Clonal Relatedness and Mutational Differences between Upper Tract and Bladder Urothelial Carcinoma


Purpose: To investigate genomic differences between urothelial carcinomas of the upper tract (UTUC) and bladder (UCB), with a focus on defining the clonal relatedness of temporally distinct tumors.

Experimental Design: We prospectively sequenced tumors and matched germline DNA using targeted next-generation sequencing methods. The cohort included 195 UTUC patients and 454 UCB patients. For a subgroup of 29 patients with UTUC and a history of a subsequent UCB, both tumors were analyzed to assess their clonal relatedness.

Results: With the progression to higher UTUC clinical state, there were fewer alterations in the RTK/RAS pathway but more alterations in TP53/MDM2. Compared with UCB, TP53, RB1, and ERBB2 were less frequently altered in UTUC (26% vs. 46%, 3% vs. 20%, 8% vs. 19%, respectively; Q < 0.001), whereas FGFR3 and HRAS were more frequently altered (40% vs. 26%, 12% vs. 4%, respectively; Q < 0.001). On the basis of an integrated analysis of tumor mutational burden, MSensor score and mutational signature, 7.2% of UTUC tumors were classified as MSI-high/MMR-deficient (MSI-H/dMMR). The risk of bladder recurrence after UTUC was significantly associated with mutations in FGFR3, KDM6A, CCND1, and TP53. Comparison of UCB with corresponding UTUC tumors from the same patient supports their clonal relatedness.

Conclusions: UTUC and UCB exhibit significant differences in the prevalence of common genomic alterations. In individual patients with a history of both tumors, UCB and UTUC were always clonally related. Genomic characterization of UTUC provides information regarding the risk of bladder recurrence and can identify tumors associated with Lynch syndrome.

Introduction

Urothelial carcinoma (UC) is the sixth most common cancer type in the United States (1). UCs of the bladder (UCB) account for the majority of UCs (90%–95%; ref. 2), whereas UCs of the upper tract (UTUC) are significantly less common, accounting for 5% to 10% (1, 3). Although both UCB and UTUC arise within the urothelium and have a similar histologic appearance, they have distinct clinical characteristics (4). UTUC is uniquely associated with several environmental risk factors (5–7) and is more common than UCB in patients with Lynch syndrome (8).

Due to the relative rarity of UTUC compared with UCB, most clinical and biological studies have focused predominantly or exclusively on bladder cancers, with the results and clinical implications extrapolated to UTUC. To date, relatively few UTUC have been examined using newer next-generation sequencing (NGS) methods and The Cancer Genome Atlas (TCGA) study of UCs excluded UTUC patients (9, 10). Small retrospective case series have, however, suggested differences in the prevalence of oncogenic driver mutations between UCB and UTUC (11, 12).

Here, we leveraged a prospective molecular characterization initiative to explore the potential clinical utility of tumor
Translational Relevance

To date, relatively few urothelial carcinomas of the upper tract (UTUC) have been examined using next-generation sequencing (NGS) methods. In this study, we sequenced 195 UTUC using a targeted NGS platform and compared the results to 454 urothelial carcinomas of the bladder (UCB). We identified significant differences in the prevalence of common genomic alterations between UTUC and UCB. Targeted NGS was a robust methodology for identifying UTUC patients whose tumors were microsatellite instability-high/mismatch-repair-deficient, the vast majority of which arose in patients with a pathogenic germline mutation in a Lynch syndrome–associated gene. In individual patients with a history of both, we found that the UCB and UTUC were always clonally related. The latter results justify the development of methods to prevent lower tract seeding during surgery and the adoption of risk-adapted surveillance for bladder recurrence in patients with UTUC.

Materials and Methods

Study samples

Written consent was obtained from all participating patients. The study was conducted in accordance with International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws, and approved by an institutional review board. In total, 195 UTUC and matched germline DNA samples from blood [including 84 UTUC samples from a prior retrospective study (ref. 11) and 111 samples collected and sequenced within the context of a prospective molecular characterization initiative. Overall, the UTUC samples included 84 tumors from patients with no muscle invasion (<pT2, 43%), 76 from patients with muscle invasion (≥pT2, 39%) and 35 from patients with metastatic disease (18%) at the time of tumor collection (Table 1). Eighty-five percent of tumors were high-grade. We performed targeted NGS analysis of matched tumor and germline DNA of at least 275 and up to 468 cancer-associated genes. The most frequently mutated genes included FGFR3 (40%), KMT2D (37%), KDM6A (32%), TP53 (26%), and ARID1A (23%; Fig. 1). We further grouped mutations by canonical pathway or functional significance (18).

Results

Genomic landscape of UTUC

To explore the genomic landscape of UTUC across the disease spectrum, we analyzed 195 UTUC tumors, including 84 samples analyzed retrospectively and reported previously (11) and 111 samples collected and sequenced within the context of a prospective molecular characterization initiative. Overall, the UTUC samples included 84 tumors from patients with no muscle invasion (<pT2, 43%), 76 from patients with muscle invasion (≥pT2, 39%) and 35 from patients with metastatic disease (18%) at the time of tumor collection (Table 1). Eighty-five percent of tumors were high-grade. We performed targeted NGS analysis of matched tumor and germline DNA of at least 275 and up to 468 cancer-associated genes. The most frequently mutated genes included FGFR3 (40%), KMT2D (37%), KDM6A (32%), TP53 (26%), and ARID1A (23%; Fig. 1). We further grouped mutations by canonical pathway or functional significance (18).

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>UTUC (N = 195)</th>
<th>Bladder (N = 454)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR), years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>67.1 (58.1-74.5)</td>
<td>67.5 (60.1-74.4)</td>
<td>0.692</td>
</tr>
<tr>
<td>Male</td>
<td>121 (62%)</td>
<td>367 (81%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>74 (38%)</td>
<td>87 (19%)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>22 (11%)</td>
<td>63 (14%)</td>
<td>0.619</td>
</tr>
<tr>
<td>Former</td>
<td>112 (58%)</td>
<td>246 (54%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>61 (37%)</td>
<td>143 (32%)</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal pelvis</td>
<td>154 (79%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Urter</td>
<td>41 (21%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;pT2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥pT2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low grade</td>
<td>84 (45%)</td>
<td>151 (33%)</td>
<td>0.055</td>
</tr>
<tr>
<td>High grade</td>
<td>76 (39%)</td>
<td>215 (47%)</td>
<td></td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;pT2</td>
<td>35 (18%)</td>
<td>90 (20%)</td>
<td></td>
</tr>
</tbody>
</table>
| ≥pT2                       | 0.692
| Metastasis                 | 165 (85%)       | 428 (94%)        |       |
| Presence of pathologic variant |               |                  |       |
| Yes                        | 86 (44%)        | 170 (37%)        | 0.186 |
| No                         | 27 (14%)        | 58 (13%)         |       |
| Abbreviation: IQR, interquartile range. |                |                  |       |
| NOTE: P values in bold are statistically significant. |                |                  |       |
In patients with higher stage disease, there were fewer alterations in the RTK/RAS pathway \((P < 0.001)\) but more alterations in TP53/MDM2 \((P < 0.001)\). The frequency of activating alterations in FGFR3 and HRAS was lower in patients with higher stage disease (63% vs. 26% and 17% vs. 3%, respectively; \(P < 0.001\)). Conversely, the frequency of alterations in TP53 and MDM2 was significantly increased in patients with higher stage disease (11% vs. 31% and 4% vs. 17%, respectively; \(P < 0.001\)). The frequency of alterations in only two other genes was significantly greater in patients with lower stage UTUC tumors: STAG2, a component of the cohesin complex that plays a role in meiosis and mitosis (24% vs. 6%, \(P < 0.001\)), and FBXW7, a component of the SCF complex involved in regulating protein degradation of several oncogenes including cyclin E and c-Myc (12% vs. 0%, \(P < 0.001\)).

When comparing the genomic profiles of UTUC based on the location of the primary tumor (renal pelvis vs. ureter), only KMT2C and KMT2D, two genes with a purported role in chromatin regulation, were significantly more frequently altered in ureteral tumors as compared with renal pelvic tumors after adjusting for multiple comparison (41% vs. 18%, \(Q = 0.023\) and 59% vs. 32%, \(Q = 0.034\), respectively).

Genomic comparison between UTUC and bladder tumors

To identify differences in the mutational landscape between upper and lower tract urothelial tumors, we compared the 195 UTUC tumors with 454 UCB tumors from patients who had no prior history of UTUC (Table 1). The spectrum of mutations identified by MSK-IMPACT in these bladder tumors was comparable to those reported by the TCGA (9, 10). Overall, TP53, RB1, and ERBB2 were significantly more frequently altered in UCB as compared with UTUC (46% vs. 26%, 20% vs. 3%, 19% vs. 8%, respectively; \(Q < 0.001\)), whereas FGFR3 and HRAS were significantly more frequently altered in UTUC (40% vs. 26%, 12% vs. 4%, respectively; \(Q < 0.001\); Fig. 2). When grouped by pathway/function, genes in the cell-cycle and TP53/MDM2 pathways were significantly more frequently altered in UCB compared with UTUC (56% vs. 43%, \(Q = 0.01\) and 55% vs. 35%, \(Q < 0.001\), respectively).

We next sought to determine if the prevalence of alterations in individual genes varied as a function of clinical disease state in UTUC and UCB (Fig. 3). For clinical state <pT2, HRAS and KMT2C were significantly more frequently altered in UTUC (17% vs. 3%, \(Q = 0.003\) and 30% vs. 12%, \(Q = 0.008\), respectively). When

Figure 1.
Overview of the genomic landscape of UTUC, stratified by clinical state and molecular pathways. The genes with significant differences in genomic alteration frequencies across clinical states are highlighted by red boxes.
limiting the analysis to only high-grade samples <pT2, HRAS was still significantly more frequently altered in UTUC as compared with UCB (22% vs. 4%, Q = 0.001). For clinical state ≥pT2, TP53 and RB1 were more frequently altered in UCB (62% vs. 39%, Q = 0.008 and 26% vs. 3%, Q < 0.001), whereas HRAS was more frequently altered in UTUC (12% vs. 2%, Q = 0.003). The TP53/MDM2 pathway was significantly more frequently altered in UCB (69% vs. 51%, Q = 0.022). For patients with metastatic disease at the time of tumor collection, RB1, ERBB2, and cell-cycle pathway–associated genes as a group were all more frequently altered in UCB (27% vs. 3%, Q = 0.031; 27% vs. 0%, Q = 0.007; 71% vs. 43%, Q = 0.015, respectively).

Patients with Lynch syndrome have germline mutations in mismatch-repair (MMR)–associated genes, which results in an increased risk for the development of tumors with microsatellite instability (MSI) and hypermutation. UC belongs to the spectrum of Lynch syndrome, but UTUC is much more frequent than UCB in patients with Lynch syndrome (8). To assess for evidence of MMR deficiency in the two groups, we calculated tumor mutational burden and MSisensor scores, a measure of somatic alteration of microsatellite regions (Supplementary Methods; refs. 16, 19). The median number of somatic mutations/Mb was significantly higher in UTUC compared with UCB [13.2 (7.4–19.1) vs. 8.8 (5.9–15.4); P < 0.001]. Overall, 6.2% (12/194) of the UTUC
samples were MSI-high (defined as an MSIsensor score $\geq 10$), with 3.1% (6/194) having an indeterminate MSIsensor score (3–10). As expected, the number of mutations/Mb was significantly higher in tumors with MSIsensor scores $\geq 10$ (median: 49.3) as compared with tumors with MSIsensor scores between 3 and 10 (median: 13.0; $P = 0.002$) or MSIsensor scores $< 3$ (median: 6; $P < 0.001$). Four patients with UCB (1.1%) had an MSIsensor score $\geq 10$, including one patient known to have Lynch syndrome and no prior history of UTUC.

UTUC is the third most prevalent cancer in Lynch syndrome (20), and current European guidelines recommend that germline DNA sequencing be considered for all UTUC patients younger than age 60 and those with a personal or familial history of Lynch-related cancers (21). However, no optimal screening strategy has been validated. In our cohort of 195 UTUC, consent to assess for germline mutations was obtained in 47 patients, typically those in whom there was clinical suspicion of a hereditary syndrome or a high MSIsensor score. Analysis of the germline sequencing data revealed that 12 of these 47 patients had a pathogenic or likely pathogenic germline mutation in a Lynch syndrome–associated gene (Supplementary Table S2). Notably, all tumors from these patients had a high tumor mutational burden (range: 22–472, median: 54.9, IQR: 32.4–67.0). Only 10 of 12 Lynch patients, however, had an MSIsensor score of $\geq 10$ (Fig. 4; Supplementary Table S2). Furthermore, of the 12 tumors with MSIsensor scores of $\geq 10$, 10 had a Lynch syndrome–associated germline mutation, one a personal history strongly suggestive of Lynch syndrome but no consent for germline analysis (patient 2; Fig. 4), and one a somatic Lynch-like MSI-high tumor (patient 1; Fig. 4).

To further characterize those tumors with evidence of hypermutation but indeterminate or low MSIsensor scores, we performed mutational signature decomposition analysis (22, 23) on all tumor samples with 10 or more single-nucleotide somatic mutations. Notably, only 6 of 12 tumors from patients with Lynch syndrome had a predominant MMR/MSI signature by mutational signature decomposition analysis, whereas the others exhibited a predominant mitotic clock (aging) signature. In the broader cohort of UTUC samples with 10 or more mutations without an MMR germline mutation, we identified evidence of a predominant AID/APOBEC signature in 20 of 30, a smoking signature in 2 of 30 and a POLE signature in 1 of 30.

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Figure 3.
Stage-by-stage comparison of the differences in the prevalence of genomic alterations between UTUC and UCB, for the genes identified at a frequency of $\geq 10\%$ at any clinical state. The genes with significant differences after multiple comparisons using the Bonferroni method are highlighted by red boxes.
As above, two patients with MSIsensor scores <10 had a Lynch syndrome–associated UTUC (patients 3 and 4; Fig. 4).

In sum, the data indicate that no single metric could identify all MMR-deficient UTUC tumors and that the positive and negative predictive value of current clinical germline testing guidelines is low (Supplementary Table S3). The data thus suggest that an integrated approach that incorporates tumor mutational burden, MSIsensor score, mutational signature analysis, and somatic and germline mutation of Lynch syndrome–associated genes is needed to accurately classify the MMR deficiency status of UTUC tumors.

Given the limitations of current clinical germline testing guides, our results also support universal tumor/normal genetic profiling in all patients with UTUC to identify those with a Lynch syndrome–associated tumor.

Clonal relatedness of lower tract recurrences in UTUC patients

Of the 195 patients with UTUC, 137 underwent radical nephroureterectomy, with 57 (42%) later developing a UCB after a median time of 7.3 months (IQR: 4.1–13.7; Supplementary Table S4). After adjusting for clinical factors associated with bladder recurrence, including sex, history of prior bladder cancer,
altered in FGFR3 (HR = 3.00; 95% CI, 1.58–5.68; \( P = 0.001 \)), KDM6A (HR = 2.27; 95% CI, 1.29–4.02; \( P = 0.005 \)), and CCND1 (HR = 3.10; 95% CI, 1.17–8.21; \( P = 0.023 \)) were significantly associated with a higher risk of developing a subsequent bladder tumor, whereas TP53 alterations were associated with a lower risk (HR = 0.32; 95% CI, 0.13–0.80; \( P = 0.014 \); Supplementary Table S5).

To determine whether the bladder tumors that arose in patients with a prior history of UTUC represented clonal recurrences or second primary tumors, we analyzed temporally distinct pairs of UTUC and UCB from 29 patients (Supplementary Table S6). Clonal relatedness between the tumors was investigated using all somatic mutation data, including synonymous mutations, as previously described (17). Sixteen patients (55%) had no prior history of UCB. All pairs of UTUC and UCB were deemed to have a shared clonal origin (\( P < 0.005 \)). We did, however, observe some lesion-to-lesion heterogeneity with only 86% of somatic mutations being present in both the initial UTUC and the subsequent bladder tumor recurrence (Fig. 5). In the 13 patients with a prior history of UCB, 75% of the mutations were found to be similar in both the UTUC and subsequent bladder tumors (Supplementary Fig. S1). Again, all pairs of UTUC and recurrent UCB were clonal (\( P < 0.005 \)). For the 7 bladder tumors collected before radical nephroureterectomy with tissue available for sequencing, 69% of mutations were shared between the initial UCB and subsequent UTUC, with all the tumor pairs again being of shared clonal origin (\( P < 0.005 \)).

**Discussion**

Although they share a similar urothelial histologic appearance, UTUC and UCB have several epidemiologic and clinical differences (4). By comparing the mutational profiles of UTUC and UCB in 649 urothelial cancer samples (195 UTUC and 454 UCB), we sought to determine whether differences in somatic mutational patterns underlie the clinical differences between the two diseases. Although the spectrum of genomic alterations was similar between UTUC and UCB, significant differences in the prevalence of mutations in individual genes were observed, including a higher frequency of FGFR3 and HRAS alterations and a lower frequency of TP53, RB1, and ERBB2 alterations in UTUC as compared with UCB. Furthermore, we found that significant differences in the mutational frequency of several genes remained after adjusting for clinical disease state.
Consistent with prior studies (25), FGFR3 alterations were more common in low-grade tumors. FGFR3 mutations in urothelial cancer typically arise in one of several hotspot locations and have been shown to be oncogenic and thus represent potential therapeutic targets. Notably, 31% of high-grade UTUC had FGFR3 alterations, a frequency significantly higher than that observed in high-grade UCB (21%). As FGFR3 and TP53 tend to be mutually exclusive, our results lend further support to the model that high-grade tumors often arise de novo, in the absence of a prior low-grade lesion, whereas some low-grade tumors with FGFR3 alterations, more frequently in the upper tract than in the bladder, progress over time to high-grade disease (26).

RB1 alterations were rarely observed in our high-grade UTUC cohort (2%), whereas RB1 inactivation is common in MIBC, where it has been associated with genomic instability (27). It is noteworthy that no single pathognomonic molecular event has been identified in UC. Overall, we found that the RTK/RAS, PIK3/AKT, cell-cycle, and TP53/MDM2 pathways were all altered in around half the tumors, with RTK/RAS and TP53/MDM2 alterations being largely mutually exclusive. Recently, a whole-exome sequencing analysis of 27 UTUC samples confirmed that there was a significantly higher frequency of mutations in the p53 and related pathways in high-grade tumors, leading to genomic instability, copy-number alterations, and disruption of the cell-cycle and apoptotic pathways, which was corroborated by protein analysis (12). However, given the complex co-mutation pattern of UC and the lack of in-depth studies on the biological role of most of the oncogenes and tumor suppressors identified in this disease, the understanding of the key co-mutational events required for progression to a high-grade, lethal phenotype will require further study.

Tumor genomic analysis can provide information that could be used by physicians to guide the clinical management of UTUC patients. For example, clinical tumor genomic profiling can prospectively identify potential therapeutic targets and thus guide treatment selection (28). Overall, over half of the urothelial tumors in the current study as well as the TCGA had potentially actionable genomic alterations, including ERBB2 amplifications and mutations and FGFR3 hotspot mutations (29). Furthermore, patients with Lynch syndrome are at increased risk for the development of UTUC, and the identification of patients with Lynch syndrome–associated tumors has treatment and screening implications for both affected patients and unaffected family members (30). Our data suggest that screening for hereditary UTUC based on clinical risk assessment or MSI status alone can miss some cases of Lynch syndrome (Supplementary Table S3). With the implementation of NGS technology in daily practice, integration of tumor mutational burden, analysis of microsatellite regions (MSI sensor score) and mutational signature could more robustly identify MMR-deficient tumors. Recently, upfront tumor sequencing in colorectal cancer has been shown to have greater sensitivity than the prior multitest approaches for Lynch syndrome screening (31). Our results support this strategy in UTUC as well. Furthermore, given the strong association between mutational burden and immunotherapy response (32), UTUC patients with microsatellite instability in the setting of MMR deficiency may represent a subpopulation of patients with a greater likelihood of benefiting from both local and systemic immunotherapies (33).

Intravesical recurrence after radical nephroureterectomy is common, with a median rate of recurrence of 22% to 47% (24), and several patient-specific and tumor-specific clinicopathologic predictors of recurrence have been identified (24). Here, we identified a strong association in multivariable analysis between the risk of recurrence and alterations in FGFR3, KDM6A, CCND1, and TP53. These findings could help identify those patients in greatest need for close monitoring or early instillation of mitomycin C (34). The pathogenesis of bladder tumors that arise after curative intent treatment of UTUC is an ongoing controversy in the field. Two different theories have been proposed: UCB could result from intraluminal seeding from the prior UTUC (35) or represent a second primary tumor in the setting of a toxin-induced, field-cancerization effect (36). Initial studies using loss-of-heterozygosity analysis reported conflicting results (37, 38). To our knowledge, this is the first study to use contemporary NGS methods to assess the clonality or multifocality of bladder tumors in patients with a history of UTUC. Our results clearly demonstrate the clonal origin of UTUC and UCB tumors that arise sequentially in individual patients with a history of both tumors. The results justify the exploration of methods to prevent lower tract seeding during radical nephroureterectomy or ureteroscopy and more rigorous surveillance for bladder recurrences after surgery, particularly in those patients with genetic features associated with lower tract recurrence (TP53-wild-type, FGFR3/KDM6A-mutant). Due to the limited efficacy of a single postoperative intravesical dose of mitomycin C (34), studies of adjuvant treatments designed to prevent bladder recurrences are also warranted in patients at highest risk for subsequent lower tract recurrence.

Although this study is the largest cohort of UTUC tumors genomically characterized to date, it has several limitations. Less frequent mutational events and structural alterations not covered in the MSK-IMPACT assay could not be detected and may have important prognostic implications, at least for individual patients. However, the majority of the genomic alterations identified by whole-exome sequencing from 27 patients with UTUC (12) could be identified using our gene panel. Furthermore, differences in gene expression due to changes in the epigenetic regulation of genes may provide added prognostic information, a possibility not addressed by our targeted DNA-sequencing approach. Finally, individual mutations in specific genes may have different biological consequences. Integration of genome, transcriptome, and proteomic analyses may thus provide further insights into the factors that drive UTUC initiation and progression.

In conclusion, a genomic comparison of UTUC and UCB in a cohort of 649 patients revealed significant differences in the prevalence of common genomic alterations. However, individual patients with a history of both tumors, we found that the UCB and UTUC were always clonally related. Genomic characterization of UTUC provides clinically relevant information, including identification of patients who could be candidates for molecularly driven clinical trials or for treatment off-label with agents approved for use in other cancer types; evaluation of the efficacy of a single postoperative intravesical dose of mitomycin C (34), studies of adjuvant therapies; and identification of those patients in need of germline analysis for Lynch syndrome. Routine implementation of tumor genomic profiling in patients with UTUC should thus be considered and prospectively evaluated.
Disclosure of Potential Conflicts of Interest

E.J. Pietzak is a consultant/advisory board member for Merck. J.E. Rosenberg has ownership interests (including patents) at Illumina; reports receiving speakers bureau honoraria from Chugai Pharma; is a consultant/advisory board member for Advicent Bio, Agencyt/Assellas, AstraZeneca, Bayer, Fortress Biotech, Lilly, Merck, BioClinTherapeutics, and Sensei Biotherapeutics; reports receiving commercial research support from Astellas, Bayer, Mirati, Roche/Genentech, and Seattle Genetics. D.F. Bajorin reports receiving speakers bureau honoraria from Merck; is a consultant/advisory board member for AstraZeneca, Eli Lilly, Fidia Farmaci, Genentech, Merck, Pfizer, and Urogen; and reports receiving commercial research grants from Merck and Novartis. J.F. Hechtman reports receiving speakers bureau honoraria from Medscape. M.F. Berger is a consultant/advisory board member for Roche. H. Al-Ahmadie is a consultant/advisory board member for Pfizer. B.H. Borchner is a consultant/advisory board member for Genentech. D.B. Solit is a consultant/advisory board member for Illumina, Loxo Oncology and Pfizer. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions


Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): F. Audenet, S. Isharwal, E.K. Cha, E.J. Pietzak, J.P. Sfakianos, A. Bagrodia, H. Al-Ahmadie, B.H. Borchner, J.A. Coleman, D.B. Solit

References


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975

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