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# Development of secondary urothelial carcinoma following complete response to immune checkpoint inhibitors

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ABSTRACT

The management of metastatic urothelial cancer is rapidly evolving since immune checkpoint inhibitors were introduced. We present the case of a patient with metastatic upper tract urothelial cancer who had a complete response to durvalumab and tremelimumab. This patient then developed multiple non-invasive papillary bladder tumours. Next-generation sequencing revealed that the tumours shared ancestry with the upper tract cancer, although there were key differences, most notably the presence of a *TP53* missense mutation in the upper tract disease that was absent in the bladder tumours. This illustrates an important practice point in the management of exceptional responders to checkpoint inhibitors.

## Introduction

The management of metastatic urothelial carcinoma (mUC) has evolved rapidly over the last 5 years with the introduction of immune checkpoint inhibitors. Agents that target the PD-1/PD-L1 axis have proven activity, and have become a standard of care in this disease. Durable responses can be observed, and long-term survival is increasingly becoming a reality. The current first-line standard of care for most patients remains cisplatin-based chemotherapy, but many randomized controlled phase III clinical trials have been conducted or are underway to attempt to improve on this standard with earlier introduction of checkpoint inhibitors.[1]

As more patients with mUC receive checkpoint inhibitors, a population of exceptional responders will gradually emerge, especially since these patients may experience prolonged survival. The long-term management of these patients remains uncertain. The case report presented here discusses management of exceptional responders in the setting of mUC with an upper tract primary, and the risk of second primary cancers in the urothelium. We performed targeted sequencing of the initial primary upper tract tumor, and of a recurrent lesion in the bladder, and highlight how these lesions share a common ancestry, but also differ in significant ways. While cystoscopic surveillance for local recurrence has not been necessary in mUC where survival has been historically short, this case shows that it may be time to revisit this paradigm.

## Case report

A 41-year old man presented with gross hematuria. He was found to have a mass involving the right renal pelvis and lower calyx. He underwent laparoscopic nephroureterectomy with retroperitoneal lymph node sampling. Pathology revealed a 3.5 cm papillary upper tract urothelial cancer (UTUC) with sarcomatoid differentiation and a 2.1 cm paracaval lymph node metastasis. The final stage was pT3 pN2 M0. Follow-up imaging after 8 weeks revealed interval development of multiple retroperitoneal and pelvic lymph node metastases, recurrence in the surgical resection bed and multiple lung metastases. The patient enrolled in a phase III clinical trial of combination checkpoint inhibitor (DANUBE[1]). Tumour testing performed at a central laboratory by the sponsor showed high PD-L1 expression. The patient received durvalumab and tremelimumab every 4 weeks for 4 cycles followed by maintenance durvalumab every 4 weeks. He had a deep partial response after 8 weeks, and by 5.5 months he had achieved a complete response. Computed tomography (CT) imaging (A) prior to nephrectomy, (B) at relapse and (C) showing complete response is shown in Fig. 1.

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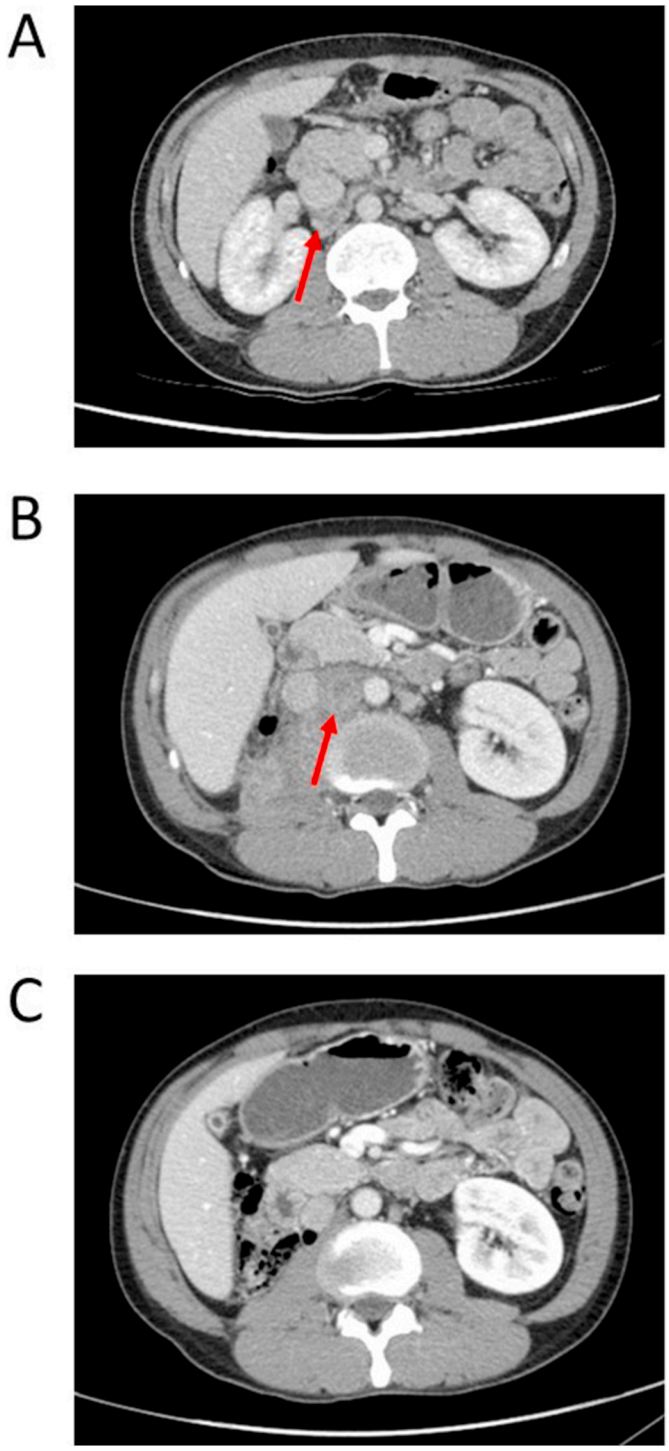


**Fig. 1.** CT imaging showing disease state prior to nephrectomy (A, with red arrow indicating resected regional lymphadenopathy), at relapse (B, with red arrow indicating aortocal lymphadenopathy) and after 5.5 months on treatment (C) showing complete response. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

After 15 months on treatment, cross sectional imaging revealed a new polypoid lesion in the right bladder wall. He underwent cystoscopy and transurethral resection of a papillary bladder tumour (TURBT) found at the right ureteral orifice. Pathology showed low-grade non-invasive papillary urothelial carcinoma (pTa).

The patient continued on treatment with single-agent durvalumab, and with regular surveillance cystoscopies. Twenty seven months after initiating treatment with checkpoint inhibitors, he developed 4 additional papillary bladder tumours. All were resected, and again showed low-grade non-invasive papillary urothelial cancer. At the time of the last follow-up forty six months since initiation of immunotherapy, the patient continues on maintenance durvalumab with no further evidence of disease recurrence.

## Methods

We performed targeted sequencing of the upper-tract malignancy, the bladder lesion, and matched germline DNA using a custom 51-gene panel in alignment with previous methods to a median depth of 445, 957, and 366, respectively. A complete list of genes sequenced is provided in Table 1, and detailed methods have been previously published.[2]

## Results

Representative histological sections and genomic data are shown in Fig. 2. Genomic analysis reveals shared alterations in *CDKN2A*, the *TERT* promoter, *ERBB3*, *ARID1A*, *FOXA2* and *RB1* with similar variant allele frequencies (VAF). The upper tract sample harbored a truncal *TP53* hotspot missense mutation, which was not present in the bladder tumour. Conversely, the bladder tumour harbored a truncal *CDKN1A* frameshift not observed in the earlier sample. Based on the 51-gene panel, the overall tumour mutation burden (TMB) was estimated at 8.70 and 6.93 mutations/Mb in the UTUC and TURBT samples, respectively; this includes silent and non-coding mutations. There were 5.79 and 4.01 protein altering mutations/Mb, respectively.

## Discussion

In this case, targeted sequencing demonstrated that these tumours share ancestry but were different clones. This supports the theory of urothelial cancer as a "field" defect and is in agreement with a recently published case series showing a similar shared ancestry for patients with localized UTUC who subsequently developed bladder UC.[3] In addition, our findings highlight the role of *TP53* mutations in the invasive phenotype, which is a well-described genomic event associated with invasiveness and worse outcomes.[4] In our case, the UTUC sample harbored a *TP53* missense mutation which was absent from the TURBT specimen; the UTUC sample also showed a more aggressive phenotype and was associated with rapid development of mUC, while the TURBT only showed non-invasive disease and the patient did not develop further metastatic disease.

Despite the exceptional response that we report, the DANUBE study did not show an overall survival benefit for the combination of durvalumab and tremelimumab in all comers. However, exploratory analyses

**Table 1**
Custom 51 gene panel for targeted sequencing of urothelial cancers.

| | | |
|---|---|---|
| RUNX3 | EGFR | MDM2 |
| ARID1A | BRAF | RB1 |
| NRAS | FGFR1 | KLF5 |
| NOTCH2 | MYC | FOXA1 |
| TXNIP | CDKN2A | AKT1 |
| NFE2L2 | FANCC | TSC2 |
| PPARG | PTCH1 | CREBBP |
| CTNNB1 | TSC1 | TP53 |
| BAP1 | RXRA | NF1 |
| PIK3CA | NOTCH1 | ERBB2 |
| TACC3 | PTEN | NOTCH3 |
| FGFR3 | HRAS | CCNE1 |
| FBXW7 | CCND1 | ERCC2 |
| TERT[a] | ATM | RUNX1 |
| PIK3R1 | KRAS | EP300 |
| APC | KMT2D | KDM6A |
| CDKN1A | ERBB3 | STAG2 |

[a] Sequencing of TERT promoter only.

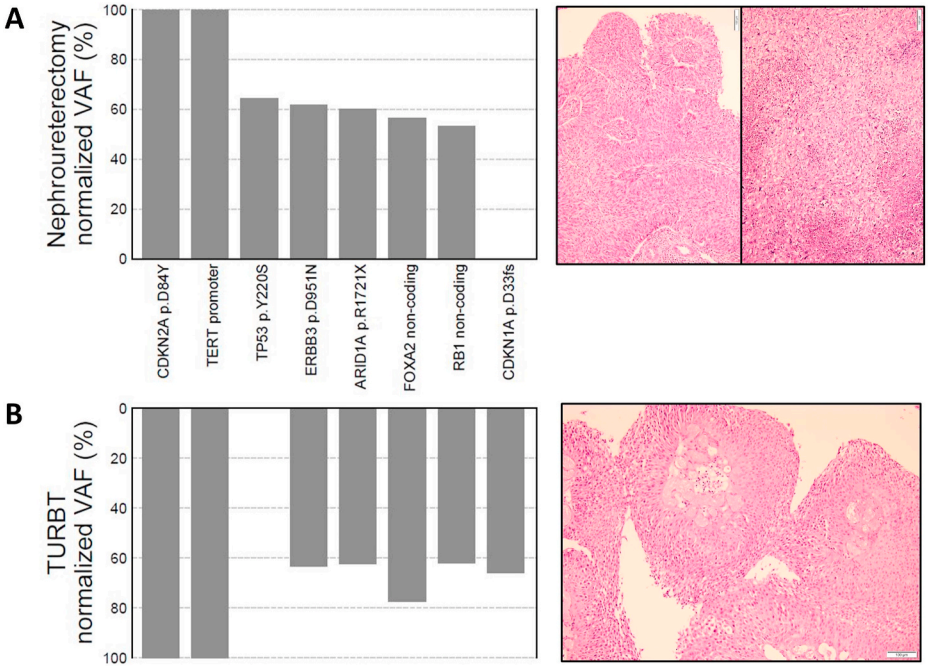


**Fig. 2.** Targeted sequencing of the UTUC (A) and TURBT (B) samples. Representative histological sections are shown for each sequenced tumour to illustrate the difference between the high-grade papillary upper tract tumour (A, left) with sarcomatoid differentiation (A, right) and the low-grade non-invasive papillary lesion form the TURBT (B). Magnification bars are 100 μm.

may lead to future studies in biomarker-defined subpopulations. In addition, current and future clinical trials evaluating checkpoint inhibitors in combination with cytotoxic and targeted therapies will only improve the long-term outlook for what was previously a disease with low survival rates. This case illustrates an important practice point for oncologists dealing with exceptional responders to immune checkpoint inhibitors. Despite adequate control of the initial advanced cancer, patients may be at risk of relapse or second primaries within the urothelial tract and selected patients with a complete response to therapy may benefit from cystoscopic follow-up and aggressive local management of recurrences. While little is known about the outcomes of these patients, it may be reasonable to follow existing guidelines for high-risk UTUC.[5]

## Consent

The patient consented to having his personal data included in this case report.

## Declaration of competing interest

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JML reports honoraria from Roche. AWW reports commercial research grant from Janssen and honoraria from AstraZeneca, Astellas, Janssen, and Merck. BJE reports honoraria from AstraZeneca, Pfizer, BMS, Roche, Merck, and Janssen. The remaining authors have nothing to declare.

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