Natera, Inc.

Post-ESMO Investor Call

October 23, 2025



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Today's speakers



Professor Thomas Powles, Lead Principal Investigator of IMvigor011
Professor of Genitourinary Oncology
Chair of Barts Cancer Centre at St. Bartholomew's Hospital



Steve Chapman, Chief Executive Officer, Natera



Mike Brophy, Chief Financial Officer, Natera



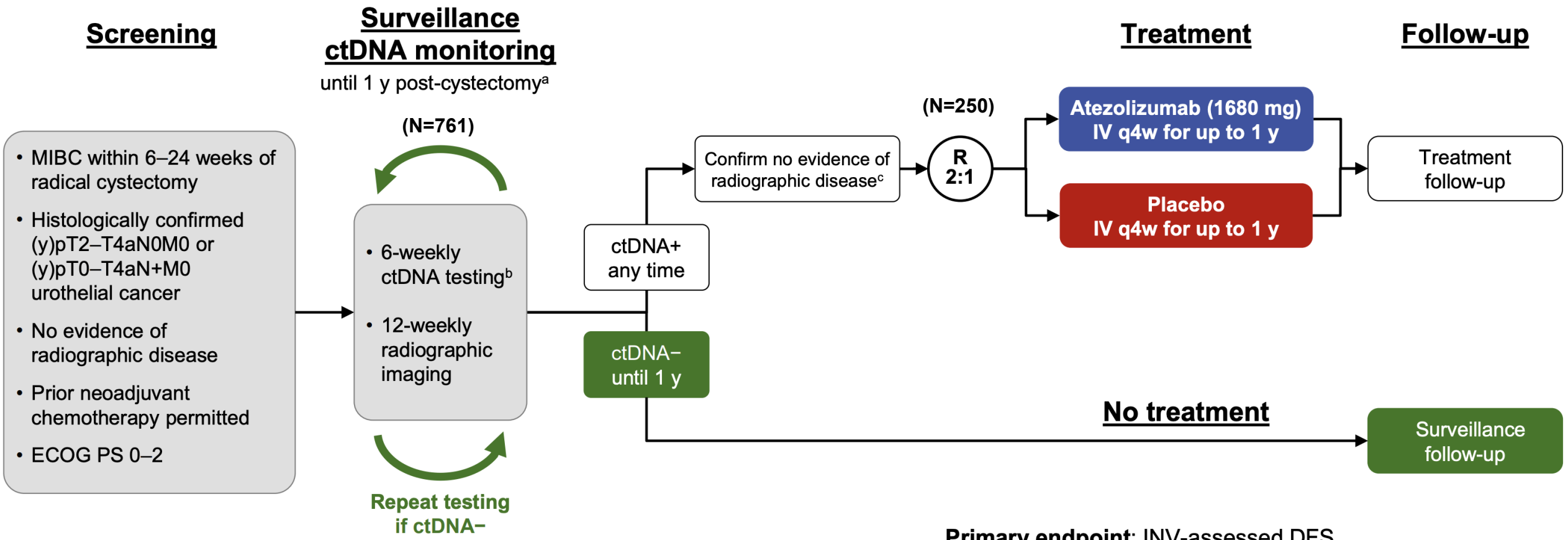
Solomon Moshkevich, President of Clinical Diagnostics, Natera



Alexey Aleshin, M.D., General Manager of Oncology & Chief Medical Officer, Natera

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IMvigor011 study design



ClinicalTrials.gov number, NCT04660344. Stratification factors were nodal status (positive vs negative), tumour stage at cystectomy (≤pT2 vs pT3/pT4), PD-L1 status (IC0/1 [<5%] vs IC2/3 [≥5%] by VENTANA SP142 immunohistochemistry assay) and time from cystectomy to first ctDNA+ sample (≤20 weeks vs >20 weeks). [a] Early versions of the protocol included a 21-mo surveillance ctDNA monitoring period.
[b] ctDNA status was determined by the Natera Signatera™ MRD test (outside of mainland China) and by the BGI MRD test (in mainland China). [c] By INV and IRF assessment. ECOG PS, Eastern Cooperative Oncology Group performance status; IC, immune cells; INV, investigator; IRF, independent review facility; IV, intravenous; mo, month; PD-L1, programmed death-ligand 1; R, randomised; y, year.
Adapted from Powles T, et al. ESMO 2021 (Abstract 3716) with permission.

Presented by: Thomas Powles, MBBS, MRCP, MD
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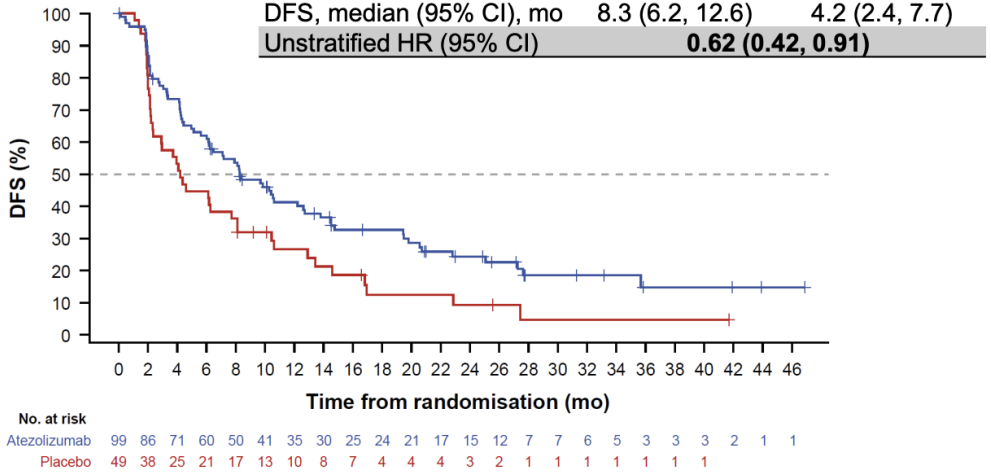
DFS and OS in subgroups based on timing of ctDNA+ test

ctDNA+ at initial test

(148/250; 59.2%)

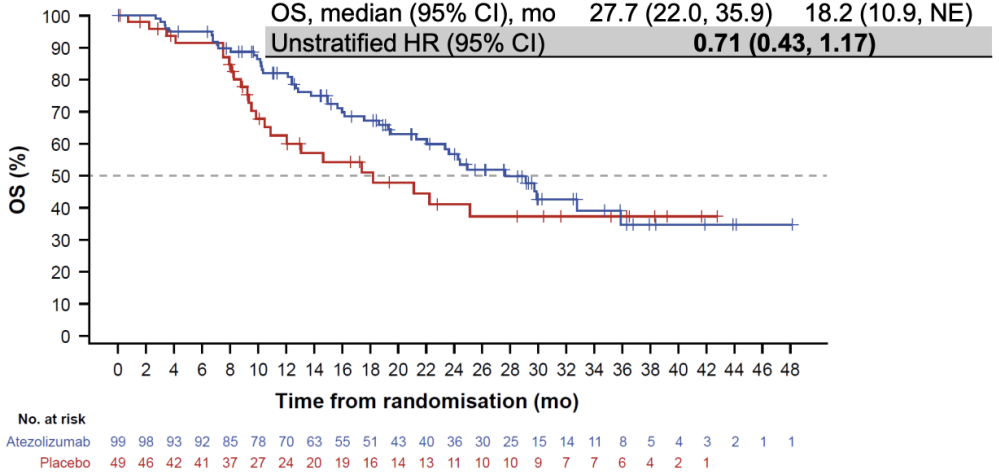
INV-assessed DFS

	Atezolizumab (n=99)	Placebo (n=49)
DFS, median (95% CI), mo	8.3 (6.2, 12.6)	4.2 (2.4, 7.7)
Unstratified HR (95% CI)	**0.62 (0.42, 0.91)**	



OS

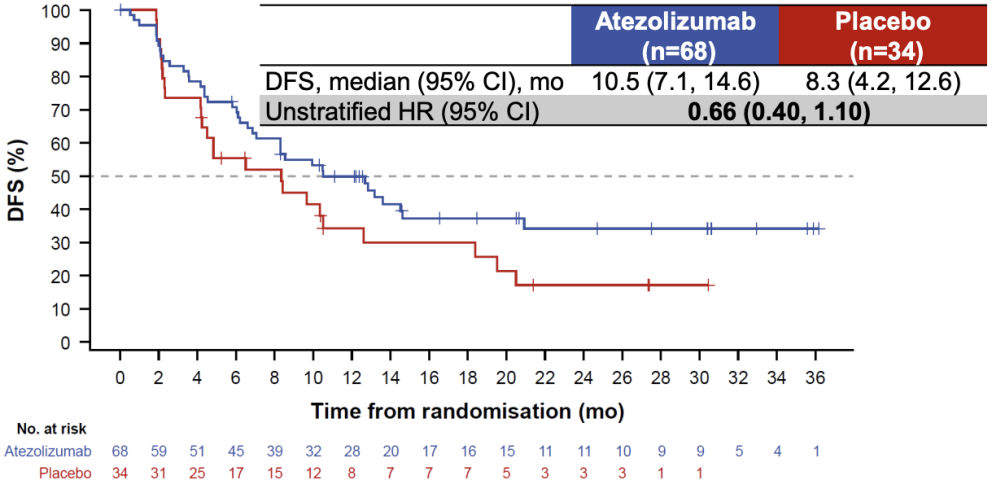
	Atezolizumab (n=99)	Placebo (n=49)
OS, median (95% CI), mo	27.7 (22.0, 35.9)	18.2 (10.9, NE)
Unstratified HR (95% CI)	**0.71 (0.43, 1.17)**	

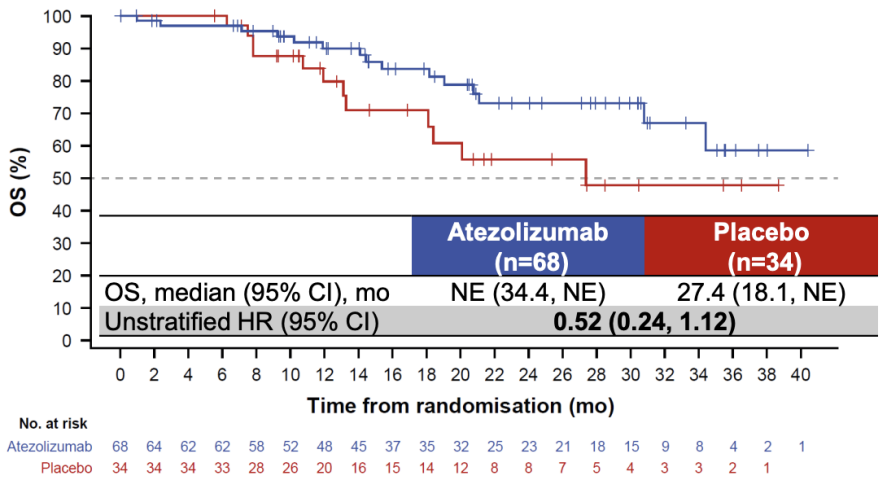


ctDNA+ at subsequent test

(102/250; 40.8%)

	Atezolizumab (n=68)	Placebo (n=34)
DFS, median (95% CI), mo	10.5 (7.1, 14.6)	8.3 (4.2, 12.6)
Unstratified HR (95% CI)	**0.66 (0.40, 1.10)**	





	Atezolizumab (n=68)	Placebo (n=34)
OS, median (95% CI), mo	NE (34.4, NE)	27.4 (18.1, NE)
Unstratified HR (95% CI)	**0.52 (0.24, 1.12)**	

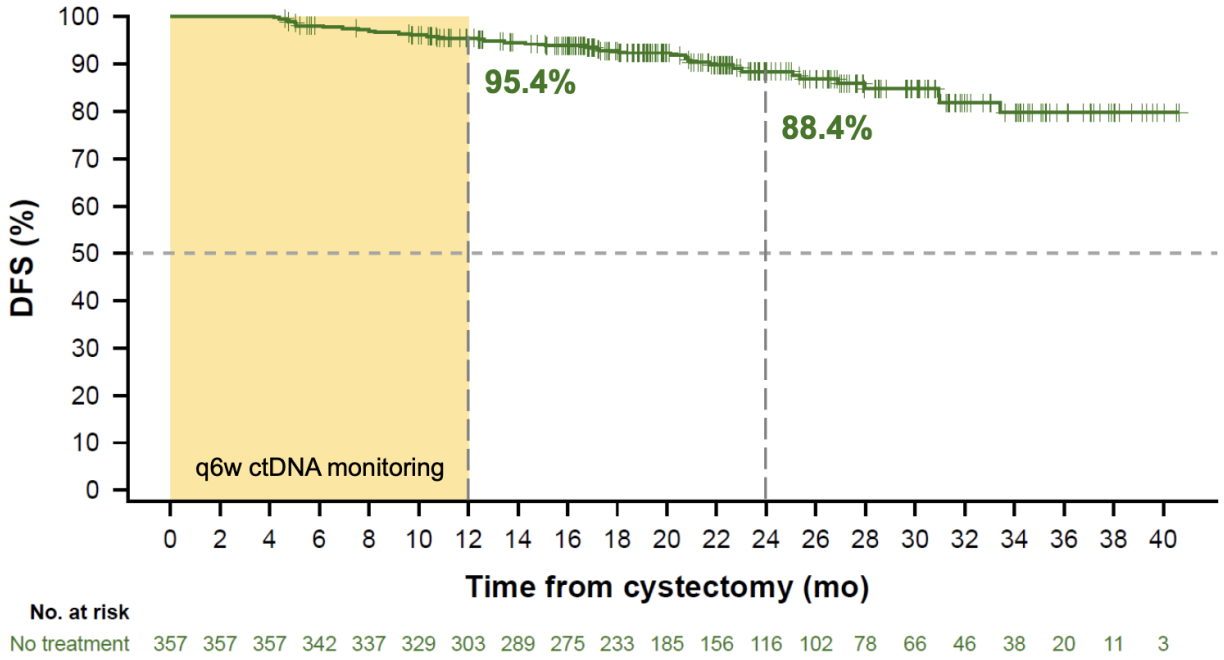
Clinical cutoff: 15 June 2025; median follow-up: 16.1 mo from randomisation. © Copyright 2025.

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DFS and OS in patients who persistently tested ctDNA−

INV-assessed DFS

	No treatment (n=357)
Events, n (%)	39 (10.9)
DFS, median (95% CI), mo	NE (NE)



No. at risk

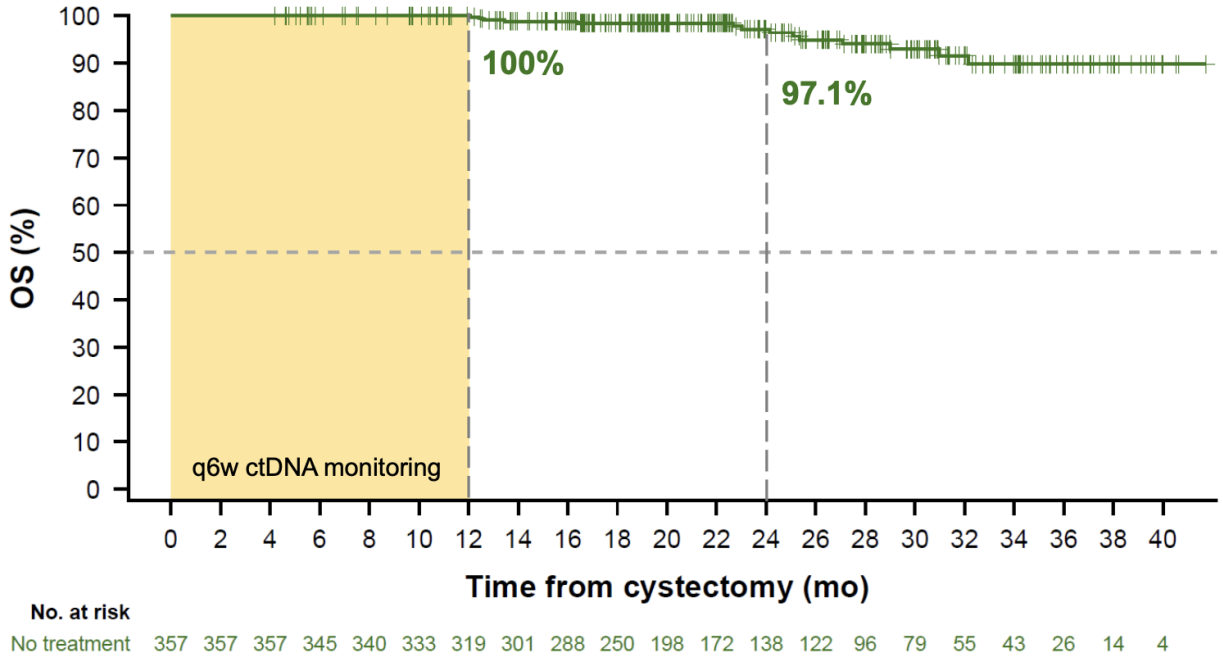
No treatment	357	357	357	342	337	329	303	289	275	233	185	156	116	102	78	66	46	38	20	11	3

8 DFS events were deaths not clearly attributed to disease recurrence

Median follow-up: 21.8 mo from cystectomy

OS

	No treatment (n=357)
Events, n (%)	14 (3.9)
OS, median (95% CI), mo	NE (NE)



No. at risk

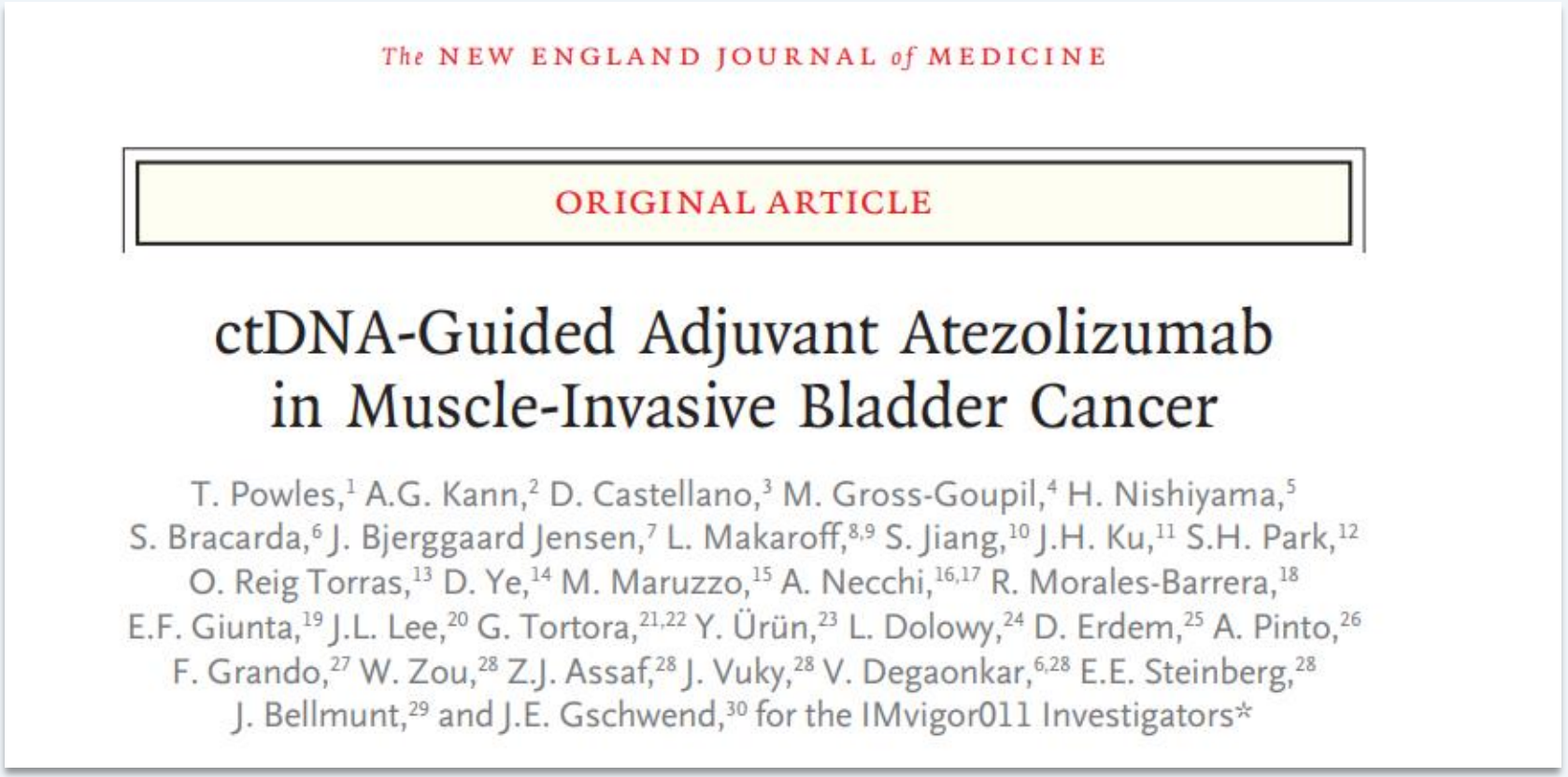
No treatment	357	357	357	345	340	333	319	301	288	250	198	172	138	122	96	79	55	43	26	14	4

15 patients (4.2%) who experienced disease recurrence during the ctDNA monitoring period were discontinued from the study and censored for OS

Clinical cutoff: 15 June 2025. To be included in the ctDNA− efficacy-evaluable population, patients must have ≥1 negative test result and no positive test result, had ≥1 post-baseline clinical outcome assessment and completed 1 y of surveillance or discontinued from surveillance without a ctDNA+ result. q6w, every 6 weeks © Copyright 2025.

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ORIGINAL ARTICLE

ctDNA-Guided Adjuvant Atezolizumab in Muscle-Invasive Bladder Cancer

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Single timepoint ctDNA analysis, no serial testing

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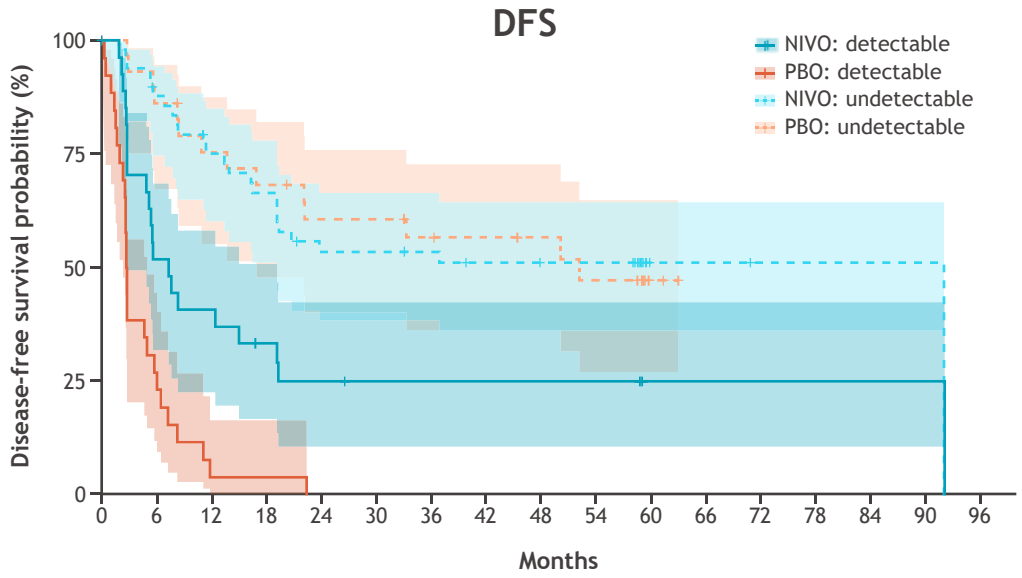
Adjuvant nivolumab vs placebo for high-risk muscle-invasive urothelial carcinoma: 5-year efficacy and ctDNA results from CheckMate 274

Matthew D. Galsky,[1] Jürgen E. Gschwend,[2] Matthew I. Milowsky,[3] Michael Schenker,[4] Begoña P. Valderrama,[5] Yoshihiko Tomita,[6] Aristotelis Bamias,[7] Thierry Lebret,[8] Shahrokh F. Shariat,[9] Se Hoon Park,[10] Mads Agerbaek,[11] Gautam Jha,[12] Frank Stenner,[13] Dingwei Ye,[14] Fabio Giudici,[15] Jessica Connors,[16] Saurabh Gupta,[16] Joshua Zhang,[16] Dean F. Bajorin,[17] Johannes Alfred Witjes[18]

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Presentation number 3068O

ctDNA detectable status relationship with DFS and OS in each treatment arm

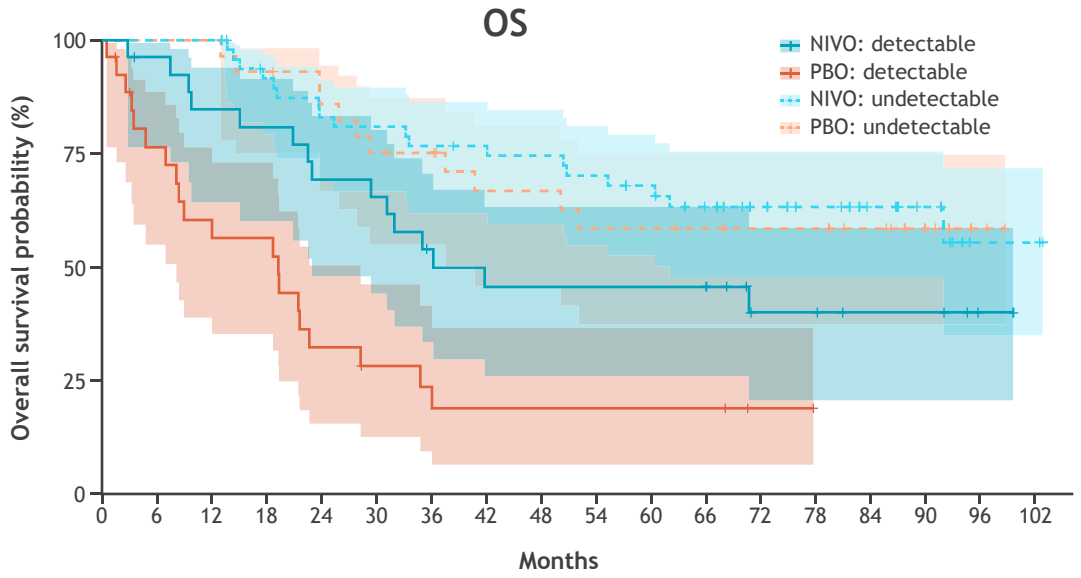


No. at risk

NIVO: detectable	27	14	11	8	6	5	5	5	5	5	1	1	1	1	1	1	0
PBO: detectable	27	7	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
NIVO: undetectable	50	42	35	31	24	24	23	21	20	20	2	2	1	1	1	1	0
PBO: undetectable	29	25	21	19	16	16	14	13	12	10	2	0	0	0	0	0	0

ctDNA detectable	NIVO (n = 27)	PBO (n = 27)
Median DFS (95% CI), months	7.4 (2.8-19.2)	2.8 (2.4-5.0)
DFS HR (95% CI)	0.35 (0.18-0.66)	

ctDNA undetectable	NIVO (n = 50)	PBO (n = 29)
Median DFS (95% CI), months	91.9 (19.2-NE)	52.2 (16.9-NE)
DFS HR (95% CI)	0.99 (0.51-1.93)	



No. at risk

NIVO: detectable	27	25	22	21	18	17	13	11	11	11	11	11	6	6	4	4	1	0
PBO: detectable	27	19	15	14	8	6	5	4	4	4	4	4	1	0	0	0	0	0
NIVO: undetectable	50	50	50	43	39	38	36	35	34	32	30	24	20	17	13	9	2	2
PBO: undetectable	29	29	29	27	24	21	20	16	16	14	14	13	12	12	10	5	2	0

ctDNA detectable	NIVO (n = 27)	PBO (n = 27)
Median OS (95% CI), months	36.2 (23.0-NE)	19.3 (8.1-28.2)
OS HR (95% CI)	0.41 (0.20-0.83)	

ctDNA undetectable	NIVO (n = 50)	PBO (n = 29)
Median OS (95% CI), months	NR (62.0-NE)	NR (40.7-NE)
OS HR (95% CI)	0.87 (0.41-1.84)	

- Within the ctDNA-detectable subgroup, NIVO improved median DFS and median OS by > 2-fold and > 1.5-fold vs PBO, respectively
- Despite a small number of samples analyzed, the trend of improvement for DFS and OS is evident in patients with detectable ctDNA

Minimum follow-up, 61.3 months; median follow-up, 41.8 months in ctDNA-evaluable patients. Post hoc exploratory analyses. Baseline ctDNA was measured using the Signatera™ assay.

Conclusions[1,2]

- Adjuvant immunotherapy improved DFS and OS by 1.5-2x in the Signatera™ ctDNA-positive groups
  - Similar treatment efficacy was observed in patients who tested positive in first test vs. subsequent tests, and those with and without neoadjuvant therapy
- Signatera ctDNA-negative patients saw no clinical benefit from adjuvant immunotherapy, and those who remained serially negative for 1y had excellent outcomes and may be spared from unnecessary treatment
- Similar approach should be considered in other histologies, expanding the adjuvant window and treating only after ctDNA positivity
- ctDNA testing methodologies have significant differences, so test performance should not be generalized without sufficient clinical data

1. Adjuvant nivolumab vs placebo for high-risk muscle-invasive urothelial carcinoma: 5-year efficacy and ctDNA results from CheckMate 274; Galsky M et al., Annals of Oncology, 2025.
2. IMvigor011: a Phase 3 trial of circulating tumour (ct)DNA-guided adjuvant atezolizumab vs placebo in muscle-invasive bladder cancer; Powles T et al., New England Journal of Medicine, 2025

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Circulating tumor DNA (ctDNA) in patients with muscle-invasive bladder cancer (MIBC) who received perioperative durvalumab (D) in NIAGARA

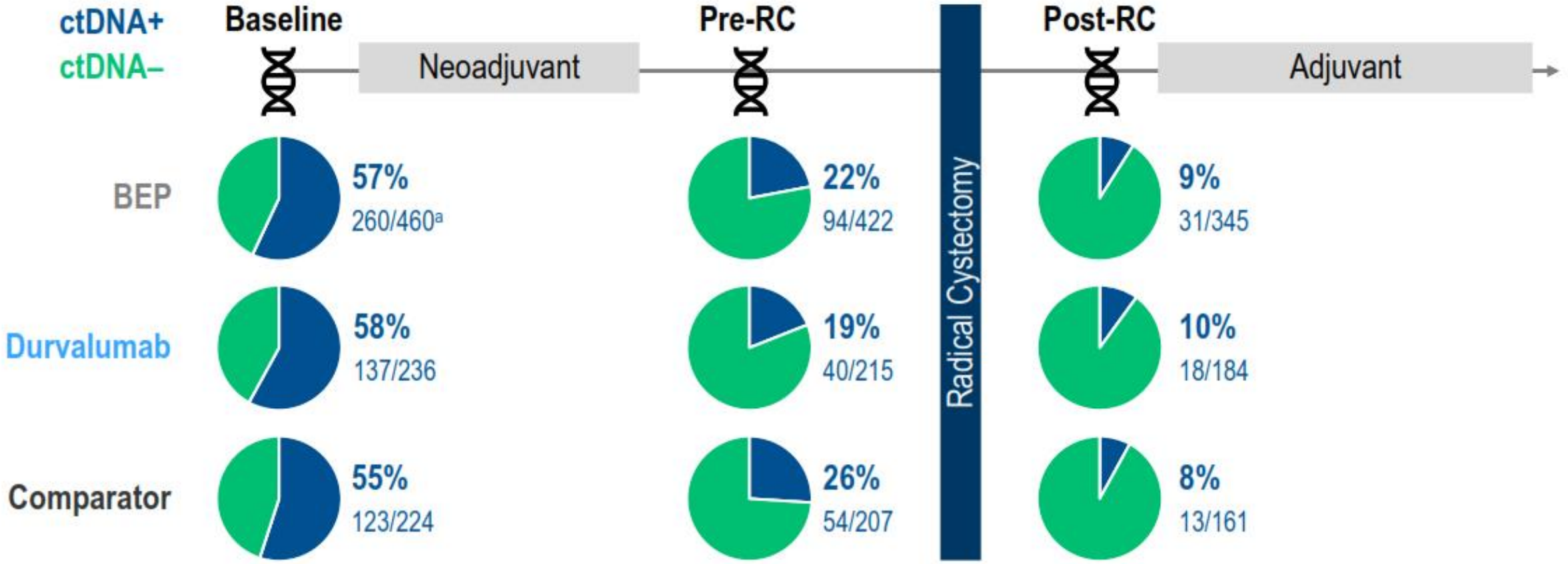
Thomas Powles,[1] Michiel S. van der Heijden,[2] Ying Wang,[3] James W. F. Catto,[4] Joshua J. Meeks,[5] Hikmat Al-Ahmadie,[6] Hiroyuki Nishiyama,[7] Agrin Moeini,[8] Toan Quang Vu,[9] Lorenzo Antonuzzo,[10] Tae-Hwan Kim,[11] Vagif Atduev,[12] Hiroaki Kikukawa,[13] Bernhard Eigl,[14] Yousef Zakharia,[15] Kazuo Nishimura,[16] Svetlana Ho,[17] Wenjing Xin,[18] Yashaswi Shrestha,[17] Matthew D. Galsky[19]

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NIAGARA: ctDNA Detection Rates

ctDNA+ rates decreased after neoadjuvant treatment and radical cystectomy

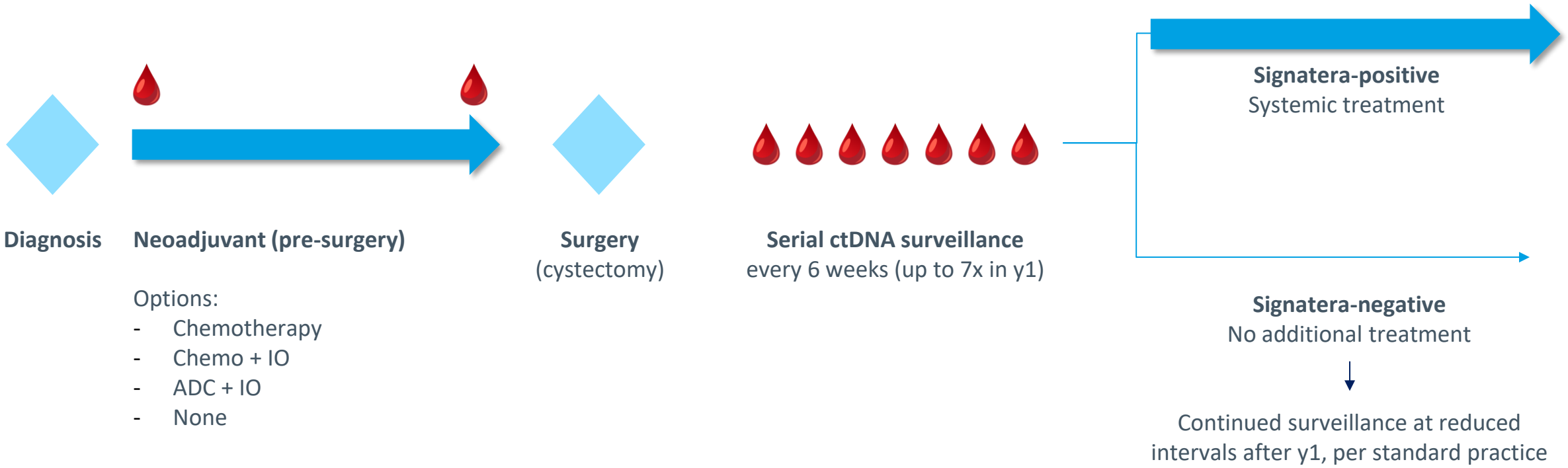


[a]The overall BEP was 462 patients, however, 2 patients did not have a baseline ctDNA assessment available.
BEP, biomarker evaluable population; ctDNA, circulating tumor DNA; RC, radical cystectomy.

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New standard of care emerging

- Adjuvant treatment decision can benefit from ctDNA guidance, regardless of neoadjuvant regimen
- The duration of ADC therapy could be tailored by ctDNA analysis in the perioperative setting
- Frequent ctDNA assessment (q6w in y1) is needed to catch MRD before visible on CT scan



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MIBC indication overview

- ~30k new MIBC patients per year in the U.S.[1,2,3], ~150k worldwide[4,5]
- Envision 10-14 tests per MIBC patient over 5-year journey, <10% penetration
- Majority of our MIBC patients have Medicare[6], opportunity to expand coverage with commercial payers
- In the US, bladder cancer physicians treat multiple other GU cancers, such as renal cell carcinoma, testicular, prostate, etc.

1. https://seer.cancer.gov/statfacts/html/urinb.html
2. Patel VG, Oh WK, Galsky MD. Treatment of muscle-invasive and advanced bladder cancer in 2020. CA Cancer *J Clin*. 2020;70(5):404-423. doi:10:3322/caac.21631
3. Kantar Health (Cerner) Report.
4. Global Cancer Observatory. Cancer Today GLOBOCAN 2022 Factsheet – Bladder [Internet; cited 2025 October].
5. Ghandour R, et al. Treatment Options and Outcomes in Nonmetastatic Muscle Invasive Bladder Cancer. Trends Cancer. 2019;5(7):426-39.
6. Natera Internal Data.

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Significant ongoing investments and clinical pipeline in MIBC

Phase 2/3 MODERN trial (Alliance A032103)

- Targeting enrollment of >3k patients from >300 clinical sites across North America
- Randomized: escalation for Signatera-positives, observation for Signatera-negatives

Phase 3 ARCHER trial (NRG-GU015)

- Randomized trial >100 sites across North America, evaluating whether a shorter course of radiation can achieve outcomes comparable to current SOC
- Signatera ctDNA incorporated prospectively as a secondary endpoint, and urine tumor DNA (utDNA) evaluated as exploratory endpoint

>20 additional studies to evaluate bladder-sparing treatment approaches, and escalation / de-escalation in other stages of disease

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Implications for future trial designs

MRD-enriched randomized trials

- Randomize Signatera-positive; observe Signatera-negative with prespecified **TOMR / conversion** triggers



Surrogate endpoints

- Incorporate **Signatera kinetics/clearance** as an **early indicator** reasonably likely to predict clinical benefit (mounting multi-tumor evidence)



Integration with new regimens

- Build **Signatera-guided** perioperative designs alongside **ADC+IO** combinations and **bladder-sparing** approaches to refine escalation/de-escalation strategies



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Summary

- IMvigor011 establishes new SOC for post-surgical Signatera-guided IO treatment
- Not all MRD assays are the same, need prospective validation
- Additional studies planned in MIBC with Signatera across entire care continuum
- TOMR concept derisked and likely applicable in other histologies

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