Novel Bladder Cancer Therapies

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Disclosures

- Bayer and J&J Advisory
- OncLive and Targeted Oncology

Bladder Cancer Outcomes

5-year relative survival rates for bladder cancer

These numbers are based on people diagnosed with bladder cancer between 2014 and 2020.

SEER* Stage	5-year Relative Survival Rate
In situ alone	97%
Localized	72%
Regional	40%
Distant	9%
All SEER stages combined	78%

American Cancer Society®

Localized Bladder Cancer

Management of Non-Muscle Invasive Bladder Cancer

- AUA Low Risk: Surveillance
- AUA Intermediate Risk: Intravesical therapy versus surveillance
- AUA High Risk: Cystectomy preferred if very-high risk, BCG if no very-high risk features

AUA Risk Stratification for Non–Muscle-Invasive Bladder Cancer*

Low Risk	Intermediate Risk	High Risk
• Papillary urothelial neoplasm of low malignant potential • Low grade urothelial carcinoma ▸ Ta and ▸ ≤3 cm and ▸ Solitary	• Low grade urothelial carcinoma ▸ T1 or ▸ >3 cm or ▸ Multifocal or ▸ Recurrence within 1 year • High grade urothelial carcinoma ▸ Ta and ▸ ≤3 cm and ▸ Solitary	• High grade urothelial carcinoma ▸ CIS or ▸ T1 or ▸ >3 cm or ▸ Multifocal • Very high risk features (any): ▸ BCG unresponsive[l] ▸ Certain histopathologic subtypes[m] ▸ Lymphovascular invasion ▸ Prostatic urethral invasion

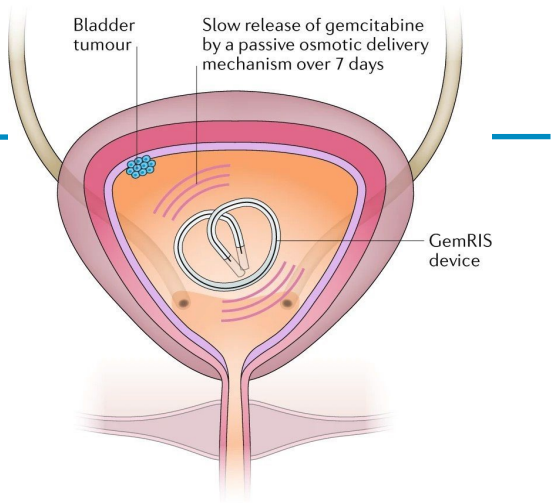
NCCN Bladder Cancer Guidelines

Localized Bladder Cancer

Management of Non-Muscle Invasive Bladder Cancer

- BCG unresponsive or intolerant:
  - Cystectomy
  - Intravesical chemotherapy: Mitomycin C, Gemcitabine, Valrubicin, Gem/Docetaxel
  - Pembrolizumab *(2020)* -> Phase II study, 46% CR at 12m
    - Systemic PD-1 inhibitor, Grade 3/4 AEs: 13%
  - Nadofaragene firadenovec-vcng *(2023)* -> Phase III study, 64% CR at 12m
    - Non-replicating adenovirus delivering IFN-2b, Grade 3/4 AEs: 4%
  - Nagopendekin alfa inbakicept-pmln + BCG *(2024)* -> Phase II/III study, 64% CR at 12m
    - IL-15 superantagonist, Grade 3/4 AEs: 3%

SunRIse-1



- Tar-200 provides the highest single agent CR rate of 82.4%, 46% at 12m
- Grade 3/4 AEs: 13%
- *FDA Approval 9/9/2025 for BCG-unresponsive high risk MIBC with CIS*

NCT04640623

Population:
- Aged ≥18 years
- Histologically confirmed HR NMIBC CIS (with or without papillary disease)
- ECOG PS of 0-2
- Persistent or recurrent disease within 12 months of completion of BCG
- Unresponsive to BCG[1,2] and not receiving RC

R

TAR-200 + Cetrelimab[b]
***Cohort 1* (N=53)**
Cohort 1 was closed

TAR-200 Monotherapy
***Cohort 2* (N=85)**
Enrollment completed

Cetrelimab[b] Monotherapy
***Cohort 3* (N=28)**
Cohort 3 was closed

Population:
- Papillary-only HR NMIBC (no CIS)[a]

TAR-200 Monotherapy
***Cohort 4* (N=52)**
Enrollment completed

TAR-200 dosing:
Q3W (indwelling) for the first 24 weeks; then Q12W through Week 96

Cohorts 1-3:
Primary end point
- Overall CR rate

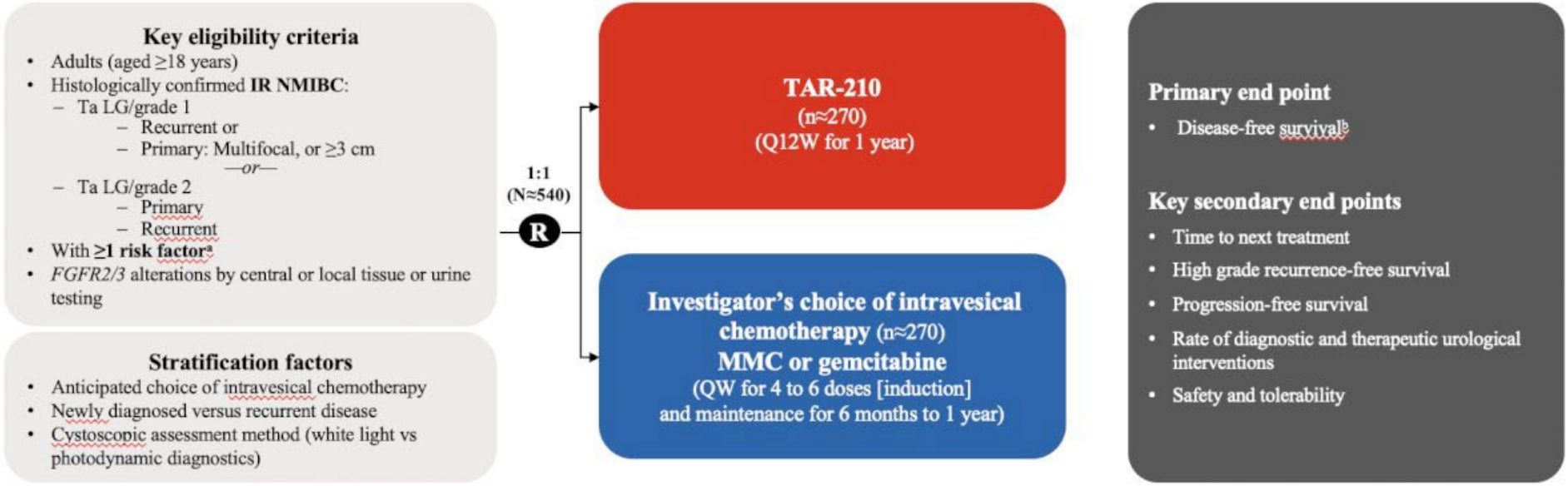
Key secondary end points
- Duration of response
- Overall survival
- Safety
- Tolerability

Cohort 4:
Primary end point
- DFS rate at 12 months

ESMO 2024

MoonRISe-1

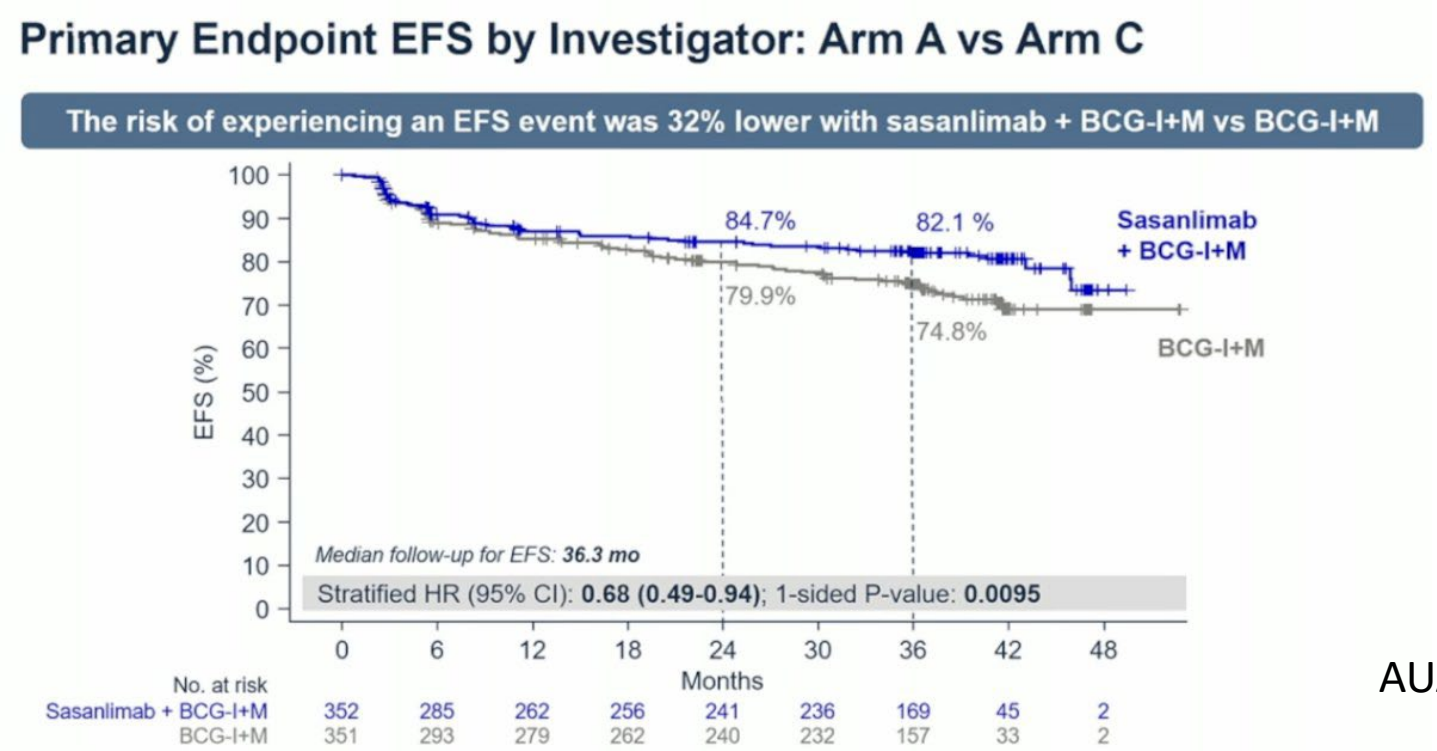
- Tar-210 Erdafitinib Intravesical Delivery System for intermediate risk NMIBC with FGFR 2/3 alterations
- FGFR 2/33 alteration prevalence in 50-80% low grade NMIBC
- *Open and recruiting at Ochsner!*



AUA 2024

CREST

- Sasanlimab, SubQ PD1 inhibitor, and BCG – *pending FDA approval*
- Complete response at 36 months: 92% (S+ BCG) vs 87.4% (BCG)
- S + BCG 32% lower EFS at 36 months, no OS benefit at 36 months
- Grade 3/4 AEs: 15%, primarily thyroid disorders, rash and hepatitis



AUA 2025

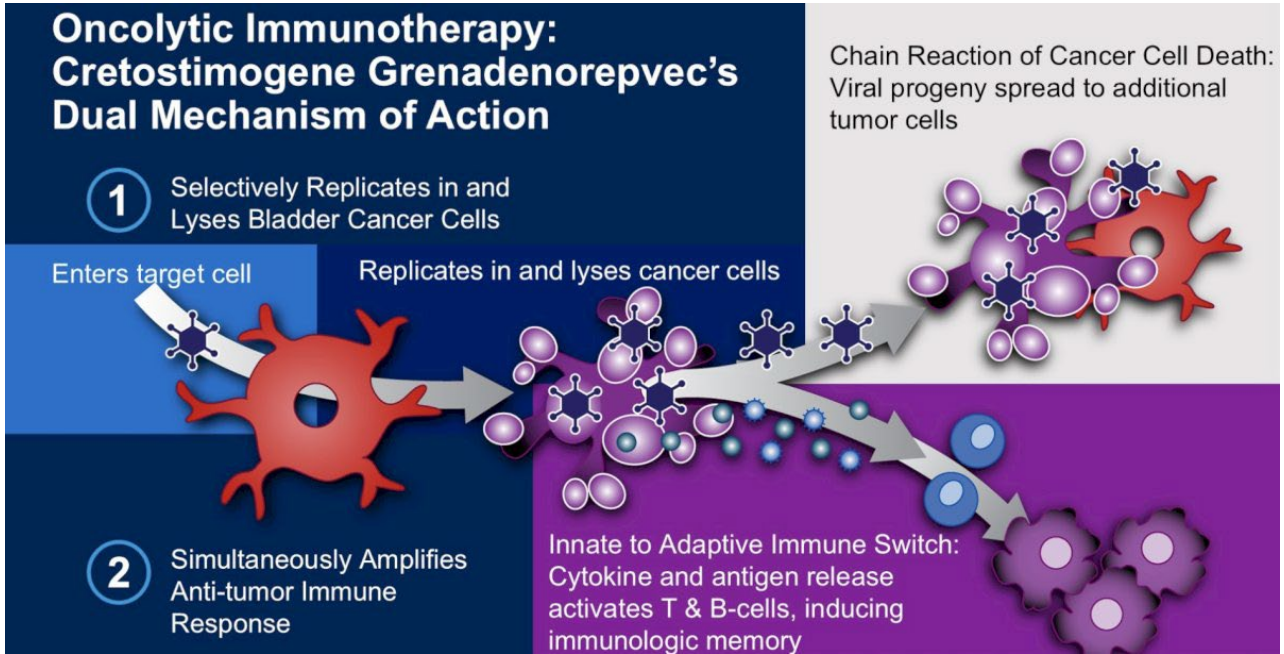
ESMO 2025 – Late Breaking Abstracts

- POTOMAC: Phase III Durvalumab & BCG
  - Durvalumab q4w up to one year, primary endpoint EFS
  - Press release 5/2025 shows improved DFS
- ALBAN: Phase III Atezolizumab & BCG
  - Atezolizumab q3w up to one year, primary endpoint is EFS

ESMO 2025 Berlin 10/17 – 10/21/25

BOND-003

- Phase III single arm study of Cretostimogene Grandenorepvec for BCG-unresponsive NMIBC, *pending FDA approval*
- Conditionally replicating oncolytic serotype 5 adenovirus
- 46.3% CR at 12 months, Grade 3/4 AEs: 0
- *CORE-008 Phase II for high risk non-muscle invasive bladder cancer open at Ochsner!*



AUA 2024

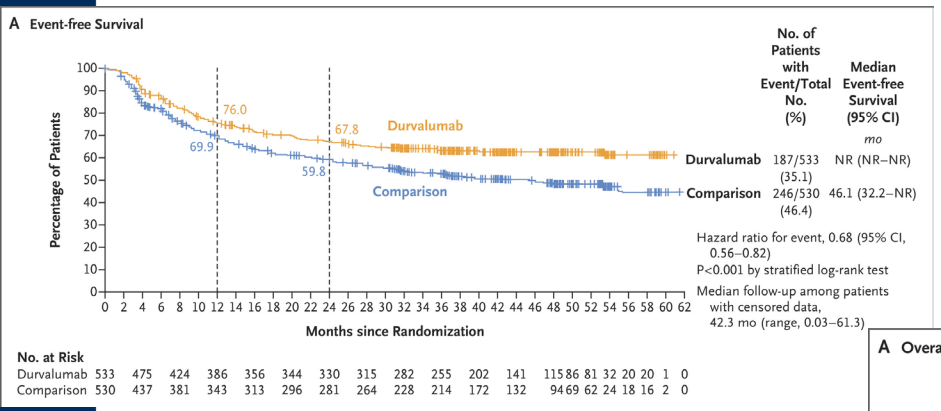
Localized Bladder Cancer

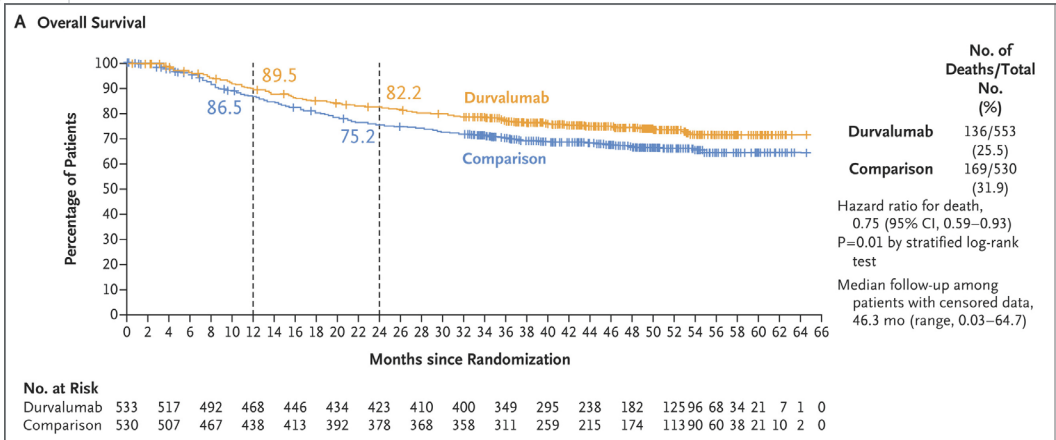
Management of Muscle Invasive Bladder Cancer

- Neoadjuvant Cisplatin-based chemotherapy if eligible -> Cystectomy
  - Adjuvant immunotherapy if eligible
  - VESPER study shows improved PFS with neoadjuvant ddMVAC x6 versus Gem/Doce x4 *(2022)*
- Bladder preservation with concurrent chemoRT after maximal TURBT
  - Ideally tumors <6 cm, no CIS, no hydronephrosis
  - Cisplatin, Gemcitabine or 5FU/Mitomycin as radiosensitizing agents

NIAGARA

- Neoadjuvant Gem/Cis/Durva -> Adjuvant Durvalumab *FDA 3/28/25*
- Key secondary endpoint shows improved OS by 25%, HR 0.75 with durvalumab arm. Grade 3/4 AEs: 40.6% G/C + D vs 40.9% G/C
- How does this fit with ddMVAC?
- Are we overtreating some patients with neoadjuvant IO?

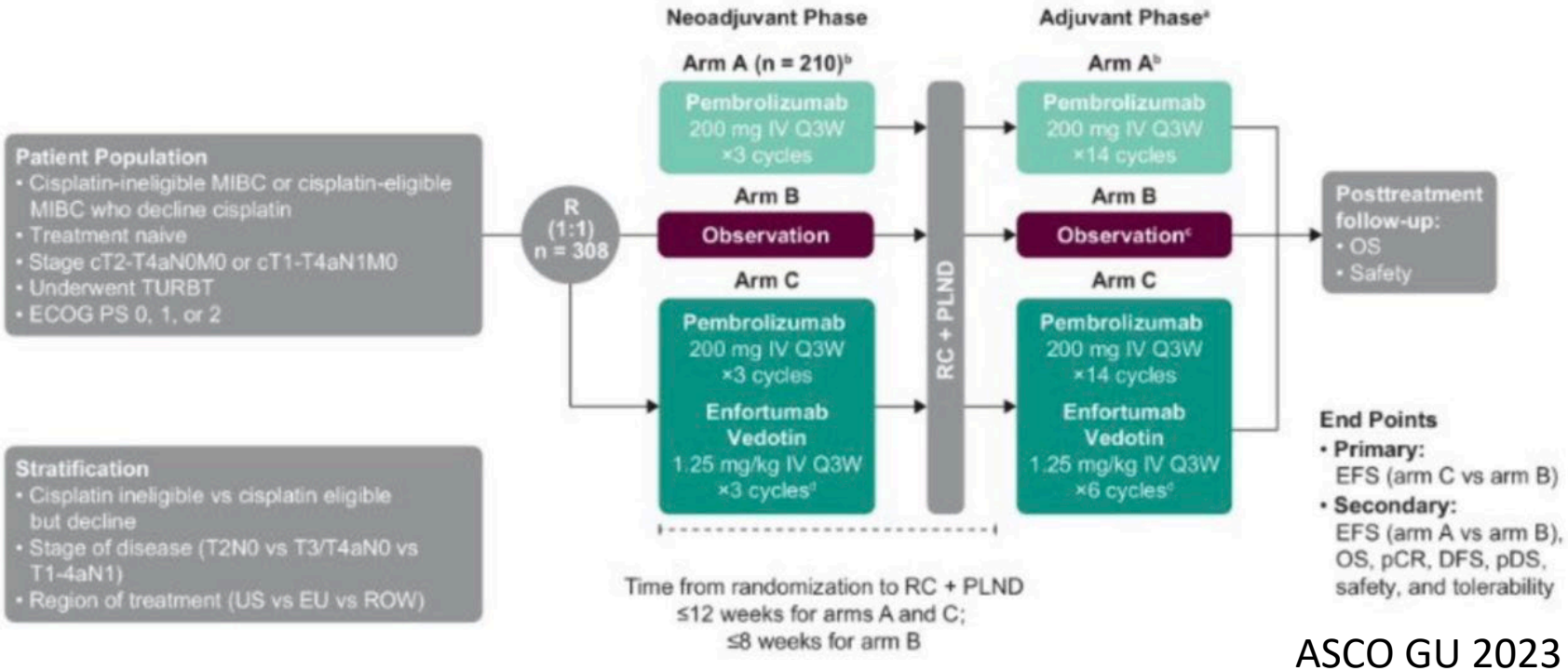




NEJM 9/15/24

ESMO 2025

- EV-303 / Keynote-905: Neoadjuvant EV/P -> Adjuvant EV/P
- 8/12/25 Press Release: EV/P has improved PFS, OS and pCR rates vs surgery alone
- How will pCR and OS compare to NIAGRA? Pembro only arm?
- EV-304/Keynote-B15 for Cisplatin eligible patients

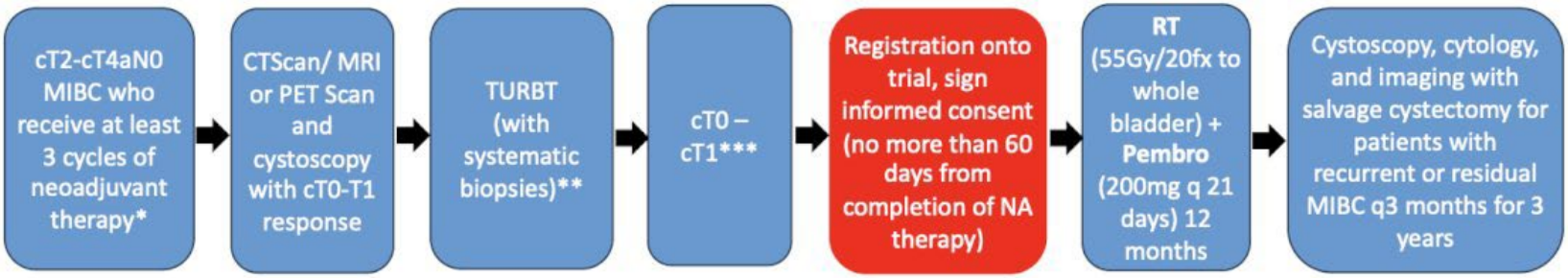


ASCO GU 2023

Bladder Sparing Approaches

- Some patients opt against surgery after neoadjuvant chemotherapy
- Paucity of prospective studies.
  - Does cT0 = pT0? Biomarkers? Does salvage/delayed surgery = upfront?
- GU 15-257(2023): Nivo/Gem/Cis x4 -> If CR Nivo q2w x8 cyles
  - 46% CR, clinical complete response for 2-year metastasis free survival was 0.97

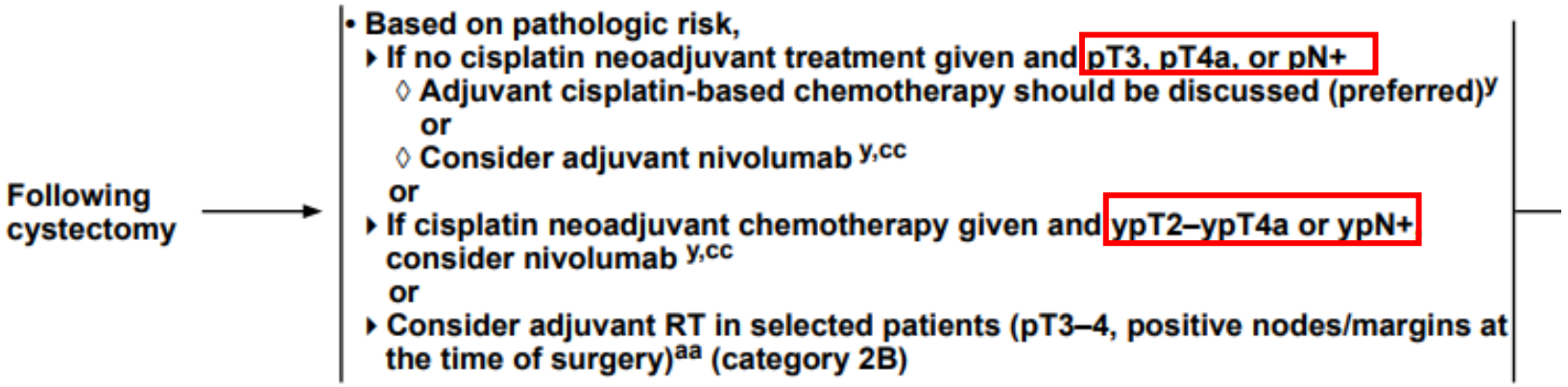
Schema | S2427 BRIGHT trial



AUA 2025

Localized Bladder Cancer

Guidelines for Adjuvant Therapy

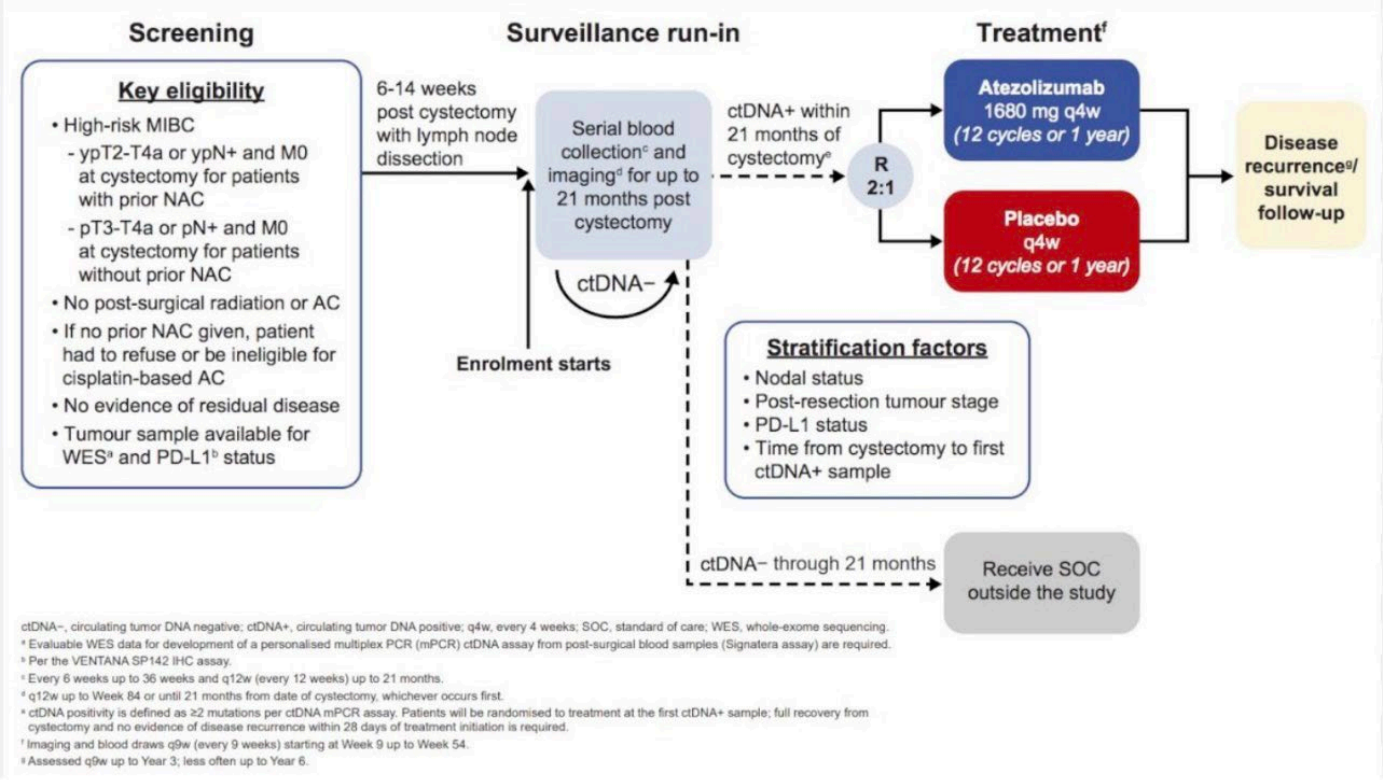


NCCN Bladder Cancer Guidelines

- CheckMate-274 – Adjuvant Nivolumab: DFS 22 months, OS 69.5 months (HR 0.76 [95% CI, 0.61 to 0.96). Grade 3/4 AEs: 17.9% vs 7.2% *(2021)*
- AMBASSADOR – Adjuvant Pembrolizumab: DFS 29 months, OS immature but trend towards insignificant (HR: 0.98, 95% CI: 0.76 – 1.26, p=0.88)). Grade 3/4 AEs: 48% vs 31% *(2024)*
  - Significant cross-over from placebo -> Nivolumab

ESMO 2025

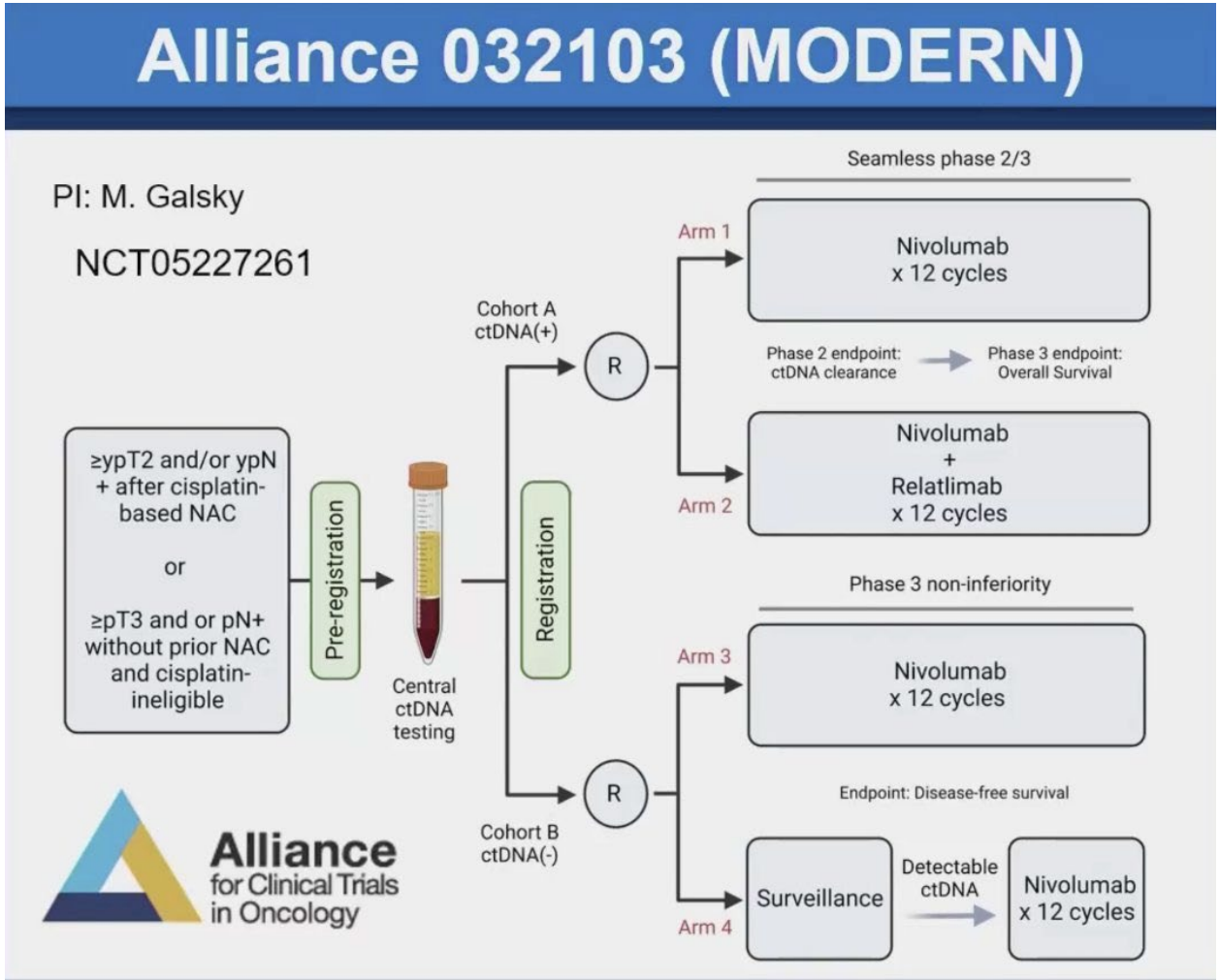
- Imvigor011: Adjuvant Atezolizumab in ctDNA+ post-cystectomy patients
- Imvigor010 Adjuvant – No DFS / OS improvement
  - Difference between PD-1 and PD-L1 inhibition?
  - Updated results shows DFS/OS benefit in ctDNA (+) population



EAU 2024

MODERN STUDY

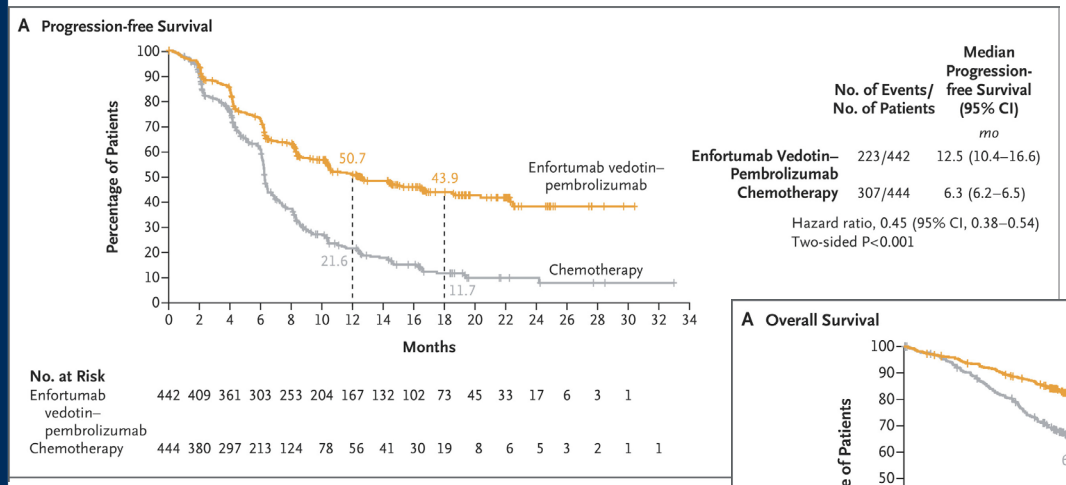
- *Currently recruiting at Ochnser!*

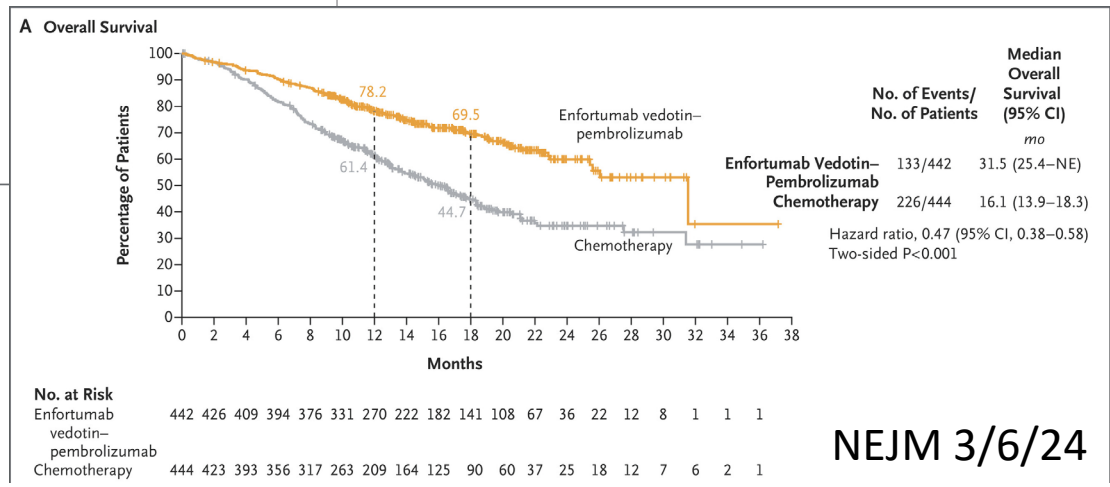


ASCO 2024

Metastatic Bladder Cancer – 1L EV/Pembro

- EV 103: Enfortumab Vedotin & Pembrolizumab versus platinum based chemotherapy in cisplatin-ineligible patients *(4/2023)*
  - Grade 3/4 AEs: 55.9% EV/P vs 69.5% chemotherapy
- EV 302: Enfortumab Vedotin & Pembrolizumab versus platinum based chemotherapy in untreated bladder cancer patients *(12/2023)*

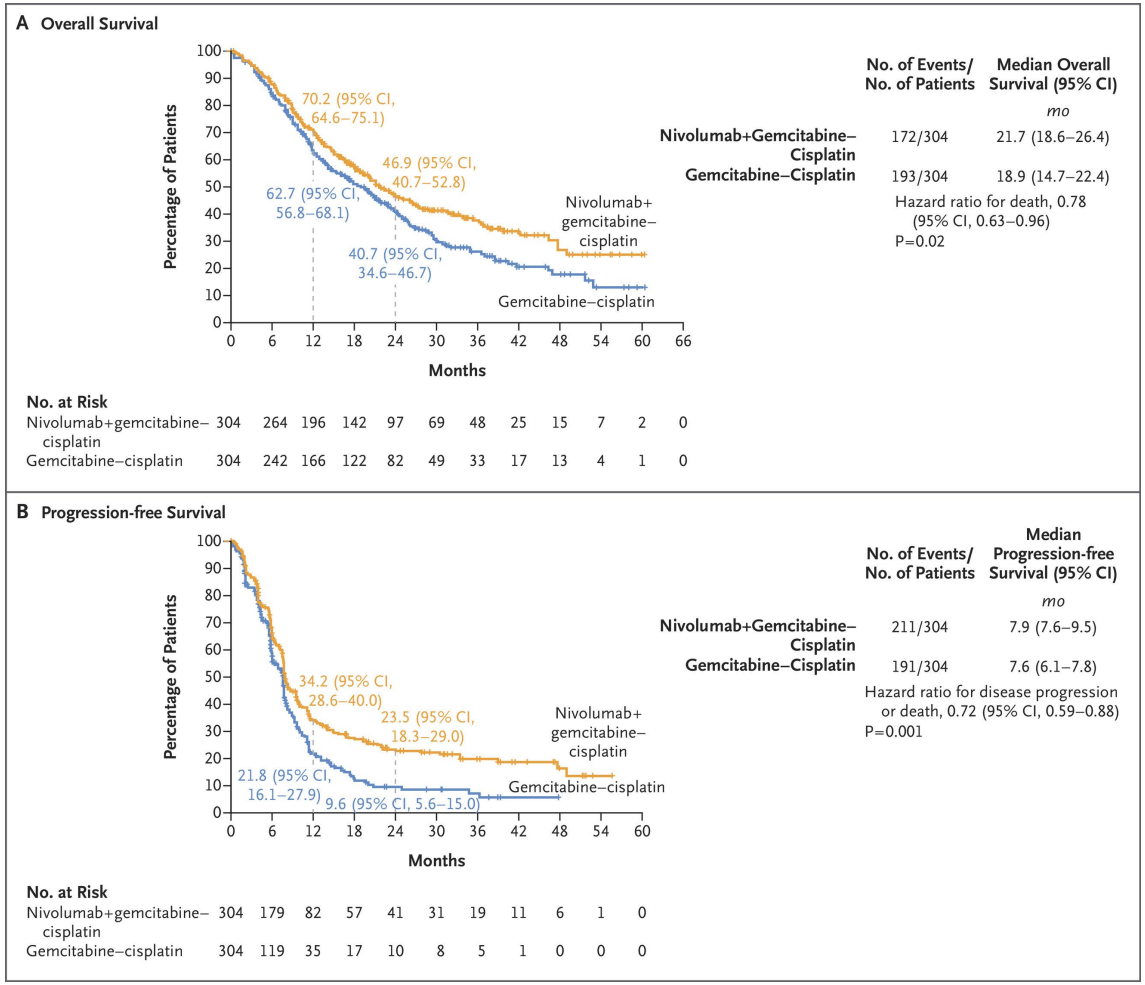




NEJM 3/6/24

Metastatic Bladder Cancer – 1L Gem/Cis/Nivo

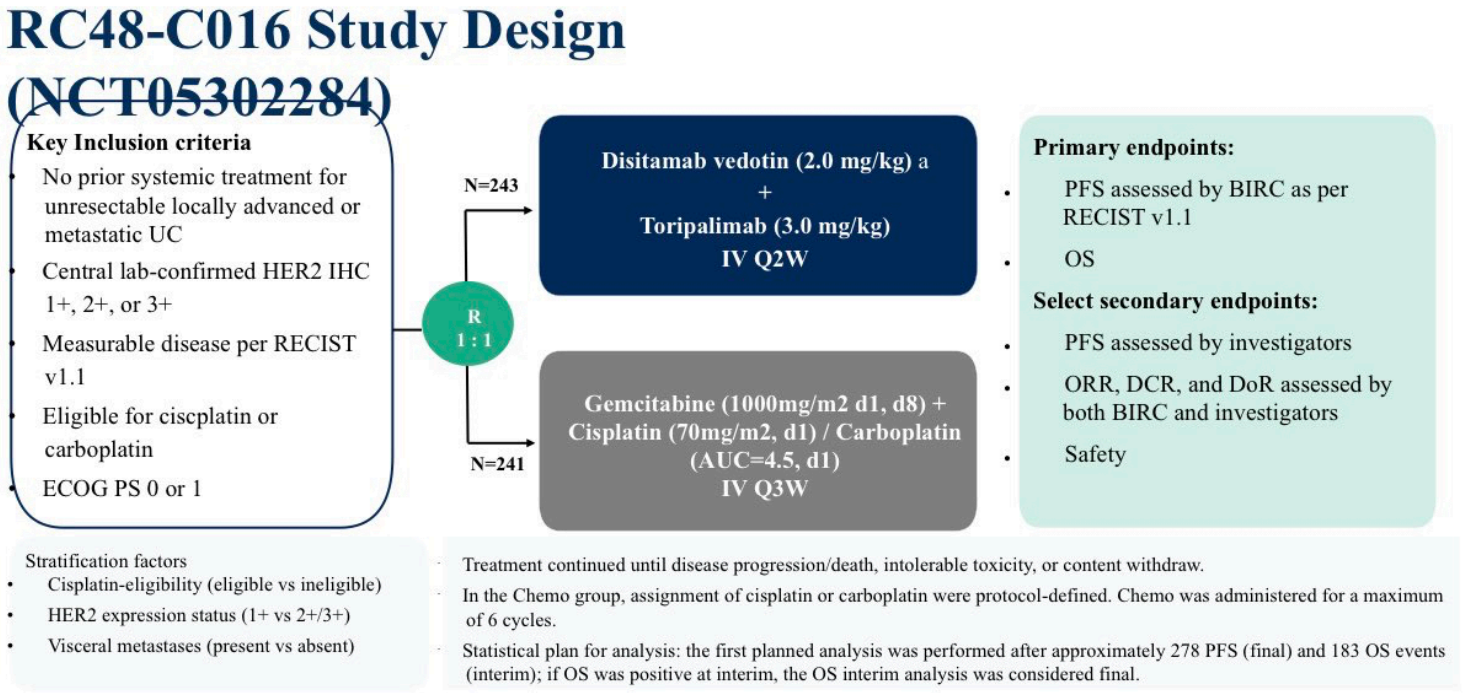
- CheckMate 901 - *FDA Approval 3/2024*
- Grade 3/4 AEs: 61.8% Nivo + G/C vs 51.7% G/C
- Included more histologic variants including adenocarcinoma, SqCC if predominate urothelial histology



NEJM 10/22/23

Metastatic Bladder Cancer – ESMO 2025

- 1L Disitimab Vedotin + Toripalimab– Phase III 1st line therapy for HER2+
- Press Release 2/2025: Positive for PFS/OS



ASCO GU 2025

Metastatic Bladder Cancer –2L Chemo

- Retrospective study out of Memorial Sloan Cancer Institute on outcomes of platinum-based chemotherapy after EV-Pembro
- Median PFS was 4.4 months, and median OS was 12 months

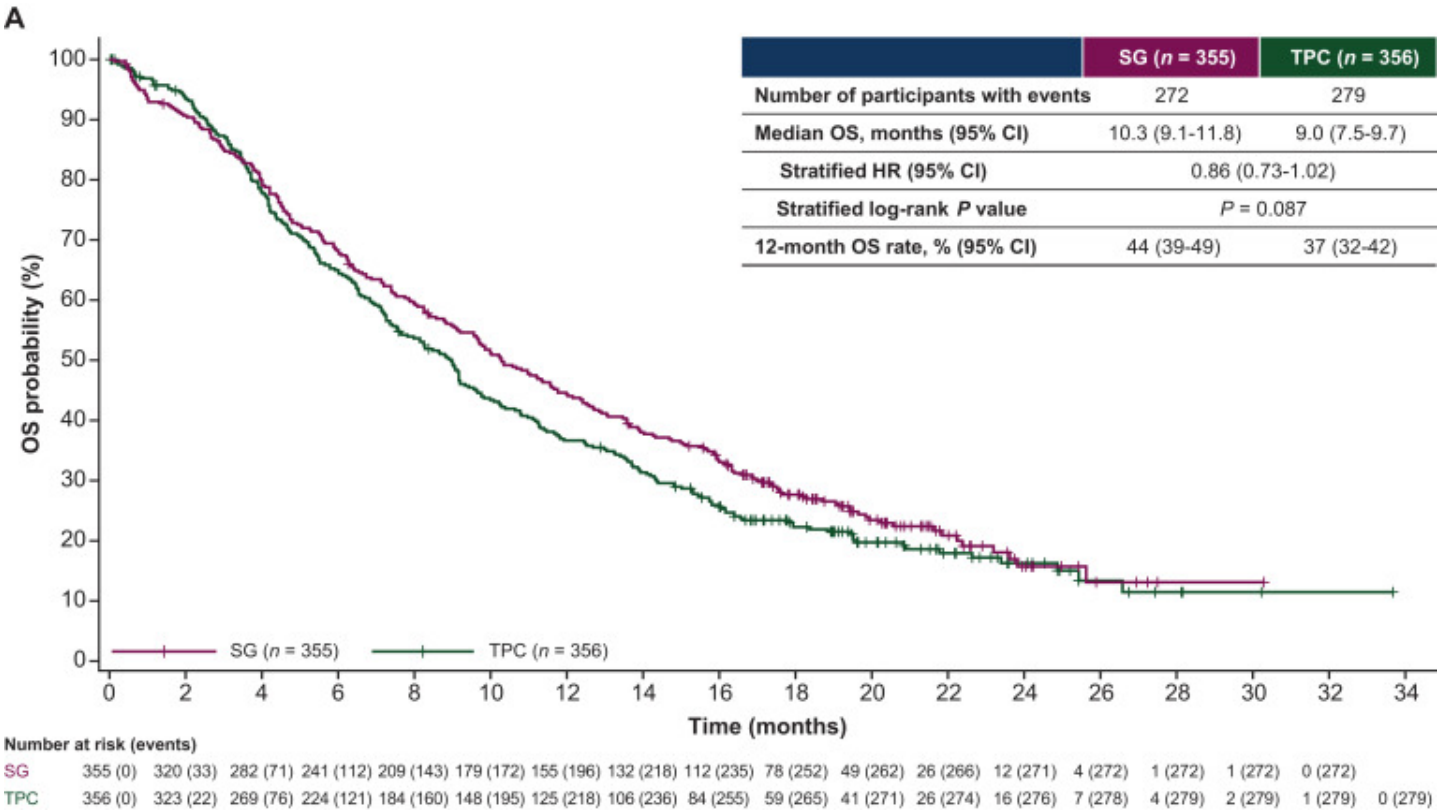
Disease response with platinum-based chemotherapy after enfortumab vedotin and pembrolizumab.

	N=38 (%)	95% CI
Observed response rate	17 (50%)	34%, 66%
Complete response	1 (2.9%)	0.15%, 17%
Partial response	16 (47%)	30%, 65%
Stable disease	6 (18%)	7.4%, 35%
Progressive disease	11 (32%)	18%, 15%

2025 ASCO Poster Presentations

Metastatic Bladder Cancer – ~~Sacituzumab~~

- TROPICS-04 Study, FDA Approval 2021. Withdrawn *10/2024*
- Sacituzumab vs 2L Investigator Choice Chemotherapy: ORR 28%
- 35% Grade 3 neutropenia, 12% febrile neutropenia, 12% G5 neutropenia
  - Low g-CSF rate

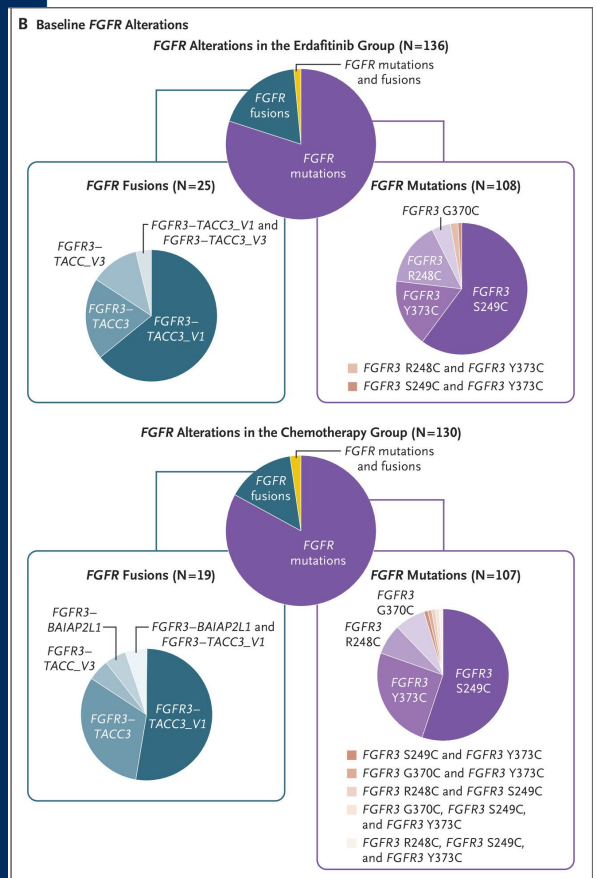


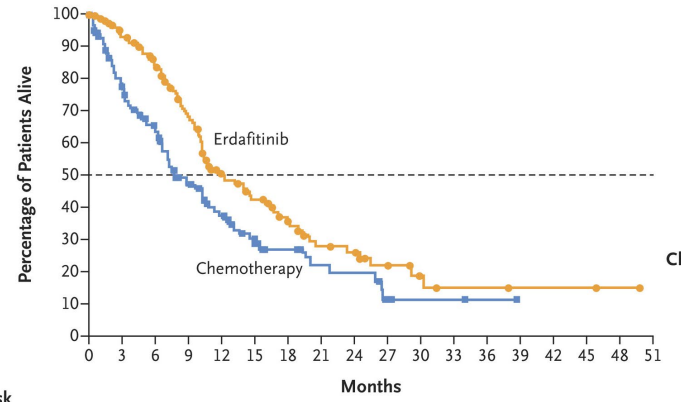
	SG (*n* = 355)	TPC (*n* = 356)
Number of participants with events	272	279
Median OS, months (95% CI)	10.3 (9.1-11.8)	9.0 (7.5-9.7)
Stratified HR (95% CI)	0.86 (0.73-1.02)	
Stratified log-rank *P* value	*P* = 0.087	
12-month OS rate, % (95% CI)	44 (39-49)	37 (32-42)

Annals of Oncology 5/2025

Metastatic Bladder Cancer –2L Erdafitinib

- THOR Study – Erdafitinib vs Chemotherapy. *FDA Approval 1/2024*
  - FGFR3 mutation in 10-20% advanced bladder cancer
  - Grade 3/4 AEs: 45.9% Erdafitinib, 46.4% chemotherapy
- Median OS – 12.1 months vs 7.8 months, HR 0.64





	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI)
		mo
Erdafitinib	77/136	12.1 (10.3–16.4)
Chemotherapy	78/130	7.8 (6.5–11.1)

Hazard ratio for death, 0.64 (95% CI, 0.47–0.88)
P=0.005

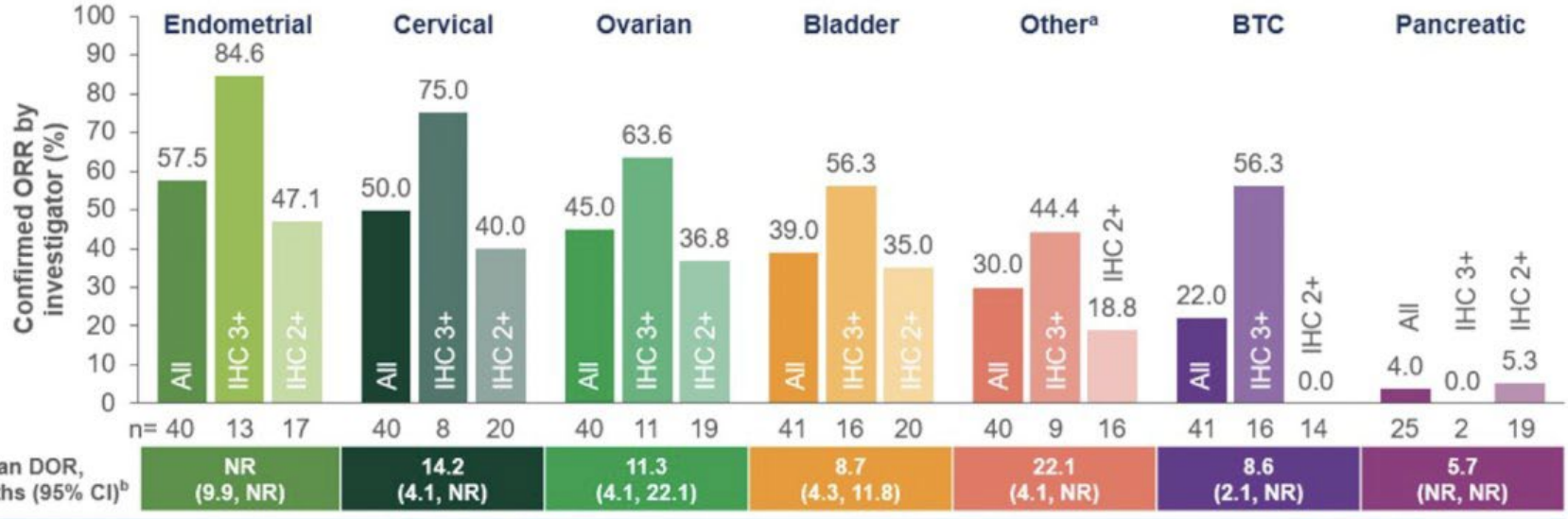
No. at Risk (no. with censored data)

Erdafitinib	136	117	97	74	46	35	25	17	15	9	5	3	3	2	2	2	1	0
	(0)	(10)	(20)	(25)	(35)	(39)	(44)	(47)	(48)	(52)	(55)	(56)	(56)	(57)	(57)	(57)	(58)	(59)
Chemotherapy	130	87	66	43	30	18	13	9	8	3	2	2	1	0	0	0	0	0
	(0)	(17)	(25)	(30)	(35)	(41)	(45)	(47)	(47)	(49)	(50)	(50)	(51)	(52)	(52)	(52)	(52)	(52)

NEJM 10/20/2023

Metastatic Bladder Cancer –2L

- DESTINY-PanTumor02, Phase II – Phase II T-DXD for Her2 2+/3+ expressing locally advanced or metastatic cancer after prior therapy or without alternative. *FDA Approval 4/2024 for Her2 3+*
- Grade 3/4 AEs: 40.8%, neutropenia and anemia



	All patients (N=267)	IHC 3+ (n=75)	IHC 2+ (n=125)
ORR, % (95% CI)	37.1 (31.3, 43.2)	61.3 (49.4, 72.4)	27.2 (19.6, 35.9)
Median DOR, months (95% CI)[b]	11.3 (9.6, 17.8)	22.1 (9.6, NR)	9.8 (4.3, 12.6)

JCO 10/23/23

Future Directions for Bladder Cancer

- Need for early molecular testing and histologic staining
- Utilization of biomarkers to evaluate early response to treatment
- SBRT for oligo-progression
- Bladder conserving approaches

Thank you!