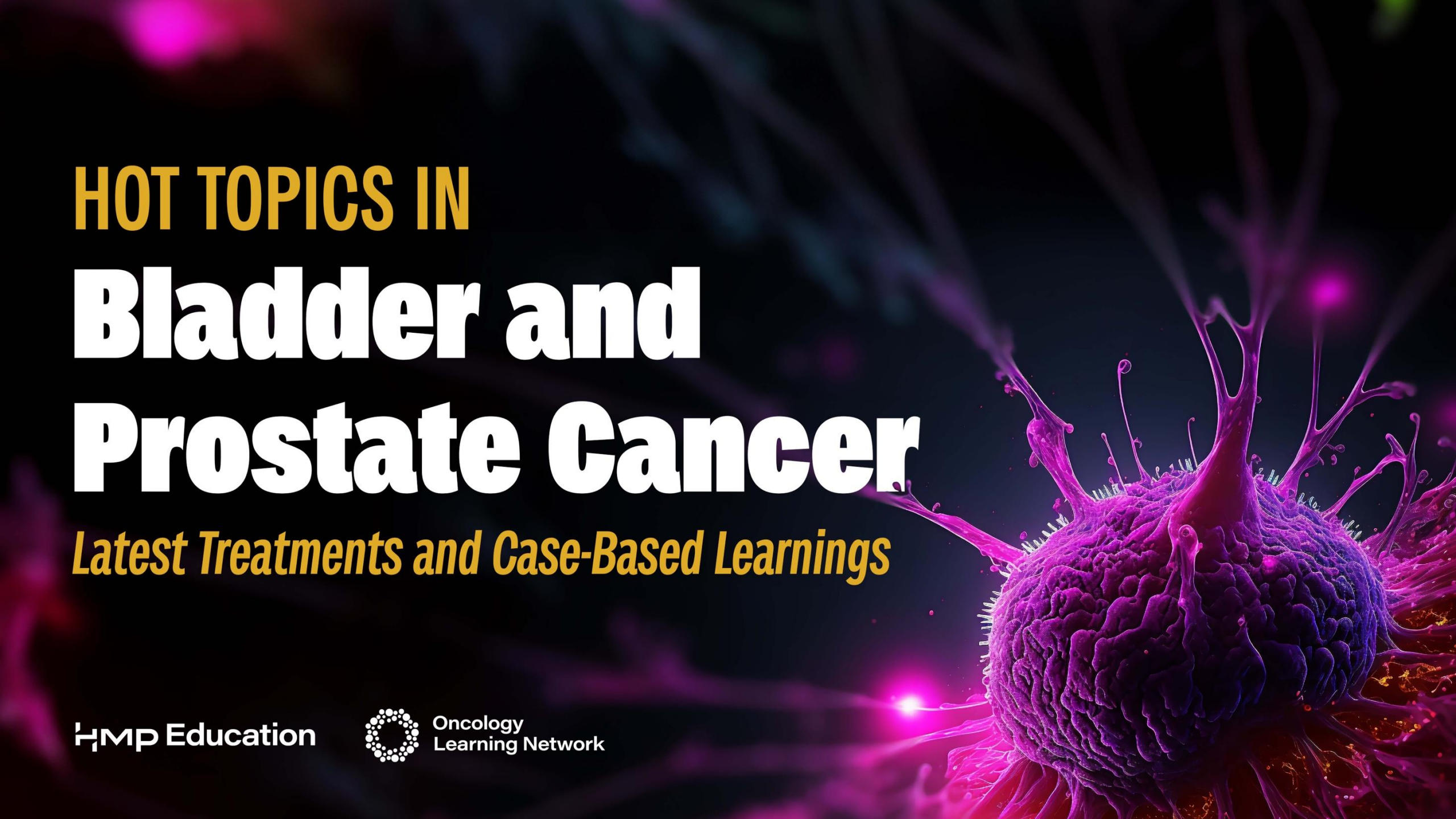
HOT TOPICS IN

Bladder and Prostate Cancer

Latest Treatments and Case-Based Learnings



HMP Education

Oncology Learning Network

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Program Information

- This program is provided by HMP Education, an HMP Global company
- Supported by an educational grant from AstraZeneca

Learning Objectives

- Describe diagnostic and prognostic biomarkers and emerging applications for next generation imaging in staging and treatment selection for MIBC, HER-2+ mUC, and de novo mHSPC
- Evaluate recent clinical trial data and its implications for treatment selection and sequencing in MIBC, HER-2+ mUC, and de novo mHSPC
- Evaluate the evolving landscape of neoadjuvant treatment in MIBC and de novo mHSPC treatment and the implications for patient care
- Implement the most current guideline recommendations and patient-centered care strategies to improve MIBC, mUC, and de novo mHSPC diagnosis, treatment, and outcomes

MIBC = muscle-invasive bladder cancer; mUC = metastatic urothelial carcinoma; mHSPC = metastatic hormone-sensitive prostate cancer.

Submit Your Questions

- Scan the QR Code to submit your questions
- Scan the QR Code at the end to complete the Post-Event Survey and be entered to win a $100 Amazon Gift Card!

Agenda

- **Overview**
  - Importance of Multidisciplinary Care in Bladder and Prostate Cancer
  - Unmet needs in MIBC and de novo mHSPC
- **Historical Approaches to MIBC**
- **Neoadjuvant MIBC**
  - Patient case study
  - Systemic therapy considerations
  - Current Clinical Trial Data
- **Advanced Metastatic UC**
  - Biomarkers and targeted therapy
- **De Novo mHSPC**
  - Overview
  - Patient case study
  - Germline/Somatic biomarker testing
  - Systemic therapy considerations
  - Current Clinical Trial Data

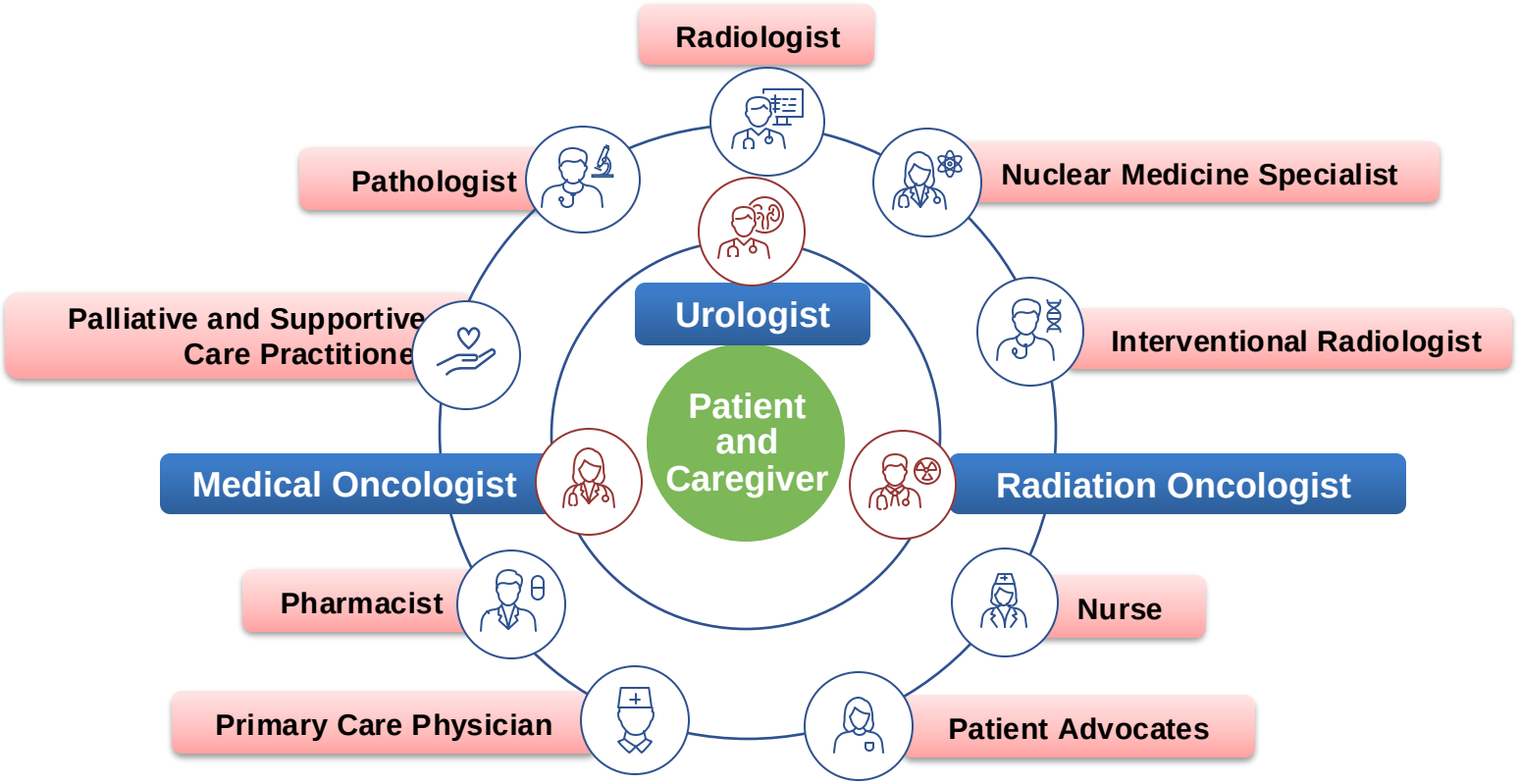
Overview & Historical Approaches

Multidisciplinary Care is Essential

"The sum total of medical knowledge is now so great and wide-spreading that it would be futile for any one man...to assume that he has even a working knowledge of any part of the whole.... The best interest of the patient is the only interest to be considered, and in order that the sick may have the benefit of advancing knowledge, union of forces is necessary.... It has become necessary to develop medicine as a cooperative science; the clinician, the specialist, and the laboratory workers uniting for the good of the patient, each assisting in elucidation of the problem at hand, and each dependent upon the other for support."

William J. Mayo, 1910

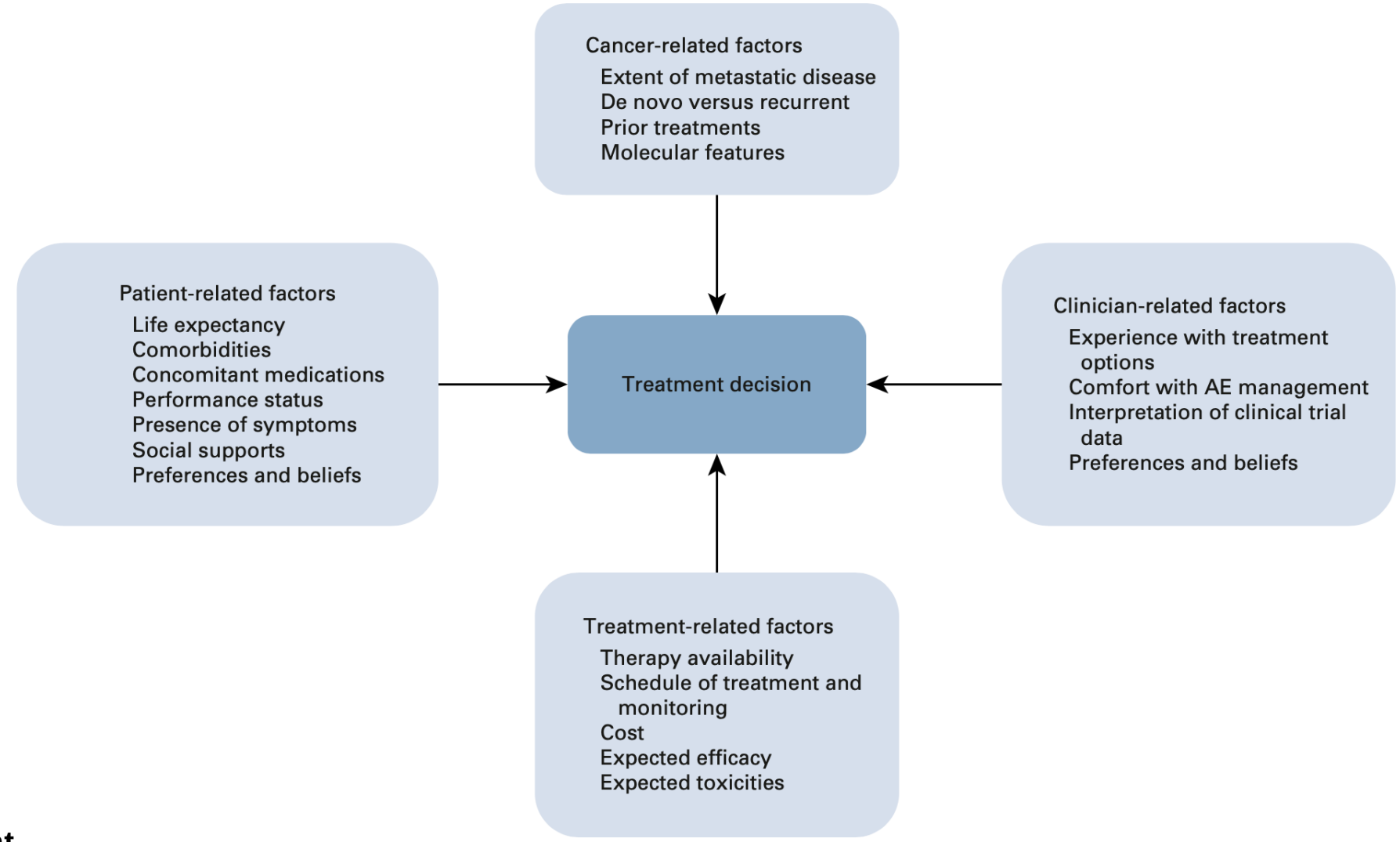
Multidisciplinary Care in Bladder and/or Prostate Cancer



Reichard, CA et al. *BJU Int.* 2019;124:811-19; Gomella, LG et al. *J Oncol Pract*. 2010;6:e5-e10; Rao, K et al. *BJU Int.* 2014;114 Suppl 1:50-4; De Luca, S et al. *Minerva Urol Nefrol.* 2019;71:576-82;. Korman, H et al. *Am J Clin Oncol.* 2013;36:121-5; Aizer, AA et al. *J Clin Oncol.* 2012;30:3071-6; Aizer, AA et al. *J Natl Compr Canc Netw.* 2013;11:1364-72; Tang, C et al. *Cancer.* 2020;126:506-14; Sciarra, A et al. *Am J Clin Exp Urol*. 2013;25;1:12-17; Aizer, AA et al. *Semin Radiat Oncol*. 2013;23:157-64; Hurwitz, LM et al. *Urol Oncol.* 2016;34:233.e17-25;. Betschart, P et al. *Oncol Res Treat.* 2019;42:366-74; Patrikidou, A et al. *Clin Transl Radiat Oncol.* 2018;12:28-33;. Magnani, T et al. *BJU Int.* 2012;110:998-1003; Colasante, A et al. *Oncol Let.* 2018;15:1823-28.;. Litton G et al. *J Oncol Pract*. 2010;6:e35-7; Hudak, JL et al. *Urol Nurs.* 2007;27:491-8.

Medical writing support for this summary was provided by Roham Sadeghimakki of Onyx (a division of Prime, London, UK) and funded by Pfizer Inc. and Astellas Pharma Inc.

Factors Contributing to Treatment Decisions



AE = adverse event.

Morgans AK, et al. *J Clin Oncol*. 2022;40(8):818-824.

Addressing the Unmet Needs

MIBC

Treatment Options
- Need for more effective and less invasive treatments
- Drug resistance remains a significant challenge
- Post-surgical complications can impact quality of life

Diagnostic Challenges
- Early detection is crucial but current tools are limited
- Accurate risk stratification is essential for tailored treatment

Quality of Life
- Post-treatment morbidity can be significant
- Improved supportive care is needed

Research and Development
- Novel therapeutic targets are needed
- Personalized medicine can improve outcomes

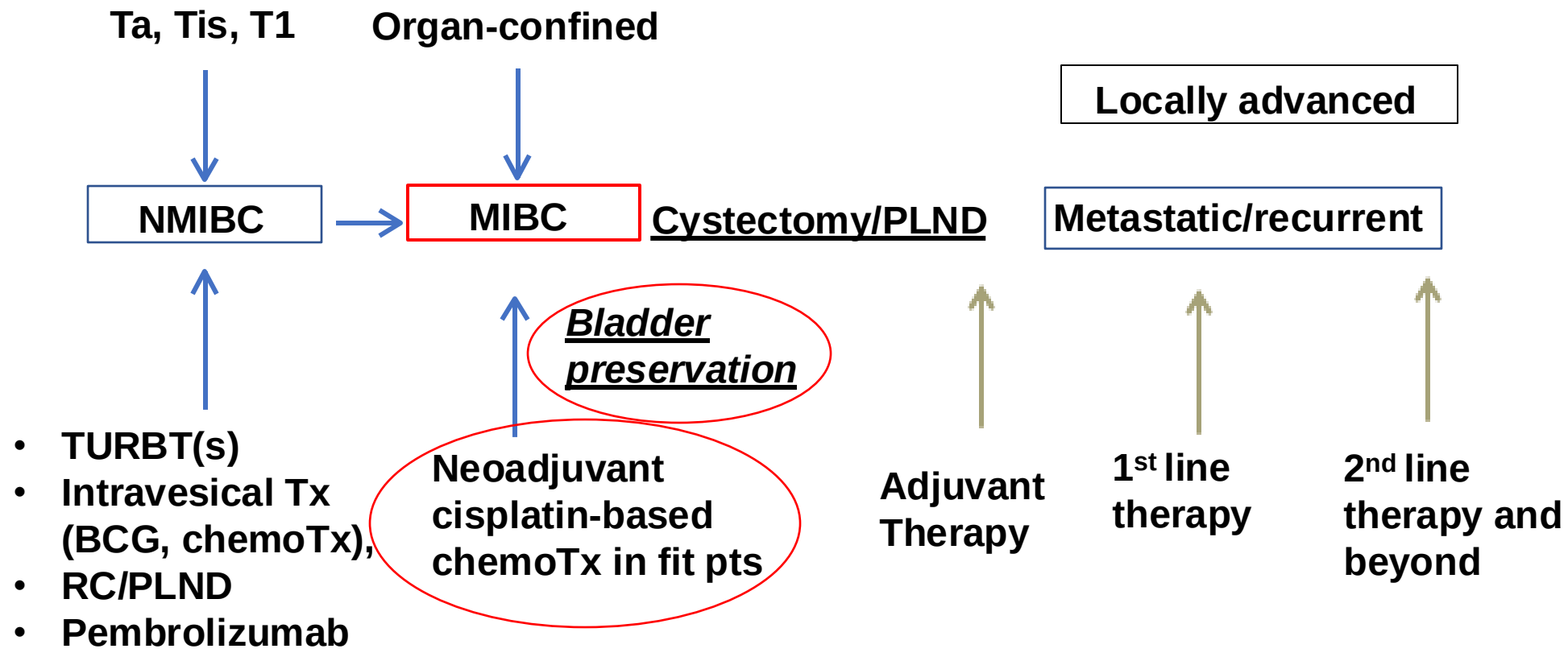
De novo mHSPC

- Therapies to **prolong time to progression from mHSPC to mCRPC**
- Newer treatment options **prolonging survival** of mHSPC and mCRPC
- **Biomarker-based approaches** to guide therapy selection/personalized treatment
- **Timely testing** (germline/somatic) to determine treatment selection

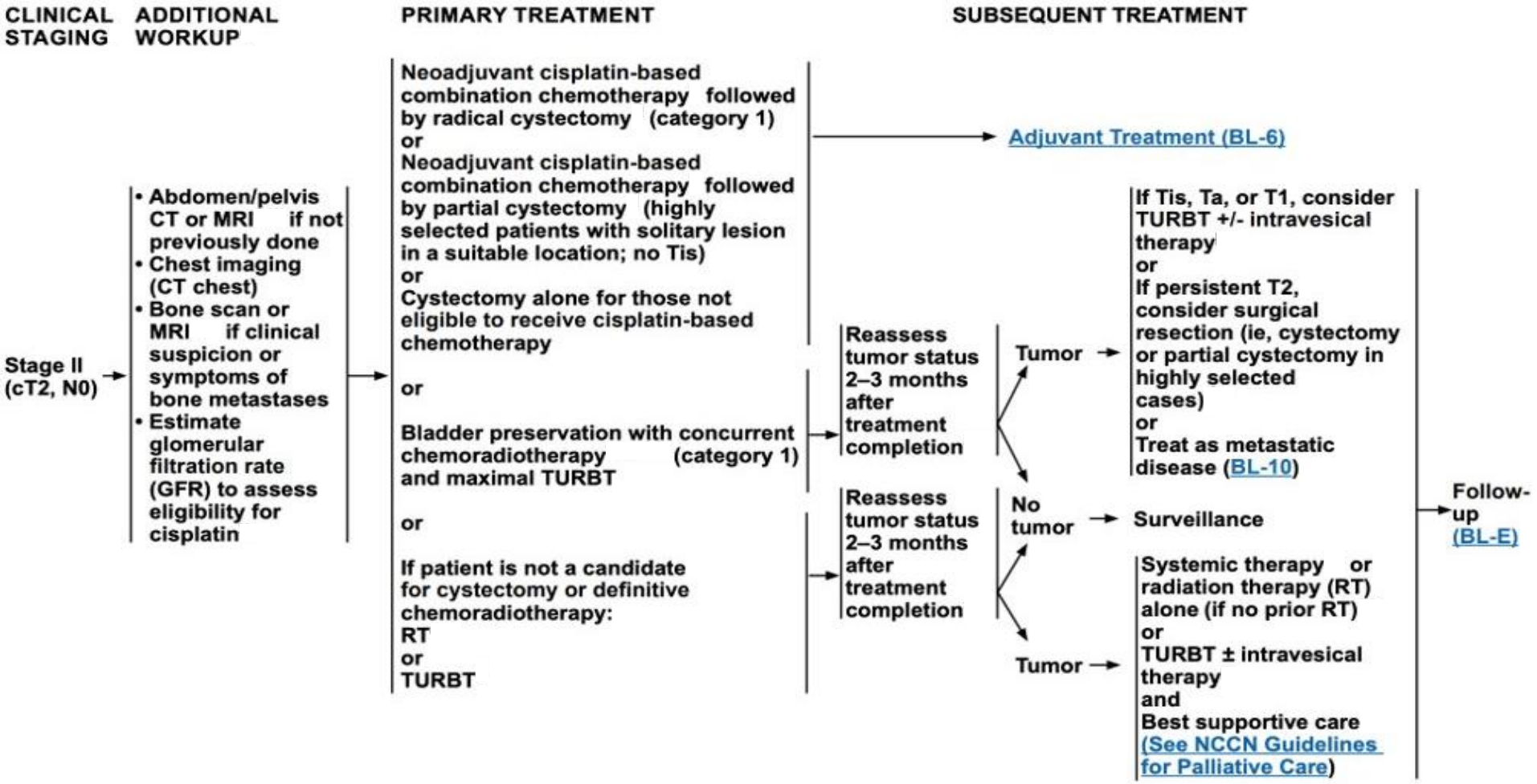
mCRPC = metastatic castration-resistant prostate cancer.

Neoadjuvant MIBC

Disease/Treatment Settings



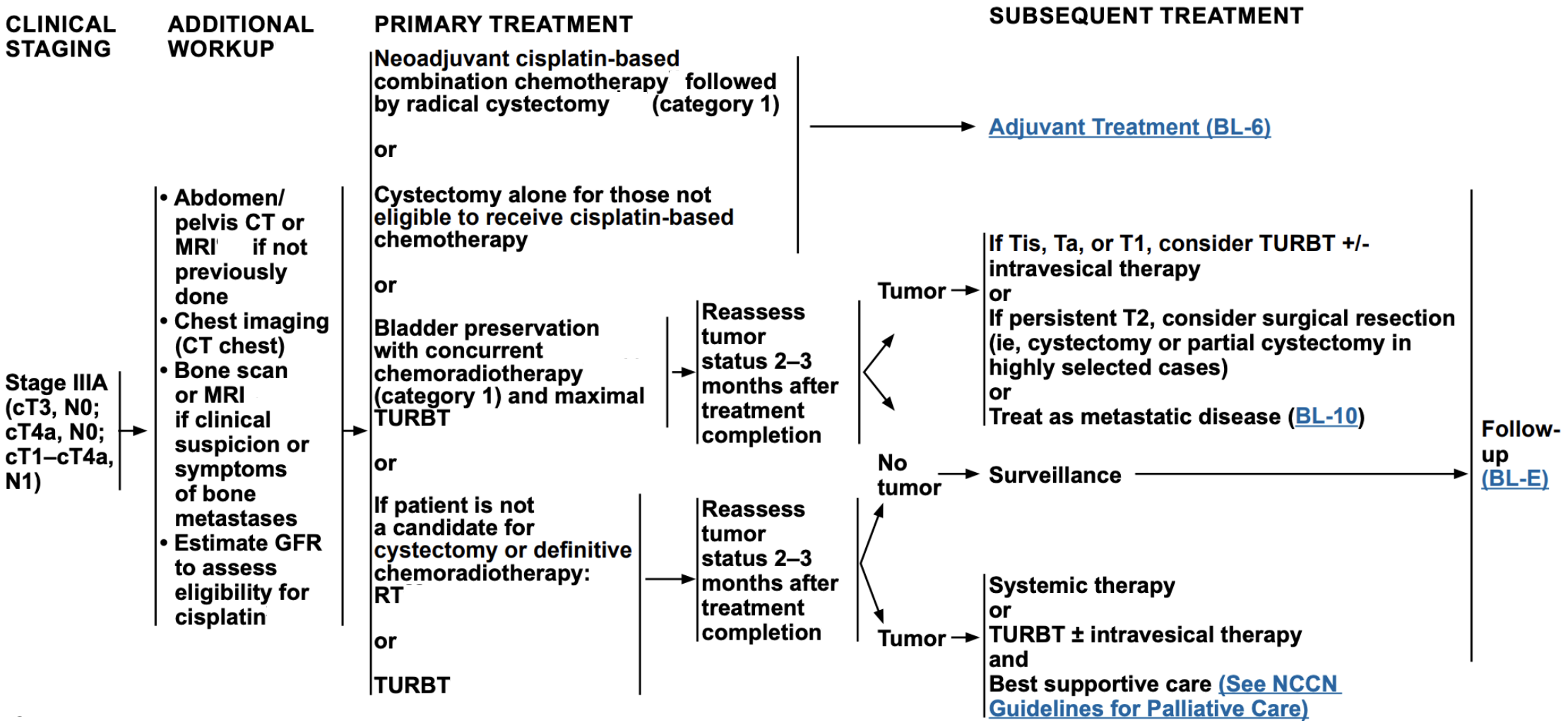
NCCN MIBC Stage II



RT = radiation therapy; MRI = magnetic resonance imaging.

National Comprehensive Cancer Network (NCCN). Accessed February 16, 2024. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.

NCCN MIBC Stage III



NCCN. Accessed February 16, 2024. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.

Patient Case

63-year-old smoker develops gross hematuria

- Cystoscopy demonstrates a large bladder mass
- TURBT demonstrates high grade urothelial cancer with muscle invasion
- CT scan of the chest/abdomen/pelvis demonstrates no evidence of metastatic disease
- Creatinine clearance is 60 mL/min

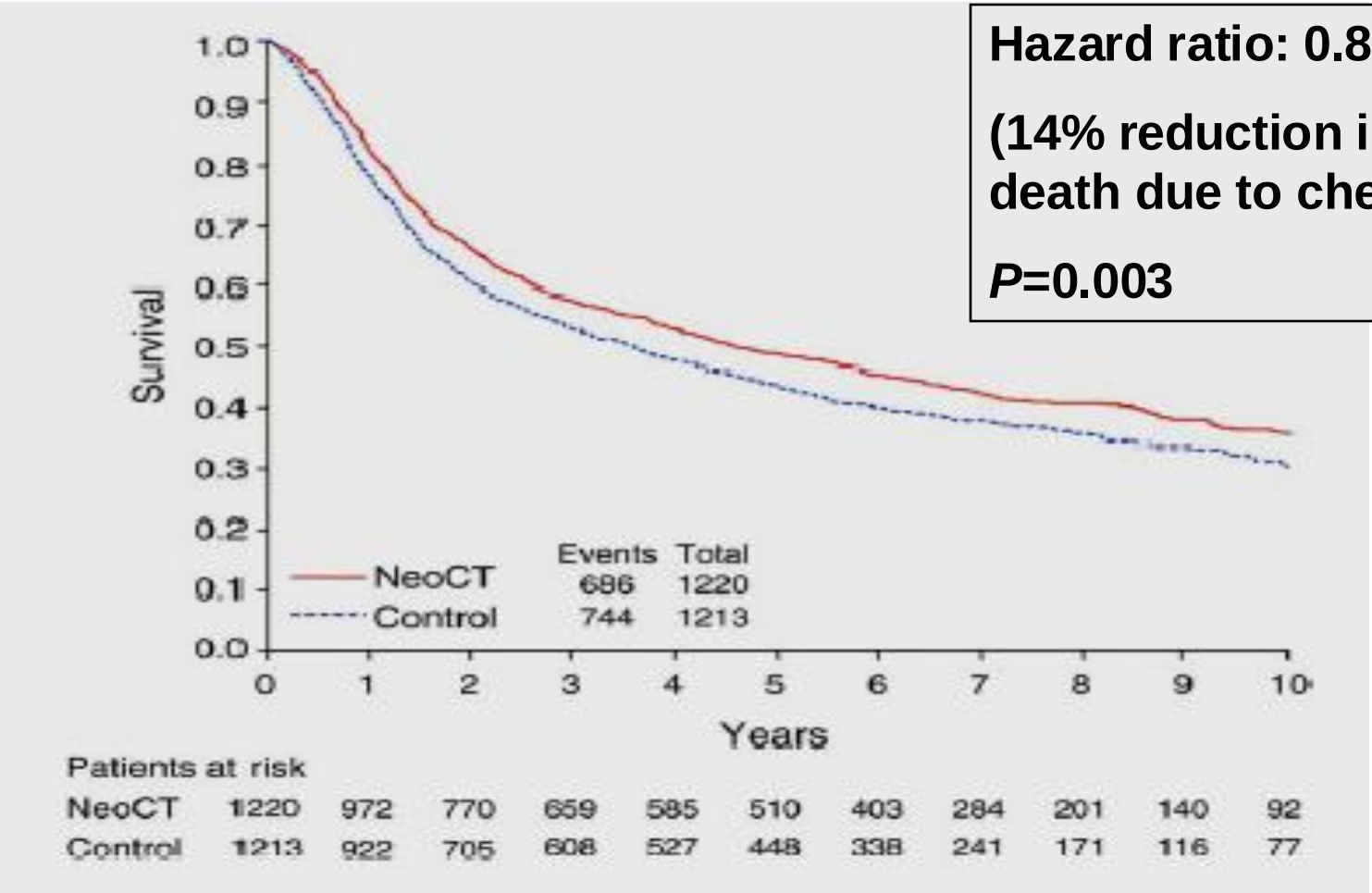
Patient Case Continued

Appropriate management options include

- Gemcitabine/cisplatin x 4 cycles followed by cystectomy
- Dose-dense neoadjuvant M-VAC for 4 cycles followed by cystectomy
- Immediate cystectomy
- Bladder preservation regimen with weekly cisplatin and radiation therapy
- NAC followed by bladder preservation

M-VAC = methotrexate, vinblastine, doxorubicin, and cisplatin; NAC = N-acetyl cysteine.

Neoadjuvant Platinum-Based Combination Chemotherapy vs None



Hazard ratio: 0.86

(14% reduction in the risk of death due to chemotherapy)

***P*=0.003**

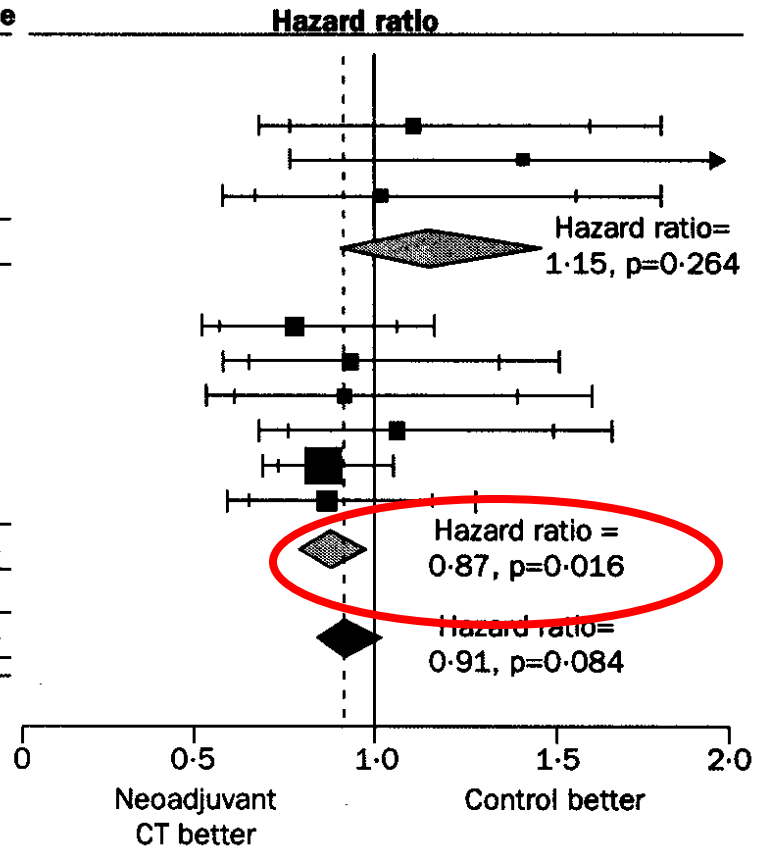
CT = chemotherapy.

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. *Eur Urol*. 2005;48(2):202-205.

Meta-Analysis:
Neoadjuvant Chemotherapy for Muscle-Invasive TCC

Trial	Number of events/total: Neoadjuvant CT	Control	O–E	Variance
Single agent platinum				
Wallace[14]	59/83	50/76	2·74	27·18
Martinez-Pineiro[9]	34/41	37/55	5·85	16·51
Raghavan[14]	43/62	38/59	0·33	20·11
Subtotal	136/186	125/190	8·92	63·80
Platinum-based combination				
Malmström[11]	68/151	84/160	−9·97	37·94
Bassi[7]	53/102	60/104	−1·95	28·13
Cortesi (unpublished)	43/82	41/71	−1·87	20·84
Sengeløv[13]	70/78	60/75	1·79	31·96
MRC/EORTC[8]	275/491	301/485	−23·69	143·61
Sherif[12]	79/158	90/159	−6·37	42·18
Subtotal	588/1062	636/1054	−42·06	304·66
Total	724/1248	761/1244	−33·14	368·45

Did not include INT-0080



n=2688

TCC = transitional cell carcinoma.

Advanced Bladder Cancer (ABC) Meta-Analysis Collaboration. *Lancet*. 2003;361(9373):1927-1934.

CheckMate-274

Phase 3 randomized, double-blind, multicenter trial of adjunctive nivolumab vs placebo in high-risk muscle invasive urothelial carcinoma

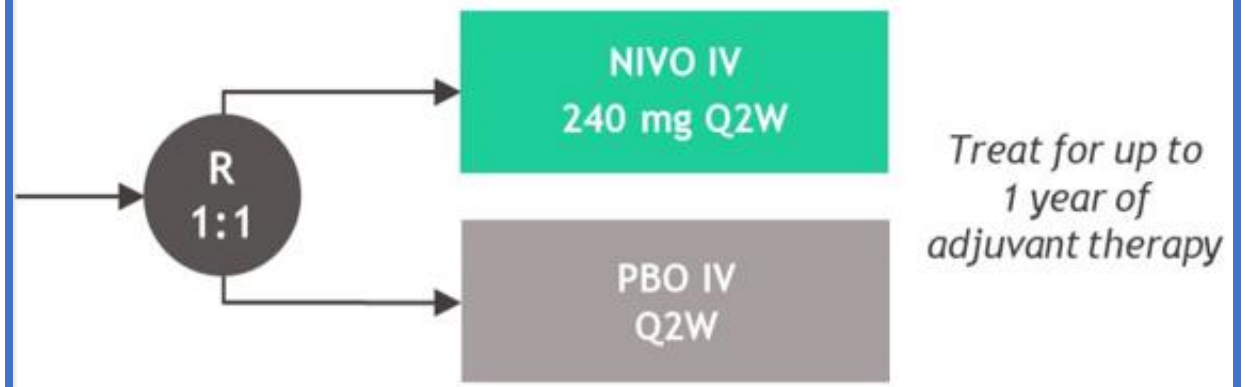
N=709

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of randomization

Median (range) follow-up[c] (ITT population),
36.1 (0.0-75.3) months (37.4 months for NIVO, 33.9 months for PBO)
Minimum follow-up[d] (ITT population), 31.6 months
Median (range) follow-up[c] (PD-L1 ≥ 1% population),
37.1 (0.0-75.3) months (39.8 months for NIVO, 33.3 months for PBO)

Stratification factors
- Tumor PD-L1 status (≥ 1% vs < 1% or indeterminate)[b]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status



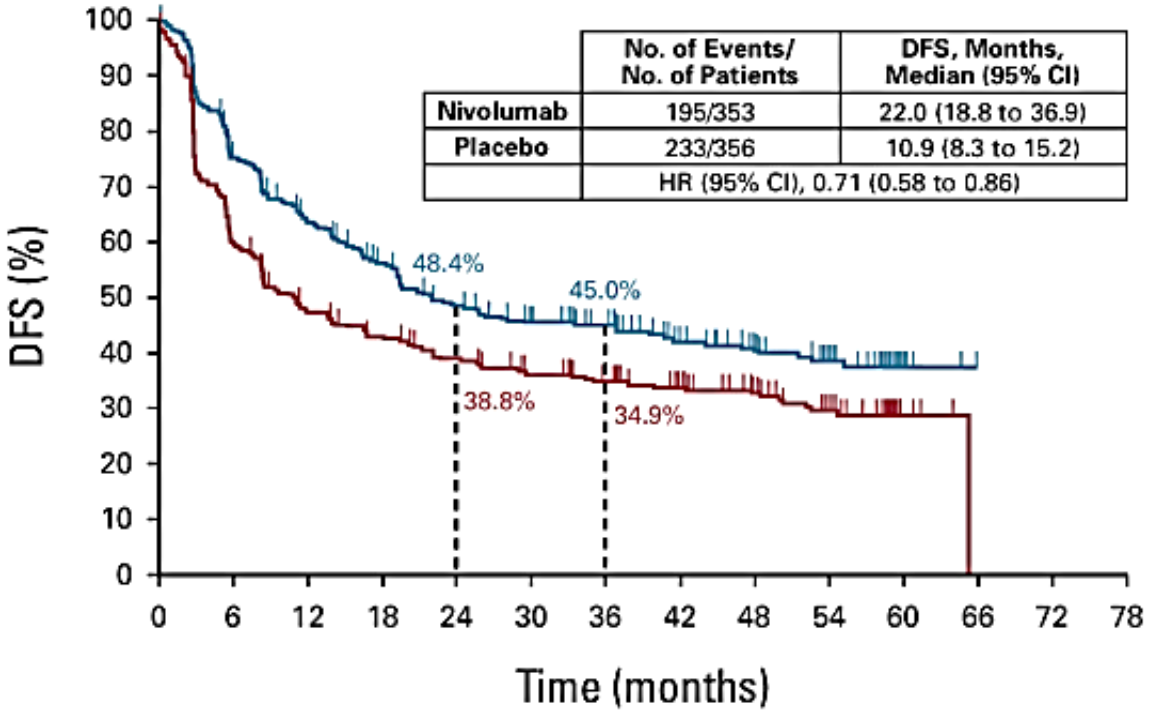
Primary endpoints: DFS in all randomized patients (ITT population) and DFS in all randomized patients with tumor PD-L1 ≥ 1%
Secondary endpoints: NUTRFS, DSS, and OS[e]
Exploratory endpoints included: DMFS, PFS2, safety, HRQoL

[a]NCT02632409; [b]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the validated Dako PD-L1 IHC 28-8 pharmDx immunohistochemistry assay; [c]Defined as time between randomization date and last known date alive (for patients who are alive) and death; [d]Defined as time from clinical cut-off date to last patient's randomization date; [e]OS will be assessed at a future database lock, OS and DSS data are not presented.
R = randomize; IV = intravenous; Q2W = every 2 weeks; DFS = disease-free survival; ITT = intent-to-treat; NUTRFS = non-urothelial tract recurrence-free survival; DSS = disease-specific survival; OS = overall survival; DMFS = distant metastasis-free survival; HRQoL = health-related quality of life.
NIH. Accessed December 4, 2024. https://clinicaltrials.gov/study/NCT02632409.

CheckMate-274 ITT Analysis

Extended median follow-up: 3 years

Primary Endpoint

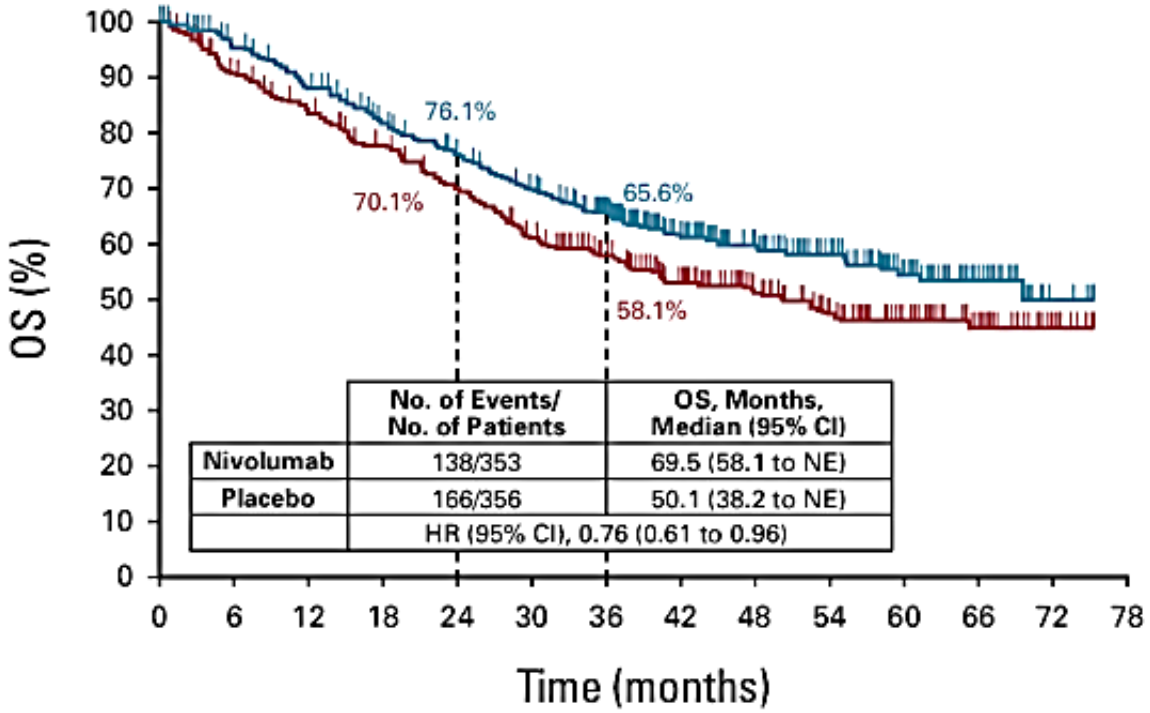


	No. of Events/ No. of Patients	DFS, Months, Median (95% CI)
Nivolumab	195/353	22.0 (18.8 to 36.9)
Placebo	233/356	10.9 (8.3 to 15.2)
	HR (95% CI), 0.71 (0.58 to 0.86)	

Number at risk

Nivolumab	353	253	208	177	150	132	113	83	57	43	4	0	0	0
Placebo	356	207	156	138	123	109	94	80	59	39	4	0	0	0

Key Secondary Endpoint



	No. of Events/ No. of Patients	OS, Months, Median (95% CI)
Nivolumab	138/353	69.5 (58.1 to NE)
Placebo	166/356	50.1 (38.2 to NE)
	HR (95% CI), 0.76 (0.61 to 0.96)	

Number at risk

Nivolumab	353	326	298	268	244	220	188	150	123	92	60	33	4	0
Placebo	356	308	281	254	226	194	167	136	109	79	56	32	10	0

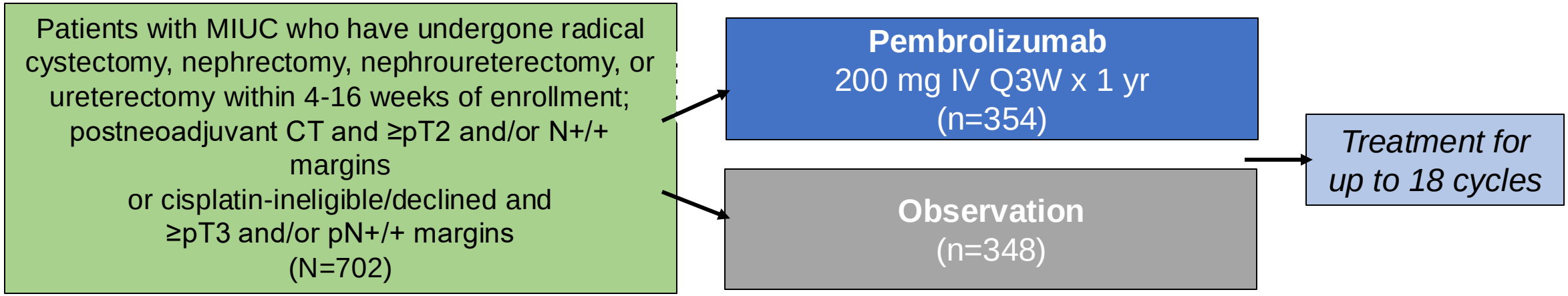
HR = hazard ratio; CI = confidence interval; NE = not estimable.

Galsky MD, et al. *J Clin Oncol.* 2024;JCO2400340.

AMBASSADOR: Adjuvant Pembrolizumab vs Observation in MIUC

Randomized phase 3 study of adjuvant pembrolizumab in high-risk MIUC

Stratified by PD-L1 status (neg vs pos), neoadjuvant CT (yes vs no), pathologic stage (pT2/3/4aN0 vs pTaN0 vs pT4bNx/N1-3 vs positive surgical margins)*

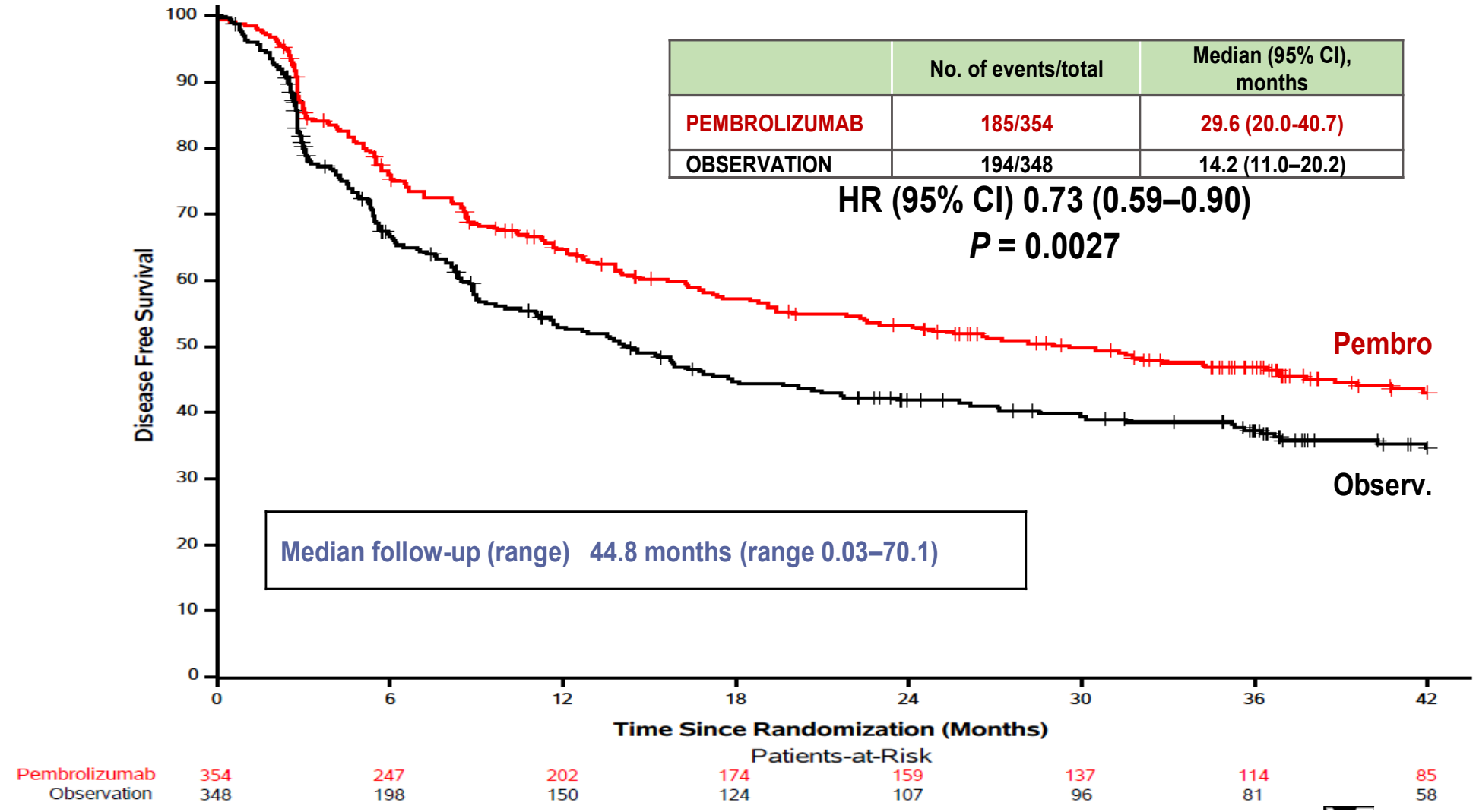


- **Primary endpoints:** OS, DFS
- **Secondary endpoints:** OS, DFS in PD-L1-positive and PD-L1-negative cohorts, safety

***PD-L1 positive: combined positive score (CPS) ≥10%.**

Apolo AB, et al. Presented at: American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO GU); January 25-27, 2024; San Francisco, California. Abstract LBA531. NIH. Accessed December 4, 2024. https://clinicaltrials.gov/study/NCT03244384.

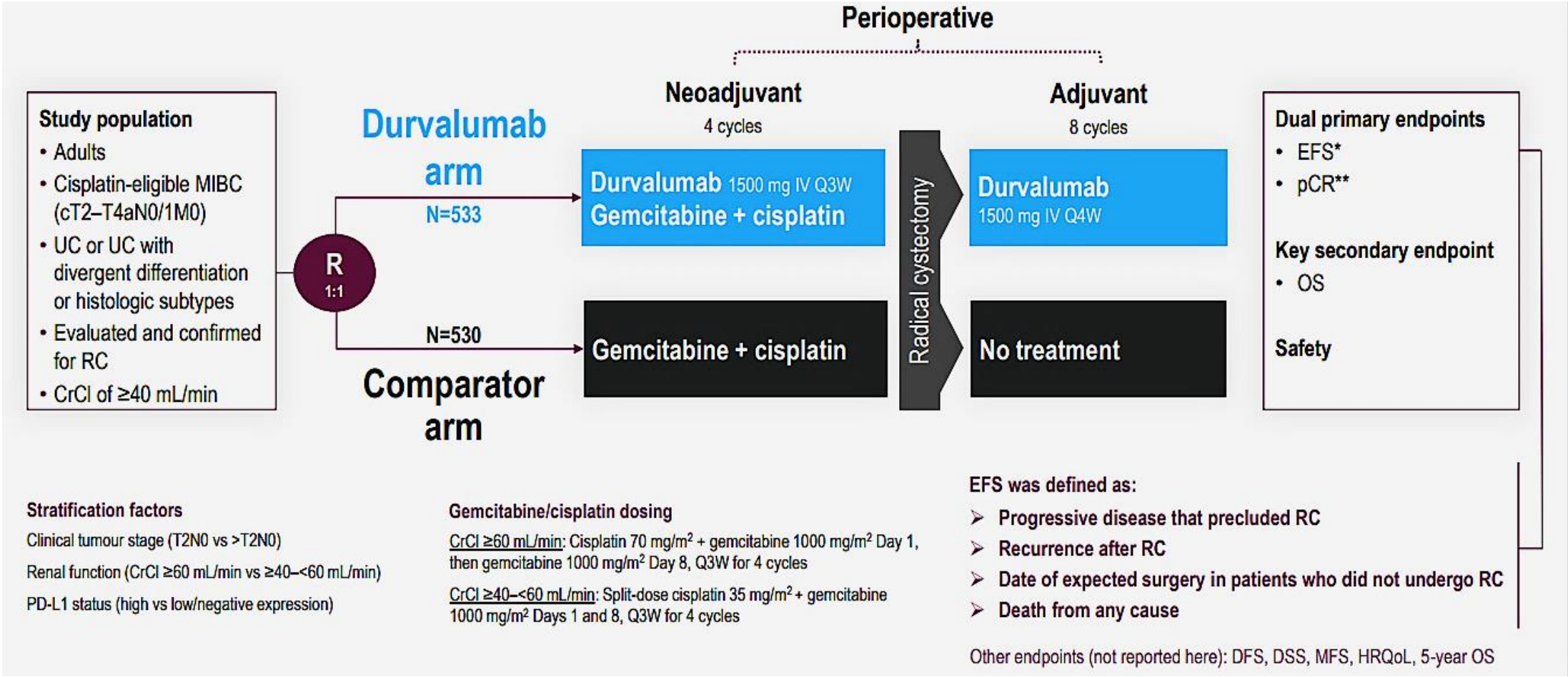
AMBASSADOR: Disease-Free Survival (ITT)



Apolo AB, et al. Presented at: ASCO GU; January 25-27, 2024; San Francisco, California. Abstract LBA531.

NIAGARA Study Design

Global Study to Determine the Efficacy and Safety of Durvalumab in Combination with Gemcitabine+Cisplatin for Neoadjuvant Treatment and Durvalumab Alone for Adjuvant Treatment in Patients with Muscle-Invasive Bladder Cancer

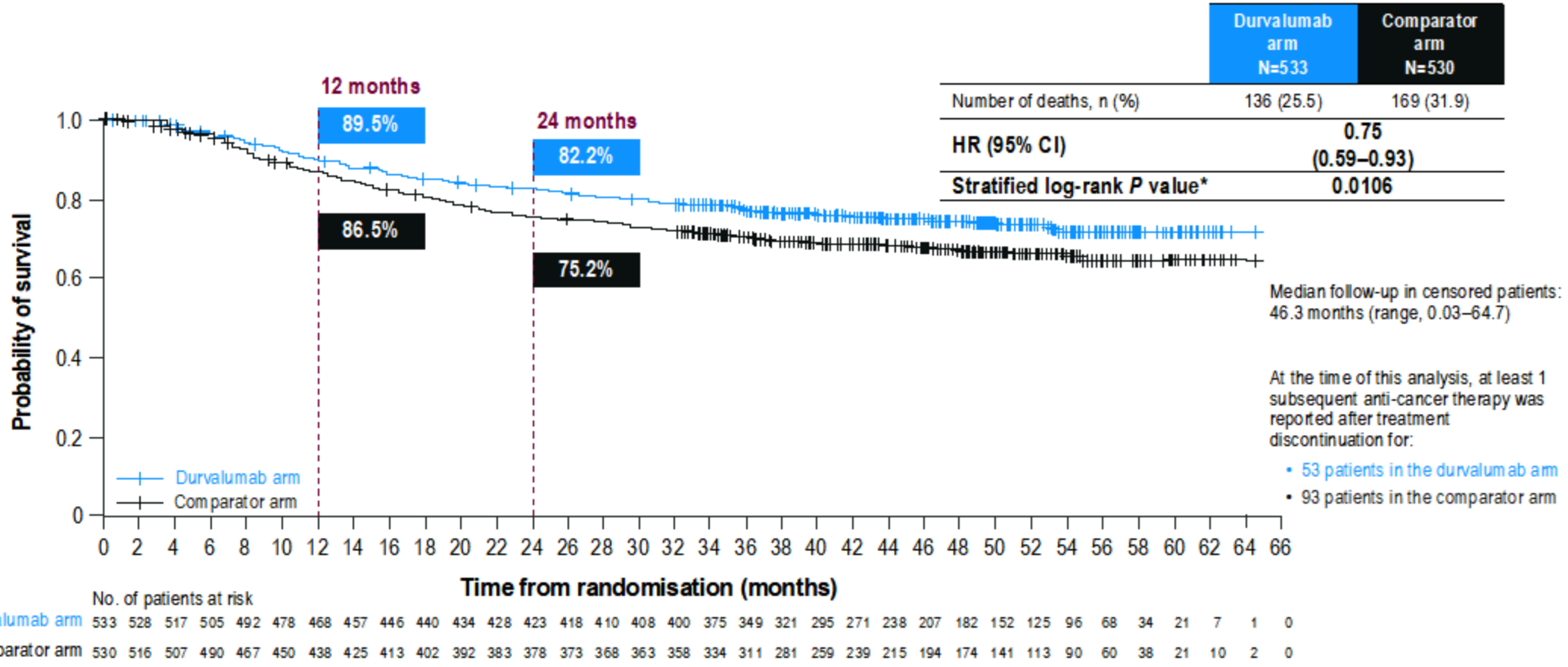


***Evaluated by blinded independent central review or central pathology review (if a biopsy was required for a suspected new lesion); **Evaluated by blinded central pathology review. pCR = pathological complete response.**

NIH. Accessed December 4, 2024. https://clinicaltrials.gov/study/NCT03732677.

NIAGARA Overall Survival (ITT)

OS is the time of randomization until death due to any cause regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy.



	Durvalumab arm N=533	Comparator arm 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	

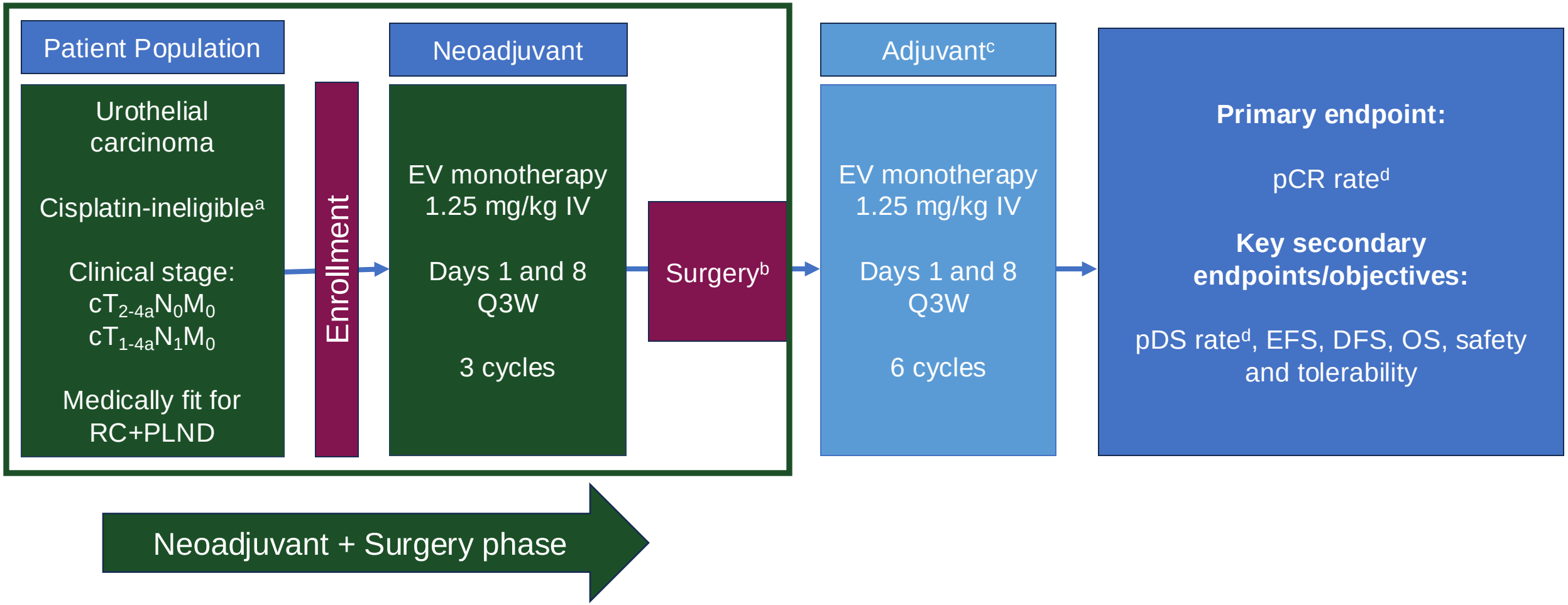
Median follow-up in censored patients: 46.3 months (range, 0.03–64.7)

At the time of this analysis, at least 1 subsequent anti-cancer therapy was reported after treatment discontinuation for:

- 53 patients in the durvalumab arm
- 93 patients in the comparator arm

***The threshold for statistical significance was based on Lan-DeMets alpha spending function with O'Brien-Fleming boundary—with the observed number of events, the boundary for declaring statistical significance was 0.01543 for a 4.9% overall 2-sided alpha. Data cutoff 29 Apr 2024.**

EV-103 Cohort L: Perioperative EV in Cisplatin-Ineligible MIBC



[a]Cisplatin ineligibility: Galsky criteria ≥1 of: GFR <60 and ≥30 mL/min, ECOG PS of 2, NCI CTCAE Version 4.03 grade ≥2 hearing loss, or NYHA Class III heart failure; [b]Surgery phase: RC+PLND and 30-day post-operative period; [c]Adjuvant phase begins 8 weeks after surgery; [d]Per central pathology review.

Sridhar S, et al. Presented at: ESMO Congress; October 22, 2023; Madrid, Spain. Abstract 2365MO.

EV-103 Cohort L
Pathological Complete Response Rate (pCR)

pCR of 34%; pDS of 42%

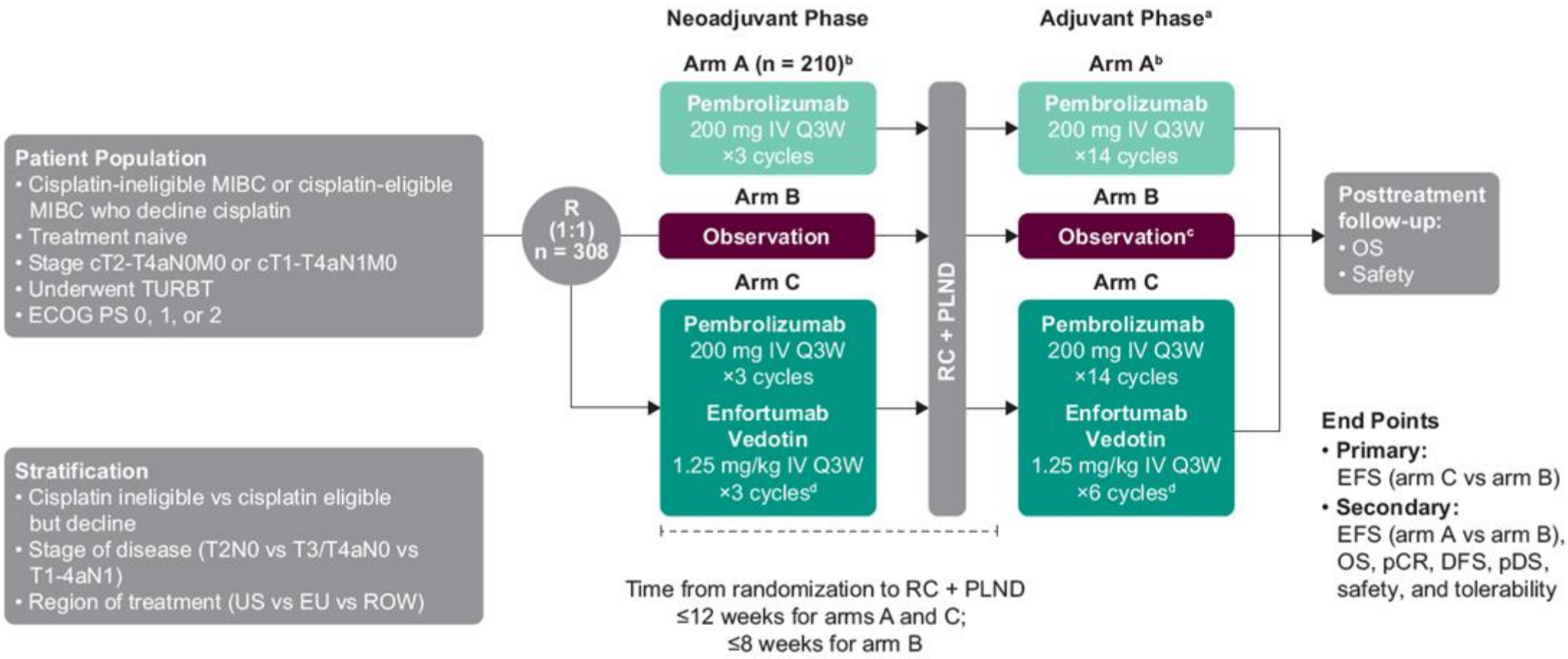
Pathological Response	Central Pathology Review (N=50[a]) n (%) [95% CI[b]]
pCR (defined as absence of viable tumor tissue: ypT0N0)	17 (34.0) [21.2, 48.8]
pDS[c] (defined as patients with <ypT2, including pT0, pTis, pTa, pT1, and N0)	21 (42.0) [28.2, 56.8]

Data cutoff date 13 Jun 2023

[a]One patient achieved clinical CR and did not undergo surgery and was excluded from pCR and pDS analyses; [b]Computed with the Clopper-Pearson method; [c]pDS included as key secondary endpoint.

Sridhar S, et al. Presented at: ESMO Congress; October 22, 2023; Madrid, Spain. Abstract 2365MO.

KEYNOTE-095/EV-303 Study Design

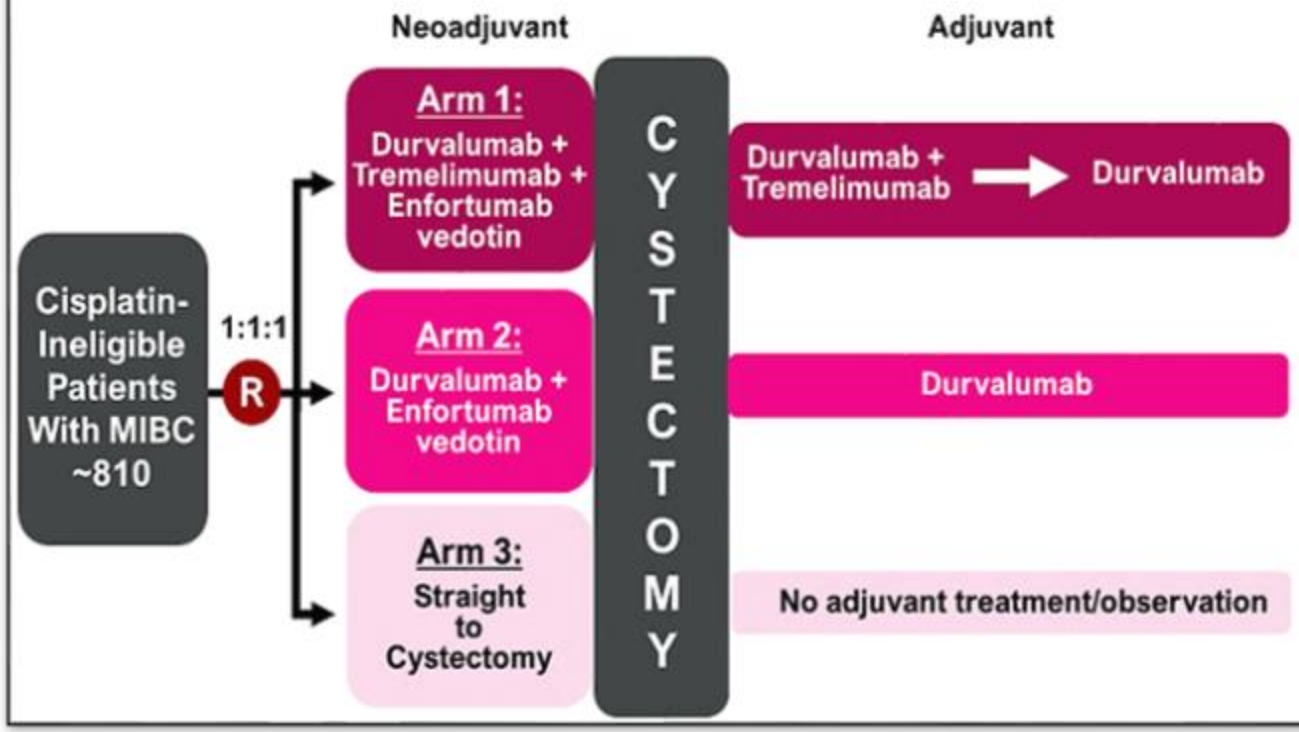


[a]Until disease progression, unacceptable AEs, intercurrent illness preventing further treatment administration, or investigator's or patient's decision to withdraw; [b]Prior to the protocol amendment 8, patients were enrolled in arm A, enrollment for that arm will be stopped once the current protocol amendment is initiated, and further randomization will focus on arms B and C; [c]Patients at high risk of recurrence after RC + PLND may receive treatment with adjuvant nivolumab per the approved product label; [d]Administered on days 1 and 8 of every 3-week cycle.

Necchi A, et al. Presented at: ASCO GU; February 16-18, 2023; San Francisco, California. Abstract LBA442. NIH. Accessed December 4, 2024. https://clinicaltrials.gov/study/NCT02625961.

VOLGA Study Design

Phase 3, Randomized, Open-Label, Multicenter Study to Determine the Efficacy and Safety of Durvalumab in Combination With Tremelimumab and Enfortumab Vedotin or Durvalumab in Combination With Enfortumab Vedotin for Perioperative Treatment in Patients Ineligible for Cisplatin Undergoing Radical Cystectomy for Muscle Invasive Bladder Cancer



Primary endpoint (D + T + EV)

- Pathologic complete response rate
- Event-free survival

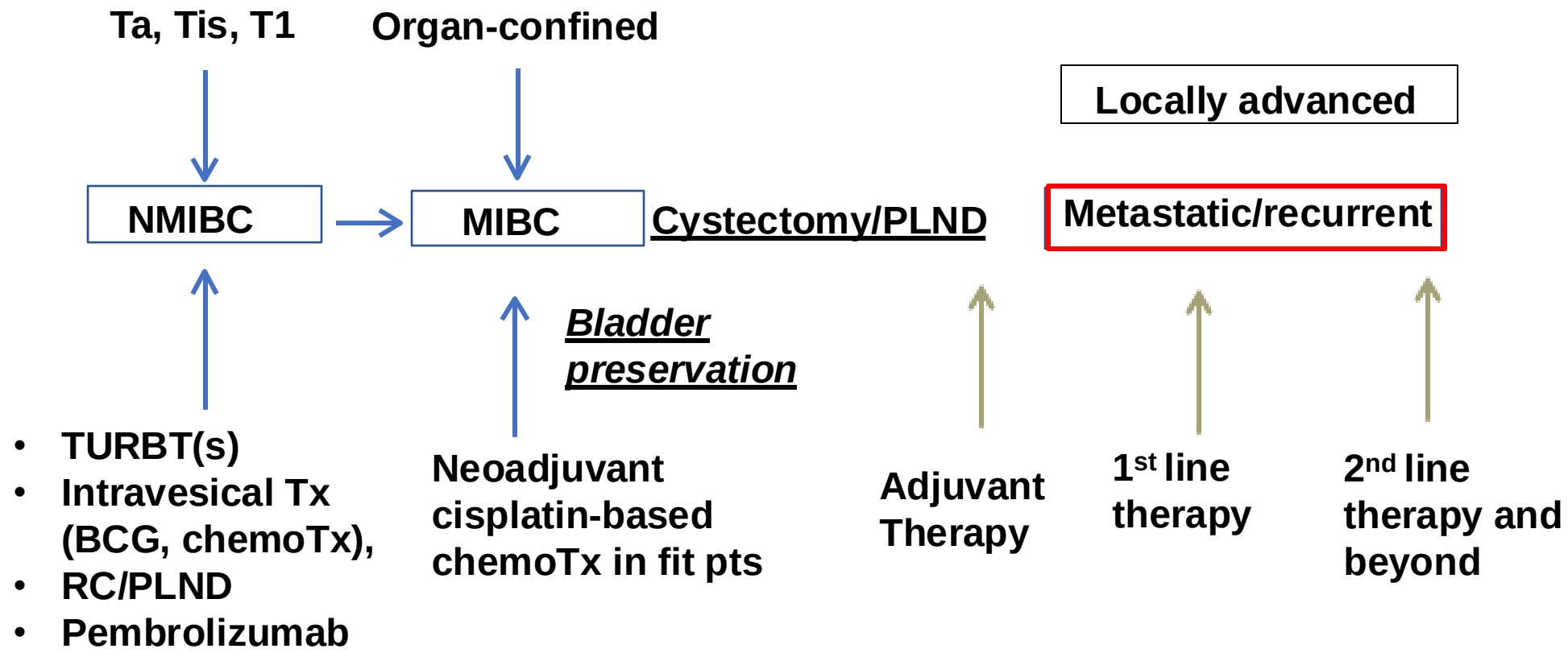
Key Secondary endpoints

- Pathologic complete response rate (D+EV)
- Event-free survival (D+EV)
- Overall survival
- Disease-free survival
- Pathologic downstaging
- Disease-specific survival

NIH. Accessed December 4, 2024. https://clinicaltrials.gov/study/NCT05628688.

Advanced Metastatic UC

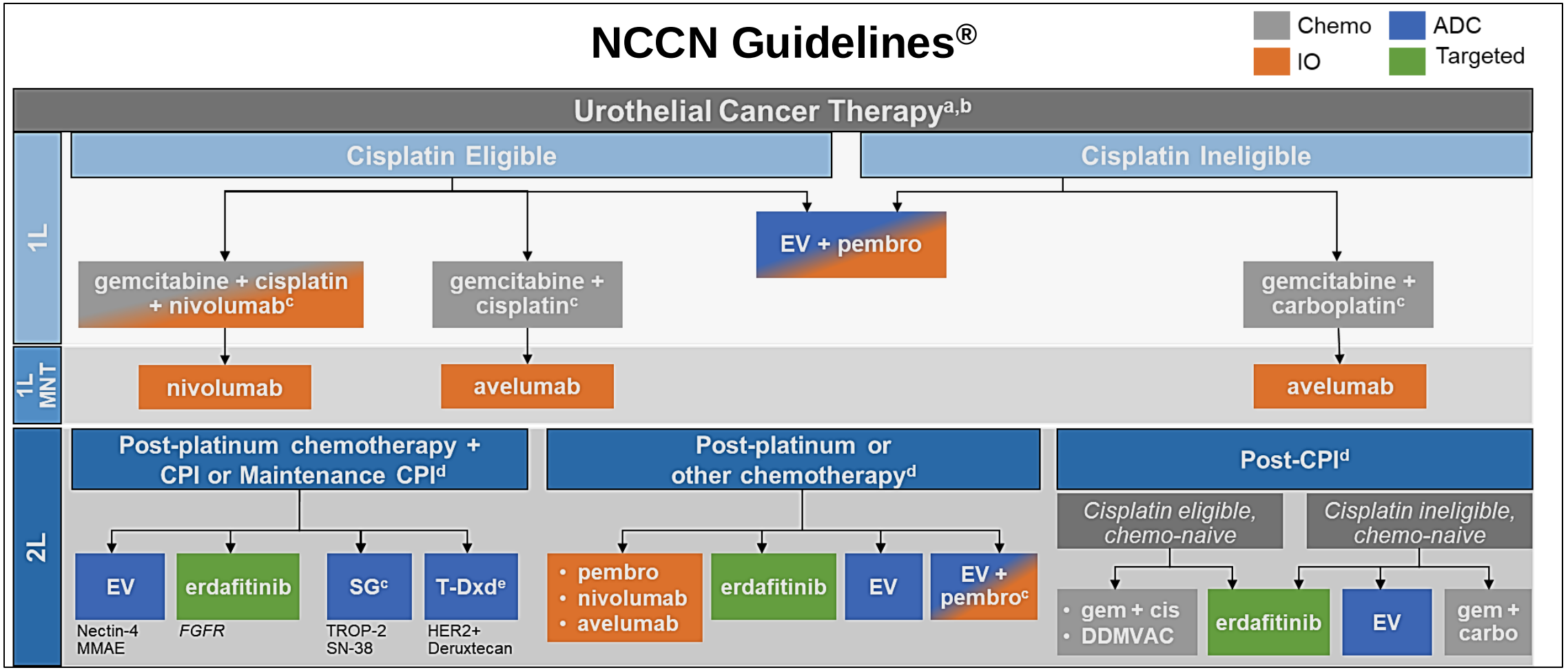
Disease/Treatment Settings



Metastatic Disease: A Paradigm Shift

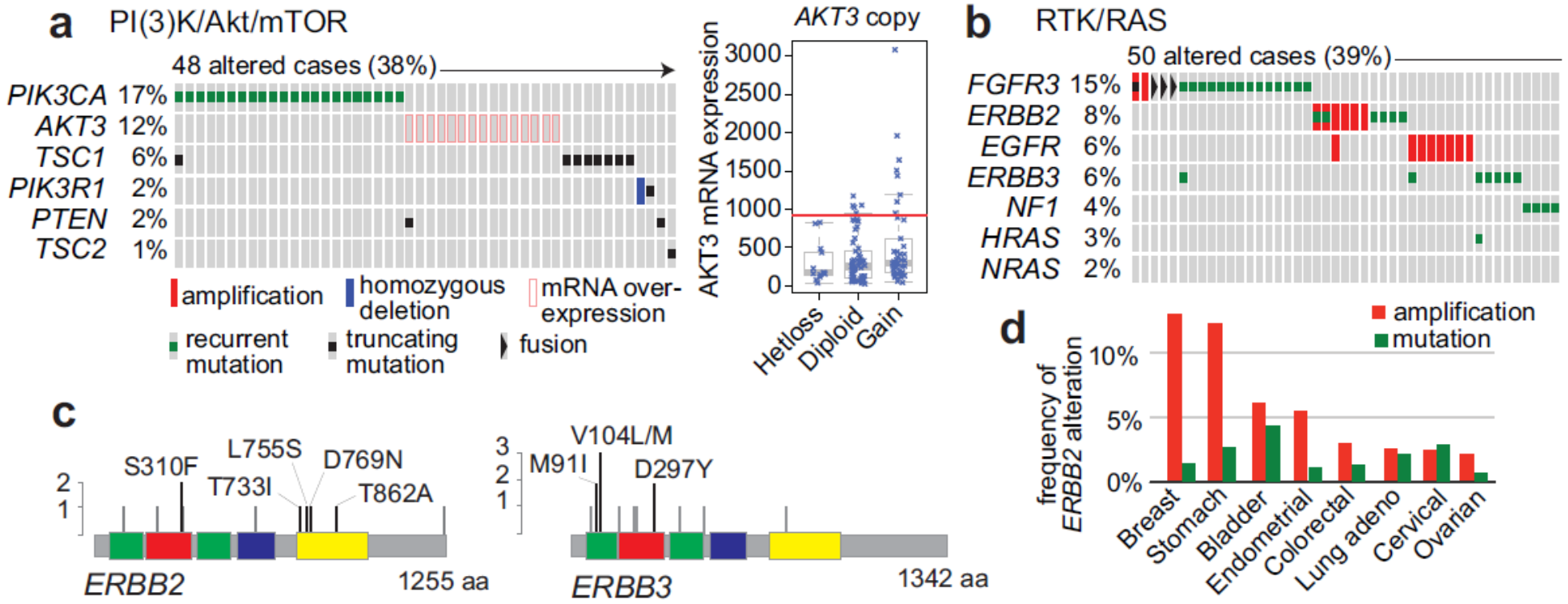
- Chemotherapeutic regimens such as gemcitabine/cisplatin and MVAC demonstrate improved survival, but only 5-10% of patients survive 5 years
- Maintenance immune therapy for responding patients increases the median survival to 27 months
- Second line immune therapy with pembrolizumab demonstrates a median survival of 12 months
- New agents need to be identified to improve survival

Current Treatment Paradigm For LA/mUC



[a]Based on preferred or alternative preferred regimens, unless indicated otherwise; [b]EV + pembrolizumab, nivolumab + gemcitabine-cisplatin, sacituzumab govitecan, and erdafitinib are not approved globally for la/mUC; [c]Included under other recommended regimens; [d]Participation in clinical trials of new agents is recommended; [e]Included under useful in certain circumstances.
1L = first-line; MNT = maintenance therapy; LA = locally advanced.
NCCN. Accessed May 21, 2024. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.

Multiple Alterations in Kinase Signaling Pathways



Cancer Genome Atlas Research Network. *Nature*. 2014;513(7517):202-209.

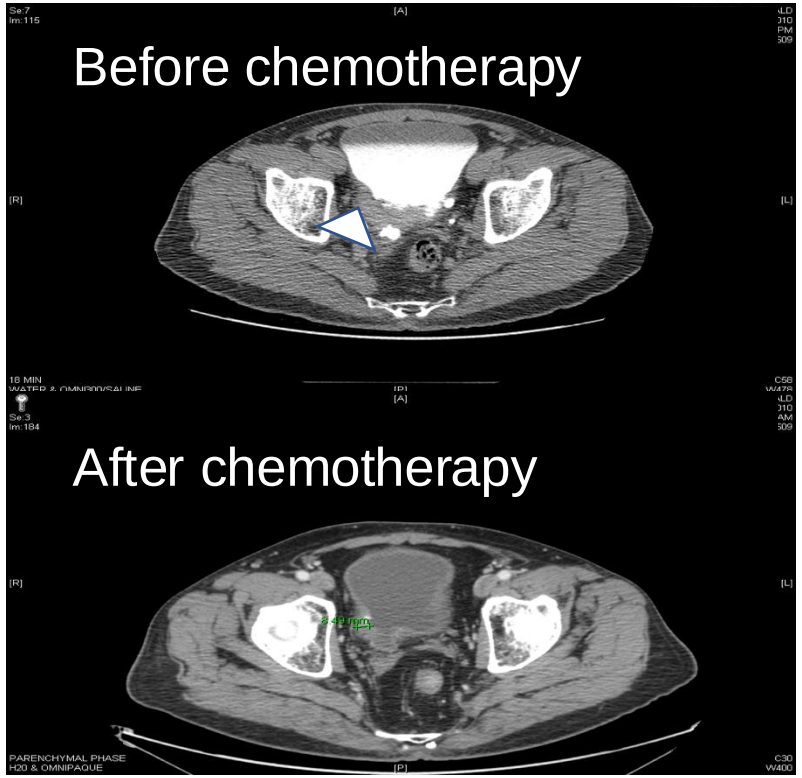
Actionable Genomic Landscape in Advanced Urothelial Carcinoma

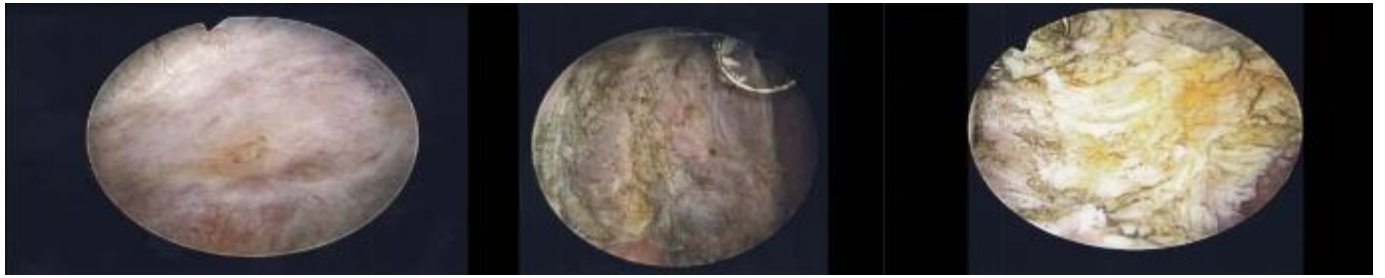
Biomarker and Somatic Alterations		NMIBC/MIBC/mUC Incidence Range	Late Stage/Approved Therapeutics	Indication/Phase/Clinical Trials, etc.	***Warnings*** Common Adverse Events
PD-L1 Positive		30-42%	Nivolumab Pembrolizumab Avelumab	CheckMate (274/901) KEYNOTE-057 JAVELIN Bladder-100	Immune-mediated reactions, diarrhea, fatigue, rash, pain, nausea, etc.
FGFR(1-4) altered Fusions/Mutations		10-70%	Erdafitinib	Approved- laUC or mUC (1-2024) NCT02365597, MoonRISe-1(P3)	Diarrhea, stomatitis Hyperphosphatemia, blood abnormalities
Nectin-4		>90%	Enfortmab Vedotin (EV) (mono/ICI combo)	EV-201, 301, 302– VOLGA, STAR-EV, etc.	***BB Warning- SJS and TEN*** Rash, fatigue, nausea, neuropathy, diarrhea, hyperglycemia, etc.
DNA Repair	ERCC2	1-5%	Platinum Radiation Therapy		
HER2 altered (mutation/amplification overexpression)		15-35%	T-Dxd	Approved HER2 Tumor Agnostic (4-2024)Destiny- PanTumor	***BB Warning- ILD, pneumonitis*** Nausea, fatigue, blood/lab abnormalities
			Disitamab Vedotin	mUC Phase-2	Nausea, fatigue, neuropathy, blood abnormalities, itching

Gerald T, et al. Presented at: ASCO GU Symposium; February 16, 2022; San Francisco, California. Abstract 525. Shah SH, et al. Presented at: ASCO GU Symposium; January 29, 2024; San Francisco, California. Abstract 574.

Patient Case Revisited

- 67 y/o man, wishes to preserve bladder
- cT2 TCC right posterior wall, compete transurethral resection (TUR) (R0)
- Received neoadjuvant therapy
- Clinical complete response (cCR)
- Negative CT scan
- Complete TUR scar, post-CT, cT0 pathology

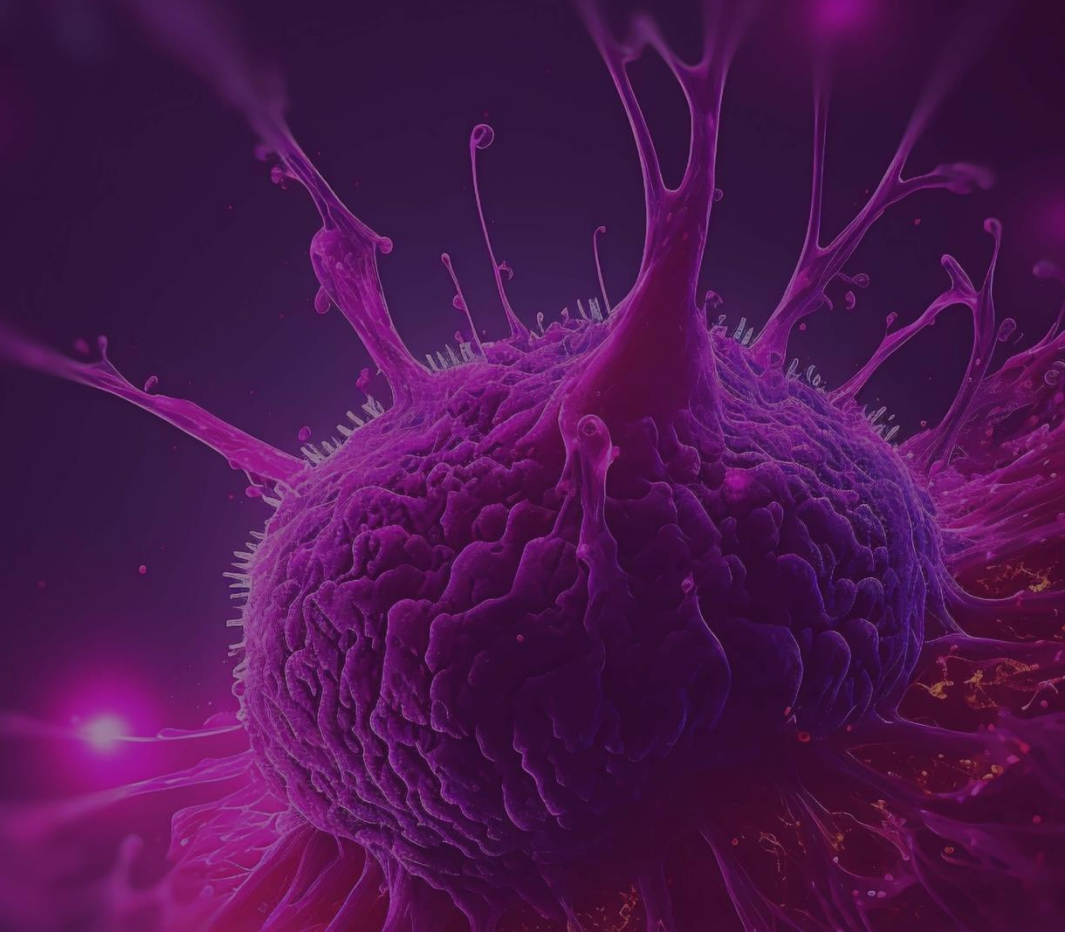




Key Learning Points

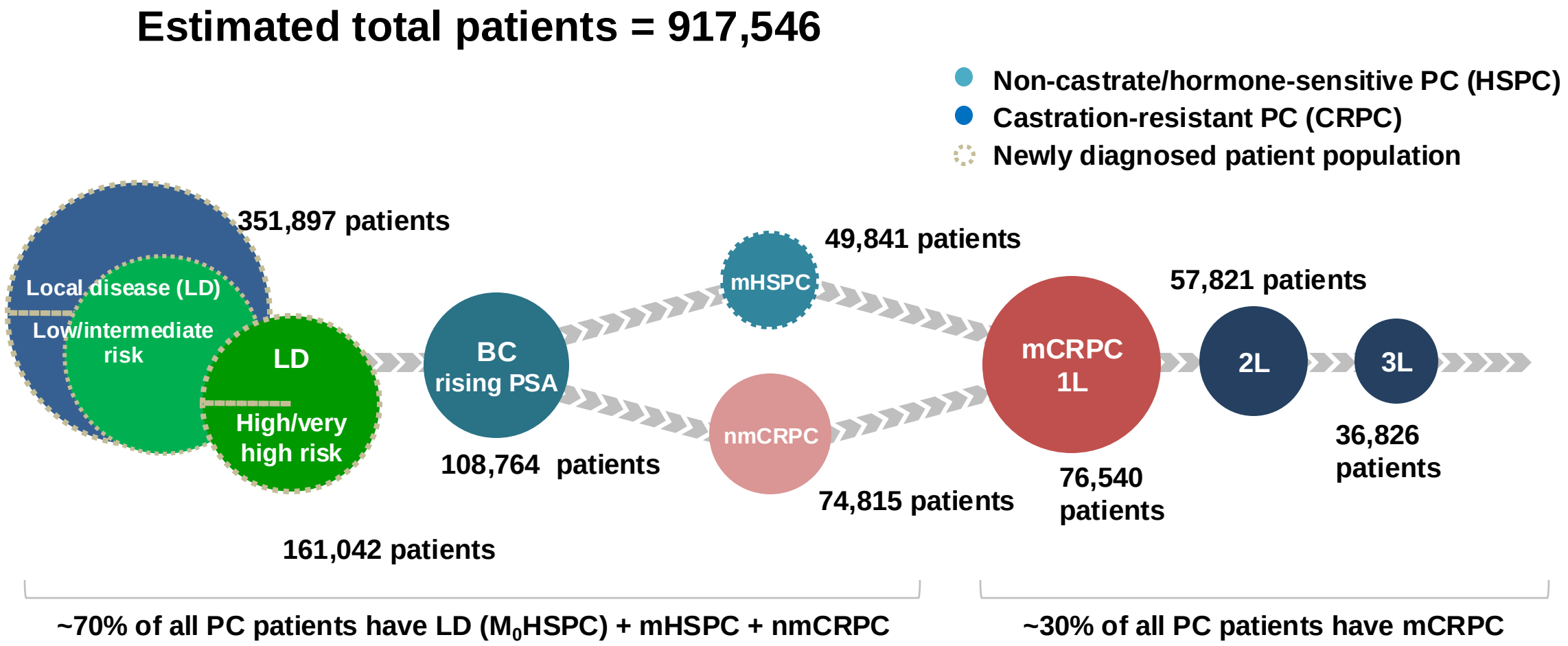
- Historically, 60-70% of patients were eligible for neoadjuvant cisplatin therapy
- 30-40% of patients were not eligible due to their renal clearance
- Newer neoadjuvant therapies in clinical trials are not dependent upon renal clearance—extending the scope of neoadjuvant therapy to more patients in the near future
- Durvalumab demonstrated statistical significance in the neoadjuvant setting providing Level 1 evidence for its future use
- Neoadjuvant Bladder Preservation may have a more prominent role in the future
- Biomarker testing of FGFR and HER-2 are crucial in therapeutic selection in advanced urothelial cancer

Questions?



De Novo mHSPC

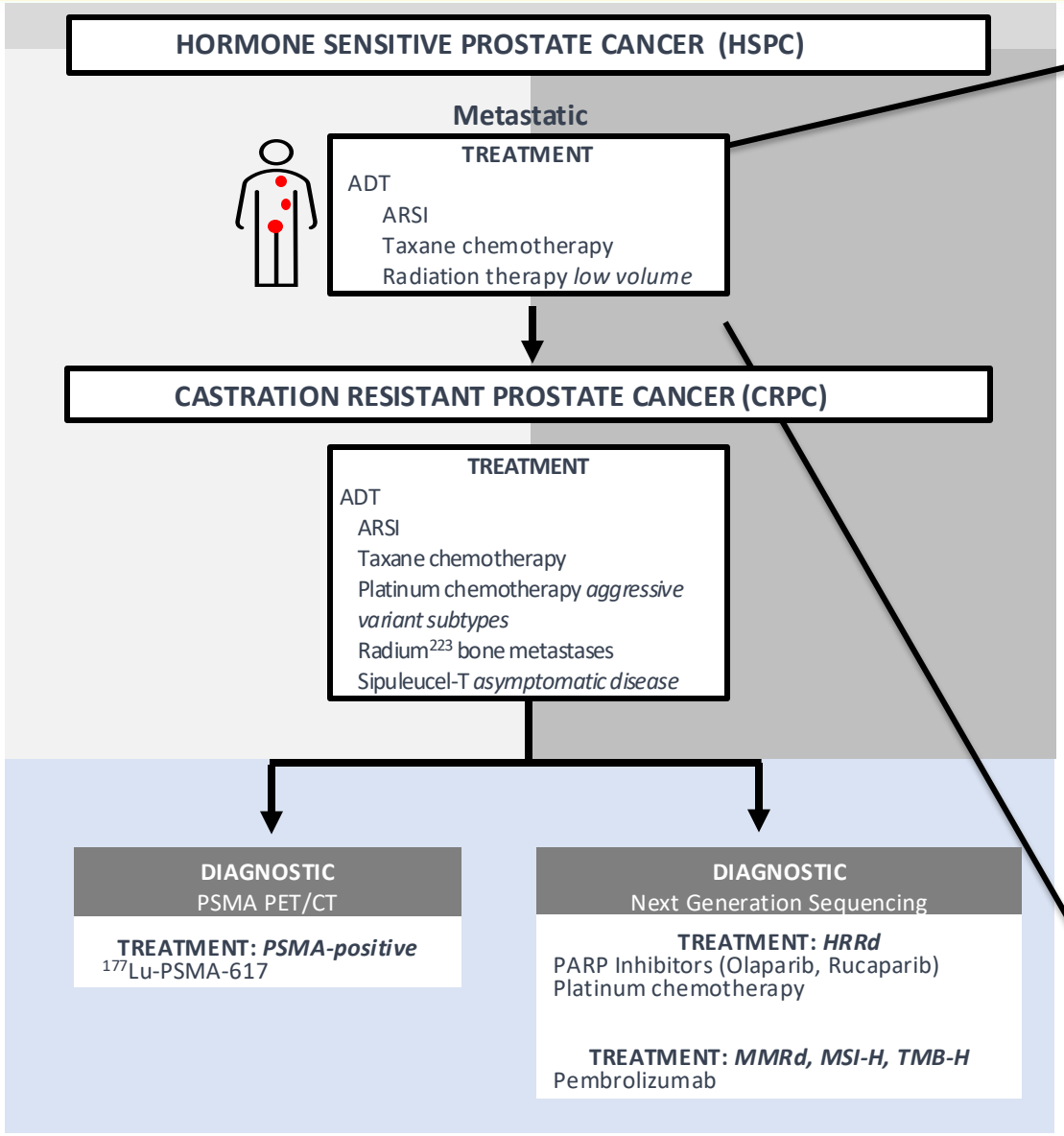
Stages of Diagnosis and Progression of Prostate Cancer

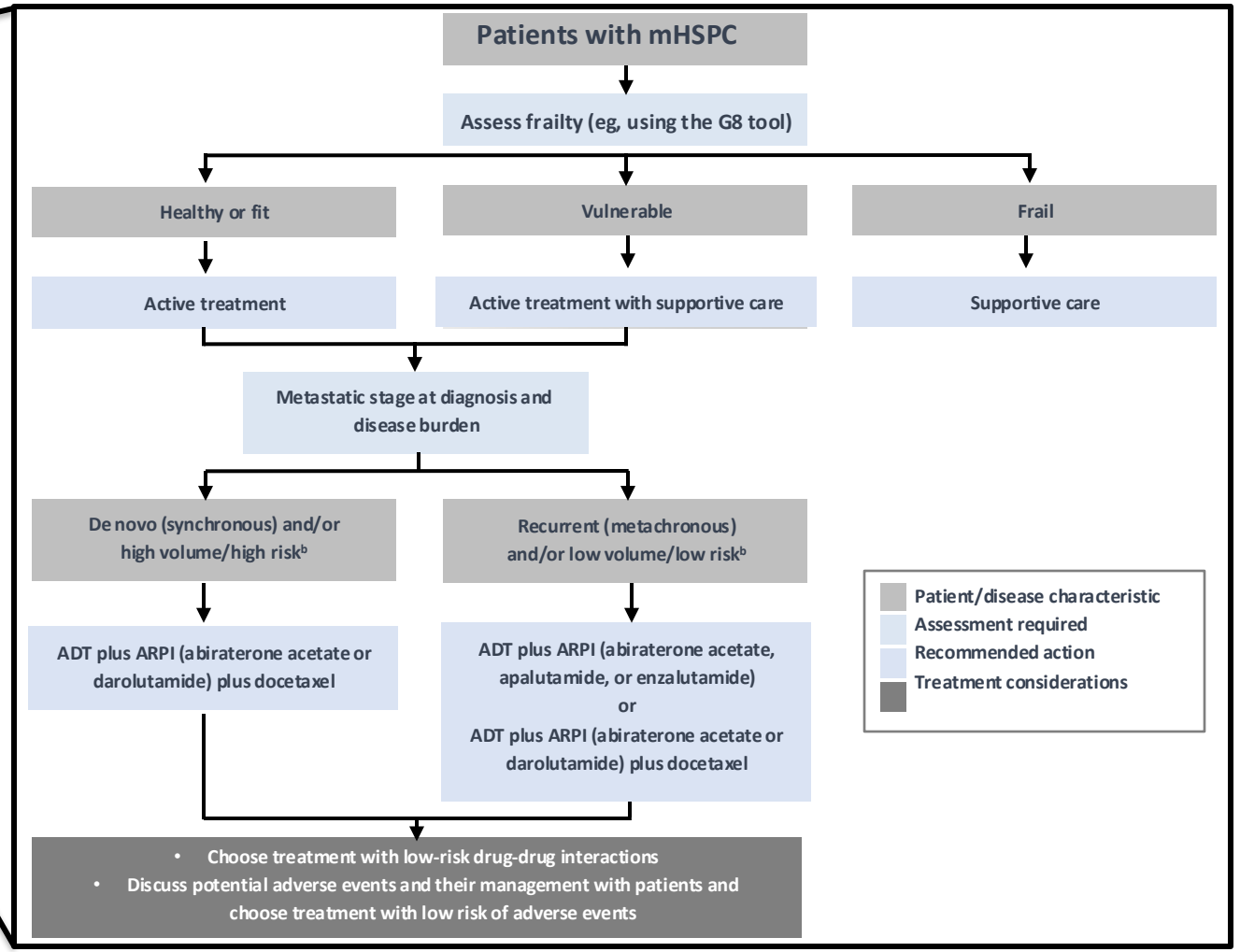


BC = biochemical control; nmCRPC = non-metastatic CRPC.

Shore N. Presented at: Health Technology Assessment International (HTAI) 2019 Annual Meeting; June 15-19, 2019; Cologne, Germany.

Advanced Prostate Cancer: *Standard of Care*

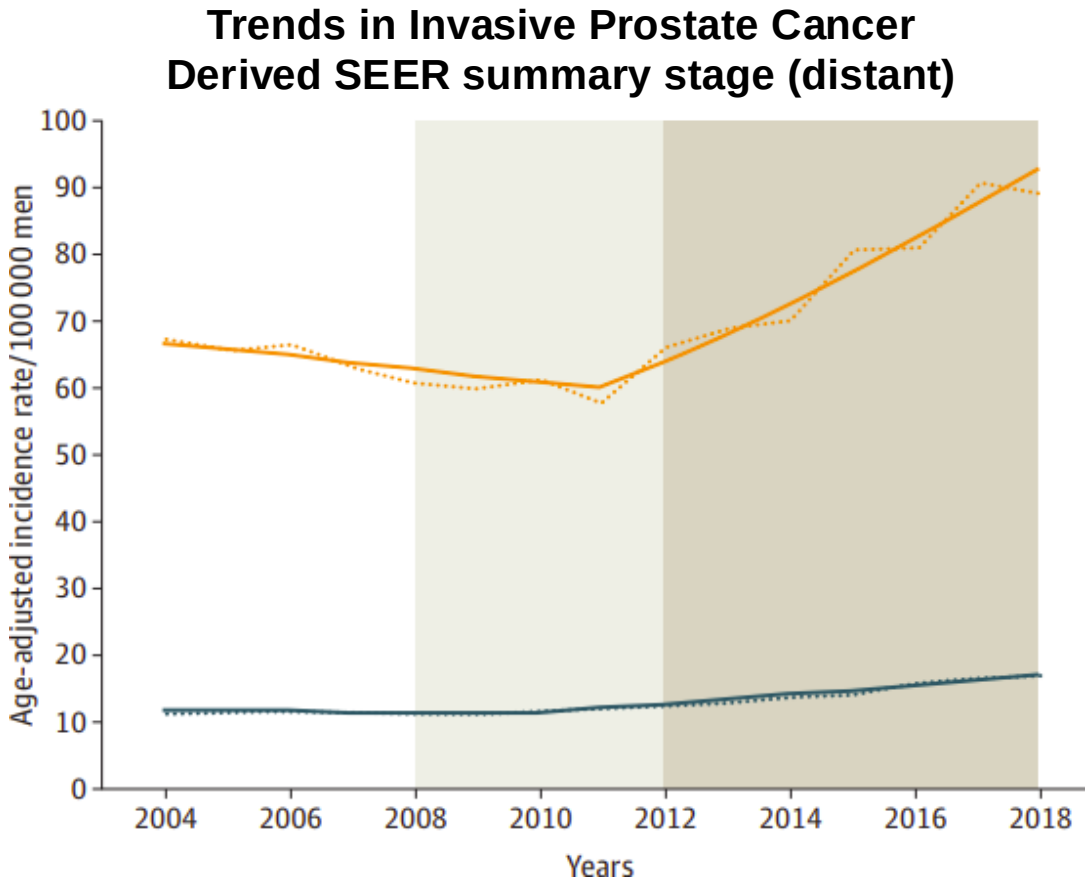




Gillette CM et al. *Cancers (Basel)*. 2023;15(9):2552. Hussain M et al. *JAMA Oncol*. 2024;10(6):807-820.

Metastatic Prostate Cancer in the US

- De novo mHSPC accounts for **5%-10% of all PCa diagnoses**
  - Likely due to new diagnostic tools (eg, PSMA-PET) and a reduction in PSA screening
- mHSPC **responsible for ~50% of PCa-related deaths**
- Multiple real-world studies have indicated that **>50% of patients still receive only ADT ± NSAAs**
  - Slow adoption of level-one evidence



The incidence rate of **metastatic PCa in men over 75 increased by 43%** from 2011 to 2018, and **by 41% in men aged 45 to 74** from 2010 to 2018.

PCa = prostate cancer; SEER = surveillance, epidemiology, and end results; USPSTF = US Preventive Services Task Force.

Piombino C et al. *Cancers (Basel)*. 2023;15(20):4945. Desai MM et al. *JAMA Netw Open.* 2022;5(3):e222246. Swami U et al. *J Urol*. 2023;209(6):1120-1131.

De Novo mHSPC Patient Case

A 59-year-old man with history of low volume metastatic adenocarcinoma of the prostate successfully controlled on ADT for 1 year presents in clinic with complaints of recent weight loss, fatigue, and mild pelvic pain radiating to the right side. At presentation, Labs are abnormal with elevated PSA 1 from baseline and HgB 12 dL/L. Upon further testing and imaging, the findings of the results reveal the following

- CT/MRI: 1 lesion in the R-femur and 2 lesions in the soft tissue in the R renal pelvis
- PSMA-PET: as above, but SUV elevated within T9-11 and 3 bilateral rib lesions

Prognosis: High-Volume vs. Low-Volume mHSPC

- mHSPC is usually categorized as a high- or low-volume disease
  - Low-volume mHSPC – anything other than that which fits the criteria for high-volume mHSPC
  - High-volume mHSPC – presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis

- PSMA PET criteria with volume quantification deliver comparable LVD/HVD discrimination with additional subgroups for unifocal, oligometastatic, and disseminated disease, critical for guidance of targeted or multimodal therapy

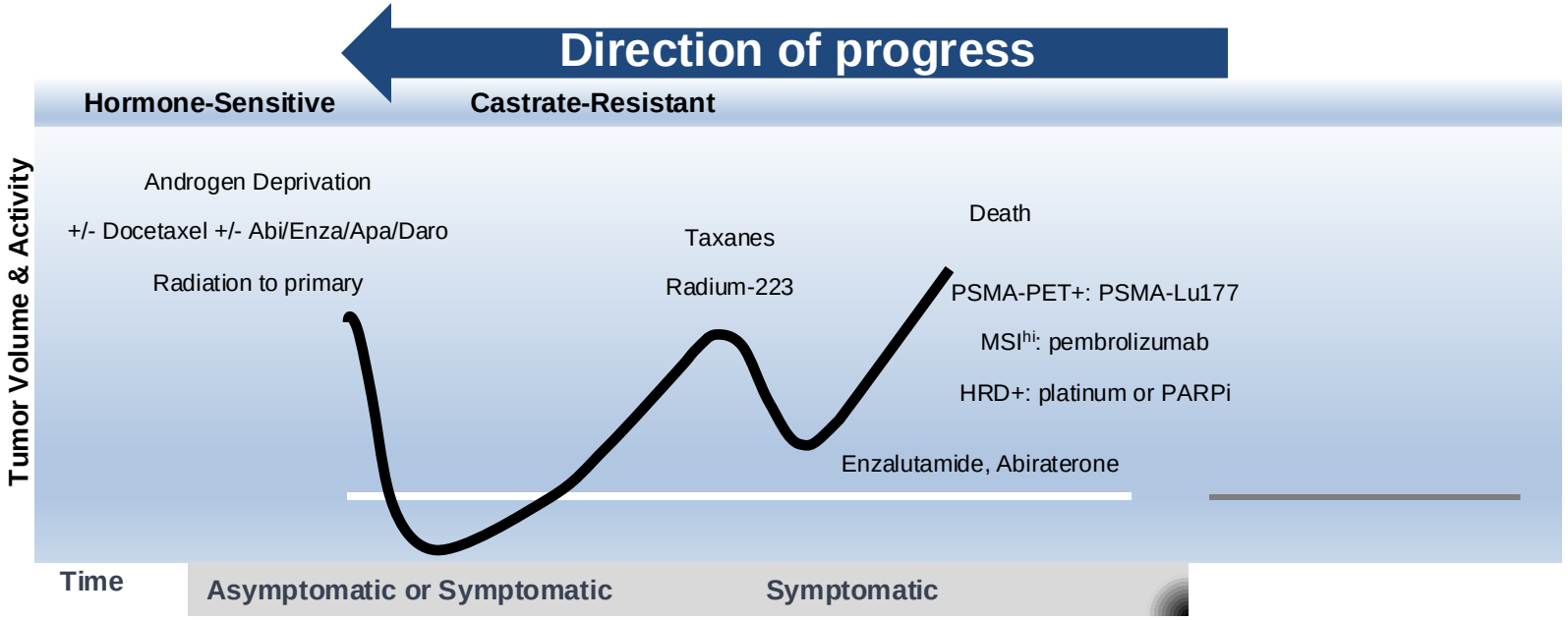
- Patients with low-volume disease have a more favorable prognosis than those with high-volume disease

Low- and high-volume metastatic diseases are associated with different outcomes; thus, management of the two forms should differ

Barbato F, et al. *J Nucl Med*. 2021;62(12):1747-1750. Oing C, Bristow RG. *ESMO Open.* 2023;8(2):101194. Verzoni E, et al. *Curr Oncol*. 2022;29(7):4578-4586.

A Need to Delay Progression for mHSPC

- Despite numerous approvals in life prolonging systemic treatment of advanced PC, metastatic disease remains incurable
- With an initial diagnosis of mHSPC, the OS is only 30% at 5 years
- *Therefore, it is crucial to prolong the time to progression for patients with mHSPC*



Oing C, Bristow RG. *ESMO Open*. 2023;8(2):101194.

Genetic/Biomarker Testing

- When should testing occur?
- How to decide on testing method/sequence?
- Should we be ordering more than one test at a time?
- If you receive a positive readout what are your next steps?

Genomic Alterations: Therapeutic, Prognostic, and Predictive Advantage in mHSPC

- **High-volume mHSPC** has evidence of **greater genomic instability relative to low-volume disease**
  - Global copy number burden and more frequent NOTCH, cell cycle, and Wnt signaling alterations
- AR aberrations detected in ctDNA at baseline associated with shorter OS
- Time to castration resistance is shorter with alterations in AR, TP53, PTEN, RB1, cell cycle, and MYC pathways
- SPOP mutations are associated with prolonged time to progression and death in patients treated with ARSIs (but not docetaxel) for mHSPC

Hamid AA, et al. *Am Soc Clin Oncol Educ Book*. 2023;43:e390166.

Somatic and Germline Testing:
Standard of Care in Prostate Cancer

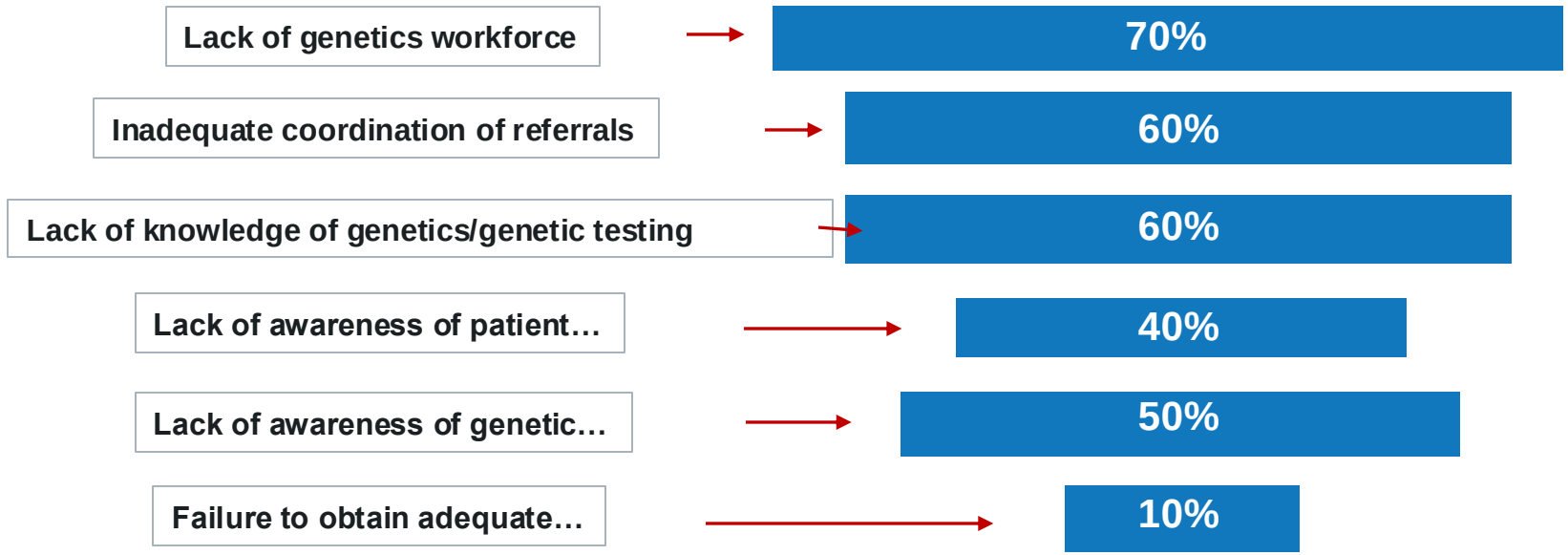
Guidelines	Somatic testing recommendations	Germline testing recommendations
NCCN Clinical Practice Guidelines in Oncology	✓	✓
ESMO 2020 Guidelines	✓	✓
AUA/ASTRO/SUO 2023 Guidelines	✓	✓
EAU 2023 Guidelines	✓	✓

Barriers to Genetic Testing for Prostate Cancer Patients

A retrospective study was performed to understand the uptake and challenges of genetic testing for PCa patients

Provider Responses:

What do you believe are the barriers for Genetic Testing?



- Only 39% of eligible PCa patients were referred, with testing completed in 11% with indications
- 30% of providers reported they would be comfortable completing genetic counseling themselves
- Lack of GC workforce (70%), lack of knowledge of genetic testing (60%), and lack of time and expertise (50%) were the most common barriers identified

Suri Y, et al. *Cancer Treat Res Commun*. 2022;32:100588.

Biomarkers in Advanced Prostate Cancer

PROGNOSTIC

- **Offer information regarding a patient's overall outcome** (ie, risk for recurrence after receiving standard treatment)
- Can help in the selection of patients for treatment but **does not predict response to a particular therapy**

- PSA
- Serum Testosterone
- HSD3B1
- Neutrophil-to-lymphocyte ratio
- CTC enumeration
- Total alkaline phosphatase
- Bone Scan Index (BSI)
- Bone metabolic markers
- PSMA
- ***PTEN* loss**

PREDICTIVE

- **Provide information regarding treatment benefit** or the **difference in outcomes between** two or more **interventions**

- PSA
- HSD3B1
- Neutrophil-to-lymphocyte ratio
- Serum testosterone
- AR splice variant
- Circulating cell-free DNA or tumor-DNA
- AR splice variant
- *ERG/SOX9*
- DNA damage repair gene alterations
- SLFN11 expression
- Bone metabolic markers
- PSMA
- HRR mutations
- ***PTEN* loss**
- MSI and dMMR
- HRR
- TMB
- PDL-1 expression

CTC = circulating tumor cell.

Asif S, et al. *Cancers (Basel)*. 2021;13(22):5723.

Treatment Selection for mHSPC

Abiraterone	Enzalutamide	Apalutamide	Darolutamide	Docetaxel
• Generic • Requires K+/LFT/BP monitoring • Concern for long-term HTN and prednisone • Less fatigue than AR antagonists • **Can intensify to triplet therapy**	• Less monitoring • Concern for neurocognitive issues	• Less monitoring • Concern for rash and neurocognitive issues	• Less monitoring • **Can intensify to triplet therapy**	• Least expensive • Completed after 6 cycles • Offer while chemo fit • Potential for new/worsened neuropathy • Can consider stopping early if exceptional responder/not tolerating chemo

- **Triplet therapy** often used in fit patients with aggressive disease or features suggesting less dependence on AR (high volume of metastatic disease, low PSA given volume of disease, high grade/poorly differentiated)

Abiraterone PI. Shpilsky. Expert Opin Pharmacother. 2021;22:1227. Fizazi. *Lancet*. 2022;399:1695. Enzalutamide PI. Ryan. *Prostate Cancer Prostatic Dis*. 2020;23:207. Apalutamide PI. Schulte. *Am Soc Clin Oncol Educ Book*. 2020;40:1. Darolutamide PI. Smith. *NEJM*. 2022;386:1132. Docetaxel PI. Thomas. *Cancers*. 2022;14:8. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. v.1.2023. Maluf. *JCO Glob Oncol*. 2021;7:559.

Improved OS in mHSPC with Treatment Intensification: **Level 1 Evidence**

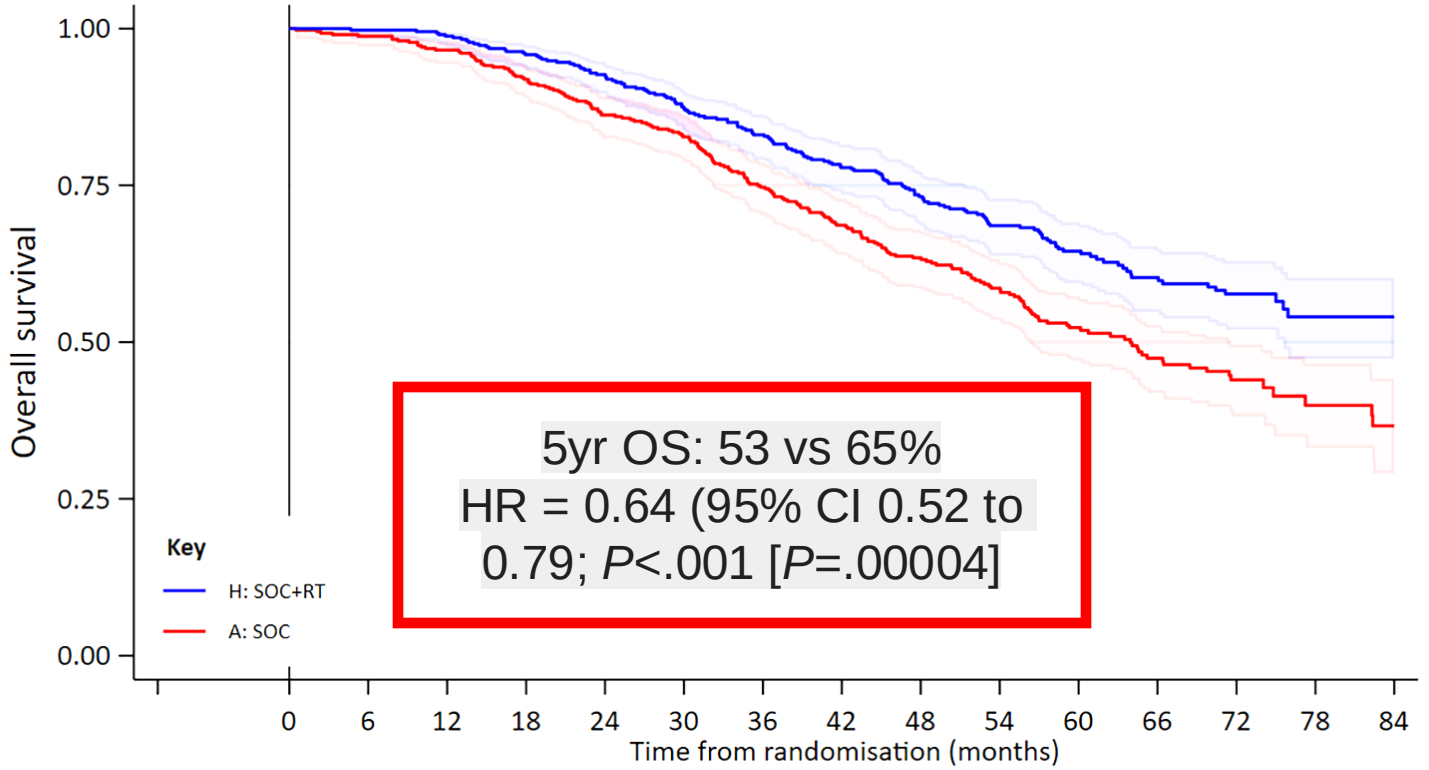
Clinical Trial(s)	Intervention	Control	Comments
STAMPEDE-H	Prostate radiation + ADT (± docetaxel)	ADT (± docetaxel)	Benefit in low-volume subgroup
GETUG-15 CHAARTED STAMPEDE-C	Docetaxel + ADT	ADT	Benefit in high-volume subgroup
LATITUDE STAMPEDE-G	Abiraterone + ADT	ADT	Similar benefits by risk group
ARCHES ENZAMET	Enzalutamide + ADT	ADT	Similar benefits by risk group
TITAN	Apalutamide + ADT	ADT	Similar benefits by risk group
ARASENS	Darolutamide + ADT + docetaxel	ADT + docetaxel	Similar OS benefit for recurrent and de novo metastatic disease
PEACE-1	Abiraterone + ADT + docetaxel (± prostate radiation)	ADT + docetaxel (± prostate radiation)	rPFS benefit for all; OS benefit in high-volume

rPFS = radiographic progression-free survival.

Parker CC, et al. *Lancet*. 2018;392(10162):2353-2366. Armstrong AJ, et al. *J Clin Oncol.* 2022;40(15):1616-1622. Davis ID, et al. *N Engl J Med.* 2019;381(2):121-131. James N, et al. *Lancet*. 2016;387(10024):1163-1177. Sweeney CJ, et al. *N Engl J Med*. 2015;373(8):737-746. Chi KN, et al. *N Engl J Med*. 2019;381(1):13-24. Fizazi K, et al. *N Engl J Med.* 2017;377(4):352-360. James ND, et al. *N Engl J Med.* 2017;377(4):338-351. Smith MR, et al. *N Engl J Med*. 2022;386(12):1132-1142. Fizazi K, et al. *Lancet*. 2022;399(10336):1695-1707.

Prostate-Directed Therapy: STAMPEDE Trial Update

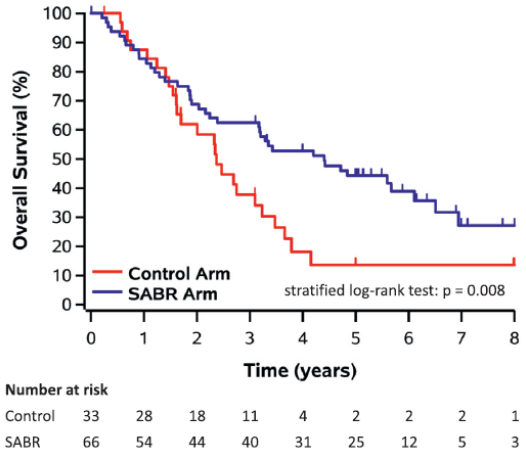
2061 pts, met PCa, 2013-16, Phase III RCT ADT +/- RT



A: SOC															
At-risk now	409	403	392	373	348	330	297	268	226	174	123	92	57	26	13
Censored now	0	1	3	3	5	9	10	15	37	73	106	127	156	184	195
Event by now	0	5	14	33	56	70	102	126	146	162	180	190	196	199	201
H: SOC+RT															
At-risk now	410	408	404	391	378	354	336	307	267	215	163	122	76	42	21
Censored now	0	1	1	2	2	4	5	13	35	71	111	143	184	215	236
Event by now	0	1	5	17	30	52	69	90	108	124	136	145	150	153	153

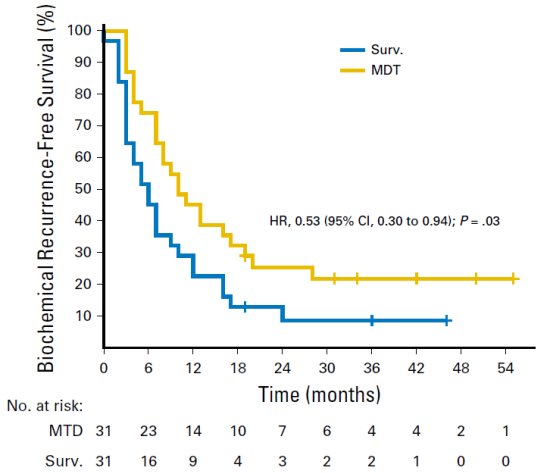
Parker C, et al. *PLoS Med*. 2022;19(6):e1003998.

Metastasis-directed Therapy (MDT) in Oligometastatic Cancer: Randomized Trials



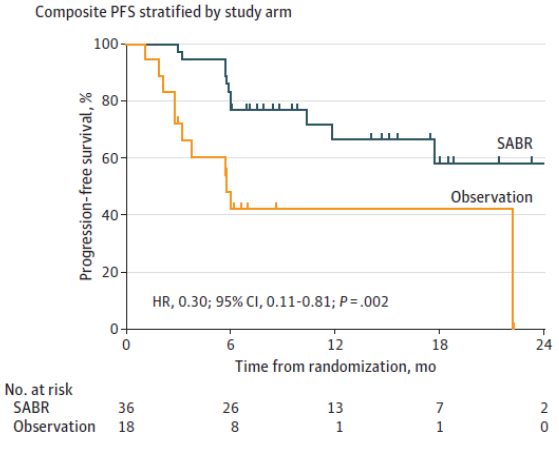
SABR-COMET
N=99
1-5 oligometastasis from various malignancies
Primary controlled
Improved OS

Harrow, IJROBP, 2022



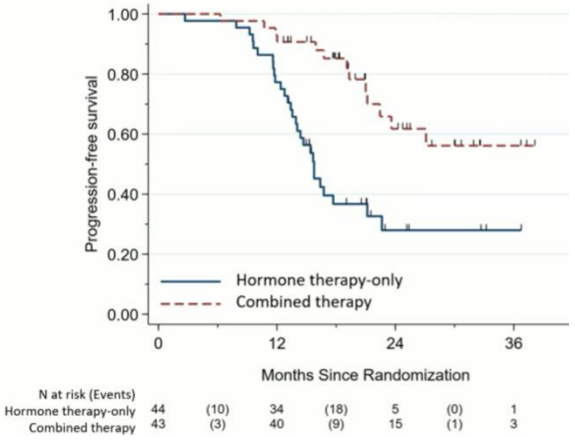
STOMP
N=62
1-3 oligometastasis from prostate cancer
Primary controlled
Improved ADT-free Survival

Ost, J Clin Oncol, 2017



ORIOLE
N=54
1-3 oligometastasis from prostate cancer
Primary controlled
Improved PFS

Phillips, JAMA Onc, 2020

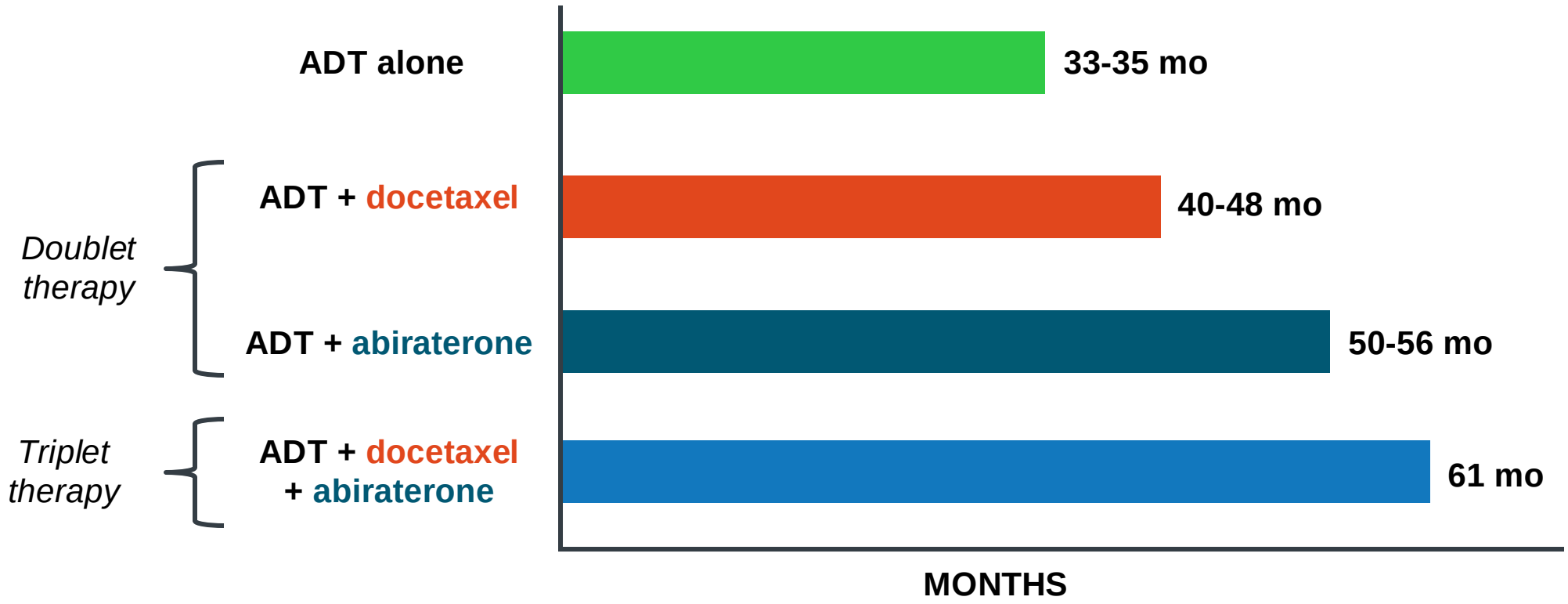


EXTEND PROSTATE INT ADT
N=87
1-5 oligometastasis from prostate cancer
Treated or Untreated Primary
Improved PFS

Tang, JAMA Oncol, 2023

Treatment Intensification in De Novo High-Volume mHSPC: Median OS

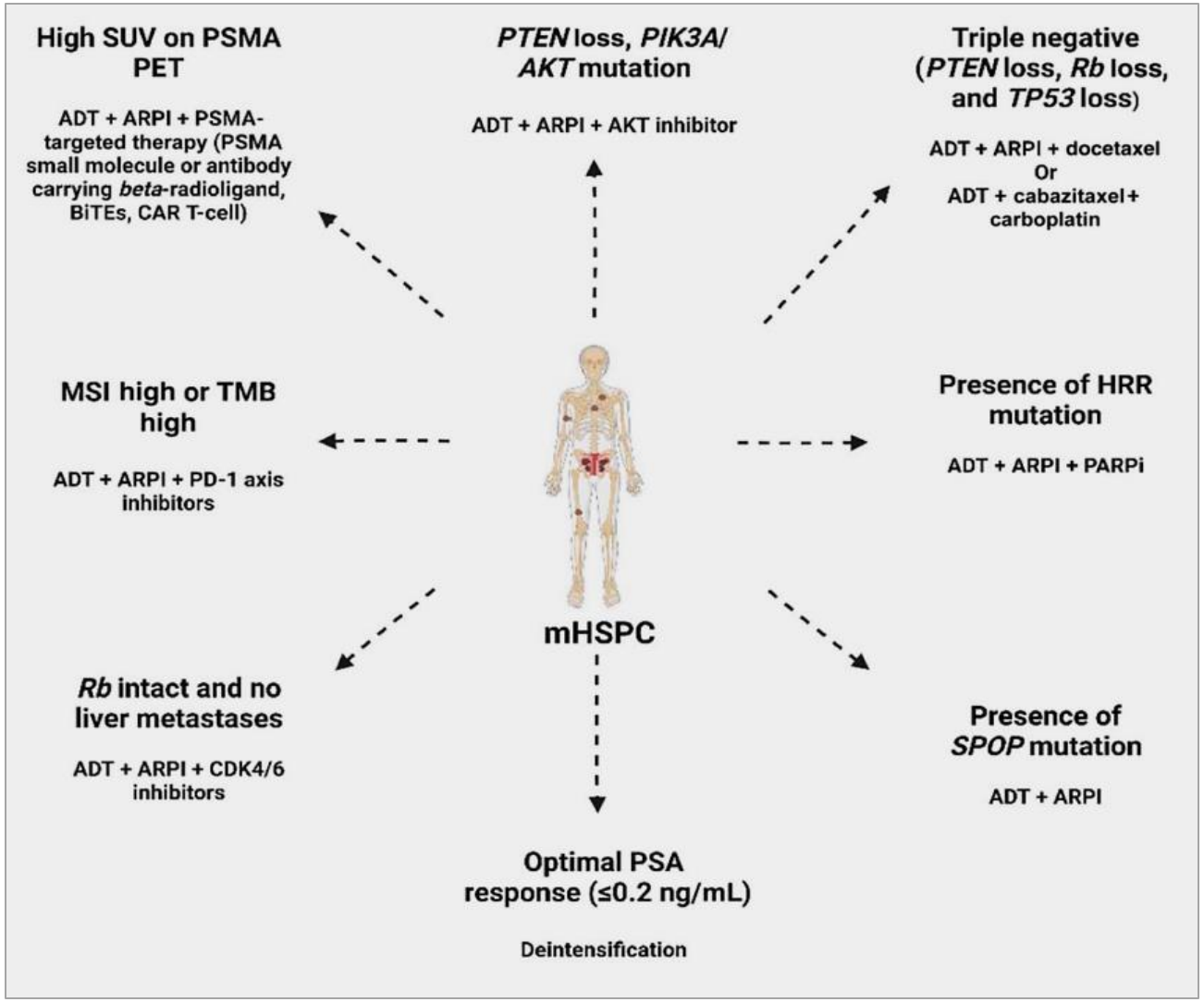
Cross-trial Comparison*: Median OS by Treatment Intensity



*Cross-trial comparisons have significant limitations. Data are shown here to generate discussion, not directly compare between trials.

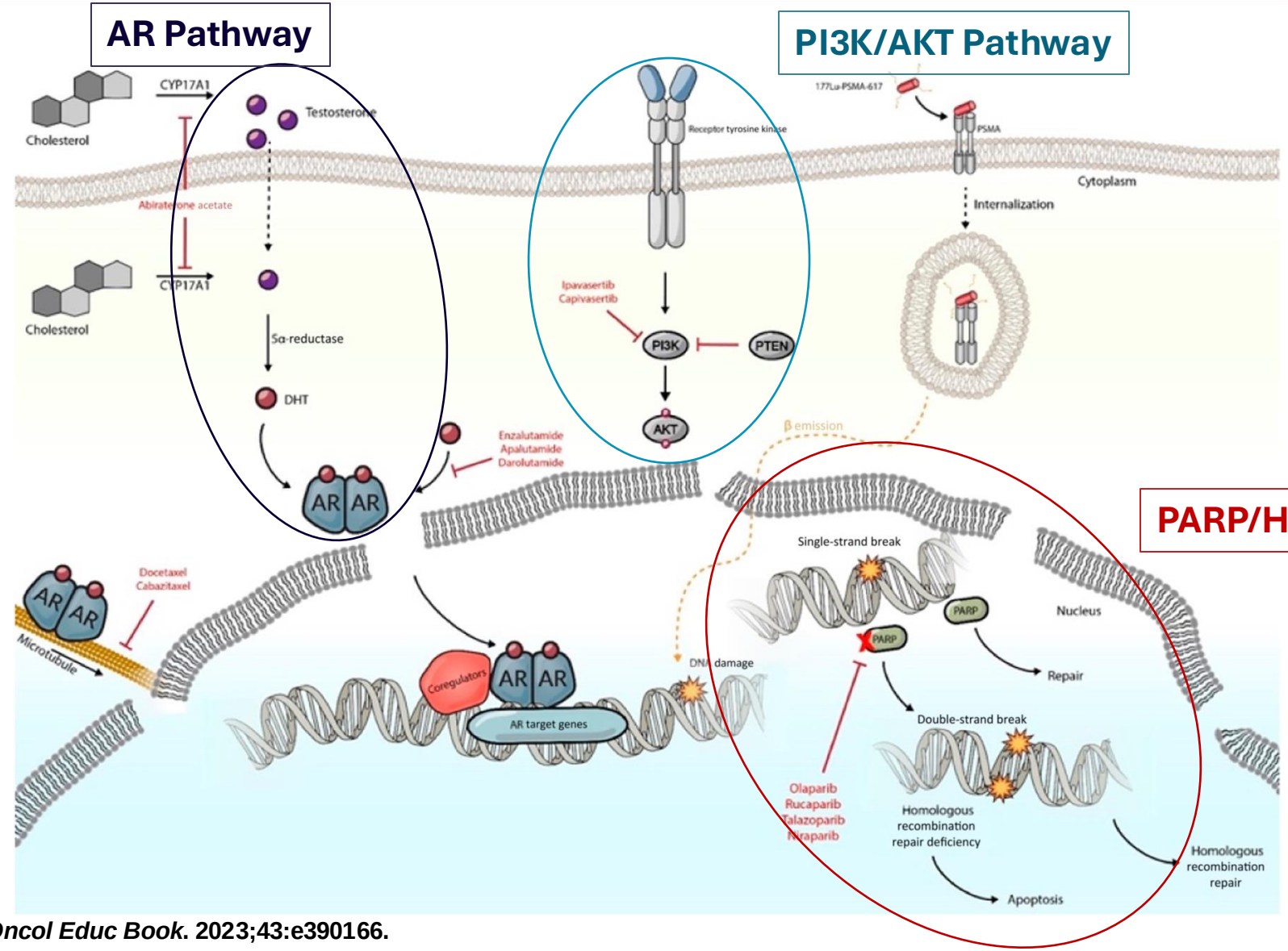
Kyriakopoulos. *J Clin Oncol*. 2018;36:1080. Gravis. *Eur Urol*. 2018;73:847. Clarke. *Ann Oncol*. 2019;30:1992. Fizazi. *Lancet*. 2022;399:1695. Fizazi. *Lancet Oncol*. 2019;20:686. James. *Int J Cancer*. 2022;151:422.

Precision Therapy Approaches in mHSPC: Potential Future



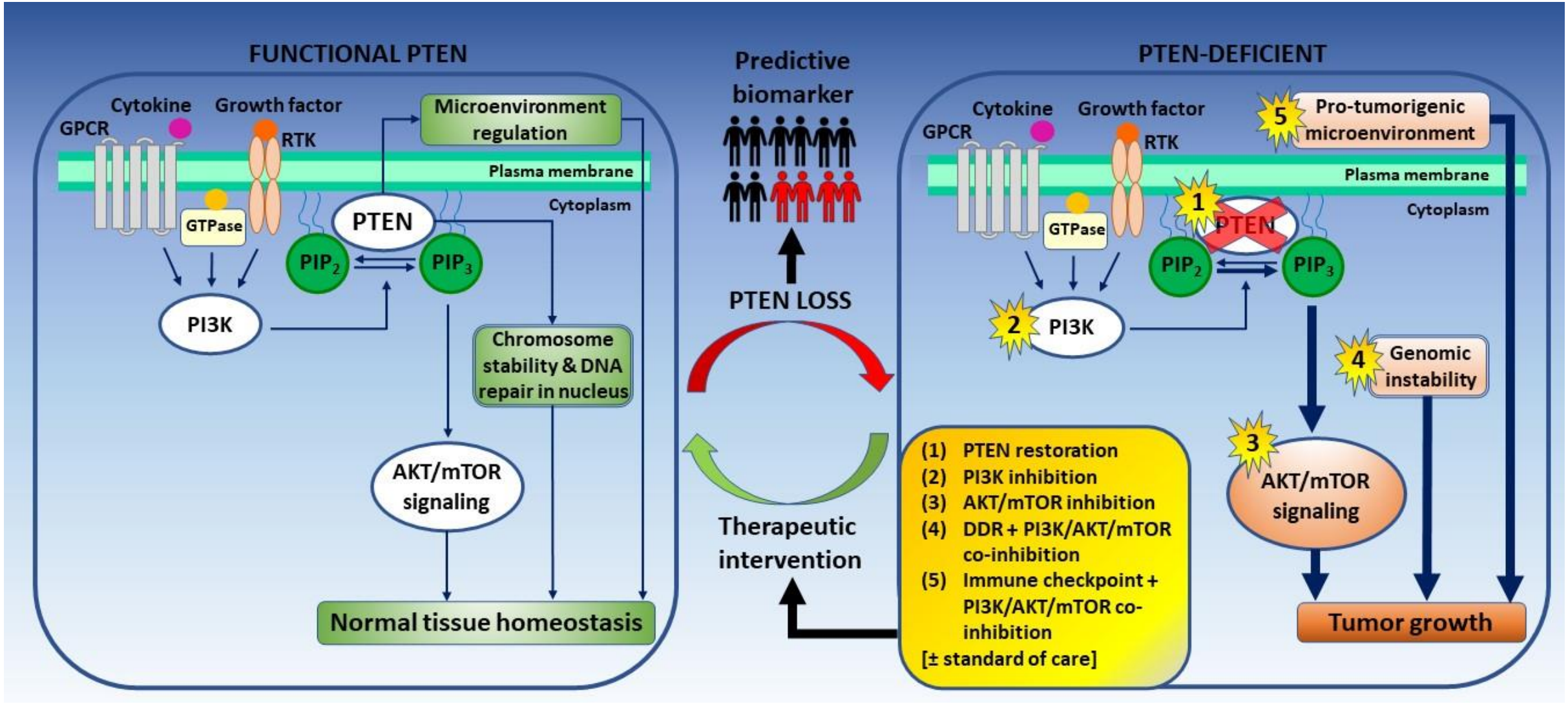
Hamid AA et al. *Am Soc Clin Oncol Educ Book*. 2023;43:e390166.

Therapeutic Targets for mHSPC



Hamid AA et al. *Am Soc Clin Oncol Educ Book*. 2023;43:e390166.

PI3K/AKT Pathway and PTEN Deficiency in PC



Turnham DJ, et al. *Cells*. 2020;9(11):2342.

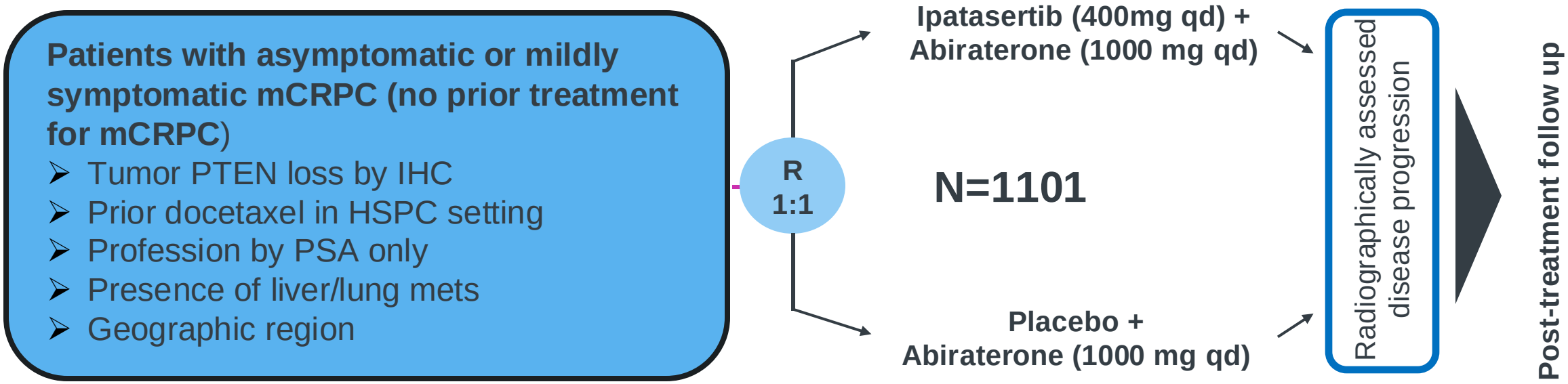
PTEN Status ***Is Associated*** with a Negative Impact on Survival in mHSPC Patients Treated with Conventional Therapies

Baseline Characteristics	
N of pts with de novo mHSPC N of pts having PTEN loss	56 22 (39%)
Median age at diagnosis	69 years (49-87)
N of pts with high-volume disease	48 (86%)
Median PSA pre-treatment	48 ng/mL (5.6-2170)
Therapies in the HSPC setting	ADT alone (n=15, 27%), ADT + Docetaxel (n=25, 44.6%), ADT + Abiraterone or Enzalutamide (n=8; 14.3%), ADT + Docetaxel + Abiraterone (n=5; 9%)

- **The prevalence of PTEN loss in *de novo* mHSPC is similar to castration-resistant disease**
- **TTCRPC is shorter among PTEN-loss patients (18 vs 26 months, HR 1.33; *P*=.07)**
- **Median OS is 40 months in PTEN loss compared to 75 months in PTEN-intact pts (HR 3.26; *P*=.01)**

Thouvenin J et al. *Ann Oncol.* 2021;32:S661.

IPATential150: *Phase III Study of Ipatasertib + Abiraterone vs Placebo + Abiraterone in mCRPC*



- **Co-primary endpoints:** Investigator-assessed rPFS (PCWG3 criteria) in **PTEN-loss (by IHC)** and ITT and populations
- Secondary endpoints: OS, TTP, Time to initiation of chemotherapy, ORR, investigator-assessed rPFS in **PTEN-loss (by NGS)** population

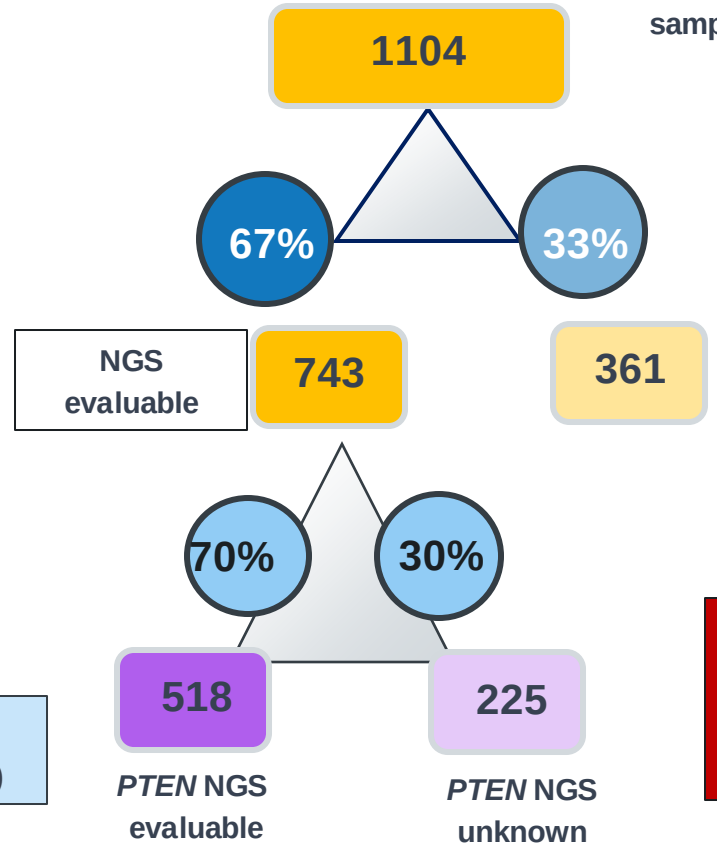
Sweeney C et al. *Lancet*. 2021;398(10295):131-142. De Bono J. IPATenial150. ESMO 2020. Available at: https://bit.ly/31s8gje.

IPATential150: *Phase III Study of Ipatasertib + Abiraterone vs Placebo + Abiraterone in mCRPC*

Definition of *PTEN* Loss by NGS

PTEN status	Sequence classification	
Loss	*PTEN*-inactivating alterations	Homozygous deletion (CN=0)
		Heterozygous deletion (CN=1)
		DN mutations
		Bi-allelic inactivation
Unknown	*PTEN*-inactivating status unknown	
Wild type	No *PTEN*-inactivating mutations	

PTEN NGS Analysis



- 44% insufficient DNA (n=158)
- 25% laboratory QC metric (n=89)
- 17% insufficient tissue (n=61)
- 15% informatic analysis failure (n=53)

- 40% *PTEN* loss (n=208)
- 60% *PTEN* wild type (n=310)

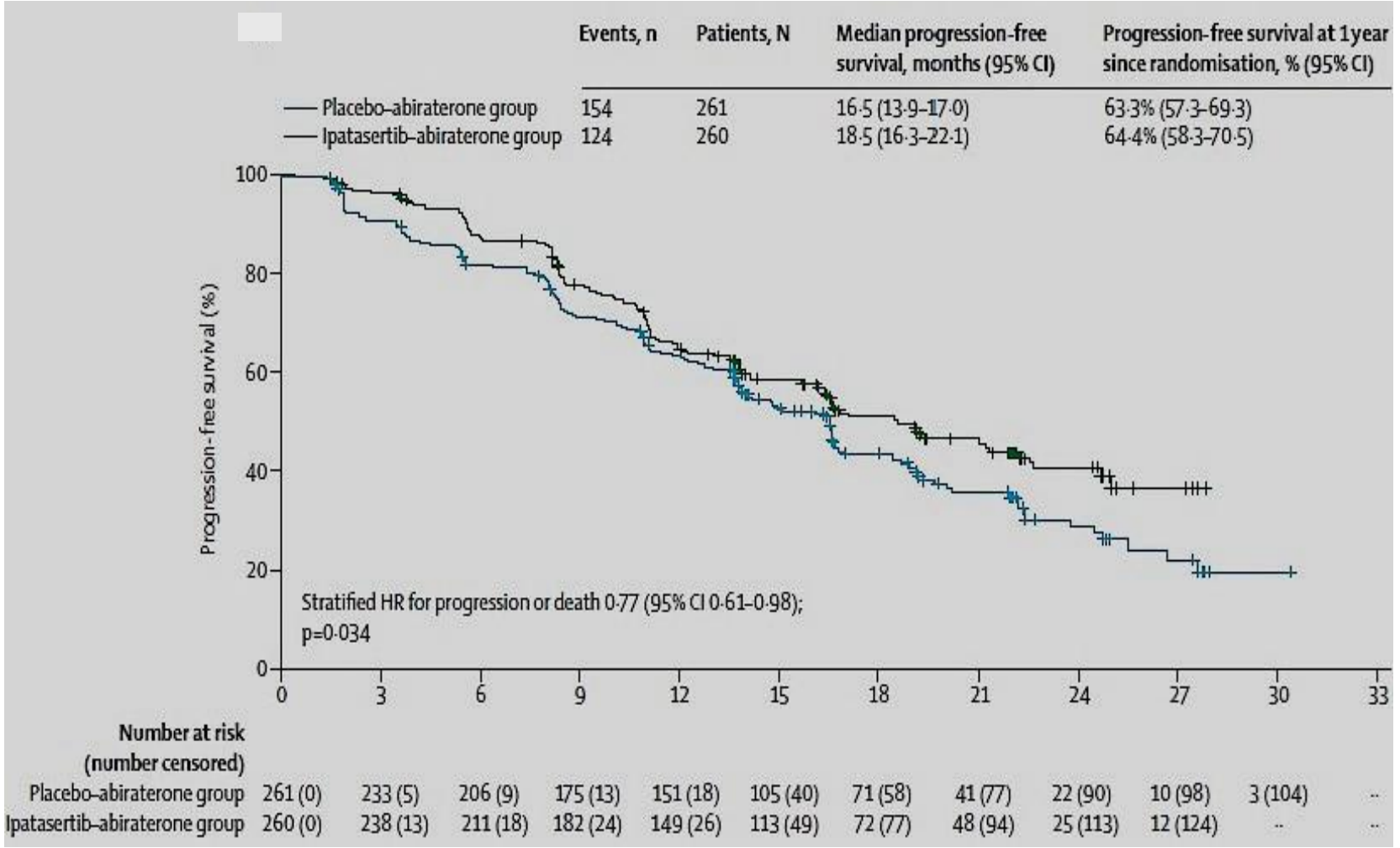
NGS assay failure rate
- IPATential150: 33%
- PROfound: 31%
- TRITON: 32%

- Out of 1101 patient samples, 67% were evaluable by NGS, and 70% of these were able to be evaluated for PTEN status
- The overall agreement between PTEN status by IHC and NGS was 85.5%
- Of the 208 samples with PTEN loss by NGS, 91.3% also showed PTEN loss by IHC

De Bono J. IPATenial150. ASCO GU 2021.

IPATential150: *Phase III Study of Ipatasertib + Abiraterone vs Placebo + Abiraterone in mCRPC*

- **Ipatasertib + abiraterone significantly improved rPFS** among patients with mCRPC with PTEN-loss tumors
- No significant difference between the groups in the ITT population
- PTEN status by IHC and NGS demonstrated good concordance
- Adverse events were consistent with the known safety profiles of each agent



Sweeney C et al. *Lancet*. 2021;398(10295):131-142. De Bono J. IPATenial150. ESMO 2020. Available at: https://bit.ly/31s8gje.

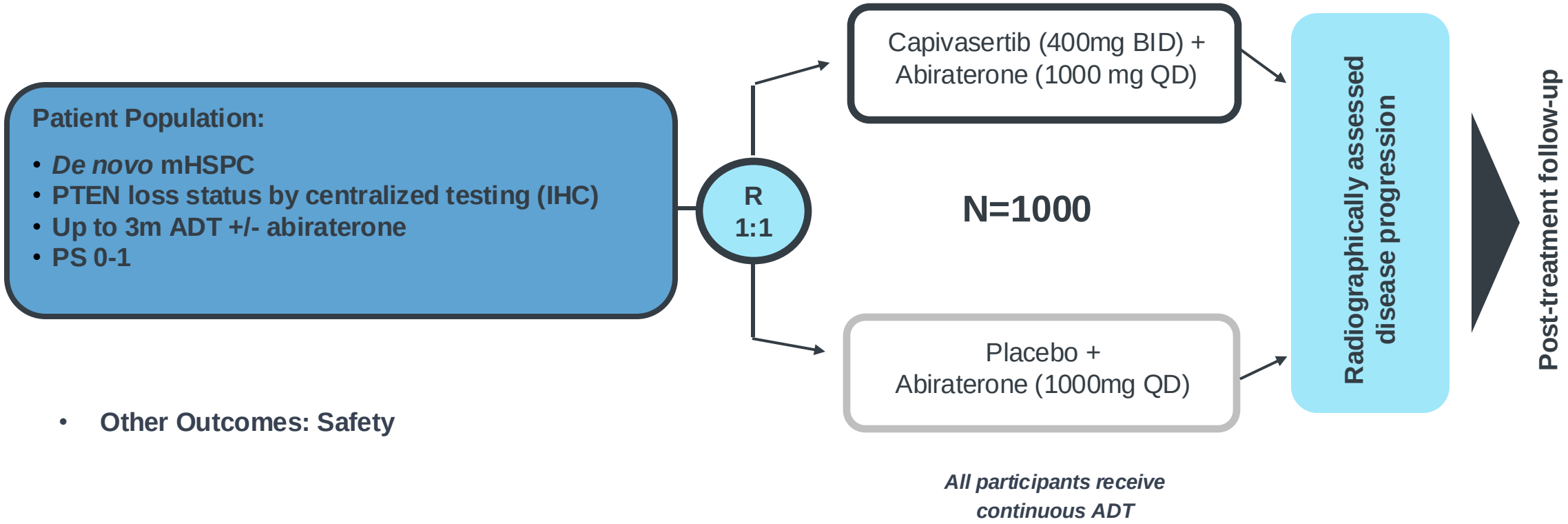
Ongoing Phase 2/3 Clinical Trials in mHSPC

Table 1

Trial	Target (n)	Inclusion Criteria	Intervention	Control	Primary End Point
CYCLONE-03 (NCT05288166) Phase III	900	- High-risk mHSPC (>=4 bone mets and/or >=1 visceral met) - Ongoing ADT Treatment naïve (or <3 months of ADT or ARSI before inclusion)	Abemaciclib + Abiraterone Acetate 1000 mg PO QD + Prednisone 5 mg PO QD	Placebo + Abiraterone Acetate 1000 mg PO QD + Prednisone 5 mg PO QD	rPFS
UpFrontPSMA (NCT04343885) Phase II	140	- High-volume PSMA-avid disease (SUVmax >15) - < 4 weeks on ADT	ADT + 177Lu-PSMA-617 IV every 6 weeks for 2 cycles, followed by Docetaxel every 3 weeks for 6 cycles	ADT + Docetaxel every 3 weeks for 6 cycles	Proportion of patients with PSA <= 0.2 ng/mL at 12 months
PSMAddition (NCT04720157) Phase III	1,126	- PSMA-positive on 68Ga-PSMA-11 PET/CT - Treatment-naïve (or up to 45 days of ADT or ARSI before inclusion)	177Lu-PSMA-617 IV every 6 weeks for 6 cycles + ADT + ARSI	ADT + ARSI	rPFS
AMPLITUDE (NCT04497844) Phase III	788	- Positive for deleterious germline or somatic HRR mutation - Ongoing ADT - Treatment naïve (or up to 45 days of ADT or AAP before inclusion)	Niraparib 200 mg PO QD + Abiraterone Acetate 1000 mg PO QD + Prednisone 5 mg PO QD	Placebo + Abiraterone Acetate 1000 mg PO QD + Prednisone 5 mg PO QD	rPFS
TALAPRO-3 (NCT04821622) Phase III	550	- Positive for deleterious germline or somatic HRR mutation - Ongoing ADT - Treatment naïve (or <3 months of ADT or ARSI before inclusion)	Talazoparib 0.5 mg PO QD + Enzalutamide 160 mg PO QD	Placebo + Enzalutamide 160 mg PO QD	rPFS
CAPItello-281 (NCT00493853) Phase III	1,000	- Synchronous mHSPC PTEN deficiency on tissue IHC - Ongoing ADT	Capivasertib 400 mg PO BID + Abiraterone Acetate 1000 mg PO QD + Prednisone 5 mg PO QD	Placebo + Abiraterone Acetate 1000 mg PO QD + Prednisone 5 mg PO QD	rPFS
PROMETHEAN (NCT05053152) Phase II	260	- Recurrent oligometastatic (1-5 lesions) prostate cancer (PET detected) after RT or RP	SABR + 6 months relugolix 120 mg QD	SABR + 6 months placebo	Conventional imaging rPFS

CAPItello-281: *Phase III Trial of Capivasertib and Abiraterone in Patients with De Novo mHSPC Characterized by PTEN Deficiency*

- **Primary endpoint:** Investigator-assessed rPFS
- **Secondary endpoints:** OS, time to start of first subsequent anticancer therapy, symptomatic skeletal event-free survival, time to pain progression



Fizazi K et al. *J Clin Oncol.* 2021;39(Suppl. 6):TPS178.

Capivasertib vs Placebo Grade ≥3 TRAEs

mHSPC Experience

TRAE	Capivasertib	Placebo	Absolute Increase vs. Placebo
Rash	33.8%	6.8%	27%
Lower Respiratory Tract Infection	18.9%	8.1%	10.8%
Neutropenia	31.1%	21.6%	9.5%
Lacrimation Increased	12.2%	2.7%	9.5%
Groin Pain	10.8%	1.4%	9.4%
Mucosal Inflammation	18.9%	10.8%	8.1%
Pyrexia	20.3%	13.5%	6.8%
Febrile Neutropenia	14.9%	8.1%	6.8%
Diarrhea	66.2%	59.5%	6.7%
Dyspepsia	13.5%	6.8%	6.7%
Anemia	16.2%	10.8%	5.4%

ProCAID clinical trial

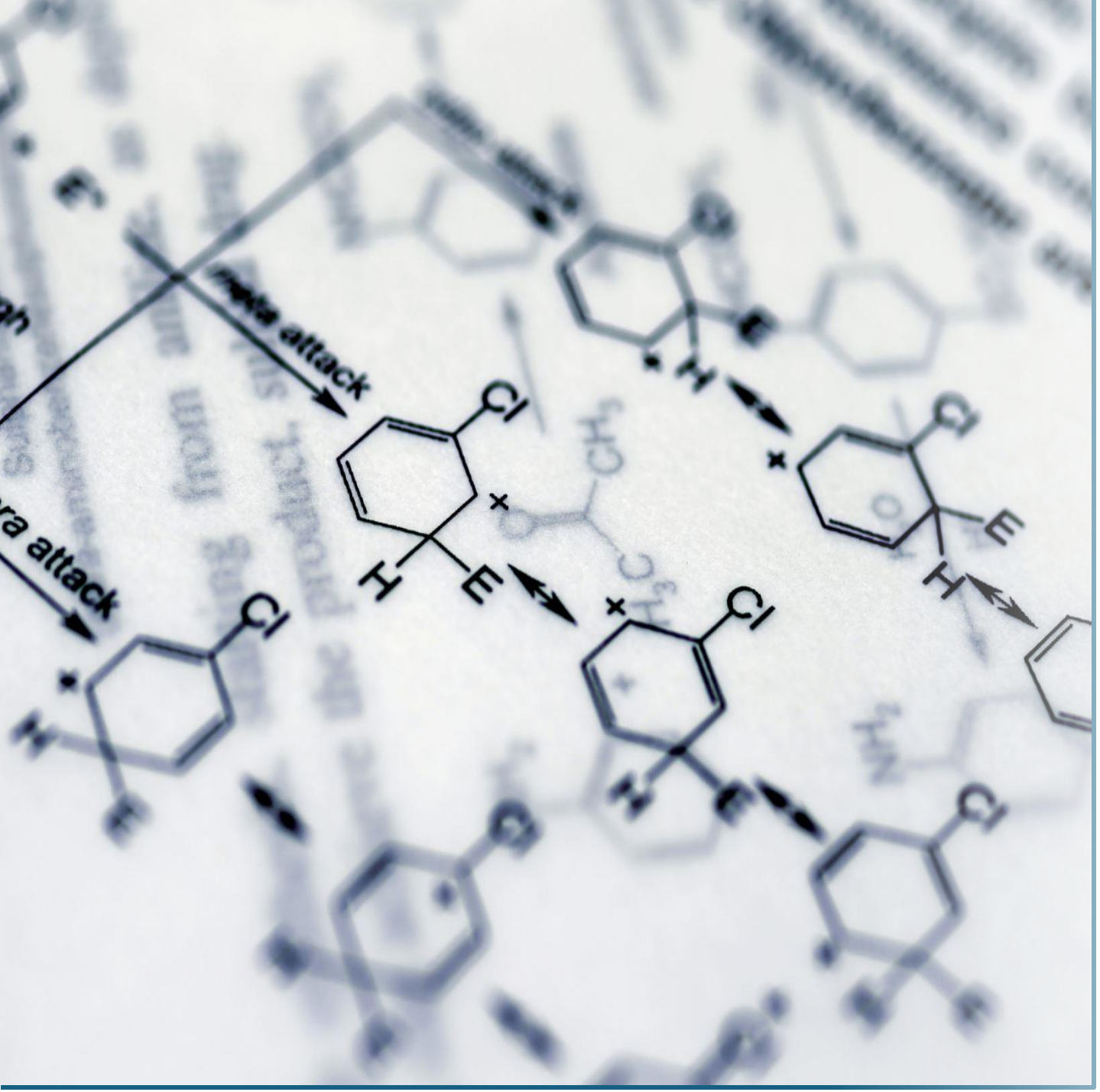
Package Insert/Breast Ca Experience

TRAE	Capivasertib	Placebo
Cutaneous	15%	0.8%
Diarrhea	12%	0.8%
Renal Injury	2.6%	0.8%
Stomatitis	1.9%	0%
Vomiting	1.9%	0.8%
Hyperglycemia	9%	0
Lymphopenia	11%	2.3%
Hypokalemia	4.5%	0%
Neutropenia	1.9%	0.8%
Anemia	16.2%	10.8%

CAPitello-291- in combination w/ Fulvestrant*

TRAE = treatment-related adverse event.

Capivasertib Package Insert. ProCAID Trial https://ascopubs.org/doi/10.1200/JCO.20.01576



CAPItello-281
November 25, 2024

Capivasertib combination in PTEN-deficient metastatic hormone-sensitive prostate cancer demonstrated statistically significant and clinically meaningful improvement in radiographic progression-free survival in CAPItello-281 Phase III trial

- **Positive high-level results** from the CAPItello-281 Phase III trial showed that capivasertib in combination with abiraterone and androgen deprivation therapy (ADT) demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of radiographic progression-free survival (rPFS) versus abiraterone and ADT with placebo in patients with PTEN-deficient *de novo* metastatic hormone-sensitive prostate cancer (mHSPC).
- Overall survival (OS) data were immature at the time of this analysis; however, the combination showed an early trend towards an OS improvement versus abiraterone and ADT with placebo. The trial will continue as planned to further assess OS as a key secondary endpoint.

Shared Decision-Making Involves Everyone

Providers

- Follow therapeutic advances
- Utilize resources and evidence to guide therapy selection
- Understand biomarker testing
- Be familiar with ongoing clinical trials for proper referrals
- Discuss with disease experts

CNC and Support Staff

- Provide detailed education to patients and staff
- Design tools to aid care teams in decision-making
- Implement protocols to mitigate shortages proactively
- Participate in tumor boards, CME, quality assurance/control, etc.

Patients

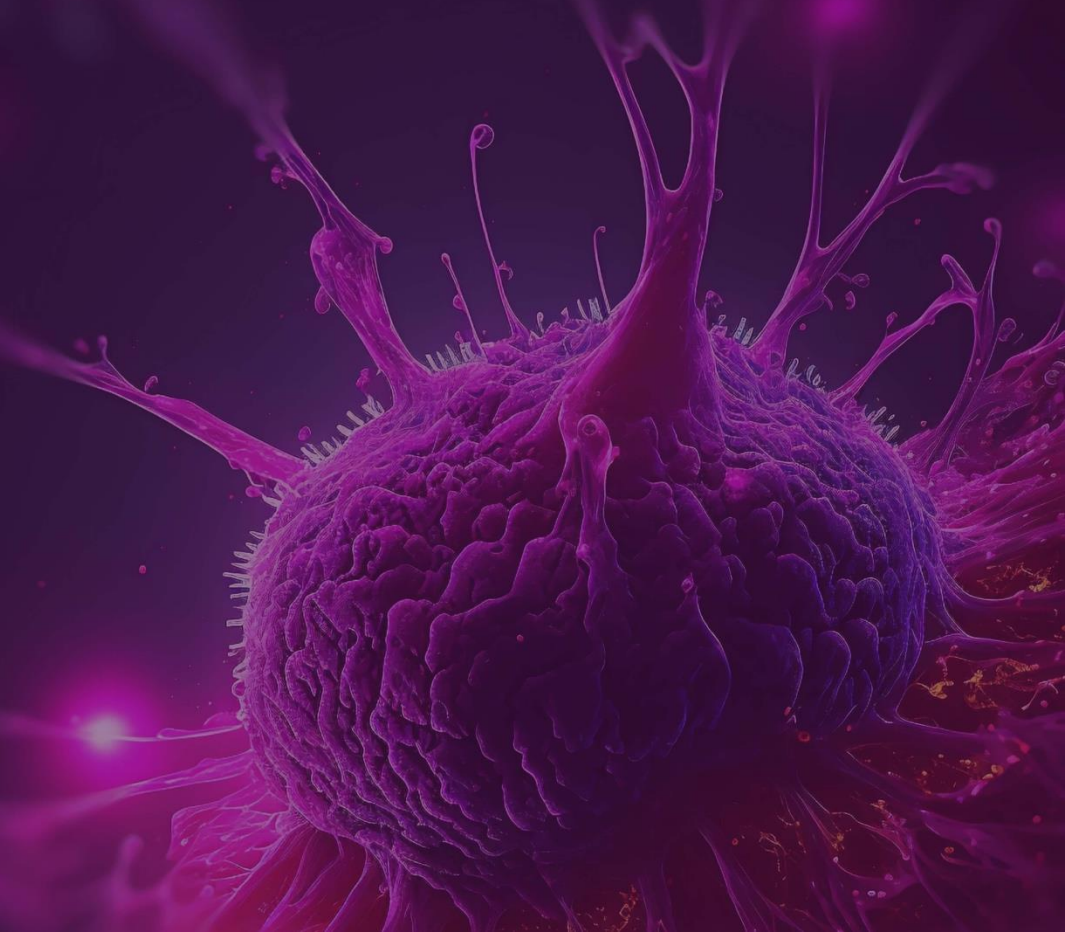
- Ask many questions
- Understand treatment selection
- Seek and enroll in clinical trials
- Anticipate, recognize, and report symptoms and changes ASAP; do not under-report…

CNC = clinical nurse coordinator; CME = continuing medical education.

Key Learning Points

- All patients must have germline/somatic testing at time of diagnosis
- There is no role for ADT monotherapy
- A fundamental challenge in treating mHSPC is the progression to castration resistance
- Additional pathway signals exist beyond the AR pathway – stay tuned
- The **CAPItello-281** trial recently reported meeting its primary endpoints when targeting the PI3K/AKT pathway and PTEN deficiency in de novo mHSPC

Questions?



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