SITC-IBCG Panel Guidelines Adjuvant Therapy

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Center for Cancer Research, National Cancer Institute
National Institutes of Health

Disclosures

- None

Research Hypothesis for Adjuvant Bladder Cancer Therapy

- Treatment decisions are based on pathological rather than clinical staging
- Treatment is used in patients with adverse pathological findings in the cystectomy specimen despite prior NAC
- A goal is to eradicate micrometastases, which may improve patient survival with an acceptable QOL

Apolo AB et al., JAMA Oncol. 2019 Dec 1;5(12):1790-1798.
Kamat AM et al., J Clin Oncol. 2023 Dec 10;41(35):5437-5447.

SITC-IBCG Panel for Adjuvant Bladder Cancer Trial Design and Endpoints

- Study Objectives
- Study Design
- Study Population
- Evaluation and Follow-Up

Apolo AB et al., JAMA Oncol. 2019 Dec 1;5(12):1790-1798.
Kamat AM et al., J Clin Oncol. 2023 Dec 10;41(35):5437-5447.

Presented by Andrea B. Apolo, MD
@apolo_andrea

SITC-IBCG Panel for Adjuvant Bladder Cancer Trial Design and Endpoints

Study Objectives

- Primary Endpoint:
  - disease-free survival (DFS)
  - overall survival (OS)
- Secondary Endpoint:
  - distant metastasis-free survival (DMFS)
  - urothelial tract–specific RFS
  - patient-reported outcomes (PRO)
  - quality-adjusted life years (QALYs)

Apolo AB et al., JAMA Oncol. 2019 Dec 1;5(12):1790-1798.
Kamat AM et al., J Clin Oncol. 2023 Dec 10;41(35):5437-5447.

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SITC-IBCG Panel for Adjuvant Bladder Cancer Trial Design and Endpoints

Study Design

- Prospective
- Randomized and Controlled
- Post-Radical Surgery

Apolo AB et al., JAMA Oncol. 2019 Dec 1;5(12):1790-1798.
Kamat AM et al., J Clin Oncol. 2023 Dec 10;41(35):5437-5447.

SITC-IBCG Panel for Adjuvant Bladder Cancer Trial Design and Endpoints

Study Design

- Consider allowing treatment post Tri-Modality Therapy (TMT)
- In cisplatin-eligible patients who have not received NAC, cisplatin-based adjuvant therapy is considered a standard (based on DFS)
- In cisplatin-ineligible patients or those who received NAC, adjuvant nivolumab is considered a standard (based on DFS)
- Plasma circulating tumor DNA (ctDNA)may stratify patients by micrometastatic disease presence after adjuvant treatment and should be an integral, integrated, or exploratory biomarker to inform future trial design

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Kamat AM et al., J Clin Oncol. 2023 Dec 10;41(35):5437-5447.

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SITC-IBCG Panel for Adjuvant Bladder Cancer Trial Design and Endpoints

Study Population

- Fit for systemic therapy
- Adequate tumor tissue available for biomarker analysis.
- Should have completed SOC treatment (ie, radical cystectomy)
- Prior neoadjuvant therapy (chemotherapy or immunotherapy) should be allowed but noted with sequencing of these agents
- Prior anti–PD-(L)1 therapy should have been administered at least 6-12months before trial inclusion if nivolumab is the comparator to avoid enrolling patients with immunotherapy-unresponsive UC
- Consider including:
  - +surgical margins (may be analyzed as a subgroup)
  - histologic subtypes/variants (may be analyzed as a subgroup)

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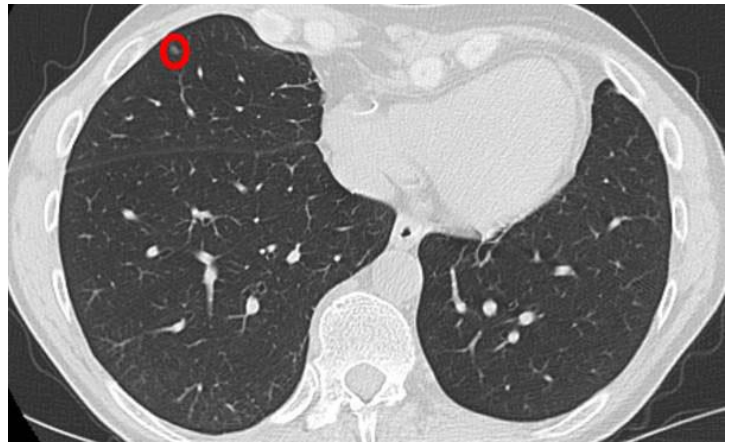
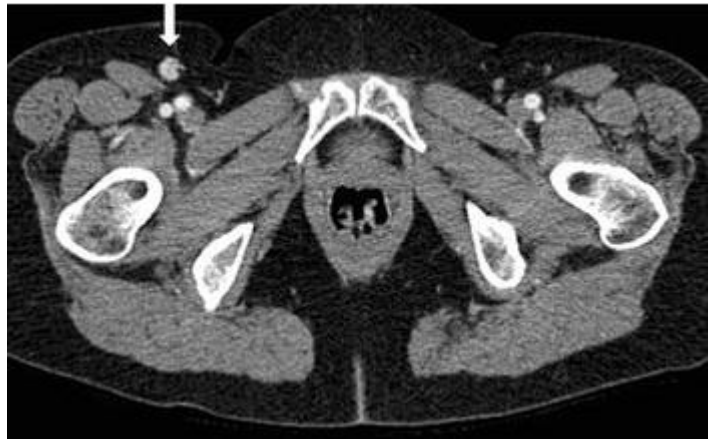
SITC-IBCG Panel for Adjuvant Bladder Cancer Trial Design and Endpoints

Evaluation and Follow-Up

- Evaluation of recurrence
  - Physical examination
  - Crosssectional imaging of the chest, abdomen, and pelvis
  - Biomarker analysis (eg, ctDNA, and others)





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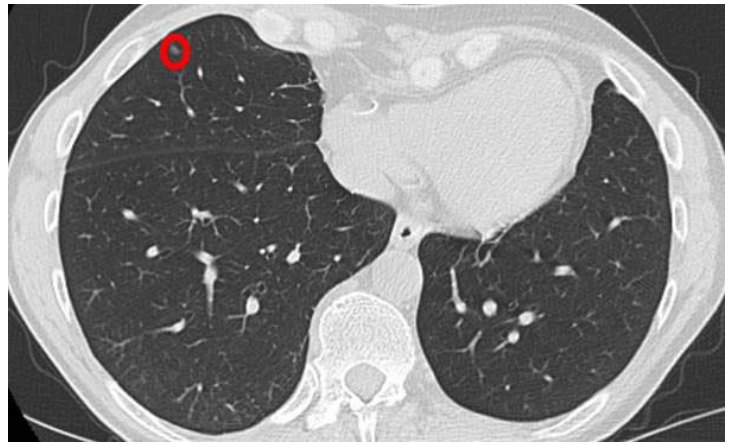
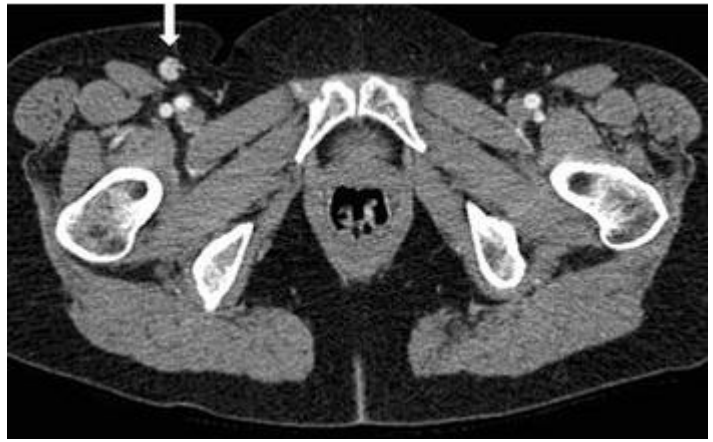
SITC-IBCG Panel for Adjuvant Bladder Cancer Trial Design and Endpoints

Evaluation and Follow-Up

- Evaluation of recurrence
  - Physical examination
  - Crosssectional imaging of the chest, abdomen, and pelvis
  - Biomarker analysis (eg, ctDNA, and others)

- Definition of recurrence





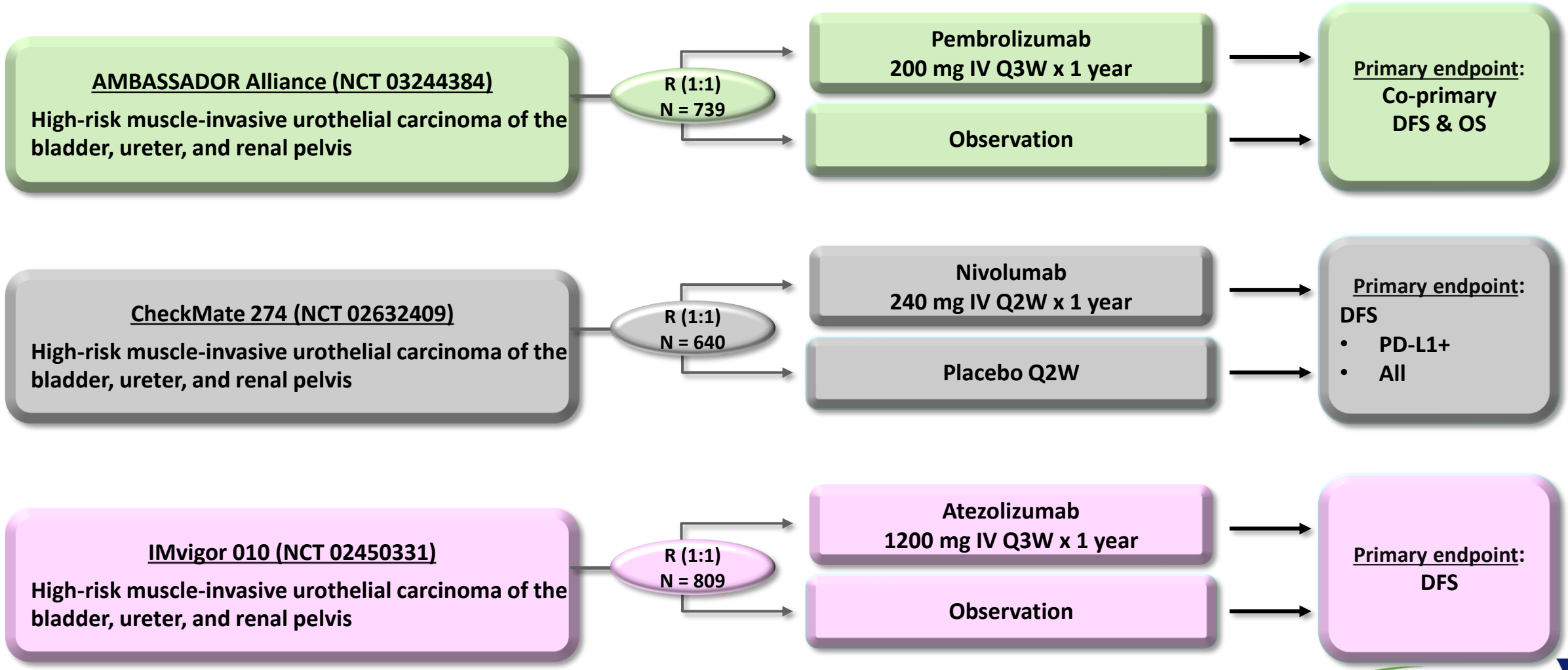
JAMA Oncology | Special Communication

Eligibility and Radiologic Assessment in Adjuvant Clinical Trials in Bladder Cancer

Andrea B. Apolo, MD; Matthew I. Milowsky, MD; Lauren Kim, MD; Brant A. Inman, MD; Ashish M. Kamat, MD; Gary Steinberg, MD; Mohammadhadi Bagheri, MD; Venkatesh P. Krishnasamy, MD; Jamie Marko, MD; Colin P. Dinney, MD; Rick Bangs, MBA; Randy F. Sweis, MD; Virginia Ellen Maher, MD; Amna Ibrahim, MD; Ke Liu, MD, PhD; Ryan Werntz, MD; Frank Cross, MA, MT; Julia A. Beaver, MD; Harpreet Singh, MD; Richard Pazdur, MD; Gideon M. Blumenthal, MD; Seth P. Lerner, MD; Dean F. Bajorin, MD; Jonathan E. Rosenberg, MD; Sundeep Agrawal, MD

Apolo AB et al., JAMA Oncol. 2019 Dec 1;5(12):1790-1798.
Kamat AM et al., J Clin Oncol. 2023 Dec 10;41(35):5437-5447.

Phase III Checkpoint-Inhibitor Adjuvant Trials in Muscle-Invasive Bladder Cancer



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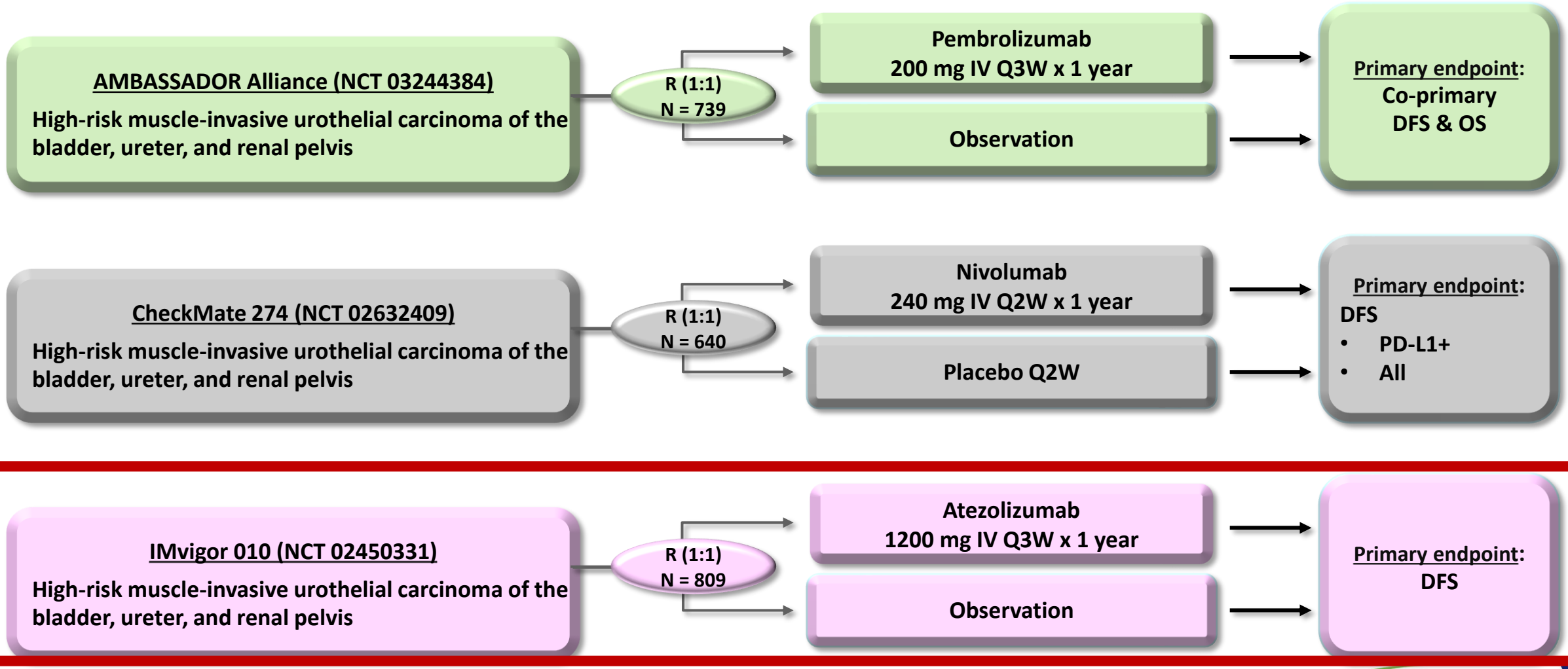
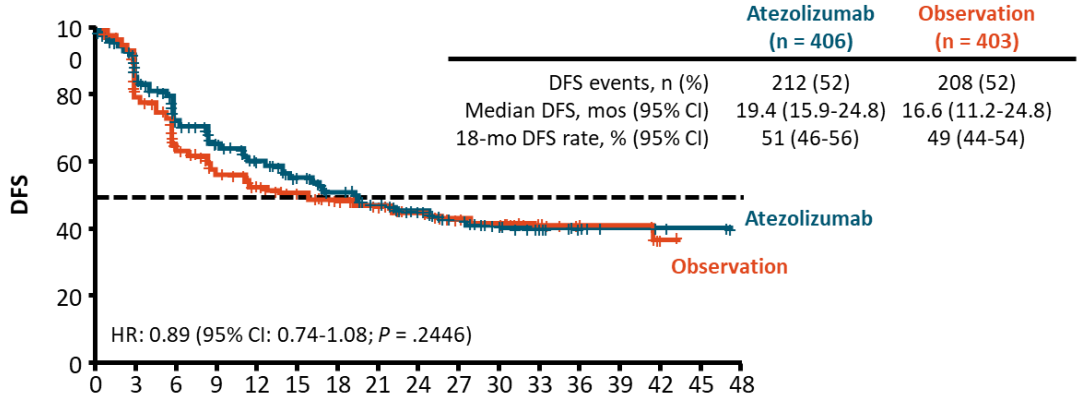
Phase III Checkpoint-Inhibitor Adjuvant Trials in Muscle-Invasive Bladder Cancer



Phase III Checkpoint-Inhibitor Adjuvant Trials in Muscle-Invasive Bladder Cancer

DFS with Adjuvant Atezolizumab vs Observation in High-Risk MIUC (ITT; Primary Endpoint)



	Atezolizumab (n = 406)	Observation (n = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS, mos (95% CI)	19.4 (15.9-24.8)	16.6 (11.2-24.8)
18-mo DFS rate, % (95% CI)	51 (46-56)	49 (44-54)

Patients at Risk, n															
Atezolizumab	40	33	28	24	22	20	16	14	11	92	67	52	15	10	3	2
Observation	6	2	1	8	3	1	9	2	5	87	67	42	17	12	2	
	40	30	24	21	18	17	15	13	10							
	3	5	0	1	8	7	6	1	9							

IMvigor 010 (NCT 02450331)

High-risk muscle-invasive urothelial carcinoma of the bladder, ureter, and renal pelvis

R (1:1)
N = 809

Atezolizumab
1200 mg IV Q3W x 1 year

Observation

Primary endpoint:
DFS

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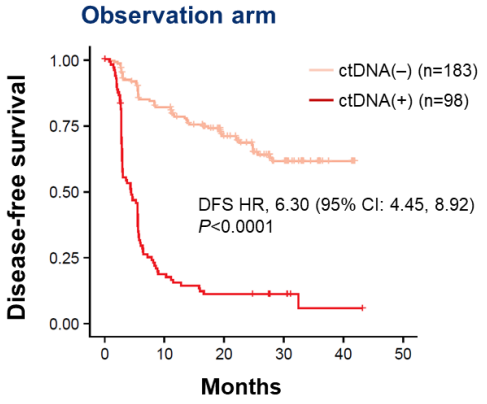
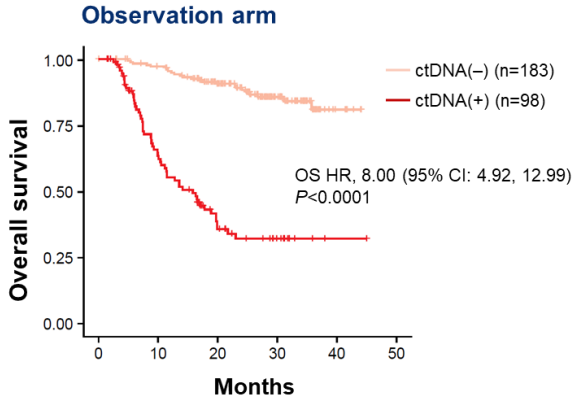
Bellmunt et al. *Lancet Oncol* 2021 Apr;22(4):525-537

Phase III Checkpoint-Inhibitor Adjuvant Trials in Muscle-Invasive Bladder Cancer

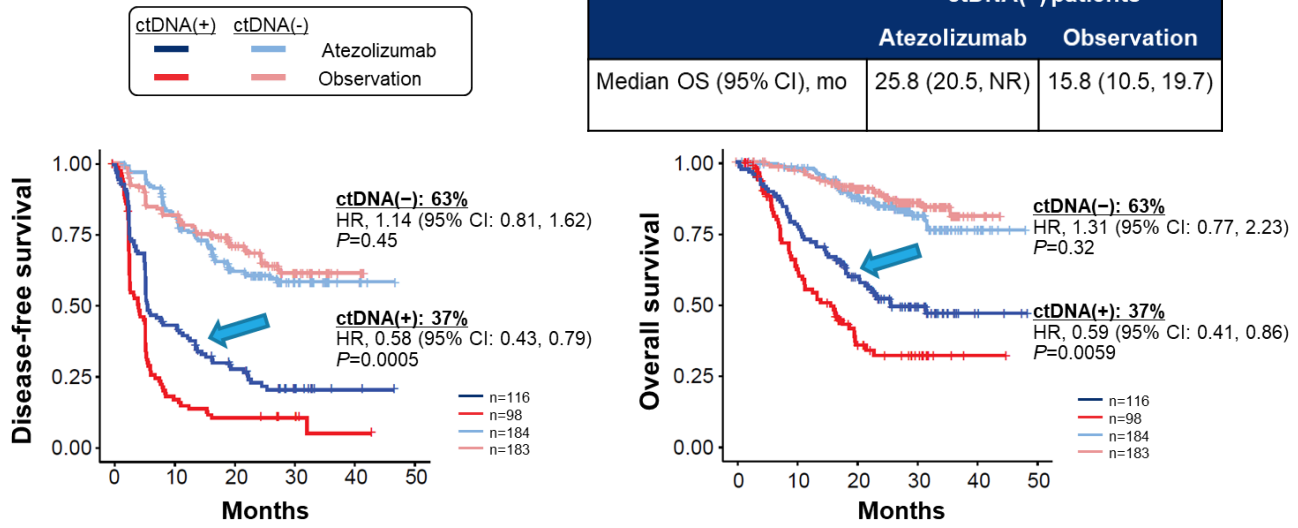
- **Prognostic value of ctDNA status in Imvigor 010**





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

	ctDNA(+) patients	
	Atezolizumab	Observation
Median OS (95% CI), mo	25.8 (20.5, NR)	15.8 (10.5, 19.7)



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Observation

Primary endpoint:
DFS

Immuno-Oncology 2020. Abstr 11.

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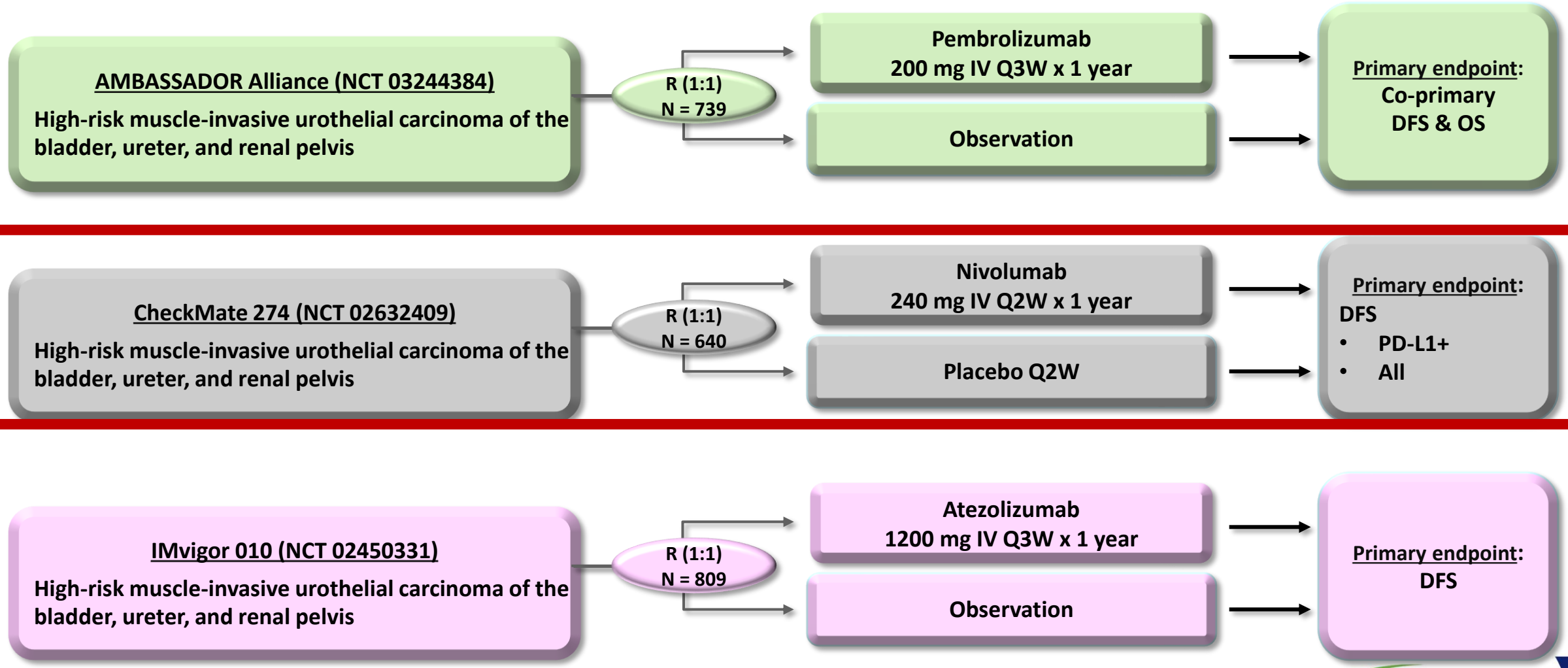
Powles. T et al., Nature volume 595, pages432–437 (2021).

Phase III Checkpoint-Inhibitor Adjuvant Trials in Muscle-Invasive Bladder Cancer



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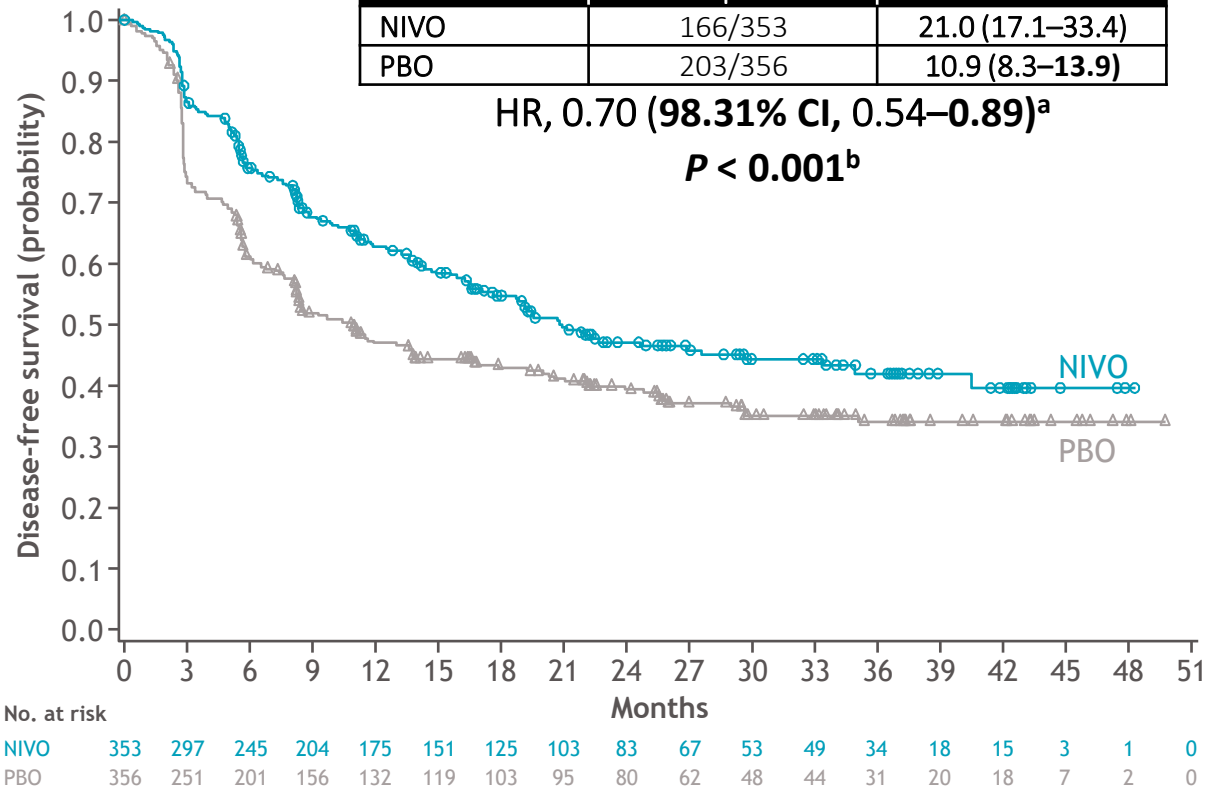
CheckMate 274: Adjuvant Nivolumab vs Placebo After Radical Surgery
Disease-free survival

• 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]



No. at risk

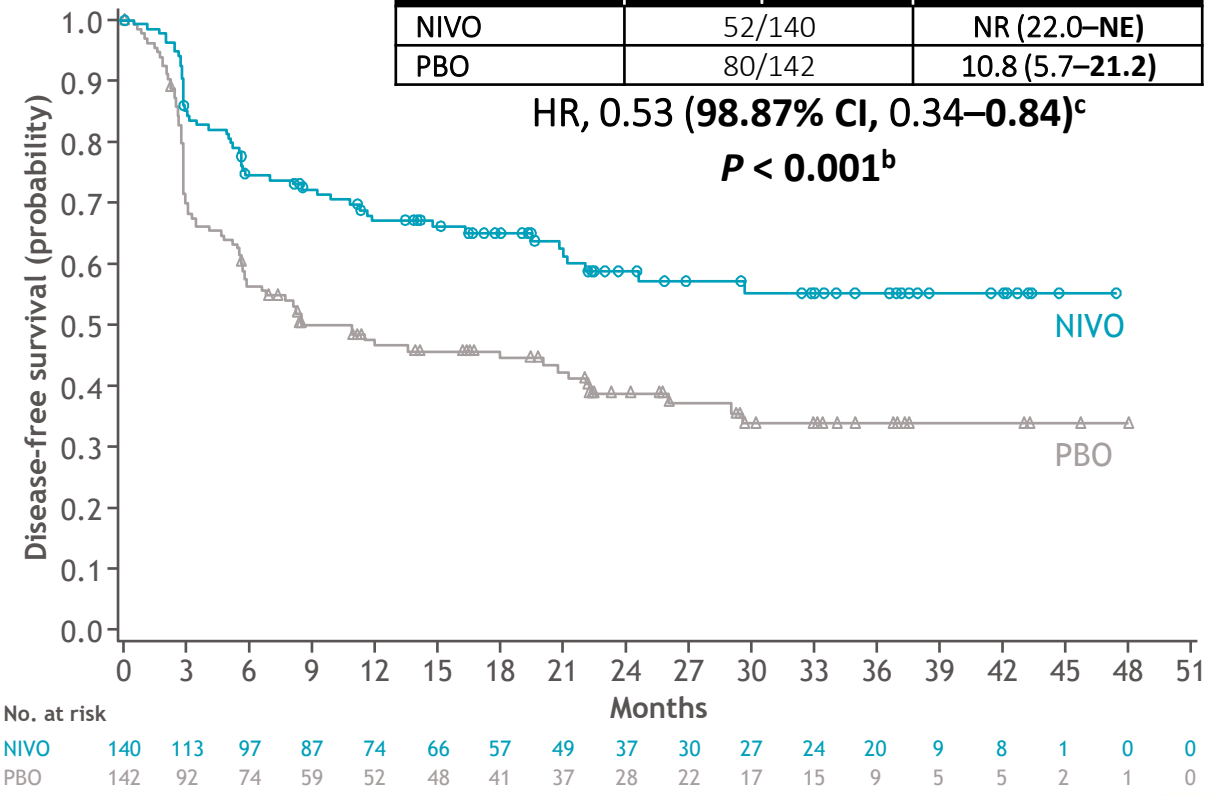
NIVO	353	297	245	204	175	151	125	103	83	67	53	49	34	18	15	3	1	0
PBO	356	251	201	156	132	119	103	95	80	62	48	44	31	20	18	7	2	0

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]



No. at risk

NIVO	140	113	97	87	74	66	57	49	37	30	27	24	20	9	8	1	0	0
PBO	142	92	74	59	52	48	41	37	28	22	17	15	9	5	5	2	1	0

Bajorin et al., N Engl J Med. 2021 Jun 3;384(22):2102-2114

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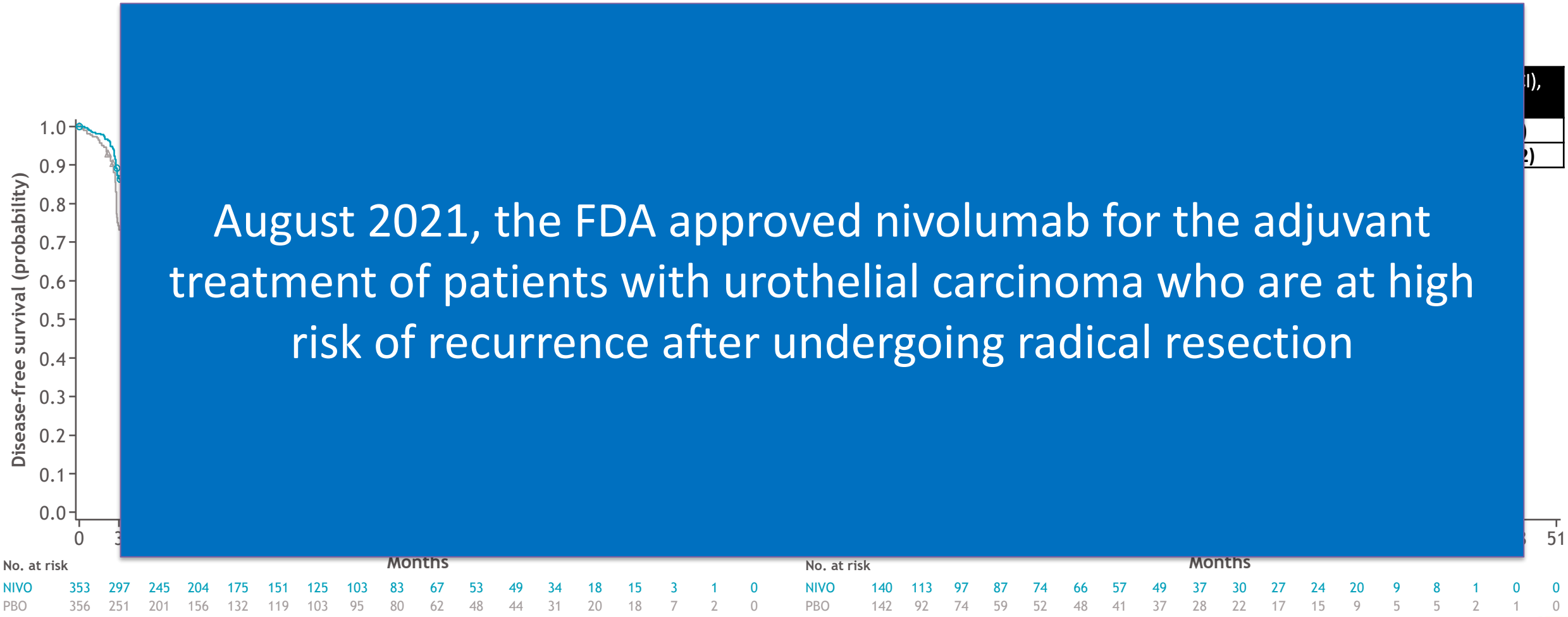
CheckMate 274: Adjuvant Nivolumab vs Placebo After Radical Surgery
Disease-free survival



August 2021, the FDA approved nivolumab for the adjuvant treatment of patients with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection

Bajorin et al., N Engl J Med. 2021 Jun 3;384(22):2102-2114

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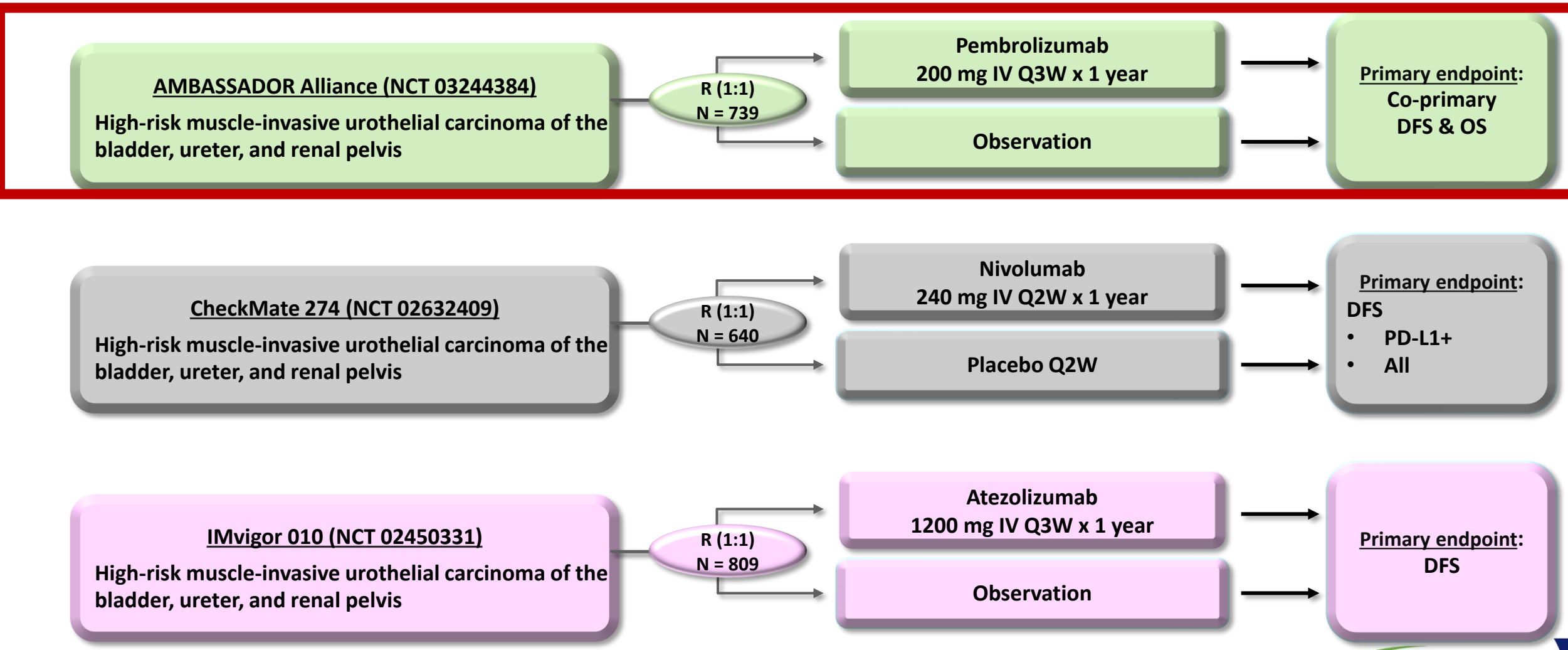

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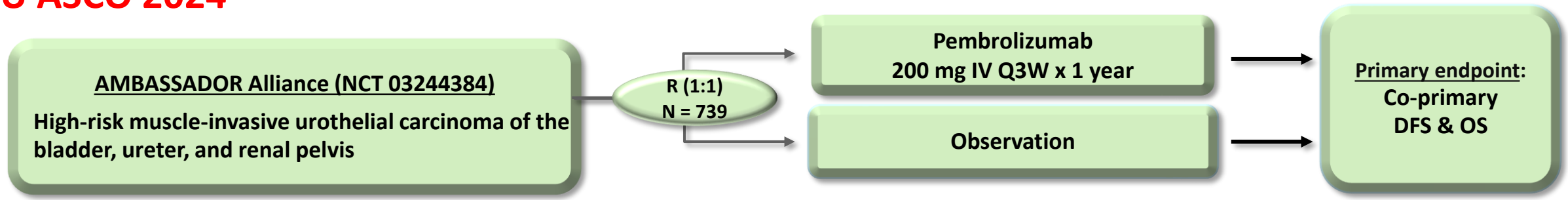
Phase III Checkpoint-Inhibitor Adjuvant Trials in Muscle-Invasive Bladder Cancer

GU ASCO 2024



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

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Apolo AB et al., GU ASCO 2024

A031501 AMBASSADOR: Patient Characteristics

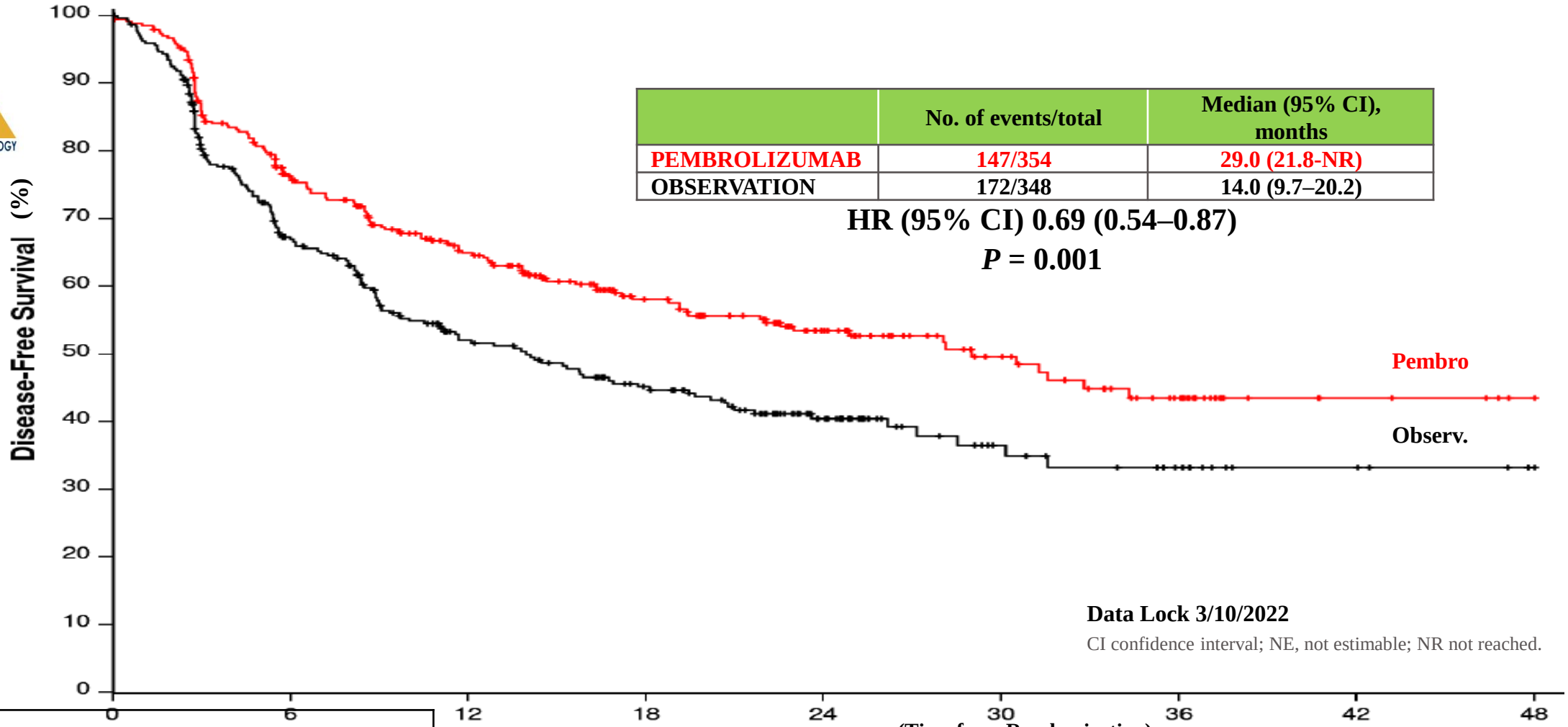
	Pembrolizumab (N=354)	Observation (N=348)
Median age, years (range)	69.0 (22.0-92.0)	68.0 (34.0-90.0)
Race		
White	323 (91.2%)	310 (89.1%)
Black or African American	14 (4.0%)	11 (3.2%)
Asian	5 (1.4%)	10 (2.9%)
American Indian or Alaskan Native	2 (0.6%)	2 (0.6%)
Not reported/Unknown	10 (2.8%)	15 (4.3%)
Gender		
Female	83 (23.4%)	95 (27.3%)
Male	271 (76.6%)	253 (72.7%)
Neoadjuvant therapy		
Yes	231 (65.3%)	218 (62.6%)
Pathologic stage		
+ Surgical margins	9 (2.5%)	8 (2.3%)
pT-any N+ (any)	180 (50.9%)	170 (48.8%)
pT2/3N0 or NX	146 (41.2%)	150 (43.1%)
pT4N0 or NX	19 (5.4%)	20 (5.8%)
PD-L1 status		
Positive (central testing, Dako 22C3, CPS ≥ 10%)	202 (57.1%)	201 (57.8%)
Primary tumor site		
Bladder	267 (75.4%)	264 (75.9%)
Urethra	6 (1.7%)	12 (3.4%)
Upper tract (renal pelvis and ureter)	81 (22.9%)	72 (20.7%)
Histology		
Variant (mixed urothelial histology excluding any neuroendocrine carcinoma)	60 (16.9%)	51 (14.7%)

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**



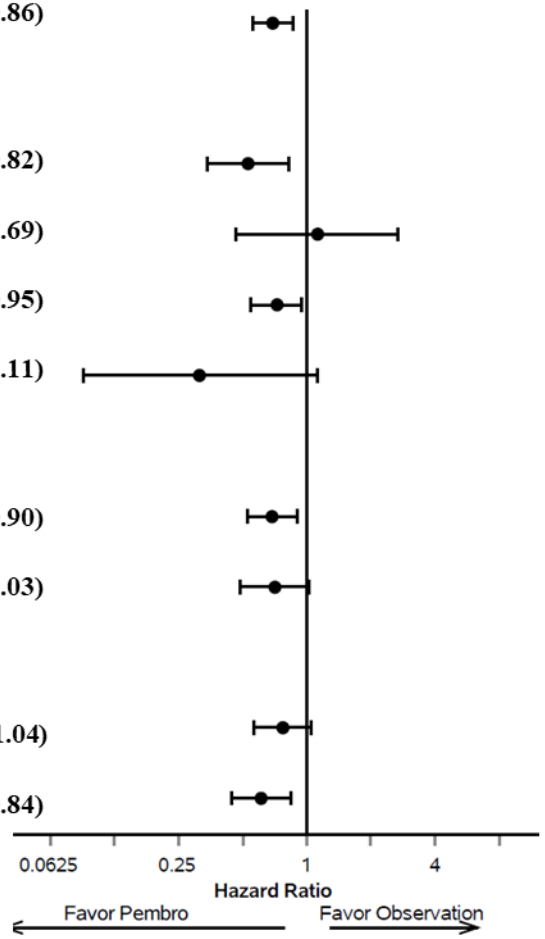
Data Lock 3/10/2022

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

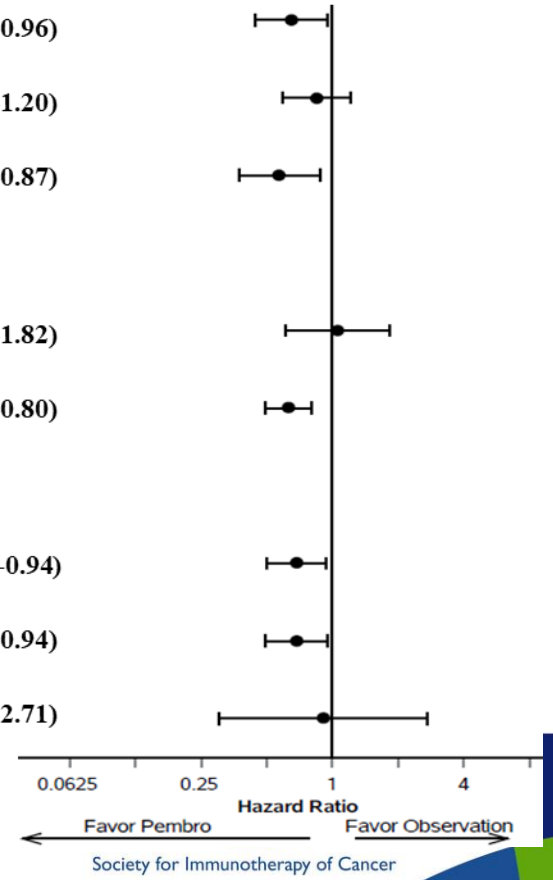
Median follow-up (range) 22.3 months (0.03-48.9)

A031501 AMBASSADOR: Disease-Free Survival Subgroups

Subgroups	Pembro	Observ	HR (95% CI)
	N events/ N patients		
Overall	147/354	172/348	0.69 (0.56-0.86)
Pathological Stage			
pT2/3N0 or NX	32/146	52/150	0.53 (0.34-0.82)
pT4N0 or NX	10/19	10/20	1.12 (0.46-2.69)
pT-any N+ (any)	100/180	103/170	0.72 (0.55-0.95)
+Surgical margins	5/9	7/8	0.31 (0.09-1.11)
Neoadjuvant Chemo			
Yes	97/231	113/218	0.69 (0.52-0.90)
No	50/123	59/130	0.70 (0.48-1.03)
PD-L1 Status			
Positive	79/202	86/201	0.77 (0.57-1.04)
Negative	68/152	86/147	0.61 (0.44-0.84)

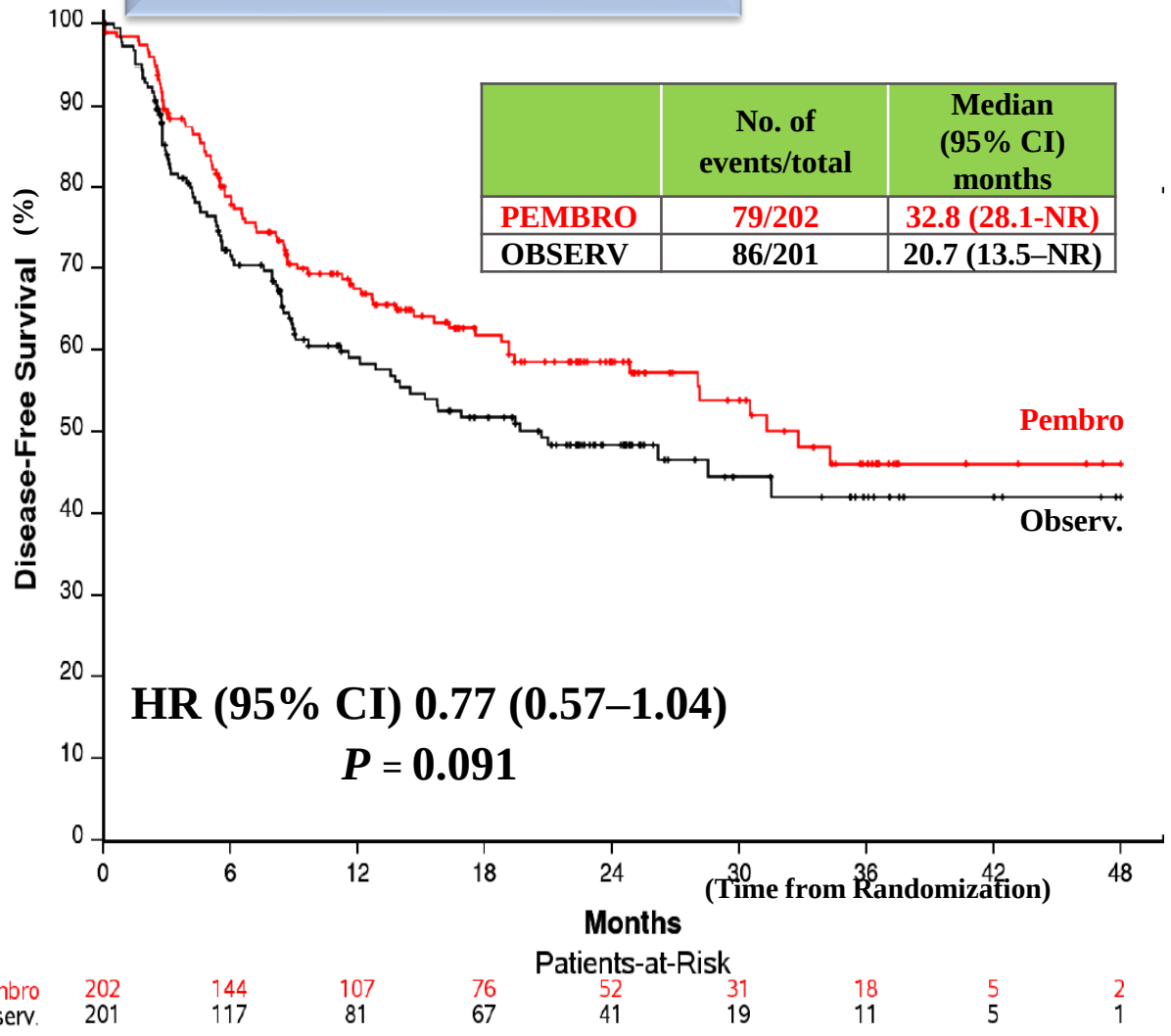


Subgroups	Pembro	Observ	HR (95% CI)
	N events/ N patients		
Age			
<65	50/120	57/125	0.65 (0.44-0.96)
65-75	62/145	62/135	0.85 (0.59-1.20)
>75	35/89	53/88	0.57 (0.37-0.87)
Primary Tumor Site			
Upper tract	29/81	23/72	1.05 (0.61-1.82)
Lower tract	118/273	149/276	0.63 (0.50-0.80)
ECOG			
0	70/184	85/179	0.68 (0.50-0.94)
1	68/151	81/157	0.68 (0.49-0.94)
2	9/19	6/12	0.91 (0.32-2.71)



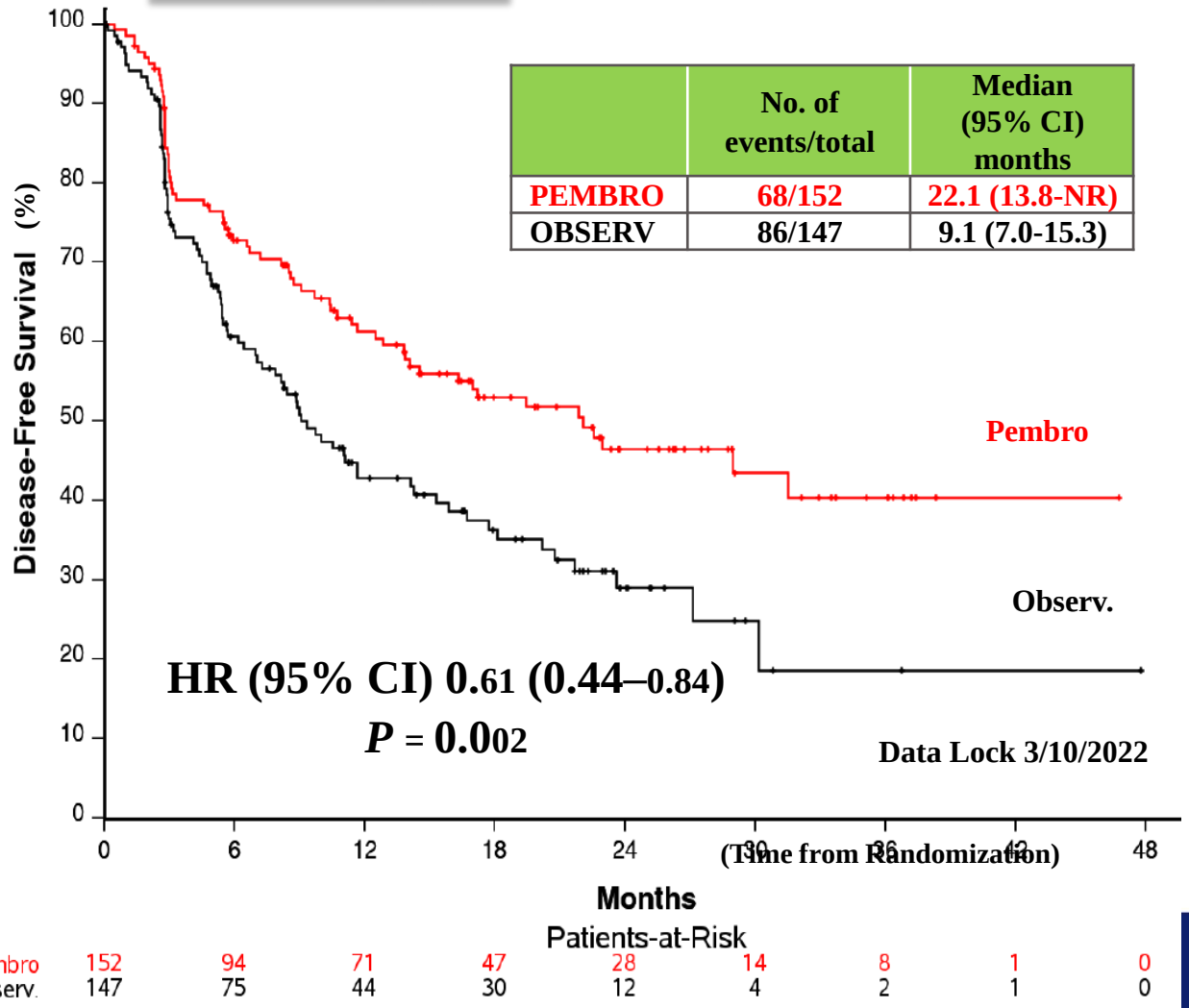
A031501 AMBASSADOR: Disease-Free Survival by PD-L1* Status

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)

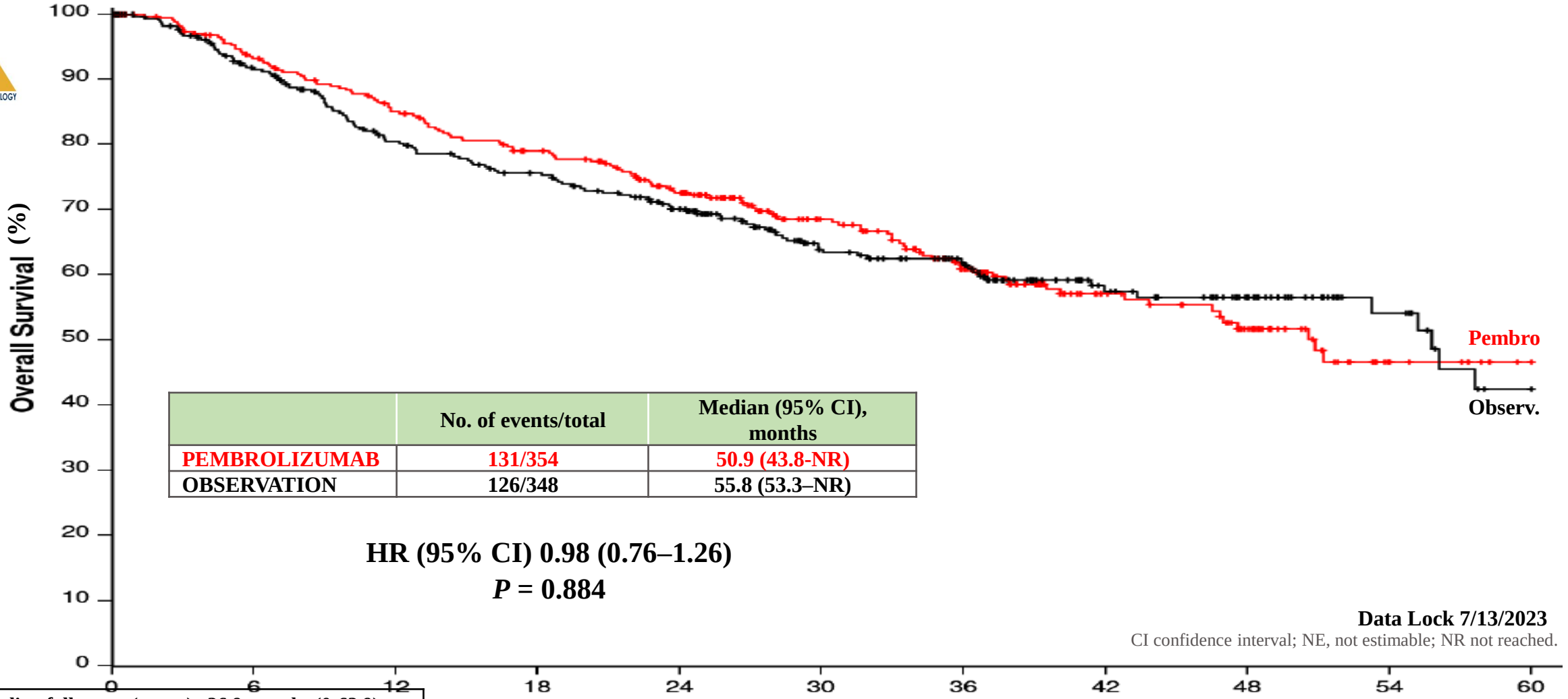
PD-L1-Negative



	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)

CI, confidence interval; NE, not estimable; NR, not reached. *Dako PD-L1 immunohistochemistry 22C3 pharmDx assay

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

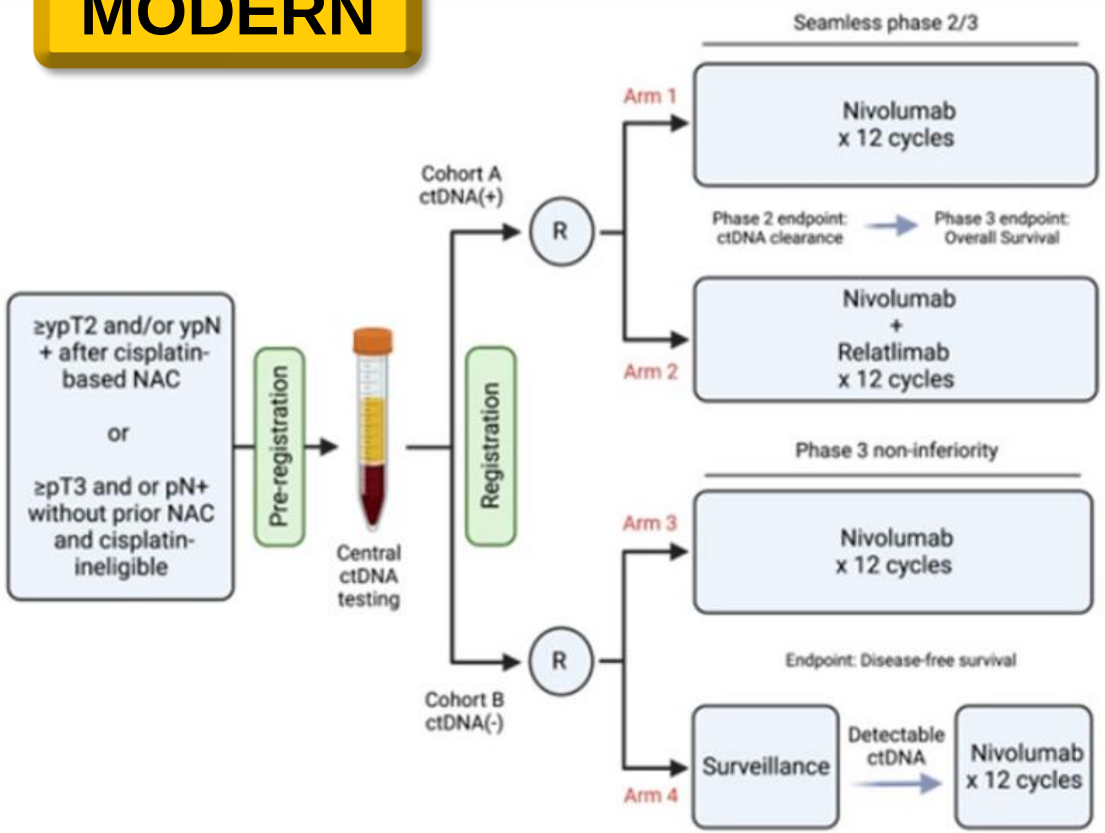
CI confidence interval; NE, not estimable; NR not reached.

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

Apolo AB et al., GU ASCO 2024

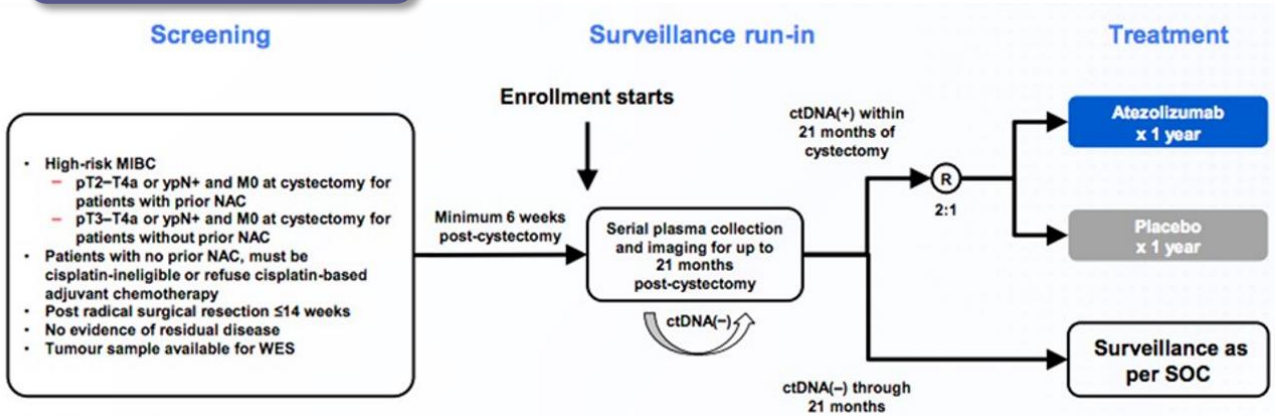
Ongoing ctDNA Based Prospective Adjuvant Bladder Cancer Studies

MODERN



ctDNA+ patients are randomized to nivo vs nivo + relatlimab
ctDNA- patients are randomized to immediate nivo vs delayed nivo when ctDNA+

IMvigor011



Stratification factors
- Nodal status (positive vs negative)
- Tumour stage after cystectomy (≤pT2 vs pT3/pT4)
- PD-L1 IHC status (IHC score of IC0/1 vs IC2/3)
- Time from cystectomy to first ctDNA(+) sample (≤20 weeks vs >20 weeks)

ctDNA+ patients are randomized to atezolizumab vs placebo

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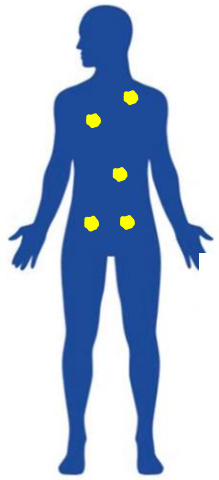
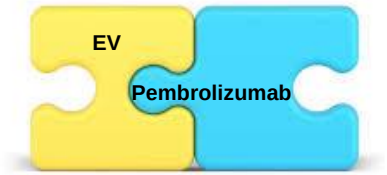
EV+pembro Is a New Standard of Care in Metastatic Bladder Cancer



First-Line

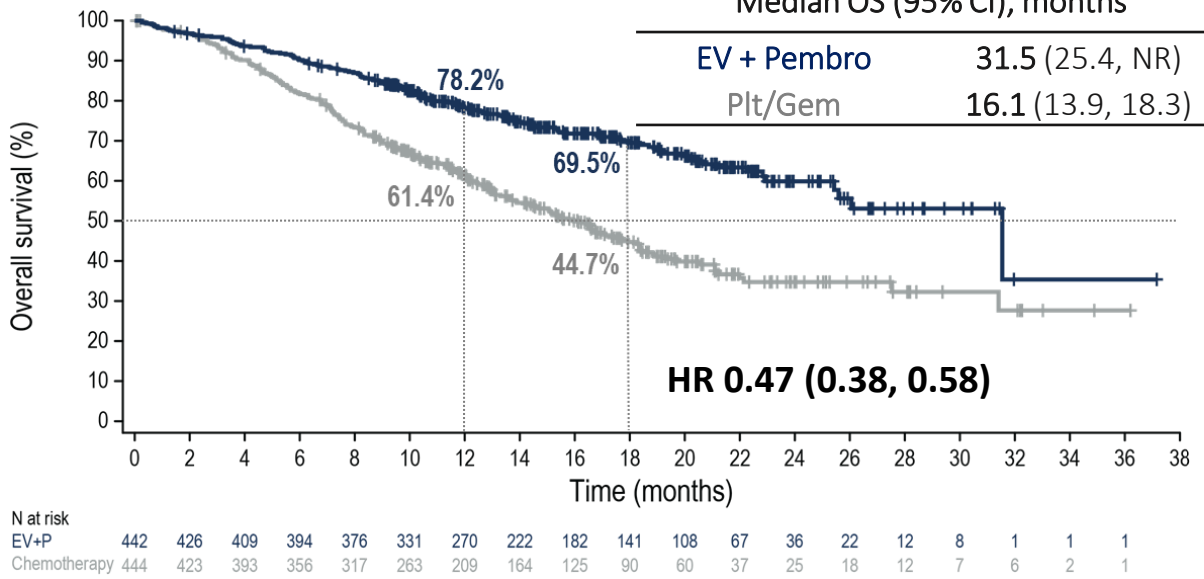
Enfortumab vedotin + Pembrolizumab



EV+Pembro vs Plt/Gem

EV-302 Study

Median OS (95% CI), months	
EV + Pembro	31.5 (25.4, NR)
Plt/Gem	16.1 (13.9, 18.3)



Powels T et al., NEJM 2024

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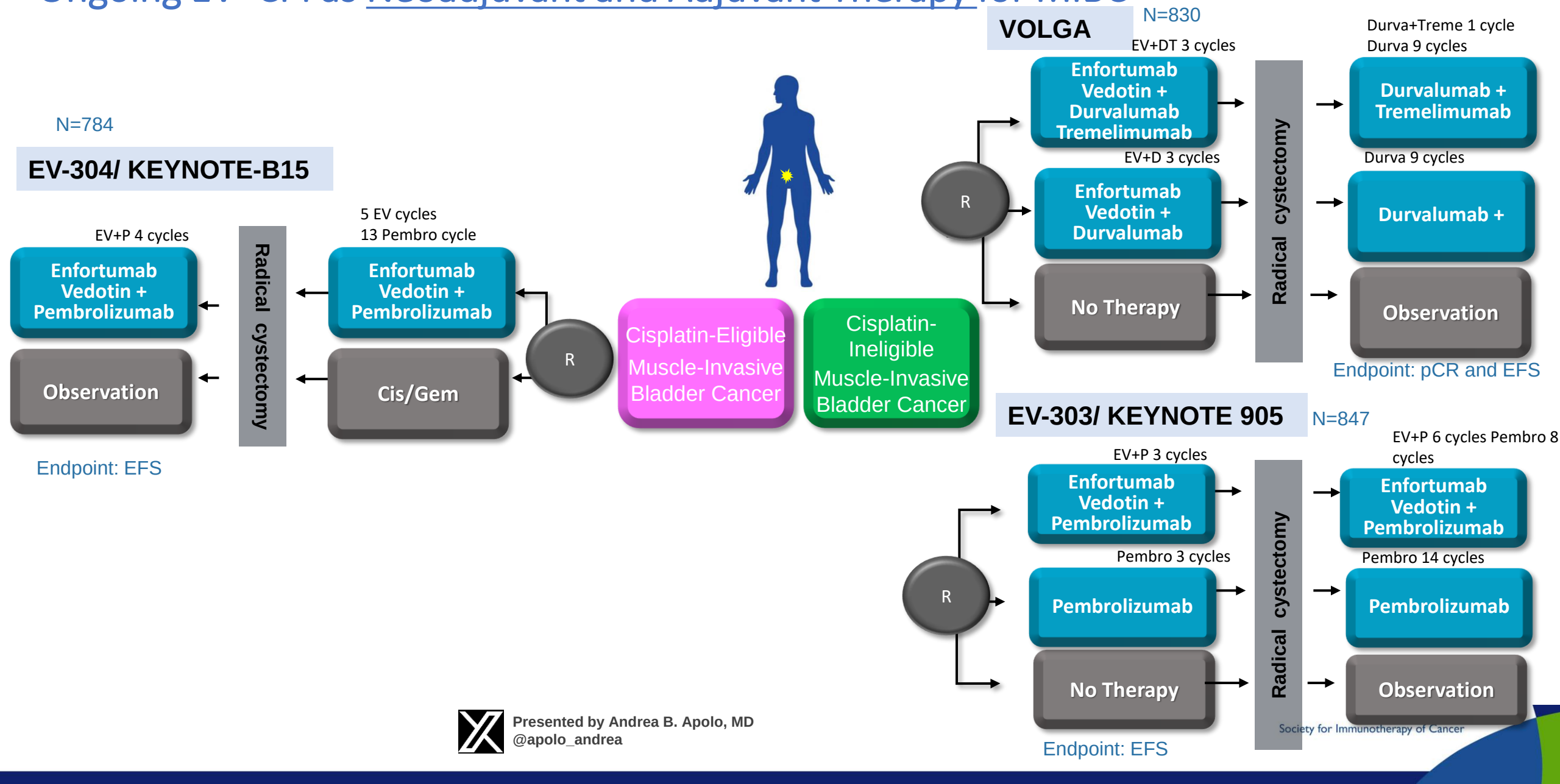
Ongoing EV+CPI as Neoadjuvant and Adjuvant Therapy for MIBC



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SITC-IBCG Panel for Adjuvant Bladder Cancer Trial Design and Endpoints

Conclusion

- Implementing a uniform approach to adjuvant bladder cancer trial design and endpoints may allow for less variability in trial conduct and result interpretation
- Biomarkers should be incorporated into adjuvant trial design and endpoints to move the field forward and select patients at highest risk and would derive the greatest benefit from therapy
- We must account for the rapidly changing landscape in bladder cancer and recognize the need for continued dialogue and adaptation

Apolo AB et al., JAMA Oncol. 2019 Dec 1;5(12):1790-1798.
Kamat AM et al., J Clin Oncol. 2023 Dec 10;41(35):5437-5447.

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