Bladder Preservation with Systemic Therapy Alone: A promising future or a false promise?

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“The best bladder is the one you’re born with”

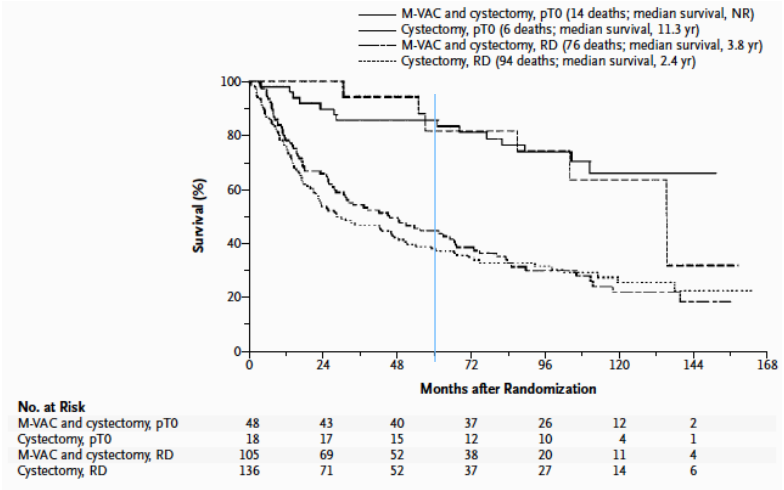
- Harry Herr, MD

Agenda

1. Response-selected patients for bladder preservation
2. Biomarker-selected patients for bladder preservation
3. Future of systemic therapy for bladder preservation

Association of Pathologic downstaging and long-term survival in MIBC

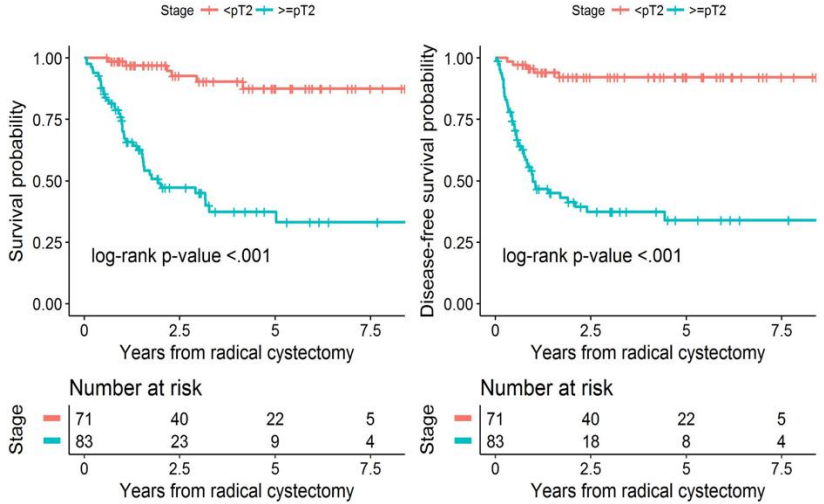
SWOG 8710
Neoadjuvant MVAC



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

Grossman, et al. *NEJM* 2003

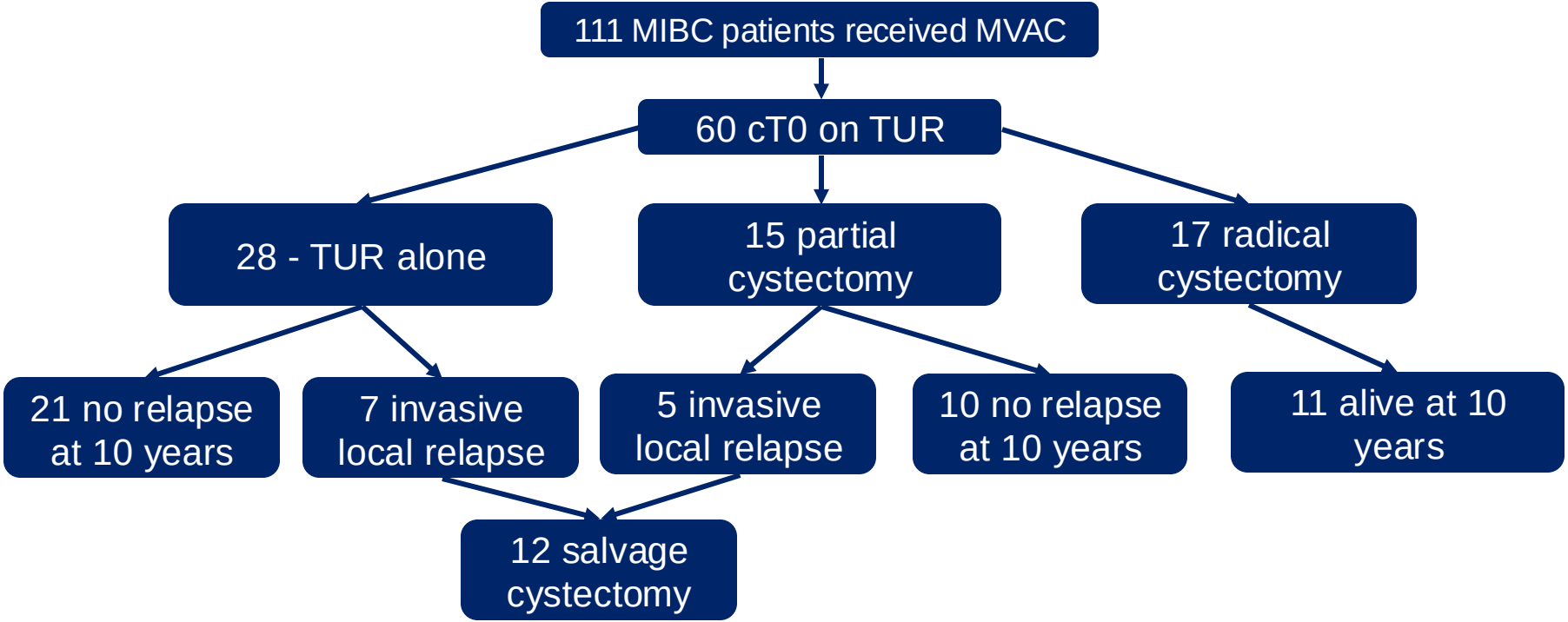
MSKCC experience
Neoadjuvant GC



Iyer et al, *Clin GU Can* 2020

Are there genomic alterations that can predict for pathologic down-staging following cisplatin-based chemotherapy in MIBC?

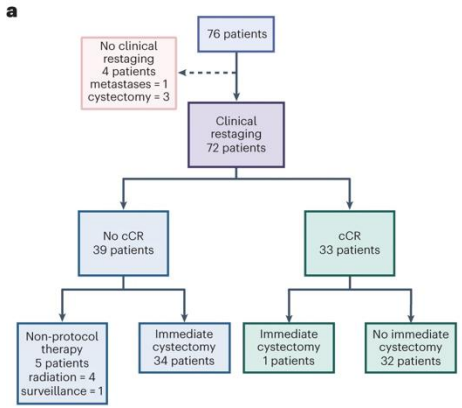
10 year follow-up of series of MVAC patients treated for MIBC

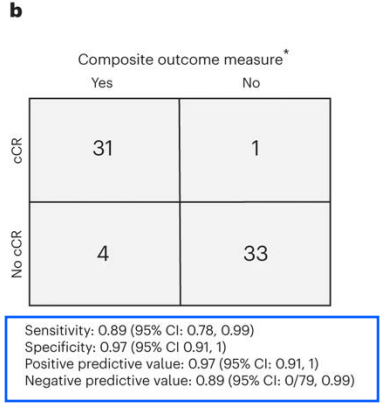


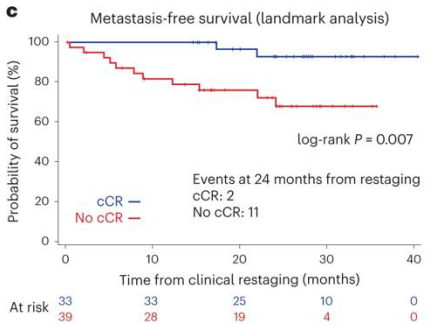
- Highly selected patients
- Meta-analysis of published data estimated 72% 5-year survival (95% CI 64-82%)

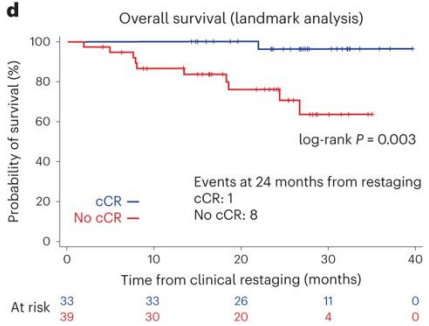
Moran, et al. *Bladder Cancer* 3, (2017) 245–258)
Herr, Bajorin, Scher. *J Clin Oncol* 16(4) 1998

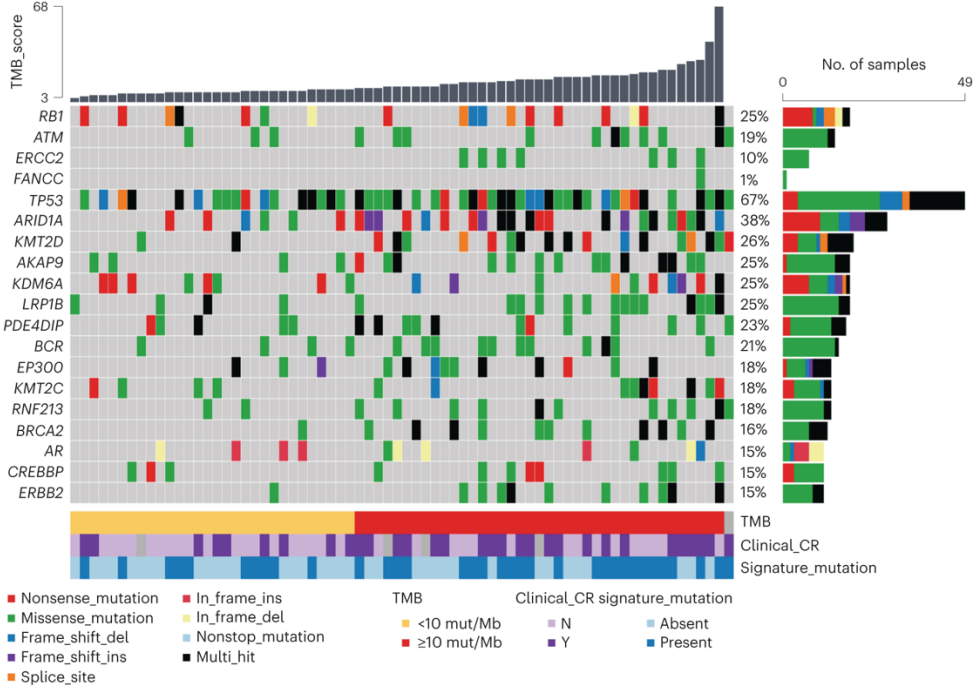
Phase 2 study of gemcitabine/cisplatin/nivolumab with selective bladder preservation







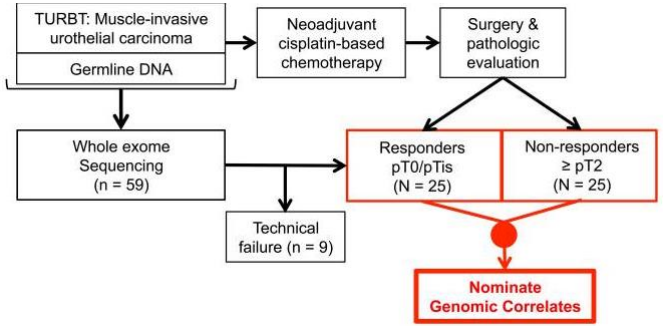


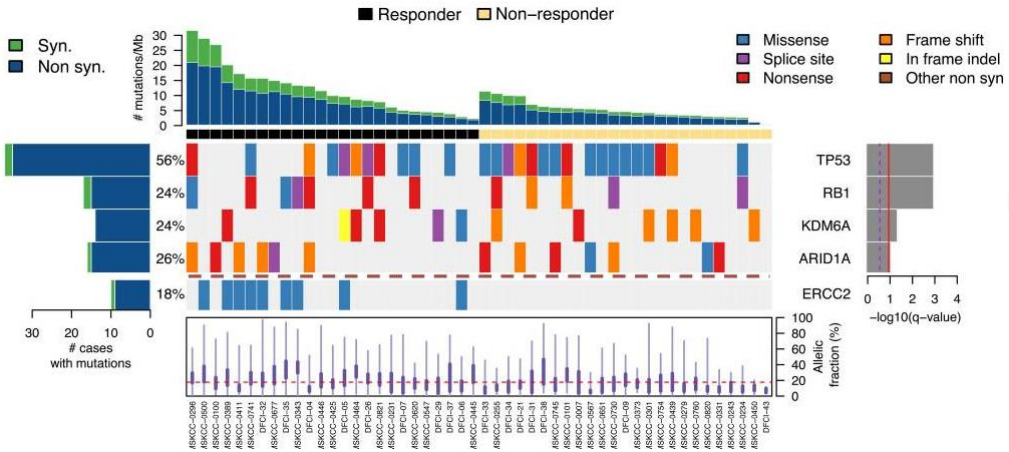


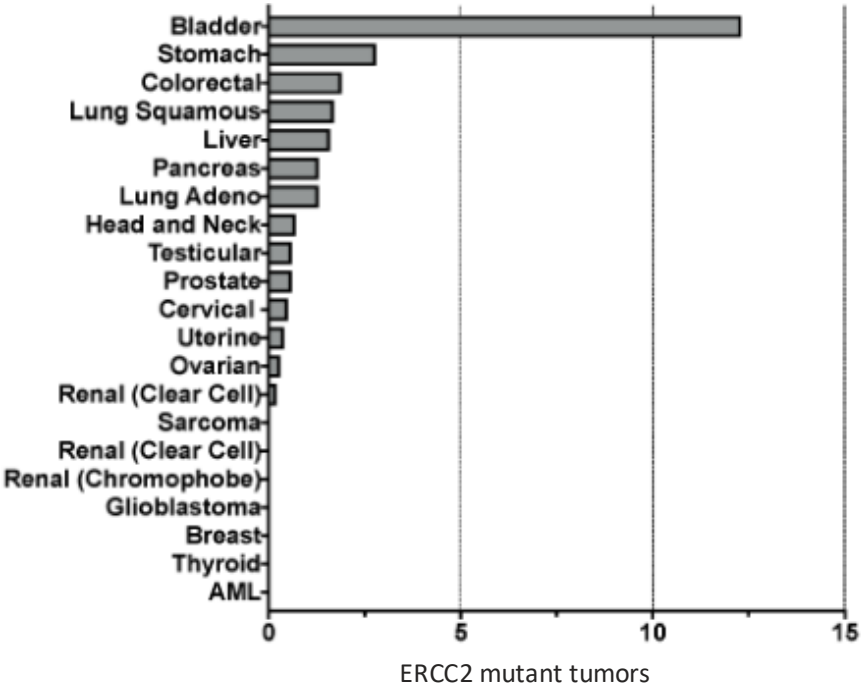
Galsky, et al. *Nature Medicine* 29, 2825–2834 (2023)

Can we use biomarkers to select patients for bladder preservation?

Outlier analysis to determine predictive biomarkers of response to chemotherapy in MIBC



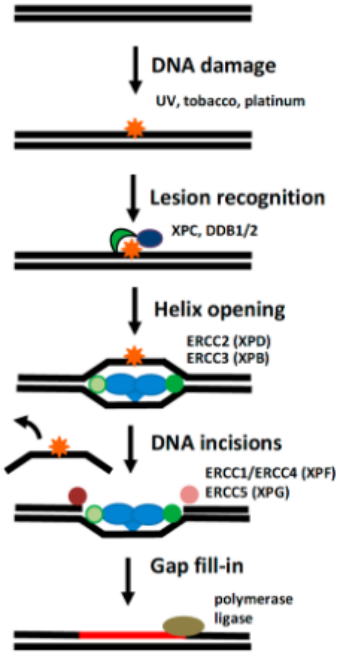




ERCC2 mutant tumors

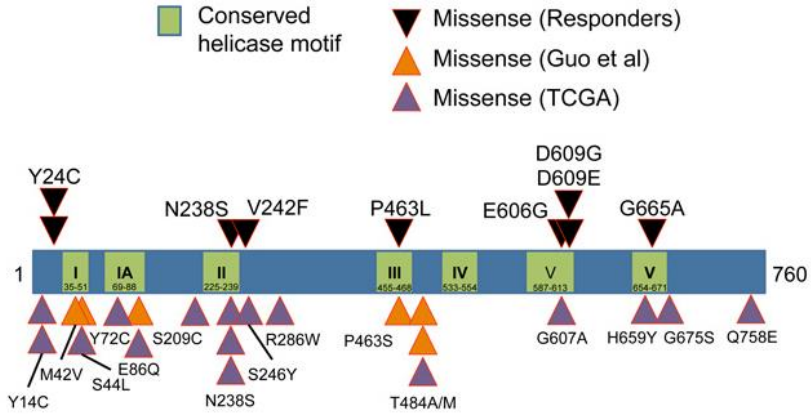
Van Allen et al, *Can Disc* 2014
Mouw, *Cancers* 2017

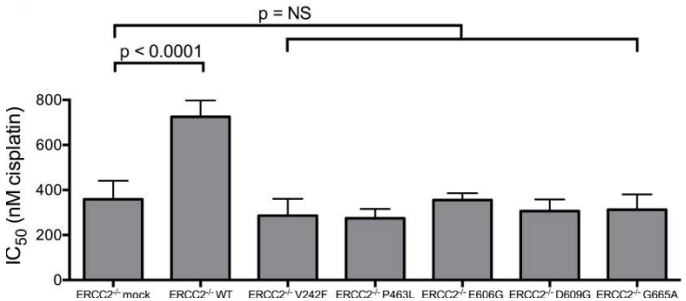
ERCC2 alterations impair nucleotide excision repair and confer cisplatin sensitivity



Autosomal recessive disorders:
Xeroderma pigmentosum
Trichothiodystrophy
Cockayne Syndrome

Hypersensitivity to UV exposure
Pigmentary changes
Skin aging/keratosis/cancer



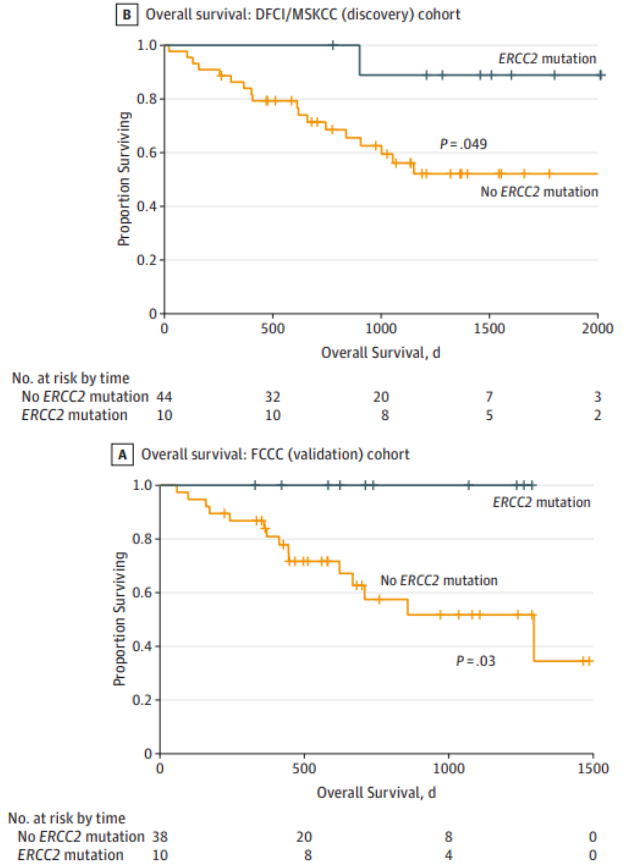


Van Allen et al, *Can Disc* 2014
Mouw, *Cancers* 2017

ERCC2 and other DDR gene alterations in MIBC

Study characteristics	Van Allen *et al.*[113]	Plimack *et al.*[114]
Number of patients	50	• Discovery cohort: 34 • Validation cohort: 24
TNM stage selection criteria	pT2–T4cN0–1M0	pT2–T4cN0–1M0
Pathological response end points	pT0/pTis versus ≥pT2	• pT0pN0cM0 versus >pT0pN0cM0 • ≤pT1pN0cM0 versus >pT1pN0cM0
NACT	GC, ddMVAC, GC-sunitinib, or ddGC	ddMVAC and ddGC
DNA-profiling technique	WES	NGS of 287 cancer-related genes
Findings	*ERCC2* mutations enriched in responders to NACT compared with nonresponders ($P<0.001$; $q<0.007$), and associated with increased mutational load (15.5 versus 5.1 mutations per Mb; $P=0.01$)	*ATM/RB1/FANCC* alterations predict response to NACT ($P<0.001$ discovery; $P=0.033$ validation)
Functional validation	*ERCC2*-deficient cell lines have increased sensitivity to cisplatin	NA

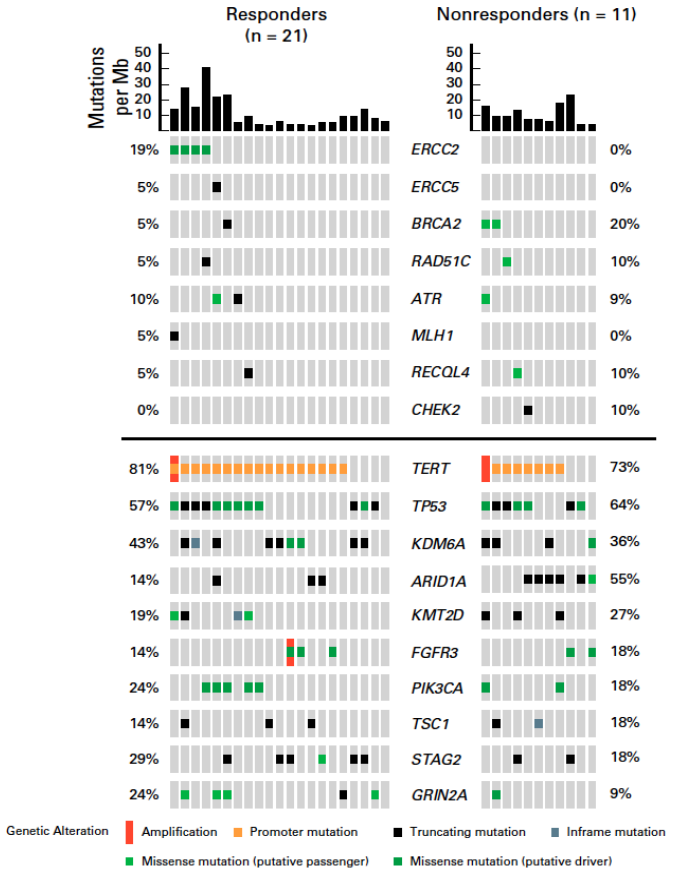
ddGC, dose-dense gemcitabine and cisplatin; ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC, gemcitabine and cisplatin; MIBC, muscle-invasive bladder cancer; NA, not applicable; NACT, neoadjuvant chemotherapy; NGS, next-generation sequencing; WES, whole-exome sequencing.

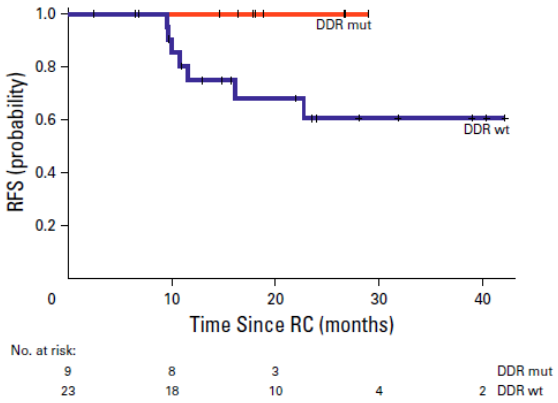


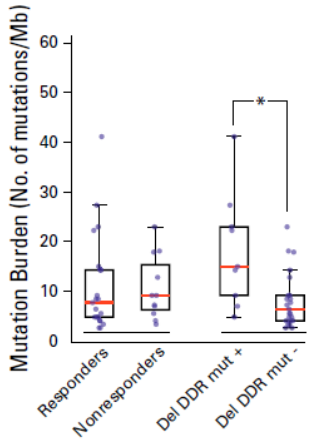
Sequencing data in 48 patients from both cohorts
ERCC2 alt: 40% of responders vs 7% of non-responders (p=0.01)

Funt et al, *Nat Rev Clin Onc* 2017 Liu et al, *JAMA Onc* 2016

ERCC2 and other DNA damage response gene alterations and cisplatin sensitivity in MIBC



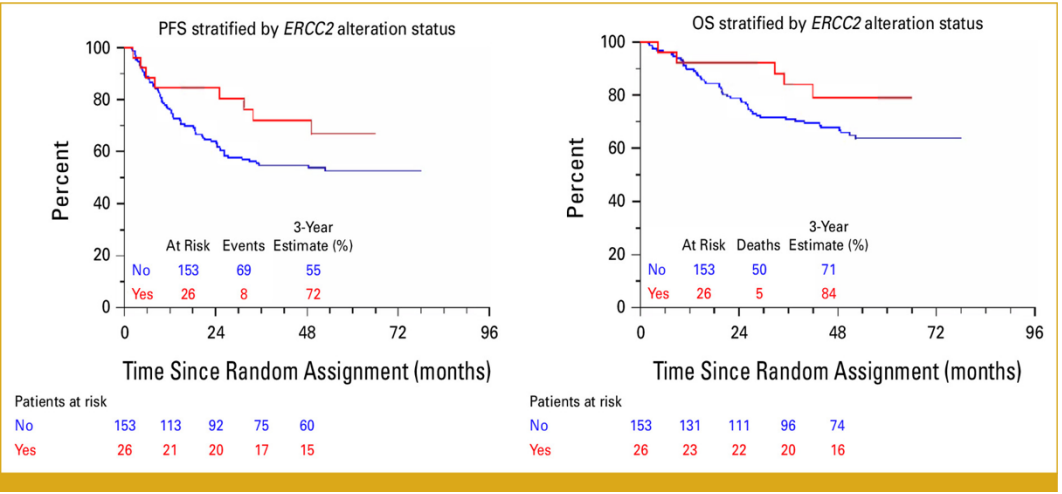




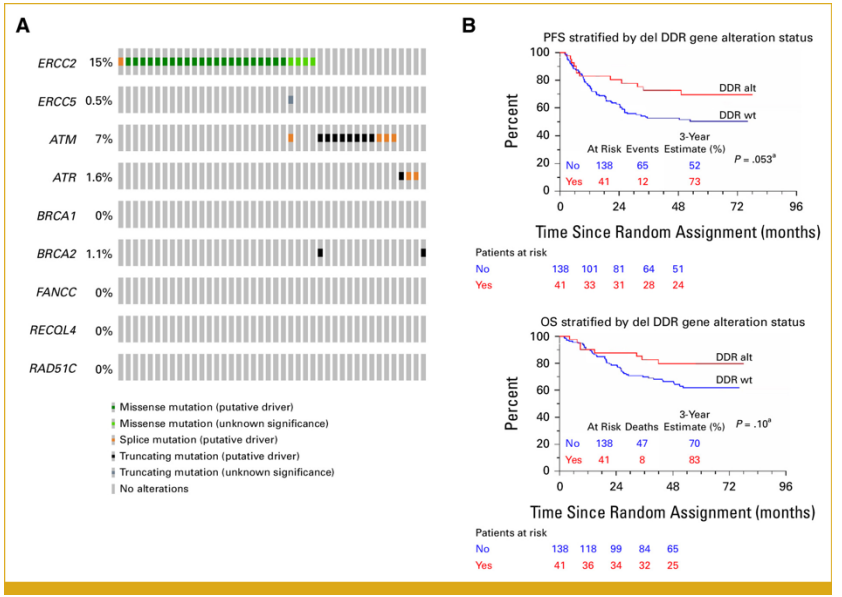
Iyer et al, *J Clin Oncol* 2018

Secondary analysis S1314: ddMVAC or GC as NAC

- MSK-IMPACT performed on pre-treatment TURBT specimens
- Presence of selected DDR mutations associated with improved PFS and trend towards improved OS
- ERCC2 mutation associated with trends towards improved PFS and OS



Iyer et al. *JCO Precis Oncol*. 2024 Nov:8:e2400287.

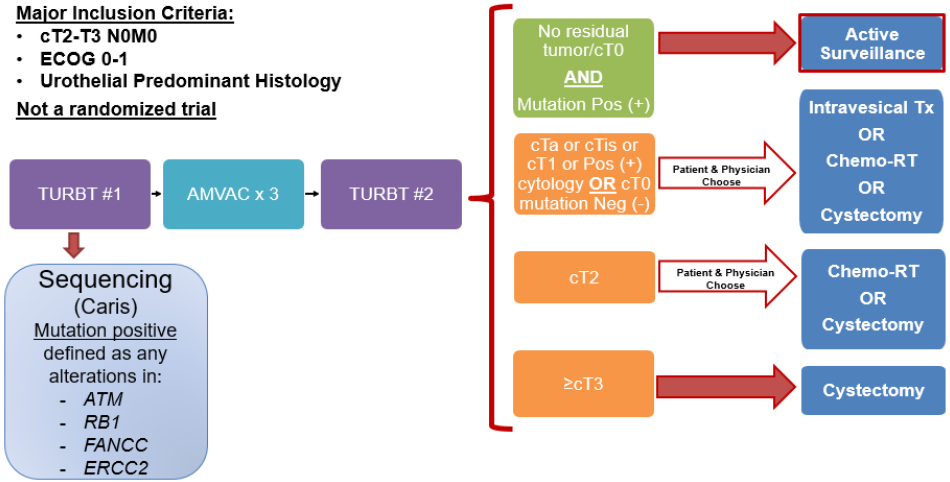


Gene	Variant?	*n*/*N* (%) with pT0	Sensitivity (95% CI) Specificity (95% CI) PPV (95% CI) NPV (95% CI)	Odds ratio (95% CI) [b] Two-sided *p* value	AUC [c]
Mutation in one or more of the 4 genes: *ATM, ERCC2, FANCC,* or *RB1*	Yes	27/56 (48)	0.79 (0.66, 0.93) 0.59 (0.48, 0.71)	5.36 (2.05, 14.02) 0.001	0.71
	No	7/49 (14)	0.48 (0.35, 0.62) 0.86 (0.73, 0.94)		
ATM	Yes	14/25 (56)	0.41 (0.25, 0.58) 0.85 (0.76, 0.93)	4.23 (1.60, 11.2) 0.004	0.66
	No	20/80 (25)	0.56 (0.35, 0.76) 0.75 (0.64, 0.84)		
ERCC2	Yes	12/18 (67)	0.35 (0.19, 0.51) 0.92 (0.82, 1.00)	5.47 (1.80, 16.6) 0.003	0.65
	No	22/87 (25)	0.67 (0.41, 0.87) 0.75 (0.64, 0.83)		
FANCC	Yes	0/4 (0)	0.00	Too few variants	
	No	34/101 (34)	0.94 (0.89, 1.00) 0.00 (0.00, 0.60) 0.66 (0.56, 0.75)		
RB1	Yes	12/25 (48)	0.35 (0.19, 0.51) 0.82 (0.73, 0.91)	2.31 (0.91, 5.86) 0.08	0.62
	No	22/80 (28)	0.48 (0.28, 0.69) 0.73 (0.61, 0.82)		

AUC = area under the curve; CI = confidence interval; NPV = negative predictive value; OR = odds ratio; PPV = positive predictive value.
[a] AUC for clinical stage alone = 0.55.
[b] OR adjusted for stratification factor T2 versus T3-4a in the logistic model.
[c] AUC including clinical stage + respective variant in the model.

Plimack et al. *Eur Urol* (2024) 86:297-300

Retain-1: Bladder Preservation with Chemotherapy alone in Biomarker-Selected Patients



RETAIN trial

Primary endpoint: 2-year MFS (>cN1 recurrence or surgically unresectable local recurrence or M1 disease)
ITT: N = 70
Mutation +: 33 (cT0 76% vs 15% in mutation negative)

2-year MFS: 77.9% (lower bound of 95% CI 62.8%)
Risk-adapted approach could not be declared non-inferior to standard approach of NAC/RC
48% of patients (n=12) on active surveillance are alive without M1 disease and their bladder intact
68% of patients (n=17) on active surveillance have recurred

Geynisman et al. J Clin Oncol. 2024 Dec 16

Retain-1 Metastasis Free Survival

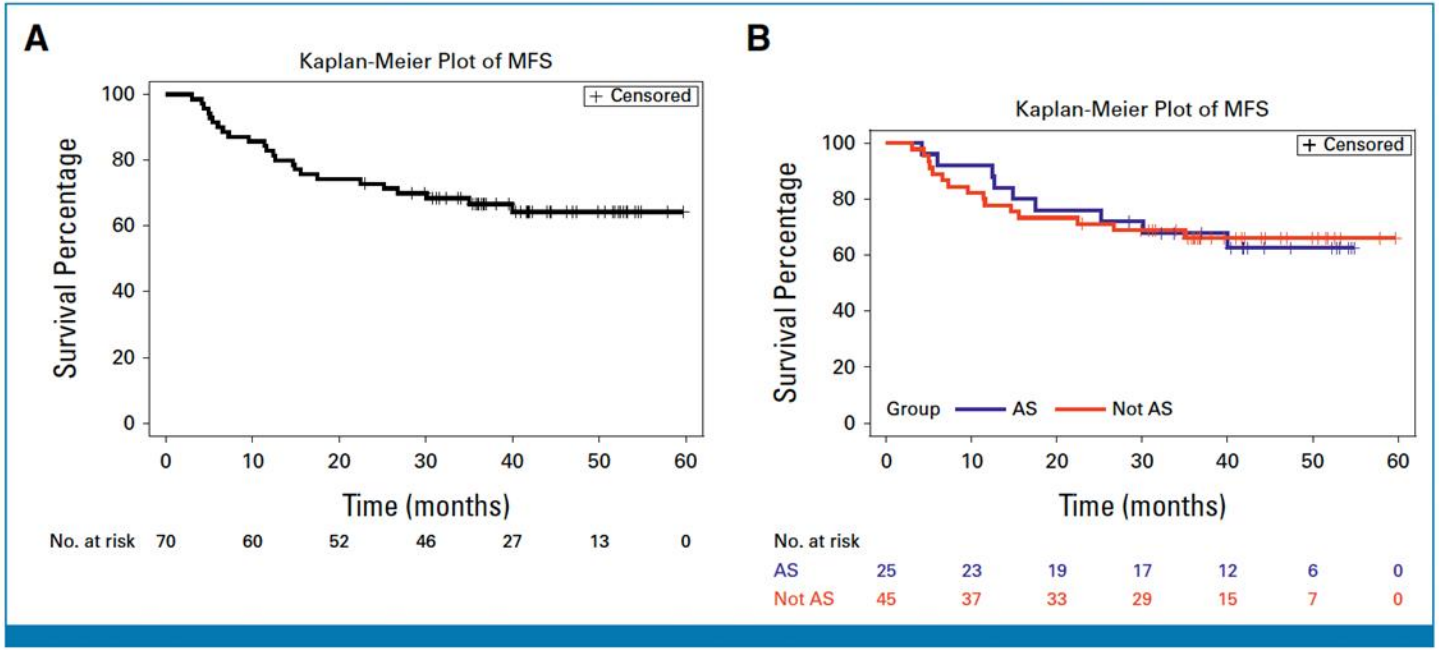


FIG 4. (A) MFS for the ITT population (N = 70) and (B) MFS in patients who began AS (blue) and patients who did not begin AS (red). AS, active surveillance; MFS, metastasis-free survival.

Geynisman et al. *J Clin Oncol*. 2024 Dec 16:

Retain-1 Overall Survival

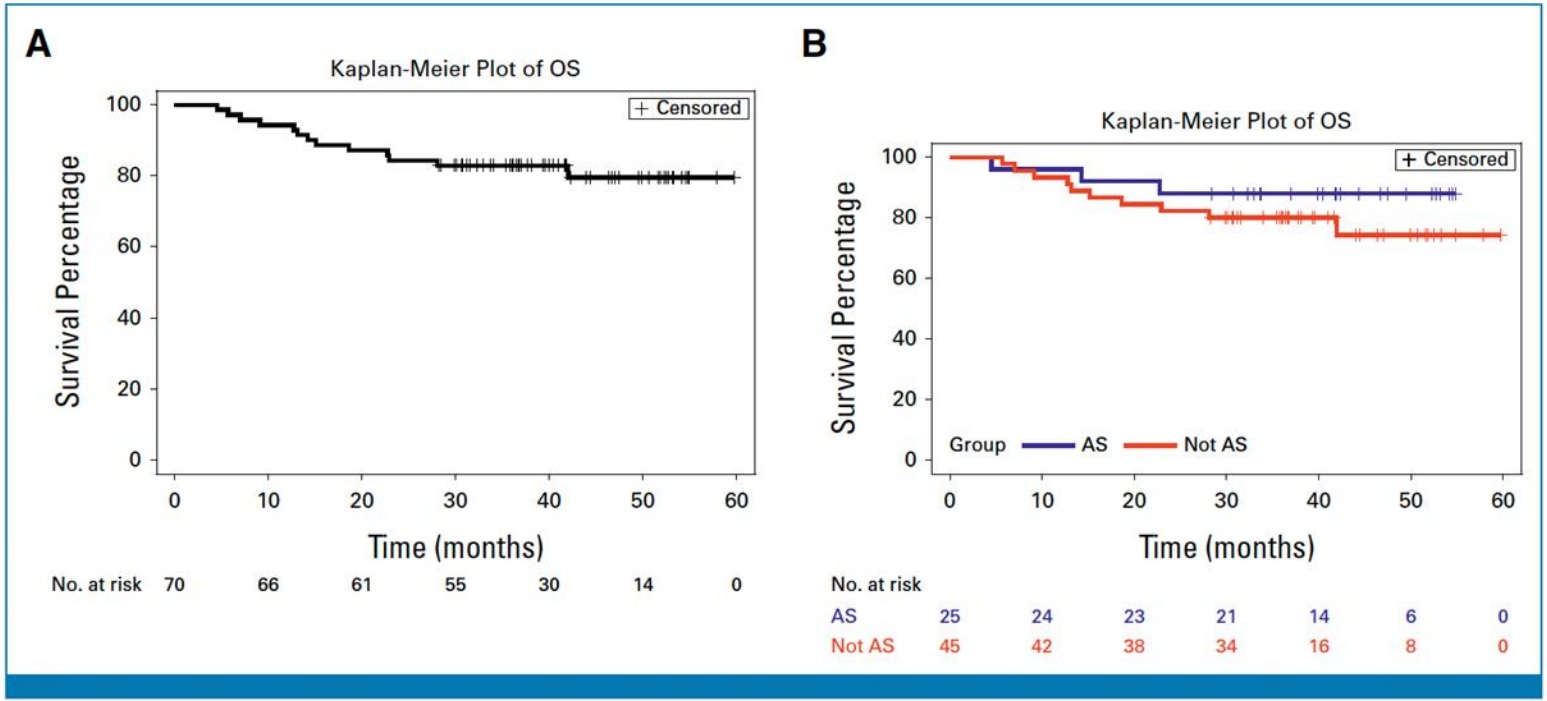
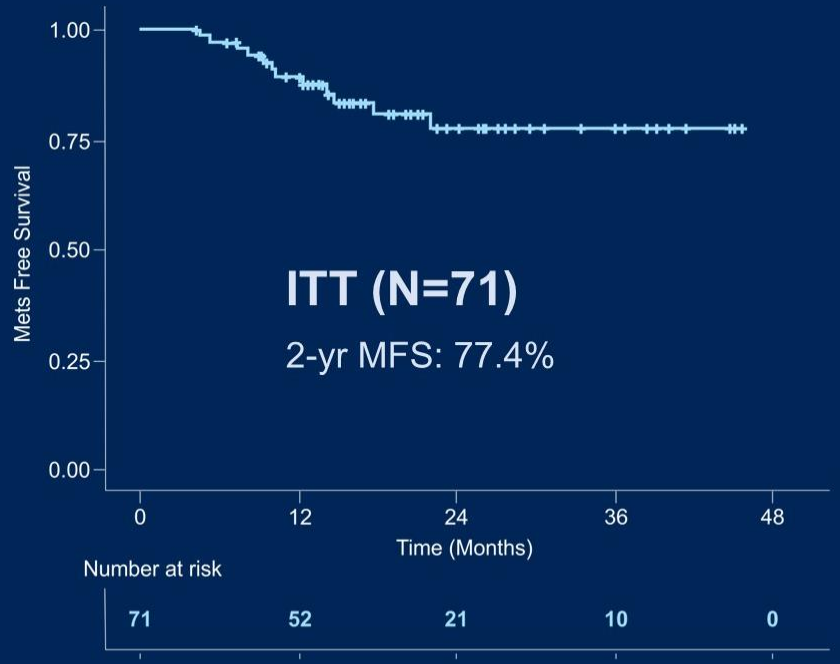
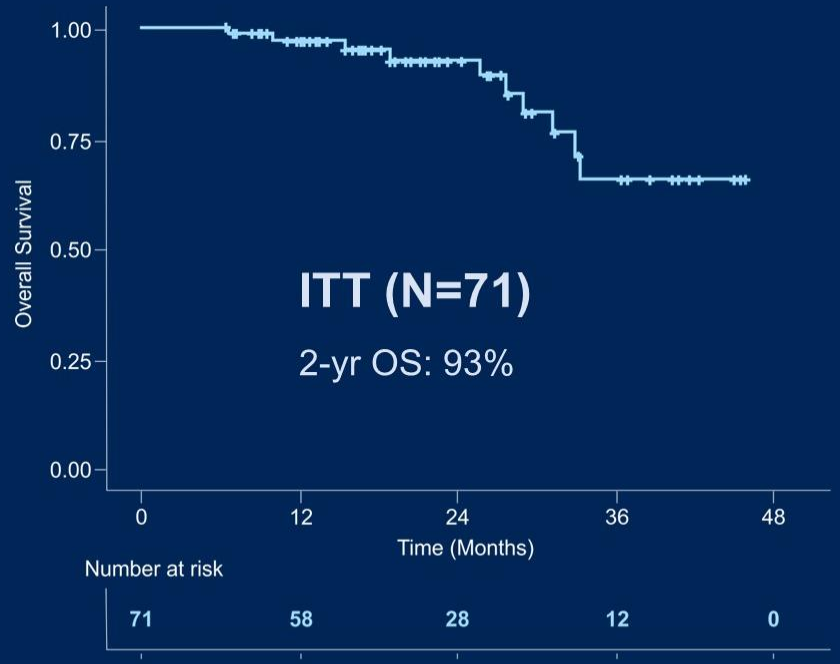


FIG 5. (A) Kaplan-Meier estimate of OS for the ITT population and (B) Kaplan-Meier estimate of OS in patients who began AS (blue) and patients who did not begin AS (red). AS, active surveillance; ITT, XXX; OS, overall survival.

Geynisman et al. *J Clin Oncol*. 2024 Dec 16:

RETAIN 2: ddMVAC + nivolumab
Metastasis-free and overall survival in ITT population

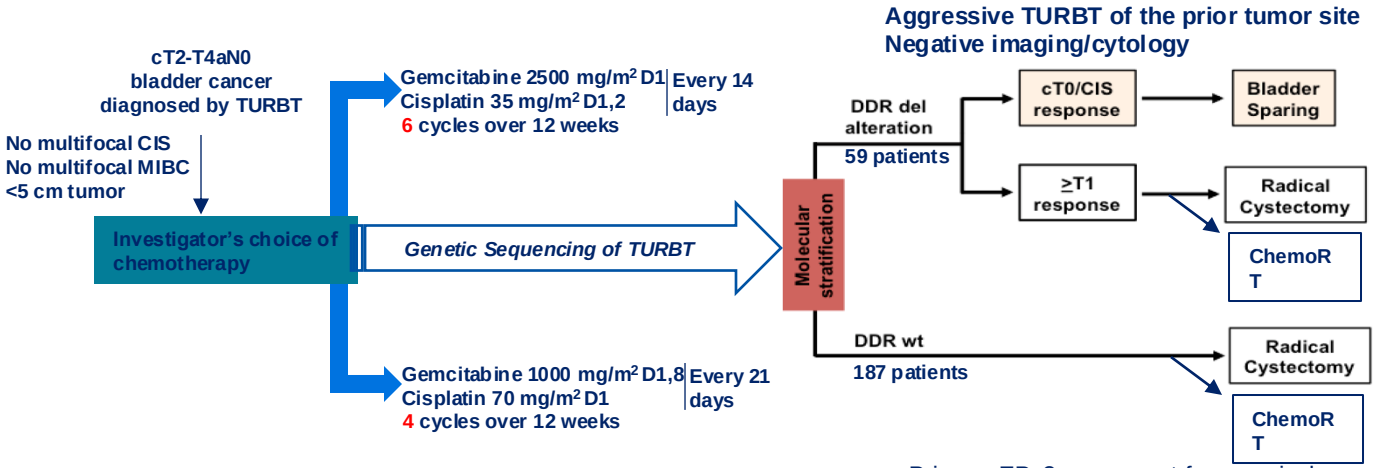




Median follow-up: 21.7 months (25th-75th percentile: 13.6 – 30.3 months)

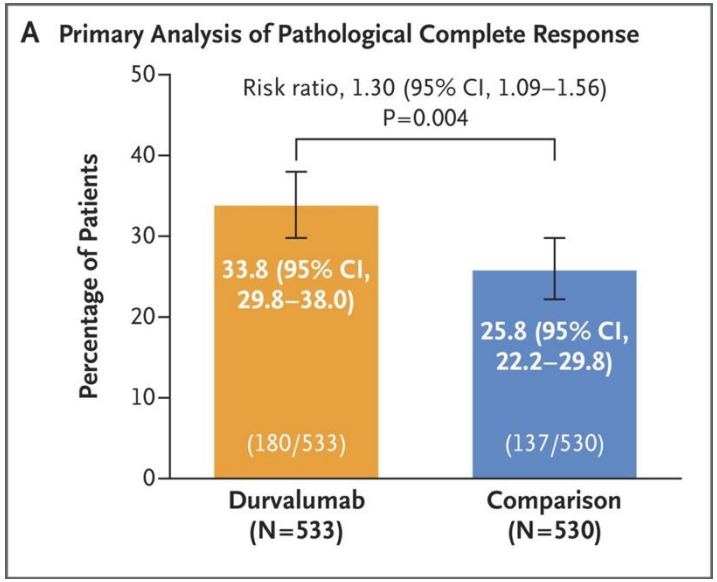
Ghatalia et al. *J Clin Oncol* 43, 2025 (suppl 5; abstr 815)

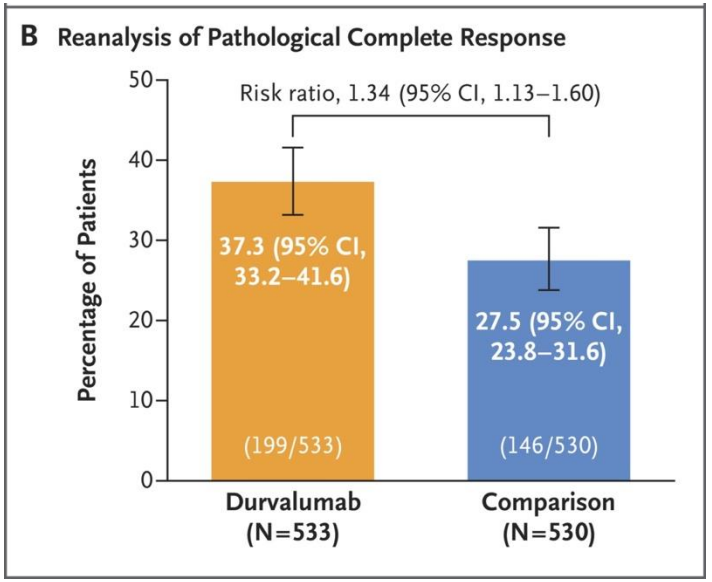
A031701: Bladder preservation following chemotherapy in patients with select DDR gene alterations



Primary EP: 3-year event-free survival
-Proportion of DDR mutant patients without invasive or metastatic recurrence following chemotherapy within the bladder sparing cohort

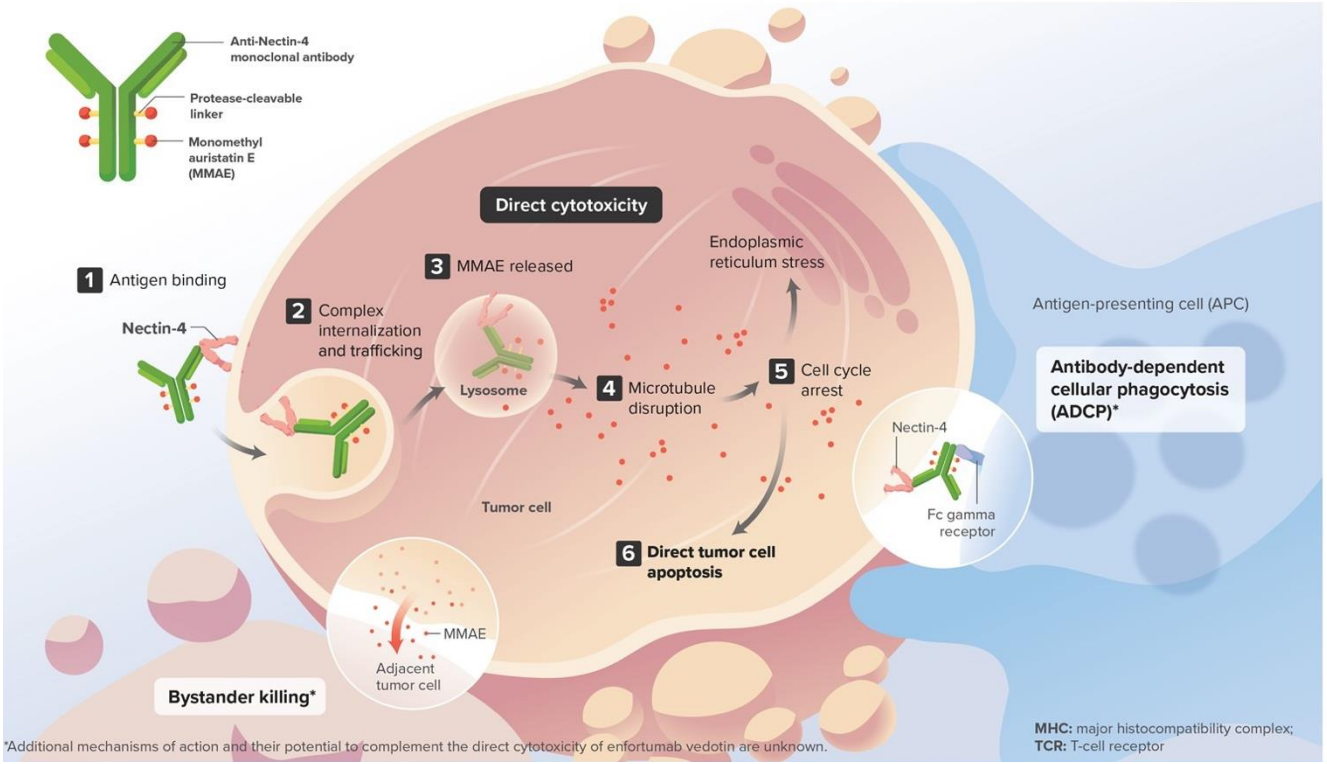
Durvalumab increases pathologic complete response rate when combined with GC





Powles et al. N Engl J Med 2024;391:1773-1786

Enfortumab vedotin: Nectin-4 directed ADC



Targets Nectin-4 which is highly expressed in urothelial cancers

IgG1 monoclonal antibody with intact Fc receptor

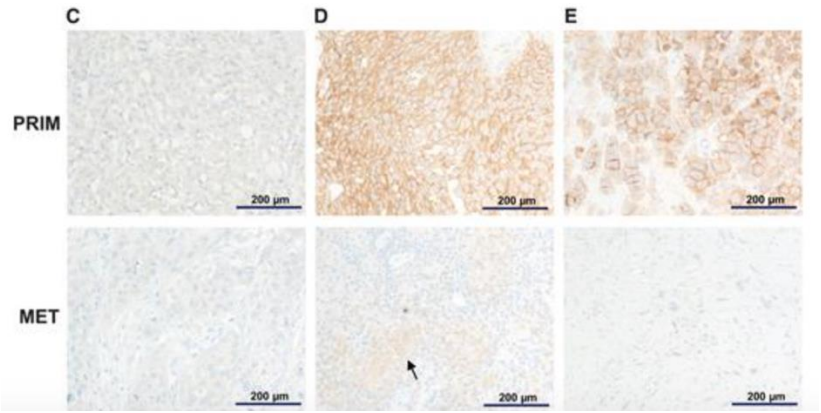
Drug : antibody ratio ~3.8

Cleavable drug linker: maleimidocaproylvaline-citrulline-p-aminobenzyloxycarbonyl

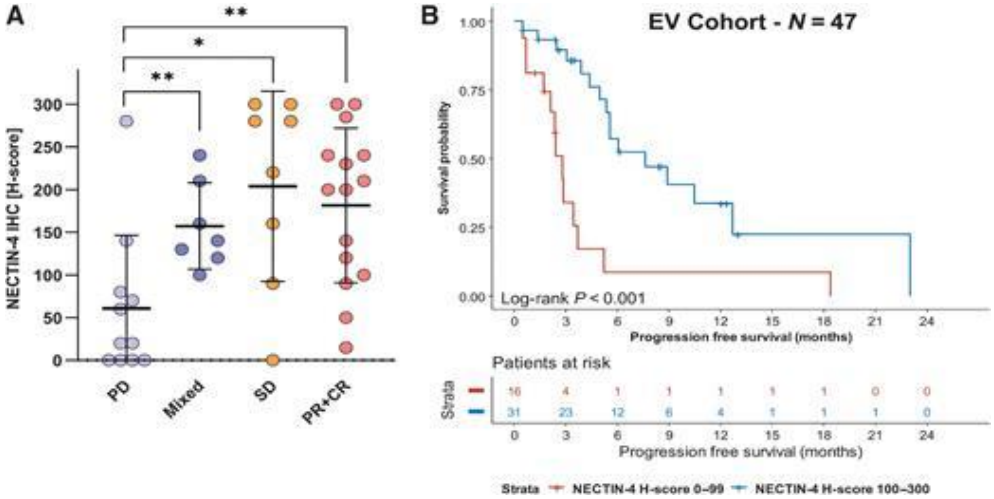
Rosenberg, et al. J Clin Oncol. 2019; 37(29):2592-2600.

Nectin-4 Expression as Proposed Biomarker of Treatment Sensitivity

Nectin-4 IHC (Primary vs. Met)

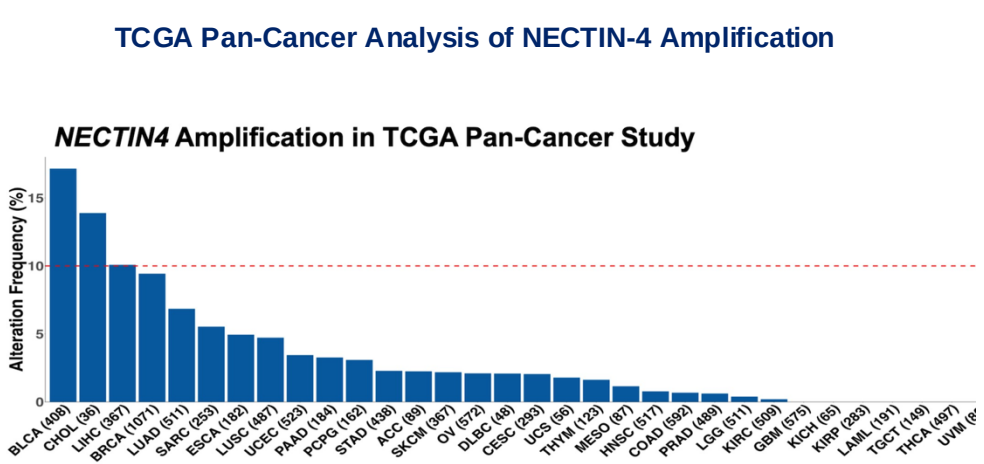


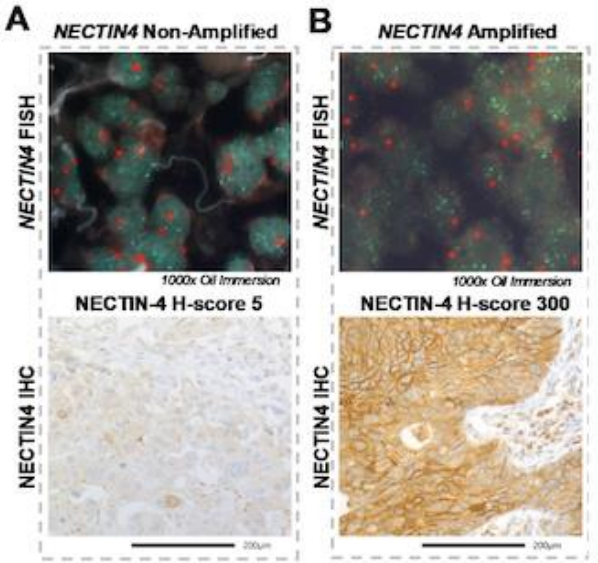
Nectin-4 IHC Association with Treatment Response



Klumper N. *Clin Cancer Res.* 2023.

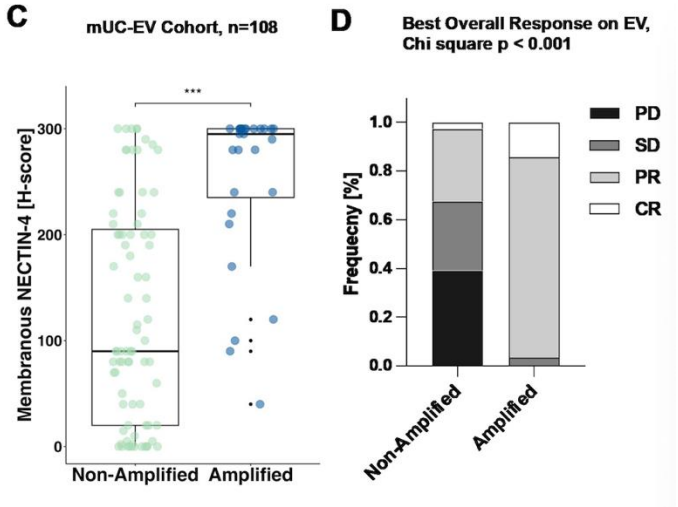
Nectin-4 Amplification as Proposed Biomarker of EV Treatment Sensitivity

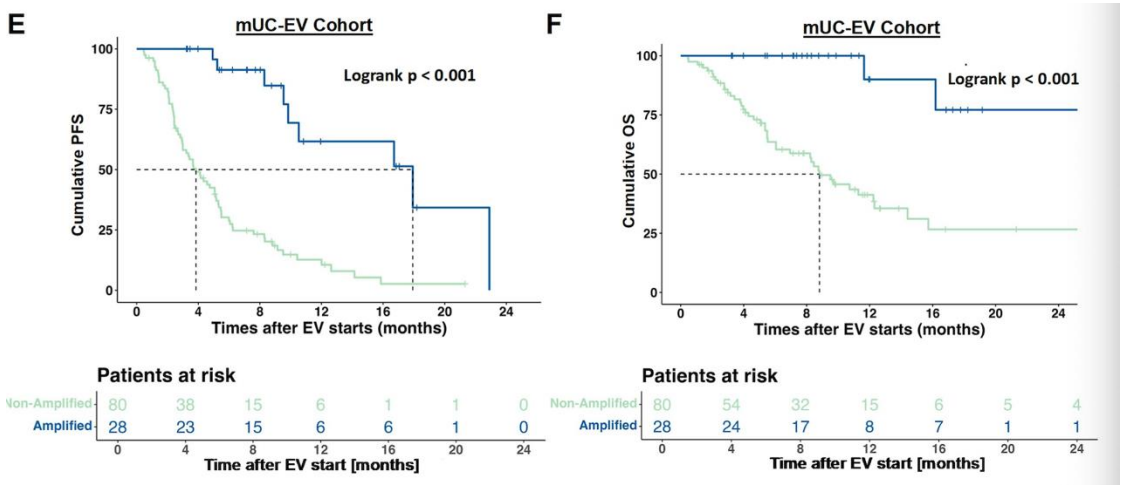




Klumper N et al. ASCO GU Symposium, 2024

Nectin-4 Amplification as Proposed Biomarker of EV Treatment Sensitivity

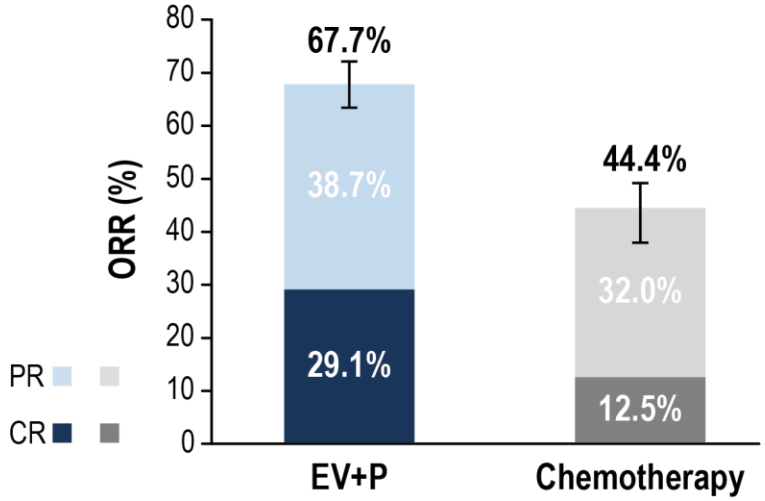




Klumper N et al. ASCO GU Symposium, 2024

EV-302: Confirmed Overall Response per BICR

Significant improvement in objective response rate was observed with EV+P



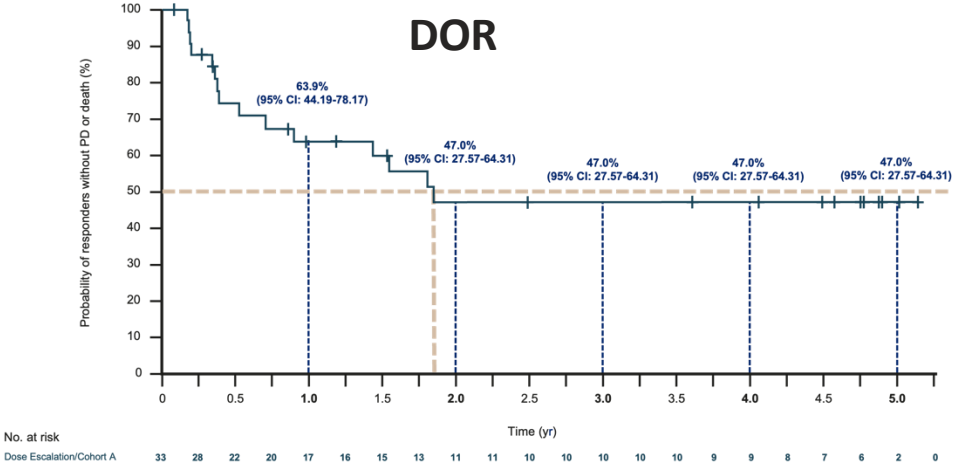
	EV+P (N=437)	Chemotherapy (N=441)
Confirmed ORR, n (%) (95% CI)	**296 (67.7) (63.1-72.1)**	**196 (44.4) (39.7-49.2)**
2-sided P value	<0.00001	
Best overall response[a], n (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Not evaluable/No assessment[b]	21 (4.8)	36 (8.2)
Median DOR (95% CI)	NR (20.2, NR)	7.0 (6.2, 10.2)

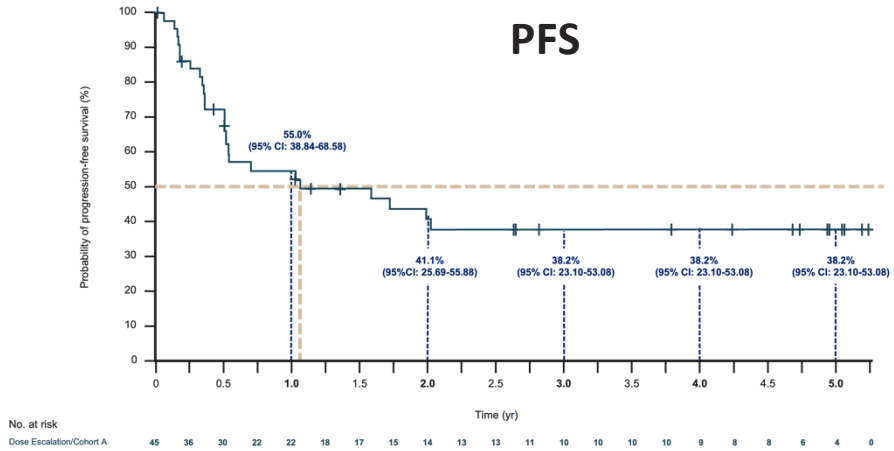
EV+P ORR is remarkably consistent across studies

Adapted from Powles et al. ESMO 2023 LBA6

Duration of response and progression free survival in EV-103 at median follow-up of 5 years

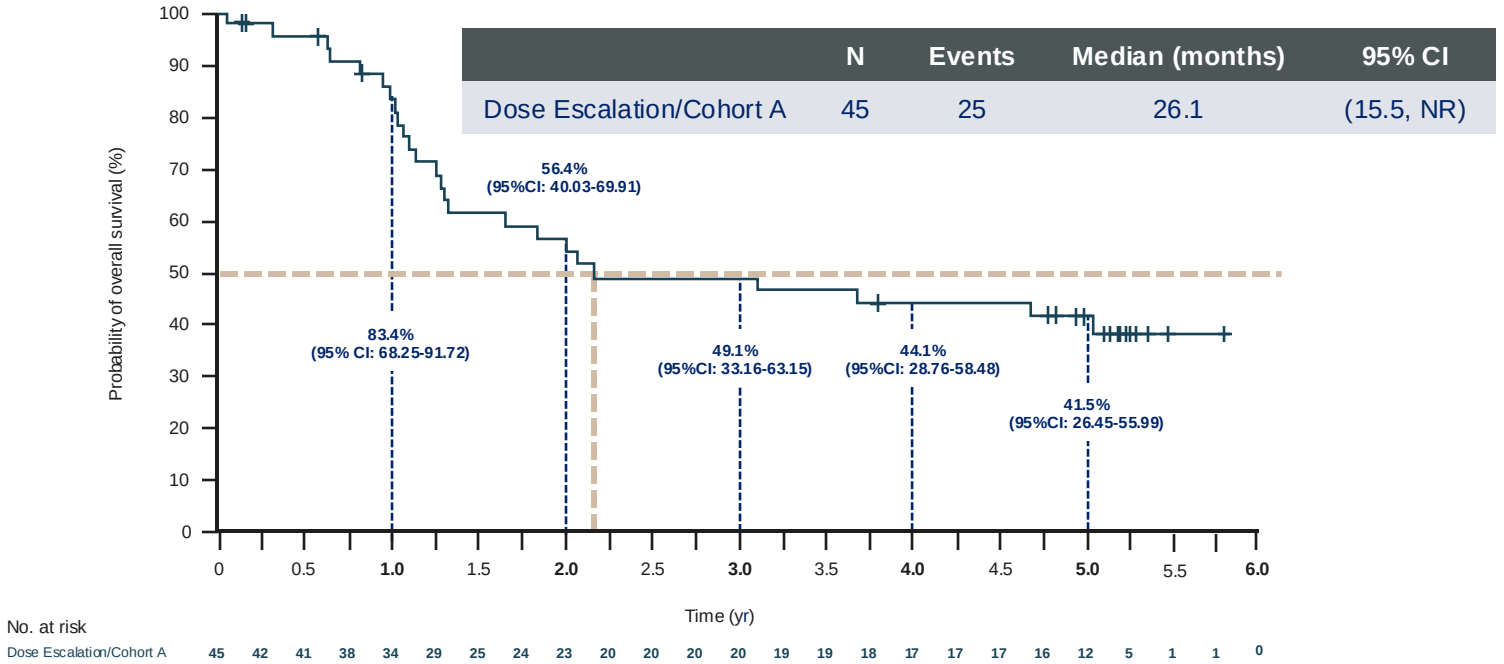
Responses durable after 2 years



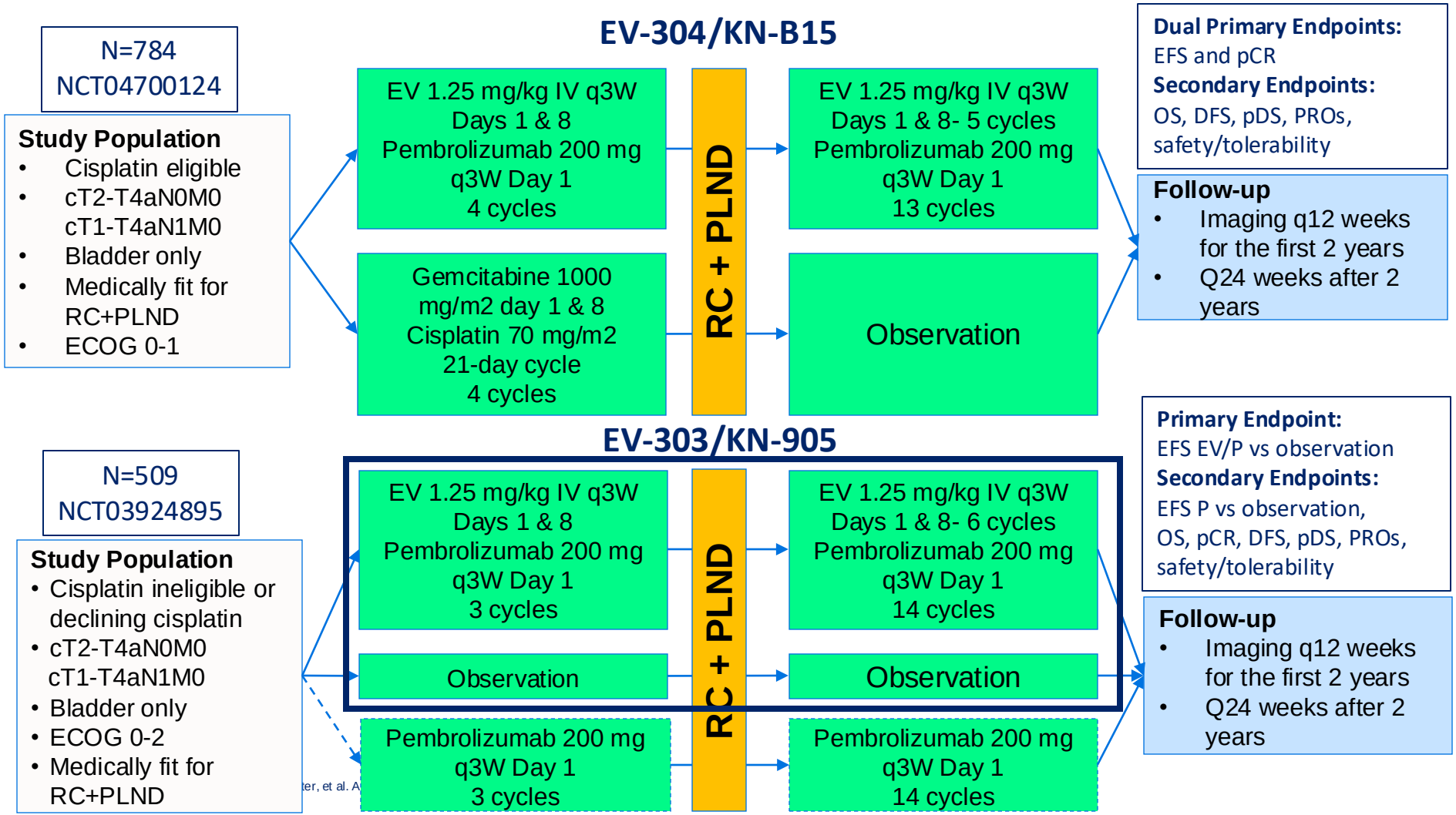


	N	Events	Median (months)	95% CI
DOR	33	15	22.1	(8.4, NR)
PFS	45	25	12.7	(6.1, NR)

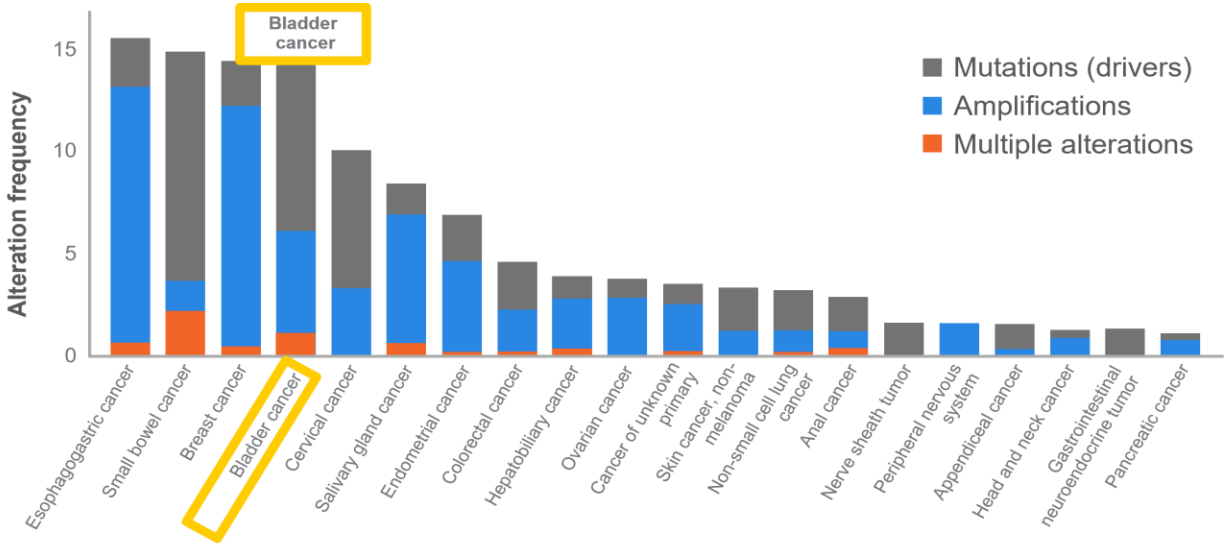
In this cisplatin-ineligible cohort, K-M estimate of 41.9% of patients were alive at 5-years follow-up



	N	Events	Median (months)	95% CI
Dose Escalation/Cohort A	45	25	26.1	(15.5, NR)


EV-304/KN-B15
N=784
NCT04700124
Study Population
• Cisplatin eligible
• cT2-T4aN0M0
cT1-T4aN1M0
• Bladder only
• Medically fit for RC+PLND
• ECOG 0-1
EV 1.25 mg/kg IV q3W
Days 1 & 8
Pembrolizumab 200 mg
q3W Day 1
4 cycles
Gemcitabine 1000 mg/m2 day 1 & 8
Cisplatin 70 mg/m2
21-day cycle
4 cycles
RC + PLND
EV 1.25 mg/kg IV q3W
Days 1 & 8- 5 cycles
Pembrolizumab 200 mg
q3W Day 1
13 cycles
Observation
Dual Primary Endpoints:
EFS and pCR
Secondary Endpoints:
OS, DFS, pDS, PROs, safety/tolerability
Follow-up
• Imaging q12 weeks for the first 2 years
• Q24 weeks after 2 years
EV-303/KN-905
N=509
NCT03924895
Study Population
• Cisplatin ineligible or declining cisplatin
• cT2-T4aN0M0
cT1-T4aN1M0
• Bladder only
• ECOG 0-2
• Medically fit for RC+PLND
EV 1.25 mg/kg IV q3W
Days 1 & 8
Pembrolizumab 200 mg
q3W Day 1
3 cycles
Observation
Pembrolizumab 200 mg
q3W Day 1
3 cycles
RC + PLND
EV 1.25 mg/kg IV q3W
Days 1 & 8- 6 cycles
Pembrolizumab 200 mg
q3W Day 1
14 cycles
Observation
Pembrolizumab 200 mg
q3W Day 1
14 cycles
Primary Endpoint:
EFS EV/P vs observation
Secondary Endpoints:
EFS P vs observation, OS, pCR, DFS, pDS, PROs, safety/tolerability
Follow-up
• Imaging q12 weeks for the first 2 years
• Q24 weeks after 2 years

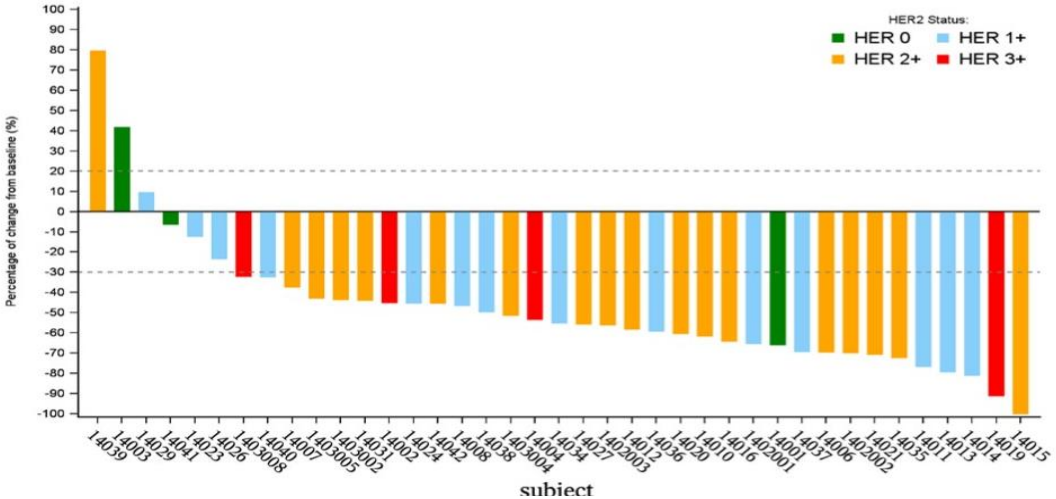
Frequency of *HER2* alterations is high in bladder cancer



- Mutations
  - 5-11% (higher frequency than breast and other cancer types)
- Amplifications
  - 6-9%
  - Can co-exist with mutations in a subset of tumors
- Overexpression in about 25-40% of UC tumors

Disitamab vedotin + Toripalimab
(IgG4 anti-PD1 monoclonal antibody)

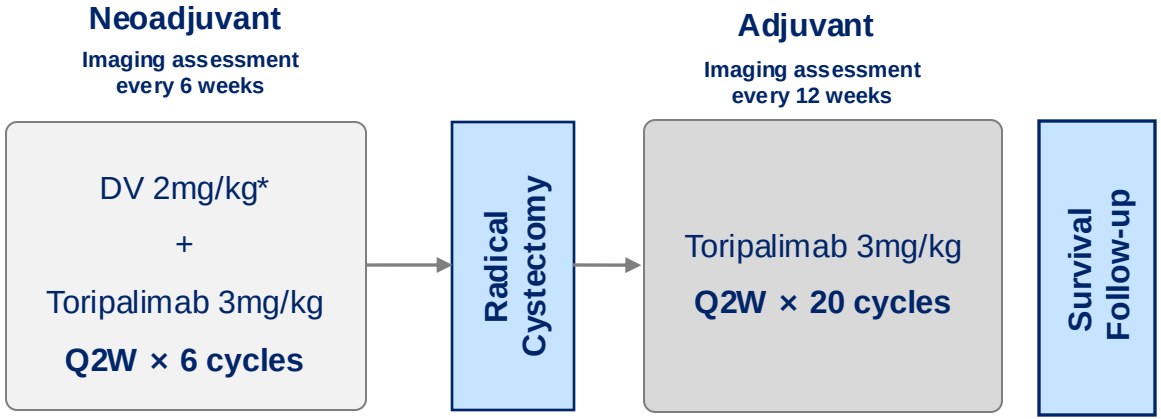
- Ph I/II study in patients with LA/mUC (n=41)
- HER2 2-3+ in 59% and PD-L1 positive in 32%
- RC48 at 1.5 or 2 mg/kg in combination with toripalimab 3 mg/kg every 2 weeks in dose escalation and expansion cohort
- TRAEs: Transaminitis, peripheral sensory neuropathy, asthenia, hypertriglyceridemia, decreased appetite
- No DLT observed and recommended dose of RC48 was 2 mg/kg



- Confirmed ORR 73.2% (95% CI 57.1, 85.8) including 9.8% CR
  - HER2 2-3+: 86.3%
  - HER2 1+: 57.1%
  - HER2 0: 33.3%
- Confirmed ORR PD-L1 positive: 66.6% ORR; PD-L1 negative: 74.1%
- Median PFS: 9.2 months; 2-year OS rate 63.2%

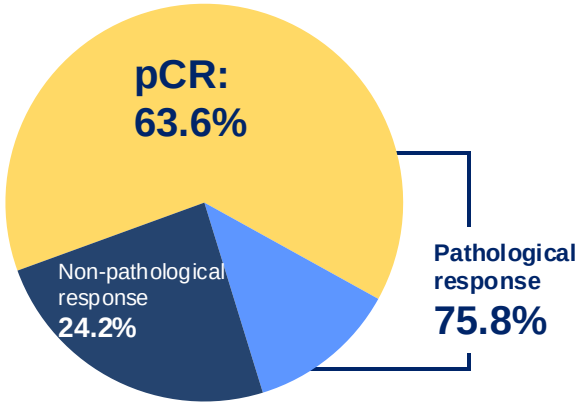
Sheng et al, *J Clin Oncol* 41, 2023 (suppl 16; abstr 4566)

Disitamab vedotin + toripalimab in MIBC



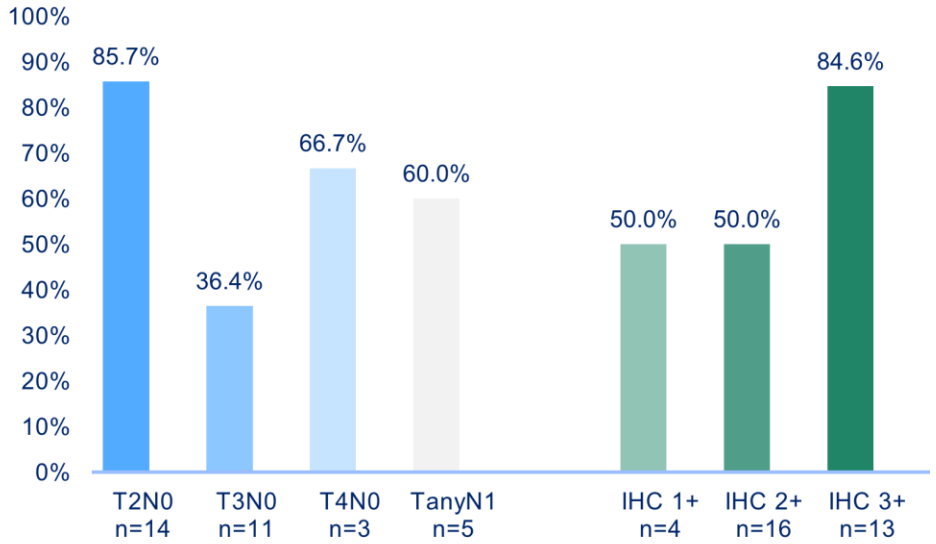
Pathological response	Surgical patients N=33*
pCR (ypT0N0), n (%)	**21 (63.6)**
95% CI	45.1-79.6
Pathological response (≤ypT1N0M0), n (%)	**25 (75.8)**
95% CI	57.7-88.9

- **Primary endpoint:** Pathologic complete response (pCR, defined as ypT0N0) rate in the patients who underwent RC.
- **Secondary endpoints:** Pathological response rate (defined as ≤ypT1N0M0)[#]; 1-year disease-free survival (DFS) rate; overall survival (OS)^; adverse events.
- **Exploratory endpoint:** event-free survival (EFS).



Sheng, et al. *J Clin Oncol* 43, 2025 (suppl 5; abstr 665)

pCR rates for different subgroups



- pCR rate for the HER2 IHC 3+ subgroup was numerically higher than those for IHC 1+ and IHC 2+ subgroups
- Is this a subgroup who would be excellent candidates for bladder sparing?

 Sheng, et al. *J Clin Oncol* 43, 2025 (suppl 5; abstr 665)

Conclusions: a bright but unrealized future

- Biomarker directed therapy remains unrealized as yet, but requires more evaluation alongside promising treatments
  - DNA repair genes, Nectin-4, Her2, others
- Clinical complete responders based on imaging, TUR, and other modalities (ctDNA, utDNA) may enrich for long-term benefit from conservative approaches
- New therapies are more potent, increasing the proportion of complete responses, expanding the playing field to more patients

Thank you!