

Redefining Curative Intent in MIBC

The Current and Future State of Bladder Preservation

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Disclosures

- Advisory board
 - Johnson and Johnson
 - Eisai
 - Bayer
 - Pfizer

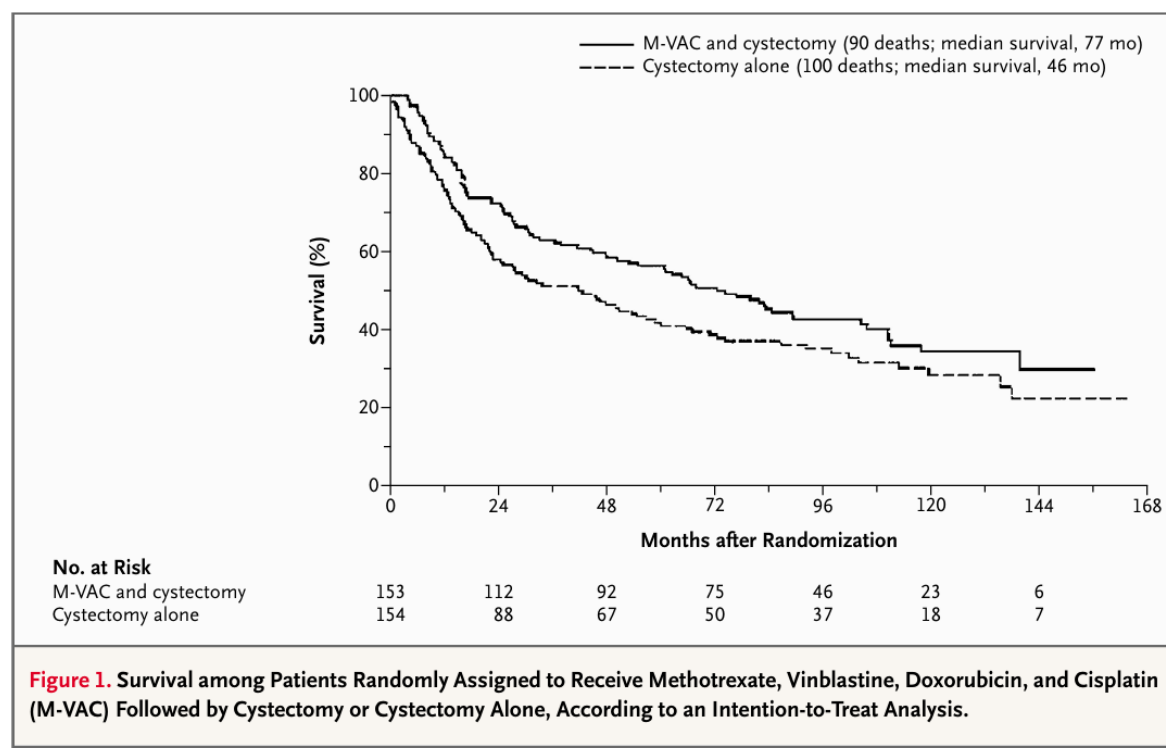
Learning Objectives

By the end of this session, participants should be able to:

- Review contemporary evidence supporting bladder-preserving approaches in MIBC.
- Identify optimal candidates for trimodality therapy.
- Discuss emerging biomarkers and response-adapted strategies.
- Examine how immunotherapy and novel systemic therapies may expand curative bladder preservation.

Muscle invasive bladder cancer is a systemic disease

SWOG 8710

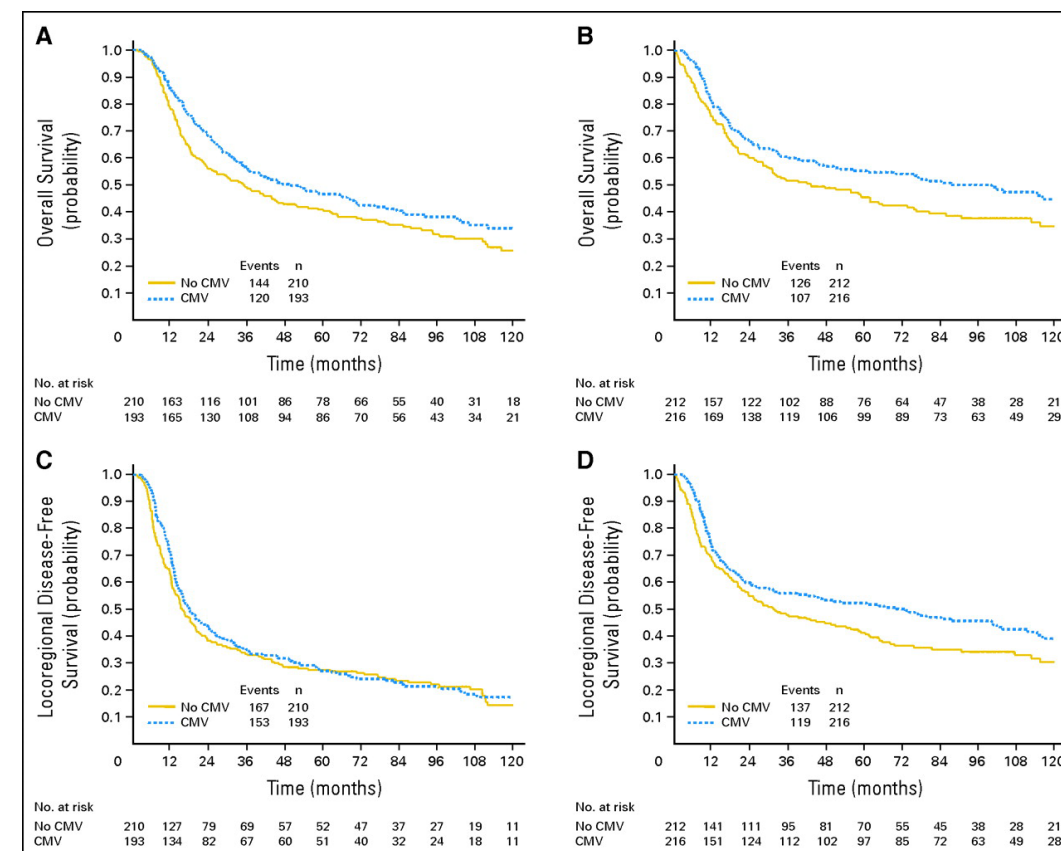


Cisplatin-based NAC was associated with:

- approximately **5% absolute overall survival benefit at 5 years**
- approximately **14% relative reduction in risk of death**

Grossman et al. N Engl J Med 2003;349:859-66.

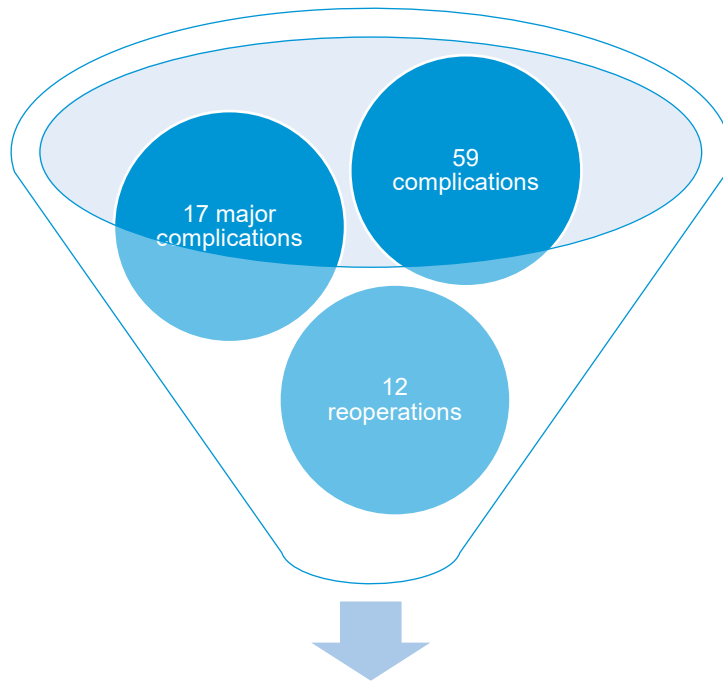
BA06-30894



BA06 30894 International Phase III Trial Assessing Neoadjuvant Cisplatin, Methotrexate, and Vinblastine Chemotherapy for Muscle-Invasive Bladder Cancer: Long-Term Results of the BA06 30894 Trial. *J Clin Oncol* 29, 2171-2177(2011).
 DOI: [10.1200/JCO.2010.32.3139](https://doi.org/10.1200/JCO.2010.32.3139)

Radical cystectomy remains morbid

100 radical cystectomy patients



5 die within 90 days

Most Common Complications

Gastrointestinal	29%
Infectious	26%
Genitourinary	16%
Wound-related	13%
Cardiac	6%

Chemoradiation as a viable bladder sparing approach

BC 2001 Trial

Phase III randomized trial (n=360)

- RT alone vs RT + concurrent 5-FU/Mitomycin-C
- Included T2-T4a N0 MIBC patients
- Neoadjuvant chemotherapy permitted but not required

Locoregional disease-free survival

- 67% vs 54% at 2 years
- HR 0.68 (p=0.03)

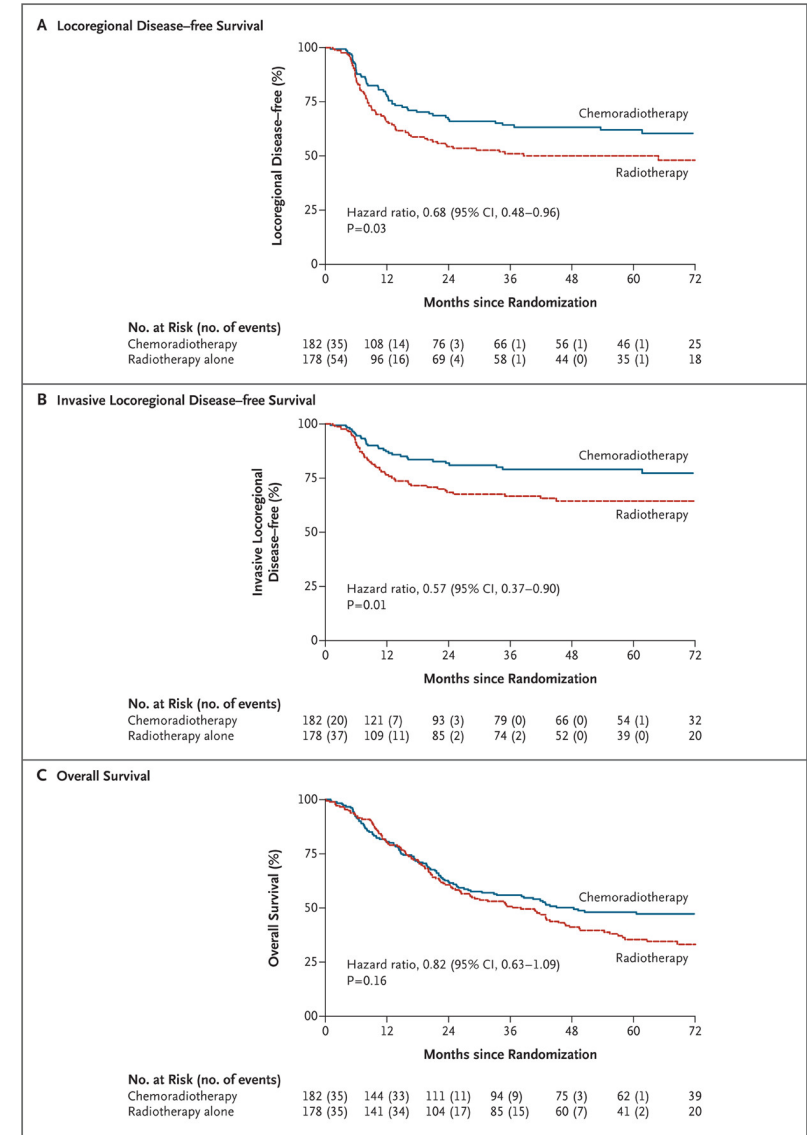
Invasive Locoregional Relapse

- 18% vs 32%
- HR 0.57 (p=0.01)

Survival

- 5-year OS: 48% vs 35%
- HR 0.82 (p=0.16)

James ND, Hussain SA, Hall E, et al. **Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer.** *New England Journal of Medicine.* 2012;366(16):1477–1488. doi:10.1056/NEJMoa1106106.



Evolution of bladder sparing treatment

RTOG commissioned a series of phase II trials designed to refine TMT strategies

RTOG enrolled 468 patients across these protocols from 1988 - 2007

MGH separately published their series of 475 patients treated with TMT from 1986 – 2013

“[T]his treatment approach results in low rates of invasive tumor recurrence (10-year invasive LF, 14%) and high long-term DSS (5- and 10-year DSS, 71% and 65%, respectively) and OS (5- and 10-year OS, 57% and 36%, respectively), with 80% of patients retaining an intact bladder at 5 years....

[T]he 5- and 10-year OS and DSS rates in contemporary RC series of clinically staged patients with T2-4a MIBC are comparable to those seen in this study and other bladder preserving studies.”

Table 1 – Protocol design and treatment

Protocol	Neoadjuvant chemotherapy	Induction	Response	Consolidation or cystectomy	Maximum RT dose to tumor (Gy)	Adjuvant chemotherapy	Pts., n (%)
MGH 180	MCV 2 cycles	CP + QD RT	CR	CP + RT	64.8	None	52 (11)
MGH 880, RTOG 8903 Arm 1	MCV 2 cycles	CP + QD RT	IR CR	Cystectomy CP + RT	64.8	None	56 (12)
MGH 880, RTOG 8903 Arm 2	None	CP + QD RT	IR CR	Cystectomy CP + RT	64.8	None	50 (11)
MGH 930A	None	CP + 5-FU + BID RT	IR CR	Cystectomy CP + 5-FU + BID RT	64.8	MCV 3 cycles	21 (4.4)
RTOG 9506	None	CP + 5-FU + BID RT	IR CR	Cystectomy CP + 5-FU + BID RT	44	None	15 (3.2)
RTOG 9706	None	CP + BID RT	IR CR	Cystectomy CP + BID RT	64.8	MCV 3 cycles	23 (4.8)
RTOG 9906	None	CP + pacl + BID RT	IR CR	Cystectomy CP + Pacl + BID RT	64.3	CP + gem 4 cycles	44 (9.3)
RTOG 0233 Arm 1	None	CP + 5-FU + BID RT	IR CR	Cystectomy CP + 5-FU + BID RT	64.3	CP + Pacl + gem 4 cycles	28 (5.9)
RTOG 0233 Arm 2	None	CP + Pacl + BID RT	IR CR	Cystectomy CP + Pacl + BID RT	64.3	CP + Pacl + gem 4 cycles	33 (6.9)
RTOG 0524 Group 2	None	Pacl + QD RT	CR	CP + RT	64.8	None	3 (0.6)
RTOG 0712 Arm 1	None	CP + 5-FU + BID RT	IR CR	Cystectomy CP + 5-FU + BID RT	64.3	CP + gem 4 cycles	18 (3.8)
RTOG 0712 Arm 2	None	Gem + QD RT	IR CR	Cystectomy Gem + RT	64	CP + gem 4 cycles	14 (2.9)
Per protocol	Varied ^a	Varied ^b	IR CR	Cystectomy Varied ^b	64–66	Varied ^c	118 (25)

BID = twice daily; CP = cisplatin; CR = complete response; Gem = gemcitabine; IR = incomplete response; MCV = methotrexate, cisplatin, vinblastine; MGH = Massachusetts General Hospital; Pacl = paclitaxel; Pts. = patients; QD = once daily; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group; 5-FU = 5-fluorouracil.

^a Ten patients received two cycles of MCV.

^b Thirty-seven patients received concurrent cisplatin; 34 patients received concurrent paclitaxel; 25 patients received concurrent cisplatin/5-FU; 16 patients received concurrent cisplatin/paclitaxel; four patients received concurrent 5- fluorouracil/mitomycin-C; one patients received concurrent gemcitabine/cisplatin; and one patient received concurrent carboplatin.

^c 34 patients received adjuvant chemotherapy.

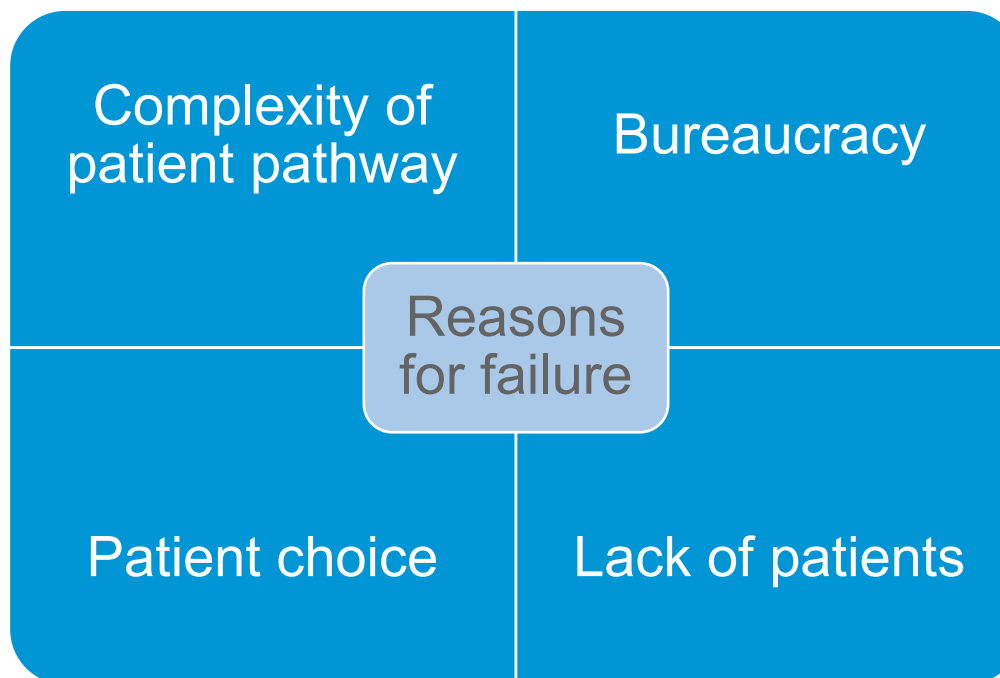
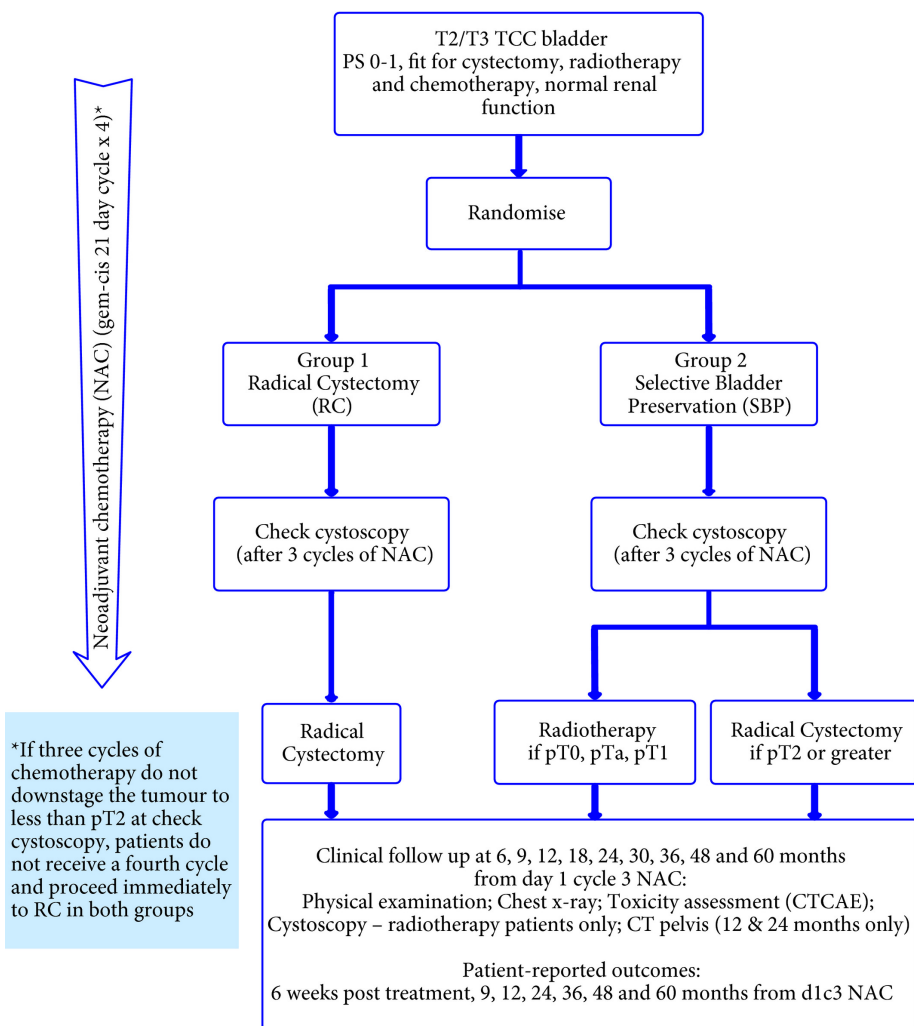
Mak RH, Hunt D, Shipley WU, et al. Bladder preservation in muscle-invasive bladder cancer: long-term outcomes of RTOG 89-03, 95-06, 97-06, 99-06, and 02-33. *Journal of Clinical Oncology*. 2014;32(34):3801-3809.

Giactalone NJ, Shipley WU, Clayman RH, et al. Long-term outcomes after bladder-preserving tri-modality therapy for patients with muscle-invasive bladder cancer: an updated analysis of the Massachusetts General Hospital experience. *European Urology*. 2017;71(6):952-960.

SPARE *attempted* to directly compare TMT to RC

Study enrolled 45 patients over 30 months

Closed to accrual by the independent trial steering committee 01/26/2010



Propensity matched analysis suggests for well selected patients, TMT is equivalent to NAC + RC

722 contemporary patients across 3 institutions

- 440 radical cystectomy
- 282 TMT patients
- Matched on age, sex, CIS, T-stage, hydronephrosis, ECOG PS, BMI, peri-treatment chemotherapy and smoking

Inclusion criteria

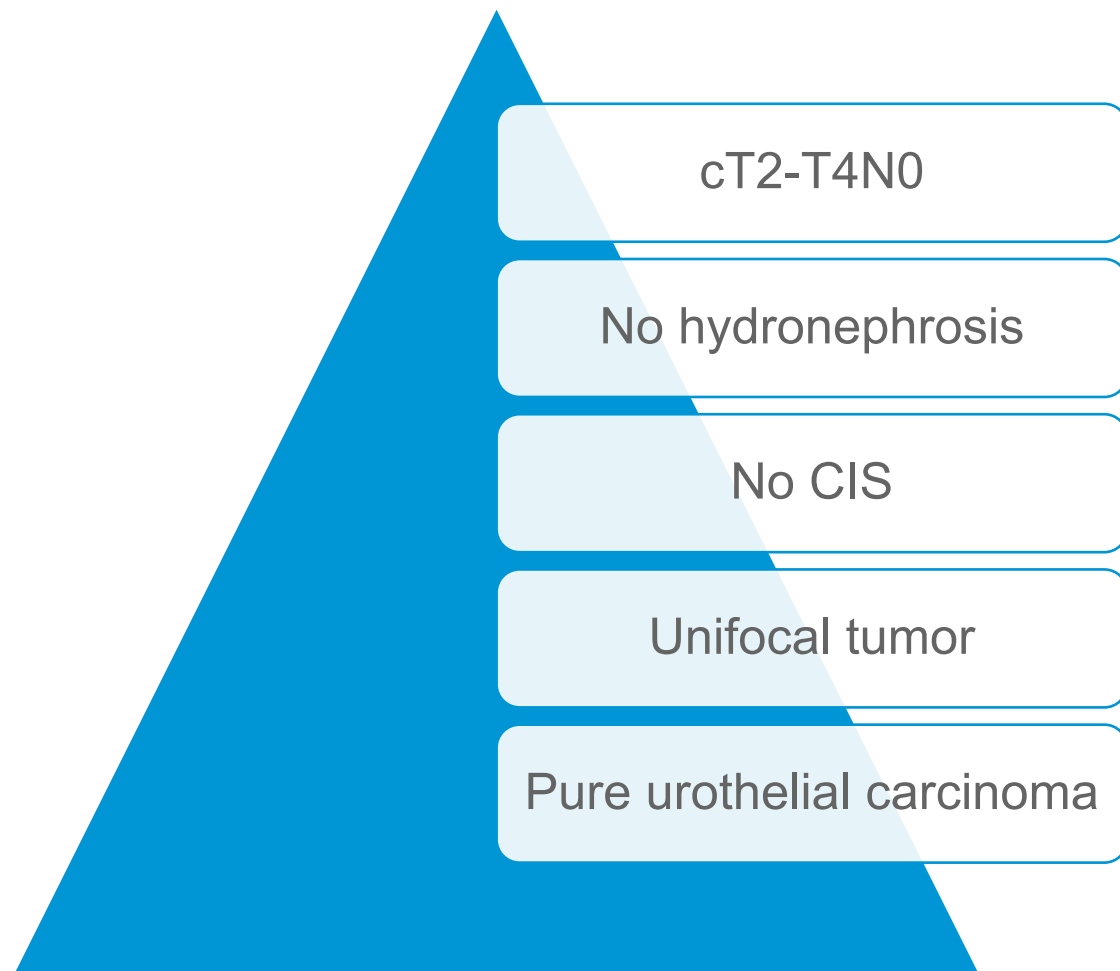
- cT2-T4N0
- <7cm
- Solitary tumor
- No bilateral hydronephrosis
- Adequate bladder function
- No extensive or multifocal CIS

Endpoint	RC	TMT
Metastasis-free survival	74%	75%
Cancer-specific survival	81-83%	84-85%
Disease-free survival	73-76%	74-76%

Salvage cystectomy: 13%

90-day mortality: RC 2.5% TMT 0%

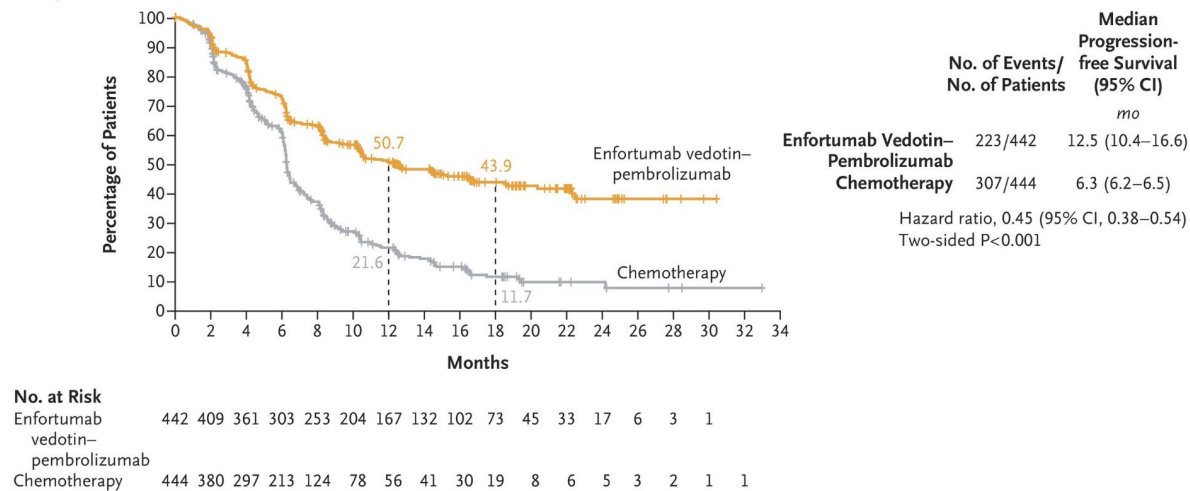
Who are 'well selected' patients for TMT



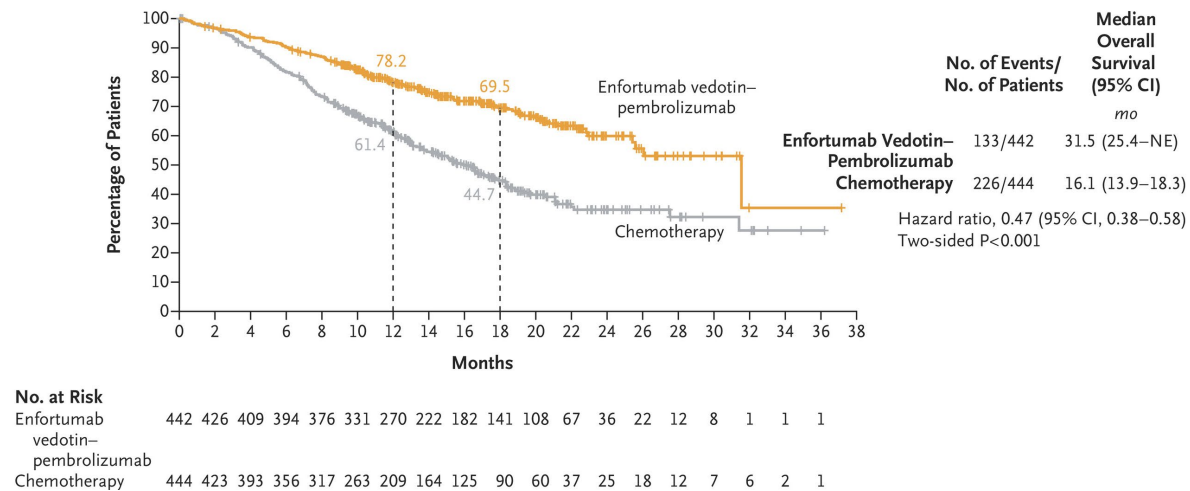


EV + P created a sea change in bladder cancer care

A Progression-free Survival



A Overall Survival



Subgroup Analysis

Subgroup	Enfortumab Vedotin-Pembrolizumab mo (no. of events/no. of patients)	Chemotherapy mo (no. of events/no. of patients)	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	12.5 (223/442)	6.3 (307/444)	0.45 (0.38–0.54)
Age			
<65 yr	12.7 (75/144)	6.4 (88/135)	0.45 (0.32–0.62)
≥65 yr	12.0 (148/298)	6.2 (219/309)	0.45 (0.36–0.56)
Race			
White	10.4 (168/308)	6.2 (207/290)	0.48 (0.39–0.60)
Other	22.3 (55/134)	6.5 (100/154)	0.39 (0.27–0.55)
Geographic region			
North America	12.0 (58/103)	6.3 (55/85)	0.56 (0.38–0.82)
Europe	10.4 (94/172)	6.3 (144/197)	0.50 (0.38–0.66)
Rest of the world	NE (71/167)	6.2 (108/162)	0.35 (0.26–0.48)
Sex			
Female	10.4 (55/98)	6.1 (74/108)	0.49 (0.34–0.71)
Male	14.6 (168/344)	6.3 (233/336)	0.44 (0.36–0.54)
ECOG performance-status score			
0	22.3 (93/223)	6.7 (146/215)	0.36 (0.28–0.48)
1 or 2	9.3 (130/219)	6.1 (161/227)	0.53 (0.42–0.68)
Primary site of origin of disease			
Upper tract	12.7 (69/135)	6.2 (70/104)	0.50 (0.35–0.71)
Lower tract	12.5 (152/305)	6.3 (236/339)	0.44 (0.35–0.54)
Liver metastases			
Present	8.2 (66/100)	6.0 (78/99)	0.53 (0.38–0.76)
Absent	16.4 (157/342)	6.4 (229/345)	0.43 (0.35–0.52)
PD-L1 expression			
Low (CPS <10)	10.5 (105/184)	6.3 (127/185)	0.50 (0.38–0.65)
High (CPS ≥10)	18.5 (116/254)	6.2 (176/254)	0.42 (0.33–0.53)
Cisplatin eligibility status			
Eligible	14.6 (117/244)	6.5 (149/234)	0.48 (0.38–0.62)
Ineligible	10.6 (106/198)	6.1 (158/210)	0.43 (0.33–0.55)
Site of metastasis			
Visceral site	10.4 (176/318)	6.2 (238/318)	0.45 (0.37–0.55)
Lymph node only	NE (38/103)	8.3 (55/104)	0.40 (0.26–0.62)
Renal function			
Normal	18.7 (38/84)	6.7 (61/95)	0.46 (0.30–0.71)
Mild impairment	12.7 (79/165)	6.3 (114/162)	0.46 (0.34–0.62)
Moderate or severe impairment	10.5 (106/193)	6.2 (132/187)	0.47 (0.36–0.61)

ctDNA MRD assays are being rapidly adopted in clinical practice



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Redefining curative intent in bladder cancer

**REMOVE
THE BLADDER**



**TARGETED
CHEMOIMMUNOTHERAPY
WITH SURGERY**



**SYSTEMIC
AND
LOCAL CONTROL**



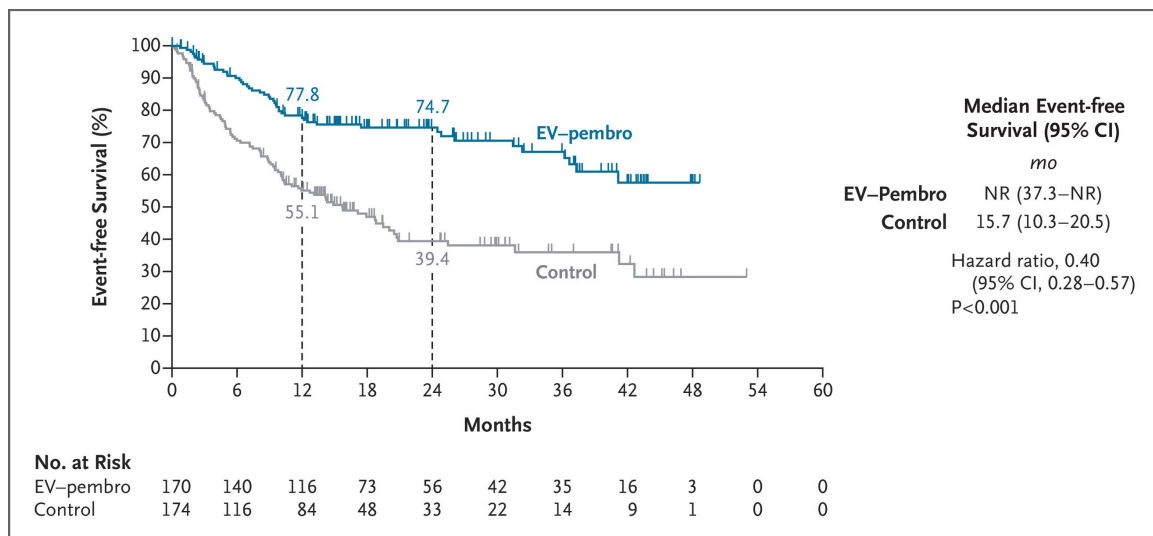
**MOLECULAR
REMISSION
ADAPTED THERAPY**



imafluo.com

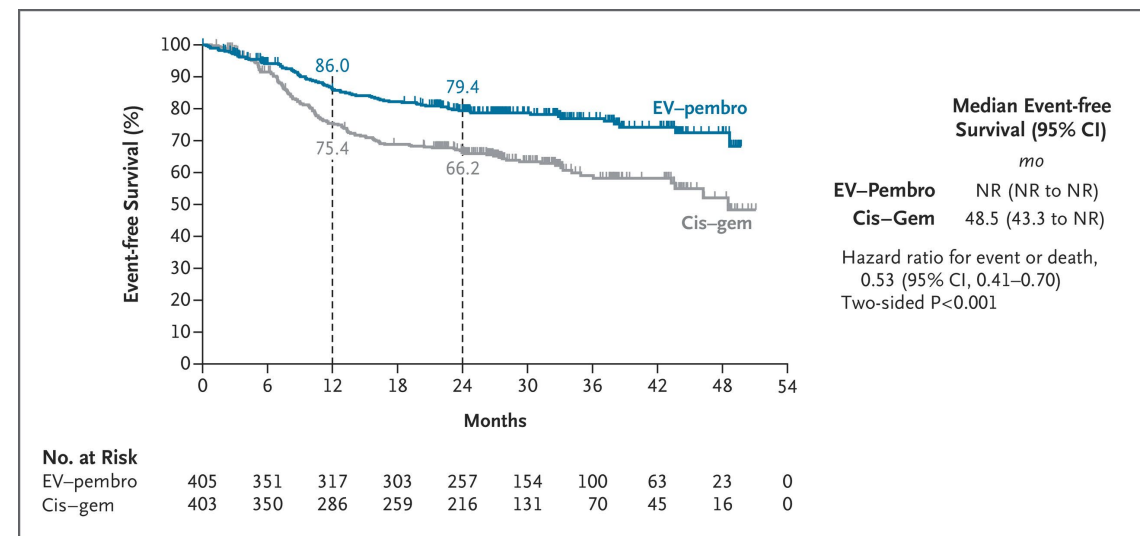
Perioperative EV + P improves surgical outcomes

Cisplatin ineligible



pCR 57.1% vs 8.6%

Cisplatin eligible



pCR 55.8% vs 32.5%

How do we incorporate EV + P into bladder sparing treatment

BRIGHT trial aims to evaluate radiation in place of surgery for patients with good response to NAC

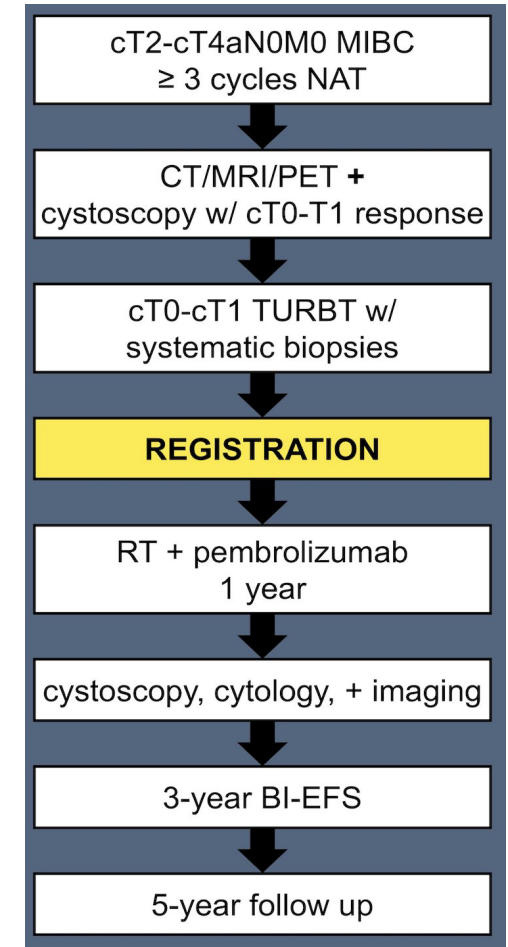
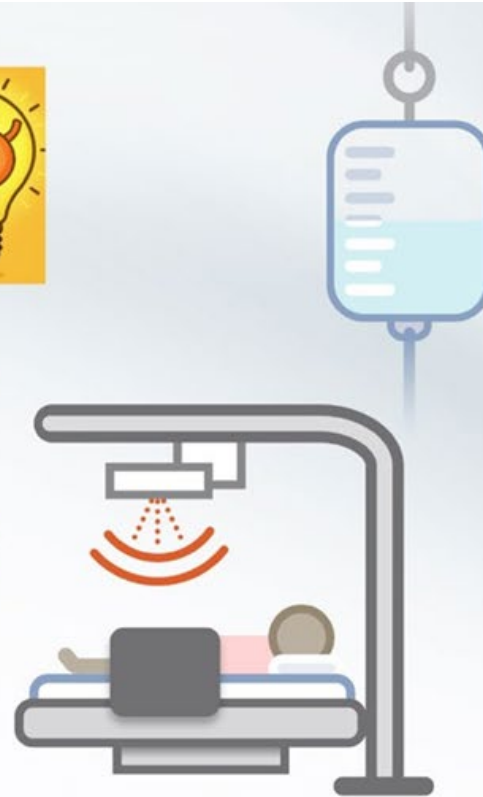


Clinical Trial S2427 (BRIGHT)



Can pembrolizumab plus radiation help people with muscle invasive bladder cancer keep their bladder?

Call 1-800-4-CANCER.
Or visit swog.org/S2427.



Open at Ochsner!

What about radiation for patients with more locally advanced disease?

Study #2024-0071

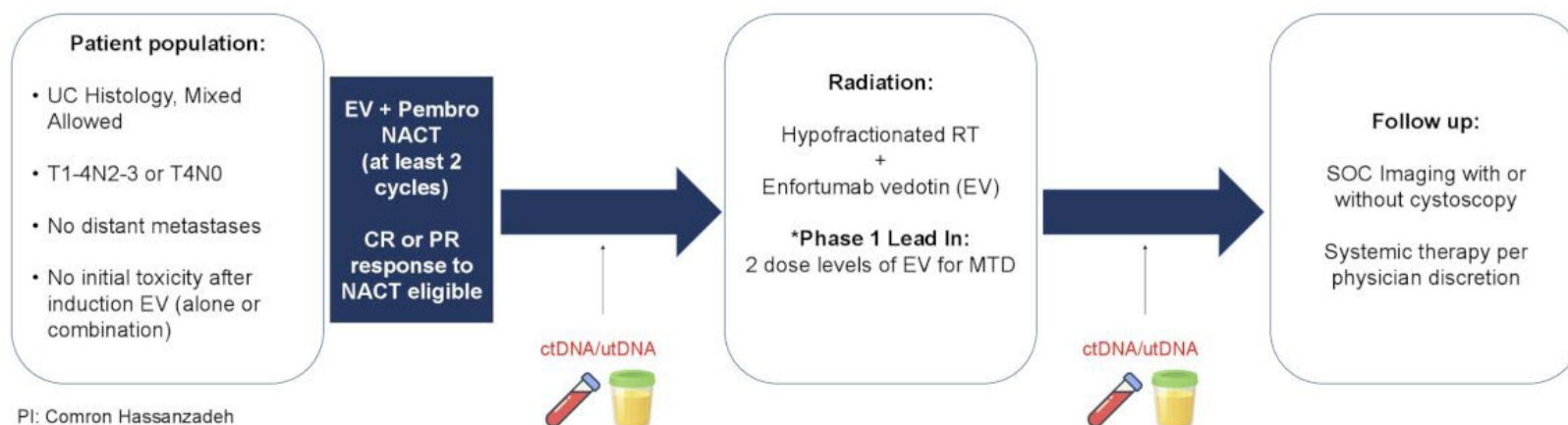
Enfortumab Vedotin with radiation for locally Advanced Bladder Cancer (CONSOLIDATE)

MD Anderson Study Status

Enrolling

Treatment Agent

Enfortumab Vedotin



Soon to be open at Ochsner!

ctDNA MRD assays are prognostic after cystectomy

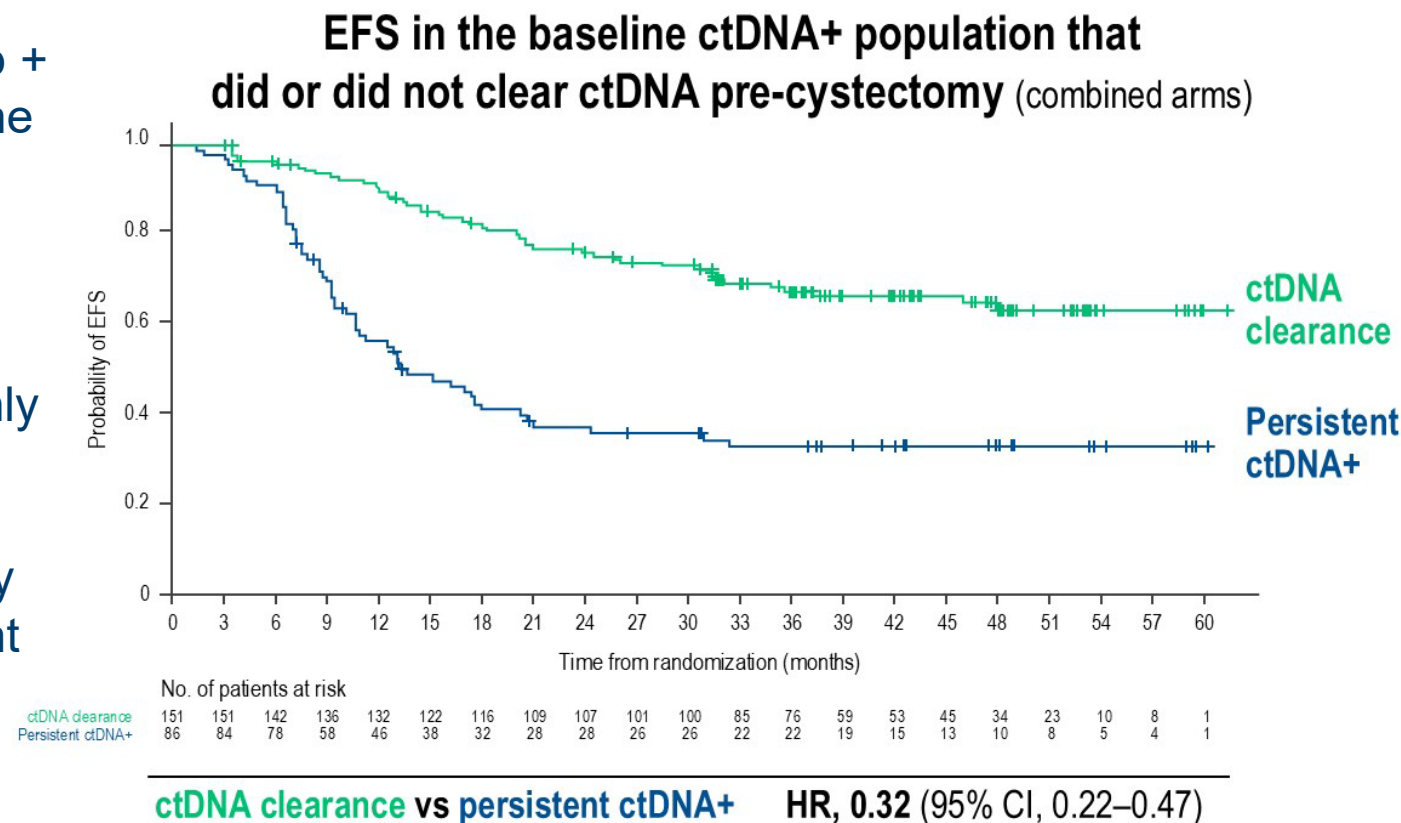
NIAGARA Trial

Phase III trial of perioperative durvalumab + NAC/cystectomy vs NAC/cystectomy alone

Perioperative durvalumab improved EFS and OS

Tumor informed MRD assays proved highly prognostic

Patients who cleared ctDNA had markedly improved outcome regardless of treatment arm



Do patients with negative ctDNA MRD assay need adjuvant therapy?

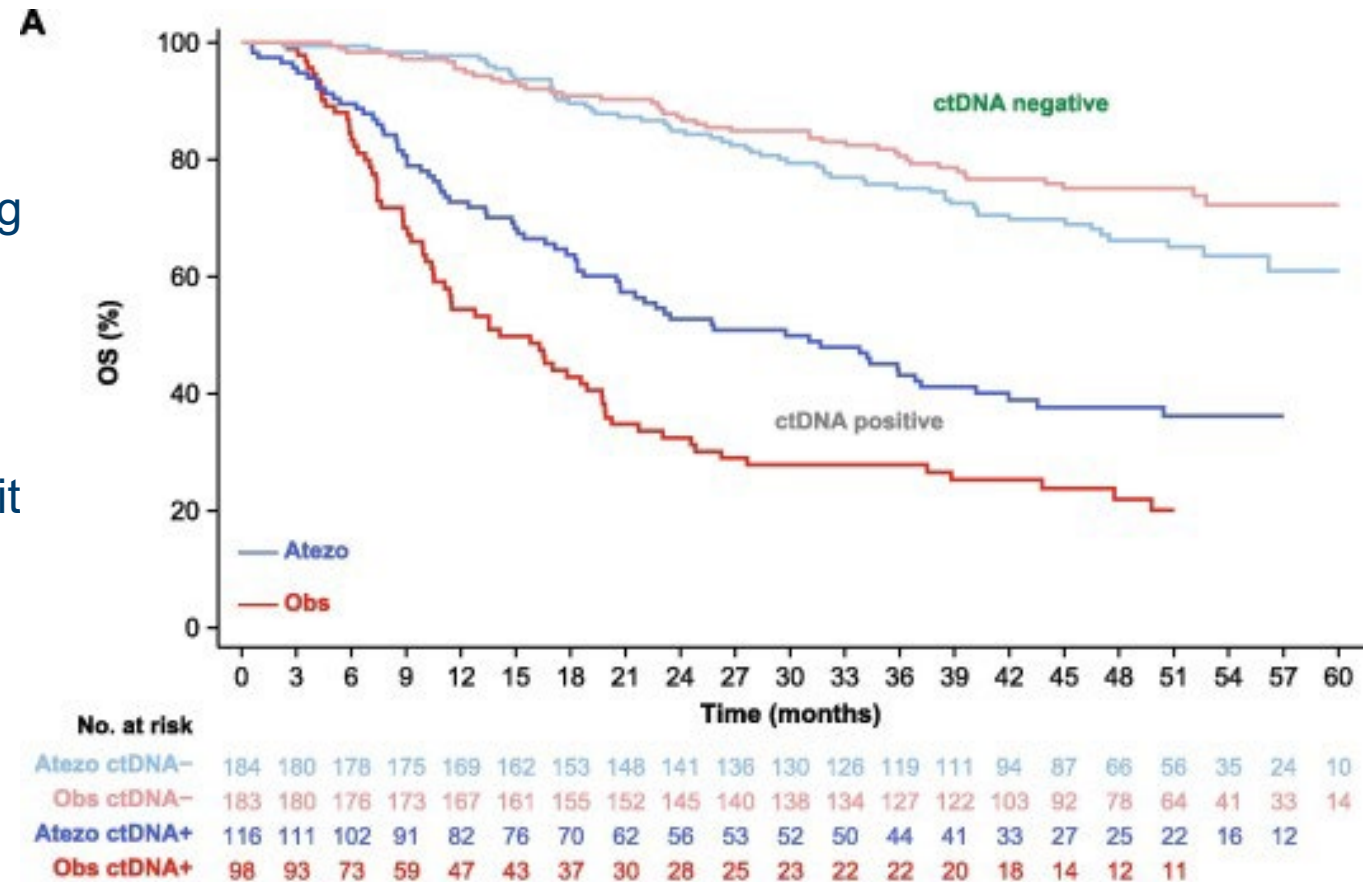
MRD assay may help select patients for adjuvant therapy

IMvigor 010

Phase III trial of adjuvant atezolizumab in unselected high-risk bladder cancer following cystectomy ([y]pT2/N+)

Did not achieve primary clinical outcome

Post-hoc analyses showed significant benefit of atezlizumab ctDNA + patients; with no benefit in ctDNA – patients



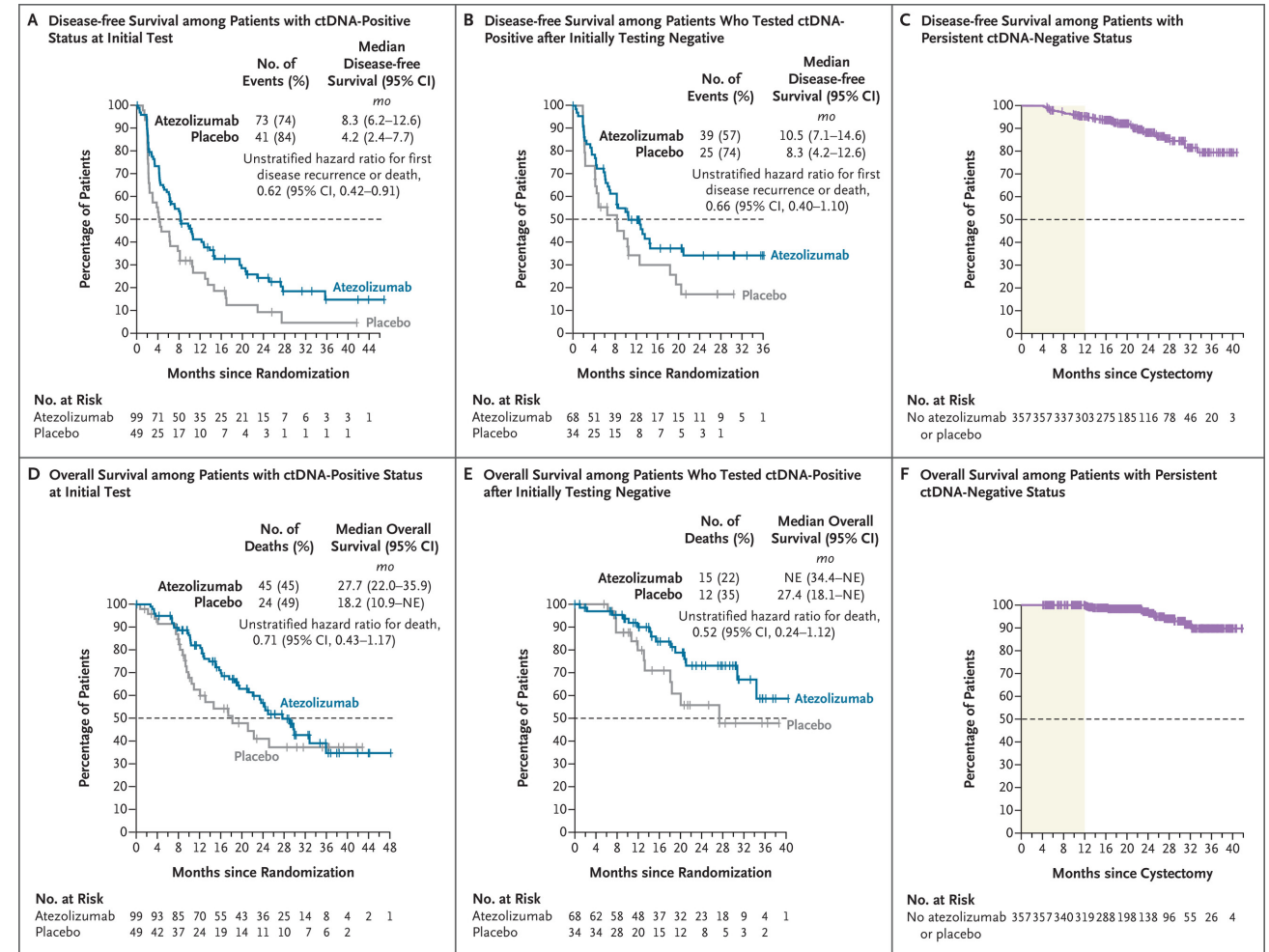
MRD assay may help select patients for adjuvant therapy

IMvigor 011

Phase III trial of adjuvant atezolizumab vs placebo in patients testing positive for ctDNA following radical cystectomy

Atezo improved mDFS to 9.9 months from compared to 4.8 months

Durabale DFS and OS in patients with persistent negative ctDNA testing



Can ctDNA status guide adjuvant therapy?

MODERN Trial

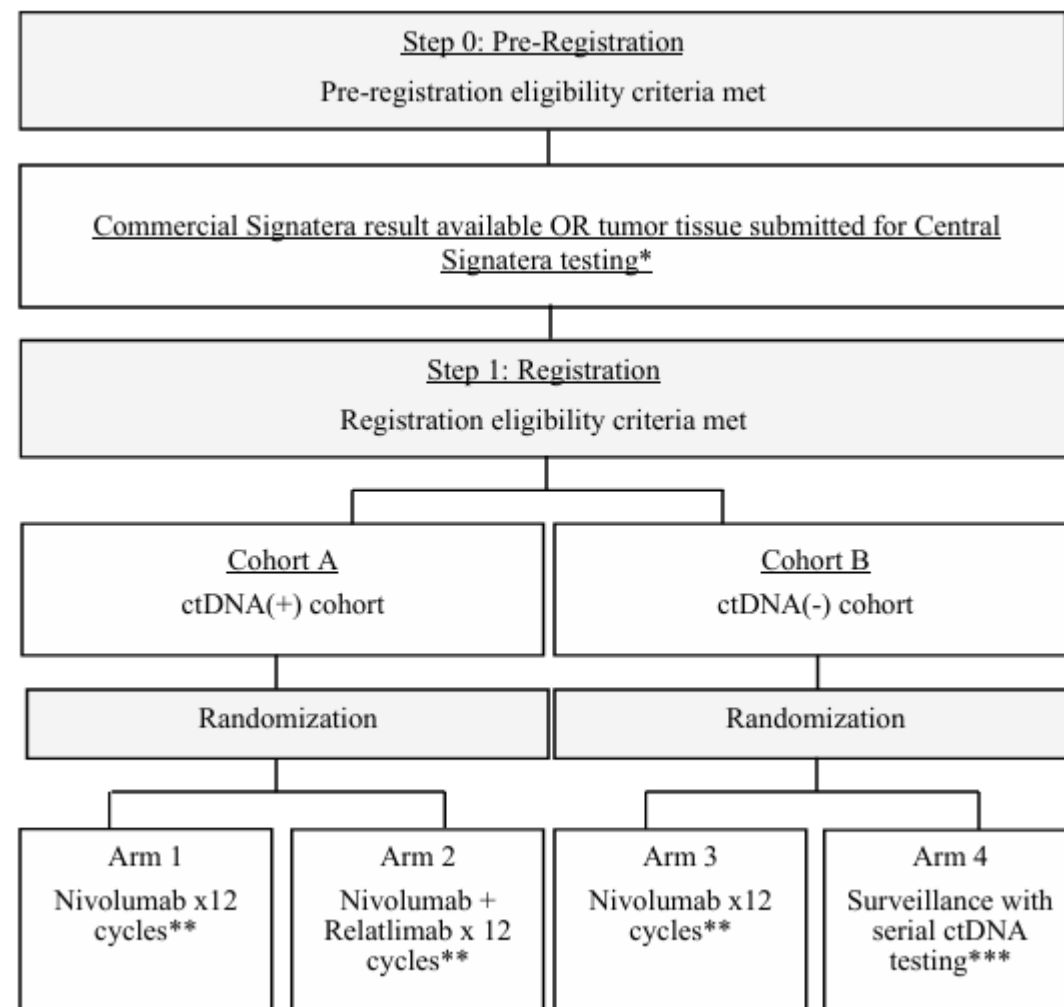
Phase III trial of ctDNA MRD adapted adjuvant therapy

High risk (ypT2/N+ or pT3/N+) urothelial carcinoma after cystectomy or radical nephroureterectomy

ctDNA MRD + patients randomize to nivolumab SOC vs intensified relatlimab/nivo

ctDNA MRD + patients randomize to nivolumab SOC vs de-escalated observation

Open at Ochsner!



ctDNA MRD assays are highly prognostic in metastatic disease

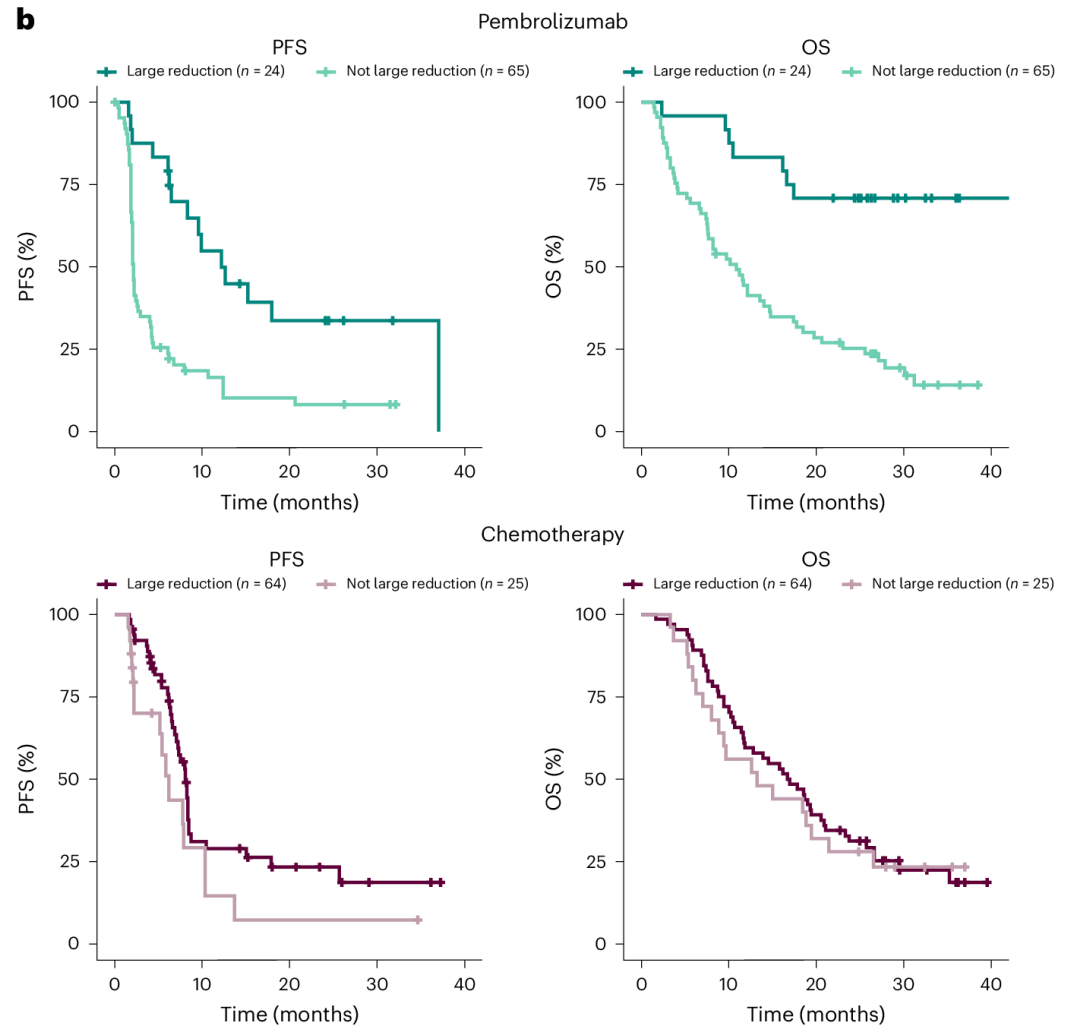
KEYNOTE 361

Phase III trial of pembrolizumab with or without platinum chemotherapy vs chemotherapy alone in 1L treatment of mUCC

Did not achieve primary clinical outcome

Post-hoc analyses showed ctDNA was strongly prognostic of outcome, particularly in patients treated with pembrolizumab

Patients with large reduction in ctDNA treated with pembro had long and durable OS

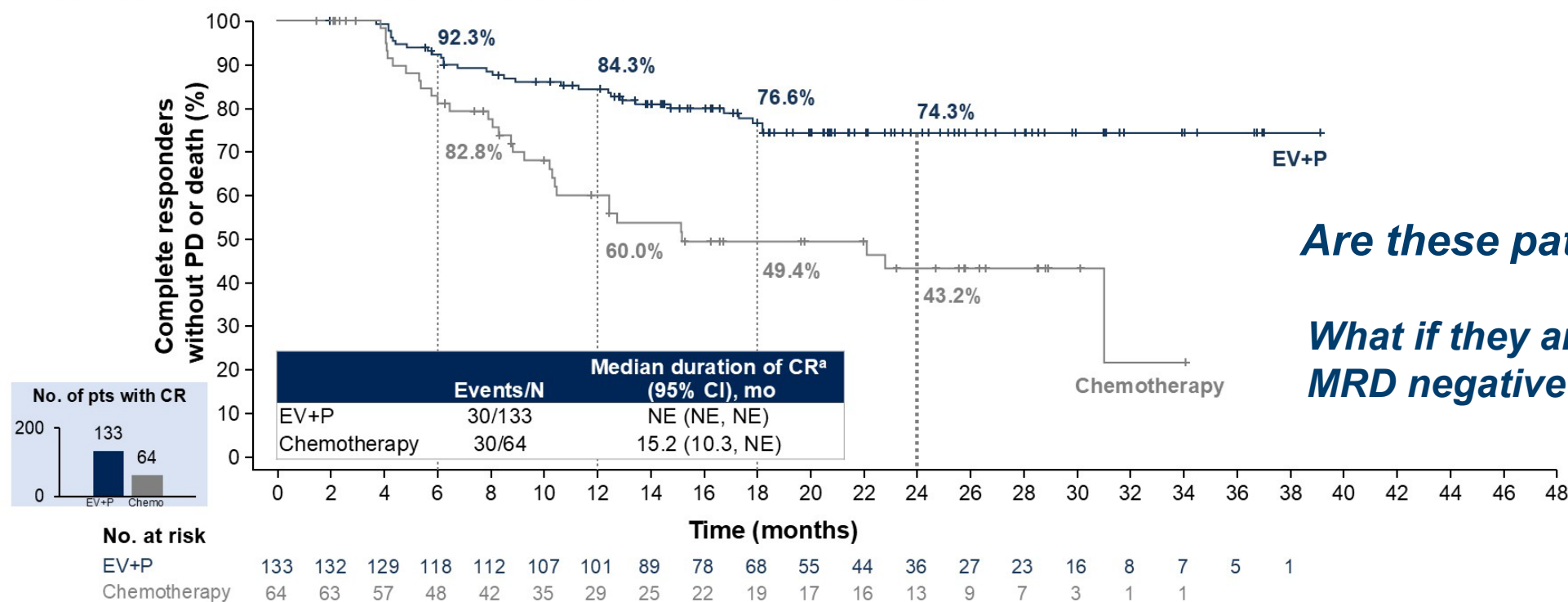


EV + P can induce durable responses in mBC

10

Duration of CR: Patients with best response of CR^{1,2}

Probability of maintained CR at 2 years was 74.3% with EV+P



- 60.2% of patients with CR in the EV+P arm and 64.1% in the chemotherapy arm were cisplatin eligible

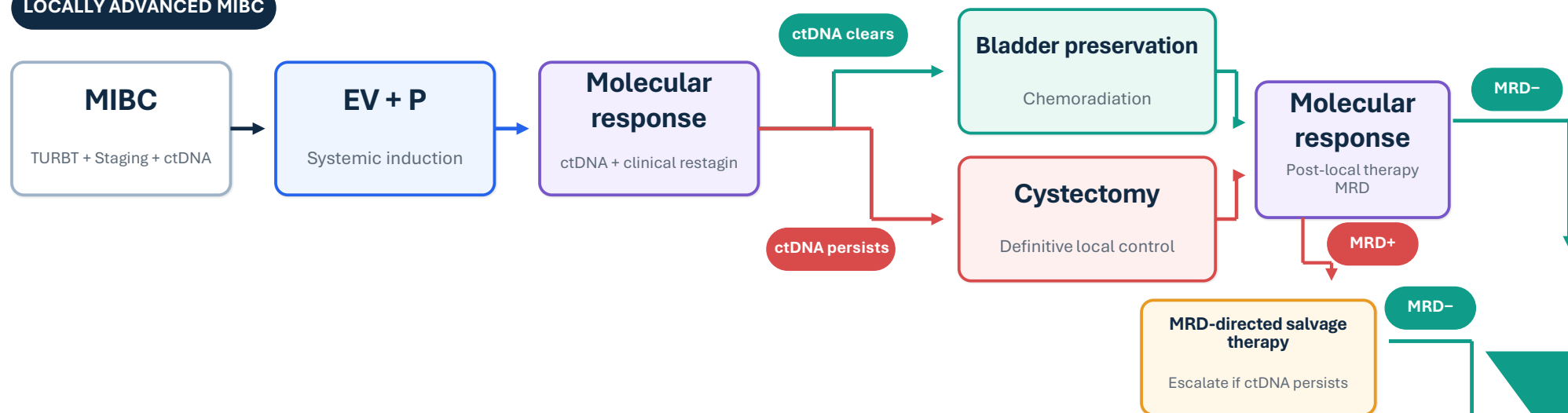
Data cutoff: August 8, 2024. NCT04223856. EV, enfortumab vedotin; P, pembrolizumab; pts, patients. ^aDuration of CR was calculated from the time of CR being achieved (not from the time of PR).

1. Powles T, et al. ASCO GU 2025 (Abstract 664). 2. Powles T, et al. Annals Oncol, In press.

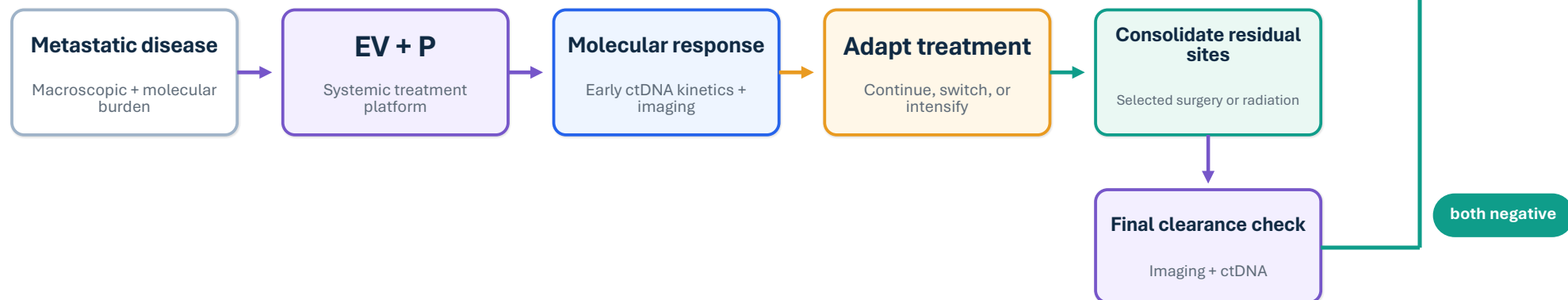


Redefining curative intent – a future state

LOCALLY ADVANCED MIBC



RELAPSED / DE NOVO METASTATIC



Thanks!

