Oncology Learning Network

Advancing Care in Genitourinary Cancers

Integrating Targeted Therapies for Metastatic Urothelial Carcinoma and Advanced Prostate Cancer

Daniel M. Geynisman MD

Chief, Genitourinary Medical Oncology
Associate Professor, Medical Oncology
Fox Chase Cancer Center, Temple Health

Faculty Disclosures

Scientific Advisory

- Exelixis, AstraZeneca

Honoraria

- National Comprehensive Cancer Network® (NCCN®), Targeted Oncology, 2nd.MD, Exelixis

Institutional Funding for Clinical Research

- Regeneron, Novartis, Arvinas

Disclosures

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration)
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity
- This activity has been independently reviewed for balance
- This CME activity includes brand names for participant clarity purposes only. No product promotion or recommendation should be inferred
- NCCN makes no warranties of any kind whatsoever regarding their content, use, or application, and disclaims any responsibility for their application or use in any way

Program Information

- Provided by HMP Education, LLC, an HMP Global Company
- Supported in part by an educational grant from Johnson & Johnson

Pre-Event Survey

Scan the QR Code to submit your questions and answer the pre-event survey

References

Learning Objectives

- Describe the underlying mechanisms of action, therapeutic benefits, and safety profiles of emerging and established treatment options for UC and advanced PCa
- Assess key prognostic and diagnostic biomarkers that identify patients at elevated risk of developing advanced PCa
- Describe the impact of mUC and its effect on patients' quality of life
- Learn to employ proactive approaches for recognizing, monitoring, and managing AEs associated with immunotherapies and targeted treatments for mUC and PCa
- Apply patient-centered decision-making principles to develop personalized treatment plans that account for both comorbidities and patient preferences

Outline

1. Introduction
   - Epidemiology of UC and PCa
   - Challenges to Care
2. Urothelial Carcinoma
   - Disease Overview
   - Diagnosis and Staging
   - Updates in localized UC
   - Advanced Disease & Clinical Guidelines
3. Advanced Prostate Cancer
   - mHSPC, nmCRPC, mCRPC
4. Side-effect management for drugs used in UC and PCa
5. Patient-Centered Care for GU Cancers

Introduction to Urothelial Carcinoma and Prostate Adenocarcinoma

Epidemiology of Urothelial Carcinoma

Estimated New Cases

Males			Females		
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All Sites	**983,160**	**100%**	**All Sites**	**934,870**	**100%**

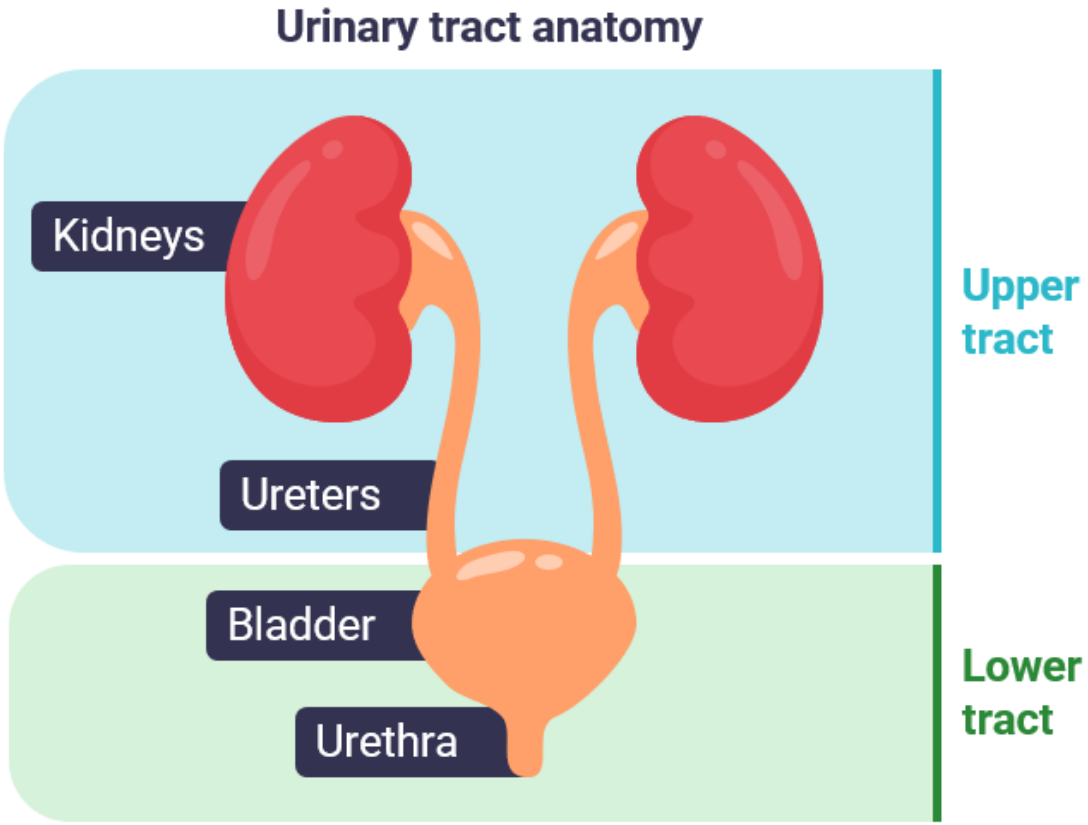
Estimated Deaths

Males			Females		
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
Leukemia	14,020	4%	Uterine corpus	12,550	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All Sites	**322,090**	**100%**	**All Sites**	**287,270**	**100%**

Siegel RL, et al. CA Cancer J Clin. 2024;74(1):12-49.

- Bladder, urethra, ureter, renal pelvis
  - Biology of upper tract disease different (enriched for *FGFR* mutations)
- Oldest median age of any solid tumor, early 70s
- ~550,000 cases worldwide, ~85,000 in the US (4.6% of all cancers), and ~17,000 deaths in the US
- 3-4 times more common in men
- Estimate of disease state at presentation in the bladder
  - Non-Muscle Invasive Bladder Cancer (NMIBC) 75%
  - Muscle-Invasive Bladder Cancer (MIBC) 25%-30%
  - Locally Advanced/Metastatic 5%

Risk Factors



- 50%-60% of all cases caused by smoking for both men and women
- Occupational exposure: aromatic amines, benzidine and their derivatives (metal workers, painters, rubber industry, leather workers, electrical workers, miners, cement workers, transport operators)
- Chronic cystitis
- Lynch Syndrome
- Iatrogenic
  - Radiation
  - Cyclophosphamide

Saginala K, et al. *Med Sci (Basel).* 2020;8(1):15.

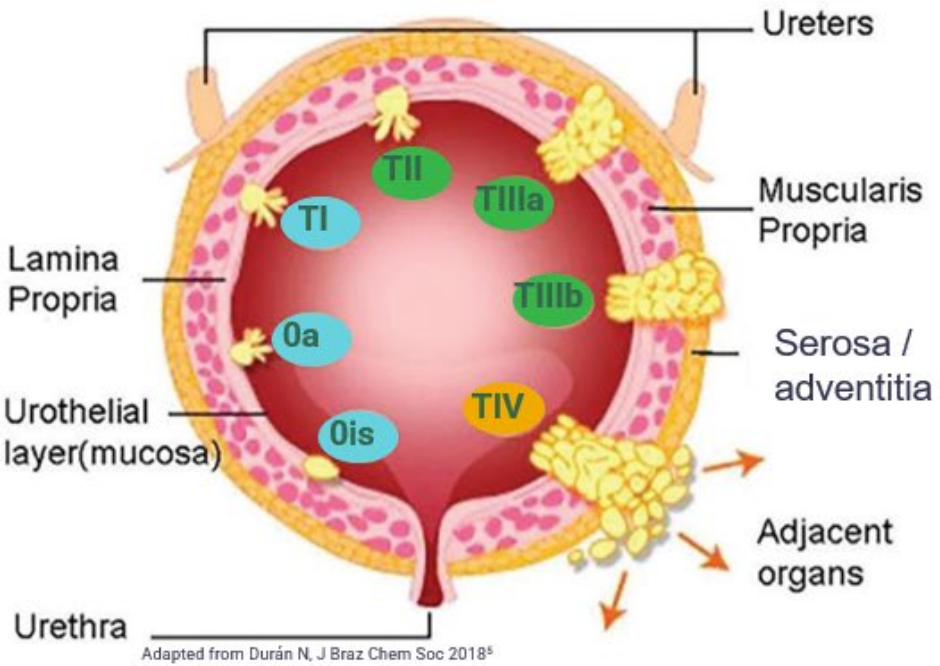
Urothelial Carcinoma: Staging

NMIBC

Stage 0is:
Carcinoma in situ

Stage 0a:
Non-invasive papillary carcinoma

Stage I:
Tumor invades subepithelial connective tissue



Adapted from Durán N, J Braz Chem Soc 2018[5]

MIBC

Stage II:
Tumor invades connective tissue and into the deep muscle layer

Stage IIIa:
Tumor invades perivesical tissue but not lymph nodes

Stage IIIb:
Tumor has spread to one of more lymph nodes

MBC

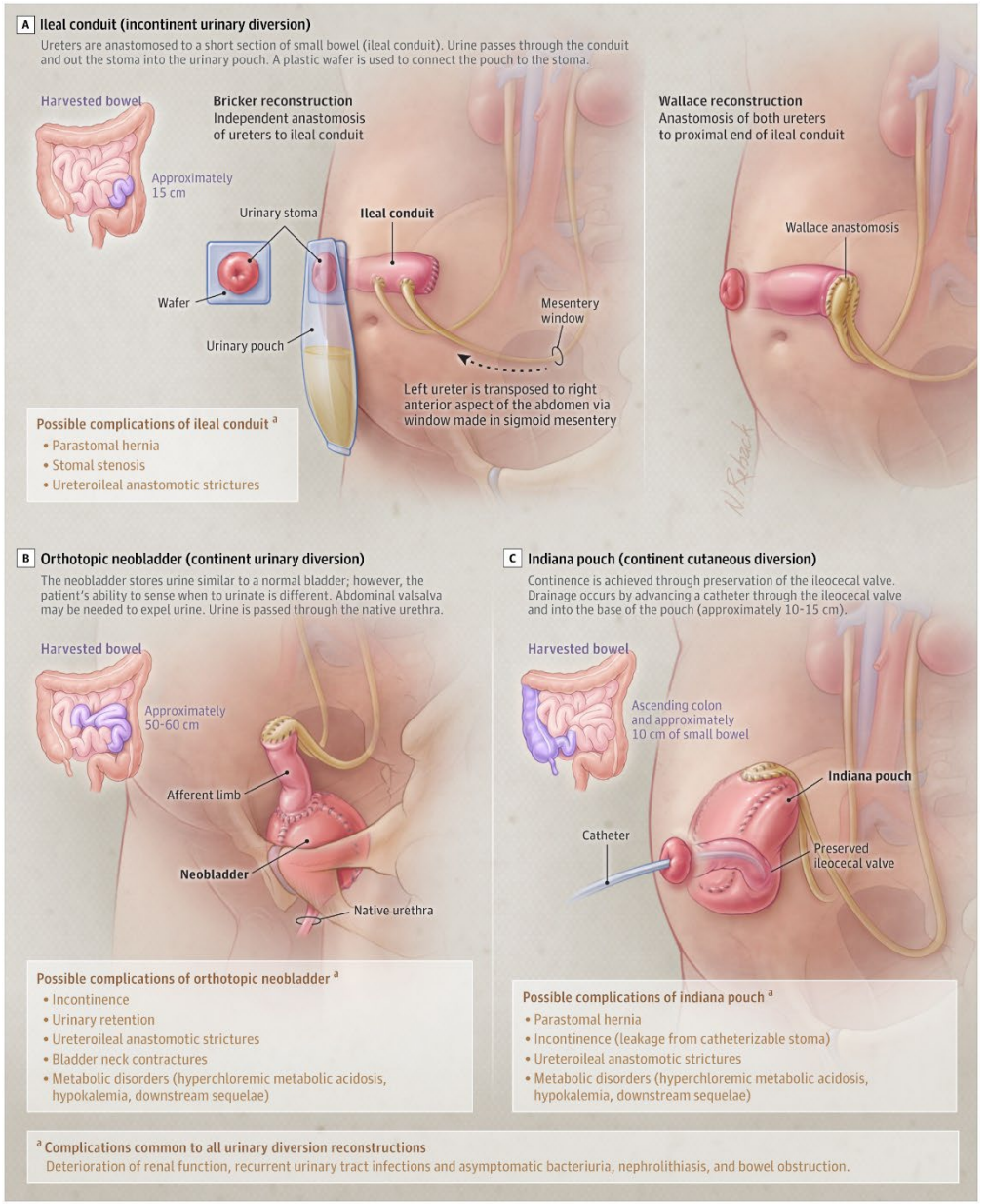
Stage IV:
Tumor invades adjacent tissues and organs

Table 2. **AJCC Prognostic Groups**

	T	N	M
Stage 0a	Ta	N0	M0
Stage 0is	CIS (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
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

Challenges in Care: UC

- Surgical
- Time
- Drug side-effects
- Cost of care
- QoL



Lenis AT, et al. *JAMA*. 2020;324(19):1980-1991.

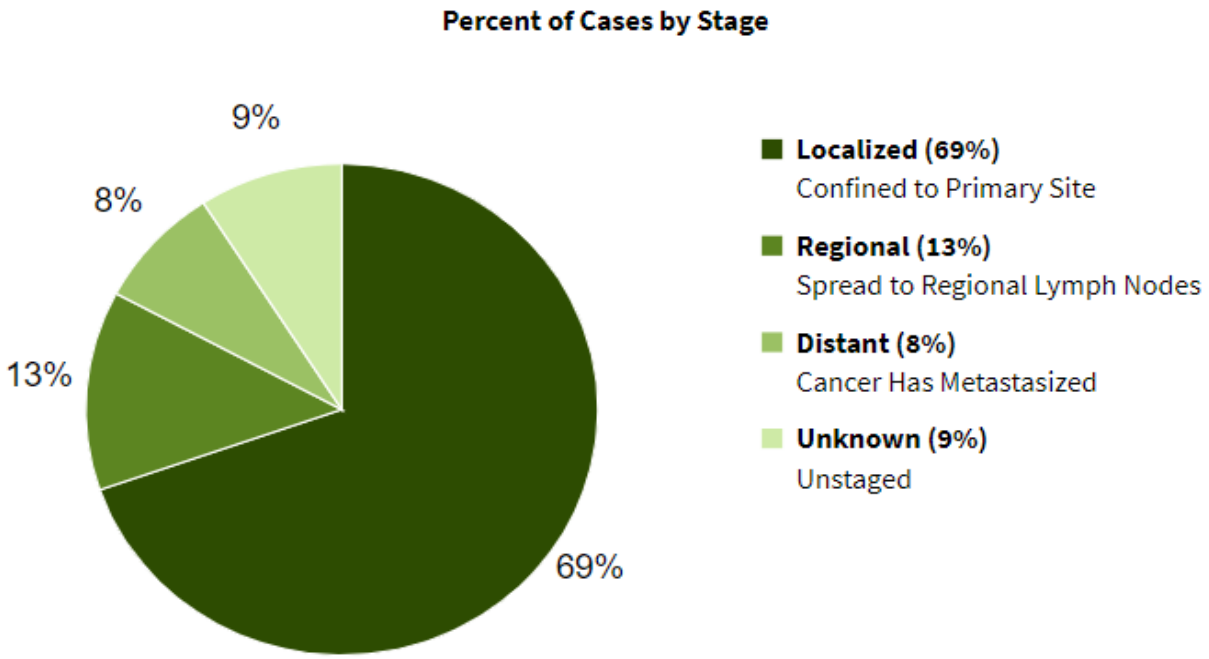
Epidemiology of Prostate Cancer

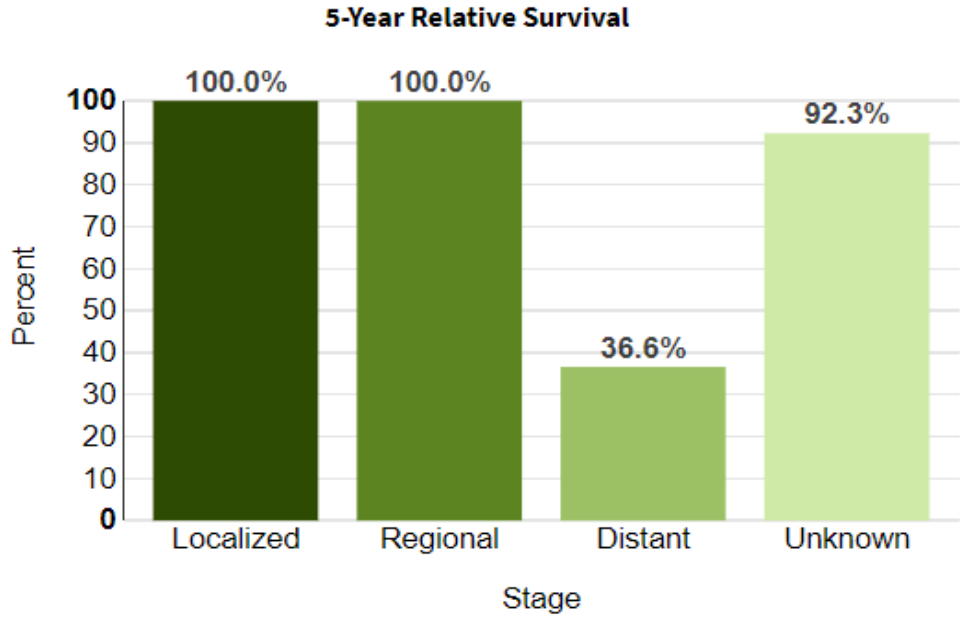
	Common Types of Cancer	Estimated New Cases 2024	Estimated Deaths 2024
1.	Breast Cancer (Female)	310,720	42,250
2.	**Prostate Cancer**	**299,010**	**35,250**
3.	Lung and Bronchus Cancer	234,580	125,070
4.	Colorectal Cancer	152,810	53,010
5.	Melanoma of the Skin	100,640	8,290
6.	Bladder Cancer	83,190	16,840
7.	Kidney and Renal Pelvis Cancer	81,610	14,390
8.	Non-Hodgkin Lymphoma	80,620	20,140
9.	Uterine Cancer	67,880	13,250
10.	Pancreatic Cancer	66,440	51,750

Prostate cancer represents 14.9% of all new cancer cases in the U.S.

NIH: National Cancer Institute – SEER. Accessed October 2025. https://seer.cancer.gov/statfacts/html/prost.html.

Epidemiology of Prostate Cancer





NIH: National Cancer Institute – SEER. Accessed October 2025. https://seer.cancer.gov/statfacts/html/prost.html.

Prostate Cancer: Staging

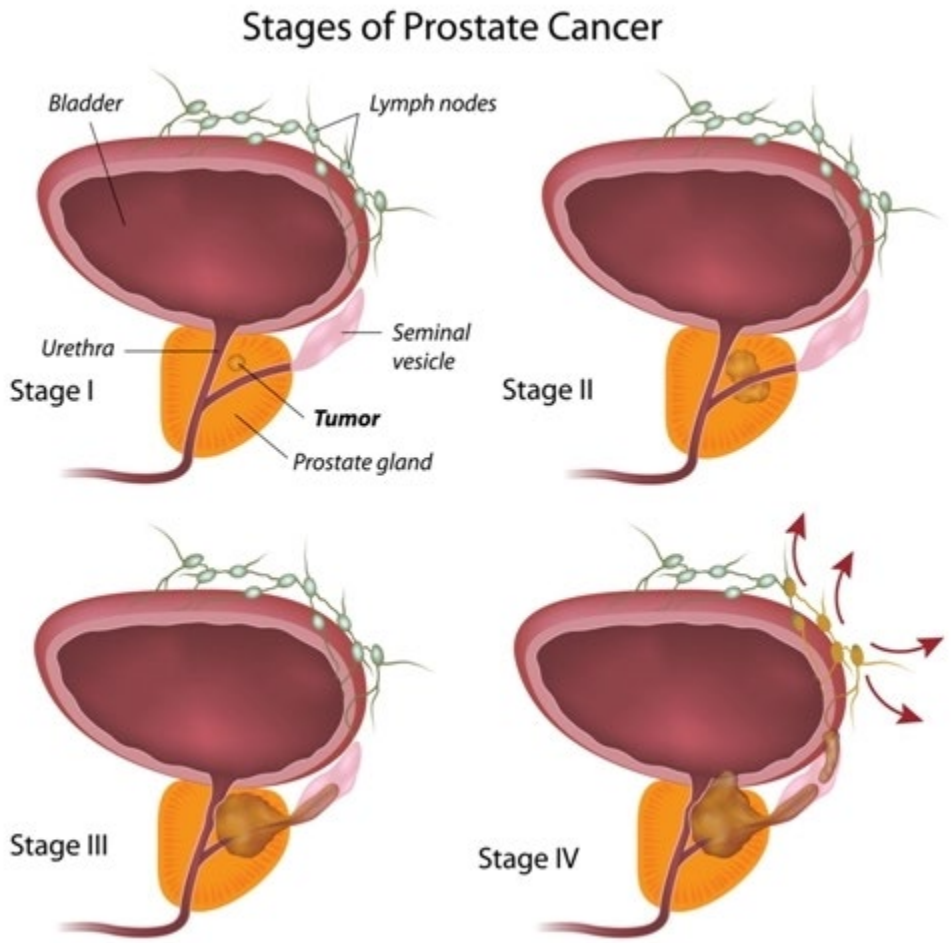


Table 2. **AJCC Prognostic Groups**

Group	T	N	M	PSA (ng/mL)	Grade Grou
Stage I	cT1a-c	N0	M0	PSA <10	1
	cT2a	N0	M0	PSA <10	1
	pT2	N0	M0	PSA <10	1
Stage IIA	cT1a-c	N0	M0	PSA ≥10 <20	1
	cT2a	N0	M0	PSA ≥10 <20	1
	pT2	N0	M0	PSA ≥10 <20	1
	cT2b	N0	M0	PSA <20	1
	cT2c	N0	M0	PSA <20	1
Stage IIB	T1-2	N0	M0	PSA <20	2
Stage IIC	T1-2	N0	M0	PSA <20	3
	T1-2	N0	M0	PSA <20	4
Stage IIIA	T1-2	N0	M0	PSA ≥20	1-4
Stage IIIB	T3-4	N0	M0	Any PSA	1-4
Stage IIIC	Any T	N0	M0	Any PSA	5
Stage IVA	Any T	N1	M0	Any PSA	Any
Stage IVB	Any T	Any N	M1	Any PSA	Any

Grade Group	Gleason Score	Gleason Pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

Prostate. In: Amin MB, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. Springer; 2017: 715-726.

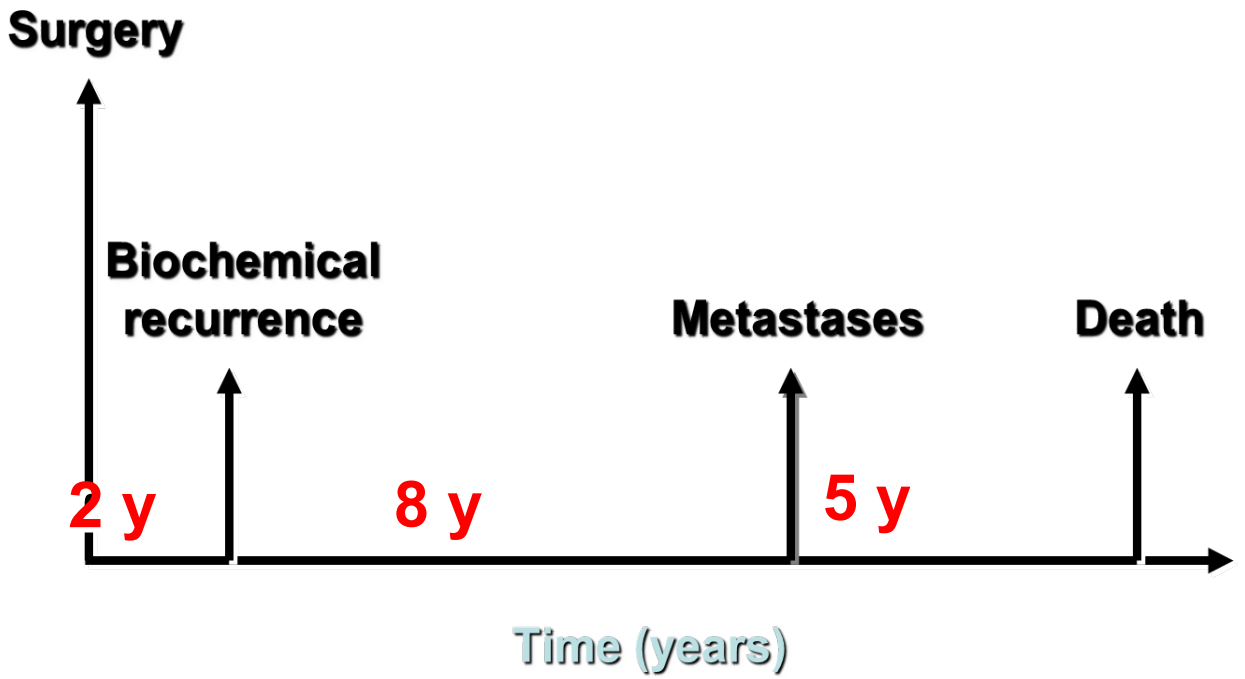
Prostate Cancer: Staging

National Comprehensive Cancer Network® (NCCN)

NCCN Guidelines® Version 2.2026
Prostate Cancer

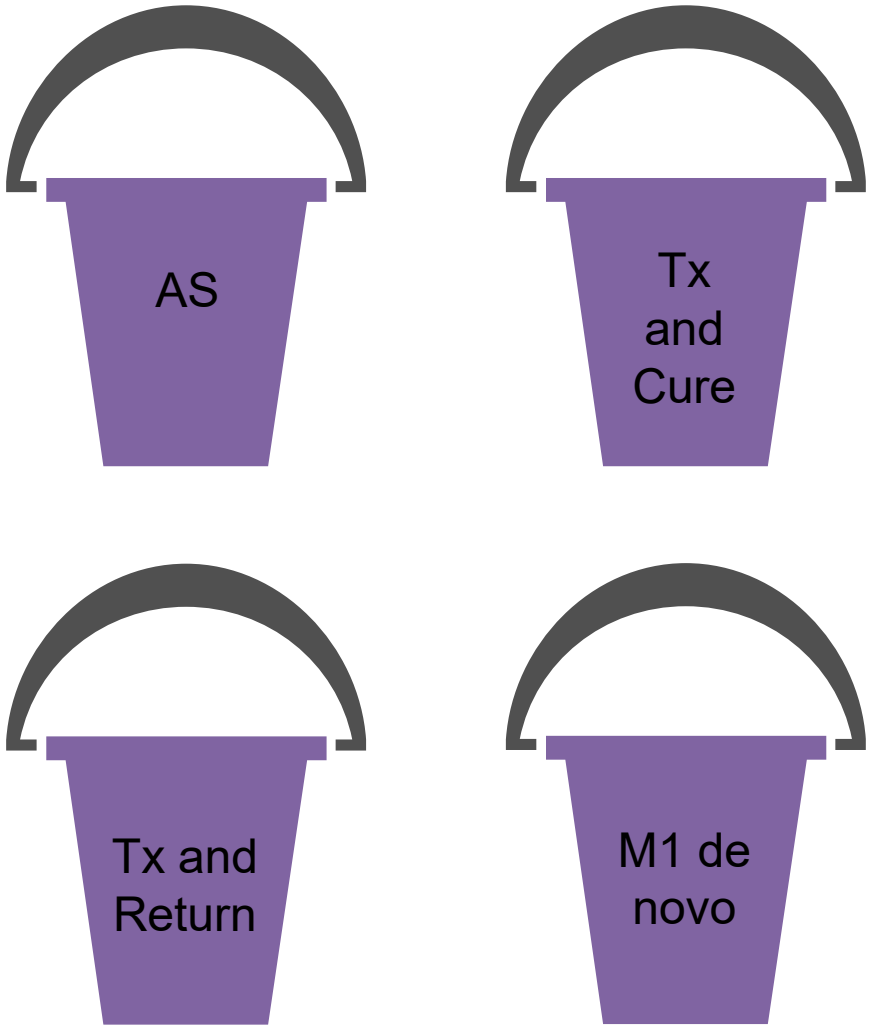
Initial Risk Stratification and Staging Workup for Clinically Localized Disease

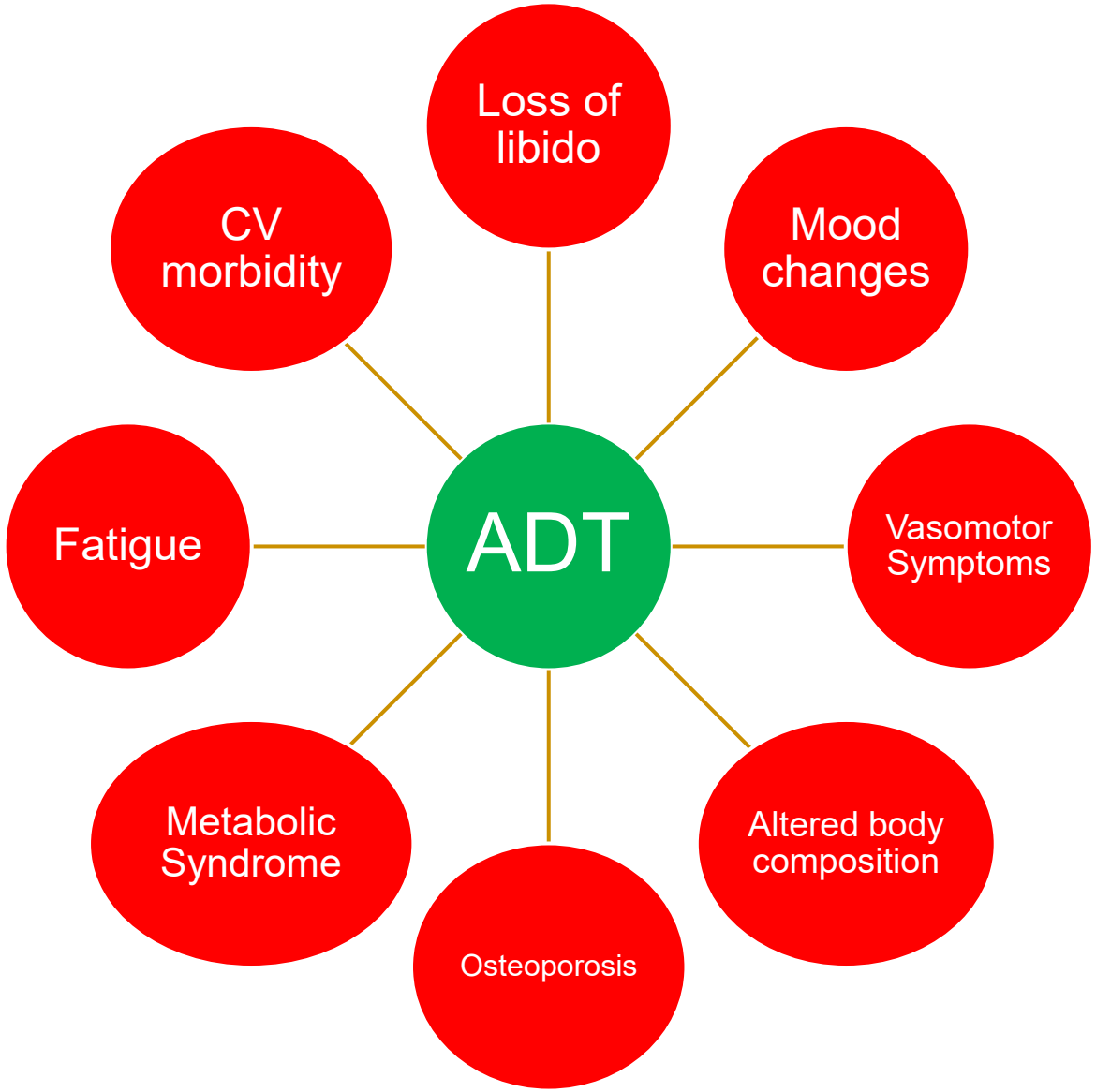
Risk Group	Clinical/Pathologic Features (Staging, ST-1)		
Low	Has all of the following: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL		
Intermediate	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ‣ cT2b–cT2c ‣ Grade Group 2 or 3 ‣ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥50% biopsy cores positive (eg, ≥6 of 12 cores)
High	Has one or more high-risk features, but does not meet criteria for very high risk: • cT3a–cT4 • Grade Group 4 or Grade Group 5 • PSA >20 ng/mL		
Very High	Has at least two of the following: • cT3–cT4 • Grade Group 4 or 5 • PSA >40 ng/mL		



N=304

Challenges in Care: PCa





NIH: National Cancer Institute – SEER. Accessed October 2025. https://seer.cancer.gov/statfacts/html/prost.html.

Urothelial Carcinoma: NMIBC

Urothelial Carcinoma: NMIBC

Risk group	
Low Risk	A primary, single, TaT1 LG/G1 tumour < 3 cm in diameter without CIS in a patient ≤ 70 years A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors
Intermediate Risk	Patients without CIS who are not included in either the low-, high-, or very high-risk groups
High Risk	All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group All CIS patients, EXCEPT those included in the very high-risk group
	Stage, grade with additional clinical risk factors: Ta LG/G2 or T1G1, no CIS with all 3 risk factors Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors T1G2 no CIS with at least 1 risk factor
Very High Risk	**Stage, grade with additional clinical risk factors:** Ta HG/G3 and CIS with all 3 risk factors T1G2 and CIS with at least 2 risk factors T1 HG/G3 and CIS with at least 1 risk factor T1 HG/G3 no CIS with all 3 risk factors

Risk Factors: Age >70, Multifocal and Recurrence
*All patients with variant histology are considered VH Risk

Risk group	Probability of Progression and 95% Confidence Interval (CI)		
	1 Year	5 Years	10 Years
New Risk Groups with WHO 2004/2016			
Low	0.06% (CI: 0.01%–0.43%)	0.93% (CI: 0.49%–1.7%)	3.7% (CI: 2.3%–5.9%)
Intermediate	1.0% (CI: 0.50%–2.0%)	4.9% (CI: 3.4%–7.0%)	8.5% (CI: 5.6%–13%)
High	3.5% (CI: 2.4%–5.2%)	9.6% (CI: 7.4%–12%)	14% (CI: 11%–18%)
Very High	16% (CI: 10%–26%)	40% (CI: 29%–54%)	53% (CI: 36%–73%)

American Urological Association

Pay Close Attention to

- ***Presence of LVI***
- ***Persistent T1 at TURBT***
- ***Variant Histology***

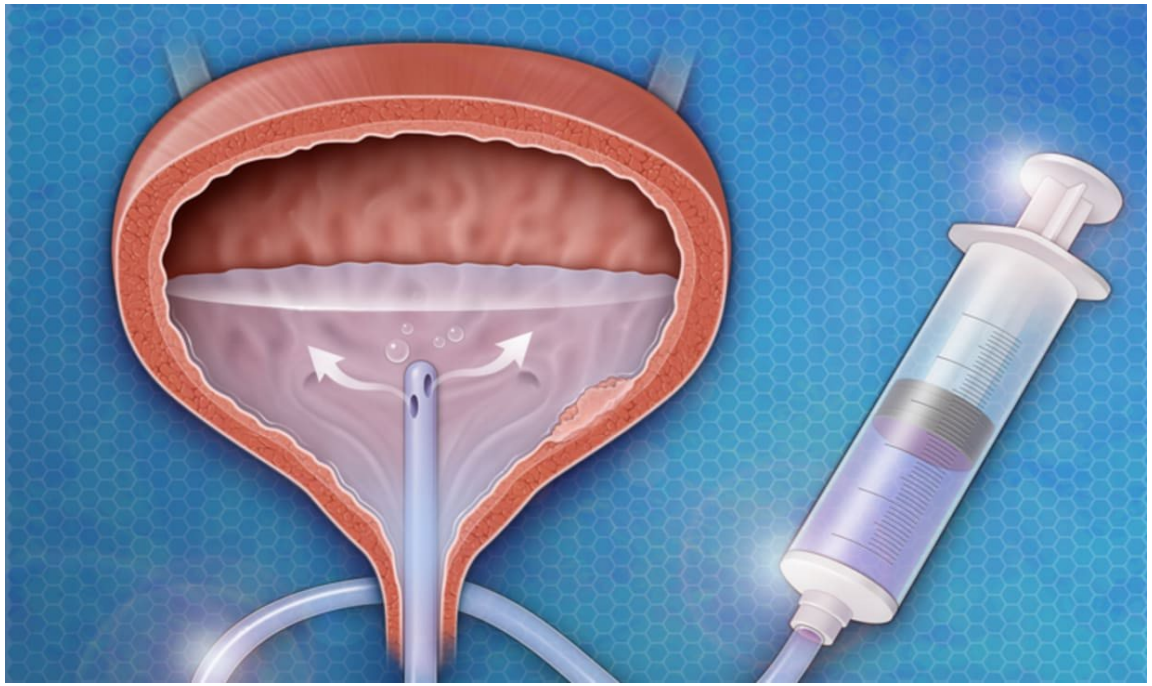
EAU. Guidelines. Accessed October 2025. https://uroweb.org/guidelines. AUA. Guidelines. Accessed October 2025. https://www.auanet.org/guidelines-and-quality/guidelines. Holzbeierlein JM, et al. *J Urol*. 2024;211(4):533-538.

Management of Low/Int-Risk Tumors

Low-Risk

- No need for adjuvant intravesical therapy
- Patients with low-risk NMIBC have a risk of recurrence of approximately 30%-40% at 5 years
- Post-TUR installation significantly decreases the odds of having a recurrence with an NNT ~ 8.5

Int-Risk

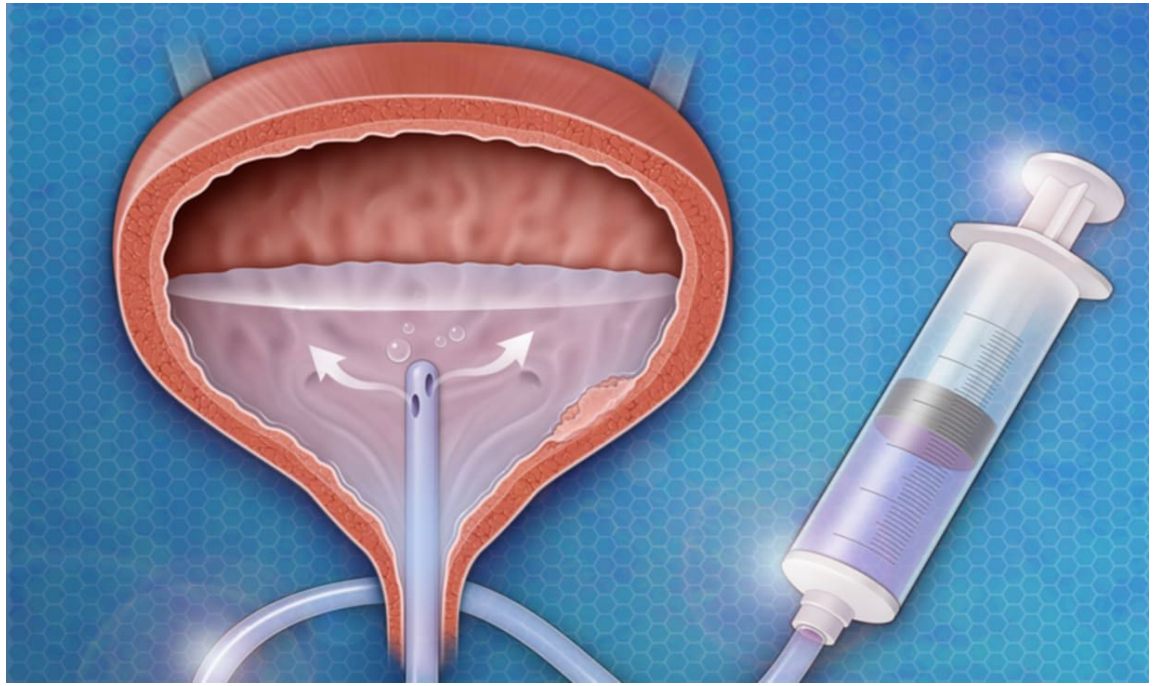


BCG Intravesical Therapy
Induction + Maintenance

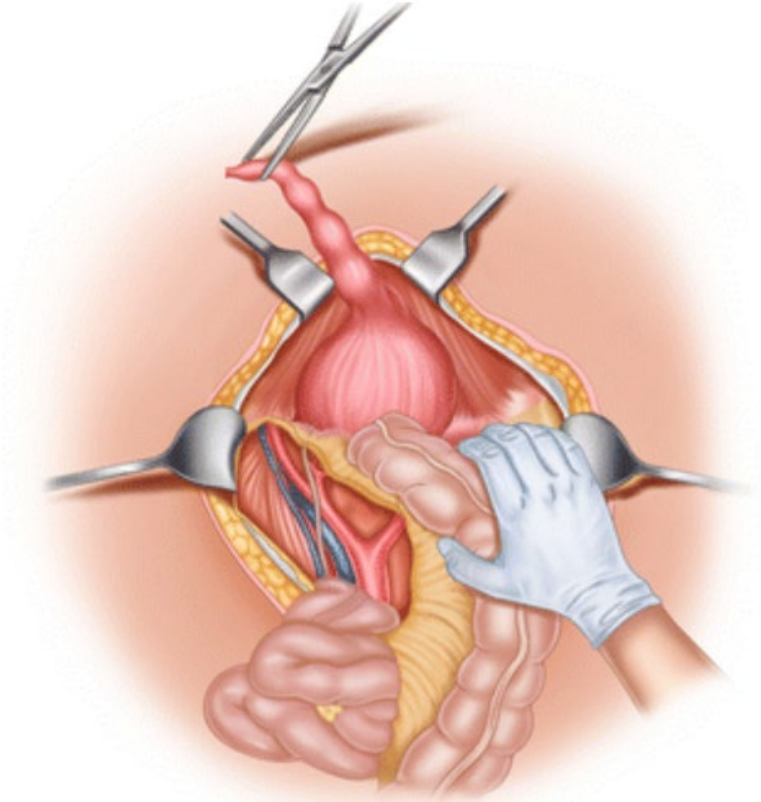
One FDA-Approved Strain:
TICE

EAU. Guidelines. Accessed October 2025. https://uroweb.org/guidelines. AUA. Guidelines. Accessed October 2025. https://www.auanet.org/guidelines-and-quality/guidelines. Holzbeierlein JM, et al. *J Urol*. 2024;211(4):533-538.

BCG naïve HR-NMIBCA



BCG Intravesical Therapy
Induction + Maintenance



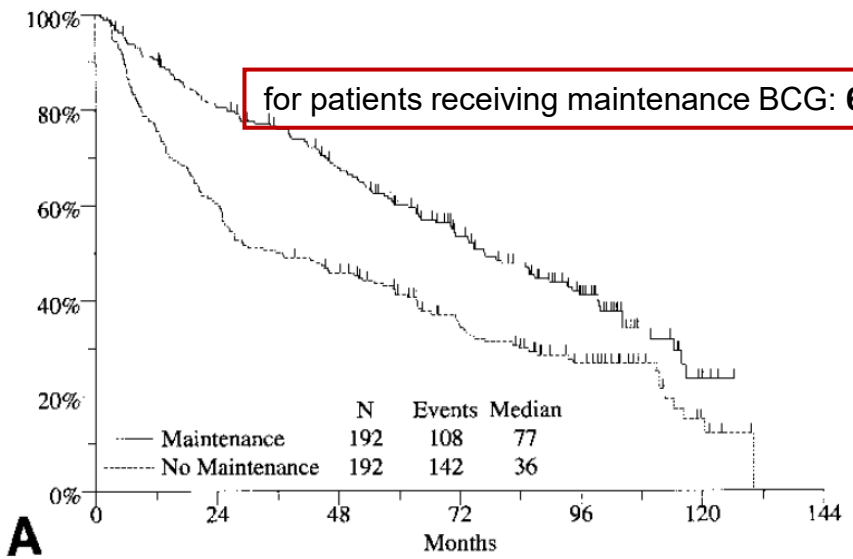
Early Cystectomy
High Volume/Persistent T1, LVI, Variant Histology

Adapted from Andres Correa.

Efficacy of BCG Intravesical Therapy in HR- NMIBCA

MAINTENANCE BACILLUS CALMETTE-GUERIN IMMUNOTHERAPY FOR RECURRENT TA, T1 AND CARCINOMA IN SITU TRANSITIONAL CELL CARCINOMA OF THE BLADDER: A RANDOMIZED SOUTHWEST ONCOLOGY GROUP STUDY

DONALD L. LAMM,*,† BRENT A. BLUMENSTEIN, JOHN D. CRISSMAN, JAMES E. MONTIE, JAMES E. GOTTESMAN, BRUCE A. LOWE, MICHAEL F. SAROSDY,‡ ROBERT D. BOHL, H. BARTON GROSSMAN,§ THOMAS M. BECK, JOSEPH T. LEIMERT AND E. DAVID CRAWFORD‖



for patients receiving maintenance BCG: **60% 5-yr RFS***

Induction (6 weekly) + Maintenance (3 weekly)

** Maintenance – 3, 6, 12, 18, 24, 30, 36 months*

Lamm DL, et al. *J Urol*. 2000;163(4):1124-1129.

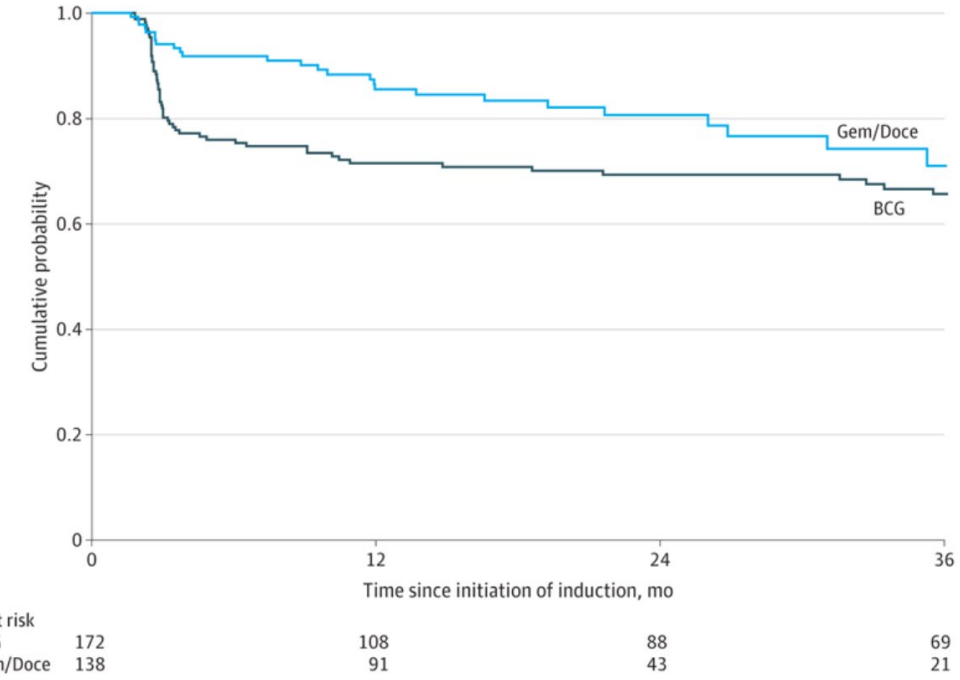
BCG-naïve HR-NMIBCA – BRIDGE Trial

Original Investigation | Urology

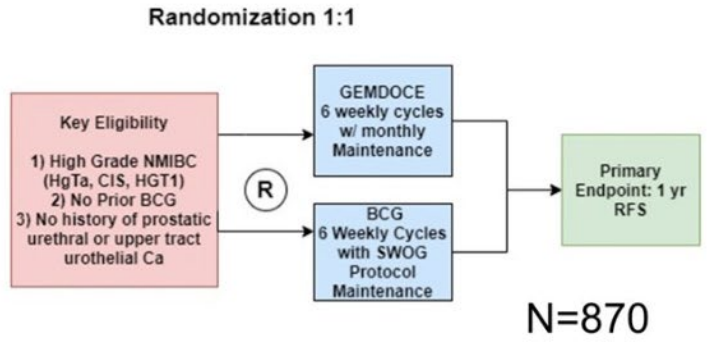
Comparison of Sequential Intravesical Gemcitabine and Docetaxel vs Bacillus Calmette-Guérin for the Treatment of Patients With High-Risk Non-Muscle-Invasive Bladder Cancer

Ian M. McElree, MS[1]; Ryan L. Steinberg, MD[2]; Sarah L. Mott, MS[3] ; et al

Figure. High-grade Recurrence-Free Survival by Treatment Group



EA8212 (BRIDGE)



McElree IM, et al. *JAMA Netw Open*. 2023;6(2):e230849.

BCG Unresponsive Approved Agents

Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study

Arjun V Balar, Ashish M Kamat, Girish S Kulkarni, Edward M Uchio, Joost L Boormans, Mathieu Roumiguié, Laurence E M Krieger, Eric A Singer, Dean F Bajorin, Petros Grivas, Ho Kyung Seo, Hiroyuki Nishiyama, Badrinath R Konety, Haojie Li, Kijoeng Nam, Ekta Kapadia, Tara Frenkl, Ronald de Wit

Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial

Stephen A Boorjian, Mehrdad Alemozaffar, Badrinath R Konety, Neal D Shore, Leonard G Gomella, Ashish M Kamat, Trinity J Bivalacqua, Jeffrey S Montgomery, Seth P Lerner, Joseph E Busby, Michael Poch, Paul L Crispen, Gary D Steinberg, Anne K Schuckman, Tracy M Downs, Robert S Svatek, Joseph Mashni Jr, Brian R Lane, Thomas J Guzzo, Gennady Bratslavsky, Lawrence I Karsh, Michael E Woods, Gordon Brown, Daniel Canter, Adam Luchey, Yair Lotan, Tracey Krupski, Brant A Inman, Michael B Williams, Michael S Cookson, Kirk A Keegan, Gerald L Andriole Jr, Alexander I Sankin, Alan Boyd, Michael A O'Donnell, David Sawutz, Richard Philipson, Ruth Coll, Vikram M Narayan, F Peter Treasure, Seppo Yla-Herttuala, Nigel R Parker, Colin P N Dinney

IL-15 Superagonist NAI in BCG-Unresponsive Non–Muscle-Invasive Bladder Cancer

Karim Chamie, M.D.,[1] Sam S. Chang, M.D.,[2] Eugene Kramolowsky, M.D.,[3] Mark L. Gonzalgo, M.D.,[4] Piyush Kumar Agarwal, M.D.,[5] Jeffrey C. Bassett, M.D.,[6] Marc Bjurlin, M.D.,[7] Michael L. Cher, M.D.,[8,9] William Clark, M.D.,[10] Barrett E. Cowan, M.D.,[11] Richard David, M.D.,[12] Evan Goldfischer, M.D.,[13] Khurshid Guru, M.D.,[14] Mark W. Jalkut, M.D.,[15] Samuel D. Kaffenberger, M.D.,[16] Jed Kaminetsky, M.D.,[17] Aaron E. Katz, M.D.,[18] Alec S. Koo, M.D.,[19] Wade J. Sexton, M.D.,[20] Sergei N. Tikhonenkov, M.D.,[21] Edouard J. Trabulsi, M.D.,[22] Andrew F. Trainer, M.D.,[23] Patricia Spilman, M.A.,[24] Megan Huang, Ph.D.,[24] Paul Bhar, M.S.,[24] Sharif A. Taha, Ph.D.,[24] Lennie Sender, M.D.,[24] Sandeep Reddy, M.D.,[24] and Patrick Soon-Shiong, M.D.[24]

TAR-200 for Bacillus Calmette-Guérin–Unresponsive High-Risk Non–Muscle-Invasive Bladder Cancer: Results From the Phase IIb SunRISe-1 Study

Siamak Daneshmand, MD[1]; Michiel S. Van der Heijden, MD, PhD[2]; Joseph M. Jacob, MD[3]; Felix Guerrero-Ramos, MD, PhD[4]; Martin Bögemann, MD[5,6]; Giuseppe Simone, MD, PhD[7]; Christopher M. Pieczonka, MD[8]; Nelson Canales Casco, MD[9]; Daniel Zainfeld, MD[10]; Philipp Spiegelhalder, MD[11]; Evanguelos Xylinas, MD[12]; David Cahn, MD[13]; Yair Lotan, MD[14]; Katie S. Murray, DO[15]; Takashi Kawahara, MD[16]; Katharine Stromberg, PhD[17]; Jason Martin, PhD[18]; Abhijit Shukla, PhD[19]; Christopher J. Cutie, MD[19]; Kristi Bertzos, PhD[20], Shalaka Hampras, PhD, MPH, MBBS[17]; Hussein Sweiti, MD[21]; and Andrea Necchi, MD[22,23]

Balar AV, et al. *Lancet Oncol*. 2021;22(7):919-930. Chamie K, et al. *NEJM Evid*. 2023;2(1):EVIDoa2200167. Boorjian SA, et al. *Lancet Oncol*. 2021;22(1):107-117. Daneshmand S, et al. *J Clin Oncol*. 2025:JCO2501651.

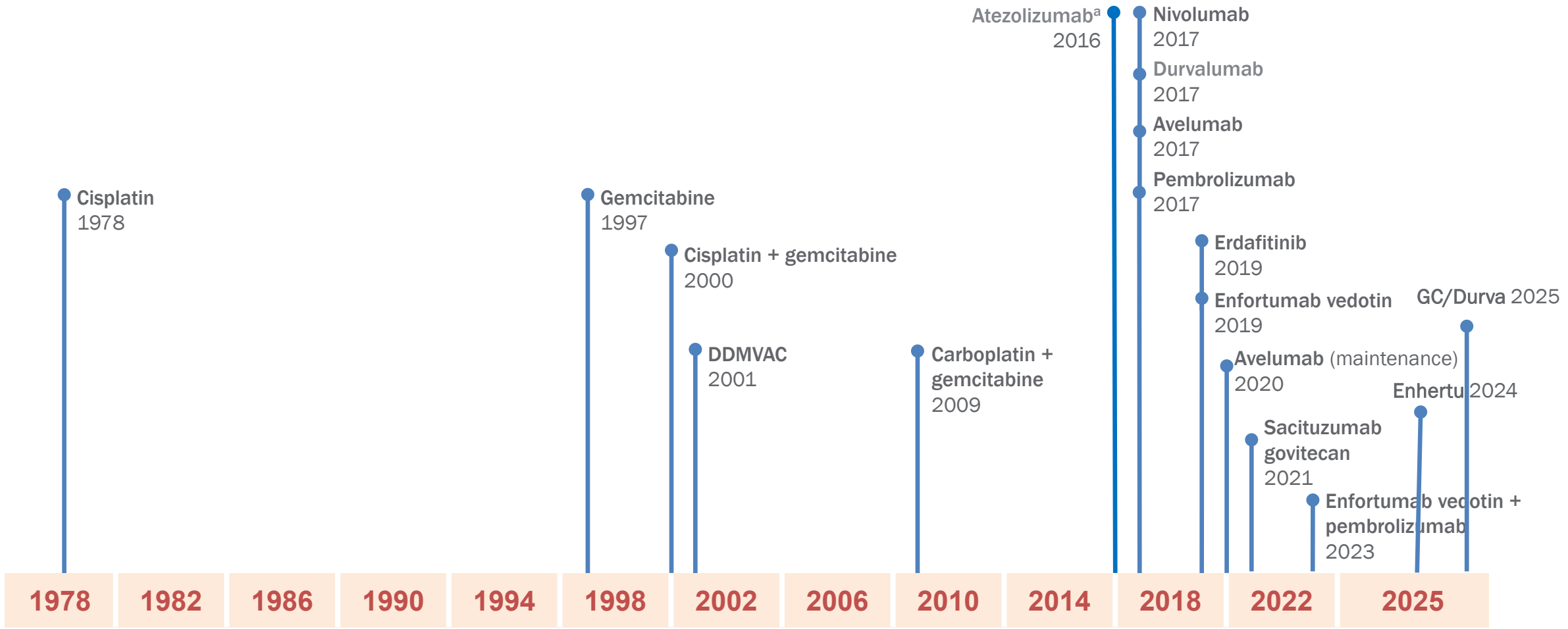
BCG Unresponsive Approved Agents

	Ferring Nadofaragene	ImmunityBio Anktiva	Janssen TAR-200	Merck Pembrolizumab
MOA	Gene therapy IFNα2b	*Combination of IL-15 superagonist + BCG*	Local delivery gemcitabine via "pretzel"	Immunotherapy PD-1 inhibitor
Stage	FDA-approved 2022	*FDA April 2024*	FDA – Approved Sept 2025	FDA-approved 2020
Trial	Phase 3	*QUILT 3.032*	SunRISe-1	KEYNOTE-057
N	103	*82*	90	96
Age (median: yrs)	72	*73*	71	73
Male	89%	*87%*	77%	84%
CR rate at 12 months	24%	45%	46.9%	19%
CR rate at 24 months	19% (14% @ 36M)	*33% (18 M)*	NR	NR
Overall Survival	80% (5-years)	*94.3% (2-years)*	94.7% (1-year)	*91% (3-years)*
Safety	4% G3+ TRAE	*20% G3 TEAE* *2% G4 TEAE* *1% G5 TEAE*	7.4% G3+ TRAE	13% G3+ TRAE

Balar AV, et al. *Lancet Oncol*. 2021;22(7):919-930. Chamie K, et al. *NEJM Evid*. 2023;2(1):EVIDoa2200167. Boorjian SA, et al. *Lancet Oncol*. 2021;22(1):107-117. Daneshmand S, et al. *J Clin Oncol*. 2025:JCO2501651.

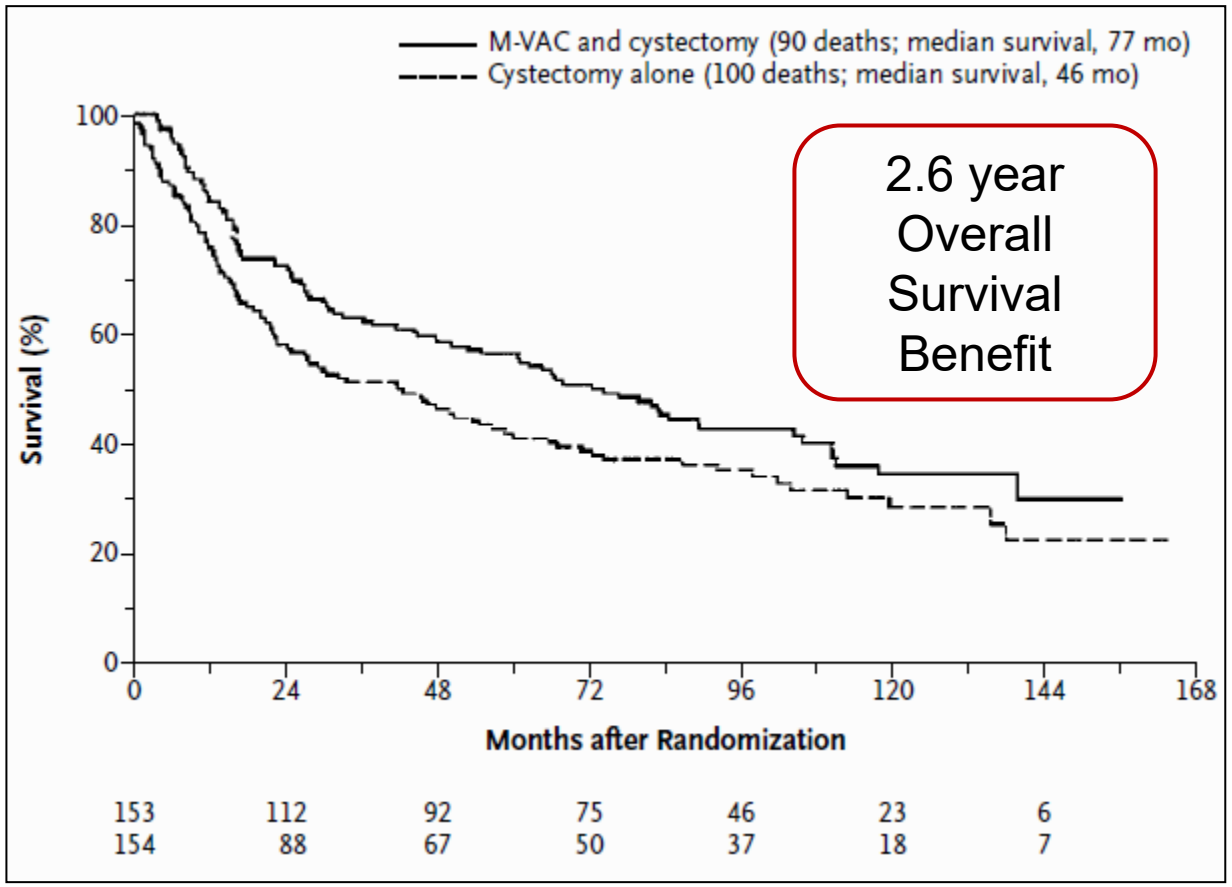
Urothelial Carcinoma: MIBC

Treatment Landscape for MIBC/mUC



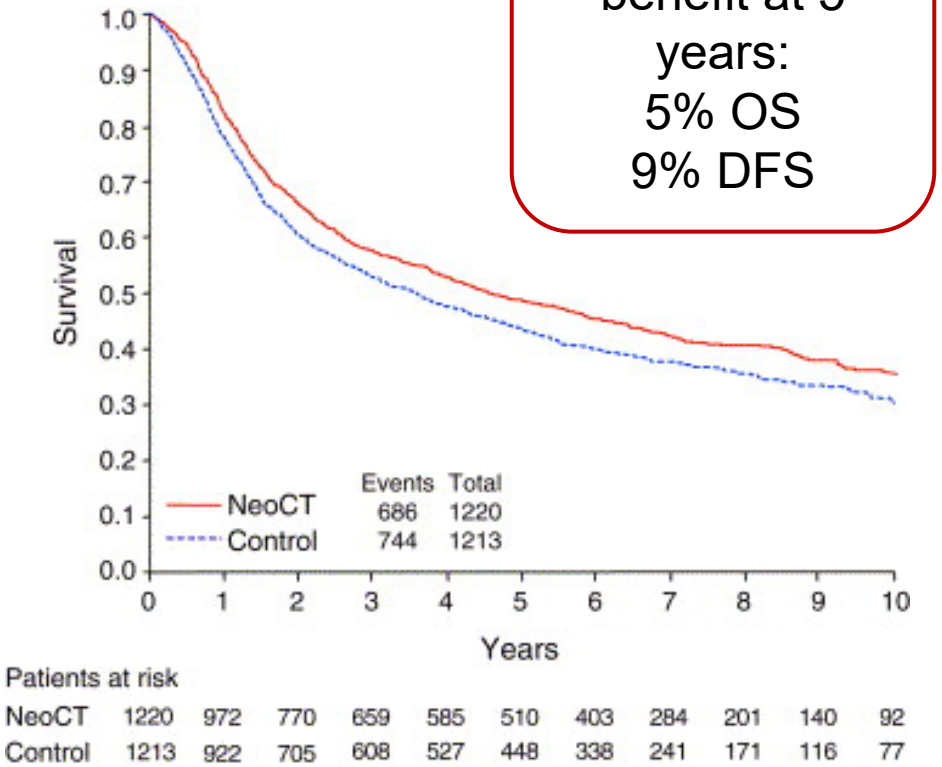
Urothelial Carcinoma: Neoadjuvant Cisplatin Chemotherapy

SWOG-8710: 3 cycles standard MVAC → Cystectomy vs. Cystectomy alone



2.6 year Overall Survival Benefit

Absolute benefit at 5 years:
5% OS
9% DFS

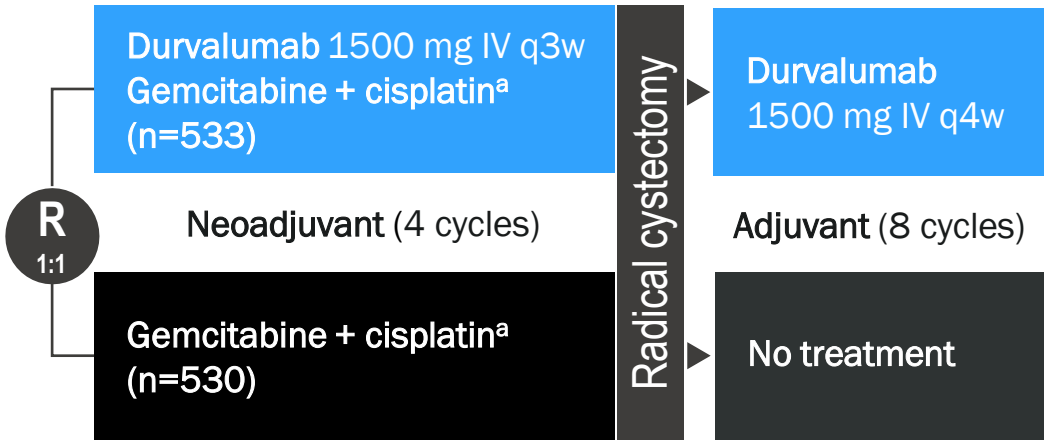


Grossman HB, et al. *N Engl J Med*. 2003;349(9):859-866. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. *Eur Urol*. 2005;48(2):202-205; discussion 205-206.

Urothelial Carcinoma: MIBC; NIAGARA

Study population

- Cisplatin-eligible MIBC (cT2–T4aN0/1M0)
- UC or UC with divergent differentiation or histologic subtypes
- Evaluated and confirmed for RC
- CrCl ≥40 mL/min



Stratification factors

- Clinical tumor stage (T2N0 vs >T2N0)
- Renal function (CrCl ≥60 mL/min vs ≥40 to <60 mL/min)
- PD-L1 status (high vs low/negative expression)

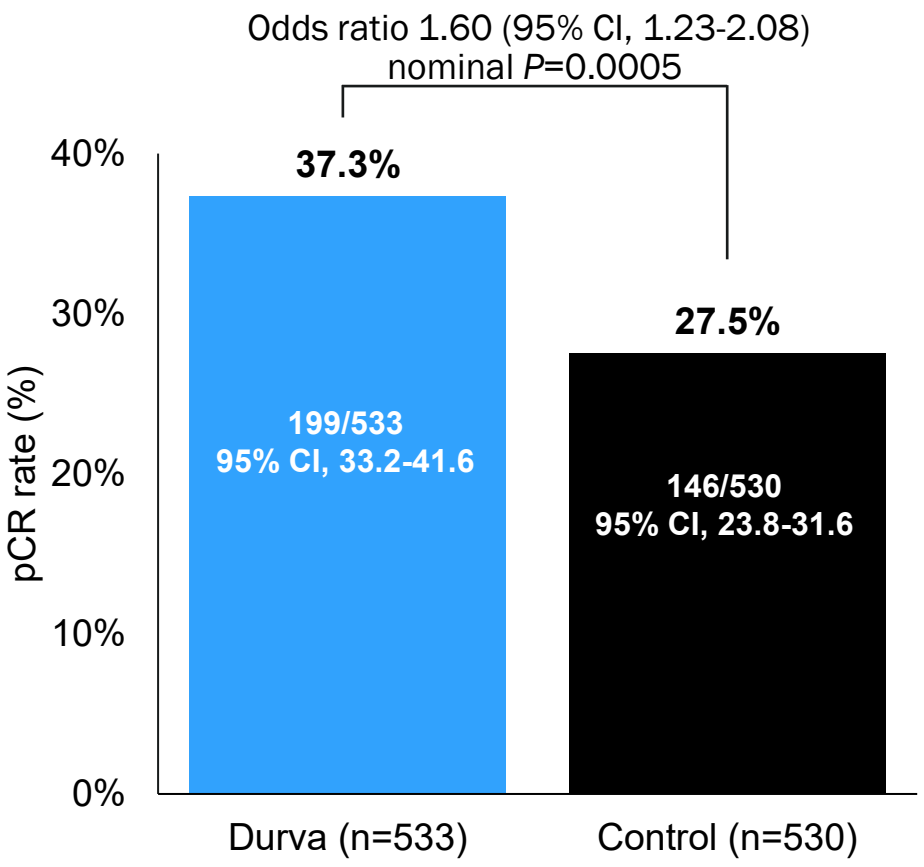
Dual primary endpoints	Key secondary endpoints
EFS and pCR	OS and safety

Characteristics, %		Durva (n=533)	Control (n=530)
Median age (range), years		65 (34-84)	66 (32-83)
Male		82	82
Race	White	66	68
	Asian	29	27
ECOG PS	0/1	78/22	78/22
Current or former smoker		71	75
Renal function	CrCl ≥60 mL/min	81	81
	CrCl ≥40 to <60 mL/min	19	19
Tumor stage	T2N0/>T2N0	40/60	40/60
PD-L1 expression	High	73	73
	Low/negative	27	27
Histology	UC	86	83
	Divergent differentiation	14	17
Regional lymph nodes	N0/N1	95/5	94/6

Powles T, et al. *N Engl J Med*. 2024;391(19):1773-1786.

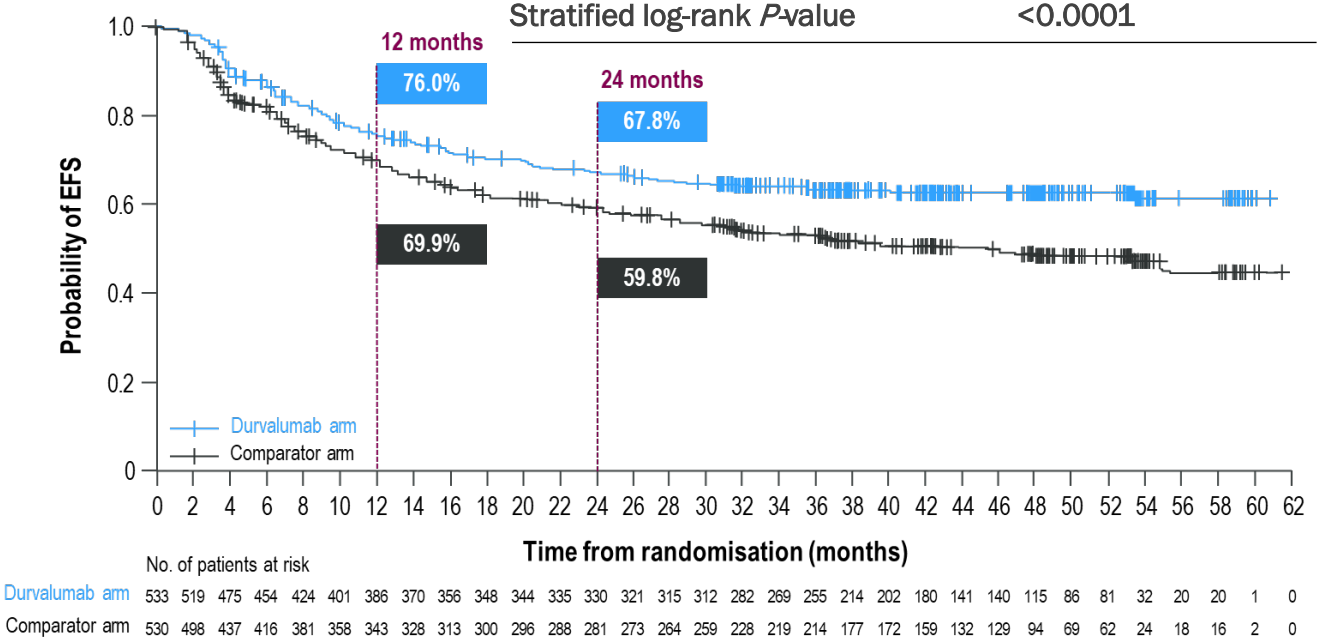
Urothelial Carcinoma: NIAGARA, EFS

pCR (ITT)



EFS by BICR (ITT)

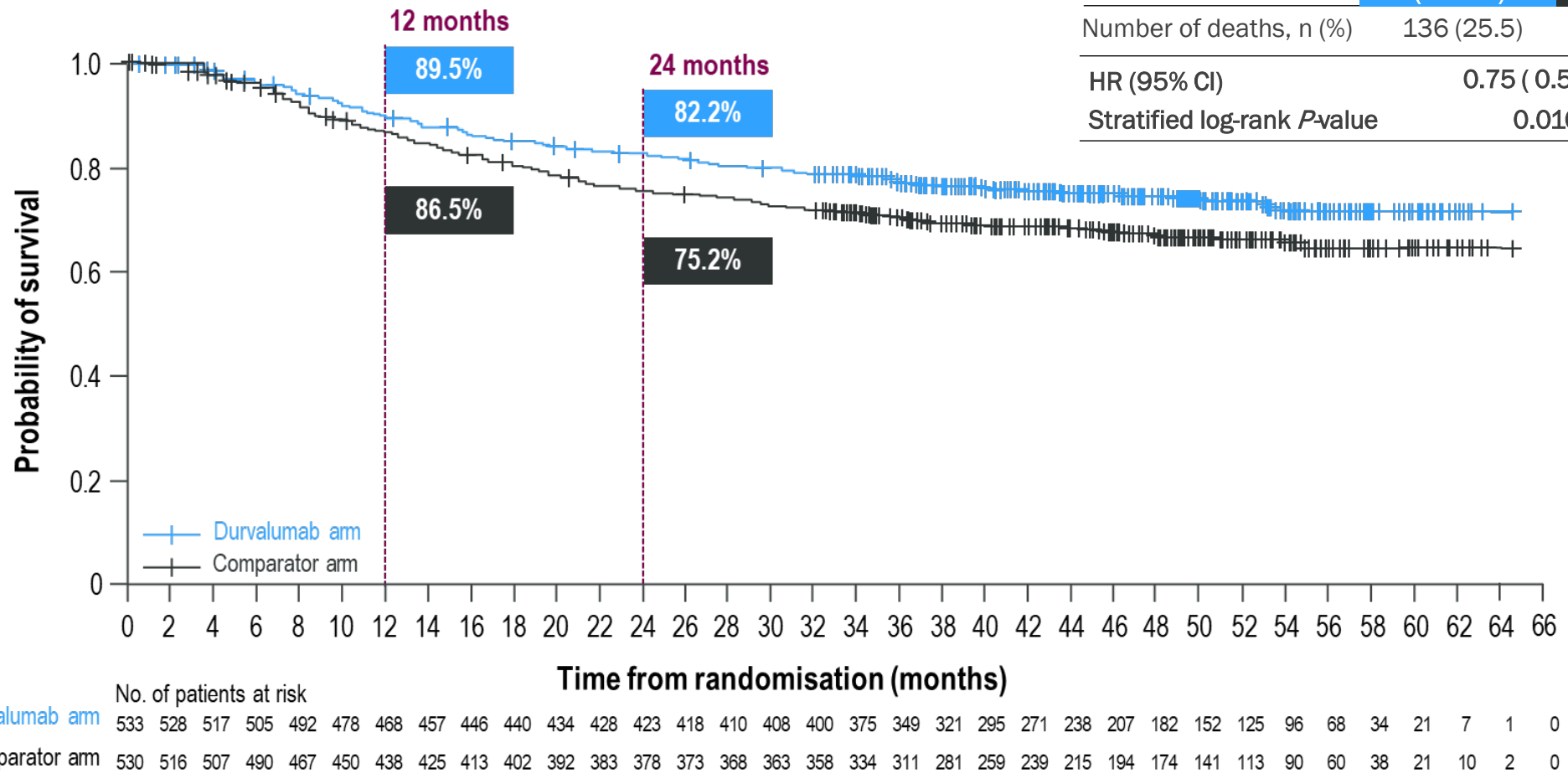
	Durva (n=533)	Control (n=530)
Number of events, n (%)	187 (35.1)	246 (46.4)
Median EFS, mo (95% CI)	NR (NR-NR)	46.1 (32.2-NR)
HR (95% CI)	0.68 (0.56-0.82)	
Stratified log-rank *P*-value	<0.0001	



Powles T, et al. *N Engl J Med*. 2024;391(19):1773-1786.

Urothelial Carcinoma: NIAGARA, OS

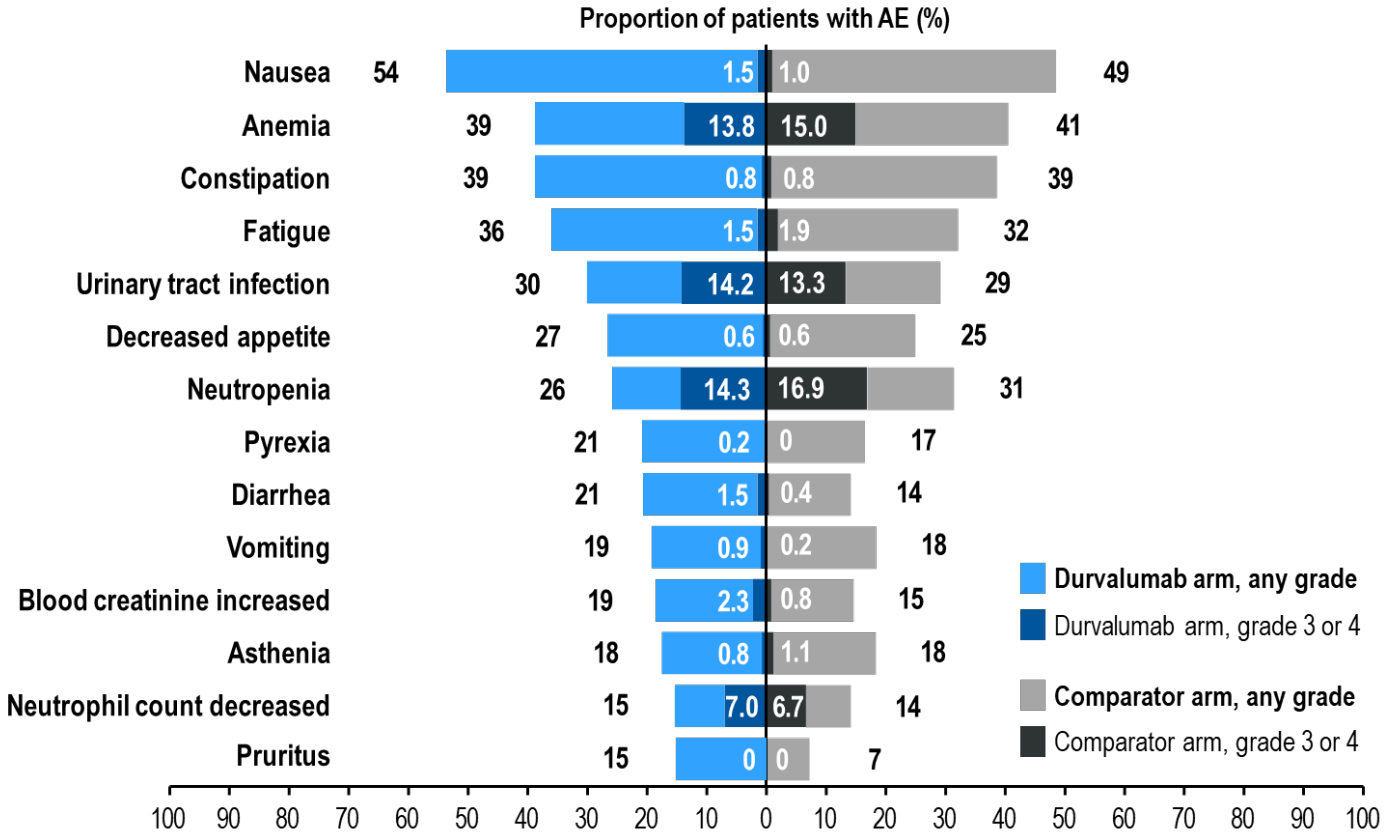
	Durva (n=533)	Control (n=530)
Number of deaths, n (%)	136 (25.5)	169 (31.9)
HR (95% CI)	0.75 (0.59-0.93)	
Stratified log-rank *P*-value	0.0106	



Powles T, et al. *N Engl J Med*. 2024;391(19):1773-1786.

Urothelial Carcinoma: NIAGARA

All Cause AEs Reported for ≥15% of Patients From Either Arm in the Overall Study Period



AEs in Overall Study Period, n (%)	Durva (n=530)	Control (n=536)
TRAE	502 (95)	487 (93)
Grade 3 or 4	215 (41)	215 (41)
Death	3 (0.6)	3 (0.6)
Any grade imAE	111 (21)	16 (3)
AE of any cause leading to:		
Discontinuation of study treatment	112 (21)	80 (15)
Discontinuation of neoadjuvant Durva	50 (9)	-
Discontinuation of NAC	72 (14)	80 (15)
Patient not undergoing RC	6 (1)	7 (1)
Delay in surgery	9 (2)	6 (1)
Discontinuation of adjuvant Durva	30/383 (8)	-

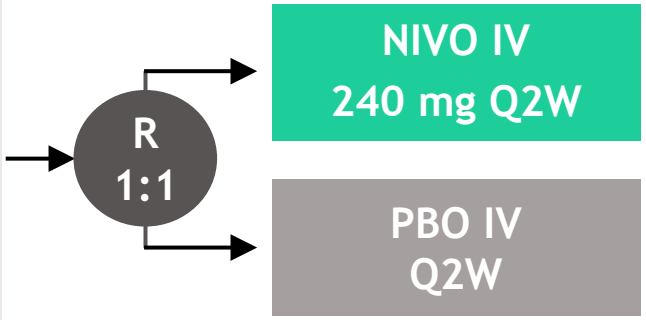
Powles T, et al. *N Engl J Med*. 2024;391(19):1773-1786.

Urothelial Carcinoma: MIBC Adjuvant

- Patients with ypT2-ypT4a or ypN+ MIUC who had NAC chemotherapy

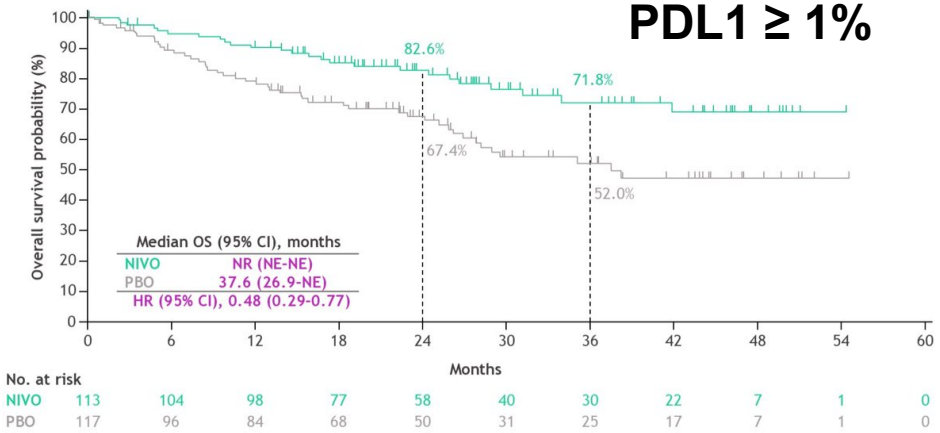
N=284

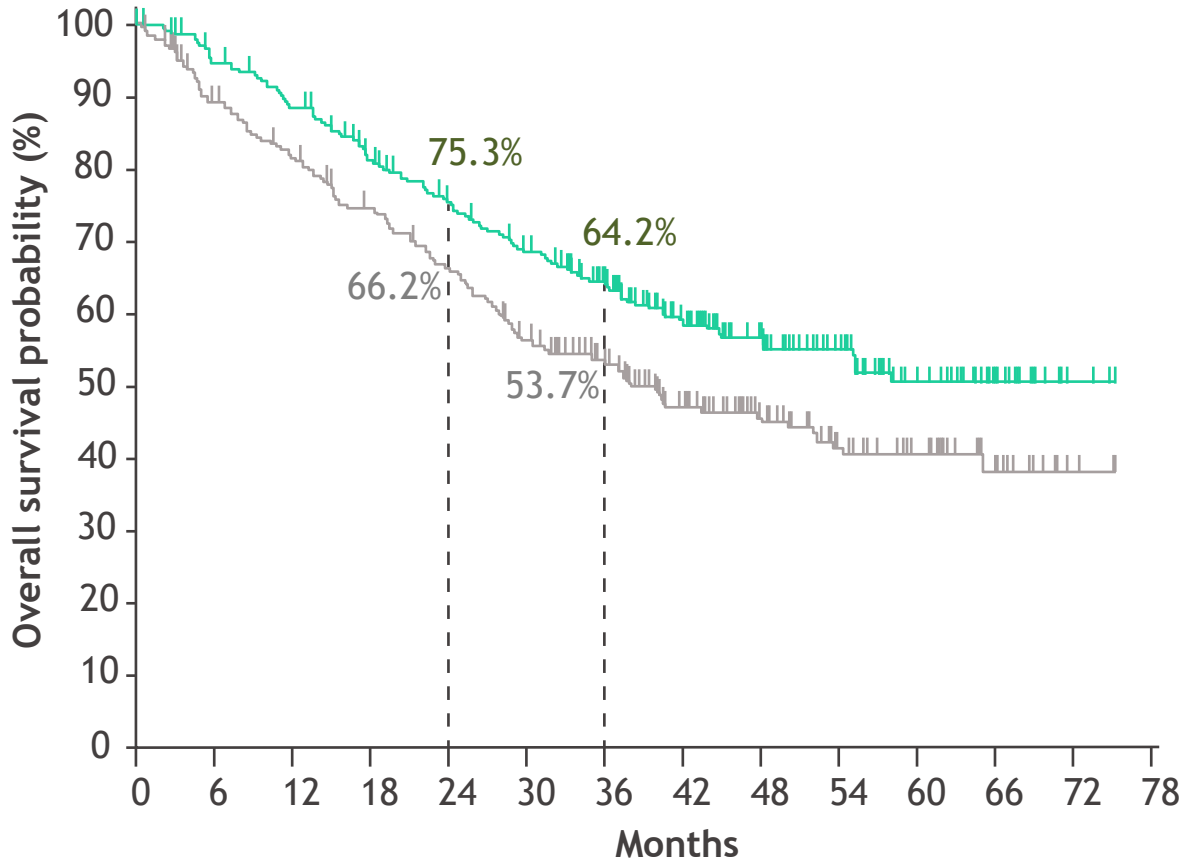
- Patients with pT3-pT4a or pN+ MIUC without prior NAC chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy



N=276

PDL1 ≥ 1%



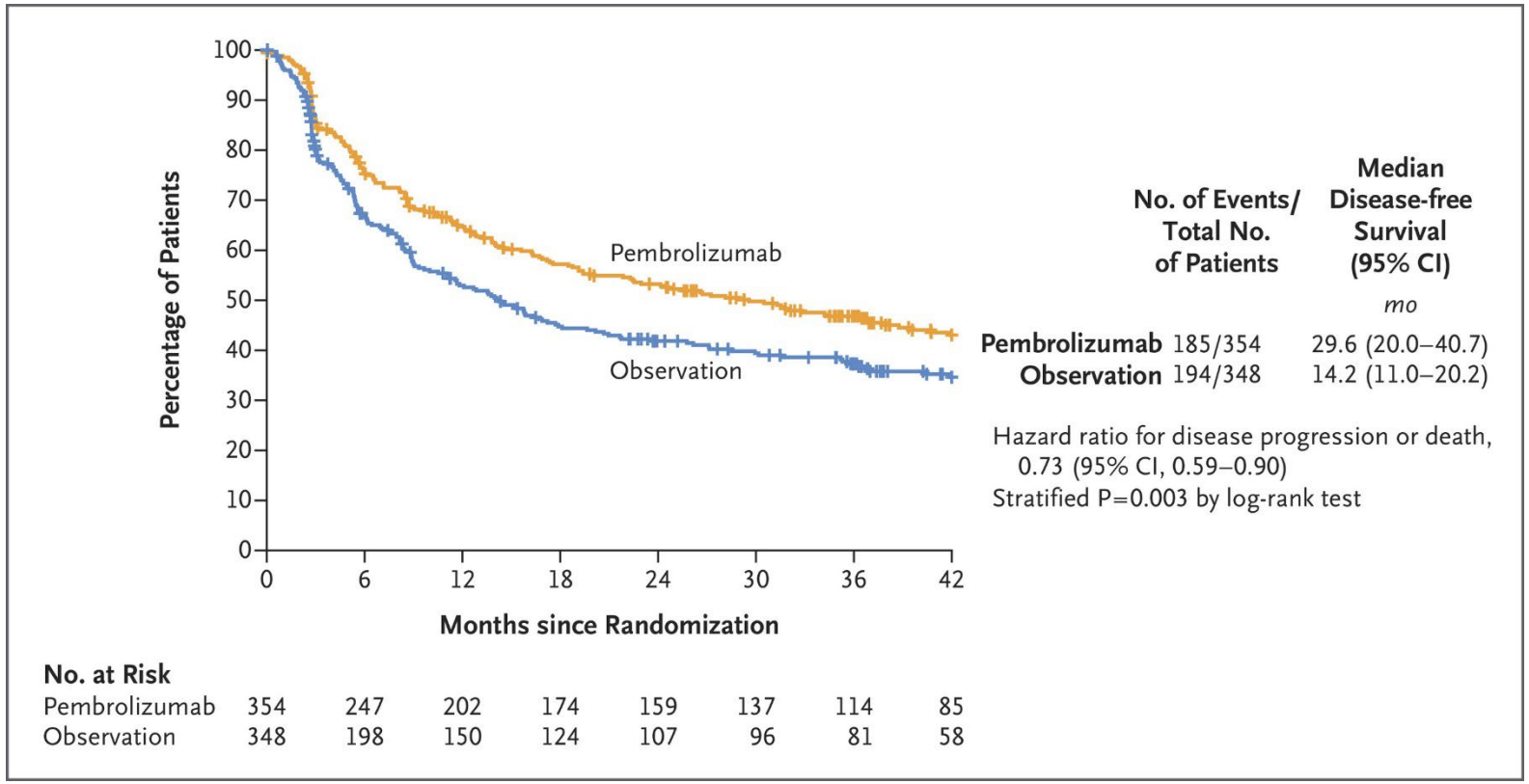


No. at risk

NIVO	279	258	239	213	193	172	145	107	81	56	34	20	3	0
PBO	281	240	218	195	172	143	119	89	65	43	31	17	6	0

Milowsky MI, et al. Oral abstract presented at: 2025 ASCO Genitourinary Cancer Symposium; Feb 13-15, 2025; San Francisco, CA.

Urothelial Carcinoma: Adjuvant



	No. of Events/ Total No. of Patients	Median Disease-free Survival (95% CI)
		mo
Pembrolizumab	185/354	29.6 (20.0–40.7)
Observation	194/348	14.2 (11.0–20.2)

Hazard ratio for disease progression or death, 0.73 (95% CI, 0.59–0.90)
Stratified P=0.003 by log-rank test

AMBASSADOR[7] Phase 3 Pembrolizumab

702

Pembro (n=354) vs observation (n=348)

- ≥ypT2 and/or ypN+/+margins (with NAC)
- ≥pT3 and/or pN+/+margins (without NAC)

- **Primary**: DFS and OS
- **Secondary**: DFS and OS in PD-L1–positive and –negative patients

Pembro	Observation
29.6 (20.0-40.7)	**14.2** (11.0-20.2)
HR 0.73 (95% CI, 0.59-0.90); *P*=0.003	

3-year survival at second interim analysis	
Pembro	**Observation**
60.8% (55.3-66.9)	**61.9%** (56.5-67.9)
HR 0.98 (95% CI, 0.76-1.26)	

Apolo AB, et al. *N Engl J Med*. 2025;392(1):45-55.

Urothelial Carcinoma: MIBC

National Comprehensive Cancer Network® (NCCN)

NCCN Guidelines Version 2.2025
Bladder Cancer

PRINCIPLES OF SYSTEMIC THERAPY

Neoadjuvant Chemotherapy (Preferred for Bladder)		Category of Evidence
Preferred regimen	**DDMVAC with growth factor support for 3-6 cycles**	Category 2A
Other recommended regimens	Gemcitabine + cisplatin for 4 cycles	Category 2A

Perioperative/Sandwich Therapy		Category of Evidence
Preferred regimen	**Gemcitabine + cisplatin + durvalumab prior to cystectomy, then durvalumab after cystectomy (for bladder cancer only)**	Category 1

Adjuvant Therapy			Category of Evidence
No previous platinum-based neoadjuvant therapy (pT3-T4a, pN+)	Preferred regimen	**DDMVAC with growth factor support for 3-6 cycles**	Category 2A
	Other recommended regimens	Gemcitabine + cisplatin for 4 cycles	Category 2A
		Nivolumab	Category 2A
		Pembrolizumab	Category 2A
Previous platinum-based neoadjuvant therapy (ypT2-4a or ypN+)	*Other recommended regimen*	Nivolumab	Category 2A
		Pembrolizumab	Category 2A

Urothelial Carcinoma: aUC

Urothelial Carcinoma: mUC until 2023

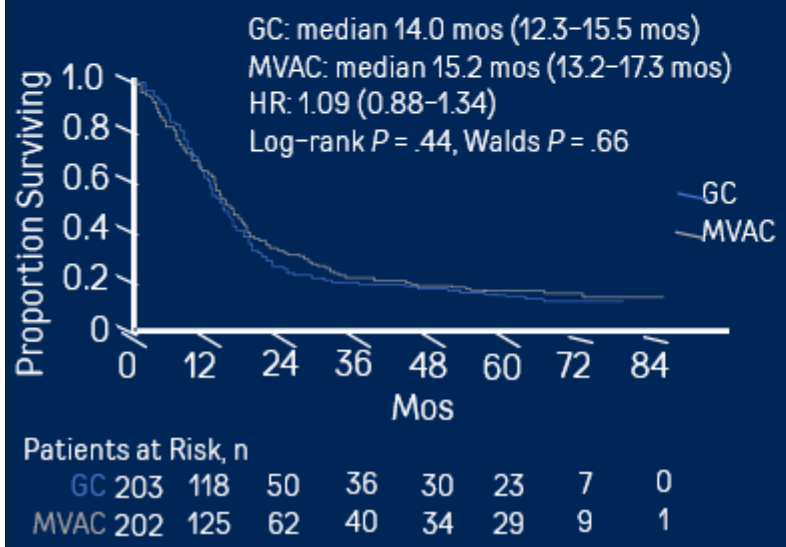
Cisplatin Eligible

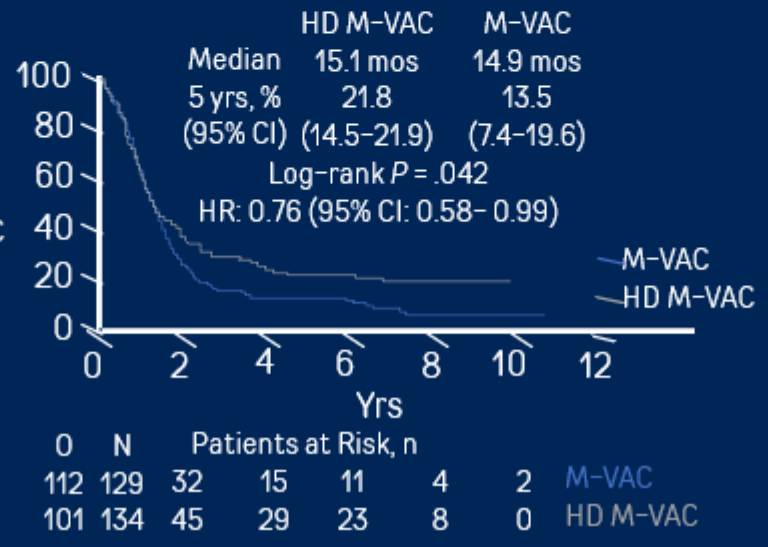
Gemcitabine + Cisplatin[1,2]
ORR: 49%
CR: 12%
Median OS: 14.0 mo

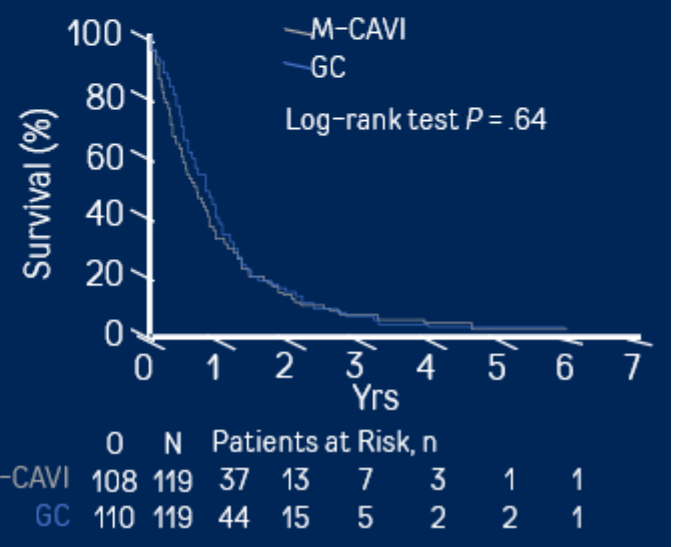
Dose Dense MVAC[3]
ORR: 72%
CR: 25%
Median OS: 15.1 mo

Cisplatin Ineligible

Gemcitabine + Carboplatin[4]
ORR: 36%
CR: 3%
Median OS: 9.3 mo

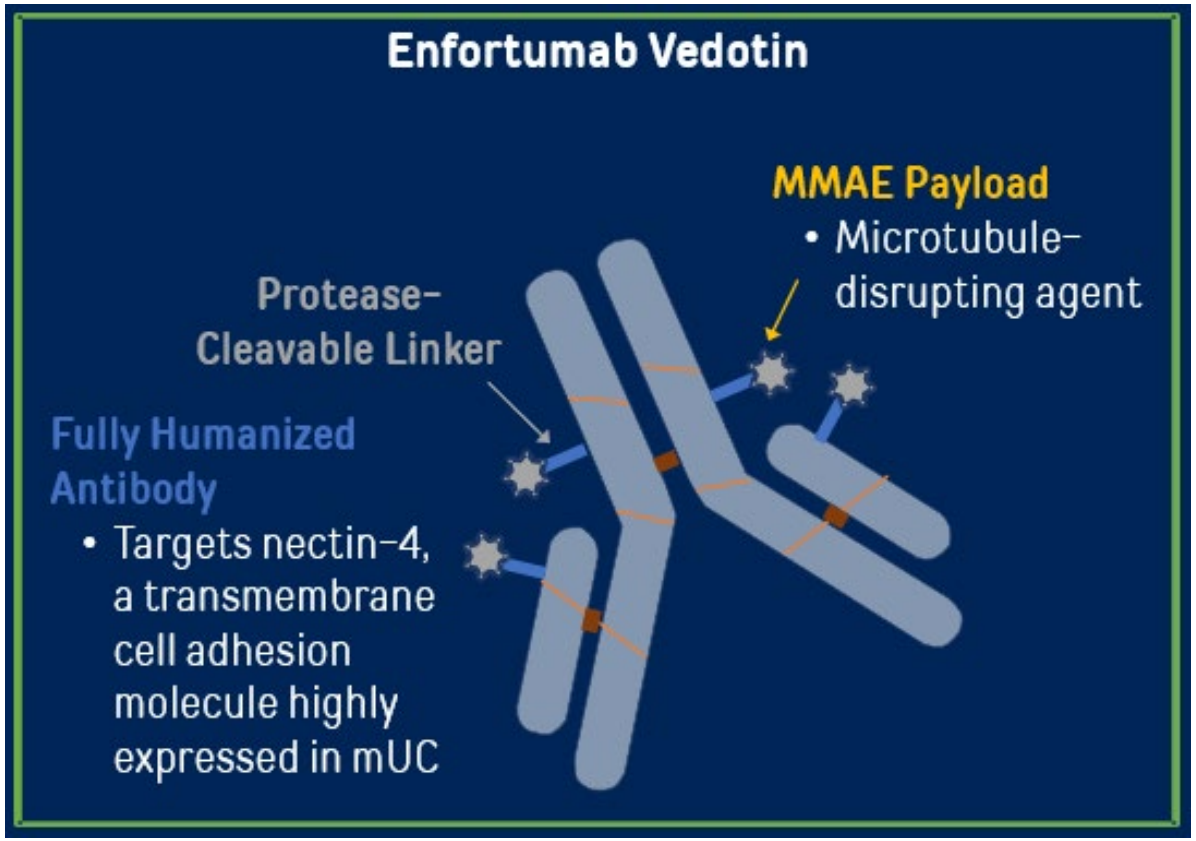




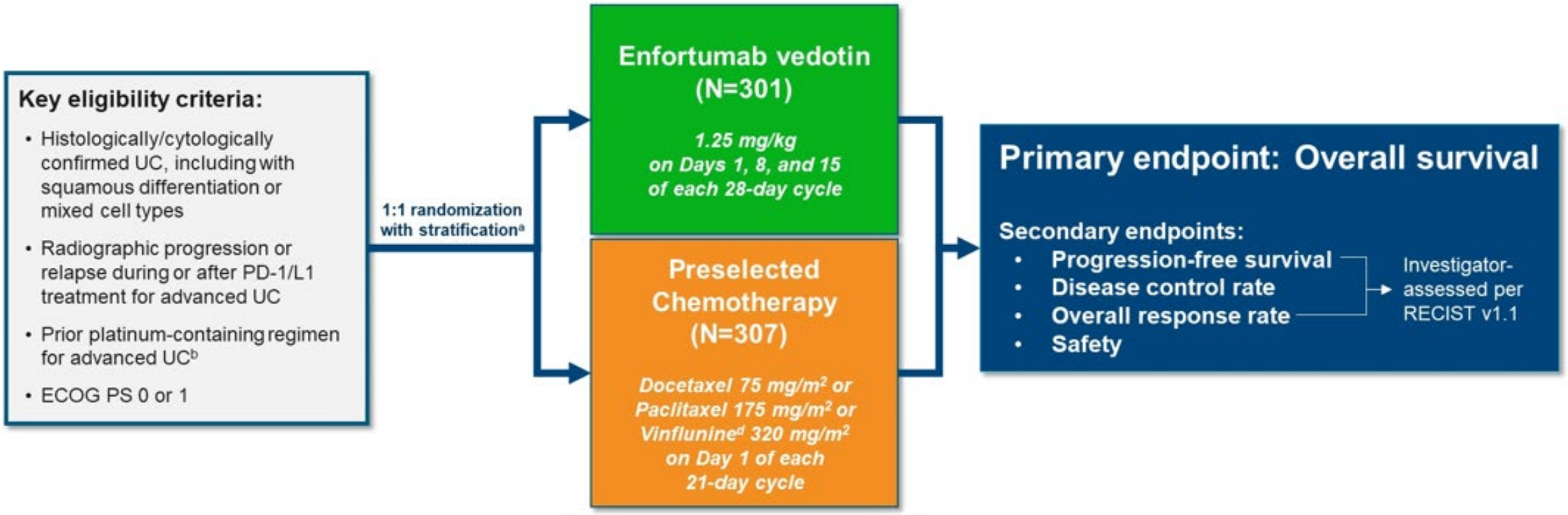


Courtesy of Pooja Ghatalia and Elizabeth Plimack.

Urothelial Carcinoma: Enfortumab Vedotin

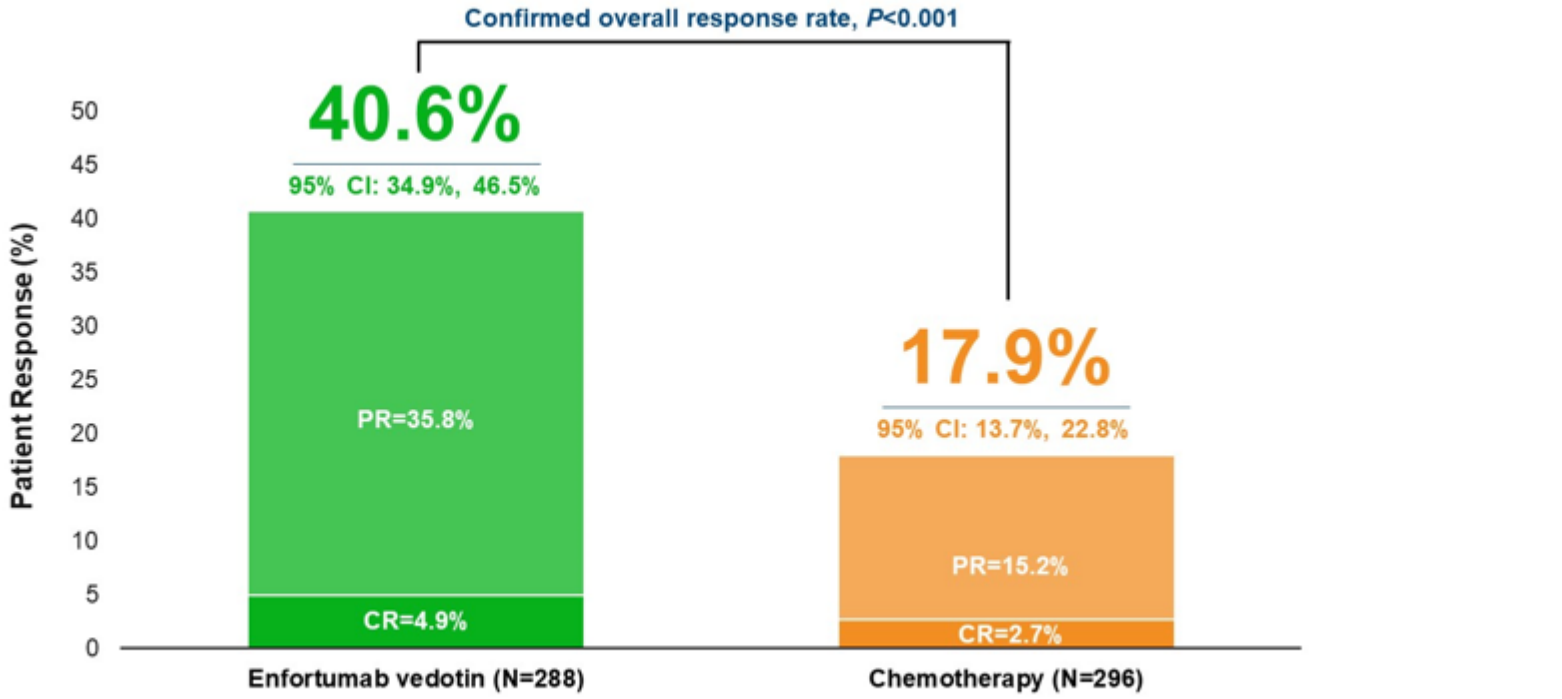


Urothelial Carcinoma: EV-301



Powles T, et al. *N Engl J Med*. 2021;384(12):1125-1135.

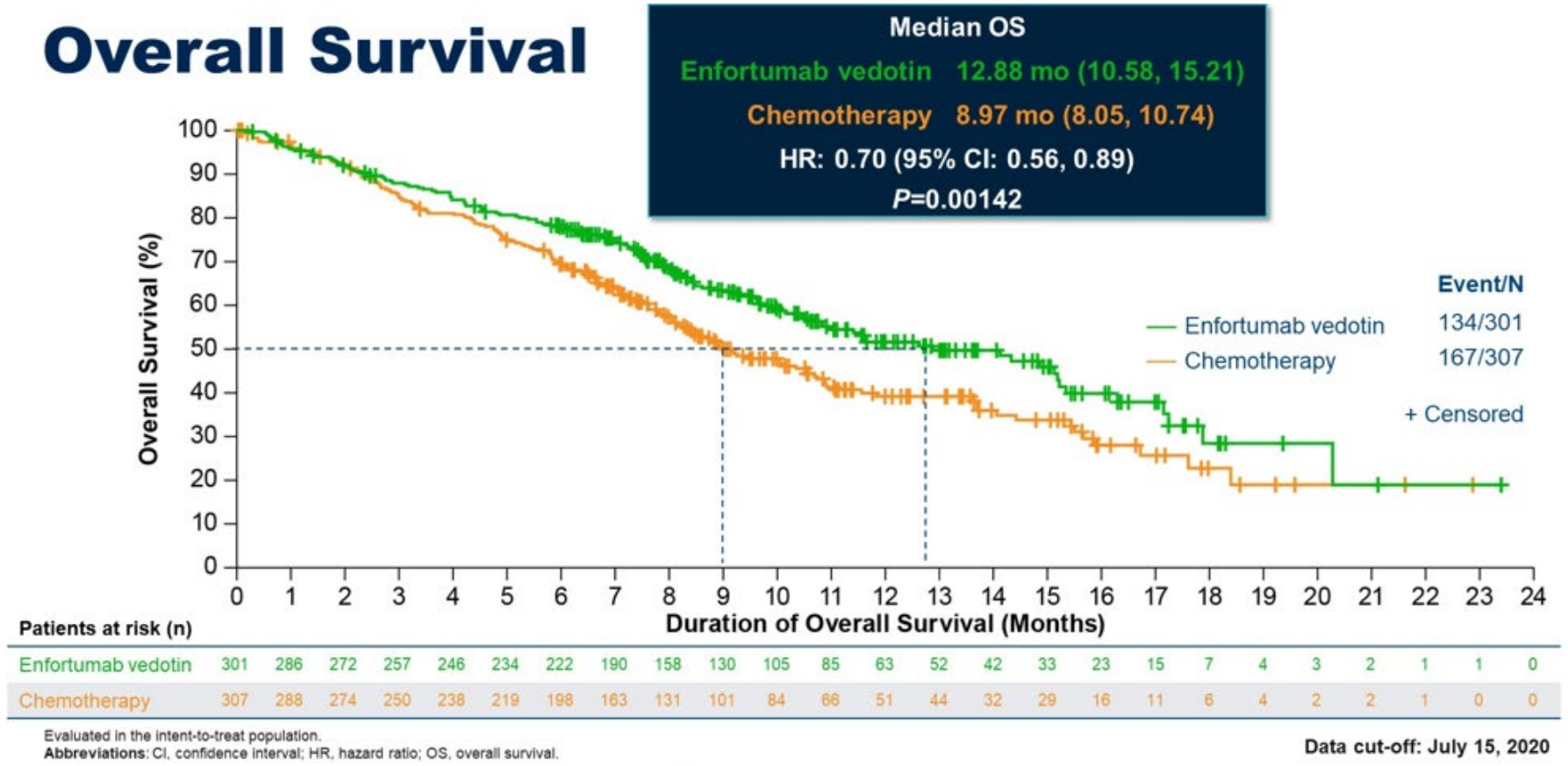
Urothelial Carcinoma: EV-301



Disease control rate,[a] % (95% CI)	71.9 (66.3, 77.0)	53.4 (47.5, 59.2)	*P*<0.001

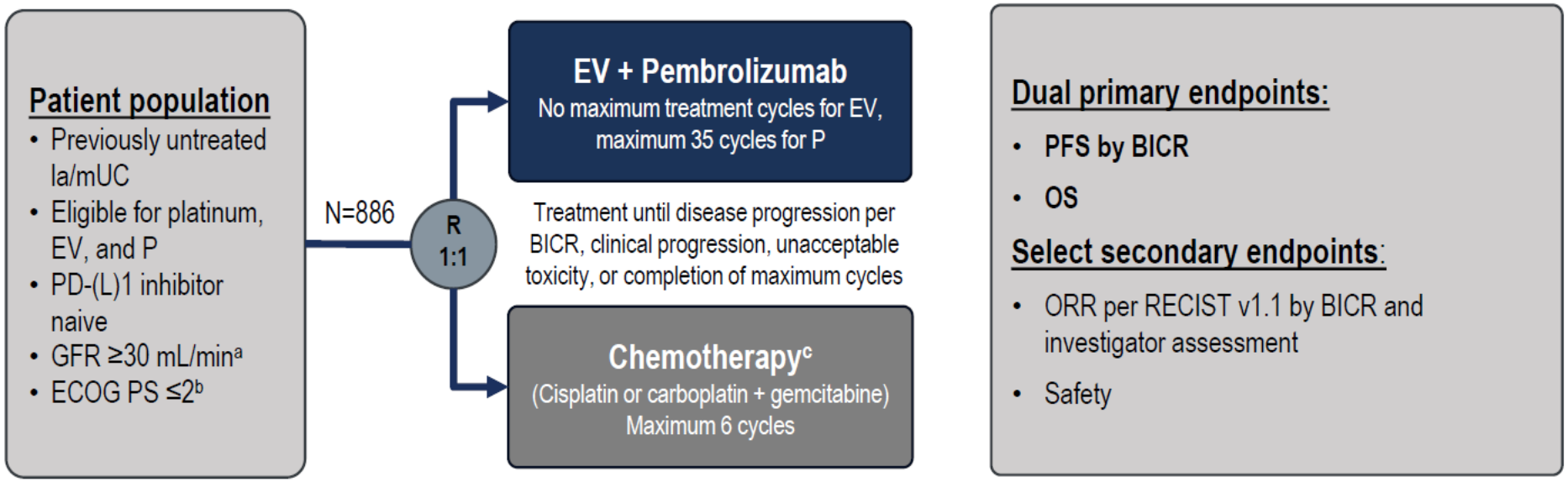
Powles T, et al. *N Engl J Med*. 2021;384(12):1125-1135.

Urothelial Carcinoma: EV-301



Powles T, et al. *N Engl J Med*. 2021;384(12):1125-1135.

Urothelial Carcinoma: EV-302



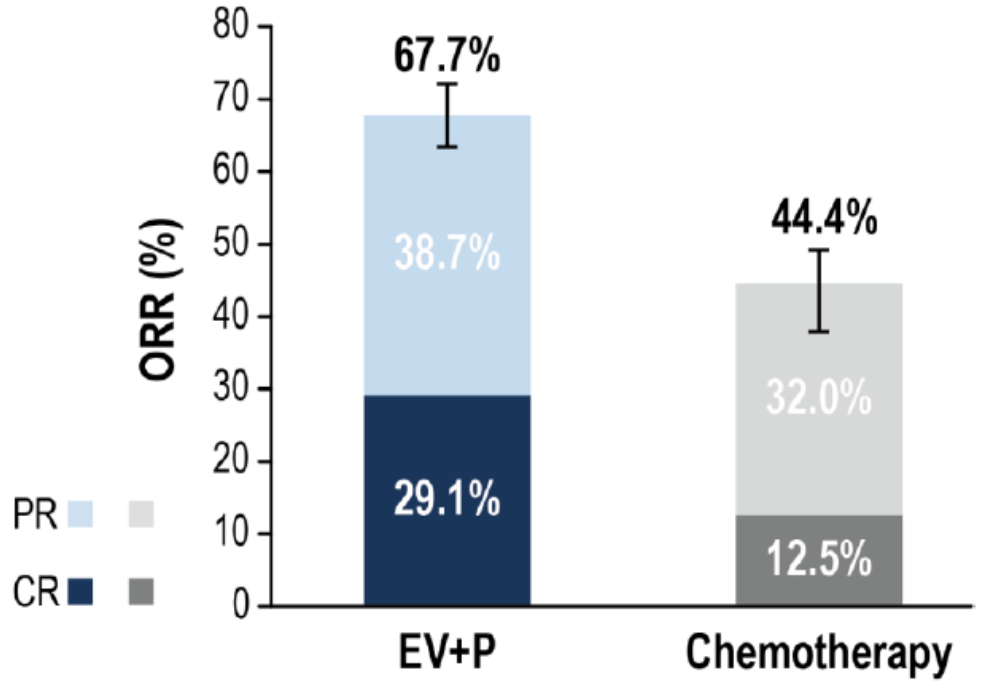
Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

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

Powles T, et al. *N Engl J Med*. 2021;384(12):1125-1135.

Urothelial Carcinoma: EV-302



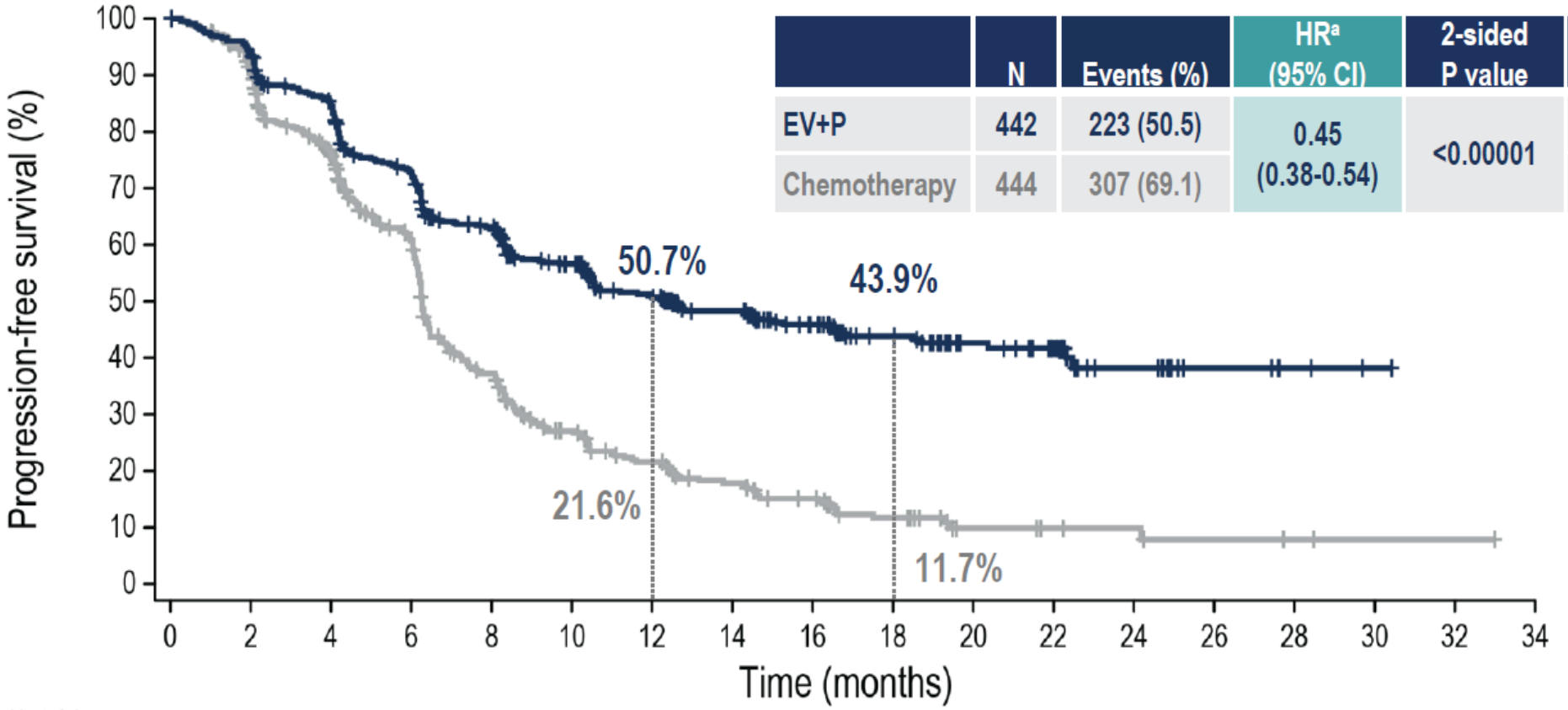
	EV+P (N=437)	Chemotherapy (N=441)
Confirmed ORR, n (%) (95% CI)	**296 (67.7) (63.1-72.1)**	**196 (44.4) (39.7-49.2)**
2-sided P value	<0.00001	
Best overall response[a], n (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive 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)

Powles T, et al. *N Engl J Med*. 2024;390(10):875-888.

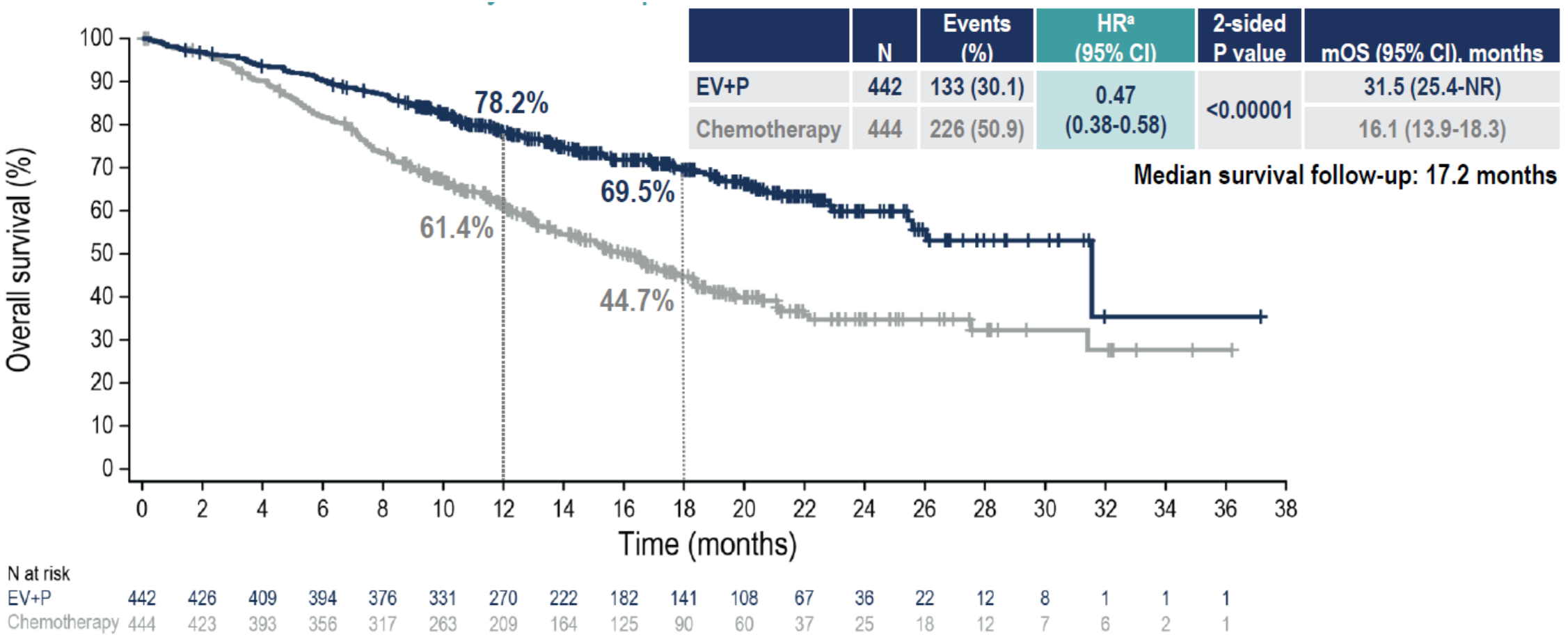
Urothelial Carcinoma: EV-302

	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)



Powles T, et al. *N Engl J Med*. 2024;390(10):875-888.

Urothelial Carcinoma: EV-302

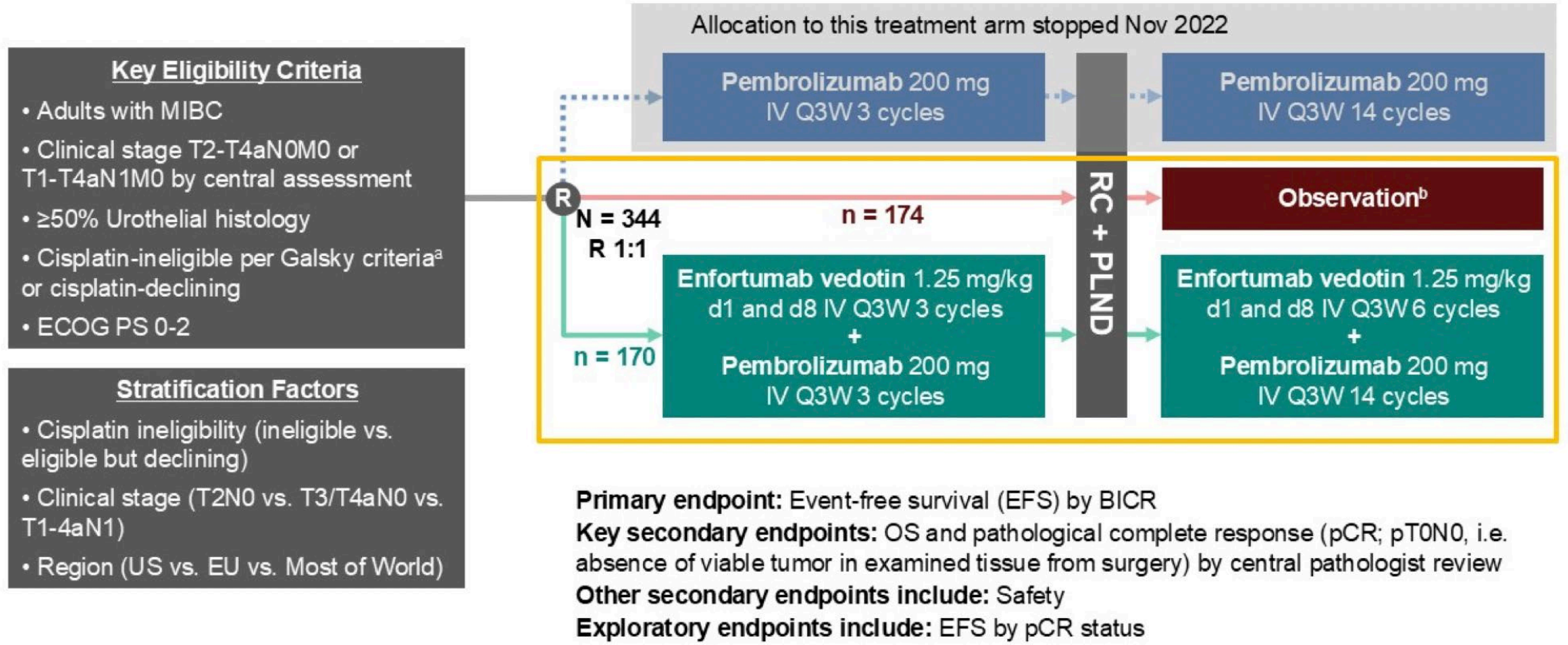


	N	Events (%)	HR[a] (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)

Median survival follow-up: 17.2 months

Powles T, et al. *N Engl J Med*. 2024;390(10):875-888.

Urothelial Carcinoma: ESMO 2025 MIBC; Keynote-905



Primary endpoint: Event-free survival (EFS) by BICR
Key secondary endpoints: OS and pathological complete response (pCR; pT0N0, i.e. absence of viable tumor in examined tissue from surgery) by central pathologist review
Other secondary endpoints include: Safety
Exploratory endpoints include: EFS by pCR status

Vulsteke C, et al. Perioperative (periop) enfortumab vedotin (EV) plus pembrolizumab (pembro) in participants (pts) with muscle-invasive bladder cancer (MIBC) who are cisplatin-ineligible: The phase 3 KEYNOTE-905 study. Presented at: ESMO Congress 2025; October 17-21, 2025; Berlin, Germany.

Urothelial Carcinoma: ESMO 2025 MIBC; Keynote-905

Baseline Characteristics

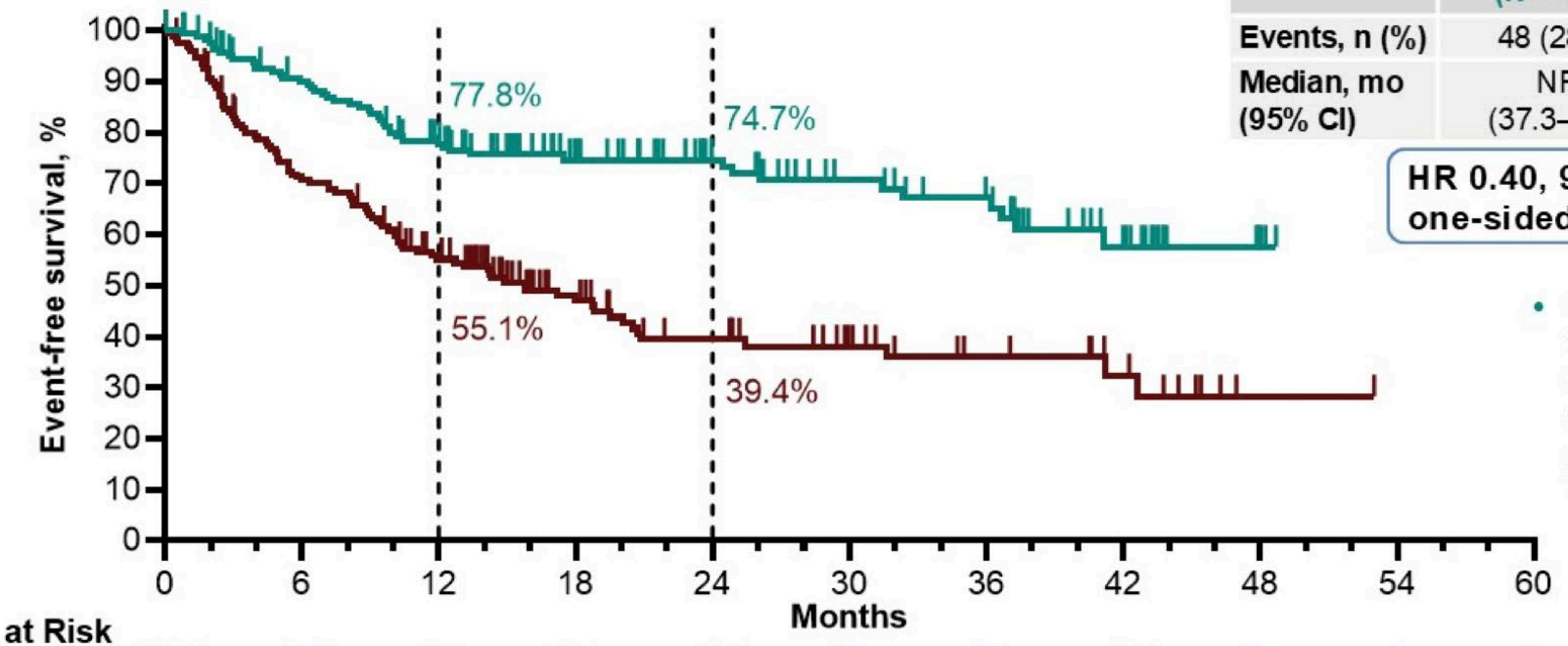
Characteristic, n (%)	EV + pembro (N = 170)	Control (N = 174)
Median age (range), years	74.0 (47–87)	72.5 (46–87)
≥65 to <75 years	63 (37.1)	77 (44.3)
≥75 years	78 (45.9)	68 (39.1)
Male	137 (80.6)	131 (75.3)
ECOG PS		
0	102 (60.0)	95 (54.6)
1	47 (27.6)	53 (30.5)
2	21 (12.4)	26 (14.9)
Region		
United States	21 (12.4)	23 (13.2)
European Union	78 (45.9)	77 (44.3)
Most of World	71 (41.8)	74 (42.5)
Cisplatin eligibility status (per Galsky criteria)		
Ineligible	142 (83.5)	139 (79.9)
Eligible but declining	28 (16.5)	35 (20.1)
PD-L1 combined positive score (CPS) ≥10[a]	80 (47.1)	83 (47.7)
Tumor stage at baseline (*centrally assessed using both pathology of TURBT specimen and imaging*)[b]		
T2N0	30 (17.6)	32 (18.4)
T3/T4aN0	133 (78.2)	132 (75.9)
T1-4aN1	7 (4.1)	10 (5.7)
Creatinine clearance		
≥60 mL/min	68 (40.0)	72 (41.4)
≥30 and <60 mL/min	102 (60.0)	101 (58.0)
<30 mL/min	0	1 (0.6)
Pure urothelial carcinoma histology	152 (89.4)	161 (92.5)

Vulsteke C, et al. Perioperative (periop) enfortumab vedotin (EV) plus pembrolizumab (pembro) in participants (pts) with muscle-invasive bladder cancer (MIBC) who are cisplatin-ineligible: The phase 3 KEYNOTE-905 study. Presented at: ESMO Congress 2025; October 17-21, 2025; Berlin, Germany.

Urothelial Carcinoma: ESMO 2025 MIBC; Keynote-905

Primary Endpoint: EFS[a] by BICR

ITT Population



	EV + pembro (N = 170)	Control (N = 174)
Events, n (%)	48 (28.2)	95 (54.6)
Median, mo (95% CI)	NR (37.3–NR)	15.7 (10.3–20.5)

HR 0.40, 95% CI 0.28–0.57, one-sided *P* <.0001*

- 29/174 pts (16.7%) in the control arm received adjuvant nivolumab as of data cutoff per local guidelines/prescribing information

No. at Risk

EV + pembro	170	140	116	73	56	42	35	16	3	0	0
Control	174	116	84	48	33	22	14	9	1	0	0

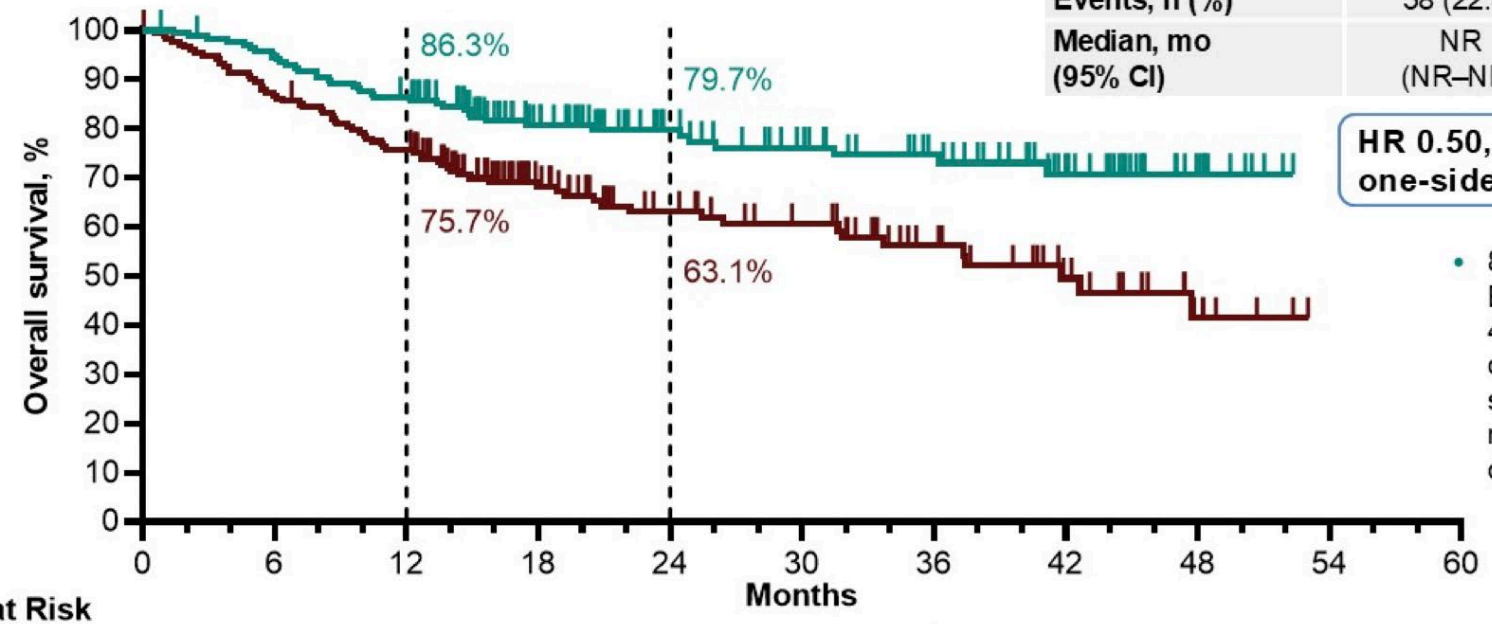
Vulsteke C, et al. Perioperative (periop) enfortumab vedotin (EV) plus pembrolizumab (pembro) in participants (pts) with muscle-invasive bladder cancer (MIBC) who are cisplatin-ineligible: The phase 3 KEYNOTE-905 study. Presented at: ESMO Congress 2025; October 17-21, 2025; Berlin, Germany.

Urothelial Carcinoma: ESMO 2025 MIBC; Keynote-905

ITT Population

	EV + pembro (N = 170)	Control (N = 174)
Events, n (%)	38 (22.4)	68 (39.1)
Median, mo (95% CI)	NR (NR–NR)	41.7 (31.8–NR)

HR 0.50, 95% CI 0.33–0.74, one-sided *P* =.0002*



No. at Risk											
EV + pembro	170	159	144	94	68	56	45	28	10	0	0
Control	174	150	130	75	54	45	30	18	6	0	0

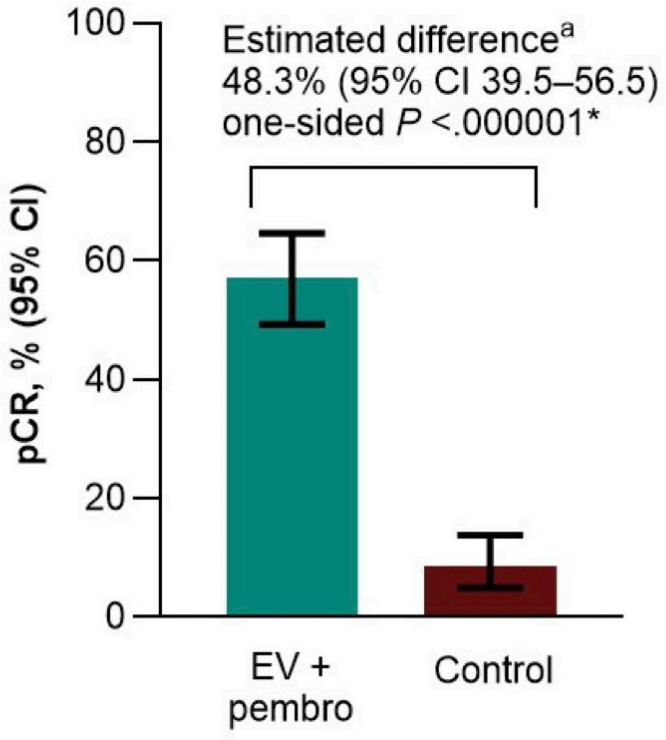
- 8/170 pts (4.7%) in the EV + pembro arm and 46/174 (26.4%) in the control arm received subsequent therapy for recurrent/metastatic disease

Vulsteke C, et al. Perioperative (periop) enfortumab vedotin (EV) plus pembrolizumab (pembro) in participants (pts) with muscle-invasive bladder cancer (MIBC) who are cisplatin-ineligible: The phase 3 KEYNOTE-905 study. Presented at: ESMO Congress 2025; October 17-21, 2025; Berlin, Germany.

Urothelial Carcinoma: ESMO 2025 MIBC; Keynote-905

Key Secondary Endpoint: pCR by Central Pathology Review

ITT Population



	EV + pembro (N = 170)	Control (N = 174)
pCR, n	97	15
pCR rate, % (95% CI)	57.1 (49.3–64.6)	8.6 (4.9–13.8)

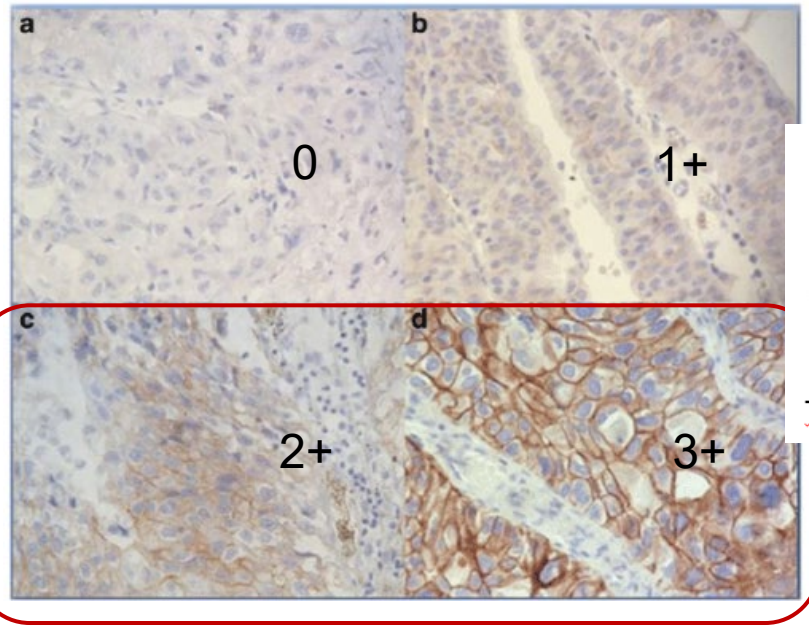
- **pCR:** absence of viable tumor (pT0N0) in examined tissue from RC + PLND
- Pts who did not undergo surgery, including those with clinical complete response after neoadjuvant therapy, were considered non-responders

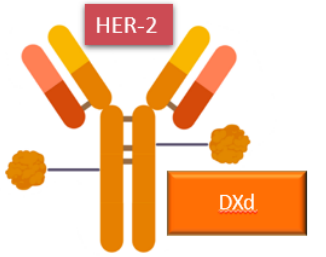
Vulsteke C, et al. Perioperative (periop) enfortumab vedotin (EV) plus pembrolizumab (pembro) in participants (pts) with muscle-invasive bladder cancer (MIBC) who are cisplatin-ineligible: The phase 3 KEYNOTE-905 study. Presented at: ESMO Congress 2025; October 17-21, 2025; Berlin, Germany.

Biomarker Directed Options

HER2: Traztuzumab Deruxtecan (Enhertu)

- Requires IHC testing (2+/3+)
- 10% Incidence in UC

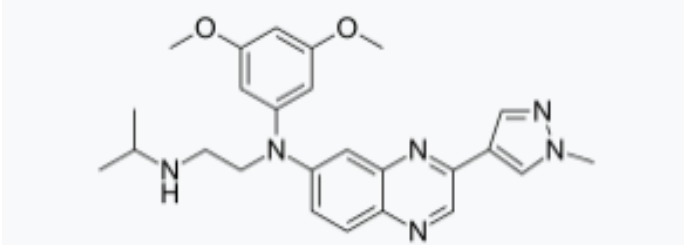




Traztuzumab Deruxtecan

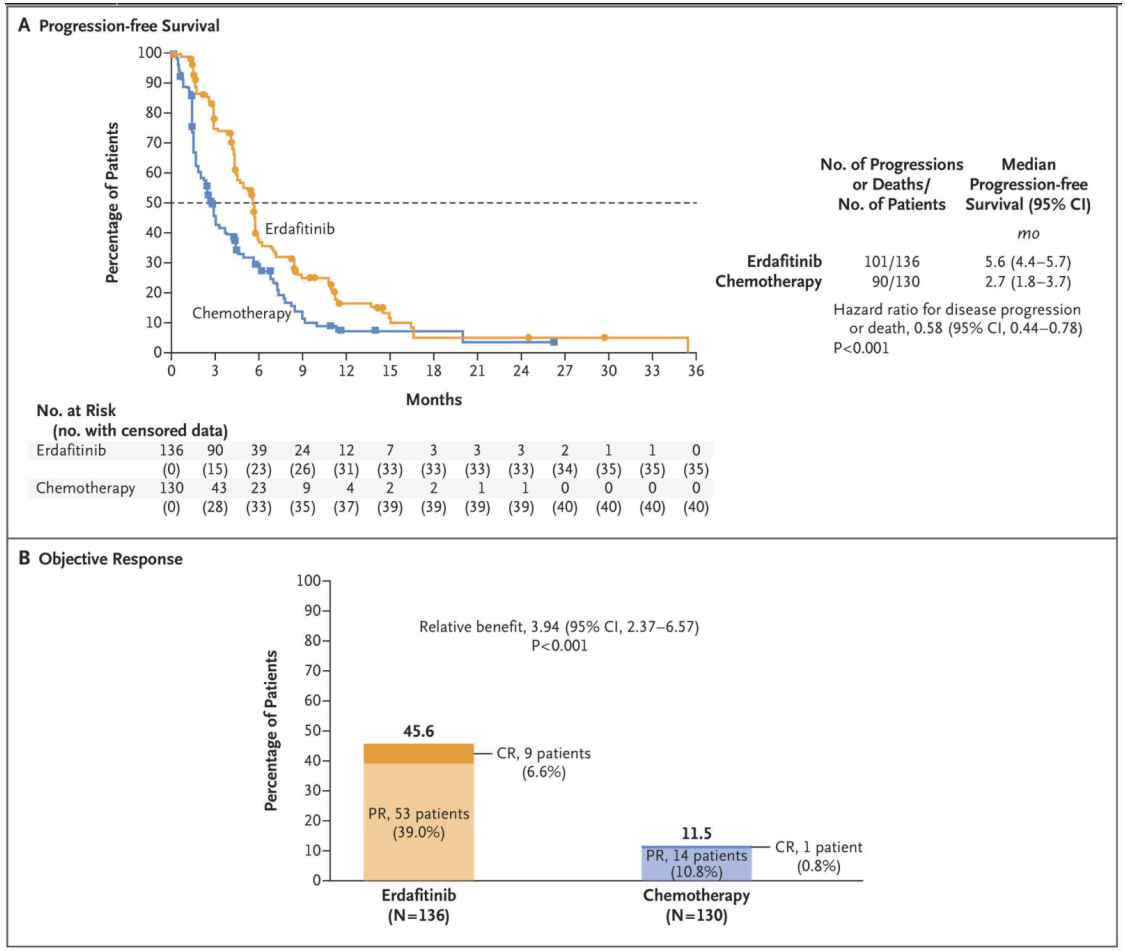
FGFR: Erdafitinib

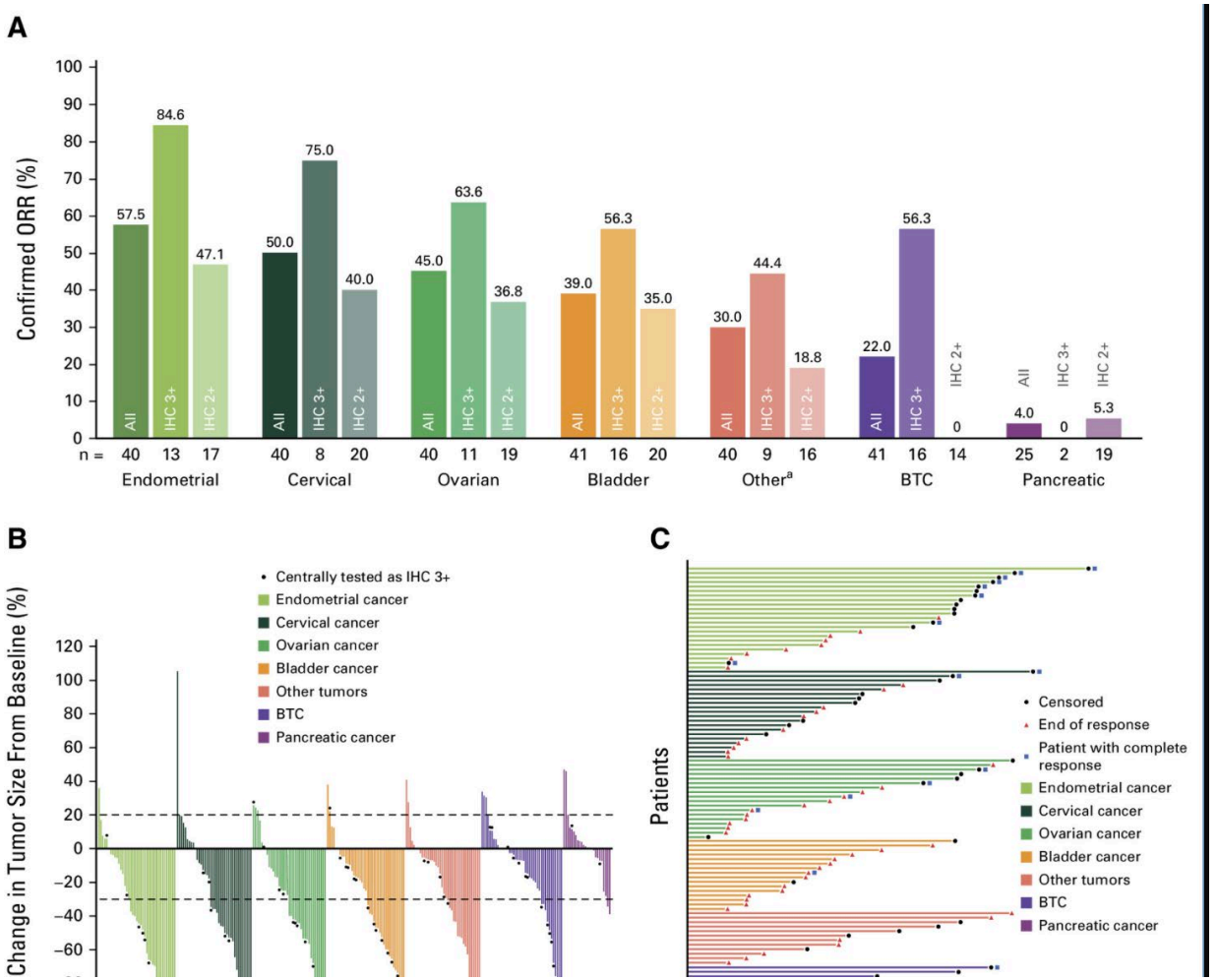
- Must have a susceptible FGFR3 mutation (R248C, S249C, G370C, or Y373C) or fusion (TACC3_V1, TACC3_V3, or BAIAP2L1)
- 10-15% incidence in UC



El Ochi MR, et al. *BMC Clin Pathol*. 2017;17:3.

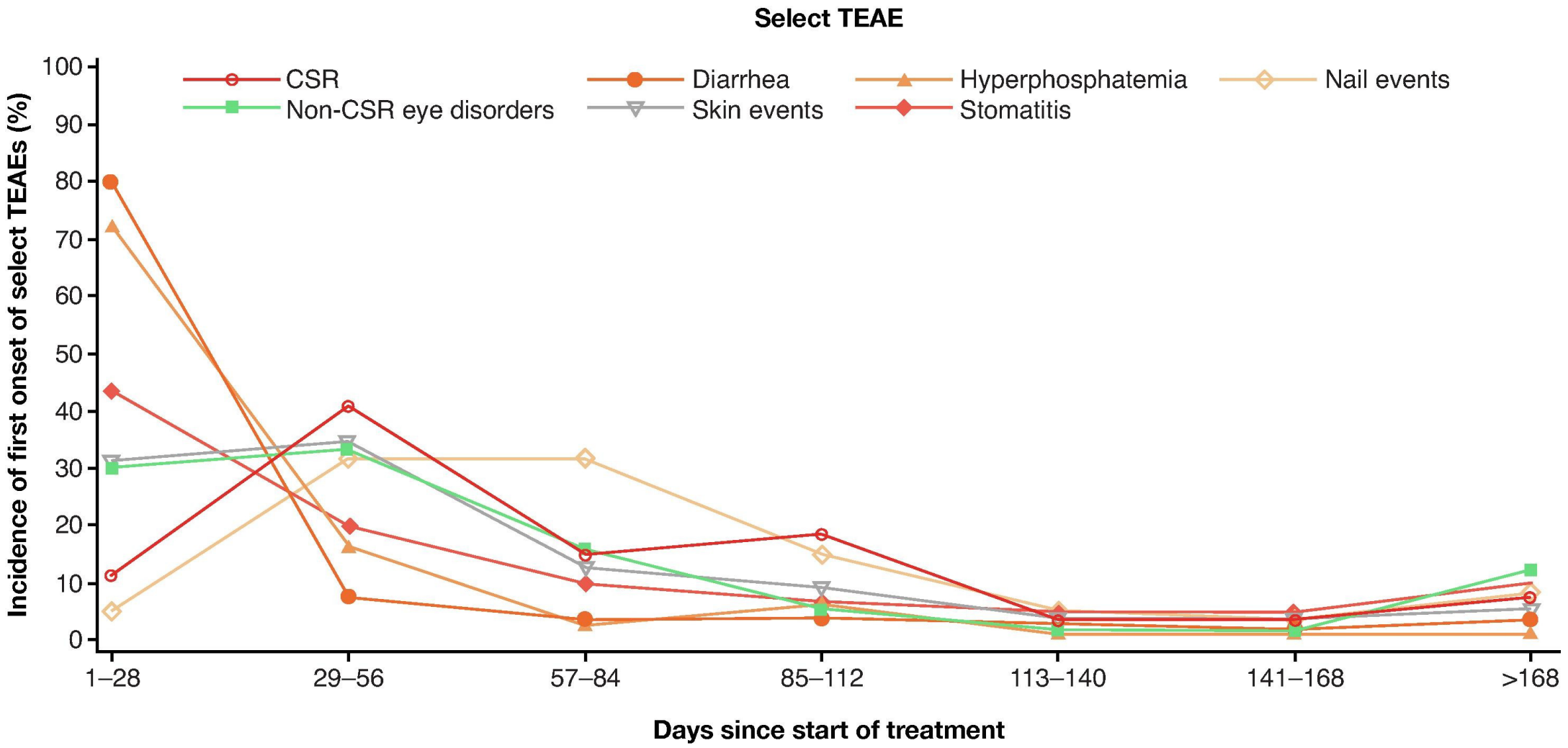
Urothelial Carcinoma: Eradafitinib & Enhertu





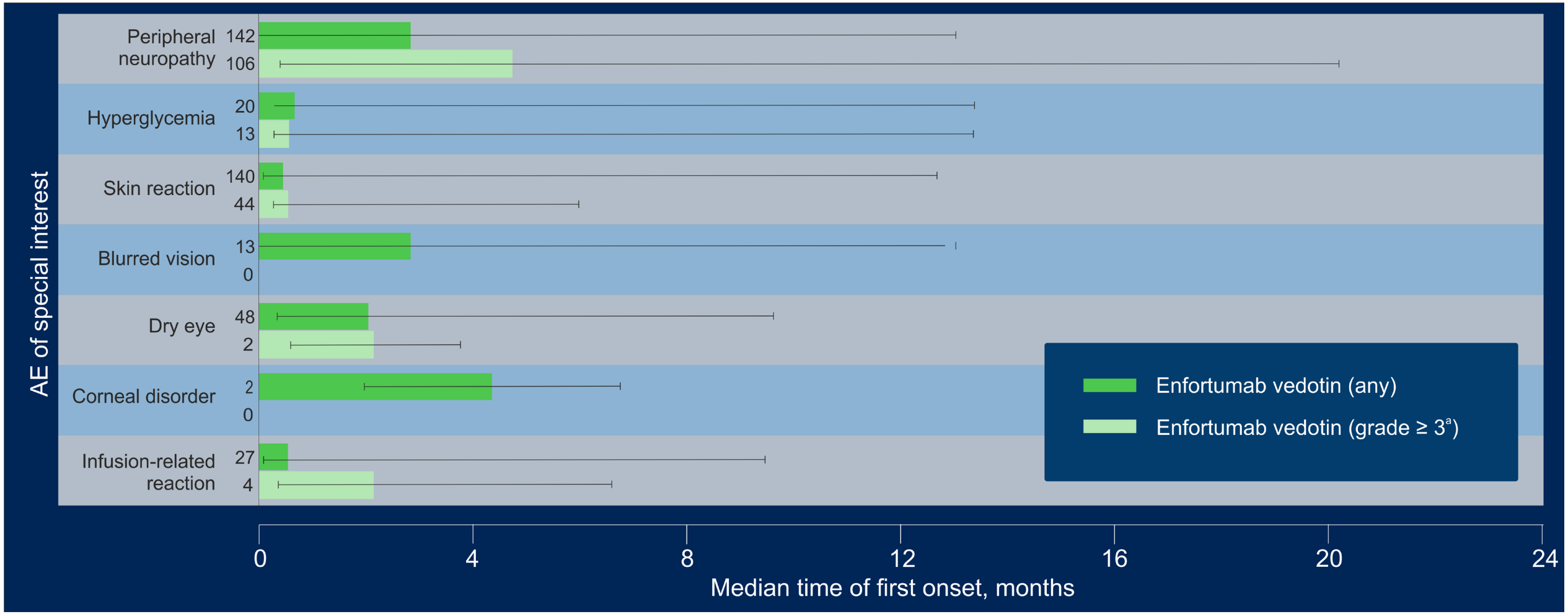
Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42(1):47-58. Loriot Y, et al. *N Engl J Med*. 2023;389(21):1961-1971.

Erdafitinib: Toxicity Profile



Siefker-Radtke AO, et al. *Eur Urol Open Sci*. 2023;50:1-9.

EV: Time of first onset of toxicity in 301



Ghatalia P, et al. Presented at: 2024 ASCO Annual Meeting; May 31-June 4, 2024; Chicago, IL.

EV: Hyperglycemia

Hyperglycemia:

- Mechanism unknown
- Occurs in 6.5% of EV treated patients
- Risk: High BMI and A1C >6.5%

<u>Pre-treatment counseling</u>

- Optimize glycemic control in patients with diabetes. Involve Endocrine

<u>On treatment monitoring</u>

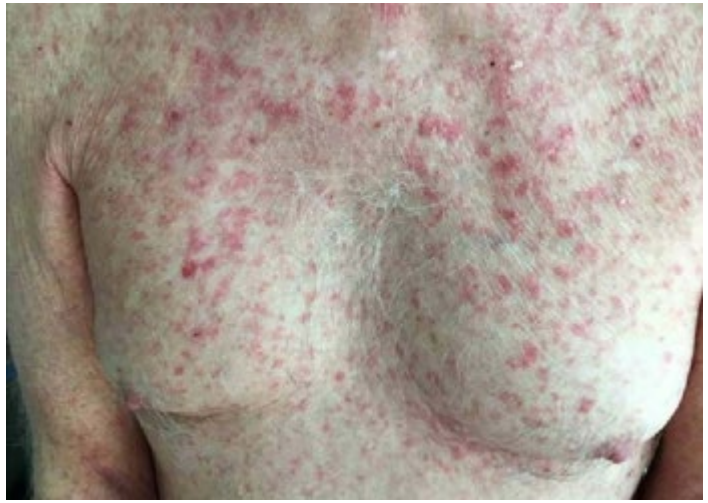
- Check glucose prior to each infusion

<u>Hyperglycemia Management Strategies</u>

- Hold EV if glucose >250
- If severe, consider steroids as could be T1DM from pembro

Ghatalia P, et al. Presented at: 2024 ASCO Annual Meeting; May 31-June 4, 2024; Chicago, IL.

EV: Skin Toxicity Management



Lacouture Oncologist 2022

- Erythematous and scaly
- Pruritic papules
- Intertriginous, flexural, acral, possible truncal

<u>Pre-treatment counseling</u>

- Remind patient to report rash and use sunscreen

<u>On treatment monitoring</u>

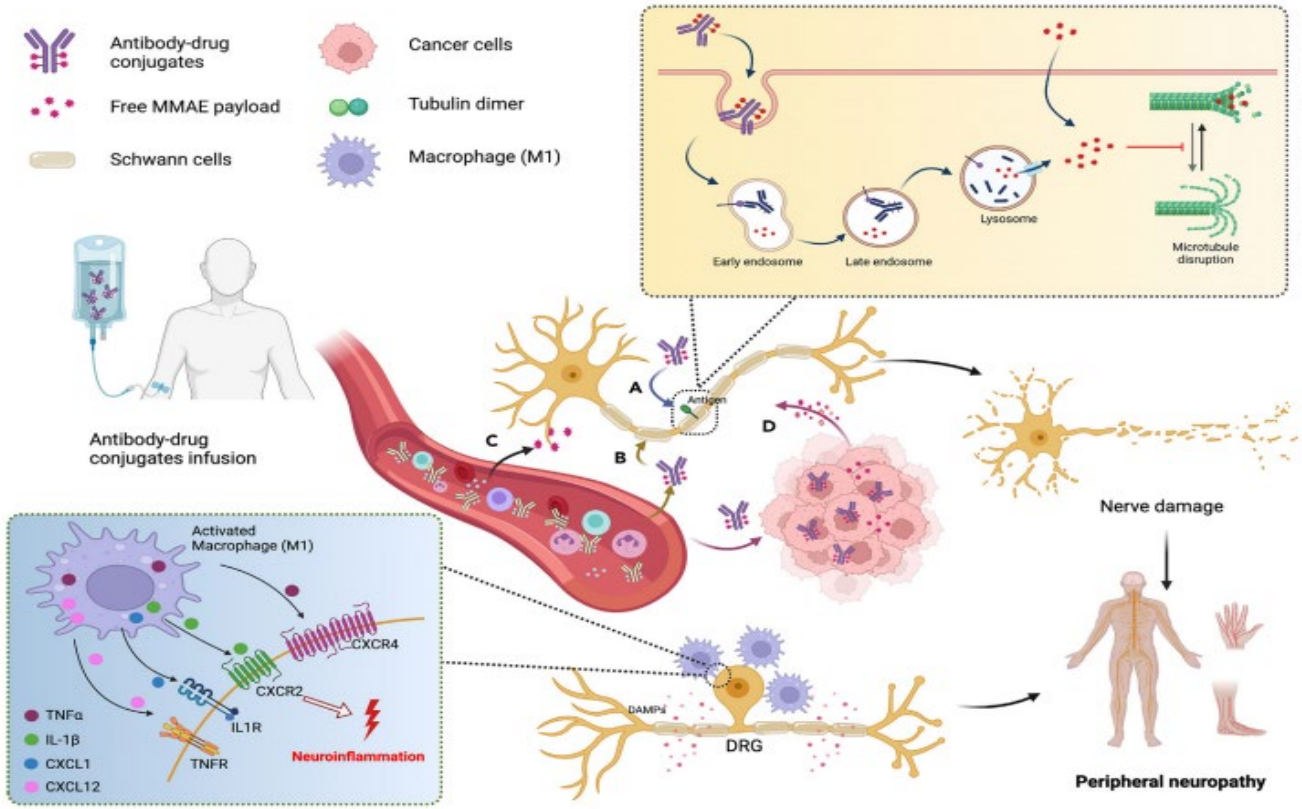
- Careful skin exam, rule out mucosal involvement / Stevens-Johnson Syndrome

<u>Rash Emergent Therapy</u>

- Topical Steroid Cream (0.1% triamcinolone)
- Hydroxyzine for Itch
- EV dose hold / dose reduction
- For refractory or extensive cases
  - Systemic Steroids
  - Dermatology referral for biologic therapy with dupilumab

Ghatalia P, et al. Presented at: 2024 ASCO Annual Meeting; May 31-June 4, 2024; Chicago, IL.

EV: Neurologic



Pre-treatment counseling

- Baseline assessment for existing neuropathy

On treatment monitoring

- Carefully ask about neuropathy at visits, ensure gait is not affected (ie, no motor neuropathy)

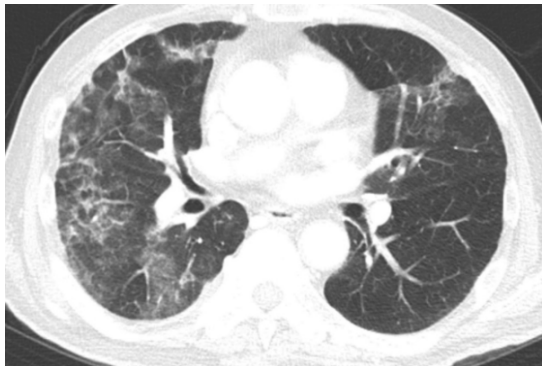
Neuropathy management strategies

- Dose holds / dose reduction / schedule extension
- Discontinue EV if excellent response and/or neuropathy interfering with ADLs
- Adjunctive therapy for neuropathic pain: gabapentin, pregabalin, duloxetine

Ghatalia P, et al. Presented at: 2024 ASCO Annual Meeting; May 31-June 4, 2024; Chicago, IL. Fu Z, et al. iScience. 2023;26(10):107778.

Pneumonitis: EV, Pembro and TDxD

Radiologic Findings



Symptoms:
Hypoxia
Cough
Dyspnea

Interstitial Lung Disease:
Traztuzumab Deruxtecan (10%)

No symptoms: Hold, restart
Symptoms: Steroids, discontinue permanently

EV mediated (median onset 3 mo):
Enfortumab Vedotin (<5%)

Immune mediated:
Pembrolizumab (<5%)

EV+ Pembrolizumab (10%)

No symptoms: Hold EV, restart at lower dose
Mild symptoms: Oral steroids, slow taper, restart at lower dose
Severe symptoms: High dose steroids discontinue permanently

Courtesy of Elizabeth R. Plimack and Pooja Ghatalia.

Prostate Cancer Disease States and Treatment Approaches

Tanya Barauskas Dorff, MD

Professor of Medicine
Department of Medical Oncology and Therapeutics Research
City of Hope Comprehensive Cancer Center

Brenda Martone, NP

Nurse Practitioner
Northwestern Medicine
Chicago, Illinois

Faculty Disclosures

Tanya Barauskas Dorff, MD:

- Consultant for Astellas, AstraZeneca, Bayer, Dendreon, Janssen, J&J, Novartis, Pfizer, Blue Earth, Foundation Medicine
- Research funding to institution from AbbVie, Amgen, AstraZeneca, Dendreon

Brenda Martone, NP: Has no financial relationships to disclose

Disclosures

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration)
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity
- This activity has been independently reviewed for balance
- This CME activity includes brand names for participant clarity purposes only. No product promotion or recommendation should be inferred
- NCCN makes no warranties of any kind whatsoever regarding their content, use, or application, and disclaims any responsibility for their application or use in any way

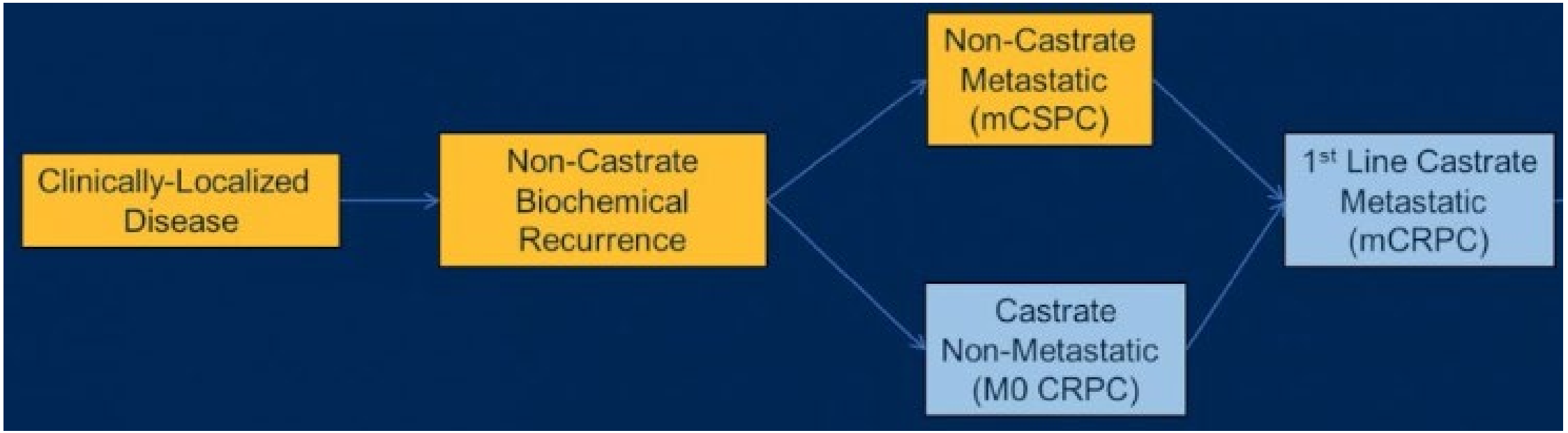
Program Information

- Provided by HMP Education, LLC, an HMP Global Company
- Supported in part by an educational grant from Johnson & Johnson

Learning Objectives

- Define the role of molecular testing in localized and advanced prostate cancer
- Identify optimal treatment intensification for patients with metastatic hormone-sensitive prostate cancer
- Determine when and how to use 177Lu-PSMA-617 radioligand therapy in mCRPC in sequence with other therapies

Disease States in Prostate Cancer



- Because of PSA, we know there is cancer sometimes before we can see it
- Giving ADT for BCR can create castration resistance before we can see the metastatic disease
- PSMA PET muddies the waters a bit between BCR and mCSPC

PSA = prostate-specific antigen; ADT = androgen deprivation therapy; BCR = biochemical recurrence; PSMA = prostate-specific membrane antigen; PET = positron emission tomography; mCSPC = metastatic castration-sensitive prostate cancer; mCRPC = (metastatic castration-resistant prostate cancer).

National Comprehensive Cancer Network® (NCCN)

NCCN Guidelines
Prostate Cancer Version 2.2025

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

Risk Group	Clinical/Pathologic Features (Staging, ST-1)			Additional Evaluation	Initial Therapy
Very Low	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • <3 positive biopsy fragments/cores, ≤50% cancer in each fragment/core • PSA density ≤0.15 ng/mL/g			• Confirmatory testing can be used to assess the appropriateness of active surveillance (PROS-F 2 of 5)	PROS-3
Low	Has all of the following but does not qualify for very low risk: • cT1–T2a • Grade Group 1 • PSA <10 ng/mL			• Confirmatory testing can be used to assess the appropriateness of active surveillance (PROS-F 2 of 5)	PROS-4
Intermediate	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▶ cT2b–T2c ▶ Grade Group 2 or 3 ▶ PSA 10–20 ng/mL	Favorable Intermediate:	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (e.g., <6 of 12 cores)	• Confirmatory testing can be used to assess the appropriateness of active surveillance (PROS-F 2 of 5)	PROS-5
		Unfavorable Intermediate:	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥50% biopsy cores positive (e.g., ≥6 of 12 cores)	• Soft tissue imaging and consider bone imaging ▶ If regional or distant metastases are found, see PROS-8 or PROS-13	PROS-6
High	Has one or more high-risk features, but does not meet criteria for very high risk: • cT3–T4 • Grade Group 4 or Grade Group 5 • PSA ≥20 ng/mL			Bone and soft tissue imaging • If regional or distant metastases are found, see PROS-8 or PROS-13	PROS-7
Very High	Has at least two of the following: • cT3–T4 • Grade Group 4 or 5 • PSA >40 ng/mL			Bone and soft tissue imaging • If regional or distant metastases are found, see PROS-8 or PROS-13	PROS-7

Footnotes for Initial Risk Stratification and Staging Workup for Clinically Localized Disease (PROS-2A).

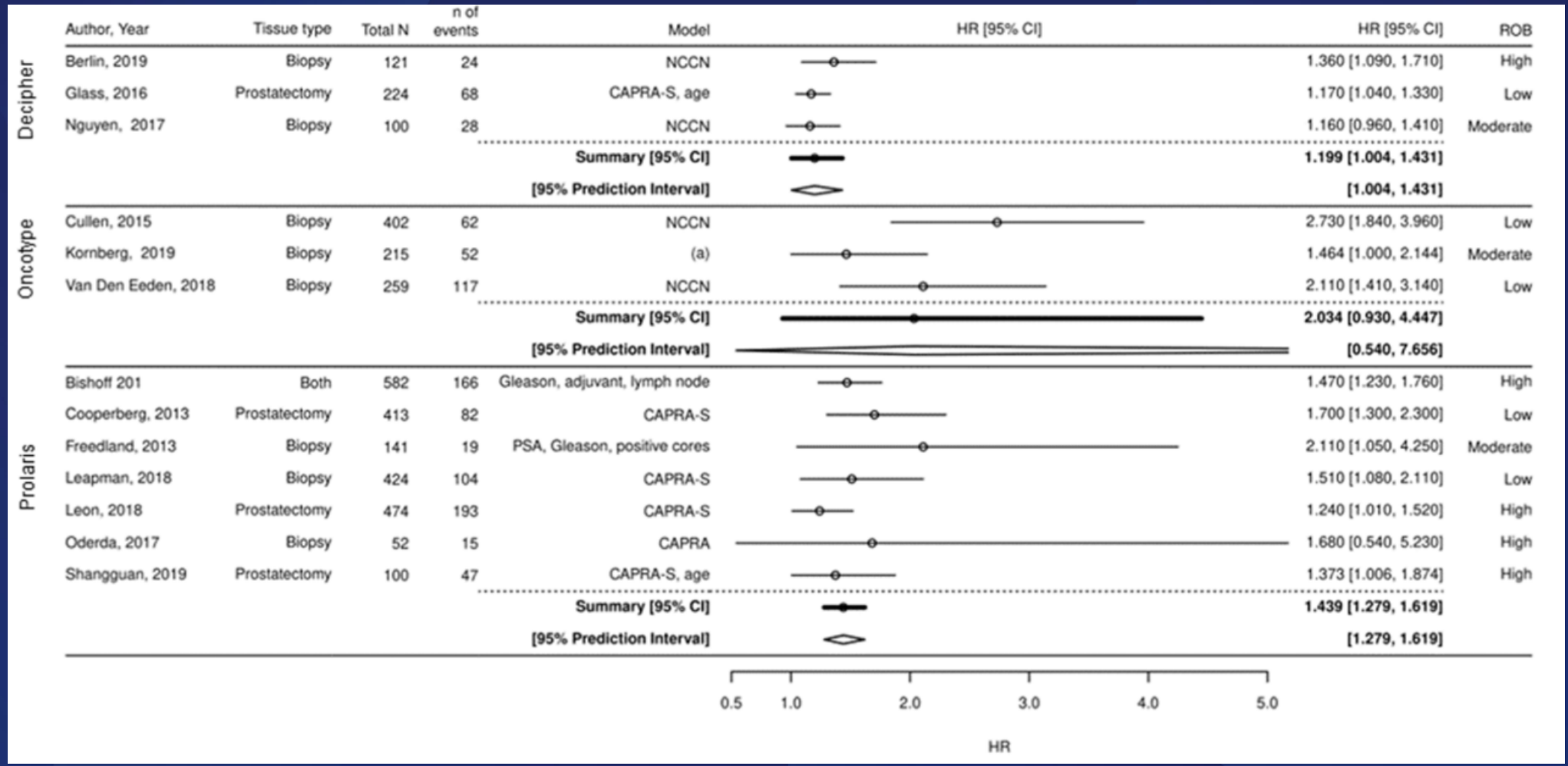
IRF = intermediate risk factor.

Molecular Testing in Localized Prostate Cancer

Decipher 22 gene RNA microarray

OncotypeDx prostate 17 genes rtPCR

Prolaris – cell cycle progression 31 genes rtPCR



Boyer MJ, et al. *Prostate Cancer Prostatic Dis*. 2025;28(1):103-111.

DECIPHER score

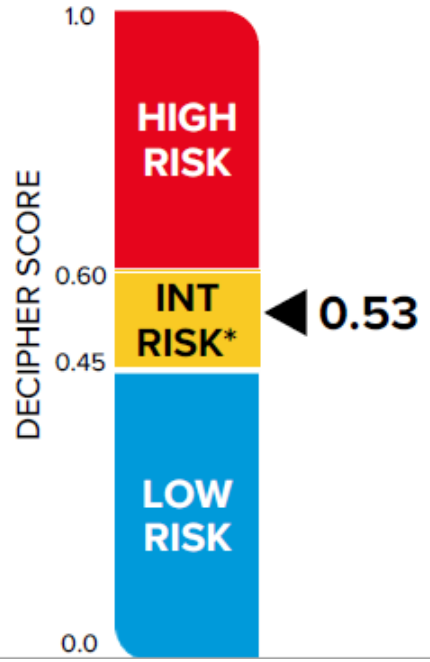
CLINICAL AND PATHOLOGY DETAILS For reference only, not used in calculation of genomic risk

Specimen: **Needle Biopsy**
Clinical Stage: **T3b**

Most Recent PSA: **0.01 ng/mL**
Gleason Score: **4 + 4**

National Comprehensive Cancer Network® (NCCN®) Risk Category: **Very High/High**

DECIPHER GENOMIC RISK RESULTS



GENOMIC RISK IS: INTERMEDIATE

3.9%	7.7%	14.1%
5-year	*10-year*	*15-year*
Risk of Metastasis with RT† or RP‡		**Risk of Prostate Cancer Mortality** with RT or RP

Clinical studies have shown that Decipher intermediate-risk patients have an average clinical risk and prognosis. Depending on life expectancy and overall health status:

- Patients receiving definitive therapy may benefit from treatment intensification.[3-5,12]

RT = radiation therapy; RP = radical prostatectomy.

Decipher. Accessed October 2025. https://decipherbio.com/decipher-prostate/physicians/biopsy-test-report/.

NRG-GU009: PARALLEL PHASE III RANDOMIZED TRIALS FOR HIGH RISK PROSTATE CANCER EVALUATING DE-INTENSIFICATION FOR LOWER GENOMIC RISK AND INTENSIFICATION OF CONCURRENT THERAPY FOR HIGHER GENOMIC RISK WITH RADIATION (PREDICT-RT*)

**Prostate RNA Expression/Decipher To Individualize Concurrent Therapy with Radiation*

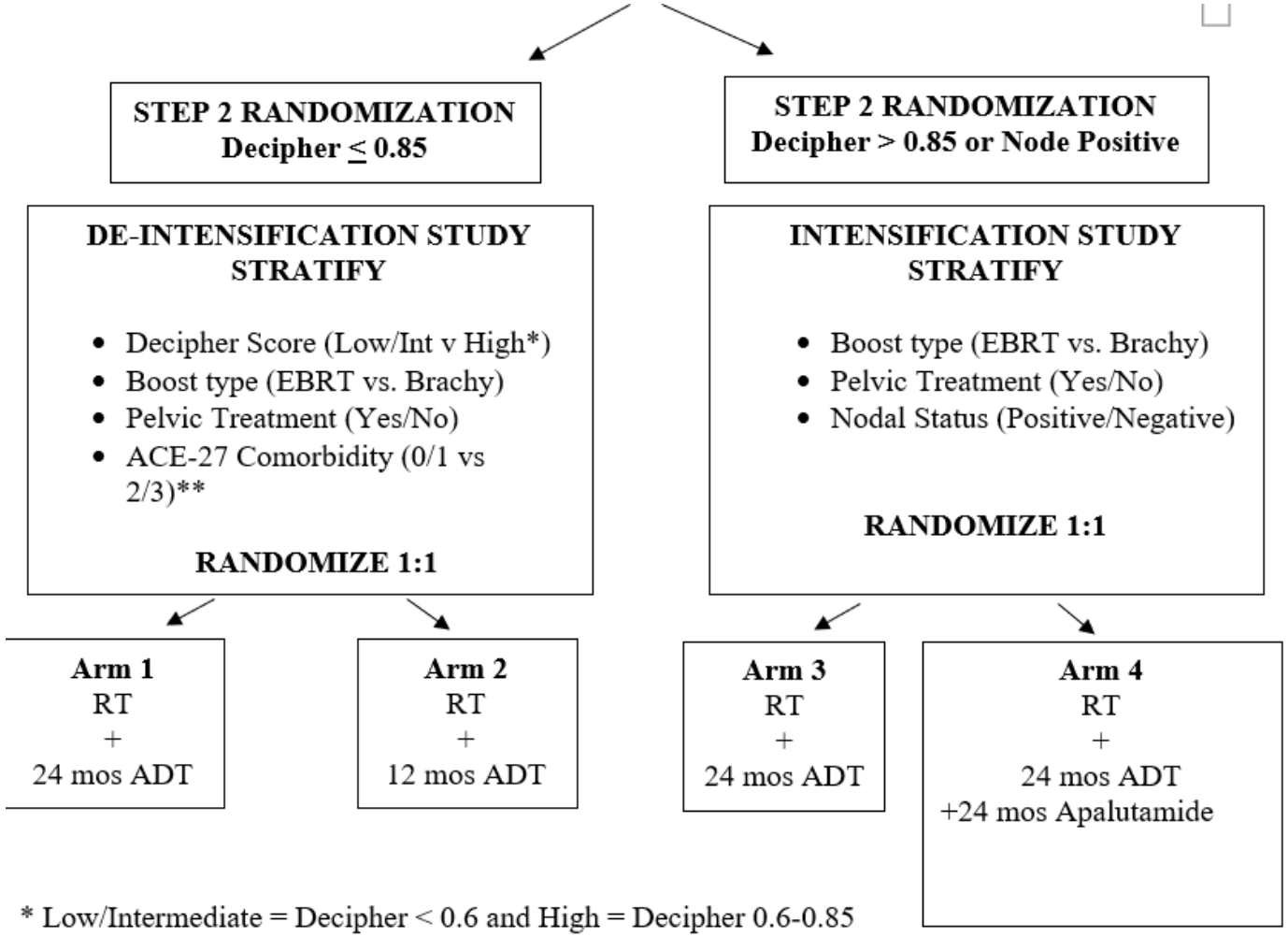
Primary Endpoint: metastasis-free survival (conventional imag)

De-Intensification add'l endpoints

- Cardiometabolic
- QOL
- Cognitive

Target accrual = 2478

PIs = Oliver Sartor & Paul Nguyen



Twitter, Instagram: @NRGOnc

National Cancer Institute: Community Oncology Research Program.

NRG Oncology. Accessed October 2025. https://www.nrgoncology.org/Clinical-Trials/Protocol/nrg-gu009-1?filter=nrg-gu009-1. UroToday. Accessed October 2025. https://www.urotoday.com/conference-highlights/astro-2022/140289-astro-2022-treatment-of-local-regional-disease-in-the-era-of-psma-pet.html.

DNA testing: Germline

Importance to Patient and Family

- Germline testing recommended for ALL patients with advanced prostate cancer and those with lower risk/ lower stage prostate cancer with family history
  - If a pathogenic variant is identified, this has impact on children and siblings, male and female
- In mCRPC pathogenic HRR alterations that are germline provide rationale to treat with PARP inhibitor
  - These are moving into earlier disease states (AMPLITUDE – mHSPC)

HRR = homologous recombination repair; PARP = poly(ADP-ribose) polymerase; mHSPC = metastatic hormone-sensitive prostate cancer.

mHSPC: Doublet therapy

Agent	Trial(s)	n	Primary endpoint	Considerations
Abiraterone	LATITUDE STAMPEDE	1199 957	OS HR 0.62 OS HR 0.62 (metastatic)	Cost effective Cardiovascular risks Prednisone 5 mg daily
Apalutamide	TITAN	1052	OS HR 0.67	
Darolutamide	**ARANOTE**	669	OS HR, 0.81 [95% CI, 0.59 to 1.12	Mostly ex-US; 10% black, 30% asian
Docetaxel	CHAARTED	820	OS HR 0.6 (signif only for hi vol)	No longer NCCN rec as doublet b/c of triplet trials
Enzalutamide	ENZAMET	1125	OS HR 0.67	**Control arm got bicalutamide** Some got docetaxel

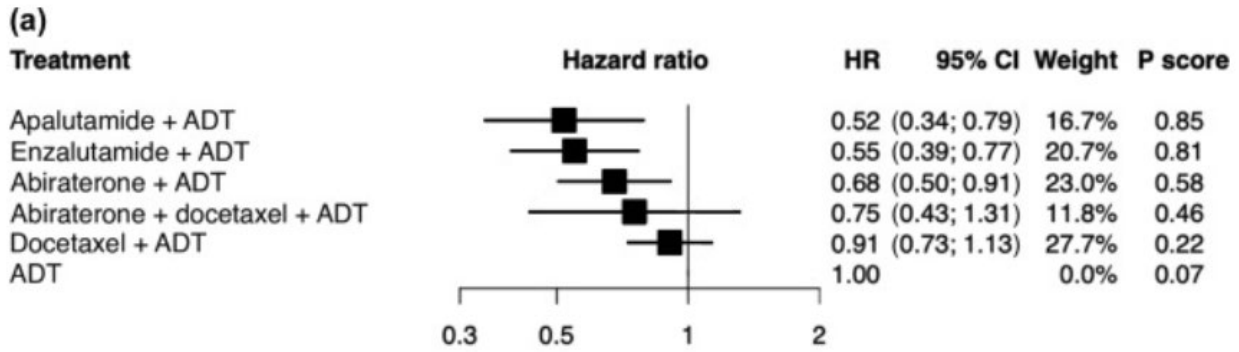
For low volume, radiation to prostate primary for synchronous improved rPFS independent of abiraterone (PEACE-1: Fizazi K et al, Lancet 2022)

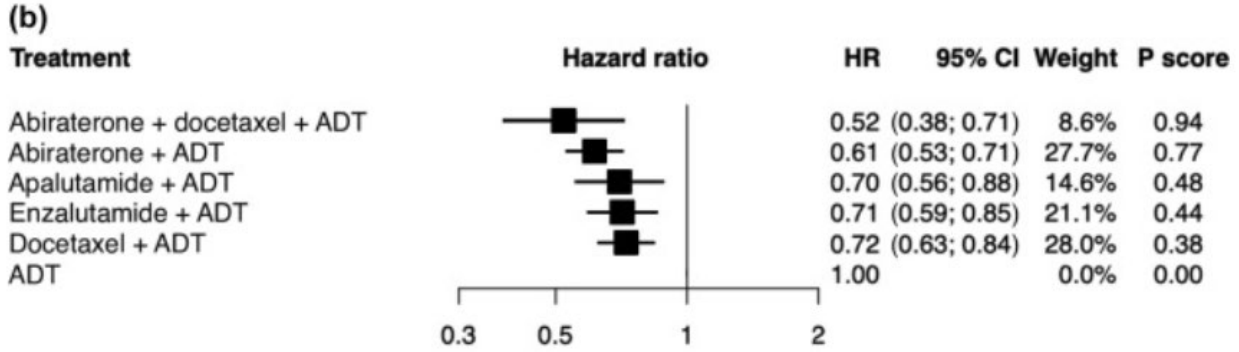
OS = overall survival; HR = hazard ratio; CI = confidence interval; rPFS = radiographic progression-free survival.

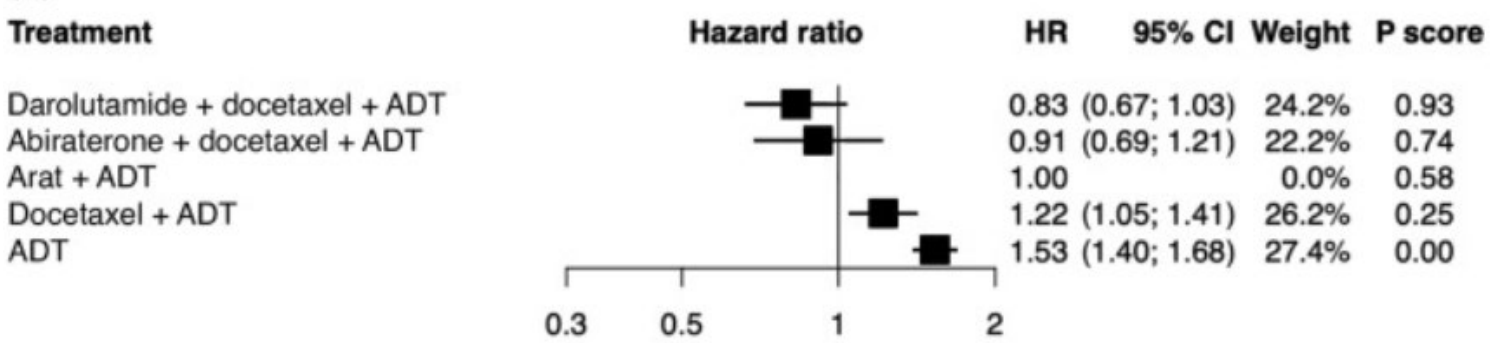
Fizazi K, et al. *N Engl J Med*. 2017;377(4):352-360. James ND, et al. *Lancet*. 2016;387(10024):1163-1177. Chi KN, et al. *N Engl J Med*. 2019;381(1):13-24. Saad F, et al. *J Clin Oncol*. 2024;42(36):4271-4281. Sweeney CJ, et al. *N Engl J Med*. 2015;373(8):737-746. Davis ID, et al. *N Engl J Med*. 2019;381(2):121-131.

Systematic meta-analysis: triplet benefit in mHSPC

- Benefit primarily in high volume (b) vs low volume (a)
- Risks must be considered
- Overall HR for OS (bottom)







Mandel P, et al. *Eur Urol Focus*. 2023;9(1):96-105.

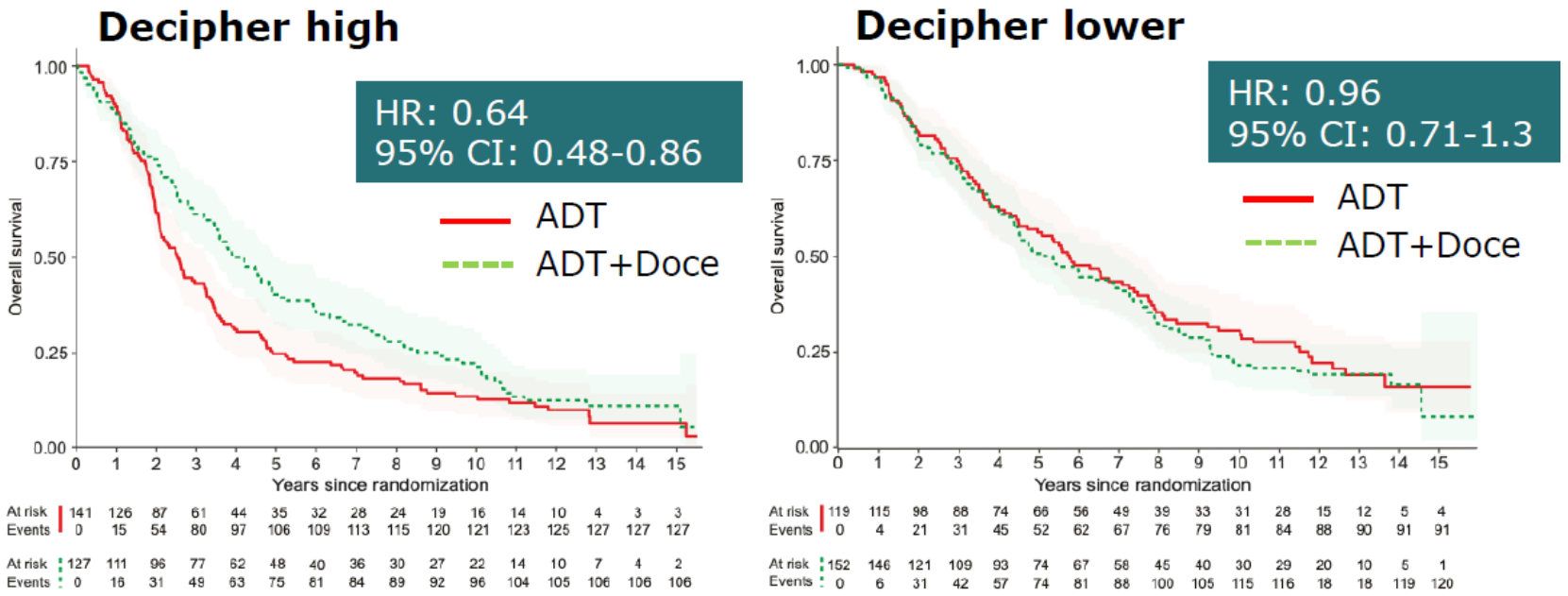
DECIPHER score shows ability to identify those who don't benefit from (docetaxel) triplet

22-gene RNA test used in localized PC

- Trained on CHAARTED

Based on samples from STAMPEDE

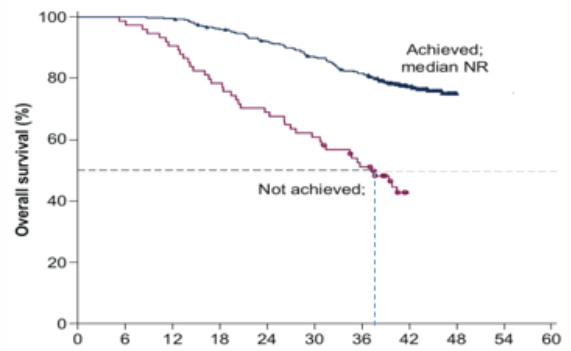
- Was not predictive for abiraterone
- Was predictive for low volume and high volume for docetaxel



Grist E, et al. Decipher mRNA score for prediction of survival benefit from docetaxel at start of androgen-deprivation therapy for advanced prostate cancer: an ancillary study of the STAMPEDE docetaxel trials. 1596O: Proffered Paper Session. Presented at: ESMO Congress 2024; September 13-17, 2024; Barcelona, Spain.

Doublet therapy is good, but PSA nadir at 7 months is prognostic for those who don't fare as well

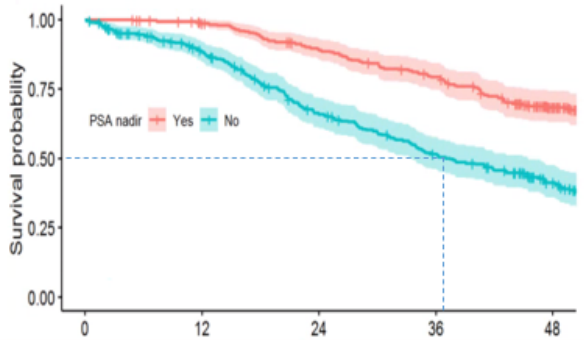
TITAN (apalutamide)



Chowdhury *et al Ann Oncol* 2023

Median OS = 37.2 mo

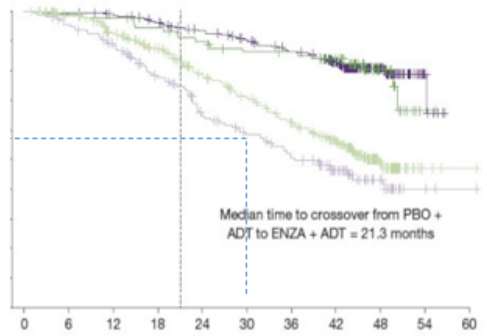
LATITUDE (abiraterone)



Roy and Ong 2024, *unpublished*
Matsubara *et al*, *Eur Urol*, 2019

Median OS = 37.5 mo

ARCHES (enzalutamide)

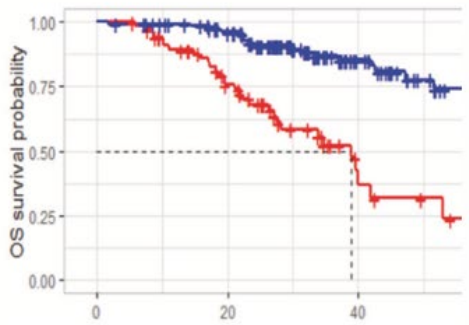


Szmulewitz *et al SESAUA* 2023

Median OS = 36.4 mo

PSA nadir >0.2 at 7 months identifies those with shorter OS

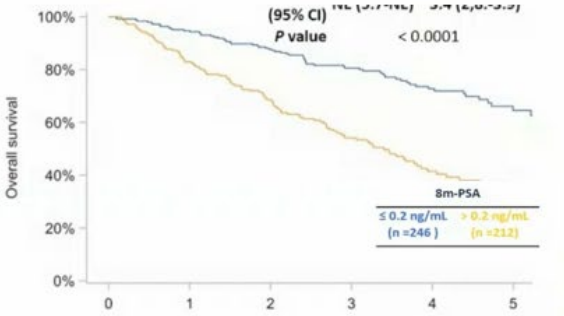
Real-World



Median OS = 38.9 mo

Gebrael *et al* Prostate Cancer and Prostatic Diseases 2023

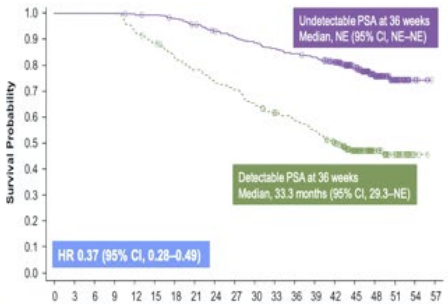
PEACE-1 (abiraterone, RT)



Median OS = 40.8 mo

Gravis Mescam *et al ESMO* 2022

ARASENS (darolutamide)



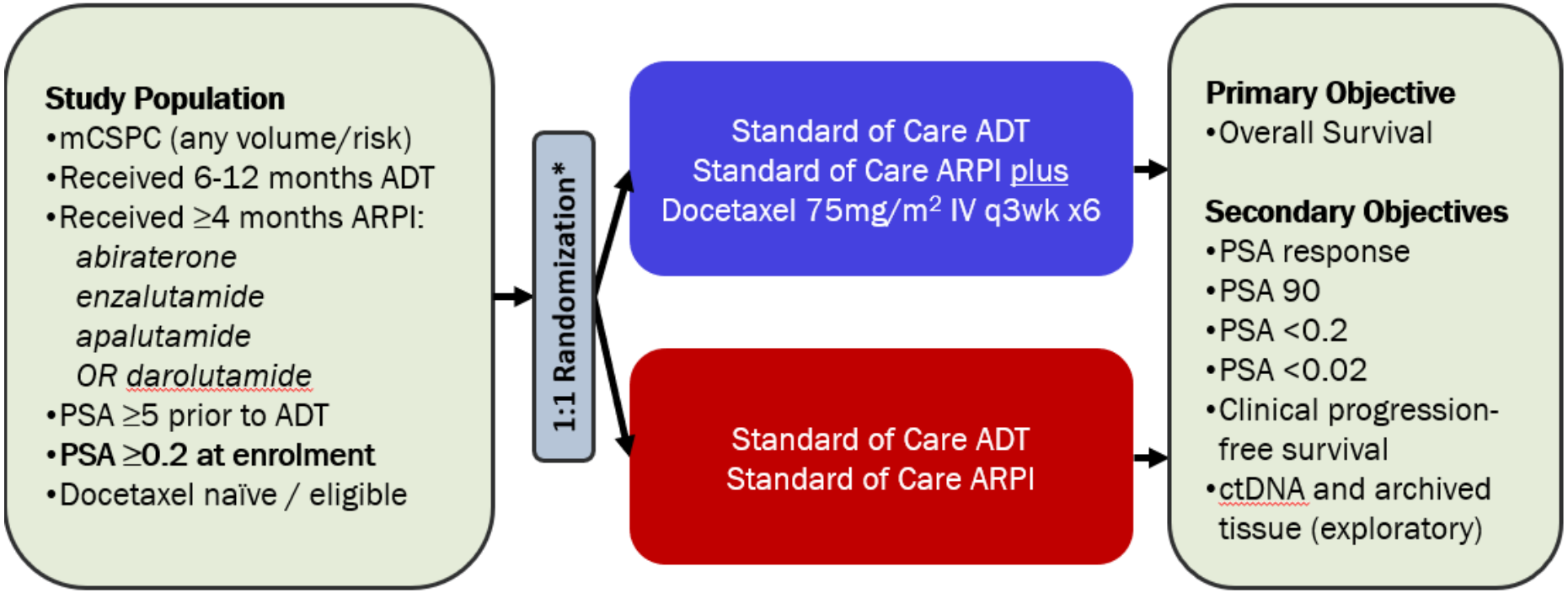
Median OS = 40.3 mo

Saad *et al AUA* 2023

Adapted from A. Sokolova

Chowdhury S, et al. *Ann Oncol*. 2023;34(5):477-485. Roy S, Ung M. 2024;Unpublished. Matsubara N, et al. *Eur Urol*. 2020;77(4):494-500. Szmulewitz RZ. Presented at: 2023 SESAUA annual meeting; March 18-21, 2026; Río Grande, PR. Gebrael G, et al. *Prostate Cancer Prostatic Dis*. 2024;27(2):279-282. Gravis-Mescam G, et al. Presented at: 2022 ESMO annual meeting; September 9-13, 2022; Paris, France. Saad F, et al. Presented at: 2023 AUA annual meeting; April 28-May 1, 2023; Chicago, IL.

Coop Groups will try to fill knowledge gaps in mHSPC: Triple Switch - using inadequate PSA nadir to selectively use triplet

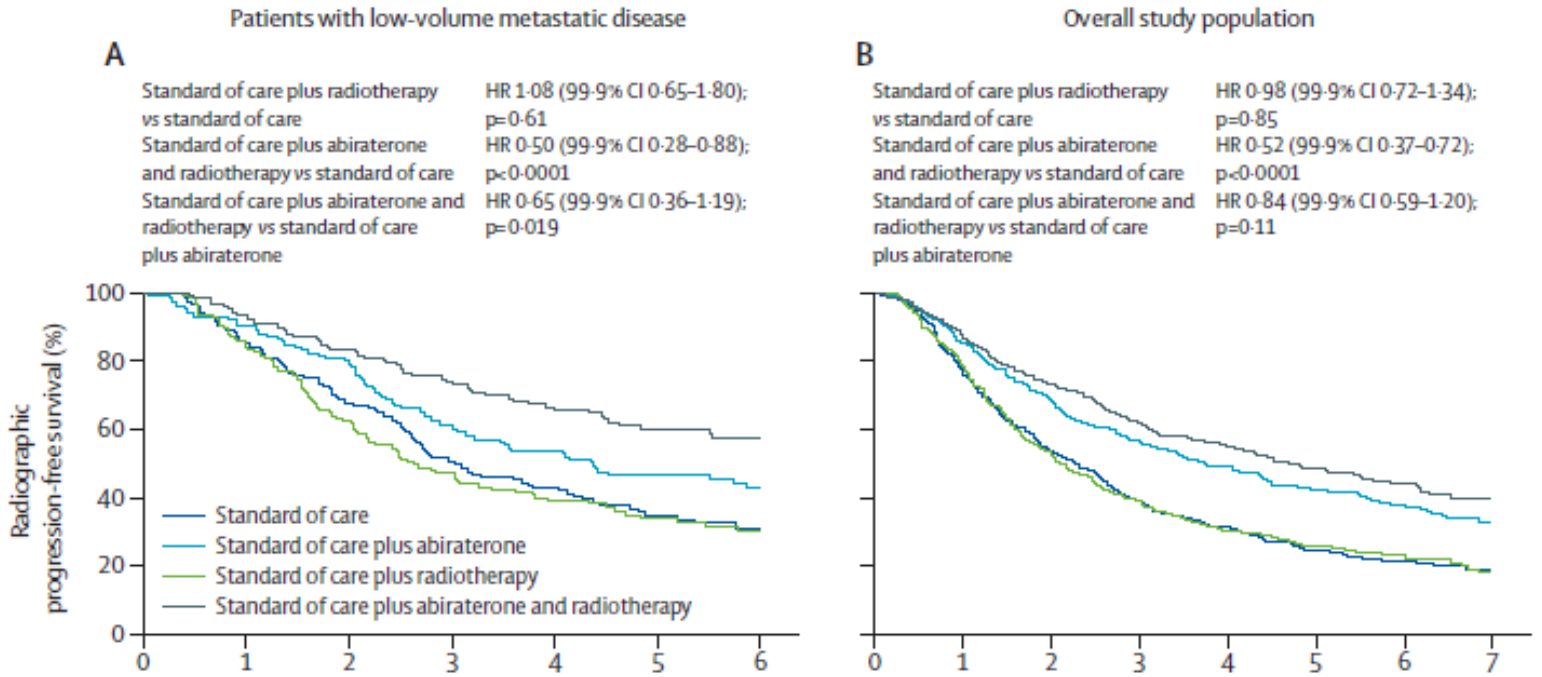


Triple Switch (PR26): *Actively enrolling*

ARPI = androgen receptor pathway inhibitor.

UroToday. Accessed October 2025. https://www.urotoday.com/conference-highlights/asco-2025/asco-2025-prostate-cancer/160788-asco-2025-triple-switch-swog-cctg-pr26-a-randomized-phase-iii-clinical-trial-for-the-addition-of-docetaxel-to-androgen-receptor-pathway-inhibitors-in-patients-with-mcspc-and-suboptimal-psa-response.html.

PEACE-1: impact of RT to prostate primary



Number at risk (number censored)

Standard of care	127 (0)	108 (0)	86 (0)	64 (0)	53 (1)	34 (11)	20 (22)	296 (0)	223 (2)	157 (2)	115 (2)	90 (4)	54 (23)	30 (41)	13 (55)
Standard of care plus abiraterone	126 (0)	113 (1)	96 (4)	73 (5)	64 (5)	46 (15)	31 (27)	292 (0)	246 (3)	195 (6)	159 (8)	139 (8)	98 (31)	63 (57)	27 (86)
Standard of care plus radiotherapy	126 (0)	105 (1)	77 (2)	58 (2)	48 (2)	36 (8)	23 (18)	293 (0)	228 (2)	152 (4)	112 (5)	86 (5)	61 (19)	34 (41)	12 (57)
Standard of care plus abiraterone and radiotherapy	126 (0)	116 (0)	105 (0)	89 (3)	79 (4)	60 (17)	34 (41)	291 (0)	249 (4)	211 (4)	174 (7)	153 (8)	108 (38)	60 (78)	26 (107)

Overall survival not improved:
6.9 years SOC +/- abi vs 7.5 years for SOC +/- RT +/- abi (HR 0.98)

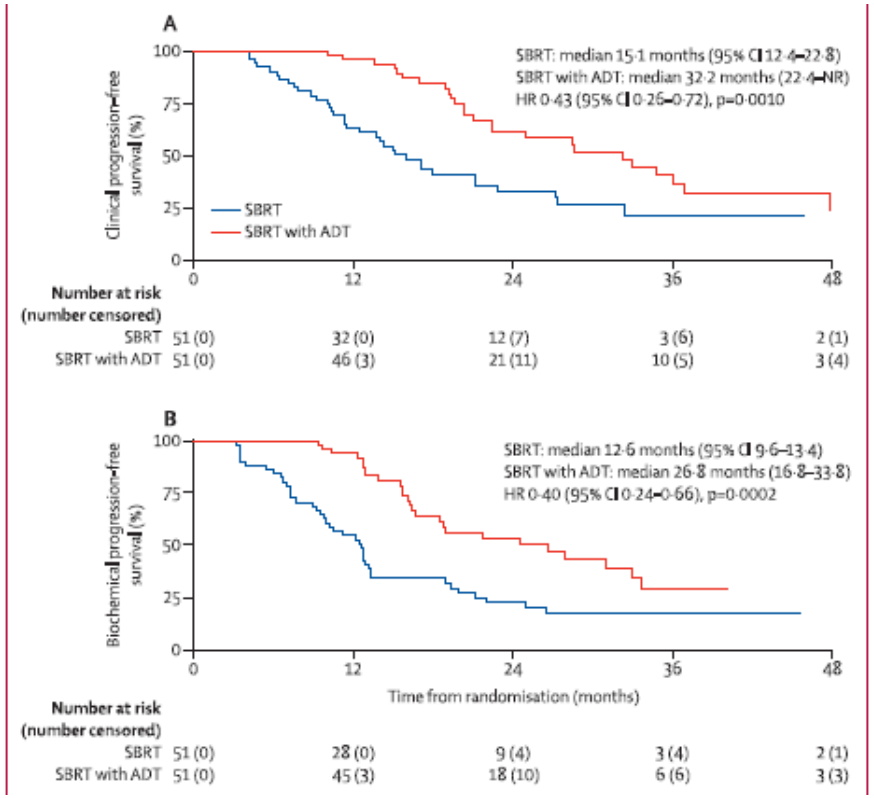
SOC = standard of care; abi = abiraterone.

Bossi A, et al. *Lancet*. 2024;404(10467):2065-2076.

Metastasis directed radiation for oligomet PCa

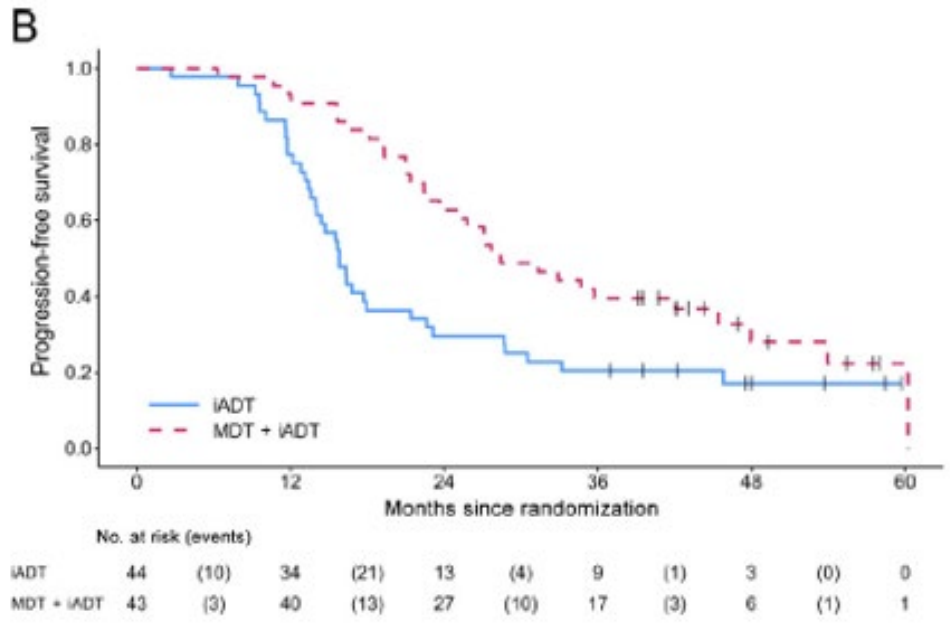
RADIOSA: SBRT + ADT vs SBRT alone

- 1-3 mets (60% PSMA PET)
- PFS 32 mo for combination,15 mo for SBRT alone (HR 0.43)



EXTEND: ADT vs ADT + SBRT

- 1-5 mets, allowed intermittent or continuous ADT
- Combined analysis: PFS 36 mo MDT + ADT vs 17 mo for ADT alone



SBRT = stereotactic body radiotherapy; PFS = progression-free survival.

Marvaso G, et al. *Lancet Oncol*. 2025;26(3):300-311. Sherry AD, et al. *Eur Urol*. 2025:S0302-2838(25)00396-3.

DNA testing: Somatic

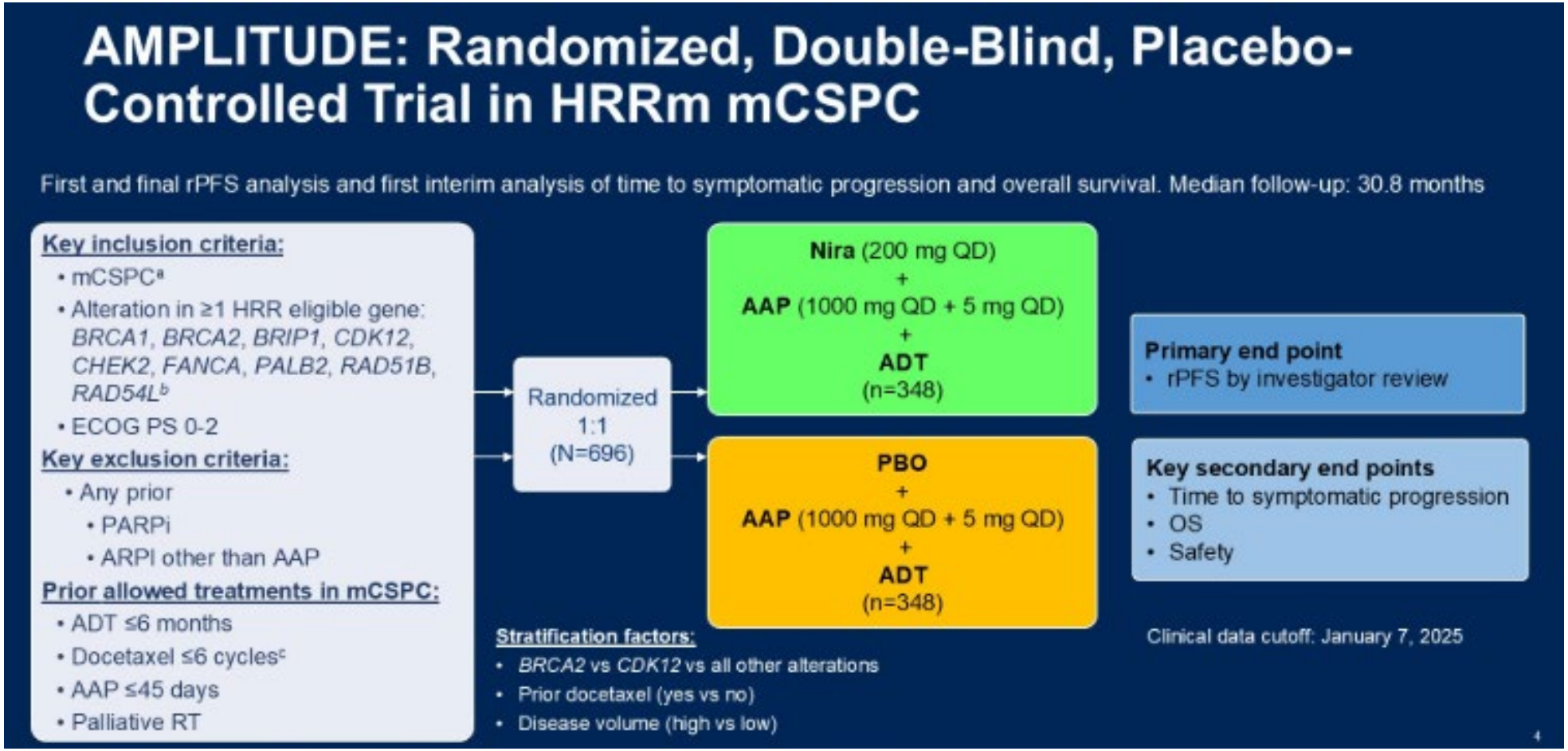
Going beyond HRR / PARPi and moving to earlier actionability!

- HRR alterations (BRCA and others) → PARP inhibitors
  - These can arise in the tumor cells, and can emerge during treatment
- MSI, high TMB → pembrolizumab
- TP53, RB1, PTEN → aggressive variant

- PTEN del → capivasertib (mHSPC)

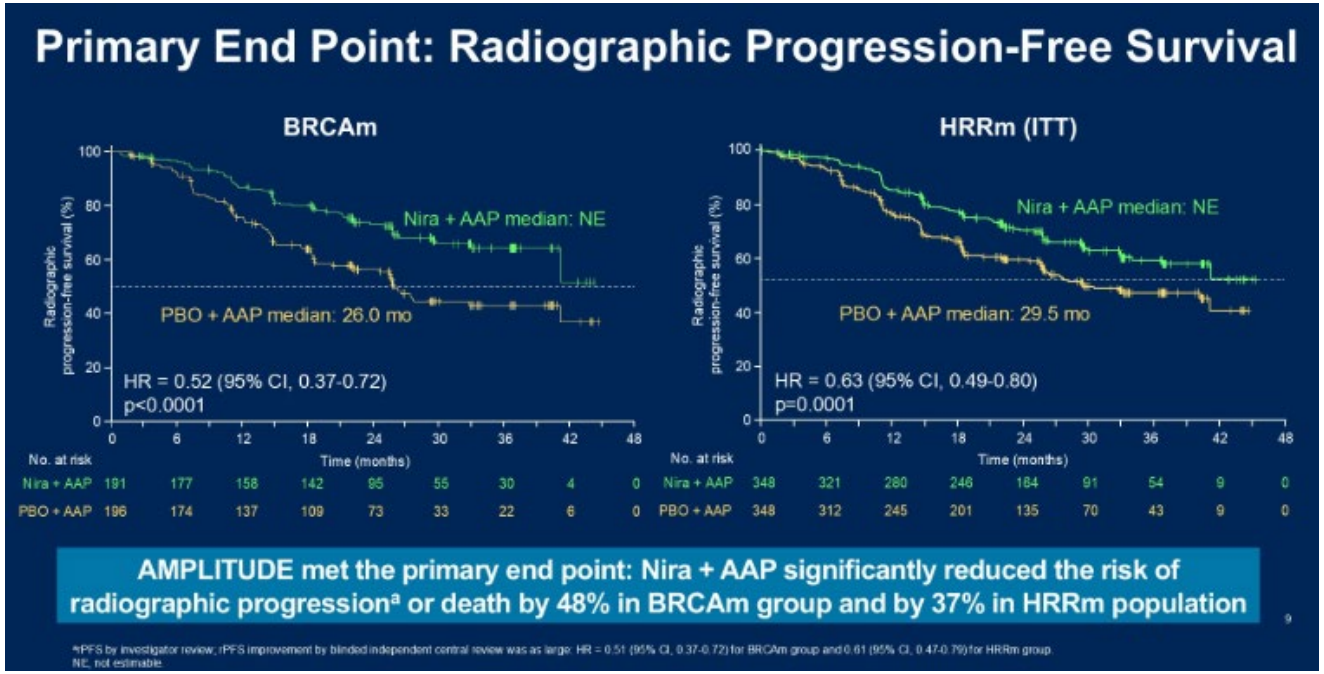
HRR = homologous recombination repair; PARPi = PARP inhibitor; BRCA = breast cancer; MSI = microsatellite instability; TMB = tumor mutational burden.

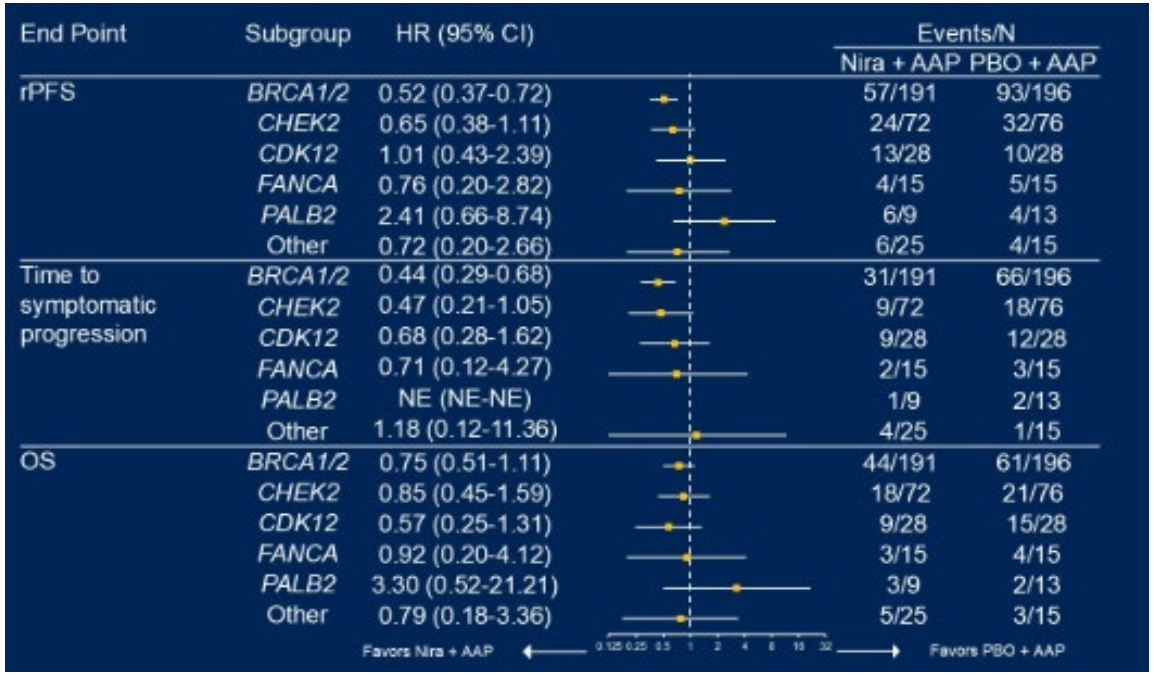
AMPLITUDE: study design



[a]Patients with lymph node-only disease are not eligible; [b]HRR gene panel was fixed prior to trial initiation based on MAGNITUDE trial and external data from the published literature; [c]Last dose 3 months prior to randomization.
AAP = abiraterone acetate plus prednisone; ECOG PS = Eastern Cooperative Oncology Group performance status; Nira = niraparib; PBO = placebo.
UroToday. Accessed October 2025. https://www.urotoday.com/conference-highlights/asco-2025/asco-2025-prostate-cancer/161080-asco-2025-phase-3-amplitude-trial-niraparib-and-abiraterone-acetate-plus-prednisone-for-metastatic-castration-sensitive-prostate-cancer-patients-with-alterations-in-homologous-recombination-repair-genes.html.

AMPLITUDE: positive for rPFS primary endpoint





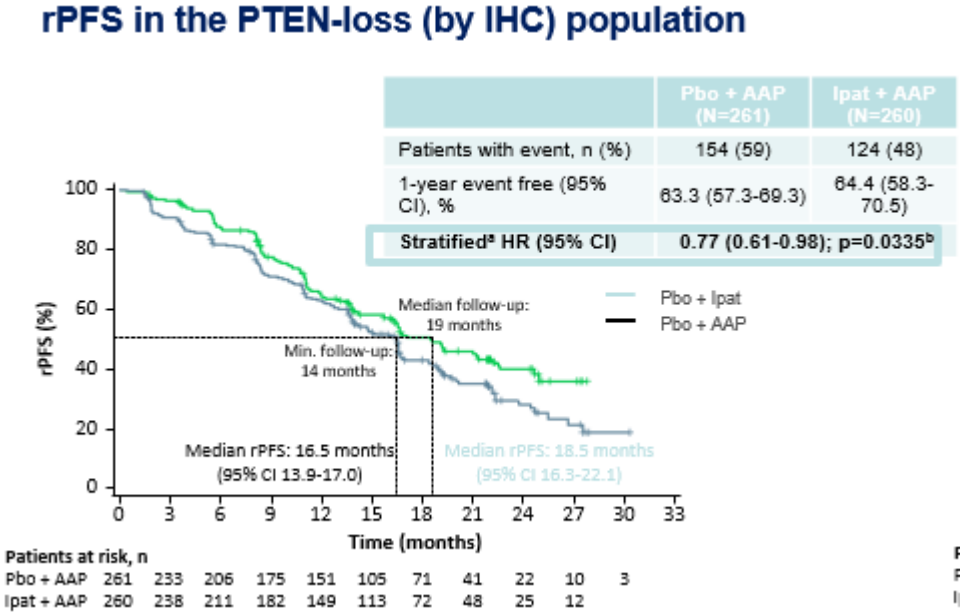
- Control arm has >2 years rPFS
- Increase in grade 3 or 4 TEAEs from 59% to 75%, SAE 13% vs 3%
- 1 MDS on niraparib arm, 0 on control

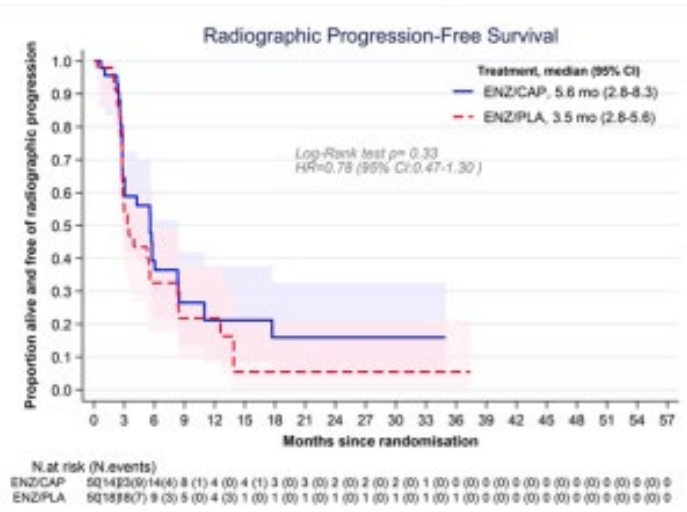
TEAE = treatment-emergent adverse events; SAE = serious adverse event; MDS = myelodysplastic syndrome.

Attard G. LBA 5006. Presented at: ASCO Annual Meeting 2025; May 30 – June 3, 2025; Chicago, IL.

Capivasertib in mHSPC: Capitello trial (press release + for rPFS)

- PI3k/AKT pathway activated in PCa (PTEN loss)
- In mCRPC abi +/- ipatasertib trial (IPaTential) was negative but molec selected population showed signal
- RE-AKT trial (enza + capivasertib) no signal but unselected and CRPC
- **Capitello is mHSPC, PTEN loss selected**



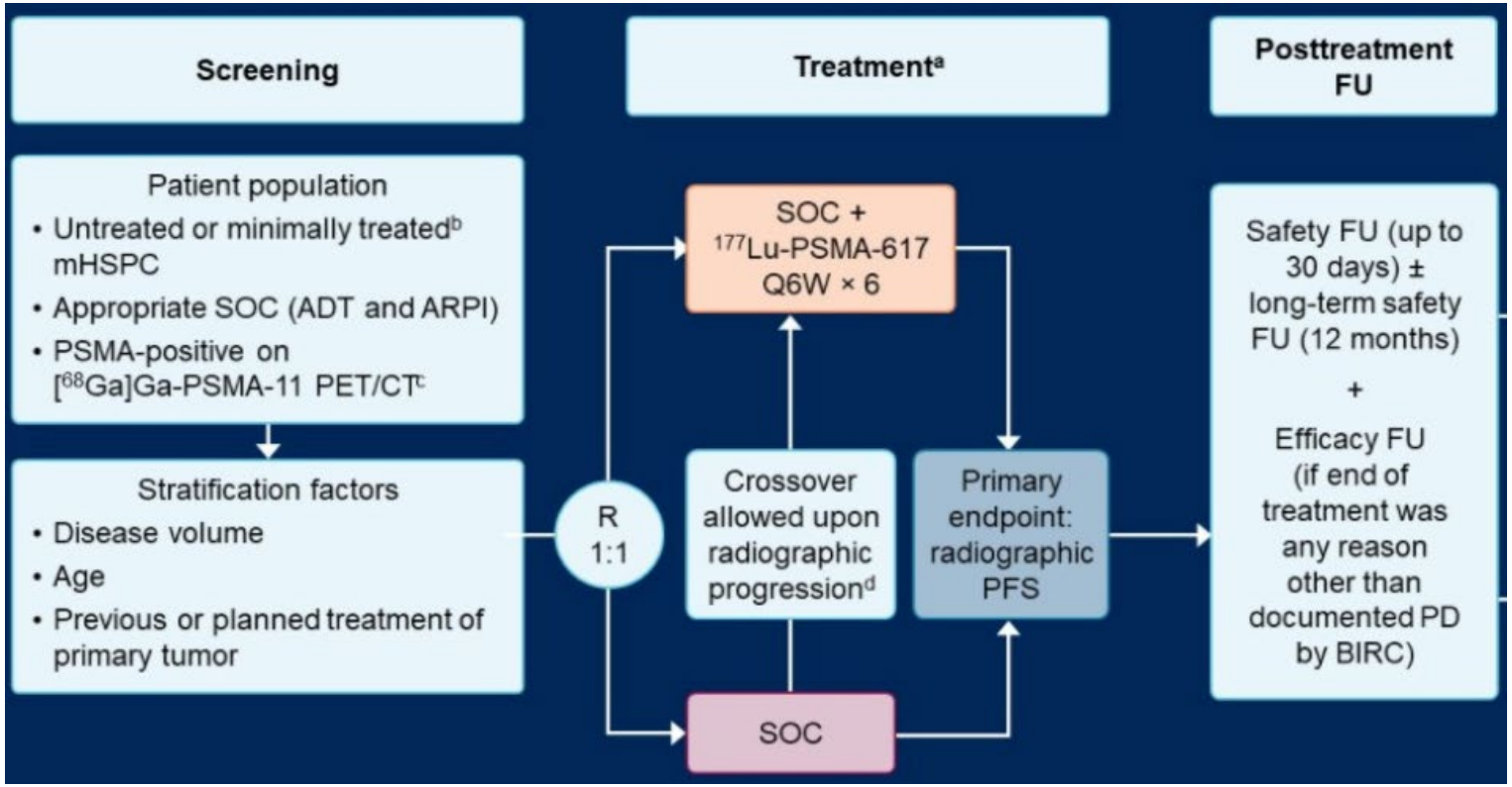


IHC = immunohistochemistry.

Sweeney C, et al. *Lancet*. 2021;398(10295):131-142. Rescigno P, et al. *Eur J Cancer*. 2024;205:114103.

PSMAddition

- PSMAFore found benefit for RLT prior to docetaxel
  - 177Lu-PSMA-617 is a highly effective agent
- But concerns in translating to mHSPC
  - VISION criteria for PSMA PET selection are not stringent
  - Dosing is same as in CRPC
  - Late (2nd malignancy) toxicity?



Completed accrual 10/2023, to be presented at ESMO 2025

RLT = radioligand therapy; FU = follow-up; PD = progressive disease; BIRC = blinded independent review committee.

mHSPC

Unmet needs

- Biomarkers to select patients for triplet vs doublet
  - Soon between various triplet options
- Categorizing patients by PSMA PET vs conventional imaging
  - Intermittent therapy vs continuous in PET–detected metastatic disease
- Response assessment by PSMA PET

- Keeping patients healthy during long-term ADT

NCI: FAST-PRO study design

- Metastatic hormone-sensitive prostate cancer starting doublet
- 6 cycles of 5-day FMD (once per month x 6 months)
- Goal: increase those who achieve PSA nadir ≤0.2 by 12 months to 81%
  - Also time to castration resistance
- And reduce incident diabetes

Freedand, Lin, Dorff multi-PI R01
21/138 accrued

FMD = fasting-mimicking diet.

How can we best mitigate negative impact of ADT on cardiovascular health?

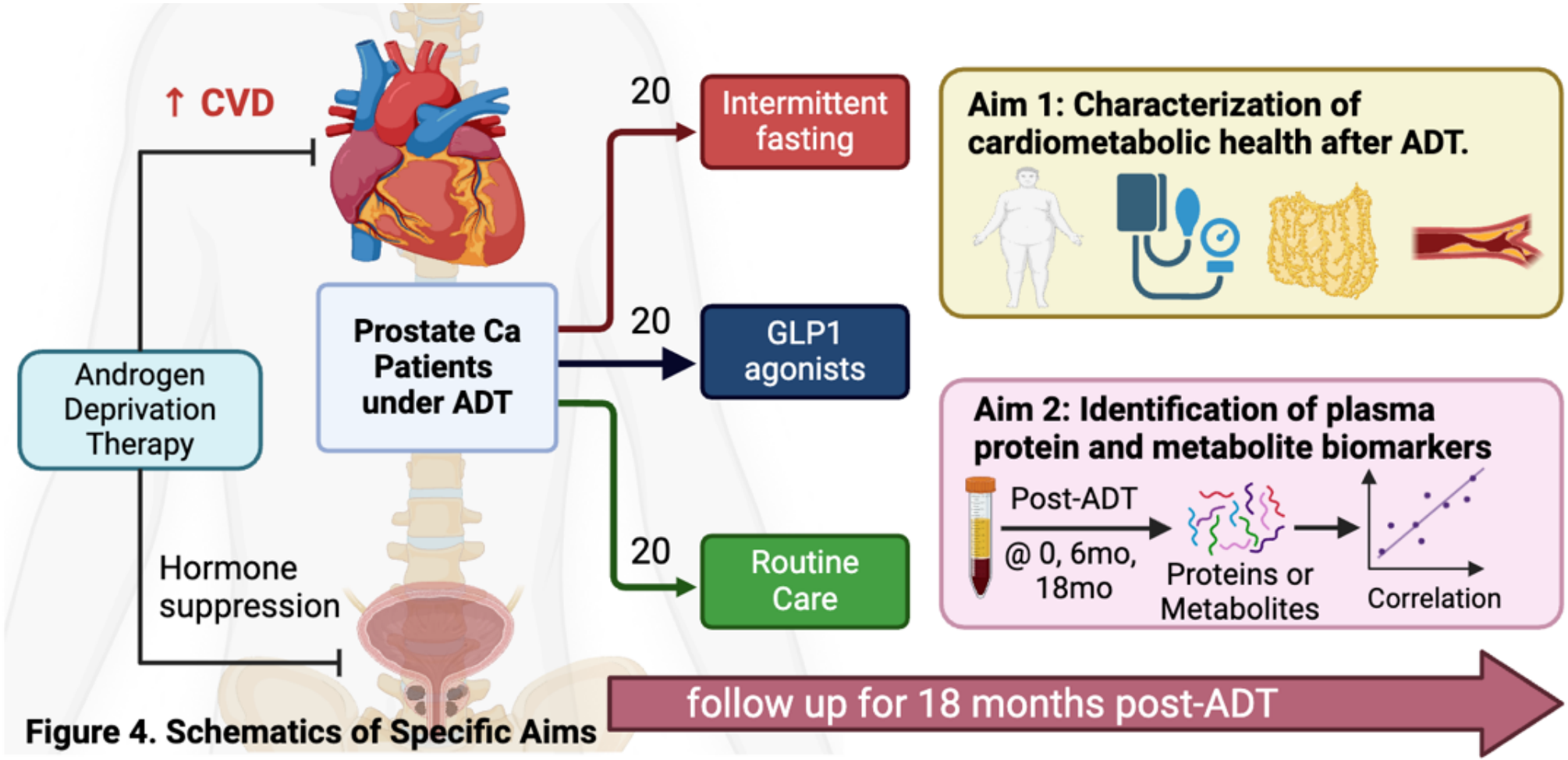


Figure 4. Schematics of Specific Aims

CVD = cardiovascular disease.

Dorff TL, Li R, Rhee J-W. Clinical Trials ID: NCT07202247.

mCRPC: current landscape

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA

Pre-ARPI	Post-ARPI / Pre-Docetaxel	Post-ARPI / Post-Docetaxel
Preferred: • Abiraterone (category 1) • Enzalutamide (category 1) **Other Recommended:** • Docetaxel (category 1) **Useful in Certain Circumstances:** • Molecular Biomarker–Directed Therapy ▸ BRCA mutation ◊ Niraparib/abiraterone (category 1) ◊ Olaparib/abiraterone (category 1) ◊ Talazoparib/enzalutamide (category 1) ▸ HRRm (other than BRCA1/2) ◊ Talazoparib/enzalutamide (category 1) • Disease State–Specific Therapy ▸ Bone metastases ◊ Radium-223/enzalutamide	**Preferred:** • Docetaxel (category 1) **Useful in Certain Circumstances:** • Molecular Biomarker–Directed Therapy ▸ BRCA mutation ◊ Olaparib (category 1, preferred) ◊ Rucaparib (category 1, preferred) ◊ Niraparib/abiraterone (category 2B) ◊ Talazoparib/enzalutamide (category 2B) ▸ HRRm (other than BRCA1/2) ◊ Olaparib ◊ Talazoparib/enzalutamide (category 2B) • Disease State–Specific Therapy ▸ PSMA-positive metastases ◊ Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) ▸ Aggressive variant ◊ Cabazitaxel/Carboplatin	**Preferred:** • Cabazitaxel (category 1) • Docetaxel rechallenge **Useful in Certain Circumstances:** • Molecular Biomarker–Directed Therapy ▸ BRCA mutation ◊ Olaparib (category 1) ◊ Rucaparib ▸ HRRm (other than BRCA1/2) ◊ Olaparib ▸ Other FDA-approved agents for tissue agnostic indications • Disease State–Specific Therapy ▸ PSMA-positive metastases ◊ Lu-177–PSMA-617 (category 1) ▸ Aggressive variant ◊ Cabazitaxel/carboplatin ▸ Palliation for symptomatic patients unable to tolerate other therapies ◊ Mitoxantrone

Treatment options in m0 CRPC

Study Name Agent	SPARTAN Apalutamide 240 mg daily	PROSPER Enzalutamide 160 mg daily	ARAMIS Darolutamide 600 mg BID
Design	2:1 apa/placebo	2:1 enza/placebo	2:1 daro/placebo
Number of pts	1207	1401	1509
Inclusion:	PSA DT <10 mo Pelvic LN <2 cm OK	PSA DT ≤10 mo -- bPSA ≥2	PSA DT ≤10 mo Pelvic LN <2cm OK bPSA ≥2
Met Free Surv	40.5 mo vs 16.2 placebo (HR 0.29)	36.6 mo vs 14.7 placebo (HR 0.07)	40.4 mo vs 18.4 placebo (HR 0.41)
Discontinuation	10.7% apa, 6.3% placebo	10% enza, 8% placebo	8.9% daro, 8.7% placebo

DT = doubling time; LN = lymph nodes; bPSA = benign PSA.

Smith MR, et al. *N Engl J Med*. 2018;378(15):1408-1418. Hussain M, et al. *N Engl J Med*. 2018;378(26):2465-2474. Fizazi K, et al. *N Engl J Med*. 2019;380(13):1235-1246.

Apa-RP Clinical Trial – Proactive Rash Management in Patients Receiving Apa

Proactive Rash Management Guide

Based on data collected in the SPARTAN and TITAN studies, **a patient-empowered rash management guide** was developed as **a proactive approach to improve rash-related outcomes**, which were evaluated in the Apa-RP study

Patients were provided with education on gentle skin care during visits and phone calls with the care team

USE

- ✓ Gentle emollients (lotion) daily after any other prescribed topical steroid lotion has dried
- ✓ Antiseptic-containing soap substitute or mild pH-neutral soap
- ✓ Sunblock (SPF 50) when outdoors
- ✓ For patients with preexisting eczema: intensify usual skin care routine

AVOID

- × Strong sun and weather extremes
- × Long, hot baths, showers, and saunas (use tepid water for bathing)
- × Alcohol-based and fragranced skin-care products

Apa-RP

- Phase 2, single-arm, multicenter study
- Treatment-naive patients with **high-risk localized prostate cancer**
- Study conducted among US urology practices
- Patients were provided with the rash management guide outlining recommended skin care practices

Radical prostatectomy followed by adjuvant Apa (240 mg) + ADT qd (N=108)

Primary Endpoint: Biochemical recurrence-free rate at 24 months, defined as PSA >0.2 ng/mL

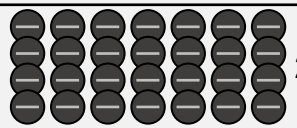
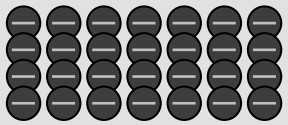
Rash-related safety data from **Apa-RP** were **compared descriptively** with data from:

- **SPARTAN** (phase 3 in nmCRPC)
- **TITAN** (phase 3 in mHSPC)

nmCRPC = non-metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer.

Shore N, et al. *Prostate Cancer Prostatic Dis*. 2025;28(3):828-831. ClinicalTrials.gov. Accessed May 30, 2025. https://www.clinicaltrials.gov/study/NCT04523207.

Dosing and Administration for ARPI in mHSPC

	Dosing		Administration	Mean Half Life	Absorption
	Daily	Weekly			
Darolutamide	**2 tablets bid** (300 mg each)	 **28 tablets**	• Swallow whole **with food**	20 hours	30% Bioavailability **enhanced** 2.0- to 2.5-fold by food
Apalutamide	**1 tablet qd** (240 mg)	 **7 tablets**	• Swallow whole **with or without food** • Can be dispersed in non-carbonated water then administered in water, orange juice, applesauce, or additional water	~3 days	100% Not impacted by food
	4 tablets qd (60 mg each)	 **28 tablets**			
Enzalutamide	**2 tablets qd** (80 mg each)	 **14 tablets**	• Swallow whole **with or without food**	5.8 days	85% (estimated)
	4 tablets or capsules qd (40 mg each)	 **28 tablets**			
Abiraterone	**2 tablets qd** (500 mg each) + 5 mg prednisone qd	 **14 tablets**	• Swallow whole **without food** –With water –No food 2 hours before and 1 hour after taking Abi	12 hours ± 5 hours	≤10% (estimated) Absorption **impacted** by fat
	4 tablets qd (250 mg each) + 5 mg prednisone qd	 **28 tablets**			

Darolutamide PI. Drugs@FDA: FDA-Approved Drugs. Accessed October 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/212099s008lbl.pdf. Apalutamide PI. Drugs@FDA: FDA-Approved Drugs. Accessed October 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/210951s016lbl.pdf. Enzalutamide PI. Drugs@FDA: FDA-Approved Drugs. Accessed October 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/203415s024,213674s012lbl.pdf. Gibbons JA, et al. *Clin Pharmacokinet*. 2015;54(10):1043-1055. Abiraterone acetate PI. FDA-Approved Drug. Janssen Biotech, Inc. Accessed October 2025. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ZYTIGA-pi.pdf. Schultz HB, et al. *Int J Pharmaceutics*. 2020;577:119069.

Adverse Events w/ ARPi in nmCRPC

Safety	SPARTAN		PROSPER		ARAMIS	
	APA (n = 803)	PBO (n = 398)	ENZA (n = 930)	PBO (n = 465)	DARO (n = 954)	PBO (n = 554)
Any AEs, n (%)	775 (96.5)	371 (93.2)	808 (87)	360 (77)	794 (83.2)	426 (76.9)
Any serious AEs, n (%)	199 (24.8)	92 (23.1)	226 (24)	85 (18)	237 (24.8)	111 (20.0)
AEs leading to discontinuation, %	11.0	7.0	9.0	6.0	8.9	8.7
AEs leading to death, n (%)	10 (1.2)	1 (0.3)	32 (3.4)	3 (0.7)	37 (3.9)	18 (3.2)
AEs (all grades), %						
Fatigue	30.4	21.1	33.0	14.0	12.1	8.7
Hypertension	24.8	19.8	12.0	5.0	6.6	5.2
Rash	23.8	5.5	0	0	2.9	0.9
Falls	15.6	9.0	11.0	4.0	4.2	4.7
Fractures	11.7	6.5	N/A	N/A	4.2	3.6
Mental impairment disorders	5.1	3.0	5.0	2.0	0.4	0.2

Smith MR et al. *N Engl J Med*. 2018;378:1408-1418. Hussain M et al. *N Engl J Med*. 2018;378:2465-2474. Fizazi K et al. *N Engl J Med*. 2019;380:1235-1246.

AE = adverse event.

Smith MR, et al. *N Engl J Med*. 2018;378(15):1408-1418. Hussain M, et al. *N Engl J* Med. 2018;378(26):2465-2474. Fizazi K, et al. *N Engl J Med*. 2019;380(13):1235-1246.

PARP inhibitors in prostate cancer: summary of approvals

Olaparib	PROFOUND	mCRPC post ARPI, pre or post docetaxel	OS HR 0.69 (crossover adjusted 0.42) for BRCA + ATM
Rucaparib	TRITON-3	mCRPC post ARPI, post doce only in HSPC	rPFS HR 0.61 (0.50 in BRCA subgroup)
Abiraterone + Olaparib	PROPEL	mCRPC without prior ARPi	OS HR 0.66 in HRR altered
Enzalutamide + Talazoparib	TALAPRO-2	mCRPC without progression on ARPi	OS HR 0·80 [95% CI 0·66-0·96] in all comers, HR 0·55 in HRR altered
Abiraterone + Niraparib	MAGNITUDE	mCRPC without progression on ARPi	OS HR 0.785, 95% CI 0.606-1.016 in HRR altered, HR 0.66 in BRCA+

- HRR alterations remain a main selection factor, either germline or somatic, and by tissue or by ctDNA
- **New indications: combination with ARPI in 1st line CRPC and soon mHSPC**

ctDNA = circulating tumor DNA.

de Bono J, et al. *N Engl J Med*. 2020;382(22):2091-2102. Fizazi K, et al. *N Engl J Med*. 2023;388(8):719-732. Saad F, et al. *Lancet Oncol*. 2023;24(10):1094-1108. Agarwal N, et al. *Lancet*. 2025;406(10502):447-460. Chi KN, et al. *Eur Urol Oncol*. 2025;8(4):986-998.

PARP inhibitors: Common Hematologic AEs

- Anemia
- Thrombocytopenia
- Neutropenia

Watch for

Worsening fatigue
Shortness of breath
s/s bleeding
s/s infection

- Monitor CBC/diff
- Consider dose holds
- Transfuse as needed
- Consider restarting at reduced dose
- Refer to package insert

Rare but serious
MDS, AML

PARP = poly(ADP-ribose) polymerase; s/s = signs and symptoms; CBC = complete blood count; MDS = myelodysplastic syndrome; AML = acute myeloid leukemia.

Common non hematologic AEs

Olaparib*	Rucaparib	Niraparib	Talazoparib*
Fatigue	Fatigue	Fatigue	Fatigue
Nausea	Nausea	Nausea	Nausea
Diarrhea	Vomiting	Vomiting	Anorexia
Anorexia	Anorexia	Anorexia	Fractures
Dizziness	Diarrhea	Constipation	Dizziness
HTN	Rash	Rash	Dysgeusia
Pneumonitis	Hepatoxicity	Insomnia	
VTE		HTN	
Hepatoxicity		PRES	
*Given in combination with abiraterone and prednisone			*given in combination with enzalutamide

HTN = hypertension; VTE = venous thromboembolism; PRES = posterior reversible encephalopathy syndrome.

Dose modifications for AEs

Dose modifications for TALZENNA® may help manage adverse reactions[1]

Adverse Reactions	Withhold TALZENNA Until Levels Resolve To	Resume TALZENNA
Hemoglobin < 8 g/dL	≥ 9 g/dL	Resume TALZENNA at a reduced dose
Platelet count < 50,000/µL	≥ 75,000/µL	Resume TALZENNA at a reduced dose
Neutrophil count < 1000/µL	≥ 1500/µL	Resume TALZENNA at a reduced dose
Non-hematologic Grade 3/4	≤ Grade 1	Consider resuming TALZENNA at a reduced dose or discontinue

♦ The TALAPRO-2 study protocol allowed for the use of supportive care growth factors and/or transfusions to help manage anemia or other cytopenia-related ARs[2]

RECOMMENDED STARTING DOSE	DOSE REDUCTIONS FOR ADVERSE REACTIONS		
	1st DOSE REDUCTION	2nd DOSE REDUCTION	3rd DOSE REDUCTION
			
0.5 mg once daily	0.35 mg once daily	0.25 mg once daily	0.1 mg once daily

Not actual size.

To manage adverse reactions (ARs), consider[1]:

DOSE INTERRUPTION OR **DOSE REDUCTION**

Consider dose interruption if a patient experiences an AR

Consider a dose reduction if a patient experiences an AR

INITIAL REDUCTION

Reduce to 150 mg 100 mg

Initial reduction to 250 mg (one 150-mg tablet and one 100-mg tablet) taken twice daily (total 500 mg daily)

FURTHER REDUCTION

Reduce to 100 mg 100 mg

Further reduction to 200 mg (two 100-mg tablets) taken twice daily (total 400 mg daily)

Tablets shown are not actual size.

COMBINATION THERAPY

LYNPARZA®
Recommended Daily Dose
300 mg (two 150-mg tablets) **taken orally, twice daily**
(total 600 mg daily) with or without food

150 mg 150 mg *2x daily*

with food or without food

+

abiraterone
1000 mg **taken orally, once daily** 500 mg 500 mg *1x daily*
Abiraterone must be taken on an empty stomach. No food should be consumed for at least 2 hours before the dose of abiraterone is taken and for at least 1 hour after the dose of abiraterone is taken.
Refer to the Prescribing Information for abiraterone for complete dosing information for that product.
without food

with
prednisone or prednisolone
5 mg **taken orally, twice daily** (total 10 mg daily) 5 mg *2x daily*
Refer to Prescribing Information for prednisone or prednisolone for complete dosing information for those products.

MONOTHERAPY

LYNPARZA®
Recommended Daily Dose
300 mg (two 150-mg tablets)
taken orally, twice daily
(total 600 mg daily)
with or without food

150 mg 150 mg *2x daily*

with food or without food

Tablets shown are not actual size.

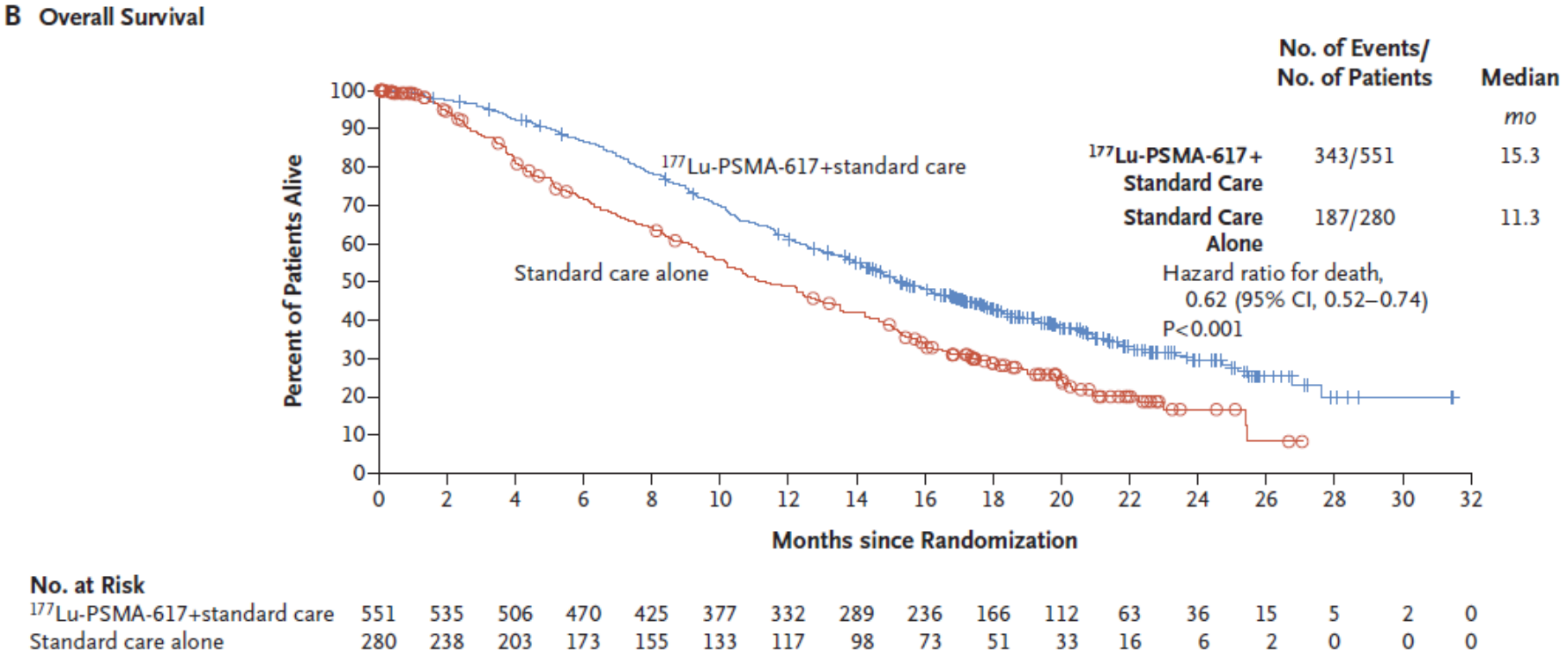
For monotherapy and combination therapy

- Continue treatment until disease progression or unacceptable toxicity.
- Inform patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice while taking LYNPARZA®.
- Patients receiving LYNPARZA® for mCRPC should also receive a GnRH analog concurrently or should have had bilateral orchiectomy.
- If a patient misses a dose of LYNPARZA®, instruct patient to take their next dose at its scheduled time. Instruct patient to swallow tablets whole. Do not chew, crush, dissolve or divide tablet.
- This is not all dosing and administration information necessary to dose LYNPARZA®. Please see full Prescribing Information.

Pfizer. Accessed October 2025. https://talzennaxtandi.pfizerpro.com/dosing/dosing-and-administration. Lynparza. Accessed October 2025. https://www.lynparzahcp.com/prostate-cancer/dosing.html.

FDA approved: Lu-177-PSMA vipivotide tetraxetan

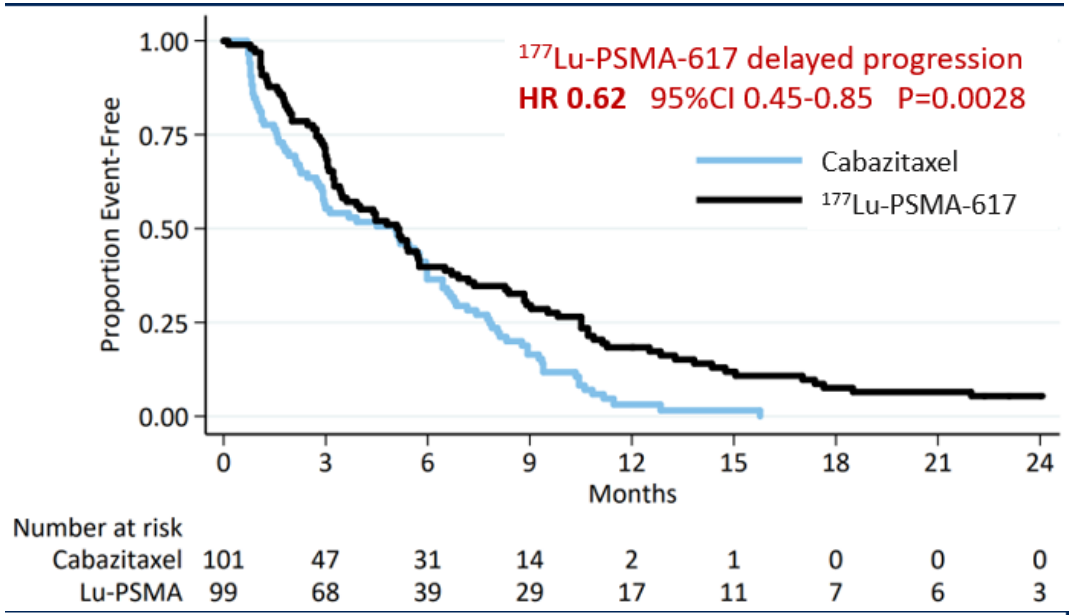
- VISION trial = phase III in post docetaxel mCRPC, randomized to "best standard care" (ARPI switch)
  - 40% with 2 prior taxane regimens

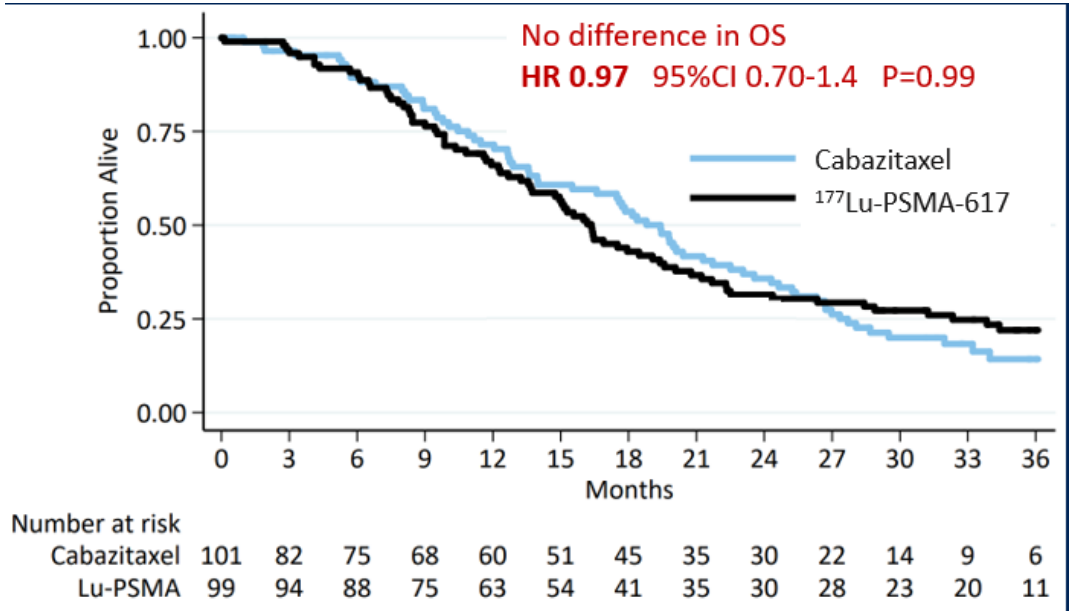


7.4 GBq every 6 weeks for up to 6 doses
- 5.7% had dose reduction, 16% interruption

Sartor O, et al. *N Engl J Med*. 2021;385(12):1091-1103.

TheraP (Lu177-PSMA-617 vs Cabazitaxel)





- **Inclusion: PSMA SUVmax >20 at any site and no FDG+/PSMA- sites (28% excluded)**

	[177Lu]Lu-PSMA-617 (n=98)		Cabazitaxel (n=85)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Fatigue	69 (70%)	5 (5%)	61 (72%)	3 (4%)
Pain*	60 (61%)	11 (11%)	52 (61%)	4 (5%)
Dry mouth	59 (60%)	0	18 (21%)	0
Diarrhoea	18 (18%)	1 (1%)	44 (52%)	4 (5%)
Nausea	39 (40%)	1 (1%)	29 (34%)	0
Thrombocytopenia	18 (18%)	11 (11%)	4 (5%)	0
Dry eyes	29 (30%)	0	3 (4%)	0
Anaemia	19 (19%)	8 (8%)	11 (13%)	7 (8%)
Neuropathy†	10 (10%)	0	22 (26%)	1 (1%)
Dysgeusia	12 (12%)	0	23 (27%)	0
Haematuria	3 (3%)	1 (1%)	12 (14%)	5 (6%)
Neutropenia‡	7 (7%)	4 (4%)	4 (5%)	11 (13%)
Insomnia	9 (9%)	0	12 (14%)	1 (1%)
Vomiting	12 (12%)	1 (1%)	10 (12%)	2 (2%)
Dizziness	4 (4%)	0	11 (13%)	0
Leukopenia	10 (10%)	1 (1%)	5 (6%)	1 (1%)
Any adverse event	53 (54%)	32 (33%)	34 (40%)	45 (53%)

Data are n (%). Events that occurred in at least 10% of participants are shown. 177Lu=Lutetium-177. PSMA=prostate-specific membrane antigen. *Including bone, buttock, chest wall, flank, neck, extremity, tumour pain, or pelvic pain. †Motor or sensory. ‡Febrile neutropenia.

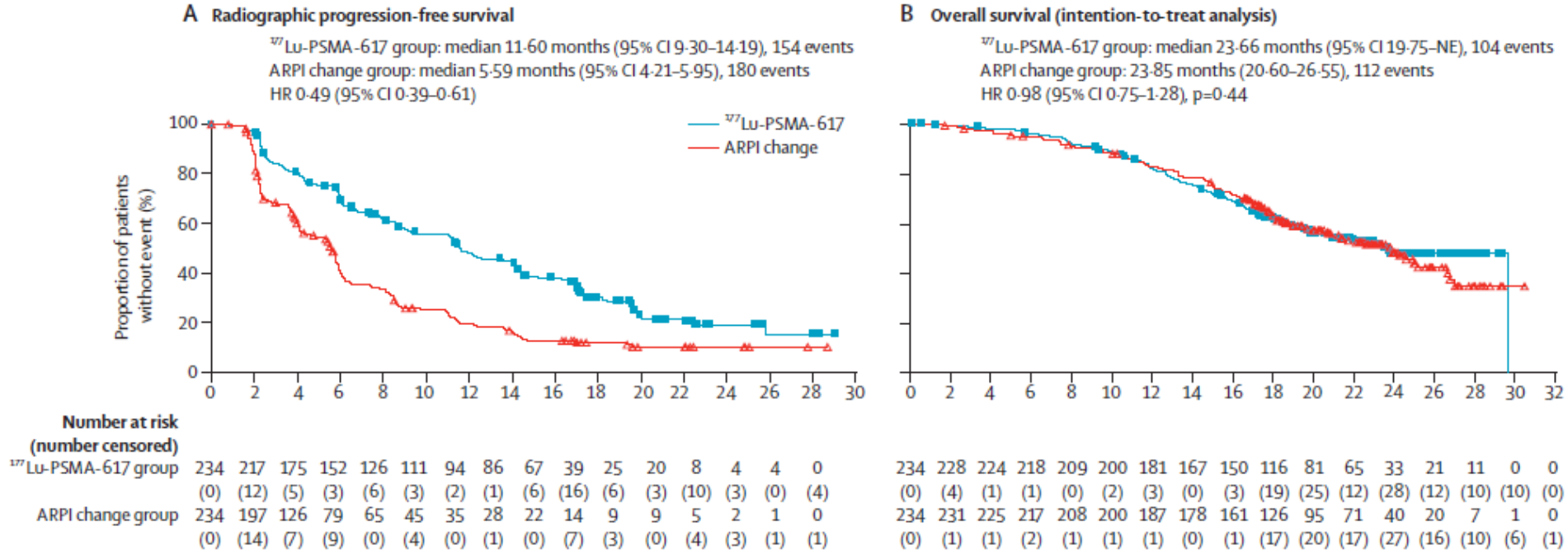
Table 2: Adverse events

SUV_{max} = maximum standardized uptake value; FDG = [^{18}F]Fluorodeoxyglucose.

Hofman MS, et al. *Lancet*. 2021;397(10276):797-804.

PSMAfore: mCRPC post ARPi, pre-docetaxel

- PSMA PET criteria same as VISION (72 excluded, n=468)
- Randomization to 177-Lu-PSMA-617 vs 2nd ARPi
  - Crossover allowed
- rPFS HR 0.41 (med 12 mo w/ PSMA RLT, 5.6 w/ 2nd ARPi)
  - ORR 41.9% with PSMA RLT vs 13% with 2nd ARPi



Morris MJ, et al. *Lancet*. 2024;404(10459):1227-1239.

Lu-177 Radiation Precautions

Stay apart. Limit close contact (less than 3 feet) with household contacts for 2 days.

- Limit close contact with children or pregnant women for 7 days

Sleep in a separate bedroom from household contacts for 3 days, from children for 7 days, or from pregnant women for 15 days.

Plan to use protection.

After each dose, there should be **no sexual activity for 7 days.** Use effective birth control over the entire course of treatment and for 14 weeks after the last dose.

Drink plenty of water before and after each dose and urinate (pee) as often as possible. This will help get rid of extra radiation in your body.

After each dose

Your body, blood, and urine give off radiation for a while after getting PLUVICTO. Always follow your doctors' instructions. Also, here are some tips to help reduce overall exposure to yourself and others:

Lu-177 Most common side effects

PSMAfore: ADVERSE REACTIONS OCCURRING AT ≥10% INCIDENCE IN PATIENTS WHO RECEIVED PLUVICTO[1,a]

	PLUVICTO (n=227)		Change in ARPI (n=232)	
Adverse reactions	All grades (%)	Grades 3 or 4 (%)	All grades (%)	Grades 3 or 4 (%)
Gastrointestinal disorders				
Dry mouth[b]	61	0.9	2.6	0
Nausea	32	0	12	0.4
Constipation	22	0.4	14	0
Diarrhea	17	0	9	0.4
Vomiting	11	0	4.7	0
Chemistry				
Fatigue[b]	53	1.3	53	5
Metabolism and nutrition disorders				
Decreased appetite	22	0	19	0.4
Musculoskeletal and connective tissue disorders				
Arthralgia	20	0	23	0.4
Back pain	14	1.3	20	1.6

	PLUVICTO[a]		Change in ARPI[b]	
Laboratory abnormalities	All grades (%)	Grades 3 or 4 (%)	All grades (%)	Grades 3 or 4 (%)
Hematology				
Decreased lymphocytes	78	27	57	12
Decreased hemoglobin	67	7[c]	50	7[c]
Decreased neutrophils	38	3.5	18	1.3
Decreased platelets	30	2.7	11	1.7
Chemistry				
Increased alkaline phosphatase	31	8	50	10[c]
Decreased estimated glomerular filtration rate	23	0.9[c]	22	3.5
Increased magnesium	19	0.9[c]	28	0[c]
Decreased calcium	18	0.9	11	0.9
Decreased sodium	11	0[c]	18	0[c]
Decreased potassium	6	0.9[c]	18	2.6

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.[13]
[b] Includes multiple similar terms.[1]

Morris MJ, et al. *Lancet*. 2024;404(10459):1227-1239.

Lu-177 dose modifications

Adverse reaction	Severity	Dosage modification
Myelosuppression (anemia, thrombocytopenia, leukopenia, or neutropenia)	Grade 2	Withhold PLUVICTO until improvement to grade 1 or baseline.
	Grade ≥3	Withhold PLUVICTO until improvement to grade 1 or baseline. Reduce PLUVICTO dose by 20% to 5.9 GBq (160 mCi).
	Recurrent grade ≥3 myelosuppression after 1 dose reduction	Permanently discontinue PLUVICTO.
Renal toxicity	Defined as: • Confirmed serum creatinine increase (grade ≥2) • Confirmed CrCl <30 mL/min; calculate using Cockcroft-Gault with actual body weight	Withhold PLUVICTO until improvement.
	Defined as: • Confirmed ≥40% increase from baseline serum creatinine, and • Confirmed >40% decrease from baseline CrCl; calculate using Cockcroft-Gault with actual body weight	Withhold PLUVICTO until improvement or return to baseline. Reduce PLUVICTO dose by 20% to 5.9 GBq (160 mCi).
	Grade ≥3 renal toxicity	Permanently discontinue PLUVICTO.
	Recurrent renal toxicity after 1 dose reduction	Permanently discontinue PLUVICTO.
Dry mouth	Grade 2	Withhold PLUVICTO until improvement or return to baseline. Consider reducing PLUVICTO dose by 20% to 5.9 GBq (160 mCi).
	Grade 3	Withhold PLUVICTO until improvement or return to baseline. Reduce PLUVICTO dose by 20% to 5.9 GBq (160 mCi).
Gastrointestinal toxicity	Grade ≥3 (not amenable to medical intervention)	Withhold PLUVICTO until improvement to grade 2 or baseline. Reduce PLUVICTO dose by 20% to 5.9 GBq (160 mCi).
	Recurrent grade ≥3 gastrointestinal toxicity after 1 dose reduction	Permanently discontinue PLUVICTO.
Fatigue	Grade ≥3	Withhold PLUVICTO until improvement to grade 2 or baseline.
Electrolyte or metabolic abnormalities	Grade ≥2	Withhold PLUVICTO until improvement to grade 1 or baseline.
Other nonhematologic toxicity	Any unacceptable toxicity	Permanently discontinue PLUVICTO.
	Any adverse reaction that requires treatment delay of >4 weeks	Permanently discontinue PLUVICTO.
	Any recurrent grade 3 or 4 or persistent and intolerable grade 2 adverse reaction after 1 dose reduction	Permanently discontinue PLUVICTO.

Pluvicto®. Accessed October 2025. www.pluvicto-hcp.com.

The most common side effects of PLUVICTO include:

- Decreased blood cell counts
- Tiredness
- Dry mouth
- Nausea
- Appetite loss
- Joint pain
- Constipation
- Back pain

Pluvicto®. Accessed October 2025. www.pluvicto-hcp.com.

Capivasertib

Monitoring:

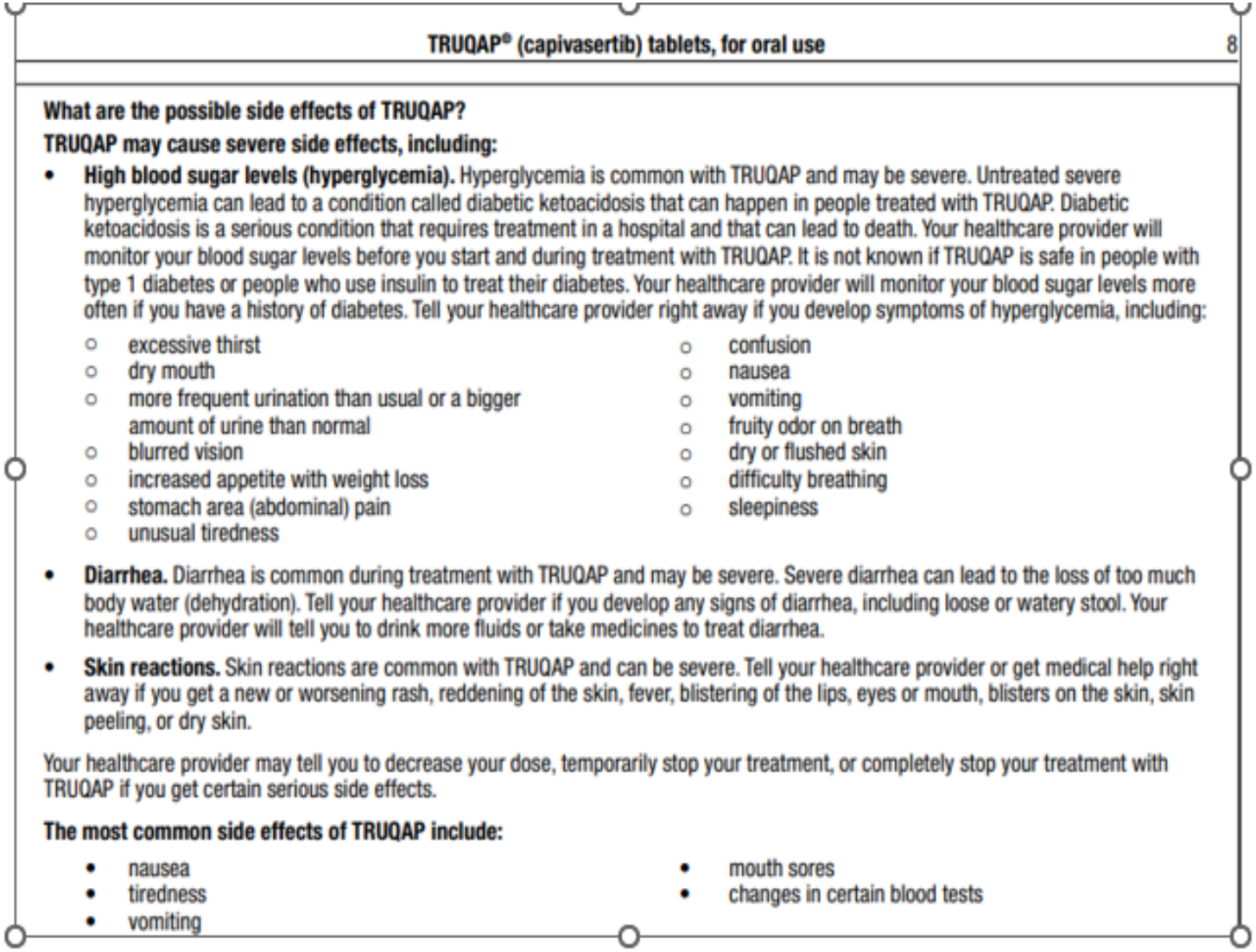
Fasting glucose: Monitor on day 3 or 4 of dosing week during the first two months of therapy

- HbA1c: check at baseline and every 3 months

Diarrhea: Loperamide and increase fluid intake

Cutaneous skin reactions: rash, erythema, dryness, blisters

- Consider referral to dermatology



TRUQAP® (capivasertib) tablets, for oral use 8

What are the possible side effects of TRUQAP?

TRUQAP may cause severe side effects, including:

- **High blood sugar levels (hyperglycemia).** Hyperglycemia is common with TRUQAP and may be severe. Untreated severe hyperglycemia can lead to a condition called diabetic ketoacidosis that can happen in people treated with TRUQAP. Diabetic ketoacidosis is a serious condition that requires treatment in a hospital and that can lead to death. Your healthcare provider will monitor your blood sugar levels before you start and during treatment with TRUQAP. It is not known if TRUQAP is safe in people with type 1 diabetes or people who use insulin to treat their diabetes. Your healthcare provider will monitor your blood sugar levels more often if you have a history of diabetes. Tell your healthcare provider right away if you develop symptoms of hyperglycemia, including:
  - excessive thirst
  - dry mouth
  - more frequent urination than usual or a bigger amount of urine than normal
  - blurred vision
  - increased appetite with weight loss
  - stomach area (abdominal) pain
  - unusual tiredness
  - confusion
  - nausea
  - vomiting
  - fruity odor on breath
  - dry or flushed skin
  - difficulty breathing
  - sleepiness
- **Diarrhea.** Diarrhea is common during treatment with TRUQAP and may be severe. Severe diarrhea can lead to the loss of too much body water (dehydration). Tell your healthcare provider if you develop any signs of diarrhea, including loose or watery stool. Your healthcare provider will tell you to drink more fluids or take medicines to treat diarrhea.
- **Skin reactions.** Skin reactions are common with TRUQAP and can be severe. Tell your healthcare provider or get medical help right away if you get a new or worsening rash, reddening of the skin, fever, blistering of the lips, eyes or mouth, blisters on the skin, skin peeling, or dry skin.

Your healthcare provider may tell you to decrease your dose, temporarily stop your treatment, or completely stop your treatment with TRUQAP if you get certain serious side effects.

The most common side effects of TRUQAP include:

- nausea
- tiredness
- vomiting
- mouth sores
- changes in certain blood tests

Fizazi K, et al. *J Clin Oncol*. 2021;39(6). Capivasertib PI. Drugs@FDA: FDA-Approved Drugs. Accessed October 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218197s002lbl.pdf.

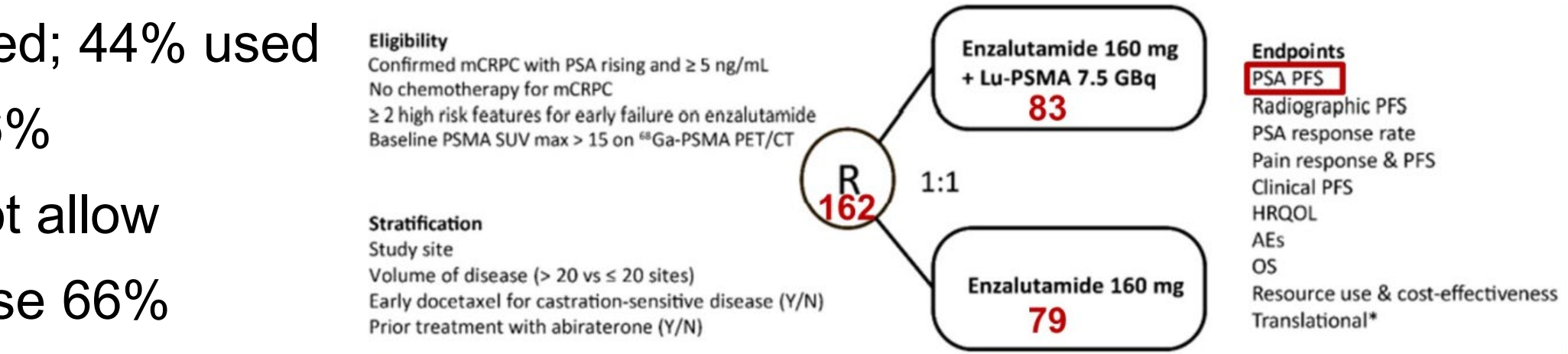
Should we give ARPi with 177Lu-PSMA-617?

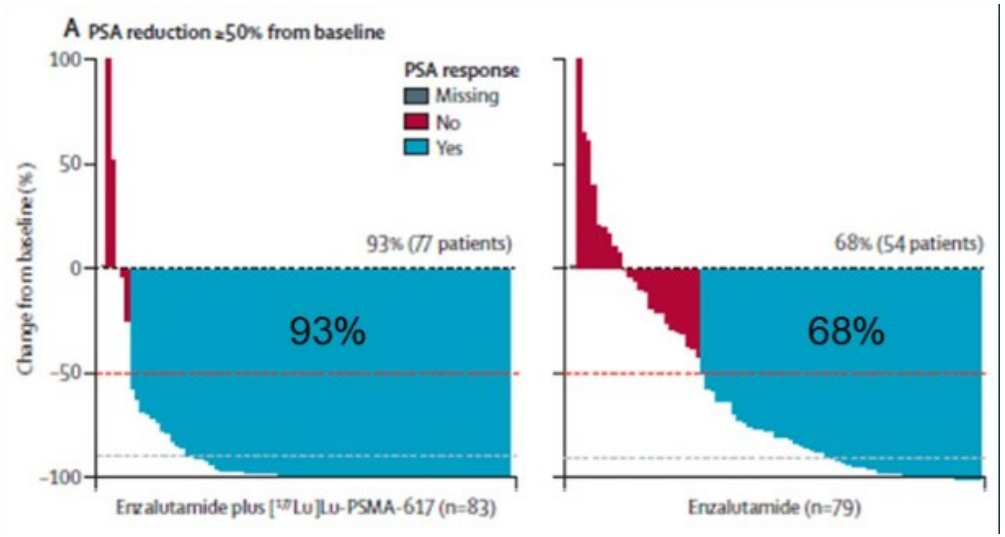
VISION allowed; 44% used

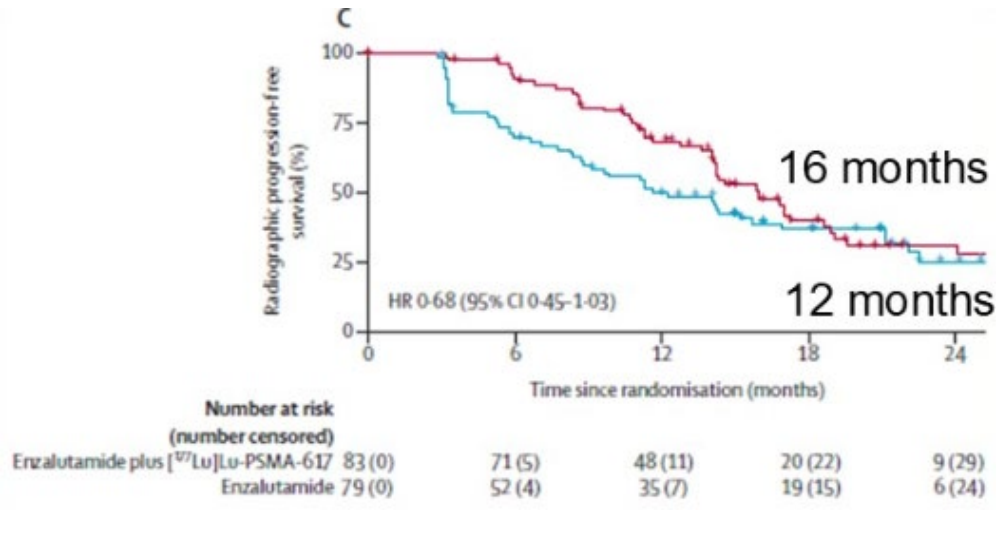
- PSA50 in 46%

TheraP did not allow

- PSA response 66%







EnzaP: benefit for adding 177Lu-PSMA vs Enza alone 1st line mCRPC

Emmett L, et al. *Lancet Oncol*. 2024;25(5):563-571.

177Lu-PSMA-617 radioligand therapy

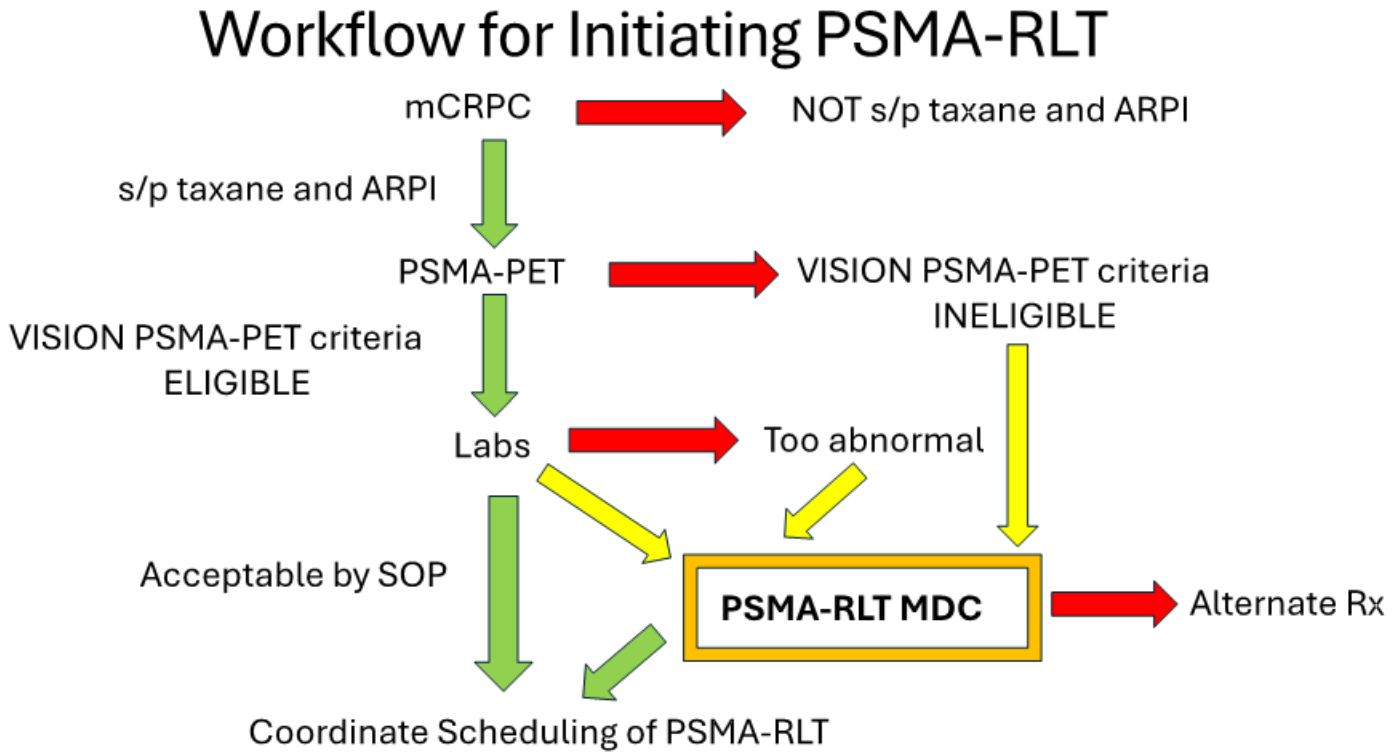
New challenges in multidisciplinary management

RLT Delivery

- PSMA PET imaging to confirm PSMA-positive tumor
- No dominant PSMA-negative metastatic lesions (ie lesions that lack PSMA uptake)
- RLT scheduling, ordering, preparation, and delivery
- Monitoring of radiation dose administered
- Radiation safety processes for handling of RLT and waste management

Patients/ Caregivers

- Education on various treatment-related considerations eg: how to minimize radiation exposure to others after discharge from hospital, how to manage AEs, when to seek care, waste management at home, etc

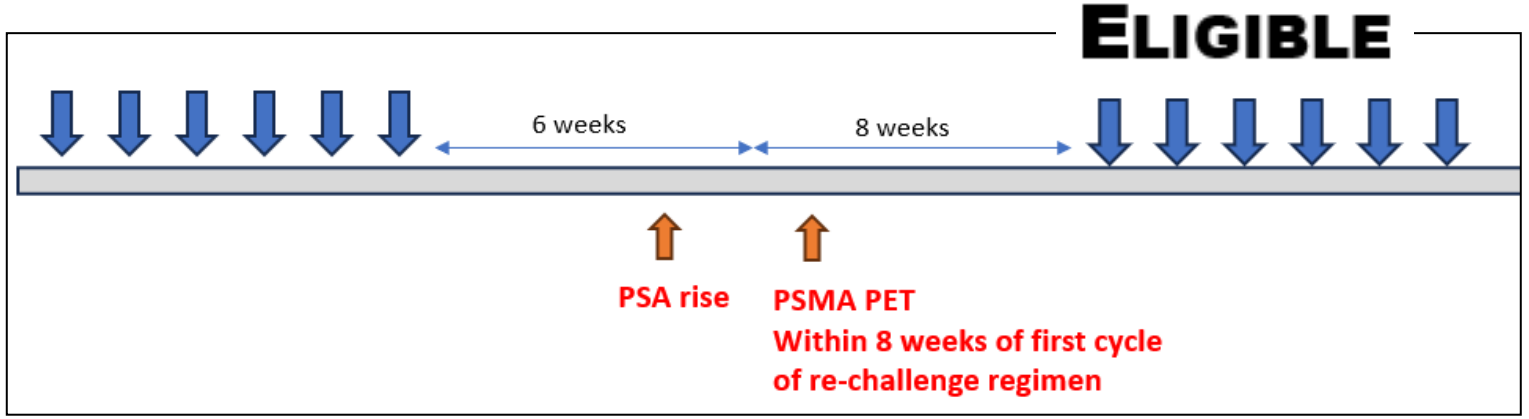


McManus HD, et al. *Prostate Cancer Prostatic Dis*. 2025;28(3):672-683. Kuo PH, et al. *J Nucl Med Technol*. 2025:jnmt.125.270053.

Ongoing trials of MORE ^{177}Lu-PSMA-617

Re-Lu (NCT06288113)

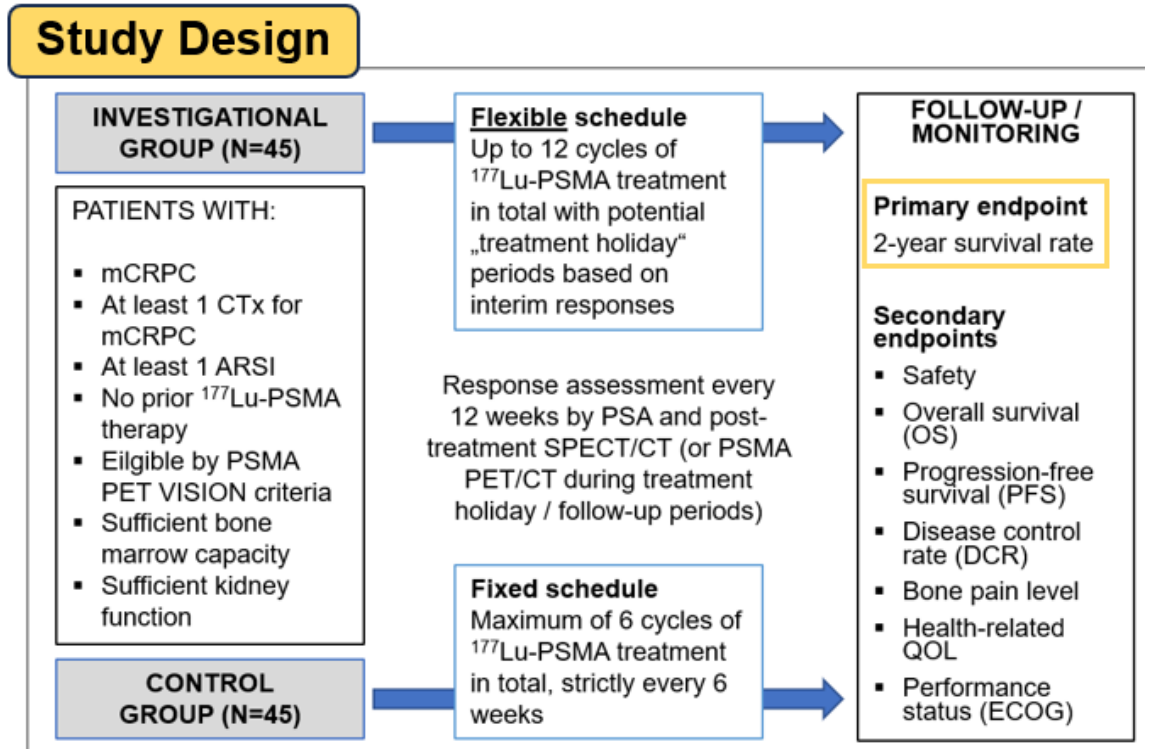
- PSA50 during the 1st round
- Received at least 4 doses



FLEX-MRT (NCT06216249)

- Up to 12 doses w/ flex timing vs std 6 at fixed 6 wk intervals

J. Calais



UCLA Health. Accessed October 2025. https://www.uclahealth.org/clinical-trials/phase-2-randomized-trial-flexible-dosing-schedule-177lu-psma. UCLA Health. Accessed October 2025. https://www.uclahealth.org/clinical-trials/re-treatment-with-177lu-psma-617-treatment-metastatic.

mCRPC

Unmet needs

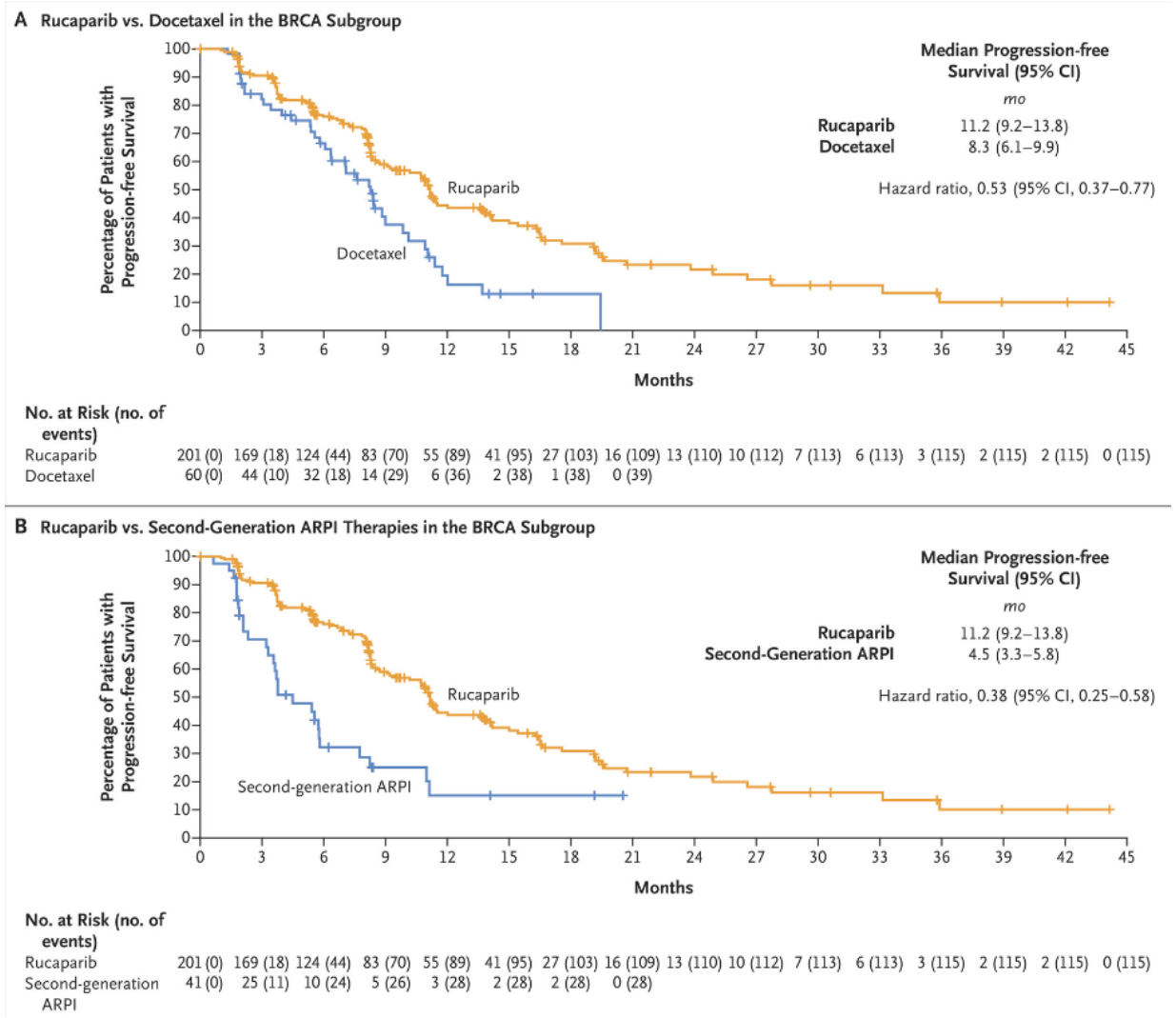
- Optimal sequencing of treatments
- Access to NGS and repeat testing where appropriate
- Wide spectrum of progression
  - Small cell, NEPC, aggressive “androgen indifferent” adeno
  - Need biopsy when new visceral metastases arise
- Lack of established treatment paradigms for NEPC

- Access to clinical trials (where we have some VERY effective options coming through!)

NGS = next-generation sequencing; NEPC = neuroendocrine prostate cancer.

Sequencing for pts w/ mCRPC and HRR alterations: PARP vs other

- TRITON-3 showed that pts with BRCA alteration do better with rucaparib than docetaxel
  - Docetaxel rPFS shorter than in unselected populations (12 months in FIRSTANA; Oudard S, et al.)
- Concern has been raised about impact of PARPi on response to 177-Lu-PSMA



Oudard S, et al. *J Clin Oncol*. 2017;35(28):3189-3197. Fizazi K, et al. *N Engl J Med*. 2023;388(8):719-732.

Noteworthy clinical trials in mCRPC

Late phase (mostly)

S2312 CARAVAN	Cabazitaxel +/- carboplatin	mCRPC post ARPI +/- docetaxel	Looking at AVPC to predict benefit
XALute: AMG509 (Xaluritamig)	Xaluritamig vs physician choice (ARPI switch or Cabazi) STEAP1 targeted BiTE	mCRPC post ARPI and docetaxel	High response rate in phase 1 expansion CRS, MSK toxicities
ABBV-969	PSMA + STEAP1 targeted ADC	mCRPC post ARPI and taxane	
AlphaBreak: FPI-2265-202	Ac225-PSMA	mCRPC after response to ^{177}Lu-PSMA-617	
JNJ-78278343	Bispecific T cell redirector targeting Hk2 (pasritamig)	Several mCRPC trials, one pre chemo, one post	Also oligomet mHSPC
MK-2400-001	B7H3 ADC vs docetaxel	mCRPC pre chemo	
CJSB462B12201	AR degrader + ^{177}Lu-PSMA-617	mCRPC eligible for ^{177}Lu-PSMA-617	

Note: bias – trials open at COH.

AVPC = aggressive variant prostate cancer; CRS = cytokine release syndrome; MSK = musculoskeletal.

Key Take-Aways

Many more therapeutic options

- Need for biomarkers to select best treatment for individual patients
  - PARP inhibitors particularly
  - Always put into context of comorbidities, life expectancy
  - Clinical trials almost always still a very good choice
- Much to learn about optimal use of PSMA-targeted radioligand therapy
  - Requires multidisciplinary coordination
- Patients with prostate cancer live many years
  - Must manage cardiovascular risk to keep patients healthy

Post-Event Survey

Scan the QR Code at the end to complete the Post-Event Survey and you'll be entered to win a $100 gift card!

References

Thank You