Bladder Cancer Management

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Objectives

- ✓ To identify the three general categories of urothelial tract tumors – NMIBC, MIBC, and metastatic – and how they differ
- ✓ To determine when neoadjuvant cisplatin-based combination chemotherapy is appropriate.
- ✓ To understand role of adjuvant therapy in treatment of MIBC.
- ✓ To understand the principles of bladder preservation therapy and patient selection.
- ✓ To understand the current treatment paradigm for advanced and metastatic UC.

Outline

- Epidemiology
- Pathology
- Diagnosis and staging
- Therapy by stage:
  - NMIBC,
  - MIBC,
  - Metastatic

Outline

- **Epidemiology**
- Pathology
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  - NMIBC,
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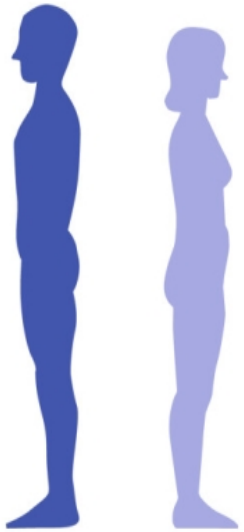
Estimated New Cases

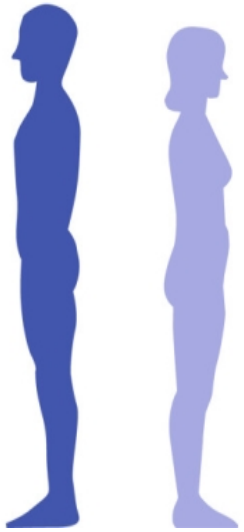
Male			Female		
Prostate	313,780	30%	Breast	316,950	32%
Lung & bronchus	110,680	11%	Lung & bronchus	115,970	12%
Colon & rectum	82,460	8%	Colon & rectum	71,810	7%
Urinary bladder	65,080	6%	Uterine corpus	69,120	7%
Melanoma of the skin	60,550	6%	Melanoma of the skin	44,410	4%
Kidney & renal pelvis	52,410	5%	Non-Hodgkin lymphoma	35,210	4%
Non-Hodgkin lymphoma	45,140	4%	Pancreas	32,490	3%
Oral cavity & pharynx	42,500	4%	Thyroid	31,350	3%
Leukemia	38,720	4%	Kidney & renal pelvis	28,570	3%
Pancreas	34,950	3%	Leukemia	28,170	3%
All sites	**1,053,250**		**All sites**	**988,660**	



19,790 cases of bladder cancer in biologic women

Estimated Deaths

Male			Female		
Lung & bronchus	64,190	20%	Lung & bronchus	60,540	21%
Prostate	35,770	11%	Breast	42,170	14%
Colon & rectum	28,900	9%	Pancreas	24,930	8%
Pancreas	27,050	8%	Colon & rectum	24,000	8%
Liver & intrahepatic bile duct	19,250	6%	Uterine corpus	13,860	5%
Leukemia	13,500	4%	Ovary	12,730	4%
Esophagus	12,940	4%	Liver & intrahepatic bile duct	10,840	4%
Urinary bladder	12,640	4%	Leukemia	10,040	3%
Non-Hodgkin lymphoma	11,060	3%	Non-Hodgkin lymphoma	8,330	3%
Brain & other nervous system	10,170	3%	Brain & other nervous system	8,160	3%
All sites	**323,900**		**All sites**	**294,220**	



4,780 in cases of bladder cancer biologic women

CA A Cancer J Clinicians, Volume: 75, Issue: 1, Pages: 10-45, First published: 16 January 2025, DOI: (10.3322/caac.21871)

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Risk Factors

Reversible

- Smoking (accounts ½ all cases)
- Workplace exposure
  - Aromatic amines used in dye industry
  - Organic chemicals used in rubber, leather, textile, and paint products
  - Hair-dresser (hair dyes)
  - Truck drivers (diesel)
- Arsenic in drinking water

Irreversible

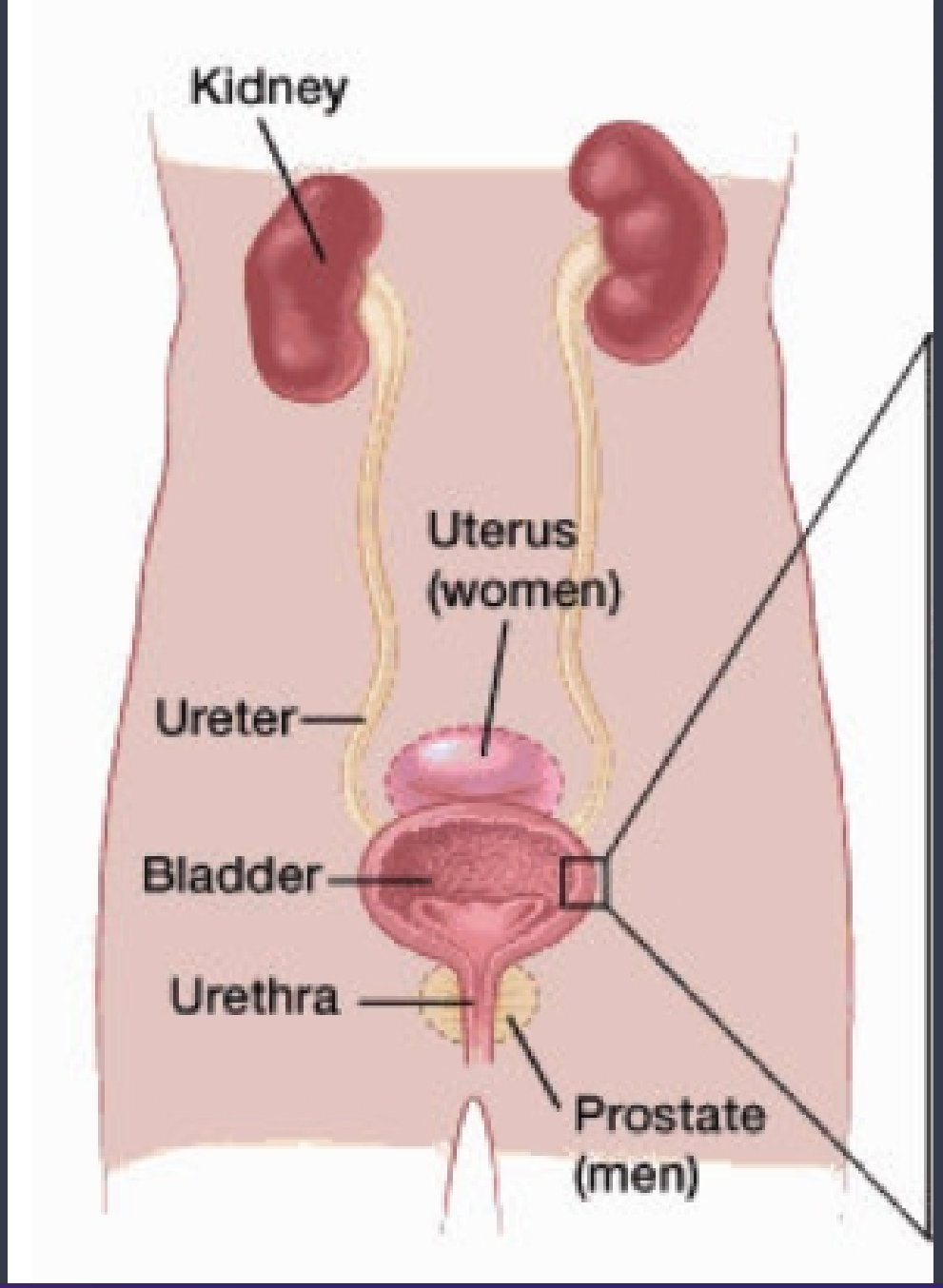
- Race and Ethnicity
- Age: 90% pts older than 55 yrs
- Biologic sex (M > F)
- Chronic bladder irritation and infections
- Genetics and family history (RB1 mutation; PTEN - Cowden disease; Lynch syndrome or HNPCC)
- Cyclophosphamide

Outline

- Epidemiology
- **Pathology**
- Diagnosis and staging
- Therapy by stage:
  - NMIBC,
  - MIBC,
  - Metastatic

Location & Pathology

- Bladder: 90% of tumors
- Upper tract urothelial cancer (UTUC): 5-7% renal pelvis (majority) and ureters
- Lower tract:
  - 92% urothelial carcinomas
  - 5% squamous cell
  - 2% adenocarcinomas (urachal)
  - 1% small cell carcinomas
- N Africa & Middle East with high prevalence of *S. haematobium,* up to 75% of tumors are pure squamous cell carcinomas.



Outline

- Epidemiology
- Pathology
- **Diagnosis and staging**
- Therapy by stage:
  - NMIBC,
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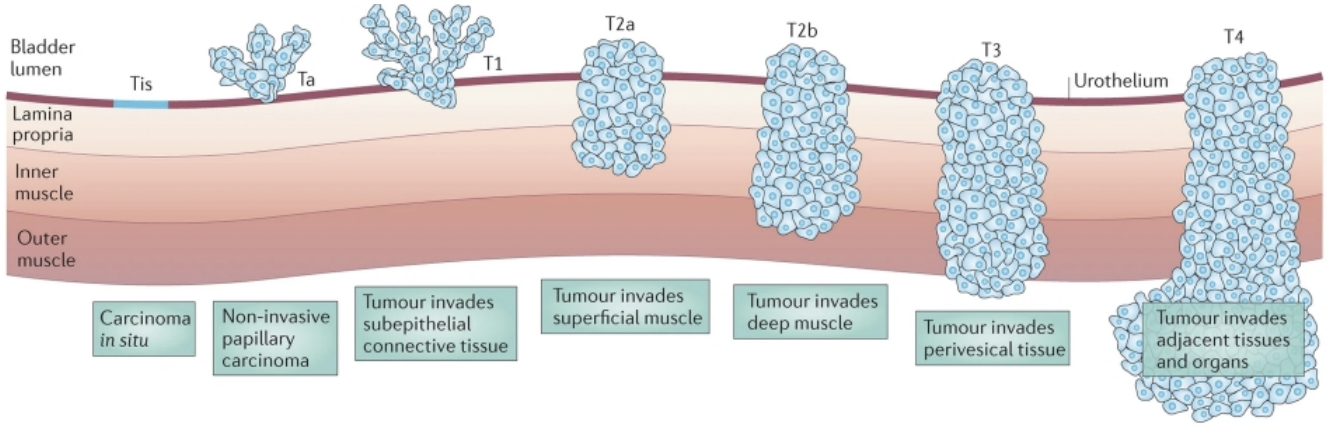
Diagnosis & Staging

- Hematuria!
- Irritative voiding symptoms in pts with RFs may be related to Tis or tumor
- Diagnosis is established by cystoscopy and biopsy
- **Key: Depth of invasion – treatment and prognosis implications**

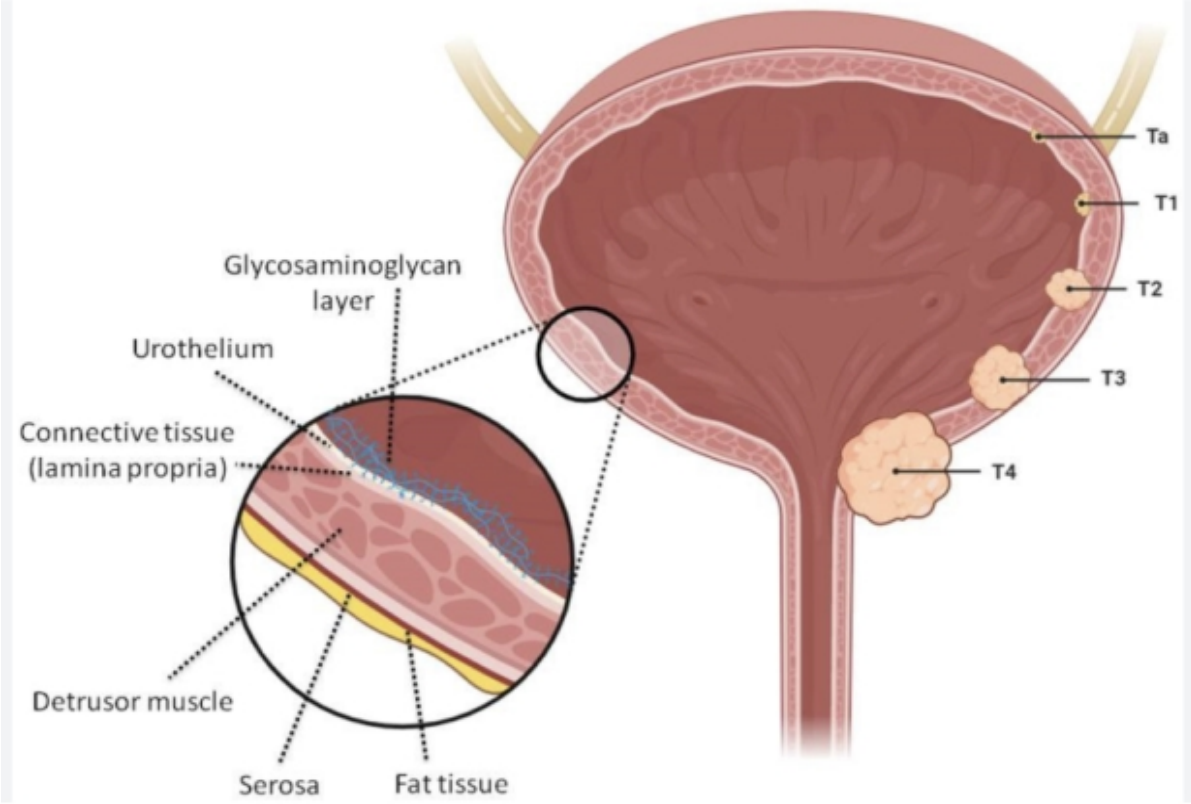
  - Ta, CIS, T1 → NMIBC (70% of cases)
  - ≥ T2 → Muscle invasive (MIBC)
  - Locally advanced/Metastatic



Challenge: depth of invasion on cystoscopy/biopsy only 50-60% correlated with cystectomy.

Diagnosis & Staging

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Urothelial carcinoma in situ: "flat tumor"
T1	Tumor invades lamina propria (subepithelial connective tissue)
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Extravesical tumor directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Extravesical tumor invades prostatic stroma, seminal vesicles, uterus, vagina
T4b	Extravesical tumor invades pelvic wall, abdominal wall



M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis
M1a	Distant metastasis limited to lymph nodes beyond the common iliacs
M1b	Non-lymph-node distant metastases

Diagnosis & Staging

***Table 2.* AJCC Prognostic Groups**

	T	N	M
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage IIIA	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
	T1-T4a	N1	M0

	T	N	M
Stage IIIB	T1-T4a	N2,N3	M0
Stage IVA	T4b	Any N	M0
	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

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  - **NMIBC,**
  - MIBC,
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NMIBC (superficial, ≤T1)

- ✓ **Ta (70%) – noninvasive papillary**
  - Usually, low-grade
  - Frequently recurs
  - Good prognosis
    - Only 6% will eventually die of bladder cancer
- ✓ **Cis (5%) – carcinoma in situ "flat tumor"**
  - Often **associated with invasive disease**
  - 60-80% develop bladder cancer
  - Only cancer for which in situ disease included in ACS case estimates b/c high likelihood of progression and recurrence
- ✓ **T1 (25%) – lamina propria invasion**
  - 50% associated with Cis
  - 50% recur at 1 year
  - 20-25% progress more invasive disease

NMIBC (superficial, ≤T1)

- Most common presentation (70-75%)
- Muscularis must be present in the specimen to call superficial disease
  - Repeat biopsy if no muscle in specimen and concern for potential invasive disease
- Primary management is resection via TURBT followed by intravesical therapy with BCG or chemotherapy
- Recurrence is very common, and surveillance cystoscopy is required
- Recurrent high-grade T1 disease associated with **40-50%** progression to T2 disease

NMIBC (superficial, ≤T1)

Pembrolizumab for BCG-unresponsive CIS or Ta/T1

- Keynote 057 open-label, single-arm Phase 2 study
- Cohort A: CIS w/ or w/o papillary tumors
- N=96
- Median f/u 36 months
- 3 mo CR: 41%
- 6 mo CR 31%
- 15 mo CR 20%
- Gr 3 TRAE: 13% (arthralgia and hyponatremia)
- No patients had progression to MIBC or metastatic disease while on study.

Mr. Smith is a 71-year-old man with a PMH remarkable for HTN, hypercholesterolemia, degenerative arthritis who presented with painless hematuria and dysuria. Cystoscopy revealed a 2 cm papillary mass on the lateral bladder wall. He underwent a which TURBT and mapping biopsies. Pathology showed high-grade urothelial carcinoma with invasion of the lamina propria. No CIS. No detrusor muscle was noted in the specimen. Imaging tests showed no evidence of metastatic disease. Laboratory test showed creatinine levels 1.0 and eGFR of 61. HBG 12.3 gr/dl. ECOG PS 0. **What do you do next?**

A. Obtain a FDG PET CT
B. Initiate induction treatment with BCG
C. Repeat TURBT
D. Consider enrollment in a clinical trial
E. Discuss early radical cystectomy

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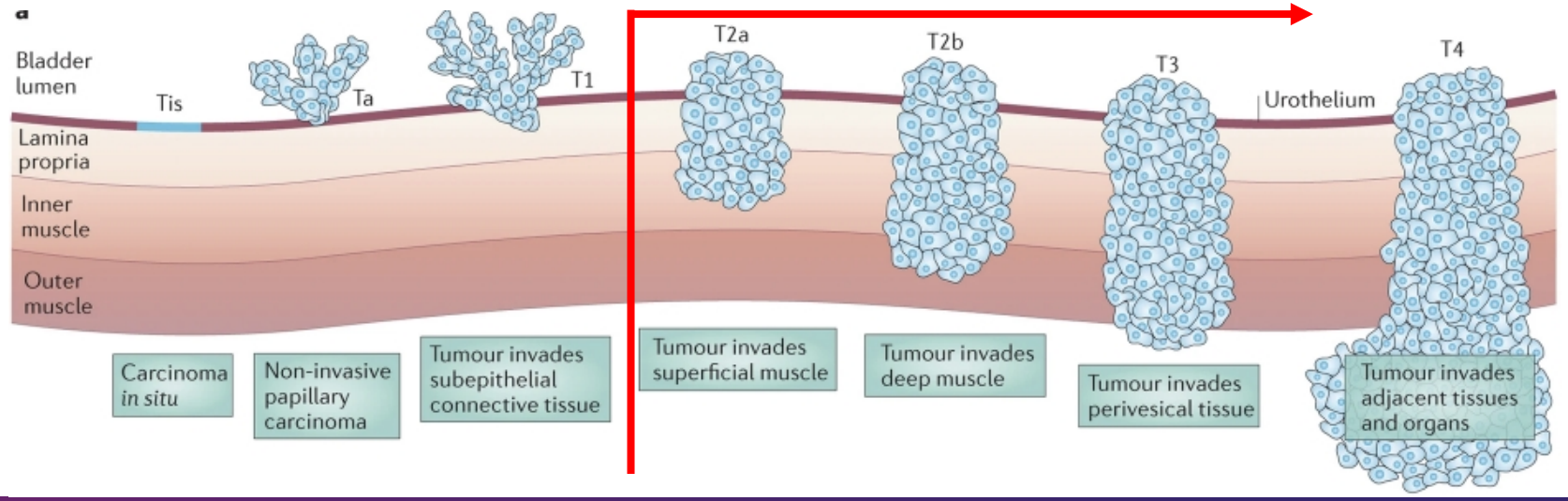
  - NMIBC,
  - **MIBC,**
  - Metastatic

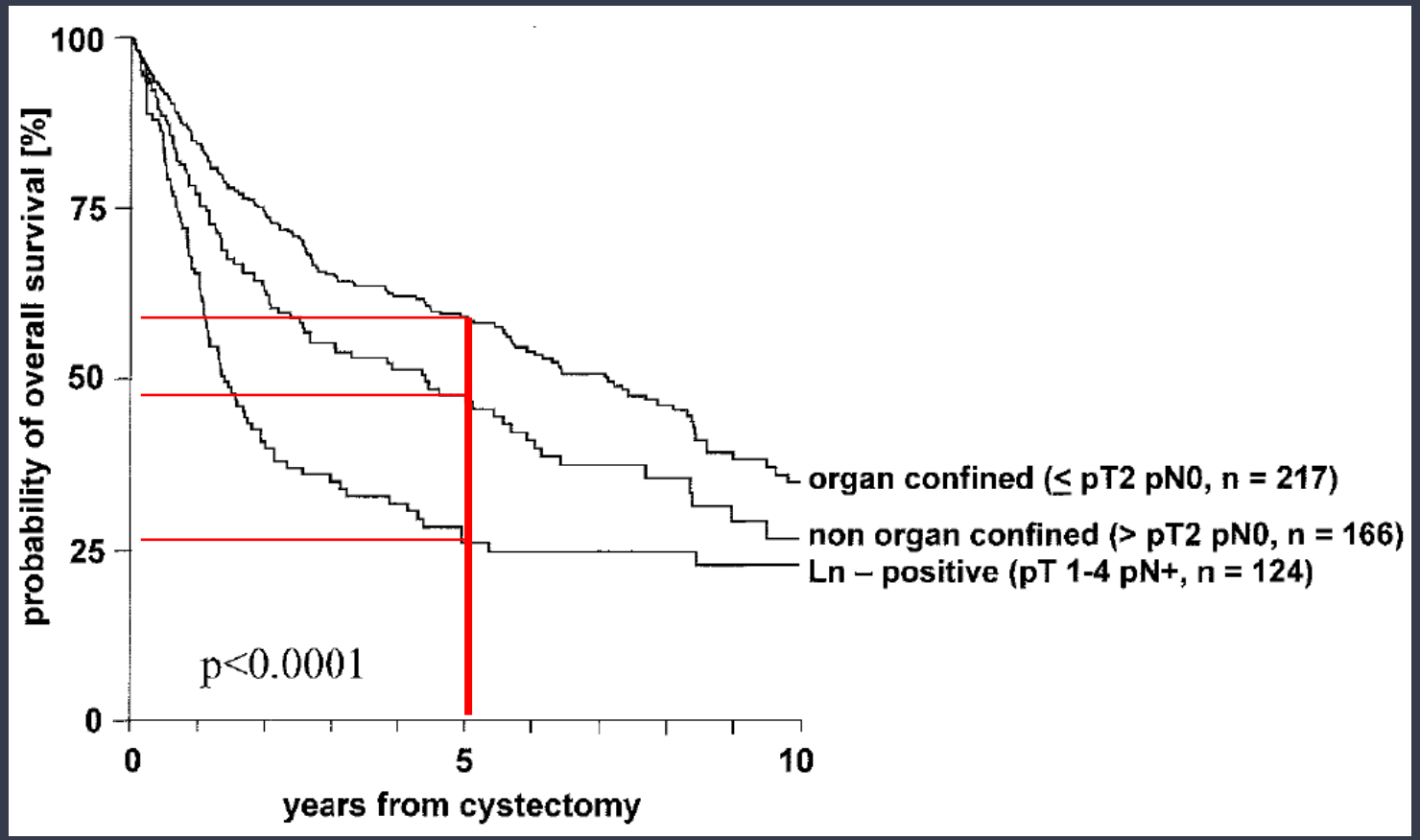
Muscle Invasive Bladder Cancer (MIBC)

- Invasion of muscularis propria
- Affects 20-25% of patients
- Primary management is cystectomy with bilateral pelvic lymphadenectomy
  - Typically following neoadjuvant cisplatin-based therapy
- Bladder sparing in <u>select patients</u>



Overall Survival by Disease Burden with Cystectomy

- ✓ 507 consecutive patients between 1985-2000
- ✓ No neoadjuvant therapy
- ✓ <u>5-year OS:</u>
  - ≤T2, N0 62%
  - >T2, N0 49%
  - T any, N+ 26%



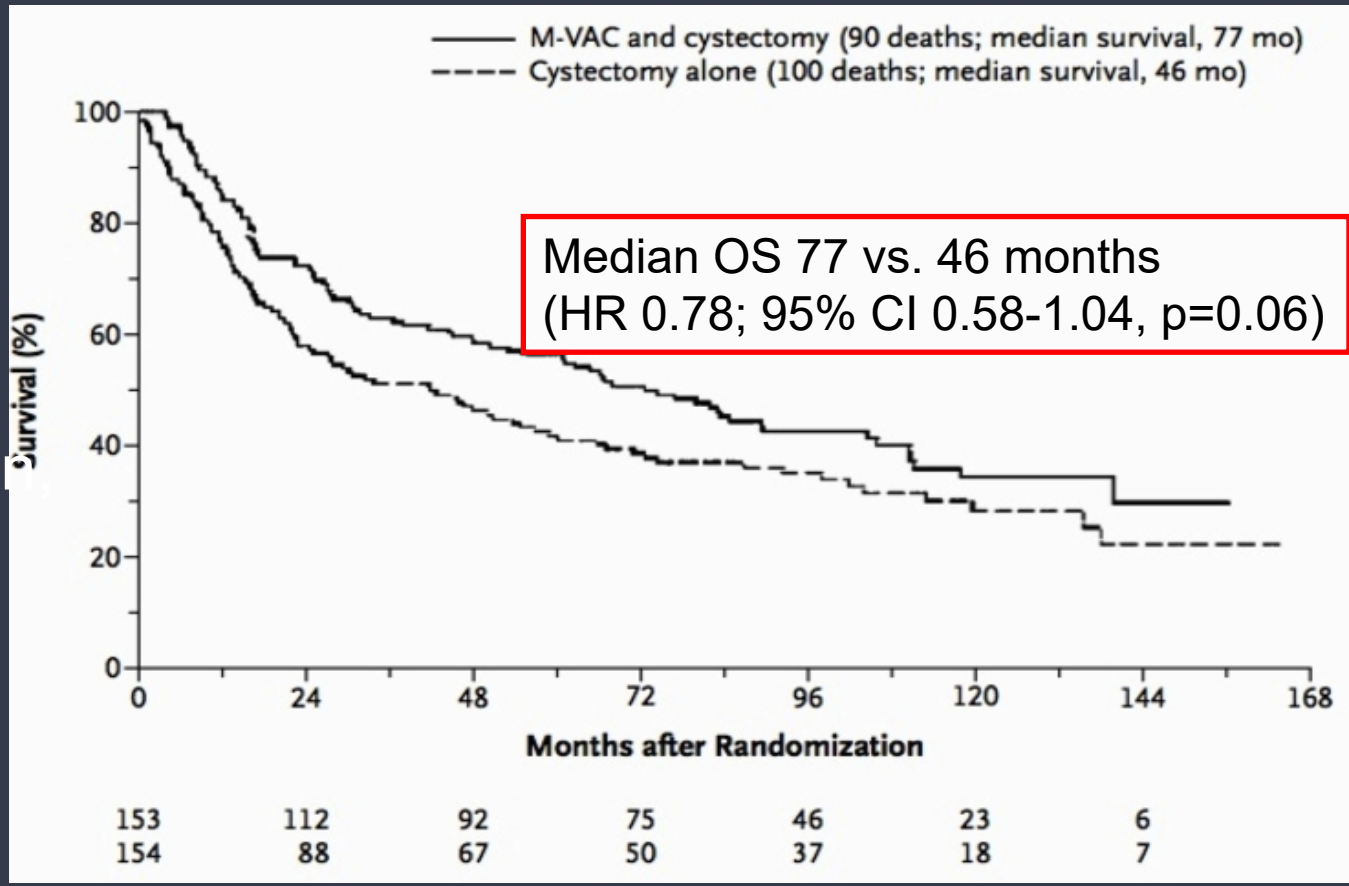
Systemic therapy in localized bladder cancer

- ✓ **Neoadjuvant therapy**
  - Advantages
    - Neoadjuvant cisplatin-based chemotherapy improves OS
    - Early therapy for micro-metastatic disease
    - Performance status / tolerance is clearly better prior to cystectomy
  - Disadvantages
    - Delay of potentially curative therapy (cystectomy)

- ✓ **Adjuvant therapy**
  - Advantages
    - Better staging and risk assessment
  - Disadvantages
    - Evidence for benefit of adjuvant therapy is not robust

SWOG-8710: Neoadjuvant MVAC + Surgery vs. Surgery

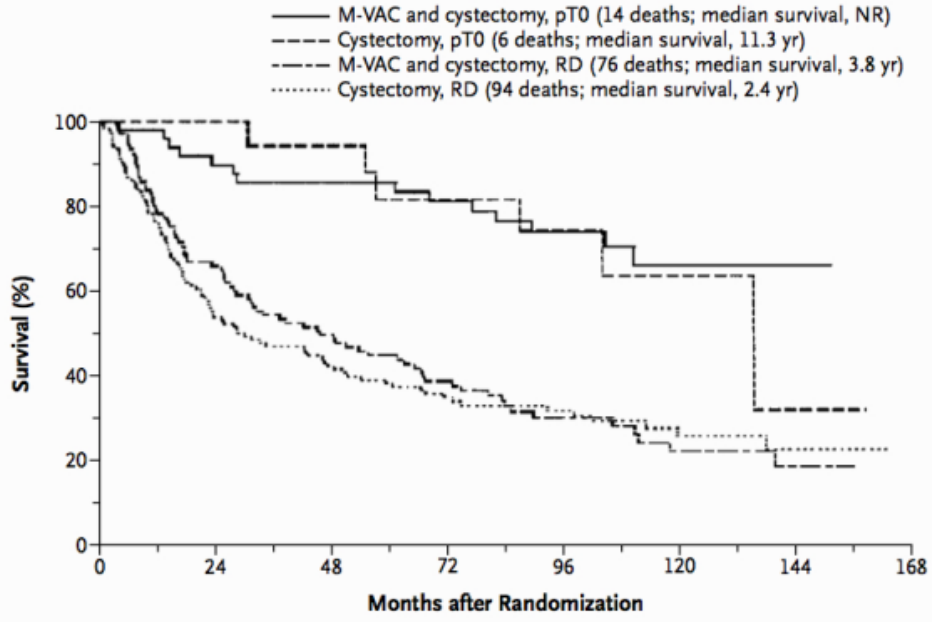
- ✓ N = 317
- ✓ Patients with T2-T4, N0
- ✓ 3 cycles of neoadjuvant MVAC (methotrexate, vinblastine, adriamycin, cisplatin)



Median OS 77 vs. 46 months
(HR 0.78; 95% CI 0.58-1.04, p=0.06)

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

SWOG-8710: Complete Responses Matter



No. at Risk

M-VAC and cystectomy, pT0	48	43	40	37	26	12	2
Cystectomy, pT0	18	17	15	12	10	4	1
M-VAC and cystectomy, RD	105	69	52	38	20	11	4
Cystectomy, RD	136	71	52	37	27	14	6

Figure 2. Survival According to Treatment Group and Whether Patients Were Pathologically Free of Cancer (pT0) or Had Residual Disease (RD) at the Time of Cystectomy.

M-VAC denotes methotrexate, vinblastine, doxorubicin, and cisplatin, and NR not reached.

- pCR rate: 38% vs. 15%
- No clear benefit unless pCR is achieved
- No accurate way to identify patients with ‘platinum-sensitive’ tumors prior to therapy

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

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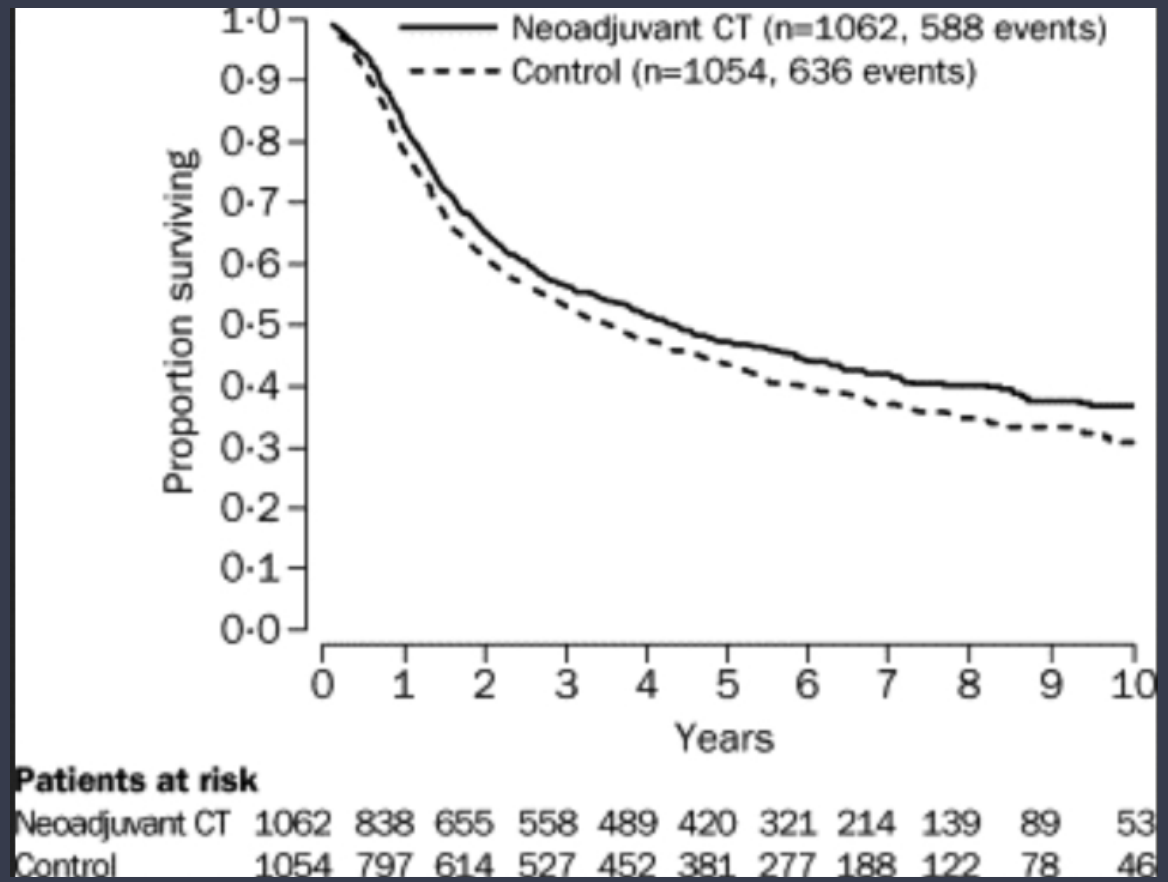
Survival benefit of NAC

- ✓ Meta-analysis of 11 randomized trials
  - Cisplatin-based chemo + local vs local therapy
- ✓ 5-yr OS benefit
  - 50% vs. 45%, HR 0.87, 95% CI: 0.78 – 0.98)
- ✓ Lower risk of recurrence
  - HR 0.81, 95% CI: 0.74 – 0.9
- ✓ Absolute disease-free survival 7%



Vale C et al. Lancet 2003.

GETUG/AFU V05 VESPER – ddMVAC wins!

Randomized Phase III Trial of Dose-dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (dd-MVAC), or Gemcitabine and Cisplatin (GC) as Perioperative Chemotherapy for Patients with MIBC: Analysis of the GETUG/AFU V05 VESPER Trial Secondary Endpoints: Chemotherapy Toxicity and Pathological Responses

Pfister et al. Eur Urol 2020

Methods

Objective: **To compare efficacy of dd-MVAC vs GC in the MIBC perioperative setting**

493 pts: randomized to dd-MVAC (248) or GC (245), 2013-2018

Results

- **NAC setting: 218 pts dd-MVAC, 219 pts GC**

NAC Outcomes

- **ypT0pN0 rate: 42% dd-MVAC vs 36% GC (p=0.2)**
- **<ypT3pN0 rate: 77% dd-MVAC vs 63% GC (p=0.001)**

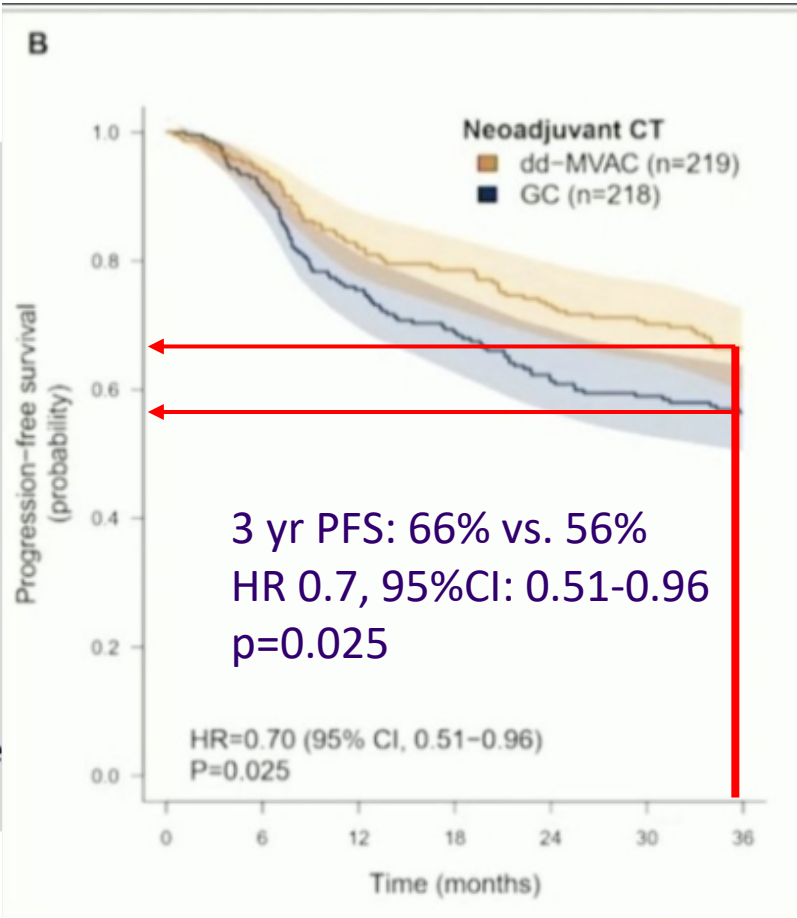
CTCAE Grade ≥3 Toxicities

- **Hematological: 52% dd-MVAC vs 55% GC**
- **N/V: 9.7% dd-MVAC vs 2.9% GC**

Conclusions

Toxicity of dd—MVAC: manageable compared to GC

Higher local control rate in the dd-MVAC arm; primary outcome of PFS expected in mid-2021



3 yr PFS: 66% vs. 56%
HR 0.7, 95%CI: 0.51-0.96
p=0.025

@EUplatinum

CHU Hôpitaux de Rouen

EUROPEAN UROLOGY
Forward faster. Together.

Pfister C et al. Euro Urol 2021. JCO 2022.

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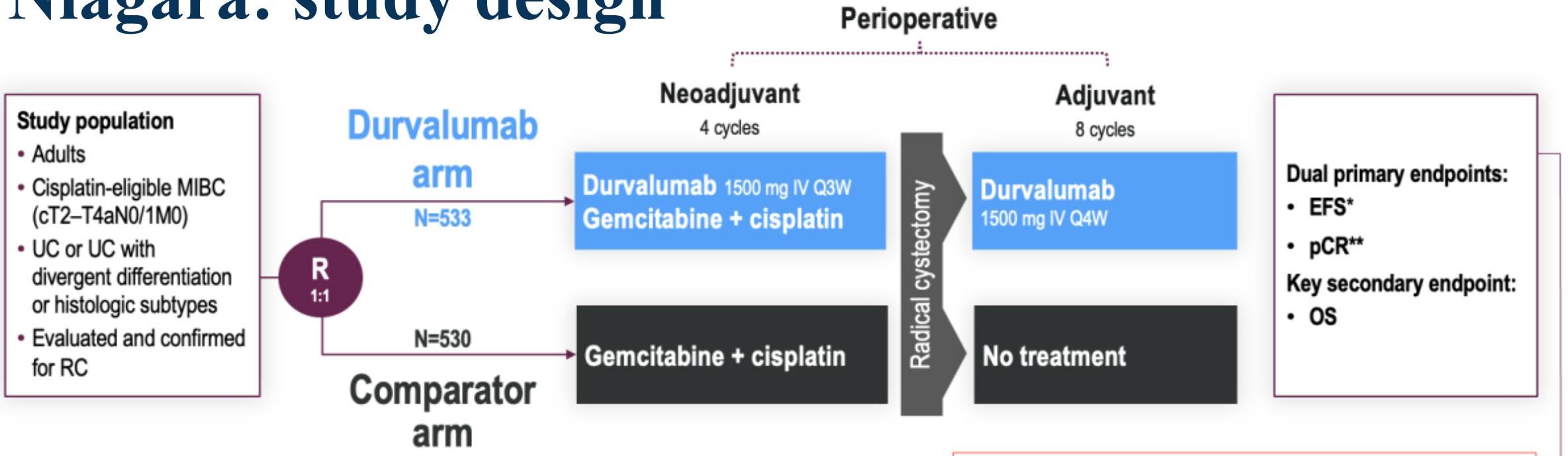
Niagara: study design



Stratification factors

Clinical tumour stage (T2N0 vs >T2N0)

Renal function (CrCl ≥60 mL/min vs ≥40–<60 mL/min)

PD-L1 status (high vs low/negative expression)

Gemcitabine/cisplatin dosing

CrCl ≥60 mL/min: Cisplatin 70 mg/m^2 + gemcitabine 1000 mg/m^2 Day 1, then gemcitabine 1000 mg/m^2 Day 8, Q3W for 4 cycles

CrCl ≥40–<60 mL/min: Split-dose cisplatin 35 mg/m^2 + gemcitabine 1000 mg/m^2 Days 1 and 8, Q3W for 4 cycles

EFS defined as:

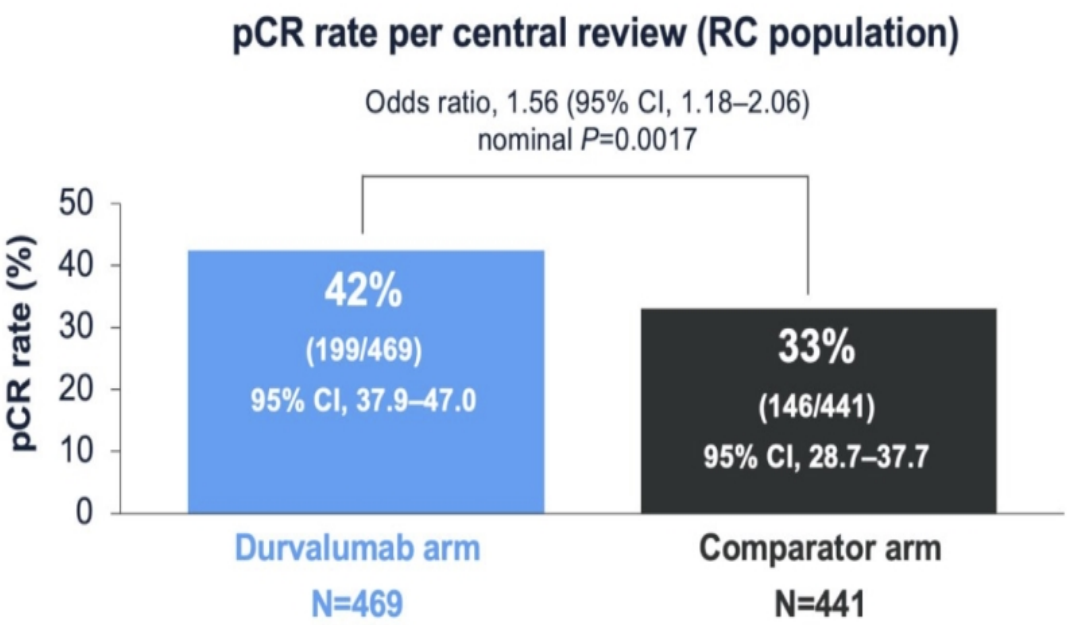
- Progressive disease that precluded RC
- Recurrence after RC
- Date of expected surgery in patients who did not undergo RC
- Death from any cause

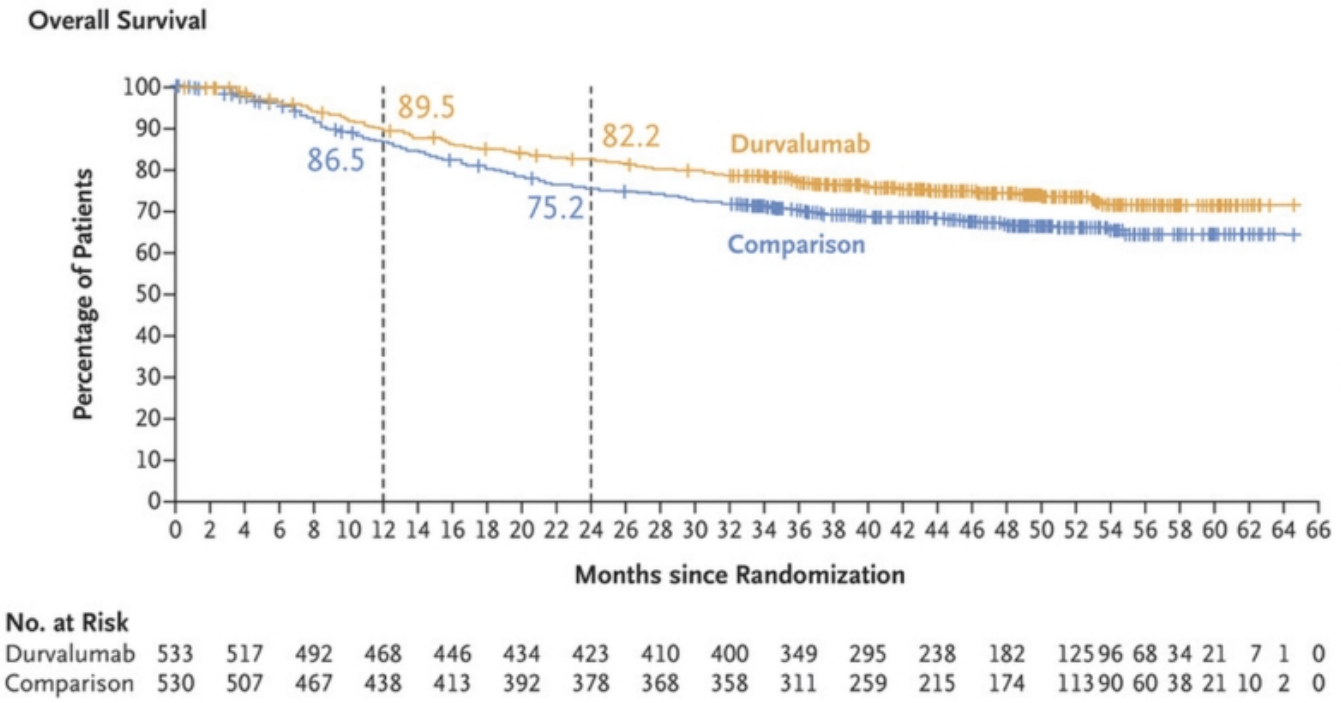
Other endpoints (not reported here):
DFS, DSS, MFS, HRQoL, 5-year OS

*Evaluated by blinded independent central review or central pathology review (if a biopsy was required for a suspected new lesion).**Evaluated by blinded central pathology review.
ClinicalTrials.gov, NCT03732677; EudraCT number, 2018-001811-59 . CrCl, creatinine clearance; DFS, disease-free survival; DSS, disease-specific survival; EFS, event-free survival ; HRQoL, health-related quality of life; IV, intravenous;
MFS, metastasis-free survival; MIBC, muscle-invasive bladder cancer; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed cell death ligand-1; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomised; RC, radical cystectomy; UC, urothelial carcinoma..

Niagara: pCR and and Event-Free Survival

Pathologic CR → Overall Survival





HR 0.75 (95% CI: 0.59-0.93)
Median FU 46.3 months (range 0.03-64.7)

Powles, T. N Engl J Med 2024;391:1773-1786

Observational Study Adjuvant Chemotherapy

VOLUME 34 · NUMBER 8 · MARCH 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Effectiveness of Adjuvant Chemotherapy for Locally Advanced Bladder Cancer

Matthew D. Galsky, Kristian D. Stensland, Erin Moshier, John P. Sfakianos, Russell B. McBride, Che-Kai Tsao, Martin Casey, Paolo Boffetta, William K. Oh, Madhu Mazumdar, and Juan P. Wisnivesky

Consider gemcitabine/cisplatin or accelerated/dose dense MVAC X 4 cycles for pT3/4 and/or pN+ if cisplatin-fit & did not receive neoadjuvant chemoTx

Defining Cisplatin-Ineligibility

- ✓ Hearing loss (measured at audiometry of 25 dB at two contiguous frequencies)
- ✓ Neuropathy (grade 2 or greater)
- ✓ Poor performance status (ECOG ≥ 2 or KPS 60-70% or less)
- ✓ Renal insufficiency (CrCl < 60 mL/min, consider 24hr Urine if eGFR borderline)
- ✓ New York Heart Association class III or greater heart failure

- ✓ Border line renal function: a split-dose administration of cisplatin may be considered (NCCN category 2B recommendation). Safer but efficacy is undefined.

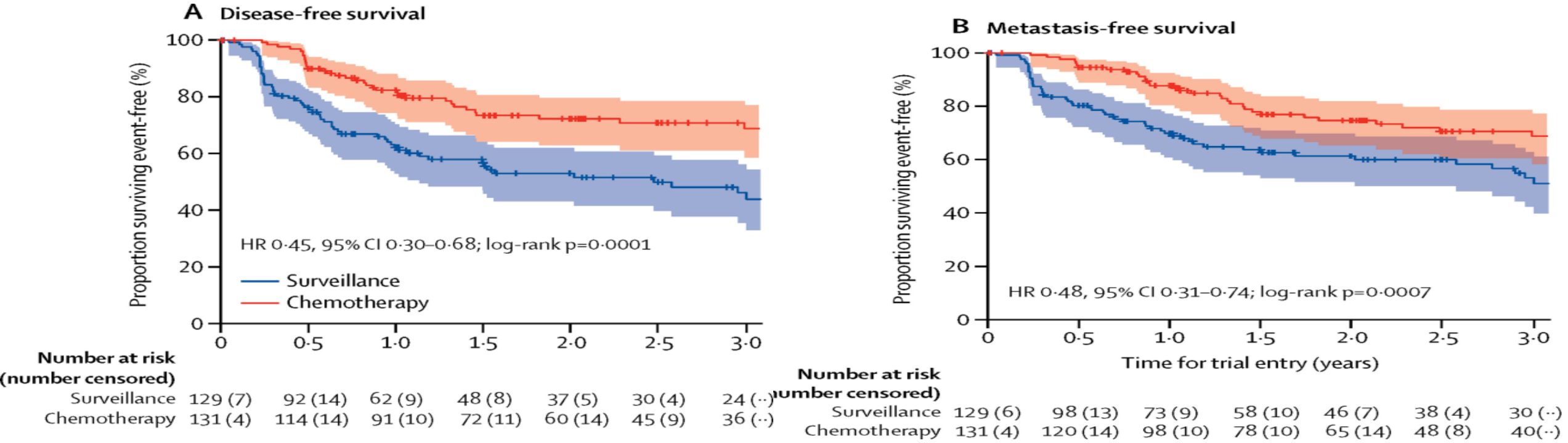
- ✓ If cisplatin-based therapy cannot be given, neoadjuvant chemotherapy is **NOT recommended**.
- ✓ Carboplatin has **NOT** demonstrated a survival benefit and **should NOT** be substituted in the perioperative setting. Cystectomy alone is appropriate.

Galsky et al. Lancet Oncology 2011.

Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial

Alison Birtle, MD, Mark Johnson, MD, Prof John Chester, PhD, Prof Robert Jones, PhD, David Dolling, PhD, Richard T Bryan, PhD, Christopher Harris, Andrew Winterbottom, Anthony Blacker, MBChB, Prof James W F Catto, PhD, Prabir Chakraborti, MD, Prof Jenny L Donovan, PhD, Paul Anthony Elliott, PhD, Ann French, MSc, Satinder Jagdev, MDRB, Benjamin Jenkins, MSc, Francis Xavier Keeley, MD, Roger Kockelbergh, MBChB, Prof Thomas Powles, PhD, Prof John Wagstaff, MD, Caroline Wilson, PhD, Rachel Todd, MSc, Rebecca Lewis, BSc, Prof Emma Hall, PhD

The Lancet
Volume 395 Issue 10232 Pages 1268-1277 (April 2020)
DOI: 10.1016/S0140-6736(20)30415-3

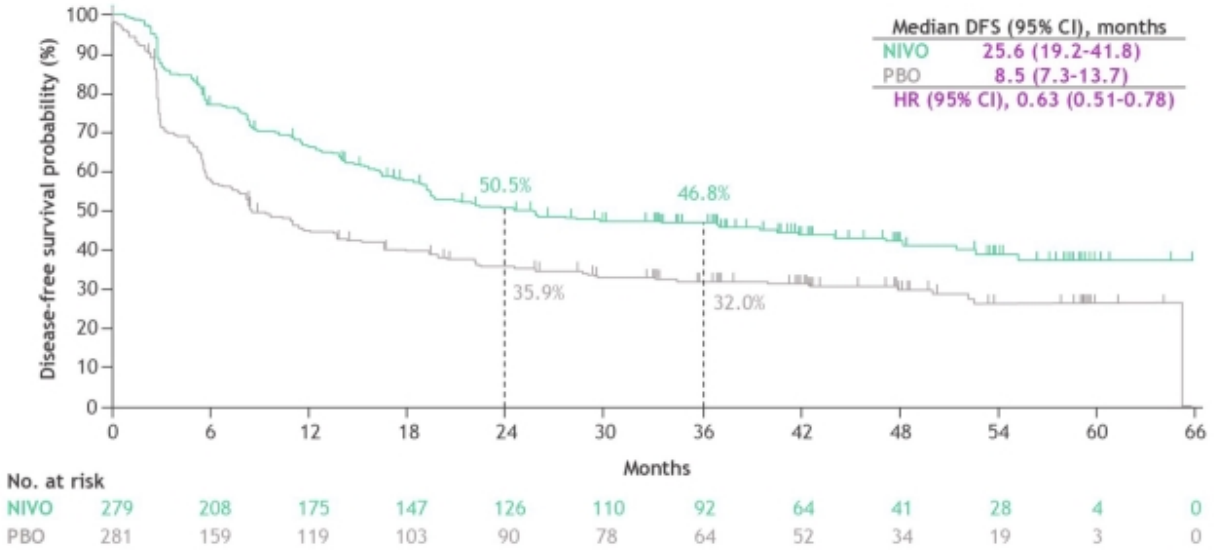


Adjuvant immunotherapy for high-risk MIBC

MIBC: ypT2-ypT4 or yN+ [prior NAC] or pT3-pT4 or N+ [prior surgery]

Checkmate 274: DFS

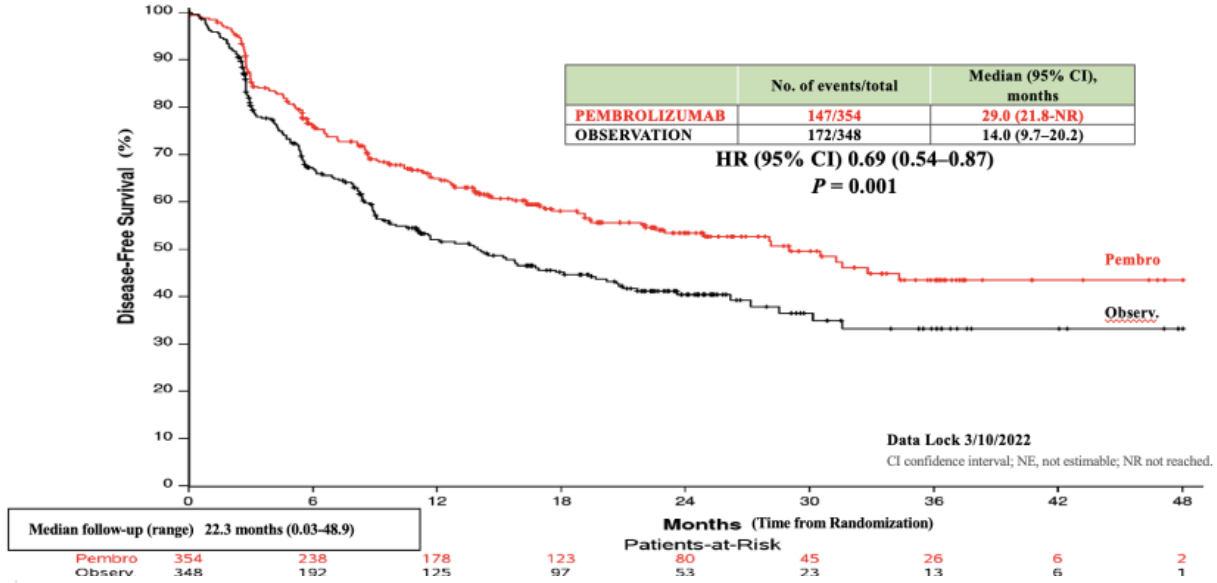
Nivolumab (240 mg intravenously) or placebo every 2 weeks for up to 1 year



Bajorin, D.F. N Engl J Med 2021;384:2102-2114

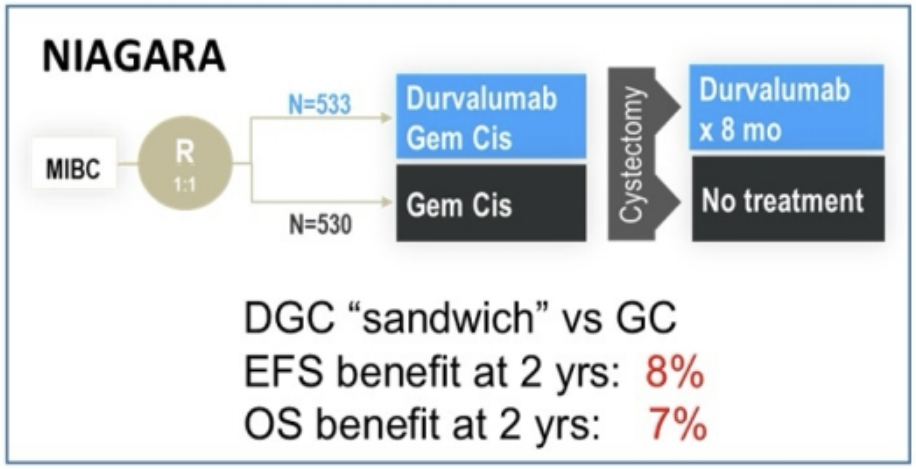
Ambassador: DFS

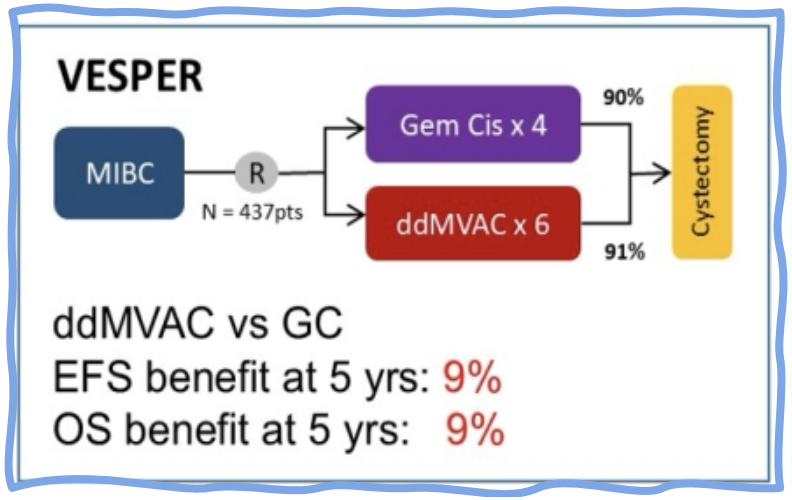
Pembrolizumab (200 mg intravenously) or placebo every 3 weeks for up to 1 year

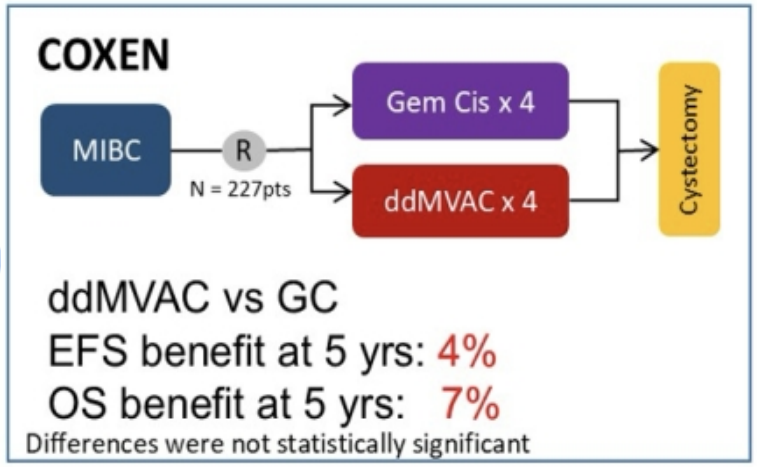


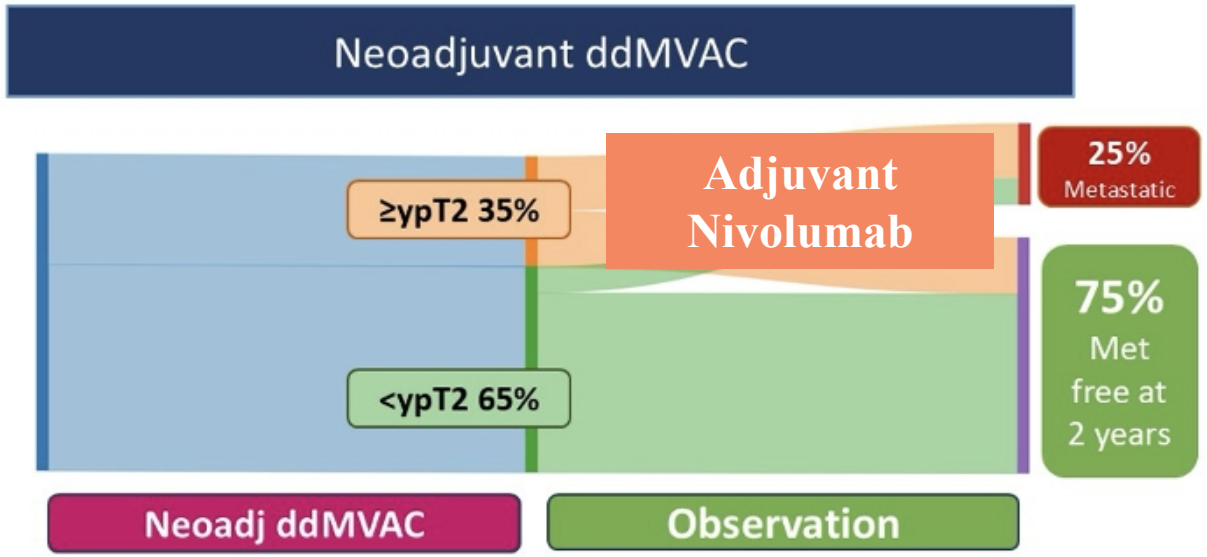
Apolo, AB. N Engl J Med 2025;392:45-55

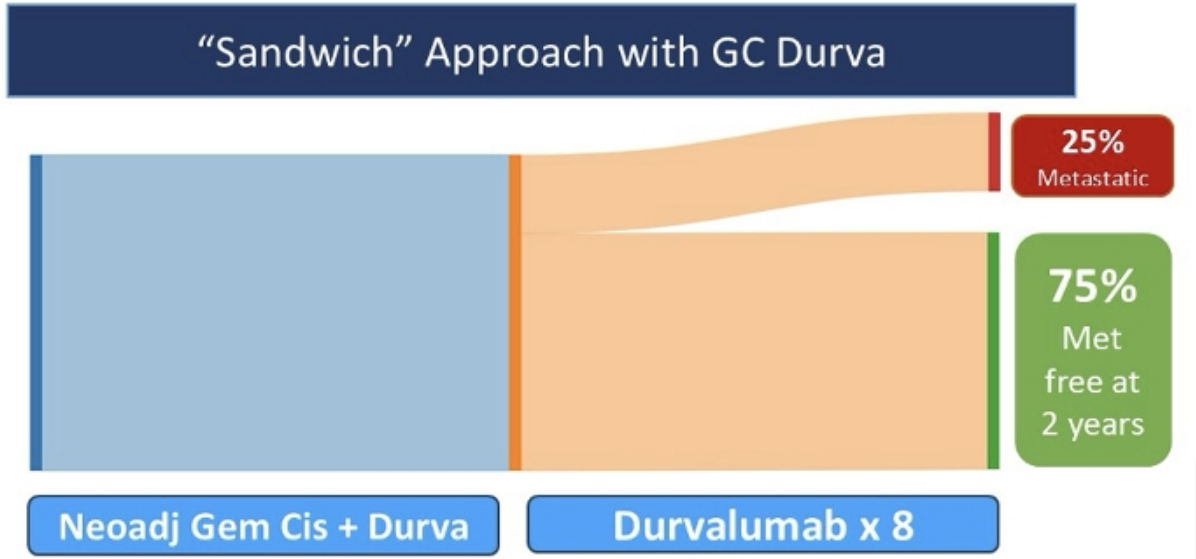
NIAGARA in the context of current treatment options











Bladder Preservation

- ✓ Bladder-preserving approaches are reasonable alternatives to cystectomy for patients who are medically unfit for surgery and those seeking alternative to radical cystectomy.
- ✓ **Generally considered if:**
  - smaller solitary tumors,
  - negative nodes,
  - no extensive or multifocal CIS,
  - no moderate or severe hydronephrosis
  - good pre-treatment bladder function
- ✓ **Trimodal therapy = maximal TURBT with concurrent chemoradiotherapy**
  - cisplatin alone or cisplatin WITH 5-FU or paclitaxel or gemcitabine, or
  - 5-FU and mitomycin, or
  - gemcitabine monotherapy

Mrs. Chang is a 67-year-old woman with a past medical history significant for hypertension, type 2 diabetes mellitus, and COPD, who presented with hematuria and dysuria. She denied other urinary symptoms. She has a 35-year history of smoking. Review of systems was otherwise unremarkable. She underwent a CT scan of the chest and CT urography, which revealed a 2 cm mass in the trigone of the bladder. The tumor showed no evidence of perivesical fat stranding or invasion of adjacent organs. There was no obstructive uropathy, and no evidence of abnormal lymph nodes or metastatic disease. She subsequently underwent cystoscopy and TURBT, which demonstrated a solitary papillary tumor located on the trigone. The lesion appeared exophytic, with frond-like projections, measuring approximately 2 cm in greatest dimension. A complete TURBT was performed. Pathology demonstrated high-grade urothelial carcinoma with detrusor muscle invasion. No CIS was identified in mapping biopsies. Laboratory testing showed an eGFR of 37 mL/min. Which of the following statements is true?

A. Neoadjuvant cisplatin-based chemotherapy with split-dose of cisplatin, with or without perioperative immune checkpoint inhibitors, is an appropriate treatment.

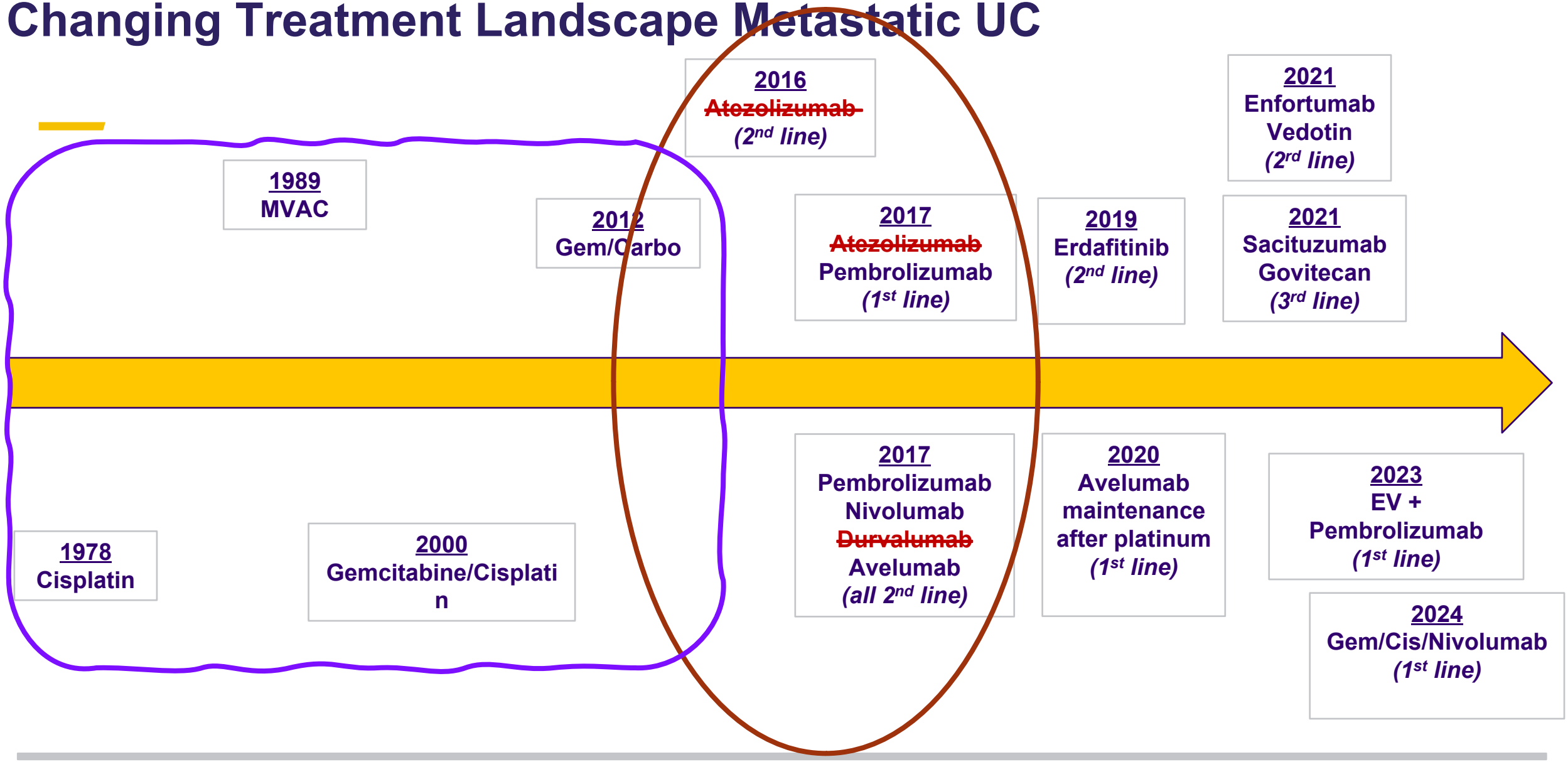
B. This patient is a candidate for trimodality therapy, using mitomycin C plus 5-FU as radiosensitizing chemotherapy.

C. Upfront cystectomy, followed by risk-adapted adjuvant nivolumab, is an appropriate treatment.

D. Intravesical BCG induction, followed by cystectomy, is an appropriate treatment.

E. B and C are true

Changing Treatment Landscape Metastatic UC



	Atezolizumab[1]	Nivolumab[2]	Pembrolizumab[3]	Avelumab[4]	Durvalumab[5]
Phase	Phase III Randomized vs chemotherapy	Phase II Single Arm	Phase III Randomized vs Chemotherpay	Phase Ib	Phase I/II
Number of Patients	931	265	542	249 (161 pts ≥ 6 mos f/u	191
Dosing	1200mg every 3 weeks	3mg/kg every 2 weeks	200mg every 3 weeks	10mg/kg every 2 weeks	10mg/kg every 2 weeks
ORR	13.4%	19.6%	21.1%	17%	17.8%
Duration of Response	63% of responses ongoing at median f/u of 21.7 mos	77% of responses ongoing at median f/u of 7 mos	72% of responses ongoing at median f/u of 14.1 mos	96% of responses ongoing at 6 mos f/u	50% of responses lasting ≥ 6 mos
Median OS	8.6 mos	8.7 mos	10.3 mos	6.5 mos	18.2 mos
Median PFS	2.1 mos	2.0 mos	2.1 mos	1.5 mos	1.5 mos
Rate of Grade 3/4 Treatment-related AEs	20%	18%	15%	8%	6.8%

1Powles T, et al. Lancet. 2018;391(10122):748-757.; 2Sharma P, et al. Lancet Oncol. 2017;18(3):312-322.; 3Bellmunt J, et al. N Engl J Med. 2017;376(11):1015-1026.; 4Patel MR, et al. Lancet Oncol. 2018;19(1):51-64.; 5Powles T, et al. JAMA Oncol. 2017;3(9):e172411

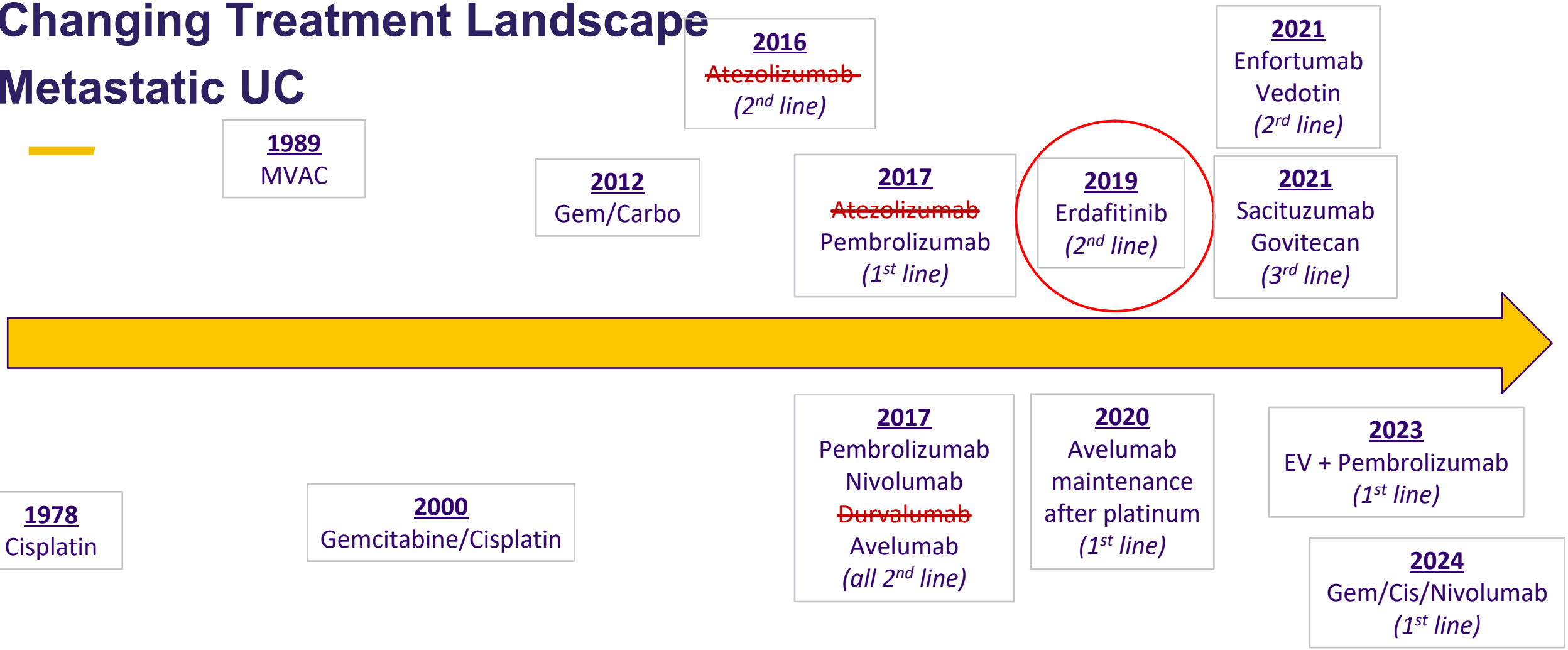
Summary of Immunotherapy in Bladder Cancer

- ✓ aPD-1 leads to ORR of 20-25%, with durable responses.
- ✓ 2nd line can use nivolumab, avelumab or pembrolizumab. However, pembrolizumab only agent with phase 3 data showing survival benefit.

PRINCIPLES OF SYSTEMIC THERAPY

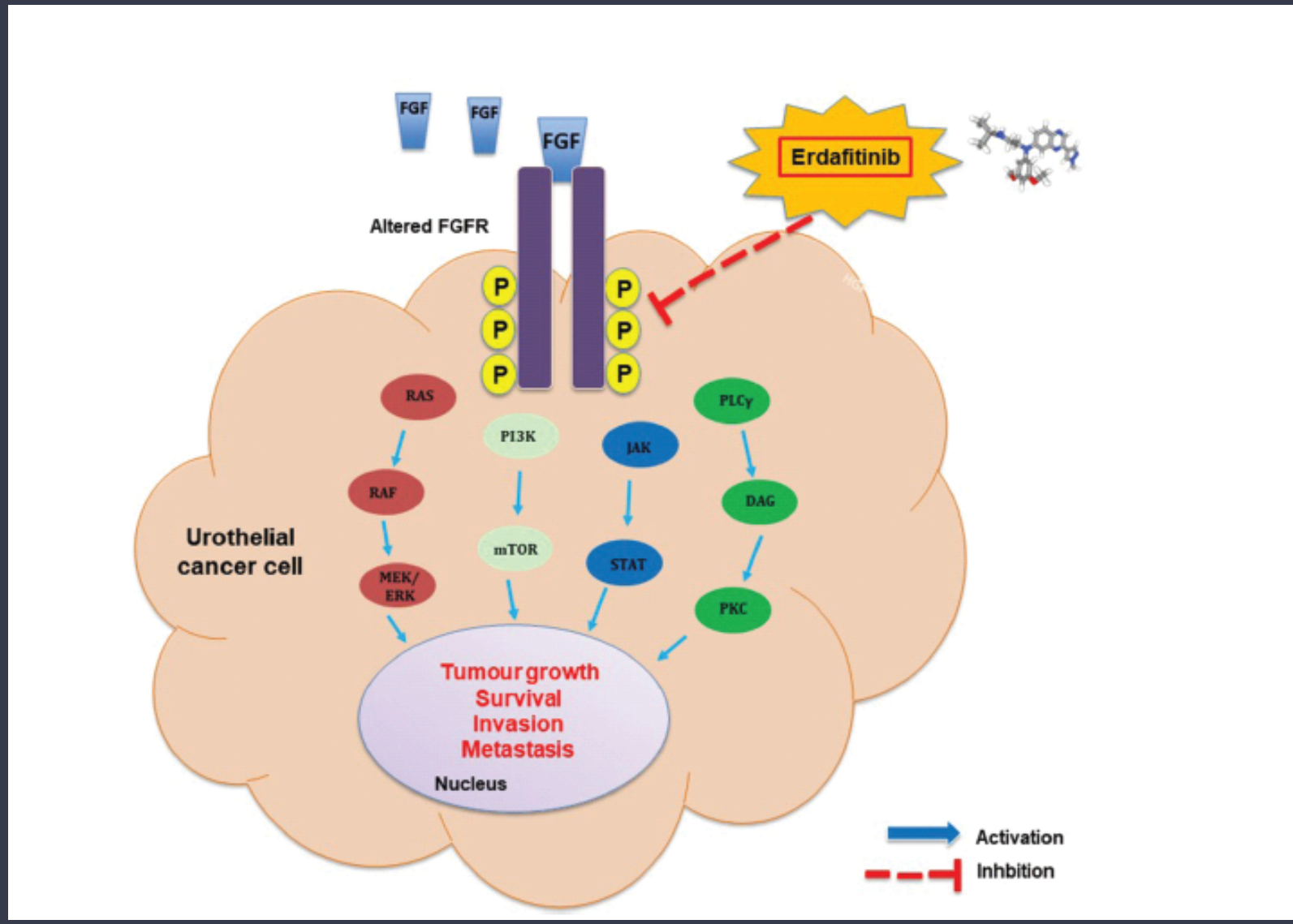
First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)		
Preferred regimen • Enfortumab vedotin-ejfv[15,16] and pembrolizumab (category 1)	**Other recommended regimens** • Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (category 1)[a,17] • Gemcitabine, cisplatin, and nivolumab (category 1) followed by nivolumab maintenance therapy[18] (category 1) • DDMVAC with growth factor support[2,10] (category 1) followed by avelumab maintenance therapy (category 1)[a,17]	**Useful in certain circumstances (cisplatin-ineligible)** • Gemcitabine and carboplatin[19] followed by avelumab maintenance therapy (category 1)[a,17] • Pembrolizumab (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy)[20] • Atezolizumab[21] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 2B)

Changing Treatment Landscape Metastatic UC



Erdafitinib targets FGFR (fibroblast growth factor receptor)

- FGFR mutations / fusions occur in ~15-20% of UC (37% UTUC).
- Approved for patient with FGFR3 genetic alterations.
- Erdafitinib a FGFR 1-4 TKI.



BLC2001: Phase 2 Trial

Pivotal Phase 2 Trial of Erdafitinib in FGFR-Altered Metastatic or Unresectable UC

- Patients with metastatic or unresectable locally advanced UC
- PD on ≥1 prior line of systemic chemotherapy or within 12 months of neoadjuvant chemotherapy or cisplatin-ineligible[a] and chemotherapy-naïve
- Prior IO therapy permitted

N=99

Central screening for FGFR fusions or mutations

Erdafitinib
10 mg/day ×
7 days on/7 days off

Erdafitinib
6 mg once daily

Erdafitinib
8 mg once daily[b]

Until PD

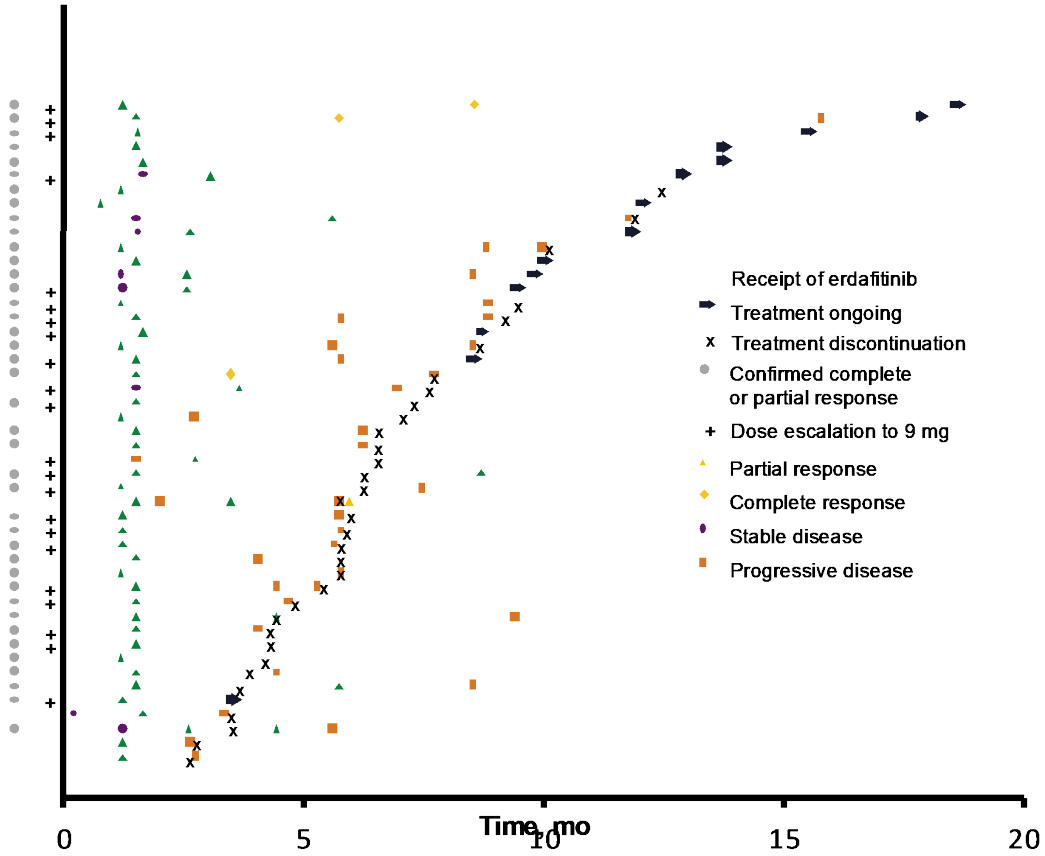
- **Primary endpoint:** ORR
- **Secondary endpoints:** PFS, OS, safety, DoR, PK, predictive biomarker evaluation

- Study has 85% power with 1-sided α=.025 to test primary hypothesis that ORR >25% in erdafitinib 8-mg arm
- Patients with ≥2 prior therapies, n=43
- Patients with visceral metastases, n=78

BLC2001: Phase 2 Trial

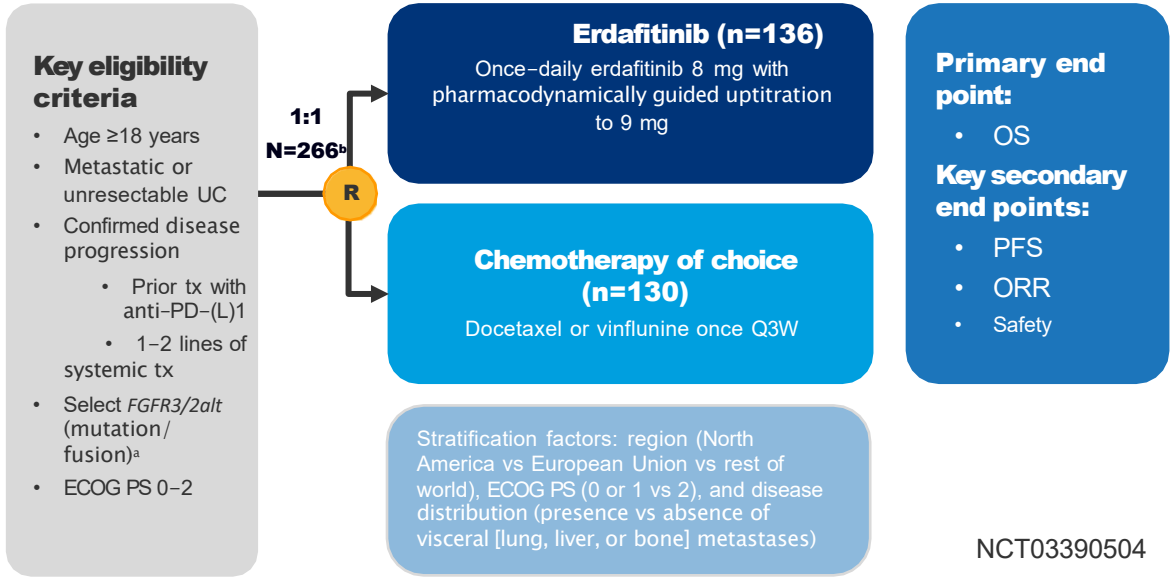
Results led to FDA approval of erdafitinib for locally advanced UC or mUC with *FGFR3* or *FGFR2* mutation or fusion after progression on ≥1 line of prior platinum-containing chemotherapy

- ✓Confirmed response rate 32.2%
  - (2.3% CR; 29.9% PR)
- ✓Among 22 pts with prior ICI, confirmed response rate 59%
- ✓Median PFS 5.5 months
- ✓Median OS was 13.8 months



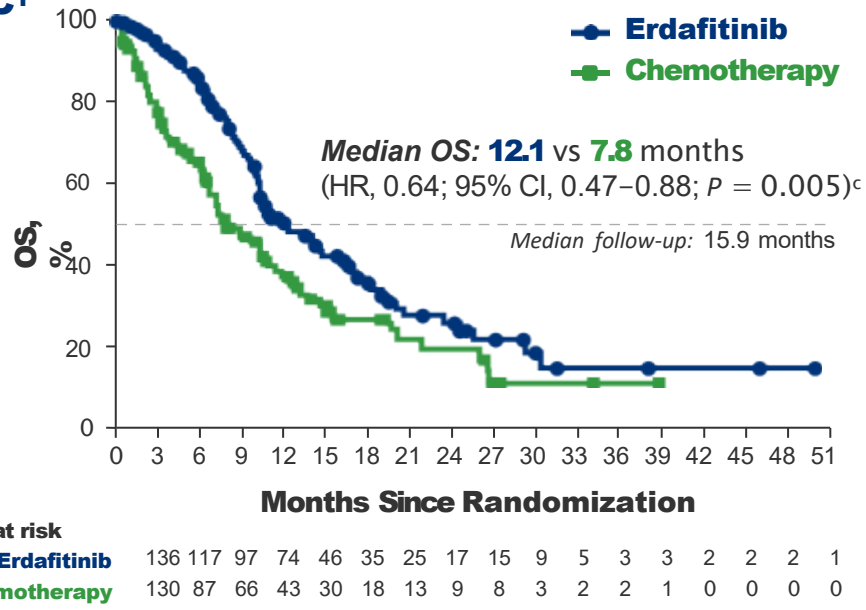
THOR Cohort 1: Erdafitinib Versus Investigator's Choice of Chemotherapy in Patients With *FGFR*-altered mUC

THOR cohort 1 study design



- Based on superior efficacy at a preplanned interim analysis, the IDMC recommended to stop the study, unblind data, and cross over patients from chemotherapy to erdafitinib

Erdafitinib demonstrated superior efficacy versus chemotherapy in patients with *FGFR*-altered mUC[1]



- ***Median PFS:*** **5.6** vs **2.7** months (HR, 0.58; 95% CI, 0.44–0.78; *P* = 0.0002)
- ***ORR:*** **45.6%** vs **11.5%** (relative risk, 3.94; 95% CI, 2.37–6.57; *P* < 0.001)

[a]Molecular eligibility can be confirmed using either central or local historical *FGFR* test results (Qiagen assay). If a patient was enrolled based on local historical testing, a tissue sample must still be submitted at the time of enrollment for retrospective confirmation (by central lab) of *FGFR* status. Tumors must have ≥1 of the following translocations: *FGFR2-BICC1*, *FGFR2-CASP7*, *FGFR3-TACC3_V1*, *FGFR3-TACC3_V3*, *FGFR3-BAIAP2L1*; or 1 of the following *FGFR3* gene mutations: R248C, S249C, G370C, Y373C; [b]Number of patients randomized at the time of the interim analysis (data cutoff January 15, 2023); [c]The significance level for stopping for efficacy was *P* = 0.019, corresponding to a HR of 0.69.

CI, confidence interval; HR, hazard ratio; IDMC, independent data monitoring committee; ECOG PS, Eastern Cooperative Oncology Group performance status; Q3W, every 3 weeks; tx, treatment; UC, urothelial cancer.

1. Loriot Y, et al. *J Clin Oncol.* 2023;41(Suppl 17):LBA4619.

Erdafitinib - Key Adverse Events

- **Hyperphosphatemia**
  - Lower starting dose and if phosphorus not to high after 2-3 weeks, increase dose
  - Restrict phosphate intake to 600-800 mg daily
- **Ocular disorders (central serous retinopathy)**
  - Led to dose interruptions/reductions in 9/14%, respectively
  - Obtain ophthalmological examinations during first four months of treatment, every 3 months afterwards, and at any time for visual symptoms.
- Other common AEs: **stomatitis**, fatigue, **diarrhea**, onycholysis, hand foot syndrome

Changing Treatment Landscape Metastatic UC

1978
Cisplatin

1989
MVAC

2000
Gemcitabine/Cisplatin

2012
Gem/Carbo

2016
~~Atezolizumab~~
(2nd line)

2017
~~Atezolizumab~~
Pembrolizumab
(1st line)

2017
Pembrolizumab
Nivolumab
~~Durvalumab~~
Avelumab
(all 2nd line)

2019
Erdafitinib
(2nd line)

2020
Avelumab
maintenance
after platinum
(1st line)

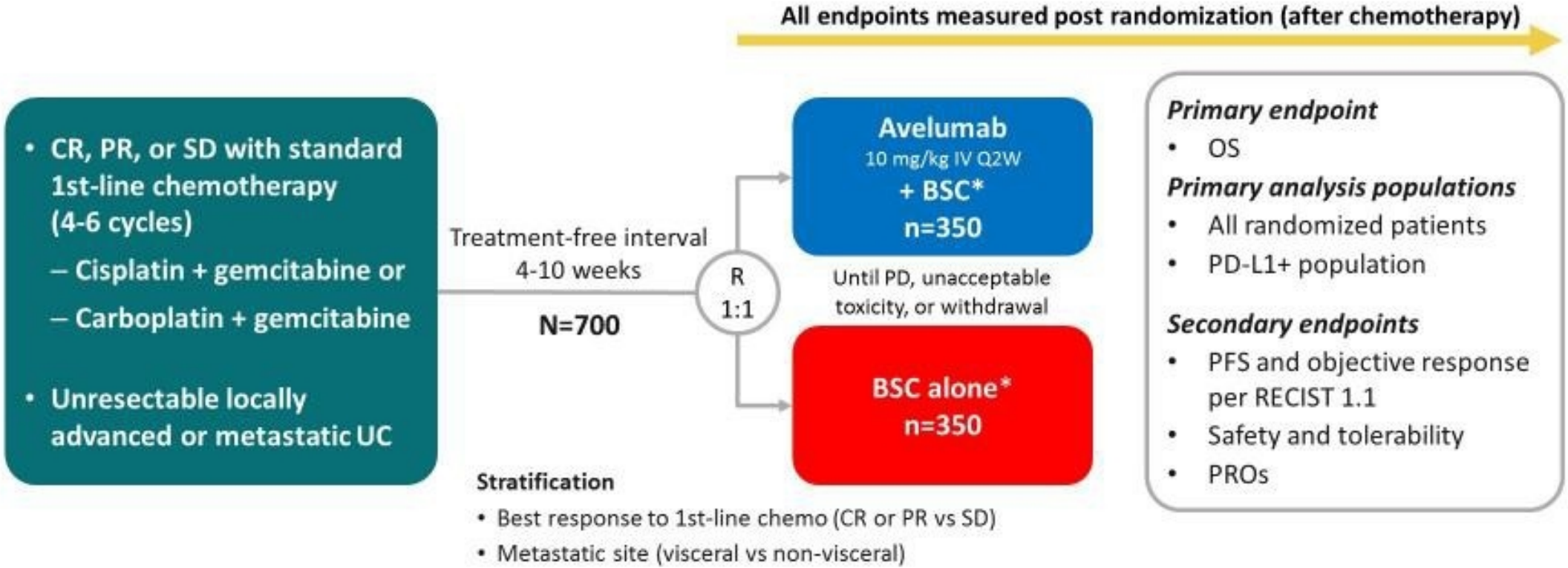
2021
Enfortumab
Vedotin
(2rd line)

2021
Sacituzumab
Govitecan
(3rd line)

2023
EV + Pembrolizumab
(1st line)

2024
Gem/Cis/Nivolumab
(1st line)

JAVELIN Bladder 100 study design (NCT02603432)



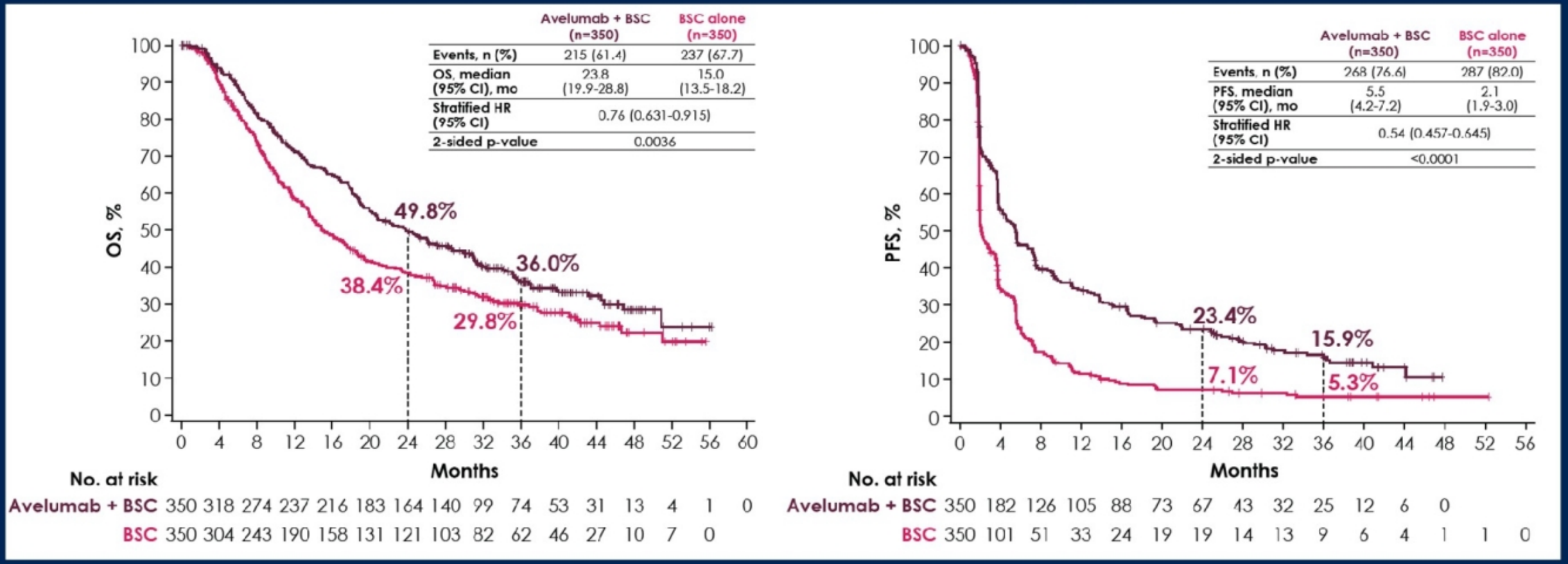
PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

BSC, best supportive care; **CR**, complete response; **IV**, intravenous; **PR**, partial response; **PRO**, patient reported outcome; **Q2W**, every 2 weeks; **R**, randomization; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumors version 1.1; **SD**, stable disease

*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

Long-term follow-up continues to show prolonged OS and PFS with avelumab + BSC vs BSC alone

OS



Investigator-assessed PFS

HR, hazard ratio.

Changing Treatment Landscape Metastatic UC

1978
Cisplatin

1989
MVAC

2000
Gemcitabine/Cisplatin

2012
Gem/Carbo

2016
~~Atezolizumab~~
(2nd line)

2017
~~Atezolizumab~~
Pembrolizumab
(1st line)

2017
Pembrolizumab
Nivolumab
~~Durvalumab~~
Avelumab
(all 2nd line)

2019
Erdafitinib
(2nd line)

2020
Avelumab
maintenance
after platinum
(1st line)

2021
Enfortumab
Vedotin
(2rd line)

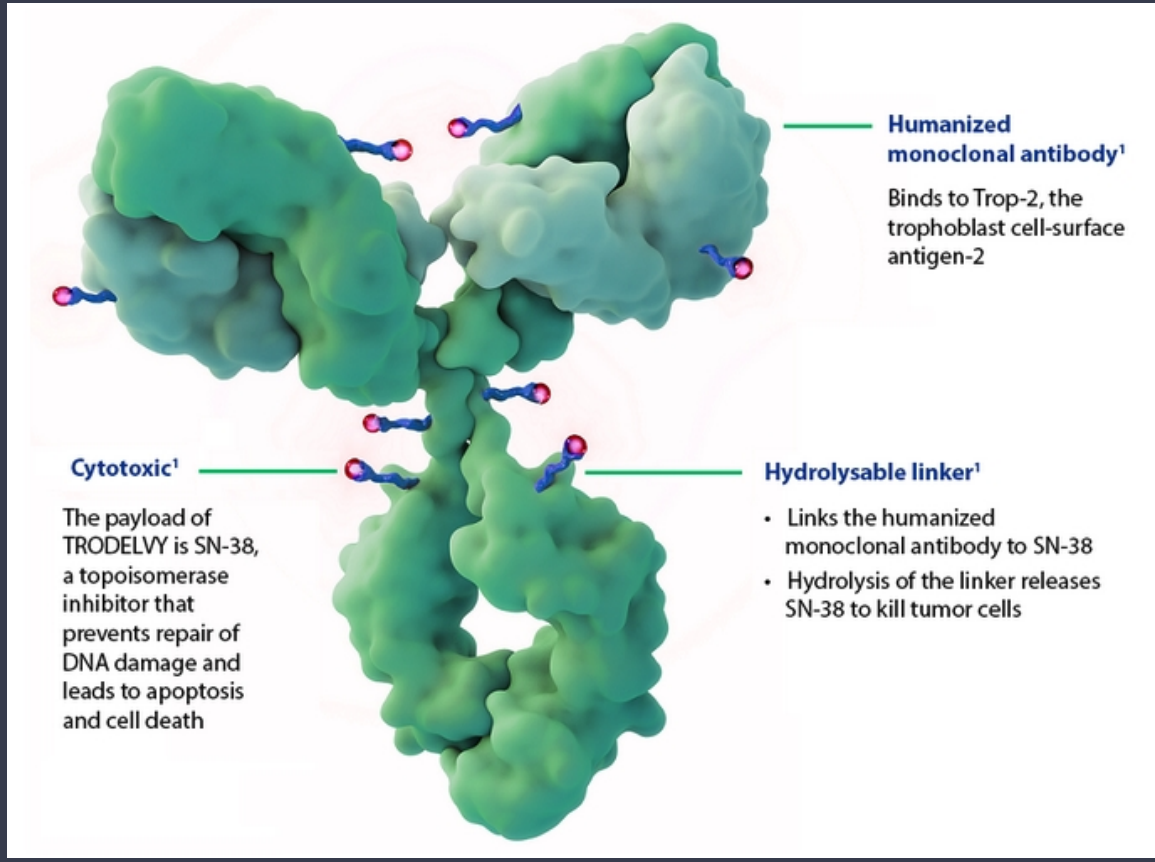
2021
Sacituzumab
Govitecan
(3rd line)

2023
EV + Pembrolizumab
(1st line)

2024
Gem/Cis/Nivolumab
(1st line)

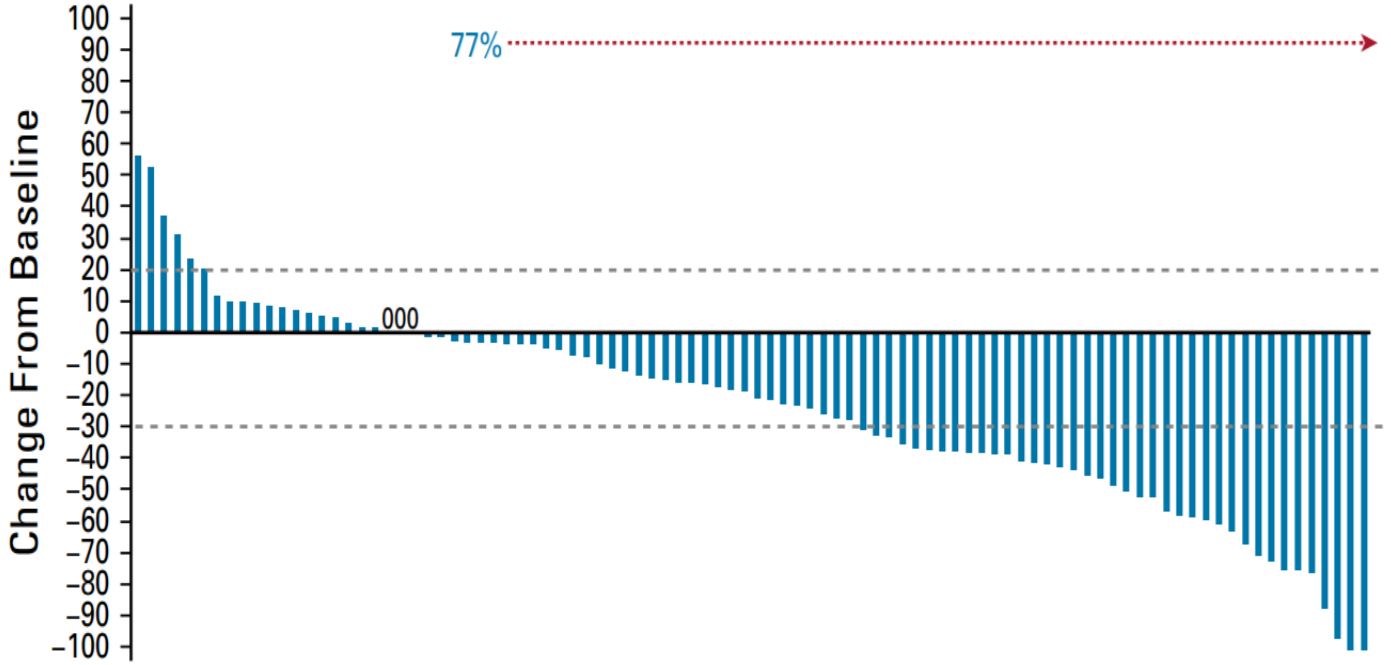
Sacituzumab Govitecan (SG)

- Targets Trop-2
  - Transmembrane glycoprotein upregulated in cancer.
- pH-dependent cleavage site
- Conjugated to SN-38 (topoisomerase 1 inhibitor)
- Approved for mTNBC



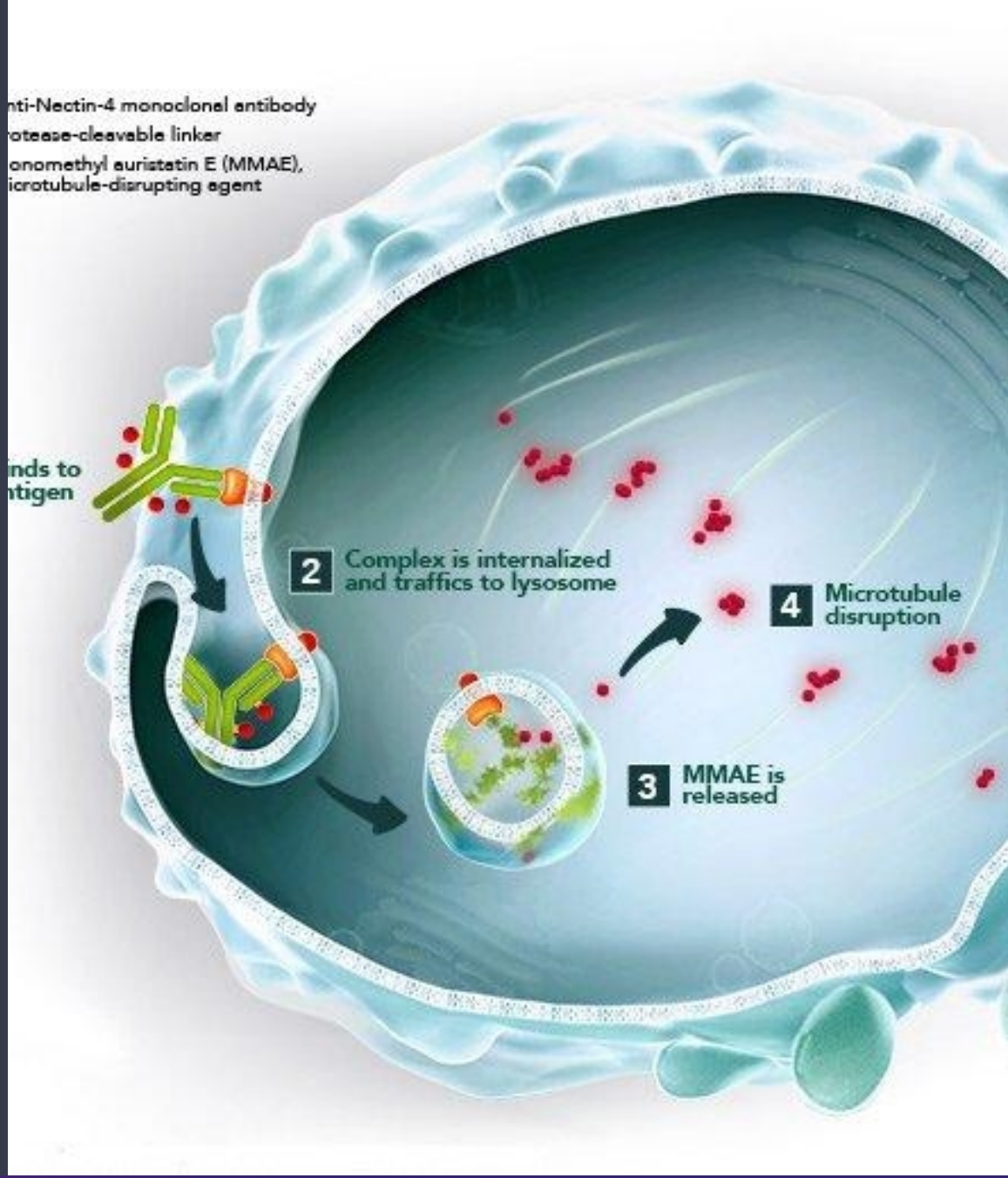
TROPHY-U-01 (Cohort 1): Phase 2 Trial

Endpoint	Cohort 1 (N=113)
ORR, No. (%) [95% CI]	**31 (27) [19, 37]**
CR, No. (%)	6 (5)
PR, No. (%)	25 (22)
Median duration of response, mo [95% CI] (range)	**7.2** [4.7, 8.6] (1.4–13.7)
Median time to onset of response, mo (range)	1.6 (1.2–2.9)

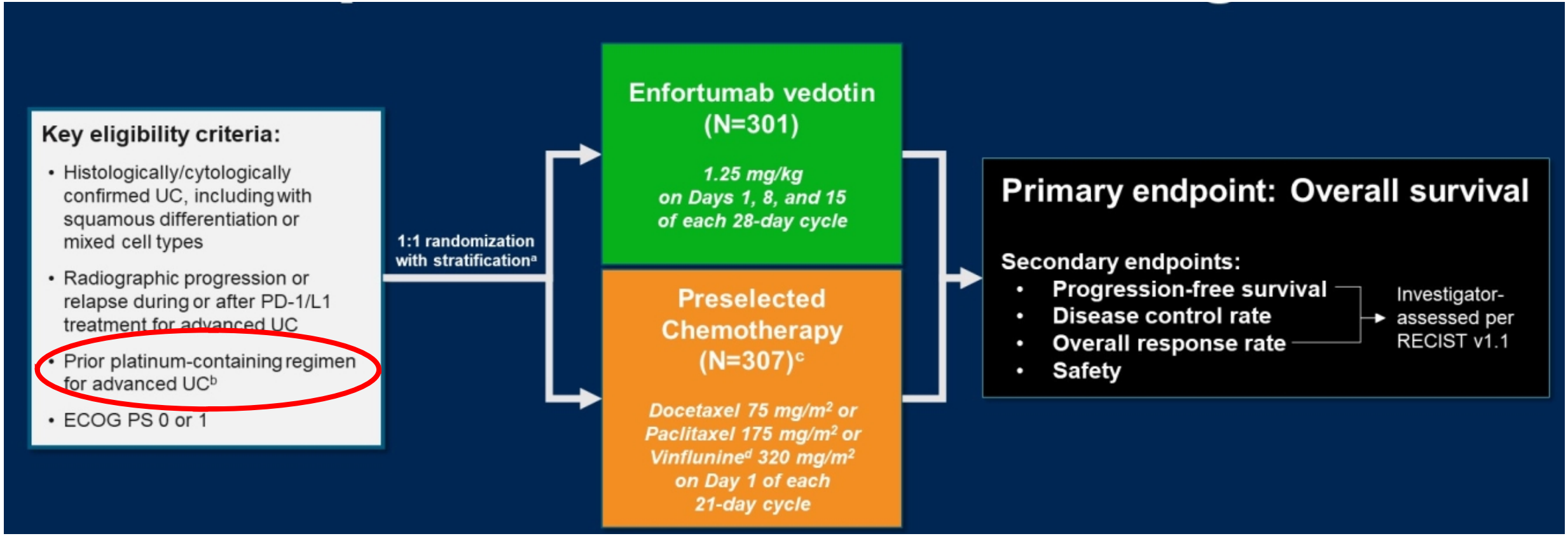


Enfortumab Vedotin (EV)

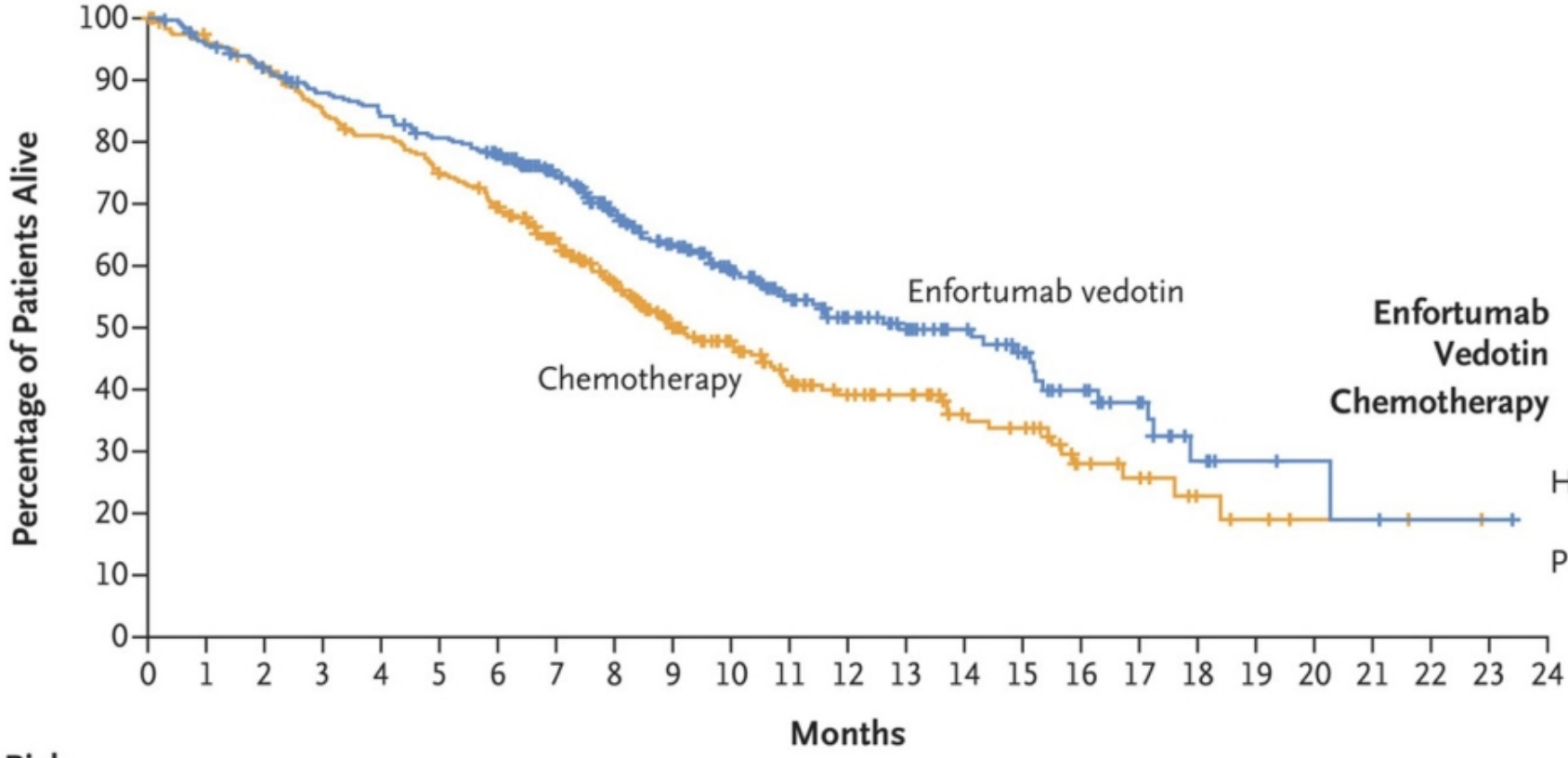
- Targets Nectin-4
  - Transmembrane adhesion molecule expressed on skin, urothelium, salivary gland ducts, esophagus, and stomach.
- Protease-cleavable linker
- Conjugated to monomethylauristatin-E (MMAE)



EV-301: Phase 3 Clinical Trial



EV-301: EV improves mOS



	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI)
		mo
Enfortumab Vedotin	134/301	12.88 (10.58–15.21)
Chemotherapy	167/307	8.97 (8.05–10.74)

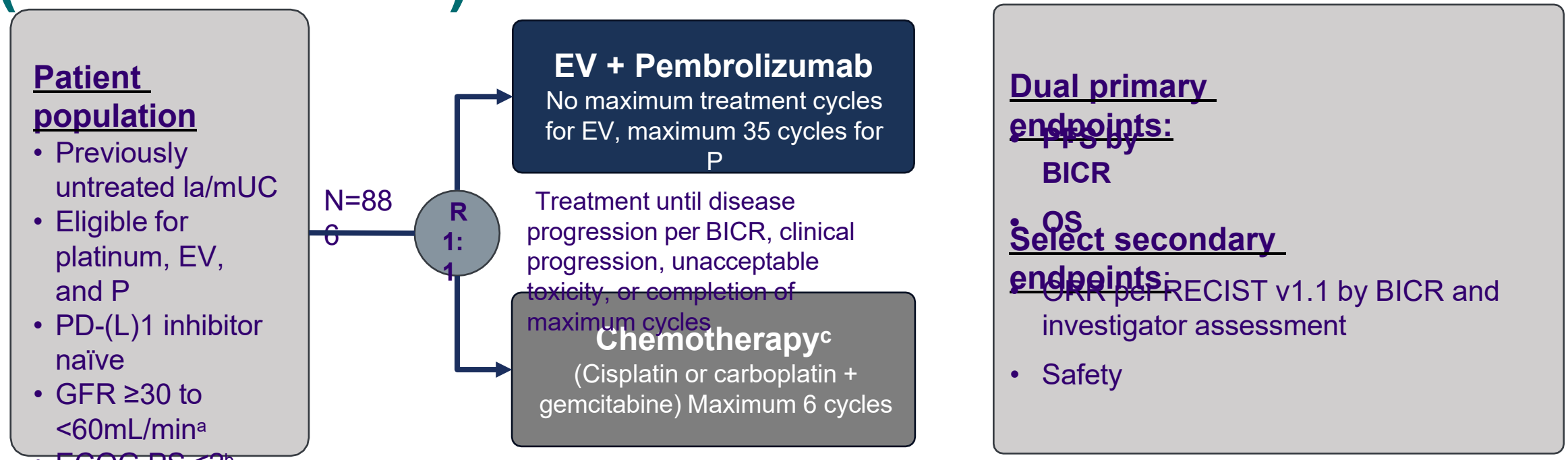
Hazard ratio for death, 0.70 (95% CI, 0.56–0.89)
P=0.001

No. at Risk																								
Enfortumab vedotin	301	286	272	257	246	234	222	190	158	130	105	85	63	52	42	33	23	15	7	4	3	2	1	1	0
Chemotherapy	307	288	274	250	238	219	198	163	131	101	84	66	51	44	32	29	16	11	6	4	2	2	1	0	0

- Progression free survival = 5.55 mo vs 3.71 mo; HR 0.62 [95%CI 0.51 – 0.75, p<0.001]
- Overall response rate = 40.6% vs 17.9%, p<0.001 (CR in 4.9% vs 2.7%)
- Disease control in 71.9% vs 53.4%, p<0.001

Powles T, et al. NEJM 2021.

EV-302/KEYNOTE-A39 (NCT04223856)



Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; patients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1

Statistical plan for analysis: the first planned analysis was performed after approximately 526 PFS (final) and 356 OS events (interim); if OS was positive at interim, the OS interim analysis was considered final

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; ORR, overall response rate; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors

[a]Measured by the Cockcroft-Gault formula, Modification of Diet in Renal Disease, or 24-hour urine

[b]Patients with ECOG PS of 2 were required to also meet the additional criteria: hemoglobin ≥10 g/dL, GFR ≥50mL/min, may not have NYHA class III heart failure

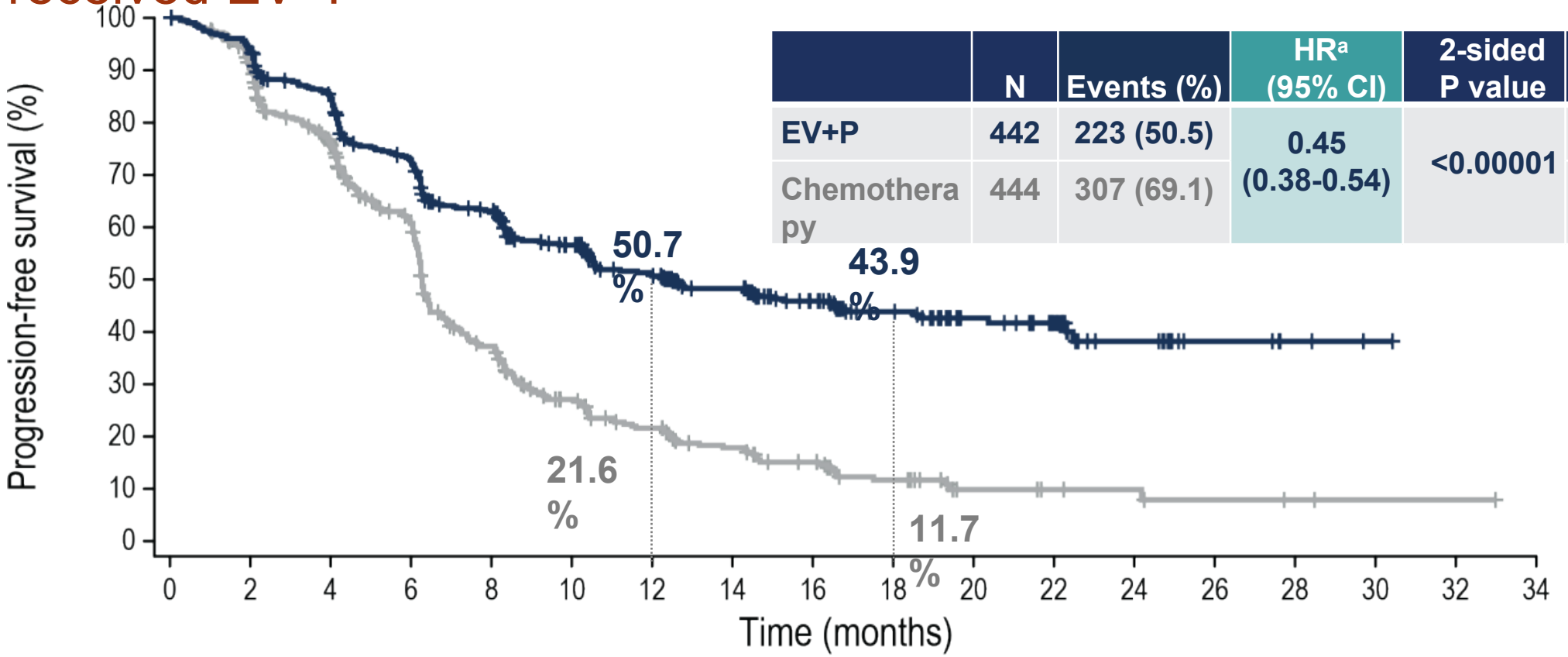
[c]Maintenance therapy could be used following completion and/or discontinuation of platinum-containing therapy

Data cutoff: 08 Aug 2023; FPI: 7 Apr 2020, LPI: 09 Nov 2022

Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mPFS (95% CI), months
EV+P	442	223 (50.5)	0.45 (0.38-0.54)	<0.00001	12.5 (10.4-16.6)
Chemotherapy	444	307 (69.1)			6.3 (6.2-6.5)



N at risk

EV+P	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1
Chemotherapy	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1	1

Data cutoff: 08 Aug 2023

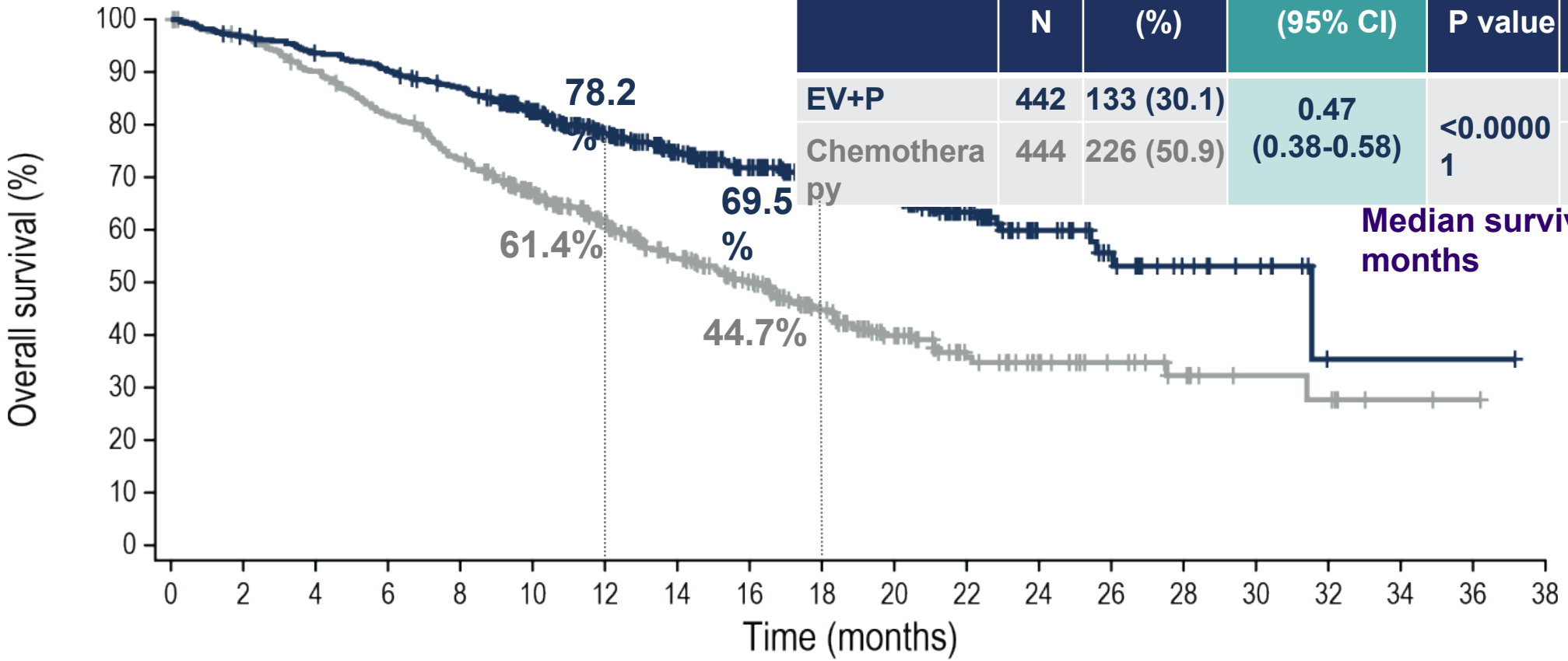
PFS at 12 and 18 months as estimated using Kaplan-Meier method HR, hazard ratio; mPFS, median progression-free survival

[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm.

Overall Survival

Risk of death was reduced by 53% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)



Median survival follow-up: 17.2 months

N at risk

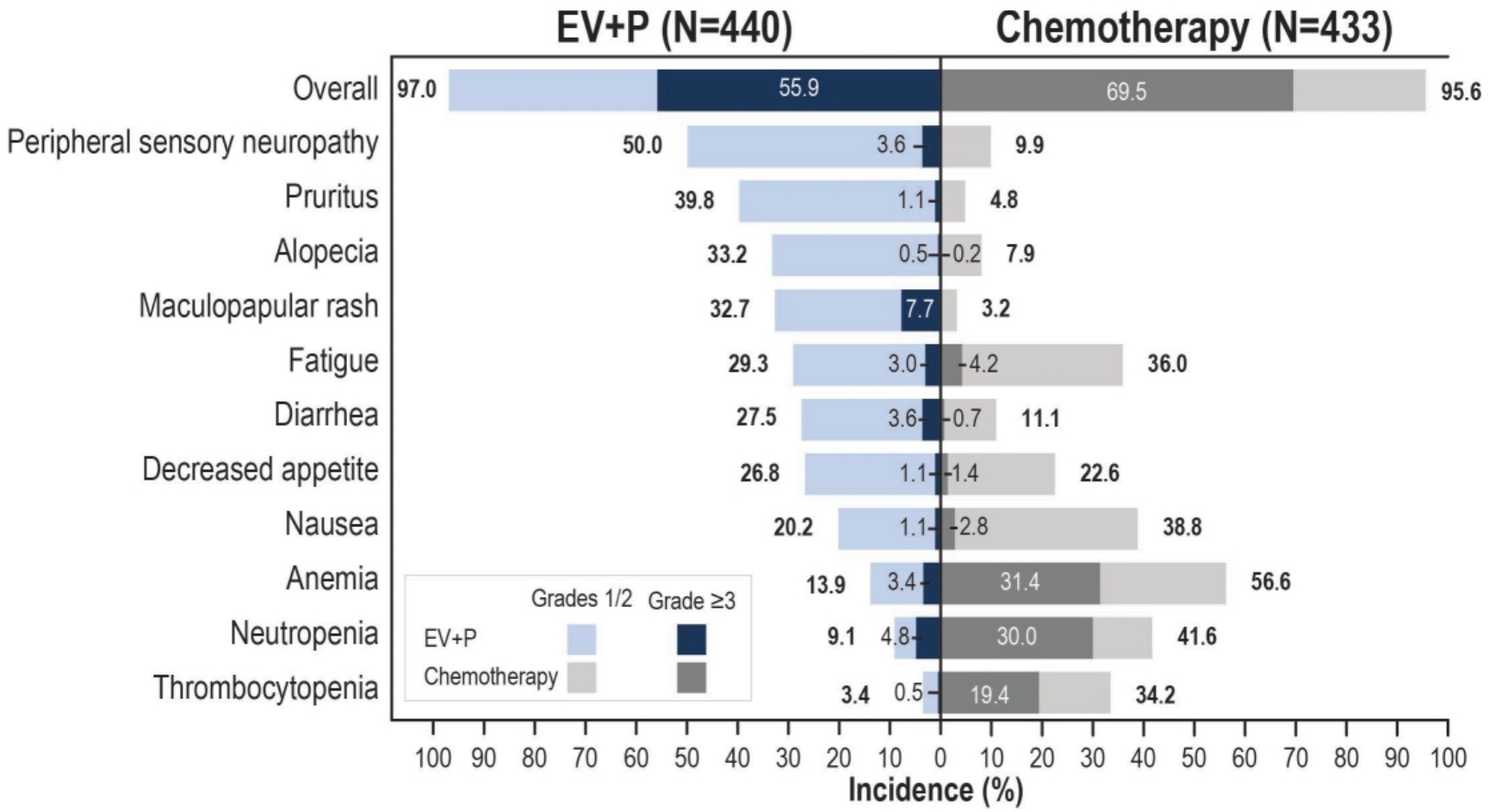
EV+P	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

Data cutoff: 08 Aug 2023

OS at 12 and 18 months was estimated using Kaplan-Meier method. [a]Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+P arm
mOS, median overall survival; NR, not reached

Treatment-Related Adverse Events

Grade ≥3 events were 56% in EV+P and 70% in chemotherapy



Serious TRAEs:
- 122 (27.7%) EV+P
- 85 (19.6%) chemotherapy

TRAEs leading to death (per investigator):
EV+P: 4 (0.9%)
- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

Chemotherapy: 4 (0.9%)
- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

Median number of cycles (range): 12.0 (1,46) for EV+P; 6.0 (1,6) for chemotherapy

Powles et al.

TRAEs shown in figure are any grade by preferred term in ≥20% of patients for any grade in either arm TRAEs, treatment-related adverse events

UW Medicine

Enfortumab Vedotin - Key Adverse Events

- **Skin reactions**
  - Occurs in > 50% with 13% grade 3-4
- **Peripheral neuropathy**
  - Occurs in > 50% with 4% grade 3-4
- **Hyperglycemia and diabetic ketoacidosis**
  - 7% develop grade 3-4 hyperglycemia
  - Hold with levels > 200 mg/dL
- **Pneumonitis**

Changing Treatment Landscape Metastatic UC

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MVAC

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Gemcitabine/Cisplatin

2012
Gem/Carbo

2016
~~Atezolizumab~~
(2nd line)

2017
Pembrolizumab
Nivolumab
~~Durvalumab~~
Avelumab
(all 2nd line)

2017
~~Atezolizumab~~
Pembrolizumab
(1st line)

2019
Erdafitinib
(2nd line)

2020
Avelumab
maintenance
after platinum
(1st line)

2021
Enfortumab
Vedotin
(2rd line)

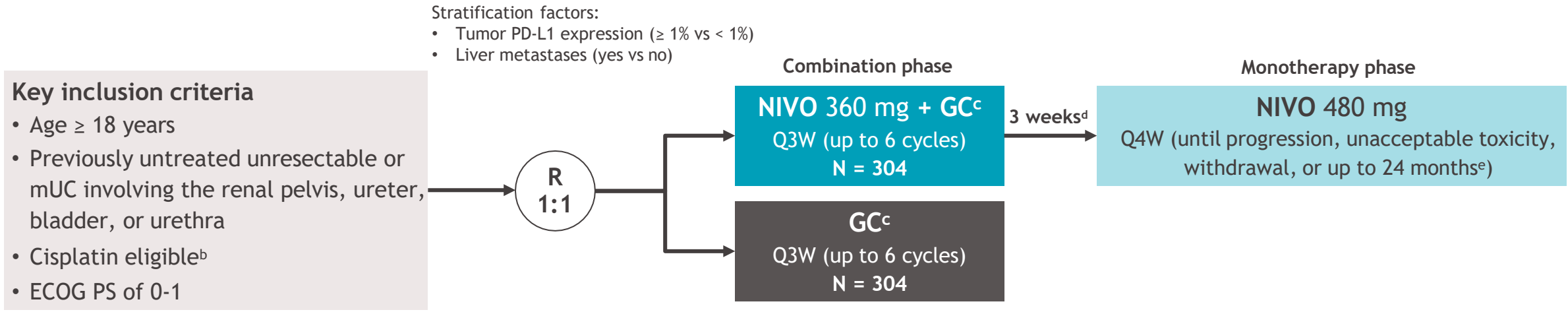
2021
Sacituzumab
Govitecan
(3rd line)

2021
Nivolumab
(Adjuvant)

2023
EV + Pembrolizumab
(1st line)

2024
Gem/Cis/Nivolumab
(1st line)

Study design (NIVO+GC vs GC in cisplatin-eligible patients)[a]



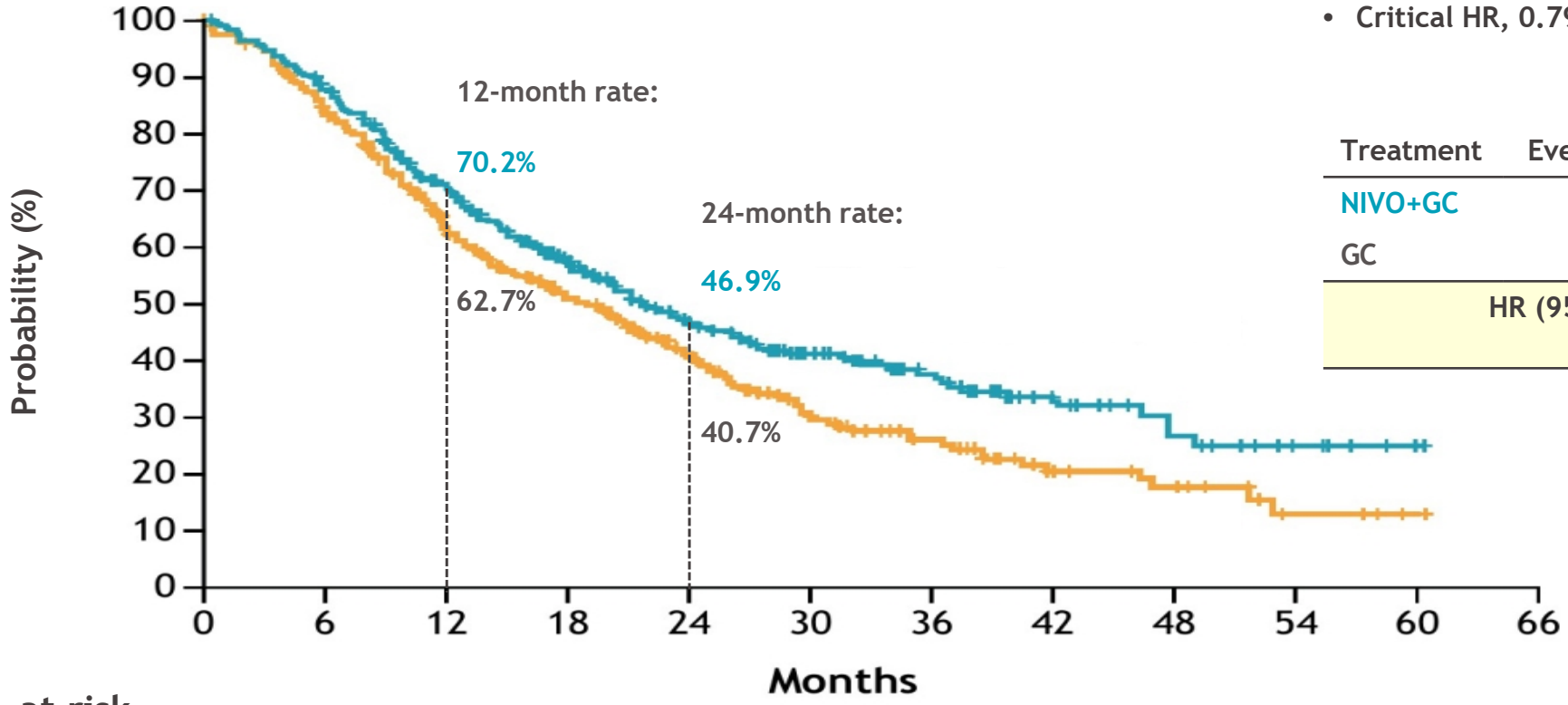
Median (range) study follow-up 33.6 (7.4–62.4) months

Primary endpoints: OS, PFS per BICR
Key secondary endpoints: OS and PFS by PD-L1 ≥ 1%, HRQoL
Key exploratory endpoints: ORR per BICR, safety

[a]Further CheckMate 901 study design details are available at https://clinicaltrials.gov/ct2/show/NCT03036098. [b]Cisplatin eligibility was determined in the study population by a GFR ≥ 60 mL/min (assessed by direct measurement, ie, creatinine clearance, or, if not available, using the Cockcroft-Gault formula), and absence of CTCAE v.4 grade ≥ 2 hearing loss and grade ≥ 2 peripheral neuropathy. [c]Patients who discontinued cisplatin alone could be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to six cycles in total). [d]NIVO monotherapy should begin 3 weeks after the last dose of NIVO+GC combination. [e]Represents a maximum of 24 months from the first dose of NIVO administered as part of the NIVO+GC combination.
BICR, blinded independent central review; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; HRQoL, health-related quality of life; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q×W, every × weeks; R, randomization.

OS (primary endpoint)

OS final analysis statistical boundaries:
- *P* value boundary, 0.0311
- Critical HR, 0.7980



Treatment	Events/patients	Median OS (95% CI), months
NIVO+GC	172/304	21.7 (18.6-26.4)
GC	193/304	18.9 (14.7-22.4)
HR (95% CI), 0.78 (0.63-0.96) *P* = 0.0171		

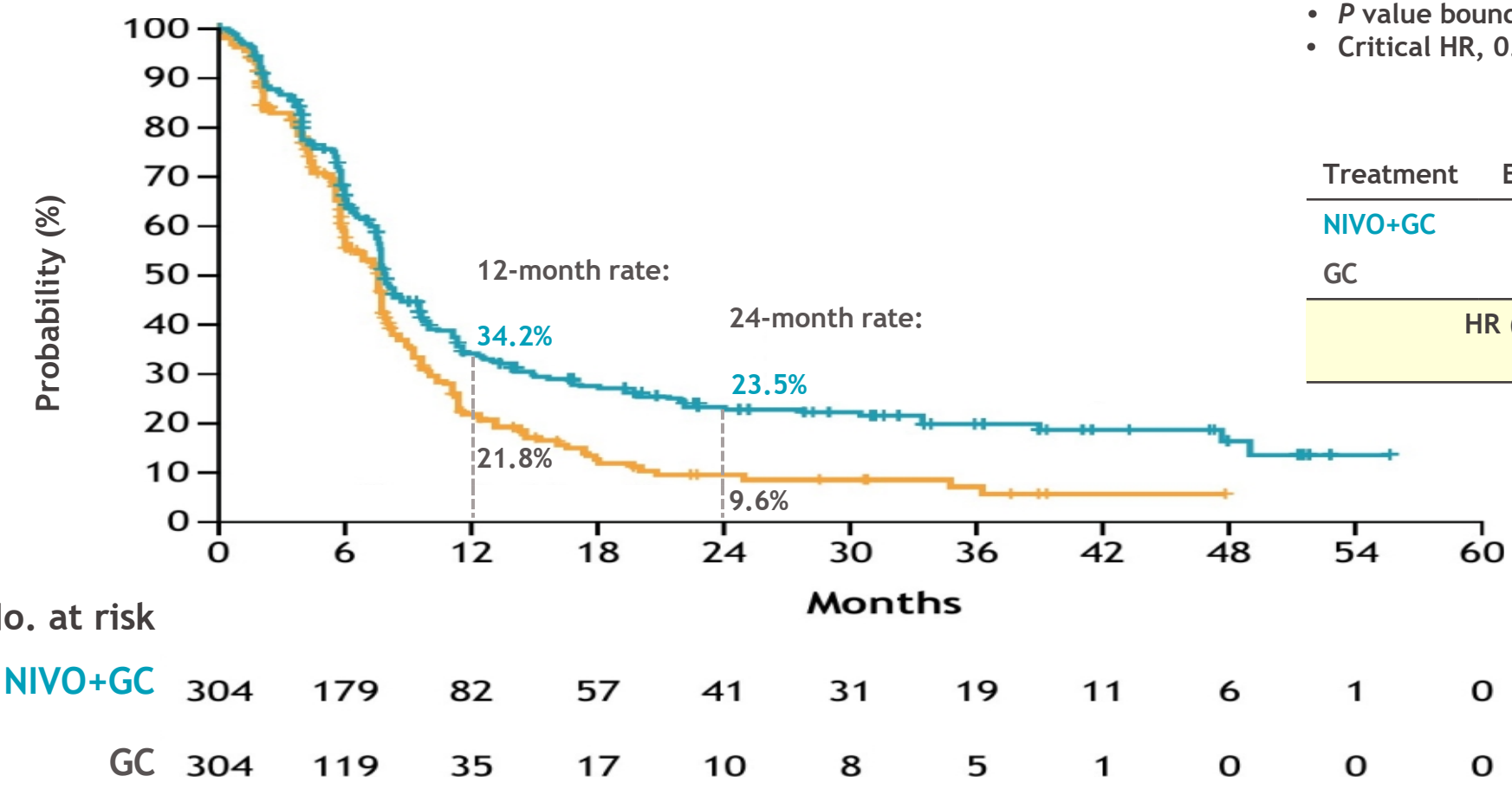
No. at risk

NIVO+GC	304	264	196	142	97	69	48	25	15	7	2	0
GC	304	242	166	122	82	49	33	17	13	4	1	0

Median (range) study follow-up was 33.6 (7.4-62.4) months. OS was estimated in all randomized patients and defined as the time from date of randomization to date of death from any cause. For patients without documented death, OS was censored on the last date the patient was known to be alive. For randomized patients with no follow-up, OS was censored at the date of randomization.

PFS per BICR (primary endpoint)

PFS final analysis statistical boundaries:
- *P* value boundary, 0.01
- Critical HR, 0.7734



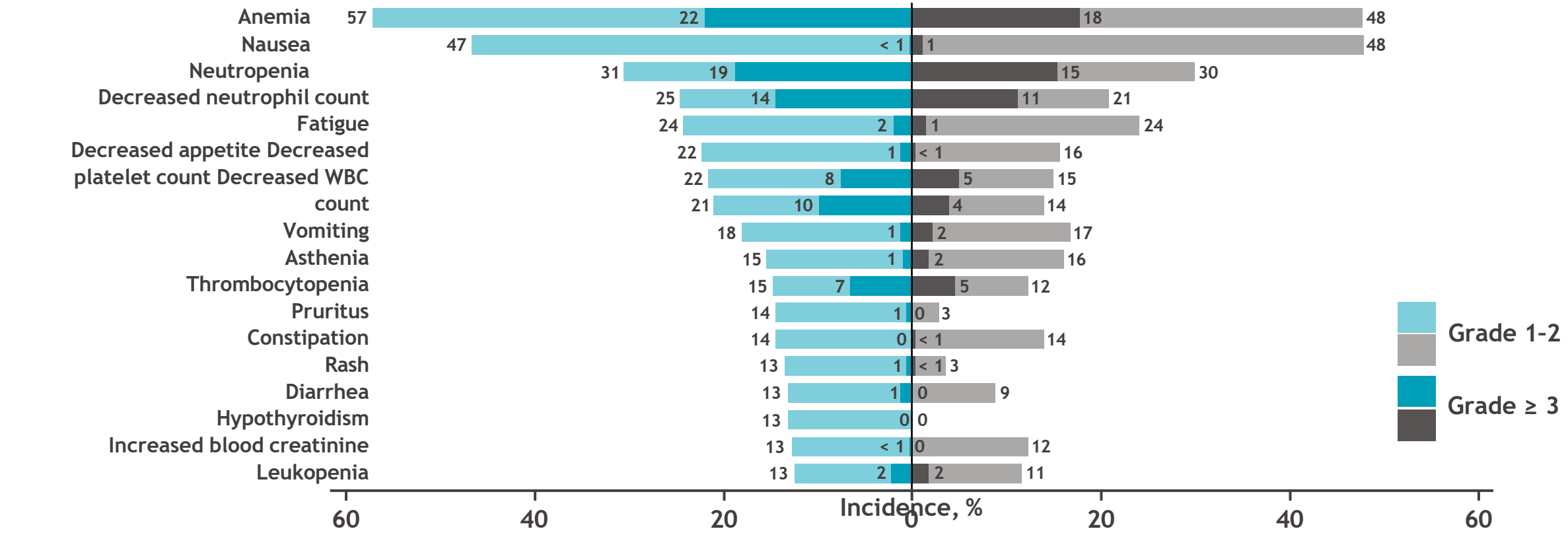
Treatment	Events/patients	Median PFS (95% CI), months
NIVO+GC	211/304	7.9 (7.6-9.5)
GC	191/304	7.6 (6.1-7.8)
HR (95% CI), 0.72 (0.59-0.88) *P* = 0.0012		

Median (range) study follow-up was 33.6 (7.4-62.4) months. PFS was estimated in all randomized patients and defined as the time from date of randomization to date of first documented disease progression (per BICR assessments using RECIST v1.1) or death due to any cause, whichever occurred first. Patients who died without reported progression were considered to have progressed on the date of death. Patients who did not progress or die were censored on the last evaluable tumor assessment date. Patients without on-study tumor assessments who did not die were censored on the date of randomization. **Patients who started any subsequent anticancer therapy without prior reported progression were censored at the last evaluable tumor assessment before initiation of subsequent anticancer therapy.**

RECIST, Response Evaluation Criteria in Solid Tumors.

Treatment-related AEs in all treated patients

	NIVO+GC (n = 304)		GC (n = 288)	
Treatment-related AE, %[a]	Any grade	Grade ≥ 3[b]	Any grade	Grade ≥ 3[b]
Any	97	62	93	52
Leading to DC	21	11	17	8



[a]Includes events that occurred in treated patients between first dose and 30 days after last dose of study therapy. Tornado plot displays individual treatment-related AEs occurring at any grade in ≥ 10% of treated patients in either arm. [b]One grade 5 event occurred in each arm (sepsis in the NIVO+GC arm and acute kidney injury in the GC arm). DC, discontinuation; WBC, white blood cell.

DESTINY-PanTumor02: T-DXd in HER2-Expressing Solid Tumors[1-4,a]

An open-label, multicenter study (NCT04482309)

Key Eligibility Criteria

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer scoring)[b]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0-1

T-DXd
5.4 mg/kg
Q3W

40 per cohort[c]

- Endometrial cancer
- Cervical cancer
- Ovarian cancer
- Bladder cancer
- Other tumors[d]
- Biliary tract cancer
- Pancreatic cancer

- **Primary endpoint:** confirmed ORR (investigator)
- **Secondary endpoints:** DOR, DCR, PFS, OS, safety
- **Exploratory analysis:** subgroup analysis by HER2 status

Baseline Characteristics

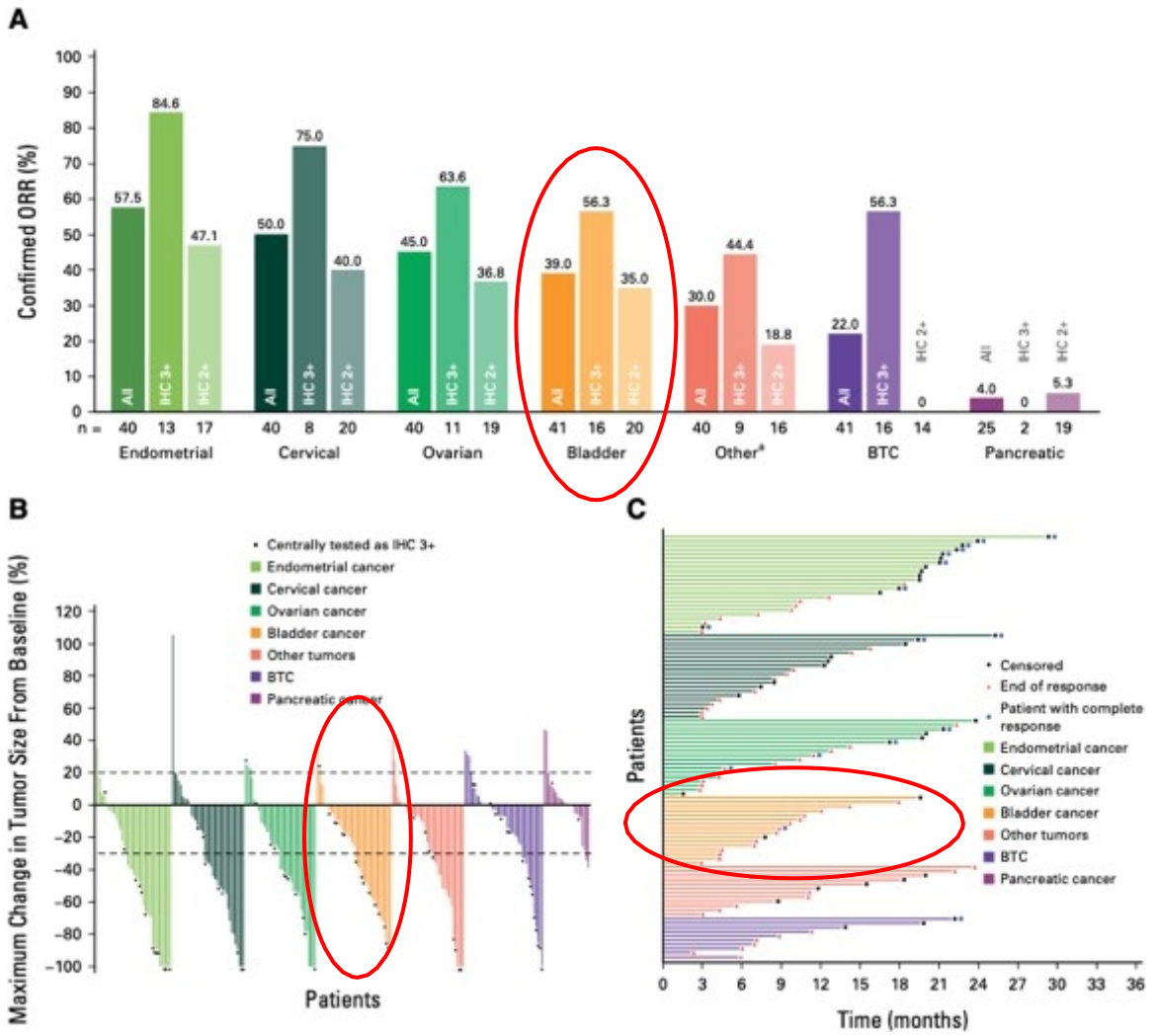
- 267 pts received treatment; 202 (75.7%) based on local HER2 testing
  - 111 (41.6%) pts were IHC 3+ based on HER2 test (local or central) at enrollment; primary efficacy analysis (all patients)
  - 75 (28.1%) pts were IHC 3+ on central testing; sensitivity analysis on efficacy endpoints (subgroup analyses)
- Median age 62 (23-85);109 (41%) pts had received ≥3 lines of therapy

[a] Primary analysis data cutoff: June 8, 2023; median follow-up: 12.75 mo. [b] Patients were eligible for either test. All patients were centrally confirmed.
[c] Planned recruitment, cohorts with no objective responses in the first 15 patients were to be closed. [d] Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, NSCLC, gastric cancer, and CRC.

1. https://clinicaltrials.gov/study/NCT04482309. 2. Hofmann M et al. *Histopathology*. 2008;52:797-805. 3. Meric-Bernstam F et al. ESMO 2023. Abstract LBA34.
4. Meric-Bernstam F et al. *J Clin Oncol*. 2024;42:47-58.

DESTINY-PanTumor02 Trial Results: UC Cohort

Tumor Response



UC Cohort Outcomes

	Overall (N=41)	HER2 IHC 3+ (n=16)	HER2 IHC 2+ (n=20)
mPFS, mo	7.0	7.4	7.8
mOS, mo	12.8	13.4	13.1
ORR, %	39.0	56.3	35.0
mDOR, mo	8.7	-	-

Meric-Bernstam F et al. *J Clin Oncol*. 2023;42:47-58.

Tumor-Agnostic FDA Approval for T-DXd[1-3]

- **Updated NCCN Guidelines for Bladder Cancer[1]**
  - Second- or subsequent-line therapy:
  - T-DXd for HER2-positive tumors (IHC 3+ or 2+)

Accelerated FDA Approval[2]

For adults with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options

1. NCCN Bladder Cancer Guidelines V4.2024. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.
2. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2.
3. ENHERTU (fam-trastuzumab deruxtecan-nxki) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.pdf.

Mr. Smith is a 71-year-old man with a PMH remarkable for HTN, hypercholesterolemia, degenerative arthritis who presented with painless hematuria. Otherwise, ROS is unremarkable. Cystoscopy revealed a 3 cm papillary mass on the lateral bladder wall, which was maximally resected via TURBT. Pathology showed high-grade urothelial carcinoma; detrusor muscle was present with invasion by the carcinoma. IHC was positive for GATA3 and p40. Staging CT of the chest and CTU scan showed enlarged retroperitoneal lymph nodes and two lung nodules consistent with metastatic disease. Laboratory test showed creatinine levels 1.7 and eGFR of 42. HBG 12.3 gr/dl. ECOG PS 1. Rest of the labs were unremarkable. No peripheral neuropathy. What of the following statements are true?

A. Initiate Enfortumab vedotin plus pembrolizumab
B. Obtain 24-hour urine
C. Recommend carboplatin-gemcitabine x 6 cycles
D. Consider cisplatin-gemcitabine in combination with nivolumab x 6 cycles and plan for maintenance nivolumab monthly for 2 years
E. A and D are true

Mrs. Johnson is a 68-year-old woman with metastatic urothelial carcinoma (UC), referred for a second opinion. Her oncologic history is notable for a diagnosis of cT2N0 MIBC two years ago. She received neoadjuvant chemotherapy with dose-dense MVAC for three cycles, followed by radical cystectomy and lymphadenectomy. Pathology revealed ypT2pN1 MIBC. She declined adjuvant therapy. Unfortunately, 10 months ago, she was diagnosed with recurrent disease. Imaging demonstrated multiple pelvic and retroperitoneal lymph nodes, along with three liver metastases. She was started on enfortumab vedotin plus pembrolizumab, which was continued until disease progression noted last month. She has residual grade 3 residual peripheral neuropathy. What of the following statements are true?

A. Obtain tumor next-generation sequencing
B. Obtain HER-2 testing
C. Recommend a FDG PET CT scan
D. Carboplatin-based chemotherapy is an appropriate next line of treatment
E. A, B and C are true
F. A, B and D are true

Summary of Treatment Approach

Disease State	Preferred Option	Other Options
Metastatic, no prior therapy (1L)	**Enfortumab-vedotin + Pembrolizumab**	**-Gem/Cis + nivolumab (cisplatin-fit)** **-Gem + (Cis or Carbo) f/b avelumab maintenance (if no progression)** ***-Pembrolizumab (platinum/EV-unfit)*** ***-Single agent chemo (platinum/EV-unfit)***
Metastatic (prior therapy)	**Platinum-based chemo (after EV/P) *OR*** **Erdafitinib (tumors with *FGFR3* activating mutation or fusion) OR** **Enfortumab-vedotin (if not used prior) OR** **Pembrolizumab (if IO not used prior)**	**-Sacituzumab-govitecan** **-T-DXd (HER2 IHC +3 or +2)**
Metastatic (≥2 prior therapies)	**Erdafitinib (tumors with *FGFR3* activating mutation or fusion) OR** **Enfortumab-vedotin (if not used prior) OR** **Sacituzumab-govitecan OR** **Pembrolizumab (if IO not used prior),** **T-DXd (HER2 IHC +3 or +2)**	***-Taxane (US)*** ***-Vinflunine (EU)***

Slide Compliments: Petros Grivas, MD, PhD

Clinical trials are critical throughout disease spectrum!

QUESTIONS?