Perioperative treatment in localized muscle-invasive bladder cancer: what should I choose?

Adjuvant therapy (guided by liquid biopsy?) is the best option

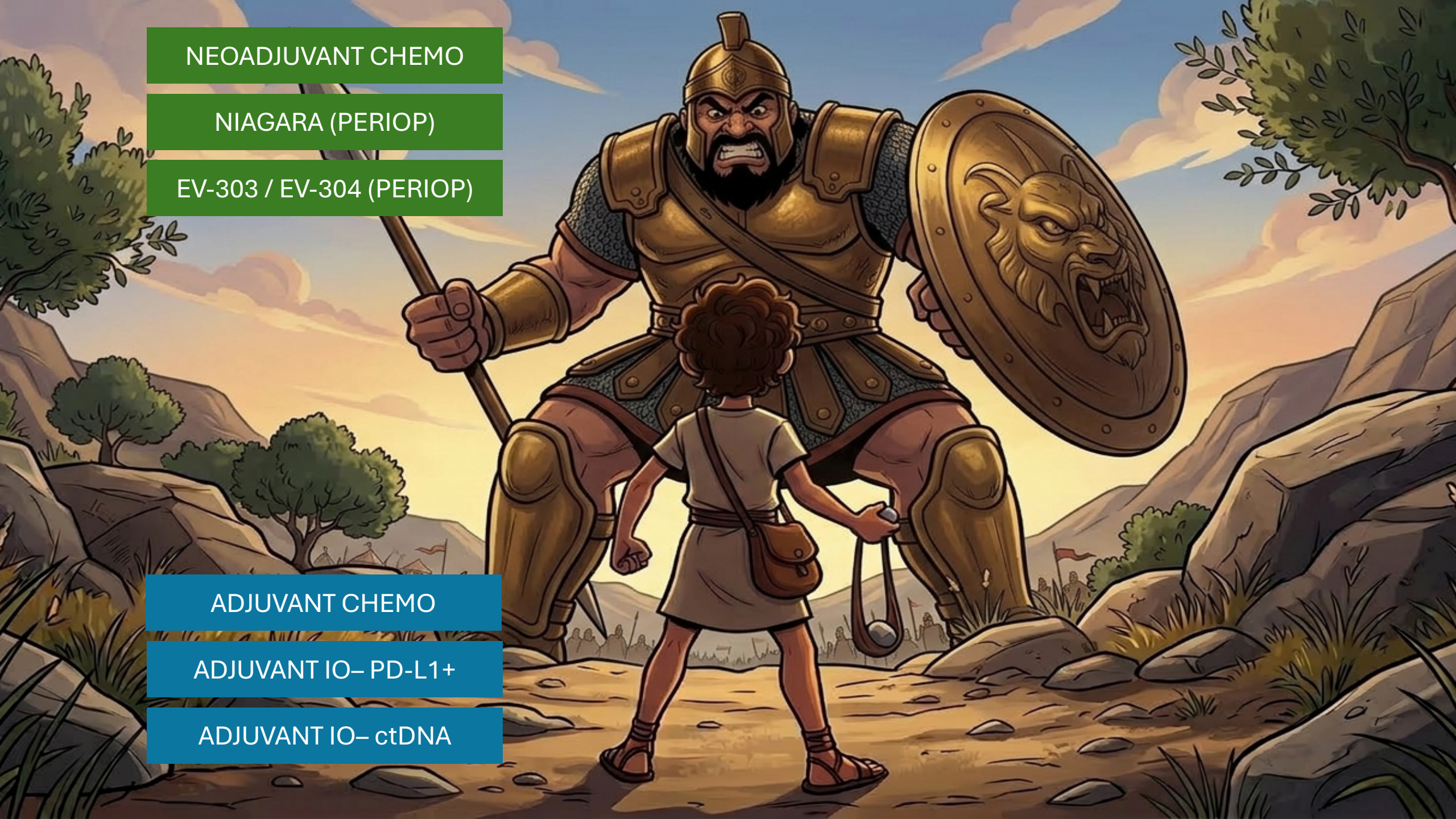
Álvaro Pinto

Medical Oncology Department, University Hospital La Paz- IdiPAZ, Madrid

Associate Professor of Medicine, Autonoma University, Madrid

Disclosures

- ***Research funding:*** *Pfizer, BMS*
- ***Advisory boards:*** *Pfizer, Novartis, Ipsen, BMS, Janssen, Astellas, Bayer, Roche, MSD, Merck, Astra Zeneca*
- ***Clinical trial payments:*** *Pfizer, Bayer, Janssen, Astellas, MSD, Clovis, Pharmacyclics, BMS, Sanofi, Astra Zeneca, Roche, Eisai, Aveo*
- ***Travel arrangements:*** *Janssen, Roche, Pfizer, BMS, Ipsen, Bayer*


NEOADJUVANT CHEMO
NIAGARA (PERIOP)
EV-303 / EV-304 (PERIOP)
ADJUVANT CHEMO
ADJUVANT IO– PD-L1+
ADJUVANT IO– ctDNA

WHY ADJUVANT THERAPY?

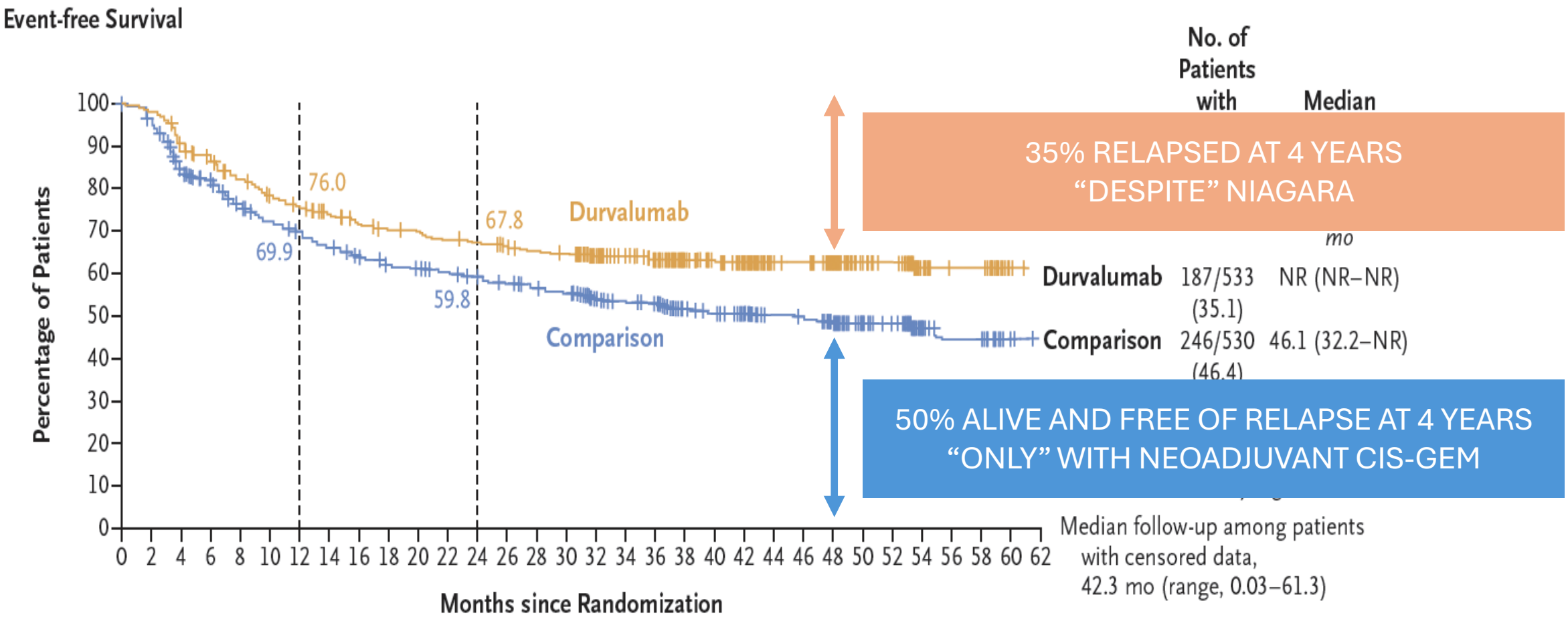
1. MORE ACCURATE PATHOLOGICAL STAGING (CYSTECTOMY)

2. PATIENTS WILL NOT MISS THE CHANCE TO GET SURGERY

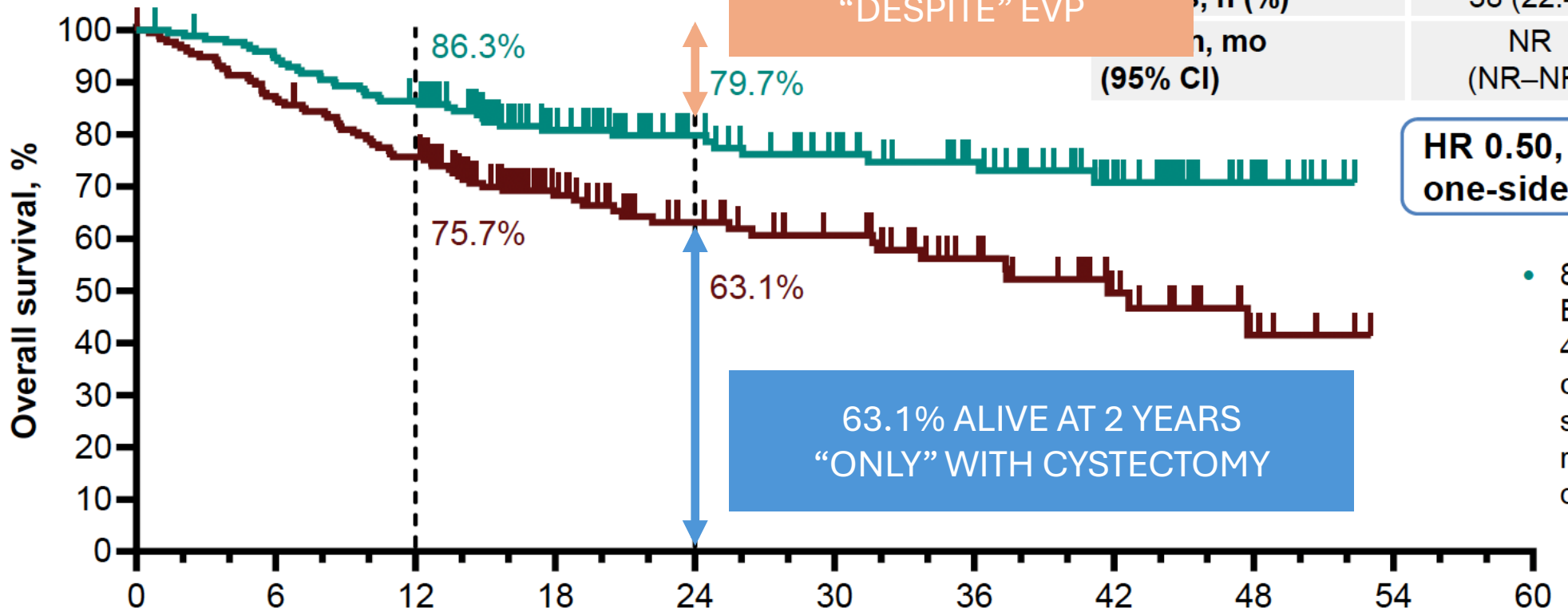
3. TREAMENT TAILORING – BIOMARKERS (ctDNA)

4. OPTIMIZATION OF THE RISK-BENEFIT RATIO OF THE THERAPEUTIC STRATEGY

NIAGARA


Event-free Survival
Percentage of Patients
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56 58 60 62
Months since Randomization
76.0
67.8
Durvalumab
69.9
59.8
Comparison
No. of Patients with
Median
mo
Durvalumab 187/533 (35.1) NR (NR–NR)
Comparison 246/530 (46.4) 46.1 (32.2–NR)
35% RELAPSED AT 4 YEARS
"DESPITE" NIAGARA
50% ALIVE AND FREE OF RELAPSE AT 4 YEARS
"ONLY" WITH NEOADJUVANT CIS-GEM
Median follow-up among patients with censored data, 42.3 mo (range, 0.03–61.3)

KN-905 / EV-303

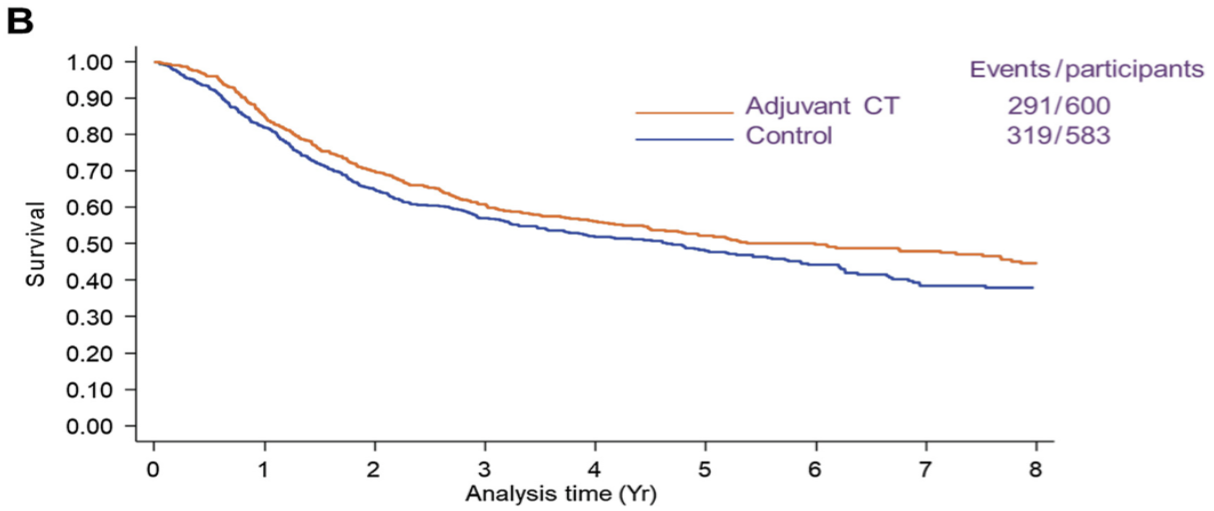


	EV + pembro (N = 170)	Control (N = 174)
s, n (%)	38 (22.4)	68 (39.1)
n, mo (95% CI)	NR (NR–NR)	41.7 (31.8–NR)

HR 0.50, 95% CI 0.33–0.74, one-sided *P* =.0002*

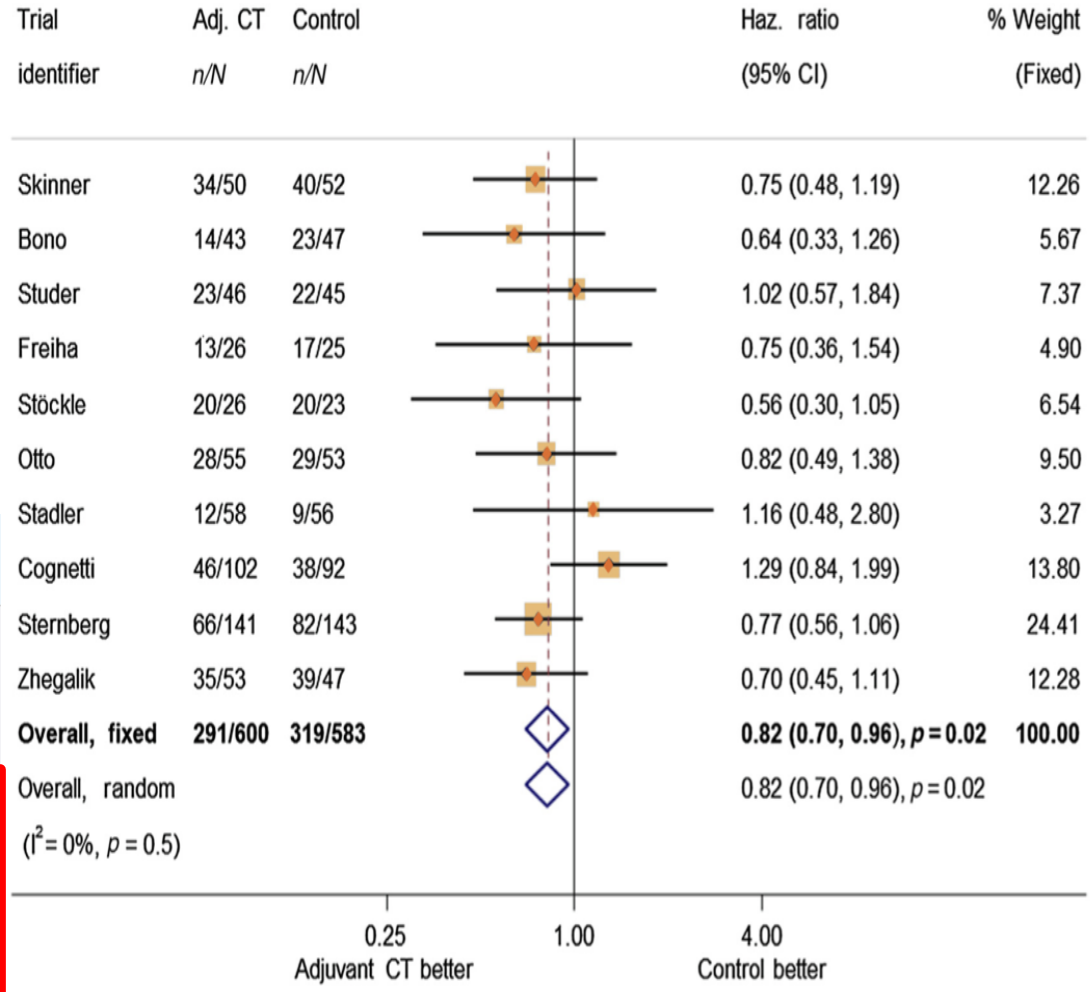
- 8/170 pts (4.7%) in the EV + pembro arm and 46/174 (26.4%) in the control arm received subsequent therapy for recurrent/metastatic disease

ADJUVANT CHEMO



Summary of evidence	LE
Adjuvant cisplatin-based chemotherapy for high-risk patients (pT3, 4 and/or or N+) without neoadjuvant treatment can be associated with improvement in DFS and OS but trials are underpowered to adequately answer this question.	2a

Recommendations	Strength rating
Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant systemic therapy has been given.	Strong



ABC Meta-Analysis Collaboration Group. Eur Urol 2022

ADJUVANT IO

N = 709

Key inclusion criteria

- ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of randomization

Stratification factors

- Tumor PD-L1 status (≥ 1% vs < 1% or indeterminate)[b]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status

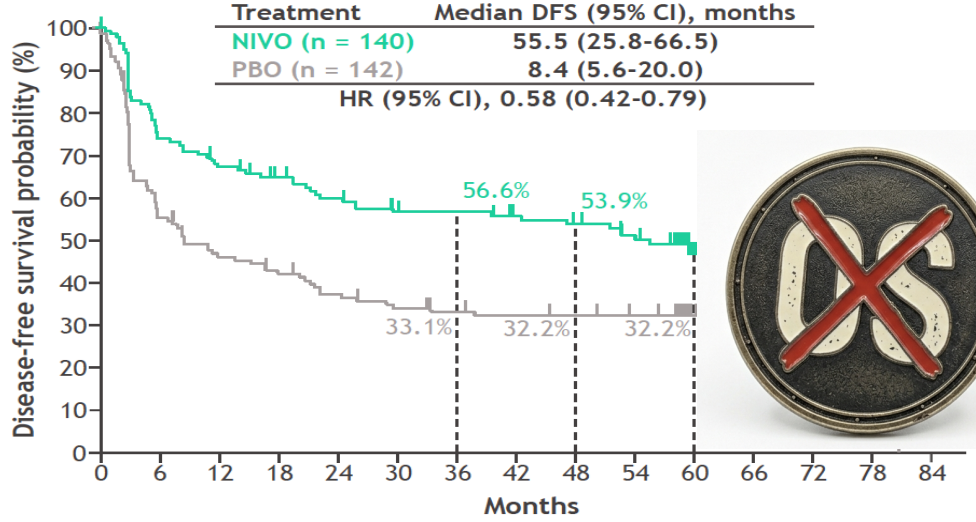
R 1:1

- NIVO IV[c] 240 mg Q2W
- PBO IV[c] Q2W

Primary endpoints: DFS in all randomized patients and DFS in all randomized patients with tumor PD-L1 ≥ 1%
Secondary endpoints presented: OS[d] and DSS
Exploratory endpoint presented: Safety

Patients with PD-L1 ≥ 1%[b]

Treatment	Median DFS (95% CI), months
NIVO (n = 140)	55.5 (25.8-66.5)
PBO (n = 142)	8.4 (5.6-20.0)
HR (95% CI), 0.58 (0.42-0.79)	



NCT03244384

Key Eligibility

- Muscle-invasive urothelial carcinoma: bladder, urethra, renal pelvis, ureter
- Post-radical surgery (cystectomy, nephrectomy, nephroureterectomy, or ureterectomy) ≥ 4 but ≤ 16 weeks
- Post-neoadjuvant chemotherapy and ≥ pT2 and/or N+/+margins
  OR
- cisplatin-ineligible or refusing and ≥ pT3 and/or pN+/+margins

Stratify

- PD-L1 status*
- Neoadjuvant chemotherapy yes/no
- Pathologic stage:
  - pT2/3/4aN0
  - pT4aN0
  - pT4bNx/N1-3
  - +surgical margins

N=739

R 1:1

- Pembrolizumab 200 mg q3W 1 year (18 cycles)
- Observation

Dual Primary Endpoints

- Disease-free survival
- Overall survival

Key Secondary Endpoints

- DFS/OS PD-L1 +/-
- Safety

Correlative Endpoints

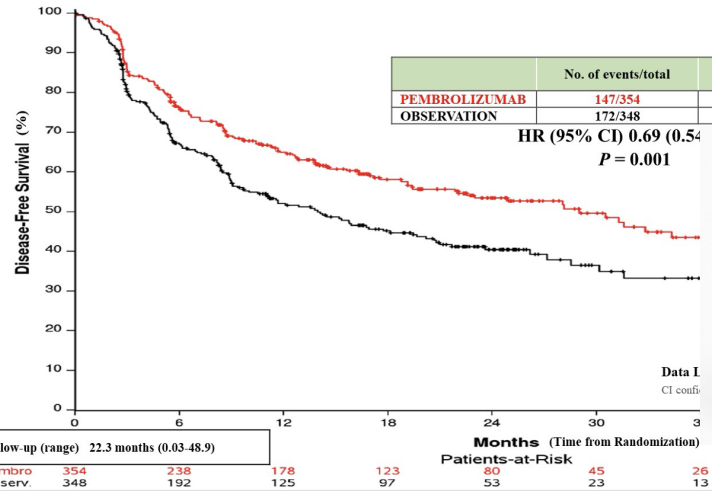
- DFS/OS ctDNA +/-
- DFS/OS immune gene signatures
- DFS/OS tumor molecular subtype
- DFS/OS TCR clonality
- QOL

*PD-L1 status was tested centrally and defined using the combined positive score: percentage of PD-L1-positive tumor cells and infiltrating immune cells relative to the total number of tumor cells. PD-L1 positive = CPS ≥ 10%, Dako PD-L1 immunohistochemistry 22C3 pharmDx assay. DFS: disease-free survival (defined as new MIUC, metastatic disease, or death without recurrence); OS: overall survival

A031501 AMBASSADOR: Disease-Free Survival (ITT)

	No. of events/total	Median (95% CI), months
PEMBROLIZUMAB	147/354	29.0 (21.8-NR)
OBSERVATION	172/348	14.0 (9.7–20.2)

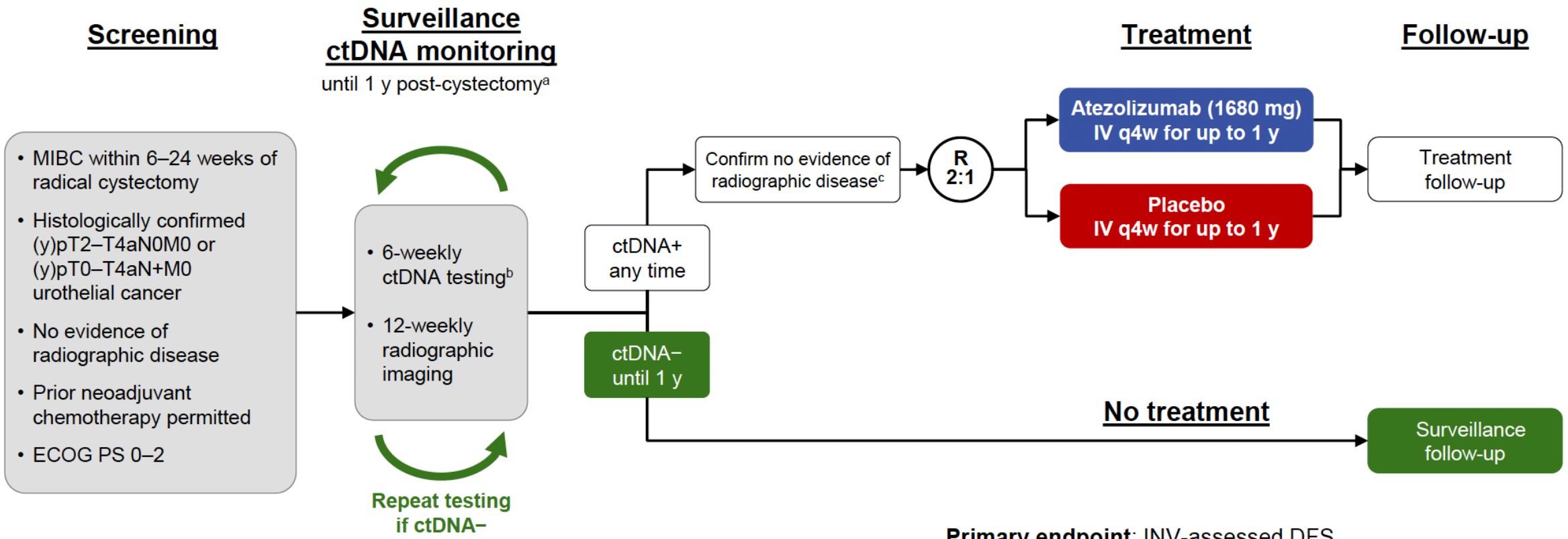
HR (95% CI) 0.69 (0.54
P = 0.001



Median follow-up (range) 22.3 months (0.03-48.9)

Galsky MD et al. Ann Oncol 2026; Apolo AB et al. N Engl J Med 2024

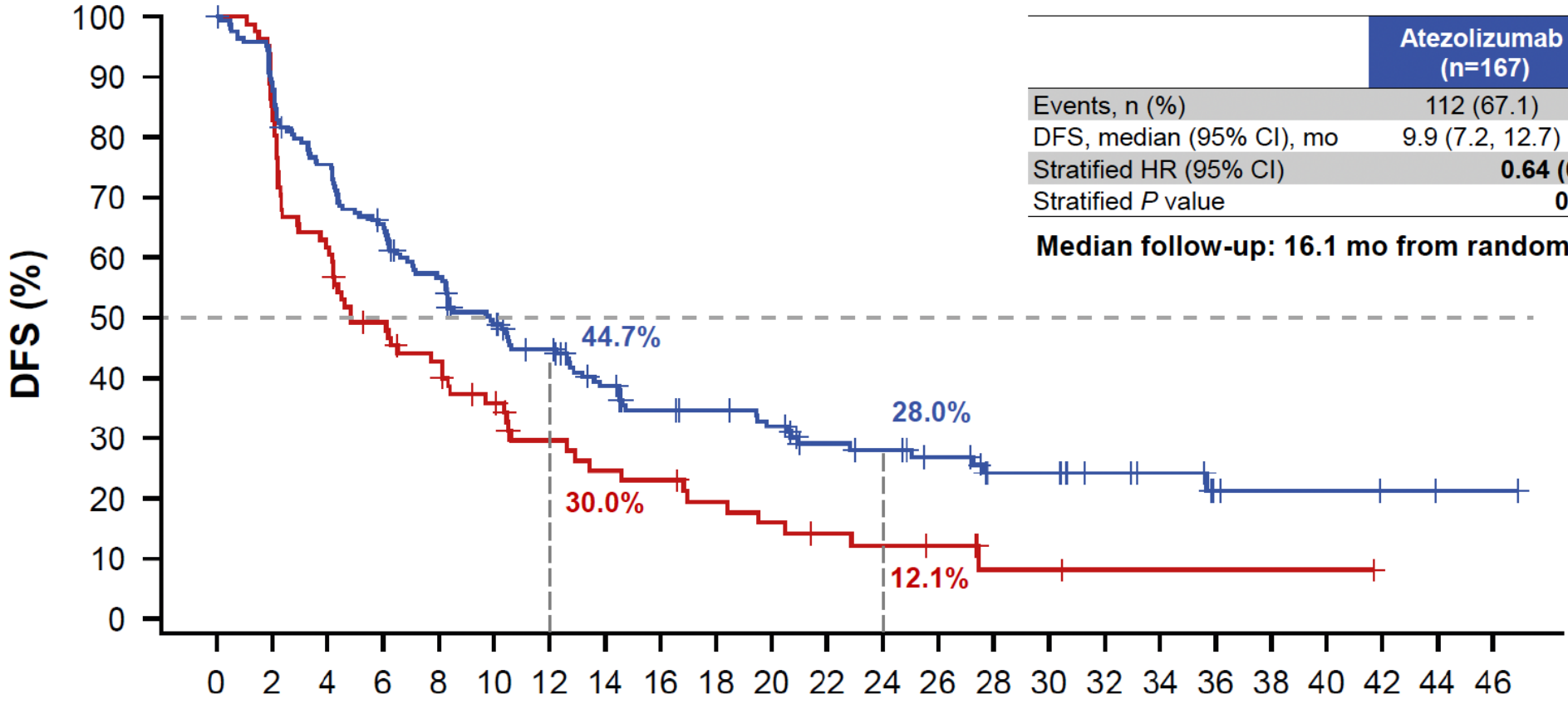
IMVIGOR-011



Primary endpoint: INV-assessed DFS
Key secondary endpoint: OS

IMVIGOR-011

INV-assessed DFS in patients who tested ctDNA+



	Atezolizumab (n=167)	Placebo (n=83)
Events, n (%)	112 (67.1)	66 (79.5)
DFS, median (95% CI), mo	9.9 (7.2, 12.7)	4.8 (4.1, 8.3)
Stratified HR (95% CI)	**0.64 (0.47, 0.87)**	
Stratified *P* value	**0.0047**	

Median follow-up: 16.1 mo from randomisation

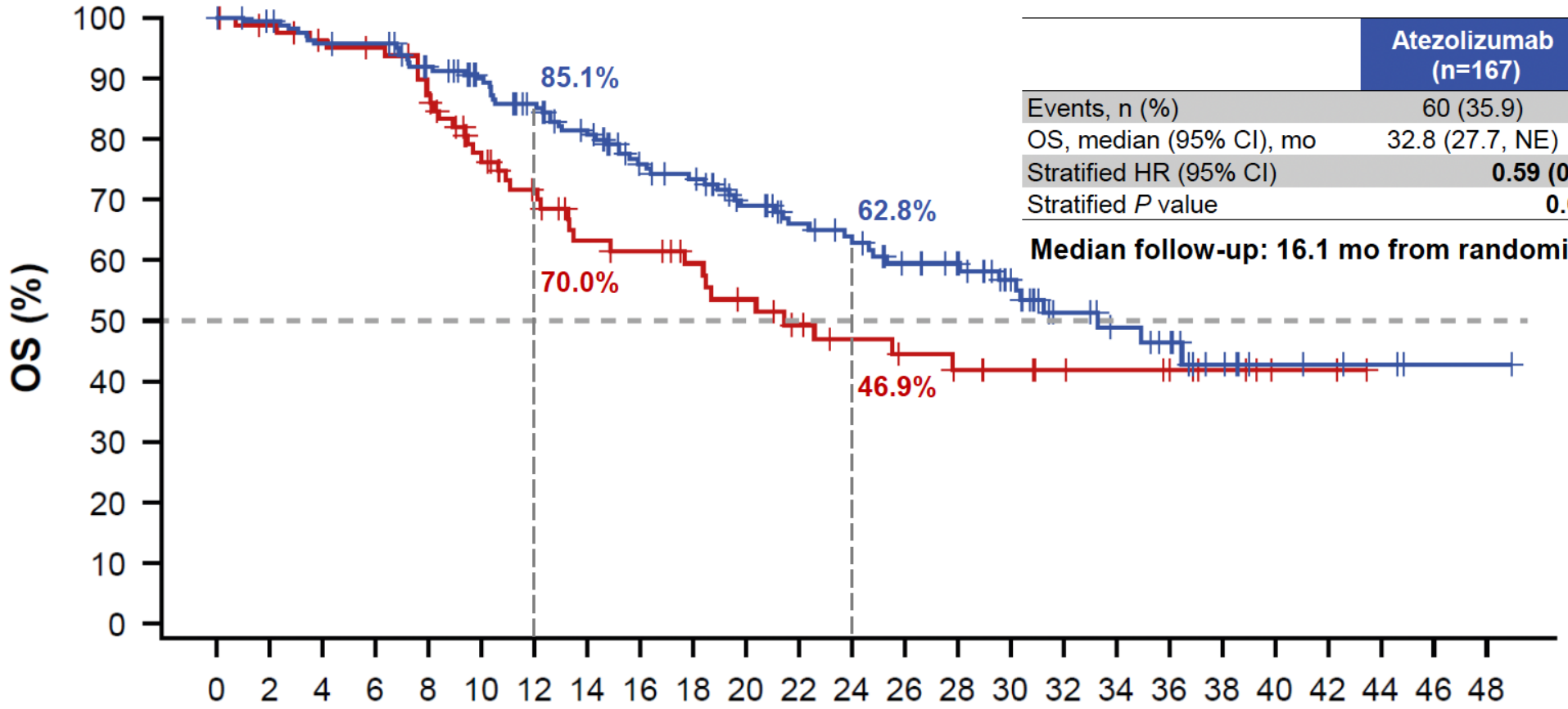
Consistent benefit in relevant secondary endpoints:

DFS per IRF:
HR, 0.66 (95% CI: 0.48, 0.91)

Distant-metastasis free survival:
HR, 0.66 (95% CI: 0.47, 0.94)

IMVIGOR-011

OS in patients who tested ctDNA+



	Atezolizumab (n=167)	Placebo (n=83)
Events, n (%)	60 (35.9)	36 (43.4)
OS, median (95% CI), mo	32.8 (27.7, NE)	21.1 (14.7,NE)
Stratified HR (95% CI)	**0.59 (0.39, 0.90)**	
Stratified *P* value	**0.0131**	

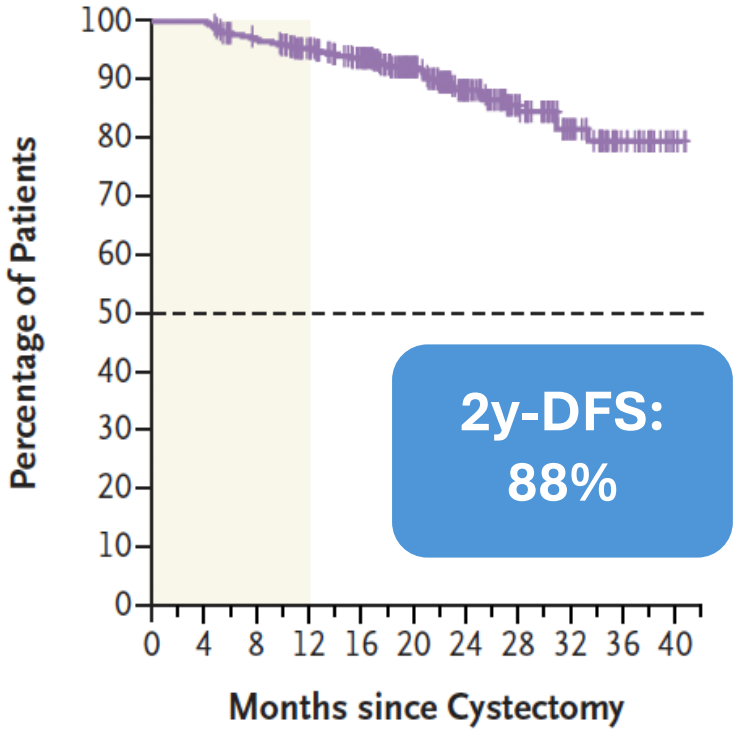
Median follow-up: 16.1 mo from randomisation

Consistent benefit in relevant secondary endpoints:

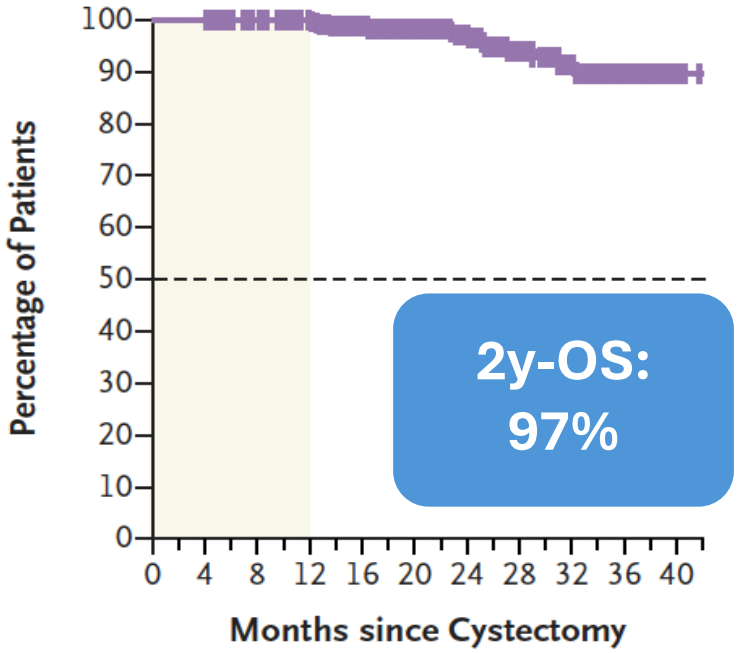
Disease-specific survival:
HR, 0.64 (95% CI: 0.40, 1.05)

IMVIGOR-011

C Disease-free Survival among Patients with Persistent ctDNA-Negative Status



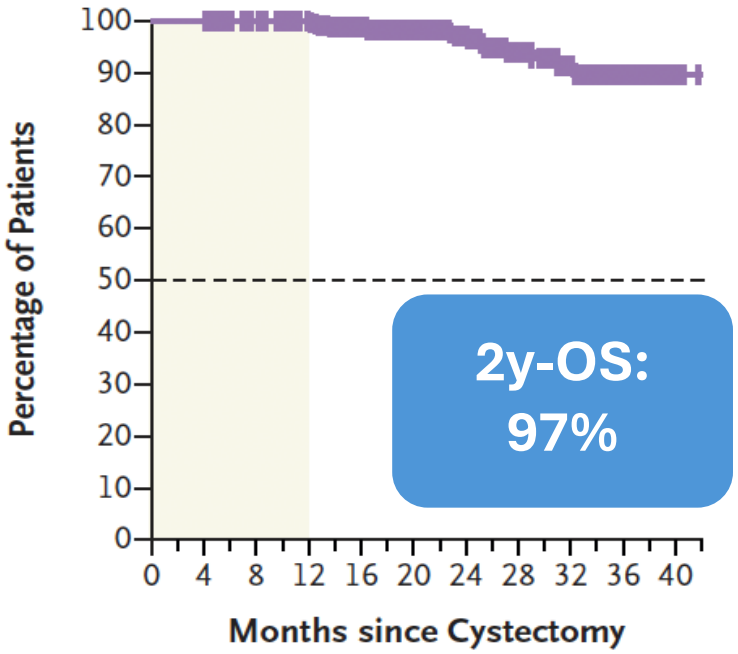
F Overall Survival among Patients with Persistent ctDNA-Negative Status



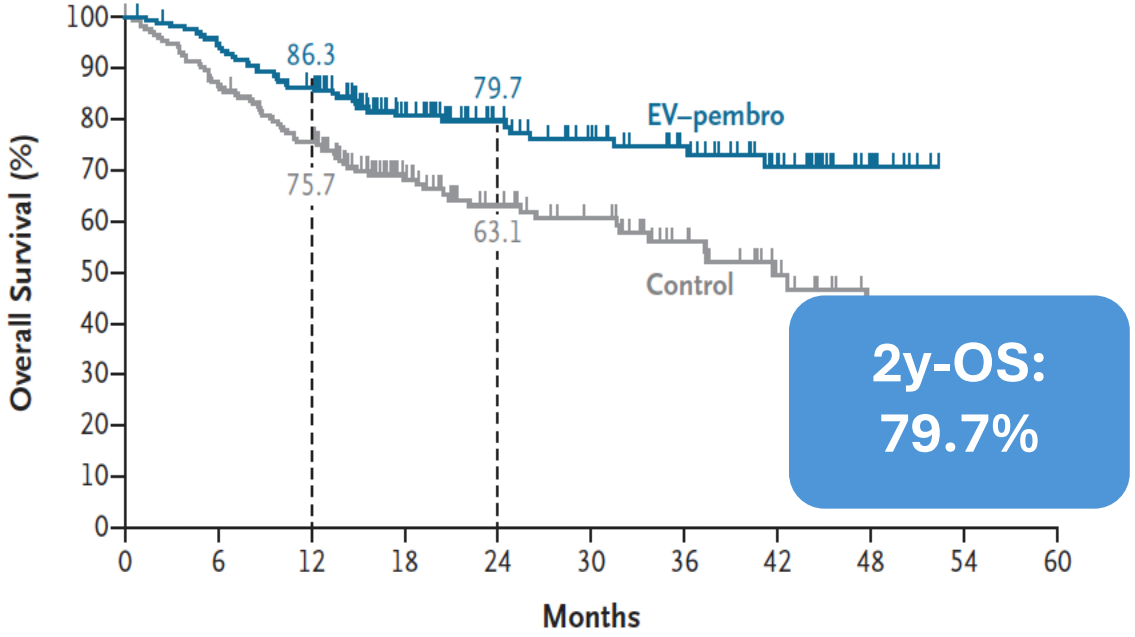
Powles T et al. NEJM 2025

IMVIGOR-011 vs EV-303

F Overall Survival among Patients with Persistent ctDNA-Negative Status



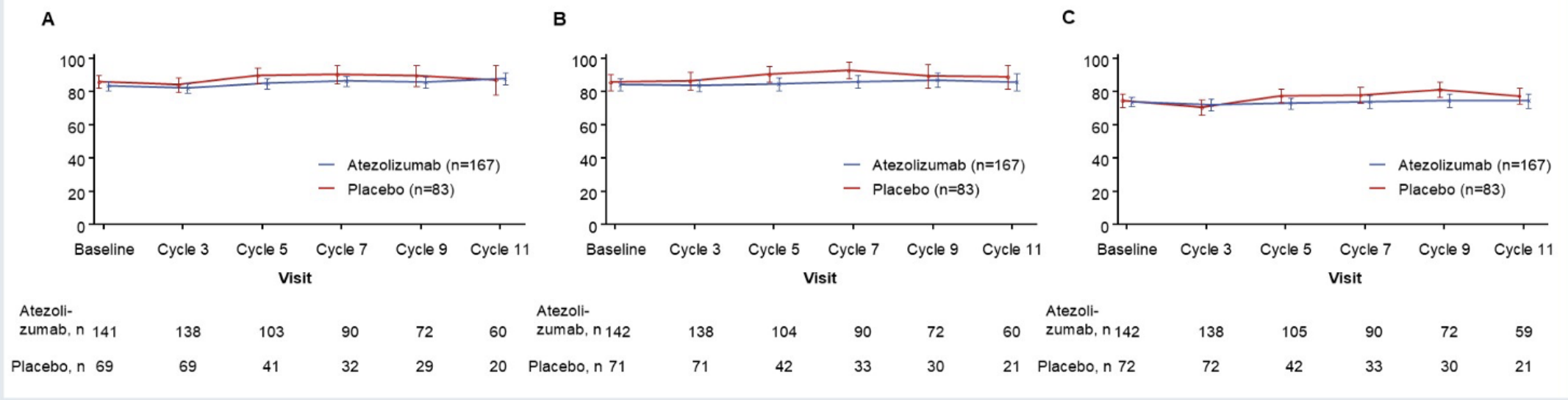
Perioperative Enfortumab Vedotin and Pembrolizumab in Bladder Cancer



IMVIGOR-011

Patient-reported outcomes from IMvigor011: A Phase 3 study of circulating tumor (ct)DNA-guided adjuvant atezolizumab vs placebo in muscle-invasive bladder cancer (MIBC)

Figure 3. Mean scores for (A) physical functioning, (B) role functioning, and (C) GHS/QoL per EORTC QLQ-C30 in randomized patients who tested ctDNA+



	Baseline	Cycle 3	Cycle 5	Cycle 7	Cycle 9	Cycle 11
Atezolizumab, n	141	138	103	90	72	60
Placebo, n	69	69	41	32	29	20

	Baseline	Cycle 3	Cycle 5	Cycle 7	Cycle 9	Cycle 11
Atezolizumab, n	142	138	104	90	72	60
Placebo, n	71	71	42	33	30	21

	Baseline	Cycle 3	Cycle 5	Cycle 7	Cycle 9	Cycle 11
Atezolizumab, n	142	138	105	90	72	59
Placebo, n	72	72	42	33	30	21

IMVIGOR-011

Cost-Effectiveness of Circulating Tumor DNA–Guided Adjuvant Atezolizumab in Muscle-Invasive Bladder Cancer Based on IMvigor011 Trial

TABLE 3. Results of Cost-Effectiveness Analysis

Strategy	Total Cost ($, USD)	Incremental Cost ($, USD)	INMB ($, USD)	QALYs	Incremental QALYs	ICER ($, USD/QALY)
SOC	131,601.74	—	—	2.92	—	—
ctDNA-guided	78,796.64	−10,514.14	72,305.10	3.05	0.13	−397,163.09 (dominant)

Abbreviations: ctDNA, circulating tumor DNA; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; QALYs, quality-adjusted life-years; SOC, standard of care; USD, US dollars.

IMVIGOR-011

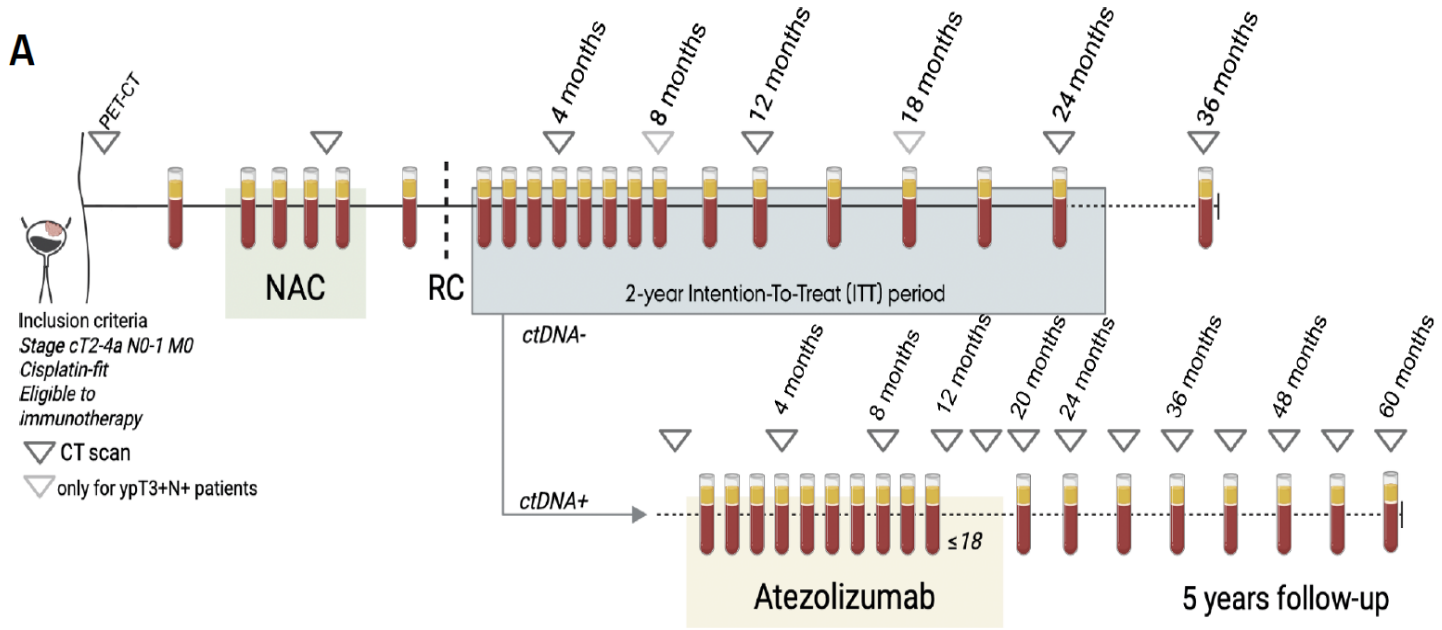
MAY 15, 2026

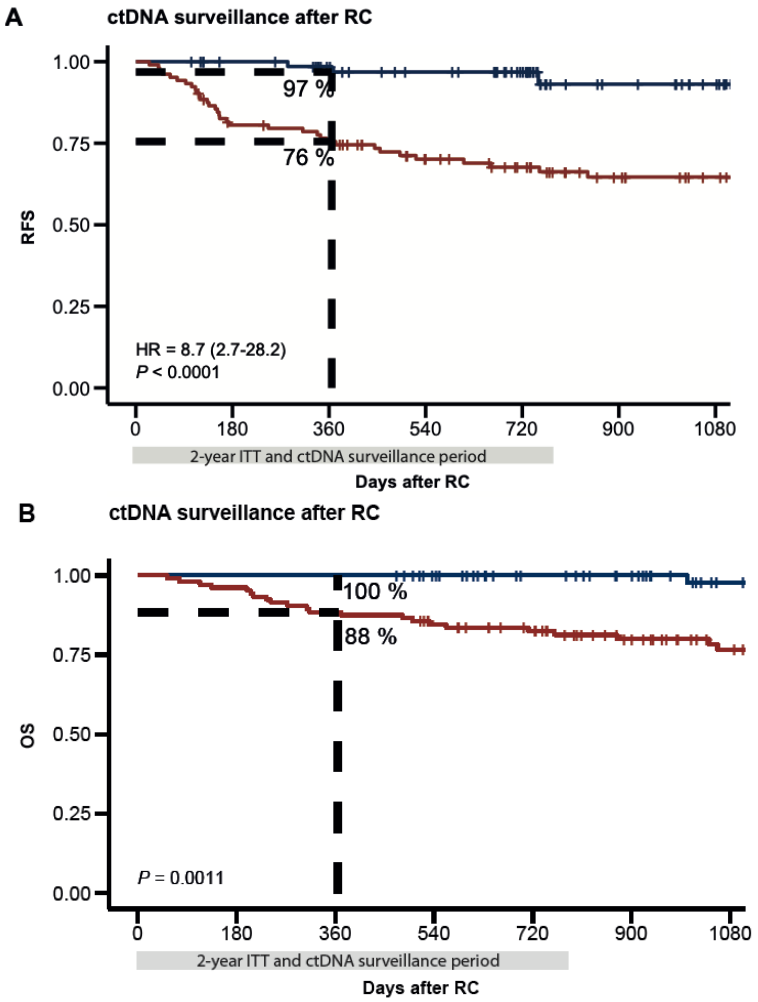
Signatera™ CDx Approved by the FDA as a Companion Diagnostic in Muscle-Invasive Bladder Cancer (MIBC)

FDA approves atezolizumab for adjuvant treatment of muscle invasive bladder cancer in patients with molecular residual disease

On May 15, 2026, the Food and Drug Administration approved atezolizumab (Tecentriq, Genentech, Inc.) and atezolizumab and hyaluronidase-tqjs (Tecentriq Hybreza, Genentech, Inc.) as adjuvant treatments for adults with muscle invasive bladder cancer (MIBC) after cystectomy who have circulating tumor DNA molecular residual disease (ctDNA MRD) as determined by an FDA-authorized test.

TOMBOLA


A
PET-CT
4 months
8 months
12 months
18 months
24 months
36 months
NAC
RC
2-year Intention-To-Treat (ITT) period
Inclusion criteria
Stage cT2-4a N0-1 M0
Cisplatin-fit
Eligible to immunotherapy
CT scan
only for ypT3+N+ patients
ctDNA-
ctDNA+
4 months
8 months
12 months
20 months
24 months
36 months
48 months
60 months
≤18
Atezolizumab
5 years follow-up


A
ctDNA surveillance after RC
RFS
1.00
0.75
0.50
0.25
0.00
97 %
76 %
HR = 8.7 (2.7-28.2)
P < 0.0001
0
180
360
540
720
900
1080
2-year ITT and ctDNA surveillance period
Days after RC
B
ctDNA surveillance after RC
OS
1.00
0.75
0.50
0.25
0.00
100 %
88 %
P = 0.0011
0
180
360
540
720
900
1080
2-year ITT and ctDNA surveillance period
Days after RC

IMVIGOR-011 vs TOMBOLA

	IMvigor011 NEJM · Oct 2025	TOMBOLA Ann Oncol · Jan 2026
DESIGN		
Phase & design	Phase III RCT, double-blind, placebo-controlled	Phase II Single-arm, open-label
Scope	Global, multinational	Danish, multicenter
N enrolled	761 (surveillance phase)	192 (178 ITT)
Median follow-up	16.1 months	34 months
POPULATION		
Tumor stage	(y)pT2–T4aN0M0 or pT0–T4aN+M0	cT2–4aN0–1M0
Prior NAC	Optional	**Mandatory**
Risk group	High-risk only	Both low- and high-risk

Powles T et al. NEJM 2025; Dyrskjot L et al. Ann Oncol 2026

IMVIGOR-011 vs TOMBOLA

	IMvigor011 NEJM · Oct 2025	TOMBOLA Ann Oncol · Jan 2026
CTDNA METHODOLOGY		
Assay	Signatera™ (Natera) — commercial tumor-informed NGS	ddPCR — local lab, tumor-informed
Testing frequency	Every 6 weeks for up to 12 months	Serial monitoring for up to 2 years post-RC
ctDNA+ rate	~40% of surveillance cohort	~58% within 2 years (63% within 4 months)
Lead time vs. imaging	ctDNA precedes radiographic recurrence	Median ~90 days before imaging-confirmed recurrence
INTERVENTION		
ctDNA+ arm	Randomized 2:1 → atezolizumab vs. placebo, q4w × 1 year	All → atezolizumab × 1 year (no comparator arm)
ctDNA− arm	Surveillance only — no treatment	Surveillance — treat only at radiographic recurrence

Powles T et al. NEJM 2025; Dyrskjot L et al. Ann Oncol 2026

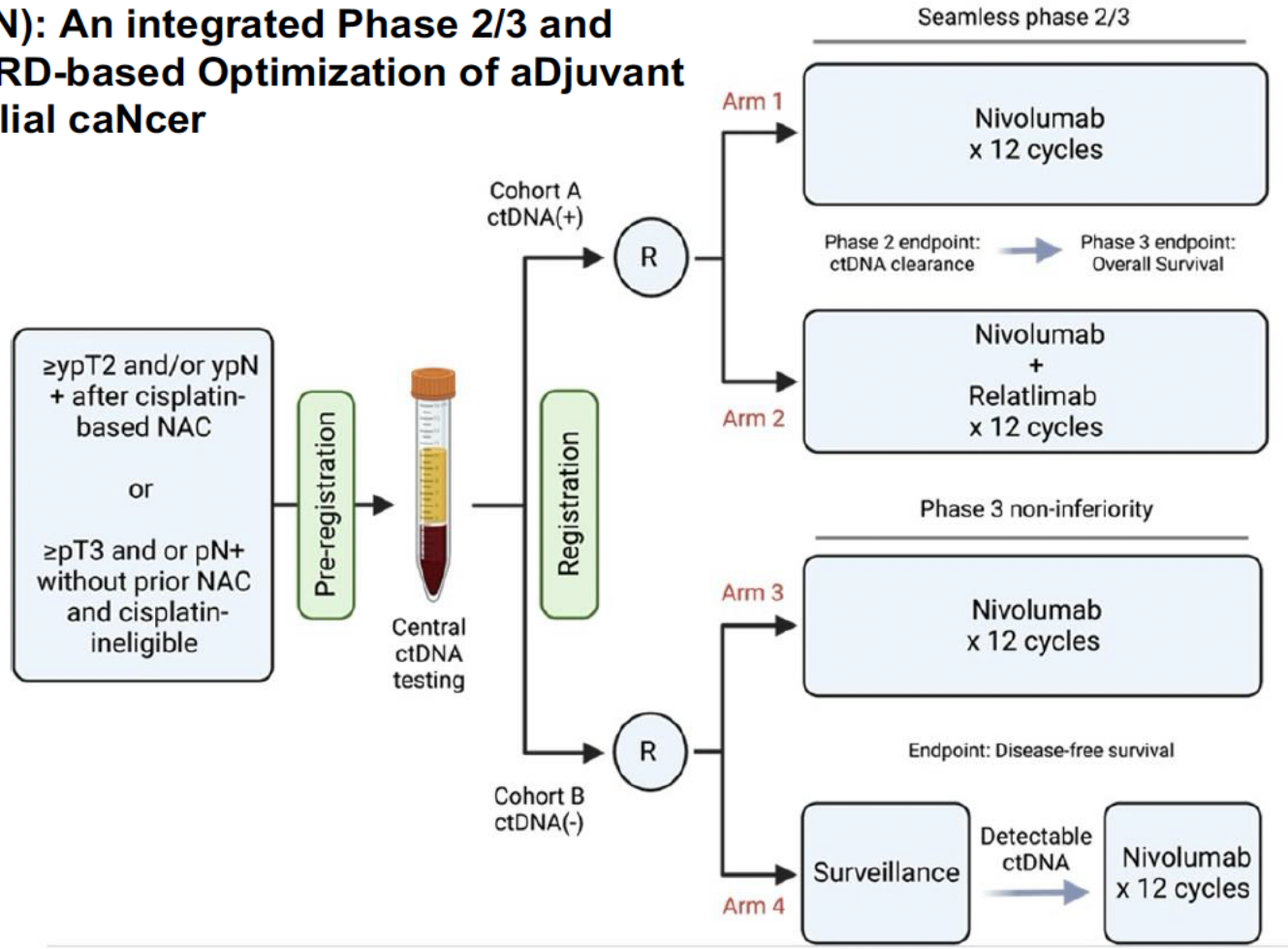
IMVIGOR-011 vs TOMBOLA

	IMvigor011 NEJM · Oct 2025	TOMBOLA Ann Oncol · Jan 2026
KEY ENDPOINTS & RESULTS		
Primary endpoint	Investigator-assessed DFS	Complete response rate (ctDNA clearance + no imaging disease)
Primary result (ctDNA+)	DFS HR 0.64 (p = 0.005) · median 9.9 vs. 4.8 mo	CR 60% (50/84) at end of treatment
Overall survival	HR 0.59 (p = 0.013) · 32.8 vs. 21.1 mo	Not a primary/key endpoint
ctDNA− outcomes	2-yr DFS 88.4% · 2-yr OS 97.1%	1-yr RFS 97%
Biomarker analyses	Limited	Rich: TGF-β signature, immune gene expression, ctDNA tumor fraction
Level of evidence	Level 1	Hypothesis-generating
Regulatory outcome	FDA approved May 2026	No regulatory submission

Powles T et al. NEJM 2025; Dyrskjot L et al. Ann Oncol 2026

MODERN (A032103)

A032103 (MODERN): An integrated Phase 2/3 and Phase 3 Trial of MRD-based Optimization of aDjuvant thErapy in uRothelial caNcer



WHICH PATIENTS NEED ADITIONAL THERAPY?

ROLE OF ESCALATION IN ctDNA+ PATIENTS?

**DO ctDNA- PATIENTS BENEFIT FROM UPFRONT IO?
OR CAN WE WAIT UNTIL CT-DNA+?**

UNANSWERED QUESTIONS…

1. WHICH PART OF THE PERIOPERATIVE STRATEGY IS REALLY NEEDED?

2. CAN WE SAFELY OMIT THE ADJUVANT PART OF THE PERIOPERATIVE STRATEGY BASED ON ctDNA?

3. IS ATEZOLIZUMAB THE BEST ADJUVANT SYSTEMIC THERAPY WE CAN OFFER TO ctDNA+ PATIENTS?

4. HOW CAN WE IMPLEMENT ctDNA TESTING IN FUTURE BLADDER-SPARING STRATEGIES?

CONCLUSIONS

ctDNA-BASED STRATEGIES ARE THE SMARTEST WAY TO OPTIMIZE THE RISK-BENEFIT RATIO IN MIBC PATIENTS RECEVING SYSTEMIC THERAPY

- **AVOID UNNECESSARY TREATMENTS**
- **IMPROVE RISK STRATIFICATION**
- **ADVANCE IN PRECISION MEDICINE**

ctDNA-BASED STRATEGIES WILL ALSO BE KEY IN THE NEAR FUTURE FOR BLADDER-SPARING APPROACHES

THANK YOU FOR YOUR ATTENTION

Álvaro Pinto

Medical Oncology Department, University Hospital La Paz- IdiPAZ, Madrid

Associate Professor of Medicine, Autonoma University, Madrid