]Division of Oncology, Department of Medicine, University of Utah, Salt Lake City, UT, USA

[i]Department of Medicine, University of Iowa, Iowa City, IA, USA

[j]Division of Oncology, Department of Medicine, University of Iowa, Iowa City, IA, USA

[k]Vall d'Hebron Institute of Oncology, Vall d' Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain

[l]Division of Hematology/Oncology, Department of Medicine, University of Virginia School of Medicine, Charlottesville, VA, USA

[m]Division of Medical Oncology, Seidman Cancer Center at Case Comprehensive Cancer Center, Cleveland, OH, USA

[n]Division of Hematology and Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

[o]Division of Medical Oncology, Duke University, Durham, NC, USA

[p]Departments of Medical Oncology and Urology, Montefiore Medical Center, Bronx, NY, USA

[q]Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

[r]Department of Clinical Therapeutics, Alexandra General Hospital, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

[s]2nd Propaedeutic Department of Internal Medicine, ATTIKON University Hospital, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

[t]Medical Oncology Department, Hospital del Mar Research Institute, Barcelona, Spain

[u]Division of Hematology/Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

[v]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[w]Department of Surgery and Cancer, Imperial College London, London, UK

[x]Department of Oncology and Nuclear Medicine, University Hospital Center Sestre Milosrdnice, School of Dental Medicine, Zagreb, Croatia

[y]Division of Hematology/Oncology, Department of Medicine, Penn State Cancer Institute, Hershey, PA, USA

[z]Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA

[aa]Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain

[bb]Department of Medicine, Section of Hematology/Oncology, Tulane University, New Orleans, LA, USA

[cc]Division of Oncology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[dd]Genitourinary Oncology Program, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Abstract

Background: While immune checkpoint inhibitors (ICIs) are approved in the first-line (1L) setting for cisplatin-unfit patients with programmed death-ligand 1 (PD-L1)-high tumors or for platinum (cisplatin/carboplatin)-unfit patients, response rates remain modest and outcomes vary with no clinically useful biomarkers (except for PD-L1).

Objective: We aimed to develop a prognostic model for overall survival (OS) in patients receiving 1L ICIs for advanced urothelial cancer (aUC) in a multicenter cohort study.

Design, setting, and participants: Patients treated with 1L ICIs for aUC across 24 institutions and five countries (in the USA and Europe) outside clinical trials were included in this study.

Outcome measurements and statistical analysis: We used a stepwise, hypothesis-driven approach using clinician-selected covariates to develop new risk scores for patients receiving ICIs in the 1L setting. Demographics, clinicopathologic data, treatment patterns, and OS were collected uniformly. Univariate Cox regression was performed on 18 covariates hypothesized to be associated with OS based on published data. Variables were retained for multivariate analysis (MVA) if they correlated with OS ($p < 0.2$) and were included in the final model if $p < 0.05$ on MVA. Retained covariates were assigned points based on the beta coefficient to create a risk score. Stratified median OS and C-statistic were calculated.

Results and limitations: Among 984 patients, 357 with a mean age of 71 yr were included in the analysis, 27% were female, 68% had pure UC, and 13% had upper tract UC. Eastern Cooperative Oncology Group performance status 2, albumin <3.5 g/dl, neutrophil:lymphocyte ratio >5, and liver metastases were significant prognostic factors on MVA and were included in the risk score. C index for new 1L risk score was 0.68 (95% confidence interval 0.65–0.71). Limitations include retrospective nature and lack of external validation.

Conclusions: We developed a new 1L ICI risk score for OS based on data from patients with aUC treated with ICIs in the USA and Europe outside of clinical trials. The score components highlight readily available factors related to tumor biology and treatment response. External validation is being pursued.

Patient summary: With multiple new treatments under development and approved for advanced urothelial carcinoma, it can be difficult to identify the best treatment sequence for each patient. The risk score may help inform treatment discussions and estimate outcomes in patients treated with first-line immune checkpoint inhibitors, while it can also impact clinical trial design and endpoints.

Keywords

1. Introduction

Bladder cancer is very common, with an estimated 81 400 new cases and 17 980 deaths in 2020 in USA [1]. Since 2016, five 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) for the treatment of advanced urothelial cancer (aUC) [2]. Pembrolizumab (anti–PD-1) and avelumab (anti–PD-L1) improved overall survival (OS) in the platinum-refractory and switch maintenance (after first-line platinum chemotherapy) settings, respectively [3,4]. Anti–PD-(L)1 ICIs also have a role in the first-line setting for cisplatin-unfit patients with high PD-L1 tumors or for platinum (cisplatin and carboplatin)-unfit patients [2]. However, outcomes for those with poor Eastern Cooperative Oncology Group (ECOG) performance status (PS) and treatment-resistant tumors remain poor [5,6]. More recently, erdafitinib, a fibroblast growth factor receptor (FGFR) inhibitor, and enfortumab vedotin, an antibody-drug conjugate against Nectin-4, both received accelerated FDA approval in treatment-refractory aUC [7,8].

Multiple clinical prognostic tools have been developed in patients with aUC treated with chemotherapy to identify prognostic factors to guide practice and inform clinical trial enrollment and risk stratification [9–17]. Two prominent tools, developed by Bajorin et al [9] and Bellmunt et al [10], have been used for prognostication of patients receiving first-line and salvage treatment, respectively. The first-line Bajorin risk score was developed in 1999, and includes PS and presence of visceral metastases (bone, lung, or liver). Few tools have been developed in patients treated with ICIs [16,17], and no tool is validated among patients with aUC treated with ICIs outside the context of clinical trials. Using a retrospective cohort of over 900 patients across 24 institutions from the USA and Europe, we developed and internally validated a new risk score for the first-line setting to prognosticate outcomes for patients with aUC treated with ICIs outside of clinical trials.

2. Patients and methods

2.1. Patient selection

We used a multi-institution cohort [5,6]. Patients were included if they had aUC (locally advanced, unresectable, or metastatic) and were treated with ICIs for this indication. Each collaborating institution independently identified consecutive patients and collected data based on a predefined and locked data collection instrument. A combination of provider-driven and electronic health record search algorithms was used. Patients were excluded from the current study if an ICI was given for alternate diagnosis or treatment setting (eg, [neo]adjuvant), they were treated with combinations or were on clinical trials, they received multiple lines of ICIs, or ICI start date or key covariates for modeling were missing. This study was approved by the institutional review board; it also followed the Declaration of Helsinki principles and local procedures at each center.

2.2. Data collection

Deidentified data including demographic, clinicopathologic, laboratory, and outcomes were collected. OS was defined as the time from ICI initiation until the date of death or the date of

censoring at the last follow-up. Patients with vital status missing were considered to be alive and censored at the date of last known follow-up.

All data were collected by a review of the electronic health record and stored using secure, web-based, standardized REDCap electronic data capture tools hosted at the Institute of Translational Health Sciences [18]. Data recorded using alternate methods were uploaded into REDCap for secure storage and standardization of variables.

2.3. Statistical analysis

A stepwise, hypothesis-driven approach of clinician-selected covariates was used to develop a new prognostic model for those receiving ICIs as first-line treatment. Univariate (UVA) Cox regression was performed on covariates hypothesized to be associated with OS. Supplementary Table 1 shows the full list of covariates tested. Continuous variables were initially tested on a continuous scale, and those that were retained for multivariate (MVA) Cox regression were transformed to a cut-point relative to the normal range or based on previously established cut-points in the literature. Variables were tested with MVA if they had a statistical relationship with OS ($p < 0.2$) and were retained if $p < 0.05$ on MVA. Each retained covariate was assigned points according to the weight of the beta coefficient to develop the final risk score.

To assess the follow-up, we used the reverse Kaplan-Meier method, and to assess the goodness of fit of the new risk model, we used a bias-corrected estimate of the Harrell's C index [19]. The C index ranges in value from 0.5 to 1.0, with a value of 0.5 indicating a very poor model, 0.7 a good model, and 1.0 a perfect fit. For internal validation, bootstrap resampling was performed with 200 samples to correct the optimism bias and obtain the 95% confidence interval (CI).

We also used the same data set to calculate an optimism-corrected estimate of the C-statistic for the first-line Bajorin model. We also calculated the hazard ratio and median OS by score for each model using the Cox regression model and Kaplan-Meier method, respectively. Analyses were performed by STATA 16.1 (StataCorp, College Station, TX, USA).

3. Results

3.1. Patient population

The study flow chart is depicted in Figure 1. Data on 984 patients across 24 institutions were collected, and 357 patients were included in this analysis. Table 1 shows baseline characteristics. The mean age was 71 yr; 75% of patients were from US sites, 68% with pure UC, and 13% with upper tract primary. The predominant ICI agent was pembrolizumab (53%). The median follow-up by the reverse Kaplan-Meier method was 22 mo. The overall response rate among patients with available data was 31% (95% CI 26–36%), median progression-free survival was 4 mo (95% CI 3–6 mo), and median OS was 12 mo (95% CI 10–14 mo).

3.2. First-line ICI model

For first-line ICIs, UVA Cox regression identified higher ECOG PS, lower albumin, lower hemoglobin, higher absolute neutrophil count, higher neutrophil:lymphocyte ratio (NLR), higher platelet count, and presence of bone or liver metastases to have a negative prognostic relationship with OS at $p < 0.2$ (Table 2). All covariates identified in UVA modeling were included in the MVA model and retained for a final model if $p < 0.05$. Continuous covariates retained were transformed to a relevant binary scale based on variable distribution in the cohort, the standard variable range, and previously established cut-points in literature. The final model identified ECOG PS ≥ 2, NLR >5, albumin <3.5 g/dl, and liver metastases as negative prognostic factors (Table 3). Since the hazard ratios (HRs) for all covariates were similar (1.52–2.44), each variable was assigned one point to develop the new first-line ICI risk score.

3.3. Model assessment

The risk score was calculated for each patient based on the retained covariates (ECOG PS ≥ 2, NLR >5, albumin <3.5 g/dl, and liver metastases) in the MVA model. Kaplan-Meier OS curves stratified by the risk score are depicted in Figure 2. A higher score was associated with shorter OS. The median OS was 23, 12, 7, and 2 mo for those with a score of 0, 1, 2, and 3+, respectively. The HR for each score group is shown in Table 4 alongside calculated HR based on the first-line Bajorin model. The optimism-corrected Harrell's C index for the new score was calculated to be 0.68 (95% CI 0.65–0.71), whereas this was 0.63 (95% CI 0.59–0.66) for the Bajorin model.

4. Discussion

A substantial number of patients who receive ICIs for aUC (either in first-line or as subsequent/salvage treatment) do not receive subsequent lines of treatment, and this generally portends a poor prognosis [20]. Therefore, if suitability for subsequent treatment after ICIs is limited, it can be useful to have predictive biomarkers to help identify patients most likely to benefit, especially as other novel treatments are approved for aUC. However, it is extremely hard to prospectively validate such biomarkers with clinical utility [7,8,21]. In this study, we used a multi-institution retrospective cohort to develop a new prognostic risk score for OS in patients with aUC treated with first-line ICIs. We identified ECOG PS ≥ 2, NLR >5, albumin <3.5 g/dl, and liver metastases as negative prognostic factors.

Biomarkers in oncology are derived from patient characteristics, such as demographic factors, disease characteristics, laboratory studies, and molecular features, and can have prognostic and/or predictive properties. Prognostic biomarkers, similar to our new risk score, are regularly identified from observational data and can help identify patients more likely to have a specific outcome (eg, OS) regardless of therapy. Conversely, predictive biomarkers should be developed in randomized clinical trials and can be used to identify response/ outcome to a specific therapy. A number of prognostic factors may have a predictive value and need to be validated prospectively for clinical utility before incorporation in practice [22].

While the new risk score is prognostic and not predictive, it may be relevant as a tool to indirectly inform treatment discussions in aUC (upon prospective validation), especially when multiple treatment options are available. For example, in the first-line setting in cisplatin-ineligible patients with PD-L1–high tumor, the risk score may potentially and indirectly be taken into account during the discussion about selection of carboplatin-based chemotherapy followed by switch maintenance avelumab compared with ICI upfront. Similarly, for patients who are platinum ineligible, the risk score could possibly and indirectly help inform the decision between ICI and palliative care or gemcitabine alone. However, these approaches should first be tested prospectively in the first-line clinical trials (eg, DANUBE, IMvigor130, Keynote361, and Checkmate901), since the predictive role of the risk score is unknown. Other ongoing or future clinical trials comparing anti–PD(L)1 with other agents may also evaluate this risk score.

The new risk score also includes elements that resemble prior prognostic models from the pre- and post-ICI era. The presence of liver metastases and worse ECOG PS are established negative prognostic clinical biomarkers, included in models developed using data from patients treated with chemotherapy. Notably, PS and visceral metastases compose the Bajorin risk factors, first identified over 20 yr ago from a retrospective cohort of patients with unresectable or metastatic UC treated with cisplatin-based chemotherapy [9]. Further, the Bellmunt score, developed in 2010, also identified hemoglobin <10 g/dl, liver metastasis, and ECOG PS >0 as negative prognostic factors among patients treated with vinflunine chemotherapy after progression with first-line platinum-based chemotherapy [10]. While the latter was not in the first-line setting, similarities (ECOG PS and liver metastases) with our novel risk score are notable. Similarly, Sonpavde et al [14] recently used data from multiple clinical trials of salvage agents after platinum-based chemotherapy to develop a prognostic nomogram and identified liver metastasis, worse ECOG PS, hemoglobin <10 g/dl, treatment-free interval of <3 mo, and albumin level of less than lower limit of normal as factors associated with shorter OS [14]. This model was developed from patients enrolled in phase II trials testing salvage systemic chemotherapy or biologic agent, but not ICIs. Here again, the similarity to our model with the overlap of ECOG PS, albumin, and liver metastases suggests that these clinical factors could be associated with more aggressive tumor biology and/or cancer burden, rather than ICI response.

More recently, two models have been reported in the ICI era. Sonpavde et al [16] used clinical data from three clinical trials of PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab) after platinum-based chemotherapy to develop a five-factor prognostic model for OS. Similar to our risk score, this model identified ECOG PS, NLR, and liver metastases as negative prognostic factors, and also included platelet count and lactate dehydrogenase. It is unknown whether NLR can be considered a surrogate of tumor (and/or host) biology and/or ICI responsiveness. A higher NLR is considered a biomarker of inflammation commonly observed in advanced solid tumors. Studies in patients with muscle-invasive bladder cancer receiving neoadjuvant chemotherapy have shown that a higher baseline lymphocyte count or a lower NLR is associated with a better chemotherapy response as well as longer disease-free survival and OS [23–25]. Black et al [23] identified NLR >3 to be associated with a decreased response to neoadjuvant chemotherapy and shorter disease-specific survival and OS in nonmetastatic muscle-invasive bladder cancer. However, NLR

had not been found to be prognostic in previous models, but it was recently associated with an ICI response in patients with aUC [17]. Sheng et al [26] found a negative association between NLR and specific circulating myeloid-derived suppressor cell subsets, as well as OS, in a recent single-center study. In addition, Nassar et al [17] used clinical and genomic data to predict response to ICIs, and identified NLR >5, visceral metastases, and single-nucleotide variant count <9 to be associated with benefit to ICIs (but not taxane chemotherapy). This aligns with our model that identified both NLR and visceral metastases as negative prognostic factors.

In terms of model concordance, our model has comparable concordance with other models. For example, the five-factor model mentioned above reported concordance of 0.69 in the discovery set, and 0.67 and 0.78 in two validation cohorts, comparable with our Harrell's C-statistic of 0.68. Notably, the Nassar et al [17] model reported a Harrell's C-statistic of 0.9, substantially higher than existing clinical models. It is possible that models using a combination of clinical and genomic data may have a better prognostic value than those using clinical data alone; however, they may have higher complexity and less practicality, and may need more patients. A number of putative biomarkers regarding ICI response are under exploration, including PD-L1 protein expression, tumor mutational burden, T-effector and regulatory cells, TGF-β, EMT and other gene signatures, DNA damage response gene and FGFR3 alterations, molecular subtypes, and T-cell clonality/diversity among others [27]. More work is needed to validate predictive biomarkers and show clinical utility [2,28–30]. As comprehensive genomic profiling becomes more frequent, future models may incorporate molecular biomarker data. Future work may also better understand different biologic subtypes of UC to help guide further prognostic and predictive biomarker development.

The strengths of our study include utilization of a large cohort of patients treated outside of clinical trials, multi-institution representation from two continents and 24 centers, and the very reasonable cohort sample size and number of events. Limitations include the retrospective nature with an inherent selection bias, lack of validation cohort, missing data, and relatively short follow-up time. We were unable to develop a risk score for patients treated in the salvage setting. We did not incorporate PD-L1 or other molecular biomarkers due to logistical challenges. Our cohort included only patients treated with ICIs, so conclusions cannot be extrapolated to other therapies. Moreover, we developed this model in a heterogeneous population. Last but not least, results from IMvigor130 [31], DANUBE [32], Checkmate901, Keynote361 [33], NILE, and EV-302 phase III trials are expected to keep shaping the treatment landscape in aUC and impact the potential clinical applications of our risk score. For example, our score may not necessarily apply to the switch maintenance anti–PD-L1 setting, which is the new standard of care based on the Javelin Bladder 100 trial (with avelumab) [4]. Despite these limitations, our study developed a prognostic model using data from patients with aUC treated with ICIs as first-line therapy outside clinical trials, which can contribute to the emerging literature and be further validated in clinical trials.

5. Conclusions

In conclusion, we developed a new risk score based on patients receiving first-line ICIs, which identified ECOG PS ≥ 2, NLR >5, albumin <3.5 g/dl, and liver metastases as negative prognostic factors. External validation is actively being pursued along with biomarker exploration. Upon further validation, this model can help inform prognostic estimates, therapy-related discussions, and clinical trial eligibility/stratification, while it may act as a "benchmark" for efficacy assessment in single-arm phase II trials in this setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Funding/Support and role of the sponsor:

contracted research from Seattle Genetics, BlueEarth Diagnostics, Nektar, AstraZeneca, and Seattle Genetics (all unrelated in the last 3 yr). Dr. A. Fröbe has a role in the advisory boards of Amgen, Astellas Pharma, Bayer, Janssen, Pfizer, Roche, and Sanofi-Genzyme. Dr. G. Sonpavde has a role in the advisory board of BMS, Exelixis, Bayer, Sanofi, Pfizer, Novartis, Eisai, Janssen, Amgen, AstraZeneca, Merck, Genentech, EMD Serono, Astellas, and Seattle Genetics; reports receiving research support to institution from AstraZeneca, Bayer, Amgen, Boehringer-Ingelheim, Janssen, Merck, Sanofi, and Pfizer; reports being an author for Uptodate; reports being in the steering committee for AstraZeneca, BMS, Astellas, Debiopharm, and Bavarian Nordic; and reports being a speaker for Onclive, Research to Practice, and Physician Education Resource (PER). Dr. E. Yu (in last 3 yr) reports consulting for Abbvie, Advanced Accelerator Applications, Amgen, AstraZeneca, Bayer, Churchill, Clovis, Dendreon, EMD Serono, Incyte, Janssen, Merck, Pharmacyclics, QED, Sanofi-Genzyme, Seattle Genetics, and Tolmar; and receiving research support to Institution from Bayer, Daiichi-Sankyo, Dendreon, Merck, Seattle Genetics, and Taiho. Dr. G. Lyman reports unrelated advisory/consulting for Agendia BV, Amgen Inc., Genomic Health, Inc., Halozyme, Inc., Mylan, Partners Healthcare, Samsung Bioepis, Pfizer Inc., and Spectrum Pharmaceuticals, Inc. Dr. P. Grivas (all unrelated in the last 3 yr) reports consulting for AstraZeneca, Bayer, Bristol-Myers Squibb, Clovis Oncology, Driver, Dyania Health, EMD Serono, Exelixis, Foundation Medicine, Genentech/Roche, Genzyme, GlaxoSmithKline, Heron Therapeutics, Immunomedics, Janssen, Merck, Mirati Therapeutics, Pfizer, Seattle Genetics, and QED Therapeutics; being in educational program (not current; with direct input in content) for Bristol-Myers Squibb; and receiving research funding to institution from AstraZeneca, Bavarian Nordic, Bayer, Bristol-Myers Squibb, Clovis Oncology, Debiopharm, Genentech/Roche, GlaxoSmithKline, Immunomedics, Kure It Cancer Research, Merck, Mirati Therapeutics, Oncogenex, Pfizer, and QED Therapeutics.

References

[1]. American Cancer Society. Key statistics for bladder cancer. https://www.cancer.org/cancer/bladder-cancer/about/key-statistics.html

[2]. Gopalakrishnan D, Koshkin VS, Ornstein MC, Papatsoris A, Grivas P. Immune checkpoint inhibitors in urothelial cancer: recent updates and future outlook. Ther Clin Risk Manag 2018;14:1019–40. [PubMed: 29892196]

[3]. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015–26. [PubMed: 28212060]

[4]. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med 2020;383:1218–30. [PubMed: 32945632]

[5]. Khaki AR, Li A, Diamantopoulos LN, et al. Impact of performance status on treatment outcomes: a real-world study of advanced urothelial cancer treated with checkpoint inhibitors. Cancer 2020;126:1208–16. [PubMed: 31829450]

[6]. Miller NJ, Khaki AR, Diamantopoulos LN, et al. Histological subtypes and response to PD-1/PD-L1 blockade in advanced urothelial cancer: a retrospective study. J Urol 2020;204:63–70. [PubMed: 31971495]

[7]. Loriot Y, Necchi A, Park SH, et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma. N Engl J Med 2019;381:338–48. [PubMed: 31340094]

[8]. Rosenberg JE, O'Donnell PH, Balar AV, et al. Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. J Clin Oncol 2019;37:2592–600. [PubMed: 31356140]

[9]. Bajorin DF, Dodd PM, Mazumdar M, et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 1999;17:3173–81. [PubMed: 10506615]

[10]. Bellmunt J, Choueiri TK, Fougeray R, et al. Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. J Clin Oncol 2010;28:1850–5. [PubMed: 20231682]

[11]. Necchi A, Sonpavde G, Lo Vullo S, et al. Nomogram-based prediction of overall survival in patients with metastatic urothelial carcinoma receiving first-line platinum-based chemotherapy: Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC). Eur Urol 2017;71:281–9. [PubMed: 27726966]

[12]. Galsky MD, Moshier E, Krege S, et al. Posttreatment prognostic nomogram for patients with metastatic urothelial cancer completing first-line cisplatin-based chemotherapy. Urol Oncol Semin Orig Investig 2014;32:48.e1–8.

[13]. Pond GR, Agarwal N, Bellmunt J, et al. A nomogram including baseline prognostic factors to estimate the activity of second-line therapy for advanced urothelial carcinoma. BJU Int 2014;113:E137–43. [PubMed: 24219029]

[14]. Sonpavde G, Pond GR, Rosenberg JE, et al. Nomogram to assess the survival benefit of new salvage agents for metastatic urothelial carcinoma in the era of immunotherapy. Clin Genitourin Cancer 2018;16:e961–7. [PubMed: 29706503]

[15]. Sonpavde G, Pond GR, Rosenberg JE, et al. Improved 5-factor prognostic classification of patients receiving salvage systemic therapy for advanced urothelial carcinoma. J Urol 2016;195:277–82. [PubMed: 26292040]

[16]. Sonpavde G, Manitz J, Chen G, et al. 5-Factor prognostic model for survival of patients with metastatic urothelial carcinoma receiving three different post-platinum PD-L1 inhibitors. J Clin Oncol 2019;37(suppl):4552.

[17]. Nassar AH, Mouw KW, Jegede O, et al. A model combining clinical and genomic factors to predict response to PD-1/PD-L1 blockade in advanced urothelial carcinoma. Br J Cancer 2020;122:555–63. [PubMed: 31857723]

[18]. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap)— a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81. [PubMed: 18929686]

[19]. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–87. [PubMed: 8668867]

[20]. Gómez de Liaño Lista A, van Dijk N, de Velasco Oria de Rueda G, et al. Clinical outcome after progressing to frontline and second-line Anti-PD-1/PD-L1 in advanced urothelial cancer. Eur Urol 2020;77:269–76. [PubMed: 31699525]

[21]. Tagawa ST, Faltas BM, Lam ET, et al. Sacituzumab govitecan (IMMU-132) in patients with previously treated metastatic urothelial cancer (mUC): Results from a phase I/II study. J Clin Oncol 2019;37(7_suppl):354.

[22]. Khaki AR, Gadi VK, Prasad V. Clinical risk during the evaluation of genomic risk for hormone-sensitive breast cancer: ignoring valuable data. J Natl Compr Cancer Netw 2019;17:1456–8.

[23]. Black AJ, Zargar H, Zargar-Shoshtari K, et al. The prognostic value of the neutrophil-to-lymphocyte ratio in patients with muscle-invasive bladder cancer treated with neoadjuvant chemotherapy and radical cystectomy. Urol Oncol 2020;38:3.e17–27.

[24]. Buisan O, Orsola A, Areal J, et al. Low pretreatment neutrophil-to-lymphocyte ratio predicts for good outcomes in patients receiving neoadjuvant chemotherapy before radical cystectomy for muscle invasive bladder cancer. Clin Genitourin Cancer 2017;15:145–51.e2. [PubMed: 27364982]

[25]. Leibowitz-Amit R, Israel A, Gal M, et al. Association between the absolute baseline lymphocyte count and response to neoadjuvant platinum-based chemotherapy in muscle-invasive bladder cancer. Clin Oncol 2016;28:790–6.

[26]. Sheng IY, Diaz-Montero CM, Rayman P, et al. Blood myeloid-derived suppressor cells correlate with neutrophil-to-lymphocyte ratio and overall survival in metastatic urothelial carcinoma. Target Oncol 2020;15:211–20. [PubMed: 32207064]

[27]. van Dijk N, Funt SA, Blank CU, Powles T, Rosenberg JE, van der Heijden MS. The cancer immunogram as a framework for personalized immunotherapy in urothelial cancer. Eur Urol 2019;75:435–44. [PubMed: 30274701]

[28]. Powles T, Morrison L. Biomarker challenges for immune checkpoint inhibitors in urothelial carcinoma. Nat Rev Urol 2018;15:585. [PubMed: 30030491]

[29]. Mendiratta P, Grivas P. Emerging biomarkers and targeted therapies in urothelial carcinoma. Ann Transl Med 2018;6:250. [PubMed: 30069452]

[30]. Grivas P, Castellano DE, O'Donnell PH, et al. Association between stromal/TGF-β/EMT gene expression signature and response to pembrolizumab monotherapy in cisplatin-ineligible patients with locally advanced (unresectable) or metastatic urothelial carcinoma. J Clin Oncol 2019;37(7_suppl):433.

[31]. Grande E, Galsky M, Arranz Arija JA, et al. IMvigor130: efficacy and safety from a Phase 3 study of atezolizumab (atezo) as monotherapy or combined with platinum-based chemotherapy (PBC) vs placebo + PBC in previously untreated locally advanced or metastatic urothelial carcinoma (mUC). Ann Oncol 2019;30(suppl_5):v851–934.

[32]. Powles TB, Van Der Heijden MS, Castellano Gauna D, et al. A phase III, randomized, open-label study of first-line durvalumab (D) with or without tremelimumab (T) vs standard of care chemotherapy in patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE). Ann Oncol 2020;31(suppl_4):S550.

[33]. Alva A, Csoszi T, Ozguroglu M, et al. Pembrolizumab (P) combined with chemotherapy (C) vs C alone as first-line (1L) therapy for advanced urothelial carcinoma (UC): KEYNOTE-361. Ann Oncol 2020;31(suppl_4):S1142–215.
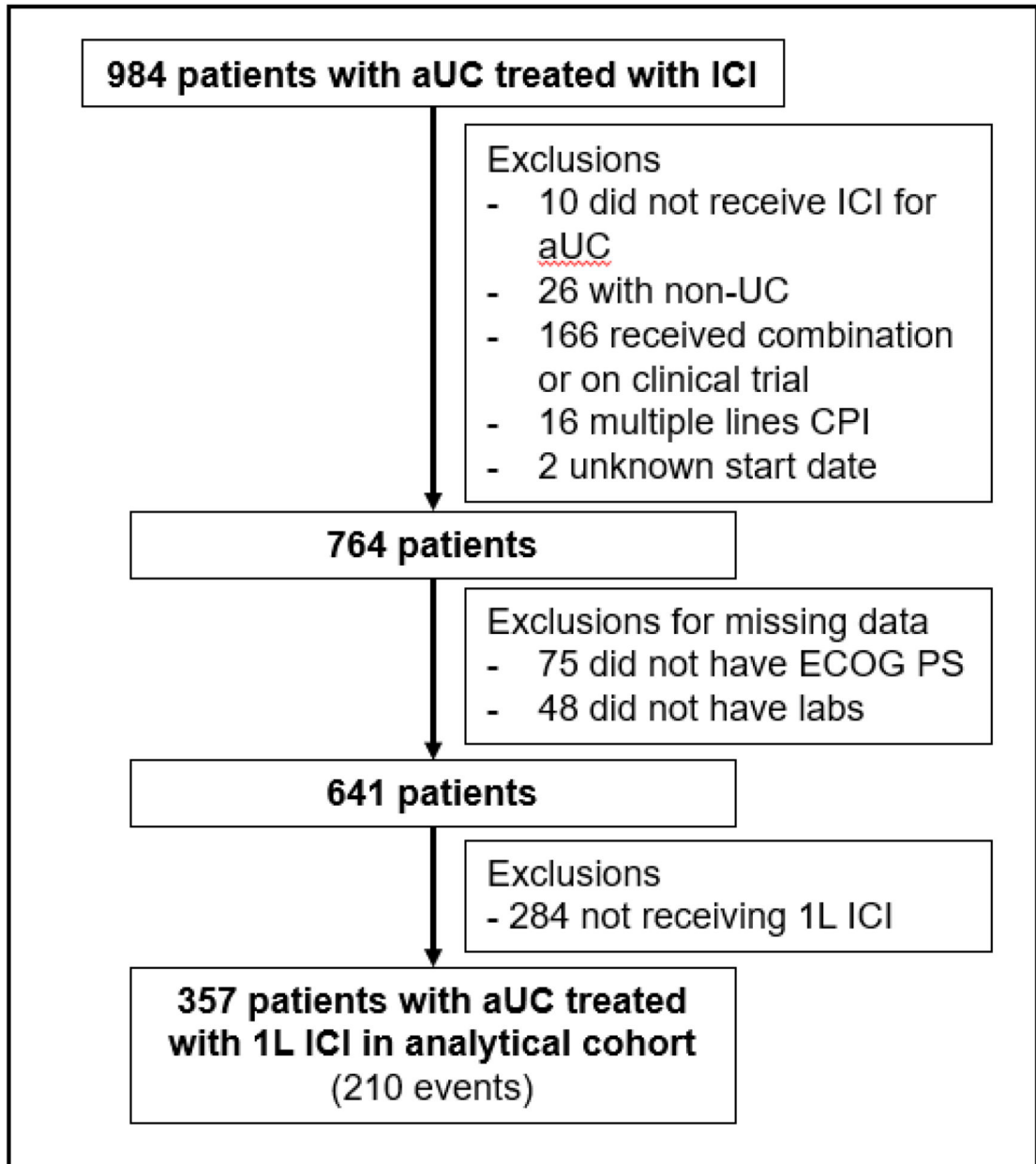
Fig. 1 –.
CONSORT diagram showing the inclusion of patients in the study. aUC = advanced urothelial cancer; ECOG = Eastern Cooperative Oncology Group; ICI = immune checkpoint inhibitor; 1L = first line; PS = performance status; UC = urothelial cancer.
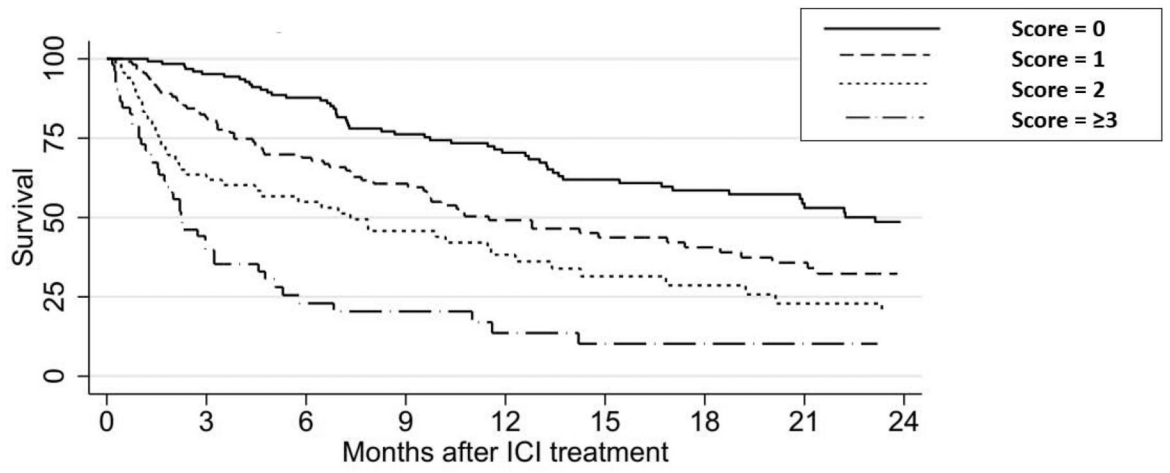
Fig. 2 –.
Kaplan-Meier curve by new first-line risk score. ICI = immune checkpoint inhibitor.

Table 1.

Baseline characteristics of patients with advanced UC treated with first line ICI included in risk score modeling

	First line ICI
	N=357
Age (year), mean (range)	71 (32–93)
Sex, n (%)	
Male	259 (73)
Female	98 (27)
Race/Ethnicity, n (%)	
Caucasian/White	263 (74)
Hispanic/Latino	43 (12)
Black/African-American	20 (6)
Asian	13 (4)
Other/Unknown	18 (5)
Smoking History, n (%)	
Yes	243 (68)
No	111 (31)
Unknown	3 (1)
Continent of treatment, n (%)	
North America (US only)	91 (25)
Europe	266 (75)
Site of Primary Disease, n (%)	
Bladder	296 (83)
Upper tract (renal pelvis or ureter)	48 (13)
Urethra	3 (1)
Unknown	10 (3)
Histology, n (%)	
Pure UC	242 (68)
UC with variant histology	115 (32)
History of extirpative surgery, n (%)	
Yes	184 (52)
No	148 (41)
Unknown	25 (7)
History of BCG, n (%)	
Yes	74 (21)
No	278 (78)
Unknown	5 (1)
Prior platinum chemotherapy, n (%)	
Yes	147 (41)
No	210 (59)
Agent received, n (%)	

	First line ICI N=357
Atezolizumab	137 (38)
Avelumab	1 (0.1)
Durvalumab	11 (3)
Nivolumab	16 (4)
Pembrolizumab	189 (53)
Unknown	3 (1)
GFR<60ml/min at ICI start, n (%)	
Yes	137 (38)
No	191 (54)
Unknown	29 (8)
Metastatic disease site at ICI start, n (%)	
Bone	81 (23)
Liver	58 (16)
Lung	107 (30)
Lymph node	243 (68)
ECOG Performance Status, n (%)	
0	80 (22)
1	176 (49)
2	90 (25)
3	9 (3)
4	2 (1)
	Median (IQR)
Albumin at ICI start (g/dL)	3.8 (3.4–4.1)
Hemoglobin at ICI start (mg/dL)	11.6 (10.0–13.1)
ALC at ICI start (x10^3/ul)	1.3 (0.9–1.8)
ANC at ICI start (x10^3/ul)	5.5 (4.1–7.3)
NLR at ICI start	4.2 (2.7–7.1)
Platelets at ICI start (x10^9/L)	254 (201–334)

Abbreviations: ALC indicates absolute lymphocyte count; ANC, absolute neutrophil count; BCG, Bacillus Calmette-Guérin; ECOG, Eastern Cooperative Oncology Group; GFR, glomerular filtration rate; ICI, immune checkpoint inhibitor; IQR, inter-quartile range; LDH, lactate dehydrogenase; NLR, neutrophil : lymphocyte ratio; PS, performance status; SD, standard deviation; UC, urothelial carcinoma.

Table 2 –

Hazard ratios and p values for covariates identified with $p < 0.2$ in univariable Cox regression for patients with advanced urothelial cancer treated with first-line immune checkpoint inhibitors

Covariate	Hazard ratio (95% CI) on UVA	p value on UVA	Hazard ratio (95% CI) on MVA	p value on MVA
ECOG PS 2+ (vs 0–1)	1.96 (1.46–2.62)	<0.001	1.61 (1.17–2.21)	0.003
Albumin[a]	0.53 (0.43–0.65)	<0.001	0.64 (0.47–0.86)	0.004
Hemoglobin[a]	0.90 (0.84–0.96)	0.001	1.00 (0.93–1.09)	0.934
ANC[a]	1.03 (1.02–1.05)	<0.001	0.98 (0.95–1.00)	0.055
NLR[a]	1.04 (1.03–1.05)	<0.001	1.04 (1.02–1.06)	<0.001
Platelet count[a]	1.00 (1.00–1.00)	0.006	1.00 (1.00–1.00)	0.401
Bone metastases	1.85 (1.37–2.52)	<0.001	1.37 (0.99–1.88)	0.055
Liver metastases	2.48 (1.78–3.44)	<0.001	2.23 (1.59–3.13)	<0.001

ANC = absolute neutrophil count; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; MVA = multivariate analysis; NLR = neutrophil to lymphocyte ratio; PS = performance status; UVA = univariate analysis.

[a]Hazard ratio represents the ratio between groups one unit apart in continuous variable.

Table 3 –

Hazard ratios for multivariate model including only covariates that make up risk score

Covariate	Hazard ratio (95% CI)
ECOG PS 2+	1.65 (1.22–2.23)
Albumin <3.5 g/dl	1.88 (1.38–2.58)
NLR >5	1.52 (1.13–2.04)
Liver metastasis	2.44 (1.75–3.39)

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; NLR = neutrophil to lymphocyte ratio; PS = performance status.

Table 4 –

Stratified median overall survival, hazard ratio, and C-statistic by prognostic model (new risk score and Bajorin)

	New risk score			Bajorin			
Score	**N**	**mOS, mo (95% CI)**	**HR (95% CI)**	**Score**	**N**	**mOS, mo (95% CI)**	**HR (95% CI)**
0	127	23 (17–32)	Ref.	0	128	23 (17–35)	Ref.
1	110	12 (9–18)	1.57 (1.10–2.23)	1	169	10 (7–13)	1.95 (1.41–2.70)
2	68	7 (3–12)	2.35 (1.60–3.47)	2	60	5 (2–7)	2.86 (1.92–4.25)
3	52	2 (2–3)	4.91 (3.28–7.35)				
Harrell's C-statistic (95% CI)		0.68 (0.65–0.71)				0.63 (0.59–0.66)	

CI = confidence interval; HR = hazard ratio; mOS = median overall survival.