What Clinicians Want to Know: Addressing Current Questions Related to Novel Treatment Approaches for Urothelial Bladder Cancer and Prostate Cancer

A CME Symposium Held in Conjunction with the 2025 ASCO® Genitourinary Cancers Symposium

Thursday, February 13, 2025
7:00 PM – 9:00 PM PT (10:00 PM – 12:00 AM ET)

Faculty (Bladder Cancer)

Terence Friedlander, MD
Matthew D Galsky, MD

Faculty (Prostate Cancer)

Neeraj Agarwal, MD, FASCO
Andrew J Armstrong, MD, ScM

Moderator

Elisabeth I Heath, MD

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Moderator

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Dr Agarwal — Disclosures
Faculty

No relevant conflicts of interest to disclose.

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Dr Armstrong — Disclosures
Faculty

Advisory Committees	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Cytogen Corporation, Janssen Biotech Inc, Merck, Myovant Sciences, Novartis, Pfizer Inc
Consulting Agreements	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Curium, Janssen Biotech Inc, Merck, Novartis, Pfizer Inc
Contracted Research	Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Janssen Biotech Inc, Merck, Novartis, Pathos, Pfizer Inc

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Dr Friedlander — Disclosures
Faculty

Advisory Committees	Aadi Bioscience, AbbVie Inc, Adaptimmune, Aktis Oncology, Astellas, Bicycle Therapeutics, Bristol Myers Squibb, Gilead Sciences Inc, Merck, Pfizer Inc, Samsung Bioepis
Consulting Agreements	Astellas, EMD Serono Inc, Pfizer Inc
Contracted Research	Bicycle Therapeutics, Genentech, a member of the Roche Group, Johnson & Johnson Pharmaceuticals, Pfizer Inc
Data and Safety Monitoring Boards/Committees	Bicycle Therapeutics

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Dr Galsky — Disclosures
Faculty

Advisory Committees	AbbVie Inc, Aktis Oncology, Alligator Bioscience, Analog Devices Inc, Asieris Pharmaceuticals, AstraZeneca Pharmaceuticals LP, Basilea Pharmaceutica Ltd, Bicycle Therapeutics, Bristol Myers Squibb, Curis Inc, Daiichi Sankyo Inc, Dragonfly Therapeutics, EMD Serono Inc, FUJIFILM Pharmaceuticals USA Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Janssen Biotech Inc, Merck, Numab Therapeutics AG, Pfizer Inc, Rappta Therapeutics, Seagen Inc, Silverback Therapeutics, UroGen Pharma, Veracyte Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Dendreon Pharmaceuticals Inc, Genentech, a member of the Roche Group, Merck, Novartis

Dr Heath — Disclosures
Moderator

Advisory/Consulting	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Sanofi
Honoraria/Paid Travel	Astellas, Bayer HealthCare Pharmaceuticals, Caris Life Sciences, Sanofi, Seagen Inc
Institutional Research Support	Amgen Inc, Arvinas, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BioXcel Therapeutics Inc, Bristol Myers Squibb, Calithera Biosciences, Caris Life Sciences, Corcept Therapeutics, Corvus Pharmaceuticals, Daiichi Sankyo Inc, Eisai Inc, Exelixis Inc, F Hoffman-La Roche Ltd, Fortis Therapeutics, Gilead Sciences Inc, GSK, Harpoon Therapeutics, Infinity Pharmaceuticals Inc, iTeos Therapeutics, Janssen Biotech Inc, Merck, Mirati Therapeutics Inc, Modra Pharmaceuticals, MSD, Novartis, Oncolys BioPharma, Peloton Therapeutics Inc, a wholly-owned subsidiary of Merck & Co Inc, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, POINT Biopharma, Seagen Inc
Steering Committees	Janssen Biotech Inc
Speakers Bureaus	Sanofi
Nonrelevant Financial Relationships	Calibr-Skaggs Institute for Innovative Medicines

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What Clinicians Want to Know: Addressing Current Questions Related to the Management of Renal Cell Carcinoma

A CME Symposium Held in Conjunction with the 2025 ASCO® Genitourinary Cancers Symposium

Friday, February 14, 2025

6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)

Faculty

Thomas E Hutson, DO, PharmD, PhD

Rana R McKay, MD

Tian Zhang, MD, MHS

Moderator

Sumanta Kumar Pal, MD

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Fourth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, February 28 to March 2, 2025

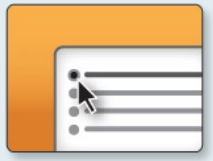
Fontainebleau Hotel, Miami Beach, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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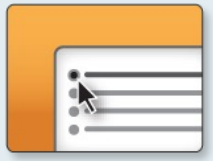
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
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Survey of General Medical Oncologists: January 29 – February 6, 2025

Results available on iPads and Zoom chat room

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Agenda

Module 1: Role of Antibody-Drug Conjugates (ADCs) in Front-Line Therapy for Metastatic Urothelial Bladder Cancer (mUBC) — Dr Friedlander

Module 2: Evidence-Based Use of ADCs for Relapsed/Refractory mUBC — Dr Galsky

Module 3: Evolving Role of Treatment Intensification with Androgen Receptor Pathway Inhibitors for Nonmetastatic and Metastatic Prostate Cancer — Dr Armstrong

Module 4: Optimal Integration of PARP Inhibitors into Therapy for Prostate Cancer — Dr Agarwal

Agenda

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Role of Antibody-Drug Conjugates (ADCs) in Front-Line Therapy for Metastatic Urothelial Bladder Cancer (mUBC)

Terence Friedlander, MD
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Robert and Virginial O'Reilly Family Endowed Chair
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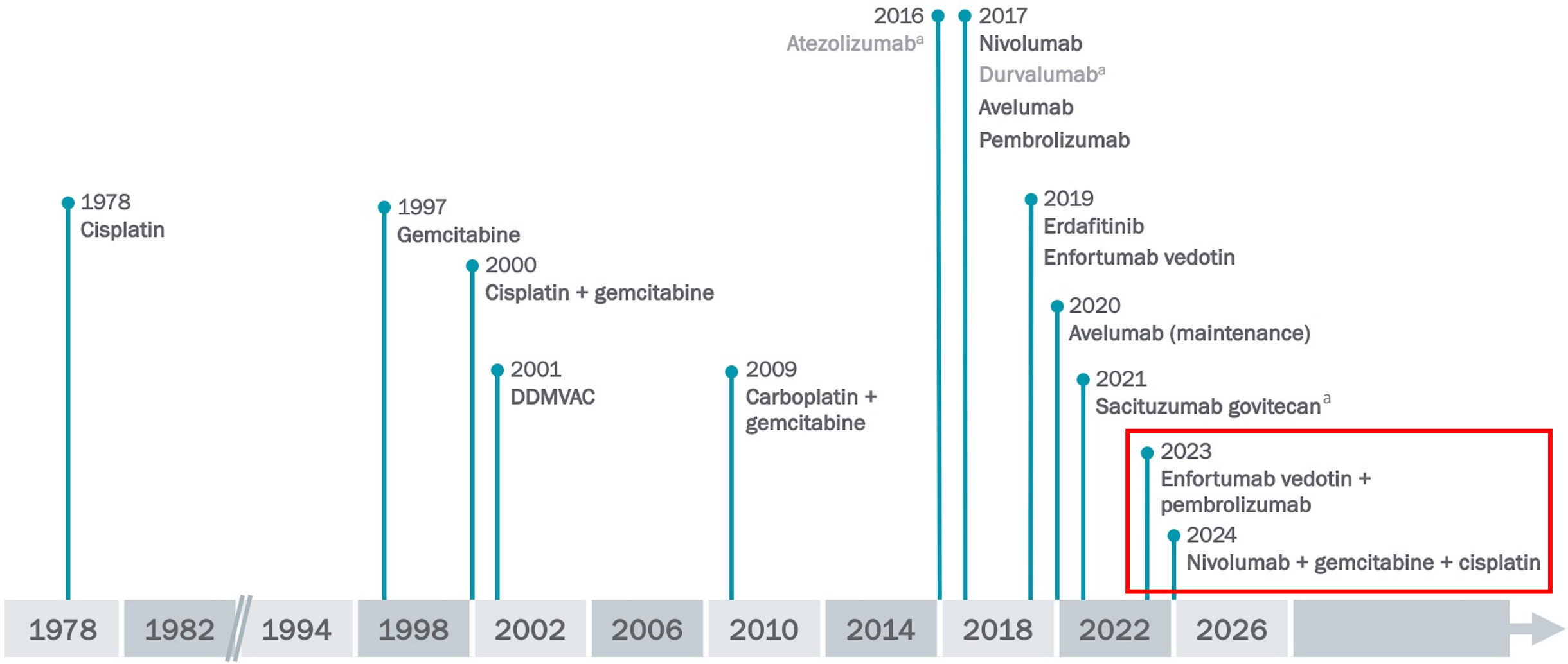
@DrTFriedlander UCSF

The Treatment Landscape for la/mUC has Evolved Rapidly



[a] No longer FDA approved; indication withdrawn

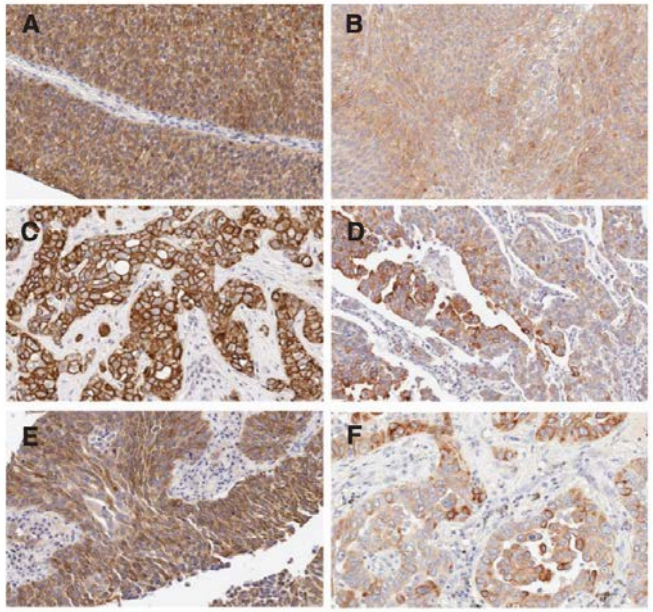
Why target Nectin-4?

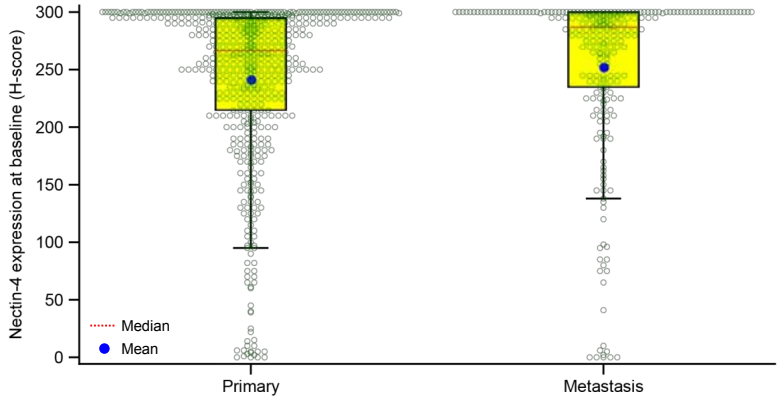
- Nectins are transmembrane cell-adhesion molecules
  - Over-expressed in multiple cancers
  - Highly expressed in **both** localized and mUC

Bladder Cancer

Breast Cancer

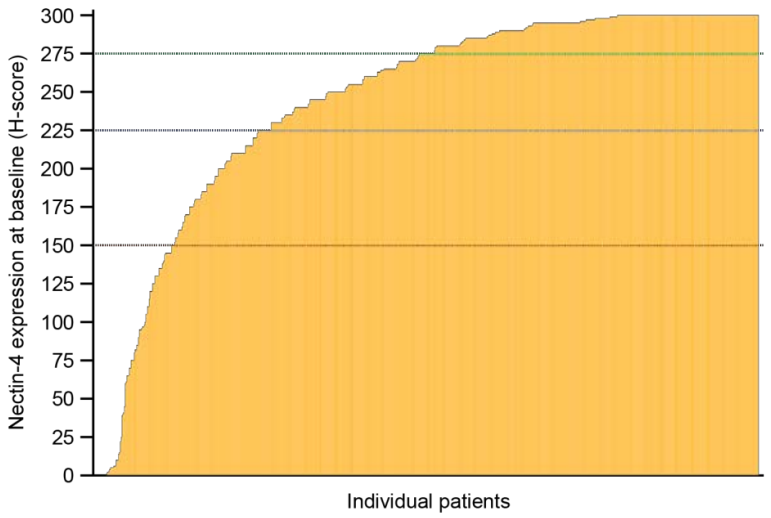
Lung Cancer





Biopsy origin	Primary (n=554)	Metastasis (n=246)
H-score, median (IQR)	267 (215-295)	287 (235-300)

H-score of Nectin-4 expression in EV-302 (n=800)



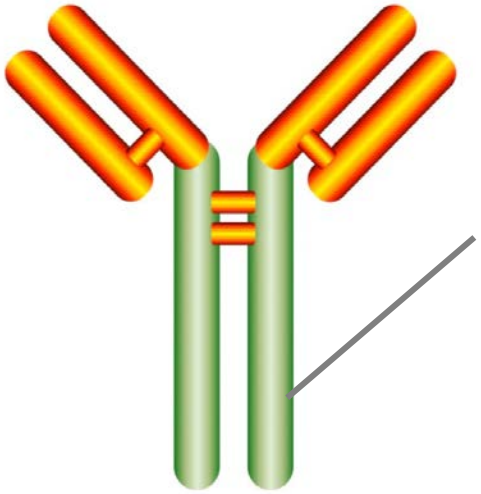
Variable	EV+P (n=394)	Chemotherapy (n=406)
H-score, median (IQR)	280 (230-298)	270 (215-297)
Subgroup, H-score, n (%)		
<150	38 (9.6)	50 (12.3)
≥150 to <225	50 (12.7)	56 (13.8)
≥225	306 (77.7)	300 (73.9)
Patients with H-score 0, n (%)	3 (0.8)	6 (1.5)

Challita-Eid, P et al. Can Res 2016, Powles et al ESMO 2024

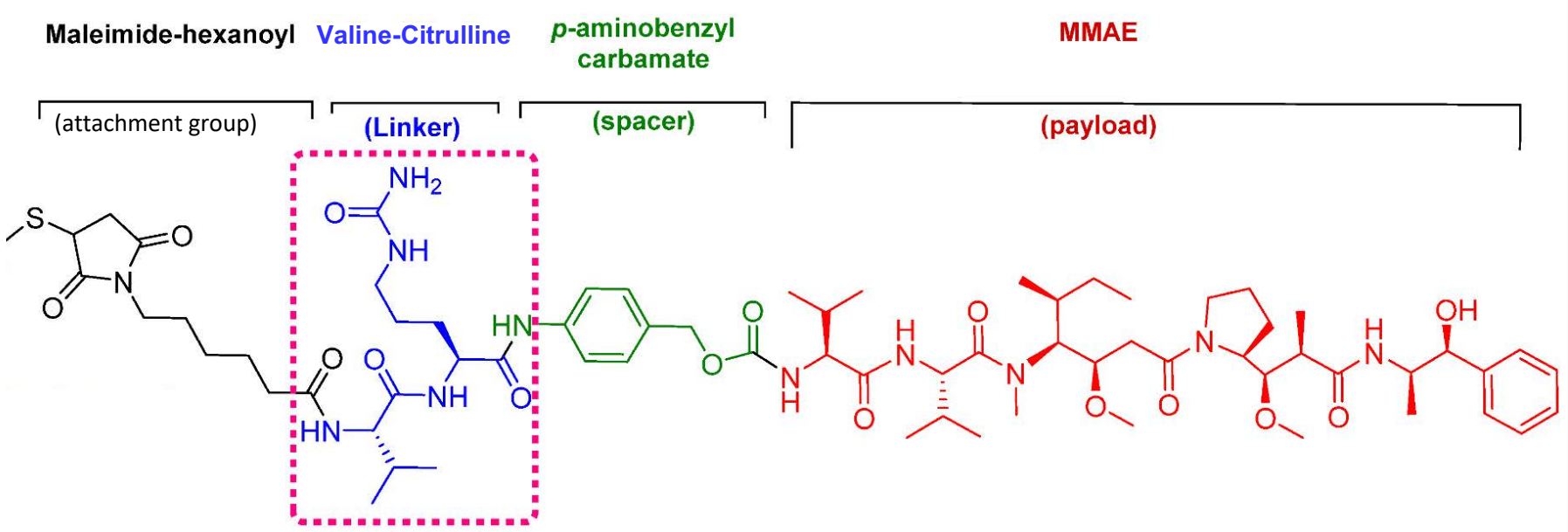
What is Enfortumab Vedotin?

Antibody-Drug Conjugate Targeting Nectin-4

Monomethyl auristatin E (MMAE) “payload”

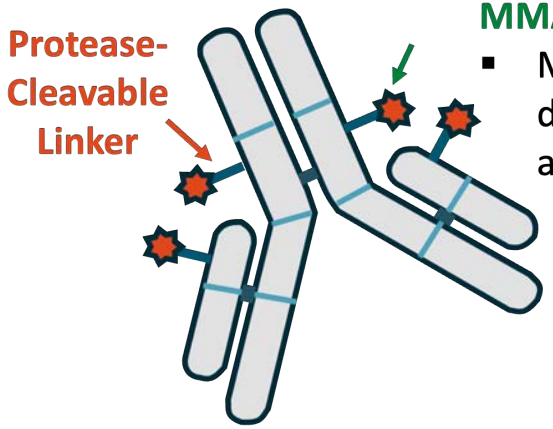


Nectin-4 antibody



Schaer et al Pharmaceuticals 2019; https://www.humimmu.com/products/anti-human-nectin-4-monoclonal-antibody

Enfortumab Vedotin: Mechanism of Action

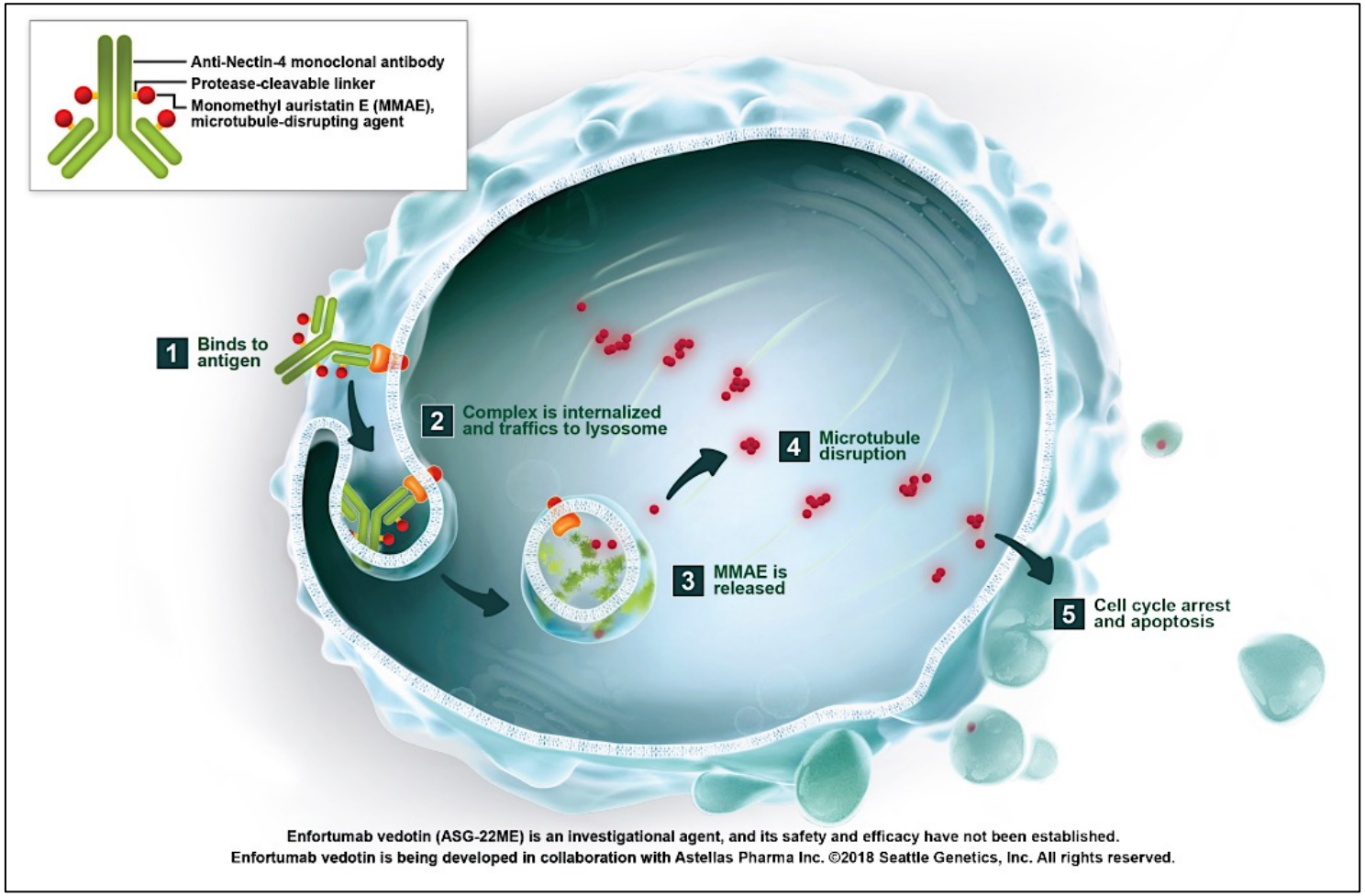


MMAE Payload

- Microtubule-disrupting agent

Fully Humanized Antibody

- Targets nectin-4, a transmembrane cell adhesion molecule highly expressed in mUBC



1. Samanta. Cell Mol Life Sci. 2015;72:645.
2. Rosenberg. JCO. 2019; 37:2592.
3. Enfortumab vedotin PI.
4. Petrylak DP, et al. 2017. J Clin Oncol 35(15_suppl): Abstract 106. ASCO 2017.

EV-301: Enfortumab Vedotin vs Chemotherapy in mUC After Platinum and Anti–PD-1/PD-L1 Therapy

- Interim analysis of international, randomized, open-label phase III trial of enfortumab vedotin, a Nectin-4–directed antibody–drug conjugate (data cutoff: July 15, 2020)

Stratified by liver mets (yes vs no), ECOG PS (0 vs 1), region (US/W Europe vs ROW)

Patients with locally advanced or metastatic histology/cytology confirmed UC; previously treated with platinum-containing CT*; radiographic progression or relapse on/after PD-(L)1 tx; ECOG PS ≤1 (N = 608)

Enfortumab Vedotin 1.25 mg/kg IV on Days 1, 8, 15 of 28-day cycles (n = 301)

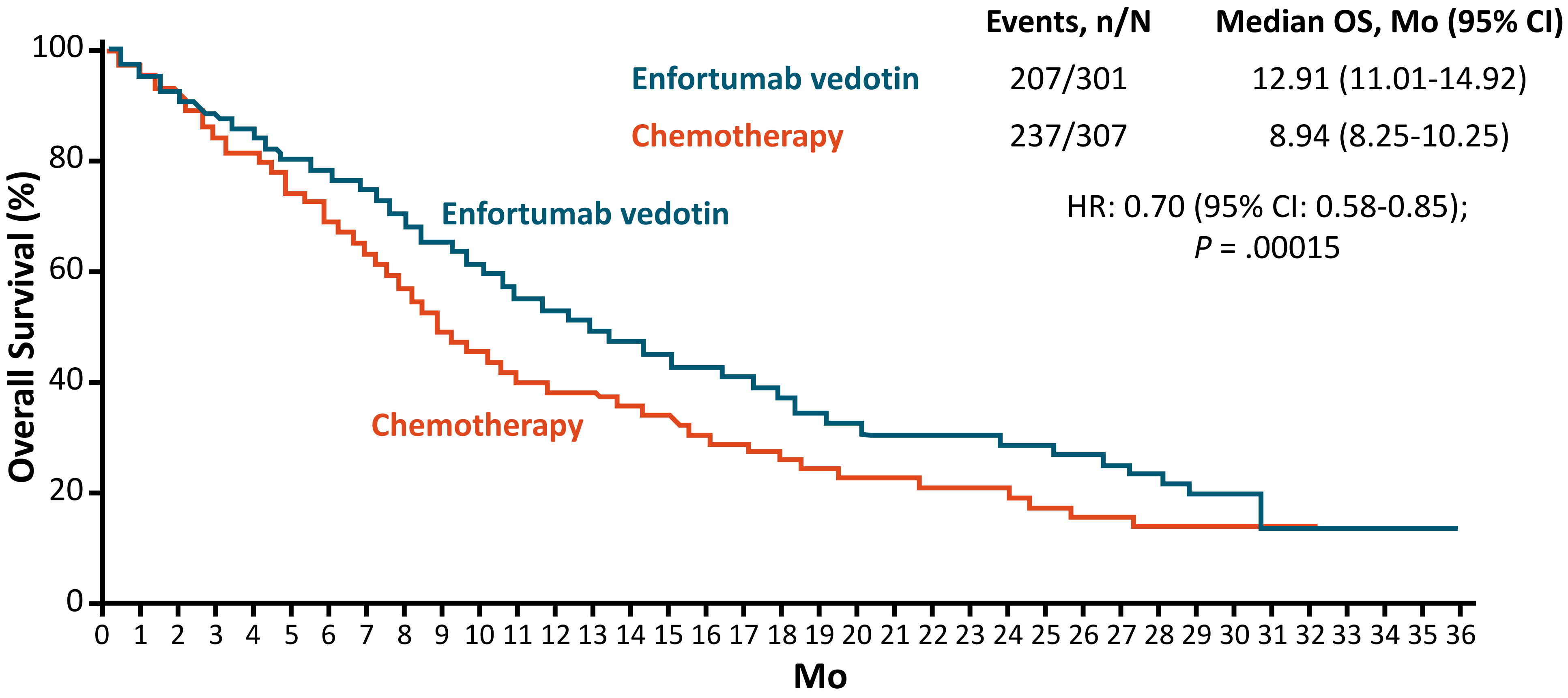
Investigator's choice of chemotherapy (taxane or vinflunine)† (n = 307)

*If used in the adjuvant/neoadjuvant setting, PD must be ≤ 12 mos of completion. †Standard docetaxel (75 mg/m^2), paclitaxel (175 mg/m^2), or vinflunine (320 mg/m^2) on Day 1 of each 21-day cycle.

- **Primary endpoint:** OS
- **Secondary endpoints:** investigator-assessed PFS, DCR, and ORR (all per RECIST 1.1); safety

1. Powles. NEJM. 2021;384:1125.
2. Rosenberg. ASCO 2022. Abstr 4516.

EV-301: OS at 24 Mo

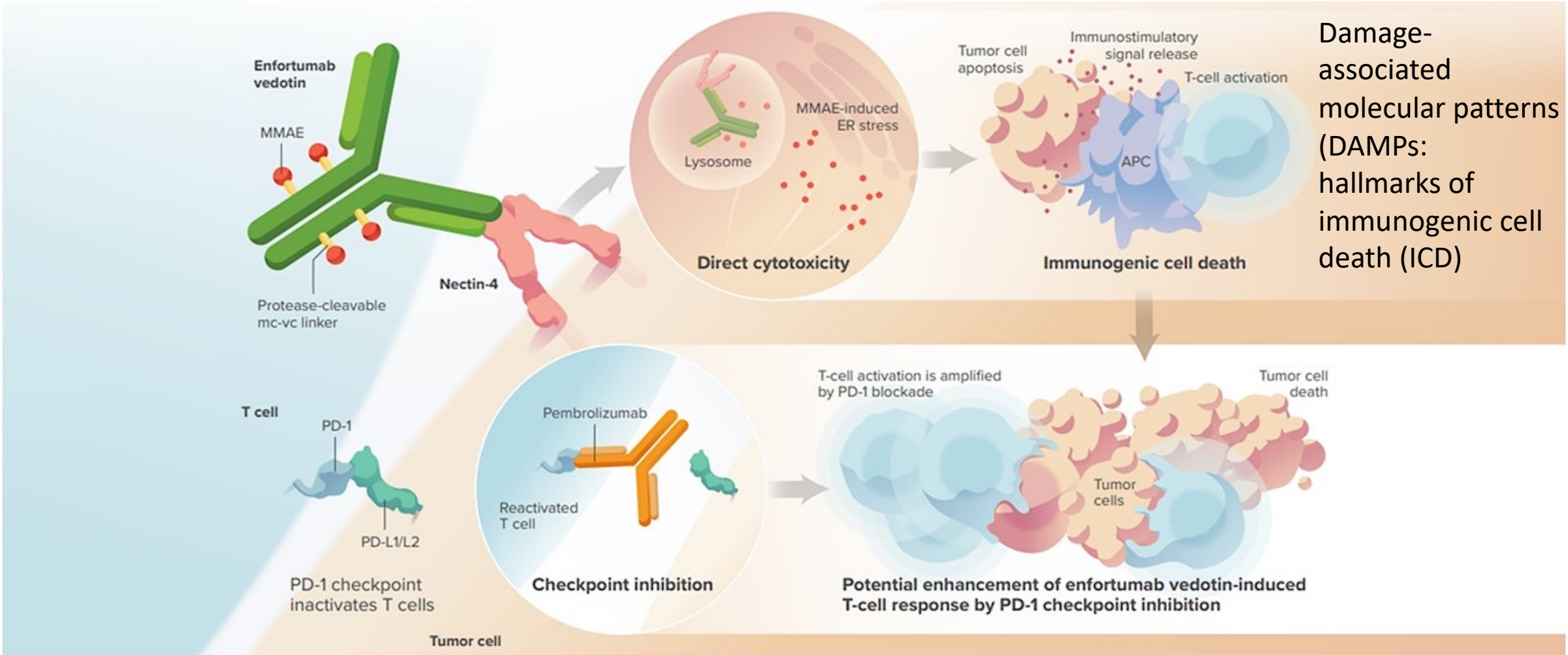


Patients at Risk, n

Mo	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Enfortumab vedotin	301	286	272	257	246	234	226	213	197	186	174	159	150	141	133	124	118	115	106	86	73	63	55	50	41	31	24	20	14	7	4	2	2	2	1	1	0
Chemotherapy	307	288	274	250	238	219	203	186	168	142	132	116	111	108	102	96	85	81	78	65	58	54	46	40	32	22	17	13	10	6	5	3	1	0	0	0	0

Rosenberg. ASCO 2022. Abstr 4516; Rosenberg et al, Ann Oncol. 2023.

Why Combine EV and Pembrolizumab?



Damage-associated molecular patterns (DAMPs: hallmarks of immunogenic cell death (ICD)

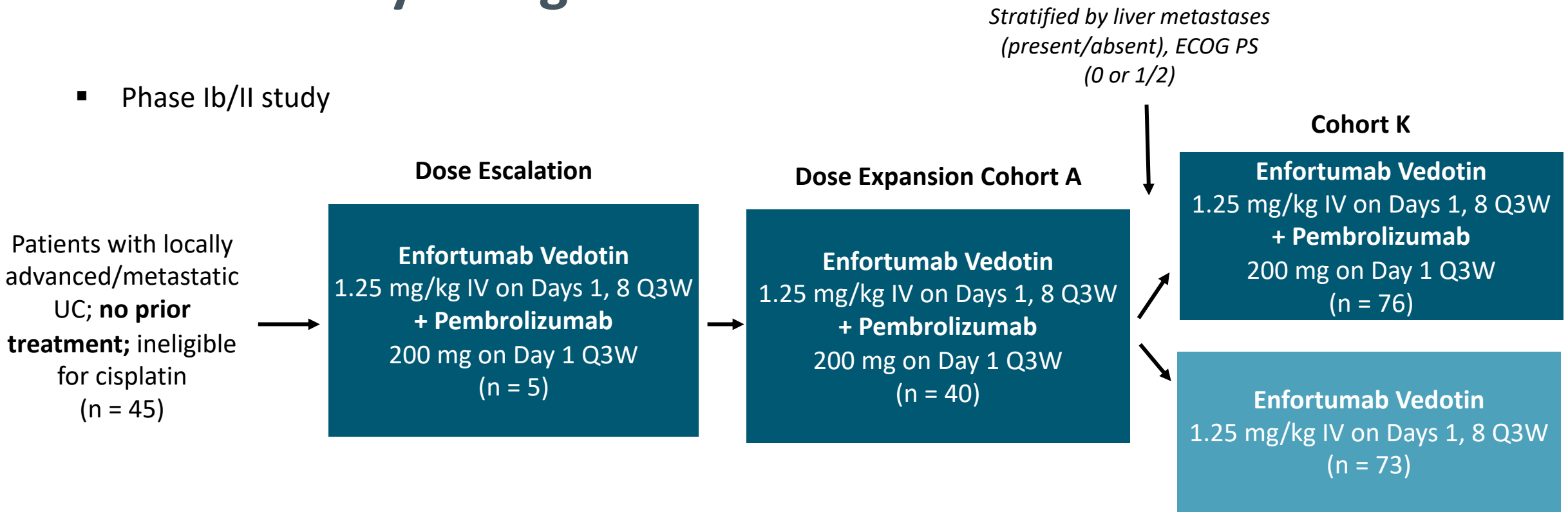
APC: antigen-presenting cell; **ER**: endoplasmic reticulum; **mc-vc**: maleimidocaproyl-valine-citrulline; **MMAE**: monomethyl auristatin E; **PD-1**: programmed cell death protein 1; **PD-L1/L2**: programmed cell death-ligands 1 and 2

Gupta et al J Clin Onc 2023 41:16_suppl, 4505-4505.

***Enfortumab vedotin plus pembrolizumab is an investigational drug combination; the safety and efficacy of the drug combination has not been established. The proposed mechanism of action for the combination is based upon preclinical studies with enfortumab vedotin and other antibody–drug conjugates. Information provided is for scientific information only and should not be interpreted as an intent to promote unapproved uses.**

EV-103 Study Design

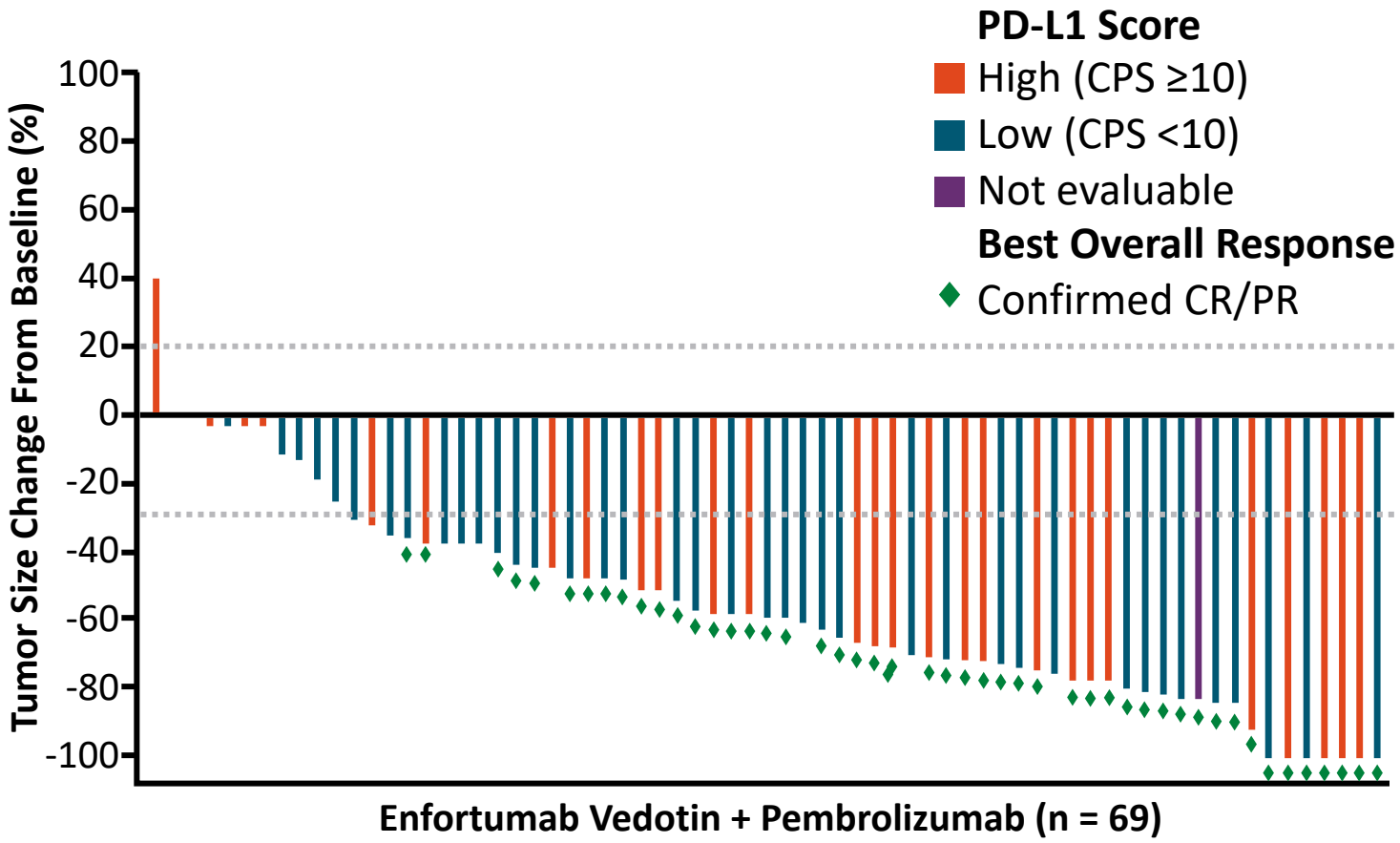
- Phase Ib/II study



- **Primary endpoint:** confirmed ORR by RECIST v1.1 per BICR
- **Key secondary endpoints:** confirmed ORR per RECIST v1.1 by investigator, DoR, DCR, PFS, OS, safety/tolerability, lab abnormalities
- **Exploratory endpoints:** biomarkers of activity including BL PD-L1 status and Nectin-4 expression, PFS on subsequent therapy by investigator, PROs

Rosenberg. ESMO 2022. Abstr LBA73.

EV-103 Cohort K: ORR by BICR



- ORR: 64.5% (95% CI 52.7-75.1)
  - 10.5% CR!
- Activity seen independently of PD-L1 status
  - 61.4% (27/44) confirmed ORR in CPS <10
  - 67.7% (21/31) confirmed ORR in CPS ≥10
- Tumor reduction observed in 97.1% of patients

Rosenberg. ESMO 2022. Abstr LBA73. O'Donnell et al, JCO 2023.

EV-302: Phase III Trial

Patient population

- Previously untreated la/mUC
- Eligible for platinum, EV, and P
- PD-(L)1 inhibitor naive
- GFR ≥30 to <60mL/min[a]
- ECOG PS ≤2[b]

N=886

R 1:1

EV + Pembrolizumab
No maximum treatment cycles for EV, maximum 35 cycles for P

Chemotherapy[c]
(Cisplatin or carboplatin + gemcitabine)
Maximum 6 cycles

Treatment until disease progression per BICR, clinical progression, unacceptable toxicity, or completion of maximum cycles

Dual primary endpoints:

- **PFS by BICR**
- **OS**

Select secondary endpoints:

- ORR per RECIST v1.1 by BICR and investigator assessment
- Safety

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

BICR, blinded independent central review; **ECOG PS**, Eastern Cooperative Oncology Group Performance Status; **EV**, enfortumab vedotin; **FPI,** first person initiated into trial; **GFR**, glomerular filtration rate; **LPI**, last person initiated into trial; **IV**, intravenous; **la/mUC,** locally advanced or metastatic urothelial carcinoma; **ORR**, overall response rate; **OS**, overall survival; **P**, pembrolizumab; **PD-L1**, programmed death-ligand 1; **PFS**, progression-free survival; **R**, randomization; **RECIST**, Response Evaluation Criteria in Solid Tumors.

[a]Measured by the Cockcroft-Gault formula, Modification of Diet in Renal Disease, or 24-hour urine.

[b]Patients with ECOG PS of 2 were required to also meet the additional criteria: hemoglobin ≥10 g/dL, GFR ≥50mL/min, may not have NYHA class III heart failure.

[c]Maintenance therapy could be used following completion and/or discontinuation of platinum-containing therapy.

Data cutoff: 08 Aug 2023
FPI: 7 Apr 2020
LPI: 09 Nov 2022

Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation) Powles et al. NEJM, 2024.

Key Demographic and Baseline Disease Characteristics

Balanced between treatment arms and representative of 1L la/mUC population

	EV+P (N=442)	Chemotherapy (N=444)
Male sex, n (%)	344 (77.8)	336 (75.7)
Age (years), median (range)	69.0 (37,87)	69.0 (22,91)
Race, n (%)		
White	308 (69.7)	290 (65.3)
Asian	99 (22.4)	92 (20.7)
Geographic location, n (%)		
North America	103 (23.3)	85 (19.1)
Europe	172 (38.9)	197 (44.4)
Rest of World	167 (37.8)	162 (36.5)
ECOG PS, n (%)		
0	223 (50.5)	215 (48.4)
1	204 (46.2)	216 (48.6)
2	15 (3.4)	11 (2.5)
Primary tumor location, n (%)		
Upper tract	135 (30.5)	104 (23.4)
Lower tract	305 (69.0)	339 (76.4)

	EV+P (N=442)	Chemotherapy (N=444)
Cisplatin eligible[a], n (%)	240 (54.3)	242 (54.5)
Metastatic category, n (%)		
Visceral metastases	318 (71.9)	318 (71.6)
Bone	81 (18.3)	102 (23.0)
Liver	100 (22.6)	99 (22.3)
Lung	170 (38.5)	157 (35.4)
Lymph node only disease	103 (23.3)	104 (23.4)
PD-L1 expression[b], n/N (%)		
High (CPS ≥ 10)	254/438 (58.0)	254/439 (57.9)
Low (CPS < 10)	184/438 (42.0)	185/439 (42.1)

1L, first-line treatment; **CPS**, combined positive score; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **EV+P**, enfortumab vedotin + pembrolizumab; **FPI,** first person initiated into trial; **IHC**, immunohistochemistry; **la/mUC**, locally advanced or metastatic urothelial carcinoma; **LPI**, last person initiated into trial; PD-L1, programmed death-ligand 1.

[a]Represents eligibility at time of randomization.

[b]CPS status was determined using the validated PD-L1 IHC 22C3 pharmDx assay at Neogenomics and Labcorp; 4 patients in the EV+P arm and 5 patients in the chemoth of inadequate tissue quality for analysis.

Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation) Powles et al. NEJM, 2024.

Data cutoff: 08 Aug 2023
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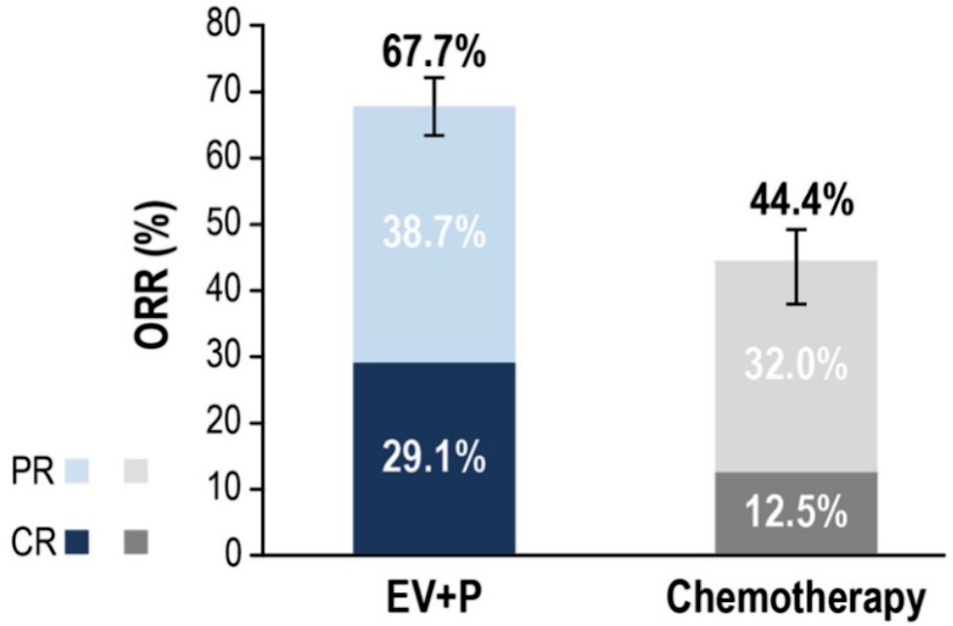
Confirmed Overall Response per BICR

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



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

Median DOR (95% CI)	NR (20.2, NR)	7.0 (6.2, 10.2)

BICR, blinded independent central review; **CI**, confidence interval; **CR**, complete response; **DOR**, duration of response; **EV+P**, enfortumab vedotin + pembrolizumab; **NR**, not reached; **ORR**, overall response rate; **PR**, partial response.

[a]Best overall response according to RECIST v1.1 per BICR. CR or PR was confirmed with repeat scans ≥28 days after initial response.

[b]Patients had either post-baseline assessment and the best overall response was determined to be not evaluable per RECIST v1.1 or no response assessment post-baseline.

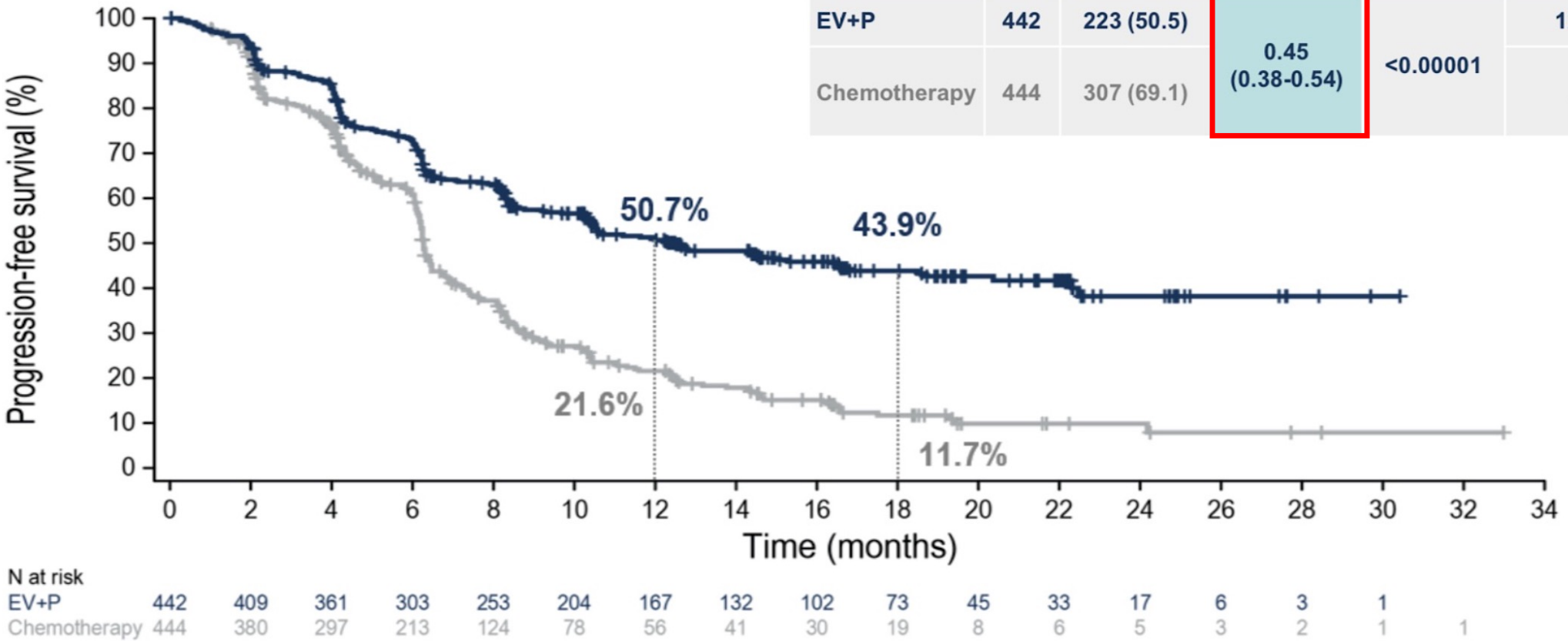
Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation) Powles et al. NEJM, 2024.

Data cutoff: 08 Aug 2023

Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P

	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)



BICR, blinded independent central review; **CI**, confidence interval; **EV+P**, enfortumab vedotin + pembrolizumab; **HR**, hazard ratio; **mPFS**, median progression-free survival.
mPFS at 12 and 18 months as estimated using Kaplan-Meier method.
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm.
Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation)

Data cutoff: 08 Aug 2023

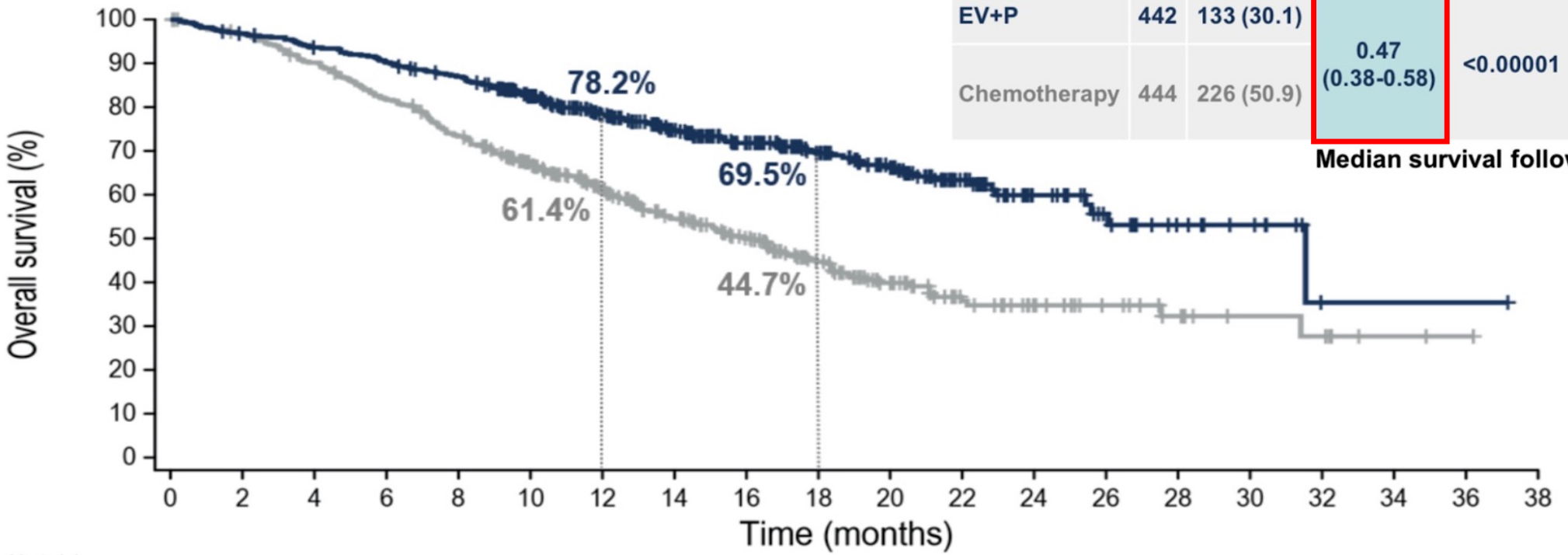
Powles et al. NEJM, 2024.

Overall Survival

Risk of death was reduced by 53% in patients who received EV+P

	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



N at risk

EV+P	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

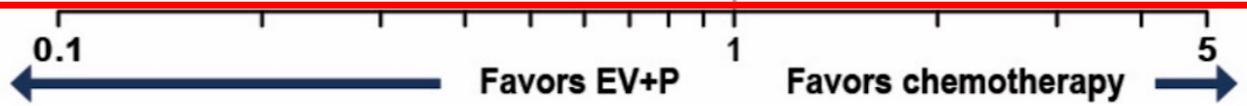
CI, confidence interval; **EV+P**, enfortumab vedotin + pembrolizumab; **HR**, hazard ratio; **mOS**, median overall survival; **NR**, not reached; **OS**, overall survival;.
OS at 12 and 18 months as estimated using Kaplan-Meier method.
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm.
Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation) Powles et al. NEJM, 2024.

Data cutoff: 08 Aug 2023

Subgroup Analysis of OS

OS benefit in select pre-specified subgroups was consistent with results in overall population

Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	133/442	226/444	0.47 (0.38-0.58)
Age			
<65 years	39/144	58/135	0.46 (0.30-0.71)
≥65 years	94/298	168/309	0.48 (0.38-0.63)
Sex			
Female	32/98	54/108	0.51 (0.32-0.80)
Male	101/344	172/336	0.47 (0.36-0.60)
ECOG PS			
0	44/223	94/215	0.36 (0.25-0.53)
1-2	89/219	131/227	0.54 (0.41-0.72)
Primary disease site of origin			
Upper tract	38/135	45/104	0.53 (0.34-0.83)
Lower tract	94/305	180/339	0.46 (0.36-0.59)
Liver metastases			
Present	43/100	67/99	0.47 (0.32-0.71)
Absent	90/342	159/345	0.47 (0.36-0.61)
PD-L1 expression			
Low (CPS <10)	53/184	99/185	0.44 (0.31-0.61)
High (CPS ≥10)	79/254	125/254	0.49 (0.37-0.66)
Cisplatin eligibility			
Eligible	69/244	106/234	0.53 (0.39-0.72)
Ineligible	64/198	120/210	0.43 (0.31-0.59)



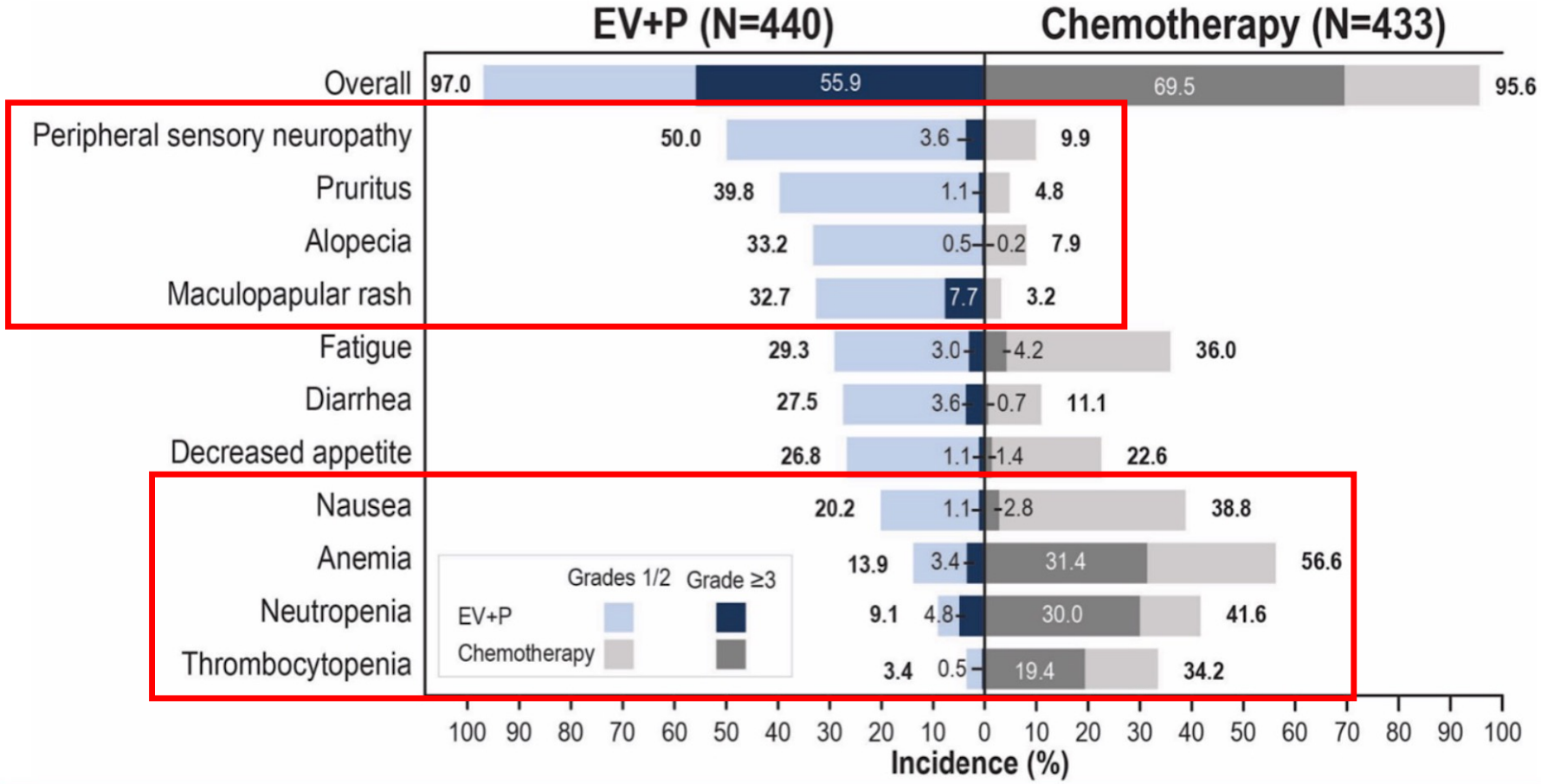
CPS, Combined Positive Score; **ECOG PS**, Eastern Cooperative Oncology Group Performance Status; **EV+P**, enfortumab vedotin + pembrolizumab; **OS**, overall survival; **PD-L1**, Programmed death-ligand 1.

Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation) Powles et al. NEJM, 2024.

Data cutoff: 08 Aug 2023

Treatment-Related Adverse Events

Grade ≥3 events were 56% in EV+P and 70% in chemotherapy



Serious TRAEs:

- 122 (27.7%) EV+P
- 85 (19.6%) chemotherapy

TRAEs leading to death (per investigator):

EV+P: 4 (0.9%)

- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

Chemotherapy: 4 (0.9%)

- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

Median number of cycles (range): 12.0 (1,46) for EV+P; 6.0 (1,6) for chemotherapy

EV+P, enfortumab vedotin + pembrolizumab; **TRAEs,** treatment-related adverse events.
TRAEs shown in figure are any grade by preferred term in ≥20% of patients for any grade in either arm.
Powles T, et al. Oral Presentation at 2023 ESMO Annual Meeting; October 20-24, 2023; Abstract #LBA6 / Presidential Symposium (Oral Presentation) Powles et al. NEJM, 2024.

Data cutoff: 08 Aug 2023

EV-302: Updated Analysis from the Phase 3 Global Study of Enfortumab Vedotin in Combination with Pembrolizumab (EV+P) vs Chemotherapy (Chemo) in Previously Untreated Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC)

Powles T et al.

Genitourinary Cancers Symposium 2025;Abstract 664.

February 14, 2025

4:10 PM – 4:15 PM PST

EV-302: Updated Analysis of Key Efficacy and Safety Outcomes

	EV+P		Chemo		EV+P vs chemo
Efficacy (intent to treat set)	n	mo	n	mo	HR (95% CI)
Median PFS	442	12.5 (95% CI, 10.4-16.6)	444	6.3 (95% CI, 6.2-6.5)	0.48 (0.41-0.57)
Median OS	442	33.8 (95% CI, 26.1-39.3)	444	15.9 (95% CI, 13.6-18.3)	0.51 (0.43-0.61)
Cisplatin eligible	244	36.7	234	18.7	0.54 (0.42-0.70)
Cisplatin ineligible	198	25.6	210	12.7	0.50 (0.39-0.64)
Liver mets present	100	19.1	99	10.1	0.56 (0.40-0.78)
Liver mets absent	342	39.3	345	18.3	0.50 (0.40-0.62)
Safety (safety analysis set)	n		n		
Grade ≥3 TRAE	440	252 (57.3%)	433	301 (69.5%)	–

Powles T et al. Genitourinary Cancers Symposium 2025;Abstract 664.

Important Questions

- Is EV + Pembro the new Standard of Care?

- How to Manage Toxicity of the EV + P regimen?

Important Questions

- **Is EV + Pembro the new Standard of Care?**

- How to Manage Toxicity of the EV + P regimen?

PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)	
Cisplatin eligible	**Preferred regimens** • Pembrolizumab and enfortumab vedotin-ejfv[15] (category 1) **Other recommended regimens** • Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (category 1)[a,13] • Nivolumab, gemcitabine, and cisplatin (category 1) followed by nivolumab maintenance therapy[14] (category 1) **Useful under certain circumstances** • DDMVAC with growth factor support (category 1)[2,8] followed by avelumab maintenance therapy (category 1)[a,13]
Cisplatin ineligible	**Preferred regimens** • Pembrolizumab and enfortumab vedotin-ejfv[15,17] (category 1) **Other recommended regimens** • Gemcitabine and carboplatin[16] followed by avelumab maintenance therapy (category 1)[a,13] **Useful under certain circumstances** • Gemcitabine[18] • Gemcitabine and paclitaxel[19] • Ifosfamide, doxorubicin, and gemcitabine[21] (for patients with good kidney function and good performance status) • Pembrolizumab[22] (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy) • Atezolizumab[20] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 2B)

PRINCIPLES OF SYSTEMIC THERAPY

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Important Questions

- Is EV + Pembro the new Standard of Care?

- **How to Manage Toxicity of the EV + P regimen?**

Special Toxicities of EV to Focus on Today

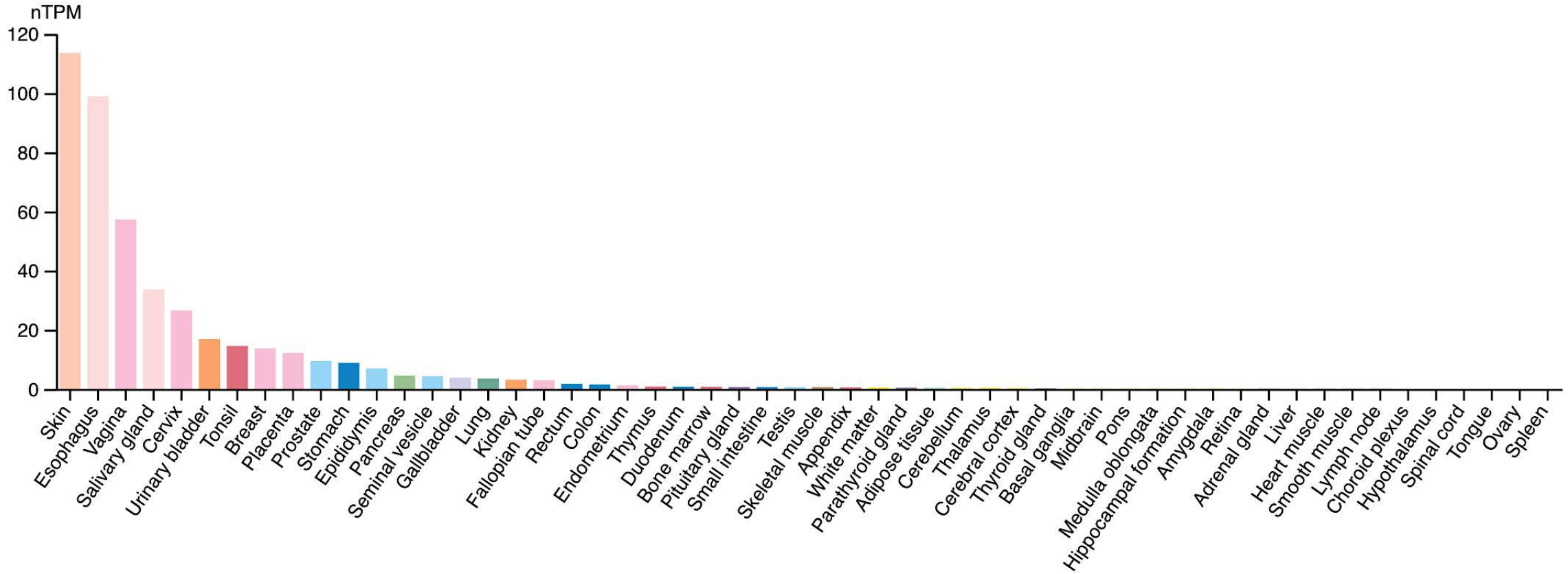
- Peripheral Neuropathy
- Rash/Dermatologic Events
- Ocular
- Pneumonitis

Nectin-4 is Expressed in the Skin

RNA EXPRESSION OVERVIEW[i]

Consensus dataset[i]

RNA tissue specificity: Tissue enhanced (esophagus, skin, vagina)



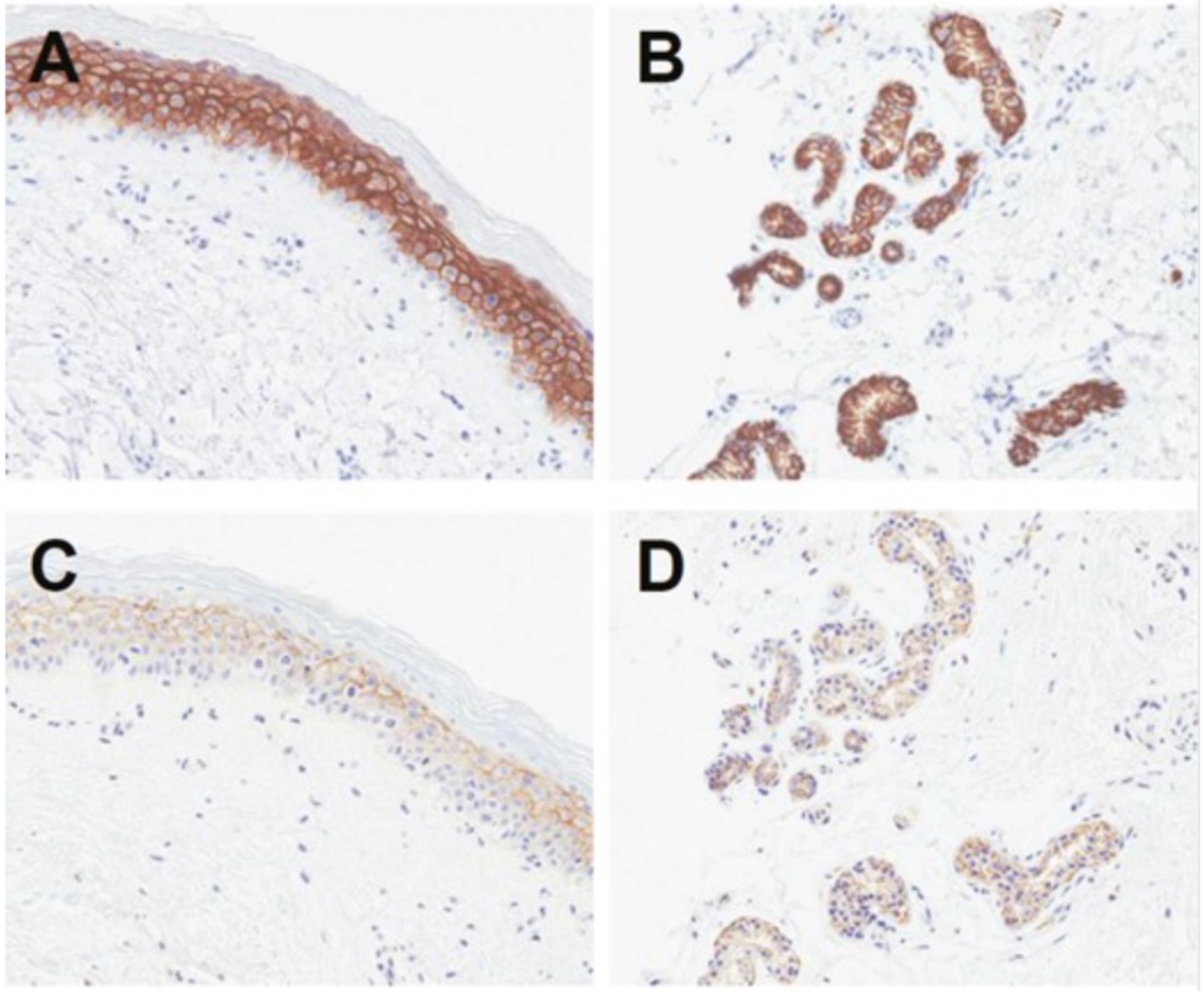
https://www.proteinatlas.org/ENSG00000143217-NECTIN4/tissue

Epidermis

Sweat Gland

Nectin-4

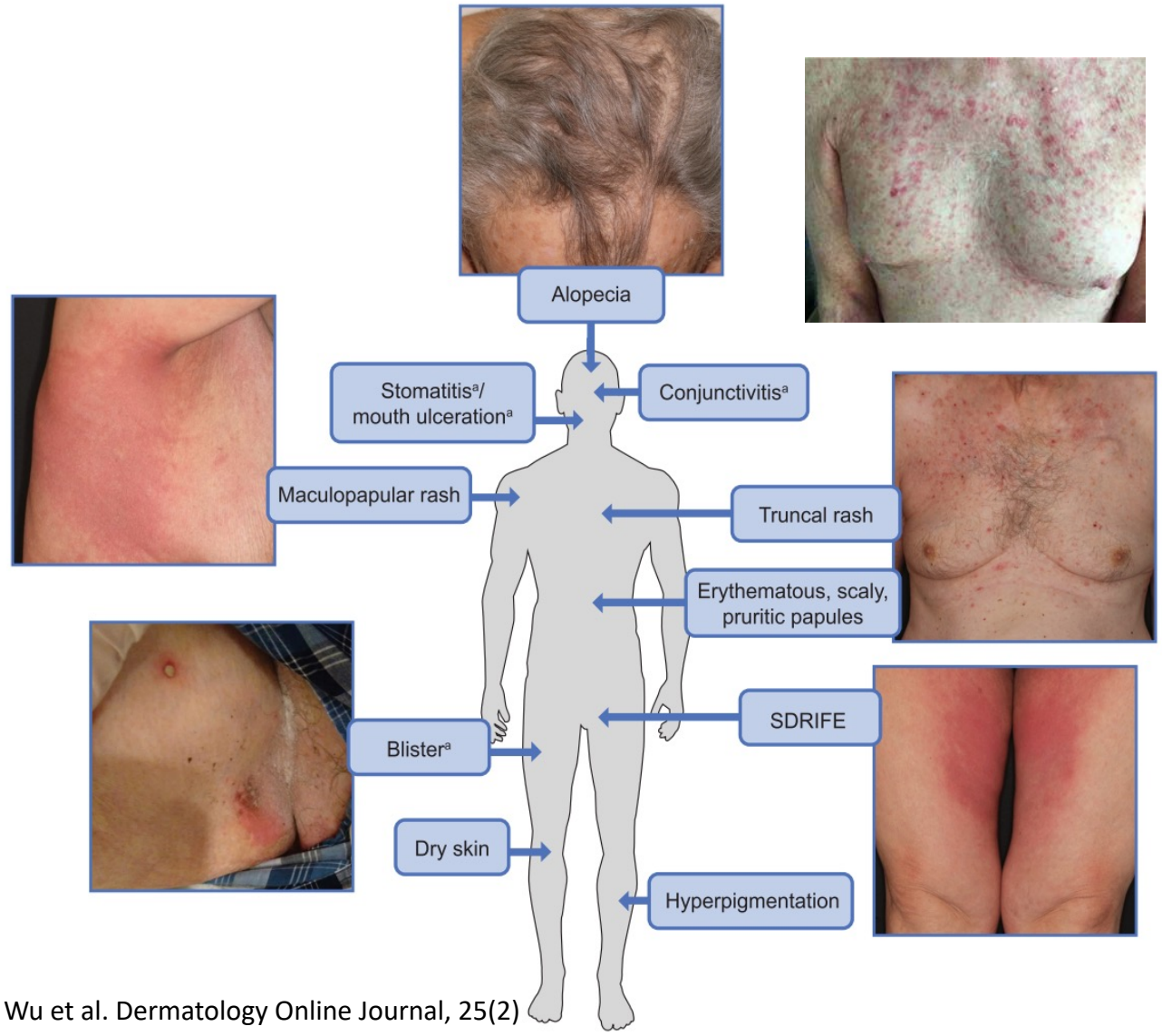
Nectin-4 + EV



Lacouture et al Oncologist, 2022

Enfortumab Skin Toxicity

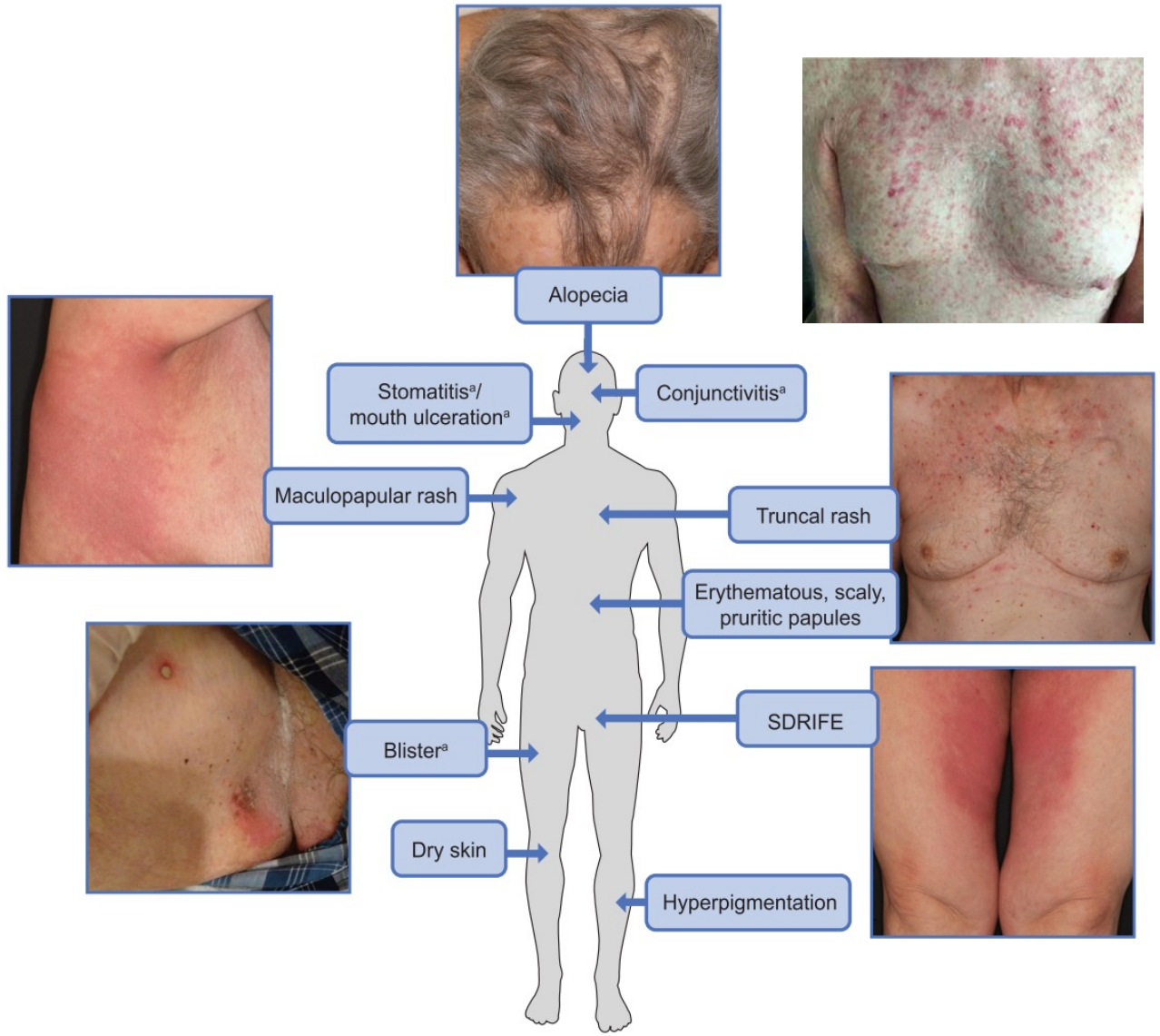
- Seen in >50% of patients
  - Usually grade 1 or 2
  - Rare serious toxicity
  - Typically occurs in cycle 1 or 2
  - Pembrolizumab dermatitis can occur later, but difficult to distinguish clinically



1. Wu et al. Dermatology Online Journal, 25(2)
2. Lacoutre et al. The Oncologist 2022
3. Geisler et al J Am Acad Dermatol 2020

Skin Toxicity Management

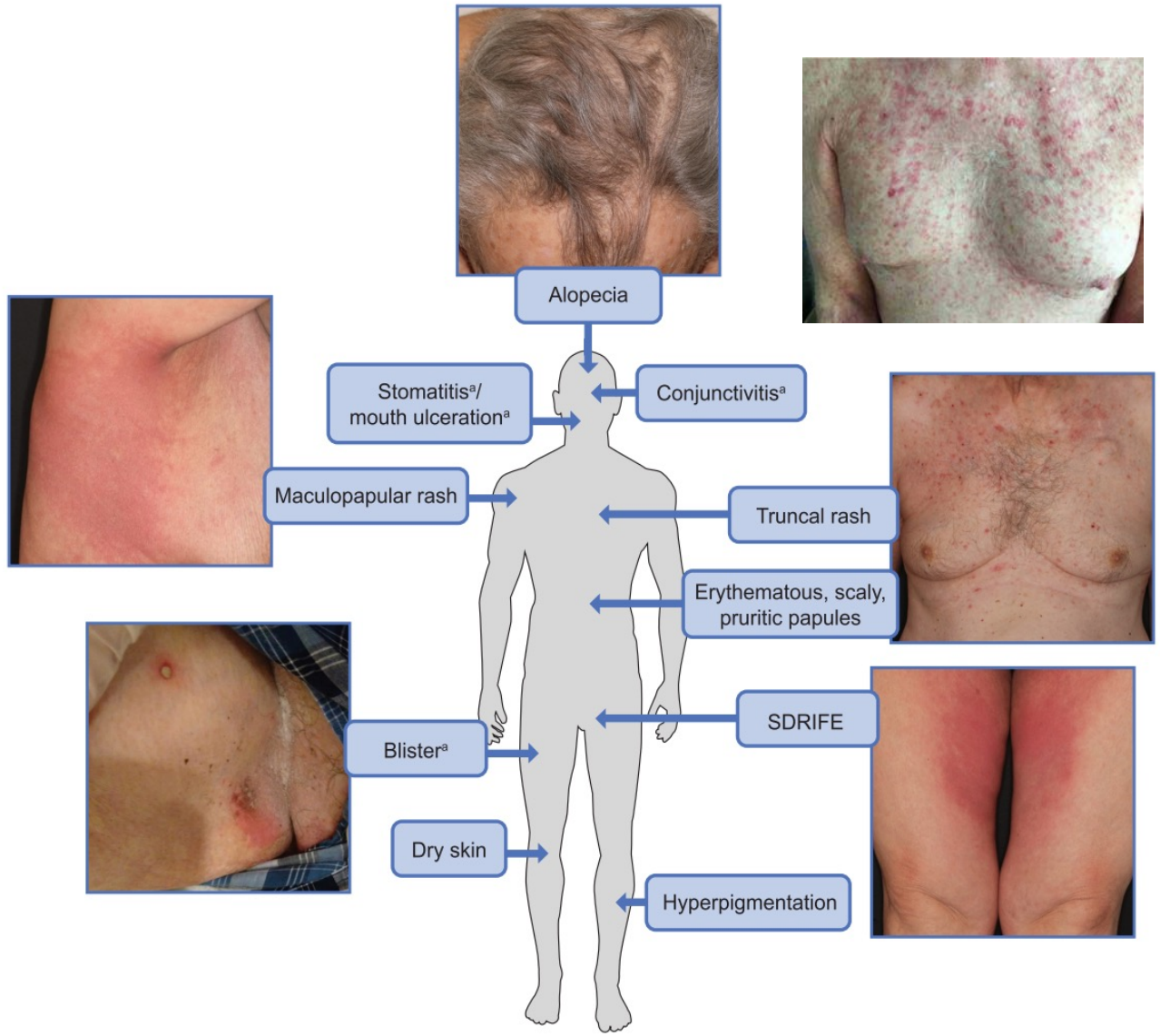
- Grade 1 (<10% body surface area, no large fold involvement, no fever)
  - High-potency topical steroids
  - Continue EV without dose reduction
  - Close reassessment



1. Wu et al. Dermatology Online Journal, 25(2)
2. Lacoutre et al. The Oncologist 2022

Skin Toxicity Management

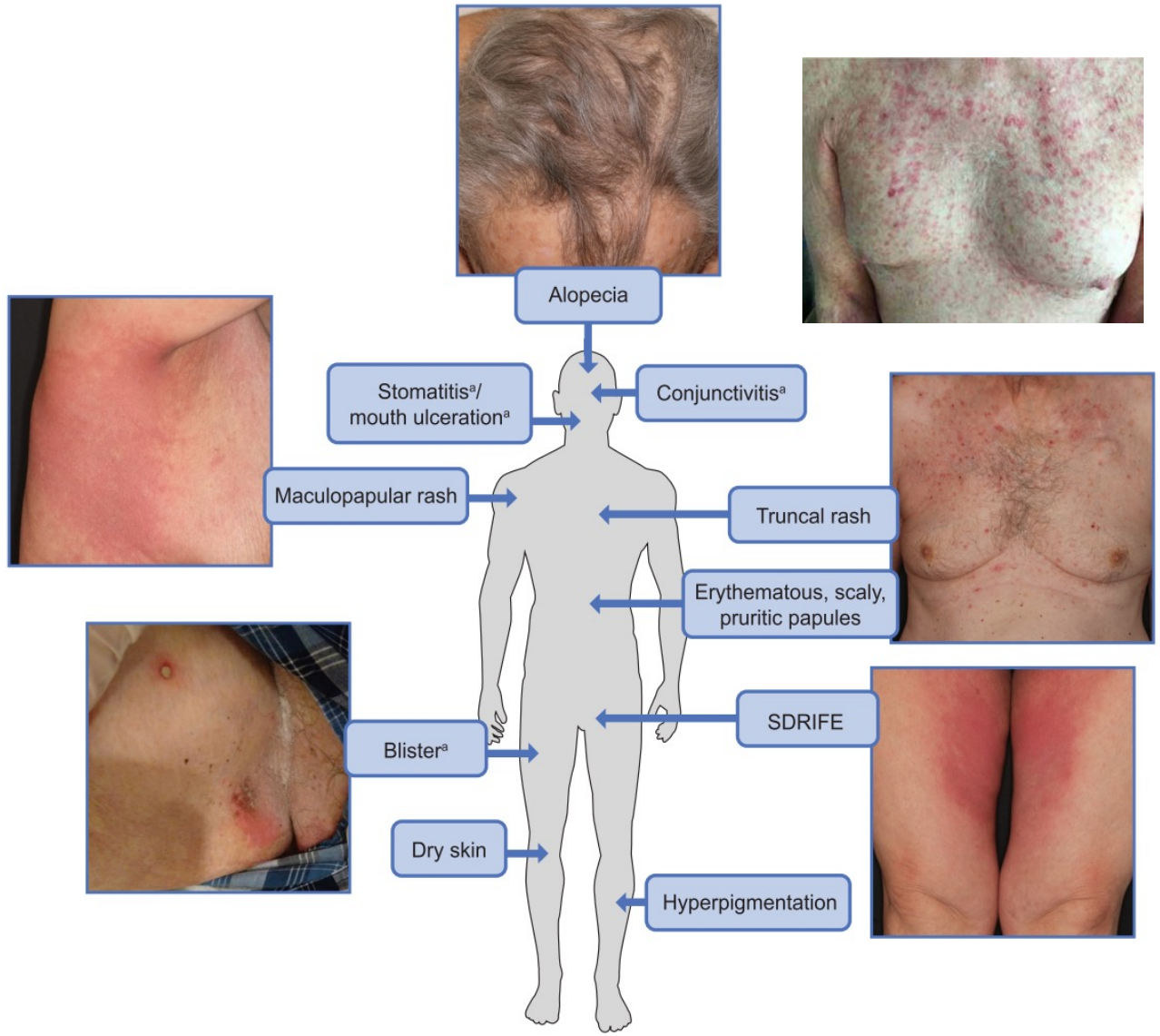
- Grade 2 (10%-30% body surface area, no large fold involvement, no fever)
  - Skin biopsy
  - High-potency systemic steroids and emollients
  - Hold EV dose until Grade 0/1
  - Close reassessment
  - Resume therapy at 1mg/kg



1. Wu et al. Dermatology Online Journal, 25(2)
2. Lacoutre et al. The Oncologist 2022

Skin Toxicity Management

- Grade 3 (>10% body surface area, and either fever, blistering, mucosal involvement, unexplained liver/kidney changes, large skinfold involvement or erythroderma)
  - Consider hospitalization
  - Skin biopsy
  - Discontinue EV permanently
  - Intravenous corticosteroids (0.5-1mg/kg), emollients, oral care



1. Wu et al. Dermatology Online Journal, 25(2)
2. Lacoutre et al. The Oncologist 2022

Outcomes of EV Cutaneous Toxicity

- EV 301
  - 11% patients had dose interruption
  - 8% led to dose reduction
  - 4% discontinued EV permanently
- EV 302
  - 1.6% discontinued EV permanently

Recommended dose reduction schedule[24]	
	Dose level
Starting dose	1.25 mg/kg up to 125 mg
First dose reduction	1.0 mg/kg up to 100 mg
Second dose reduction	0.75 mg/kg up to 75 mg
Third dose reduction	0.5 mg/kg up to 50 mg

Powles. NEJM. 2021;384:1125. Rosenberg. ASCO 2022. Abstr 4516.

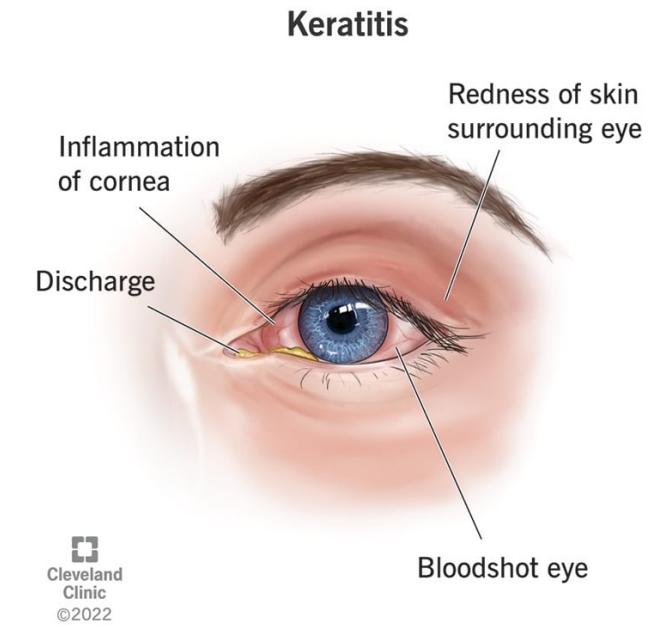
Enfortumab: Neuropathy

- Sensory Neuropathy is Common (~50% of patients)
  - Grade 1: 25%
  - Grade 2: 25%
  - Grade 3+: 3.6%
- Median onset 2.4 mo
- Can improve with dose reductions or delays (Gr2+). Early recognition is key
- Motor neuropathies occur too (10% any grade)

Powles et al NEJM 2024

Enfortumab: Other Important Toxicities

- Ocular
  - Dry eye/keratitis/lacrimation/blurred vision
  - Treatment: Lubricating eye drops, ophthalmologic corticosteroids
  - Ophthalmology referral



- Hyperglycemia
  - Class effects of MMAE
  - Deaths reported due to diabetic ketoacidosis
  - Do not treat if A1c >8%, or BG >250mg/dl
  - Endocrinology referral, good DM management

EV Toxicity: Take home points

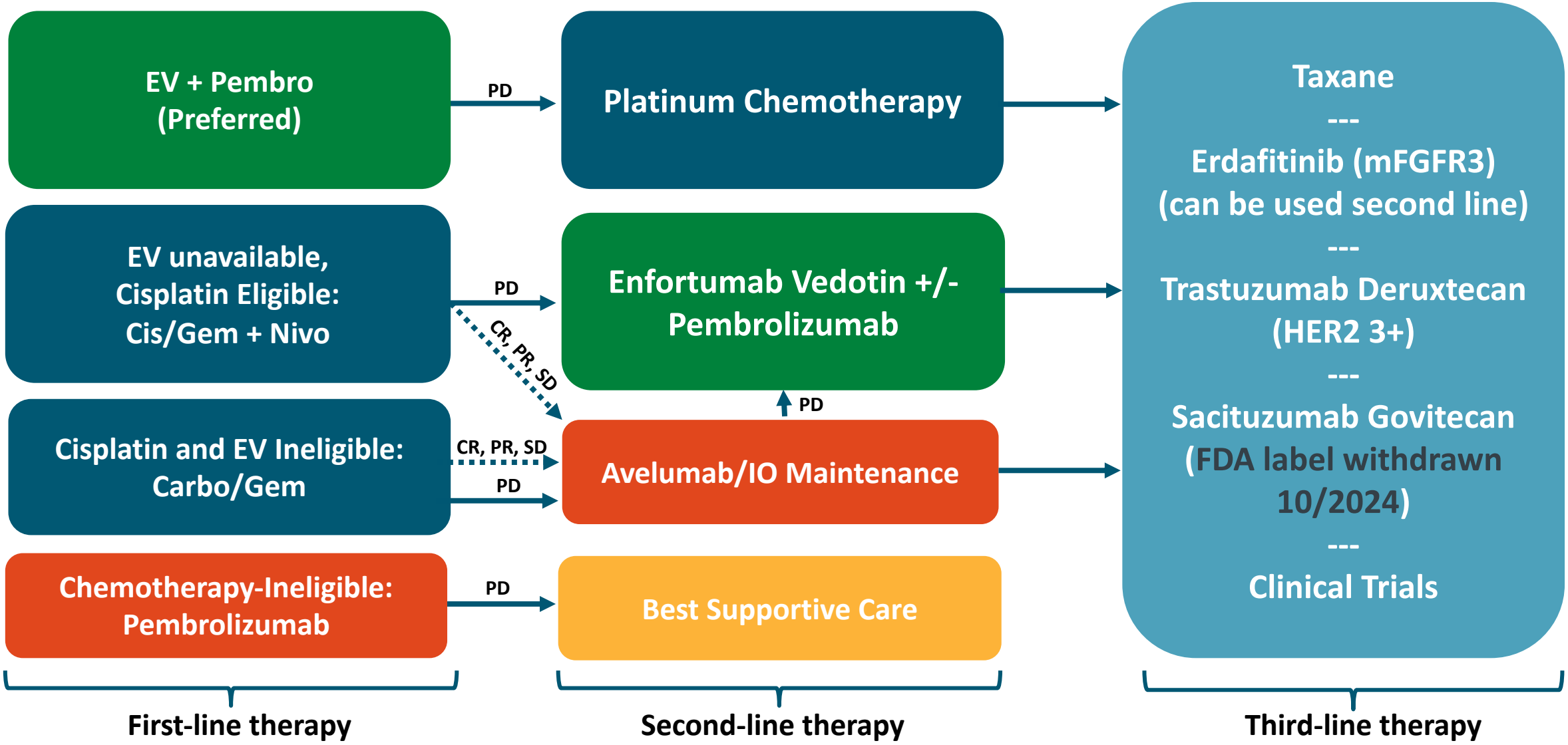
- Peripheral neuropathy and rash are common (~50% of patients)
- Patient education and monitoring are key
- Low threshold to dose-reduce & dose delay, and work with consultants
  - Dermatology
  - Neurology
  - Ophthalmology / Endocrinology
- Many adverse events improve with dose modification
- Avoid EV in patients with baseline Gr 2 neuropathy, or A1c >8%, or BS of >13.9 mmol/L (>250mg/dL)

Selected Ongoing Trials of ADCs + Immunotherapy in mUC

Treatments	Alias	Ph	Population	Primary Endpoint	NCT Number
Disitamab Vedotin + Pembrolizumab	DV-001	III	1st line HER2+	PFS, OS	NCT05911295
Disitamab Vedotin + Toripalimab		III	1st line HER2+	PFS, OS	NCT05302284
Zelenectide Pevedotin + Pembro	DURAVELO-2	III	1st line	PFS	NCT06225596
EV + SG + Pembrolizumab	DAD-IO	II	1st line	ORR	NCT04724018
Datopotamab-DXd + Volrustomig or Rilvegostomig	TROPION-Pan Tumor 03	II	1st or 2nd line	ORR, AEs	NCT05489211
SG + Avelumab	JAVELIN Bl. Medley	II	1st line	PFS, AEs	NCT05327530
EV + Pembro + Sacituzumab TMT or investigational agents	KEYMAKER-U04	I/II	1st line	ORR, PFS	NCT05845814
EV or SG + Atezolizumab	MORPHEUS-UC	Ib/II	Post-platinum	ORR	NCT03869190
SG + Zimberelimab (aPD-1) + Domvanalimab (aTIGIT)	TROPHY-U01 Cohort 7	I/II	1st line	ORR	NCT03547973
BGB-C354 (B7-H3 ADC) + Tislelizumab		I	Later line	AEs, ORR	NCT06422520

EV: Enfortumab Vedotin. SG: Sacituzumab Govitecan

How Will I Treat mUC in 2025?



Conclusions

- Multiple combination therapies are available in the first-line setting
  - EV plus Pembrolizumab
  - Cisplatin-based chemotherapy plus Nivolumab
  - Platinum-based chemotherapy → maintenance Avelumab
- Understanding how to best select patients, and use of novel biomarkers could impact its use
- Dose delays and dose modifications can be helpful in management
  - Attention especially to neuropathy & rash
- Much more to come!

Questions from General Medical Oncologists

- In what cases would you rather use a cisplatin-based regimen or nivolumab/chemotherapy rather than EV/pembro? It seems like EV/pembro is now everyone's preferred regimen. Are there any patients outside of those with autoimmune disease that you would not use front-line EV/pembro?
- What is the efficacy of EV/pembro in patients who develop metastatic disease after adjuvant immunotherapy? Do the experts still prefer EV/pembro in this setting? How does disease-free interval affect your thinking?
- If a patient is ineligible for IO therapy, should we consider EV alone or gem/cis in the first line?

Questions from General Medical Oncologists

- 81 y/o F, frail, presented with urinary retention. An 8-cm mass was found. Cystoscopy and biopsy found invasive cancer with squamous features. PD-L1 30%. TMB 6. MRI showed the tumor invading to the suprapubic bone. Bone biopsy was negative. CT showed 3 small lung nodules — the largest is 7 mm. I plan single-agent pembro. What would the investigators do? For which patients would you still consider pembro monotherapy instead of EV/pembro, particularly with modern data but considering possible morbidities?
- If a patient has a complete response and is in remission, when can we stop EV and pembrolizumab? Is anyone using MRD to determine when to stop both drugs or just one drug?

Questions from General Medical Oncologists

- When administering EV/pembro, if you hold/discontinue the EV for toxicity do you stop the pembro as well? Or do you continue pembro as a single agent until progression/toxicity?
- How do you manage cutaneous toxicity in patients on EV/pembro? Do the experts adjust dosing interval?
- For patients with mUBC on EV/pembro with pre-existing Grade 1 neuropathy, do you start them at a reduced dose or standard dose? Are there any treatments to mitigate neuropathy?
- Is there any data on the effectiveness of neoadjuvant EV/pembro?

Agenda

Module 1: Role of Antibody-Drug Conjugates (ADCs) in Front-Line Therapy for Metastatic Urothelial Bladder Cancer (mUBC) — Dr Friedlander

Module 2: Evidence-Based Use of ADCs for Relapsed/Refractory mUBC — Dr Galsky

Module 3: Evolving Role of Treatment Intensification with Androgen Receptor Pathway Inhibitors for Nonmetastatic and Metastatic Prostate Cancer — Dr Armstrong

Module 4: Optimal Integration of PARP Inhibitors into Therapy for Prostate Cancer — Dr Agarwal

Evidence-Based Use of ADCs for Relapsed/Refractory Metastatic Urothelial Bladder Cancer

Matthew D. Galsky, MD FASCO

Lillian and Henry Stratton Professor of Medicine

Icahn School of Medicine at Mount Sinai

Director, Genitourinary Medical Oncology

Associate Director, Translational Research

Tisch Cancer Institute

@MattGalsky

EV-301 Trial

Phase 3

- Adult patients with locally advanced or mUC
- ECOG PS ≤1
- Prior platinum-containing chemotherapy
- PD during or after checkpoint inhibitor treatment

R

N = ~550

Enfortumab vedotin
1.25 mg/kg IV over 30 min
on d 1, 8, and 15 of each
28-d cycle

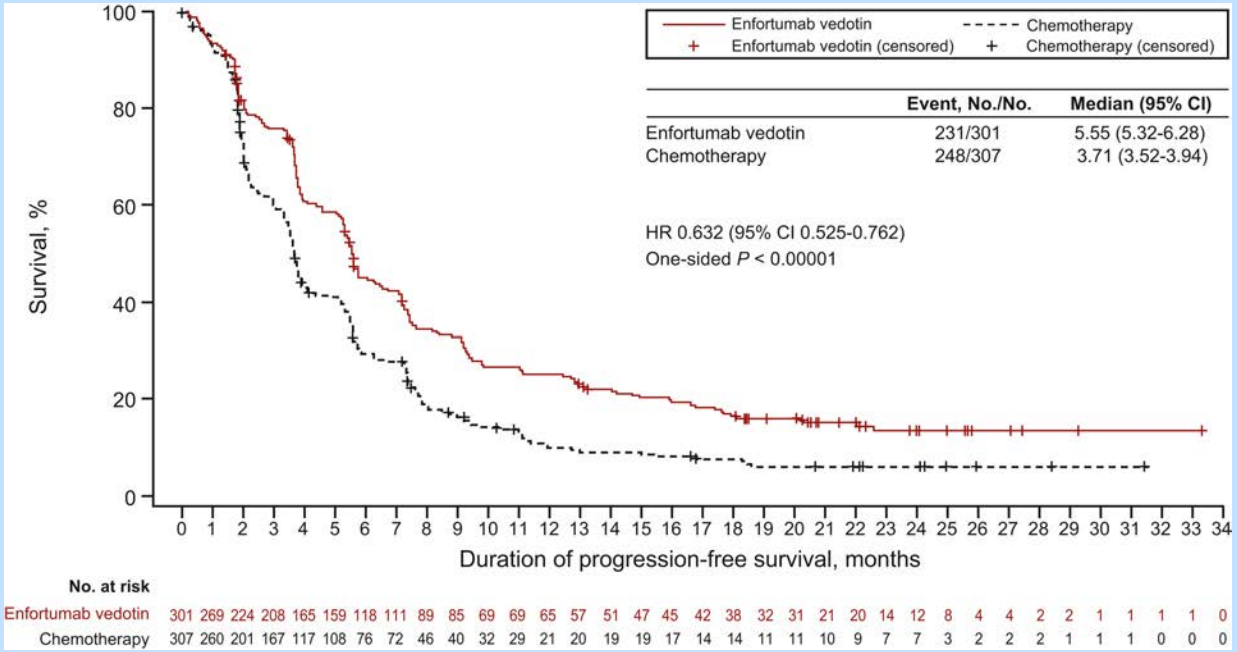
Investigator's choice:
docetaxel, paclitaxel, or vinflunine
(European Union only) IV
on d 1 of each 21-d cycle

- Treatment with study drug until radiologic disease progression, intolerance, or other discontinuation criterion is met
- Radiologic assessment of tumor response status at baseline and every 8 wk

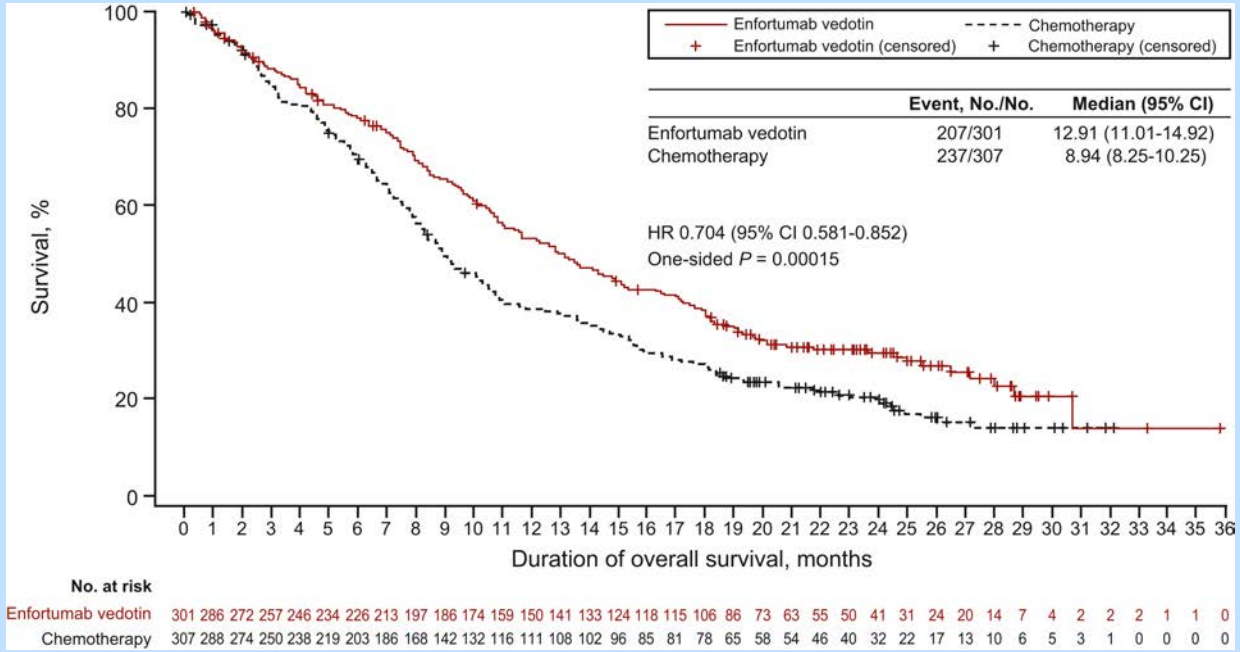
- **Primary endpoint:** OS
- **Secondary endpoints:** PFS, DOR, ORR, safety/tolerability, QOL

EV-301 Trial – 24 month follow-up

Progression-free survival



Overall survival



Rosenberg et al, Ann Oncol, 2023

Is HER2 a good target for ADCs in UC?

Location	Her 2 IHC*		
	≥1+	2+	3+
Primary (n = 114)	84 (74%)	36 (32%)	5 (4%)
Lymph node (n = 38)	35 (92%)	17 (45%)	4 (11%)

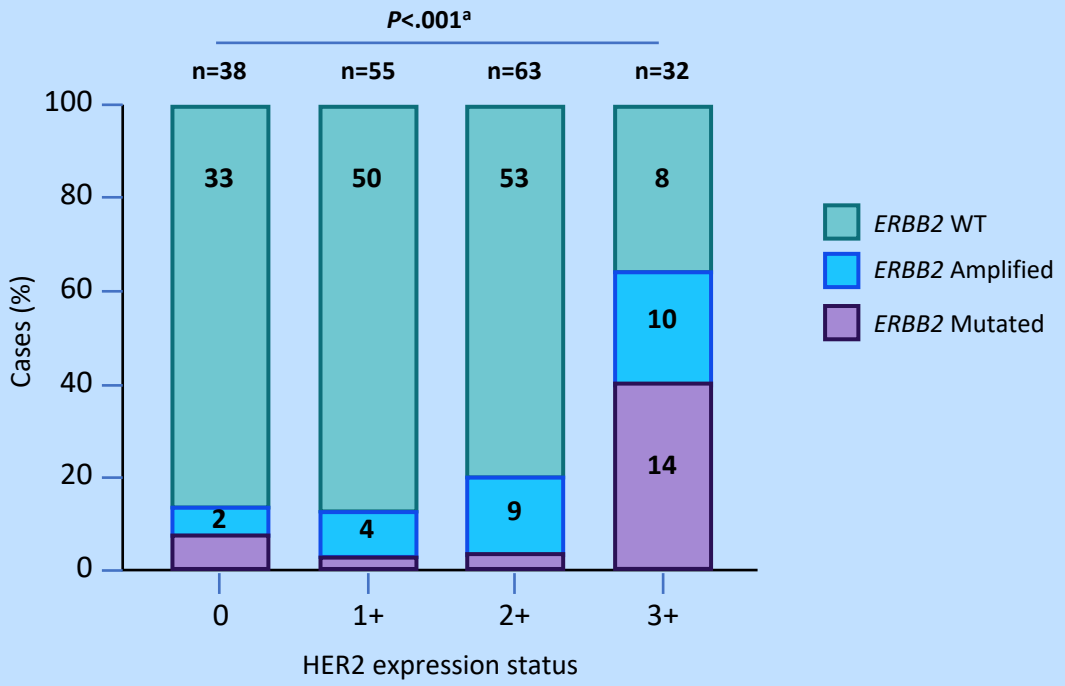
*Dako HercepTest system

Press, ASCO, 2013

Relationship Between *HER2* Alteration by NGS and HER2 Expression by IHC

HER2 IHC

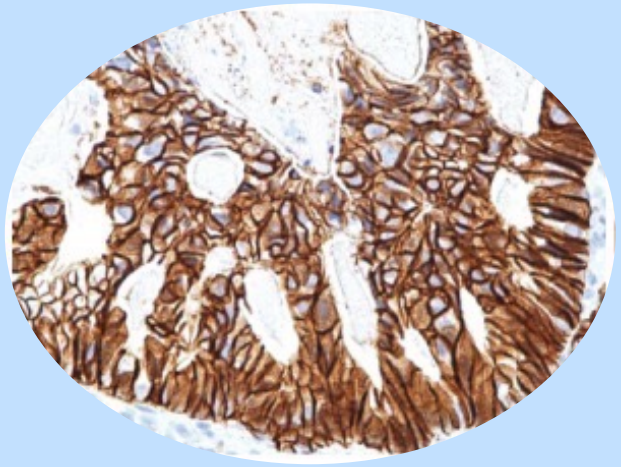
0 = 18.8%
1+ = 29.7%
2+ = 33.7%
3+ = 17.8%



ERBB2 alterations (mutations and/or amplifications) were identified by MSK IMPACT in ≈20% of urothelial cancers

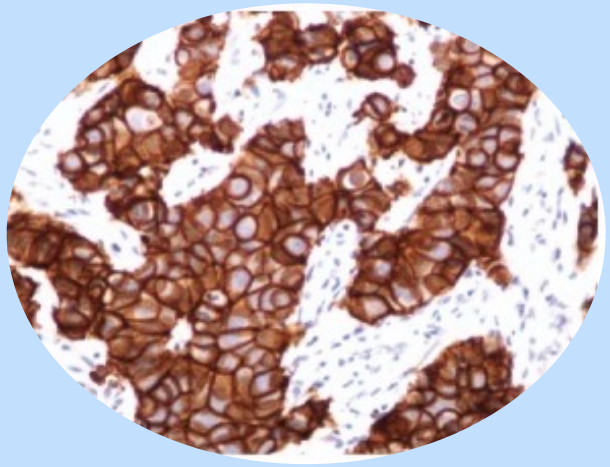
Aggen et al, ASCO GU 2023

Not all HER2 expression is created equally



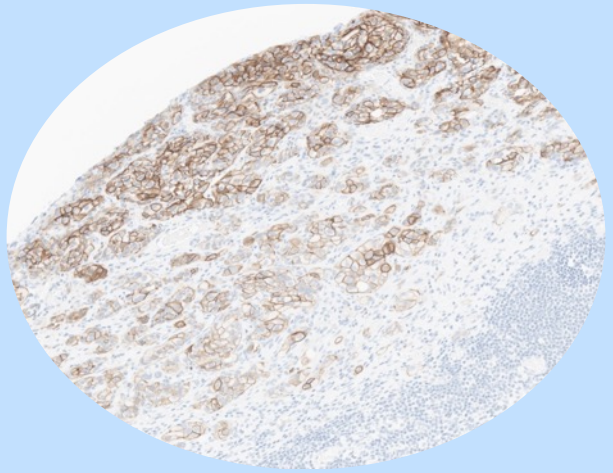
Gastric Cancer

- “U” shaped
- Patchy



Breast Cancer

- Circular
- Homogenous



Bladder Cancer

- Circular
- Patchy

Abrahao-Machado, World J Gastroenterol, 2016
Bladder photomicrograph courtesy of Hikmat Al-Ahmadie

Anti-HER2 Antibody-Drug Conjugates

	Antibody	Payload	Linker
Trastuzumab emtansine (T-DM1)	Trastuzumab	DM1	Lysine-SMCC
Trastuzumab deruxtecan	Trastuzumab	DXd	Cleavable
Disitamab vedotin (RC48)	Disitamab	MMAE	Cleavable
MRG002	Humanized anti-HER2	MMAE	Cleavable
SYD985	Trastuzumab	Seco-duocarmycin	Cleavable

Anti-HER2 Antibody-Drug Conjugates

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MRG002	Humanized anti-HER2	MMAE	Cleavable
SYD985	Trastuzumab	Seco-duocarmycin	Cleavable

Phase II DESTINY-PanTumor02
Trastuzumab Deruxtecan

T-DXd
5.4 mg/kg Q3W

40 per cohort[b]

- Endometrial cancer
- Cervical cancer
- Ovarian cancer
- Bladder cancer
- Other tumors[c]
- Biliary tract cancer
- Pancreatic cancer

Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- DOR, DCR, PFS, OS
- Safety

Exploratory analysis

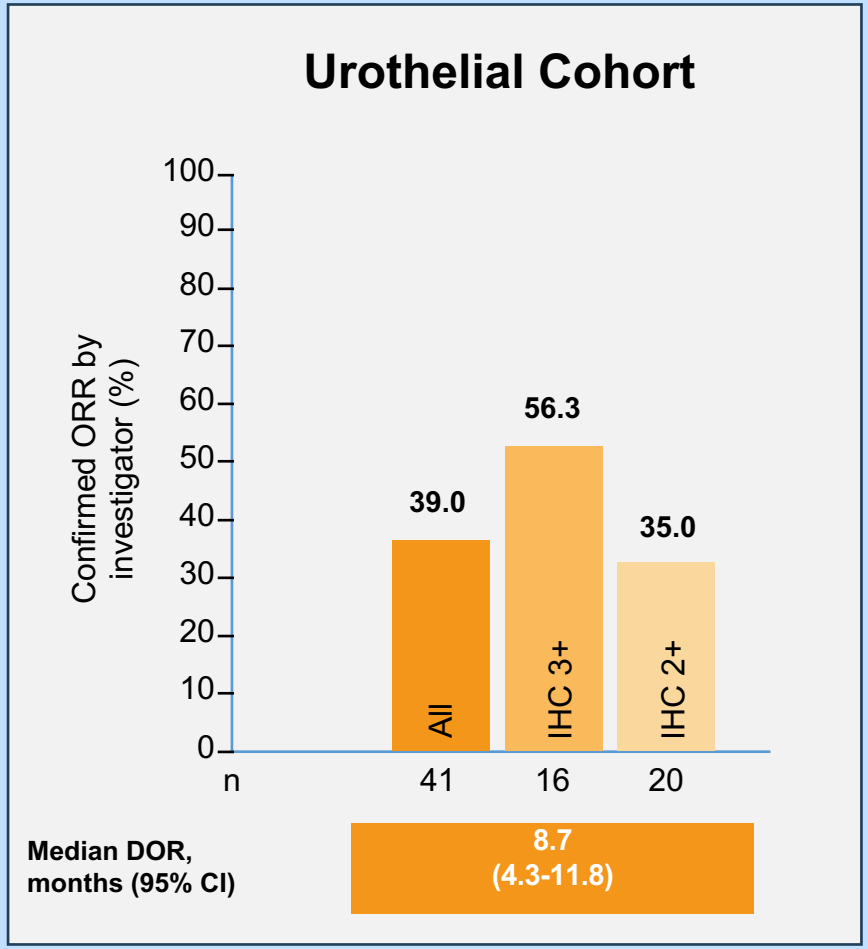
- Subgroup analyses by HER2 status

Primary analysis
data cutoff: Jun 8, 2023
Median follow up: 12.75 mo

HercepTest™, 2017 ASCO/CAP gastric scoring guidelines, local testing permitted

Meric-Bernstam et al, ESMO,2023

Phase II DESTINY-PanTumor02
Trastuzumab Deruxtecan

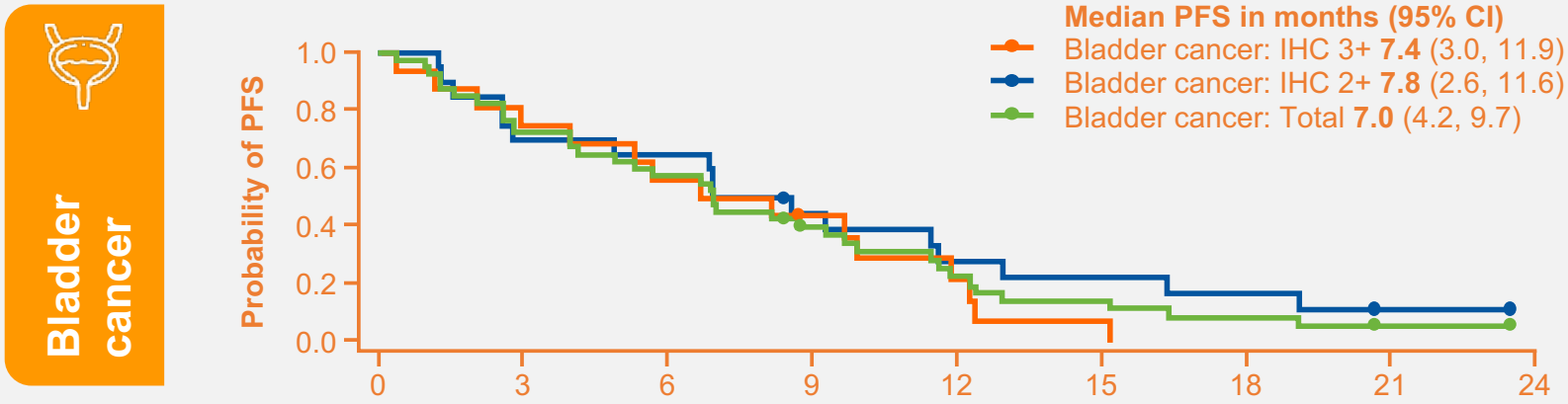


All Patients

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

Meric-Bernstam et al, ESMO,2023; Meric-Bernstam et al, JCO 2024.

Phase II DESTINY-PanTumor02 Trastuzumab Deruxtecan



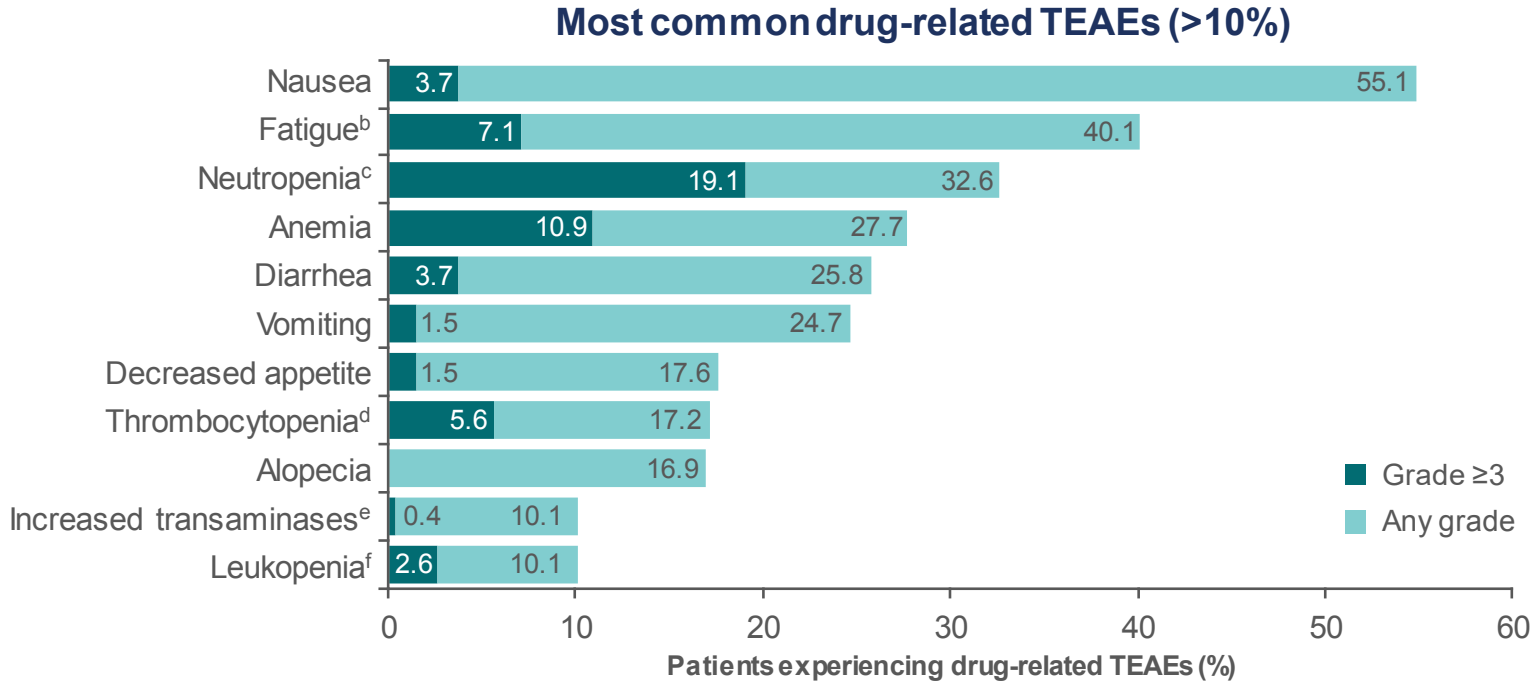
Number at risk, month

Bladder cancer: IHC 3+	16	12	9	6	3	1	0		
Bladder cancer: IHC 2+	20	14	13	8	5	4	3	1	0
Bladder cancer: Total	41	29	23	14	8	5	3	1	0

Meric-Bernstam et al, ESMO,2023; Meric-Bernstam et al, JCO 2024.

Phase II DESTINY-PanTumor02 Trastuzumab Deruxtecan

n (%)	All patients (N=267)
Any drug-related TEAEs	226 (84.6)
Drug-related TEAEs Grade ≥3	109 (40.8)
Serious drug-related TEAEs	36 (13.5)
Drug-related TEAEs associated with dose discontinuations	23 (8.6)
Drug-related TEAEs associated with dose interruptions	54 (20.2)
Drug-related TEAEs associated with dose reductions	54 (20.2)
Drug-related TEAEs associated with deaths	4 (1.5)[a]



ILD/pneumonitis adjudicated as T-DXd related, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
All patients (N=267)	7 (2.6)	17 (6.4)	1 (0.4)	0	3 (1.1)	28 (10.5)

Meric-Bernstam et al, ESMO,2023; Meric-Bernstam et al, JCO 2024.

DESTINY-PanTumor01 Study

Patients with unresectable or metastatic solid tumors with *HER2* mutations; progression on or after previous therapy and no other acceptable treatment options;
prior HER2 therapy was allowed
N = 131
(Maximum 20 any tumor type)

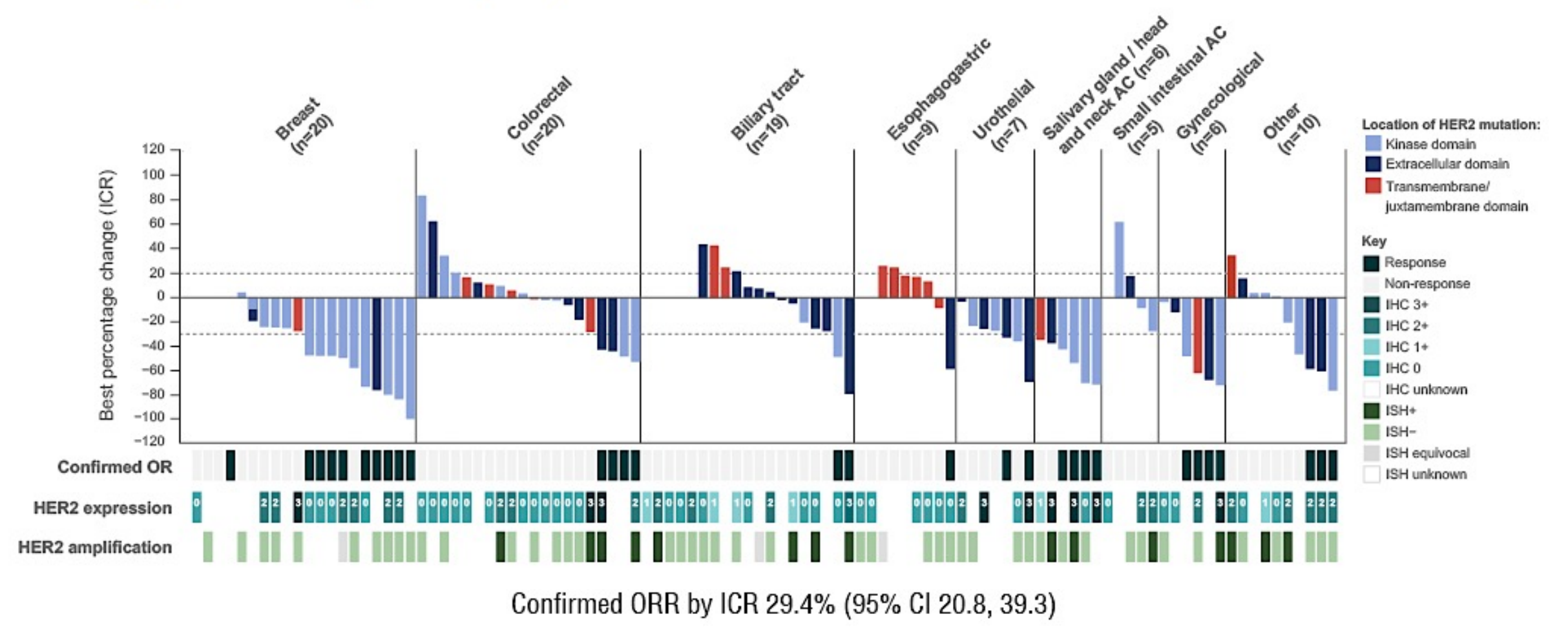
→ T-DXd
5.4 mg/kg Q3W

Prespecified *HER2* Mutations	
Extracellular domain	S310F/Y
Transmembrane/ Juxtamembrane domain	G660D R678Q
Kinase domain	L755S D769H/Y Y772_A775dup A775_G776insYVMA V77L G778_P780 dup P780_Y81insGSP V842I T862A

- **Primary endpoint**: confirmed ORR by ICR
- **Secondary endpoints**: DoR, DCR, confirmed ORR by investigator, PFS, OS, safety

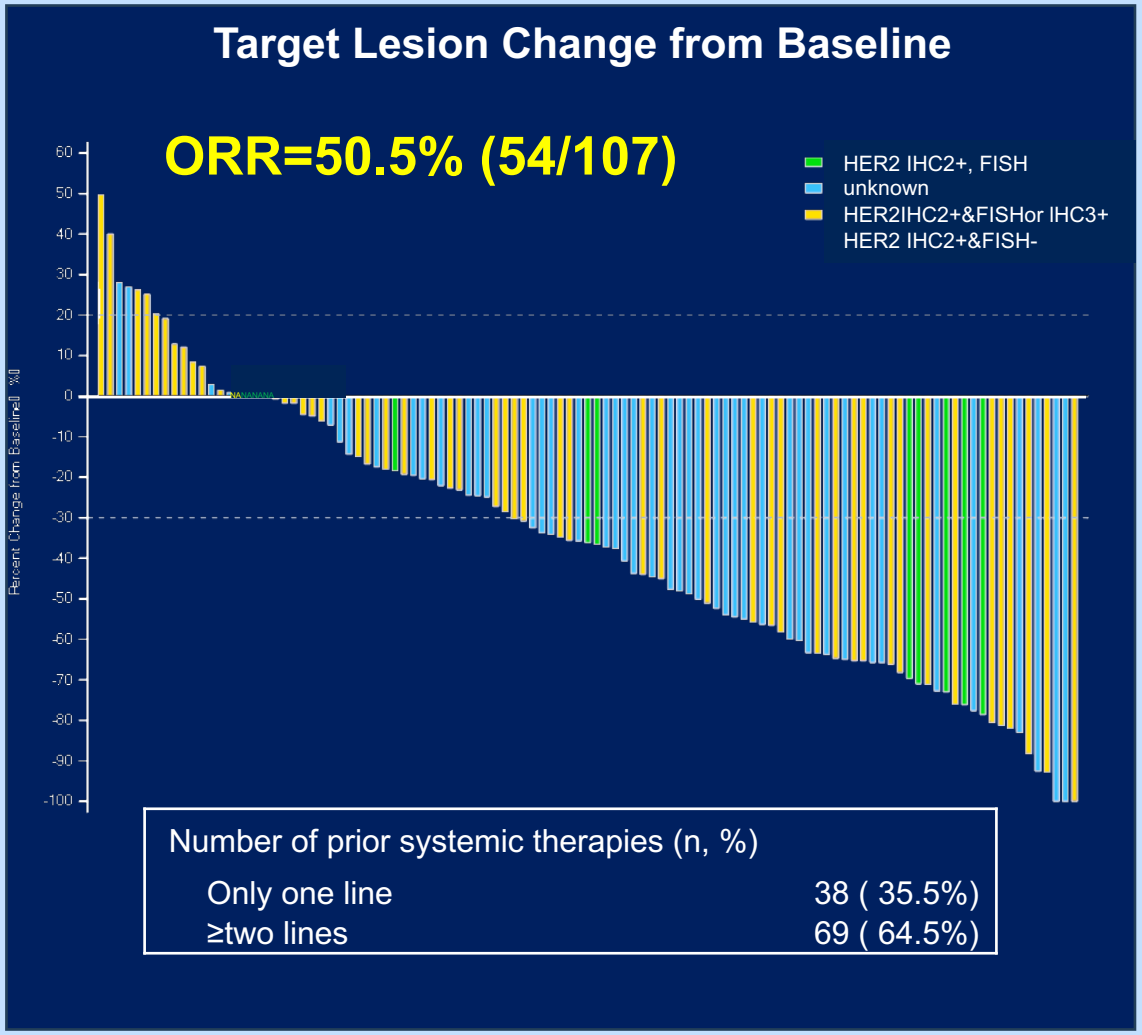
Li. ESMO 2023. Abstr 654O; Li et al. Lancet Oncol, 2024.

DESTINY-PanTumor01 Study



Li. ESMO 2023. Abstr 654O; Li et al. Lancet Oncol, 2024.

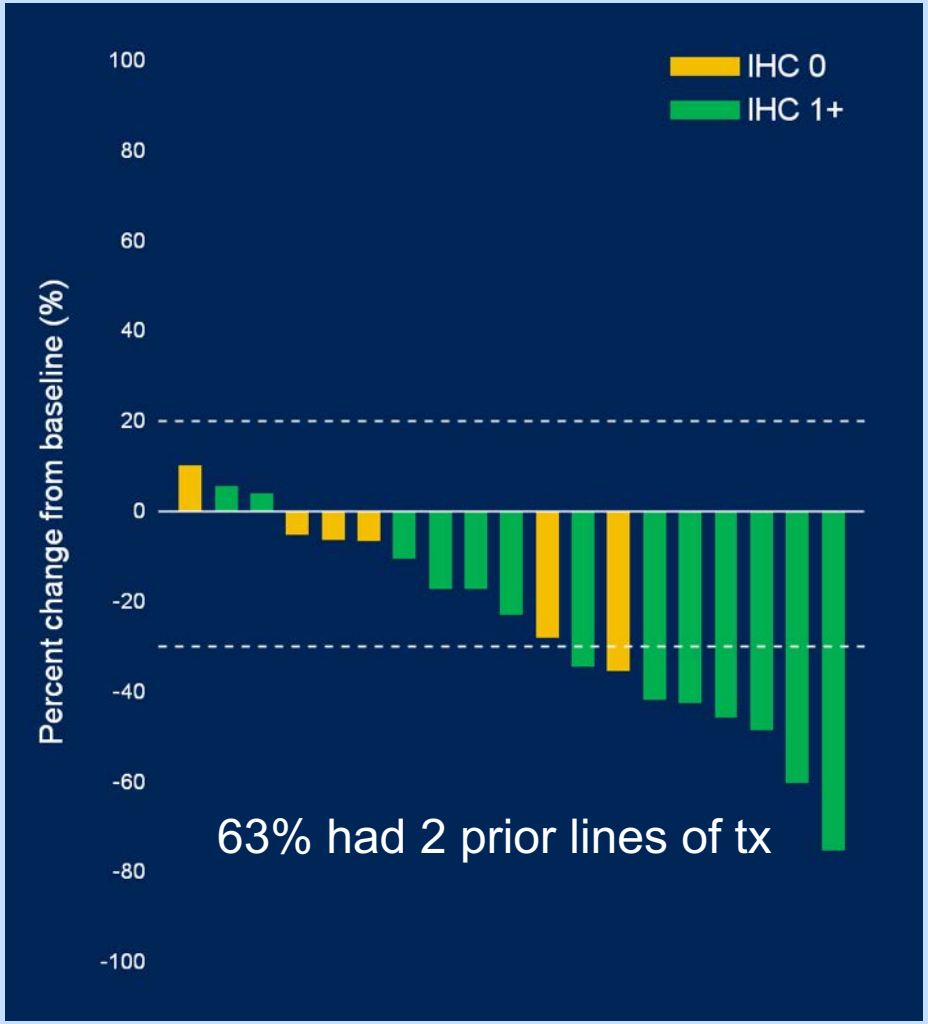
RC48 (Disitamab Vedotin) in HER2 2-3+ mUC



Subgroups	cORR (%, 95% CI)
HER2 status	
IHC2+FISH+ or IHC3+ (n=45)	62.2% (46.5%, 76.2%)
IHC2+FISH- (n=53)	39.6% (26.5%, 54.0%)
Metastasis site	
Visceral Metastasis (n=97)	51.5% (41.2%, 61.8%)
Metastasis to Liver (n=48)	52.1% (37.2%, 66.7%)
Prior therapies	
Post PD1/PDL1 Treatments (n=27)	55.6% (35.3%, 74.5%)
Post 1 line of Chemotherapy (n=38)	50.0% (33.4%, 66.6%)
Post ≥2 Lines of Chemotherapy (n=69)	50.7% (38.4%, 63.0%)

Sheng et al, ASCO, 2022. Sheng et al, JCO, 2023.

RC48 (Disitamab Vedotin) in HER2 1+ mUC



Confirmed ORR	
n (%)	5 (26.3%)
95%CI	9.1%, 51.2%

Subgroups	cORR (%, 95% CI)
IHC 0 (n=6)	0
IHC 1+ (n=13)	38.5 (13.9, 68.4)

Xu et al, ASCO, 2022

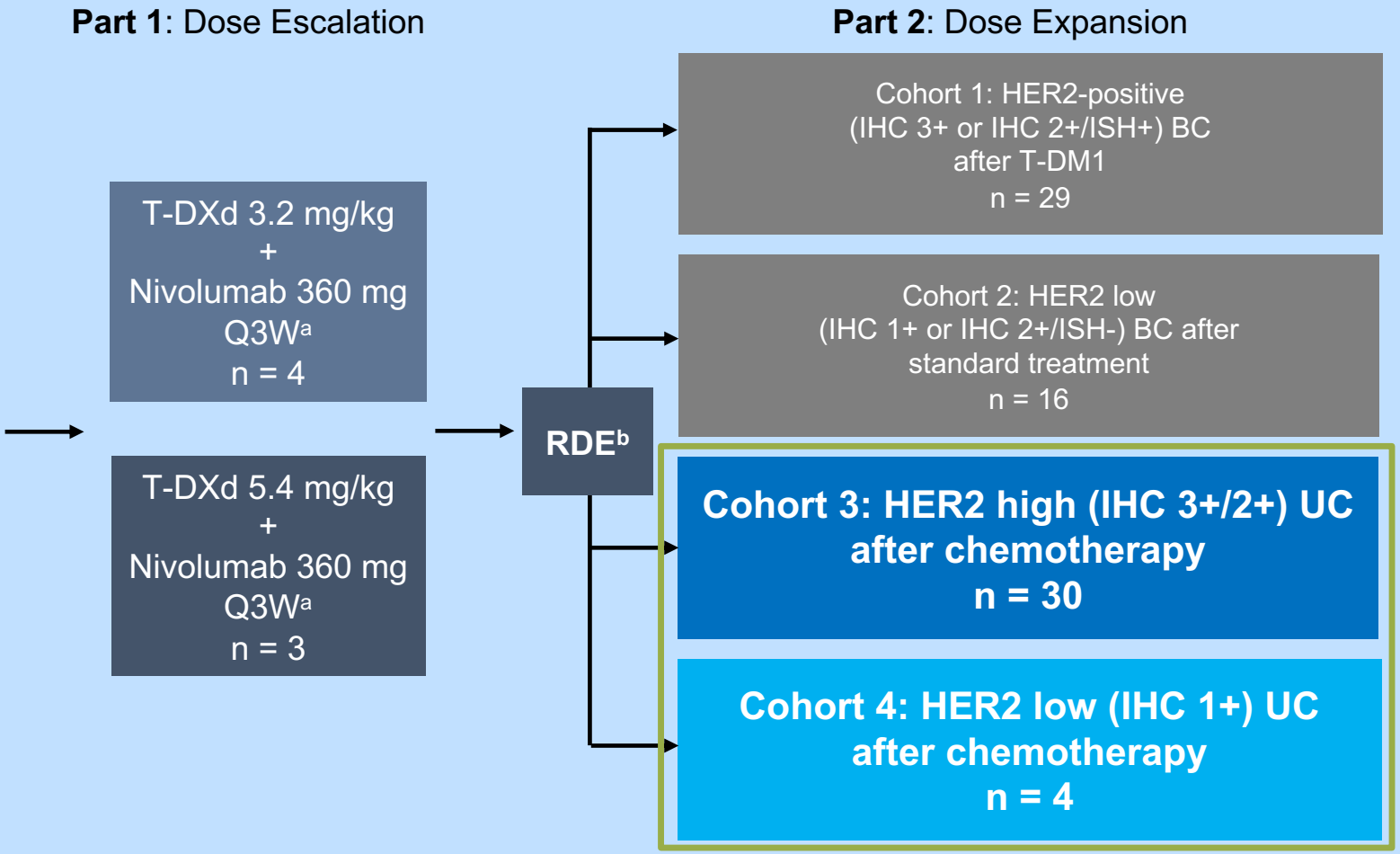
AEs differ based on target and payload

Adverse Event	Disitamab Vedotin	Enfortumab Vedotin	Trastuzumab Deruxtecan
Neuropathy	+	+	-
↑ AST	+	-/+	-
↓ neutrophils	+	-/+	+
Rash	-/+	+	-
↑ glucose	+	+	-
Diarrhea	-	-	+
Pneumonitis	-	-	+

Trastuzumab Deruxtecan + Nivolumab

Key Eligibility Criteria

- HER2-expressing advanced/metastatic BC or UC (centrally confirmed)
- ECOG PS 0 or 1
- ≥1 measurable lesion per RECIST v1.1
- No prior T-DXd or I-O
- To be eligible for part 1, patients must meet additional cohort specific criteria of part 2



Primary endpoint
- Part 1: MTD or RDE
- Part 2: ORR[c] by ICR

Secondary endpoints
- DOR by ICR, DCR, PFS by ICR, TTR by ICR, OS, investigator-assessed ORR[c]
- PK/PD
- Safety and tolerability

Exploratory endpoint
- Biomarkers of response[d]

Galsky et al, ASCO GU, 2022

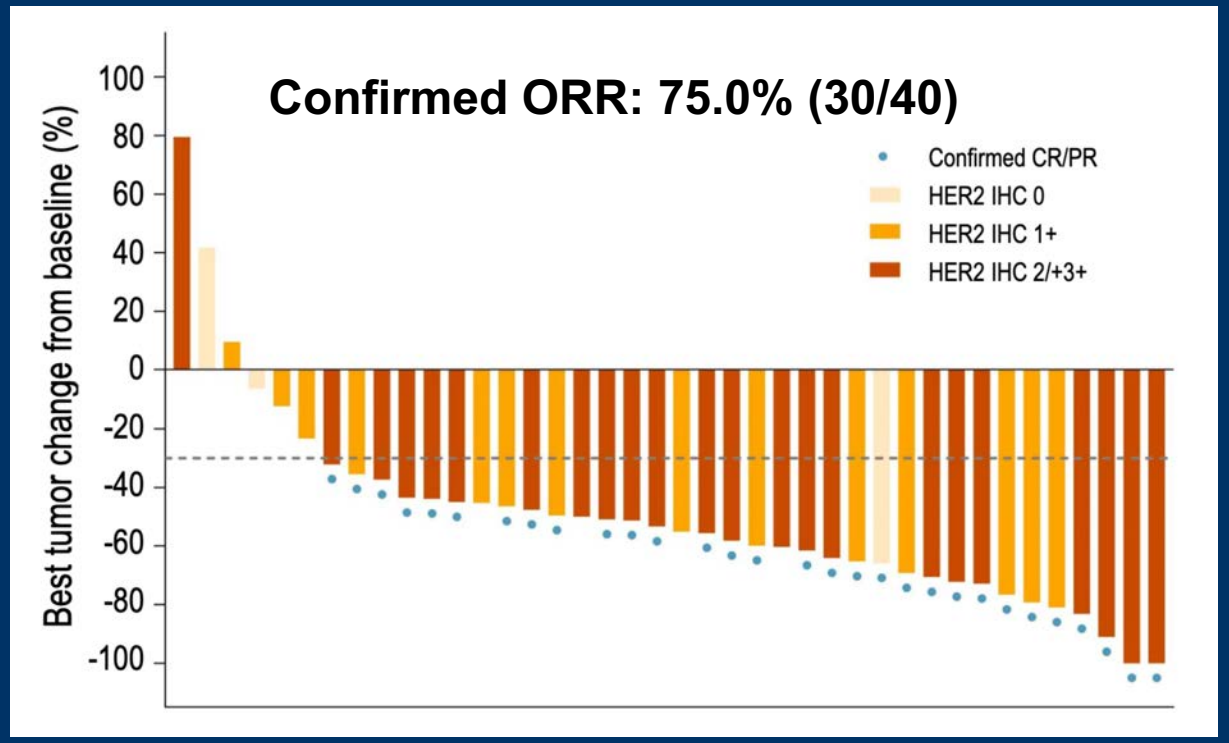
Trastuzumab Deruxtecan + Nivolumab

	Cohort 3: HER2-high n=30	Cohort 4: HER2-low n=4
cORR (CR + PR), n (%) [95% CI]	11 (36.7) [19.9-56.1]	–
Best overall response, n (%)		
CR	4 (13.3)	0
PR	7 (23.3)	2 (50.0)
SD	12 (40.0)	1 (25.0)
PD	5 (16.7)	1 (25.0)
NE	2 (6.7)	0
DoR, median (95% CI), months	13.1 (4.1-NE)	NE
TTR, median (range), months	1.9 (1.2-6.9)	–
PFS, median (95% CI), months	6.9 (2.7-14.4)	NE
OS, median (95% CI), months	11.0 (7.2-NE)	NE
Treatment duration, median (range), months		
T-DXd	3.9 (1-21)	–
Nivolumab	4.1 (1-20)	–

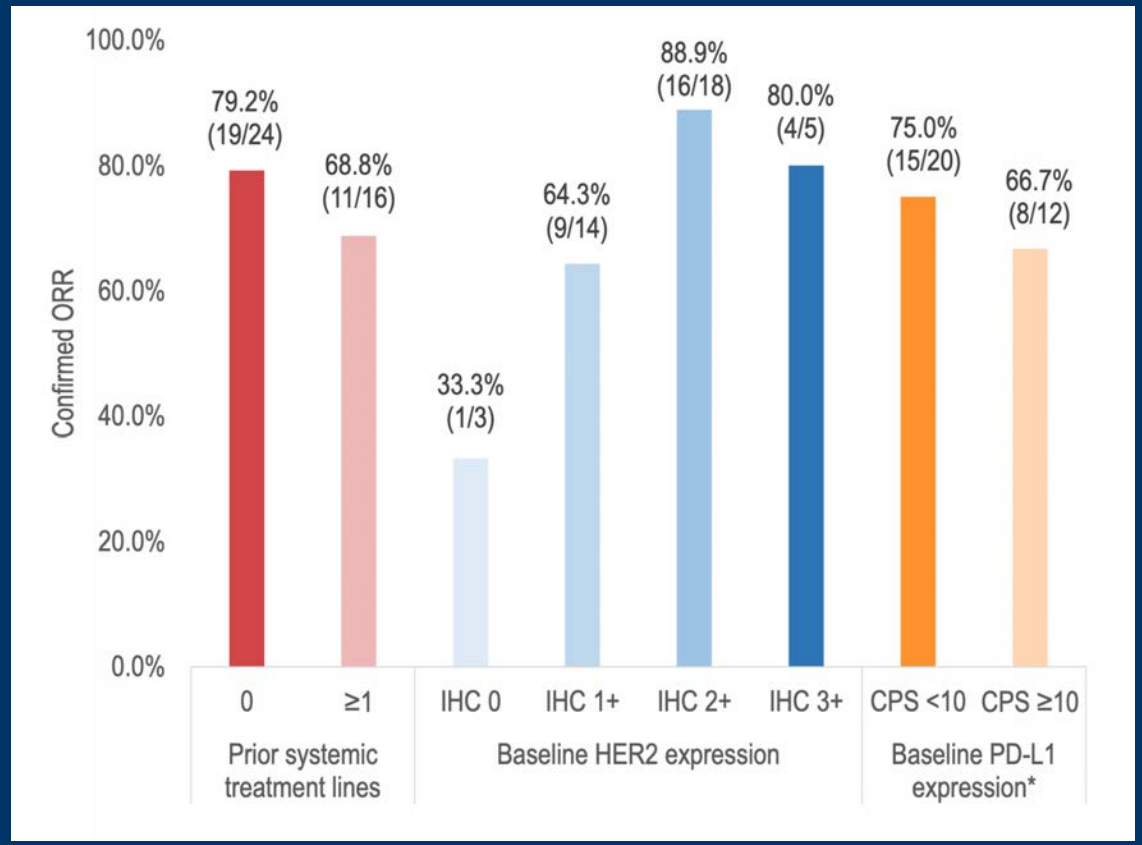
- **36.7%** cORR
- **HER2 IHC 3+: 62.5% (5/8)** patients had a confirmed objective response, including 2 CR (25%)
- HER2 IHC 2+: 27.3% (6/22) patients had a confirmed objective response, including 2 CR (9.1%
- **6.9** months, mPFS
- **11** months, mOS

Galsky et al, ASCO GU, 2022. Hamilton et al, Clin Cancer Res, 2024.

RC48 + Toripalimab

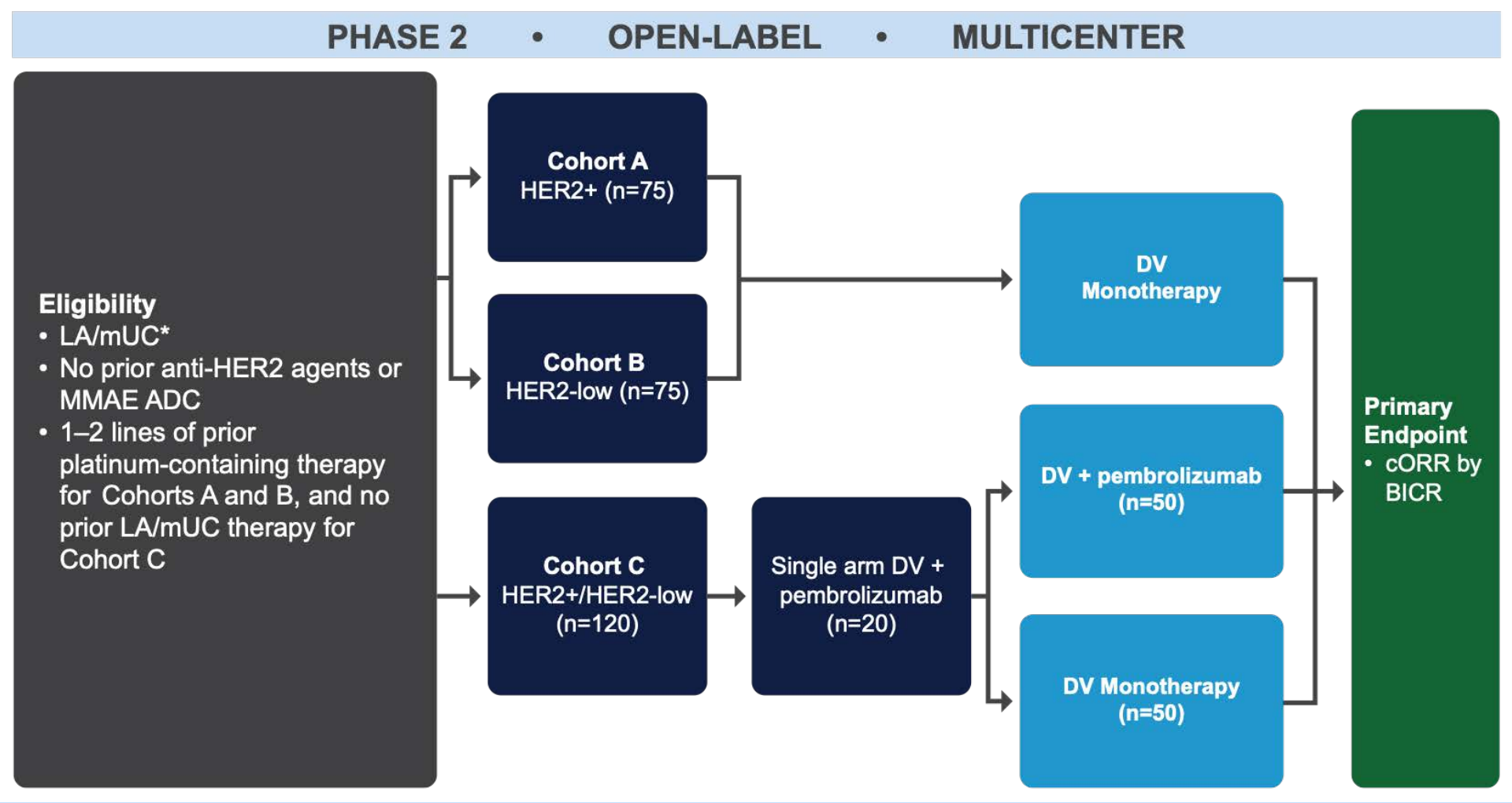


Prior systemic treatment (n,%)	
0 Line	24 (60.98%)
≥1 Lines	16 (39.02%)



Zhou et al, ESMO, 2024

RC48 G001



Gastric cancer scoring algorithm

Galsky et al, SITC, 2022

RC48 G001

RC48G001 Cohort C Study Design

ITT Population (N=170)

Previously untreated HER2-positive/ HER2-low expressing la/mUC

Eligibility

- Age ≥18 years
- la/mUC
- HER2 status:[a]
  - HER2-positive: IHC 3+, ***or*** IHC 2+ and ISH-positive
  - HER2-low: IHC 2+ and ISH-negative, ***or*** IHC 1+
- ECOG PS of 0-2[b]

[a] HER2 IHC status will be determined by central laboratory.
[b] ECOG PS of 2 was allowed if hemoglobin ≥10 g/dL and CrCl ≥50 mL/min.

Part 1 (Safety Run-In)

Disitamab vedotin Q2W + pembrolizumab Q6W
6-week cycles

N=20

Part 2 (Randomized; Currently Enrolling)

R 1:1

Disitamab vedotin Q2W + pembrolizumab Q6W
6-week cycles

n=75

Disitamab vedotin Q2W
6-week cycles

n=75

Primary Endpoint

- cORR per BICR

Secondary Endpoints

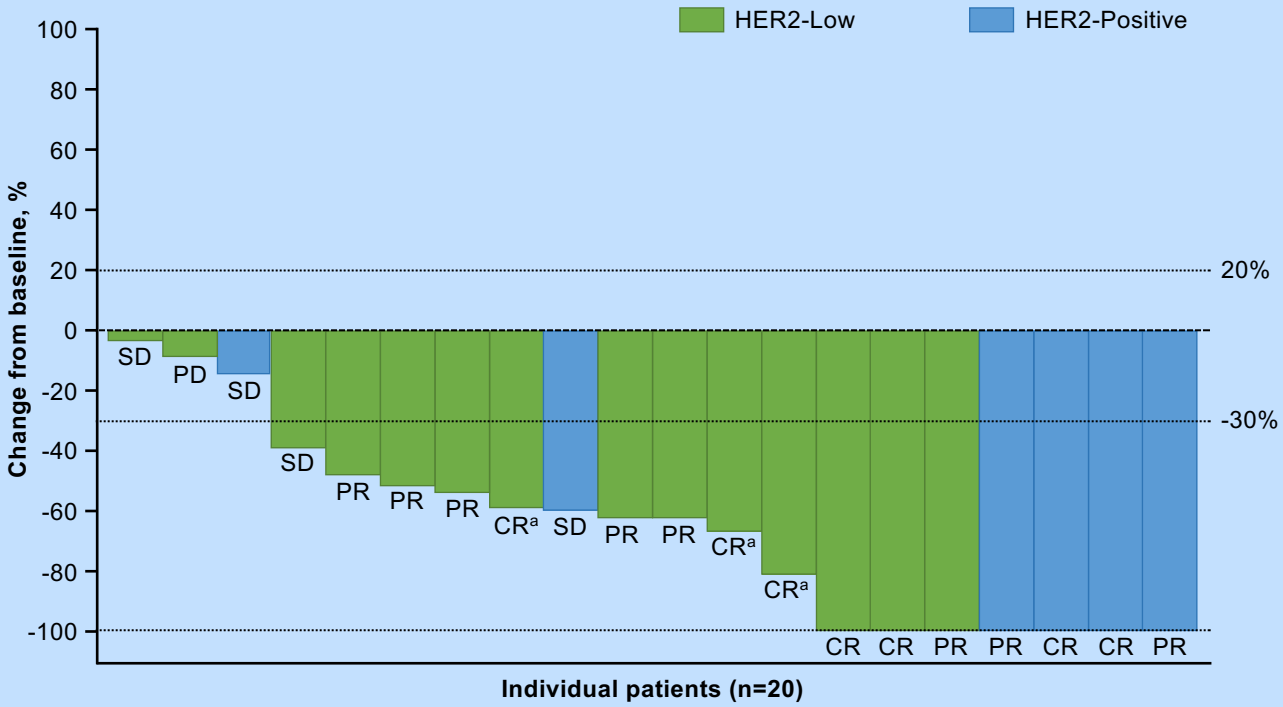
- cORR per investigator assessment
- DOR, PFS, DCR per BICR and investigator
- OS
- Safety

Disease assessments Q8W from C1D1 for 72 weeks, then Q12W until progression per BICR

Galsky et al, ESMO, 2024

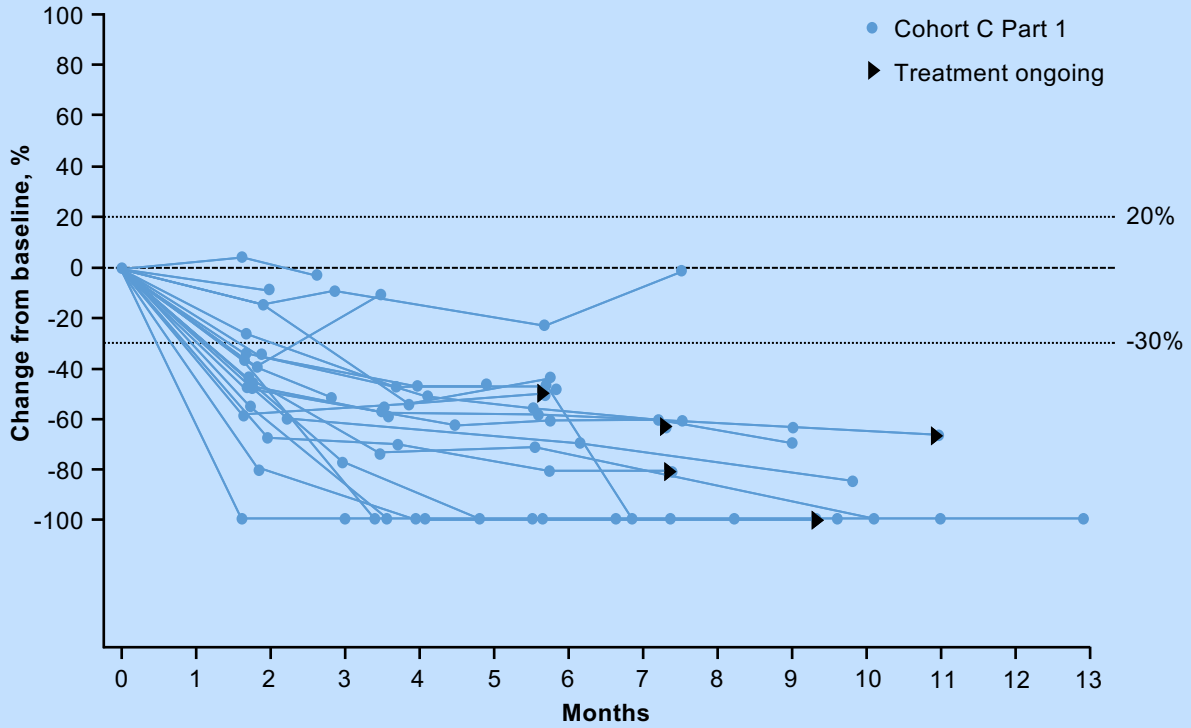
RC48 G001

Best Percent Change in Sum of Diameters From Baseline per BICR



HER2-Positive Group	n=6
Confirmed ORR, n (%)[a]	4 (66.7) [95% CI: 22.3-95.7]
HER2-Low Group	**n=14**
Confirmed ORR, n (%)[a]	11 (78.6) [95% CI: 49.2-95.3]

Percent Change in Sum of Diameters From Baseline Over Time per BICR



Galsky et al, ESMO, 2024

Is there something special about MMAE?

Regimen	Payload	N	Population	HER2	ORR
Enfortumab vedotin + Pembrolizumab	MMAE (tubulin)	43	Cis-ineligible, tx naive	All	64.5%
Disitamab vedotin + Toripalimab	MMAE (tubulin)	39	60% tx naive	All	75%
Trastuzumab deruxtecan + Nivolumab	DXd (Topo I)	26	Progressed despite prior platinum	2+ or 3+	36.7%
Sacitizumab govitecan + Pembrolizumab	SN38 (Topo I)	41	Progressed despite prior platinum	All	41%

O'Donnel et al, JCO 2023; Zhou et al, ESMO, 2024
Hamilton et al, Clin Cancer Res 2024; Grivas et al, JCO 2024

Summary

- EV demonstrates durable single-agent activity in a subset of patients
- While targeting aberrant signaling downstream of HER2 in UC has been met with limited success, HER2-directed ADCs validate HER-2 as an important target in UC
- Practical and scientific questions pose challenges:
  - Should/can we harmonize HER2 assays/scoring in UC?
  - Are EV and DV cross-resistant?
  - Should HER2 ADCs be combined with PD-1/PD-L1 blockade?
  - Should HER2 ADCs be developed solely in HER2 2+ and 3+?
  - Will these drugs ultimately have a role as first-line treatment?

Questions from General Medical Oncologists

- **62 y/o with metastatic bladder cancer s/p EV+pembro followed by cisplatin and gemcitabine with continued progression. What is the next line of management for this patient? How should we select second- and third-line treatment now that EV/pembro has been brought into earlier line treatment?**
- **Do the experts consider rechallenging with EV in later lines after first-line EV/pembro?**
- **Will you consider the EV/pembro combo for patients whose disease progresses while on avelumab maintenance, or is EV monotherapy sufficient?**

Questions from General Medical Oncologists

- Patient in his 70s, ECOG 2, with MIBC. Declined cystectomy and received chemo RT. Declined salvage cystectomy for subsequent recurrent muscle-invasive disease. Started EV/pembro but significant difficulty tolerating. Declined further chemo and now on pembro. What would the investigators treat with after EV/pembro?
- Should relapsed patients be tested a second or third time for development of an actionable mutation? Do you do molecular testing with each progression?
- Can we use archival tissue to assess HER2? Do we need retest HER2 similar to gastric cancer?

RTP
RESEARCH
TO PRACTICE

Questions from General Medical Oncologists

- Where in the treatment sequence would you place T-DXd? Would you sequence two ADCs — like EV immediately followed by T-DXd?
- Does the real-world risk of pneumonitis match the clinical trial data among patients treated with trastuzumab deruxtecan? Are there any concerns regarding increased risk for pneumonitis with recent pembro exposure? How often do you monitor?
- How does disitamab vedotin compare to T-DXd in efficacy and toxicities? How should we sequence this with T-DXd if approved?
- What is the efficacy of disitamab vedotin after using EV? How do the toxicity profiles compare between EV and disitamab vedotin?

Agenda

Module 1: Role of Antibody-Drug Conjugates (ADCs) in Front-Line Therapy for Metastatic Urothelial Bladder Cancer (mUBC) — Dr Friedlander

Module 2: Evidence-Based Use of ADCs for Relapsed/Refractory mUBC — Dr Galsky

Module 3: Evolving Role of Treatment Intensification with Androgen Receptor Pathway Inhibitors for Nonmetastatic and Metastatic Prostate Cancer — Dr Armstrong

Module 4: Optimal Integration of PARP Inhibitors into Therapy for Prostate Cancer — Dr Agarwal

Evolving Role of Treatment Intensification with Androgen Receptor (AR) Pathway Inhibitors for Patients with Nonmetastatic and Metastatic Prostate Cancer

Andrew J Armstrong MD ScM FACP
Neil Love, ASCO GU 2025
Professor of Medicine, Surgery,
Pharmacology and Cancer Biology
Director of Research
Duke Cancer Institute's Center for Prostate and Urologic Cancers

Duke Cancer Institute
Center For Prostate & Urologic Cancers

Major Updates

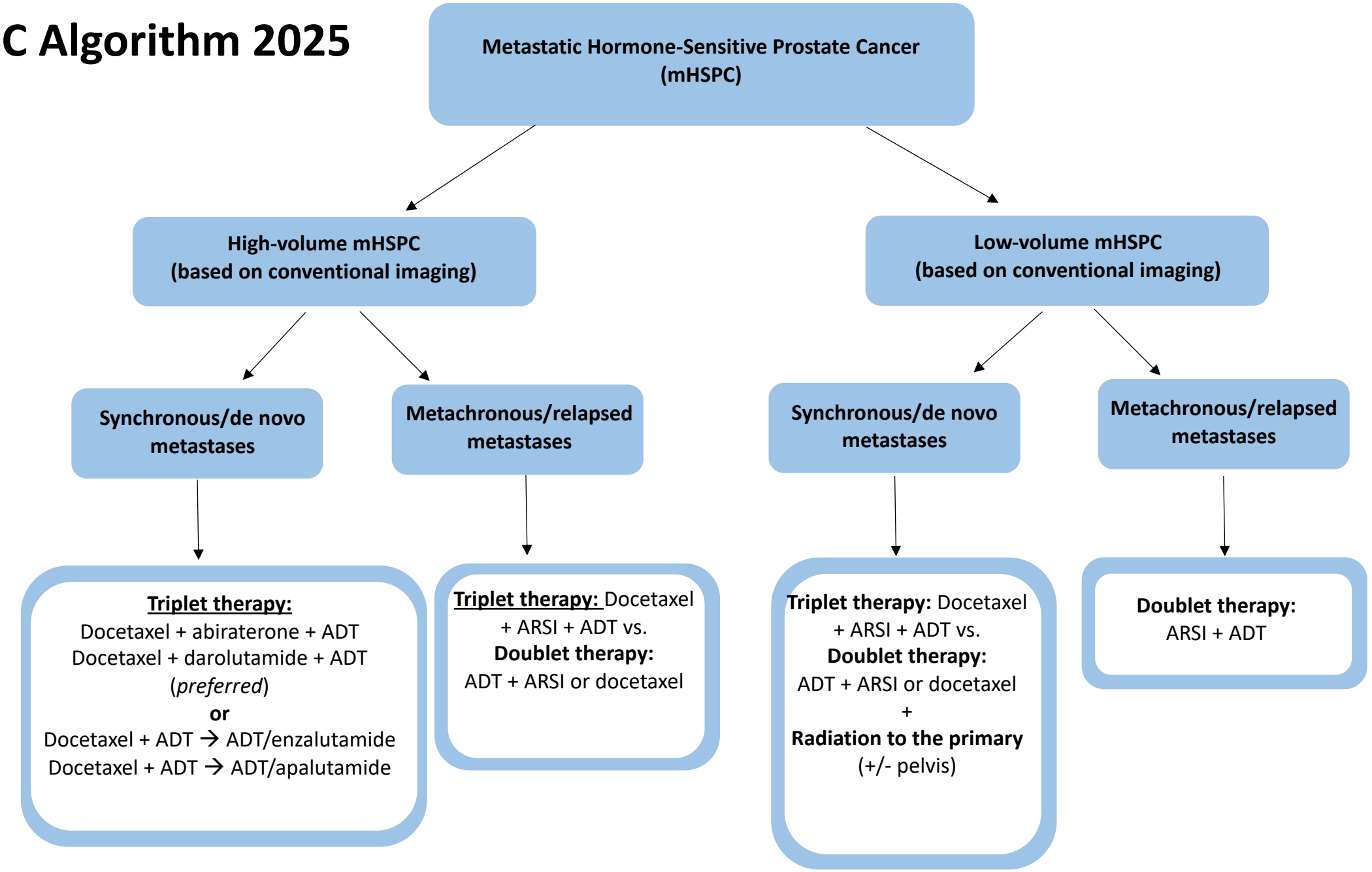
- Major efficacy and safety findings from the Phase III EMBARK trial in nmHSPC
- Extended follow-up data with abiraterone, enzalutamide and apalutamide in combination with ADT for patients with mHSPC
- Published outcomes from the Phase III ARANOTE study evaluating the addition of darolutamide to ADT for patients with mHSPC
- Key efficacy and safety data from the Phase III ARASENS trial evaluating darolutamide in combination with docetaxel and ADT for mHSPC

mHSPC Therapies with Proven Survival Benefit

Therapy	Prior Docetaxel	Comparator	FFS/PFS benefit, HR, p-value	OS benefit, HR; p-value
Radiation to the Primary	No	No radiation, ADT alone +/- docetaxel	Yes: low volume HR 0.59 p<0.0001	Yes: low volume HR 0.68 p=0.007
Enzalutamide ARCHES ENZAMET	 18% 44-45%	 Placebo/ADT ADT/Bicalutamide	 Yes HR 0.39 p<0.0001 Yes HR 0.39 p<0.0001	 Yes HR 0.66 p<0.0001 all volumes Yes HR 0.67 p=0.002 all volumes
Docetaxel/prednisone: STAMPEDE	No	ADT	Yes HR 0.61 p<0.0001	Yes HR 0.76 p=0.005 all volumes
Docetaxel: CHAARTED	No	ADT	Yes HR 0.61 p<0.0001	Yes HR 0.63 p<0.001 high volume HR 1.04 low volume
Docetaxel/Abiraterone	Yes	Docetaxel/ADT	Yes HR 0.47-0.58 p=0.006, <0.0001	Yes HR 0.72 p=0.019 high volume de novo
Apalutamide	11%	Placebo/ADT	Yes HR 0.48 p<0.001	Yes HR 0.67 p=0.0053 all volumes
Abiraterone/Prednisone LATITUDE	No	Prednisone	Yes HR 0.47 p<0.0001	Yes HR 0.66 p<0.001 high risk
Abiraterone/Prednisone STAMPEDE	No	Prednisone	Yes HR 0.31 p<0.0001	Yes HR 0.61 p<0.001 all risk/volumes
Abiraterone/prednisone (PEACE-1)	100% (concurrent)	**ADT/Docetaxel**	Yes HR 0.50 p<0.0001	Yes HR 0.75 p=0.017; HV: HR 0.72 p=0.019
Darolutamide	100% (concurrent)	Placebo/ADT/ Docetaxel	Yes CRPC HR 0.35 p<0.0001	Yes HR 0.675 p<0.0001 de novo 86%

Parker et al Lancet 2018; Armstrong et al JCO 2019 and ESMO/JCO 2021; Davis et al NEJM 2019; James N et al Lancet 2015; Sweeney et al NEJM 2015; Chi KN et al NEJM 2019; Fizazi K et al NEJM 2017; James et al NEJM 2017; Smith MR et al NEJM 2022; Fizazi K et al Lancet 2022

mHSPC Algorithm 2025



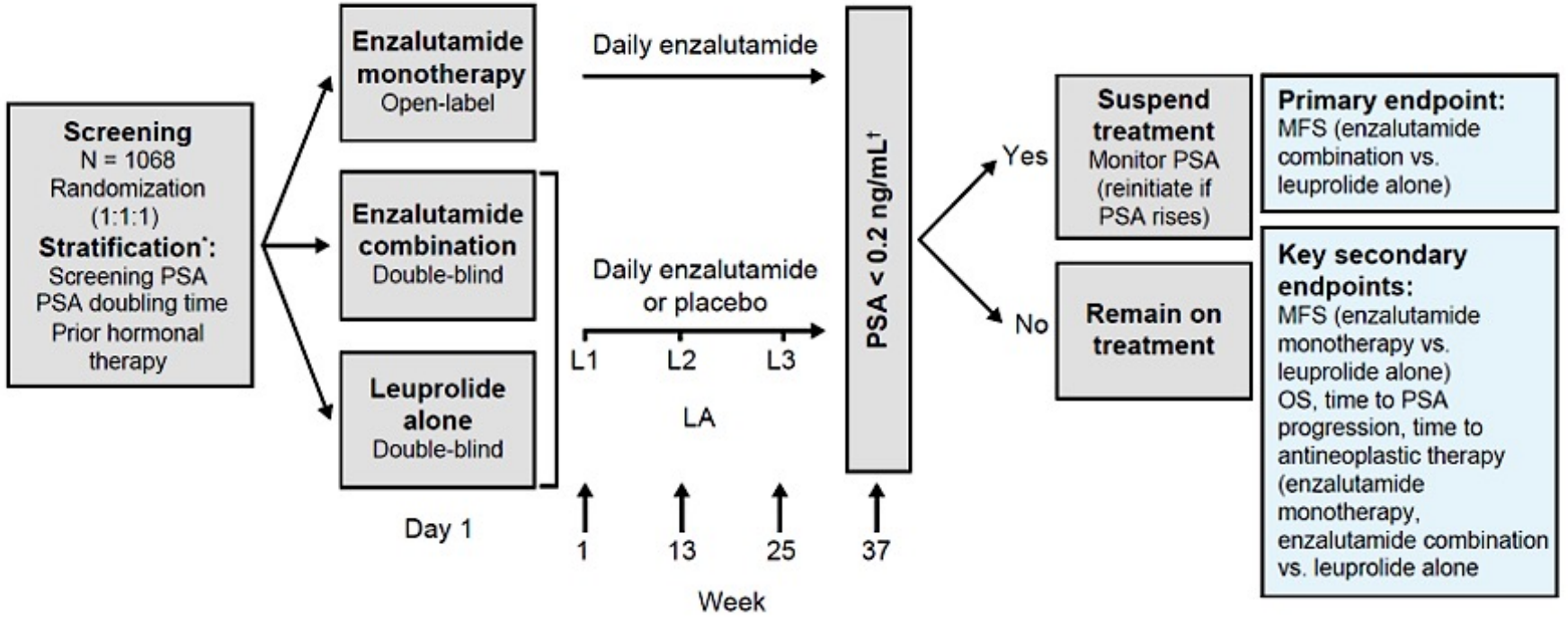
McManus and Armstrong, JCO 2023

Biochemically recurrent prostate cancer: EMBARK

High-risk PSA recurrence:

PSADT<9 mo

No PSMA PET imaging, but N0 M0 on CT/MRI/BS



*Stratification by screening PSA (≤10 ng per milliliter vs. >10 ng per milliliter), PSA doubling time (≤3 months vs. >3 to ≤9 months), and prior hormonal therapy (yes vs. no).

†Study treatment was suspended once if the PSA was less than 0.2 ng per milliliter at week 36 and restarted when PSA was greater than or equal to 5.0 ng per milliliter for those without prior radical prostatectomy and greater than or equal to 2 ng per milliliter for those with prior radical prostatectomy.

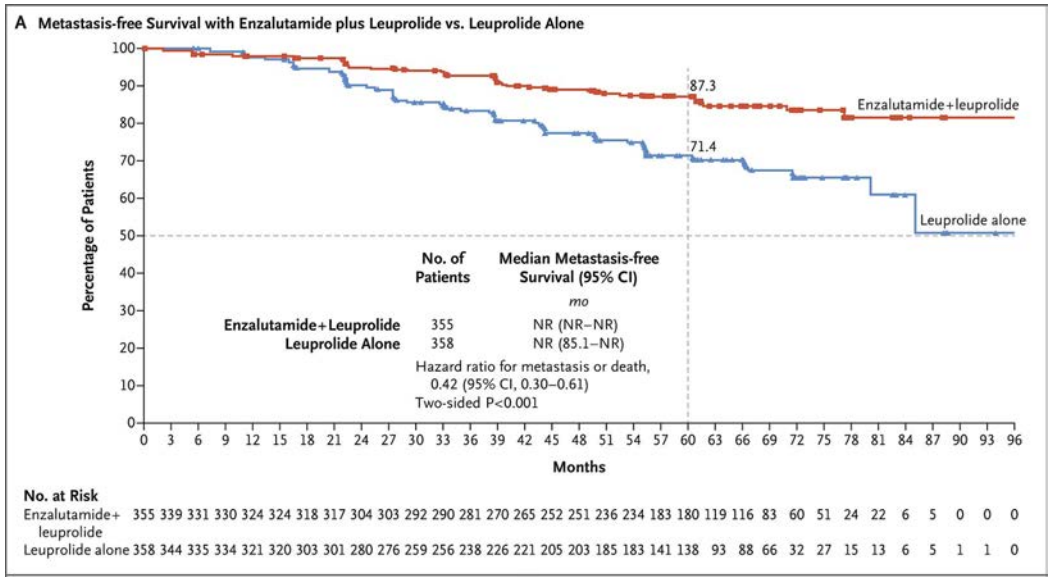
Freedland SJ, de Almeida Luz M, De Giorgi U, et al. *N Engl J Med*. 2023;389(16):1453-1465.

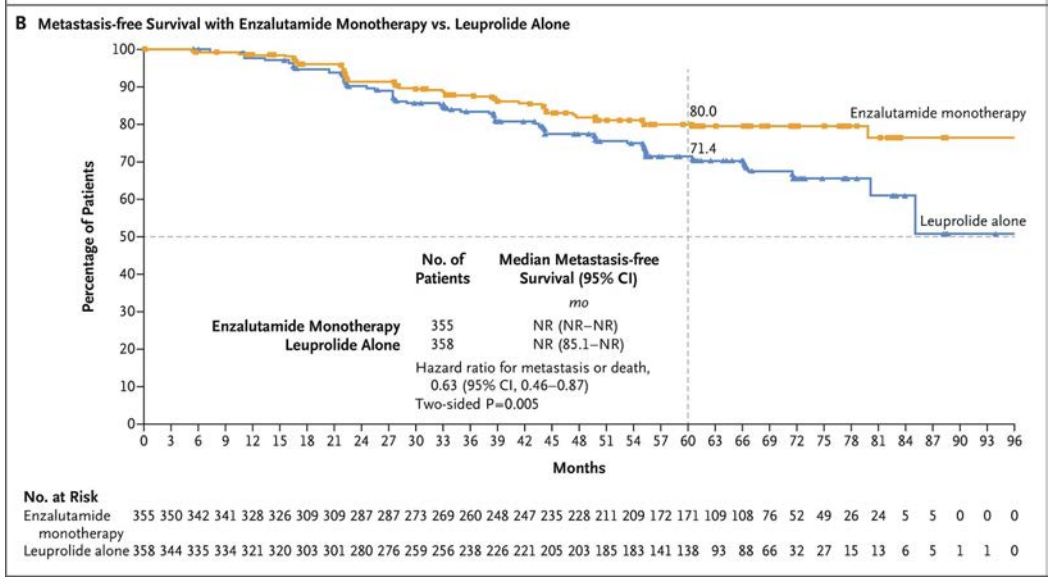
Biochemically recurrent prostate cancer: EMBARK

87 v 71% MFS at 5 years

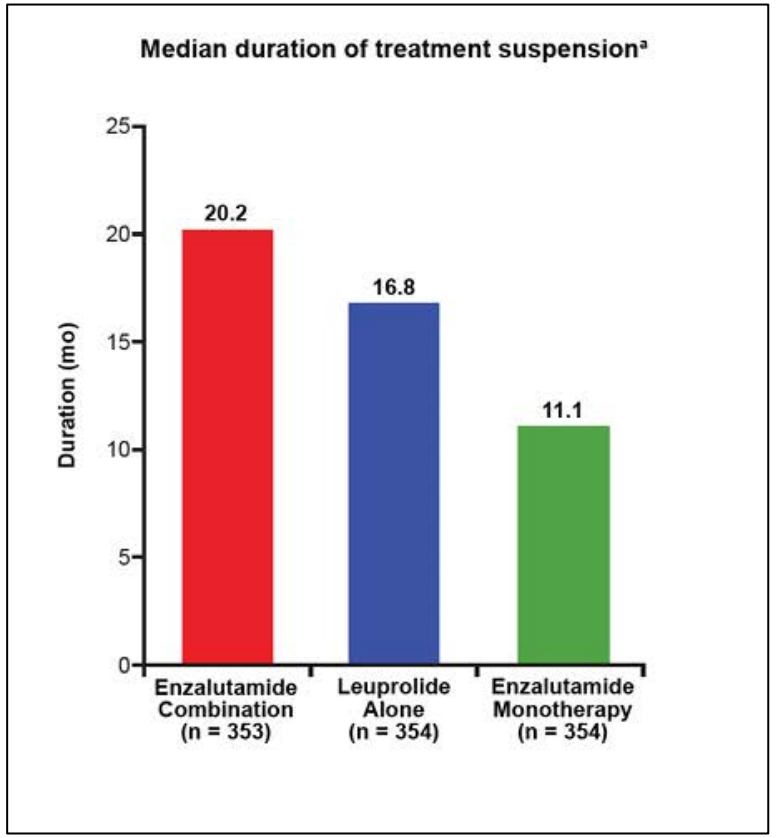
If PSA undetectable (<0.2 ng/mL) at week 36, treatment was held – resumed when PSA >5 (RT) or >2 (surgery)

80 v 71% MFS at 5 years





ADT alone – 50% without metastasis at 8 years



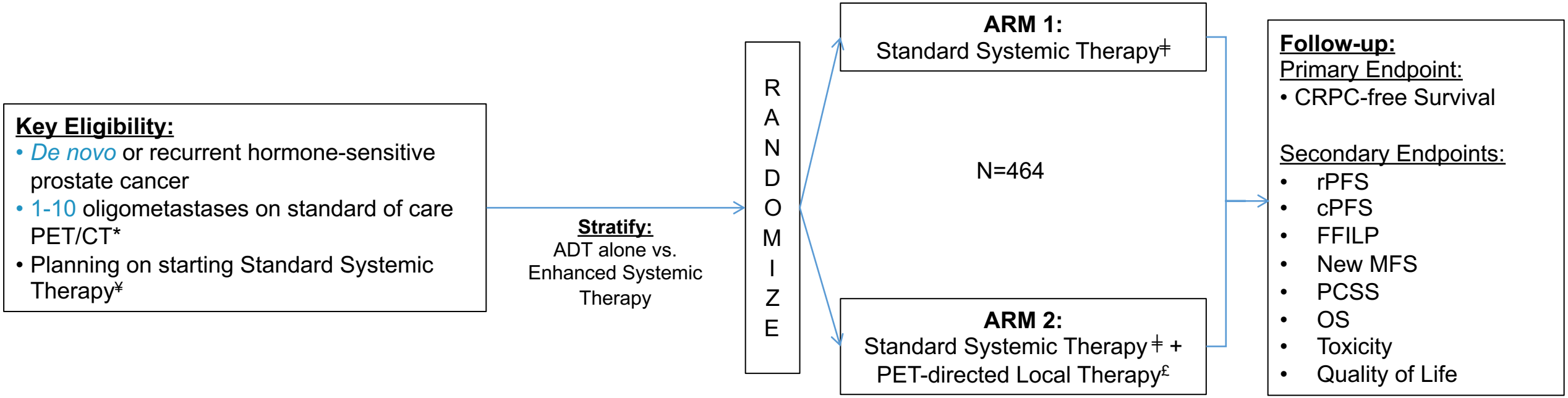
Freedland SJ, de Almeida Luz M, De Giorgi U, et al. *N Engl J Med*. 2023;389(16):1453-1465.

Challenging Questions

- **How do we handle PSMA PET + but conventional imaging negative mHSPC?**
  - 80% of EMBARK patients would be PSMA PET N1/M1 (40% M1, 19-36% polymetastatic)*
  - Treat as M1 (ARCHES, TITAN, LATITUDE/STAMPEDE, ARANOTE) or treat as M0 (EMBARK, MDT)?
  - OR, treat as M1.5 and consider both approaches (short duration of therapy, treatment holidays, MDT)
- **Which patients require ADT/ARPI doublet vs triplet therapy vs ADT monotherapy or MDT alone? And which ARPI?**
  - Disease volume, synchronous vs metachronous disease, number of mets on PSMA PET/CT imaging, patient preferences, comorbidities, frailty, drug-drug interactions
  - How to handle oligoprogressive disease, oligo-mCRPC?
- **Optimal candidates for prostate RT in the setting of mHSPC**
  - Disease volume based on CT, BS NOT PSMA PET from STAMPEDE. I do not recommend withholding life-prolonging prostate RT in such low volume patients by conventional imaging until new data is available using PSMA PET to define disease volume and RT benefit
  - What about the palliative benefits in high volume patients? PEACE-1 may provide support for this.

*Holzgreve A et al JAMA NO 2025

VA STARPORT Study Schema



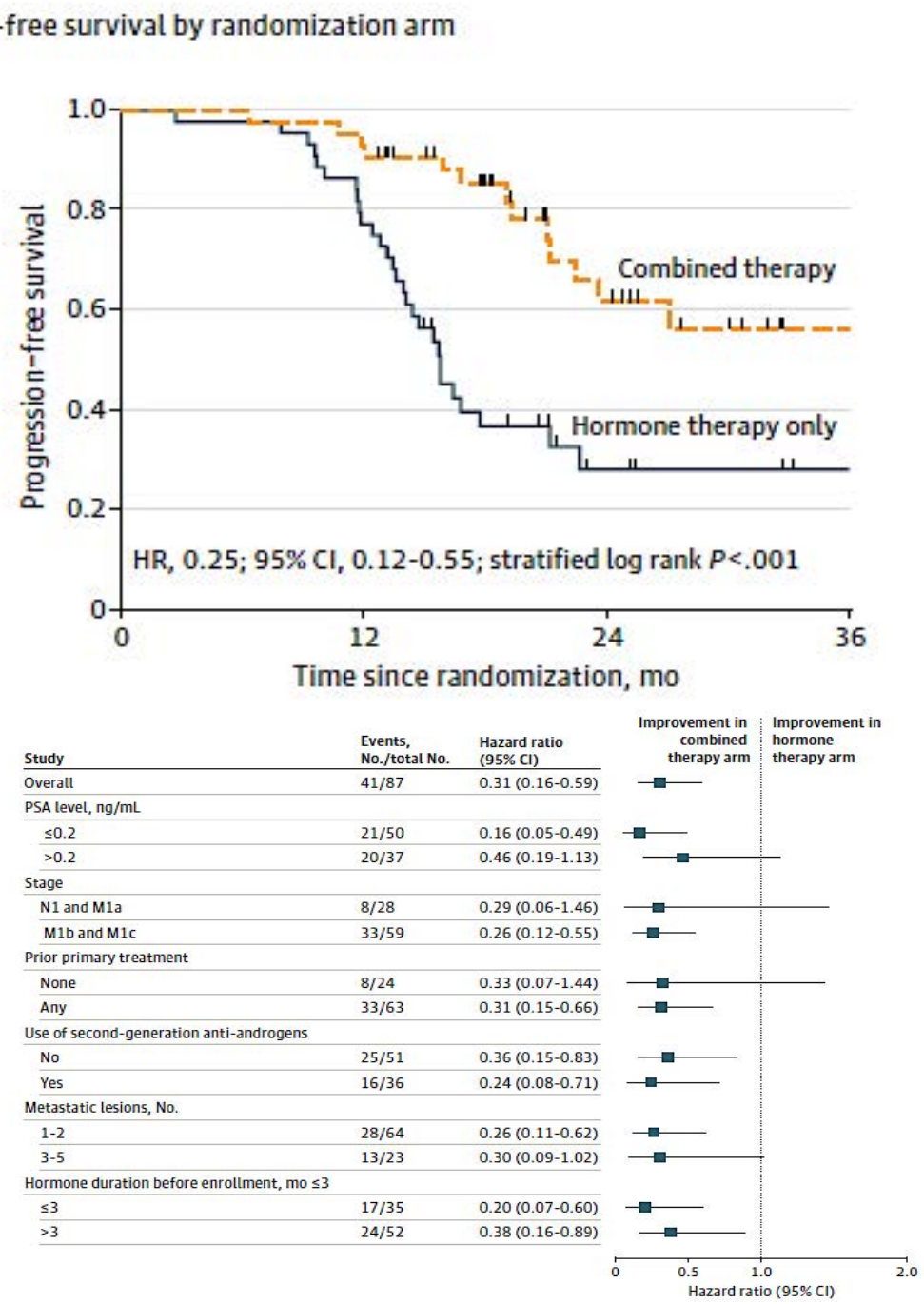
Study goals:

- Does addition of MDT to systemic therapy affect outcomes? (CRPC-free survival)
- All mets up to 10 to be treated
- PSMA-PET detected metastases only

PI Abhi Solanki, Hines VA

EXTEND Study

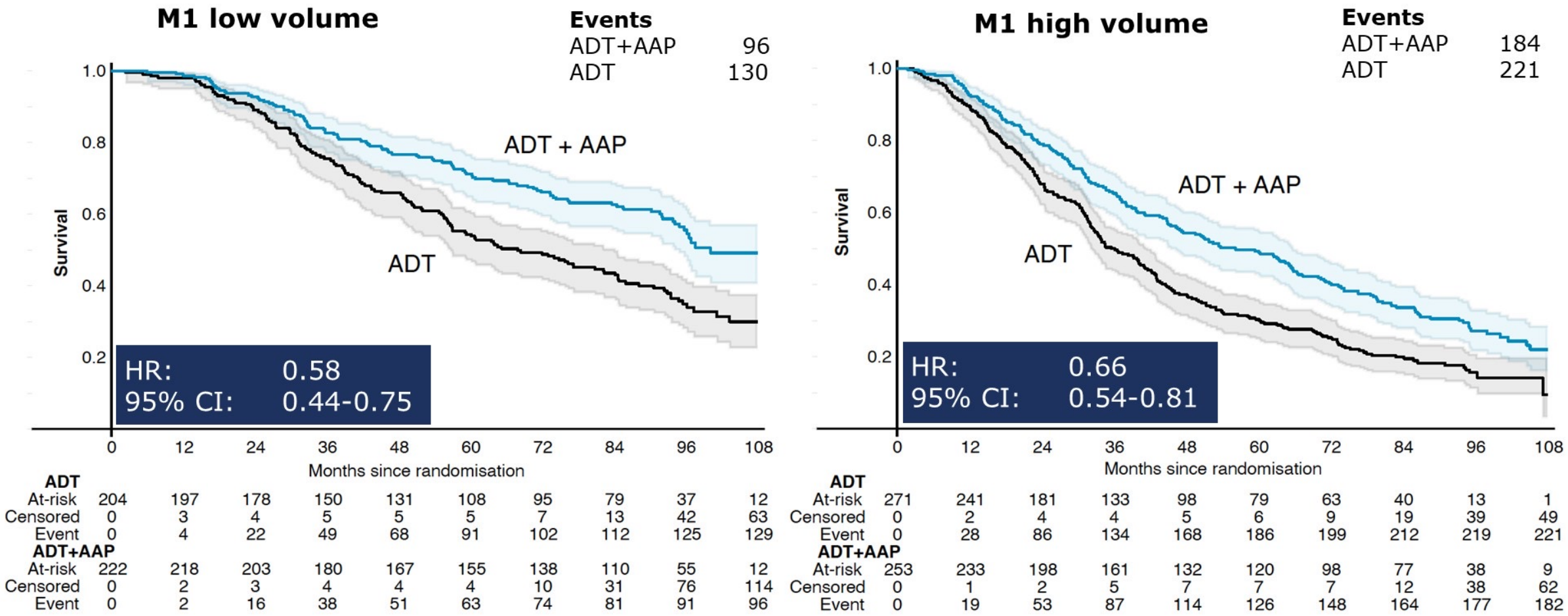
- Phase 2 trial of men with mHSPC, randomized 1:1 to MDT or ADT alone, with a planned break after 6 mo of therapy (intermittent ADT) n=87 2-18-2020
- Up to 5 sites (typically 1-2) including prostate identified by CT, BS, or fluciclovine PET (25%)
- All sites targeted
- No potent AR inhibition given in about 60% of patients
- Primary endpoint PFS improvement includes imaging, PSA, clinical progression or death
- No survival data available, most data is based on PSA endpoints
- No QOL differences noted



Tang C et al JAMA Oncol 2023

Updates: Abiraterone, Enzalutamide, Apalutamide

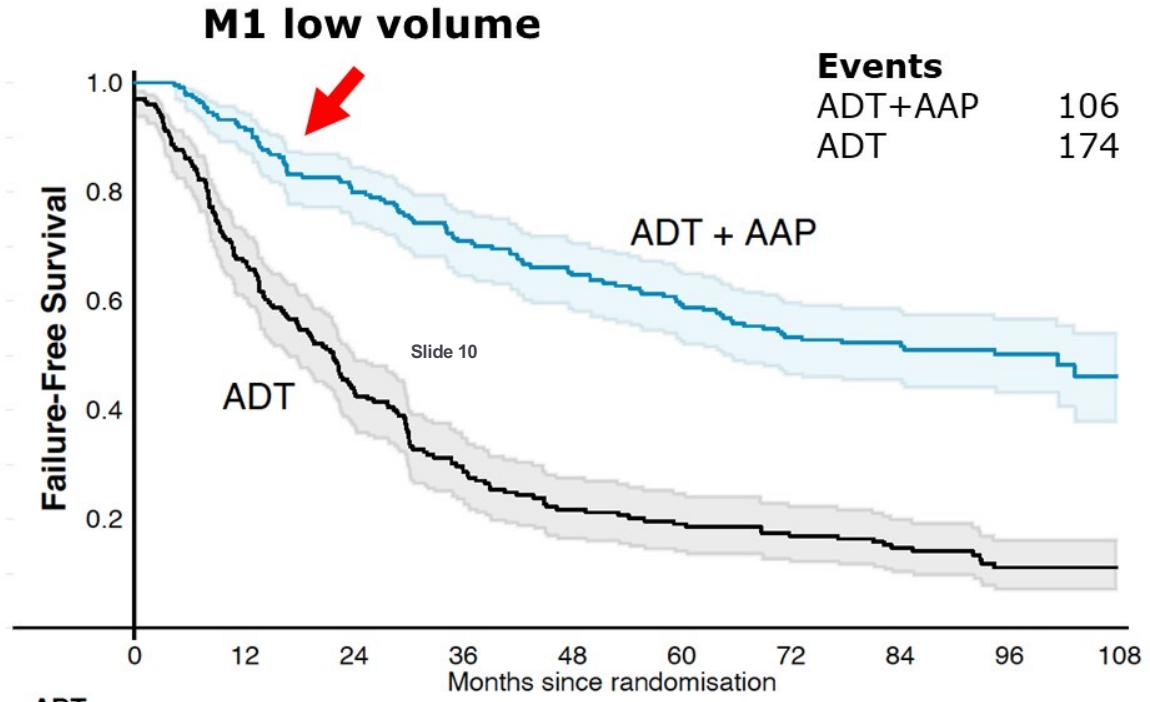
M1 split by met volume, overall survival



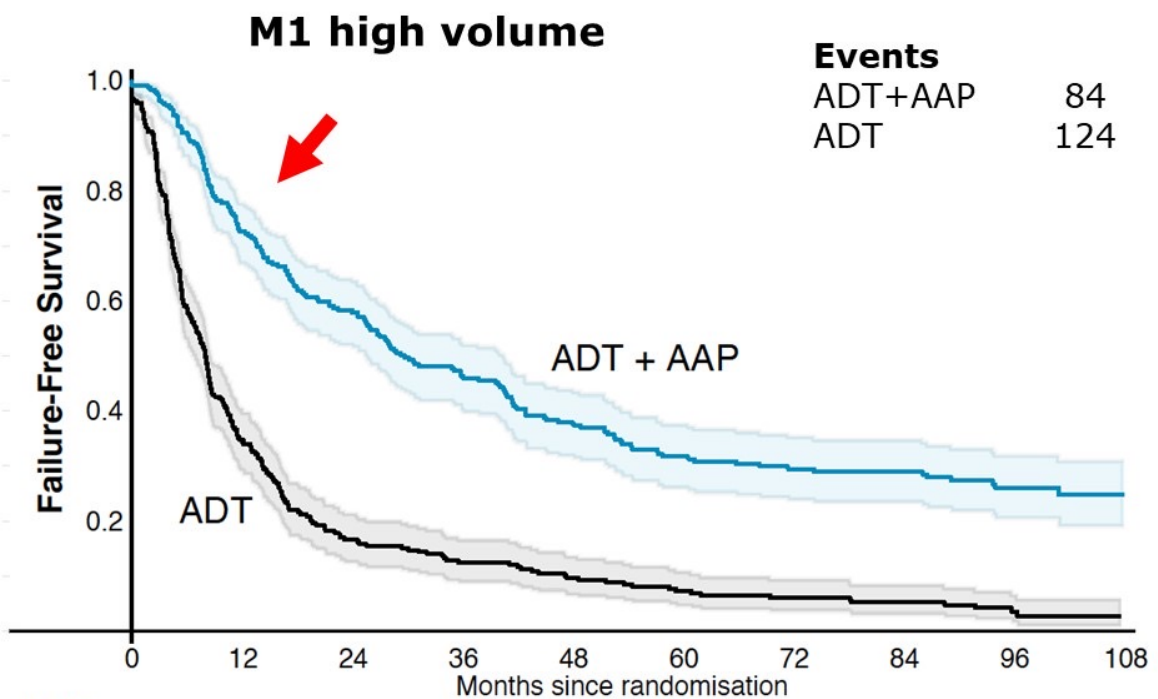
Median follow-up: 96 months (IQR: 86-107)

Met volume defined on scans retrieved after completion of randomization, using "CHAARTED" criteria
AAP, abiraterone acetate + prednisolone; ENZ, enzalutamide, Kaplan-Meier estimates with 95% CI in lighter shade

Treatment intensification + ADT + ARSI



ADT										
At-risk	204	134	87	56	41	35	31	25	13	7
Censored	0	4	5	8	8	9	9	11	18	24
Event	0	66	112	140	155	160	164	168	173	173
ADT+AAP										
At-risk	222	202	172	149	134	120	104	85	40	7
Censored	0	2	6	10	13	15	19	36	78	109
Event	0	18	44	63	75	87	99	101	104	106



ADT										
At-risk	271	93	44	32	25	18	15	12	4	0
Censored	0	3	4	5	5	6	6	7	12	15
Event	0	175	223	234	241	247	250	252	255	256
ADT+AAP										
At-risk	253	183	144	110	88	71	64	55	28	7
Censored	0	1	4	9	11	14	16	24	46	66
Event	0	69	105	134	154	168	173	174	179	180

Failure-free-survival = biochemical failure, local progression, distant metastases, or death from prostate cancer

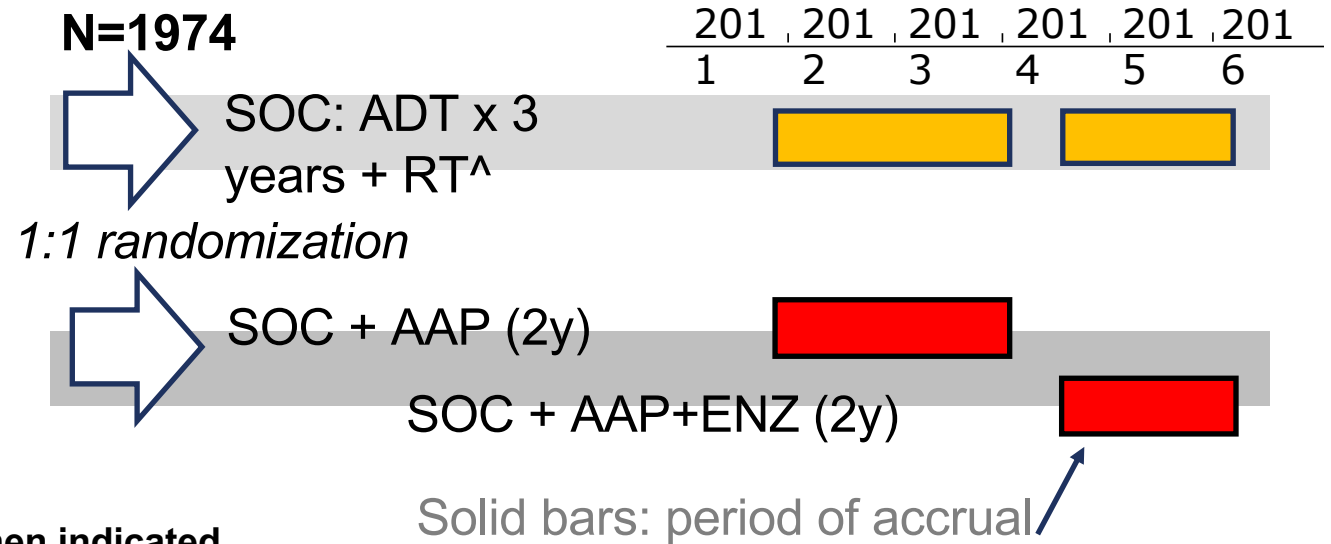
Kaplan-Meier estimates with 95% CI in lighter shade

Examples of Phase III trials targeting poor prognostic groups that are recruiting/planned:
BRCA2^{-}/DRD: AMPLITUDE (NCT03748641), TALAPRO-3 (NCT04821622), STAMPEDE; PTEN loss: CAPItello-281 (NCT04493853)

STAMPEDE Update: M0 disease

M0 pts in AAP comparison: continued FU with no further efficacy inspections

2019: amended the reporting plan to split M1 and M0, power the primary endpoint on MFS, meta-analyse with new data from AAP + ENZ comparison



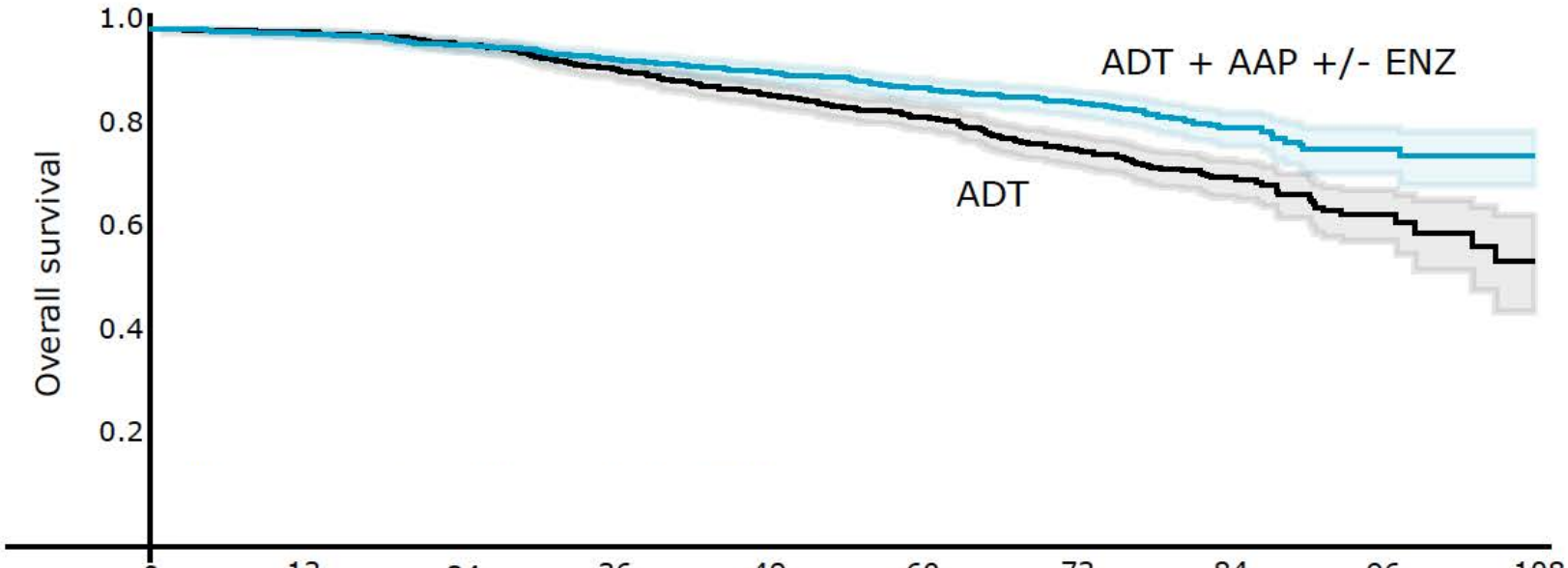
- No overlapping controls
- Same protocol and eligibility criteria
- 2 years AAP+/-ENZ
- No evidence of OS benefit with AAP+/-ENZ in mCRPC

^ When indicated

ESMO = European Society for Medical Oncology; FU = fluorouracil.

Attard G, et al. *Eur Urol.* 2021;80(4):522-523. Jayaram AK, et al. *Ann Oncol*. 2019;30(7 Suppl):vii3-vii4. Morris MJ, et al. *J Clin Oncol.* 2019;37(15 Suppl):5008.

Overall Survival



Events
147 ADT+AAP +/- ENZ
236 ADT

HR: 0.60
95% CI 0.48 to 0.73
P value 9.3×10^{-7}

6-year survival improved from 77% to 86%

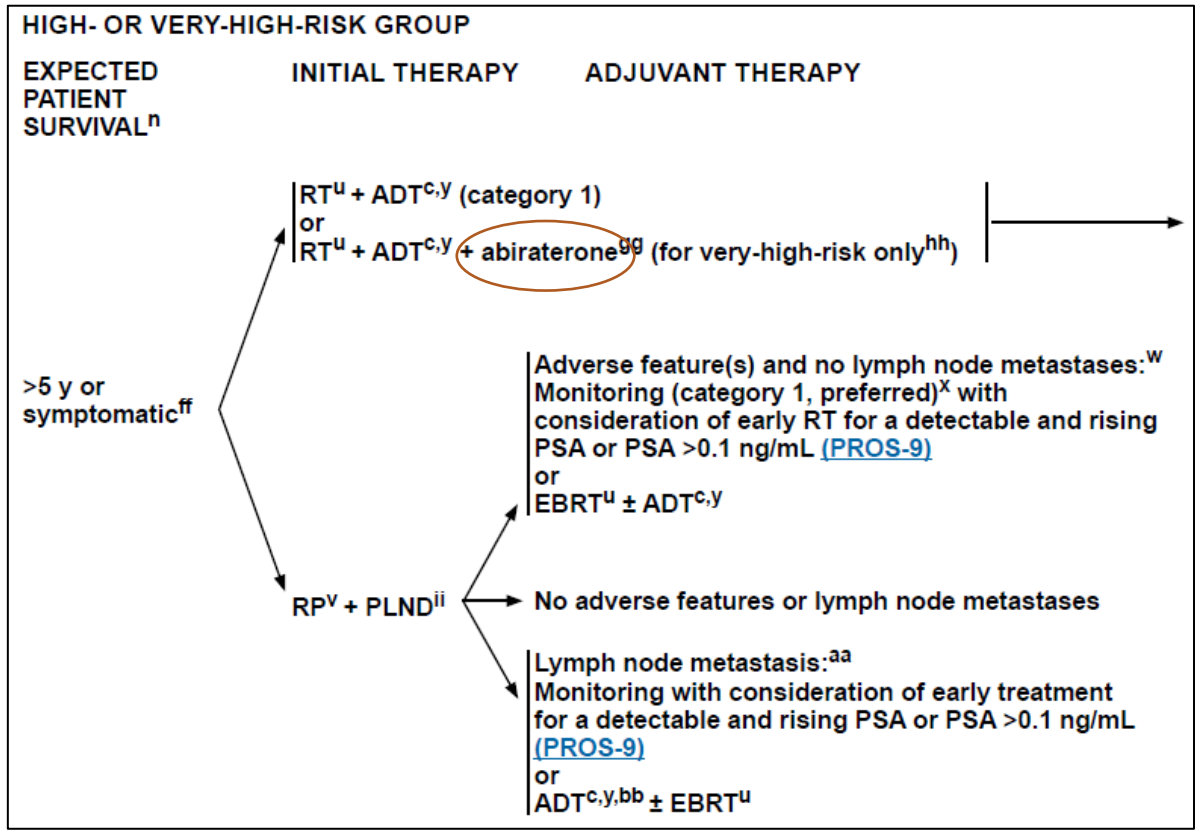
SOC										
At-risk	988	974	947	901	837	610	368	200	63	10
Censored	0	8	11	14	28	216	421	568	693	742
Event	0	6	30	73	123	162	199	220	232	236
SOC+AAP+/-ENZ										
At-risk	986	956	928	899	861	645	386	205	74	16
Censored	0	21	29	32	46	234	477	641	766	823
Event	0	9	29	55	79	107	123	140	146	147

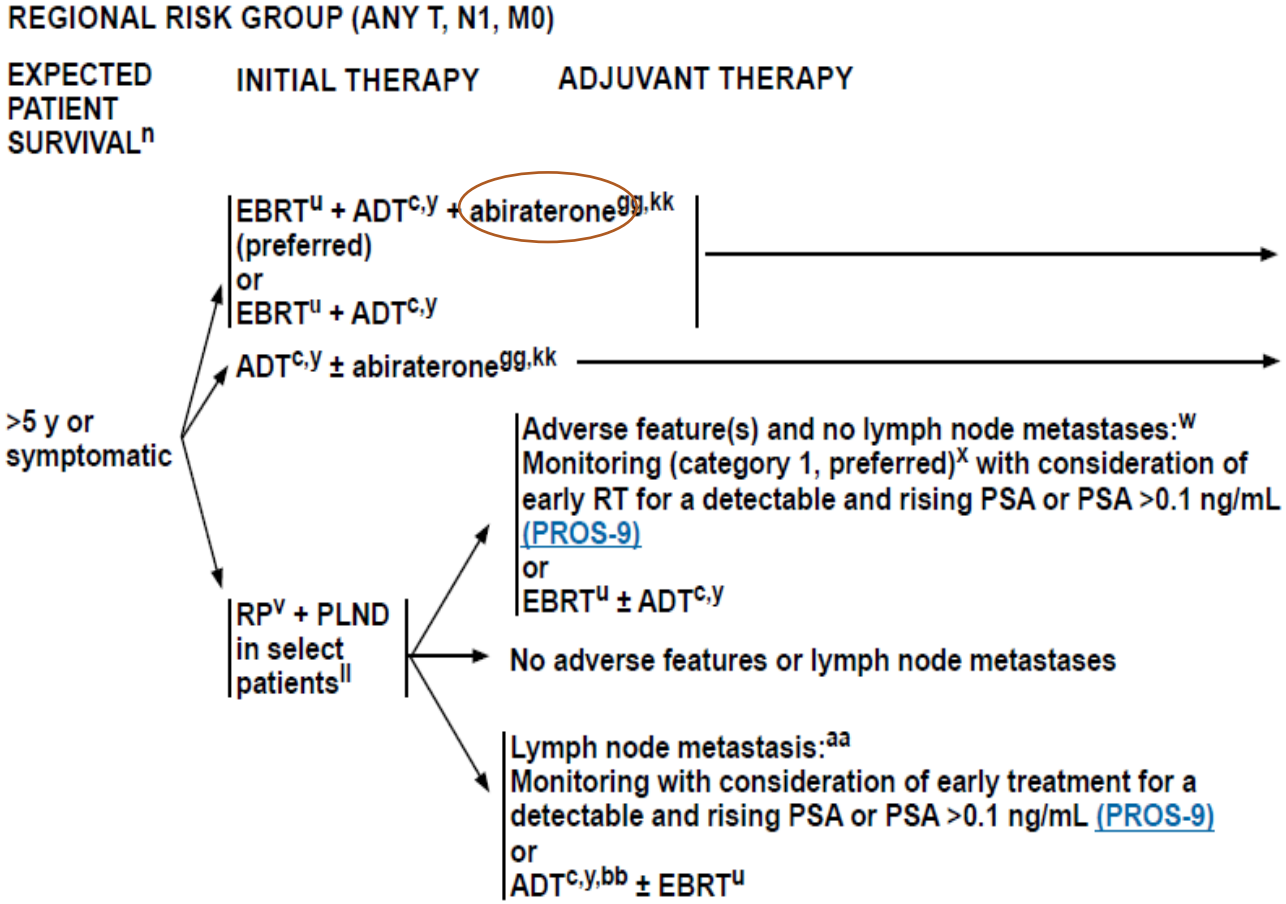
Kaplan-Meier estimates with 95% CI in lighter shade

Non-proportional hazards *P*=0.1

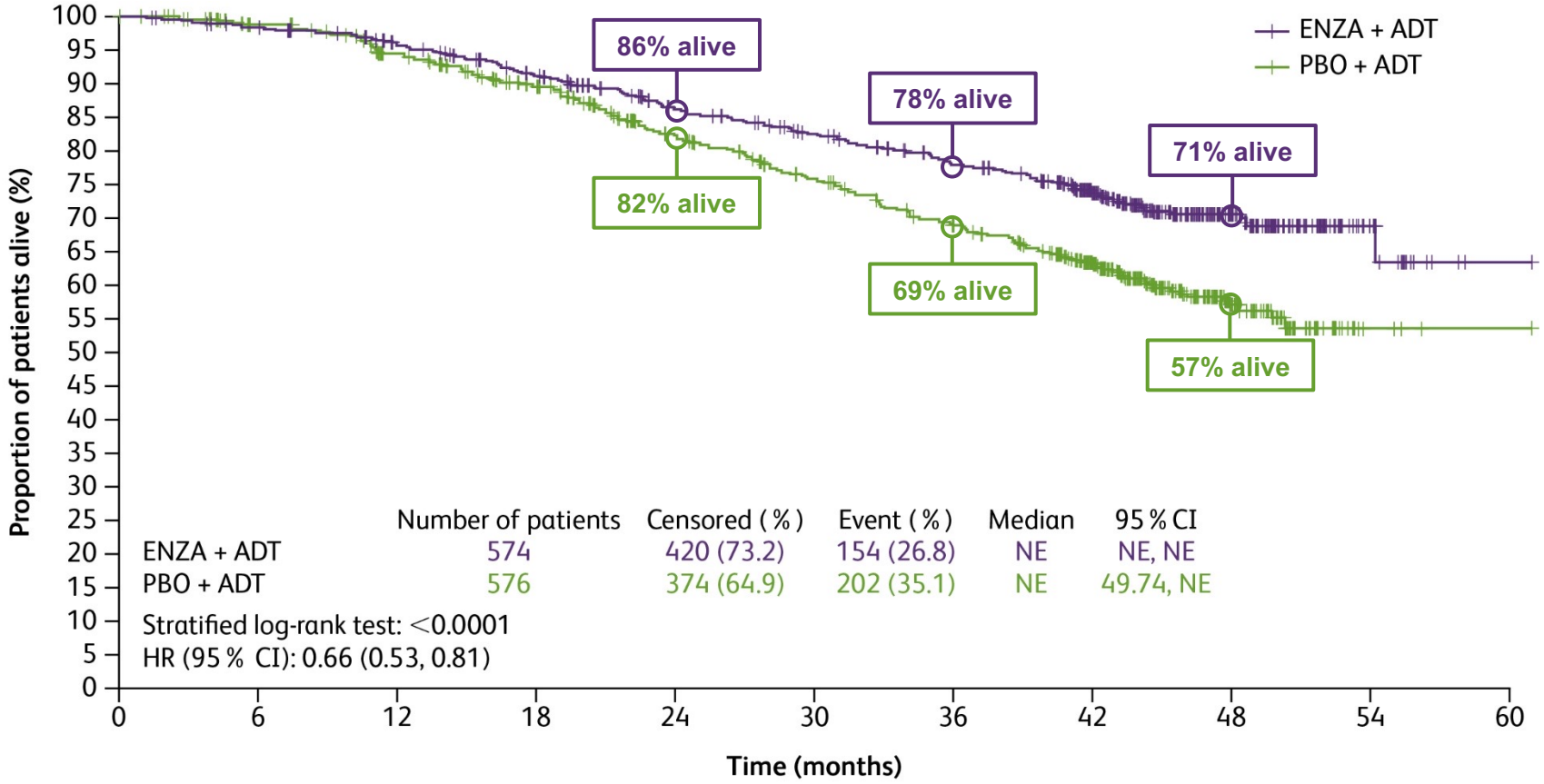
Jayaram AK, et al. *Ann Oncol*. 2019;30(7 Suppl):vii3-vii4. Attard et al Lancet 2021

NCCN Guidelines: High risk disease





Overall survival with Enzalutamide (ARCHES)



Patients at risk											
ENZA + ADT	574	559	535	498	457	427	396	316	120	17	1
PBO + ADT	576	548	511	468	404	363	322	232	80	4	1

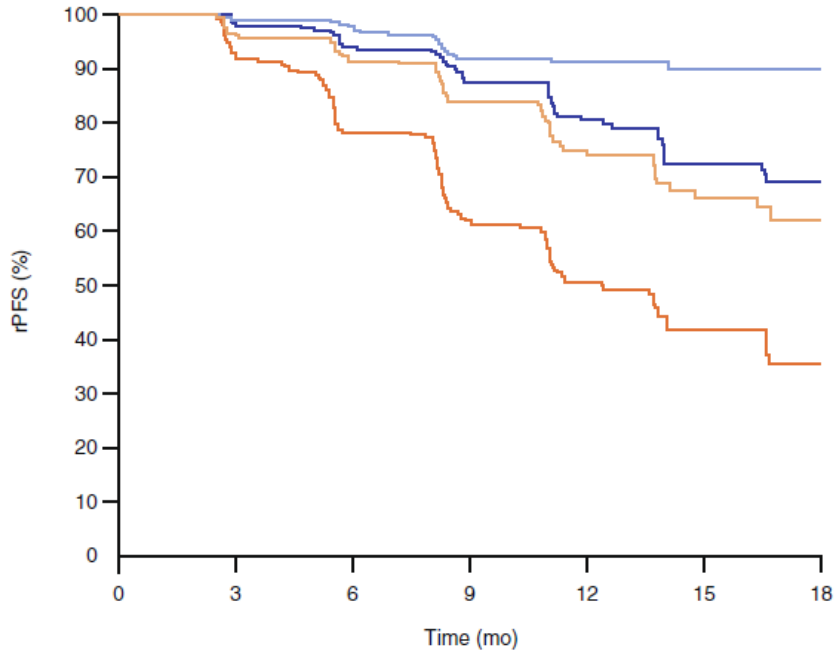
- **As of May 28, 2021: 356 deaths (enzalutamide plus ADT, 154; placebo plus ADT, 202) were observed**
- **Median follow-up time: 44.6 mo**
- **Median treatment duration:**
  - **Enzalutamide plus ADT: 40.2 mo**
  - **Placebo plus ADT: 13.8 mo**
  - **Placebo plus ADT crossover: 23.9 mo**

Armstrong AJ et al JCO 2022

ADT=androgen deprivation therapy; CI=confidence interval; ENZA=enzalutamide; HR=hazard ratio; ITT=intent-to-treat; NE=not evaluable; PBO=placebo.

- **Enzalutamide plus ADT significantly improved overall survival by 34% vs placebo plus ADT**

ARCHES Oligometastatic Analysis

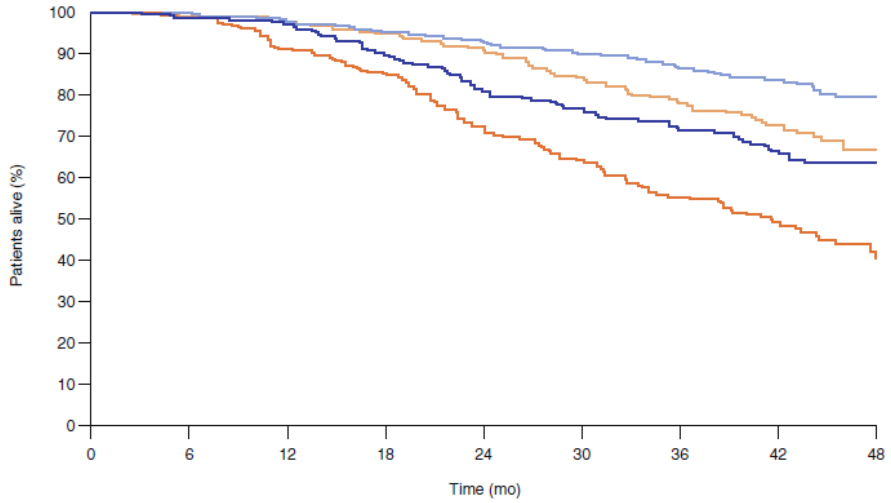


Patients with ≤5 metastases

	ENZA + ADT (n = 244)	PBO + ADT (n = 221)
Median, mo (95% CI)	NR (NE–NE)	NR (19.02–NE)
HR (95% CI)	0.27 (0.16–0.46)	

Patients with ≥6 metastases

	ENZA + ADT (n = 220)	PBO + ADT (n = 242)
Median, mo (95% CI)	NR (NE–NE)	12.45 (11.04–14.06)
HR (95% CI)	0.33 (0.23–0.46)	

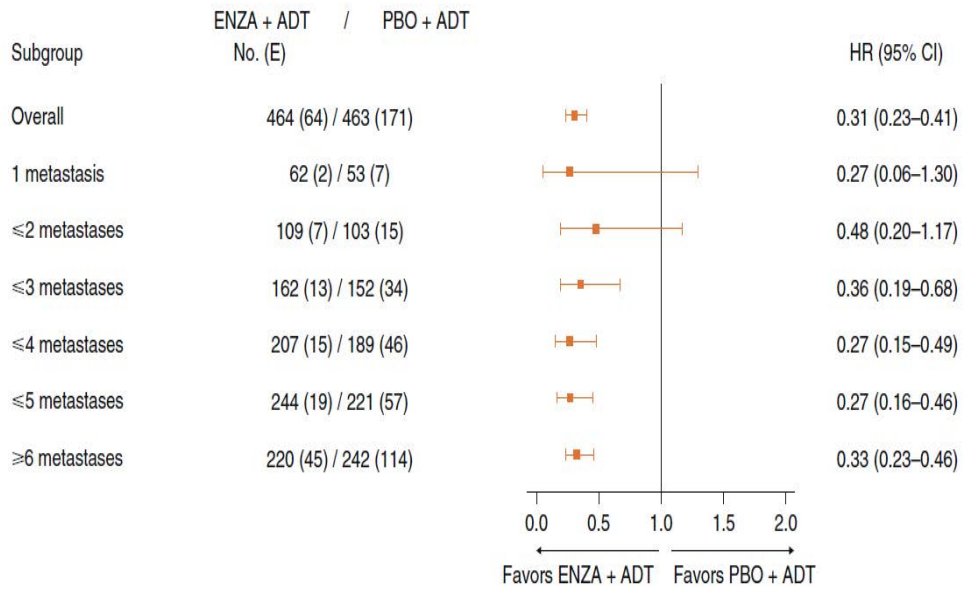


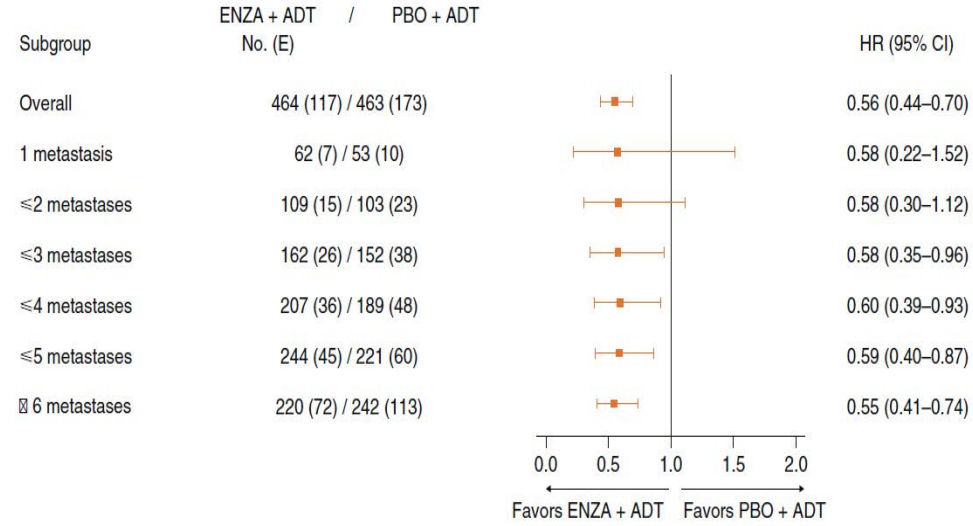
Patients with ≤5 metastases

	ENZA + ADT (n = 244)	PBO + ADT (n = 221)
Median, mo (95% CI)	NR (NE–NE)	NR (NE–NE)
HR (95% CI)	0.59 (0.40–0.87)	

Patients with ≥6 metastases

	ENZA + ADT (n = 220)	PBO + ADT (n = 242)
Median, mo (95% CI)	NR (NE–NE)	41.56 (34.07–47.70)
HR (95% CI)	0.55 (0.41–0.74)	





Armstrong et al Eur Urol 2023

Assessing risk: PSA decline

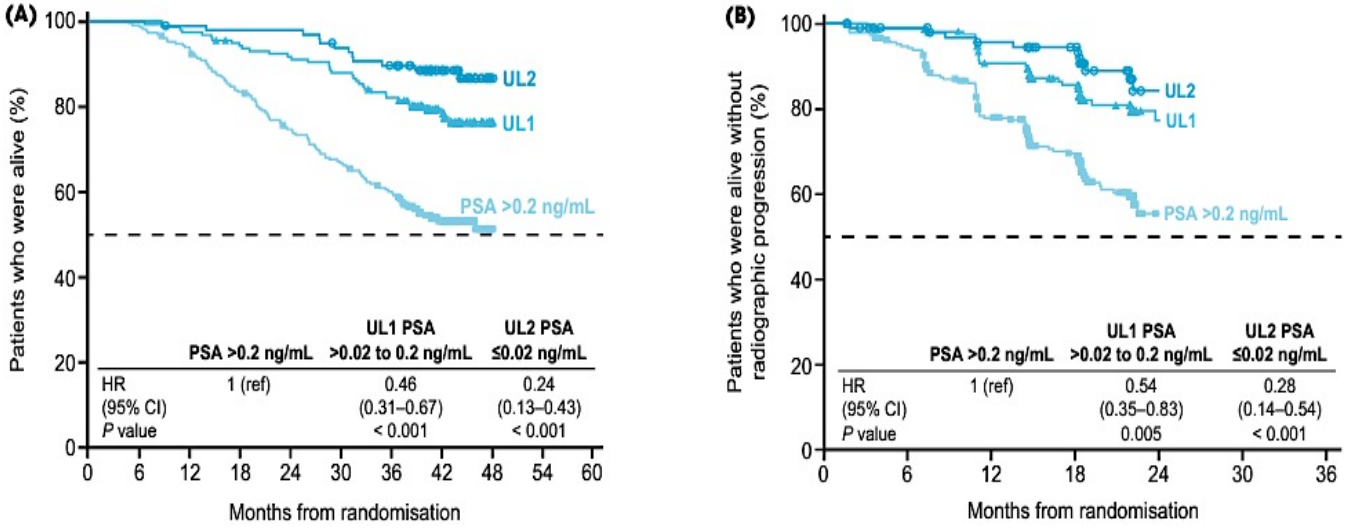
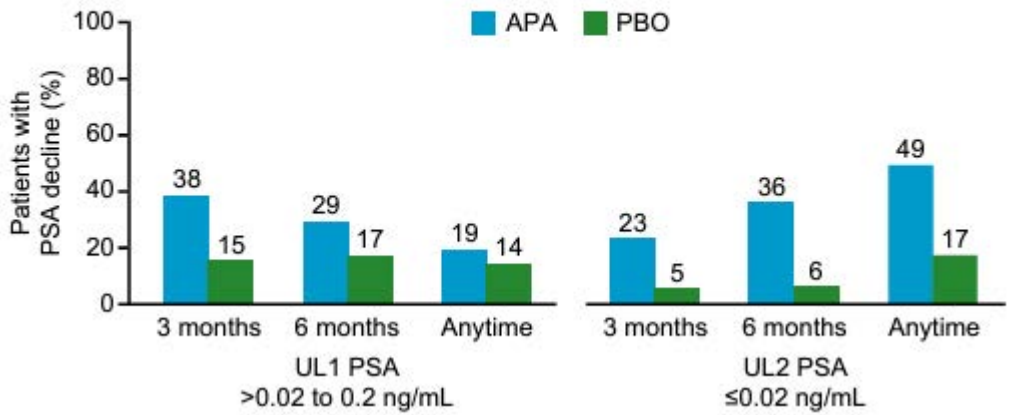
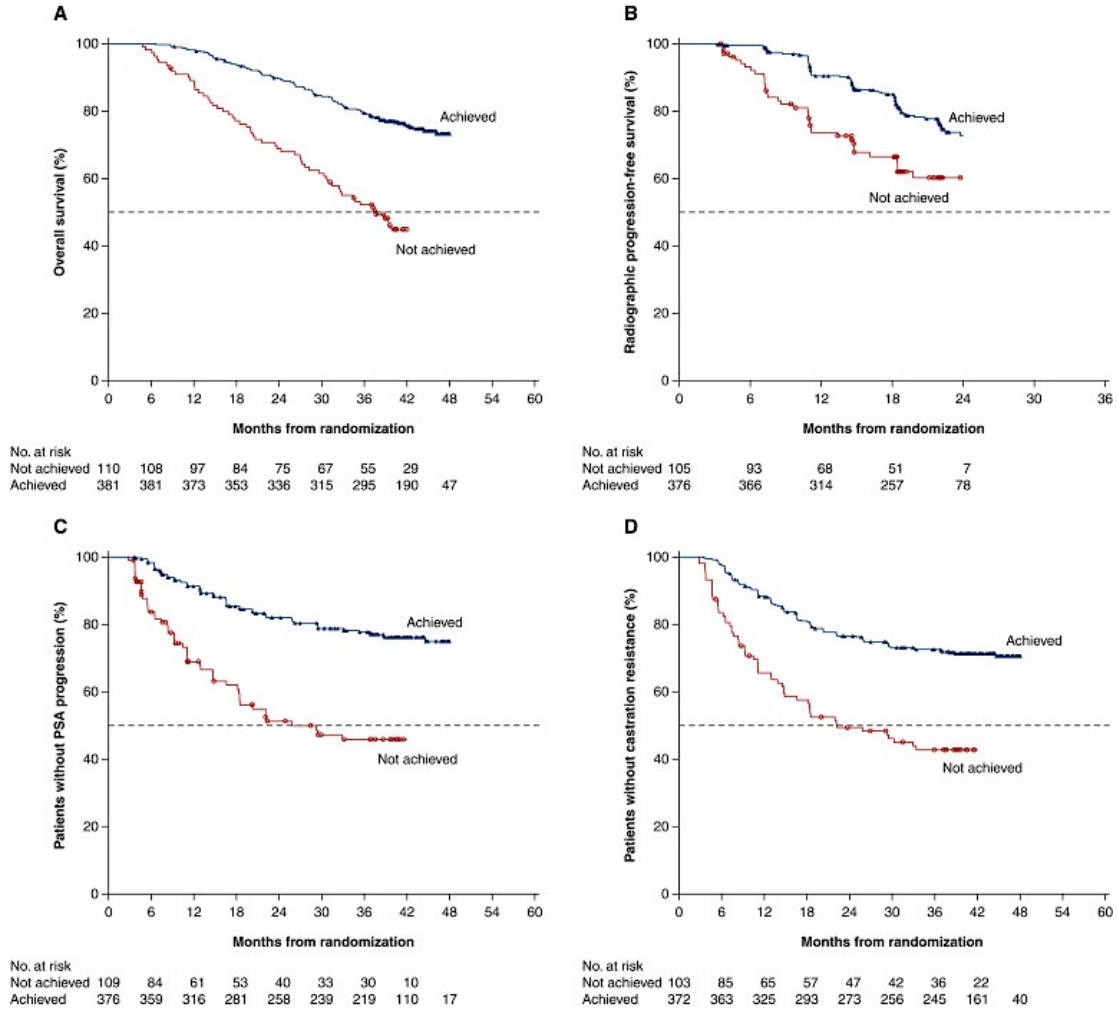


Fig. 1 The PSA decline to UL1 (>0.02 to 0.2 ng/mL) and UL2 (≤0.02 ng/mL) levels over time. APA, apalutamide; PBO, placebo.

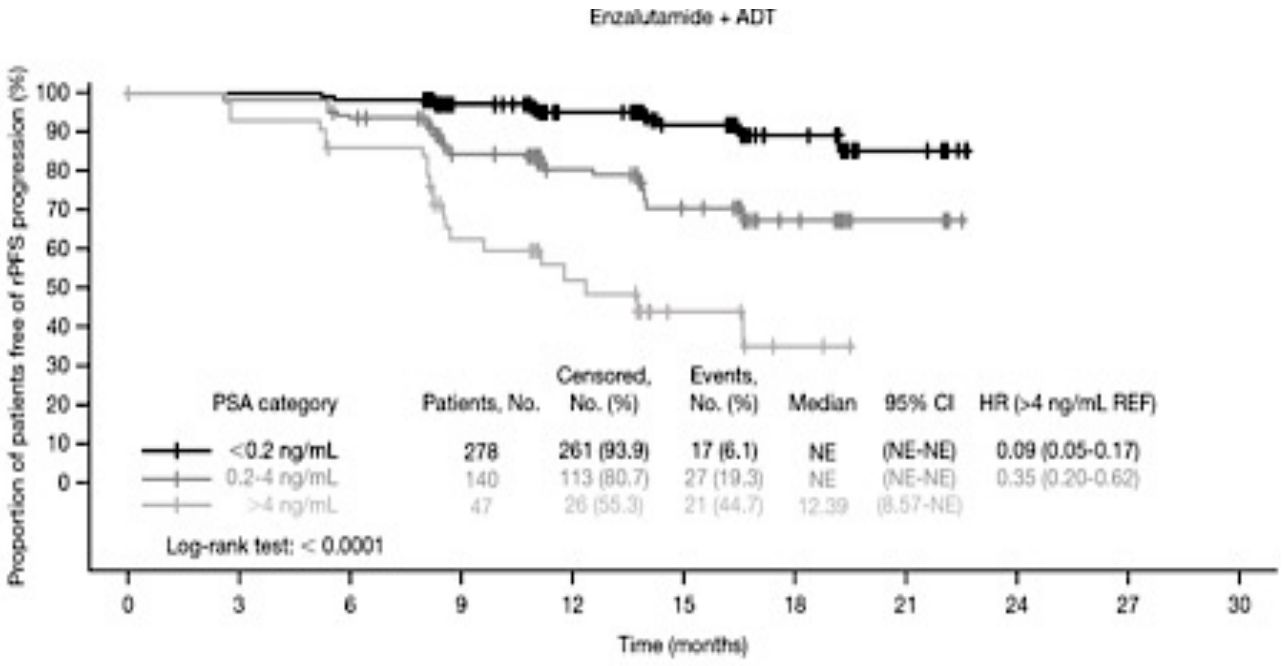


Merseburger AS et al BJUI Int 2024

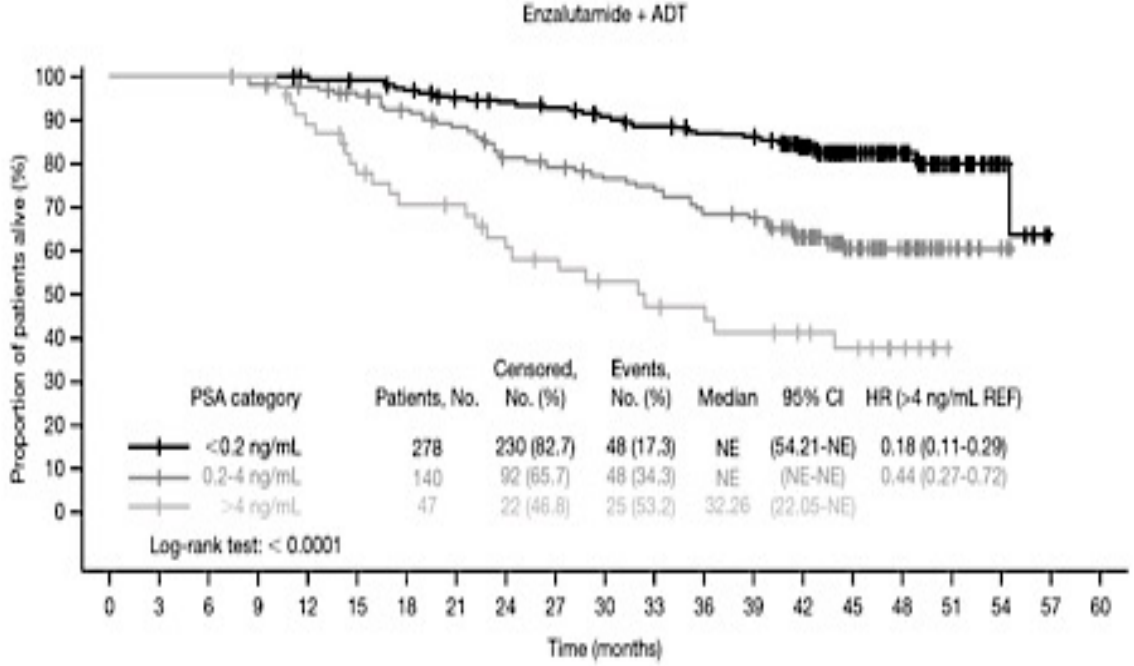


TITAN (apalutamide)
Deep PSA decline (>90% decline or <0.2ng/mL) at 3 months

PSA Nadir at 6 Months: ARCHES



rPFS



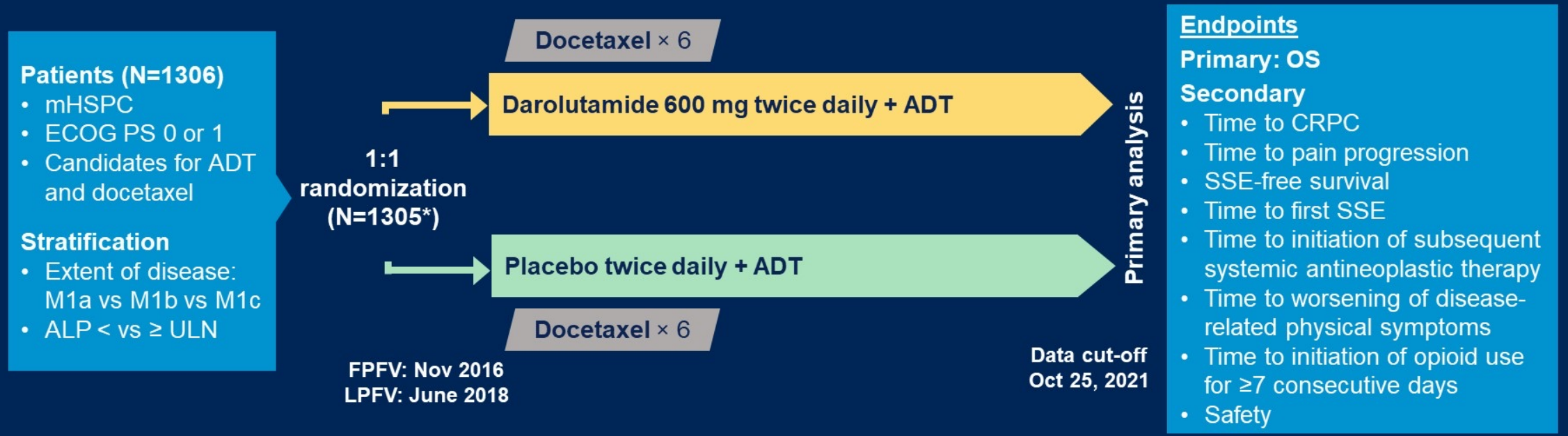
OS

Armstrong AJ et al submitted, ESMO 2022

Darolutamide

ARASENS Study Design

Global, randomized, double-blind, placebo-controlled phase III study (NCT02799602)

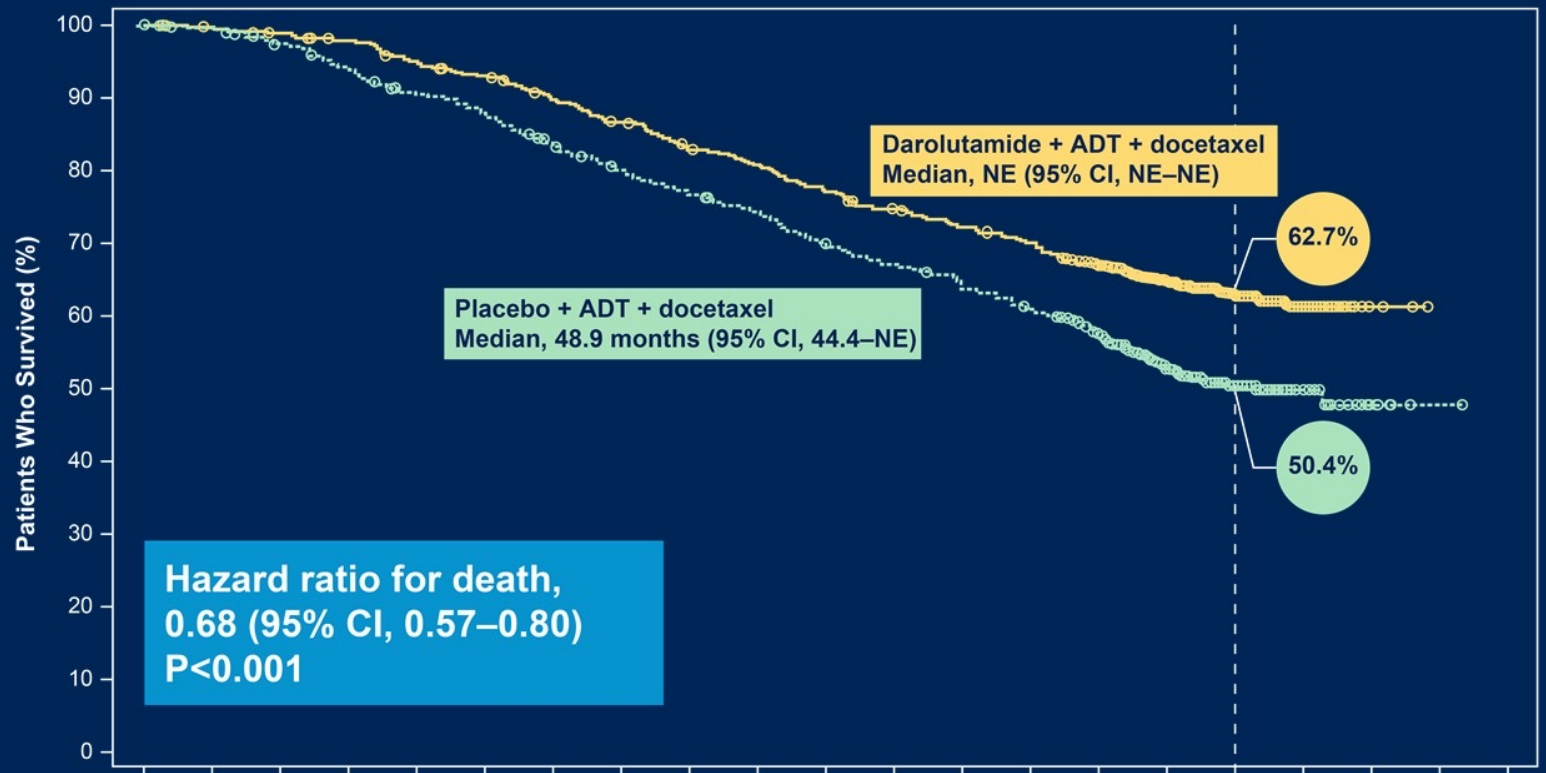


- The primary analysis was planned to occur after ~509 deaths
- Secondary efficacy endpoints were tested hierarchically

*One enrolled patient was excluded from all analysis sets because of Good Clinical Practice violations. ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FPFV, first patient first visit; LPFV, last patient first visit; M1a, nonregional lymph node metastases only; M1b, bone metastases ± lymph node metastases; M1c, visceral metastases ± lymph node or bone metastases; Q3W, every 3 weeks; SSE, symptomatic skeletal event; ULN, upper limit of normal.

ARASENS Primary Endpoint*: Overall Survival

Darolutamide significantly reduced the risk of death by 32.5%



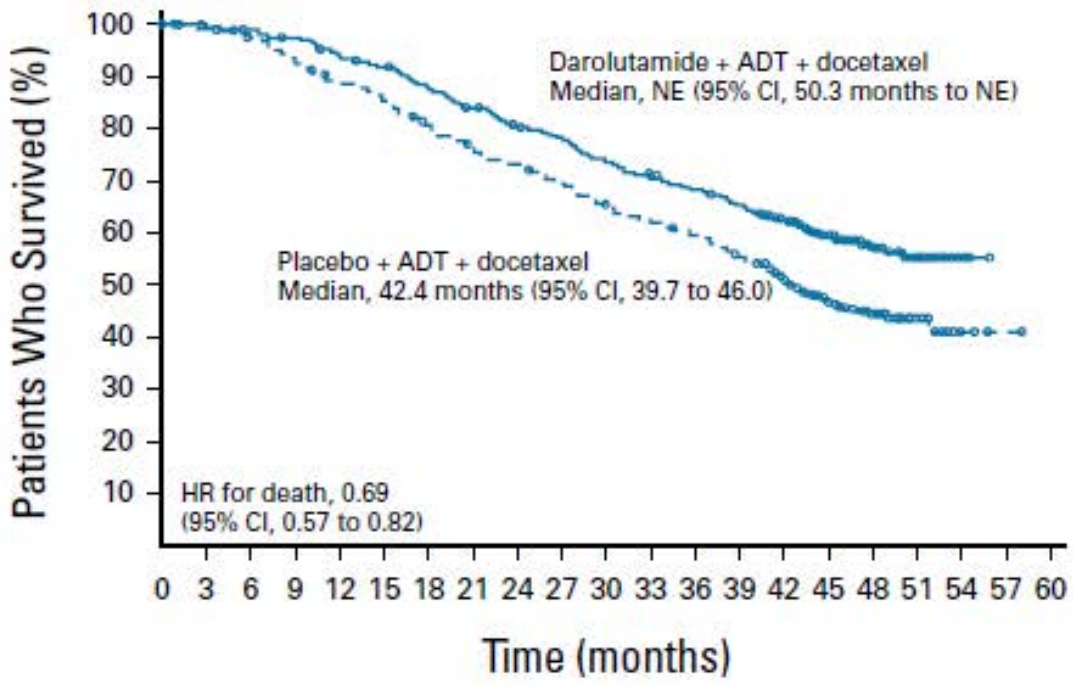
No. at Risk

Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

*Primary analysis occurred after 533 deaths (darolutamide, 229; placebo, 304). CI, confidence interval; NE, not estimable.

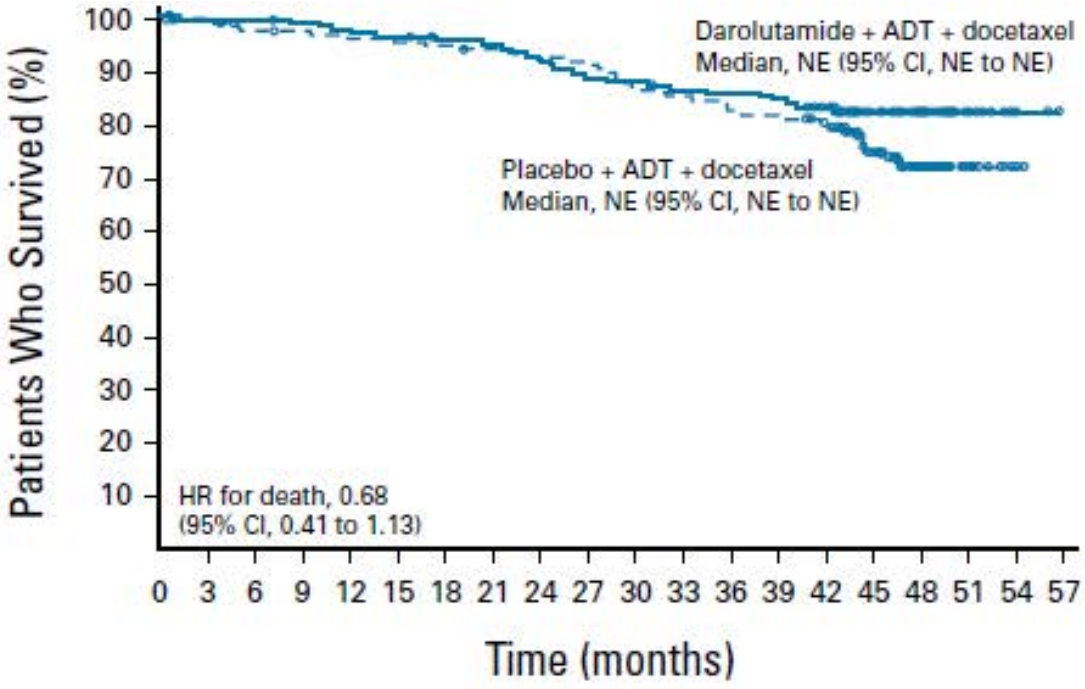
Smith et al NEJM 2023

ARASENS by Volume



No. of high-volume patients at risk:

Darolutamide	497	494	486	479	462	449	429	408	389	378	356	341	326	312	285	193	103	43	6	0	0
Placebo	508	502	491	469	444	430	401	378	358	341	319	304	286	269	233	153	72	23	4	1	0



No. of low-volume patients at risk:

Darolutamide	154	151	151	148	146	144	141	140	136	131	130	127	126	124	117	74	36	13	3	0
Placebo	146	144	139	138	136	135	134	132	130	129	122	120	116	114	107	65	35	14	2	0

Hussain et al JCO 2023

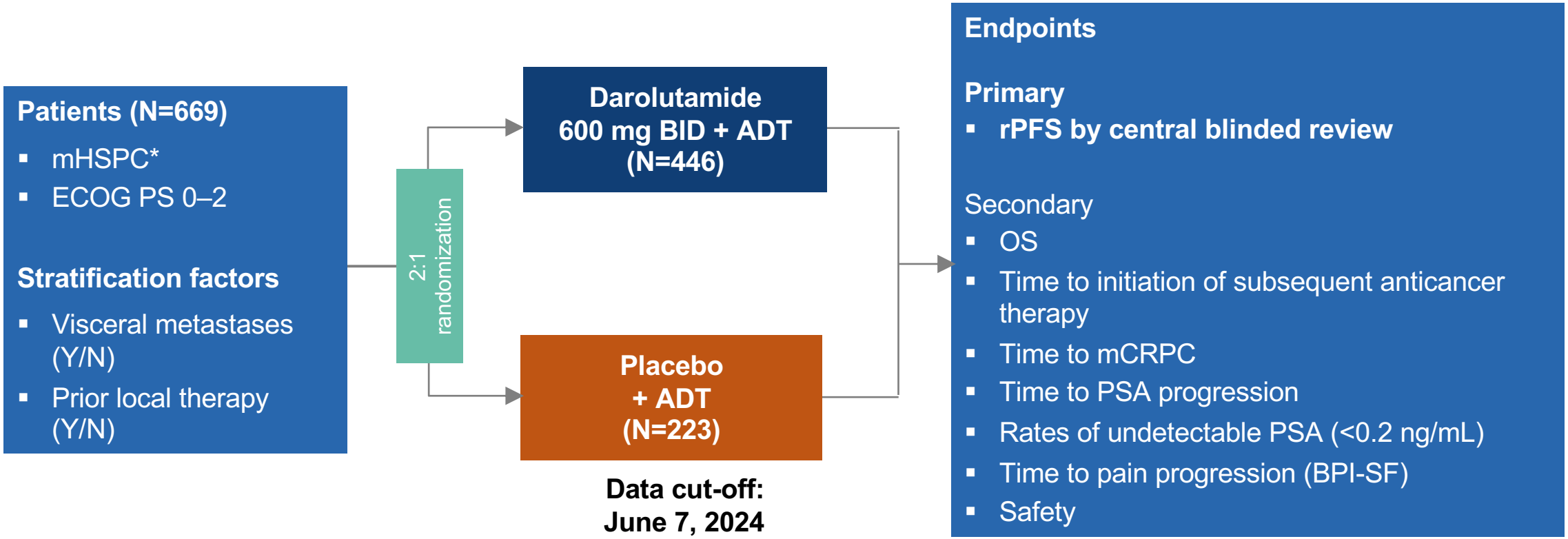
Adverse Events of Special Interest for AR Pathway Inhibitors

AEs associated with AR pathway inhibitor therapy	Darolutamide + ADT + docetaxel (n=652)		Placebo + ADT + docetaxel (n=650)	
	Patients, n (%)	EAIR/100 PY*	Patients, n (%)	EAIR/100 PY*
Fatigue	216 (33.1)	12.5	214 (32.9)	17.8
Bone fracture	49 (7.5)	2.8	33 (5.1)	2.7
Falls	43 (6.6)	2.5	30 (4.6)	2.5
Rash†	108 (16.6)	6.2	88 (13.5)	7.3
Diabetes mellitus and hyperglycemia‡	99 (15.2)	5.7	93 (14.3)	7.7
Weight decreased	22 (3.4)	1.3	35 (5.4)	2.9
Vasodilatation and flushing	133 (20.4)	7.7	141 (21.7)	11.7
Breast disorders/gynecomastia‡	21 (3.2)	1.2	10 (1.5)	0.8
Hypertension‡	89 (13.7)	5.1	60 (9.2)	5.0
Cardiac disorder‡	71 (10.9)	4.1	76 (11.7)	6.3
Cerebral ischemia	8 (1.2)	0.5	8 (1.2)	0.7
Mental impairment disorder‡	23 (3.5)	1.3	15 (2.3)	1.2
Depressed mood disorder‡	21 (3.2)	1.2	24 (3.7)	2.0
Seizure	4 (0.6)	0.2	1 (0.2)	0.1

*EAIR is the number of patients with a given AE divided by the total darolutamide/placebo treatment duration of all patients in years and expressed in 100 PY. †This category combines the following MedDRA terms: rash, maculopapular rash, drug eruption, pruritic rash, erythematous rash, macular rash, papular rash, follicular rash, pustular rash, and vesicular rash. ‡This category is a MedDRA High-Level Group Term. EAIR, exposure-adjusted incidence rate; PY, patient year.

ARANOTE Study Design

Global, randomized, double-blind, placebo-controlled, phase 3 study



ClinicalTrials.gov: NCT04736199

*Metastatic disease confirmed by conventional imaging method as a positive ^{99m}Tc-phosphonate bone scan or soft tissue/visceral metastases on contrast-enhanced abdominal/pelvic/chest CT or MRI scan, assessed by central review.
BPI-SF, Brief Pain Inventory-Short Form.

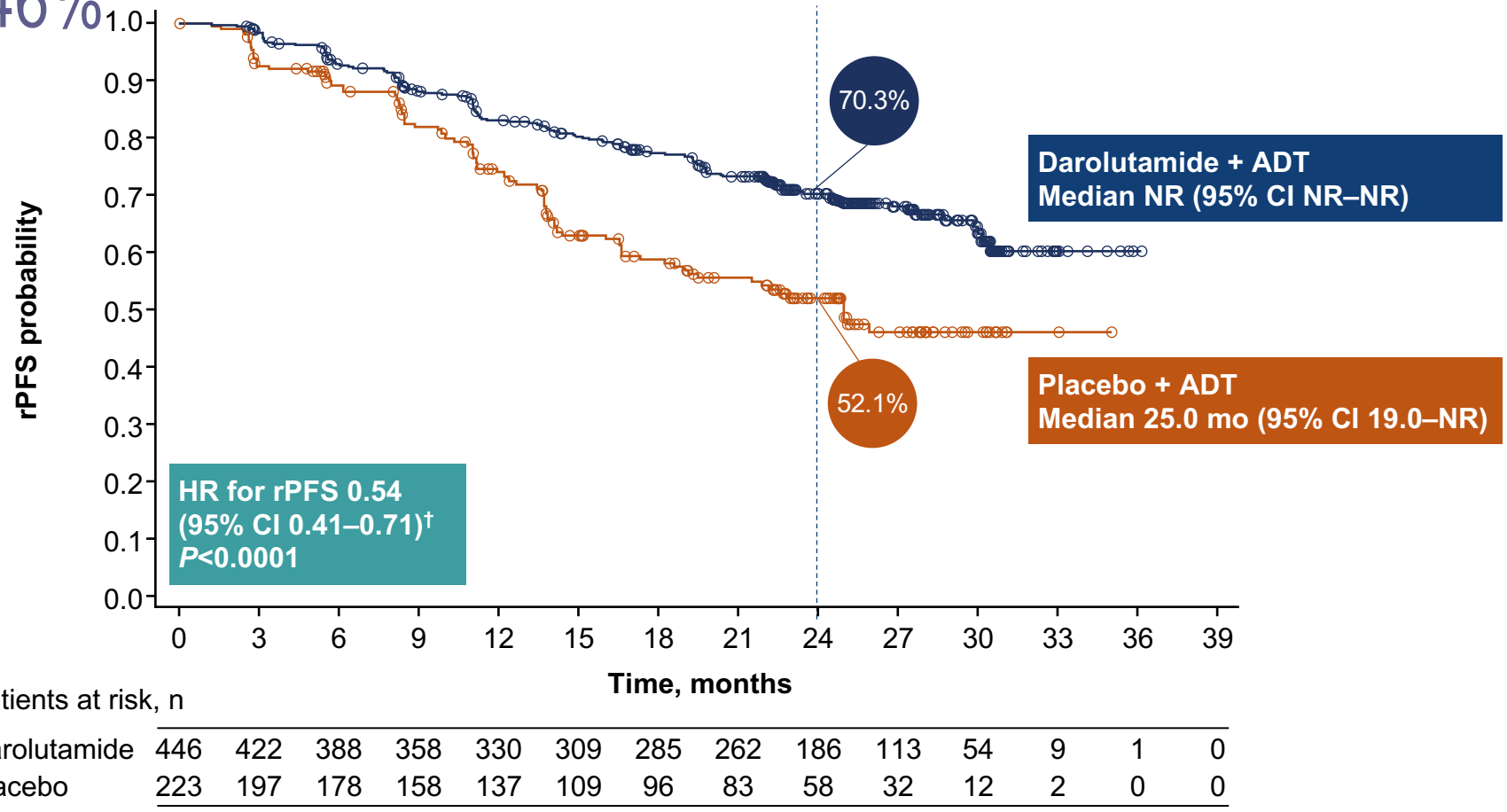
Baseline Demographics and Disease Characteristics

		Darolutamide + ADT (n=446)	Placebo + ADT (n=223)
Age, years	Median (range)	70 (43–93)	70 (45–91)
Race, n (%)	White	251 (56.3)	125 (56.1)
	Asian	144 (32.3)	65 (29.1)
	Black	41 (9.2)	24 (10.8)
	Other	10 (2.2)	9 (4.0)
Region, n (%)	Asia	141 (31.6)	63 (28.3)
	Latin America	119 (26.7)	72 (32.3)
	Europe and Rest of World	186 (41.7)	88 (39.5)
ECOG PS, n (%)	0	235 (52.7)	98 (43.9)
	1–2	211 (47.3)	125 (56.1)
Gleason score at initial diagnosis, n (%)	≥8	311 (69.7)	146 (65.5)
Serum PSA, ng/mL	Median (range)	21.4 (0.02–15,915)	21.2 (0.02–8533)
Metastases at initial diagnosis, n (%)	Yes (de novo)	317 (71.1)	168 (75.3)
	No (recurrent)	100 (22.4)	45 (20.2)
Disease volume, n (%)*	High	315 (70.6)	157 (70.4)
	Low	131 (29.4)	66 (29.6)
Visceral metastases, n (%)	Yes	53 (11.9)	27 (12.1)
	No	393 (88.1)	196 (87.9)
Prior local therapy, n (%)	Yes	80 (17.9)	40 (17.9)
	No	366 (82.1)	183 (82.1)

*Disease volume defined by CHAARTED criteria: presence of visceral metastases and/or ≥4 bone metastases with ≥1 beyond vertebral bodies and pelvis (Sweeney CJ, et al. *N Engl J Med* 2015;373:737–746).

ARANOTE Primary Endpoint: rPFS*

Darolutamide significantly reduced the risk of radiological progression or death by 46%



Patients at risk, n

Darolutamide	446	422	388	358	330	309	285	262	186	113	54	9	1	0
Placebo	223	197	178	158	137	109	96	83	58	32	12	2	0	0

BARCELONA 2024 ESMO congress

Median follow-up: darolutamide group 25.3 months; placebo group 25.0 months

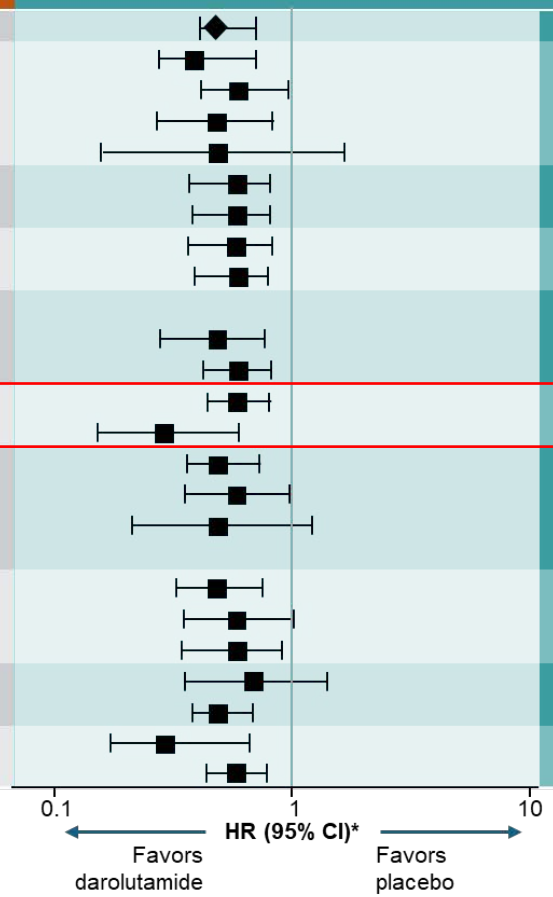
*Primary analysis occurred after 222 events (darolutamide 128; placebo 94).

†HR and 95% CI were calculated using the Cox model stratified on visceral metastases (Y/N) and prior therapy (Y/N).

ARANOTE rPFS: Subgroup Analyses

Consistent benefit of darolutamide across all subgroups

rPFS		Darolutamide (n=446) Events/Patients, n/N	Darolutamide (n=446) Median, months	Placebo (n=223) Events/Patients, n/N	Placebo (n=223) Median, months	HR (95% CI)*
Overall population		128/446	NR	94/223	25.0	0.54 (0.41–0.71)
Age subgroups, years	<65	37/118	NR	32/65	14.2	0.44 (0.27–0.71)
	65–74	53/193	NR	35/96	NR	0.64 (0.41–0.98)
	75–84	29/117	NR	22/52	NR	0.48 (0.27–0.83)
	≥85	9/18	27.4	5/10	19.2	0.51 (0.16–1.66)
Baseline PSA values	< median	58/216	NR	44/111	26.0	0.55 (0.37–0.81)
	≥ median	67/220	NR	47/108	22.9	0.55 (0.38–0.80)
ECOG PS at baseline	0	61/235	NR	37/98	NR	0.55 (0.37–0.83)
	≥1	67/211	NR	57/125	22.6	0.56 (0.39–0.79)
Gleason score at initial diagnosis	Missing/not assessed	5/13	NR	4/10	13.8	
	<8	32/122	NR	30/67	22.9	0.46 (0.28–0.75)
	≥8	91/311	NR	60/146	25.1	0.58 (0.42–0.81)
Disease volume	High volume	113/315	30.2	75/157	19.2	0.60 (0.44–0.80)
	Low volume	15/131	NR	19/66	NR	0.30 (0.15–0.60)
Race	White	76/251	NR	55/125	22.2	0.52 (0.36–0.73)
	Asian	38/144	NR	24/65	25.0	0.59 (0.35–0.98)
	Black	10/41	NR	10/24	NR	0.51 (0.21–1.23)
	Other	4/10	NR	5/9	13.7	
Geographic region	Europe and RoW	56/186	NR	39/88	22.6	0.50 (0.33–0.75)
	Asia	37/141	NR	23/63	25.0	0.60 (0.35–1.01)
	Latin America	35/119	NR	32/72	25.1	0.56 (0.35–0.90)
Visceral metastases	Yes	21/53	NR	13/27	25.0	0.71 (0.35–1.41)
	No	107/393	NR	81/196	25.0	0.52 (0.39–0.69)
Prior local therapy	Yes	19/80	NR	18/40	19.5	0.34 (0.17–0.66)
	No	109/366	NR	76/183	25.0	0.59 (0.44–0.79)



BARCELONA 2024 ESMO congress

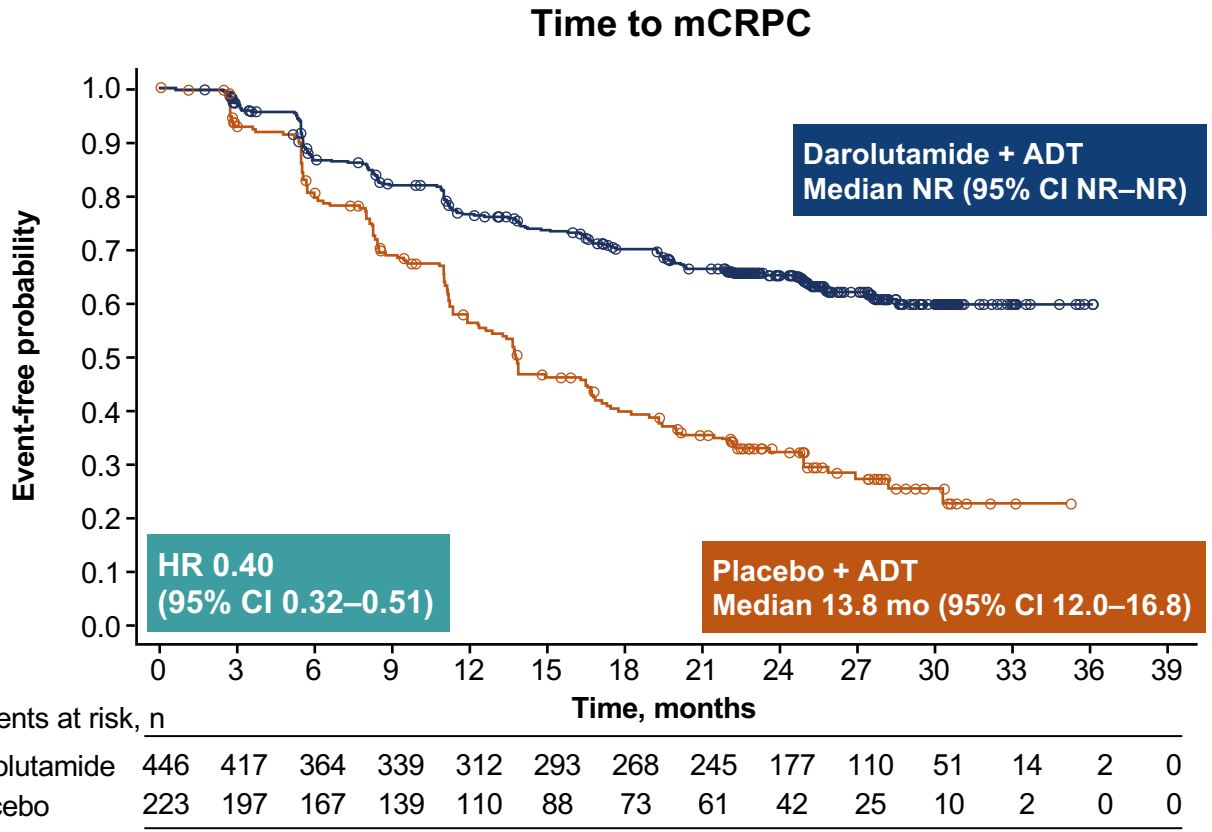
*HR and 95% CI were calculated from univariate analysis using unstratified Cox regression.

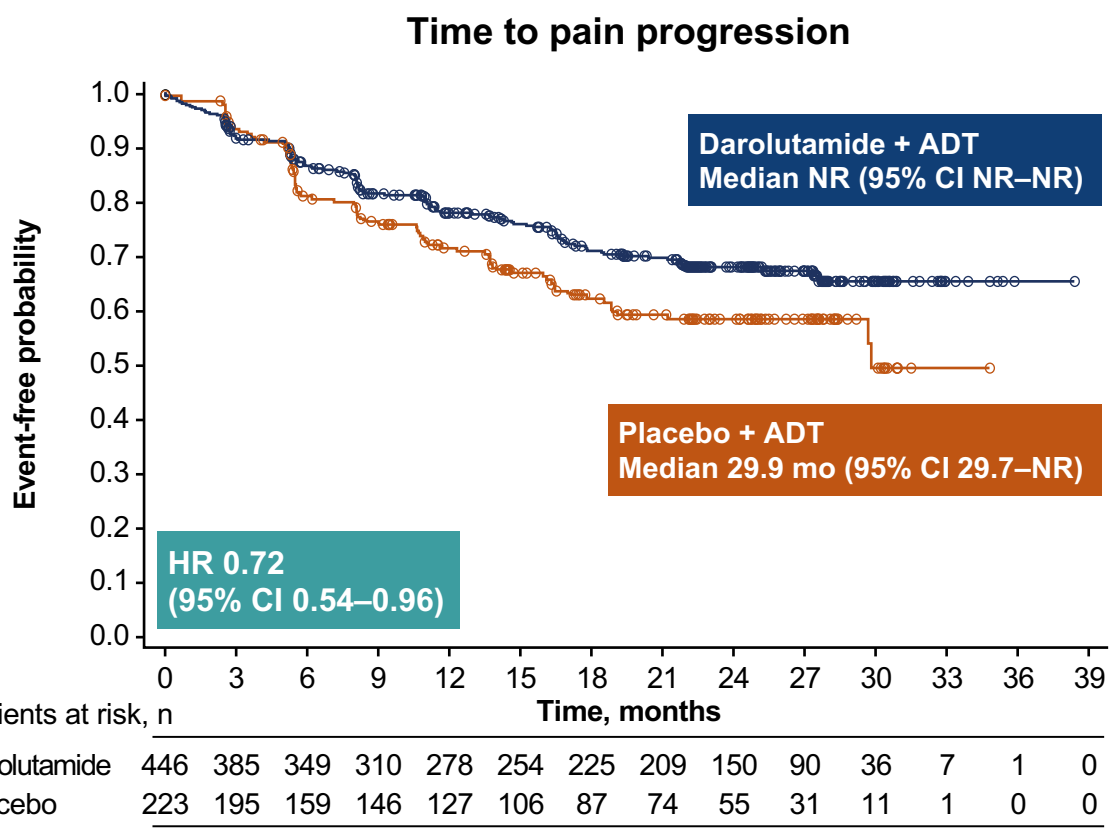
TEAEs associated with ARPIs were generally similar between treatment groups

TEAEs	Darolutamide + ADT (n=445)		Placebo + ADT (n=221)	
	Incidence, %	EAIR/100 PY	Incidence, %	EAIR/100 PY
Fatigue	5.6	3.2	8.1	5.7
Mental impairment disorder	1.6	0.9	0.5	0.3
Hypertension	9.4	5.5	9.5	6.7
Cardiac arrhythmias	8.8	5.1	6.8	4.7
Coronary artery disorders	3.6	2.0	1.4	0.9
Heart failure	0.9	0.5	0.9	0.6
Falls, including accident	1.3	0.8	0.9	0.6
Bone fracture	4.0	2.3	2.3	1.5
Vasodilatation and flushing	9.2	5.6	7.2	5.0
Diabetes mellitus and hyperglycemia	9.0	5.3	9.5	6.7
Rash	4.3	2.4	3.6	2.4

EAIR, exposure-adjusted incidence rate; PY, patient years.

Darolutamide delayed time to mCRPC and pain progression





Summary: Darolutamide

- ARASENS population was largely de novo high volume mHSPC
- ARANOTE was a much broader and diverse population
- Very well tolerated and thus a reasonable safe and effective choice for most men with mHSPC
- Darolutamide dosed concurrently with docetaxel/ADT at 600 mg twice daily with food
- OS immature in ARANOTE and due to cross over and availability of ARPIs will likely never be positive

Abiraterone vs. Enzalutamide vs. Apalutamide vs Darolutamide

Abiraterone acetate

- Requires prednisone
- Mineralocorticoid excess
- Liver and electrolyte monitoring required
- BP monitoring required
- Some CV risk (afib, others)
- Bone density monitoring recommended (fracture risk)
- Exercise recommended (fatigue, muscle loss)
- Beneficial in high and low volume/risk patients
- Can be safely given with RT

Enzalutamide, Apalutamide, Darolutamide

- No prednisone requirement
- No mineralocorticoid excess
- No liver/electrolyte monitoring required
- BP monitoring required
- Fatigue, fracture risk
- Bone density monitoring recommended (fracture risk)
- Exercise recommended (fatigue, muscle loss)
- Minimal seizure risk <1%, but careful in patients with h/o seizures, strokes
- Apalutamide rash in ~30% can be significant (not enzalutamide)
- Beneficial in high and low volume/risk patients
- Can be safely given with RT

What's next?

- More STAMPEDE arms: estradiol patches, metformin, RT to PSMA PET+ sites
- Lu^{177}-PSMA-617: PSMAddition
- Movement of potent AR inhibitors to nmHSPC setting
  - ENZARAD, ATLAS, DASL-HICAP, NRG 008/9/10 (PREDICT)
- Trials of PARP inhibitors in mHSPC (AMPLITUDE, TALAPRO-3, others)
- Trials of ADT/ARSI +- Akt inhibition in PTEN null mHSPC (CAPITello)
- No benefits: zoledronic acid, denosumab, abi+ enza, celecoxib, pembrolizumab (KEYNOTE-991)

Conclusions

- The standard of care for low volume mHSPC based on conventional imaging is doublet ADT/ARPI (LEVEL 1 EVIDENCE, SURVIVAL BENEFIT)
  - Radiation to the primary for those with synchronous metastases
  - Radiation to metastatic sites may be beneficial but is presently under study!
  - STAMPEDE 2 Treatment Arm S: Stereotactic Ablative Body Radiotherapy (SABR), a type of radiotherapy to up to 5 PSMA PET + sites
- Many patients would love to have a treatment holiday or to stop therapy altogether if remission is achieved in this setting
  - EMBARK, EXTEND trials establish this proof of concept
  - New trials are needed to test MDT in the setting of brief ADT/ARPI use in this oligomet HSPC setting with the goal of maintaining survival but extending treatment free intervals!

Questions from General Medical Oncologists

- **Would you use enzalutamide for all patients eligible per the EMBARK trial? In what setting would you use enza with and without ADT in nmHSPC? Why? When do you stop therapy, and when do you resume?**
- **78 y/o man who has CNS issues but meets EMBARK criteria. What would you recommend?**
- **How do you manage the gynecomastia with enzalutamide monotherapy in nmHSPC? Prophylactically?**
- **Can enzalutamide be replaced with other agents such as darolutamide in nmHSPC?**

Questions from General Medical Oncologists

- Many patients do not tolerate the full 160-mg enzalutamide dosing due to fatigue or dizziness. Do the investigators start high and dose reduce or start low and dose escalate? What's the lowest dose we can give and yet have therapeutic benefits?
- Side effects aside, is there any ARPI that stands out as the "best in class" in mHSPC? How do you select among them?
- In what group of patients, if any, would you choose to start with ADT alone rather than combination therapy for mHSPC? Is there a role for single-agent AR blockers in patients who had side effects from ADT (like worsening CHF)?

Questions from General Medical Oncologists

- **Like intermittent ADT, would you consider intermittent ARPI as well as intermittent ADT in a 90-year-old with mHSPC?**
- **For which patients would you utilize the ARASENS regimen? Are any patients still appropriate for docetaxel alone? What would push one to offer the addition of docetaxel to ADT + second-generation antiandrogen in older patients?**
- **Should we employ 4 vs 6 cycles of taxane in triplet therapy? If someone has only a minimal response to triple therapy, do you ever give additional cycles of chemotherapy?**

Agenda

Module 1: Role of Antibody-Drug Conjugates (ADCs) in Front-Line Therapy for Metastatic Urothelial Bladder Cancer (mUBC) — Dr Friedlander

Module 2: Evidence-Based Use of ADCs for Relapsed/Refractory mUBC — Dr Galsky

Module 3: Evolving Role of Treatment Intensification with Androgen Receptor Pathway Inhibitors for Nonmetastatic and Metastatic Prostate Cancer — Dr Armstrong

Module 4: Optimal Integration of PARP Inhibitors into Therapy for Prostate Cancer — Dr Agarwal

RTP RESEARCH TO PRACTICE

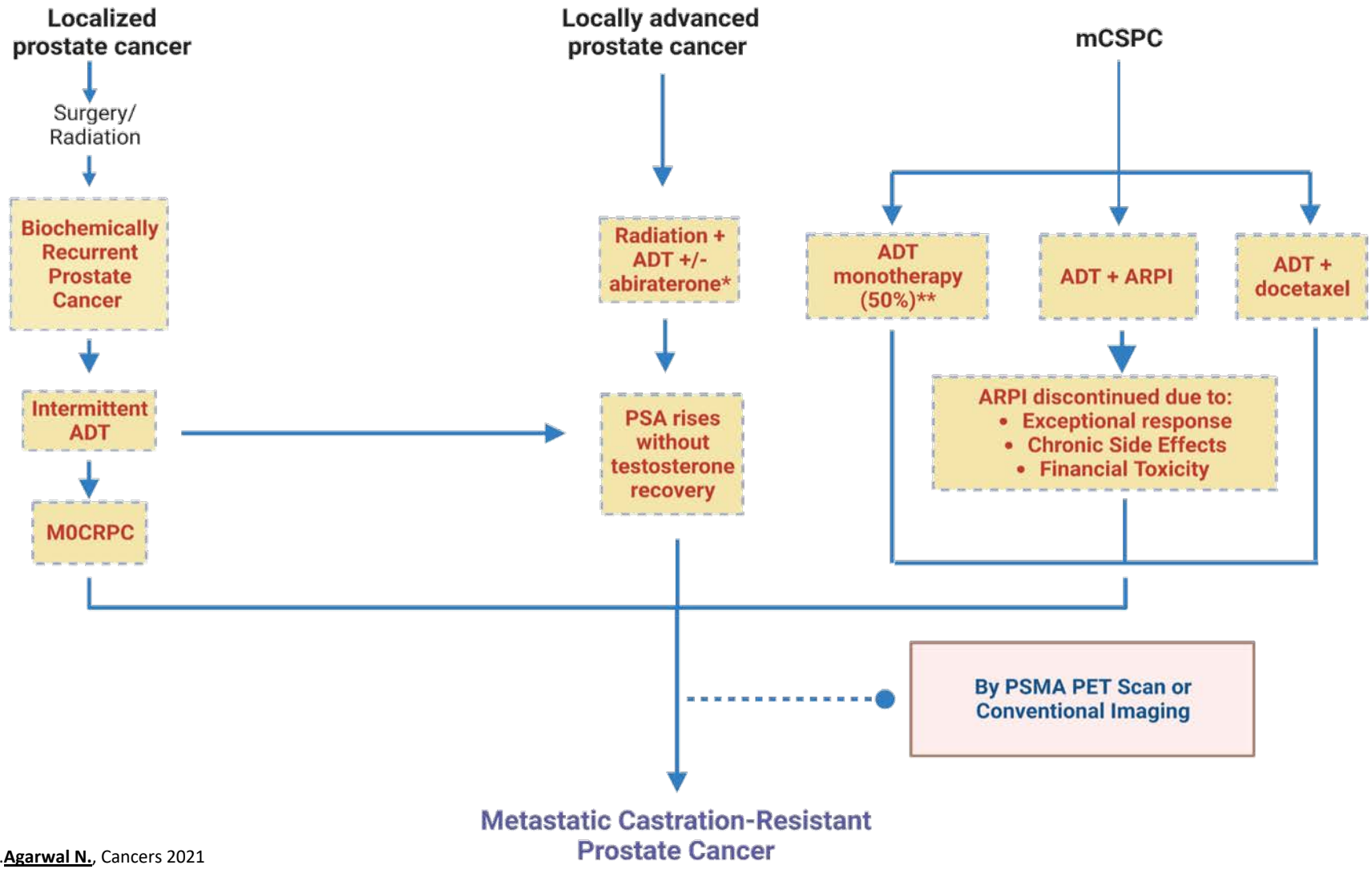
Optimal Integration of PARP Inhibitors Into the Care of Patients with Prostate Cancer

Neeraj Agarwal, MD, FASCO
Professor of Medicine (Medical Oncology)
Senior Director for Clinical Translation, Huntsman Cancer Institute (HCI)
HCI Presidential Endowed Chair of Cancer Research
Director, Center of Investigational Therapeutics
Director, Genitourinary Oncology Program
Huntsman Cancer Institute, University of Utah (NCI-CCC)

Learning Objectives

- Biological rationale for combining PARP inhibitors with AR pathway inhibitors in prostate cancer
- Efficacy and safety results of Phase III trials combining PARP inhibitors with AR pathway inhibitors
- Results of the Phase II BRCAAway trial
- Ongoing Phase III studies evaluating PARP inhibitors in combination with AR pathway inhibitors in earlier settings

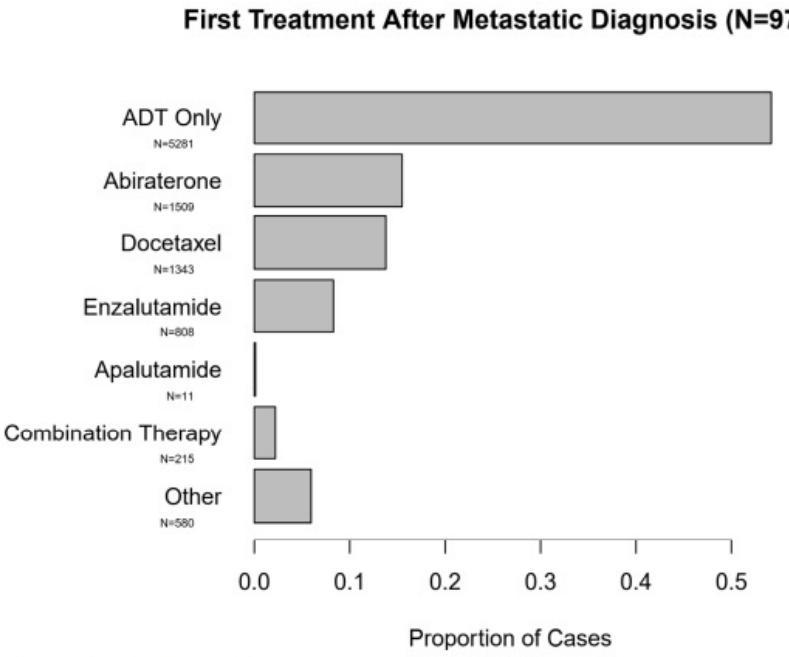
Pathways to Metastatic Castration-Resistant Prostate Cancer Without Progression on an ARPI

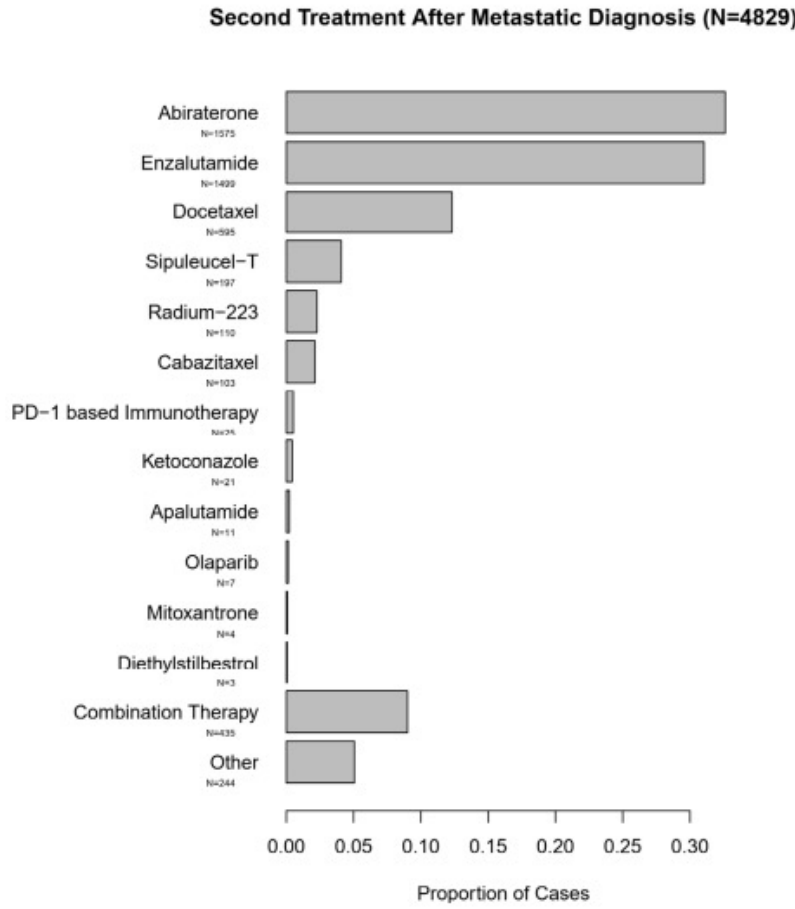


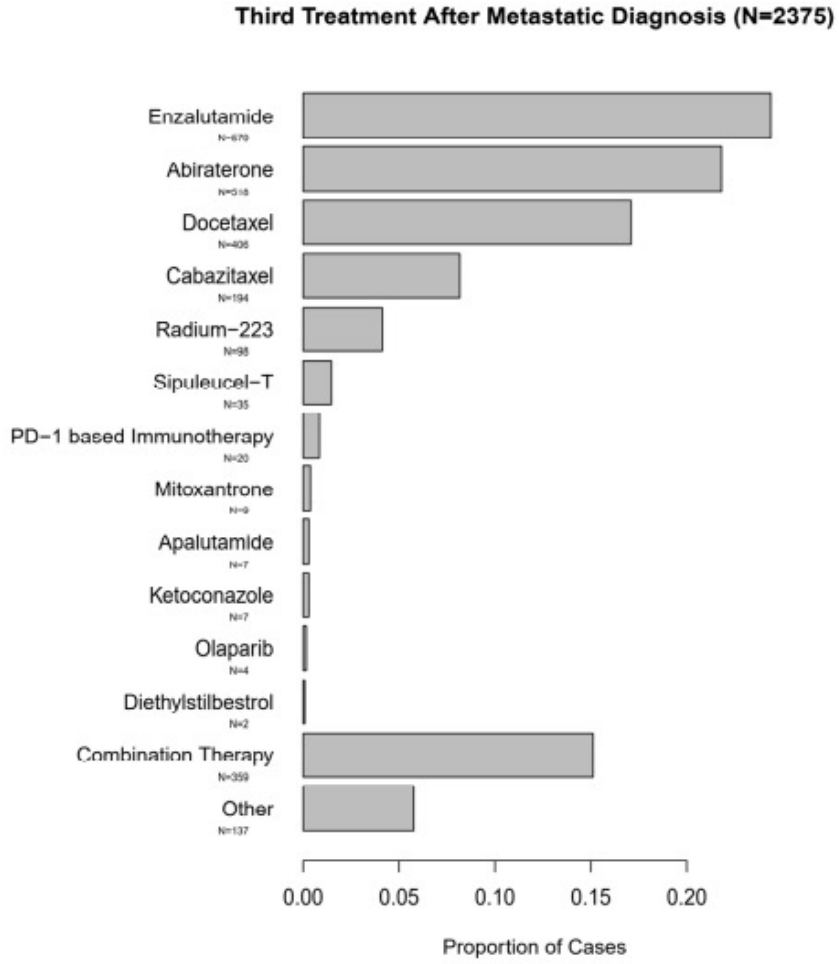
*Limited Duration of 2 years **Swami U...**Agarwal N.**, Cancers 2021

Abbreviations: ADT: androgen deprivation therapy; ARPI: androgen receptor pathway inhibitor; mCSPC: metastatic castration-sensitive prostate cancer; M0CRPC: non-metastatic castration-resistant prostate cancer; PSMA: prostate specific membrane antigen.

First, second, and third treatment after metastatic diagnosis







Swami U, …, Agarwal N. *Cancers* 2021

The rationale for combining PARPi with ARPI

ARPIs induce a phenotype resembling HRR deficiency

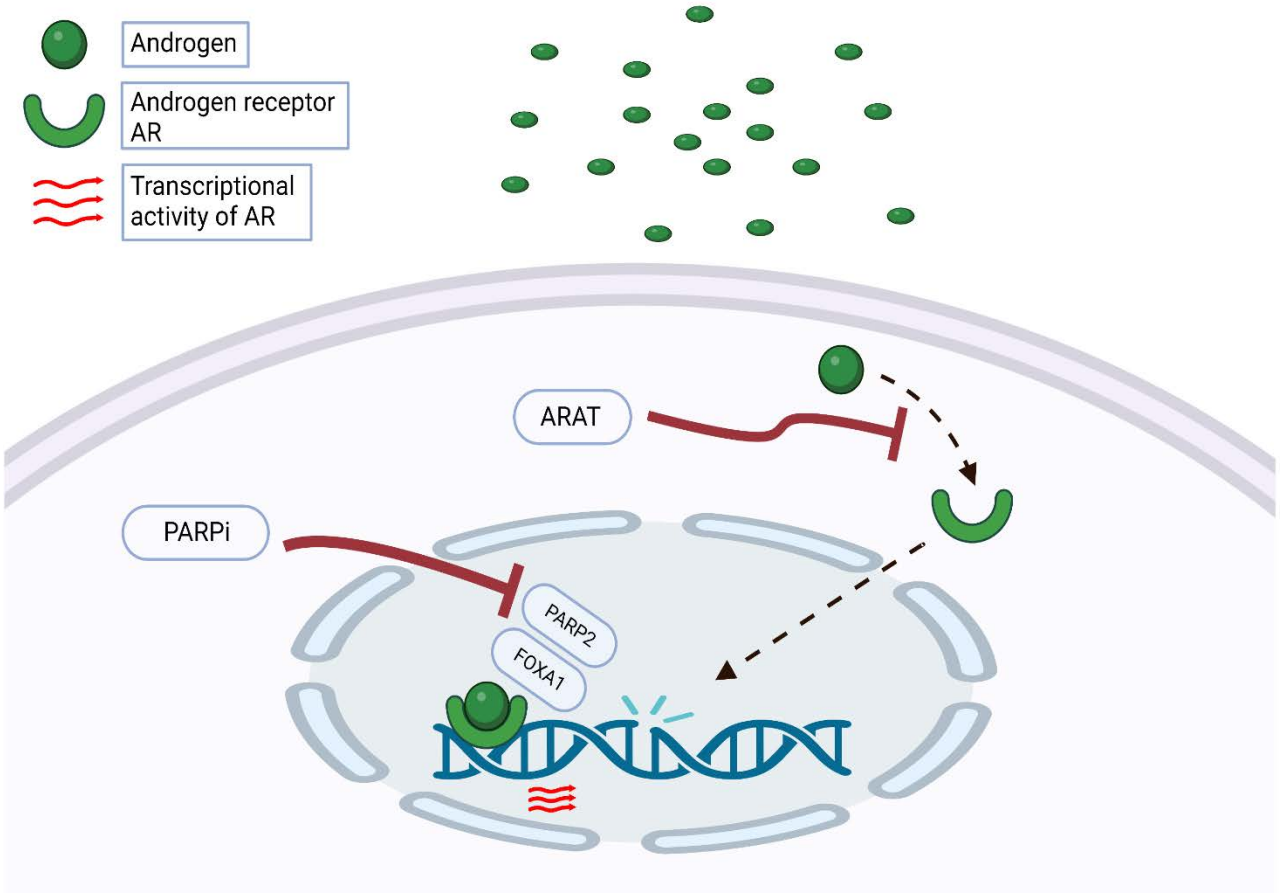
Suppressed AR function causes an upregulation of PARP

ARPIs prime tumor cells for PARP inhibition

PARP augments AR activity

PARP inhibitors may attenuate resistance to ARPIs

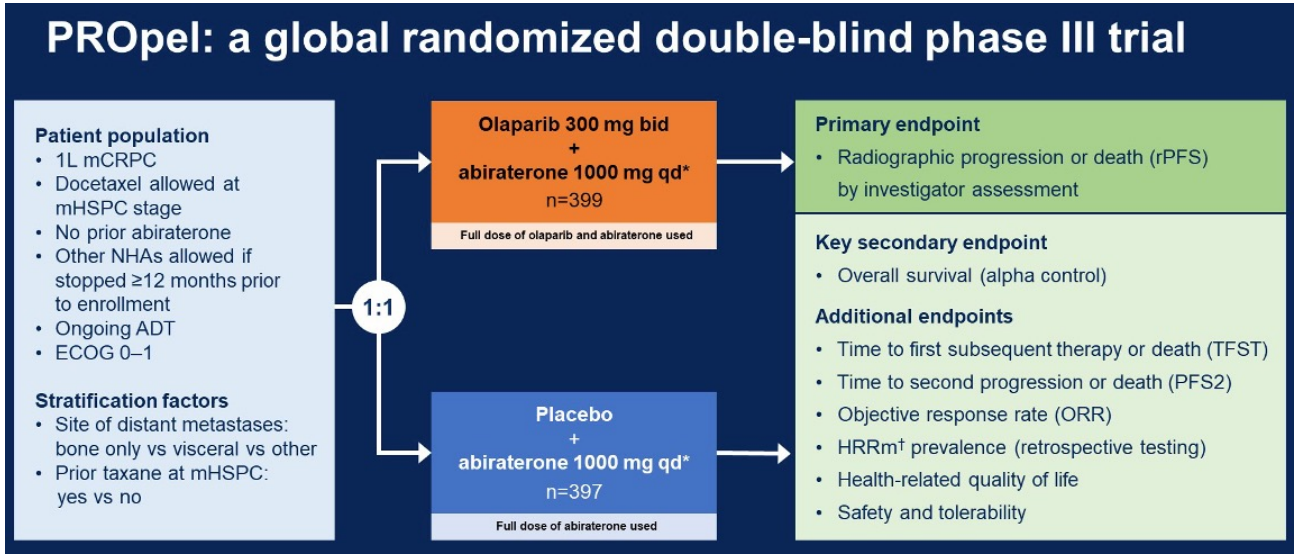
PARP inhibitors extend the benefits of ARPIs



1. Adapted from Bin Gui et al., *PNAS* 2019 June, DOI https://doi.org/10.1073/pnas.1908547116
2. **Agarwal N**, et al European Journal of Cancer, 2023.

Phase 3 PARPi + ARPI Trials Design

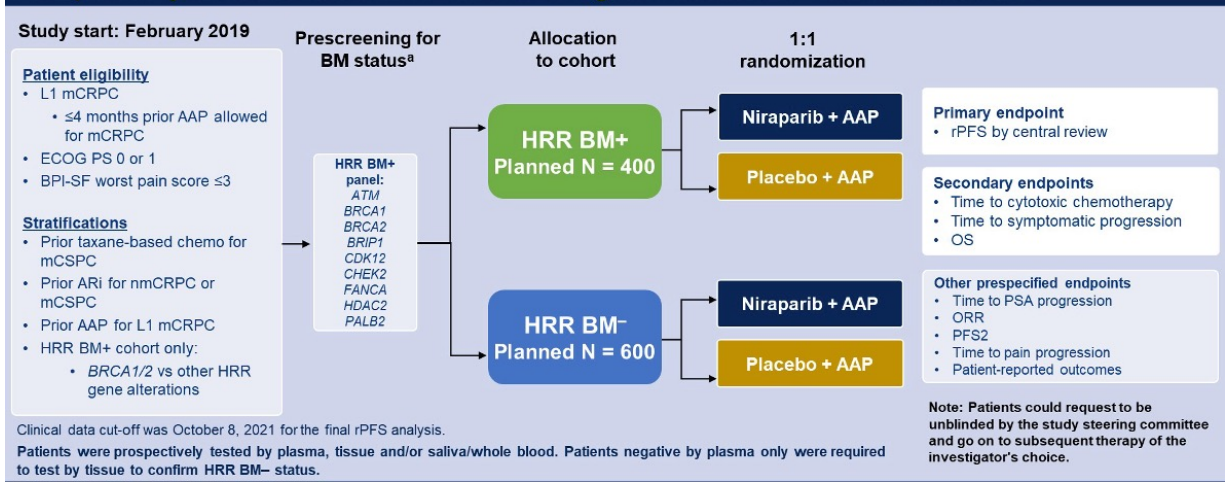
PROpel: a global randomized double-blind phase III trial



Clarke, NW. *et al.* ***NEJM Evidence,*** 2022

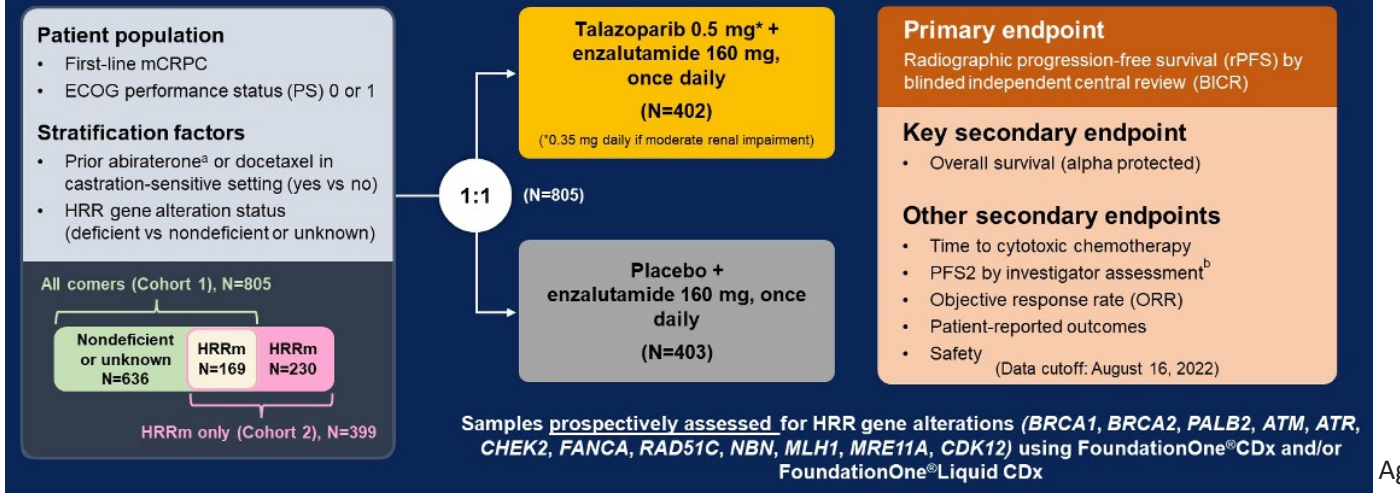
MAGNITUDE: Randomized, Double-Blind, Placebo-Controlled Study

Prospectively selected biomarker cohorts designed to test HRR BM+ and HRR BM–



Chi, KN. *et al*. ***JCO,*** 2022

TALAPRO-2: A Randomized, Double-blind, Placebo-Controlled Study



Agarwal, N. *et al.* ***Lancet,*** 2023.

PROpel

NEJM Evidence

Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer

Authors: Noel W. Clarke, M.B.B.S., Ch.M., F.R.C.S. , Andrew J. Armstrong, Sc.M., M.D., Antoine Thiery-Vuillemin, M.D., Ph.D., Mototsugu Oya, M.D., Neal Shore, M.D., Eugenia Loredo, M.D., Giuseppe Procopio, M.D., Juliana de Menezes, M.D., Gustavo Girotto, M.D., Cagatay Arslan, M.D., Niven Mehra, M.D., Ph.D., Francis Parnis, F.R.A.C.P., Emma Brown, M.D., Friederike Schlürmann, M.D., Jae Y. Joung, M.D., Ph.D., Mikio Sugimoto, M.D., Ph.D., Juan A. Virizuela, M.D., Ph.D., Urban Emmenegger, M.D., Jiri Navratil, M.D., Gary L. Buchschacher, Jr., M.D., Ph.D., Christian Poehlein, M.D., Elizabeth A. Harrington, Ph.D., Chintu Desai, Ph.D., Jinyu Kang, M.D., Fred Saad, M.D., F.R.C.S.

Clarke NW et al., **NEJM Evidence**, 2022

THE LANCET Oncology

ARTICLES | VOLUME 24, ISSUE 10, P1094-1108, OCTOBER 2023 Download Full Issue

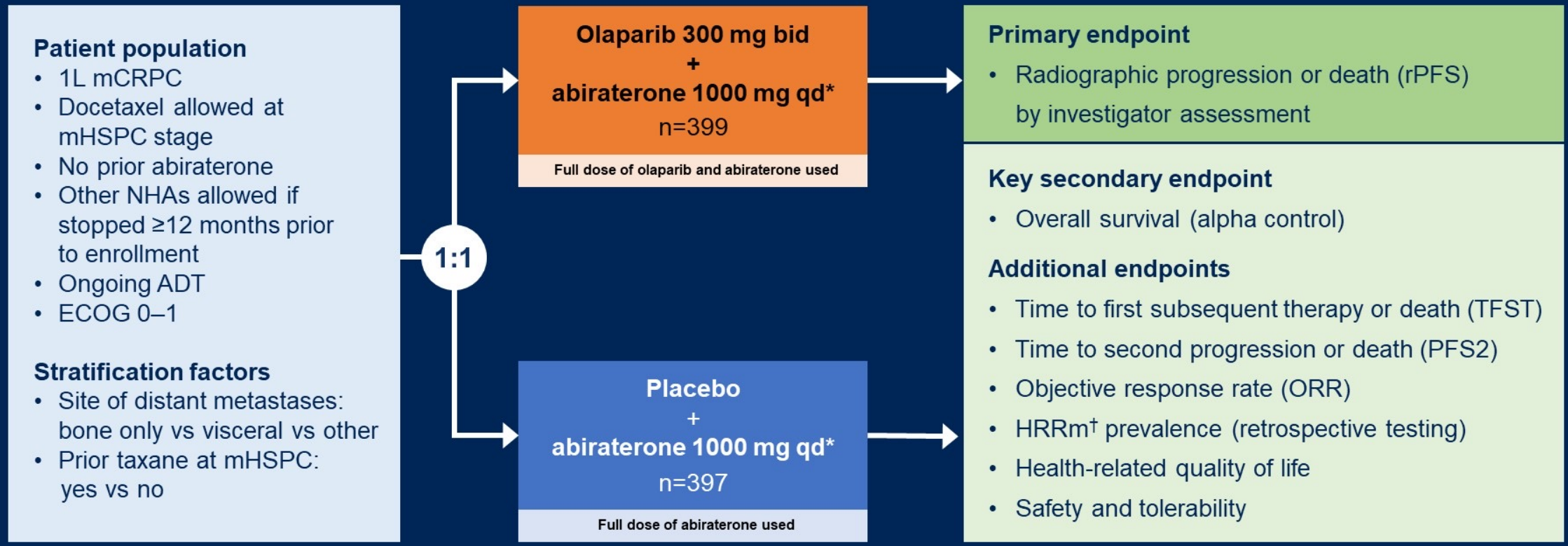
Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial

Prof Fred Saad, MD • Prof Noel W Clarke, ChM • Prof Mototsugu Oya, MD • Neal Shore, MD • Giuseppe Procopio, MD • João Daniel Guedes, MD • et al. Show all authors

Published: September 12, 2023 • DOI: https://doi.org/10.1016/S1470-2045(23)00382-0 • Check for updates

Saad F et al., **The Lancet Oncology**, 2023

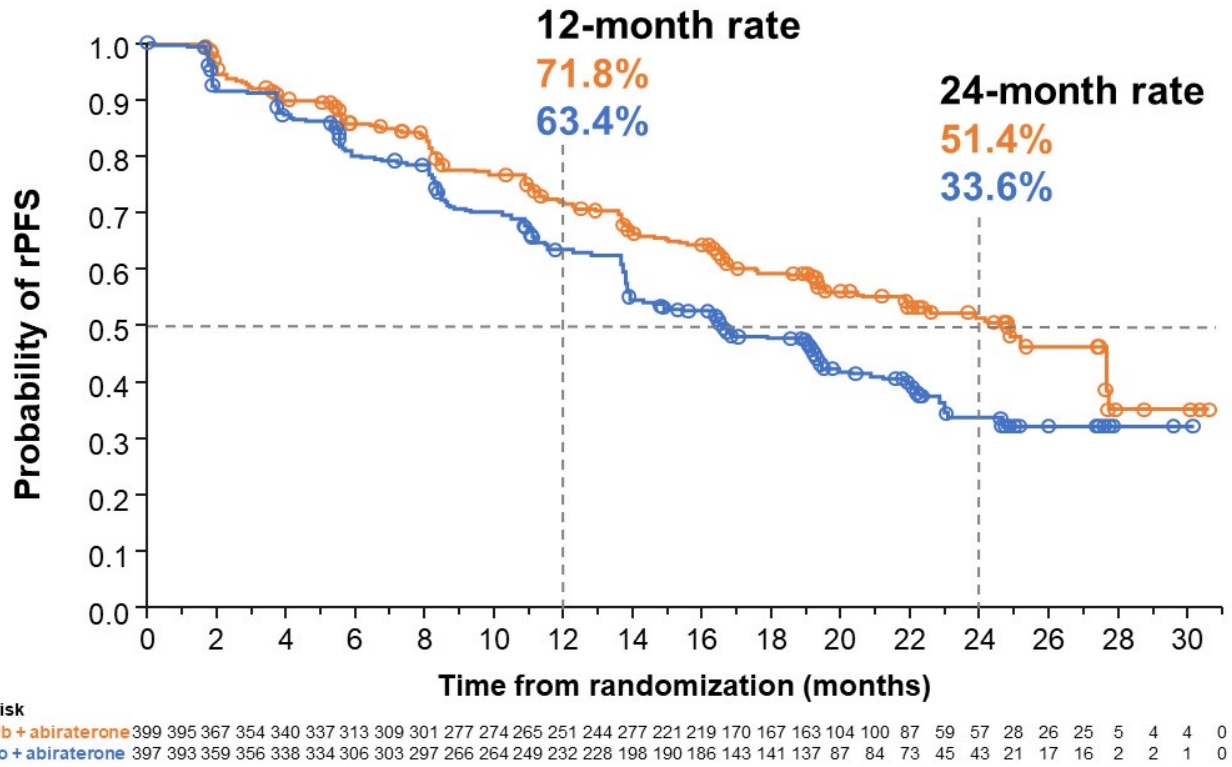
PROpel: a global randomized double-blind phase III trial



First patient randomized: Nov 2018; Last patient randomized: Mar 2020; DCO1: July 30, 2021, for interim analysis of rPFS and OS.
Multiple testing procedure is used in this study: 1-sided alpha of 0.025 fully allocated to rPFS. If the rPFS result is statistically significant, OS to be tested in a hierarchical fashion with alpha passed on to OS.
Please access the ***Supplement*** via the QR code at the end of this presentation for more details.
*In combination with prednisone or prednisolone 5 mg bid. †HRRm, homologous recombination repair mutation, including 14 genes panel.
ADT, androgen deprivation therapy; bid, twice daily; ECOG, Eastern Cooperative Oncology Group; mHSPC, metastatic hormone sensitive prostate cancer; qd, daily

PROpel primary endpoint: rPFS by investigator-assessment

34% risk reduction of progression or death with olaparib + abiraterone



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS (months)	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); *P*<0.0001	

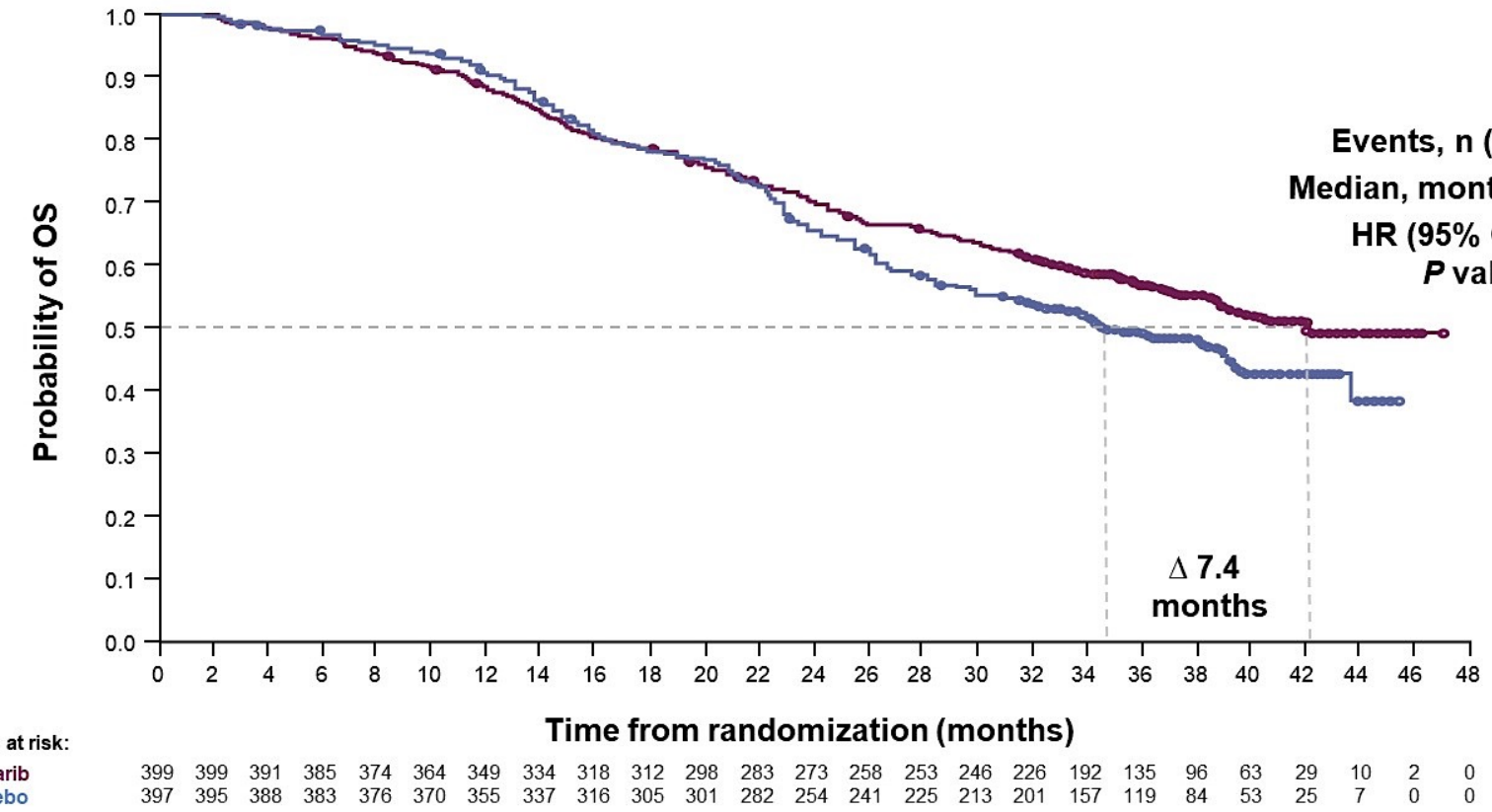
Pre-specified 2-sided alpha: 0.0324

Median rPFS improvement of 8.2 months favors olaparib + abiraterone*

Events: 394; Maturity 49.5%
*In combination with prednisone or prednisolone
CI, confidence interval; HR, hazard ratio.

PROpel: OS at final pre-specified analysis (DCO3)

In the ITT population, median OS was >7 months longer in the abiraterone + olaparib arm



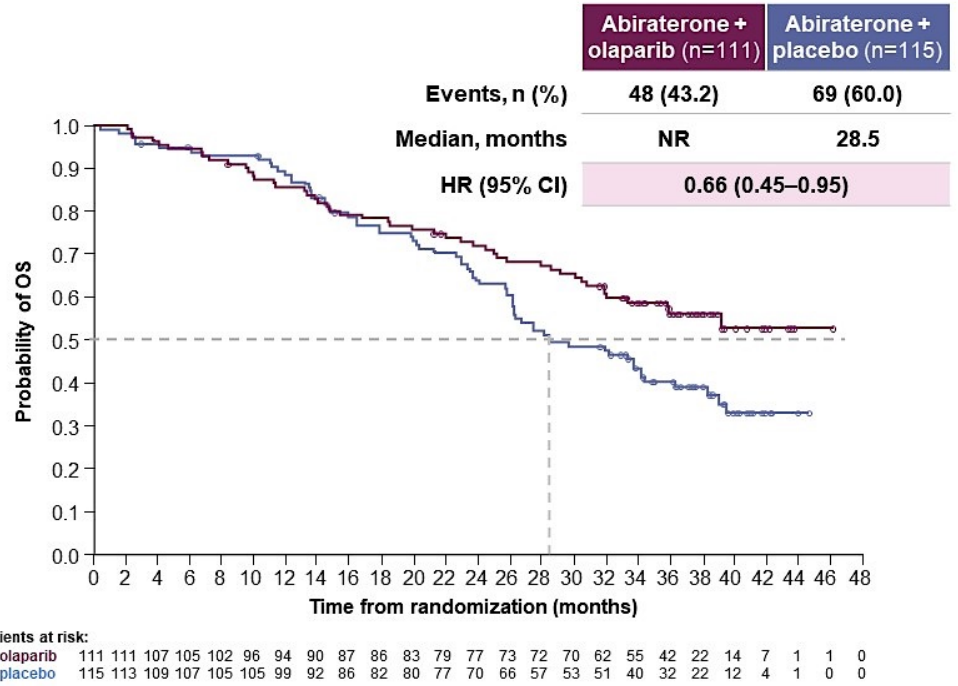
	Abiraterone + olaparib (n=399)	Abiraterone + placebo (n=397)
Events, n (%)	176 (44.1)	205 (51.6)
Median, months	42.1	34.7
HR (95% CI)	0.81 (0.67–1.00)	
P value	0.0544	
2-sided boundary for significance	0.0377	
	47.9% maturity	

DCO3: 12 October 2022.
Median (range) duration of follow-up for censored patients at DCO3 was 36.6 months (8.3–47.0) in the abiraterone + olaparib arm and 36.5 months (2.9–45.3) in the abiraterone + placebo arm.

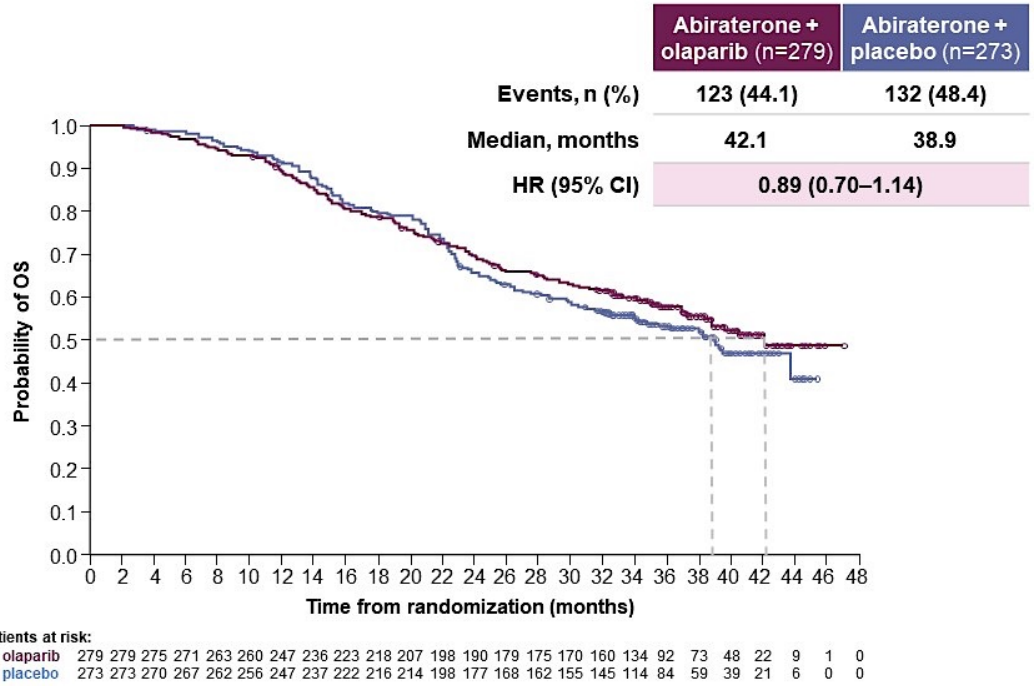
PROpel: OS in HRRm and non-HRRm subgroups (DCO3)

A trend towards OS benefit was observed across HRRm and non-HRRm subgroups

HRRm (28.4% of ITT population)



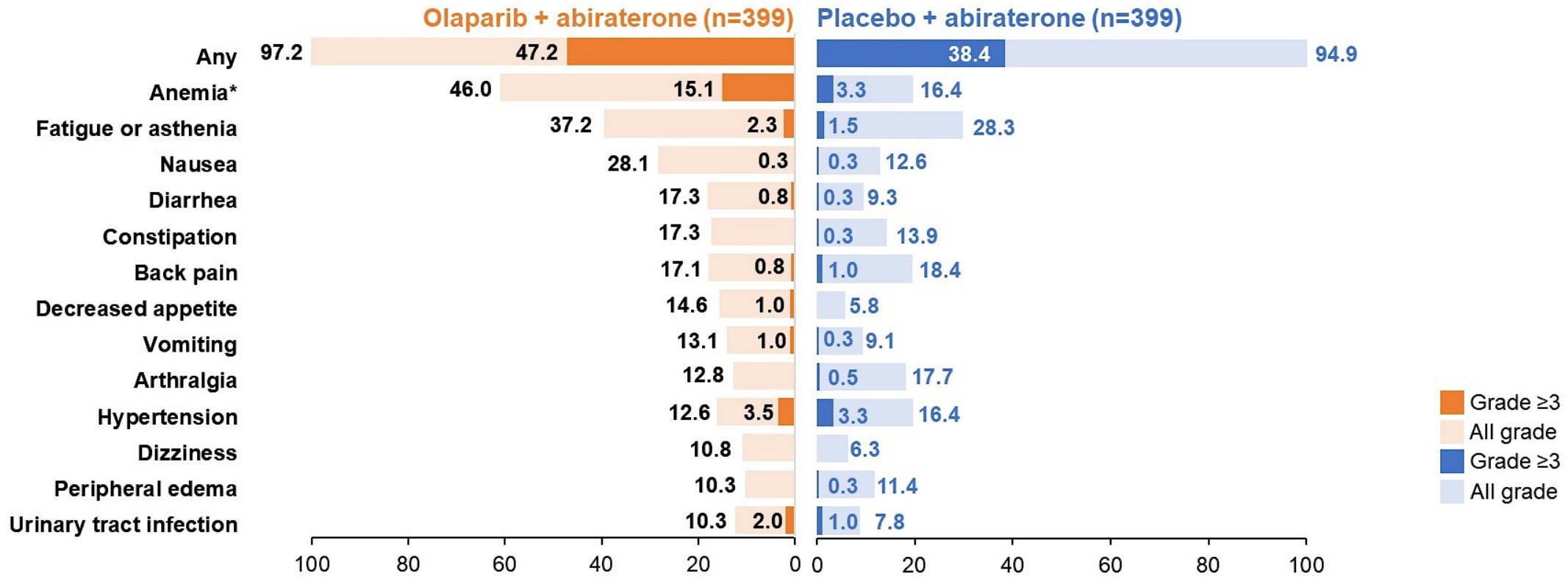
Non-HRRm (69.3% of ITT population)



DCO3: 12 October 2022.
The preplanned tumor tissue and plasma ctDNA testing was conducted after randomization and before primary analysis. Results from tumor tissue and plasma ctDNA were combined to determine patients HRRm status (see supplement for more details). 18 patients had unknown HRRm status.

PROpel: most common adverse events

AE profile was consistent with the known toxicity profiles for the individual drugs



Safety was assessed through the reporting of AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03) and laboratory assessments.
*Anemia category includes anemia, decreased hemoglobin level, decreased red-cell count, decreased hematocrit level, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, and normocytic anemia.

MAGNITUDE

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer

Kim N. Chi, MD[1]; Dana Rathkopf, MD[2]; Matthew R. Smith, MD[3]; Eleni Efstathiou, MD[4]; Gerhardt Attard, MD[5]; David Olmos, MD[6]; Ji Youl Lee, MD[7]; Eric J. Small, MD[8]; Andrea J. Pereira de Santana Gomes, MD[9]; Guilhem Roubaud, MD[10]; Marniza Saad, MD[11]; Bogdan Zurawski, MD[12]; Valerii Sakalo, MD[13]; Gary E. Mason, MD[14]; Peter Francis, MD[15]; George Wang, MS, MAS[14]; Daphne Wu, PhD[16]; Brooke Diorio, PhD[17]; Angela Lopez-Gitlitz, MD[16]; and Shahneen Sandhu, MD[18]; on behalf of the MAGNITUDE Principal Investigators

Chi KN et al., **JCO**, 2023

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial☆

K. N. Chi[1*], S. Sandhu[2,3], M. R. Smith[4,5], G. Attard[6,7], M. Saad[8], D. Olmos[9], E. Castro[10], G. Roubaud[11], A. J. Pereira de Santana Gomes[12], E. J. Small[13], D. E. Rathkopf[14,15], H. Gurney[16], W. Jung[17], G. E. Mason[18], S. Dibaj[19], D. Wu[20], B. Diorio[21], K. Urtishak[18], A. del Corral[22], P. Francis[23], W. Kim[20] & E. Efstathiou[24]

Chi KN et al., **Annals of Oncology**, 2023

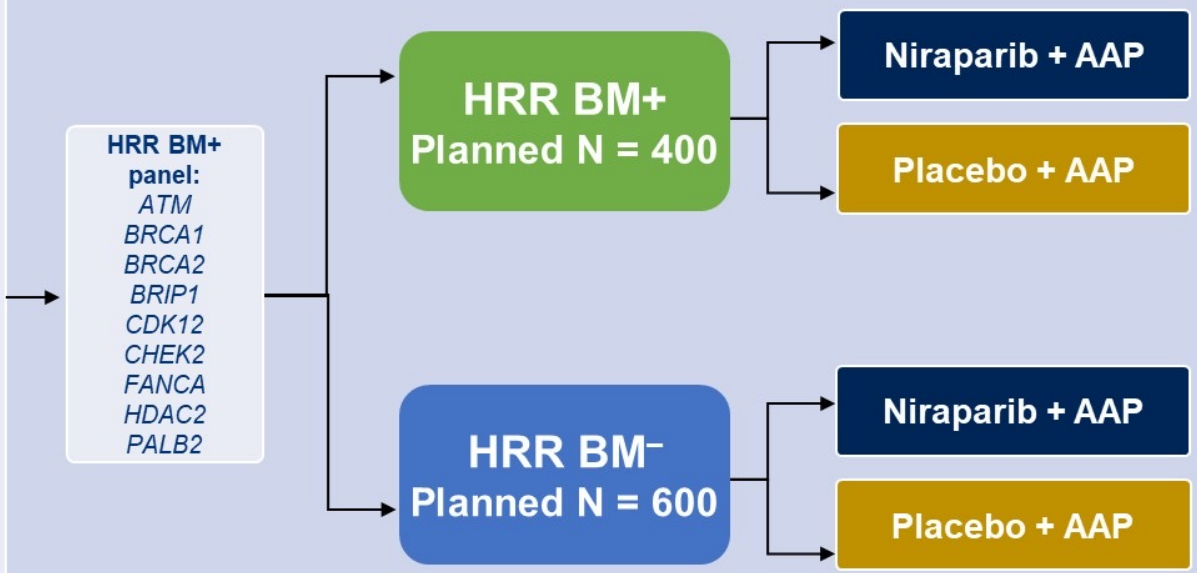
MAGNITUDE: Randomized, Double-Blind, Placebo-Controlled Study

Prospectively selected biomarker cohorts designed to test HRR BM+ and HRR BM–

Study start: February 2019

Patient eligibility
- L1 mCRPC
  - ≤4 months prior AAP allowed for mCRPC
- ECOG PS 0 or 1
- BPI-SF worst pain score ≤3

Stratifications
- Prior taxane-based chemo for mCSPC
- Prior ARi for nmCRPC or mCSPC
- Prior AAP for L1 mCRPC
- HRR BM+ cohort only:
  - *BRCA1/2* vs other HRR gene alterations



Primary endpoint
- rPFS by central review

Secondary endpoints
- Time to cytotoxic chemotherapy
- Time to symptomatic progression
- OS

Other prespecified endpoints
- Time to PSA progression
- ORR
- PFS2
- Time to pain progression
- Patient-reported outcomes

Note: Patients could request to be unblinded by the study steering committee and go on to subsequent therapy of the investigator's choice.

Clinical data cut-off was October 8, 2021 for the final rPFS analysis.

Patients were prospectively tested by plasma, tissue and/or saliva/whole blood. Patients negative by plasma only were required to test by tissue to confirm HRR BM– status.

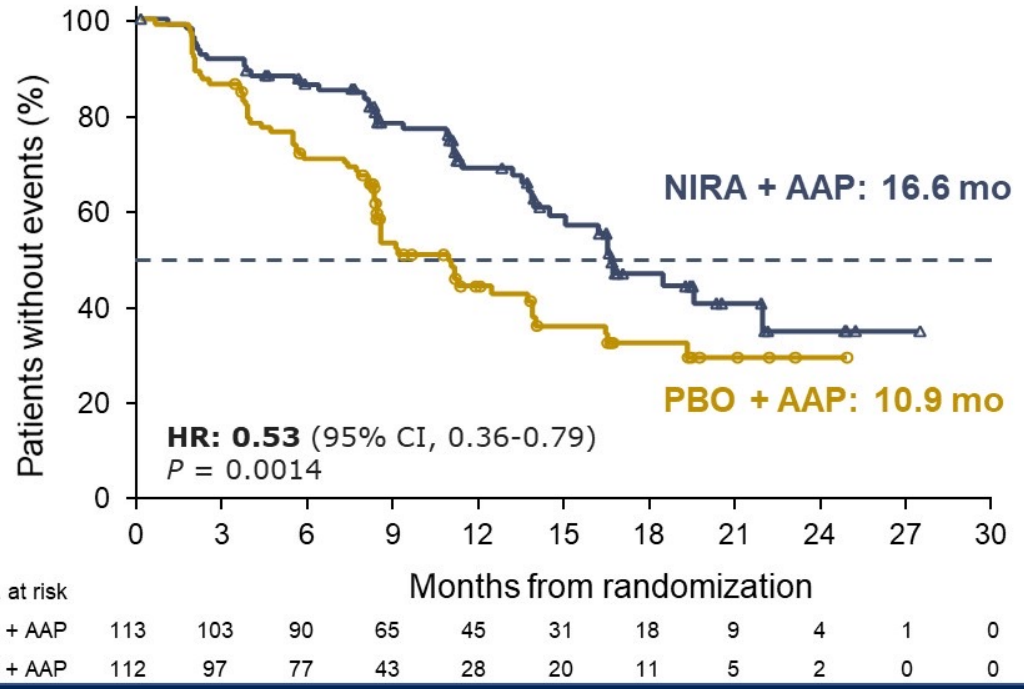
AAP, abiraterone acetate + prednisone/prednisolone; AR, androgen receptor; ARi, androgen receptor inhibitor; BM, biomarker; BPI-SF, Brief Pain Inventory–Short Form; ctDNA, circulating tumor deoxyribonucleic acid; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; L1, first line; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on first subsequent therapy; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

[a]Tissue and Plasma assays: FoundationOne tissue test (FoundationOne®CDx), Resolution Bioscience liquid test (ctDNA), AmoyDx blood and tissue assays, Invitae germline testing (blood/saliva), local lab biomarker test results demonstrating a pathogenic germline or somatic alteration listed in the study biomarker gene panel.

MAGNITUDE *BRCA1/2-mutated*: Primary Endpoint

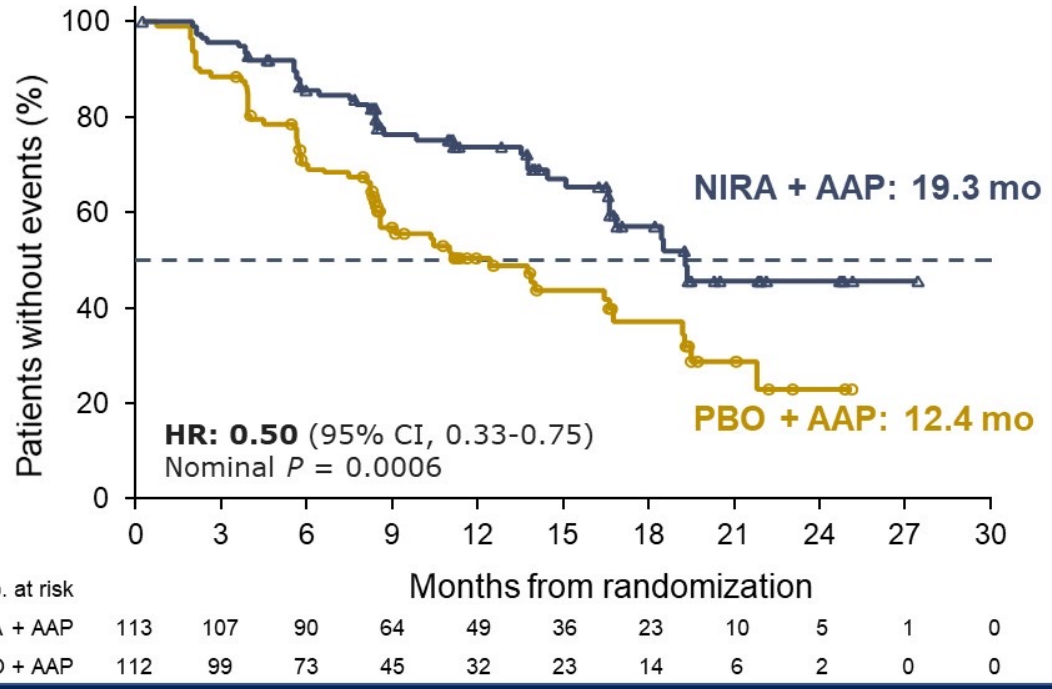
NIRA + AAP Significantly Reduced the Risk of Progression or Death by 47%

rPFS assessed by central review



No. at risk											
NIRA + AAP	113	103	90	65	45	31	18	9	4	1	0
PBO + AAP	112	97	77	43	28	20	11	5	2	0	0

rPFS assessed by investigator



No. at risk											
NIRA + AAP	113	107	90	64	49	36	23	10	5	1	0
PBO + AAP	112	99	73	45	32	23	14	6	2	0	0

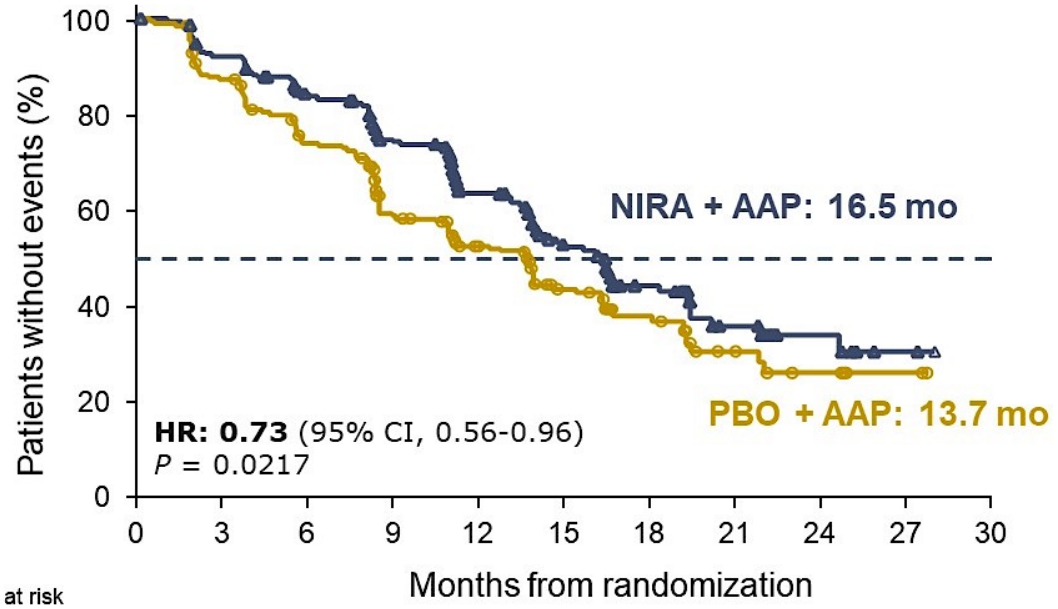
Median follow-up 16.7 months

AAP, abiraterone acetate + prednisone/prednisolone; CI, confidence interval; HR, hazard ratio; NIRA, niraparib; PBO, placebo; rPFS, radiographic progression-free survival.

MAGNITUDE All HRR BM+: Primary Endpoint

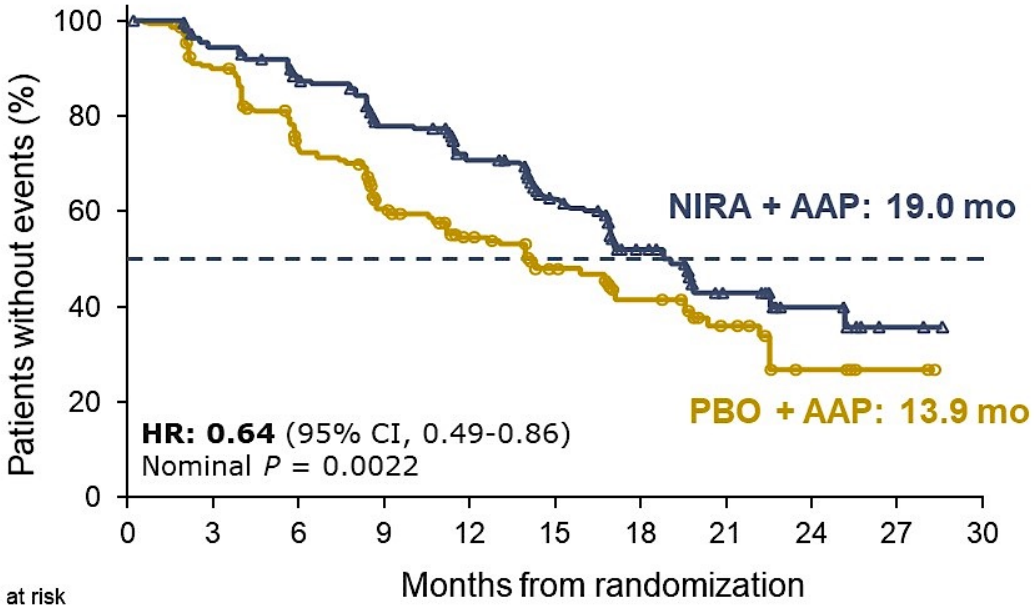
NIRA + AAP Significantly Reduced the Risk of Progression or Death by 27%

rPFS assessed by central review



No. at risk											
NIRA + AAP	212	192	167	129	96	64	45	21	10	2	0
PBO + AAP	211	182	149	102	78	53	35	15	9	2	0

rPFS assessed by investigator

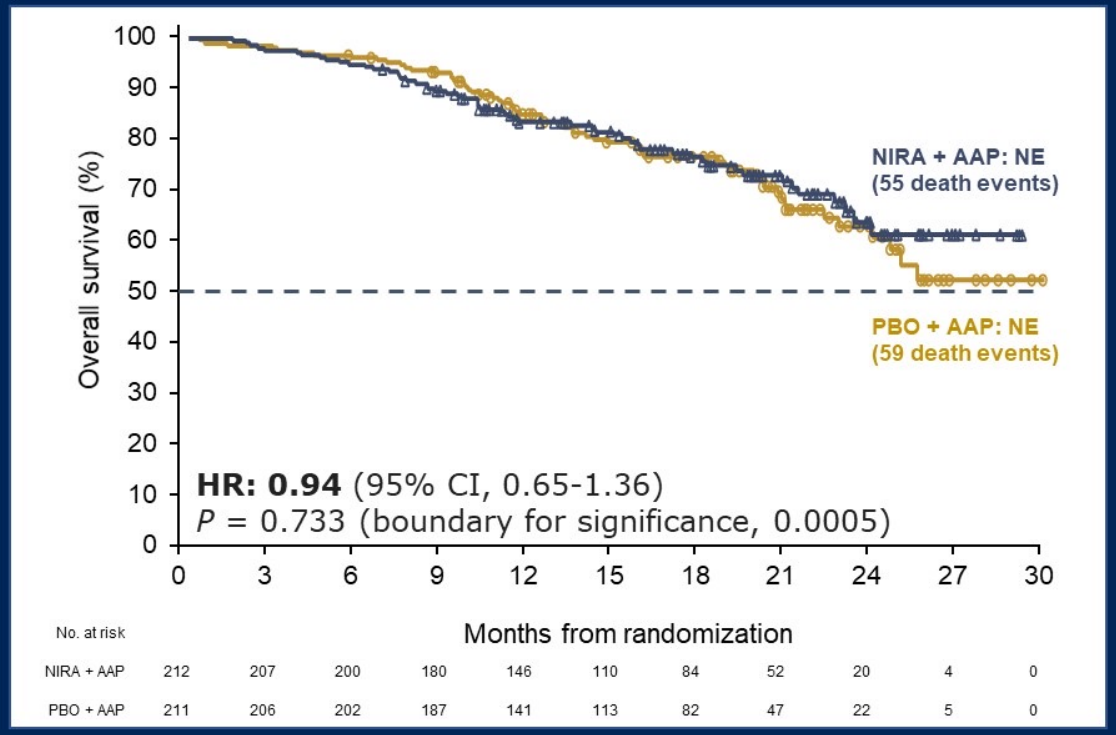


No. at risk											
NIRA + AAP	212	197	174	136	108	75	50	23	11	2	0
PBO + AAP	211	187	145	103	81	58	41	20	9	2	0

Median follow-up 18.6 months

AAP, abiraterone acetate + prednisone/prednisolone; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; NIRA, niraparib; PBO, placebo; rPFS, radiographic progression-free survival.

MAGNITUDE All HRR BM+: Overall Survival
First Interim Analysis With Median Follow-up of 18.6 Months



Pre-specified Overall Survival Multivariate Analysis

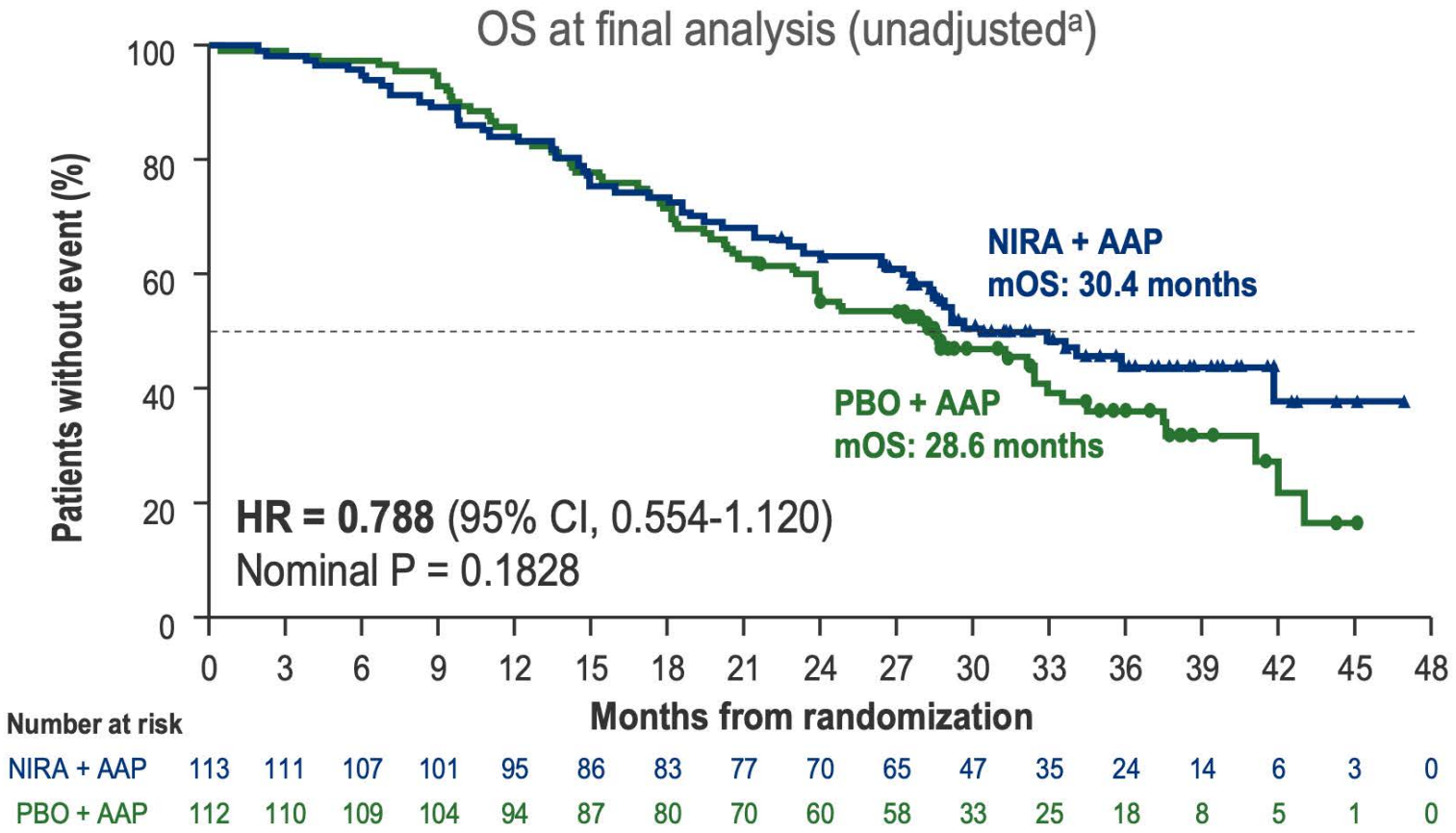
- A multivariate analysis accounting for baseline characteristics shows overall survival favors the NIRA + AAP arm
- Overall survival **HR = 0.767** (95% CI, 0.525-1.119; nominal *P* = 0.1682)

27% of deaths in the study population observed at overall survival interim analysis and thus these data are immature

AAP, abiraterone acetate + prednisone/prednisolone; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; NE, not estimable; NIRA, niraparib; PBO, placebo.

MAGNITUDE Final Analysis

Secondary endpoint: OS favored NIRA + AAP over PBO + AAP in *BRCA*+ patients



[a]Does not account for baseline imbalances. mOS, median overall survival.

Preplanned multivariate analysis (MVA) using prespecified prognostic factors supported an OS benefit of NIRA + AAP

MVA: HR = 0.663 (95% CI, 0.464-0.947); nominal P = 0.0237

MADRID 2023 ESMO congress

Dr Kim Chi

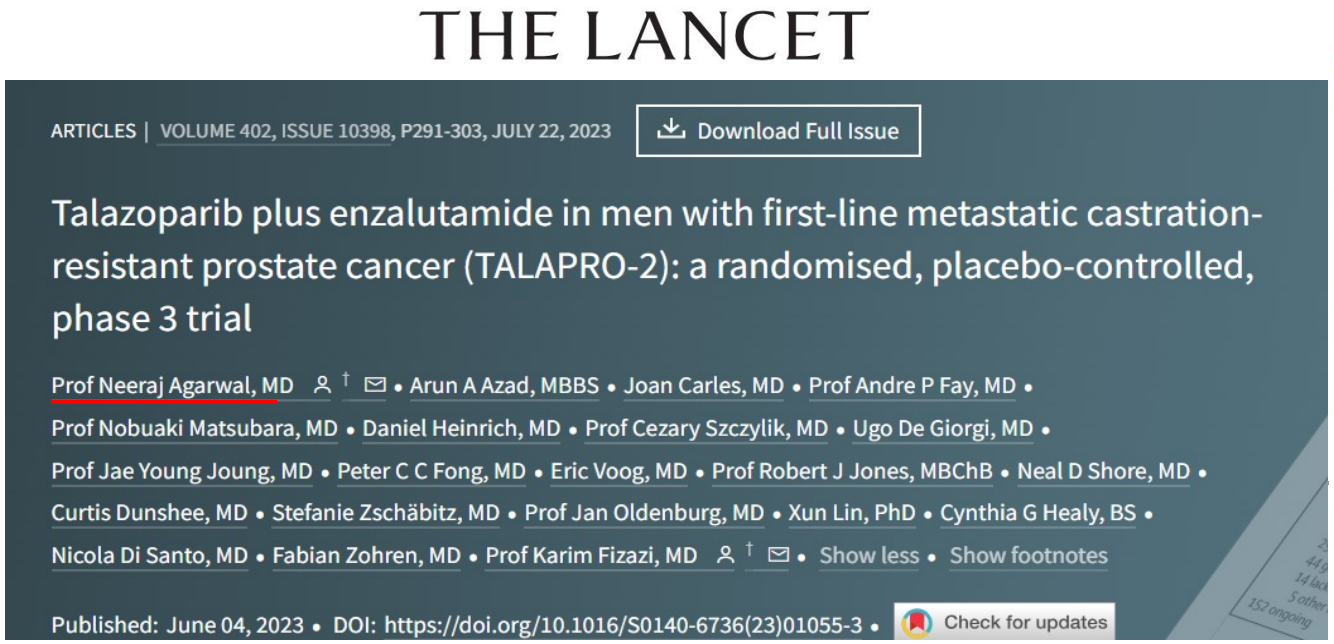
MAGNITUDE: TEAEs in HRR+ Patients (occurring in >10% of patients)

	NIRA + AAP (n = 212)			PBO + AAP (n = 211)		
Event	All Grades, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)	All Grades, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)
Patients with ≥1 SAE	76 (35.8)			52 (24.6)		
Any TEAEs	210 (99.1)	119 (56.1)	23 (10.8)	199 (94.3)	90 (42.7)	8 (3.8)
Anemia	98 (46.2)	60 (28.3)	3 (1.4)	43 (20.4)	16 (7.6)	0
Hypertension	66 (31.1)	31 (14.6)	0	44 (20.9)	26 (12.3)	0
Constipation	65 (30.7)	0	0	29 (13.7)	0	0
Fatigue	56 (26.4)	7 (3.3)	0	35 (16.6)	9 (4.3)	0
Nausea	50 (23.6)	1 (0.5)	0	29 (13.7)	0	0
Thrombocytopenia	45 (21.2)	6 (2.8)	8 (3.8)	18 (8.5)	5 (2.4)	0
Dyspnea	34 (16.0)	4 (1.9)	0	12 (5.7)	2 (0.9)	0
Asthenia	33 (15.6)	1 (0.5)	1 (0.5)	19 (9.0)	1 (0.5)	0
Back pain	31 (14.6)	5 (2.4)	0	44 (20.9)	2 (0.9)	0
Decreased appetite	30 (14.2)	1 (0.5)	0	13 (6.2)	1 (0.5)	0
Hypokalemia	29 (13.7)	6 (2.8)	0	20 (9.5)	6 (2.8)	0
Neutropenia	29 (13.7)	11 (5.2)	3 (1.4)	12 (5.7)	3 (1.4)	0
Vomiting	28 (13.2)	1 (0.5)	0	14 (6.6)	1 (0.5)	0
Arthralgia	28 (13.2)	1 (0.5)	0	20 (9.5)	1 (0.5)	0
Dizziness	24 (11.3)	1 (0.5)	0	12 (5.7)	0	0
Insomnia	22 (10.4)	0	0	8 (3.8)	0	0
Leukopenia	22 (10.4)	4 (1.9)	0	5 (2.4)	1 (0.5)	0
Bone pain	21 (9.9)	3 (1.4)	0	24 (11.4)	1 (0.5)	0
Fall	11 (5.2)	2 (0.9)	0	26 (12.3)	6 (2.8)	0

NOTE. Grade 5 TEAEs in the NIRA 1 AAP, group, No. (%): dyspnea, 1 (0.5).

Abbreviations: AAP, abiraterone acetate with prednisone; HRR, homologous recombination repair; NIRA, niraparib; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

TALAPRO-2



THE LANCET

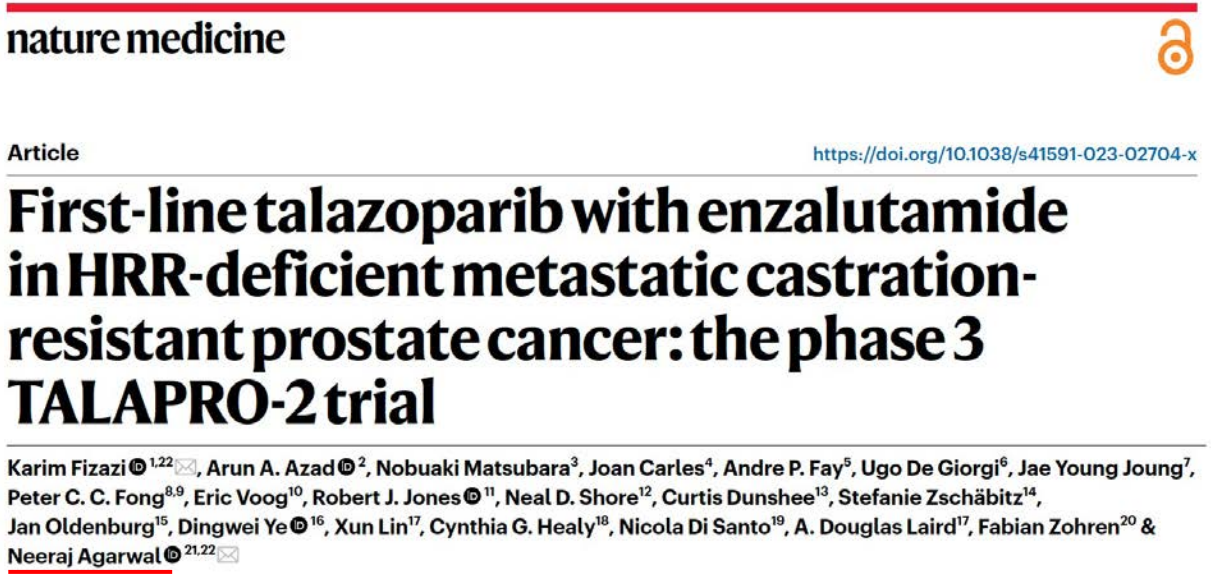
ARTICLES | VOLUME 402, ISSUE 10398, P291-303, JULY 22, 2023 Download Full Issue

Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial

Prof Neeraj Agarwal, MD † • Arun A Azad, MBBS • Joan Carles, MD • Prof Andre P Fay, MD • Prof Nobuaki Matsubara, MD • Daniel Heinrich, MD • Prof Cezary Szczylik, MD • Ugo De Giorgi, MD • Prof Jae Young Joung, MD • Peter C C Fong, MD • Eric Voog, MD • Prof Robert J Jones, MBChB • Neal D Shore, MD • Curtis Dunshee, MD • Stefanie Zschäbitz, MD • Prof Jan Oldenburg, MD • Xun Lin, PhD • Cynthia G Healy, BS • Nicola Di Santo, MD • Fabian Zohren, MD • Prof Karim Fizazi, MD † • Show less • Show footnotes

Published: June 04, 2023 • DOI: https://doi.org/10.1016/S0140-6736(23)01055-3 • Check for updates

Agarwal N. et al., ***The Lancet***, 2023



nature medicine

Article https://doi.org/10.1038/s41591-023-02704-x

First-line talazoparib with enzalutamide in HRR-deficient metastatic castration-resistant prostate cancer: the phase 3 TALAPRO-2 trial

Karim Fizazi[1,22], Arun A. Azad[2], Nobuaki Matsubara[3], Joan Carles[4], Andre P. Fay[5], Ugo De Giorgi[6], Jae Young Joung[7], Peter C. C. Fong[8,9], Eric Voog[10], Robert J. Jones[11], Neal D. Shore[12], Curtis Dunshee[13], Stefanie Zschäbitz[14], Jan Oldenburg[15], Dingwei Ye[16], Xun Lin[17], Cynthia G. Healy[18], Nicola Di Santo[19], A. Douglas Laird[17], Fabian Zohren[20] & Neeraj Agarwal[21,22]

Fizazi K, …, **Agarwal N.**, ***Nature medicine***, 2023

TALAPRO-2: Trial Design

HRR-deficient cohort is being presented today in poster D15
Statistically significant and clinically meaningful improvement in OS

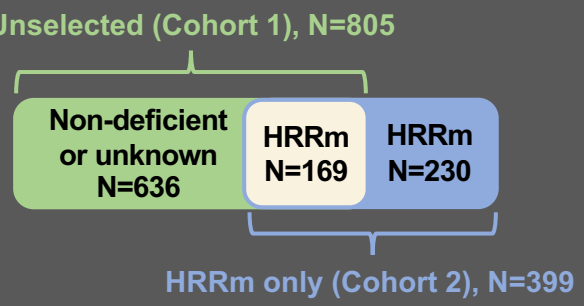
Patient population

- 1L mCRPC
- ECOG 0 or 1
- Ongoing androgen deprivation therapy

Stratification factors

- Prior abiraterone[a] or docetaxel for CSPC (yes vs no)
- HRR gene alteration status (deficient vs non-deficient or unknown)[b]

Sequential enrollment in two cohorts:



1:1

Talazoparib + enzalutamide (N=402)

Unselected Cohort 1 (N=805)

Placebo + enzalutamide (N=403)

Primary endpoint

- rPFS by BICR

Key secondary endpoint

- OS (alpha protected)

Other secondary endpoints

- Time to cytotoxic chemotherapy
- PFS2
- ORR
- Patient-reported outcomes
- Safety

Samples **prospectively assessed** for HRR gene alterations
(ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, NBN, MLH1, MRE11A, PALB2, RAD51C)
using FoundationOne/FoundationOne®CDx and FoundationOne®Liquid CDx

Analysis timeline: (unselected)

DCO1: Aug 16, 2022
rPFS (primary)

DCO2: March 28, 2023
OS (interim)

DCO3: Sept 3, 2024
OS (final) current

[a]Prior orteronel was received by two patients in each treatment arm in Cohort 1 and one patient in each treatment arm in Cohort 2. [b]Unselected cohort only.
BICR=blinded independent central review; CSPC=castration-sensitive prostate cancer; DCO=data cutoff; ORR=objective response rate; PFS2=time to second progression or death.

Source of Tumor DNA for Assessment and Baseline HRR Gene Alterations

Tissue source for prospective HRR gene alteration testing, n (%)	Talazoparib + Enzalutamide (N=402)	Placebo + Enzalutamide (N=403)
Tumor tissue	**402 (100.0)**	**403 (100.0)**
Tumor tissue and blood (circulating tumor DNA)	**57 (14.2)**	**58 (14.4)**

BRCA1/2 gene alterations were detected in 7.3% of patients across both arms

HRR gene alterations by prospective tumor tissue testing, n (%)[1]	Talazoparib + Enzalutamide (N=402)	Placebo + Enzalutamide (N=403)
1 or more alterations in the corresponding gene	**85 (21.1)**	**82 (20.3)**
CDK12	**23 (5.7)**	**29 (7.2)**
BRCA2	**23 (5.7)**	**28 (6.9)**
ATM	**23 (5.7)**	**14 (3.5)**
CHEK2	**6 (1.5)**	**5 (1.2)**
BRCA1	**5 (1.2)**	**4 (1.0)**
Other (*ATR*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*)	**14 (3.5)**	**13 (3.2)**

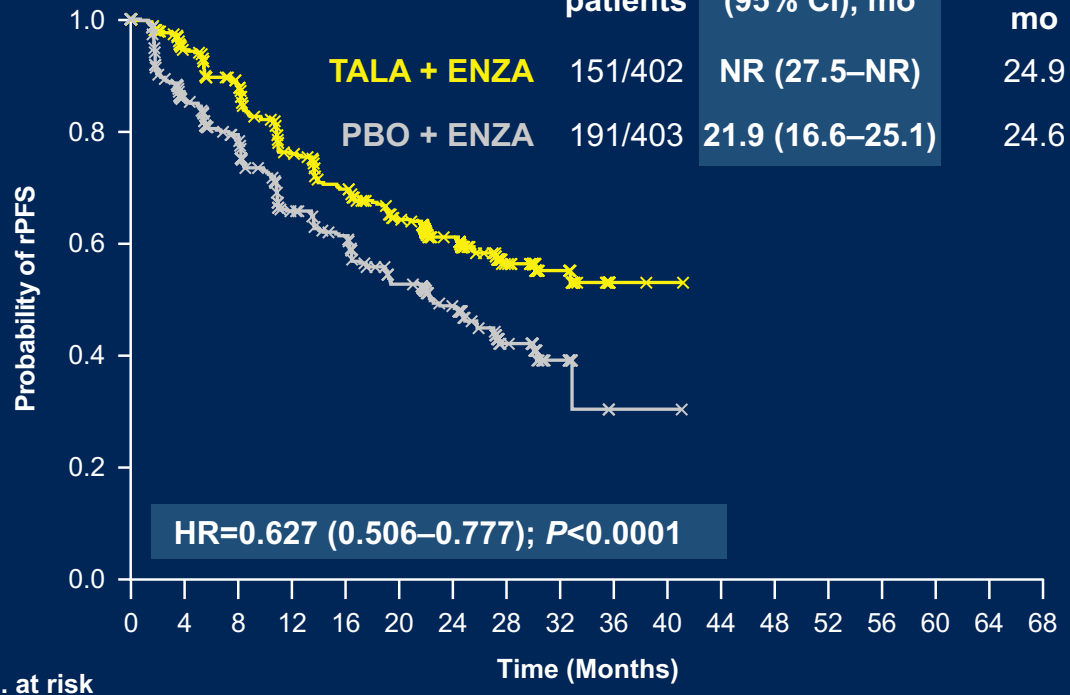
Data cutoff: August 16, 2022. 1. Agarwal N, et al. *Lancet.* 2023;402:291-303.

Primary Endpoint: rPFS by BICR

Statistically significant and clinically meaningful benefit maintained with ~2 years of additional follow-up

Primary analysis (DCO: Aug 16, 2022)[1]

	Events/ patients	Median rPFS (95% CI), mo	Median follow-up, mo
TALA + ENZA	151/402	NR (27.5–NR)	24.9
PBO + ENZA	191/403	21.9 (16.6–25.1)	24.6

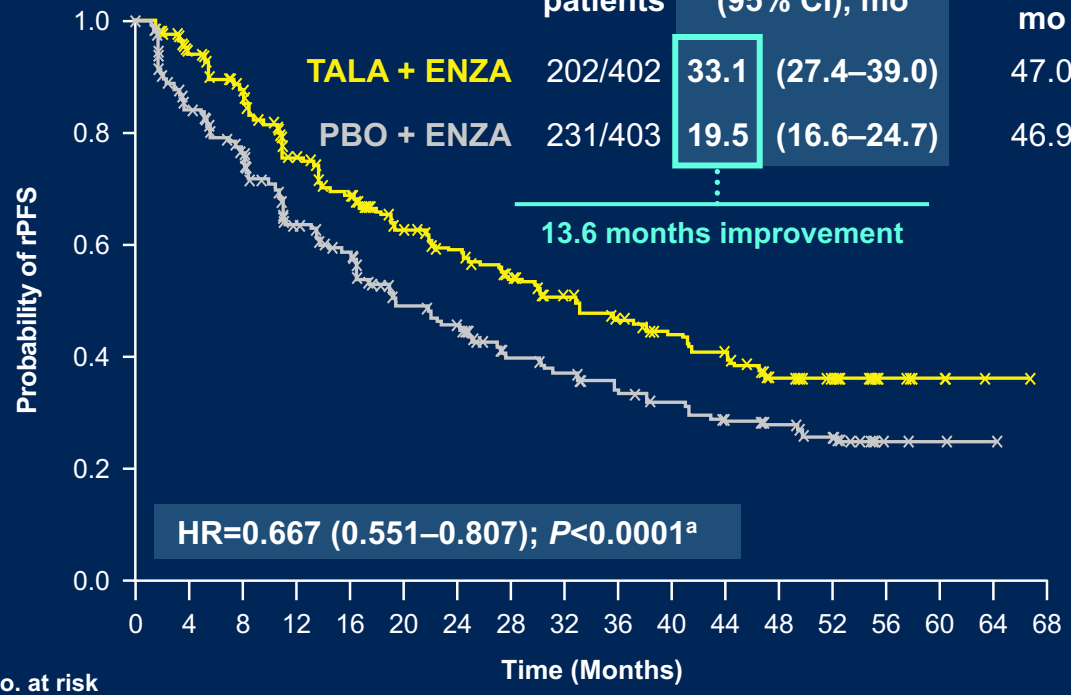


No. at risk

TALA + ENZA	402	353	318	256	226	193	136	67	29	2	1	0	0	0	0	0	0
PBO + ENZA	403	311	272	200	179	140	96	43	14	1	1	0	0	0	0	0	0

Update (DCO: Sept 3, 2024)

	Events/ patients	Median rPFS (95% CI), mo	Median follow-up, mo
TALA + ENZA	202/402	33.1 (27.4–39.0)	47.0
PBO + ENZA	231/403	19.5 (16.6–24.7)	46.9



No. at risk

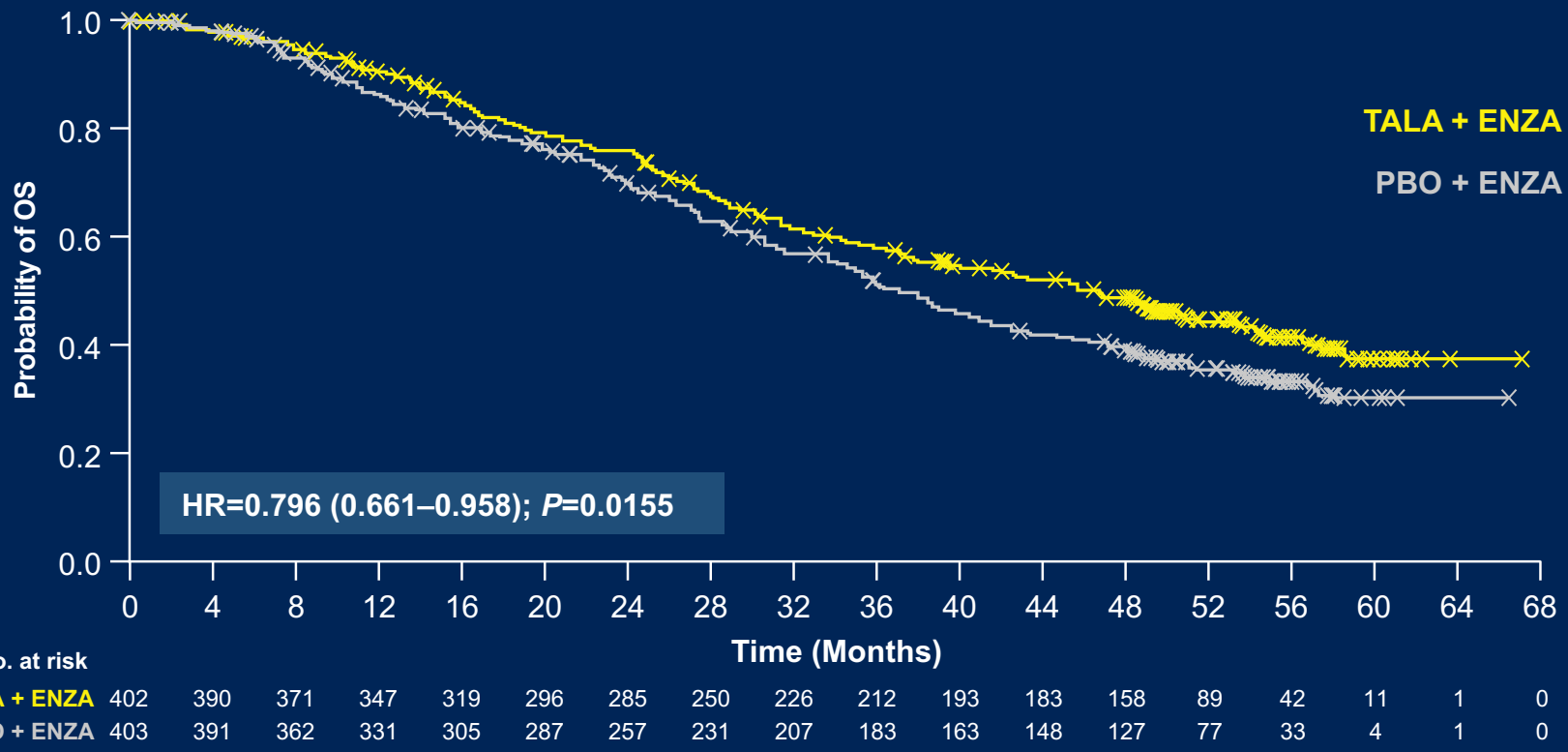
TALA + ENZA	402	353	318	257	228	196	180	155	138	122	108	101	63	50	13	7	1	0
PBO + ENZA	403	312	273	201	180	138	128	100	92	81	72	66	44	35	5	2	1	0

Stratified hazard ratios (HRs) and 2-sided *P* values are reported throughout this presentation unless otherwise stated.

[a]**The updated rPFS data are descriptive.** DCO=data cutoff; ENZA=enzalutamide; NR=not reached; PBO=placebo; TALA=talazoparib. 1. **Reproduced with permission from** Agarwal N, et al. *Lancet.* 2023;402:291-303.

Overall Survival (Final Analysis)

20.4% reduction in risk of death, >8 months improvement in median OS



	Events/patients	Median OS (95% CI), mo
TALA + ENZA	211/402	45.8 (39.4–50.8)
PBO + ENZA	243/403	37.0 (34.1–40.4)

8.8 months improvement

Median follow-up for OS was 52.5 months

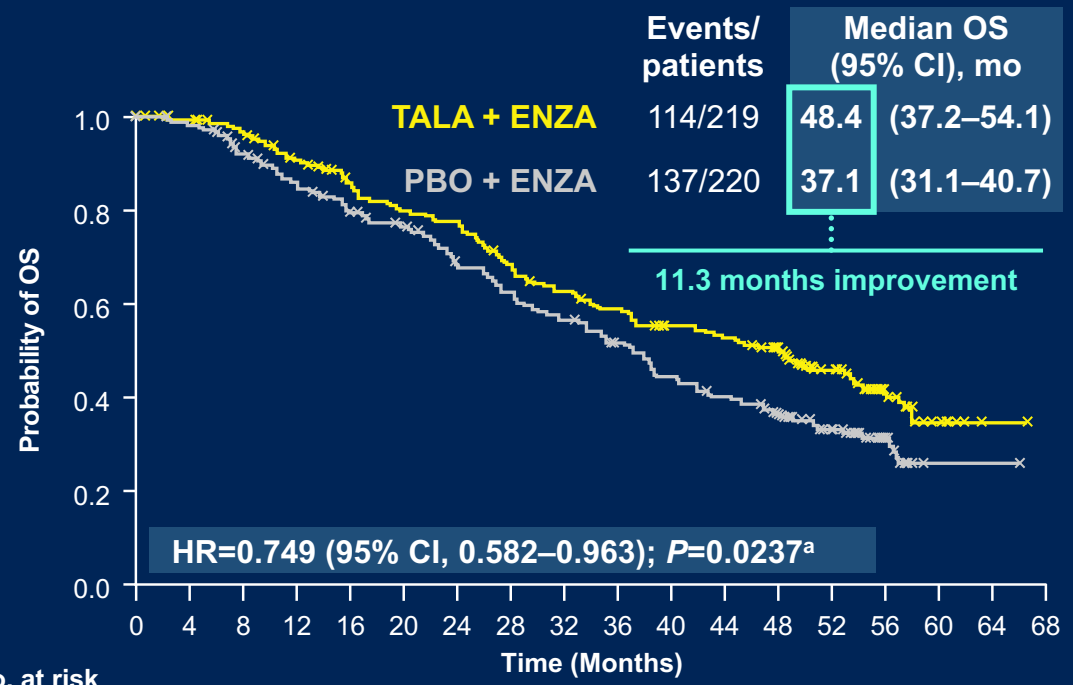
For statistical significance at the final overall survival analysis, the stratified log-rank 2-sided *P* value needed to be ≤0.022 based on a group sequential design with O'Brien-Fleming spending function.

Data cutoff: September 3, 2024.

Overall Survival in Subgroups With No Alterations Detected by Both ctDNA and Tumor Tissue

Clinically meaningful reduction in risk of death in patients without *BRCA* or HRR alterations

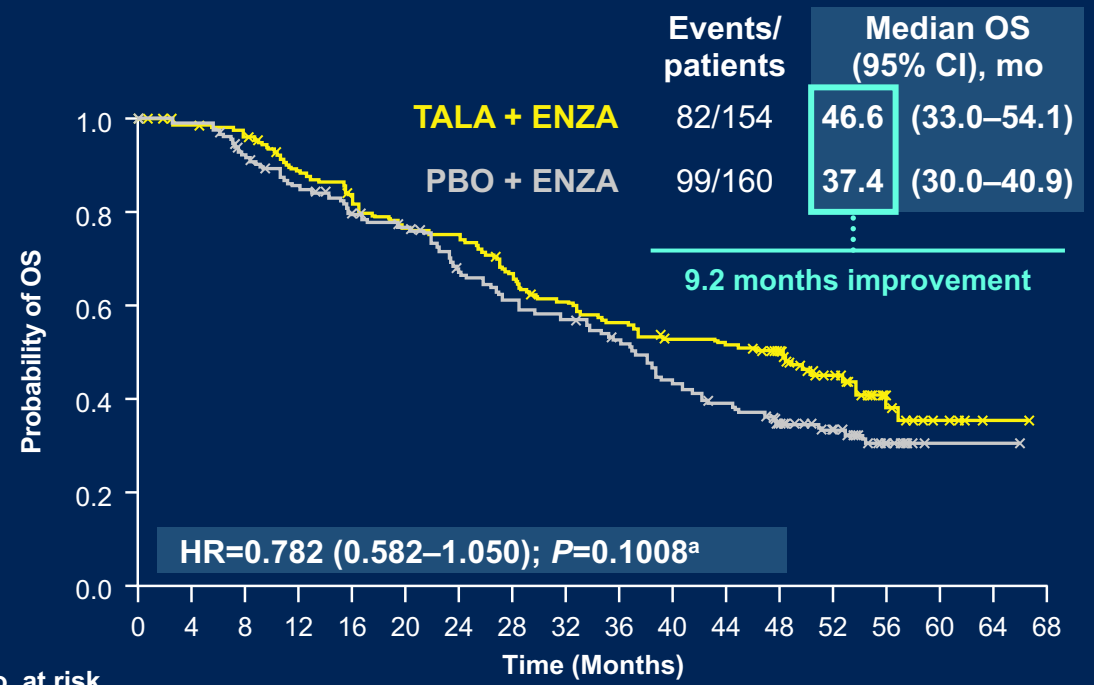
No *BRCA* alteration detected



No. at risk

TALA + ENZA	219	213	204	187	172	159	155	135	123	114	102	99	89	51	26	7	1	0
PBO + ENZA	220	214	196	179	164	155	135	121	110	98	84	75	63	39	20	1	1	0

No HRR alteration detected



No. at risk

TALA + ENZA	154	148	142	128	120	110	108	95	85	79	72	71	64	36	19	5	1	0
PBO + ENZA	160	156	143	131	120	113	97	87	81	73	61	53	44	29	14	1	1	0

Post hoc analysis employing all available test results of prescreening/screening samples including both prospective and retrospective analyses.

Data cutoff: September 3, 2024. [a]Reported *P* values are nominal and descriptive.

Summary of TEAEs

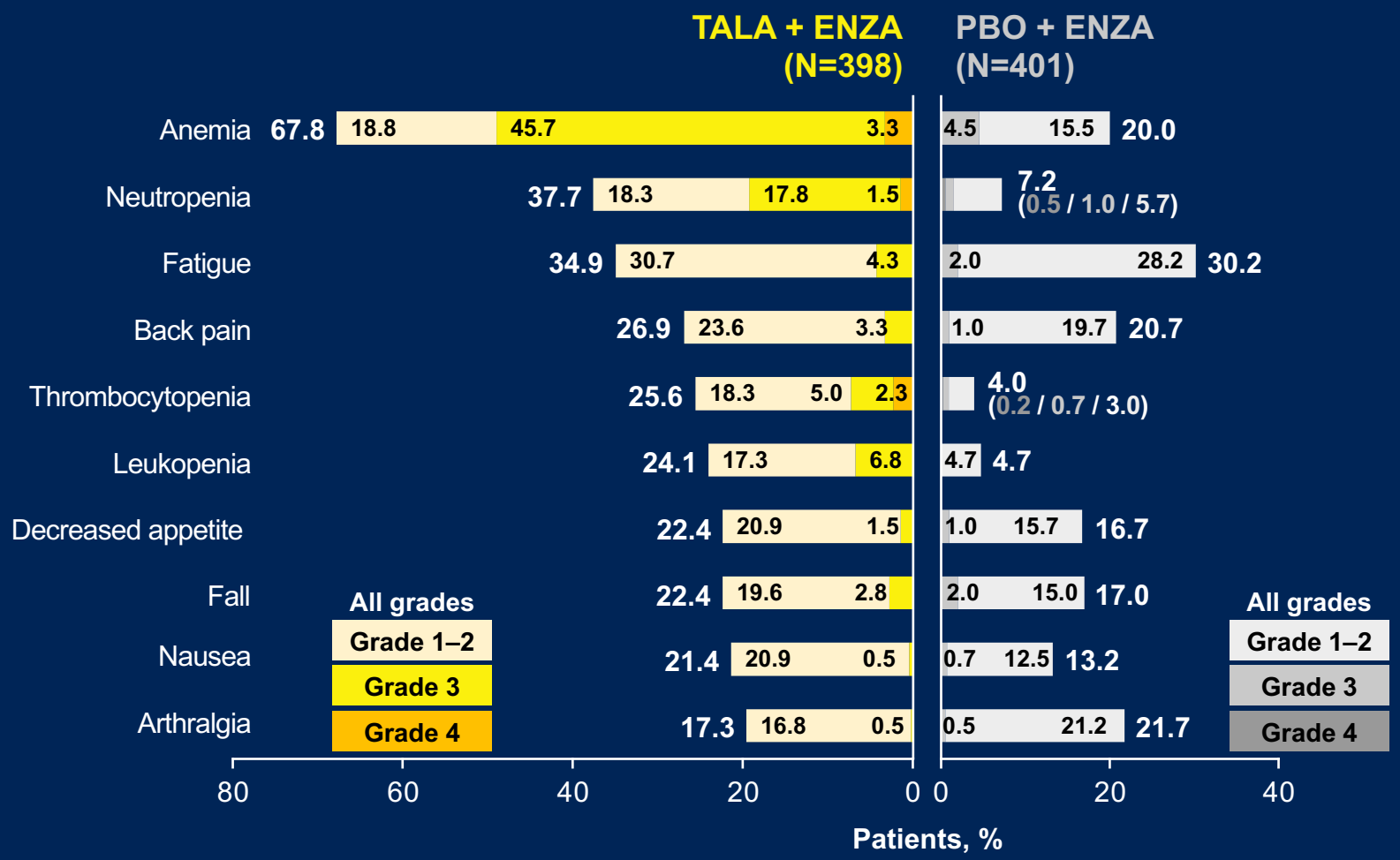
TEAEs, n (%)	TALA + ENZA (N=398)	PBO + ENZA (N=401)
Any TEAE	**394 (99.0)**	**384 (95.8)**
Treatment-related	**360 (90.5)**	**286 (71.3)**
SAEs	**182 (45.7)**	**126 (31.4)**
Treatment-related	**85 (21.4)**	**13 (3.2)**
Grade 3–4 TEAEs	**302 (75.9)**	**179 (44.6)**
Grade 5 TEAEs	**14 (3.5)**	**20 (5.0)**
Treatment-related	**1 (0.3)**	**2 (0.5)**
Dose interruption of talazoparib or placebo due to AE	**260 (65.3)**	**99 (24.7)**
Dose reduction of talazoparib or placebo due to AE[a]	**217 (54.5)**	**29 (7.2)**
Discontinuation of talazoparib or placebo due to AE	**86 (21.6)**	**52 (13.0)**

No new safety findings were identified after an additional 2 years of follow-up

- No additional cases of MDS or AML in the talazoparib group; n=1 of each previously reported
- Rate of discontinuation of talazoparib due to AEs was similar to that in the primary analysis
- In exposure-adjusted analyses, rate of venous embolic and thrombotic events was unchanged with longer follow-up (2.4 per 100 participant-years)

[a]**The median relative dose intensity of talazoparib remained >80%.**
AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Most Common All-Cause TEAEs



In the talazoparib arm:

- 49.0% had grade 1–2 anemia at baseline
- Most common TEAEs leading to a dose reduction of talazoparib were:
  - Anemia (46.2%)
  - Neutropenia (16.3%)
  - Thrombocytopenia (6.2%)
- Grade 3–4 anemia
  - Reported in 49.0% of patients
  - Median time to onset was 3.3 months
  - 42.2% received an RBC transfusion (median of two transfusions)
- 8.5% discontinued talazoparib due to anemia
- Median duration of treatment with talazoparib was 19.7 months

Figure includes TEAEs reported in ≥20% of patients in either arm.

Conclusions

- TALAPRO-2 is the first PARPi plus ARPI combination study to show a statistically significant and clinically meaningful improvement in OS vs standard-of-care ARPI in mCRPC – in patients unselected (cohort 1) and selected for HRR gene alterations (cohort 2 – poster D15)
  - Median OS in the talazoparib group was 45.8 months – **8.8 months longer** than active control
- Median OS with talazoparib plus enzalutamide was similar across the ITT, and HRR-deficient and HRR–non-deficient subgroup populations, ranging from 46 to 47 months
- Median rPFS in the talazoparib group was 33.1 months – **13.6 months longer** than active control
- No new safety signals were identified with extended follow-up

These data support talazoparib plus enzalutamide as a standard-of-care initial treatment option for mCRPC

Phase 3 Combination trials of PARP inhibitors with an APRI

	PROpel (N = 796)	MAGNITUDE (N = 423)	TALAPRO-2 (Cohort 1: N = 805)	TALAPRO-2 (Cohort 2: N = 399)
Trial population mCRPC 1st line	Docetaxel / ARSI in mCSPC setting allowed (ARSI without progression and > 12 months ago)	Docetaxel / ARSI in mCSPC setting allowed ; Abiraterone in mCRPC allowed if given < 4 months	Docetaxel / Abiraterone in mCSPC setting allowed	
Design and randomization	1 : 1 randomisation Abiraterone + olaparib (n = 399) vs abiraterone + placebo (n = 397)	Cohort 1: HRR cohort 1 : 1 randomisation abiraterone + niraparib (n = 212) vs abiraterone + placebo (n = 211) Cohort 2: non-HRR cohort (closed prematurely because of futility)	All-comer population 1 : 1 randomisation Enzalutamide + talazoparib (n = 402) vs enzalutamide + placebo (n = 403)	HRR cohort 1 : 1 randomisation Enzalutamide + talazoparib (n = 200) vs enzalutamide + placebo (n = 199)
HRR analysis	Tissue or ctDNA / retrospective	100% tissue / prospective	100% tissue / prospective	99.5% tissue / prospective 0.5% ctDNA or unspecified tissue source / prospective
Primary endpoint	rPFS (investigator review)	rPFS (central review)	rPFS (central review)	rPFS (central review)
rPFS, HR (95% CI)				
All comers	HR 0.66 (0.54-0.81)	NR	HR 0.63 (0.51-0.78)	Not included
HRR -ve	HR 0.76 (0.6-0.97)	HR 1.09 (0.75-1.57)	HR 0.70 (0.54-0.89)	Not included
HRR +ve	HR 0.50 (0.34-0.73)	HR 0.73 (0.56-0.96)	HR 0.46 (0.30-0.70)	HR 0.45 (0.33-0.61)
BRCA+	HR 0.23 (0.12-0.43)	HR 0.53 (0.36-0.79)	HR 0.23 (0.10-0.53)	HR 0.20 (0.11-0.36)
ORR (all comers)	58% vs 48%	60% vs 28% (only HRR+ pts)	61.7% vs 43.9%	67% vs 40%
OS (all comers)	HR 0.81 (0.67-1)	HR 0.66 (0.46-0.95) (only for BRCA 1/2)	**HR 0.80 (0.66–0.96)**	**HR 0.62 (0.48–0.81)**
FDA approval; EMA approval	**mCRPC with BRCA1/2 mutations; mCRPC when chemotherapy is not indicated**	**mCRPC with BRCA1/2 mutations**	**mCRPC with any HRR mutations; mCRPC when chemotherapy is not clinically indicated**	
Publication	Clarke N….Saad F. ***NEJM Evidence***, 2022	Chi K….Sandhu S. ***JCO***, 2023	**Agarwal N**….Fizazi K. ***Lancet***, 2023	Fizazi K….**Agarwal N.** ***Nature medicine***, 2023

ASCO Genitourinary Cancers Symposium

Abstract # 19

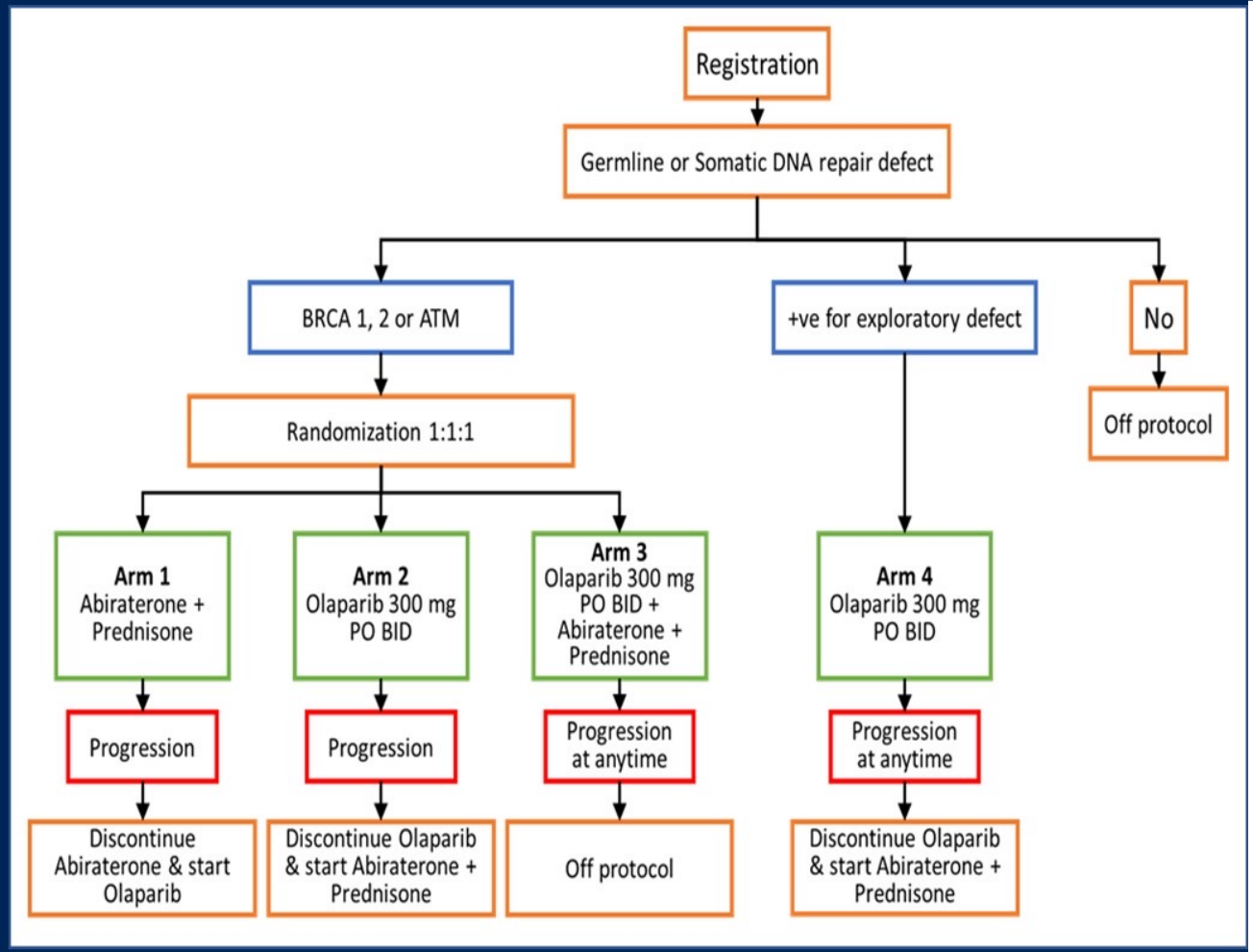
BRCAAway: A Randomized Phase 2 Trial of Abiraterone, Olaparib, or Abiraterone + Olaparib in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) bearing Homologous Recombination-Repair Mutations (HRRm)

Maha Hussain*, MD, FACP, FASCO, Masha Kocherginsky, PhD, Neeraj Agarwal, MD, Nabil Adra, MD, Jingsong Zhang, MD, PhD, Channing Judith Paller, MD, Joel Picus, MD, Zachery R Reichert, MD, PhD, Russell Zelig Szmulewitz, MD, Scott T. Tagawa, MD, Timothy Kuzel, MD, Latifa Bazzi, MPH, Stephanie Daignault-Newton, MS, Young E. Whang, MD, PhD, Robert Dreicer, MD, Ryan D. Stephenson, DO, Matthew Rettig, MD, Daniel H. Shevrin, MD, Arul Chinnaiyan, MD, PhD, Emmanuel S. Antonarakis, MD

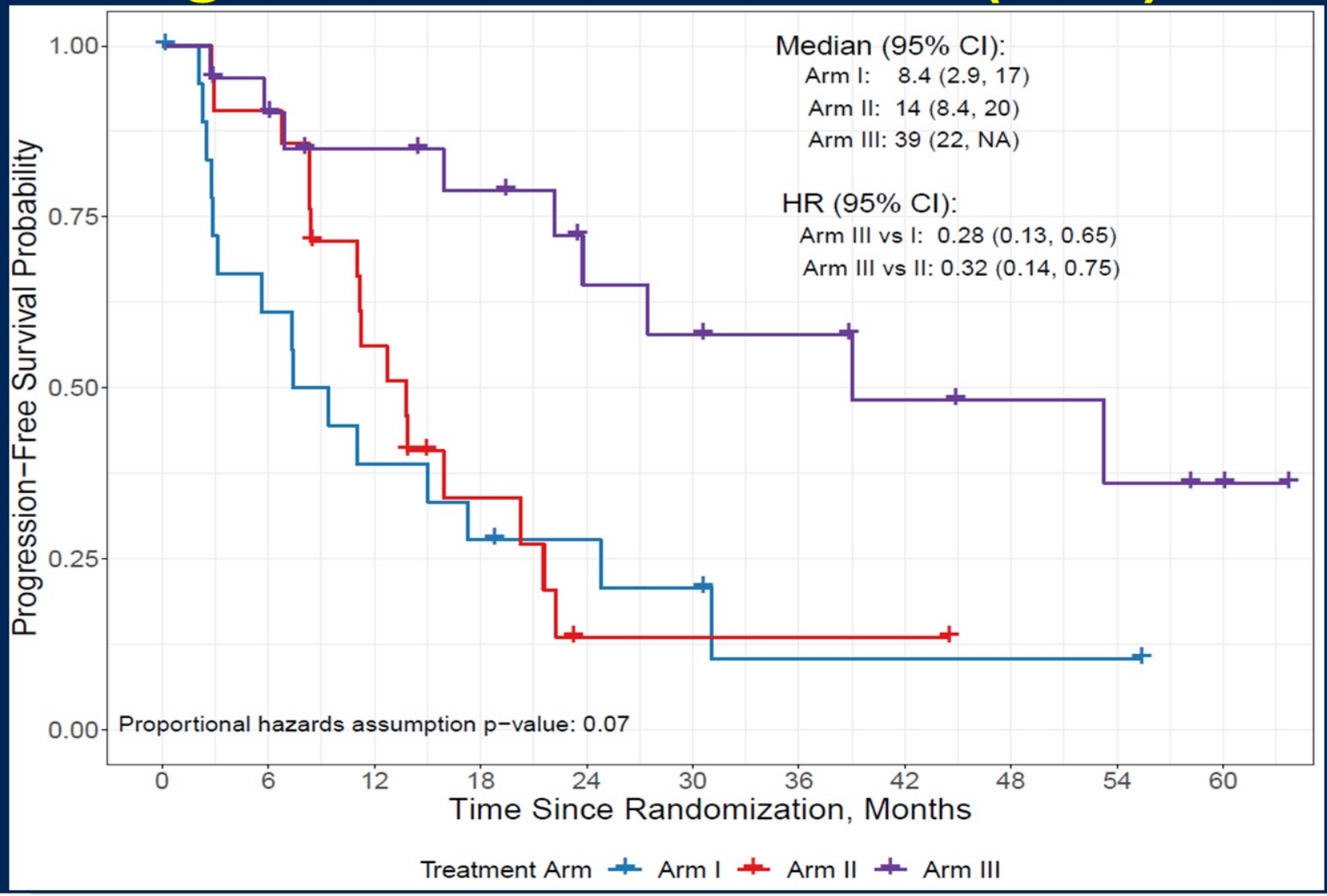
pcctc
The Prostate Cancer Clinical Trials Consortium

Methods & Study Design

- **Eligibility:** mCRPC, no prior exposure to PARP-I, AR-I, or chemotherapy for mCRPC, washout of antiandrogen (for mHSPC), radiation, and other investigational agents.
- Eligible pts underwent tumor next-generation sequencing (NGS) & germline testing; pts with inactivating BRCA1/2 and/or ATM alterations were randomized 1:1:1 to:
  - Arm I: abiraterone (1000 mg qd) + prednisone (5mg bid),
  - Arm II: olaparib (300 mg bid)
  - Arm III: olaparib + abiraterone/prednisone
- Arm I and II pts could cross over at progression.



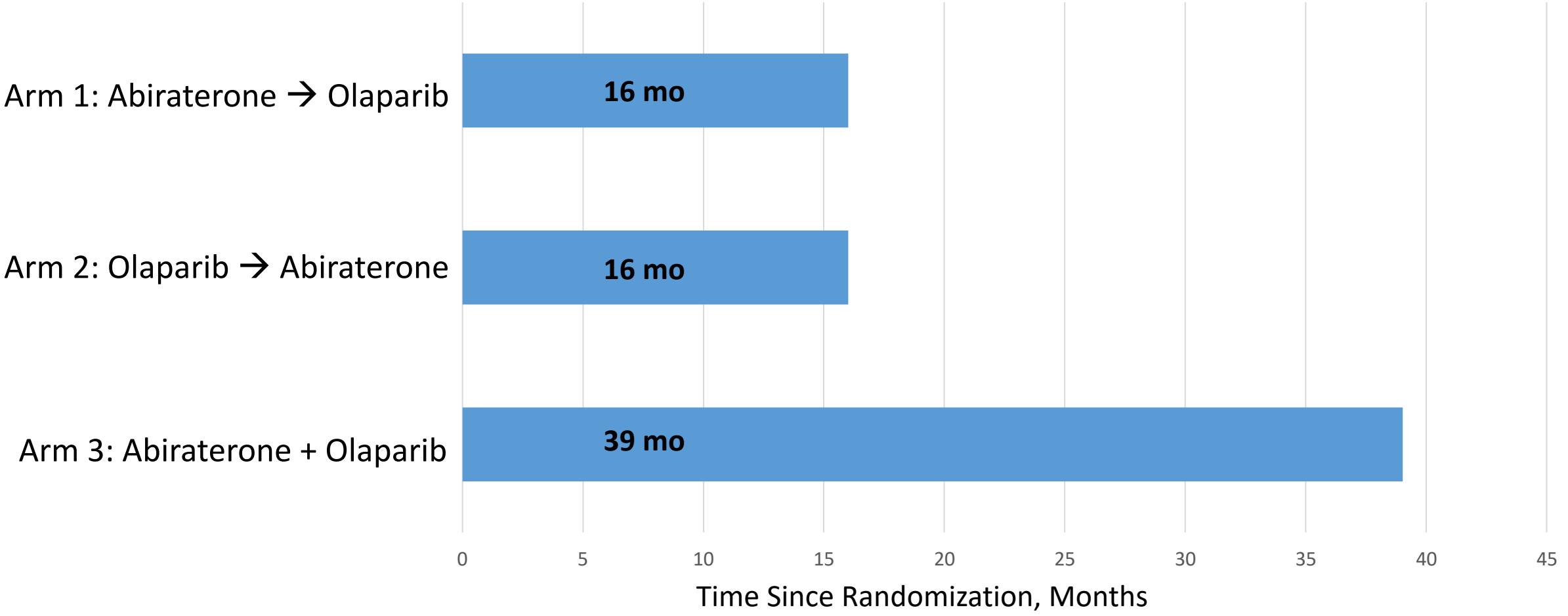
Progression-Free Survival (PFS)



PFS: time from randomization until first progression or death.

Proportional hazards assumption was not met for Arm I versus II comparison.

Median PFS from Randomization to End of Crossover Treatment



Hussain M., ASCO GU 2024

Phase 3 trial of PARPi + ARPI in 1st line mCRPC and mHSPC

mCRPC

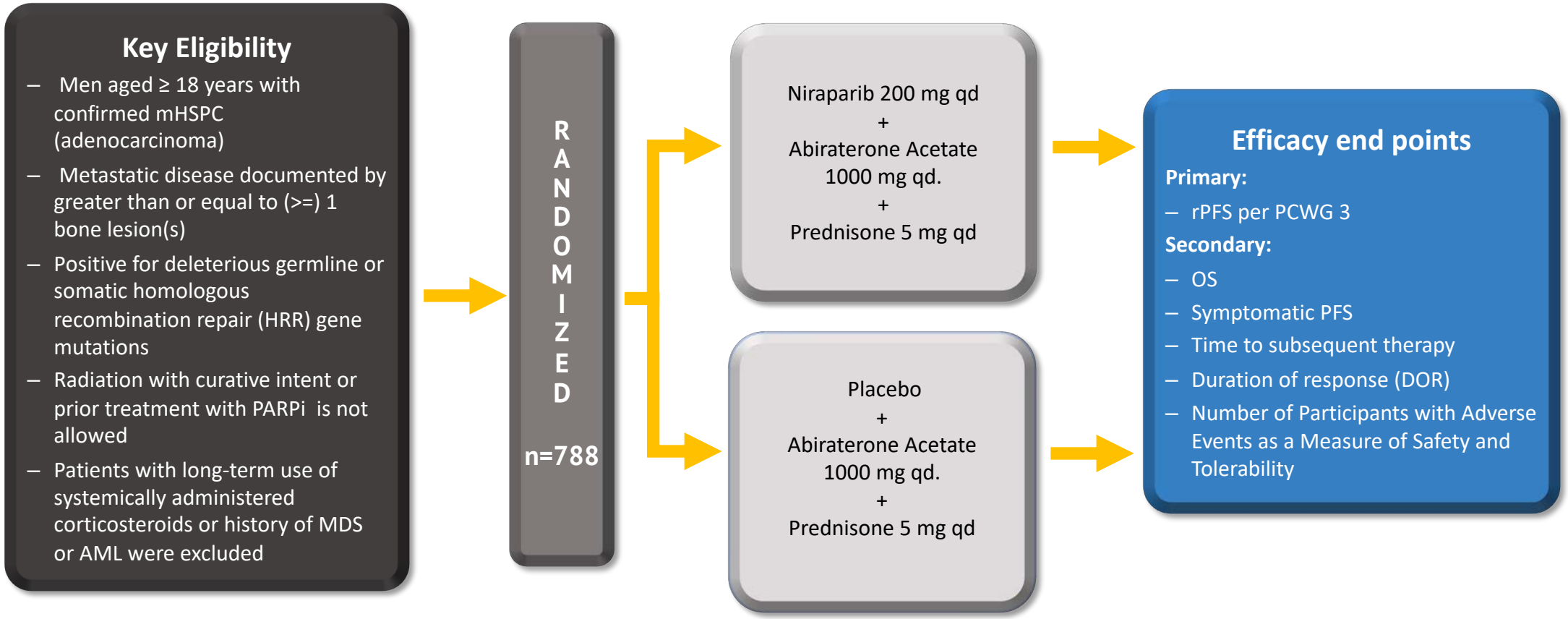
PROpel: Abiraterone + Olaparib[1]	Published
MAGNITUDE: Abiraterone + Niraparib[2]	Presented
TALAPRO-2: Enzalutamide + Talazoparib[3]	Published
CASPAR: Enzalutamide + Rucaparib	Terminated

mHSPC

TALAPRO3: Enzalutamide + Talazoparib	Ongoing
Amplitude: Abiraterone + Niraparib	Ongoing

1- Clarke NW et al., NEJM Evidence. 2022 Aug 23; 2-2022 Genitourinary cancers symposium (ASCO GU). Abstract #12; 3- Agarwal N et al., The Lancet. 2023 June 4

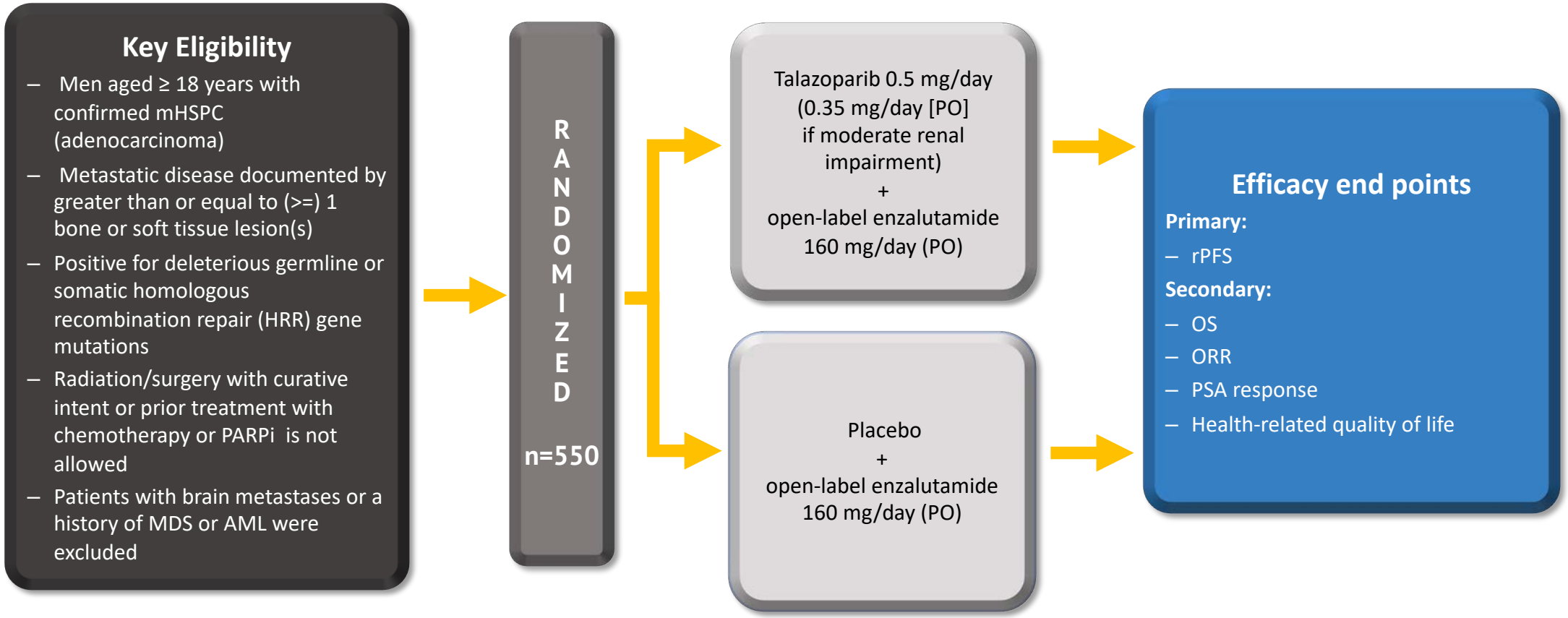
AMPLITUDE (Niraparib) : Phase 3 Trial Design (mHSPC)



www.clinicaltrials.gov: (NCT04497844)

Rathkopf et al., 2021, ABSTRACT TPS 176 ASCO-GU

TALAPRO-3 (Talazoparib) : Phase 3 Trial Design (mHSPC)



www.clinicaltrials.gov: (NCT04821622)

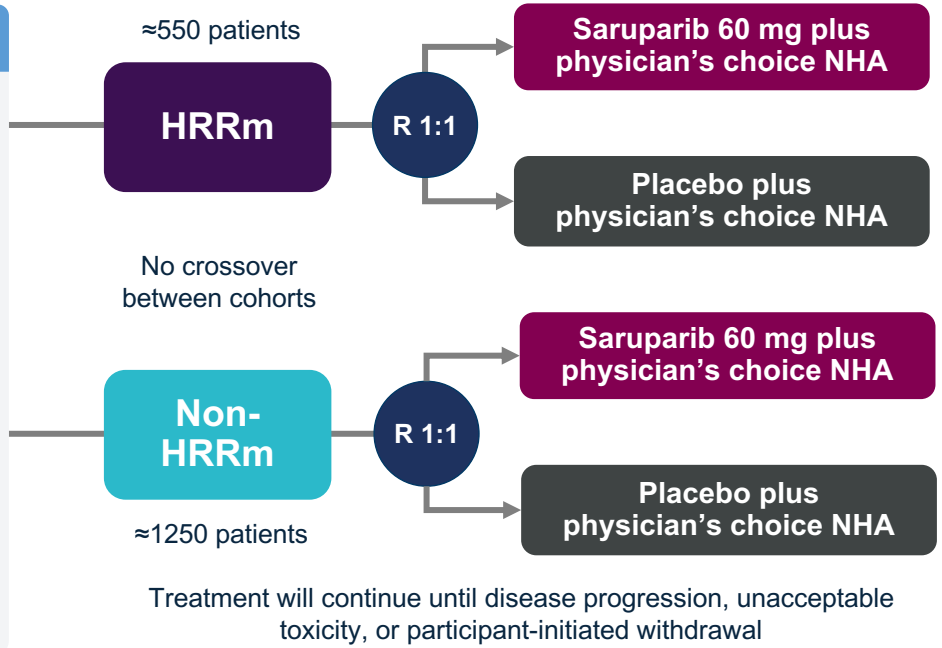
1 Agarwal et al., 2022, ABSTRACT TPS 221 ASCO-GU

EvoPAR-Prostate01 : Phase 3 Trial Design (mHSPC)

A Phase III, 2-cohort, 2-arm, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of saruparib plus physician's choice of NHA (abiraterone, darolutamide, or enzalutamide) versus placebo plus physician's choice of NHA in participants with mCSPC

Eligibility criteria

- Aged ≥18 years
- Histologically confirmed mCSPC (*de novo* or recurrent low- or high-volume disease)
- ECOG PS 0–1
- Prospectively defined HRRm status*
- Must be receiving ADT throughout the study or have undergone bilateral orchiectomy, and must be suitable for treatment with NHAs
- No prior treatment with PARP inhibitors, CT, or NHAs in the metastatic setting†
- No suspected or prior history of myelodysplastic syndrome/acute myeloid leukemia



Treatment will continue until disease progression, unacceptable toxicity, or participant-initiated withdrawal

Select endpoints

HRRm cohort
- rPFS
- OS

Non-HRRm cohort
- rPFS
- OS

Statistical analyses

rPFS and OS will be tested for each cohort separately using a stratified log-rank test

www.clinicaltrials.gov: (NCT06120491)

Agarwal N. *et al*, ***AUA*** 2024

My take on the PARPi plus ARPI in mCRPC

- Many patients with new mCRPC will not have disease progression on a prior ARPI in the next 5-7 years: 1) patients progressing from localized prostate cancer with BCR, 2) patients with locally advanced prostate cancer receiving limited duration ARPI, and 3) patients with mHSPC not receiving ARPI at all or until progression

- How I select a given combination: 1) For new mCRPC with BRCA1/2 mutations, I use the PARPi combinations based on my selection of the partner ARPI; 2) For new mCRPC with non-BRCA1/2 HRRm, I use enzalutamide plus talazoparib

- Based on the results of the BRCAAway trial, the upfront combination of an ARPI+PARPi seems more efficacious than the sequencing of ARPI followed by a PARPI

- All patients with advanced prostate cancer should undergo tumor genomic profiling and germline testing

- Next steps:
  - Elucidation of the mechanism of response in HRRm-negative patients, and
  - Mechanism of resistance to PARPi

Questions from General Medical Oncologists

- 65 y/o man s/p radical prostatectomy. Receiving ADT for PSA progression (still M0), now with symptomatic bone metastases on PSMA PET. BRCA2 germline mutation. What treatment would you recommend?
- Would you use the PARP inhibitor/ARPI combinations for somatic BRCA or PALB2 mutations? Do you apply this approach broadly to all the genes covered as HRD? Should those with ATM alterations still receive PARP given the less drastic effect?
- Any differences in response for BRCA1 vs BRCA2? I have a patient with BRCA2 who responded well to the combination compared to BRCA1 mutations with less response. Why is this?

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Questions from General Medical Oncologists

- **Are the experts using PARP inhibitor and ARPI combination therapy in patients without HRR mutations? When do you favor this approach?**
- **What are the practical applications of the findings in Phase III trials of combination PARP + ARPI, as most patients are exposed to ARPIs in a prior line of therapy? Would you use this strategy for a patient who develops mets after EBRT followed by ADT and abiraterone for N1 disease (BRCA2)? What about for a patient who received the EMBARK strategy? Does it matter whether they progressed on or after the ARPI?**

Questions from General Medical Oncologists

- 63 y/o M, gBRCA2, ADT + enzalutamide for mHSPC to the bone but discontinued enzalutamide due to poor tolerability. Now with new bone lesions causing pain. What would the panel recommend? What if he had progressed while still on ADT + enzalutamide?
- Should we use PARPi combined with androgen pathway inhibitors up front or sequence them?
- I would like to know how investigators choose which PARPi to use. Personal comfort/preference, or do the data support one over the other? Is there a subset of patients with particular mutations that would benefit more from one combination than the other?

What Clinicians Want to Know: Addressing Current Questions Related to the Management of Renal Cell Carcinoma

A CME Symposium Held in Conjunction with the 2025 ASCO® Genitourinary Cancers Symposium

Friday, February 14, 2025

6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)

Faculty

Thomas E Hutson, DO, PharmD, PhD

Rana R McKay, MD

Tian Zhang, MD, MHS

Moderator

Sumanta Kumar Pal, MD

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Online/Zoom attendees: The CME credit link is posted in the chat room.

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