

Alterations in DNA Damage Response and Repair Genes as Potential Marker of Clinical Benefit From PD-1/PD-L1 Blockade in Advanced Urothelial Cancers

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A B S T R A C T

Purpose

Alterations in DNA damage response and repair (DDR) genes are associated with increased mutation load and improved clinical outcomes in platinum-treated metastatic urothelial carcinoma. We examined the relationship between DDR alterations and response to PD-1/PD-L1 blockade.

Methods

Detailed demographic, treatment response, and long-term outcome data were collected on patients with metastatic urothelial carcinoma treated with atezolizumab or nivolumab who had targeted exon sequencing performed on pre-immunotherapy tumor specimens. Presence of DDR alterations was correlated with best objective response per Response Evaluation Criteria in Solid Tumors (RECIST) and progression-free and overall survival.

Results

Sixty patients with urothelial cancer enrolled in prospective trials of anti-PD-1/PD-L1 antibodies met inclusion criteria. Any DDR and known or likely deleterious DDR mutations were identified in 28 (47%) and 15 (25%) patients, respectively. The presence of any DDR alteration was associated with a higher response rate (67.9% v 18.8%; $P < .001$). A higher response rate was observed in patients whose tumors harbored known or likely deleterious DDR alterations (80%) compared with DDR alterations of unknown significance (54%) and in those whose tumors were wild-type for DDR genes (19%; $P < .001$). The correlation remained significant in multivariable analysis that included presence of visceral metastases. DDR alterations also were associated with longer progression-free and overall survival.

Conclusion

DDR alterations are independently associated with response to PD-1/PD-L1 blockade in patients with metastatic urothelial carcinoma. These observations warrant additional study, including prospective validation and exploration of the interaction between tumor DDR alteration and other tumor/host biomarkers of immunotherapy response.

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INTRODUCTION

The recent approval of immune checkpoint inhibitors that target the PD-1/PD-L1 axis (atezolizumab,¹ nivolumab,^{2,3} durvalumab,⁴ avelumab,⁵ and pembrolizumab⁶) has revolutionized the management of metastatic urothelial carcinoma (mUC). Although response rates are relatively low (15% to 24%), responders can experience durable disease control compared with prior systemic agents. The identification of clinically useful biomarkers that

identify patients most likely to benefit from immune checkpoint blockade (ICB) remains an ongoing challenge. PD-L1 expression assessed by immunohistochemistry (IHC) is not a robust predictive biomarker of response to ICB in mUC. Features of the host (tumor-infiltrating lymphocytes, T-cell receptor clonality) and tumor (molecular subtypes, mutation load [ML]) currently are being evaluated as predictive biomarkers for ICB in multiple cancer types.⁷⁻¹⁰ Higher ML has been associated with an increased objective response rate (ORR) in patients with

ASSOCIATED CONTENT



See accompanying article on page 1710



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urothelial cancer treated with atezolizumab,^{7,9} although high ML does not guarantee response, and low ML does not preclude response.

Urothelial carcinoma displays a complex genomic landscape,¹¹ including defective DNA damage response and repair (DDR) at the somatic genomic level.¹²⁻¹⁵ Alterations in DDR genes are associated with an elevated ML,^{13,16} increased tumor-infiltrating lymphocytes,¹⁷ and enhanced platinum responsiveness, which lead to a higher likelihood of pathologic downstaging in neoadjuvantly treated bladder cancers^{12,14,18,19} and improved survival outcomes in the metastatic setting.¹³ On the basis of these observations, we hypothesized that the presence of DDR gene mutations is associated with clinical benefit from anti-PD-1/PD-L1 immune checkpoint inhibitors in patients with mUC.

METHODS

Study Design and Patients

After institutional review board approval, we identified patients with a histologically confirmed diagnosis of mUC enrolled in prospective clinical trials of anti-PD-1/PD-L1 monotherapy (ClinicalTrials.gov identifiers: NCT02553642, NCT01928394, and NCT02108652) with identical eligibility criteria. Two of these studies have been reported previously.^{1,2} Informed consent was obtained before tumor sequencing as part of a genomic profiling protocol.

The primary objective of this analysis was to examine the effect of DDR gene alterations on ORR. The secondary objective was to assess correlations between DDR alterations and both progression-free survival (PFS) and overall survival (OS). Two separate analyses of DDR alterations were performed: any DDR alterations and known or likely deleterious DDR alterations defined as hot spot point mutations or loss-of-function alterations in tumor suppressor genes.

Data Collection

Baseline clinical characteristics were extracted, including sex, age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), hemoglobin, sites of metastatic disease at the start of anti-PD-1/PD-L1, time since last platinum-based therapy, prior systemic therapies for metastatic disease, and anti-PD-1/PD-L1 agent received. The primary outcome of interest was ORR, defined as the proportion of patients who achieved a radiographically confirmed complete or partial response as their best response to anti-PD-1/PD-L by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

The Bellmunt risk factors (ECOG PS > 0, hemoglobin < 10 g/dL, and liver metastases) were used to define subgroups on the basis of the presence of zero to three prognostic factors.²⁰ Visceral metastasis was defined as liver, lung, bone, or non-nodal soft tissue metastasis.

Tumor Sequencing

Tumor sequencing was performed using the Memorial Sloan Kettering Integrated Molecular Profiling of Actionable Cancer Targets (MSK-IMPACT) clinical sequencing assay.^{21,22} MSK-IMPACT is a hybridization capture-based next-generation sequencing platform that is Food and Drug Administration (FDA) approved and performed in a Clinical Laboratory Improvement Amendments-certified laboratory. Patients were analyzed using one of three versions of the assay, each of which examines all exons and selected introns within 341; 410; and most recently, 468 genes. Beginning in April 2016, a companion protocol was offered to patients at physician discretion to analyze further selected germline regions to identify potentially heritable pathogenic germline variants associated with cancer predisposition syndromes.²³

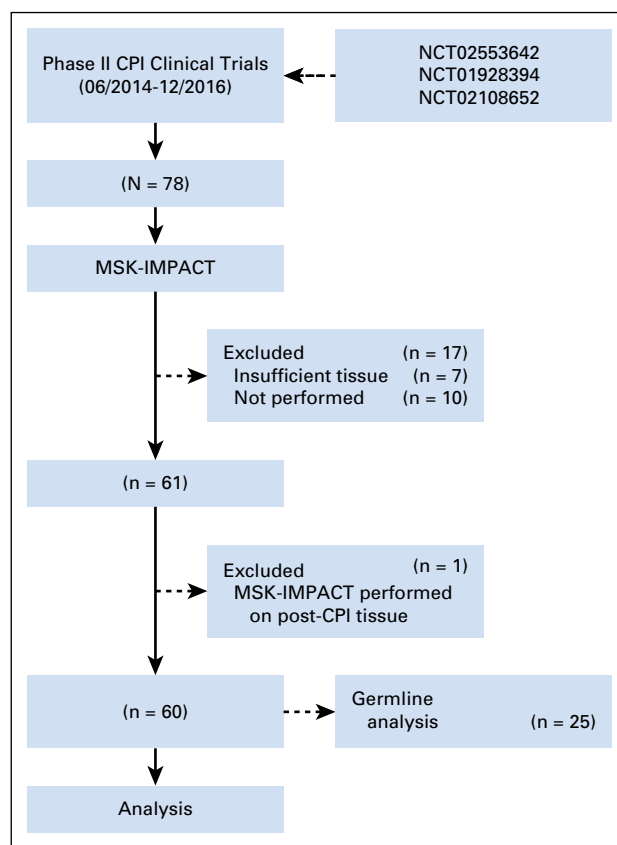


Fig 1. Flow diagram of the study. CPI, checkpoint inhibitor; MSK-IMPACT, Memorial Sloan Kettering Integrated Molecular Profiling of Actionable Cancer Targets.

DDR Genes and Determination of Deleterious Mutation Status

Thirty-four genes within the MSK-IMPACT panel were previously identified as DDR related¹³ according to PubMed searches and the National Center for Biotechnology Information Gene and BioSystems Databases (Data Supplement). All 34 genes were covered in all three versions of MSK-IMPACT.

All loss-of-function alterations were considered deleterious, including deletions, nonsense mutations, and frameshift or splice site alterations. For missense mutations, deleterious status was determined by manual review for their documentation in the Catalogue of Somatic Mutations in Cancer,²⁴ algorithmically determined recurrent hot spot mutations,^{25,26} and annotation of oncogenicity by OncoKB.^{27, 28} On the basis of previous work, all *ERCC2* missense mutations within or near conserved helicase domains were considered deleterious.¹⁴

Determination of ML

ML was determined by the number of nonsynonymous protein-coding mutations identified by MSK-IMPACT divided by the total sequenced genome length in megabases. Copy number gene alterations and structural rearrangements were excluded. The number of mutations detected through MSK-IMPACT was previously shown to correlate with total ML in the urothelial The Cancer Genome Atlas data set¹³ and on whole-exome sequencing.²²

Statistical Methods

Patients were divided into subgroups on the basis of DDR alteration status: deleterious DDR alterations, DDR alterations of unknown significance, and wild-type DDR genes. Baseline characteristics were compared by

DNA Damage Repair Genes and Immunotherapy in Urothelial Cancer

Table 1. Baseline Patient Characteristics

Variable	Cohort				P
	Entire Cohort	Deleterious DDR	Other DDR	Wild-Type DDR	
No. of patients	60	15	13	32	
Median age, years (range)	67.0 (31.6-83.5)	66.0 (31.6-80.0)	68.1 (53.9-77.8)	67.3 (41.2-83.5)	.720
Sex					
Male	53 (88.3)	14 (93.3)	12 (92.3)	27 (84.4)	.660
Female	7 (11.7)	1 (6.7)	1 (7.7)	5 (15.6)	—
Primary site					
Bladder	45 (75)	11 (73.3)	12 (92.3)	22 (68.8)	.630
Renal pelvis	11 (18.3)	2 (13.3)	1 (7.7)	8 (25.0)	—
Ureter	2 (3.3)	1 (6.7)	0 (0.0)	1 (3.1)	—
Urethra	2 (3.3)	1 (6.7)	0 (0.0)	1 (3.1)	—
ECOG performance status					
0	15 (25)	9 (60.0)	0 (0.0)	6 (18.8)	.001
1	45 (75)	6 (40.0)	13 (100)	26 (81.3)	—
Hemoglobin < 10 g/dL					
No	50 (83.3)	12 (80.0)	12 (92.3)	26 (81.3)	.730
Yes	10 (16.7)	3 (20.0)	1 (7.7)	6 (18.8)	—
Bellmunt prognostic group					
0-1	41 (68.3)	13 (86.7)	9 (69.2)	19 (59.4)	.183
≥ 2	19 (31.7)	2 (13.3)	4 (30.8)	13 (40.6)	—
Liver					
Yes	16 (26.7)	0 (0.0)	4 (30.8)	12 (37.5)	.011
No	44 (73.3)	15 (100.0)	9 (69.2)	20 (62.5)	—
Lung					
Yes	20 (33.3)	5 (33.3)	5 (38.5)	10 (31.3)	.930
No	40 (66.7)	10 (66.7)	8 (61.5)	22 (68.8)	—
Bones					
Yes	19 (31.7)	5 (33.3)	3 (23.1)	11 (34.4)	.820
No	41 (68.3)	10 (66.7)	10 (76.9)	21 (65.6)	—
Nodes					
Yes	41 (68.3)	13 (86.7)	8 (61.5)	20 (62.5)	.230
No	19 (31.7)	2 (13.3)	5 (38.5)	12 (37.5)	—
Other					
Yes	20 (33.3)	2 (13.3)	7 (53.8)	11 (34.4)	.090
No	40 (66.7)	13 (86.7)	6 (46.2)	21 (65.6)	—
Visceral					
Yes	46 (76.7)	10 (66.7)	10 (76.9)	26 (81.3)	.470
No	14 (23.3)	5 (33.3)	3 (23.1)	6 (18.8)	—
Median metastatic sites (range)	2 (1-5)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-5.0)	.410
No. of previous lines of systemic therapy in the metastatic setting					
0	5 (8.3)	2 (13.3)	2 (15.4)	1 (3.1)	.290
1	47 (78.3)	10 (66.7)	9 (69.2)	28 (87.5)	—
2	7 (11.7)	2 (13.3)	2 (15.4)	3 (9.4)	—
≥ 3	1 (1.7)	1 (6.7)	0 (0.0)	0 (0.0)	—
Previous therapy with platinum-based regimen					
Cisplatin based	27 (45)	6 (40.0)	4 (30.8)	17 (53.1)	.310
Carboplatin based	11 (18.3)	4 (26.7)	1 (7.7)	6 (18.8)	—
(Neo)adjuvant chemotherapy within 12 months	17 (28.3)	3 (20.0)	6 (46.2)	8 (25.0)	—
Refused first-line chemotherapy	5 (8.3)	2 (13.3)	2 (15.4)	1 (3.1)	—
Median platinum-free interval (range)	9.21 (0.33-150)	5.33 (0.92-41.4)	18.4 (1.12-121)	9.21 (0.33-150)	.300
Target					
Anti-PD-L1	17 (28.3)	4 (26.7)	6 (46.2)	7 (21.9)	.260
Anti-PD-1	43 (71.7)	11 (73.3)	7 (53.8)	25 (78.1)	—
Median mutations/Mb (range)	7.35 (0.0-201.0)	19.4 (2.8-201.0)	10.2 (2.8-21.7)	5.72 (0.0-23.5)	< .001
Median copy number–altered genes (range)	3.00 (0.0-13.0)	2.00 (0.0-13.0)	3.00 (0.0-9.0)	3.00 (0.0-12.0)	.660

NOTE. Values are No. (%) or No. (range) unless otherwise noted.

Abbreviations: DDR, DNA damage response and repair; ECOG, Eastern Cooperative Oncology Group; Mb, megabase.

using Fisher’s exact test for categorical variables and Wilcoxon rank sum test for continuous variables. Response data were prospectively assessed by using RECIST version 1.1 during the conduct of the respective clinical trials and retrieved for this study. Logistic regression was used to test for associations between factors of interest and objective response, with results presented as odds ratios (ORs) and 95% Wald CIs.

OS was calculated from protocol registration date until the date of death or last follow-up. Patients still alive at last follow-up were censored for OS. PFS was calculated from the registration date to the date of progression, death, or last follow-up. Patients alive and without progression were censored for PFS. Both PFS and OS were estimated by Cox proportional hazards regression and graphically by Kaplan-Meier method.

Comparisons of PFS and OS between groups were performed by using the log-rank test.

For multivariable analyses, variables or parameters that achieved a level of significance $\leq .05$ were entered into multivariable models and removed if they were no longer significant at $\alpha = .05$ in the presence of other variables. Akaike information criterion (AIC) was used to compare multivariable logistic regression models for objective response. AIC assesses relative goodness of fit between models. Lower values of AIC indicate a better fit and predictive value. All tests were two-sided, and $P < .05$ was considered significant. All analyses were conducted with SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

Patient Cohort

Seventy-eight patients with mUC were enrolled in three separate prospective anti-PD-1/PD-L1 studies between April 2014 and December 2016. Eighteen patients were excluded: 10 in whom MSK-IMPACT was not performed, seven in whom there was inadequate tissue or DNA for sequencing, and one in whom sequencing was performed on tumor tissue obtained after PD-1/PD-L1 treatment. Sixty patients, therefore, were available for analysis (Fig 1). The median age of the cohort was 67 years (range, 32 to 84 years), and the majority of patients were male (88.3%). Fifteen patients (25.0%) had an ECOG PS of 0, and the rest had an ECOG PS of 1. Most patients (76.7%) had visceral metastases. Five patients were treated with first-line anti-PD-1/PD-L1, and 17 were treated after progression within 12 months of neoadjuvant cisplatin-based chemotherapy. Median time from the end of platinum-based chemotherapy to anti-PD-1/PD-L1 was 9.2 months (range, 0.3 to 150.0 months). Most patients (71.7%) received the anti-PD-1 nivolumab, whereas the rest were treated with the anti-PD-L1 atezolizumab (Table 1).

DDR Gene Alteration Status

All sequenced tumors were obtained before the start of anti-PD-1/PD-L1, with a median time of 9.6 months (range, 0.1 to 104.6 months) from specimen acquisition to the start

of treatment. Twenty-five patients (41.7%) also underwent analysis of germline sequences, with reporting of known and likely pathogenic germline variants in the electronic medical record.

Overall, 74 DDR gene alterations were observed in 28 patients (46.7%), with a median of one DDR alteration per patient (range, one to 34; Data Supplement). Twenty-seven deleterious DDR gene alterations were observed in 15 patients (25.0%). The most commonly altered genes were *ATM* ($n = 7$); *POLE* ($n = 3$); and *BRCA2*, *ERCC2*, *FANCA*, and *MSH6* ($n = 2$ each; Data Supplement). Two patients harbored pathogenic germline DDR gene alterations (one with *MSH2* and the other with both *CHEK2* and *BRCA1*). For the patient with germline *MSH2* alteration, copy neutral loss of heterozygosity was noted in the tumor. For the patient with *CHEK2/BRCA1* alterations, no loss of heterozygosity was observed in the tumor. Both alterations (*BRCA1* E23Vfs*17 and *CHEK2* S428F) were previously shown to be deleterious.^{29,30}

We also examined the distribution of the 27 deleterious DDR alterations by pathways or mechanisms. Genes involved in double-strand break detection ($n = 8$) or repair ($n = 7$), mismatch repair (MMR; $n = 5$), and nucleotide excision repair ($n = 3$; Data Supplement) were the most commonly involved. In summary, 16.7% of patients (10 of 60) harbored deleterious alterations in genes that involved the double-strand break detection/repair mechanisms and 5.0% (three of 60) in MMR pathways, one of which harbored three deleterious MMR gene alterations.

Association Between DDR Status and Observed Clinical Phenotypes

In a comparison of clinical characteristics among patients with deleterious DDR alterations, non-deleterious DDR alterations, and no DDR alterations, those with deleterious DDR alterations had better ECOG PS (0 v 1: 60.0% v 0.0% v 18.8%; $P < .001$) and lower incidence of hepatic involvement (0.0% v 30.8% v 37.5%; $P = .011$; Table 1). Consistent with prior observations, deleterious DDR alterations were associated with higher ML ($P < .001$; Data Supplement).

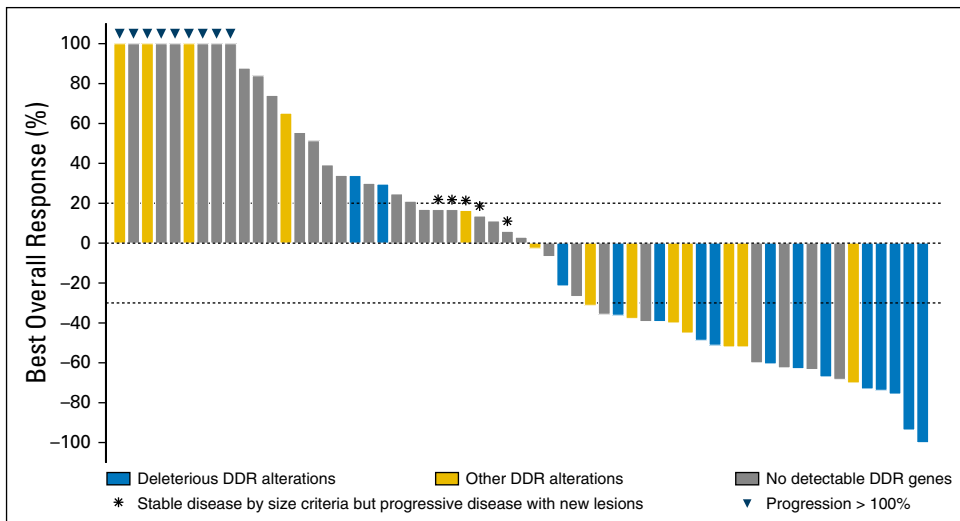


Fig 2. Waterfall plot of observed best responses from anti-PD-1/PD-L1 checkpoint inhibitors. DDR, DNA damage response and repair.

Association Between DDR Status and Response to ICB

Best objective responses for all patients are depicted in Fig 2. Objective responses were observed in 25 patients during anti-PD-1/PD-L1, which corresponds to an ORR of 41.7%. The presence of DDR alterations was associated with a higher ORR than those without any DDR alterations (67.9% v 18.8%; $P < .001$). The finding of a known/likely deleterious DDR alteration was associated with an ORR of 80% versus 53.9% for patients with DDR alterations of unknown significance and 18.8% for those without DDR alterations ($P < .001$).

In univariable logistic regression analysis, the presence of visceral metastasis was inversely associated with ORR, whereas DDR status and ML were associated with responses from immune checkpoint inhibitors (Table 2). As a result of collinearity between DDR alteration status and ML, the latter was not entered into the final multivariable model. In this model, DDR status and visceral metastases remained independent predictors of ORR. Compared with those without DDR alterations, deleterious DDR alterations were associated with an OR of 19.02 for objective

response ($P < .001$), whereas DDR alterations of unknown significance were associated with an OR of 5.79 ($P = .024$; Table 2).

In alternative multivariable models where ML was included in place of DDR status, ML and visceral metastases were independent predictors for responses, with an AIC value of 70.25 versus 66.09 for the model with DDR alteration status. This finding suggests that models that incorporate DDR alterations provide more information than those that use ML. DDR status also was an independent predictor for objective response when controlled for ML (Data Supplement).

Survival Outcomes and the Effect of DDR Alteration Status

With a median follow-up of 19.6 months, 40 events were recorded, and 34 patients died. Median PFS and OS for the entire cohort were 4.5 and 15.8 months, respectively (Data Supplement).

For patients with deleterious DDR alterations, median PFS was not reached, and the 12-month PFS rate was 56.6%. Median PFS for

Table 2. Univariable and Multivariable Analyses of Objective Response

Parameter	Univariable Analysis			Multivariable Analysis		
	OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>
Age	1.00	0.95 to 1.06	.935			
Sex						
Male v female	1.06	0.21 to 5.20	.946			
Primary site						
Bladder/urethra v upper tract	1.26	0.36 to 4.39	.712			
ECOG performance status						
0 v 1	0.76	0.23 to 2.47	.651			
Hemoglobin < 10 g/dL						
Yes v no	0.29	0.06 to 1.52	.144			
Bellmunt prognostic score						
0-1 v 2	0.53	0.16 to 1.64	.276			
Liver						
Yes v no	0.55	0.16 to 1.83	.327			
Lung						
Yes v no	0.47	0.15 to 1.48	.199			
Bones						
Yes v no	0.75	0.24 to 2.28	.606			
Nodes						
Yes v no	1.87	0.60 to 5.88	.284			
Other						
Yes v no	0.66	0.22 to 2.00	.460			
Visceral						
Yes v no	0.19	0.05 to 0.72	.014	0.16	0.03 to 0.78	.023
No. of metastatic sites						
Continuous variable	0.70	0.38 to 1.26	.228			
No. of previous lines of systemic therapy in the metastatic setting						
Continuous variable	1.86	0.69 to 4.96	.217			
Platinum-free interval						
Continuous variable	1.00	0.98 to 1.03	.681			
Target						
Anti-PD-L1 v anti-PD-1	0.97	0.31 to 3.04	.961			
Mutations/Mb						
Continuous variable	1.10	1.02 to 1.19	.017			
Copy number alterations						
Continuous variable	0.87	0.74 to 1.04	.127			
DDR						
Other DDR v wild type	5.06	1.24 to 20.63	.024	5.79	1.26 to 26.58	.024
Deleterious DDR v wild type	17.33	3.70 to 81.30	< .001	19.02	3.65 to 99.17	< .001

NOTE. Mutation load is not included in multivariable analysis because of collinearity with DDR alteration status.

Abbreviations: DDR, DNA damage repair and response; ECOG, Eastern Cooperative Oncology Group; Mb, megabase; OR, odds ratio.

those with DDR alterations of unknown significance and for those without DDR gene alterations was 15.7 and 2.9 months, respectively (Fig 3A). In univariable analysis, hemoglobin < 10 g/dL, ML, and DDR alteration status were significantly associated with PFS. In a multivariable model, hemoglobin < 10 g/dL remained an independent poor prognostic indicator for PFS. Deleterious DDR alterations were significantly associated with improvement in PFS compared with patients without detectable alterations (hazard ratio [HR], 0.20; 95% CI, 0.08 to 0.50; $P < .001$), whereas DDR alterations of unknown significance showed borderline improvement in PFS (HR, 0.44; 95% CI, 0.19 to 1.04; $P = .062$; Table 3).

The median OS was not reached for patients with deleterious DDR alterations, with 71.5% alive at 12 months, whereas the median OS for those with DDR alterations of unknown significance or no detectable DDR alterations were 23.0 and 9.3 months, respectively (Fig 3B). In a univariable analysis, hemoglobin < 10 g/dL, visceral metastases, and DDR status were associated with OS. In multivariable analysis, hemoglobin < 10 g/dL and visceral metastases remained independent prognostic indicators for poorer OS. Deleterious DDR alterations conferred superior OS compared with no detectable DDR gene alterations (HR, 0.27; 95% CI, 0.10 to 0.73; $P = .001$). Patients with DDR alterations of unknown significance showed borderline improvement in OS compared with unaltered DDR genes (HR, 0.46; 95% CI, 0.18 to 1.19; $P = .109$), which suggests that some of the alterations of unknown significance may be functional variants (Table 4). Additional multivariable analyses for PFS and OS with ML in place of DDR status, stratification by DDR status, and stratification by ML showed that DDR-containing models remained a superior predictor of outcomes compared with ML (Data Supplement; Table 4).

DISCUSSION

In this study, we observed that alterations in a panel of DDR genes were strongly associated with clinical benefit among patients with

mUC treated with anti-PD-1/PD-L1. DDR genes are frequently altered in urothelial cancers and were observed in 46.7% of tumors in the study cohort of which 25.0% were considered deleterious. Association with clinical outcomes was more pronounced in tumors with deleterious DDR alterations than in those with variants of unknown significance in DDR-associated genes. Conversely, the association was not observed with non-DDR genes (Data Supplement).

This study represents one of the first reports to examine the association between ICB response and defective DDR mechanisms beyond MMR deficiency. In MMR-deficient tumors, pembrolizumab was associated with an ORR of 50% among 12 cancer types studied (none of which were mUC), which led to FDA approval of pembrolizumab regardless of primary tumor site.³¹⁻³³ However, deleterious alterations in MMR pathway occurred in 5% of the current study cohort (18.5% of all deleterious DDR alterations). In mUC, genes involved in double-strand break detection and repair mechanisms were most frequently altered, which represent two thirds of the observed deleterious DDR alterations. These tumors derived clinical benefit from ICB, which is consistent with observations from a series of 38 patients with metastatic melanoma where responders to anti-PD-1 were enriched for *BRCA2* mutations (28% v 6%).³⁴ However, whether DDR alterations beyond MMR deficiency represent a disease-agnostic phenomenon remains unknown.

To date, no validated predictive biomarkers of response to anti-PD1/PD-L1 exist in mUC. Although these agents function by interrupting PD-1/PD-L1 signaling, which increases cytotoxic T-cell-mediated antitumor responses,^{10,35} tumor or immune cell PD-L1 expression in mUC by IHC does not have a clearly reproducible relationship to treatment response. Despite FDA approval of two PD-L1 IHC companion diagnostics, multiple PD-L1 IHC assays have demonstrated conflicting data in mUC, and their clinical utility remains unproven.^{2-6,9}

ML was previously shown to be associated with clinical benefit in mUC.^{7,9} However, ML is a continuous variable without a clearly defined cut point below which responses do not occur and above

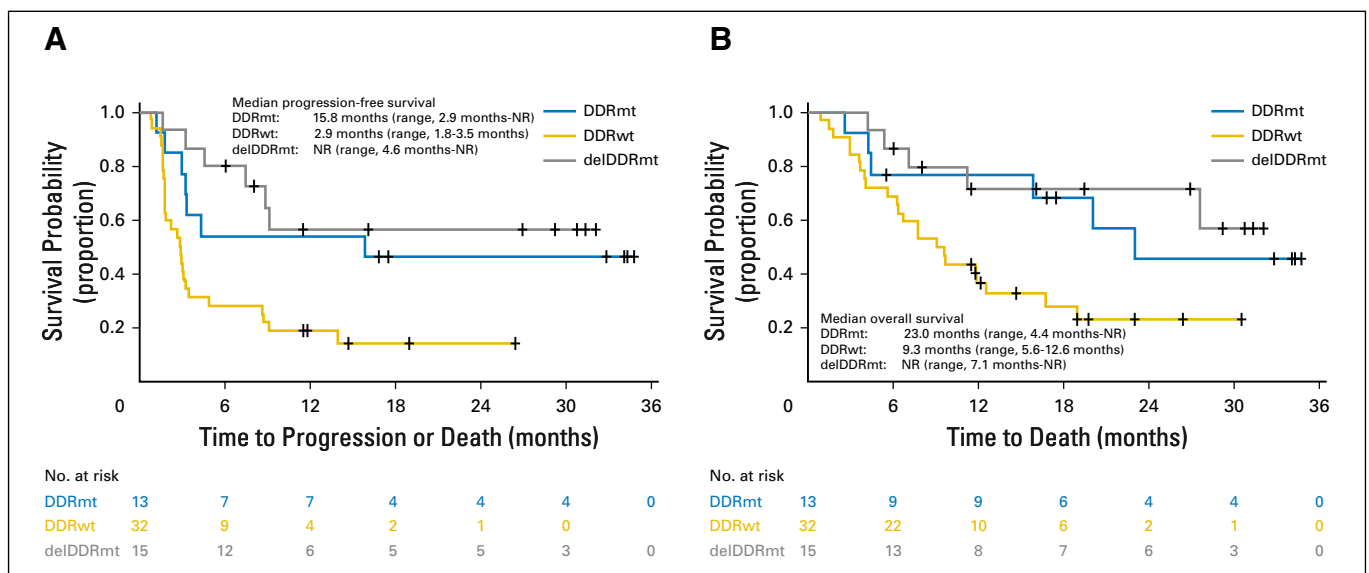


Fig 3. (A) Progression-free survival by DNA damage response and repair (DDR) alteration status. (B) Overall survival by DDR alteration status. delDDRmt, deleterious DDR alterations; DDRmt, nondeleterious DDR alterations; DDRwt, nondetectable DDR gene alterations; NR, not reached.

Table 3. Univariable and Multivariable Analyses of Progression-Free Survival

Parameter	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	P	HR	95% CI	P
Age	1.00	0.97 to 1.03	.866			
Sex						
Male v female	1.23	0.48 to 3.14	.667			
Primary site						
Bladder/urethra v upper tract	1.00	0.50 to 2.24	.995			
ECOG performance status						
1 v 0	1.11	0.53 to 2.33	.789			
Hemoglobin < 10 g/dL						
Yes v no	3.15	1.46 to 6.81	.004	4.30	1.89 to 9.78	< .001
Bellmunt prognostic score						
0-1 v ≥ 2	0.53	0.28 to 1.04	.063			
Liver						
Yes v no	1.79	0.91 to 3.54	.092			
Lung						
Yes v no	1.38	0.72 to 2.62	.331			
Bones						
Yes v no	1.06	0.54 to 2.05	.872			
Nodes						
Yes v no	0.83	0.43 to 1.61	.584			
Other						
Yes v no	0.90	0.45 to 1.76	.750			
Visceral						
Yes v no	1.77	0.81 to 3.85	.150			
No. of metastatic sites						
Continuous variable	1.16	0.83 to 1.60	.384			
No. of previous lines of systemic therapy in the metastatic setting						
Continuous variable	0.93	0.53 to 1.63	.792			
Platinum-free interval						
Continuous variable	1.00	0.98 to 1.01	.540			
Target						
Anti-PD-L1 v anti-PD-1	0.79	0.39 to 1.58	.503			
Mutation load						
Continuous variable	0.95	0.91 to 1.00	.029			
Copy number alterations						
Continuous variable	1.08	1.00 to 1.17	.057			
DDR						
Other DDR v wild type	0.38	0.16 to 0.89	.025	0.44	0.19 to 1.04	.062
Deleterious DDR v wild type	0.25	0.10 to 0.62	.003	0.20	0.08 to 0.50	< .001

NOTE. Mutation load is not included in the multivariable analysis because of collinearity with DDR alteration status. Abbreviations: DDR, DNA damage repair and response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

which response is guaranteed. In contrast, DDR mutations are easily detected with next-generation sequencing assays, and their presence in the current data set was strongly associated with anti-PD-1/PD-L1 response. In this cohort, DDR status was superior to ML at predicting responses, PFS, and OS in various multivariable models and remained significant when controlling for ML. However, because of the observed collinearity of DDR alterations and ML, mutual independence among these features could not be demonstrated.

Other non-neoantigen- and/or ML-based mechanisms have been postulated to account for the additional influence of DDR alterations on ICB treatment outcome.³⁶ For example, the stimulator of interferon genes (STING) pathway was initially described as a host response to viral infection and potential etiology for autoimmune diseases.³⁷ The STING pathway induces innate host response in preclinical cancer models³⁸⁻⁴⁰ and is activated upon contact with cytosolic DNA fragments, which culminate in a type 1 interferon response. Accumulation of cytosolic DNA fragments

that arise from defective DDR mechanisms provides triggers to prime the STING pathway for activation.^{41,42} In a PD-1/PD-L1 blockade-resistant mouse model, exposure to synthetic DNA fragments leads to STING-dependent antitumor activity in combination with anti-PD-1, which further supports this hypothesis⁴³ but awaits confirmation and replication in a clinical setting.

Contrary to previous reports, hepatic metastasis was not associated with poorer outcomes in the current study likely because of sample size. We did observe an association between deleterious DDR status and an absence of hepatic metastasis, which supports our previous observation in platinum-treated mUCs (wild-type DDR, 20.0%; more than one DDR alteration, 0.0% to 7.7%)¹³ and suggests a biologic basis worthy of additional investigation.

This retrospective analysis of prospectively treated patients has several limitations. First, the patients had better prognostic features and extended follow-up, which likely accounts for the higher ORR

Table 4. Univariable and Multivariable Analyses of Overall Survival

Parameter	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Age	1.00	0.97 to 1.04	.816			
Sex						
Male v female	1.45	0.50 to 4.17	.492			
Primary site						
Bladder/urethra v upper tract	1.14	0.52 to 2.84	.760			
ECOG performance status						
1 v 0	1.15	0.52 to 2.54	.735			
Hemoglobin < 10 g/dL						
Yes v no	4.04	1.76 to 9.27	< .001	7.41	2.88 to 19.10	< .001
Bellmunt prognostic score						
0-1 v ≥ 2	0.58	0.29 to 1.21	.140			
Liver						
Yes v no	1.55	0.74 to 3.24	.250			
Lung						
Yes v no	1.56	0.77 to 3.15	.219			
Bones						
Yes v no	1.27	0.62 to 2.60	.521			
Nodes						
Yes v no	0.84	0.42 to 1.71	.637			
Other						
Yes v no	1.07	0.53 to 2.16	.851			
Visceral						
Yes v no	2.76	1.06 to 7.18	.037	3.53	1.31 to 9.57	.013
No. of metastatic sites						
Continuous variable	1.27	0.89 to 1.80	.186			
No. of previous lines of systemic therapy in the metastatic setting						
Continuous variable	1.16	0.63 to 2.14	.633			
Platinum-free interval						
Continuous variable	1.00	0.98 to 1.01	.564			
Target						
Anti-PD-L1 v anti-PD-1	0.74	0.36 to 1.55	.427			
Mutation load						
Continuous variable	0.95	0.91 to 1.00	.052			
Copy number alterations						
Continuous variable	1.06	0.97 to 1.16	.192			
DDR						
Other DDR v wild type	0.41	0.16 to 1.03	.057	0.46	0.18 to 1.19	.109
Deleterious DDR v wild type	0.30	0.11 to 0.80	.016	0.27	0.10 to 0.73	.010

NOTE. Mutation load is not included in multivariable analysis because of collinearity with DDR alteration status.

Abbreviations: DDR, DNA damage repair and response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

observed (Data Supplement). Second, the MSK-IMPACT assay does not include all known DDR genes; thus, additional low-frequency DDR genes might also contribute to improved clinical outcomes. Moreover, many missense mutations may have little or no effect on protein function; this is likely the basis for the weaker correlation between clinical outcomes and identified DDR alterations of unknown significance. Functional defects in individual genes, pathways, or mechanisms of DDR also are not likely to have an equal effect on DDR capability, and a larger cohort size is needed to determine whether the predictive value of mutations in individual DDR genes vary. Finally, this single-center study and our cohort were identified on the basis of sequential patients who underwent tumor sequencing with MSK-IMPACT rather than all patients enrolled in anti-PD-1/PD-L1 clinical trials, which might yield selection bias.

In conclusion, this study shows that patients with DDR gene alterations are more likely to experience objective responses, longer PFS, and improved OS than patients with wild-type DDR genes.

Whether the association is predictive or prognostic should be investigated further in larger data sets from randomized studies that have led to the FDA approval of several anti-PD-1/PD-L1 agents. In addition, we plan to validate these findings prospectively in an upcoming randomized phase II study of atezolizumab or atezolizumab plus bevacizumab in mUC. Additional investigation is warranted to evaluate the mechanisms that link DDR alterations (beyond MMR), ML and neoantigen load, and immunotherapy response. If validated in other studies, DDR alterations may represent a useful predictive biomarker of response to anti-PD-1/PD-L1 in urothelial carcinoma.

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Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Alterations in DNA Damage Response and Repair Genes as Potential Marker of Clinical Benefit From PD-1/PD-L1 Blockade in Advanced Urothelial Cancers

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