Bladder Cancer

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Disclosures

- Institutional research funding: Astra Zeneca, BMS, Barinthus, Macrogenics, Crescendo Biologics, Janssen, Amgen, Promicell
- Consulting: Seagen, ImmunityBio, Daiichi-Sankyo, GSK

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 (and evolving) treatment paradigm for locally advanced / metastatic UC.

Outline

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

Outline

- **Epidemiology**
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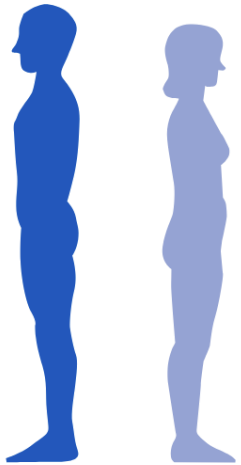
Figure 3. Leading Sites of New Cancer Cases and Deaths – 2024 Estimates

Estimated New Cases

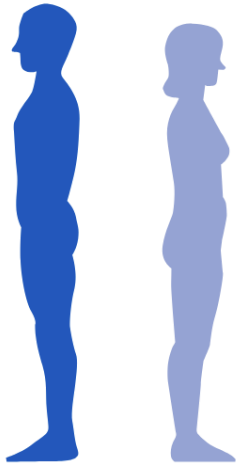
Male			Female		
Prostate	299,010	29%	Breast	310,720	32%
Lung & bronchus	116,310	11%	Lung & bronchus	118,270	12%
Colon & rectum	81,540	8%	Colon & rectum	71,270	7%
Urinary bladder	63,070	6%	Uterine corpus	67,880	7%
Melanoma of the skin	59,170	6%	Melanoma of the skin	41,470	4%
Kidney & renal pelvis	52,380	5%	Non-Hodgkin lymphoma	36,030	4%
Non-Hodgkin lymphoma	44,590	4%	Pancreas	31,910	3%
Oral cavity & pharynx	41,510	4%	Thyroid	31,520	3%
Leukemia	36,450	4%	Kidney & renal pelvis	29,230	3%
Pancreas	34,530	3%	Leukemia	26,320	3%
All sites	**1,029,080**		**All sites**	**972,060**	



20,120 in biologic women

Estimated Deaths

Male			Female		
Lung & bronchus	65,790	20%	Lung & bronchus	59,280	21%
Prostate	35,250	11%	Breast	42,250	15%
Colon & rectum	28,700	9%	Pancreas	24,480	8%
Pancreas	27,270	8%	Colon & rectum	24,310	8%
Liver & intrahepatic bile duct	19,120	6%	Uterine corpus	13,250	5%
Leukemia	13,640	4%	Ovary	12,740	4%
Esophagus	12,880	4%	Liver & intrahepatic bile duct	10,720	4%
Urinary bladder	12,290	4%	Leukemia	10,030	3%
Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,360	3%
Brain & other nervous system	10,690	3%	Brain & other nervous system	8,070	3%
All sites	**322,800**		**All sites**	**288,920**	



4,550 in biologic women

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

Risk Factors

Reversible (somewhat)

- 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

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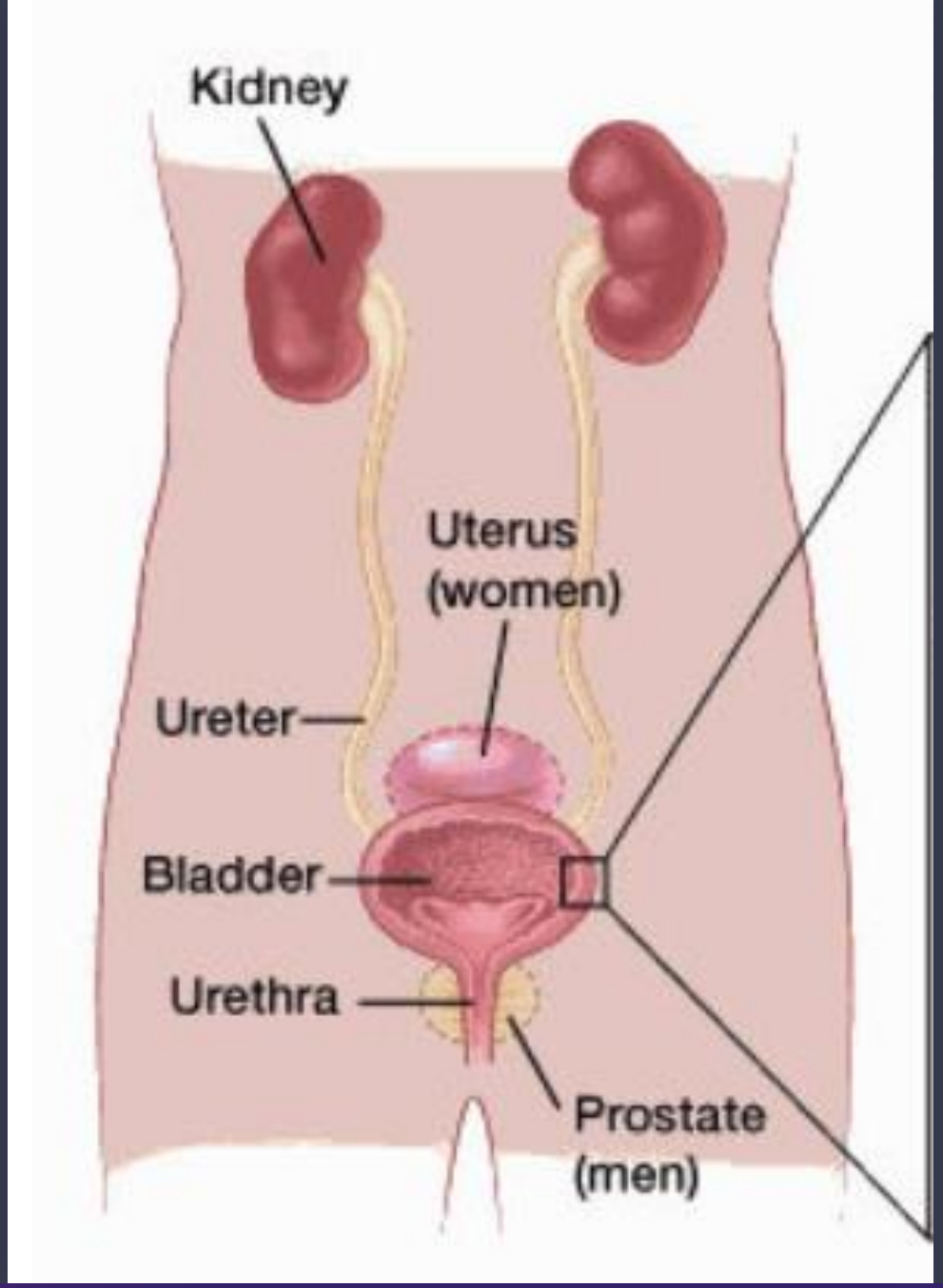
Location & Pathology

- 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:
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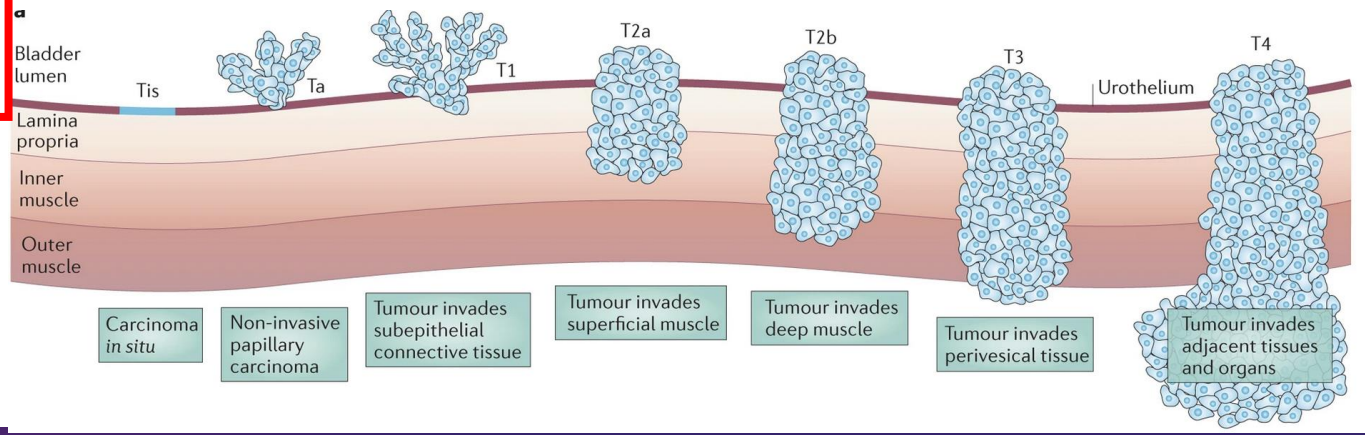
Diagnosis & Staging

- Hematuria!
- Irritative voiding symptoms in pts with RFs (tobacco use) 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

Problem: 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

N	Regional Lymph Nodes
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes

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

AJCC TNM Staging System for Bladder Cancer 8th ed., 2017.

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 (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.

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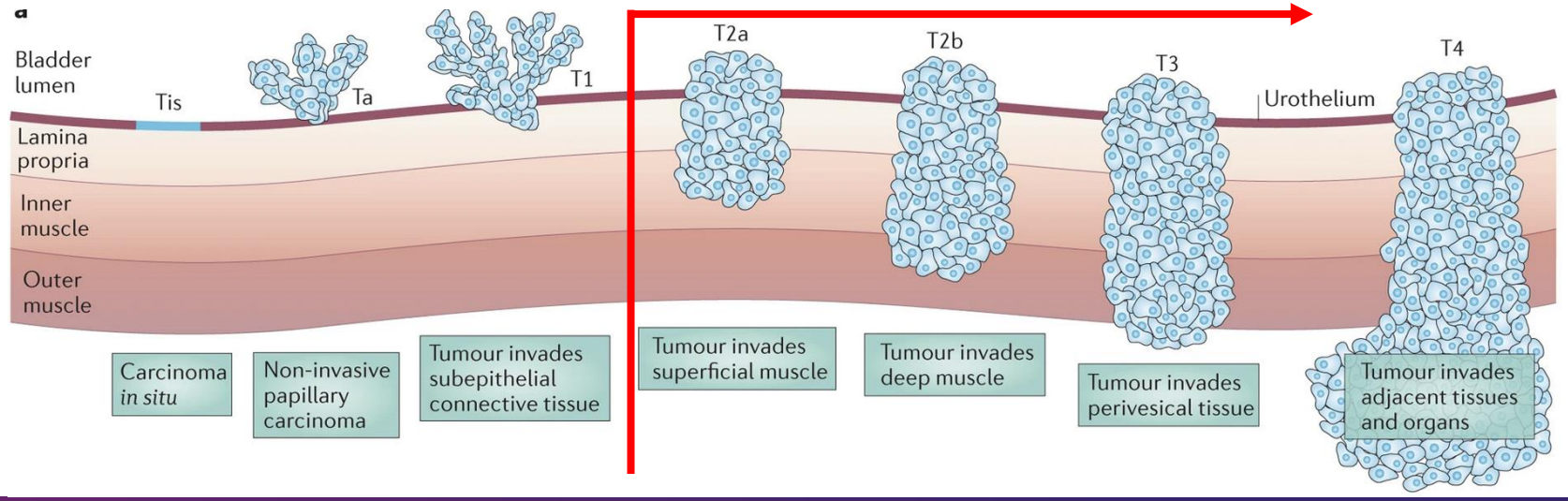
Muscle Invasive Bladder Cancer (MIBC)

- 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>



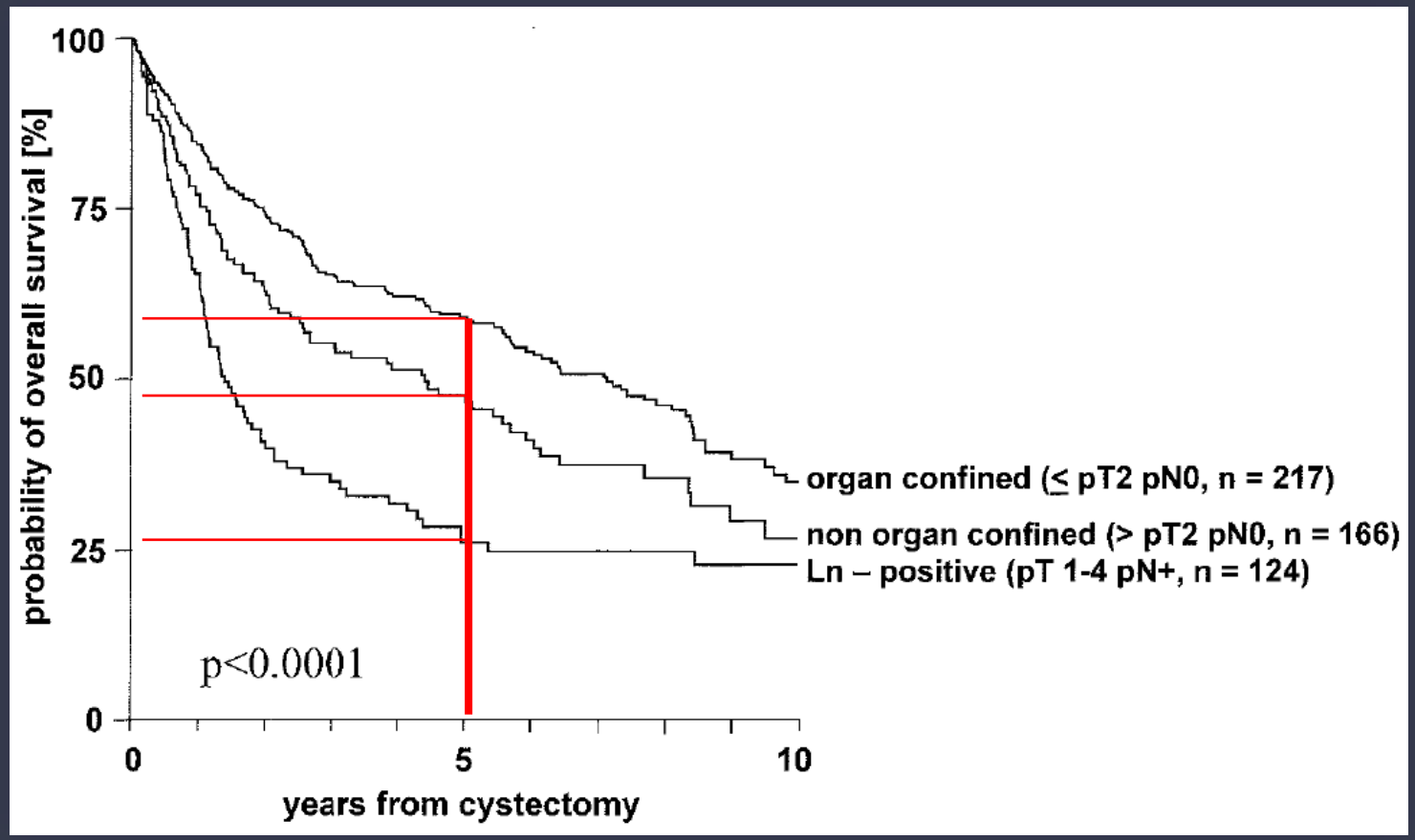
Overall Survival by Disease Burden with Cystectomy

507 consecutive patients between 1985-2000

No neoadjuvant therapy

5-year OS:

- ≤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 micrometastatic disease
- Performance status / tolerance is clearly better prior to cystectomy

Disadvantages

- Delay of potentially curative therapy (cystectomy)

Adjuvant therapy

Advantages

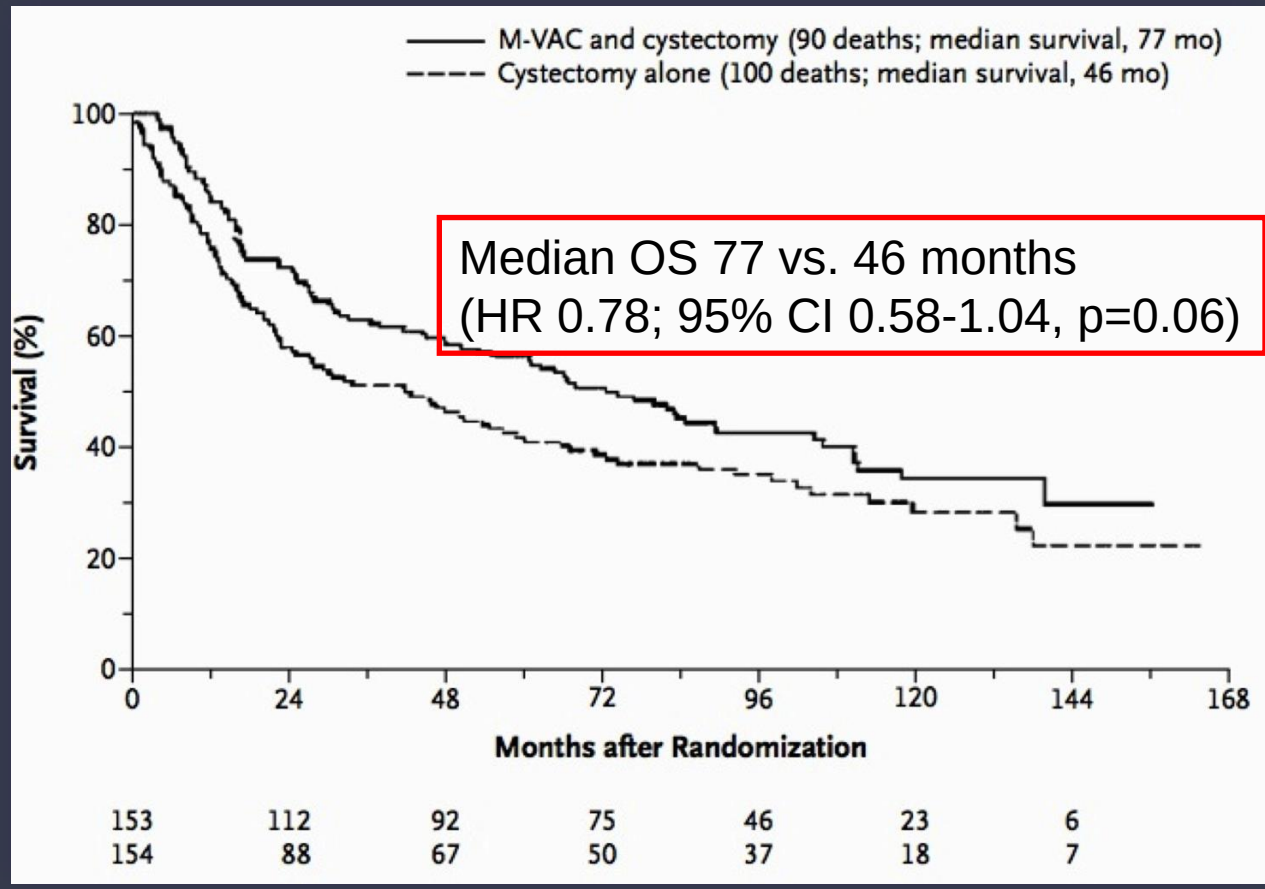
- Better staging and risk assessment

Disadvantages

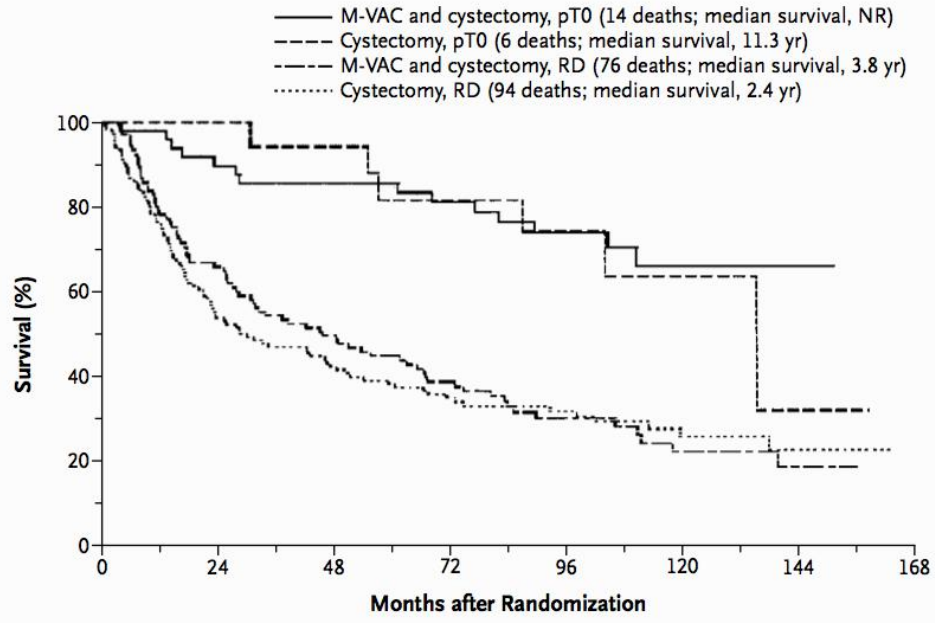
- Evidence for benefit of adjuvant therapy is not robust

SWOG-8710: Neoadjuvant MVAC + Surgery vs. Surgery

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



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

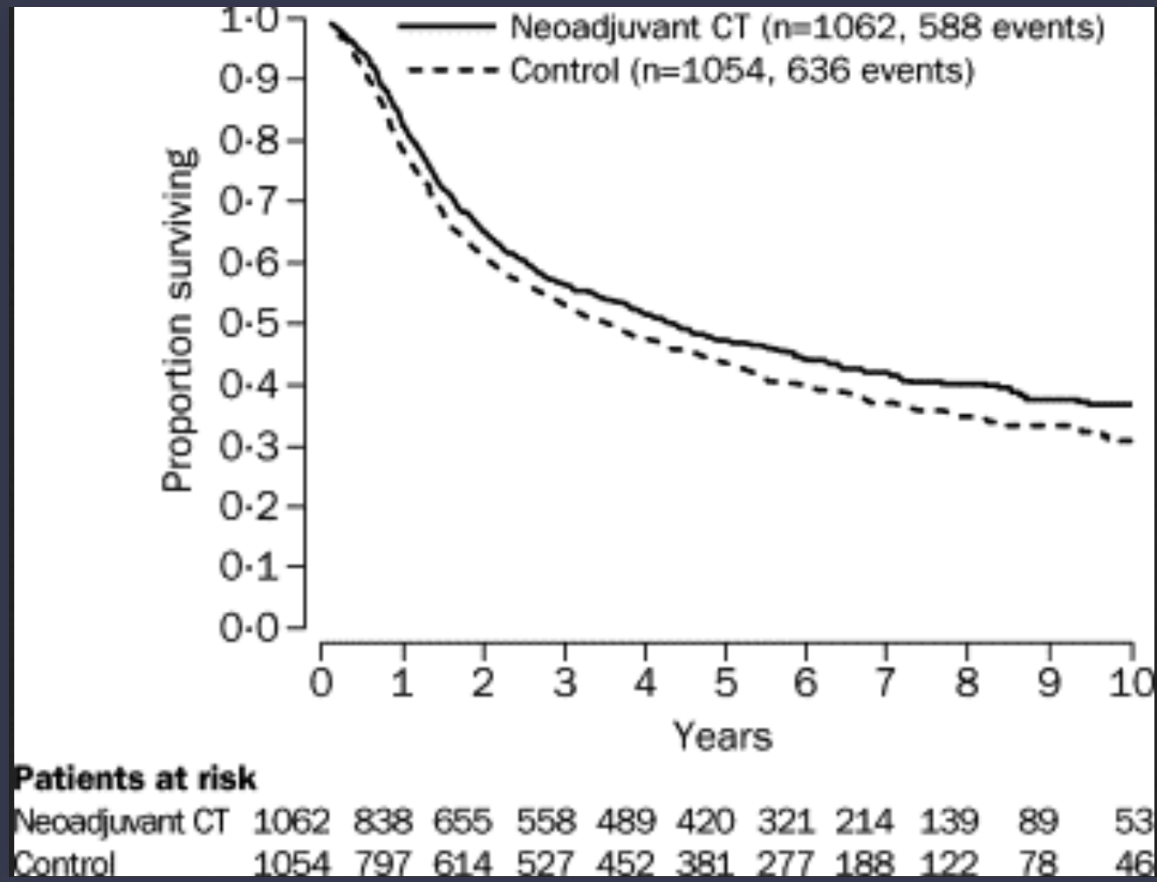
No accurate way to identify patients with 'platinum-sensitive' tumors prior to therapy **YET**

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

UW Medicine

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.

Neoadjuvant Regimens – aMVAC (w/ GF)

- Methotrexate (30 mg/m^2),
- vinblastine (3 mg/m^2),
- doxorubicin (30 mg/m^2),
- cisplatin (70 mg/m^2),
- Growth factor (G-CSF)
- Cycle length 14 days, for 3-6 cycles (4 cycles most common)

- Multicenter phase II trial included pT2 – cT4a tumor staging with N0 and N1 MIBC
- N=44
- Three cycles ddMVAC with pegfilgrastim → RC and lymph node dissection
- Compared favorably to historical control of neoadj classic MVAC
- No Grade 3 or 4 renal toxicities or toxicity-related deaths

- Pathologic downstaging in 49% of patients receiving neoadjuvant ddMVAC

Neoadjuvant Regimens - GC

- Gemcitabine (1000 mg/m^2 on days 1, 8)
- cisplatin (70 mg/m^2 on day 1)
- Cycle length 21 days for 4 cycles.

- Investigated in small phase II or retrospective studies.

- Overall GC is effective and well-tolerated.

- Some studies report lower pathologic response compared to MVAC and lack of demonstrated OS benefit due to short f/u.

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)**

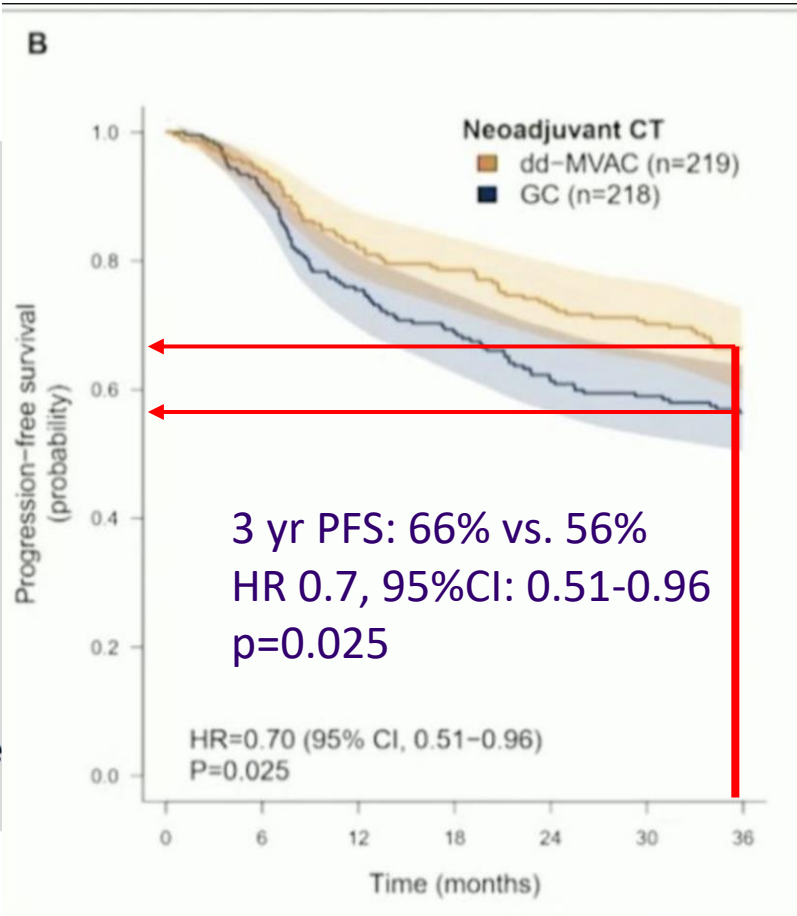
CTCAE Grade ≥3 Toxicities

- **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.

NIAGRA trial: press release (ESMO 2024)

- **Neoadjuvant Durvalumab + chemo** vs. neoadjuvant chemo in MIBC
- Statistically significant & clinically meaningful improvement in event-free survival & overall survival (primary & secondary endpoint) in this phase III trial (NCT03732677): data to be presented ESMO 2024

Ongoing peri-op phase III trials evaluating chemo + ICI vs chemo:

-Gem/Cis +/- pembrolizumab

-Gem/Cis +/- nivolumab

Ongoing peri-op phase III trials evaluating EV + ICI:

-Keynote B15, Keynote 905, VOLGA

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.

Problems with Adjuvant Chemotherapy Studies

- Split results in the existing studies
- Small under-powered studies
- Serious methodological flaws
- Early stopping of patient entry
- Confusing statistical analyses
- Reporting of questionable results

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

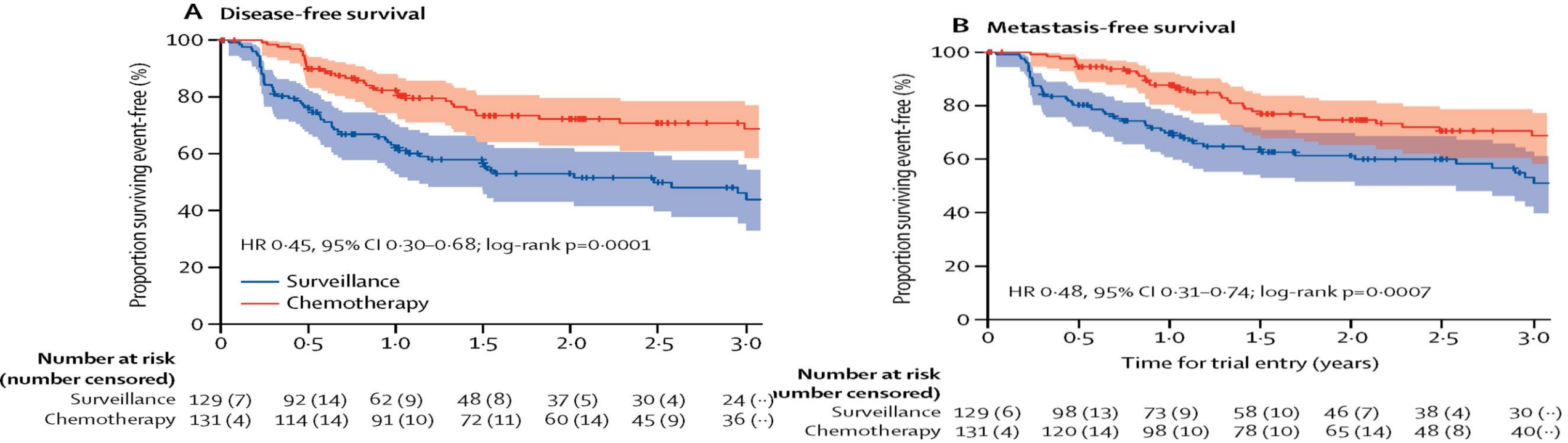
Matthew D. Galsky, Kristian D. Stensland, Erin Moshier, John P. Sfakianos, Russell B. McBride, Che-Kai Tsao, Martin Casey, Paolo Boffetta, William K. Oh, Madhu Mazumdar, and Juan P. Wisnivesky

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

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 Nivolumab

Phase 3 Checkmate 274

- Adjuvant nivolumab vs. placebo in patients with high-risk MIUC
- N = 709
- Inclusion:
  - ypT2-ypT4a or ypN+ (who had **prior NAC)**
  - pT3-pT4a or pN+ **without prior NAC** and not eligible or refuse adj cisplatin
- Stratification on PD-L1 status, prior NAC, nodal status
- Randomized 1:1 to nivolumab IV 240mg Q2W vs. placebo for 1 year of adjuvant therapy

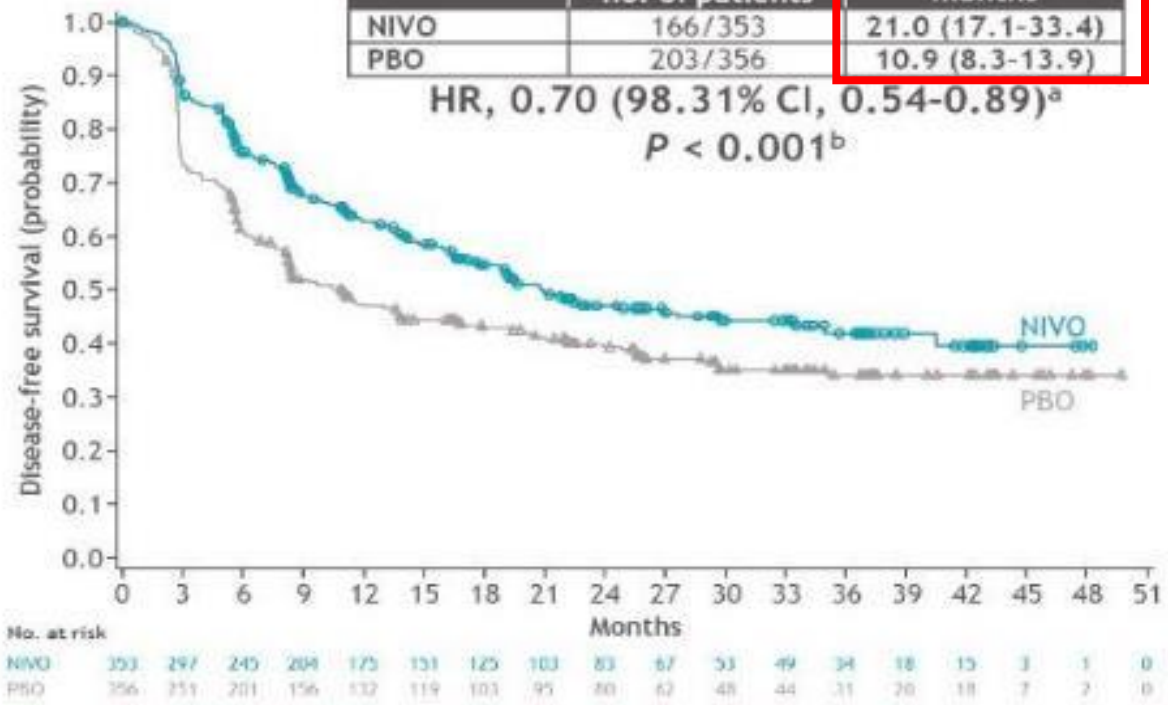
Disease-free survival

ITT

	No. of events/ no. of patients	Median (95% CI), months
NIVO	166/353	21.0 (17.1-33.4)
PBO	203/356	10.9 (8.3-13.9)

HR, 0.70 (98.31% CI, 0.54-0.89)[a]

P < 0.001[b]

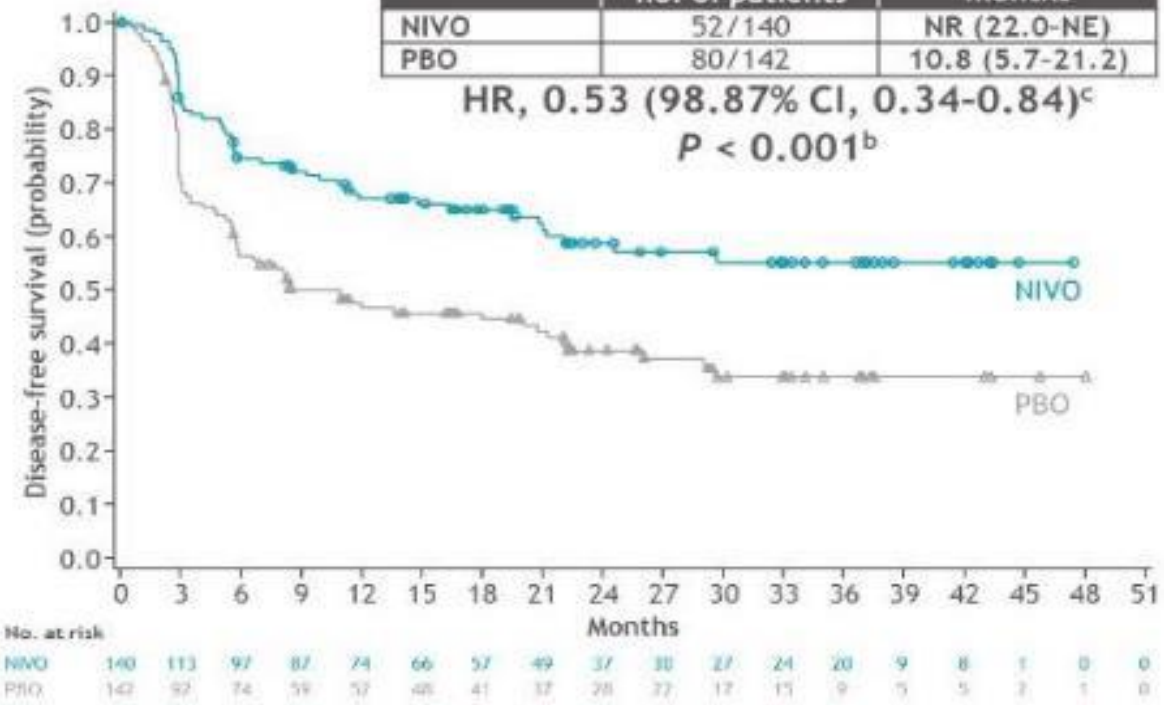


PD-L1 ≥ 1%

	No. of events/ no. of patients	Median (95% CI), months
NIVO	52/140	NR (22.0-NE)
PBO	80/142	10.8 (5.7-21.2)

HR, 0.53 (98.87% CI, 0.34-0.84)[c]

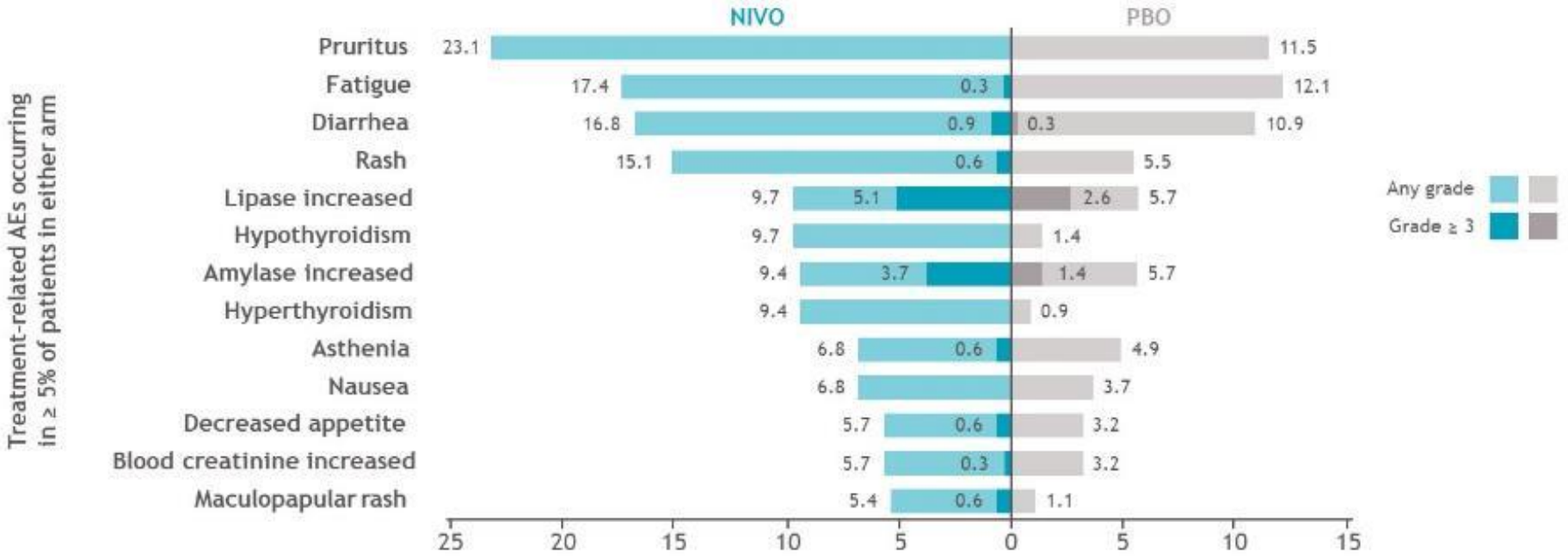
P < 0.001[b]



Minimum follow-up, 5.9 months.
DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
[a]HR, 0.695 (98.31% CI, 0.541-0.894). [b]Based on a 2-sided stratified logrank test. [c]HR, 0.535 (98.87% CI, 0.340-0.842).
CI, confidence interval; NE, not estimable; NR, not reached.

Safety summary in all treated patients

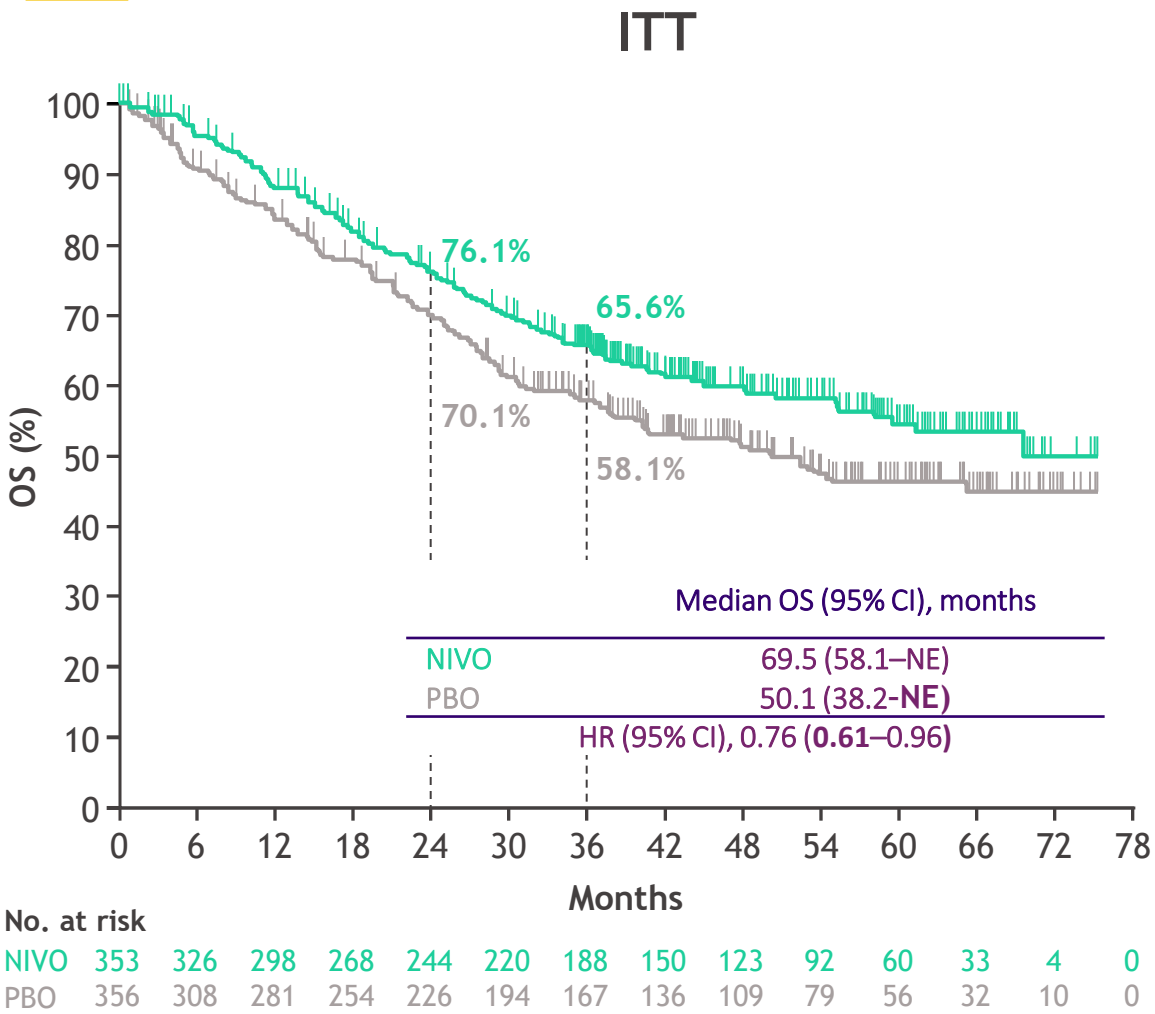
	NIVO (N = 351)[a]		PBO (N = 348)[a]	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any-cause AEs, %	98.9	42.7	95.4	36.8
Treatment-related AEs,[b] %	77.5	17.9	55.5	7.2
Treatment-related AEs leading to discontinuation, %	12.8	7.1	2.0	1.4

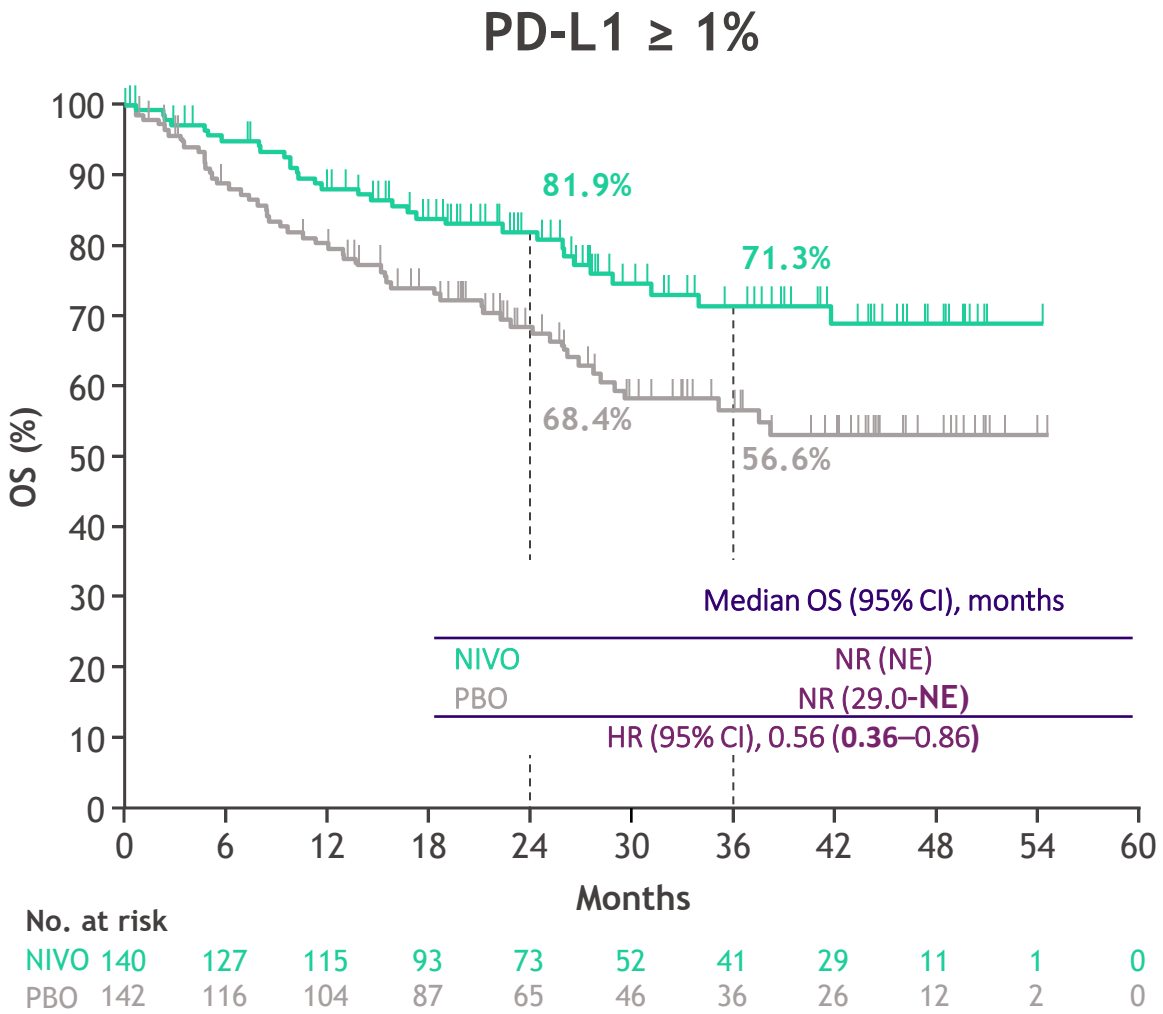


[a]Includes all treated patients. [b]There were 2 treatment-related deaths due to pneumonitis in the NIVO arm. There were no treatment-related deaths in the PBO arm. Includes events reported between the first dose and 30 days after the last dose of study therapy.

Adjuvant Nivolumab: Overall survival (Interim)

- Interim OS data favored NIVO versus PBO in the ITT and tumor PD-L1 ≥ 1% populations





Adjuvant Pembrolizumab

A031501 AMBASSADOR: Study Design

Phase 3 randomized, open label, multicenter study of adjuvant pembrolizumab vs observation in patients with high-risk muscle-invasive urothelial carcinoma (MIUC)

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

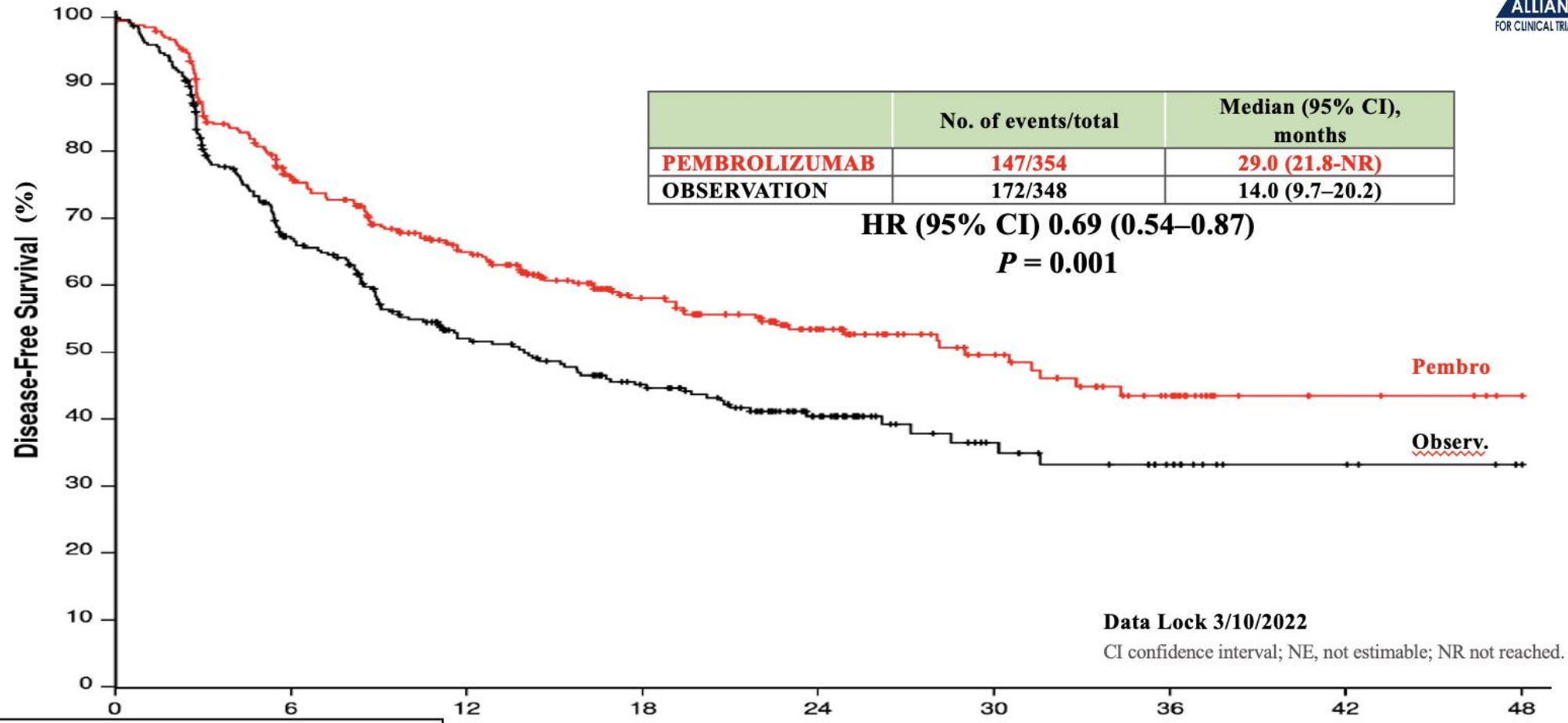
*PD-L1 status was tested centrally and defined using the combined positive score: percentage of PD-L1-positive tumor cells and infiltrating immune cells relative to the total number of tumor cells. PD-L1 positive = CPS ≥ 10%, Dako PD-L1 immunohistochemistry 22C3 pharmDx assay. DFS: disease-free survival (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 (0.54–0.87)

***P* = 0.001**



Data Lock 3/10/2022

CI confidence interval; NE, not estimable; NR not reached.

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

Patients-at-Risk

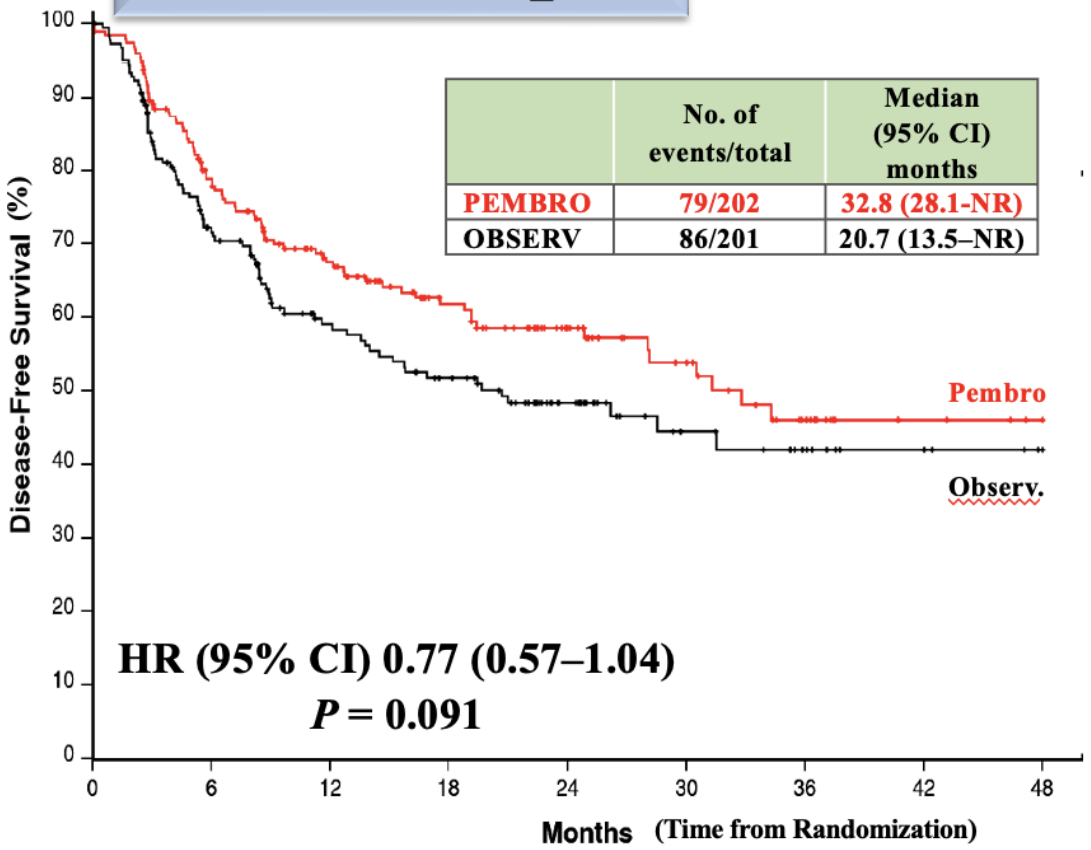
Pembro	354	238	178	123	80	45	26	6	2
Observ.	348	192	125	97	53	23	13	6	1

PRESENTED BY: Andrea B. Apolo, MD

@apolo_andrea

A031501 AMBASSADOR: Disease-Free Survival by PD-L1* Status

PD-L1-Positive CPS ≥ 10%

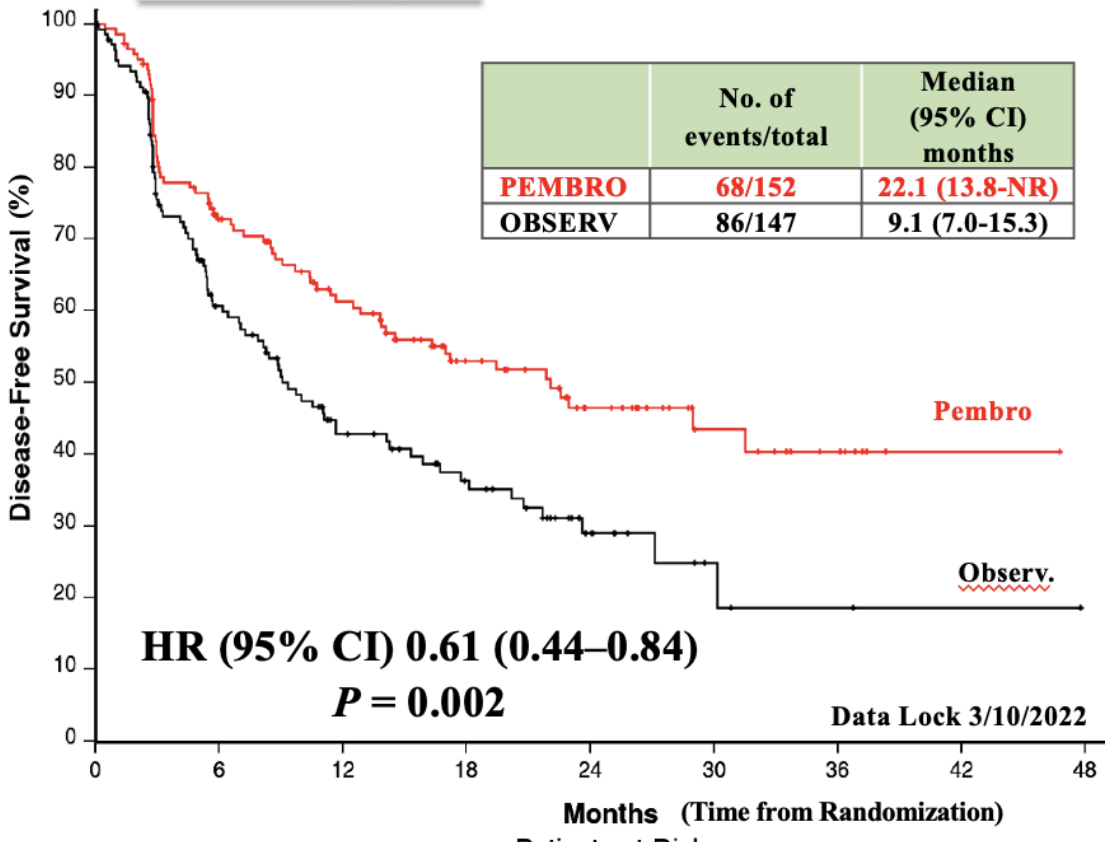


	No. of events/total	Median (95% CI) months
PEMBRO	79/202	32.8 (28.1-NR)
OBSERV	86/201	20.7 (13.5–NR)

Patients-at-Risk

Pembro	202	144	107	76	52	31	18	5	2
Observ.	201	117	81	67	41	19	11	5	1

PD-L1-Negative



	No. of events/total	Median (95% CI) months
PEMBRO	68/152	22.1 (13.8-NR)
OBSERV	86/147	9.1 (7.0-15.3)

Patients-at-Risk

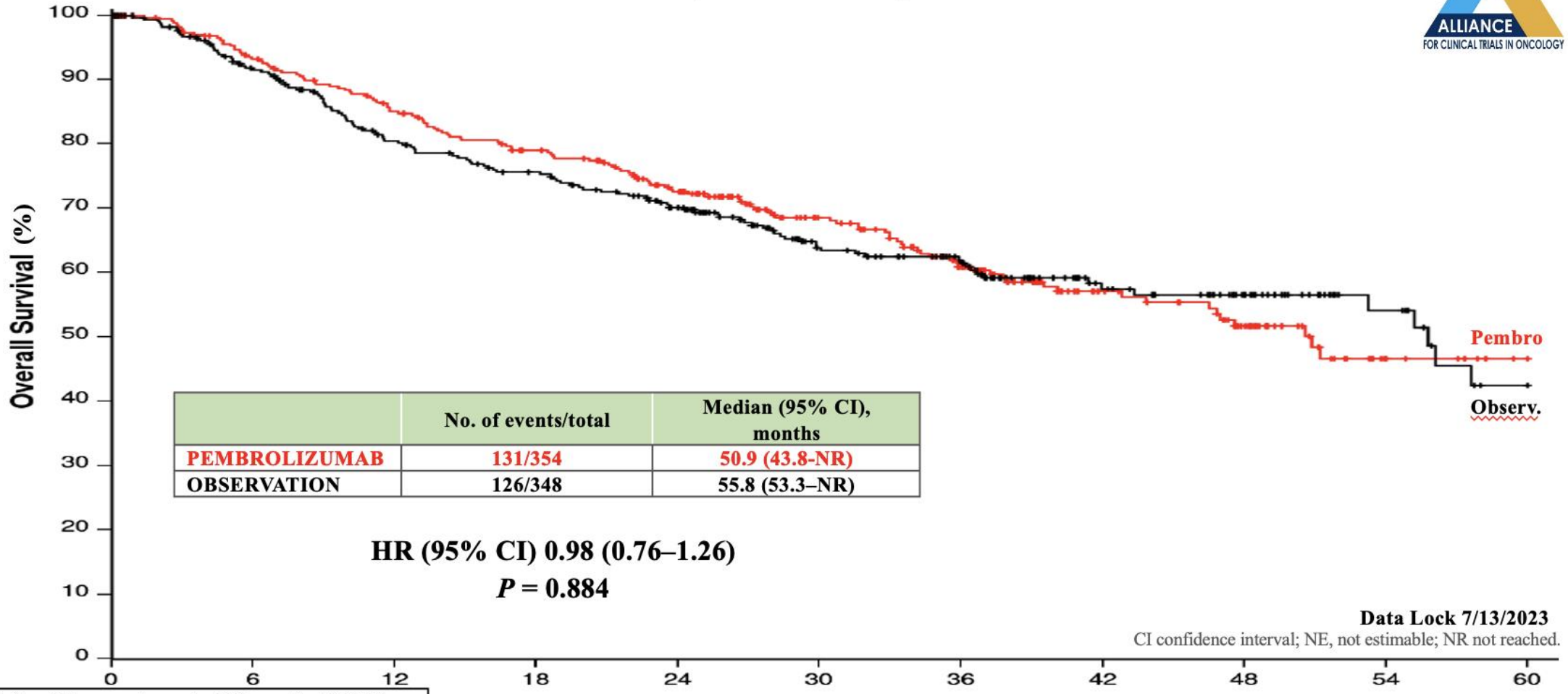
Pembro	152	94	71	47	28	14	8	1	0
Observ.	147	75	44	30	12	4	2	1	0

*Dako PD-L1 immunohistochemistry 22C3 pharmDx assay

CI, confidence interval; NE, not estimable; NR, not reached.

Data Lock 3/10/2022

A031501 AMBASSADOR: (interim) Overall Survival



	No. of events/total	Median (95% CI), months
PEMBROLIZUMAB	131/354	50.9 (43.8-NR)
OBSERVATION	126/348	55.8 (53.3–NR)

HR (95% CI) 0.98 (0.76–1.26)

***P* = 0.884**

Data Lock 7/13/2023

CI confidence interval; NE, not estimable; NR not reached.

Median follow-up (range) 36.9 months (0-63.9)

Patients-at-Risk

Pembro	354	313	280	253	218	152	115	69	50	17	10
Observ.	348	296	249	227	195	139	117	65	45	23	12

Summary Adjuvant Treatment

- If cisplatin-based **NAC has NOT been given** and tumor is pT3, pT4, or pN+ :

  → adjuvant cisplatin-based chemotherapy is the preferred approach, although nivolumab may be considered (FDA approved).

- If cisplatin-based **NAC has been given** and tumor is ypT2-ypT4a or ypN+ :

  → nivolumab may be considered. Balancing effects at delayed progression with side effects.

- Adjuvant pembrolizumab prolonged DFS vs. observation regardless of PD-L1 in AMBASSADOR trial (no OS benefit in premature analysis; FDA approval??)

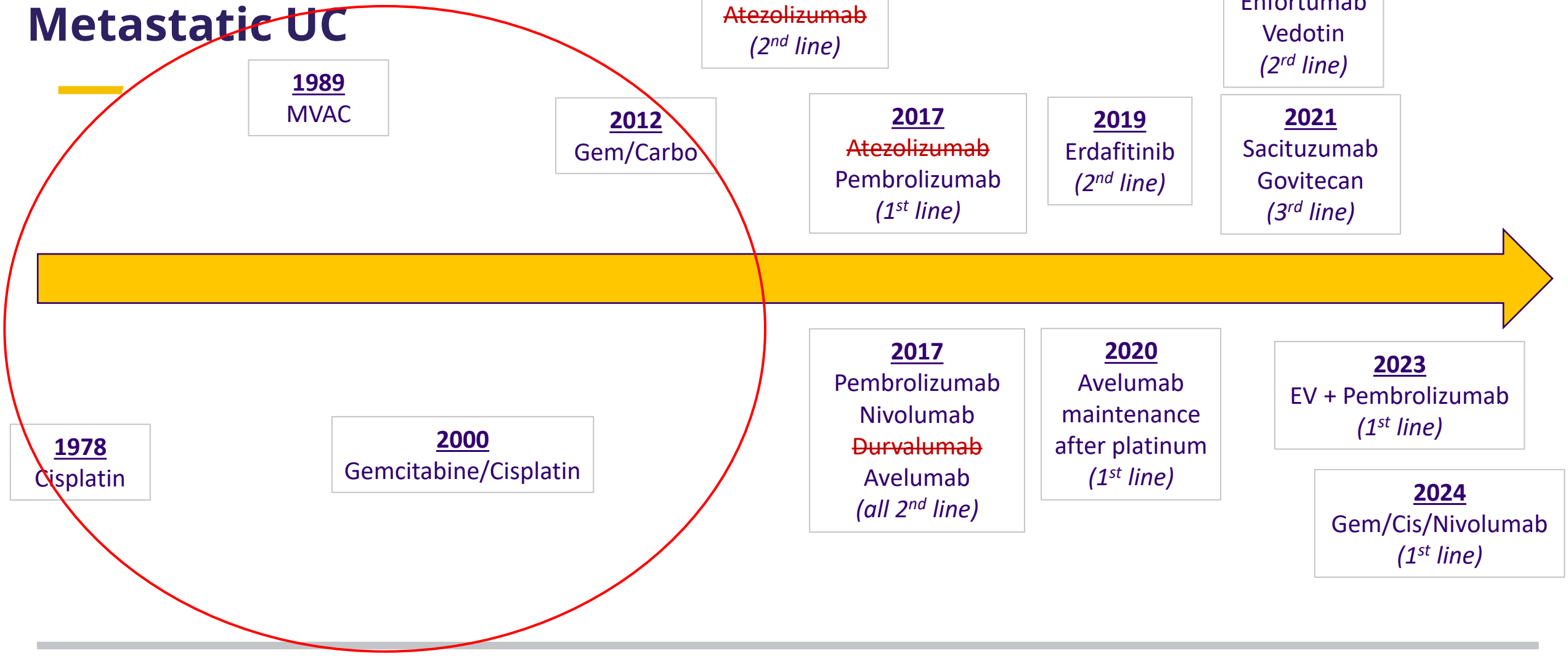
Bladder Preservation

- Bladder-preserving approaches are reasonable alternatives to cystectomy for patients who are medically unfit for surgery and those seeking alternative to radical cystectomy.
- <u>Generally considered if:</u>
  - 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

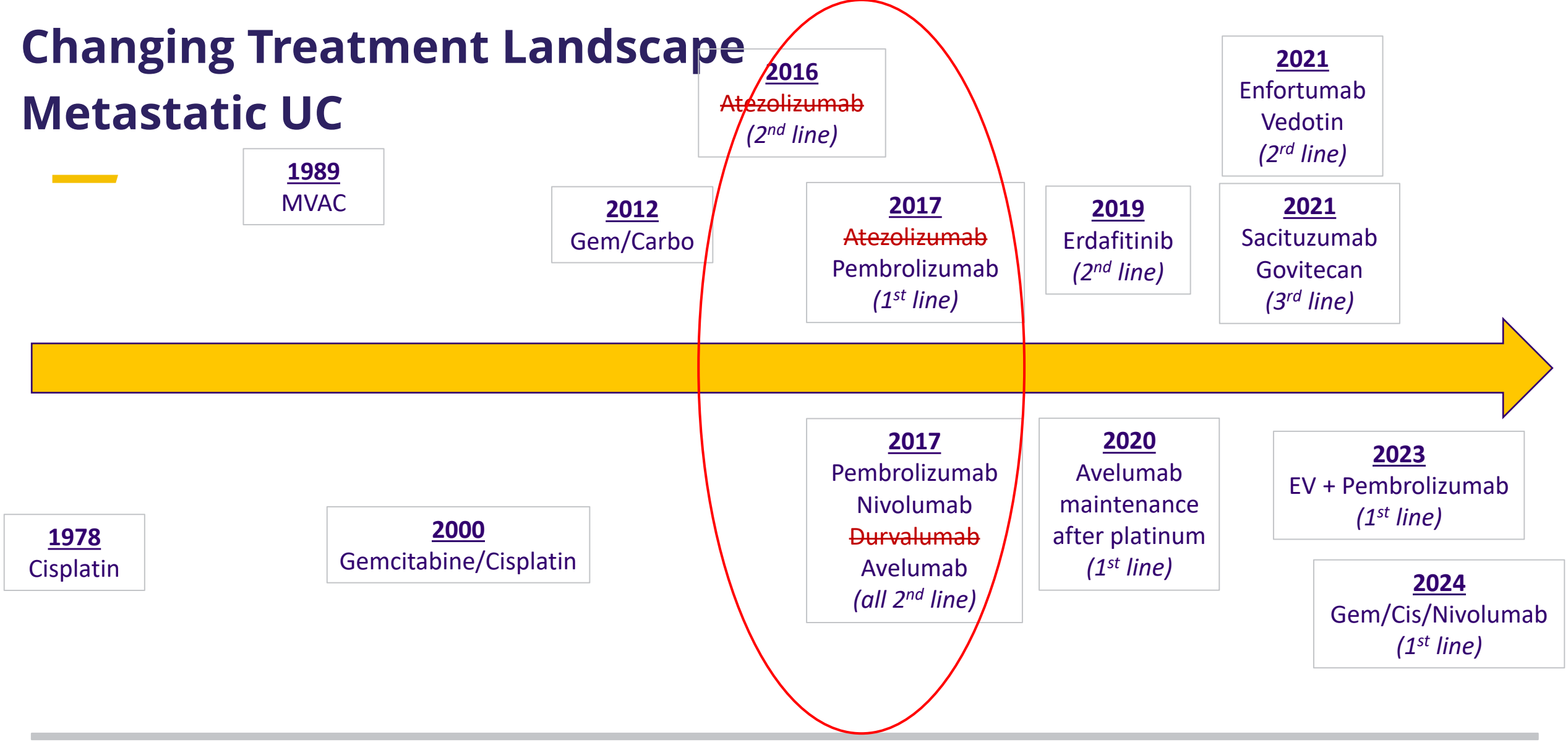
Outline

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

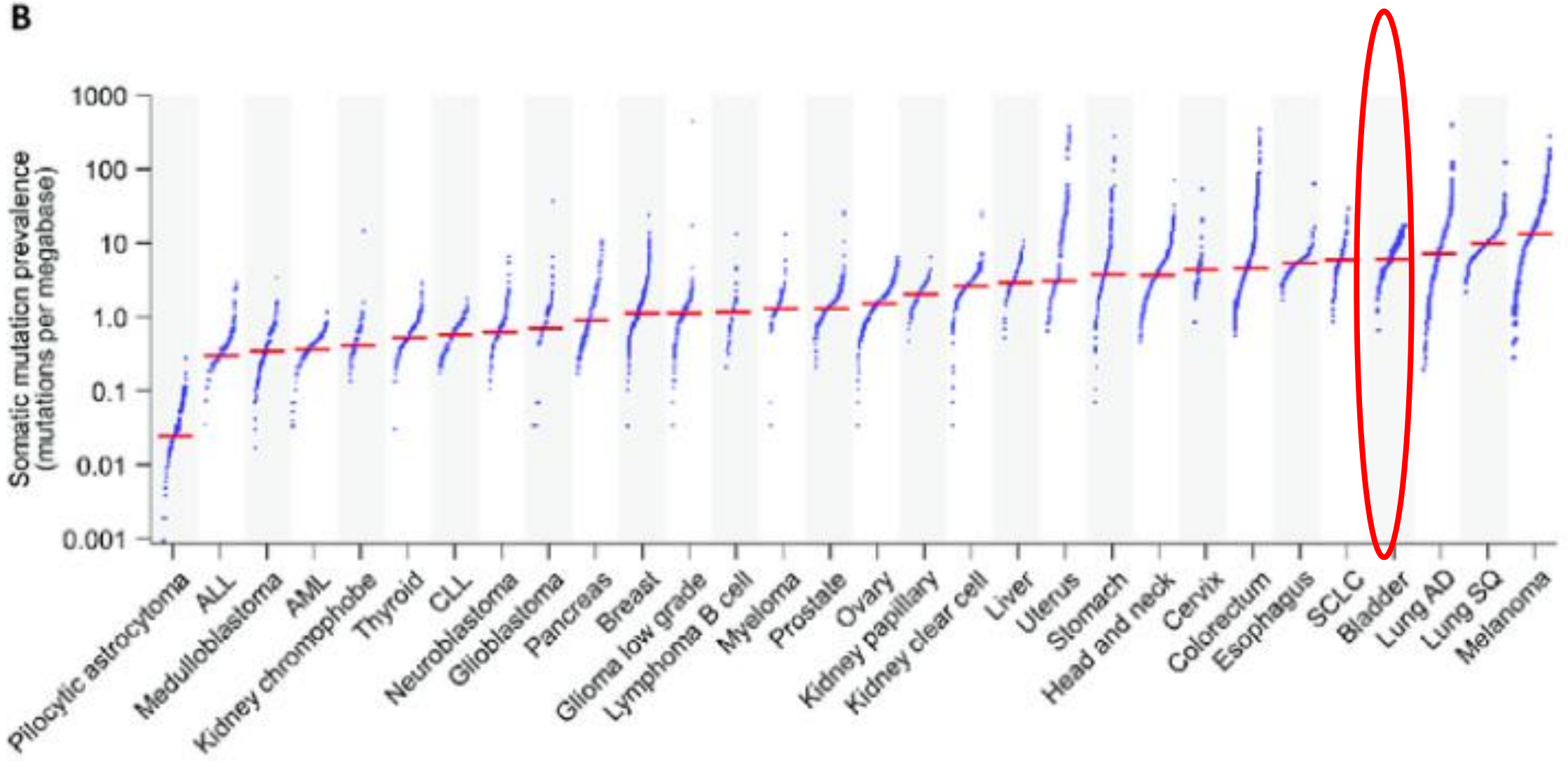
Changing Treatment Landscape Metastatic UC



Changing Treatment Landscape Metastatic UC



Bladder Tumors Have High Tumor Mutational Burden



Alexandrov LB, Nature 2013.

	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.
- Chemotherapy followed by maintenance avelumab was standard of care 2020-2023.
- Combination chemotherapy + aPD-1 does not improve survival….CM901!
- For platinum-ineligible patients, 1L pembro + EV (or pembro alone).
- 2nd line can use nivolumab, avelumab or pembrolizumab. However, pembro only agent with phase 3 data showing survival benefit.

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)

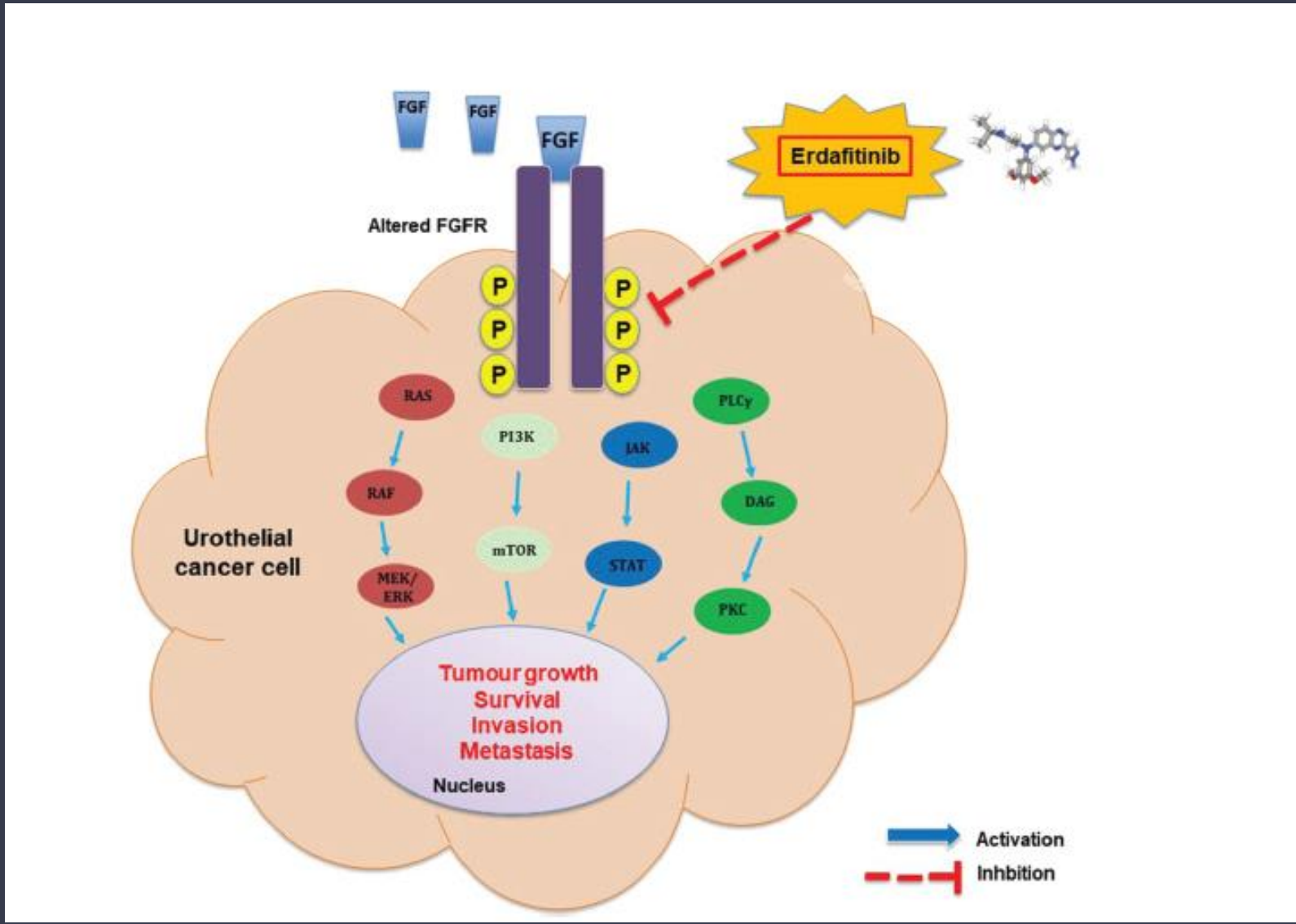
2021
Sacituzumab
Govitecan
(3rd line)

2023
EV + Pembrolizumab
(1st line)

2024
Gem/Cis/Nivolumab
(1st line)

Erdafitinib targets FGFR (fibroblast growth factor receptor)

- FGFR mutations / fusions occur in ~15-20% of UC (37% UTUC).
- Approved for patient with mutations in FGFR3 and/or FGFR2 or FGFR3 gene fusions.
- 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

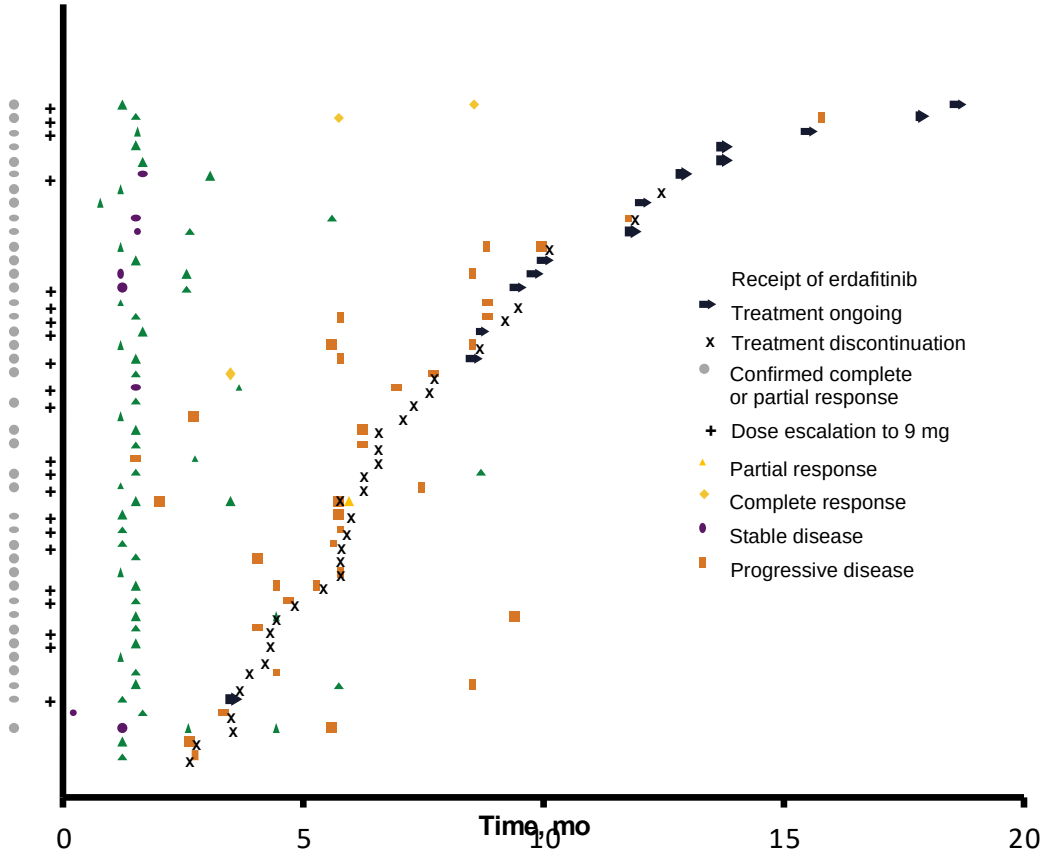
- **Primary endpoint:** ORR
- **Secondary endpoints:** PFS, OS, safety, DoR, PK, predictive biomarker evaluation

- 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

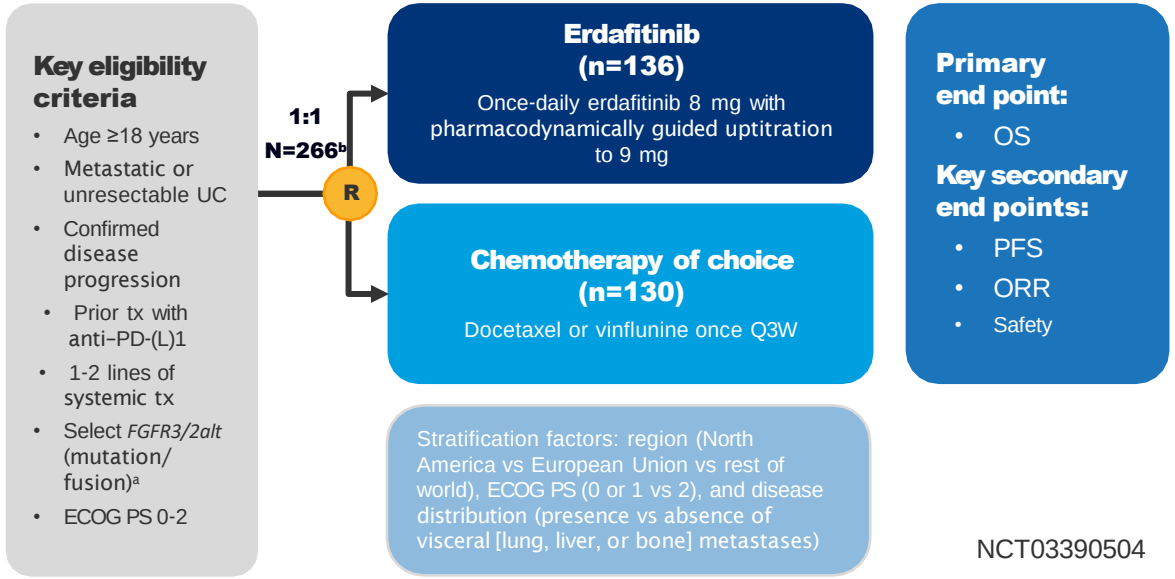
Results led to FDA approval of erdafitinib for locally advanced UC or mUC with *FGFR3* or *FGFR2* mutation or fusion after progression on ≥1 line of prior platinum-containing chemotherapy

- 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



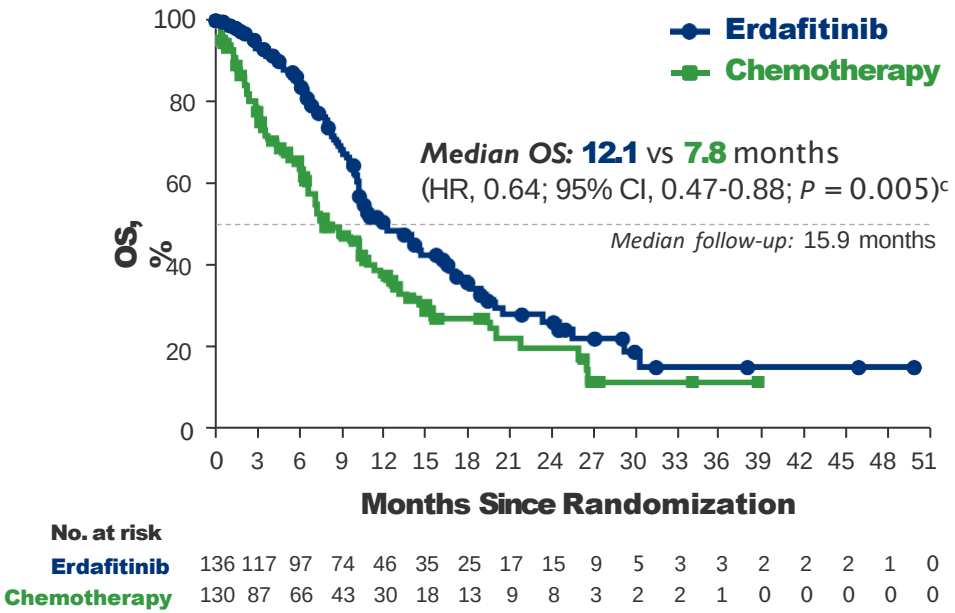
THOR Cohort 1: Erdafitinib Versus Investigator's Choice of Chemotherapy in Patients With *FGFR*-altered mUC

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 not 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

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Cisplatin

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MVAC

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Gemcitabine/Cisplatin

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2016
~~Atezolizumab~~
(2nd line)

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

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EV + Pembrolizumab
(1st line)

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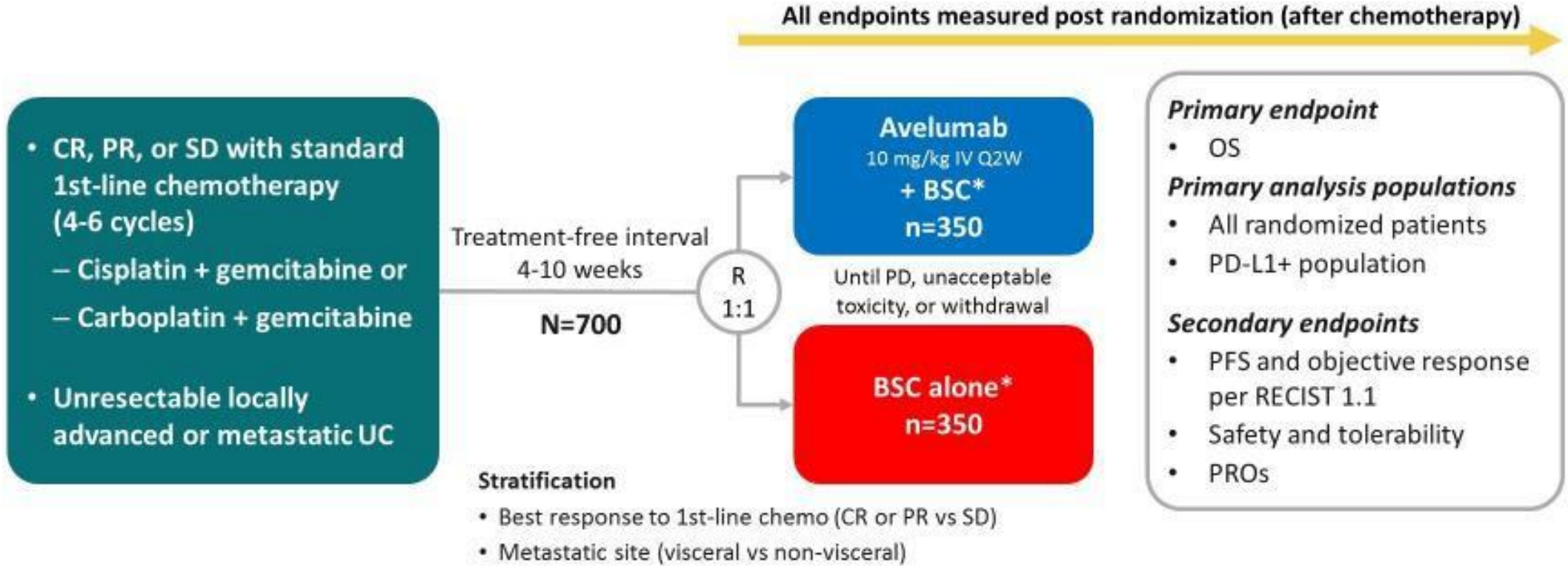
Gem/Cis/Nivolumab
(1st line)

JAVELIN Bladder 100 study design (NCT02603432)



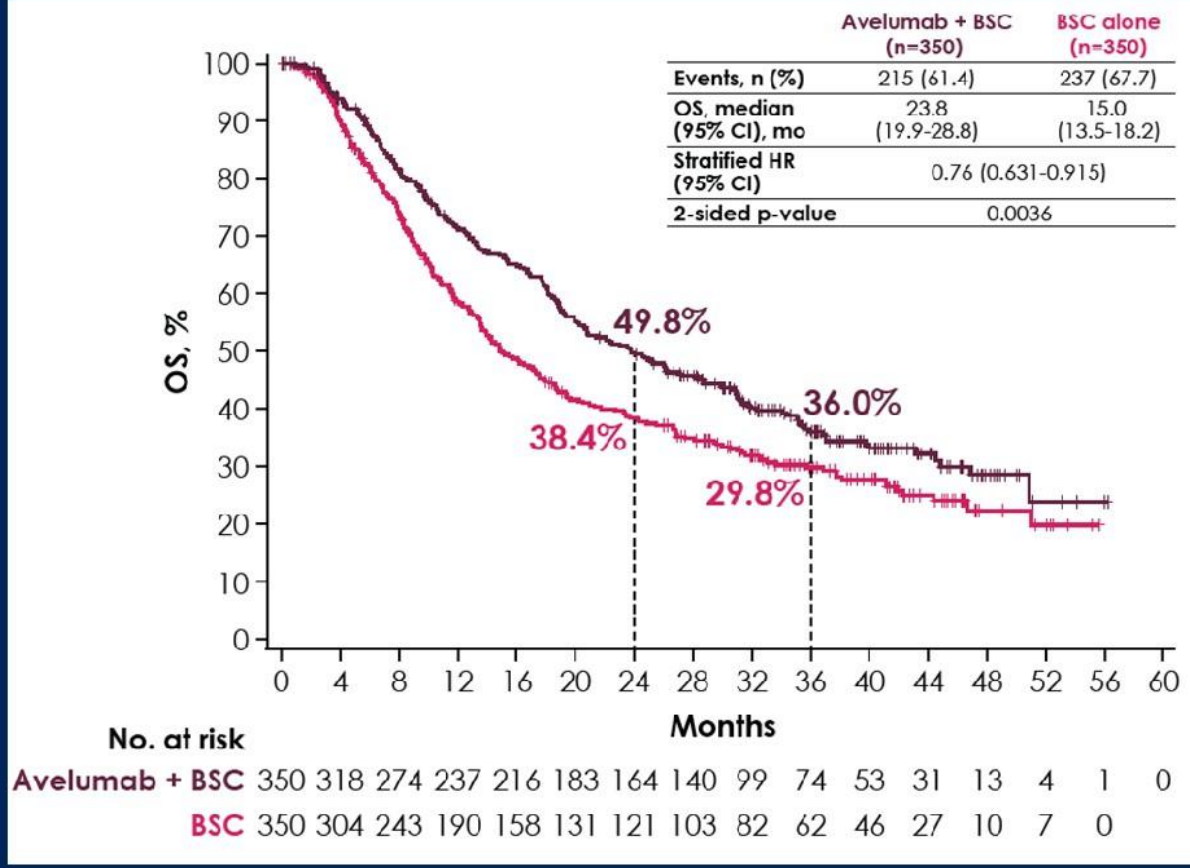
PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

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

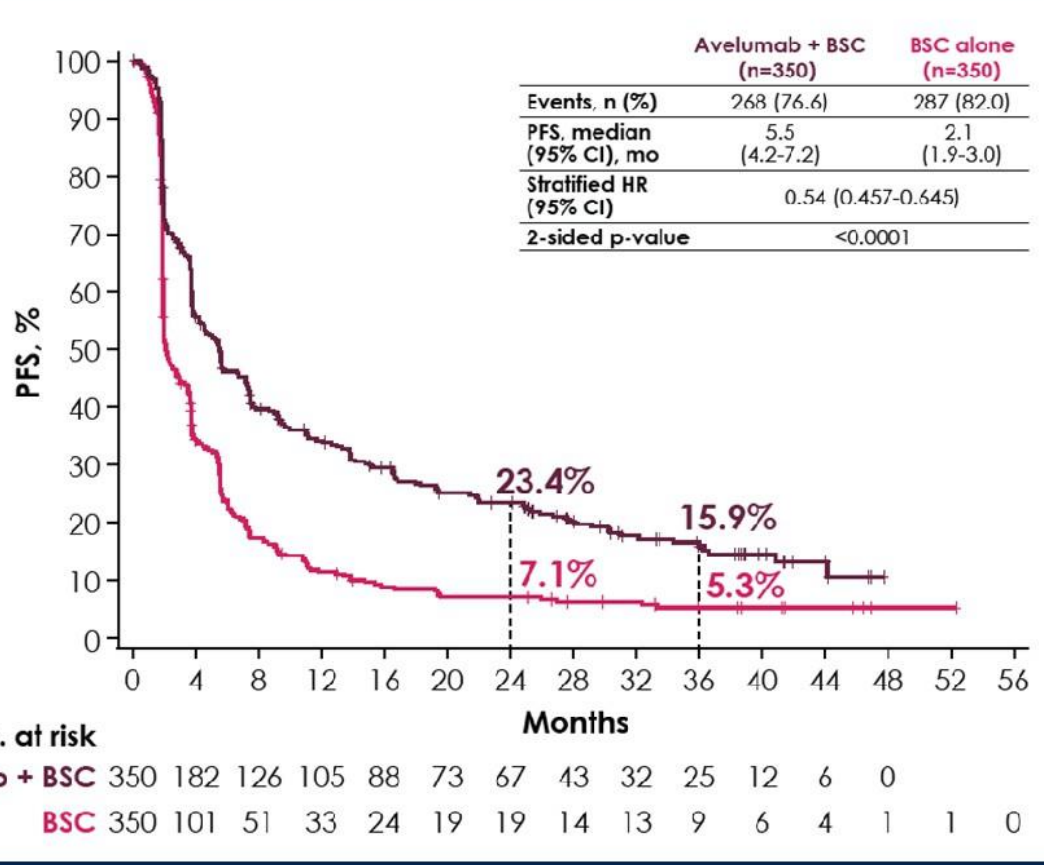
*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

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

OS



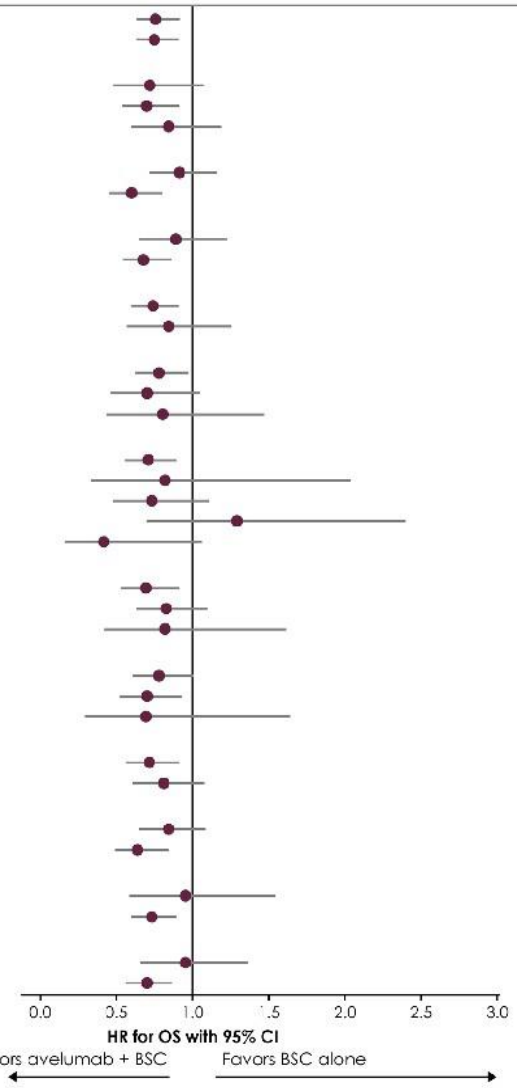
Investigator-assessed PFS



HR, hazard ratio.

OS favored avelumab + BSC vs BSC alone across subgroups

Subgroup	No. of events/no. of patients: Avelumab + BSC	BSC	HR for OS (95% CI)*
All patients (stratified†)	215/350	237/350	0.76 (0.631-0.915)
All patients (unstratified)	215/350	237/350	0.75 (0.627-0.908)
Best response to 1L chemotherapy			
CR	43/90	54/89	0.72 (0.482-1.076)
PR	108/163	117/163	0.70 (0.541-0.914)
SD	64/97	66/98	0.84 (0.596-1.188)
Metastatic disease site when initiating 1L chemotherapy			
Visceral	130/191	130/191	0.91 (0.713-1.162)
Nonvisceral	85/159	107/159	0.60 (0.451-0.798)
Age			
<65 years	85/129	71/107	0.89 (0.651-1.224)
≥65 years	130/221	166/243	0.68 (0.544-0.862)
Sex			
Male	163/266	189/275	0.74 (0.596-0.908)
Female	52/84	48/75	0.84 (0.568-1.250)
Race			
White	151/232	162/238	0.78 (0.625-0.975)
Asian	41/75	55/81	0.70 (0.464-1.044)
Other	23/43	20/31	0.80 (0.435-1.470)
Pooled geographic region			
Europe	136/214	146/203	0.71 (0.558-0.892)
North America	7/12	14/22	0.82 (0.330-2.035)
Asia	40/73	49/74	0.73 (0.479-1.108)
Australasia	23/34	18/37	1.29 (0.697-2.398)
Rest of the world	9/17	10/14	0.42 (0.163-1.061)
PD-L1 status at baseline			
Positive	102/189	108/169	0.69 (0.530-0.912)
Negative	101/139	100/131	0.83 (0.630-1.096)
Unknown	12/22	29/50	0.82 (0.418-1.614)
1L chemotherapy regimen			
Gemcitabine + cisplatin	108/183	134/206	0.78 (0.607-1.008)
Gemcitabine + carboplatin	97/147	91/122	0.70 (0.523-0.929)
Gemcitabine + carboplatin + cisplatin‡	10/20	11/20	0.69 (0.294-1.639)
ECOG performance status			
0	125/213	141/211	0.72 (0.563-0.913)
≥1	90/137	96/139	0.81 (0.606-1.078)
Creatinine clearance at baseline			
≥60 mL/min	113/181	125/196	0.84 (0.652-1.085)
<60 mL/min	101/168	109/148	0.64 (0.491-0.845)
Liver lesions at baseline			
Yes	33/43	33/44	0.95 (0.585-1.541)
No	182/307	204/306	0.73 (0.597-0.892)
Lung lesions at baseline			
Yes	59/83	57/83	0.95 (0.658-1.364)
No	156/267	180/267	0.70 (0.564-0.866)



ECOG, Eastern Cooperative Oncology Group. *HRs and CIs were calculated using a Cox proportional hazards model. †Stratified by best response to 1L chemotherapy (CR or PR vs SD) and metastatic disease site when initiating 1L chemotherapy (visceral vs nonvisceral). ‡Patients who switched platinum regimens while receiving 1L chemotherapy.

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Gem/Carbo

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~~Atezolizumab~~
(2nd line)

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

2017
Pembrolizumab
Nivolumab
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Avelumab
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Erdafitinib
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Govitecan
(3rd line)

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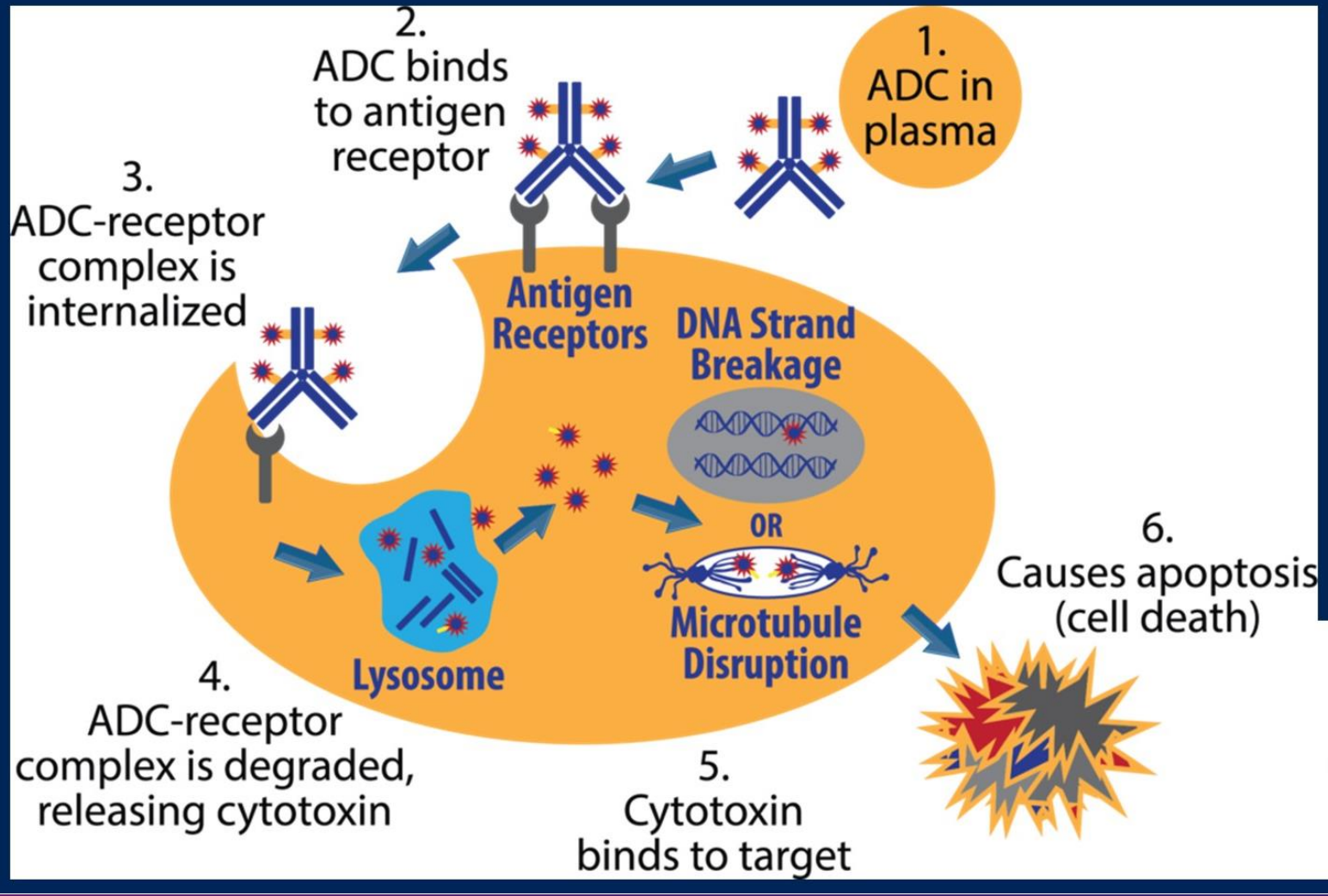
EV + Pembrolizumab
(1st line)

2024
Gem/Cis/Nivolumab
(1st line)

Antibody Drug Conjugates (ADC)



NJBio
https://njbio.com/antibody-drug-conjugates/

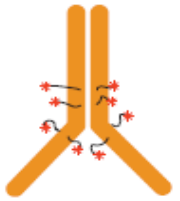
Antibody Drug Conjugates (ADC) in Bladder Cancer

Enfortumab vedotin

Target: Nectin-4, a type 1 transmembrane cell adhesion molecule overexpressed in epithelial cancers
Linker: Protease cleavable
Payload: MMAE

FDA approved: For treatment of patients with locally advanced or metastatic urothelial cancer who had prior treatment with PD-L1 inhibitor and platinum-containing chemotherapy regimen or ineligible for chemotherapy

Sacituzumab govitecan

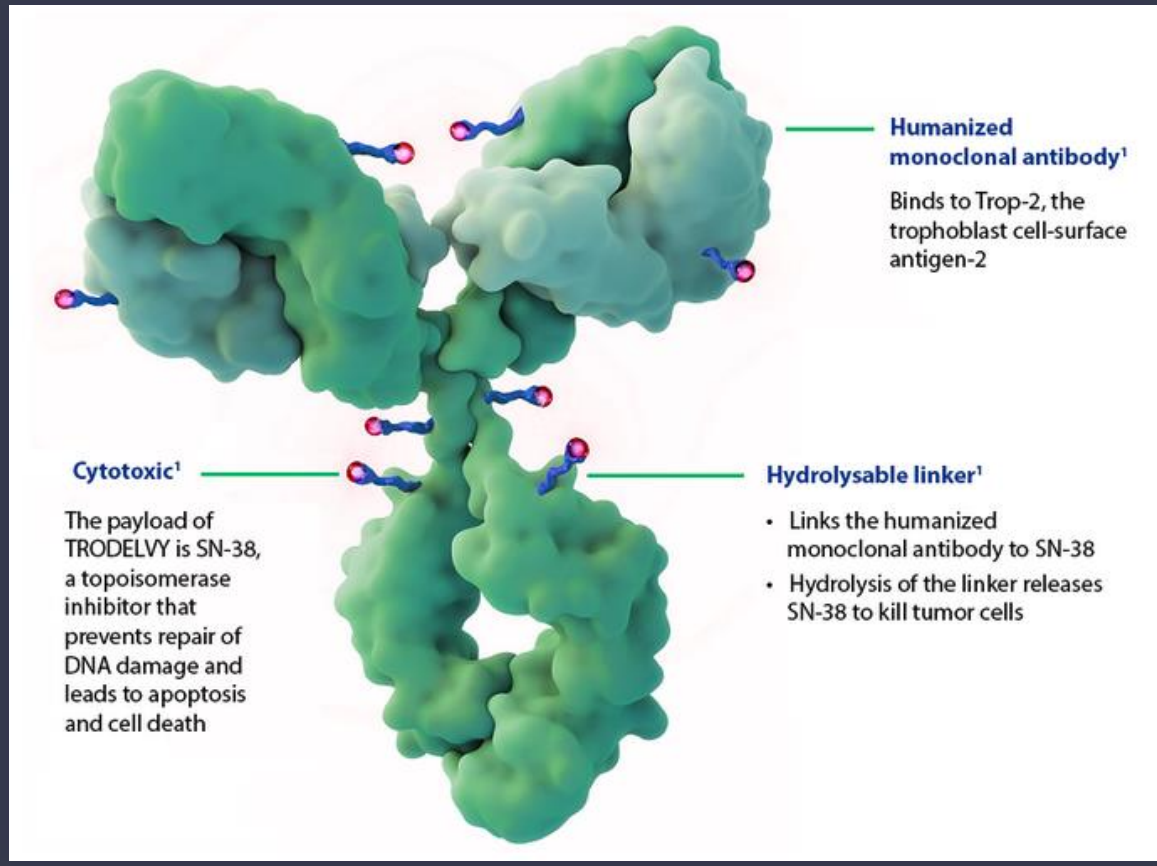


Target: Trop-2, an epithelial cell-surface glycoprotein highly expressed in muscle-invasive disease
Linker: Hydrolysable
Payload: SN-38, the active metabolite of irinotecan

FDA accelerated approval: For treatment of patients with locally advanced or metastatic urothelial cancer who had prior treatment with PD-L1 inhibitor and platinum-containing chemotherapy regimen

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 Is a Registrational, Open-Label, Multicohort Phase 2 Trial in Patients With mUC

TROPHY U-01

Cohort 1* (~100 patients): patients with mUC who progressed after prior platinum-based and CPI-based therapies — SG 10 mg/kg Days 1 and 8, every 21 days

Cohort 2 (~40 patients): patients with mUC ineligible for cisplatin-based therapy and who progressed after prior CPI-based therapies — SG 10 mg/kg Days 1 and 8, every 21 days

Cohort 3[a]: mUC CPI-naïve patients who progressed after prior platinum-based chemotherapy — SG 10 mg/kg Days 1 and 8, every 21 days; Pembrolizumab 200 mg day 1 every 21 days

Cohort 4 (up to 60 patients): mUC platinum-naïve patients — SG Days 1 and 8, every 21 days; Cisplatin[b]

Cohort 5 (up to 60 patients): mUC platinum-naïve patients — SG Days 1 and 8, every 21 days; Cisplatin[c] Avelumab 800 mg every 2 weeks

Continue treatment in the absence of unacceptable toxicity or disease progression

Continue until a maximum of 6 cycles has been completed,[d] disease progression, lack of clinical benefit, toxicity, or withdrawal of consent

→ **Maintenance avelumab (800 mg every 2 weeks) with SG (Days 1 and 8 every 21 days) for those without disease progression**

Primary Endpoint:
Objective response rate per RECIST 1.1 criteria

Key Secondary Endpoints:
Safety/tolerability, DOR, PFS, OS

Key Inclusion Criteria: Age ≥18 years, ECOG of 0/1, creatinine clearance (CrCl) ≥30 mL/min,[b,c] adequate hepatic function
Key Exclusion Criteria: Immunodeficiency, active Hepatitis B or C, active secondary malignancy, or active brain metastases

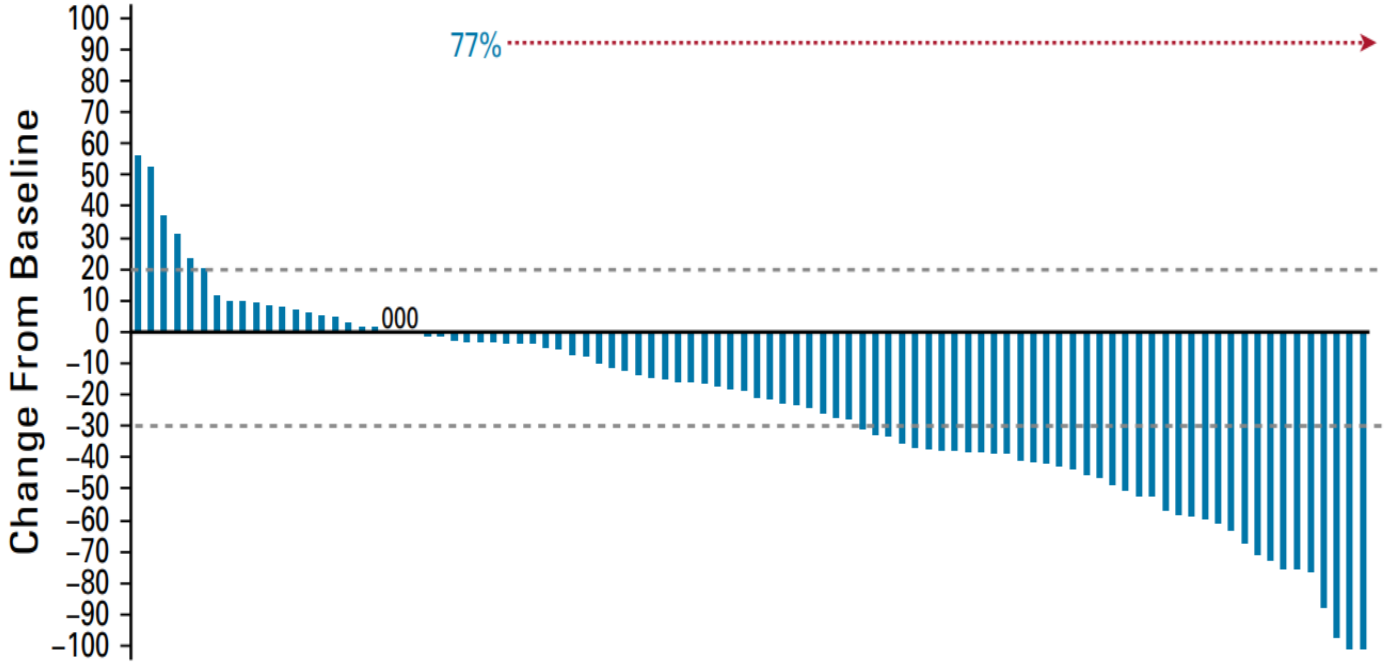
***Accelerated FDA approval for treatment of patients with locally advanced or mUC who previously received platinum-containing chemotherapy and PD-1/L1 inhibitor[1]**

[a]Exclusions for Cohort 3 only: active autoimmune disease or history of interstitial lung disease. [b]In patients with CrCl ≥60 mL/min; [c]In patients with creatinine clearance 50–60 mL/min. [d]For patients who have not progressed, maintenance therapy will begin with infusions of avelumab (800 mg every 2 weeks beginning cycle 1, day 1 and every 2 weeks thereafter) followed by SG on days 1 and 8 every 21 days.
CBR, clinical benefit rate; CPI, checkpoint inhibitor; CrCl, creatinine clearance; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mUC, metastatic urothelial cancer; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan.

1. TRODELVY™ (sacituzumab govitecan-hziy). Prescribing Information. Immunomedics, Inc.; April 2021; EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973. IMMU-132-06 study.

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)



TROPHY-U-01 Cohort 3

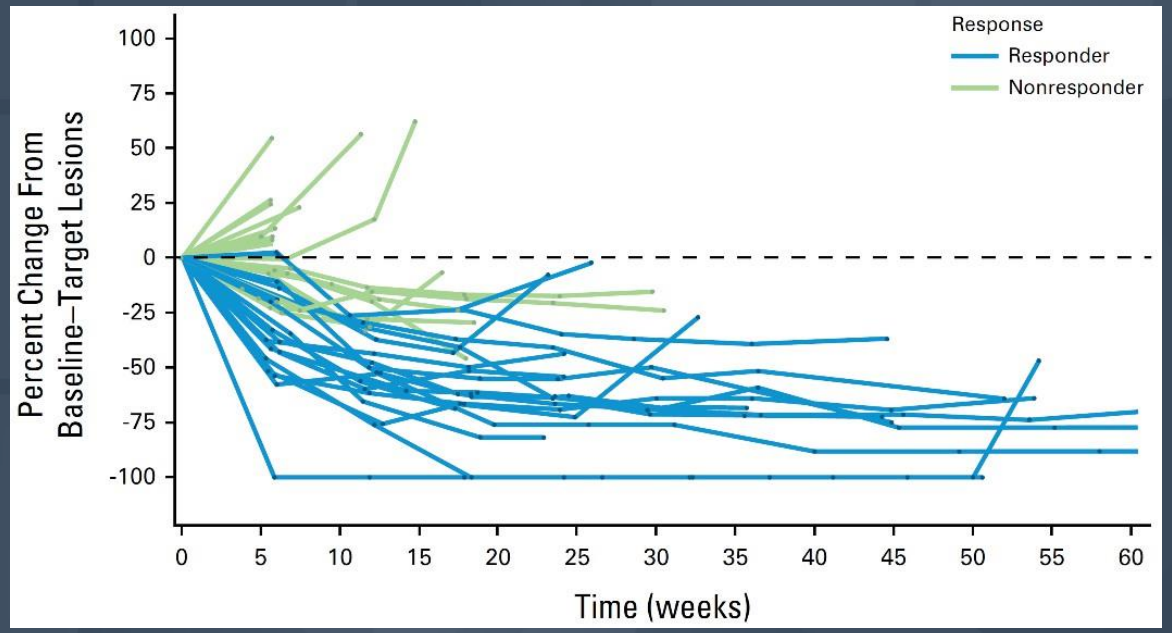
Open-label, phase 2 trial

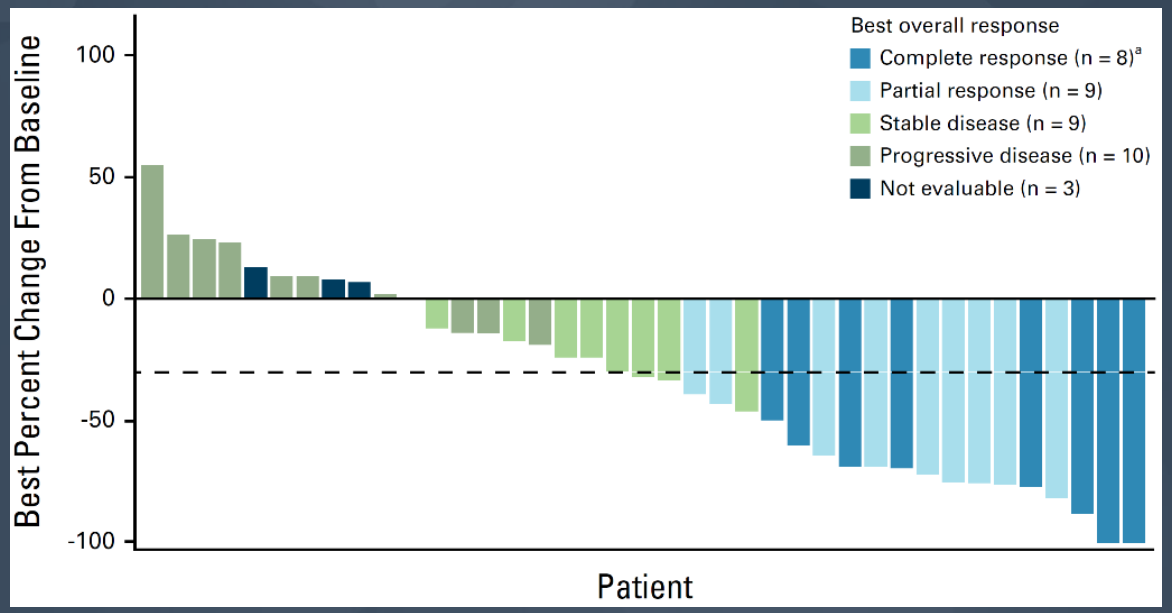
Primary endpoint: ORR (central review)
Secondary endpoints included: PFS, CBR, DOR, safety
Median follow-up: 14.8 mo

TROPHY-U-01 Trial Cohort 3 Results

Endpoint	Cohort 1
ORR, %	41
CR, %	20
PR, %	21
mDOR, mo	11.1
mPFS, mo	5.3
mOS, mo	12.7

Primary Endpoint Was Met



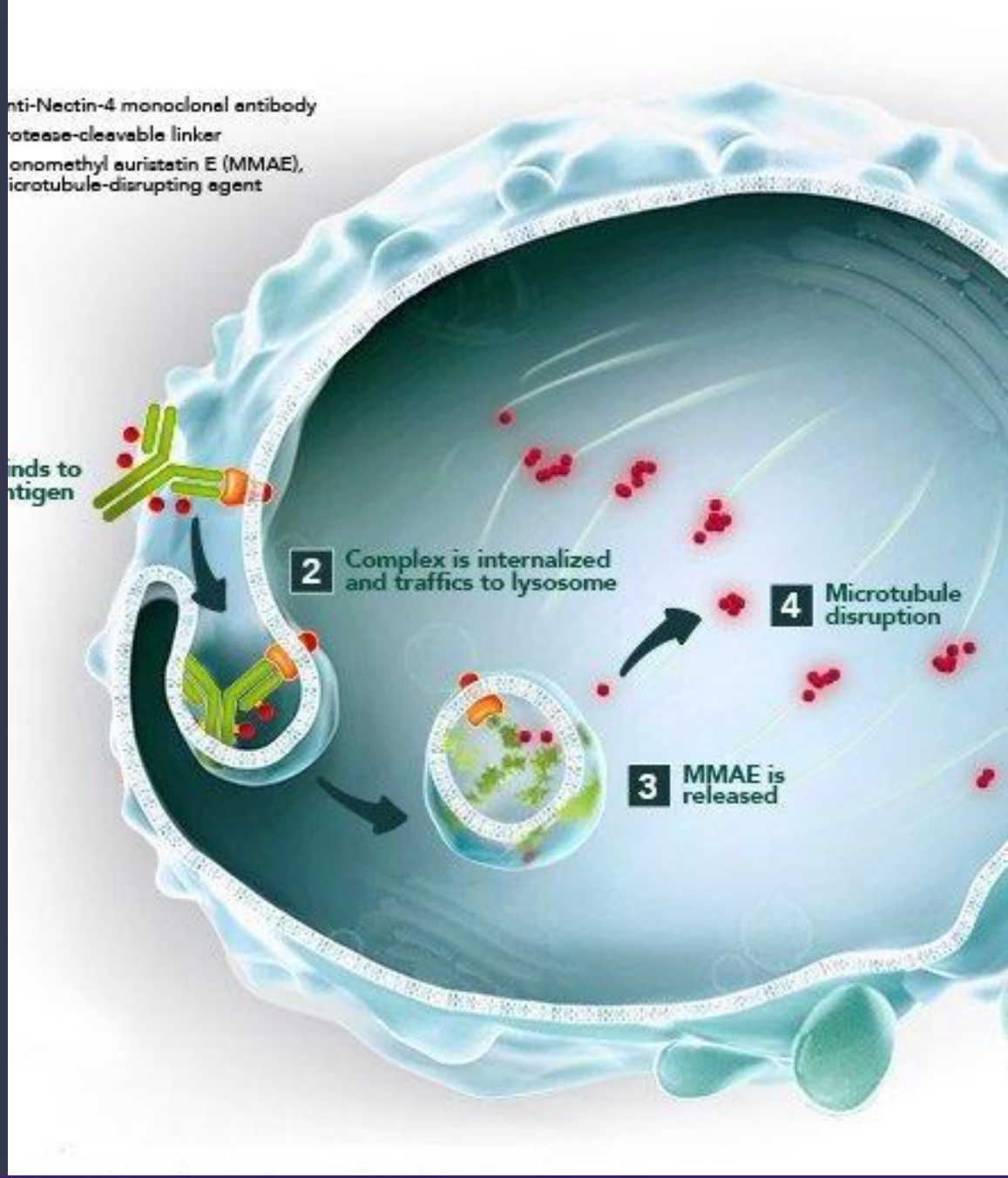


Sacituzumab Govitecan - Key Adverse Events

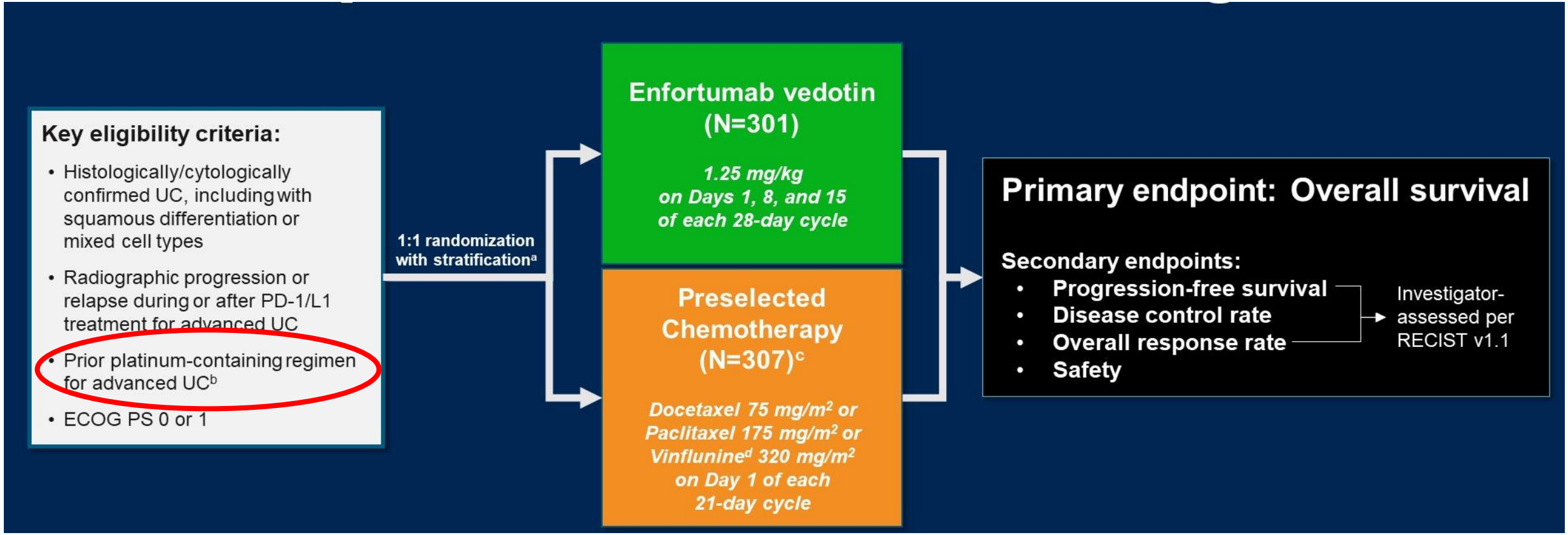
- Neutropenia
  - Occurs in > 60% with > 40% grade 3-4
  - Febrile neutropenia in 7% (including fatal cases)
- Diarrhea
  - Occurs in > 60% w/ 12% grade 3-4
- Nausea and vomiting
  - Occurs in > 60%, grade 3-4 in 4%
  - May require 2-3 anti-nausea medications
- Hypersensitivity grade 3-4 in 2% - premedication recommended

Enfortumab Vedotin (EV)

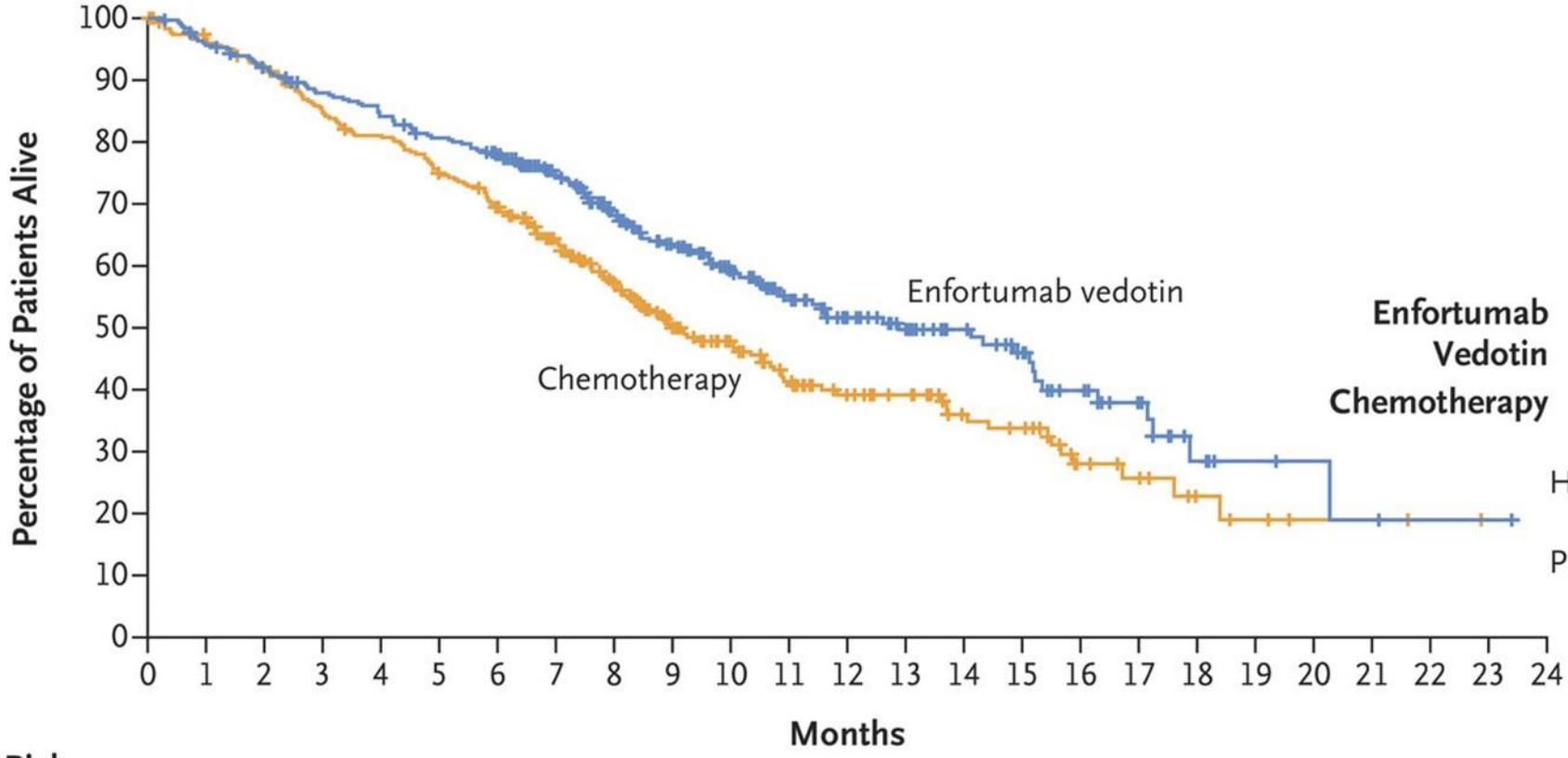
- Targets Nectin-4
  - Transmembrane adhesion molecule expressed on **skin, urothelium, salivary gland ducts, esophagus, and stomach**.
- Protease-cleavable linker
- Conjugated to monomethylauristatin-E (MMAE)



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

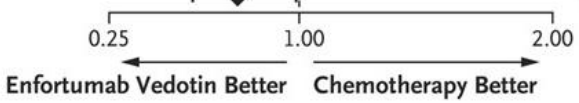
- Progression free survival = 5.55 mo vs 3.71 mo; HR 0.62 [95%CI 0.51 – 0.75, p<0.001]
- Overall response rate = 40.6% vs 17.9%, p<0.001 (CR in 4.9% vs 2.7%)
- Disease control in 71.9% vs 53.4%, p<0.001

Powles T, et al. NEJM 2021.

EV-301: Benefit across all subgroups

B Deaths According to Subgroup

Subgroup	Enfortumab Vedotin	Chemotherapy	Hazard Ratio (95% CI)
	no. of deaths/no. of patients		
All patients	134/301	167/307	0.70 (0.56–0.89)
Age group			
<65 yr	49/108	66/111	0.68 (0.47–0.99)
≥65 yr	85/193	101/196	0.75 (0.56–1.00)
<75 yr	109/249	128/239	0.69 (0.53–0.89)
≥75 yr	25/52	39/68	0.91 (0.55–1.51)
Sex			
Male	101/238	132/232	0.61 (0.47–0.79)
Female	33/63	35/75	1.17 (0.72–1.89)
Geographic region			
Western Europe	57/126	72/129	0.76 (0.53–1.07)
United States	25/43	25/44	0.88 (0.51–1.54)
Rest of the world	52/132	70/134	0.64 (0.45–0.92)
ECOG performance-status score			
0	40/120	46/124	0.81 (0.53–1.24)
1	94/181	121/183	0.67 (0.51–0.87)
Liver metastasis			
Yes	53/93	63/95	0.66 (0.46–0.96)
No	81/208	104/212	0.73 (0.55–0.98)
Preselected chemotherapy			
Paclitaxel	63/141	59/112	0.71 (0.49–1.01)
Docetaxel	41/87	67/117	0.71 (0.48–1.04)
Vinflunine	30/73	41/78	0.77 (0.48–1.24)
Primary site of tumor			
Upper urinary tract	44/98	52/107	0.85 (0.57–1.27)
Bladder or other site	90/203	115/200	0.67 (0.51–0.88)
Previous systemic therapies			
1–2	115/262	147/270	0.69 (0.54–0.88)
≥3	19/39	20/37	0.88 (0.47–1.64)
Best response among patients who previously received CPI treatment			
Response	18/61	23/50	0.63 (0.34–1.17)
No response	100/207	120/215	0.76 (0.58–0.99)



Powles et al. NEJM 2021.

UW Medicine

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)

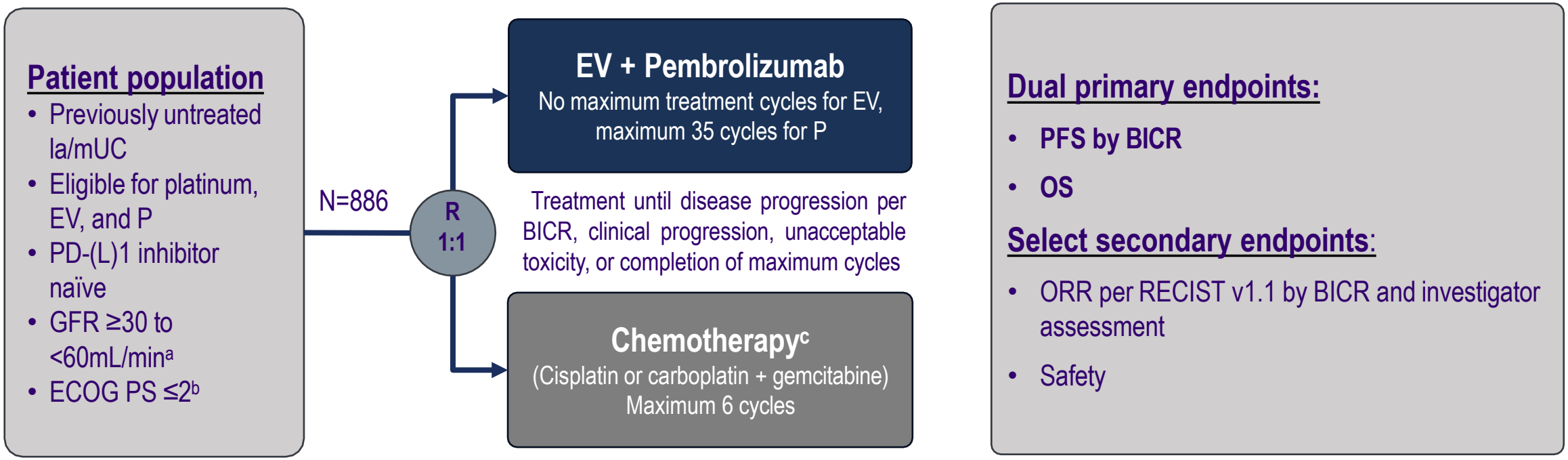
2021
Sacituzumab
Govitecan
(3rd line)

2021
Nivolumab
(Adjuvant)

2023
EV + Pembrolizumab
(1st line)

2024
Gem/Cis/Nivolumab
(1st line)

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

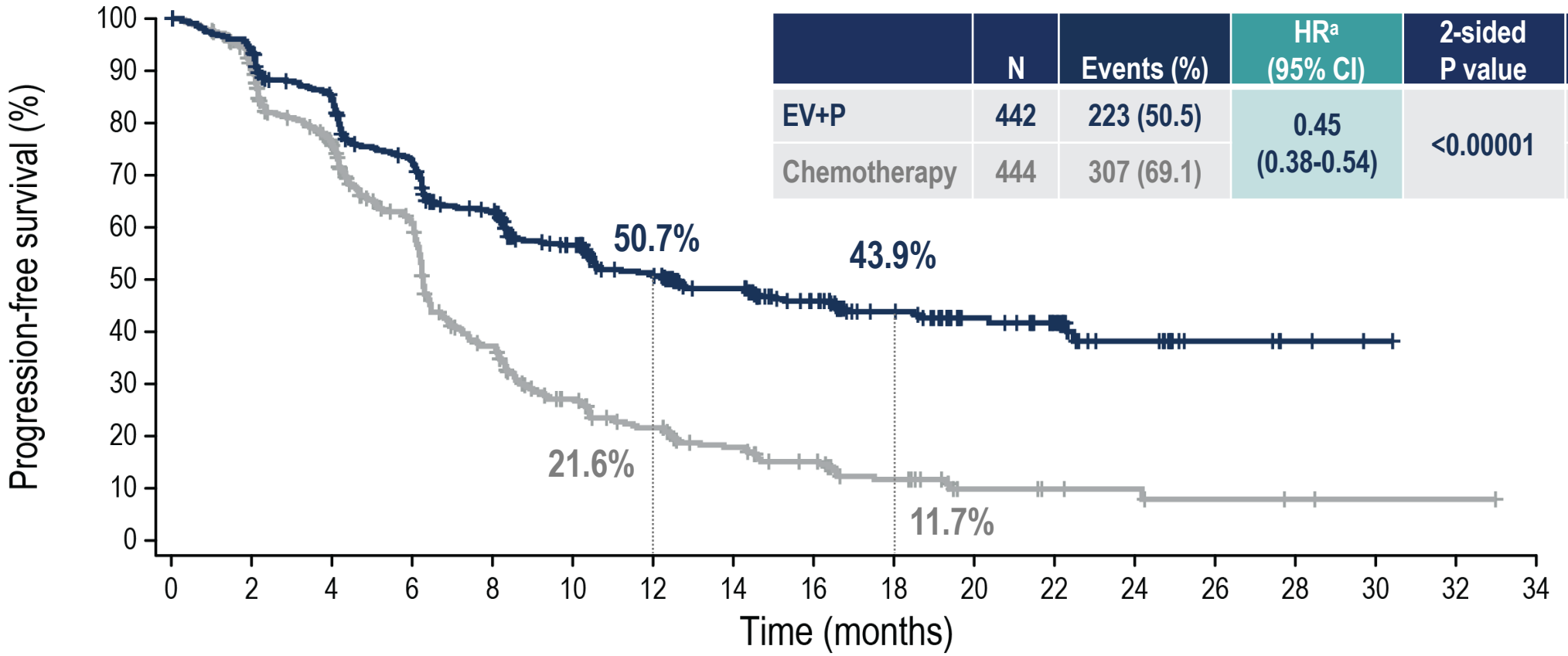
BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; ORR, overall response rate; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors
[a]Measured by the Cockcroft-Gault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

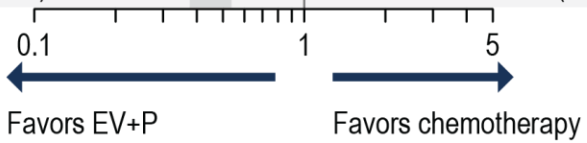
PFS at 12 and 18 months as estimated using Kaplan-Meier method
HR, hazard ratio; mPFS, median progression-free survival
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm

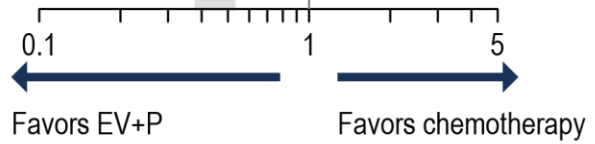
Subgroup Analysis of PFS by BICR

PFS benefit in all pre-specified subgroups was consistent with results in overall population

Subgroup	mPFS, months (Events/N) EV+P	Chemotherapy	Hazard Ratio (95% CI)
Overall	12.5 (223/442)	6.3 (307/444)	0.45 (0.38–0.54)
Age			
<65 years	12.7 (75/144)	6.4 (88/135)	0.45 (0.32–0.62)
≥65 years	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)
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 world	NR (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 PS			
0	22.3 (93/223)	6.7 (146/215)	0.36 (0.28–0.48)
1-2	9.3 (130/219)	6.1 (161/227)	0.53 (0.42–0.68)
Primary disease site of origin			
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)

Subgroup	mPFS, months (Events/N) EV+P	Chemotherapy	Hazard Ratio (95% CI)
Overall	12.5 (223/442)	6.3 (307/444)	0.45 (0.38–0.54)
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			
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)
Metastatic disease site			
Visceral metastases	10.4 (176/318)	6.2 (238/318)	0.45 (0.37–0.55)
Lymph node only	NR (38/103)	8.3 (55/104)	0.40 (0.26–0.62)
Renal function[a]			
Normal	18.7 (38/84)	6.7 (61/95)	0.46 (0.30–0.71)
Mild	12.7 (79/165)	6.3 (114/162)	0.46 (0.34–0.62)
Moderate/Severe	10.5 (106/193)	6.2 (132/187)	0.47 (0.36–0.61)





Data cutoff: 08 August 2023

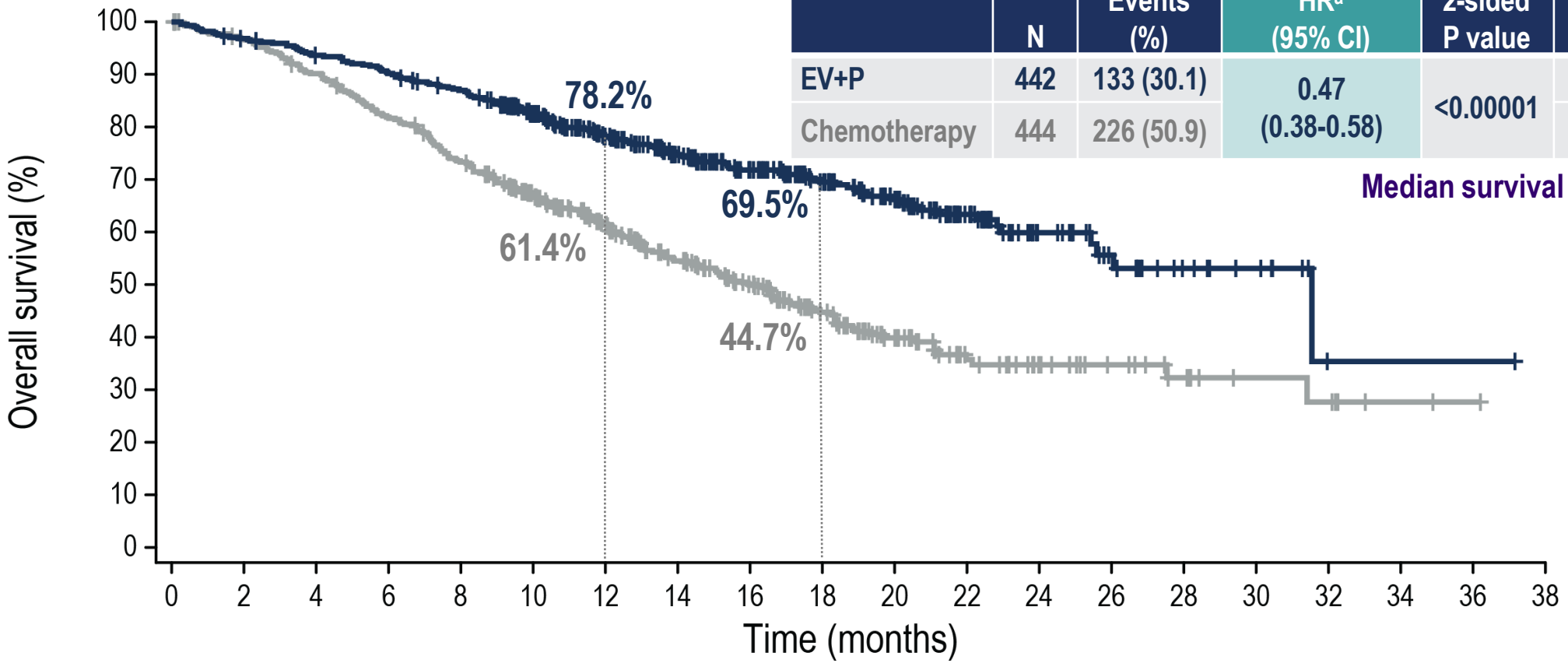
[a]Renal function categories defined as: Normal (≥90 mL/min), Mild (≥60 to <90 mL/min), Moderate/Severe (≥15 to <60 mL/min)

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

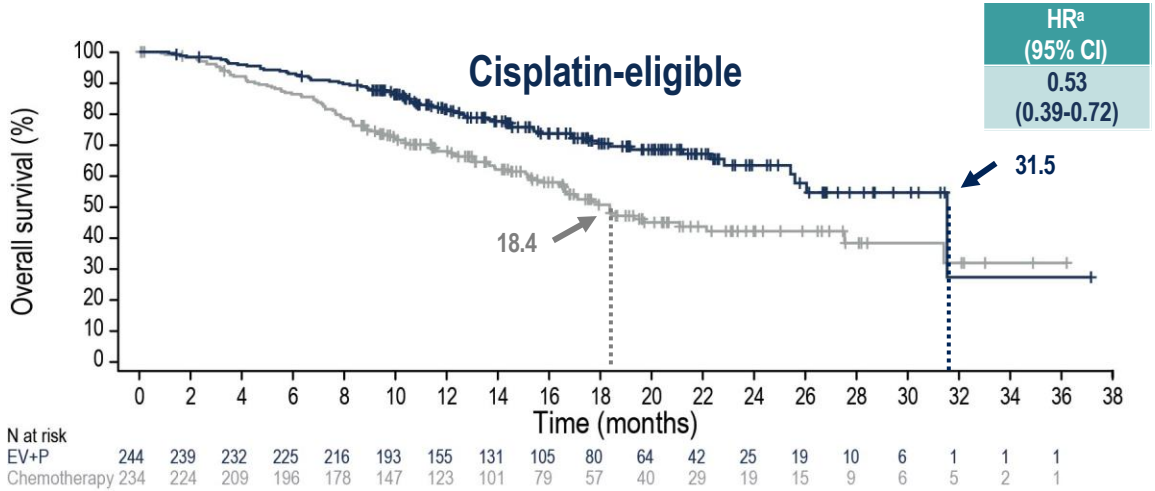
EV+P	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

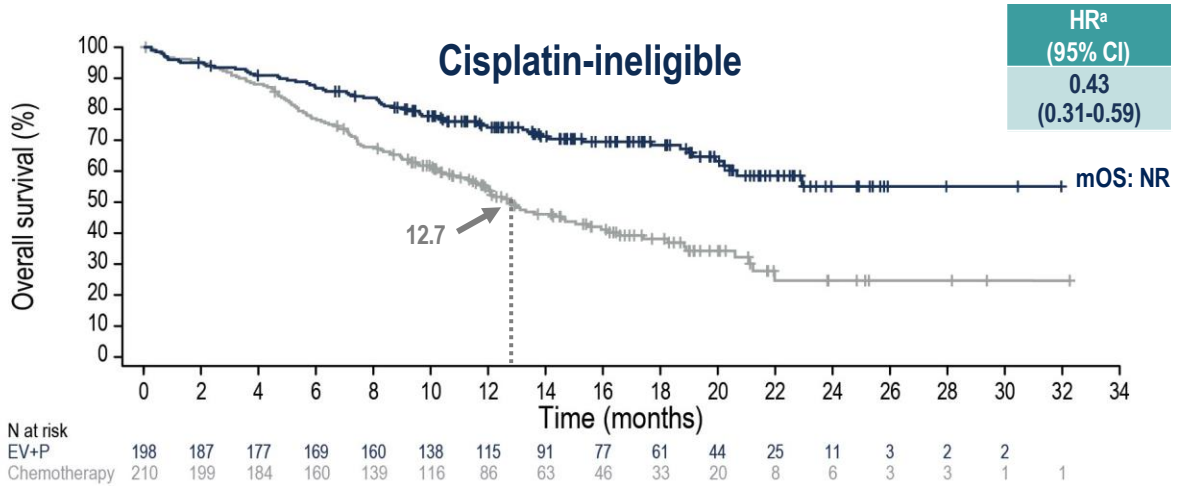
Data cutoff: 08 Aug 2023

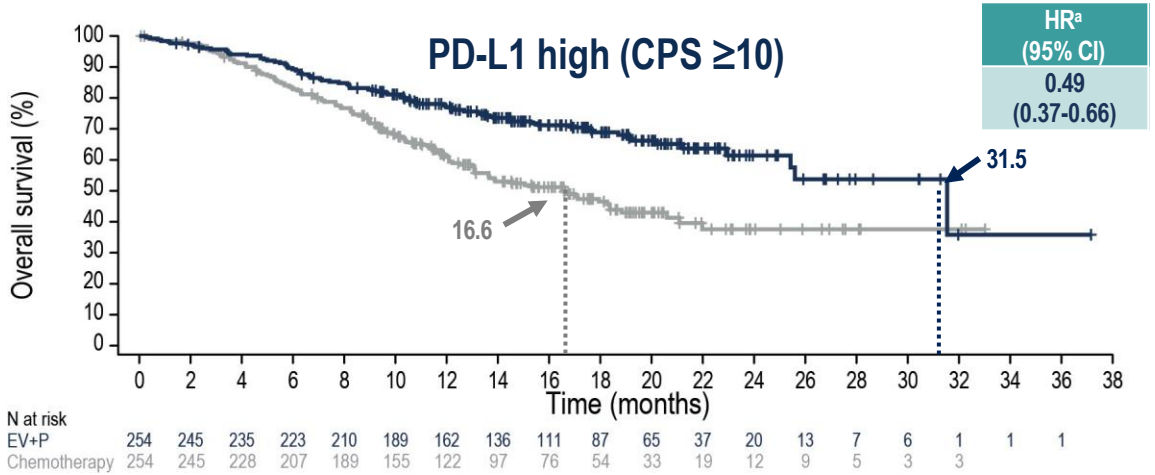
OS at 12 and 18 months was estimated using Kaplan-Meier method
mOS, median overall survival; NR, not reached
[a]Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+P arm

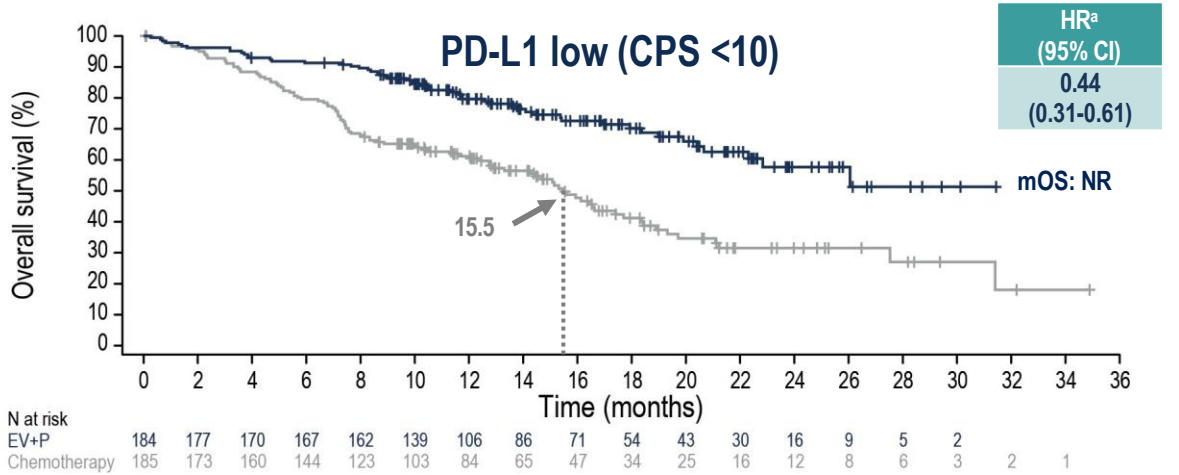
OS Subgroup Analysis: Cisplatin Eligibility and PD-L1 Expression

OS benefit was consistent with the overall population regardless of cisplatin eligibility or PD-L1 expression status







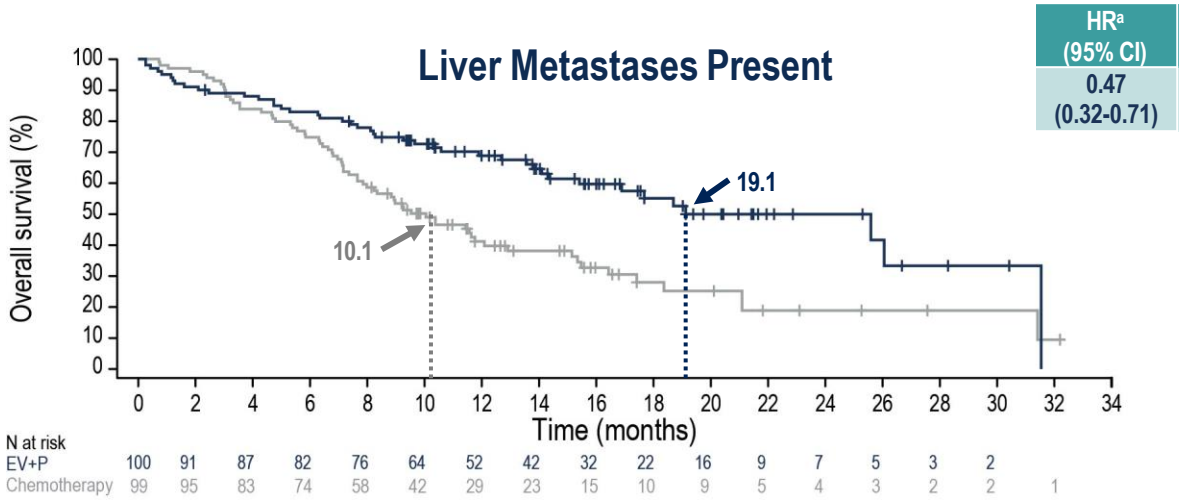


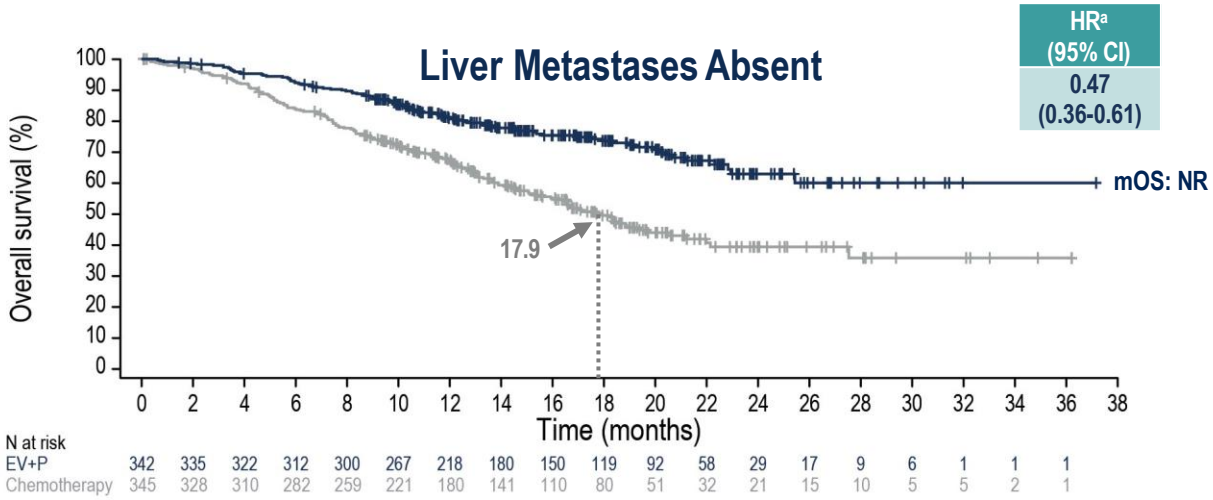
Data cutoff: 08 August 2023

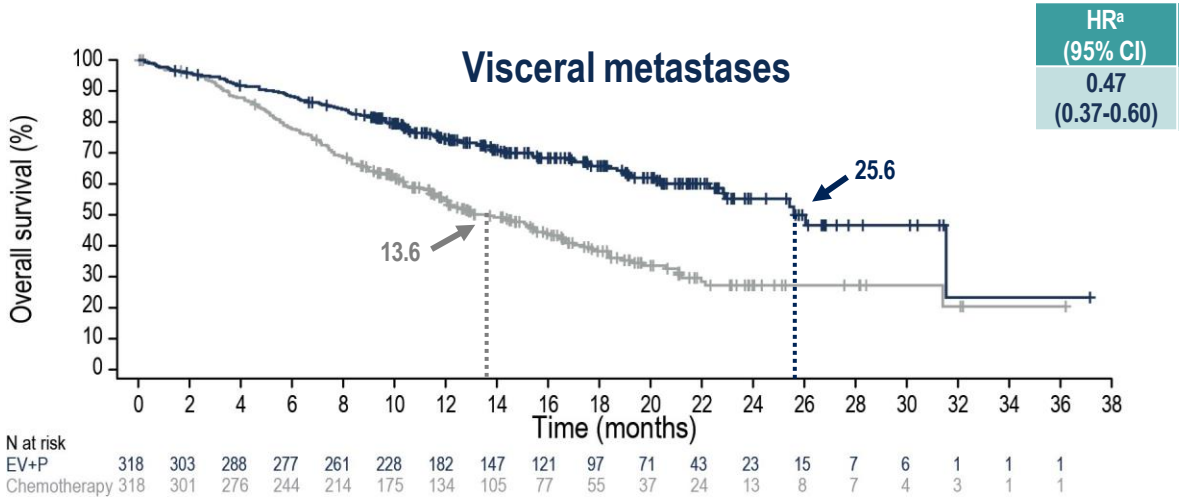
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm

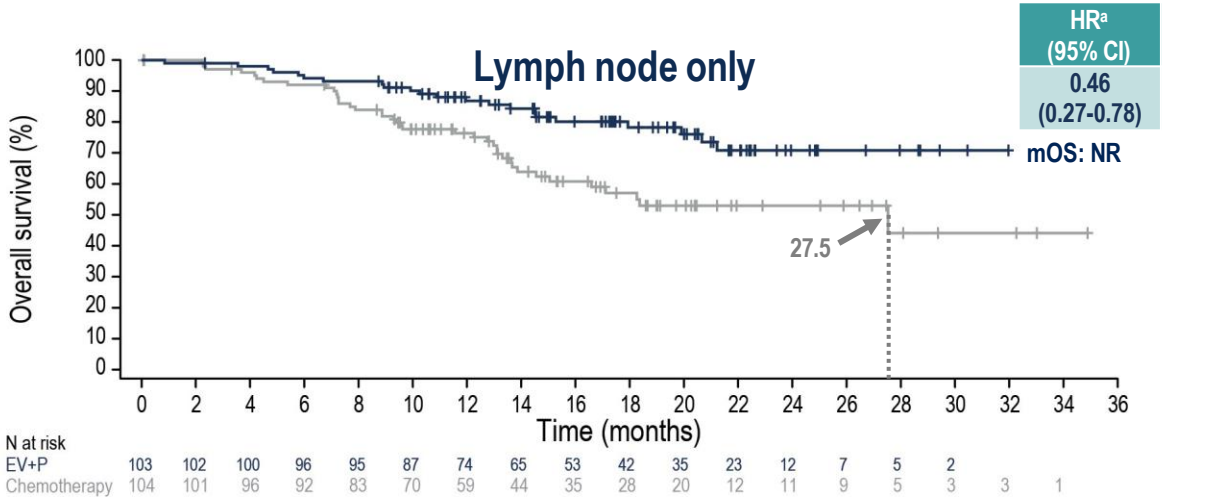
OS Subgroup Analysis: Liver Metastases and Metastatic Disease Site

OS benefit was consistent with the overall population regardless of the presence or absence of liver or visceral metastases







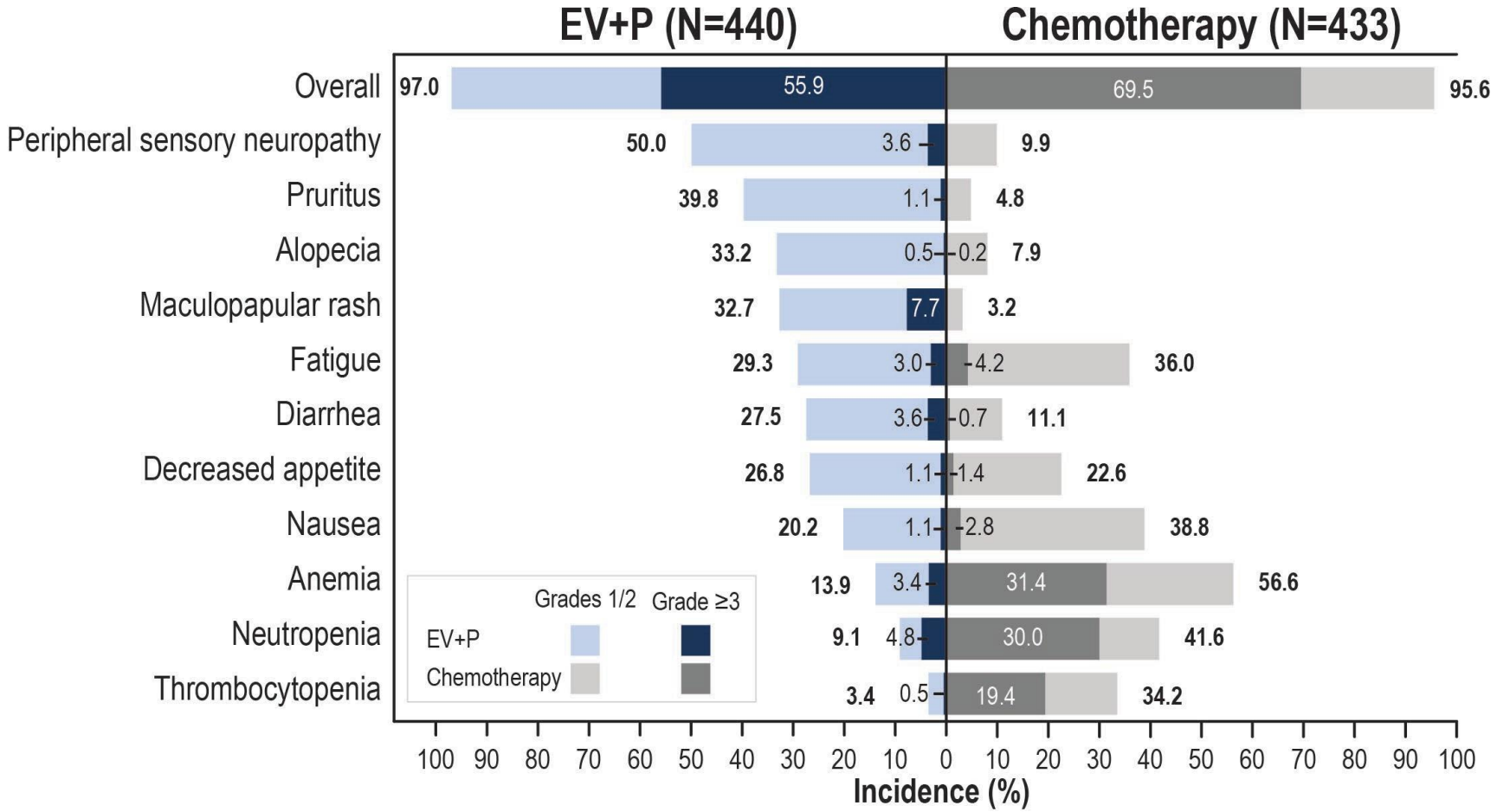


Data cutoff: 08 August 2023

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

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

Data cutoff: 08 Aug 2023

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

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

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)

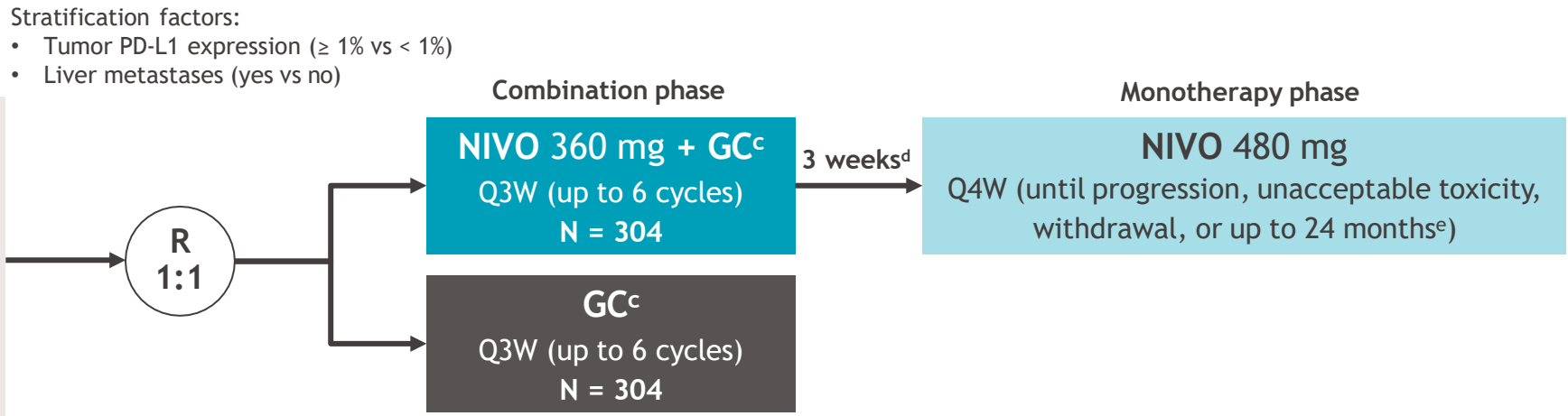
2021
Sacituzumab
Govitecan
(3rd line)

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]



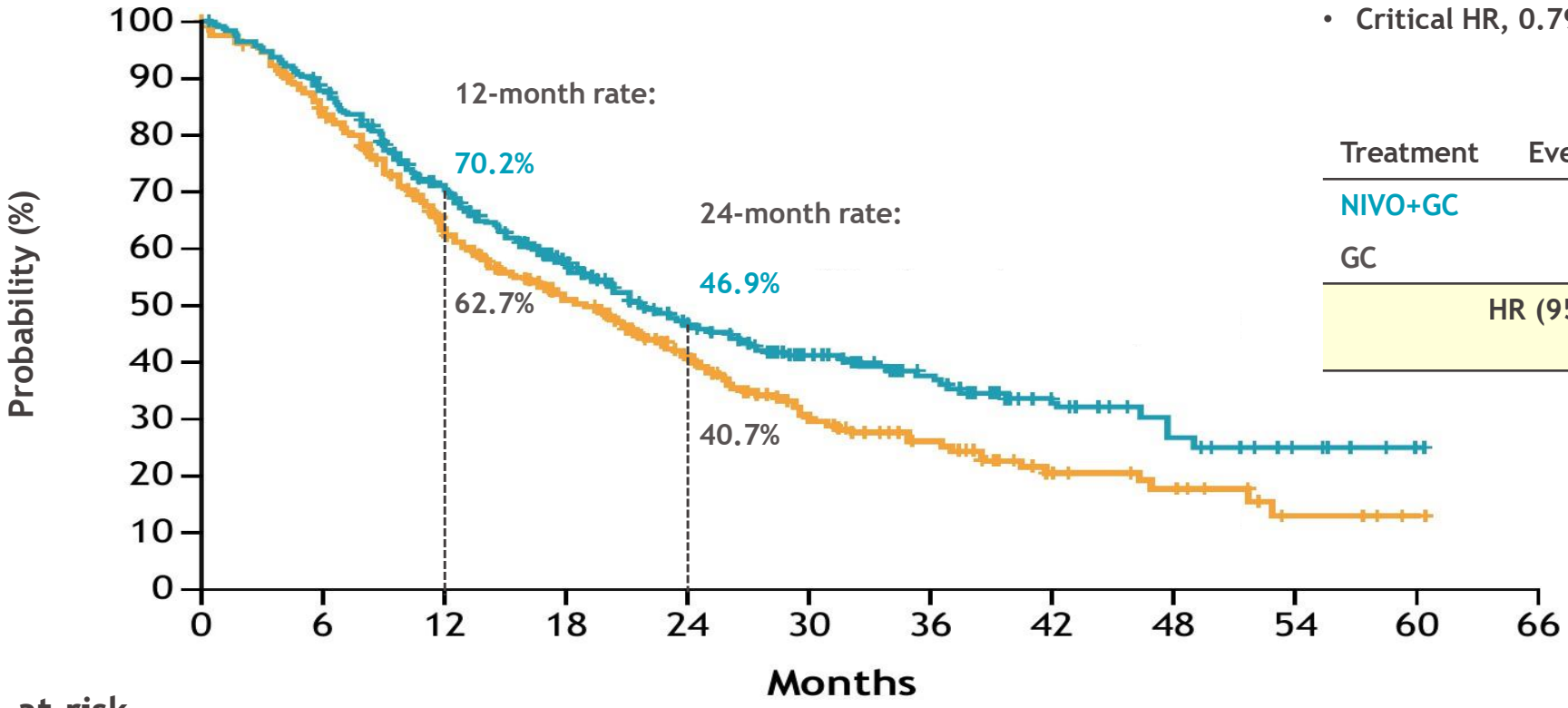
Median (range) study follow-up 33.6 (7.4–62.4) months

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		

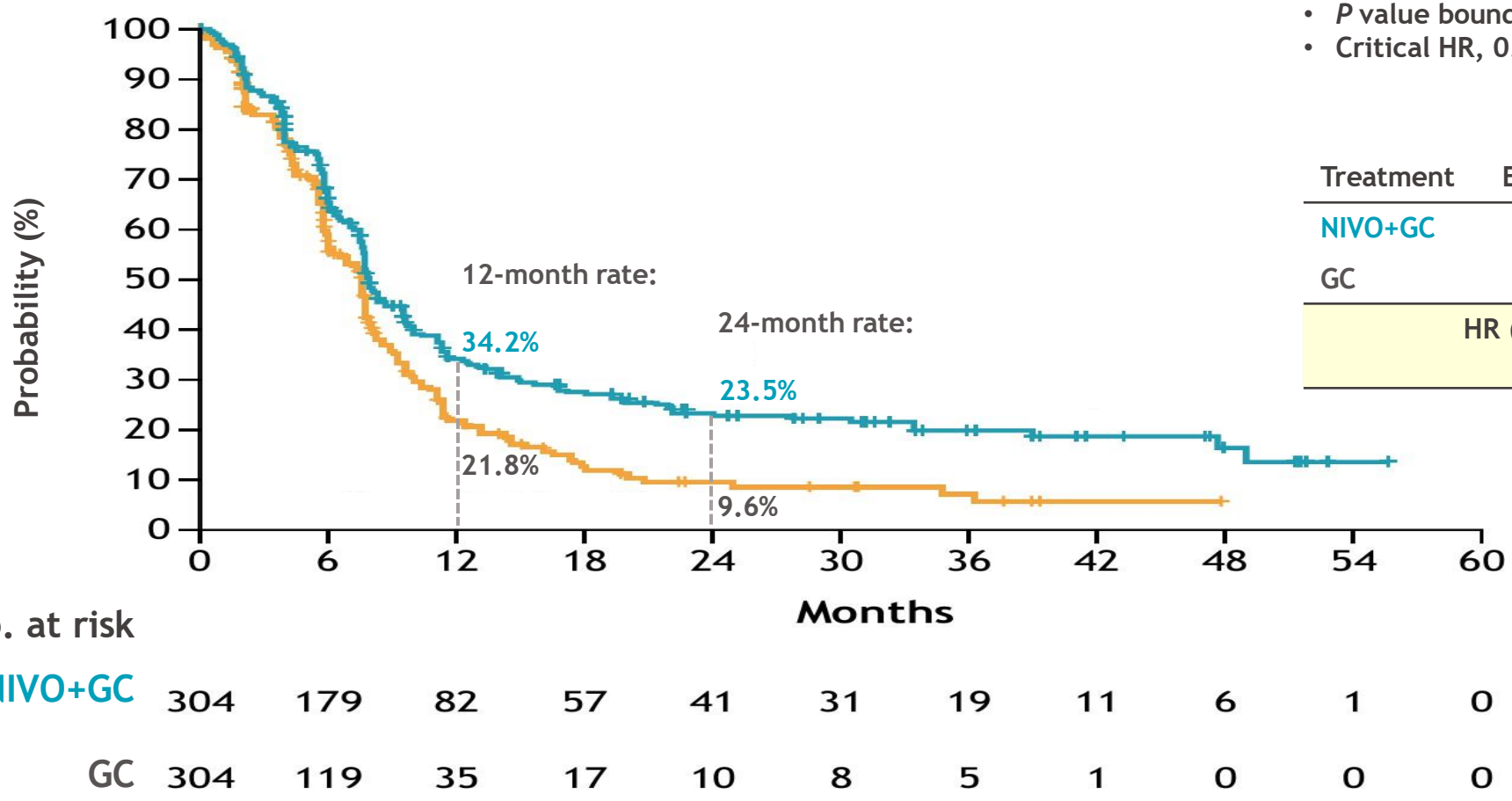
No. at risk

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



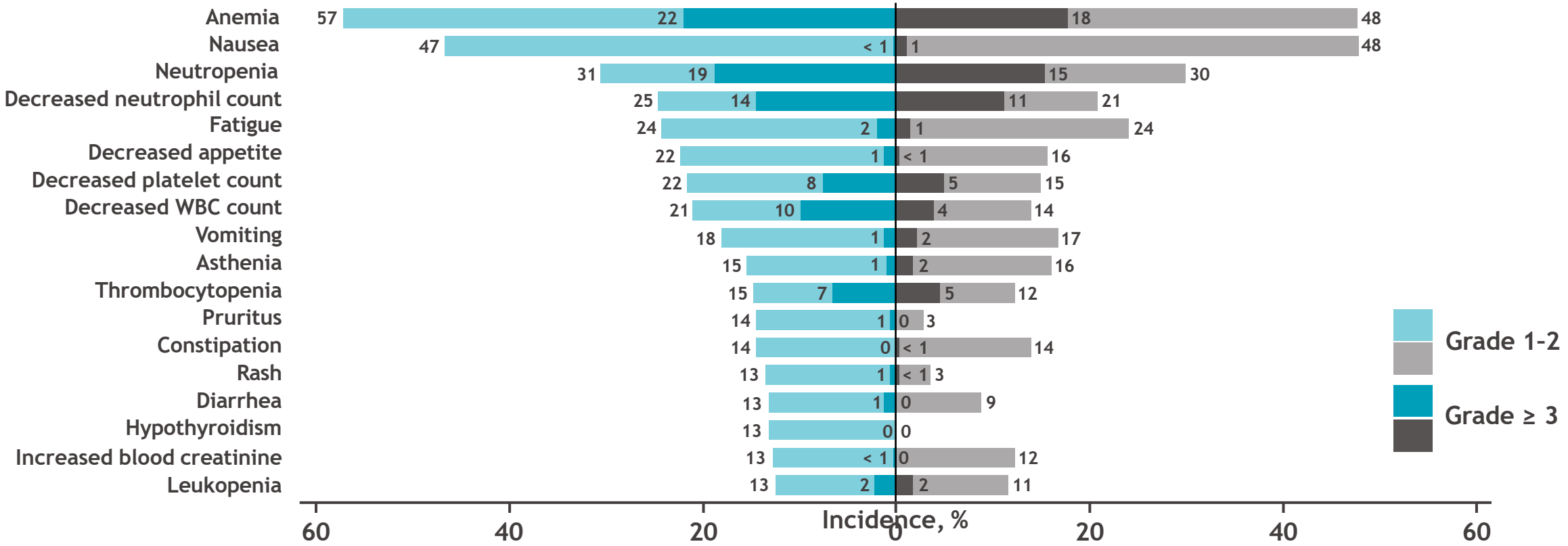
Treatment	Events/patients	Median PFS (95% CI), months
NIVO+GC	211/304	7.9 (7.6-9.5)
GC	191/304	7.6 (6.1-7.8)
HR (95% CI), 0.72 (0.59-0.88) *P* = 0.0012		

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

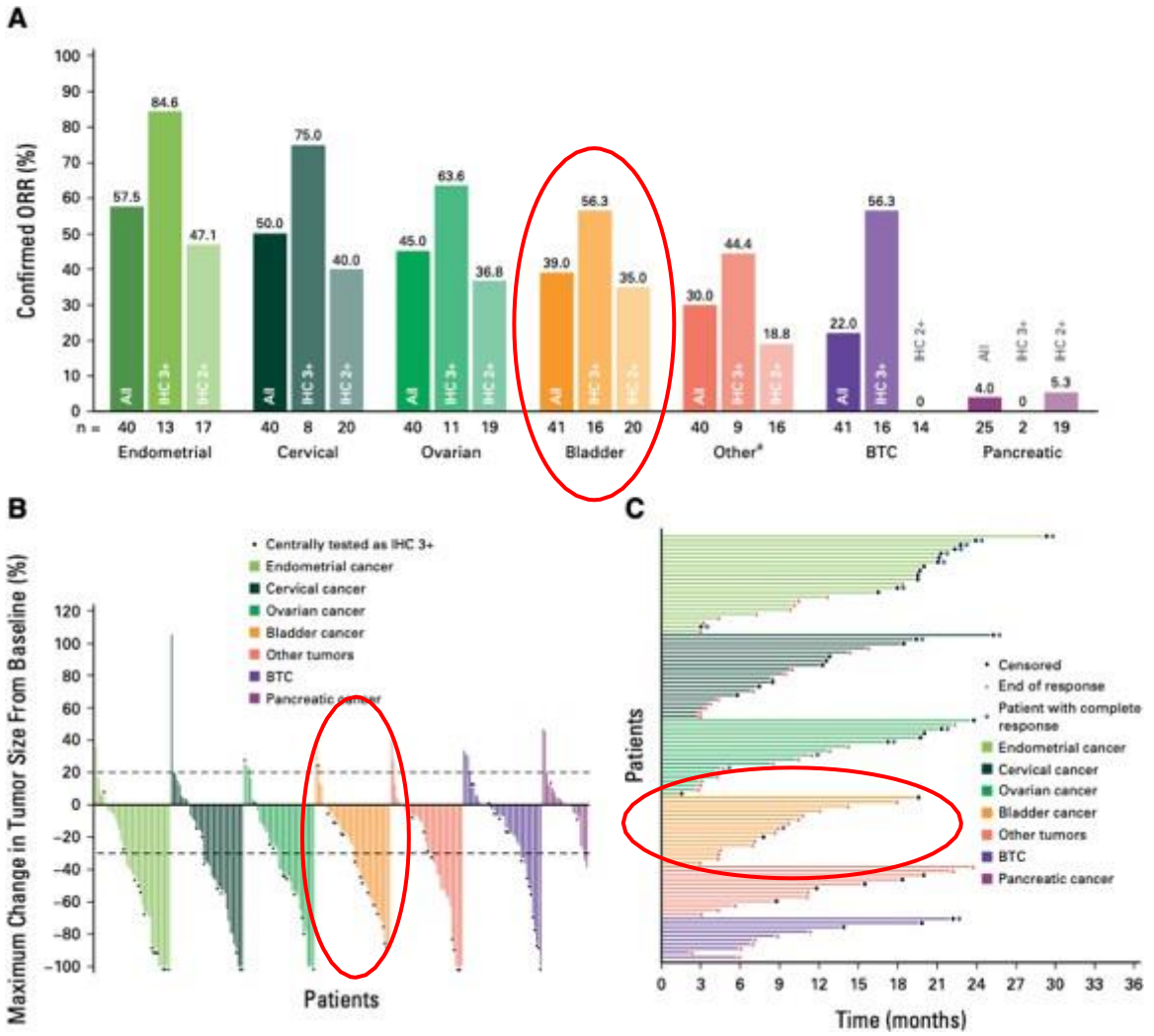
- 267 pts received treatment; 202 (75.7%) based on local HER2 testing
  - 111 (41.6%) pts were IHC 3+ based on HER2 test (local or central) at enrollment; primary efficacy analysis (all patients)
  - 75 (28.1%) pts were IHC 3+ on central testing; sensitivity analysis on efficacy endpoints (subgroup analyses)
- 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

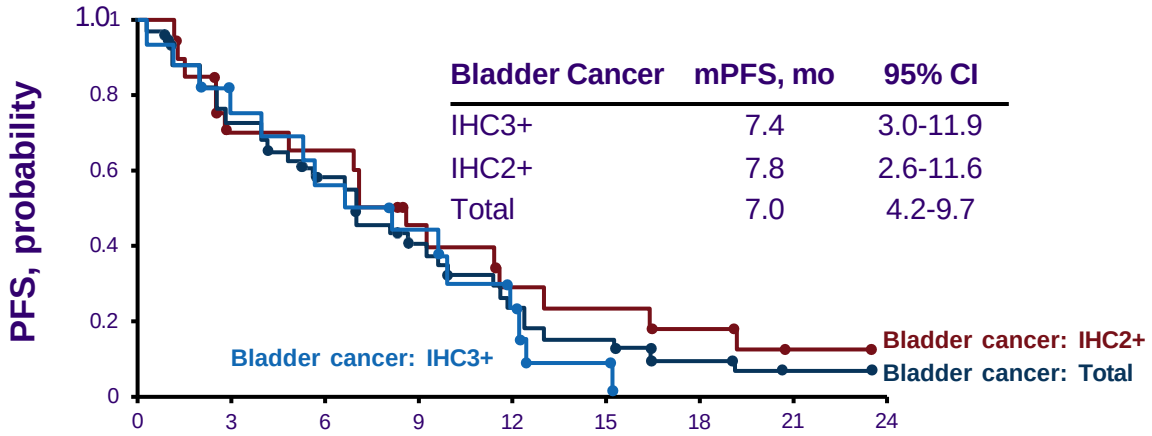


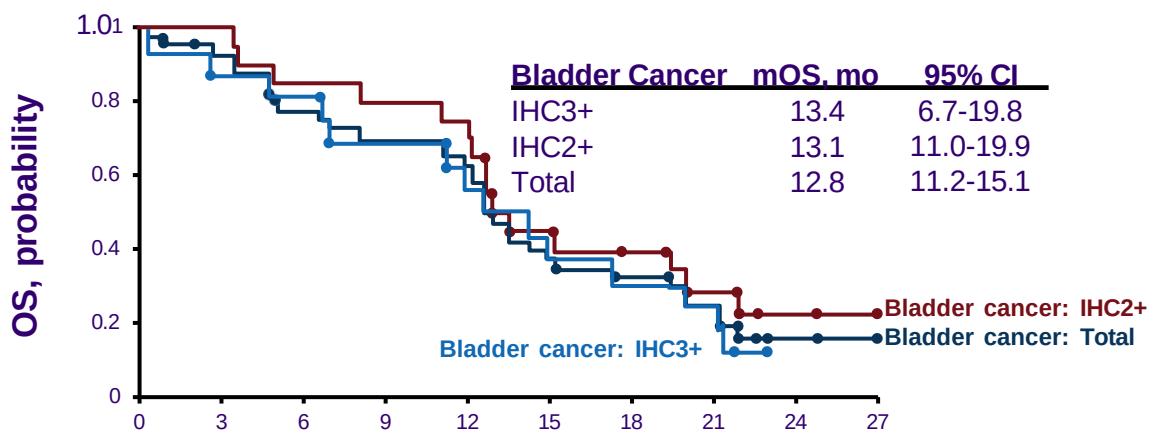
UC Cohort Outcomes

	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.

T-DXd: PFS & OS in Bladder Cohort





No. at Risk

Bladder cancer: IHC 3+	16	12	9	6	3	1	0		
Bladder cancer: IHC 2+	20	14	13	8	5	4	3	1	0
Bladder cancer: Total	41	29	23	14	8	5	3	1	0

No. at Risk

Bladder cancer: IHC 3+	16	14	13	11	9	6	5	4	0	
Bladder cancer: IHC 2+	20	20	17	16	15	9	7	5	2	0
Bladder cancer: Total	41	37	31	28	25	15	12	9	2	0

- Across all cohorts, median PFS 6.9 mo
- mPFS in Bladder cohort 7.0 mo
  - 7.8 mo for IHC2+, 7.4 mo for IHC3+

- Across all cohorts, median OS 13.4 mo
- mOS in Bladder cohort was 12.8mo
  - 13.1mo for IHC2+, 13.4 mo for IHC3+

1. 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.

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)
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)	*-Taxane (US)* *-Vinflunine (EU)*

Slide Compliments: Petros Grivas, MD, PhD

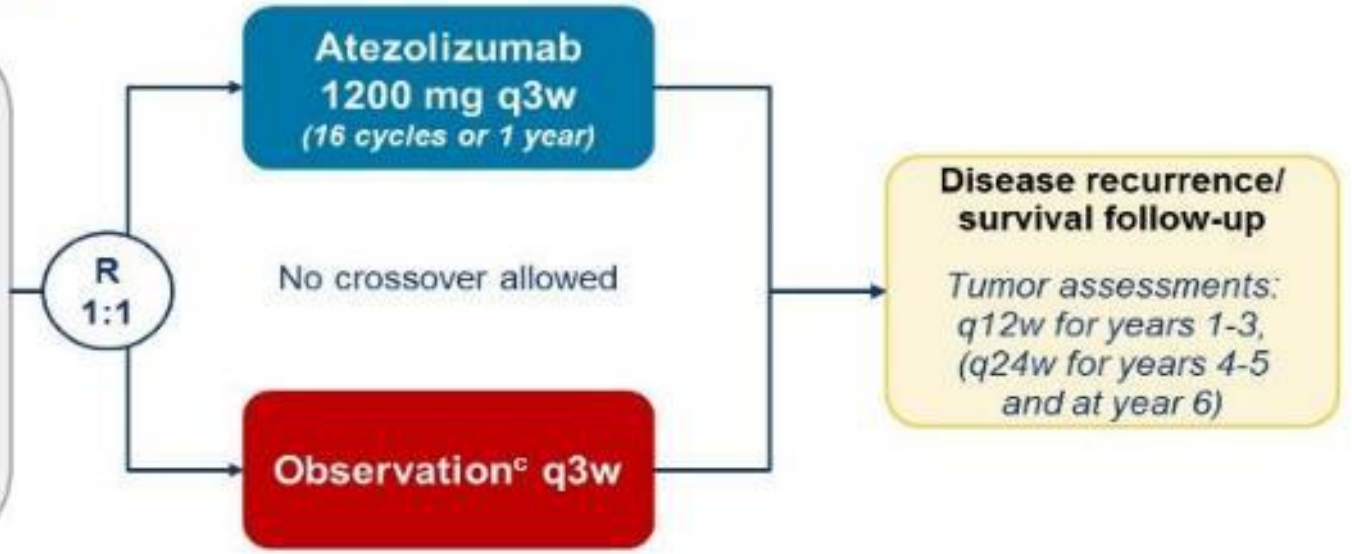
Clinical trials are critical throughout disease spectrum!

QUESTIONS?

IMvigor010 Study Design

Key eligibility[a]

- **High-risk MIUC (bladder, renal pelvis, ureter)**
- **Radical cystectomy/nephroureterectomy with LN dissection** within ≤ 14 weeks
  - **ypT2-T4a or ypN+** for patients treated with **NAC**[b]
  - **pT3-T4a or pN+** for patients **not treated with NAC**[b]
- No postsurgical radiation or AC
- If no prior NAC given, patient had to be ineligible for, or declined, cisplatin-based AC
- ECOG PS 0-2
- **Tissue sample for PD-L1 testing**



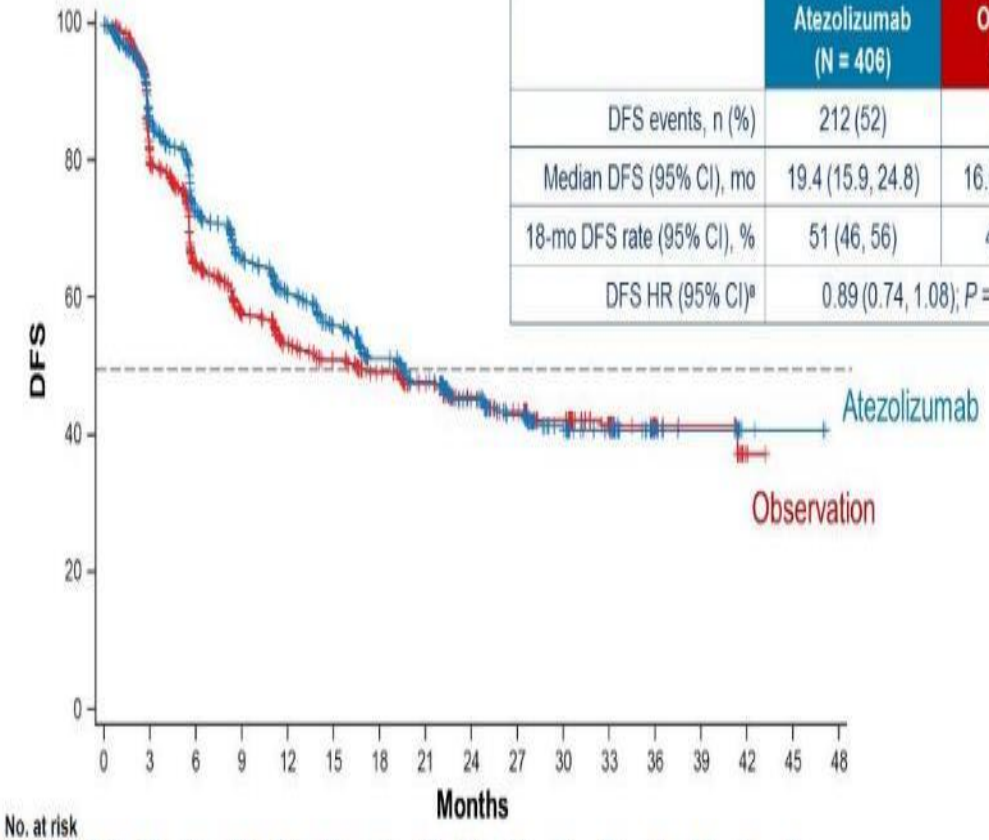
Stratification factors

- Number of LNs resected (< 10 vs ≥ 10)
- Prior NAC (Yes vs No)
- LN status (+ vs –)
- Tumor stage (≤ pT2 vs pT3/pT4)
- PD-L1 status[a] (IC0/1 vs IC2/3)

- **Primary endpoint:** DFS (ITT population)
- **Key secondary endpoint:** OS (ITT population)
- **Exploratory analyses:** Biomarkers including PD-L1 status
- **Safety**

AC, adjuvant chemotherapy; DFS, disease-free survival; ITT, intention to treat; LN, lymph node; MIUC, muscle-invasive UC. [a] Protocol amendments broadened eligibility to "all-comers" (initially, only PD-L1–selected patients were enrolled [IC2/3: PD-L1 expression on tumor-infiltrating immune cells (IC) ≥ 5% of tumor area [VENTANA SP142 IHC assay]) and to patients with MIUC (initially, only patients with muscle-invasive bladder cancer were enrolled). [b] Upper-tract UC staging: ypT2-4 or ypN+ (with NAC) and pT3-4 or pN+ (without NAC). [c] Alternating clinic visits and phone calls.

DFS in ITT Population

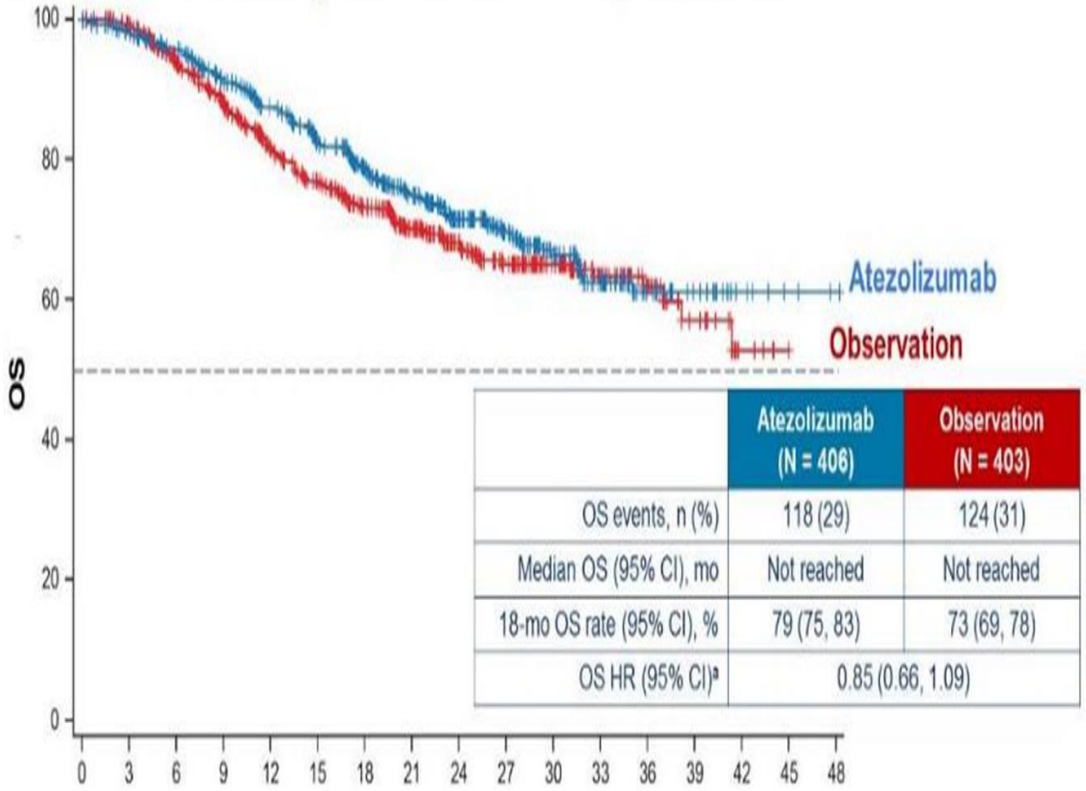


	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); *P* = 0.2446[b]	

No. at risk																
Atezolizumab	406	332	281	248	223	201	169	142	115	92	67	52	15	10	3	2
Observation	403	305	240	211	188	177	156	131	109	87	67	42	17	12	2	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. [a] Stratified by post-resection tumor stage, nodal status and PD-L1 status. [b] 2-sided.

Interim OS Analysis in ITT Population



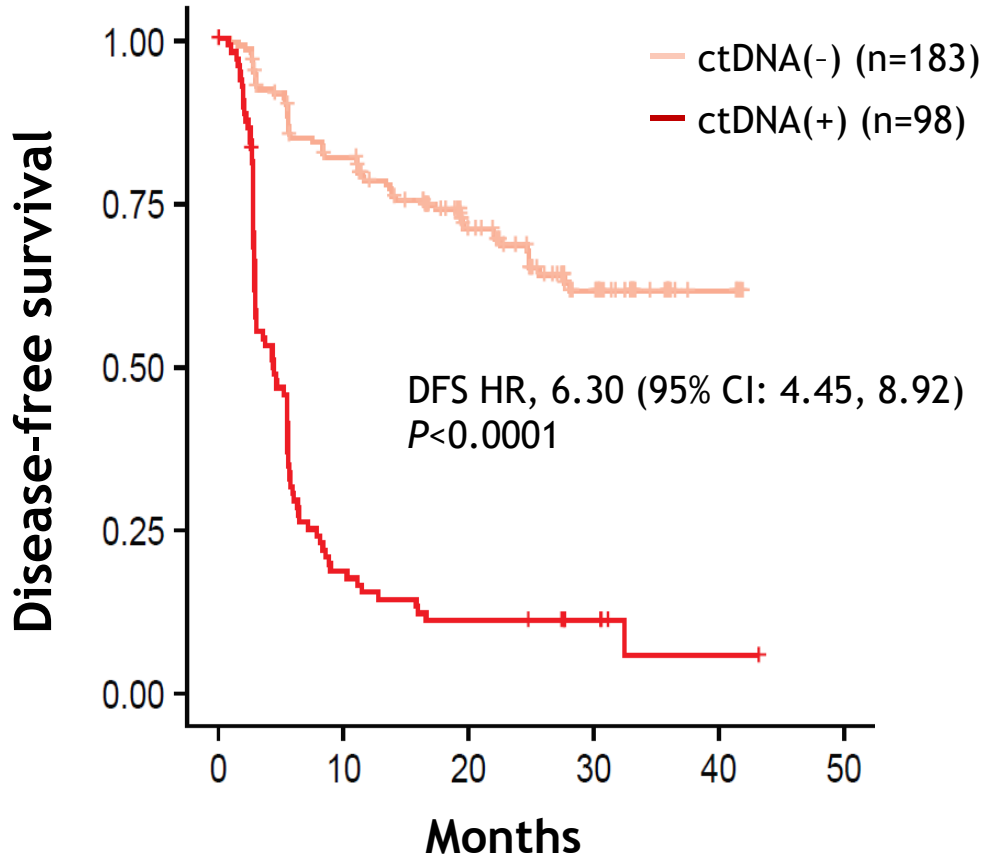
	Atezolizumab (N = 406)	Observation (N = 403)
OS events, n (%)	118 (29)	124 (31)
Median OS (95% CI), mo	Not reached	Not reached
18-mo OS rate (95% CI), %	79 (75, 83)	73 (69, 78)
OS HR (95% CI)[a]	0.85 (0.66, 1.09)	

No. at risk																
Atezolizumab	406	383	369	350	328	306	267	229	185	144	100	72	35	22	8	4	2
Observation	403	377	345	318	289	270	235	199	163	134	100	65	36	20	6	1	

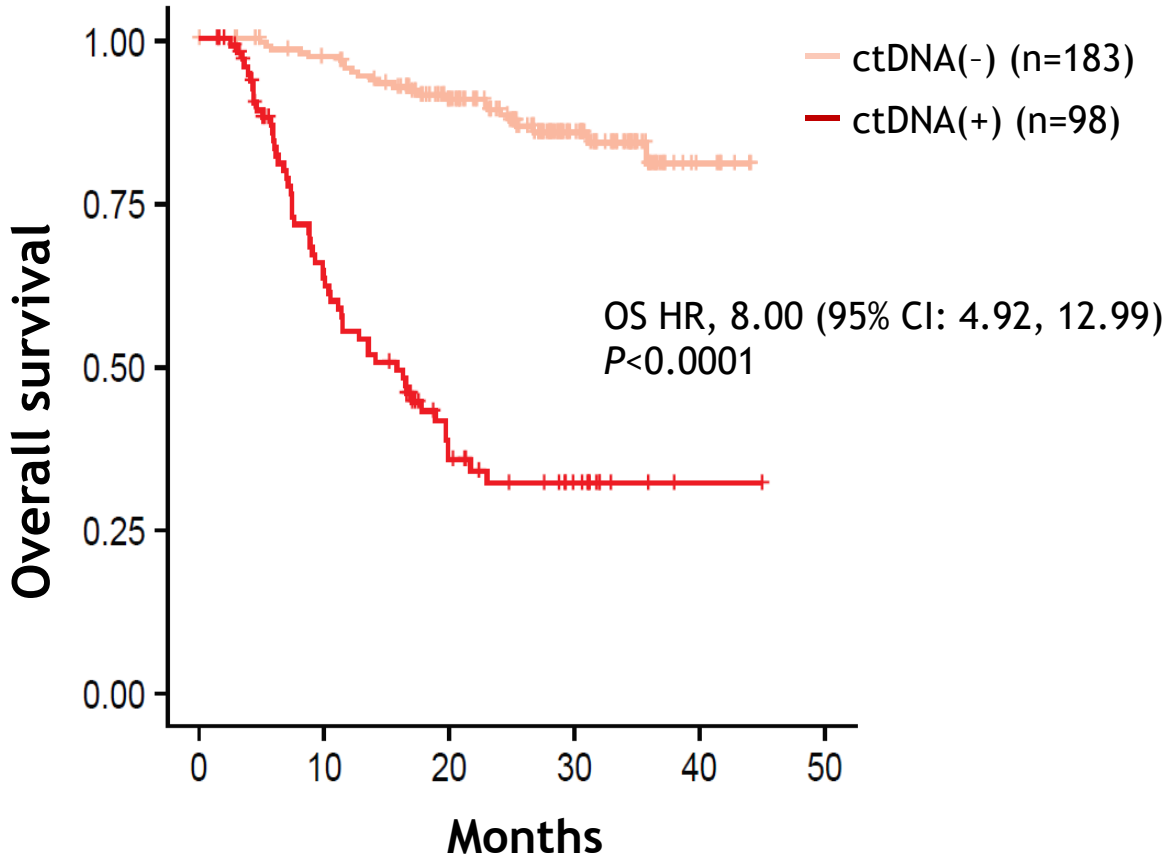
Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. Most common subsequent non-protocol therapies included immunotherapy (9% in atezolizumab arm vs 21% in observation arm), chemotherapy (27% vs 25%) and targeted therapy (5% vs 2%). [a] OS results are shown for descriptive purposes only. HR stratified by tumor stage, nodal status and PD-L1 status.

ctDNA(+) portends poor prognosis

Observation arm

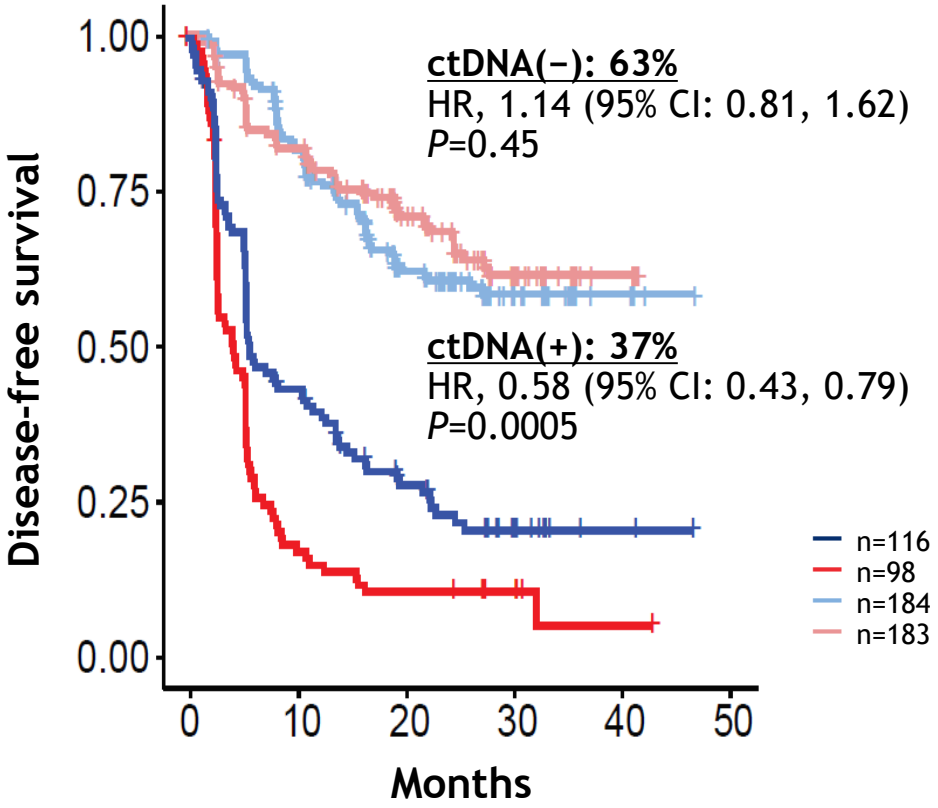


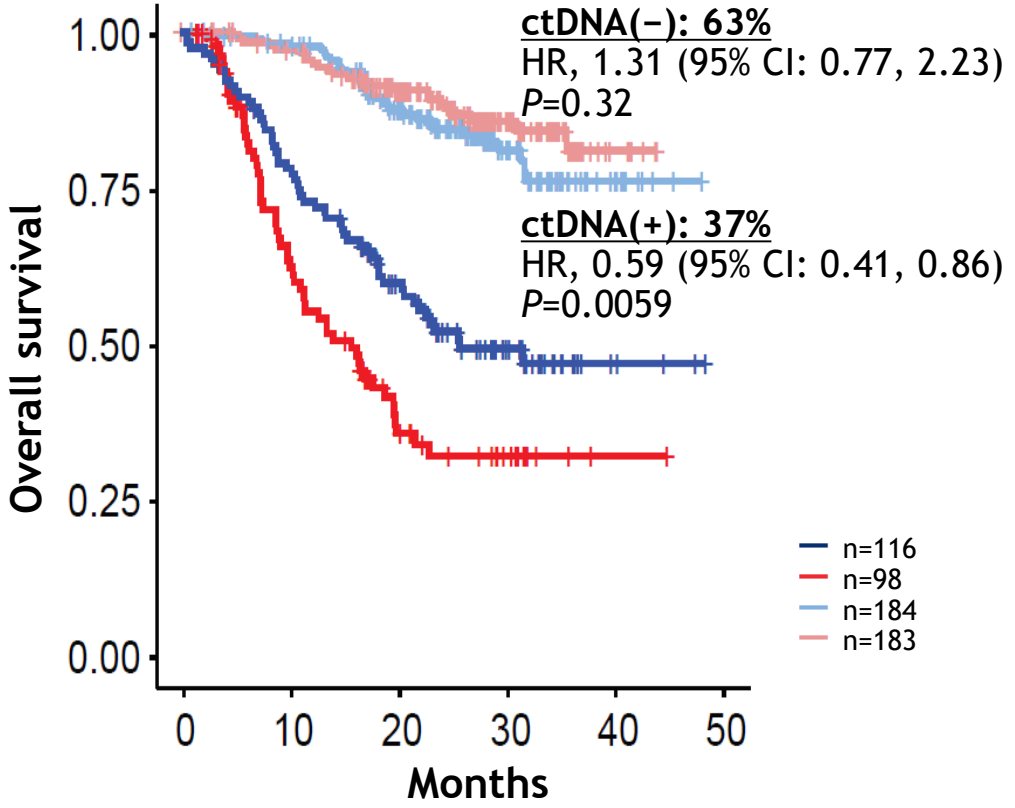
Observation arm



- IMvigor010 confirmed the prognostic value of ctDNA status

ctDNA(+) associated with improved DFS and OS with atezolizumab vs observation





IMVigor 011 (NCT04660344)

After cystectomy

ypT2 and/or ypN+

or

pT3 and/or pN+
(cisplatin-ineligible)