available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Urothelial Cancer – Editor's Choice

Programmed Death-1 or Programmed Death Ligand-1 Blockade in Patients with Platinum-resistant Metastatic Urothelial Cancer: A Systematic Review and Meta-analysis

Scot A. Niglio [a,†], *Rachel Jia* [b,†], *Jiayi Ji* [b], *Samuel Ruder* [c], *Vaibhav G. Patel* [a], *Alberto Martini* [d], *John P. Sfakianos* [d], *Kathryn E. Marqueen* [a], *Nikhil Waingankar* [d], *Reza Mehrazin* [d], *Peter Wiklund* [d,e], *William K. Oh* [a], *Madhu Mazumdar* [b], *Bart S. Ferket* [b,†], *Matthew D. Galsky* [a,†,*]

[a] *Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA;* [b] *Institute for Health Care Delivery Science, Population Health Science and Policy, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA;* [c] *Internal Medicine, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA;* [d] *Urology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA;* [e] *Urology, Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden*

Article info

Article history:
Accepted May 23, 2019

Associate Editor:
James Catto

Statistical Editor:
Andrew Vickers

Keywords:
Bladder cancer
Immune checkpoint blockade
Meta-analysis
Programmed death-1 blockade
Programmed death ligand-1 blockade
Urothelial cancer

Abstract

Context: Several anti-programmed death-1 (anti-PD-1) and anti-programmed death ligand-1 (anti-PD-L1) antibodies have been approved by regulatory authorities for treatment of platinum-resistant metastatic urothelial cancer (mUC). The impact of these therapies on survival, and comparability of PD-1 versus PD-L1 blockade are unknown.
Objective: To determine the restricted mean survival time (RMST) of patients with platinum-resistant mUC treated with PD-1/PD-L1 inhibitors and to compare RMSTs in patients treated with PD-1 versus PD-L1 inhibitors.
Evidence acquisition: We searched for phase 1, 2, and 3 clinical trials that assessed PD-1 or PD-L1 inhibition for patients with platinum-resistant mUC. Literature review and study selection, data abstraction, and risk of bias assessment were performed by two reviewers. Survival data were reconstructed using an algorithm that derives individual time-to-event data from published Kaplan-Meier curves. The RMST with 95% confidence interval (CIs) was calculated.
Evidence synthesis: From 836 references, six clinical trials were included. Survival data were reconstructed for 1315 and 736 patients treated with PD-1/PD-L1 inhibitors and chemotherapy, respectively. The RMSTs with PD-1/PD-L1 blockade up to 12 and 18 mo of follow-up were 7.8 mo (95% CI 7.6, 8.1) and 10 mo (95% CI 9.7, 10.5), respectively. A network meta-analysis of two randomized trials revealed no significant difference in the RMST up to 18 mo with PD-1 versus PD-L1 blockade (1.0 mo; 95% CI −0.5, 2.3 mo). Using reconstructed survival data from all six trials, the RMSTs with PD-1 versus PD-L1 blockade up to 12 and 18 mo follow-up were 7.8 mo (95% CI 7.7, 8.2) versus 7.8 mo (95% CI 7.5, 8.2) and 10.1 mo (95% CI 9.6, 10.7) versus 10 mo (95% CI 9.5, 10.6), respectively.
Conclusions: Our RMST estimates may be used as benchmarks to contextualize survival outcomes and inform future trial design with PD-1/PD-L1 inhibitors. PD-1 versus PD-L1 blockade in patients with mUC yields comparable survival outcomes.
Patient summary: In this study, we found that outcomes for patients with metastatic bladder cancer treated with programmed death-1 and programmed death ligand-1 inhibitors, who received prior platinum-based chemotherapy, were similar.

[1] These authors contributed equally.

* Corresponding author. Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, New York, NY 10029, USA. Tel. +1 212 659 5452; Fax: +1 646 537 9639.
E-mail address: matthew.galsky@mssm.edu (M.D. Galsky).

https://doi.org/10.1016/j.eururo.2019.05.037
0302-2838/

1. Introduction

Platinum-based chemotherapy is the standard first-line treatment for metastatic urothelial cancer (mUC) [1]. While mUC is a relatively chemosensitive disease, response durations are generally short and the vast majority of patients ultimately experience disease progression [2,3]. Treatment options for patients with mUC progressing despite first-line chemotherapy have historically been limited. However, the therapeutic landscape has recently experienced a dramatic shift with the development of immune checkpoint inhibitors (CPIs). The European Commission approved two programmed death-1 (PD-1) inhibitors (nivolumab and pembrolizumab) and one programmed death ligand-1 (PD-L1) inhibitor (atezolizumab) for the treatment of platinum-resistant mUC in 2017 [4–6], while the United States Food and Drug Administration approved two PD-1 inhibitors (nivolumab and pembrolizumab) and three PD-L1 inhibitors (atezolizumab, durvalumab, and avelumab) for the treatment of platinum-resistant mUC between 2016 and 2017 [7–15].

The rapid introduction of five new therapies into the treatment armamentarium for mUC has raised several questions regarding their use highly unlikely to be addressed in randomized clinical trials. Among these key clinical and scientific questions is whether there are differences between therapeutic blockades of the ligand PD-L1 versus the receptor PD-1. While these subclasses of immune CPIs disrupt different aspects of the same ligand-receptor interaction, both mechanistic (eg, blockade of additional ligand-receptor interactions such as PD-L2-PD-1 with PD-1, but not with PD-L1, inhibitors) and pharmacological considerations could theoretically lead to a difference in patient outcome.

Establishing the efficacy of novel therapies for the treatment of cancer has historically focused on demonstrating improvements in median survival or hazard rates relative to another therapy. However, these traditional measures are limited by (1) suboptimal characterization of the potential clinical benefit of therapies with atypical response kinetics and/or response proportions insufficient to impact the median, and (2) reliance of interpretation of hazard ratios on the distribution of events over time and satisfying the proportional hazard assumption [16]. PD-1/PD-L1 blockade in mUC and other advanced solid tumors is characterized by prolonged responses in a small subset of patients, and trials randomizing patients to PD-1/PD-L1 blockade versus cytotoxic chemotherapy consistently demonstrate violation of the proportional hazard assumptions, with early crossing of the survival curves limiting the validity of hazard ratios and producing treatment effects that are difficult to interpret. The restricted mean survival time (RMST), which involves measurement of average life expectancy until a predefined follow-up time (ie, area under the survival curve), is an alternative approach to survival analysis that may overcome these limitations [17]. In an attempt to establish benchmarks for survival outcomes with PD-1/PD-L1 blockade in patients with platinum-resistant mUC to inform future trials and to contextualize the efficacy of PD-1 versus PD-L1 blockade, we performed a meta-analysis utilizing reconstructed survival data derived from clinical trials with PD-1/PD-L1 blockade and a network meta-analysis of randomized phase 3 trials to indirectly compare PD-1 versus PD-L1 blockade, with a focus on the RMST.

2. Evidence acquisition

2.1. Endpoint and objectives

The primary endpoint of the analysis was the RMST, which is a measure of average survival time to a specific time point and may be estimated by the area under the survival curve [17,18]. The primary objectives were to estimate RMSTs up to 6, 12, and 18 mo of follow-up in patients with mUC treated with PD-1 or PD-L1 blockade by performing a meta-analysis of all trials using reconstructed survival data, and to compare the RMST of patients with mUC treated with PD-1 versus PD-L1 blockade by performing a network meta-analysis of randomized phase 3 trials.

2.2. Study eligibility and identification

We used a defined protocol and conducted our systematic review following Methodological Expectations of Cochrane Intervention Reviews, and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria [19,20]. Experts from clinical epidemiology, medical oncology, and urology designed the protocol and conducted the review. We searched PubMed, MEDLINE, and SCOPUS databases, and the Cochrane Register for Controlled Trials for phase 1, 2, and 3 clinical trials reporting on PD-1 or PDL-1 inhibition in mUC from the inception of each database until May 31, 2018. We included articles published in the English language using the following terms: phase 1, phase 2, phase 3, PD-1, PD-L1, urothelial, transitional cell, bladder, cancer, neoplasm, tumor, atezolizumab, avelumab, cemiplimab, durvalumab, pembrolizumab, and nivolumab.

To be eligible for the analysis, clinical trials must have evaluated PD-1 or PD-L1 blockade in patients with mUC progressing despite prior platinum-based chemotherapy. Further, given our approach utilizing reconstructed survival data (described below) studies must have included Kaplan-Meier (KM) curves for overall survival. Reconstructed survival data refer to the use of published KM curves to “reverse engineer” individual data points regarding the survival and follow-up of patients analyzed in the respective trial [21]. Given the heterogeneity in PD-L1 assays, including various diagnostic PD-L1 antibodies, cellular populations scored (ie, tumor cells, immune cells, or both), and cut-points defining “positive” testing, coupled with the lack of routine clinical use of PD-L1 testing in the platinum-resistant mUC setting and paucity of published KM curves stratified by PD-L1 testing, we did not focus our analysis on subpopulations of patients with tumors harboring increased PD-L1 expression but performed an exploratory analysis of the “PD-1-high” population.

2.3. Data extraction

For each publication, we extracted data on the following parameters: trial name, author, phase, sample size, intervention, baseline patient and tumor characteristics, progression-free survival, and overall survival. Two authors (S.N. and S.R.) extracted data independently, and any disagreement was resolved by consensus among reviewers. We digitally scanned KM curves from each publication and reconstructed survival data using an algorithm that maps from digitized published KM curves back to individual data by finding numerical solutions to the inverted KM equations, using information, where available, on the number of events and number of patients at risk [22]. The intraclass correlation coefficient was calculated to assess agreement among the pairs of available reconstructed and published data on median survival time and number of deaths.

2.4. Study quality, publication bias, and heterogeneity

Methodological quality of included trials was independently assessed by two authors (S.N. and V.P.) using the modified Downs and Black checklist for the assessment of the methodological quality of both randomized and nonrandomized studies [23,24]. The following categories for study quality scores have been suggested: excellent (26–28), good (20–25), fair (15–19), and poor ($\leq$14) [25,26].

To assess for publication bias, we constructed a funnel plot of the estimated RMST versus the estimated RMST precision, that is, reciprocal of standard error, based on patients with PD-1 or PD-L1 blockade across all trials. Tests for funnel plot asymmetry and study heterogeneity were not performed due to caution provided in literature against underpowered tests for publication bias [27].

2.5. Statistical analysis

To estimate RMSTs up to 6, 12, and 18 mo of follow-up in patients receiving PD-1/PD-L1 blockade using survival data from all trials, we employed a reconstructed survival data meta-analysis method to derive the pooled survival probability curve [28]. This method assumes that the number of deaths in each prespecified unit of follow-up time (0.5 mo) follows a negative binomial distribution. Furthermore, it models the correlation of the number of events across time units within each study and heterogeneity between studies by a gamma frailty process. For determining RMSTs over the three prespecified time intervals, we estimated the area under the survival probability curve using the trapezoidal rule. We obtained 95% confidence intervals (CIs) using the bootstrap method.

For the randomized phase 3 trials comparing PD-1 or PD-L1 blockade versus chemotherapy, we tested the proportional hazard assumption using the Grambsch and Therneau [29] test on the reconstructed datasets to support the use of the RMST as the primary endpoint of the network meta-analysis. An indirect comparison of RMSTs between PD-1 blockade-treated and PD-L1 blockade-treated patients was made using the randomized phase 3 trials with chemotherapy as the common comparator within a triangular-shaped network meta-analysis [30]. A linear regression model was fit on the arm-level RMST estimates with fixed study effects. The standard errors of arm-level RMSTs in each study were estimated using pseudovalue methods as implemented in the "survRM2" package to account for censoring [31,32]. As 18 mo was the common maximum follow-up time across the four study arms, we chose to estimate the 18-mo arm-level RMST to allow the pairwise comparison of treatment effects over the maximum common study period [33]. Given longer follow-up available for IMVigor 211, we additionally estimated the delta-RMST of atezolizumab relative to chemotherapy up to 24 mo.

All analyses were performed using R software with the "survRM2" and "metafor" packages [34].

3. Evidence synthesis

3.1. Study eligibility and identification

We identified 836 references from electronic database searches, from which we selected 30 potentially relevant publications for full-text evaluation. The reasons for study exclusion are outlined in Fig. 1. The final dataset included six trials encompassing 1315 patients with platinum-resistant mUC treated with PD-1 or PD-L1 blockade and 736 patients treated with chemotherapy.

3.2. Trial and patient characteristics

Characteristics of the included trials are detailed in Table 1. Among the six included trials, there was one phase IB, two phase I/II, one single-arm phase II, and two phase 3 trials reporting objective response rates with PD-1/PD-L1 blockade ranging from 13% to 25%. Eligibility criteria for the six included trials were highly similar, as shown in Supplementary Table 1. Baseline patient and tumor characteristics are summarized in Table 2. Compared with randomized studies, early-phase studies enrolled more heavily pretreated patients and patients with higher Eastern Cooperative Oncology Group performance status scores (chi-square test for testing equality of distribution yield $p < 0.001$ for each risk factor) [35].

3.3. Study quality, publication bias, and heterogeneity

According to the modified Downs and Black checklist for the assessment of methodological quality, four studies were scored as fair quality and two as good quality. Results of scoring are provided in Supplementary Table 2. The funnel plot demonstrating the estimated RMST versus the estimated RMST precision is shown in Supplementary Figure 1.

3.4. Reconstructed versus published survival data

The survival data reconstructed from the KM curves from each publication demonstrated excellent agreement with the data reported in each publication (Supplementary

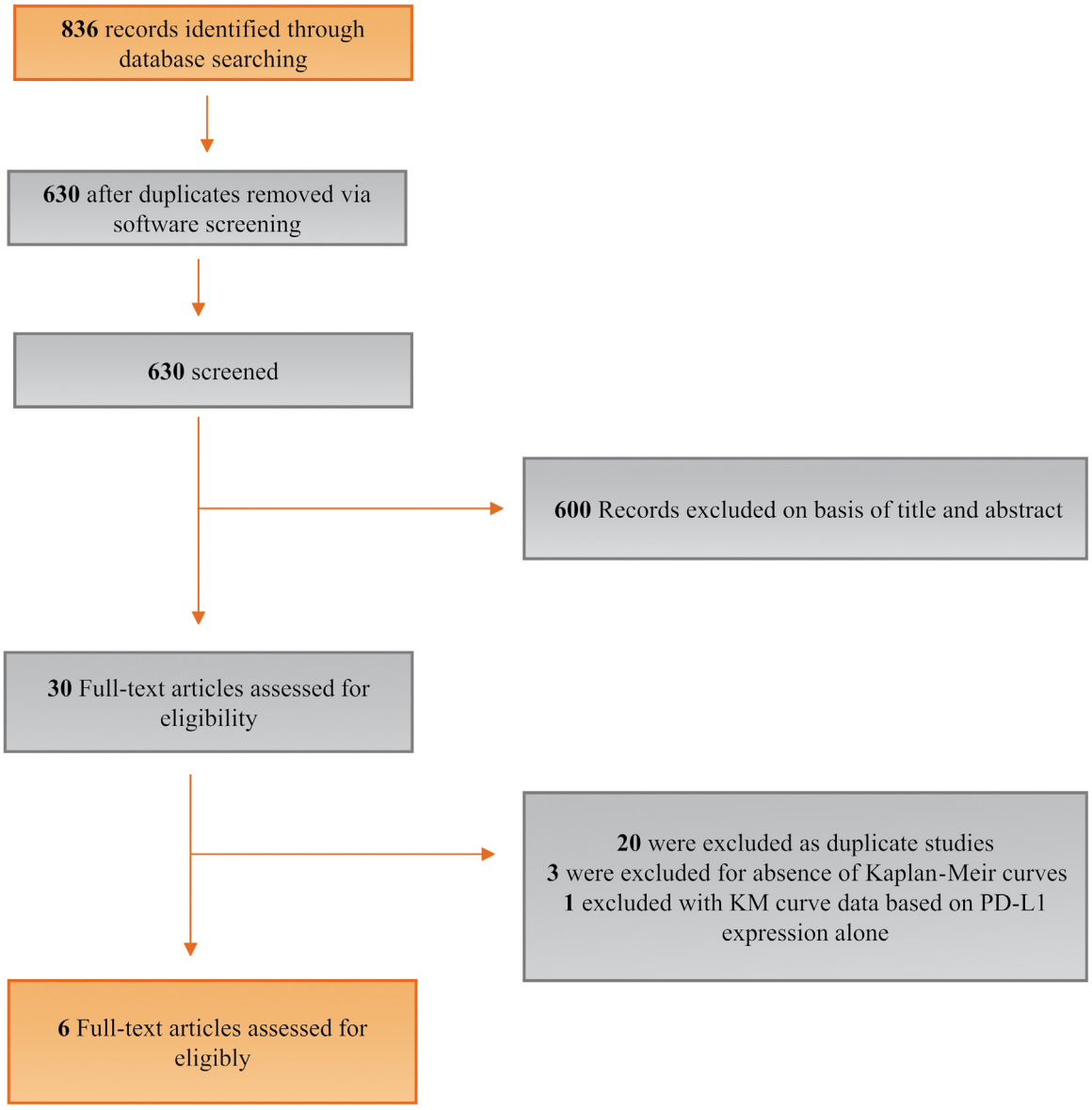

Fig. 1 – Flow diagram of systematic literature review and included versus excluded studies. KM = Kaplan-Meier; PD-L1 = programmed death ligand-1.

Table 1 – Characteristics of included trials

Trial	Phase	Treatment	Target	*N*	Median follow-up (mo)	Objective response rate (95% CI)	
						All	PD-L1 "high"
Javelin Solid Tumor [11]	IB	Avelumab 10 mg/kg IV every 2 wk	PD-L1	44	16.5	18% (8–33)	54% (25–81)
Checkmate 032 [15]	I/II	Nivolumab 3 mg/kg IV every 2 wk	PD-1	78	15	24% (15–35)	24% (9–45)
Study 1108 [12]	I/II	Durvalumab 10 mg/kg IV every 2 wk	PD-L1	191	5.8	18% (13–24)	28% (19–38)
Checkmate 275 [14]	II	Nivolumab 3 mg/kg IV every 2 wk	PD-1	265	7	20% (15–25)	28% (19–40)
IMVigor 211 [10]	III	Atezolizumab 1200 mg IV every 3 wk [a]	PD-L1	467[b]	17	13% (10–17)	23% (16–32)
Keynote-045 [13]	III	Pembrolizumab 200 mg IV every 3 wk[a]	PD-1	270[c]	14	21% (16–27)	22% (13–33)

CI = confidence interval; IV = intravenous; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1.
[a] Standard of care chemotherapy was at treating physician's discretion and could include paclitaxel (175 mg/m^2), docetaxel (75 mg/m^2), or vinflunine (320 mg/m^2), all administered intravenously every 3 wk.
[b] IMVigor2 11: atezolizumab, *n* = 467; chemotherapy, *n* = 464.
[c] Keynote-045: pembrolizumab, *n* = 270; chemotherapy, *n* = 272.

Table 2 – Baseline characteristics of patients in included trials

Characteristic	Trial (Drug)					
	Javelin [11] (Avelumab)	Checkmate 032 [15] (Nivolumab)	Study 1108 [12] (Durvalumab)	Checkmate 275 [14] (Nivolumab)	IMVigor 211 [10] (Atezolizumab)	Keynote-045 [13] (Pembrolizumab)
Median age (yr)	68	66	67	66	67	67
ECOG PS (%)						
0	43	54	33	54	47	44
≥1	57	46	67	46	53	53
Sites of metastases (%)						
Visceral metastases	75	78	93	84	77	89
Liver metastases	NR	26	43	28	30	34
LN-only metastases	NR	17	7	16	12	NR
≥2 Prior therapies (%)	54	67	33	29	19	20
Hemoglobin <10 g/dl (%)	NR	14%	22	18	14	16

ECOG PS = Eastern Cooperative Oncology Group performance status; LN-only = lymph node only; NR = not reported.

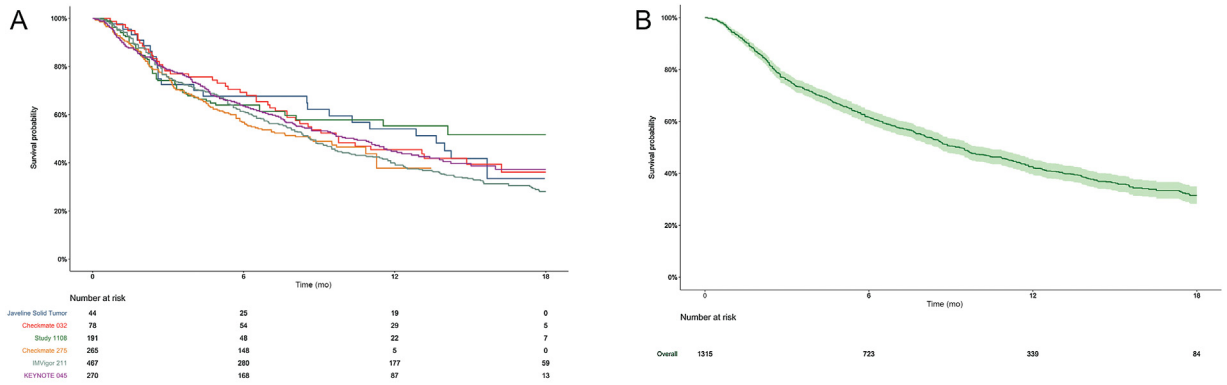

Fig. 2 – Overall survival of patients with platinum-resistant mUC using reconstructed survival data derived from (A) six individual studies with PD-1/PD-L1 blockade and (B) summary survival curve for the six studies (shaded area representing the 95% confidence bands based on 1000 bootstrap simulations). mUC = metastatic urothelial cancer; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1.

Table 3). The intraclass correlation coefficient for interobserver agreement on calculated and reported median survival time and number of events as continuous variables was >0.99 (95% CI 0.99, 1).

3.5. RMST with PD-1/PD-L1 blockade

The KM curves of patients with platinum-resistant mUC enrolled in individual trials with PD-1 or PD-L1 blockade, using reconstructed survival data, are shown in Fig. 2A, and the summary KM curve representing all 1315 patients treated with either PD-1/PD-L1 blockade is shown in Fig. 2B. Overall survival probabilities with PD-1/PD-L1 blockade at 6, 12, and 18 mo were 62% (95% CI 59%, 65%), 42% (95% CI 40%, 46%), and 31% (95% CI 28%, 35%), respectively. The RMSTs with PD-1/PD-L1 blockade up to 6, 12, and 18 mo of follow-up were 4.8 mo (95% CI 4.7, 4.9), 7.8 mo (95% CI 7.6, 8.1), and 10 mo (95% CI 9.7, 10.5), respectively.

Additional analyses were performed in subsets of patients based on the type of trial or based on PD-L1 expression. The KM curves of patients enrolled in phase I/II versus phase III trials, using reconstructed survival data, are shown in Supplementary Figure 2.

3.6. PD-1 versus PD-L1 blockade

The Grambsch and Therneau [29] test on the reconstructed datasets from the two randomized trials comparing PD-1 or PD-L1 blockade versus chemotherapy (Keynote-045 and IMVigor 211) yielded p values of 0.009 and <0.001, respectively, confirming violation of the proportional hazard assumption.

A network meta-analysis was performed using data from the two randomized trials comparing PD-1 or PD-L1 blockade (n = 270 and n = 467, respectively) with chemotherapy (n = 736). There was no significant difference in the RMST up to 18 mo for patients treated with PD-1 versus PD-L1 blockade (Table 3). The KM curves obtained using reconstructed data from each of the study arms are shown in Supplementary Figure 4.

Reconstructed survival patient data from the three trials exploring PD-1 blockade (n = 613 patients) versus data from the three trials exploring PD-L1 blockade (n = 702 patients) confirmed highly similar survival outcomes with PD-1 and PD-L1 blockade. Using reconstructed survival data from all six trials, the RMSTs with PD-1 versus PD-L1 blockade up to 12 and 18 mo follow-up were 7.8 mo (95% CI 7.7, 8.2) versus

Table 3 – Network meta-analysis of Keynote-045 [13] and IMVigor 211 [10] trials

Arms	ΔRMST up to 18-mo follow-up (95% CI)
PD-1 blockade vs chemotherapy	1.6 (0.4, 2.7) mo
PD-L1 blockade vs chemotherapy[a]	0.6 (−0.2, 1.4) mo
PD-1 blockade vs PD-L1 blockade	1 (−0.5, 2.3) mo

CI = confidence interval; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1; RMST = restricted mean survival time.
[a] ΔRMST (mo) at maximum available follow-up for IMVigor 211 [10], 24 mo, with PD-L1 blockade versus chemotherapy was 1.3 mo (95% CI 0.2–2.3; $p = 0.02$).

7.8 mo (95% CI 7.5, 8.2) and 10.1 mo (95% CI 9.6, 10.7) versus 10 mo (95% CI 9.5, 10.6), respectively.

4. Conclusions

The European regulatory approval of three PD-1/PD-L1 inhibitors and US regulatory approval of five PD-1/PD-L1 inhibitors for the treatment of platinum-resistant mUC has rapidly expanded the treatment armamentarium for this disease. However, availability of several immune CPIs, representing two therapeutic subclasses, has raised uncertainties about the optimal treatment approach, appropriate backbones for further drug development, and benchmarks for future trial design. A key question, relevant to both the laboratory and the clinic, is whether there are differences between therapeutic blockade of PD-1 and PD-L1 in patients with mUC. Herein, we performed a meta-analysis to define survival outcomes with PD-1/PD-L1 blockade in mUC and to facilitate the design of future clinical trials. Further, we performed a network meta-analysis and a pooled analysis of reconstructed survival data from six trials, demonstrating comparable survival outcomes with PD-1 versus PD-L1 blockade.

There are several potential strengths to our analysis. A critical, yet underexplored, issue in contextualizing the survival impact of immune checkpoint blockade in mUC and other advanced solid tumors is how to optimally measure the treatment effect of such therapies. While the ratio of hazards between two treatment groups using a Cox regression model is most commonly utilized, the validity of this approach is dependent on the hazards being proportional to one another over time. Survival curves that cross and/or demonstrate late separation, such as those routinely encountered in comparisons of immune checkpoint blockade versus chemotherapy in advanced solid tumors, are not adequately summarized by hazard ratios. Indeed, the primary analysis and reporting of both Keynote-045 and IMVigor 211 centered on hazard ratios despite both datasets violating the proportional hazard assumption. Therefore, we focused on the RMST as the endpoint and established benchmarks for this endpoint for future trial design. The RMST not only surmounts the limitations of conventional survival analyses in the setting of nonproportional hazards, but has also been considered a more intuitive and clinically meaningful interpretation of treatment effect [17]. To overcome the lack of publicly available actual individual patient data from contemporary cancer clinical trials, we used a novel approach to reconstruct survival data from published KM curves and demonstrated excellent agreement with survival data reported in each publication. Of note, a network meta-analysis of CPI trials in non-small cell lung cancer, although using a very different methodology in a different disease, also did not find a significance difference in survival of patients treated with PD-1 versus PD-L1 blockade [36].

There are potential limitations to our analysis. Of primary importance, there have been only two completed randomized trials comparing PD-1/PD-L1 inhibitors versus other therapies in mUC, limiting the data available for inclusion in the network meta-analysis. Salanti et al. [37] previously reported a framework for evaluating the quality of evidence from network meta-analyses; while complete application of this framework is limited by the small number of studies in our network meta-analysis, the two randomized trials included in our network meta-analysis had highly similar enrollment criteria (Supplementary Tables 4 and 5), representing the only two randomized trials in this setting completed to date, and involved a single intermediate treatment (ie, standard chemotherapy) to facilitate an indirect comparison. Further, we strengthened the results of the network meta-analysis with a pooled analysis, including single-arm trials exploring PD-1 and PD-L1 inhibitors in mUC, which, notwithstanding the limitations of cross trial comparisons, demonstrated similar survival outcomes between the therapeutic subclasses. A small difference in outcomes with PD-1 versus PD-L1 blockade cannot be excluded based on our analysis. However, a randomized trial of PD-1 versus PD-L1 blockade is unlikely to occur, and because only a minority of patients responds to these treatments, resources are likely much better focused on strategies to more meaningfully extend the benefits of immune checkpoint blockade to broader groups of patients. We acknowledge that there could be subtle differences among different drugs within the therapeutic subclasses of PD-1 and PD-L1 inhibitors, but we were unable to address such potential differences with the available data. Our subgroup analyses based on PD-L1 expression was limited by the substantial heterogeneity to the assays utilized in the individual trials; however, there is currently no defined role for PD-L1 testing in the platinum-resistant setting.

Using a novel approach to generate reconstructed survival data and an approach to survival analysis that may overcome the limitations of nonproportional hazards, we establish benchmarks for the RMST in patients with platinum-resistant mUC treated with PD-1/PD-L1 blockade and demonstrate highly similar survival outcomes with PD-1 versus PD-L1 blockade. These findings may have important implications regarding clinical practice and clinical trial design.

Author contributions: Dr. Matthew Galsky, Dr. Bart Ferket, Dr. Rachel Jia, and Dr. Scot Niglio had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Galsky, Ferket, Jia, Niglio.
Acquisition of data: Ferket, Galsky, Jia, Niglio, Ji, Ruder, Patel.
Analysis and interpretation of data: Ferket, Galsky, Jia, Niglio.
Drafting of the manuscript: Ferket, Galsky, Jia, Niglio.
Critical revision of the manuscript for important intellectual content: Niglio, Jia, Ruder, Patel, Martini, Sfakianos, Marqueen, Waingankar, Mehrazin, Wiklund, Oh, Mazumdar, Ferket, Galsky.
Statistical analysis: Jia.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Ferket, Galsky.
Other: None.

Financial disclosures: Matthew D. Galsky certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Scot Niglio's domestic partner is employed by STEMCELL Technologies. William Oh has disclosures from AstraZeneca, Bayer, CheckPoint Sciences, Janssen, Sanofi, Sema4, and Tyme Technologies. Matthew D. Galsky has served on an advisory board for Janssen, Dendreon, Merck, GlaxoSmithKline, Lilly, Astellas, Genentech, Bristol-Myers Squibb, Novartis, Pfizer, EMD Serono, AstraZeneca, Seattle Genetics, Incyte, Aileron Therapeutics, Dracen, and Inovio Pharmaceuticals; has received research funding from Janssen, Dendreon, Novartis, Bristol-Myers Squibb, Merck, AstraZeneca, and Genentech/Roche; and is a cofounder of RAPPTA Therapeutics. Rachel Jia, Jiayi Ji, Samuel Ruder, Vaibhav Patel, Alberto Martini, John P. Sfakianos, Kathryn E. Marqueen, Nikhil Waingankar, Reza Mehrazin, Peter Wiklund, Madhu Mazumdar, and Bart Ferket have nothing to disclose.

Funding/Support and role of the sponsor: None.

Acknowledgments: We would like to acknowledge Rachel Pinotti, MLIS, and Celine Soudant, MLIS, of the Levy Library at the Icahn School of Medicine at Mount Sinai, for invaluable guidance in developing and executing the search strategies for this research.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2019.05.037.

References

[1] National Cancer Institute Surveillance Epidemiology and End Results Program. Cancer stat facts: bladder cancer. 2018.
[2] De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 2012;30:191–9.
[3] Seront E, Machiels JP. Molecular biology and targeted therapies for urothelial carcinoma. Cancer Treat Rev 2015;41:341–53.
[4] European Commission. Union Register of medicinal products for human use: pembrolizumab, KEYTRUDA. http://ec.europa.eu/health/documents/community-register/html/h1024.htm.
[5] European Commission. Union Register of medicinal products for human use: Atezolizumab, Tecentriq. http://ec.europa.eu/health/documents/community-register/html/h1220.htm.
[6] European Commission. Union Register of medicinal products for human use: Nivolumab, Opdivo. http://ec.europa.eu/health/documents/community-register/html/h1014.htm.
[7] NCI-Staff. FDA approves immunotherapy drugs for patients with bladder cancer. https://www.cancer.gov/news-events/cancer-currents-blog/2017/approvals-fda-checkpoint-bladder.
[8] Powles T, Eder JP, Fine GD, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014;515:558–62.
[9] Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.
[10] Powles T, Duran I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2018;391:748–57.
[11] Apolo AB, Infante JR, Balmanoukian A, et al. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a multicenter, phase Ib study. J Clin Oncol 2017;35:2117–24.
[12] Powles T, O'Donnell PH, Massard C, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. JAMA Oncol 2017;3:e172411.
[13] 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.
[14] Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol 2017;18:312–22.
[15] Sharma P, Callahan M, Bono P, et al. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. Lancet Oncol 2016;17:1590–8.
[16] Cox DR. Regression models life-tables. J Royal Stat Soc Ser B (Methodol) 1972;34:187–202.
[17] Pak K, Uno H, Kim D, et al. Interpretability of cancer clinical trial results using restricted mean survival time as an alternative to the hazard ratio. JAMA Oncol 2017;3:1692–6.
[18] Zhao L, Claggett B, Tian L, et al. On the restricted mean survival time curve in survival analysis. Biometrics 2016;72:215–21.
[19] Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane; Collaboration; 2011.
[20] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
[21] Stewart LA, Tierney JF. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. Eval Health Prof 2002;25:76–97.
[22] Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.
[23] Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Commun Health 1998;52:377–84.
[24] Trac MH, McArthur E, Jandoc R, et al. Macrolide antibiotics and the risk of ventricular arrhythmia in older adults. CMAJ Can Med Assoc J 2016;188:E120–9.

[25] Silverman SR, Schertz LA, Yuen HK, Lowman JD, Bickel CS. Systematic review of the methodological quality and outcome measures utilized in exercise interventions for adults with spinal cord injury. Spinal Cord 2012;50:718.
[26] Hooper P, Jutai JW, Strong G, Russell-Minda E. Age-related macular degeneration and low-vision rehabilitation: a systematic review. Can J Ophthalmol 2008;43:180–7.
[27] Ioannidis JPA, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. CMAJ Can Med Assoc J 2007;176:1091–6.
[28] Taghavi R. Individual patient data meta-analysis of time-to-event outcomes: an application of a Poisson-gamma-frailty model. Universiteit Leiden; 2014.
[29] Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515–26.
[30] Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. Stat Methods Med Res 2008;17:279–301.
[31] Tian L, Zhao L, Wei LJ. Predicting the restricted mean event time with the subject's baseline covariates in survival analysis. Biostatistics 2014;15:222–33.
[32] Uno H. Vignette for survRM2 package: comparing two survival curves using the restricted mean survival time. https://cran.r-project.org/web/packages/survRM2/vignettes/survRM2-vignette3-2.html.
[33] Klein JP, Gerster M, Andersen PK, Tarima S, Perme MP. SAS and R functions to compute pseudo-values for censored data regression. Comput Methods Programs Biomed 2008;89:289–300.
[34] R. Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation Statistical Computing; 2018.
[35] Pond GR, Niegisch G, Rosenberg JE, et al. New 6-factor prognostic model for patients (pts) with advanced urothelial carcinoma (UC) receiving post-platinum atezolizumab. J Clin Oncol 2018;36:413.
[36] You W, Liu M, Miao JD, et al. A network meta-analysis comparing the efficacy and safety of anti-PD-1 with anti-PD-L1 in non-small cell lung cancer. J Cancer 2018;9:1200–6.
[37] Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT. Evaluating the quality of evidence from a network meta-analysis. PLoS One 2014;9:e99682.