Editorial Commentary

Towards circulating tumor DNA-guided treatment of muscle-invasive bladder cancer

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Cancer cells release cell-free DNA with tumor specific molecular alterations into circulation [circulating tumor DNA (ctDNA)]. Multiple studies have documented the potential biomarker value of ctDNA for detection of minimal residual disease in multiple cancer types (1-3)—including bladder cancer (4). The short half-life of ctDNA in circulation [below 2 hours (5)] makes it possible to use ctDNA for real-time tracking of tumor burden following surgery and through oncological treatments.

To use ctDNA measurements for clinical decision making, it is imperative to conduct clinical ctDNA-guided intervention trials to demonstrate clinical value. In colon cancer, results from the randomized DYNAMIC trial have demonstrated that ctDNA-guided management of patients with stage II colon cancer reduced the number of patients receiving adjuvant chemotherapy without compromising recurrence-free survival (6). ctDNA-guided trials in muscle-invasive bladder cancer (MIBC) are currently ongoing (*Table 1*) (7-9) and these are strongly supported by recent exploratory sub-analyses of data from finalized clinical trials, demonstrating the utility of ctDNA for guiding treatment decisions in MIBC (10,11).

IMvigor010 (NCT02450331), a multi-centre, open-label, randomized, phase 3 trial, evaluated adjuvant atezolizumab [anti-programmed death-ligand 1 (anti-PD-L1)] versus observation in patients with MIBC (12). The intention-to-treat (ITT) population included 809 patients who were enrolled within 14 weeks after radical cystectomy (RC) and were randomized (1:1) to receive atezolizumab every 3 weeks for 16 cycles or up to 1 year (n=406) or undergo observation (n=403). The trial did not reach its primary endpoint of improved disease-free survival (DFS) with adjuvant atezolizumab (12). ctDNA was retrospectively evaluated in the biomarker-evaluable population (BEP; n=581) at baseline [cycle 1 day 1 (C1D1)] and 6 weeks after randomization [cycle 3 day 1 (C3D1)] using Natera's Signatera assay (11). Of note, patients who were ctDNA positive at C1D1 had improved DFS and overall survival (OS) in the atezolizumab arm compared with the observation arm, while no difference between treatment arms were observed for the patients without detectable ctDNA (11). Now, with a median follow-up of 46.8 months for the IMvigor010 ITT population, Powles *et al.* recently presented updated OS by ctDNA status in *European Urology* (13). No difference in OS between treatment arms was observed. However, with the updated follow-up in the ctDNA BEP, it was confirmed that ctDNA positivity identifies high-risk patients and patients who benefit from adjuvant atezolizumab. Patients who were ctDNA positive at C1D1 had longer OS with atezolizumab

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Table 1 Ongoing ctDNA-guided intervention trials in MIBC

Trial	Start	Patient group	# patients	Study type	ctDNA method	Intervention	Primary endpoint
TOMBOLA (7)	2020	cT2-4a UC at TURBT, NAC treatment	282	Interventional	Tumor-informed ddPCR	ctDNA+: adjuvant atezolizumab; ctDNA–: ctDNA-based surveillance	Response rate
IMvigor011 (8)	2021	≥ ypT2 UC and/or N+ after NAC; ≥ pT2 UC and/or N+ without prior NAC	520	Randomized, interventional	Tumor-informed 16-plex NGS	ctDNA+: randomized to adjuvant atezolizumab or no adjuvant therapy; ctDNA–: ctDNA-based surveillance	DFS
MODERN (9)	2024	≥ ypT2 UC and/or N+ after NAC; ≥ pT3 UC and/or N+ without prior NAC and cisplatin-ineligible	1,190	Randomized, interventional	Tumor-informed 16-plex NGS	ctDNA+ (cohort A): randomized to adjuvant nivolumab or nivolumab + relatlimab; ctDNA– (cohort B): randomized to adjuvant nivolumab or ctDNA-based surveillance	Cohort A: ctDNA clearance, OS; cohort B: DFS

ctDNA, circulating tumor DNA; MIBC, muscle-invasive bladder cancer; UC, urothelial carcinoma; TURBT, transurethral resection of bladder tumor; NAC, neoadjuvant chemotherapy; ddPCR, droplet digital polymerase chain reaction; NGS, next generation sequencing; DFS, disease-free survival; OS, overall survival.

{median OS: 29.8 months [95% confidence interval (CI): 20.7–40.2]} compared with observation [median OS: 14.1 months (95% CI: 10.5–19.7); hazard ratio (HR) 0.59 (95% CI: 0.42–0.83)] (13). Notably, ctDNA positivity was the only feature of the evaluated baseline characteristics that was found to be significantly associated with a difference in OS between treatment arms, thus outperforming features such as tumor stage, nodal status, tumor mutational burden and PD-L1 status. Furthermore, a difference in OS between treatment arms was particularly observed for ctDNA-positive patients with a high tumor PD-L1 expression [≥5% of tumor area; HR 0.51 (95% CI: 0.30–0.85)] compared with ctDNA-positive patients with a lower tumor PD-L1 expression [<5% of tumor area; HR 0.75 (95% CI: 0.49–1.16)].

Powles *et al.* reported a recurrence rate of 32% among patients without detectable ctDNA in the observation arm (13). As discussed by the authors, this can be due to limited assay sensitivity at the C1D1 time point. The recurrence rate among ctDNA-negative patients is high compared to previous studies; however, these also used the accumulated ctDNA status across multiple time points following RC (14,15). Increased test sensitivity may be reached in future prospective trials designed specifically for ctDNA-guided treatment through longitudinal monitoring of ctDNA and optimized tissue and plasma collection protocols.

Although Powles *et al.* reported that a higher proportion of patients in the observation arm than in the atezolizumab arm received subsequent immunotherapy at recurrence detection (24% versus 11%, respectively), early adjuvant treatment with atezolizumab still provided a survival benefit. Furthermore, adverse effects were more frequent in the atezolizumab arm among both ctDNA positive and negative patients, highlighting the importance of sparing patients (i.e., ctDNA-negative patients) from the associated toxicity of adjuvant immunotherapy if they are unlikely to have a clinical benefit from the treatment.

What now awaits, is to document the clinical benefit of ctDNA-guided adjuvant treatment in prospective, ctDNA-guided intervention trials (*Figure 1*). Although ctDNA testing is already being used in, e.g., the U.S. to support clinical decisions, we still need to demonstrate: (I) survival benefit of ctDNA-guided treatment; (II) better quality-of-life by ctDNA-assisted disease monitoring; (III) decreased expenses to health care systems by refined administration of expensive and toxic treatments, to avoid overtreatment and unnecessary adverse effects for patients who are unlikely to benefit from treatment without compromising patient outcome.

This is currently being evaluated in two ongoing

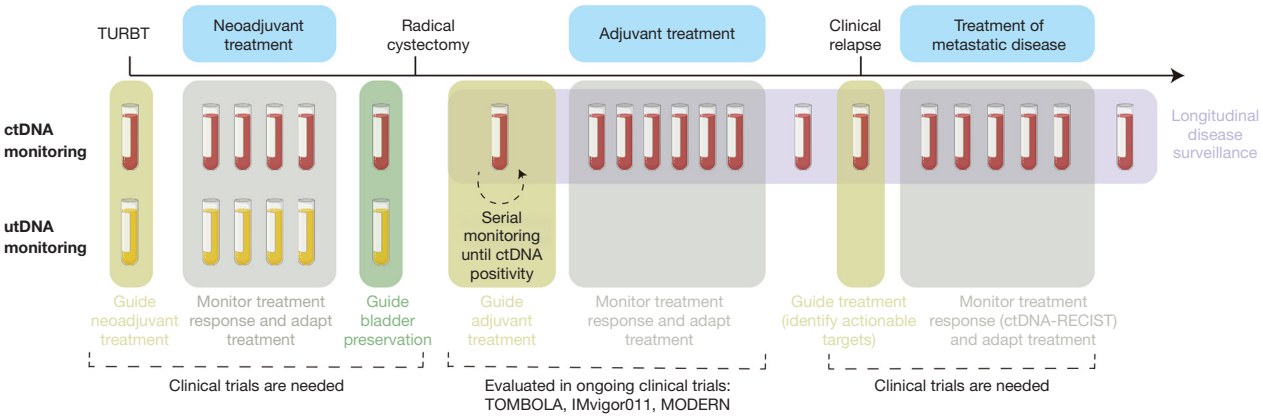

Figure 1 Potential ctDNA-guided treatment of patients with MIBC. Schematic overview of a standard disease course for a patient with MIBC who have metastatic relapse after radical cystectomy. ctDNA and utDNA analyses may be used to guide neoadjuvant treatment and bladder preservation strategies. Plasma samples collected after radical cystectomy may be used to guide adjuvant treatment and for longitudinal disease surveillance. Plasma samples collected during treatment may inform on treatment response and treatments may be adapted accordingly. It is indicated in which settings clinical trials are currently going and where clinical trials are still needed. Blood and urine sample icons are from biorender.com. TURBT, transurethral resection of bladder tumor; ctDNA, circulating tumor DNA; utDNA, urinary tumor-derived DNA; RECIST, Response Evaluation Criteria in Solid Tumors; MIBC, muscle-invasive bladder cancer.

trials, TOMBOLA (NCT04138628) (7) and IMvigor011 (NCT04660344; *Table 1*) (8). TOMBOLA is a non-randomized, phase 3, ctDNA-guided intervention trial conducted nationally in Denmark (7). Patients with MIBC are followed by ctDNA analysis (tumor-informed ddPCR assays) of monthly-drawn blood samples after RC and treatment with atezolizumab is initiated if a patient is tested ctDNA positive. IMvigor011 is an international, randomized, phase 3 trial evaluating ctDNA-guided treatment with adjuvant atezolizumab compared with placebo in patients with high-risk MIBC (8). Patients are followed by ctDNA analysis (tumor-informed Signatera assays) of blood samples collected every six weeks. At detection of ctDNA (along with regular imaging), patients are randomized (2:1) to treatment with atezolizumab or placebo. In TOMBOLA, the primary endpoint is complete response after treatment as measured by ctDNA negativity and regular imaging, whereas the primary endpoint of IMvigor011 is DFS. A key difference between TOMBOLA and IMvigor011, besides the difference in endpoint and TOMBOLA being non-randomized, is the included study population. All patients in TOMBOLA have received neoadjuvant chemotherapy (NAC) whereas patients enrolled in IMvigor011 may or may not have received platinum-based NAC. Patients receiving NAC in the IMvigor011 trial have more high-risk disease compared to patients in TOMBOLA, as patients receiving NAC in IMvigor011 are included based on having ypT2-4aN0 or ypT0-4aN+ and M0 at RC, whereas TOMBOLA recruits patients with cT2-4a at transurethral resection of bladder tumor (TURBT). For patients without prior NAC treatment in IMvigor011, pT2-4aN0 or pT0-4aN+ and M0 at RC are required for inclusion. Upon completion of the trials, we anticipate that the disparity in clinical trial endpoints and varying risks of the included patient cohorts will contribute to a comprehensive understanding regarding the significance of using ctDNA to guide adjuvant treatment strategies.

In addition, the MODERN trial (NCT05987241) initiated patient recruitment in February, 2024 and will further add to the building evidence on the perspectives of ctDNA-guided treatment of MIBC (*Table 1*) (9). MODERN is a randomized, phase 2/3 trial evaluating ctDNA-guided adjuvant treatment in patients with MIBC. Patients with detectable ctDNA after RC (cohort A) are randomized to receive adjuvant nivolumab (anti-PD-1) alone or in combination with relatlimab (LAG-3 inhibitor). Patients without detectable ctDNA (cohort B) are randomized to adjuvant nivolumab or ctDNA-based surveillance. The primary endpoints are ctDNA clearance and OS for cohort A and DFS for cohort B (9). MODERN will further increase our understanding of treatment escalation and de-escalation based on ctDNA status.

Besides guiding adjuvant treatment, ctDNA may also hold the potential to guide bladder preservation approaches—potentially,

in combination with urinary tumor-derived DNA (utDNA) measurements (*Figure 1*) (16,17). Furthermore, treatment de-escalation before RC (e.g., NAC) may also be very important, as we anticipate that a high proportion of patients receive unnecessary treatments with huge adverse effects since only around 45% of patients have a pathologic response to NAC (18,19). However, data in this clinical setting is still lacking, although retrospective studies suggest that de-escalation may be possible (14). One overarching concern is, however, that patients who may benefit the most from NAC have micrometastatic disease not detected by current ctDNA strategies, and consequently, there is a risk of removing treatment from the patients that actually benefit the most. Thus, this needs to be investigated in larger detail. Finally, ctDNA may help guide decisions during systemic treatments in the future (*Figure 1*). Currently, decisions are based on the imaging-based Response Evaluation Criteria in Solid Tumors (RECIST), which is a suboptimal surrogate marker for the ultimate clinical endpoint, OS. A ctDNA-RECIST measure that utilizes ctDNA dynamics during treatment may provide a better tool or supplement to current strategies (20).

In conclusion, ctDNA has been proven to be a very strong biomarker in retrospective and prospective studies for risk assessment in MIBC, and ongoing clinical trials will soon determine the clinical value of ctDNA-guided treatment. Based on current data, we believe that ctDNA analyses will revolutionize cancer treatment to better administer the right treatments to the right patients.

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