natera™ | Signatera™ Residual disease test (MRD)

Covered by Medicare

BLADDER CANCER

Identify MIBC patients who may benefit from adjuvant therapy after cystectomy

How do you determine which patients are likely to recur after cystectomy without adjuvant treatment?

Many patients are cured by surgery alone but receive potentially unnecessary adjuvant therapy toxicity, while other patients don't receive potentially beneficial treatment until they have progressed clinically[1]

Existing tools fall short at identifying remaining residual disease and recurrence early before patients become symptomatic

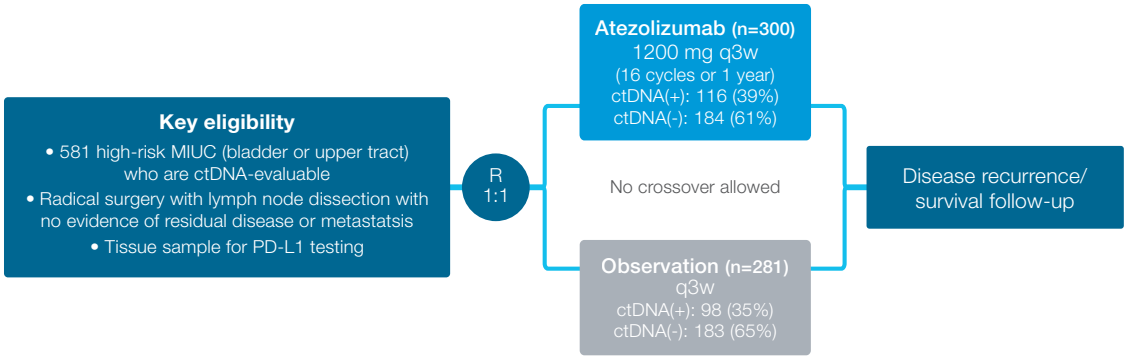
Up to 50% of patients will develop metastases following cystectomy for localized disease and it can be difficult to determine response to immunotherapy treatment quickly[2]

Signatera™ testing may help inform which patients will benefit from adjuvant therapy, if they are responding to immunotherapy, or if they are relapsing — before standard of care tools[1,3,4]

Neoadjuvant response monitoring	Postsurgical MRD assessment	Surveillance	Metastatic treatment response monitoring
Lack of ctDNA clearance during neoadjuvant treatment may be a better predictor of recurrence than pathologic response.[3]	Post cystectomy MRD assessment can identify which patients may benefit from adjuvant treatment[1,5]	ctDNA can detect recurrence up to 245 days before clinical progression (median 96 days)[3]	98% of patients with an increase in ctDNA after 2 cycles of immunotherapy did not derive an objective response[4]

IMvigor010: The first large, randomized study that demonstrated the predictive power of ctDNA in solid tumors[1]

A prespecified ctDNA marker analysis was performed on the intent-to-treat (ITT) population with Signatera™ at the post-surgery and the 6-week on-treatment timepoints.



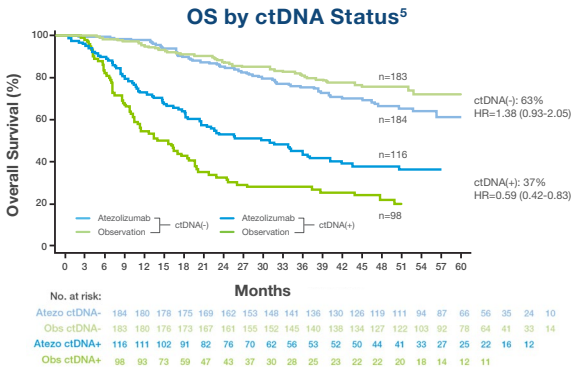
- IMvigor010 did not meet its primary endpoint (DFS in the Intention To Treat (ITT) population)
- PD-L1 and TMB biomarkers did not identify patients benefiting from atezolizumab vs observation in the ITT population

ctDNA-positive patients treated with adjuvant immunotherapy achieved a 42% increase in DFS vs. patients in the observation arm

Signatera™ ctDNA positivity after cystectomy may predict adjuvant immunotherapy treatment benefit[1,5]

Key results from extended follow-up published in European Urology:[5]

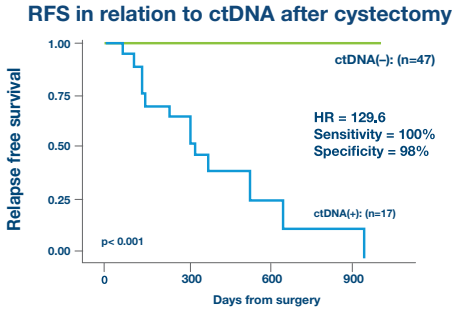
- >110% survival benefit observed in ctDNA-positive patients treated with atezolizumab (OS, HR 0.59).[5]
- No treatment benefit was observed in ctDNA-negative patients treated with atezolizumab (OS, HR 1.38)[5]
- 37% of patients were ctDNA-positive at C1D1 and ctDNA positivity predicted benefit from immunotherapy at 46.8-month median follow-up (OS, HR=0.59)[5]
- >75% of patients with detectable ctDNA post-surgery in the observation arm recurred by 20 month follow up[1]



Natera and Aarhus University Study: Longitudinal ctDNA status after cystectomy was predictive of relapse[3]

Key Results:

- Signatera™ ctDNA status at all assessed timepoints (before neoadjuvant chemo, before cystectomy, and after cystectomy) was highly prognostic of outcomes
- ctDNA was a stronger predictive factor for recurrence than lymph node status or pathologic staging
- Lead time to clinical recurrence of up to 245 days (median=96 days)
- Patients with serial negative ctDNA after cystectomy had 100% OS

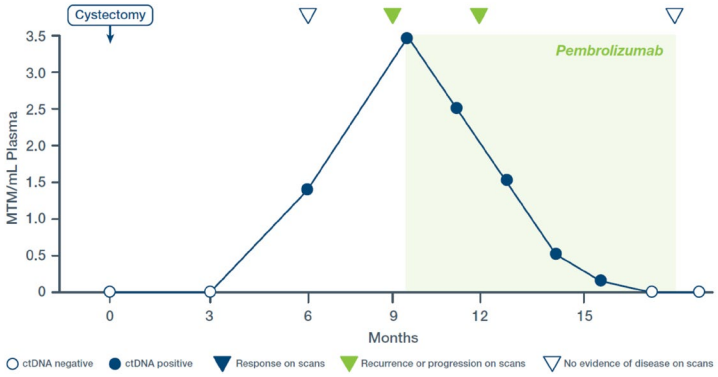


Metastatic bladder cancer case review*

Is the tumor truly progressing?

- **Age:** 71
- **Original diagnosis:** pT3N0M0 muscle-invasive bladder cancer
- **Treatment course:** Preexisting renal insufficiency precluded the use of neoadjuvant cisplatin-based chemotherapy. Patient underwent radical cystectomy
- **Monitoring:** Two postoperative ctDNA tests were negative

*Case features modified to protect patient confidentiality. No treatment recommendations are made or should be implied.



Signatera™ can be run at any time point on the core biopsy or surgical resection and is covered by Medicare and a growing number of commercial payers for MIBC patients and any patient being treated with immunotherapy

Learn more about Natera's Oncology Portfolio:

Empower™ Hereditary cancer test

Empower™ for hereditary cancer testing which analyzes up to 81 genes across 12+ common hereditary cancers (panel can also be customizable, up to 190 genes) to help guide surgical and therapeutic decisions.

Altera™ Tumor genomic profile

Add on Altera™ Genomic Profiling test which utilizes whole-exome and whole-transcriptome sequencing to identify clinically relevant biomarkers that may help guide treatment selection for advanced cancer patients– no additional sample needed.

Learn more at: natera.com/oncology

References: 1. Powles T, et al. *Nature.* 2021;595(7867):432-437. https://doi.org/10.1038/s41586-021-03642-9. **2.** Svatek RS, et al. *Can Urol Assoc J.* 2009. doi: 10.5489/cuaj.1203. **3.** Christensen E, et al. *J Clin Oncol.* 2019. doi: 10.1200/JCO.18.02052. **4.** Bratman SV, et al. *Nature Cancer.* 2020;1(9):873-881. **5.** Powles T, et al. *European Urology.* 2023; https://doi.org/10.1016/j.eururo.2023.06.007

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