FDA is committed to ensuring digital accessibility for people with disabilities. We are continually improving the user experience for everyone and applying the relevant accessibility standards. At the time of initial posting on **May 16, 2025**, the attached **Event Materials** may not be fully accessible to users using assistive technology. A fully accessible version of the **Event Materials** is in preparation and will be posted as soon as it is ready. We regret any inconvenience that this may cause our readers.

Please let us know if you encounter accessibility barriers by contacting **Division of Advisory Committee and Consultant Management (DACCM)** at:

- **ODAC@fda.hhs.gov**

TALZENNA® in Combination With Enzalutamide for the Treatment of Adult Patients With mCRPC

United States Food and Drug Administration
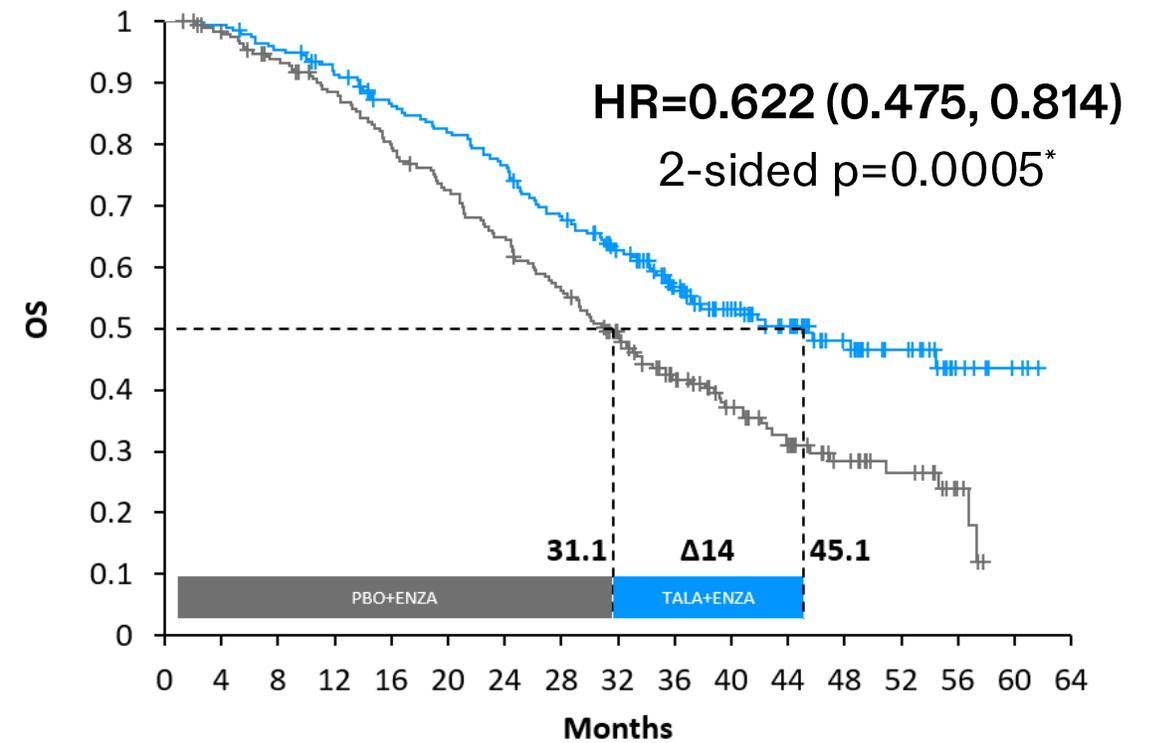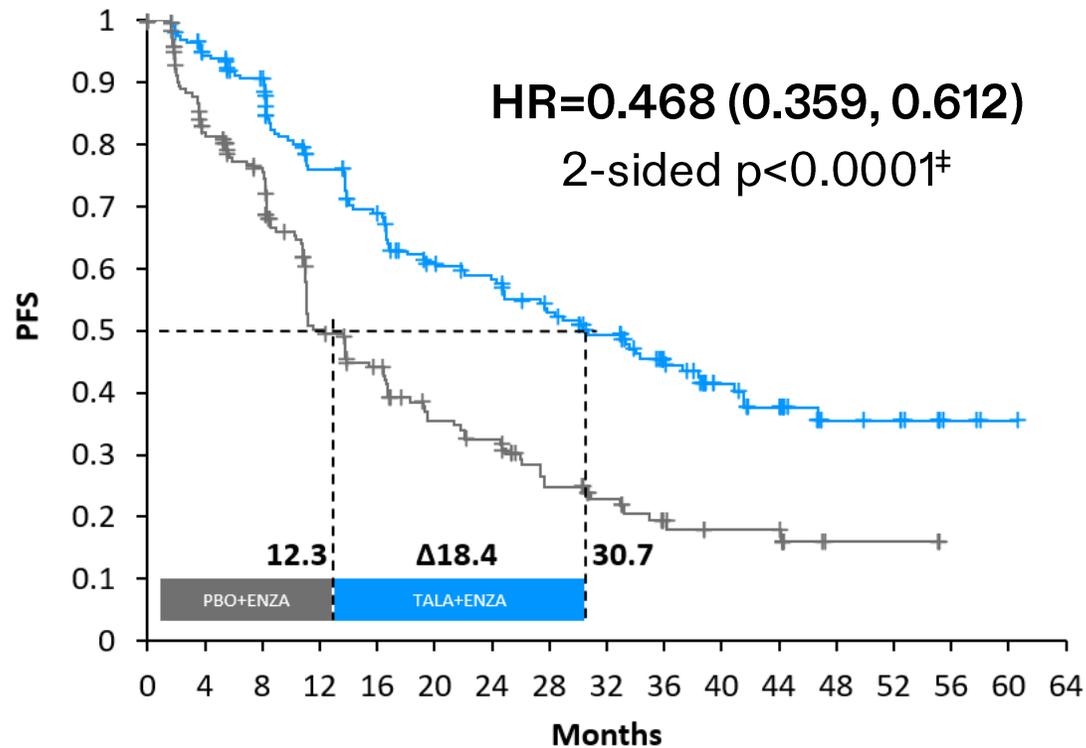Oncologic Drugs Advisory Committee

May 21, 2025

Introduction

Johanna Bendell, MD

Chief Development Officer
Oncology Research and Development
Pfizer Inc.

Pfizer

Current Indication

TALZENNA® (talazoparib) is indicated in combination with enzalutamide
for the treatment of adult patients with HRR gene-mutated mCRPC.

HR=0.468 (0.359, 0.612)
2-sided p<0.0001‡

12.3 Δ18.4 30.7
PBO+ENZA TALA+ENZA

HR=0.622 (0.475, 0.814)
2-sided p=0.0005*

31.1 Δ14 45.1
PBO+ENZA TALA+ENZA

‡ Descriptive p-value at updated analysis.
* The 2-sided critical OS p-value at the final analysis in September 2024 is 0.024
mCRPC=metastatic castrate resistant prostate cancer.

Proposed Indication Under Review Today

TALZENNA® (talazoparib) is indicated in combination with enzalutamide for the treatment of adult patients with mCRPC

mCRPC=metastatic castrate resistant prostate cancer.

Agenda

Unmet Need
Pedro Barata, MD, MSc, FACP

Associate Professor of Medicine
Case Western Reserve University
School of Medicine
Case Comprehensive Cancer Center
Cleveland, Ohio

Efficacy and Safety
Dana Kennedy, PharmD, BCOP

Vice President,
GU Therapeutic Area Head
Oncology Research and Development
Pfizer Inc.

Clinical Perspective
Neeraj Agarwal, MD, FASCO

Professor of Medicine & Presidential
Endowed Chair of Cancer Research
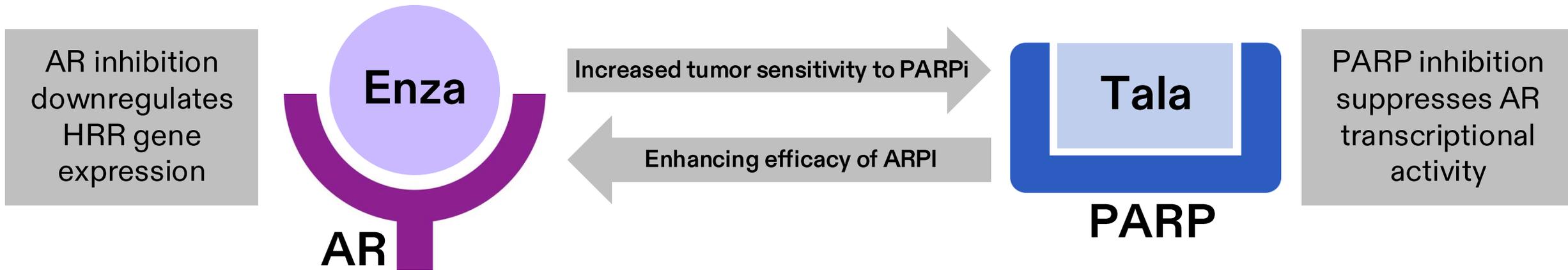Huntsman Cancer Institute
University of Utah

GU Medical Oncologist
Alicia K. Morgans, MD, MPH, FASCO

Associate Professor
Harvard Medical School
Director, Survivorship Program
Dana-Farber Cancer Institute

Biological Rationale Differentiates Talazoparib and Enzalutamide Combination in Unselected mCRPC

AR inhibition downregulates HRR gene expression		
Enza / **AR**	Increased tumor sensitivity to PARPi → ← Enhancing efficacy of ARPI	**Tala** / **PARP**
		PARP inhibition suppresses AR transcriptional activity

The Co-inhibition of AR and PARP Sensitizes Cancer Cells to Both Treatments, Making the Combination More Effective Than Either Agent Alone—With or Without HRR Gene Alterations

Data from Agarwal N, et al. *Eur J Cancer*. 2023;192:113249.
AR=androgen receptor; ARPI=androgen receptor pathway inhibitor; Enza=enzalutamide; HRR=homologous recombination repair; PARP=poly (ADP-ribose) polymerase; Tala=talazoparib.

TALAPRO-2 Designed to Evaluate Talazoparib and Enzalutamide in Selected and Unselected mCRPC Populations
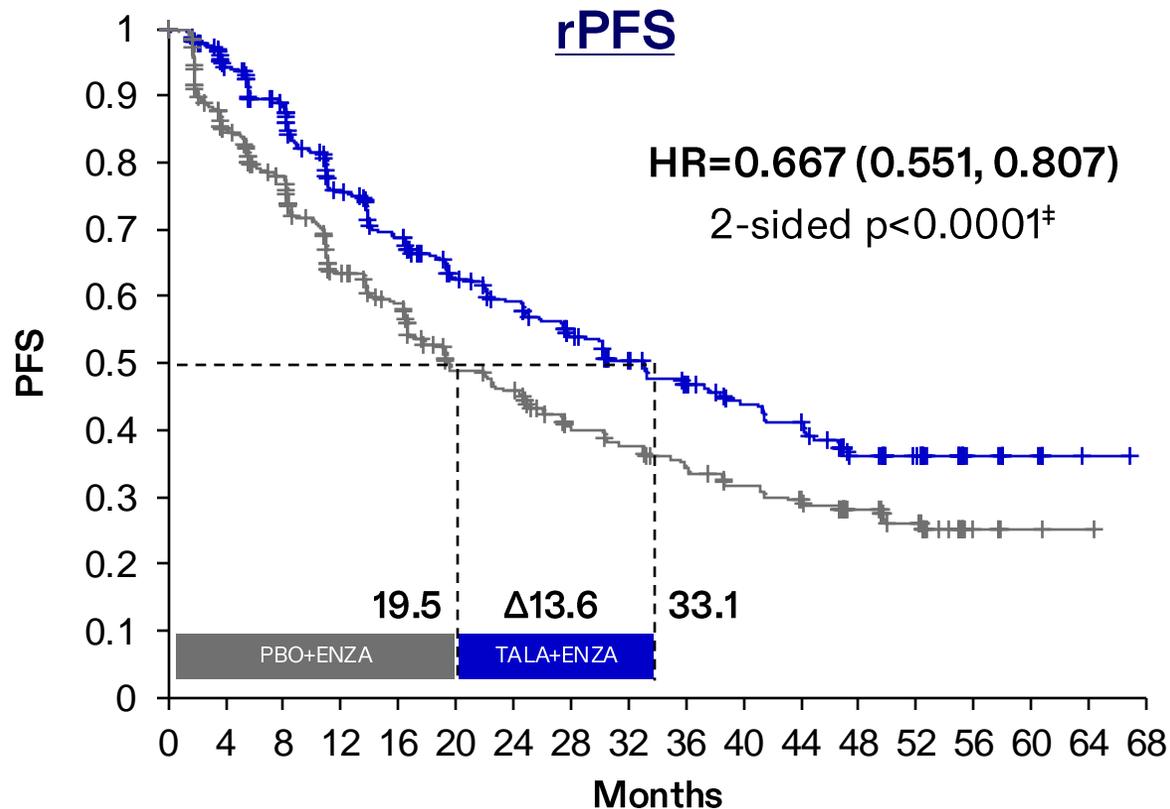
Unselected (Cohort 1): Basis for Proposed Indication

Non-HRRm / Unknown N=636	HRRm N=169	HRRm N=230

HRRm Selected (Cohort 2): Basis for Current Indication

July
FDA Meeting
Primary Endpoint
(rPFS) Agreement

Dec
sNDA
(Final rPFS)
Submission

Dec
sNDA (Final OS)
Submission:
Unselected Indication

Feb
Priority
Review
Granted

2017	2018	2019	2022	2023	2024	2025

Mar
FDA Meeting
Unselected (Cohort 1)
Agreement

Nov
FDA Pre-sNDA
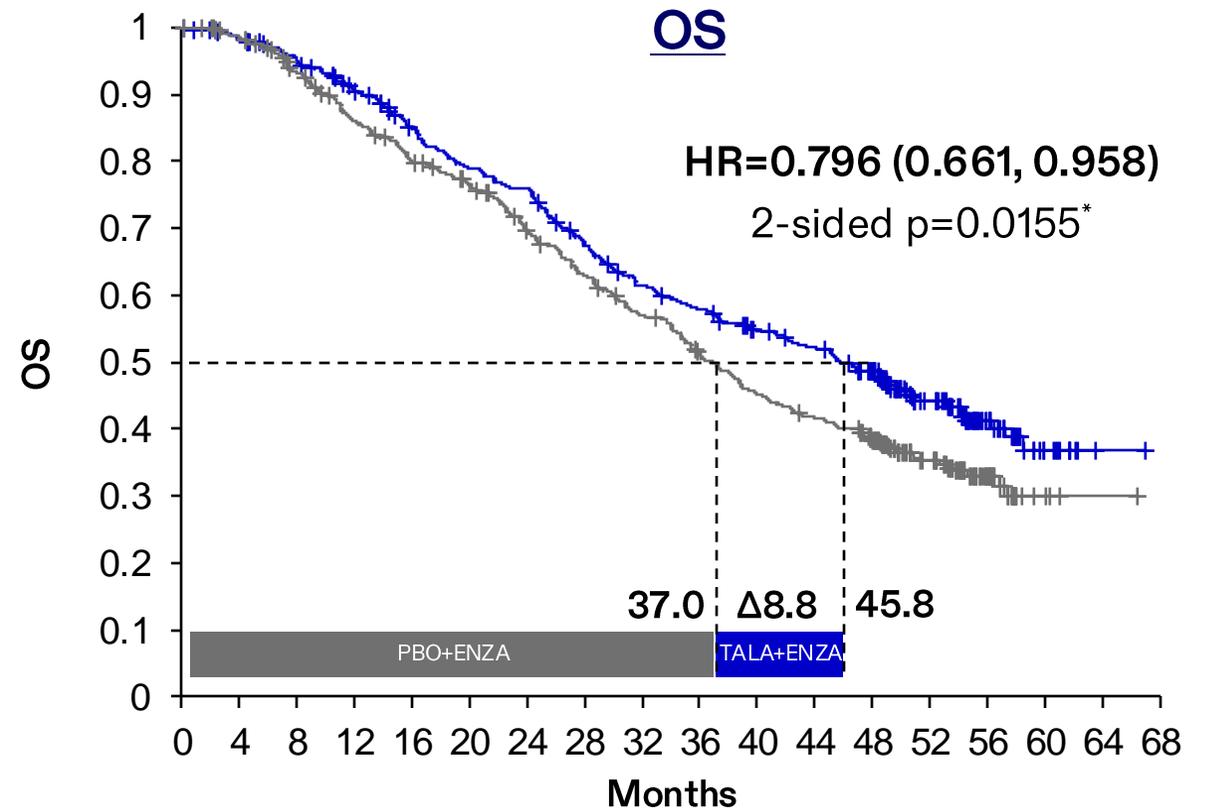Meeting

June
HRRm mCRPC
Indication
Approval

Nov
FDA Pre-sNDA
Meeting

HRRm=homologous recombination repair gene mutated; OS=overall survival; rPFS=radiographic progression-free survival.

rPFS and OS Benefit in Unselected Patients (Proposed Indication)

rPFS

HR=0.667 (0.551, 0.807)

2-sided p<0.0001‡

19.5   Δ13.6   33.1

PBO+ENZA   TALA+ENZA

PFS

Months

Patients at risk

402	318	228	180	138	108	63	13	1
403	273	180	128	92	72	44	5	1

OS

HR=0.796 (0.661, 0.958)

2-sided p=0.0155*

37.0   Δ8.8   45.8

PBO+ENZA   TALA+ENZA

OS

Months

Patients at risk

402	371	319	285	226	193	158	42	1
403	362	305	257	207	163	127	33	1

‡ Descriptive p-value at updated analysis.

* The 2-sided critical p-value for OS at the final analysis in September 2024 is 0.022

Prospectively Defined Stratified Non-HRRm Subgroup

rPFS

HR=0.739 (0.595, 0.918)

2-sided p=0.0061‡

22.4   Δ10.9   33.3

PBO+ENZA   TALA+ENZA
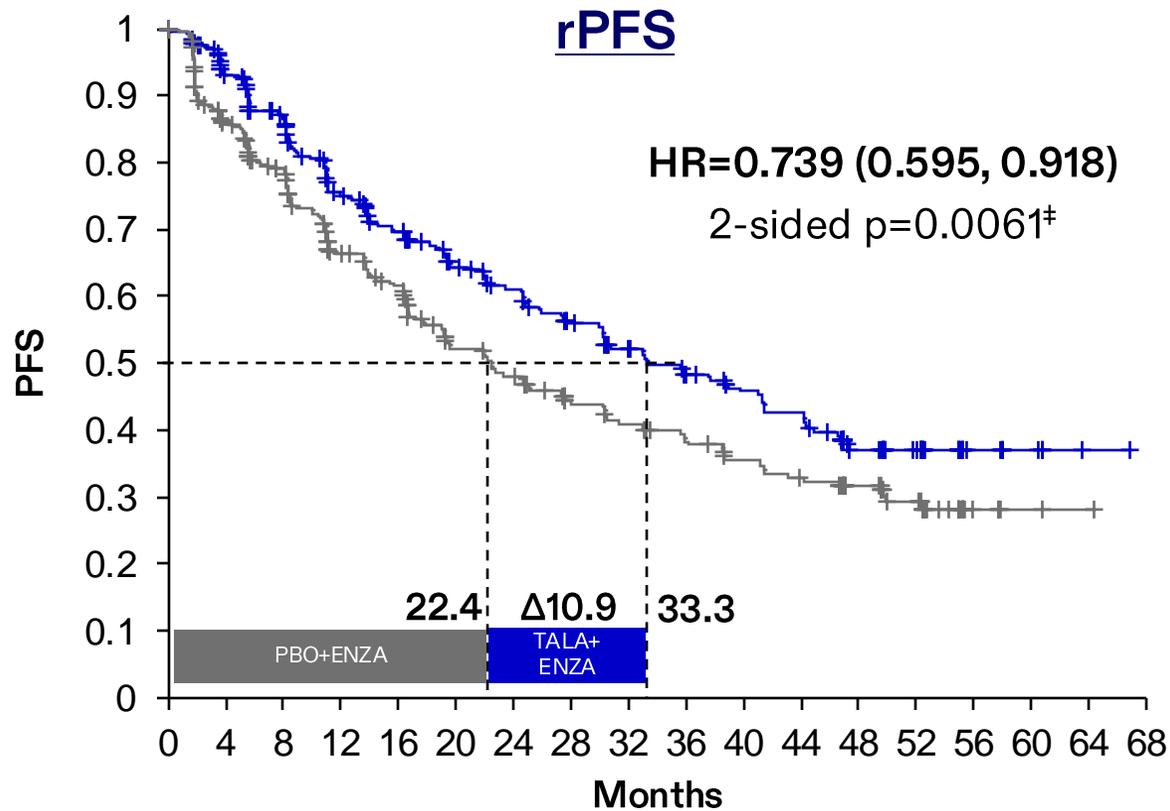
Patients at risk

| 317 | 243 | 179 | 143 | 111 | 89 | 51 | 10 | 1 |
| 319 | 219 | 151 | 108 | 81 | 65 | 42 | 5 | 1 |

OS

HR=0.878 (0.713, 1.080)

2-sided p=0.2183‡

38.3   Δ7.2   45.5

PBO+ENZA   TALA+ENZA
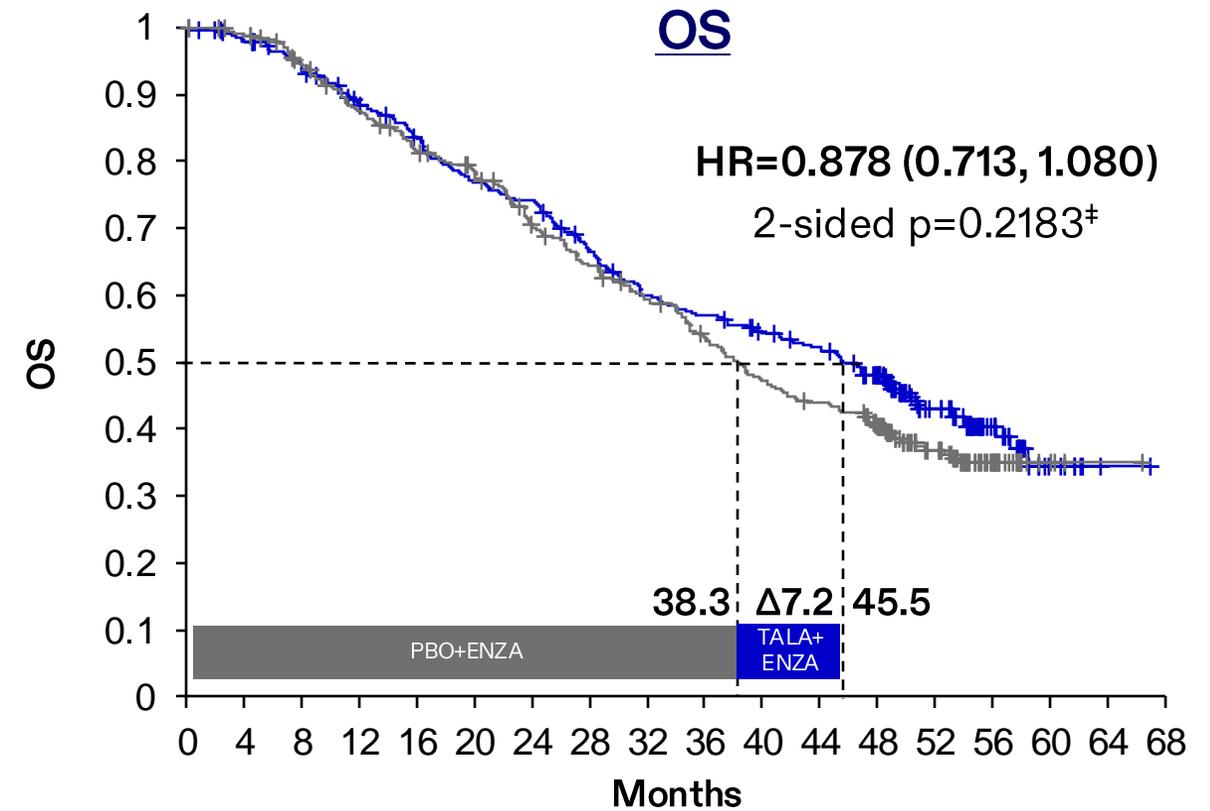
Patients at risk

| 317 | 288 | 249 | 222 | 176 | 155 | 125 | 34 | 1 |
| 319 | 292 | 248 | 208 | 172 | 136 | 106 | 28 | 1 |

‡ Compared to nominal level 0.05 without multiplicity adjustment.

Benefit–Risk Assessment

There remains an unmet need in patients with mCRPC, who are often symptomatic with advanced disease

There is a well-documented scientific rationale for the differentiated MOA of the combination of talazoparib and enzalutamide in non-HRRm tumors

Efficacy data in patients with non-HRRm mCRPC are clinically meaningful and reflect a true treatment effect that is unlikely due to chance alone

Anemia is well managed with dose modifications, and there were no clinically meaningful differences between treatment arms in patient reported outcomes
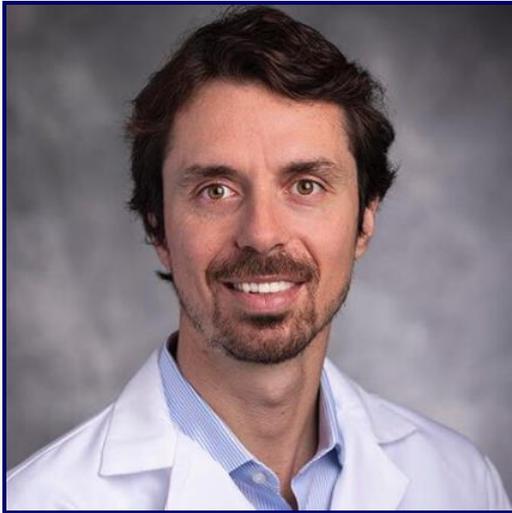
Treatment Landscape

Pedro Barata, MD, MSc, FACP

Associate Professor of Medicine
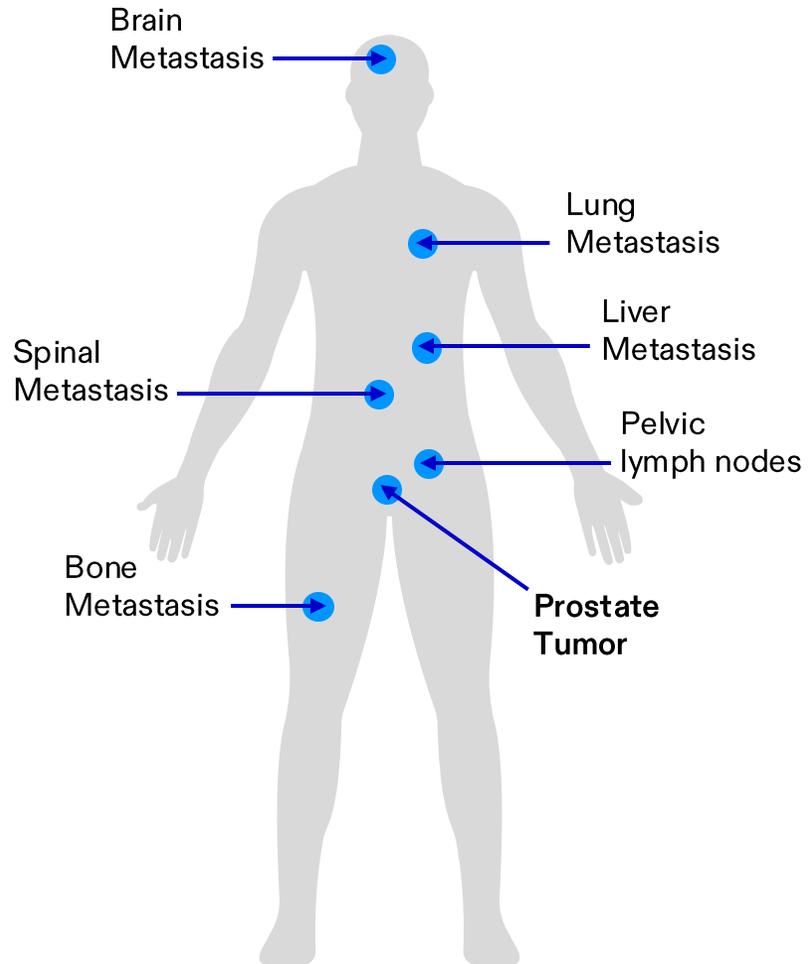Case Western Reserve University School of Medicine
Case Comprehensive Cancer Center
Cleveland, Ohio

mCRPC is an Aggressive and Fatal Disease

Brain Metastasis

Lung Metastasis

Liver Metastasis

Spinal Metastasis

Pelvic lymph nodes

Bone Metastasis

Prostate Tumor

Potential metastatic sites	Common (≥80%): Pelvic lymph nodes and bone Uncommon (≤11%): Distant lymph nodes, liver, lungs, brain and dura[1]
Disease symptoms	Urinary incontinence, decreased libido, bone pain, fatigue, weight loss, and weakness[1]
Quality of life	Depression, anxiety, decreased physical and emotional functioning[2,3]
Probability of being alive 5 years after diagnosis	<40%[4]
Treatment priorities	Delay disease progression, delay decline in QoL, prolong survival[5]

QoL=quality of life.

1. Rebello RJ, et al. *Nat Rev Dis Primers.* 2021;7(1):9; 2. Rönningås U, et al. *BMC Palliat Care.* 2024;23(1):80; 3. Fallowfield L, et al. *Nat Rev Clin Oncol.* 2016;13:643-650; 4. American Cancer Society. Cancer Facts & Figures 2025; 5. George DJ, et al. *Cancer Med.* 2023;(5):6040-6055.

Common First–Line Therapies for mCRPC

Combinations
5.6%

PARPi
2.1%

Radiopharmaceuticals
3.1%

Immunotherapy
4.6%

Chemotherapy
22.3%

ARPI
62.2%
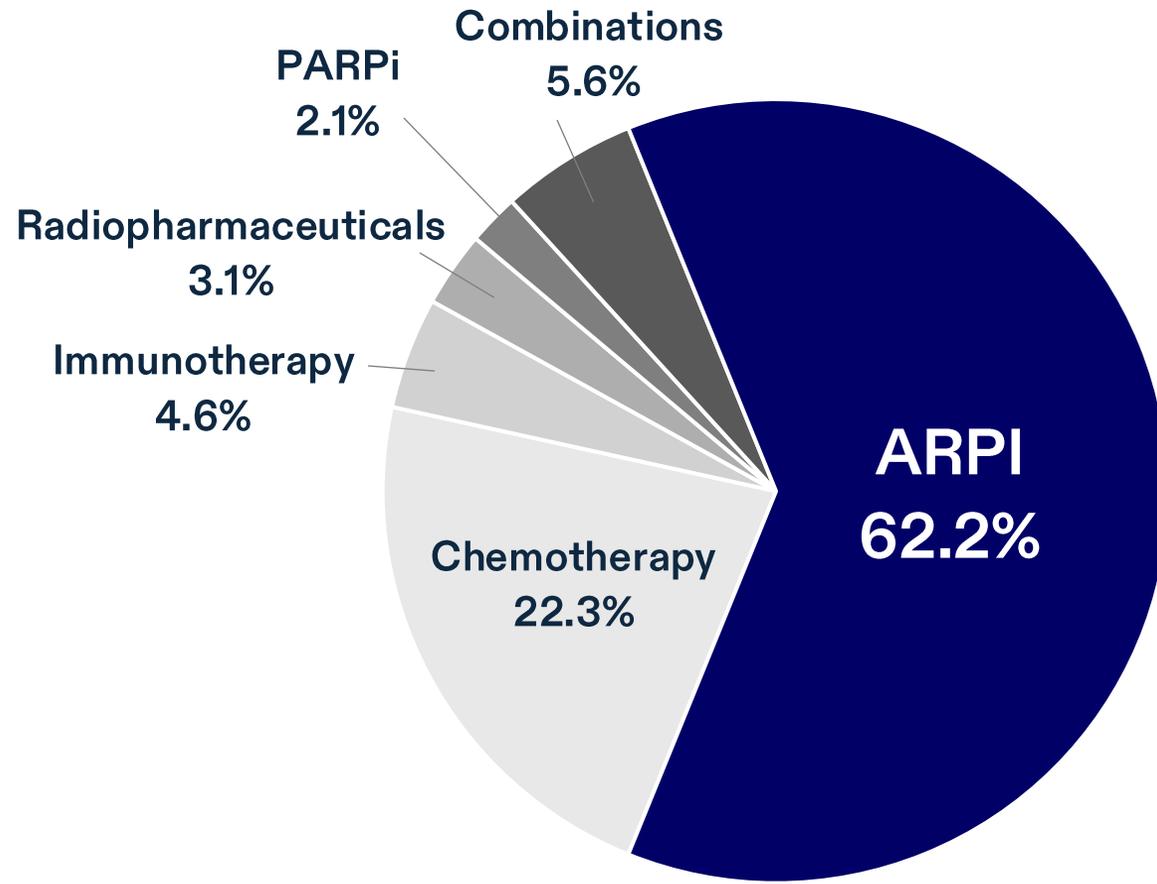
- Genetic testing identifies important biomarkers in subpopulations of patients with predictive and prognostic value (eg, HRRm[1,2]; TP53/Rb1/PTEN[3]; MSI/dMMR[4,5])

- Most mCRPC patients do not have a known predictive biomarker and are commonly treated with ARPIs[6]

ARPI=androgen receptor pathway inhibitor.
1. Azad AA, et al. *Eur J Cancer*. 2024;213:115078; 2. Hussain M, et al. *N Engl J Med*. 2020;383(24):2345-2357; 3. Corn PG, et al. *Lancet Oncol*. 2019;20(10):1432-1443; 4. Abida W, et al. *JAMA Oncol*. 2019;5(4):471-478;
5. Barata P, et al. *J Immunotherapy Cancer*. 2020;8(2):e001065; 6. Data from Raval AD, et al. *J Clin Oncol*. 2025;43(5),99-99.

First-Line Therapy is the Best Chance to Improve Outcomes

US Real-World mCRPC Treatment Patterns[1]
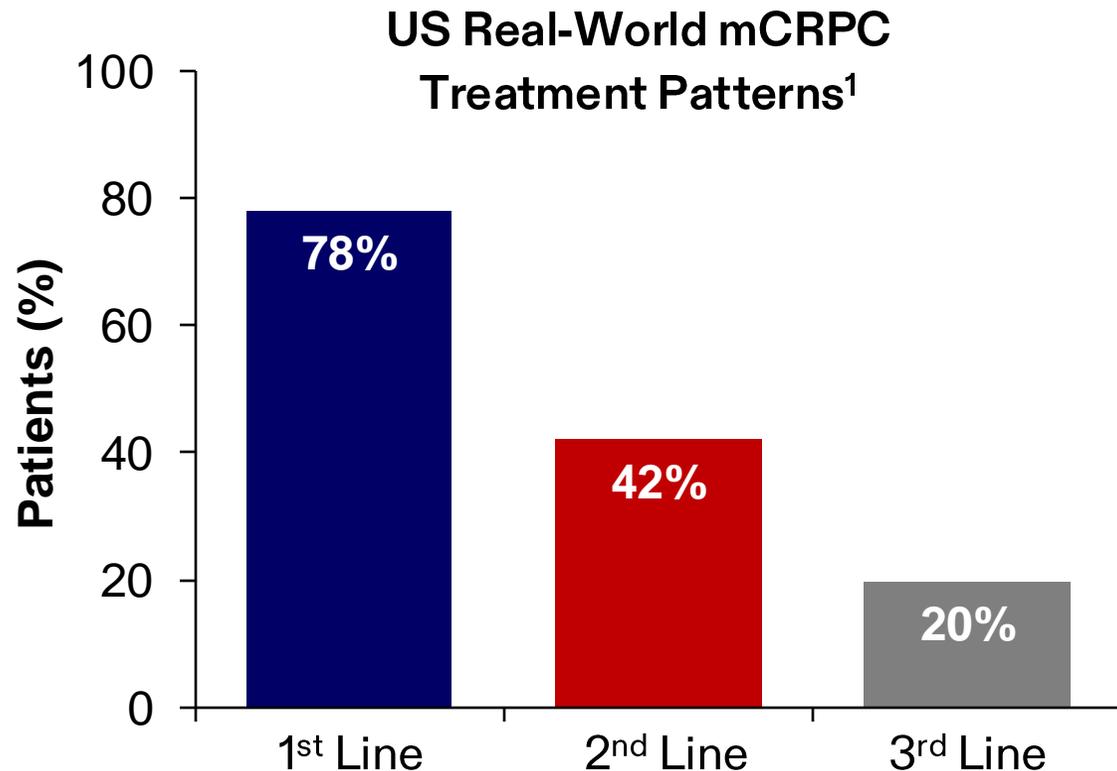
- **<50%** of mCRPC patients receive more than 1 line of therapy[1]

- **Optimal first-line therapy** is critical to improve outcomes of mCRPC patients

1. Freedland SJ, et al. *Prostate Cancer Prostatic Dis.* 2024;27(2):327-333.

Survival Outcomes of Patients with mCRPC Receiving ARPIs

Clinical Trials

- PREVAIL, 2014[1] (enzalutamide)
- COU-AA-302, 2015[2] (abiraterone)
- Alliance A031201, 2023[3] (enzalutamide)
- ACIS, 2021[4] (abiraterone)
- PROpel, 2023[5] (abiraterone)
- PEACE-3, 2024[6] (enzalutamide)

Real-World Evidence

- VA RWE, 2021[7] (enzalutamide)
- VA RWE, 2021[7] (abiraterone)
- Flatiron RWE, 2021[8] (ARPI)
- US Medicare RWE, 2023[9] (ARPI)
- Flatiron RWE, 2024[10] (ARPI)

X-axis: 0 4 8 12 16 20 24 28 32 **36**

Median Overall Survival (months)

- Clinical trials over the past decade consistently show median OS **<36 months**[1-6]

- Real-world median OS is **lower**[7-10]

1. Armstrong AJ, et al. *Eur Urol*. 2020;78(3):347-357; 2. Ryan CJ, et al. *Lancet Oncol*. 2015;16(2):152-160; 3. Morris MJ, et al. *J Clin Oncol*. 2023;41(18):3352-3362; 4. Saad F, et al. *J Clin Oncol*. 2021;39(15 suppl). Abst 5037; 5. Saad F, et al. *Lancet Oncol*. 2023;24(10):1094-1108; 6. Gillessen S, et al. ESMO Congress 2024. Abstract LBA1. Presented September 13, 2024; 7. Tagawa ST, et al. *Prostate Cancer Prostatic Dis*. 2021;24(4):1032-1040; 8. Shore ND, et al. *Adv Ther*. 2021;38(8):4520-4540; 9. Freedland SJ, et al. *Prostate Cancer Prostatic Dis*. 2024;27(2):327-333; 10. Swami U, et al. *J Urol*. 2024;211(5S):e1115.

Biological Rationale for Talazoparib and Enzalutamide Combination in Unselected mCRPC

Inhibition of AR gene expression decreases expression of DNA repair genes[1]

AR–associated genes
- KLK3
- TMPRSS2
- AR

HRR–associated genes
- RAD21
- ATAG2
- RAD51AP1
- FANCF
- RAD50
- RAD51C
- FEN1
- MRE11A

0 h 24 h 48 h
AR RNAi

High expression ▭ Low expression
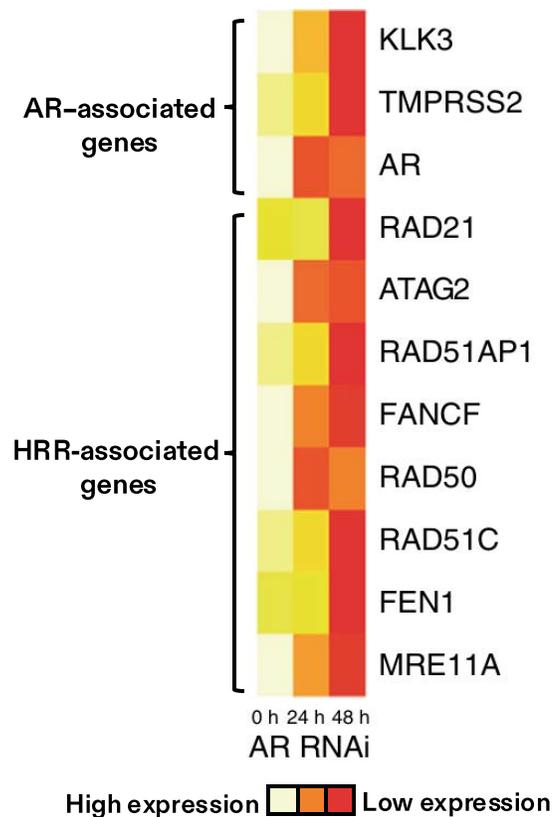
Inhibition of PARP decreases androgen receptor activity[2]

AR Activity

- PARP Proficient
- PARP Deficient
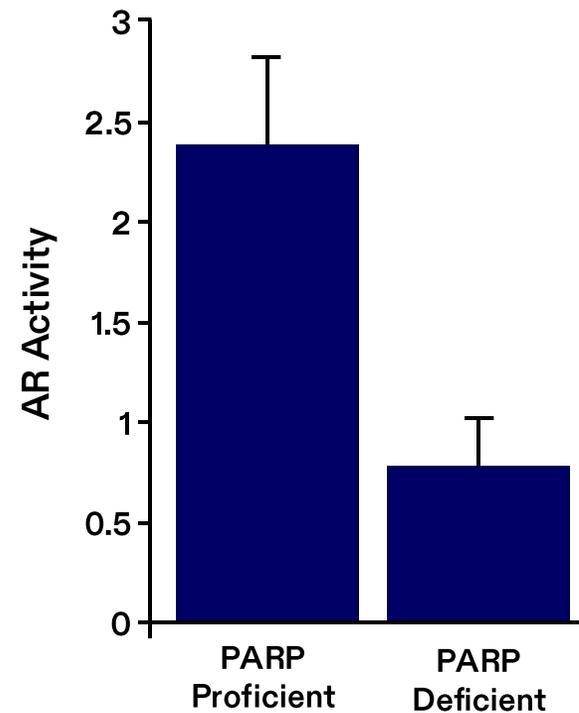
PARPi with enzalutamide inhibits HRR-proficient prostate tumor growth better than either agent alone[3]

Tumor Volume vs Days of Treatment

- Vehicle
- PARPi alone
- ENZA alone
- ENZA + PARPi

1. Reprinted from Asim M, et al. *Nat Commun.* 2017;8(1):374; 2. Reprinted from Cancer Discovery, Copyright 2012, 2(12), 1134-1149, Schiewer MJ, et al., Dual roles of PARP-1 promote cancer growth and progression, with permission from AACR; 3. Reprinted from Albertella MR, et al. Abstract 4201: Combination of the PARP1-selective inhibitor saruparib with androgen receptor pathway inhibition provides combination benefit in preclinical models of prostate cancer with or without homologous recombination repair deficiency. *Cancer Res.* 2025;85(8 suppl 1):4201.

Biology Elucidated Over a Decade of Research

Identification of HRR and AR pathway interaction

1.

Control
Castration
PARPi
Castration + PARPi

Tumors doubling (%)
Days of Treatment

2.

Control
DNA damage
ADT
DNA damage + ADT

Relative cell number
Day
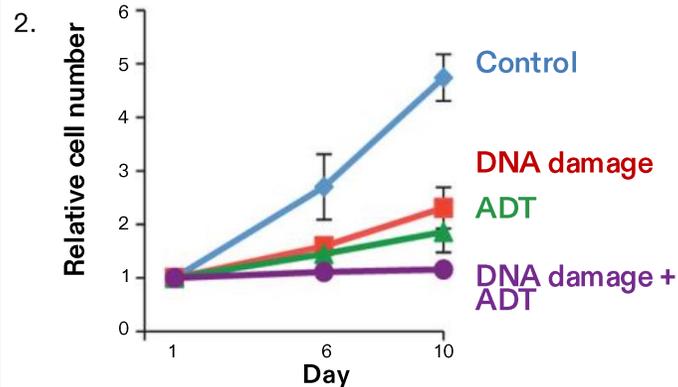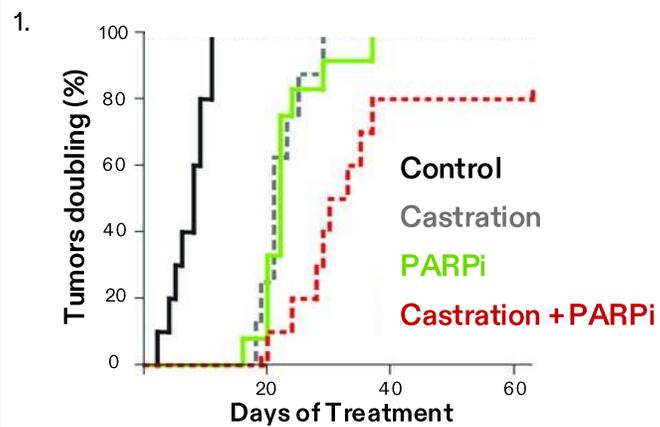
Association of AR pathway activity and HRR gene expression in human prostate cancer

3. **Upregulation of AR-associated DNA repair genes in primary prostate cancers**

Low expression   High expression
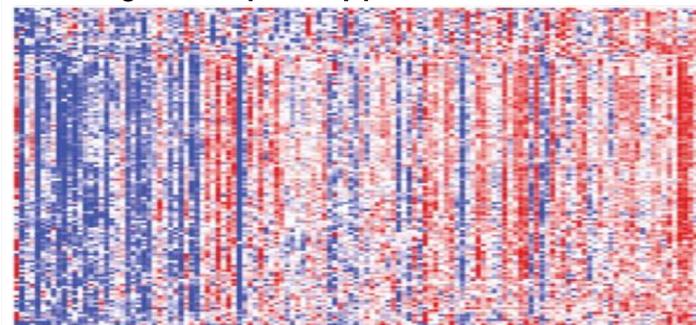
4. **Upregulation of HRR gene expression in CRPC**

Hormone-naïve prostate cancer   CRPC

Low expression   High expression
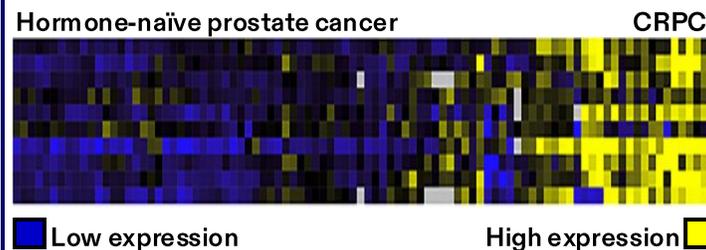
Therapeutic co-inhibition in HRR-proficient animal models

5.

PARPi alone
Vehicle
Bicalutamide
Bicalutamide + PARPi

Tumor Volume
Weeks of Treatment

6.

Vehicle
AR coactivator inhibitor
PARPi
AR coactivator inhibitor + PARPi

Active cell growth
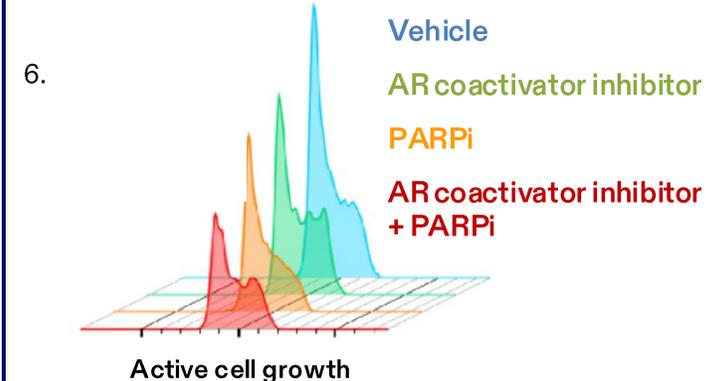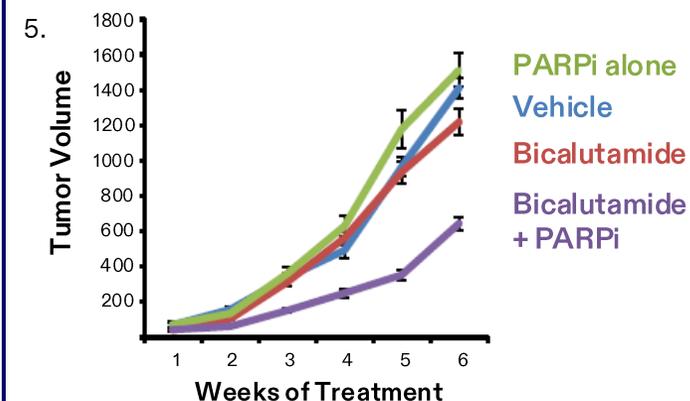
Conclusions

Overall survival of patients with mCRPC is less than 3 years; progress is needed

First chance to treat is the best opportunity to improve outcomes of patients with mCRPC

Enzalutamide is a backbone of metastatic prostate cancer treatment with a well-established safety profile, supporting new combination strategies in this setting

Strong biologic rationale for the combination of enzalutamide + talazoparib, including tumors without HRR mutations, due to cross-talk between the two pathways

Patients and physicians should have access to life-prolonging therapies

Efficacy and Safety

Dana Kennedy, PharmD, BCOP

Vice President, GU Therapeutic Area Head
Oncology Research and Development
Pfizer Inc.

TALAPRO-2: Trial Design in 1L mCRPC

Cohort 1: Unselected
N=805

Nondeficient or Unknown N=636 | **HRRm N=169** | **HRRm N=230**

Cohort 2: HRRm Selected
N=399

1:1

Talazoparib + Enzalutamide (N=402)

Placebo + Enzalutamide (N=403)

1:1

Talazoparib + Enzalutamide (N=200)

Placebo + Enzalutamide (N=199)
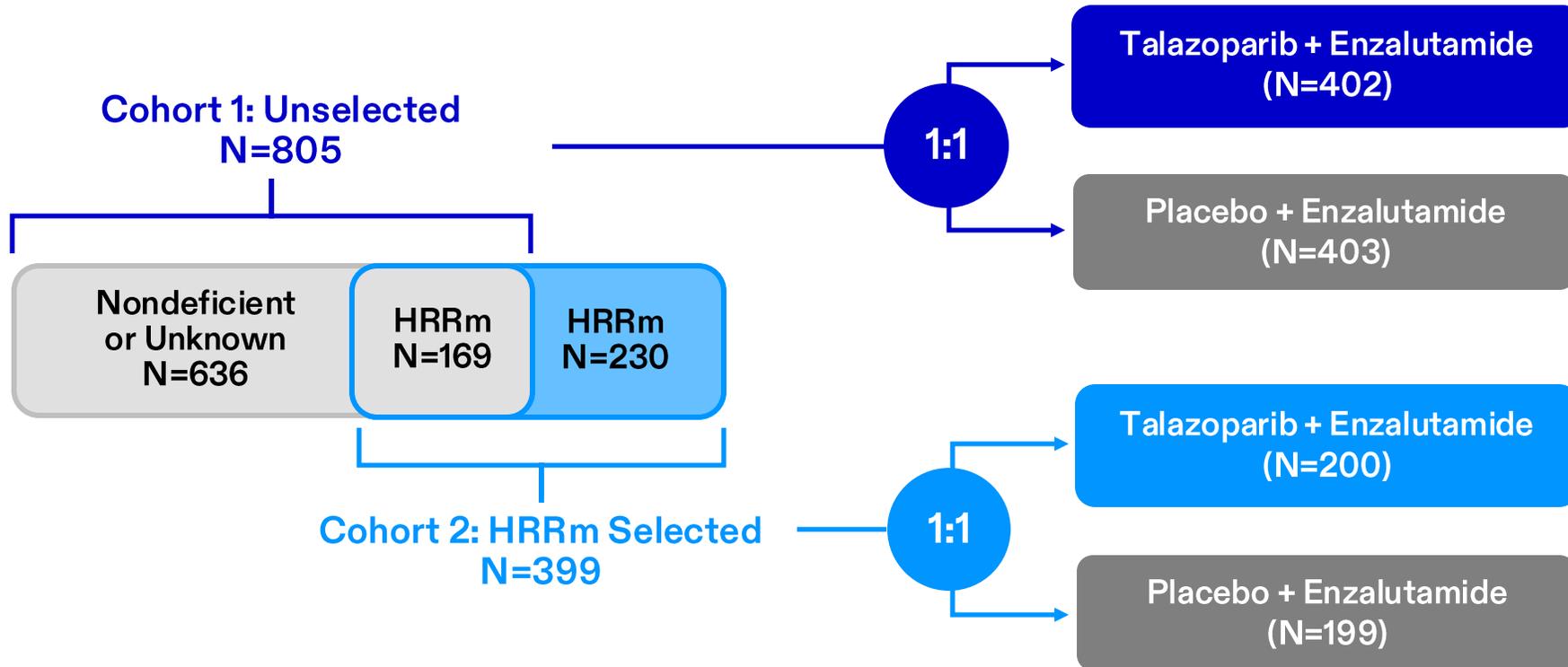
Primary endpoint
- rPFS by BICR

Key secondary endpoint
- OS (alpha protected)

Other secondary endpoints
- Time to cytotoxic chemotherapy
- PFS2
- ORR
- PROs
- Safety

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

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

TALAPRO-2: Clinical Assumptions and Statistical Analysis

Statistical Testing Hierarchy

α=0.05 (2-sided)

0.025

0.025

rPFS Unselected

Target HR=0.696; Power=85%

rPFS HRRm Selected

Target HR=0.64; Power=85%

OS Unselected

Target HR=0.75; Power=78%

OS HRRm Selected

Target HR=0.75; Power=36%

	DCO1 August 16, 2022	DCO2 October 3, 2022	DCO3 March 28, 2023	DCO4 September 3, 2024
rPFS Analysis Unselected	Final ~333 rPFS events			
OS Analysis Unselected	Interim		Interim ~327 OS events	Final ~438 OS events
rPFS Analysis HRRm		Interim → Final ~157 rPFS events		
OS Analysis HRRm		Interim		Final

Efficacy boundaries at interim and final OS analyses were determined based on the O'Brien Fleming alpha spending function.
Subgroup analyses in patients without HRRm were pre-specified without multiplicity adjustment.

Statistically Significant and Clinically Meaningful rPFS Benefit in Unselected Patients (Proposed Indication)

Primary rPFS
(DCO Aug 2022)

HR=0.627 (0.506, 0.777)

2-sided p<0.0001*

PFS

21.9   ‖ PBO+ENZA ‖ TALA + ENZA ‖ Not Reached

Months

Patients at risk

| 402 | 318 | 226 | 136 | 29 | 1 | 0 | 0 | 0 |
| 403 | 272 | 179 | 96 | 14 | 1 | 0 | 0 | 0 |
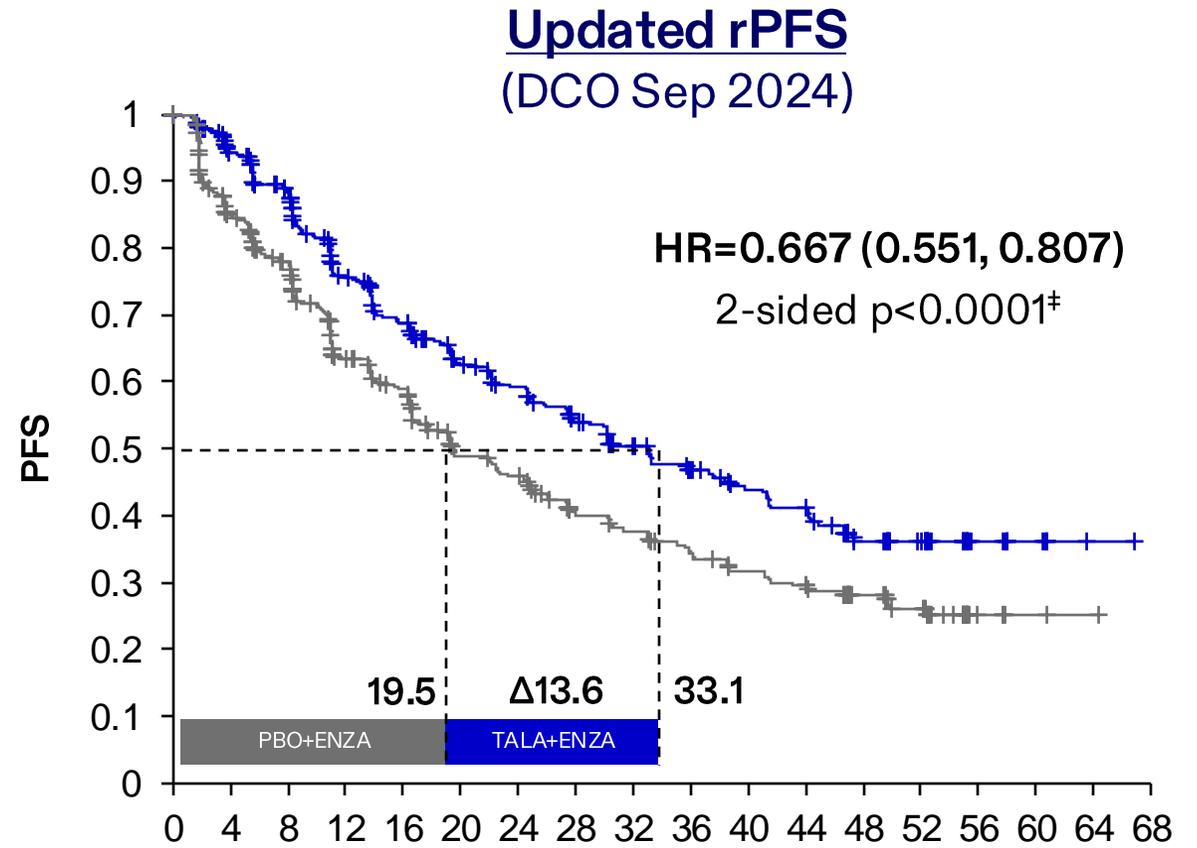
Updated rPFS
(DCO Sep 2024)

HR=0.667 (0.551, 0.807)

2-sided p<0.0001‡

PFS

19.5   Δ13.6   33.1   ‖ PBO+ENZA ‖ TALA+ENZA ‖

Months

Patients at risk

| 402 | 318 | 228 | 180 | 138 | 108 | 63 | 13 | 1 |
| 403 | 273 | 180 | 128 | 92 | 72 | 44 | 5 | 1 |

* The 2-sided critical p-value for rPFS at the final analysis in August 2022 is 0.025
‡ Descriptive p-value at updated analysis.

Unselected (Cohort 1)
Consistent rPFS Treatment Effect in Prespecified Subgroups

Sensitivity Analysis	N	← Favors TALA + ENZA Favors PBO + ENZA →	Hazard Ratio (95% CI)
All Patients	805		0.667 (0.551, 0.807)
Age: ≥70	480		0.698 (0.546, 0.892)
Age: <70	325		0.672 (0.499, 0.905)
ECOG Status: 0	530		0.705 (0.560, 0.889)
ECOG Status: 1	275		0.653 (0.471, 0.907)
Gleason Score: <8	230		0.609 (0.414, 0.896)
Gleason Score: ≥8	564		0.719 (0.577, 0.895)
Stage at Diagnosis: M0	357		0.692 (0.524, 0.914)
Stage at Diagnosis: M1	441		0.692 (0.533, 0.899)
HRRm Deficient	169		0.496 (0.334, 0.734)
HRRm Neg/Unk	636		0.740 (0.596, 0.919)
Prior Taxane/Abiraterone: YES	219		0.538 (0.377, 0.766)
Prior Taxane/Abiraterone: NO	586		0.758 (0.606, 0.949)

rPFS HR

Overall Survival Benefit in Unselected Patients (Proposed Indication)

HR=0.796 (0.661, 0.958)

2-sided p=0.0155*

37.0   Δ8.8   45.8

PBO+ENZA   TALA+ENZA

Months
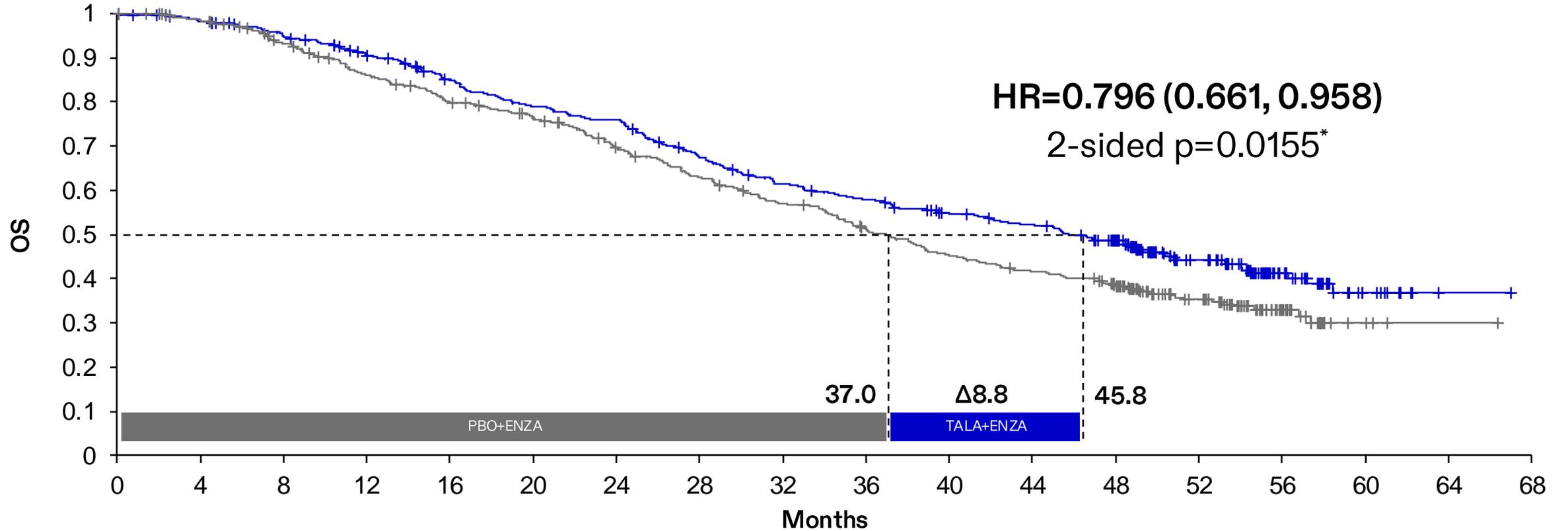
Patients at risk

402	390	371	347	319	296	285	250	226	212	193	183	158	89	42	11	1	0
403	391	362	331	305	287	257	231	207	183	163	148	127	77	33	4	1	0

* The 2-sided critical p-value for OS at the final analysis in September 2024 is 0.022

Unselected (Cohort 1)
Favorable Overall Survival Across Prespecified Subgroups

Sensitivity Analysis	N	← Favors TALA + ENZA Favors PBO + ENZA →	Hazard Ratio (95% CI)
All Patients	805		0.796 (0.661, 0.958)
Age: ≥70	480		0.797 (0.633, 1.004)
Age: <70	325		0.778 (0.571, 1.059)
ECOG Status: 0	530		0.842 (0.669, 1.061)
ECOG Status: 1	275		0.700 (0.514, 0.952)
Gleason Score: <8	230		0.895 (0.622, 1.289)
Gleason Score: ≥8	564		0.769 (0.619, 0.955)
Stage at Diagnosis: M0	357		0.828 (0.627, 1.093)
Stage at Diagnosis: M1	441		0.781 (0.609, 1.003)
HRRm Deficient	169		0.542 (0.361, 0.814)
HRRm Neg/Unk	636		0.874 (0.711, 1.076)
Prior Taxane/Abiraterone: YES	219		0.663 (0.467, 0.940)
Prior Taxane/Abiraterone: NO	586		0.853 (0.686, 1.060)

OS HR

Unselected (Cohort 1)
Meaningful Improvement in Secondary Endpoints

	Unselected (N=805)	
	TALA + ENZA (N=402)	PBO + ENZA (N=403)
Confirmed PSA 50 response	84.6%	72.2%
Confirmed ORR per RECIST 1.1	60.5%[a]	43.8%[b]
Confirmed CR	37.0%[c]	20.8%[d]

Median time to (months):			HR (95% CI)
PSA progression	28.1	17.5	0.69 (0.57, 0.84)
First subsequent therapy	NR	28.5	0.57 (0.47, 0.71)
First cytotoxic chemotherapy	NR	56.1	0.57 (0.45, 0.72)
PFS2	43.4	34.2	0.79 (0.66, 0.94)

[a] Value represents 72/119 patients.
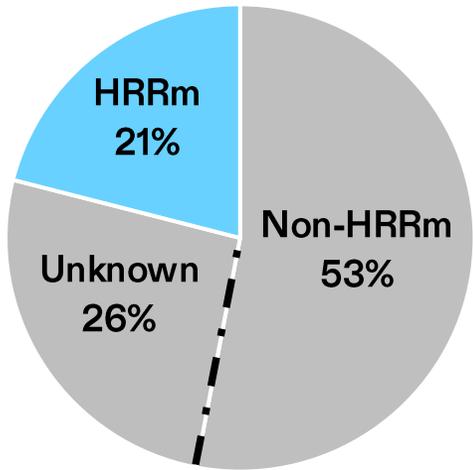[b] Value represents 57/130 patients.
[c] Value represents 44/119 patients.
[d] Value represents 27/130 patients.

Non-HRRm/Unknown Subgroup (Cohort 1)
PROSPECTIVE Genomic Stratified Subgroups

PROSPECTIVE HRR Stratification (By Either Test)

Pie chart:
- HRRm 21%
- Unknown 26%
- Non-HRRm 53%

Primarily Informed by Tumor Testing

rPFS

HR=0.739 (0.595, 0.918)
2-sided p=0.0061‡

22.4 Δ10.9 33.3

PBO+ENZA   TALA+ENZA

OS

HR=0.878 (0.713, 1.080)
2-sided p=0.2183‡

38.3 Δ7.2 45.5

PBO+ENZA   TALA+ENZA
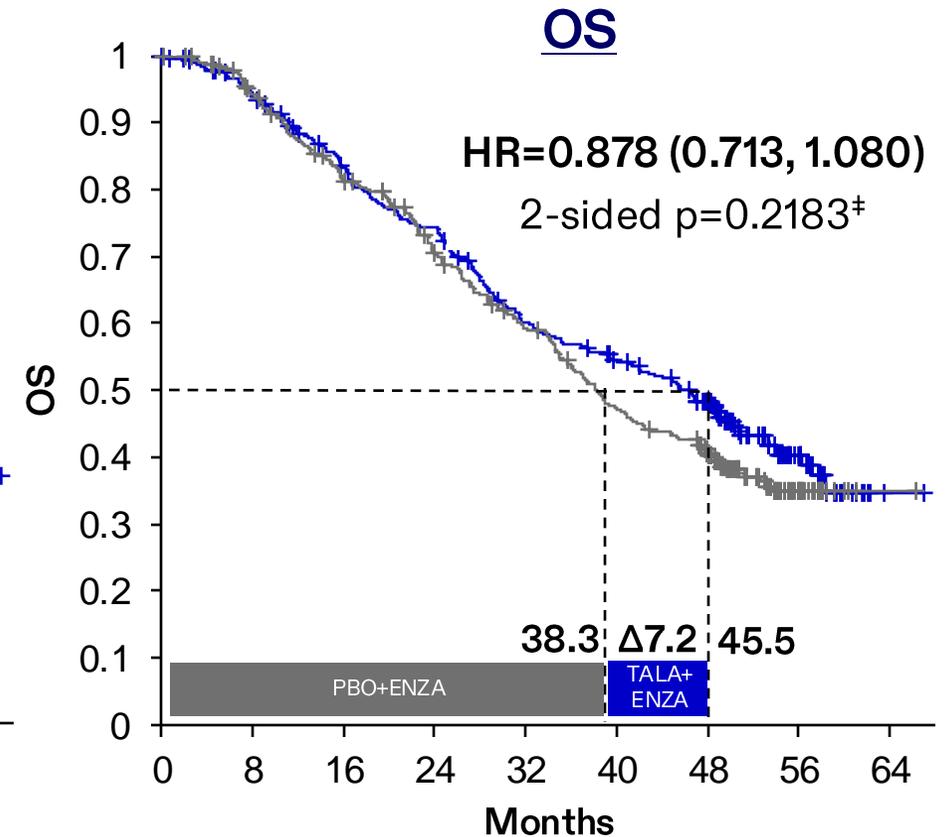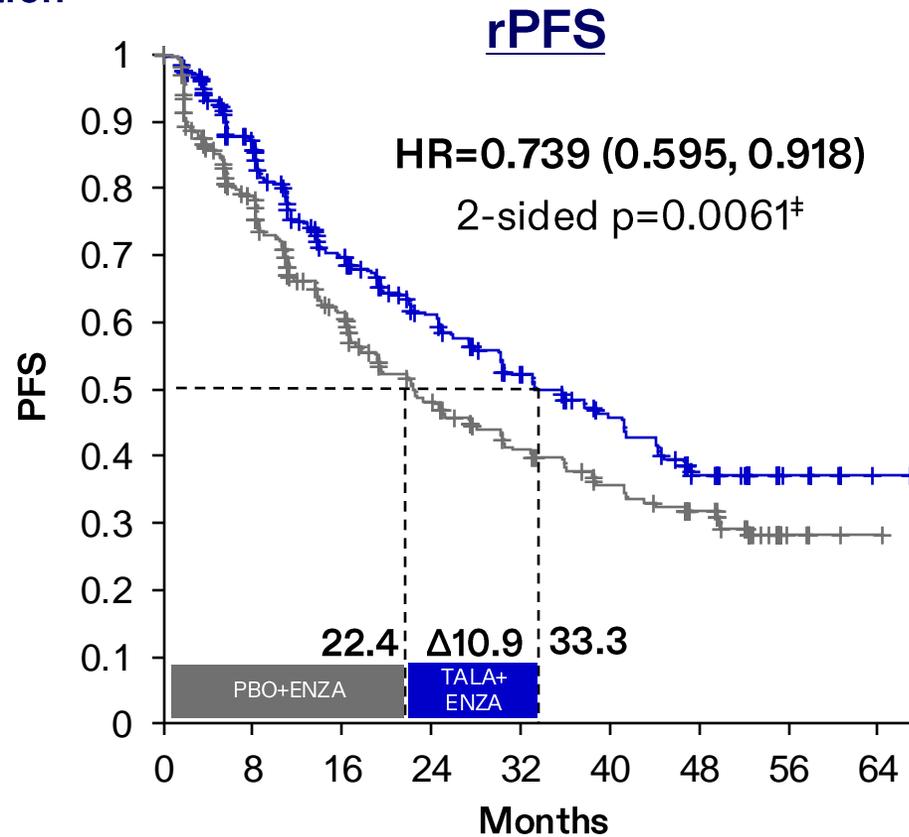
‡ Compared to nominal level 0.05 without multiplicity adjustment.

Unselected (Cohort 1)
Exploratory Genomic Subgroups: Stringent Definition

ALL Baseline Tumor and ctDNA Samples

1 or 2 Positive Tests
(either tissue or ctDNA)

HRRm
33%

Non-HRRm
39%

2 Negative Tests
(both tissue and ctDNA)

2 Unknown Tests
(both tissue and ctDNA)

5%

Non-HRRm
23%

1 Negative, 1 Unknown Test
(either tissue or ctDNA)

No Detectable HRRm by ctDNA and Tissue (Cohort 1)
Non-HRRm Subgroup: Treatment Effect Favors Combination

rPFS

HR=0.757 (0.553, 1.035)
2-sided p=0.0800‡

19.4　Δ13.7　33.1

PBO+ENZA　TALA+ENZA

Months
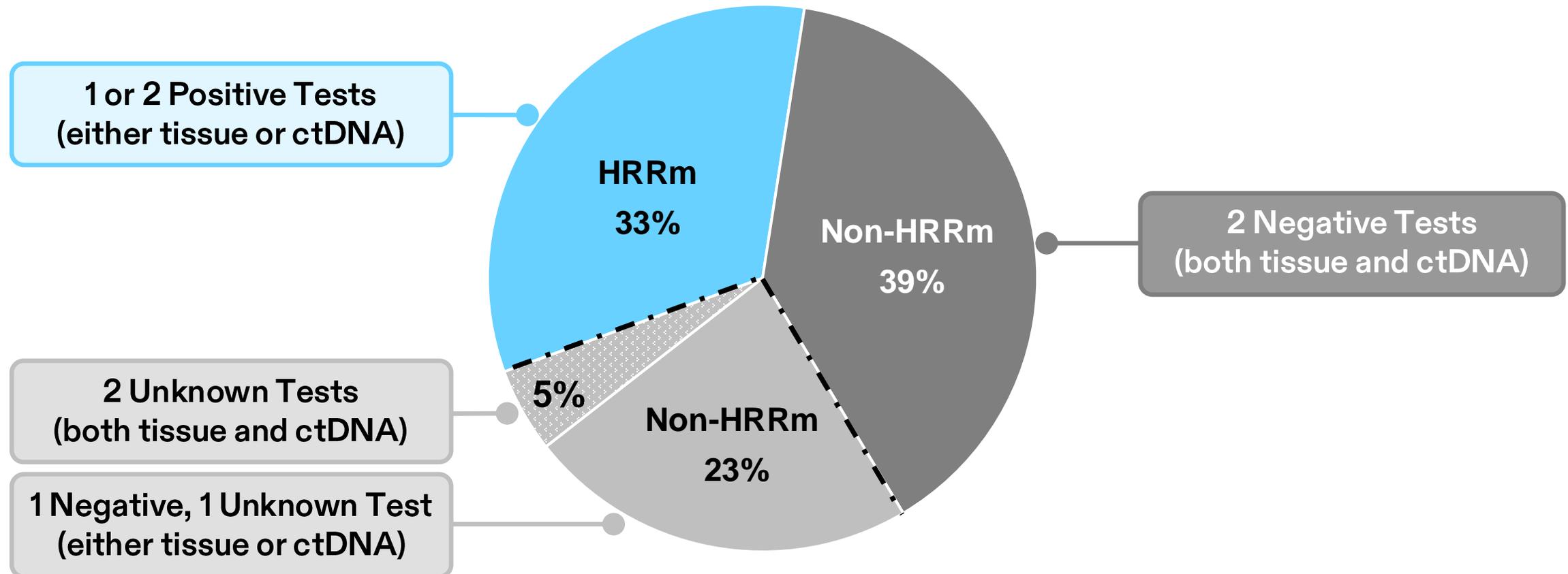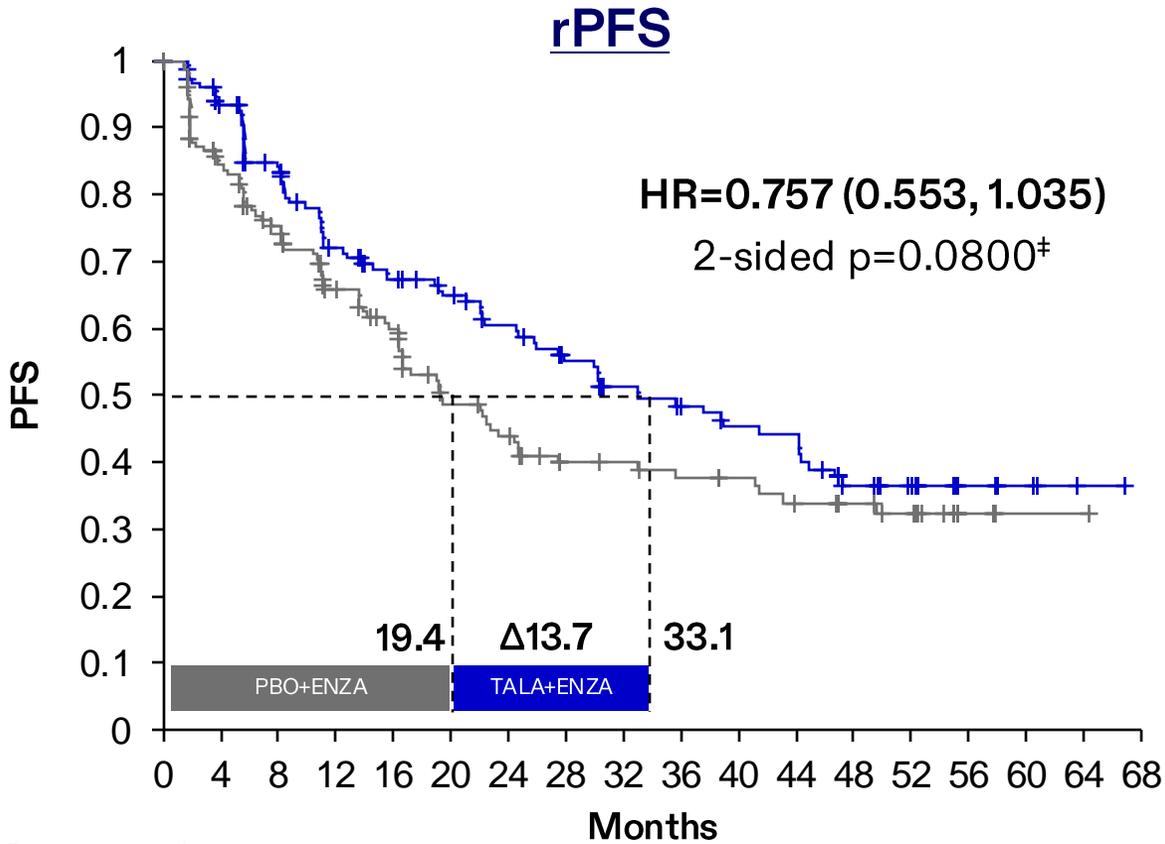
Patients at risk

154	116	84	69	52	43	25	7	1
160	105	72	47	35	30	21	4	1

OS

HR=0.782 (0.582, 1.050)
2-sided p=0.1008‡

37.4　Δ9.2　46.6

PBO+ENZA　TALA+ENZA

Months
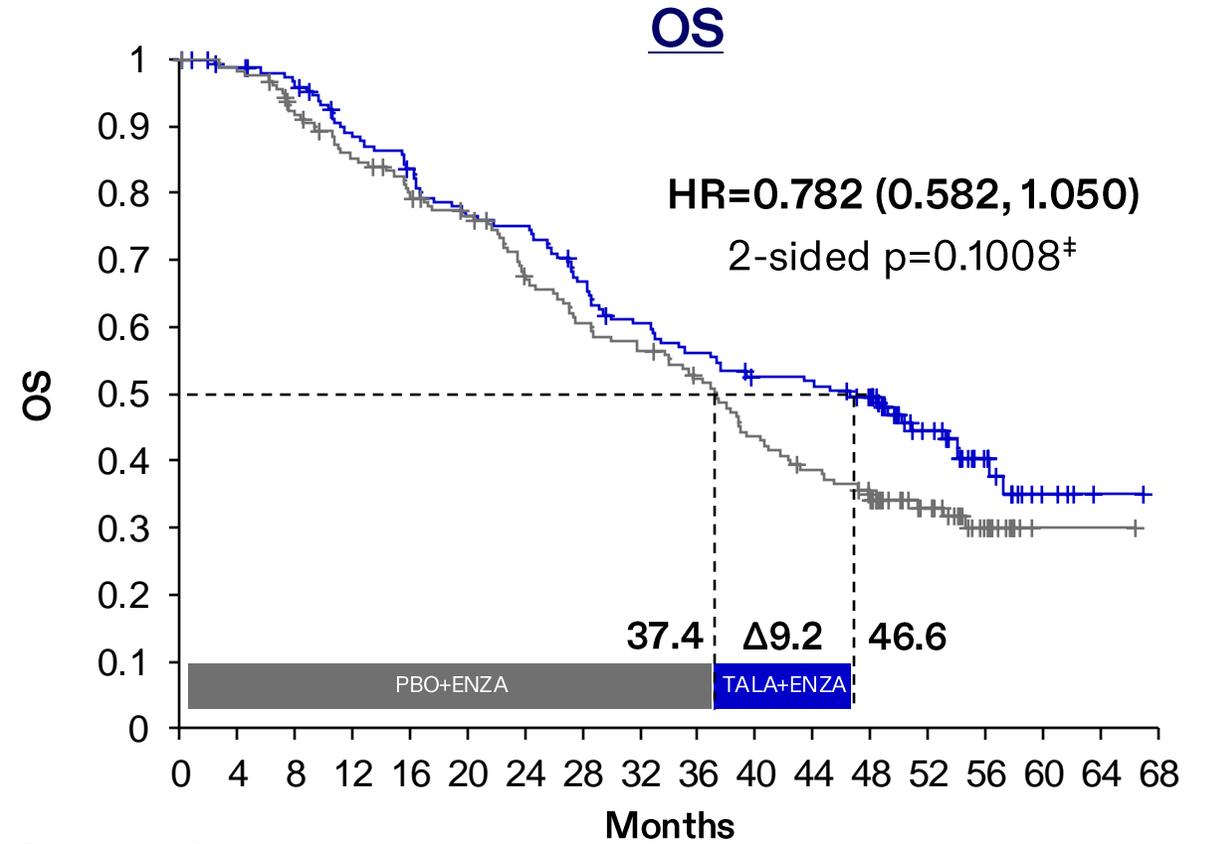
Patients at risk

154	142	120	108	85	72	64	19	1
160	143	120	97	81	61	44	14	1

‡ Compared to nominal level 0.05 without multiplicity adjustment.

No Detectable HRRm by ctDNA and Tissue (Cohort 1)
Non-HRRm Subgroup: Improvement in Secondary Endpoints

	No HRRm by Two Tests (N=314)	
	TALA + ENZA (N=154)	PBO + ENZA (N=160)
Confirmed PSA 50 response	84.3%	71.2%
Confirmed ORR per RECIST 1.1	54.0%[a]	35.7%[b]
Confirmed CR	32.0%[c]	14.3%[d]

Median time to (months):			HR (95% CI)
PSA progression	28.6	17.5	0.78 (0.56, 1.08)
First subsequent therapy	NR	25.6	0.49 (0.34, 0.69)
First cytotoxic chemotherapy	NR	36.2	0.40 (0.27, 0.60)
PFS2	44.1	35.0	0.75 (0.56, 1.00)

[a] Value represents 27/50 patients.
[b] Value represents 20/56 patients.
[c] Value represents 16/50 patients.
[d] Value represents 8/56 patients.

Unselected (Cohort 1) – Stringent Definition Based on ctDNA and Tissue
Median rPFS by Subgroup

Legend: ■ Talazoparib + Enzalutamide   ■ Placebo + Enzalutamide

ITT
- N=402 — 33.1
- N=403 — 19.5
- HR 0.667

HRRm Subgroup
- N=130 — 27.7
- N=136 — 16.5
- HR 0.527

Non-HRRm Subgroup
- N=154 — 33.1
- N=160 — 19.4
- HR 0.757

HRRm Undetermined Subgroup
- N=118 — 35.8
- N=107 — 27.6
- HR 0.747

X-axis: Months (0, 5, 10, 15, 20, 25, 30, 35)
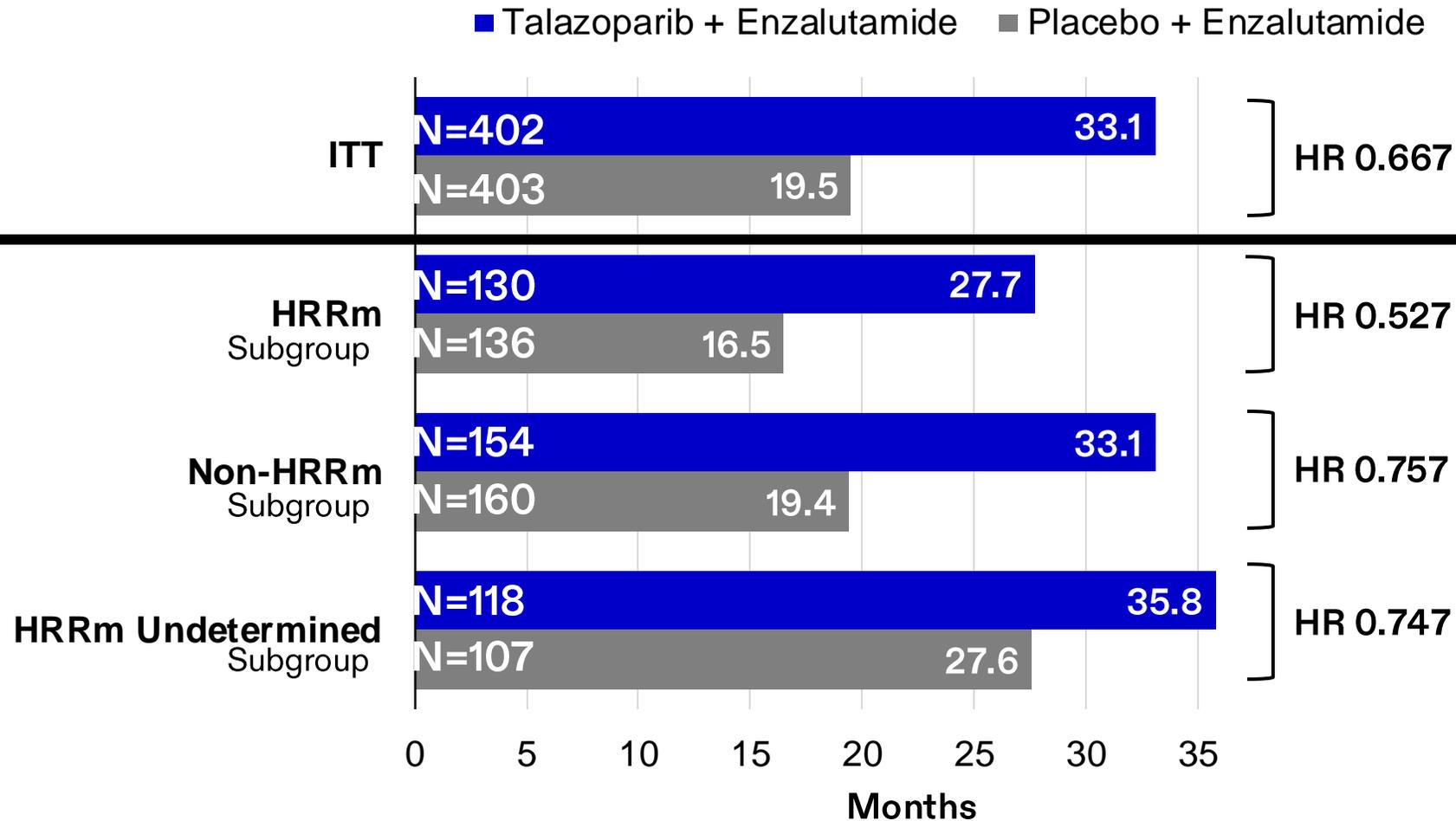
Unselected (Cohort 1) – Stringent Definition Based on ctDNA and Tissue
Median Overall Survival by Subgroup

■ Talazoparib + Enzalutamide   ■ Placebo + Enzalutamide

ITT
- N=402 — 45.8
- N=403 — 37.0
- HR 0.796

HRRm Subgroup
- N=130 — 45.1
- N=136 — 33.3
- HR 0.641

Non-HRRm Subgroup
- N=154 — 46.6
- N=160 — 37.4
- HR 0.782

HRRm Undetermined Subgroup
- N=118 — 46.6
- N=107 — 47.3
- HR 1.064

Months
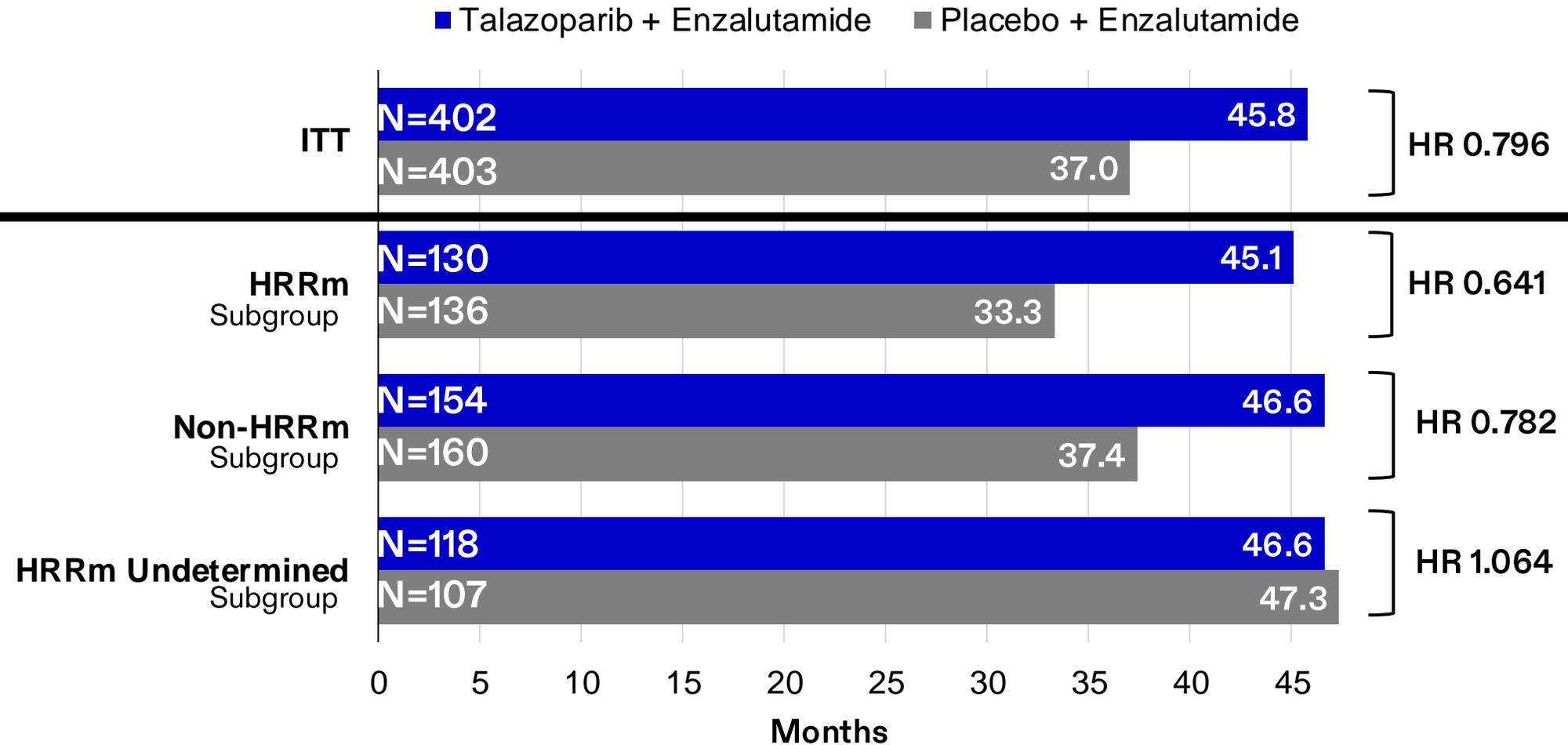
Efficacy Summary

TALAPRO–2 was designed to determine the treatment effect of adding talazoparib to enzalutamide in an unselected mCRPC population

Progression–free survival was significantly prolonged with a median improvement of 13.6 months
- 20% reduction in the risk of death is statistically significant and clinically meaningful
- Favorable treatment effect demonstrated across efficacy endpoints in the non-HRRm subgroup

The efficacy results from the TALAPRO–2 final analysis demonstrate a meaningful treatment benefit for talazoparib and enzalutamide in a well–defined mCRPC population

Safety Profiles of Talazoparib and Enzalutamide Are Well Established

Safety Profile Includes:

Talazoparib[a]
- Hematologic (Anemia)
  [Target Mediated Toxicity]

Enzalutamide[b]
- Musculoskeletal pain
- Fatigue

- At initial US approval TALAPRO-2 safety database (2023)
  - 398 patients in **Cohort 1 (Unselected)**
  - 198 patients in **Cohort 2 (HRRm Only)**

- Additional 24 months of follow-up shows consistent safety profile

[a] Talazoparib USPI. [b] Enzalutamide USPI.

Unselected (Cohort 1)

Longer Exposure with Talazoparib and Enzalutamide

	Talazoparib + Enzalutamide (N=398)	Placebo + Enzalutamide (N=401)
Talazoparib / Placebo		
Median duration of treatment	19.8 months	16.1 months
Median relative dose intensity	82%	100%
Enzalutamide		
Median duration of treatment	22.4 months	16.6 months
Median relative dose intensity	99%	100%

Unselected (Cohort 1)
Overview of Treatment-Emergent Adverse Events

	Talazoparib + Enzalutamide (N=398)	Placebo + Enzalutamide (N=401)
Any TEAE	394 (99.0%)	384 (95.8%)
Maximum Grade 3 or 4 TEAEs	302 (75.9%)	179 (44.6%)
Maximum Grade 5 TEAEs	14 (3.5%)	20 (5.0%)
Any Serious TEAE	182 (45.7%)	126 (31.4%)
TEAEs Leading to Discontinuation		
Talazoparib/Placebo	86 (21.6%)	52 (13.0%)
Enzalutamide	53 (13.3%)	48 (12.0%)
TEAEs Leading to Dose Reduction		
Talazoparib/Placebo	217 (54.5%)	29 (7.2%)
Enzalutamide	61 (15.3%)	33 (8.2%)
TEAEs Leading to Dose Interruptions		
Talazoparib/Placebo	260 (65.3%)	99 (24.7%)
Enzalutamide	175 (44.0%)	91 (22.7%)

TEAE=treatment-emergent adverse event.

Unselected (Cohort 1)
Summary of TEAEs (≥15%): Consistent with Known Safety Profiles

TALA + ENZA (N=398)   PBO + ENZA (N=401)

Event	TALA + ENZA (%)	Grade 3	Grade 4	PBO Grade 3	PBO + ENZA (%)
Anemia	67.8	49.0	3.3	4.5	20.0
Neutrophil count decreased	37.7	19.3	1.5	1.5	7.2
Fatigue	34.9	4.3		2.0	30.2
Back pain	26.9	3.3		1.0	20.7
Platelet count decreased	25.6	7.3 2.3		1	4.0
White blood cell count decreased	24.1	6.8		0	4.7
Decreased appetite	22.4	1.5		1.0	16.7
Fall	22.4	2.8		2.0	17.0
Nausea	21.4	0.5		0.7	13.2
Constipation	19.6	0.3		0.5	18.2
Arthralgia	17.3	0.5		0.5	21.7
Diarrhea	15.8	0.3		0.2	15.0
Asthenia	15.3	3.0		1.0	9.5
Hypertension	15.3	6.3		8.2	17.0

Legend:
- All Grades
- Grade 3
- Grade 4

X-axis: Patients, % (100 80 60 40 20 0 20 40 60 80 100)

Unselected (Cohort 1) – Talazoparib + Enzalutamide Arm
Incidence of Anemia Decreases Over Time

	TALA + ENZA (N=398)	PBO + ENZA (N=401)
Patients with Grade 1-2 anemia at baseline	49%	55%

Patients With Anemia (y-axis, 0% to 20%)

Weeks (x-axis, 0 to 300)

Legend: All Grades (black), Grade 3-4 (green)

Patients at Risk

| TALA + ENZA | 398 | 358 | 314 | 265 | 222 | 198 | 175 | 157 | 133 | 122 | 109 | 66 | 34 | 10 | 2 | 1 |
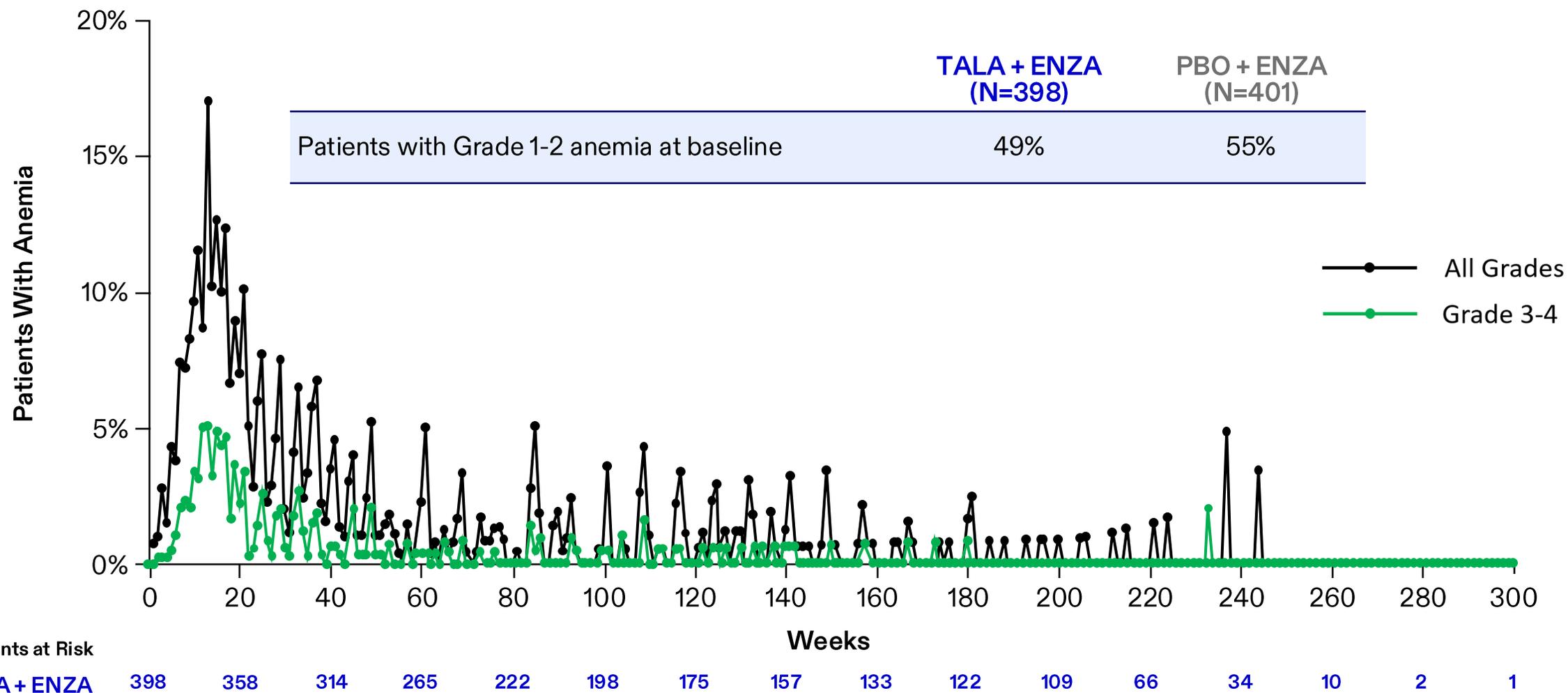
Unselected (Cohort 1) – Talazoparib + Enzalutamide Arm
Hemoglobin Change From Baseline Occurs Early and Improves Over Time
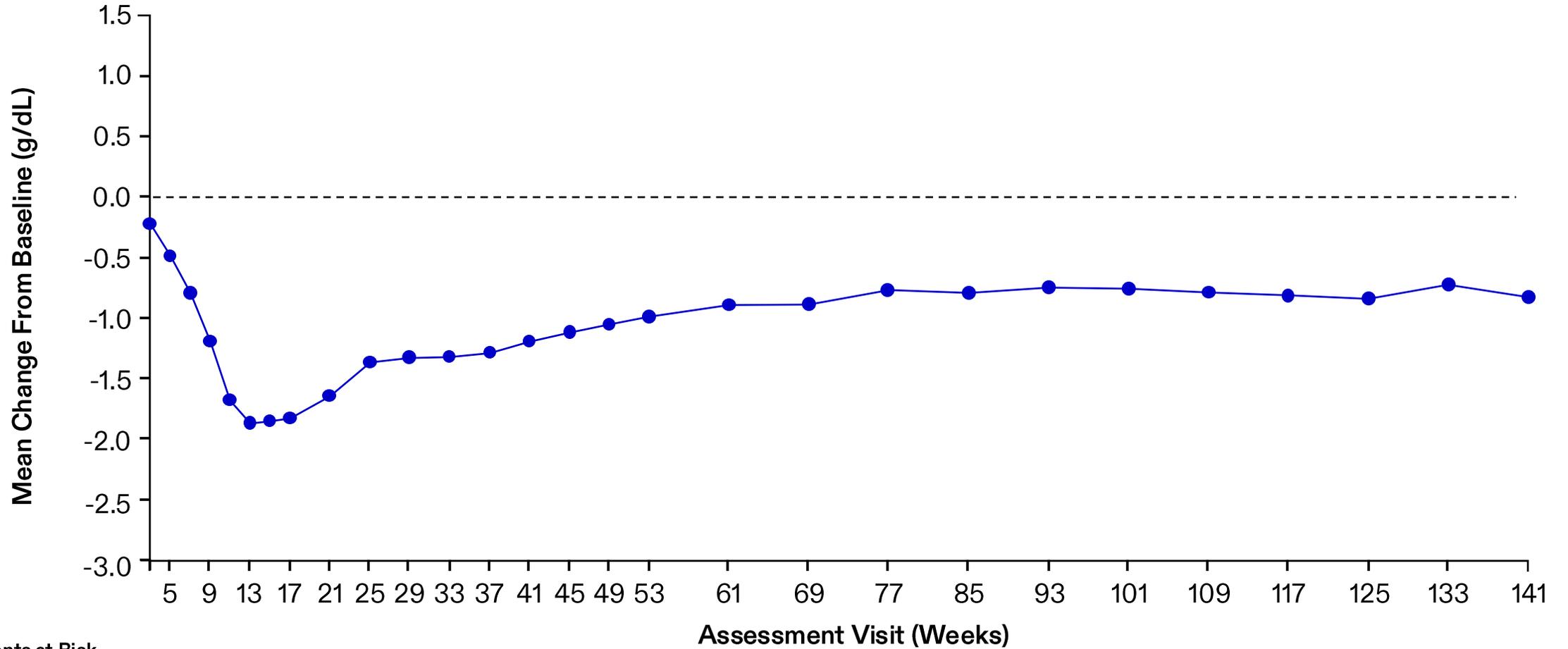
Patients at Risk

| TALA + ENZA | 393 | 385 | 373 | 366 | 353 | 350 | 344 | 337 | 325 | 307 | 292 | 289 | 274 | 258 | 236 | 226 | 216 | 207 | 196 | 190 | 178 | 165 | 159 | 153 |

Unselected (Cohort 1) – Talazoparib + Enzalutamide Arm
Incidence of Transfusions Decreases Over Time

Patients at Risk

| TALA + ENZA | 398 | 358 | 314 | 265 | 222 | 198 | 175 | 157 | 133 | 122 | 109 | 66 | 34 | 10 | 2 | 1 |
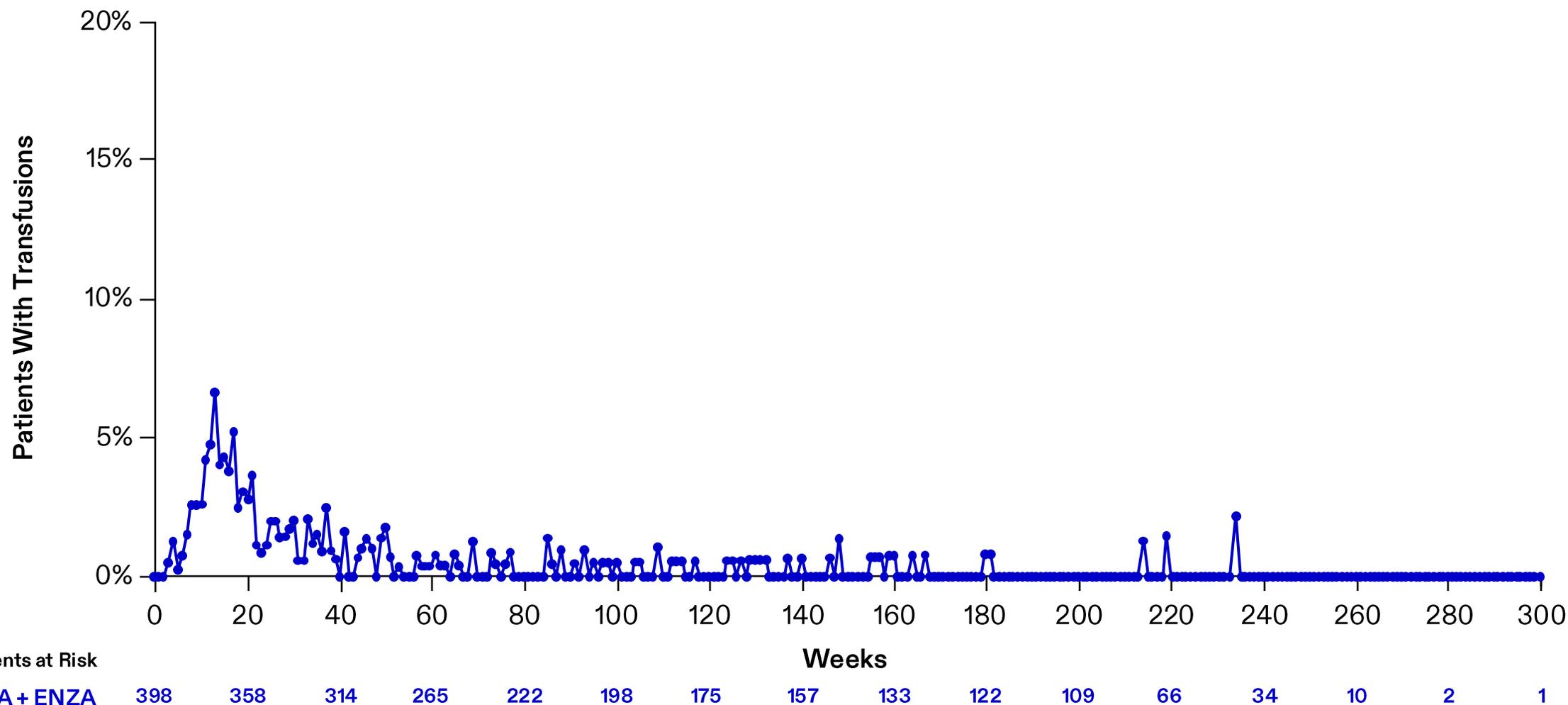
Unselected (Cohort 1)
Anemia is Manageable With Dose Modifications

	Talazoparib + Enzalutamide (N=398)	Placebo + Enzalutamide (N=401)
Dose discontinuation due to anemia[a]	34 (8.5%)	6 (1.5%)
Dose reduction due to anemia	177 (44.5%)	6 (1.5%)
Dose interruption due to anemia	185 (46.5%)	10 (2.5%)

Median Relative Dose Intensity for Talazoparib was 82%

[a] Refers to permanent discontinuation of talazoparib/placebo.

Unselected (Cohort 1) – Talazoparib + Enzalutamide Arm

Safety Profile is Consistent With Additional 24 Months of Follow-up

Legend:
Gr 1-2 / Gr ≥3
- Primary Analysis (Aug 2022)
- Final Analysis (Sept 2024)

Y-axis: Patients, %

Data values by category:

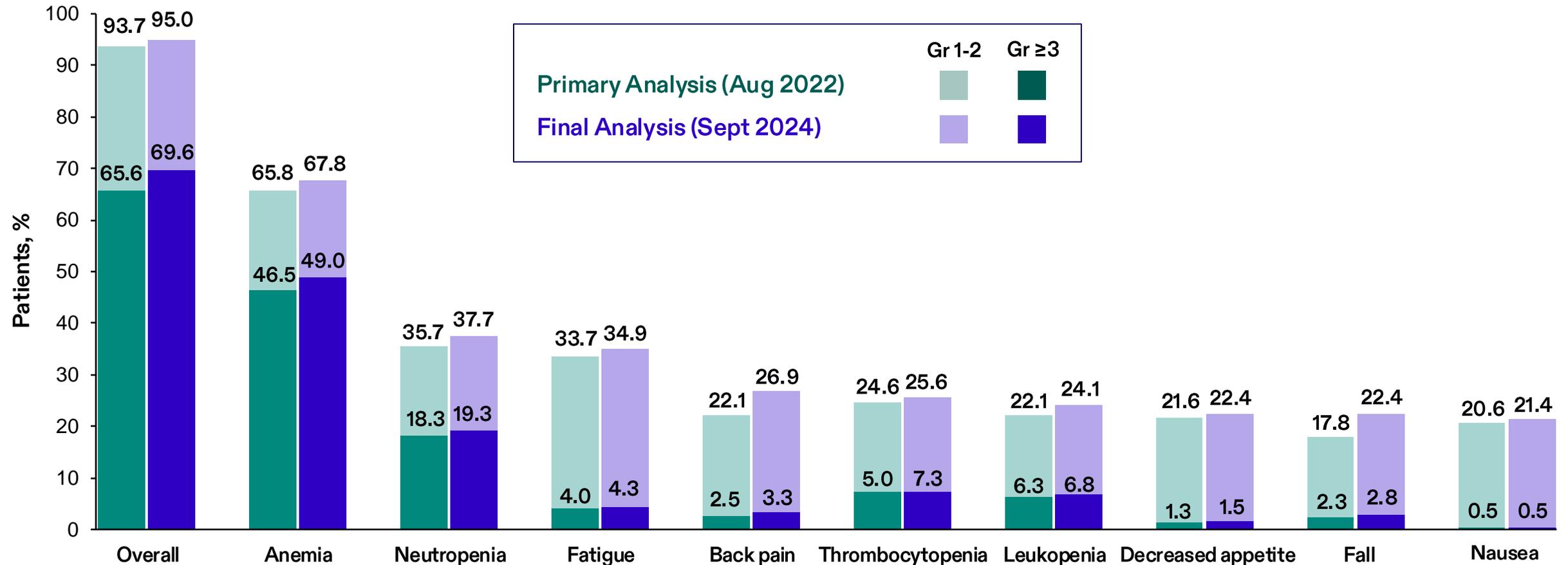| Category	Overall	Anemia	Neutropenia	Fatigue	Back pain	Thrombocytopenia	Leukopenia	Decreased appetite	Fall	Nausea
Primary total	93.7	65.8	35.7	33.7	22.1	24.6	22.1	21.6	17.8	20.6
Final total	95.0	67.8	37.7	34.9	26.9	25.6	24.1	22.4	22.4	21.4
Primary Gr ≥3	65.6	46.5	18.3	4.0	2.5	5.0	6.3	1.3	2.3	0.5
Final Gr ≥3	69.6	49.0	19.3	4.3	3.3	7.3	6.8	1.5	2.8	0.5

Figure includes TEAEs reported in ≥20% of patients in either analysis.
Agarwal N, et al. *Lancet.* 2023;402:291-303.

Unselected (Cohort 1)
Adverse Events of Special Interest

Preferred Term	Talazoparib + Enzalutamide (N=398)	Placebo + Enzalutamide (N=401)
	Grade ≥3	Grade ≥3
Venous thrombotic/embolic events	13 (3.3%)	3 (0.7%)
Second primary malignancies	11 (2.8%)	17 (4.2%)
Pneumonitis	1 (0.3%)	0
Myelodysplastic syndrome/ Acute myeloid leukemia	2 (0.5%)[a]	0

No New Cases of MDS/AML with 24 Months of Additional Follow-up

[a] Includes one case of AML reported outside of safety reporting period.

Unselected (Cohort 1) – EORTC QLQ-C30
Patient Reported Global Health Status/Quality of Life

Improvement

- Talazoparib + Enzalutamide
- Placebo + Enzalutamide

Mean Change From Baseline (y-axis: 40, 30, 20, 10, 0, -10, -20, -30, -40)

Worsening

Assessment Visit (Weeks): 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 61, 69, 77, 85, 93, 101, 109

Patients at Risk

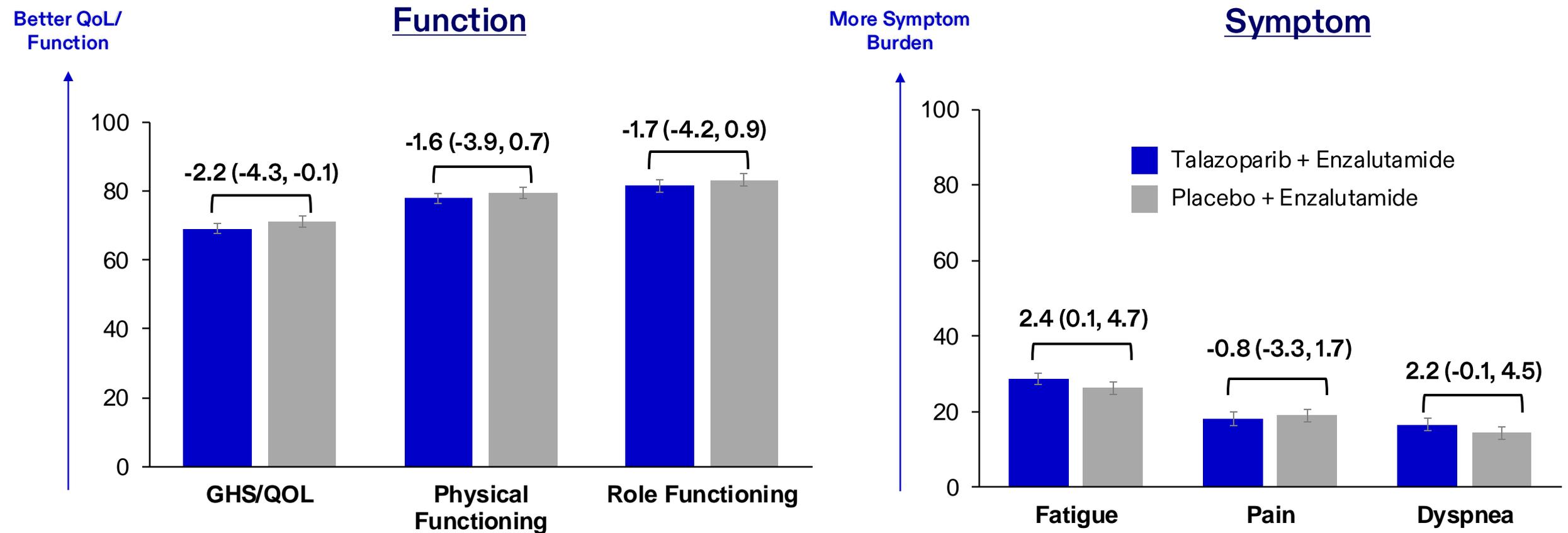|	5	9	13	17	21	25	29	33	37	41	45	49	53	61	69	77	85	93	101	109
TALA + ENZA	307	302	289	295	279	279	272	276	272	262	243	238	232	218	199	186	179	176	162	159
PBO + ENZA	316	305	285	279	270	260	243	236	229	222	212	203	196	180	169	150	138	132	122	113
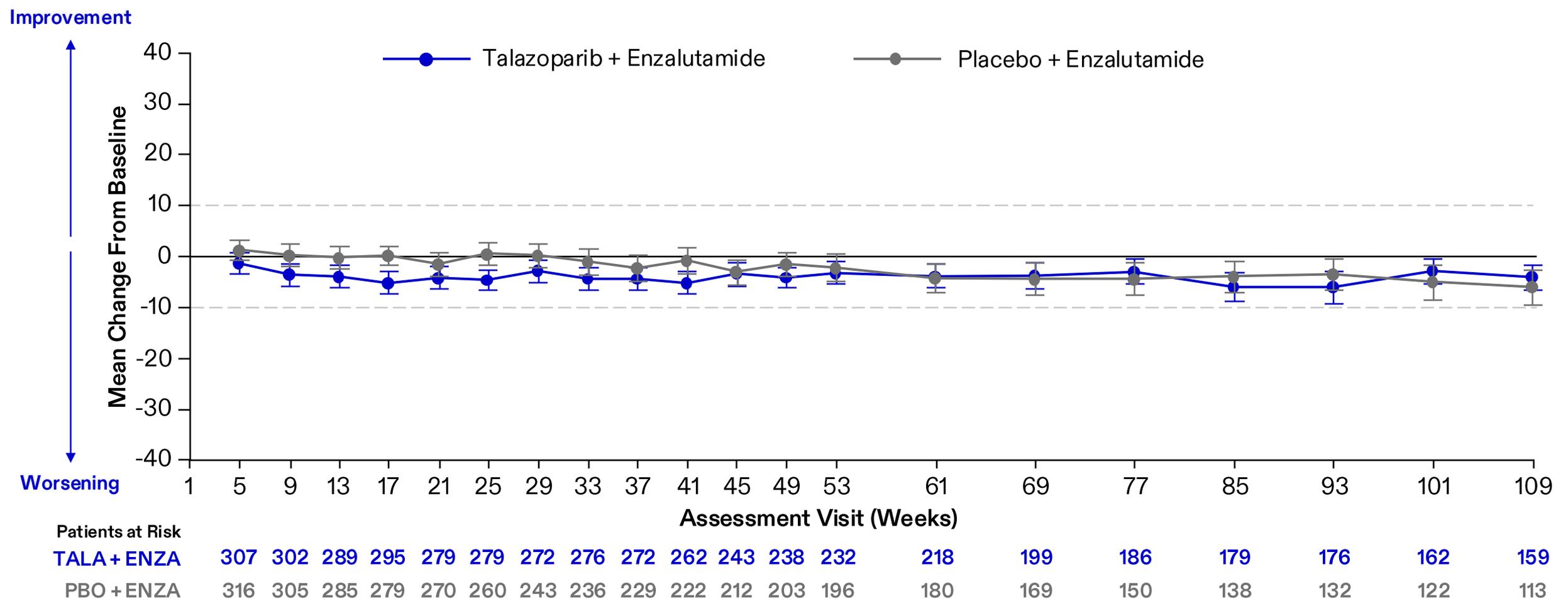
No Clinically Meaningful Difference Between Treatment Arms

GHS/QoL, Global Health Status/ Quality of Life.
Observed mean change from baseline in the first 2 years.

Unselected (Cohort 1) – EORTC QLQ-C30
Patient Reported Functioning and Symptoms

Better QoL/Function

Function

More Symptom Burden

Symptom

Function panel:
- GHS/QOL: -2.2 (-4.3, -0.1)
- Physical Functioning: -1.6 (-3.9, 0.7)
- Role Functioning: -1.7 (-4.2, 0.9)

Legend:
- Talazoparib + Enzalutamide
- Placebo + Enzalutamide

Symptom panel:
- Fatigue: 2.4 (0.1, 4.7)
- Pain: -0.8 (-3.3, 1.7)
- Dyspnea: 2.2 (-0.1, 4.5)

No Clinically Meaningful Difference Between Treatment Arms

Longitudinal mixed effect model of all on-treatment visits.

Unselected (Cohort 1) – EORTC QLQ-C30 – Talazoparib + Enzalutamide Arm
Patient Reported Global Health Status/Quality of Life

Patients at Risk																					
No Anemia/Gr 1-2 Anemia	148	148	139	148	139	139	134	137	138	130	121	117	121	108	102	96	96	96	96	90	84
Gr 3-4 Anemia	159	154	150	147	140	140	138	139	134	132	122	121	111	110	97	90	83	80	72	75
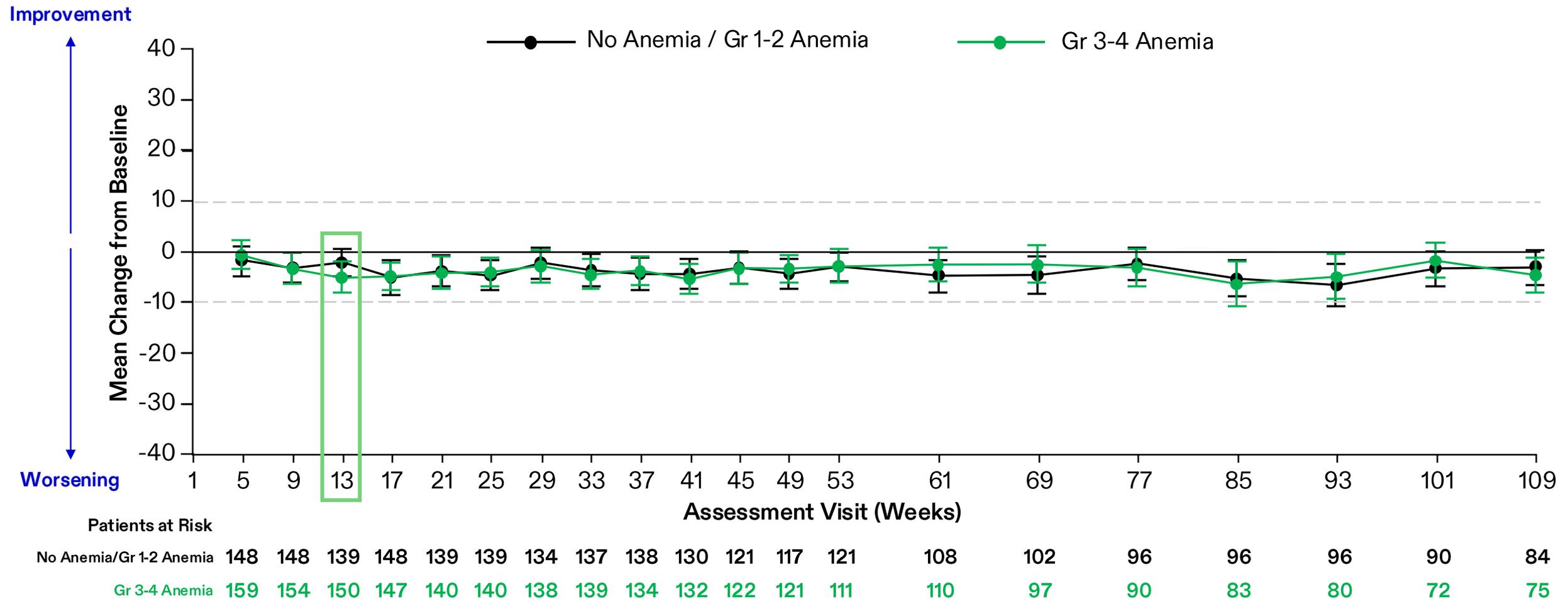
No Clinically Meaningful Difference With vs Without Grade 3-4 Anemia

Mean observed change from baseline based on status of treatment emergent grade 3-4 anemia in first two years.

Safety Summary

Safety profile of talazoparib and enzalutamide is well–established
- Safety profile of the combination is consistent with the known profiles of the individual agents
- Safety remains unchanged with 24 months of additional follow-up

Anemia is the most common AE related to talazoparib
- Occurs early and is manageable with dose modifications and supportive care
- GHS/QoL scores were similar among patients experiencing Grade 3-4 anemia and those who did not

No evidence of substantive toxicity that impacted the duration of treatment, the ability to receive subsequent therapies, or overall survival

Clinical Perspective

Neeraj Agarwal, MD, FASCO

Professor of Medicine
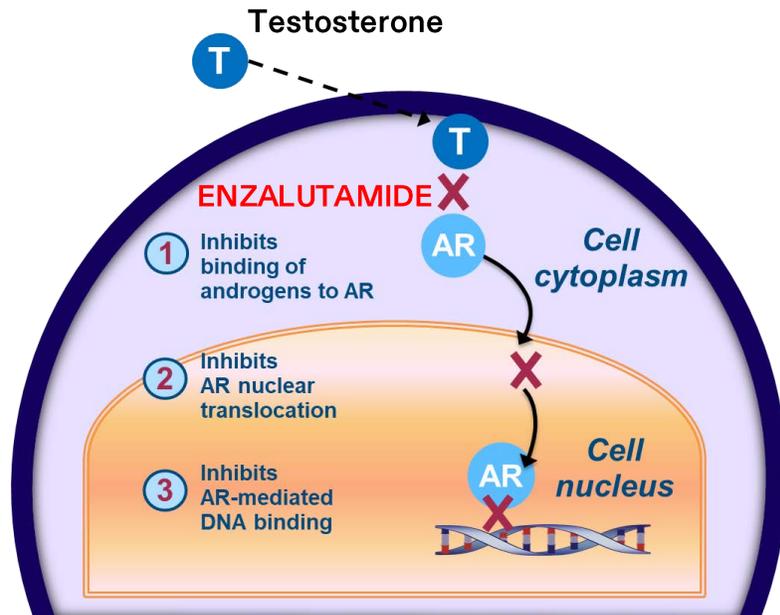Presidential Endowed Chair of Cancer Research
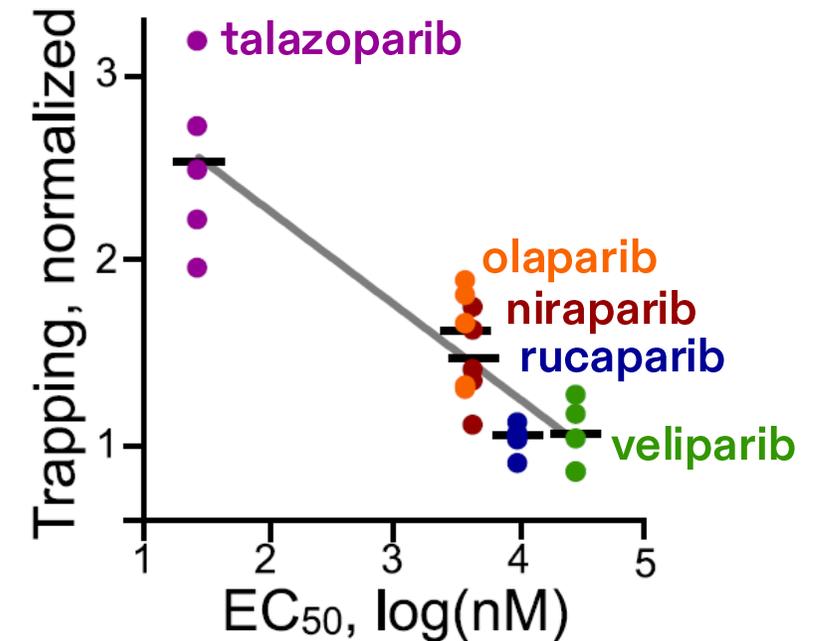Huntsman Cancer Institute
University of Utah

Why is Talazoparib + Enzalutamide Different from Other PARPi + ARPi Combinations?

Enzalutamide directly inhibits the androgen receptor[1,2,3]

Testosterone

ENZALUTAMIDE

① Inhibits binding of androgens to AR

② Inhibits AR nuclear translocation

③ Inhibits AR-mediated DNA binding

Cell cytoplasm

Cell nucleus

Talazoparib is the most potent PARP trapper[4]

talazoparib

olaparib

niraparib

rucaparib

veliparib

ARPI=androgen receptor pathway inhibitor.
1. Chen Y, et al. *Lancet Oncol.* 2009;10(10):981–991; 2. La J, et al. *JAMA Network Open.* 2024;7(8):e2428444; 3. George DJ, et al. *Prostate Cancer Prostatic Dis.* 2024;27:756–764;
4. Reprinted from *Cell Chemical Biology*, 31(7), Gopal, A.A., et al., PARP trapping is governed by the PARP inhibitor dissociation rate constant, 1373-1382 e10, Copyright 2024 with permission from Elsevier.
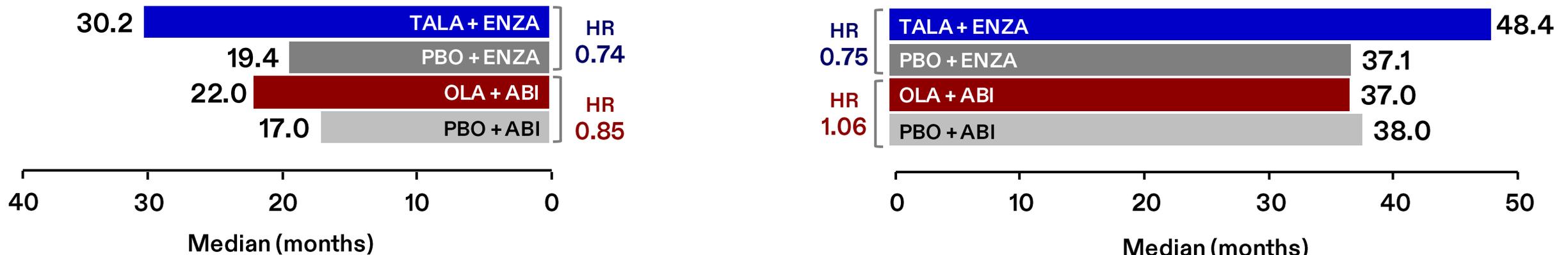
TALAPRO–2 Results Differ from PROpel[1,2]

rPFS[a]
Primary endpoint

Overall Survival
Key secondary endpoint

Unselected ITT

	rPFS			OS
33.1	TALA + ENZA	HR 0.67	HR 0.80	TALA + ENZA	45.8
19.5	PBO + ENZA			PBO + ENZA	37.0
24.8	OLA + ABI	HR 0.66	HR 0.81	OLA + ABI	42.1
16.6	PBO + ABI			PBO + ABI	34.7

Non-BRCAm Subgroup[b]
(Based on 2 Tests)

	rPFS			OS
30.2	TALA + ENZA	HR 0.74	HR 0.75	TALA + ENZA	48.4
19.4	PBO + ENZA			PBO + ENZA	37.1
22.0	OLA + ABI	HR 0.85	HR 1.06	OLA + ABI	37.0
17.0	PBO + ABI			PBO + ABI	38.0

40   30   20   10   0
Median (months)
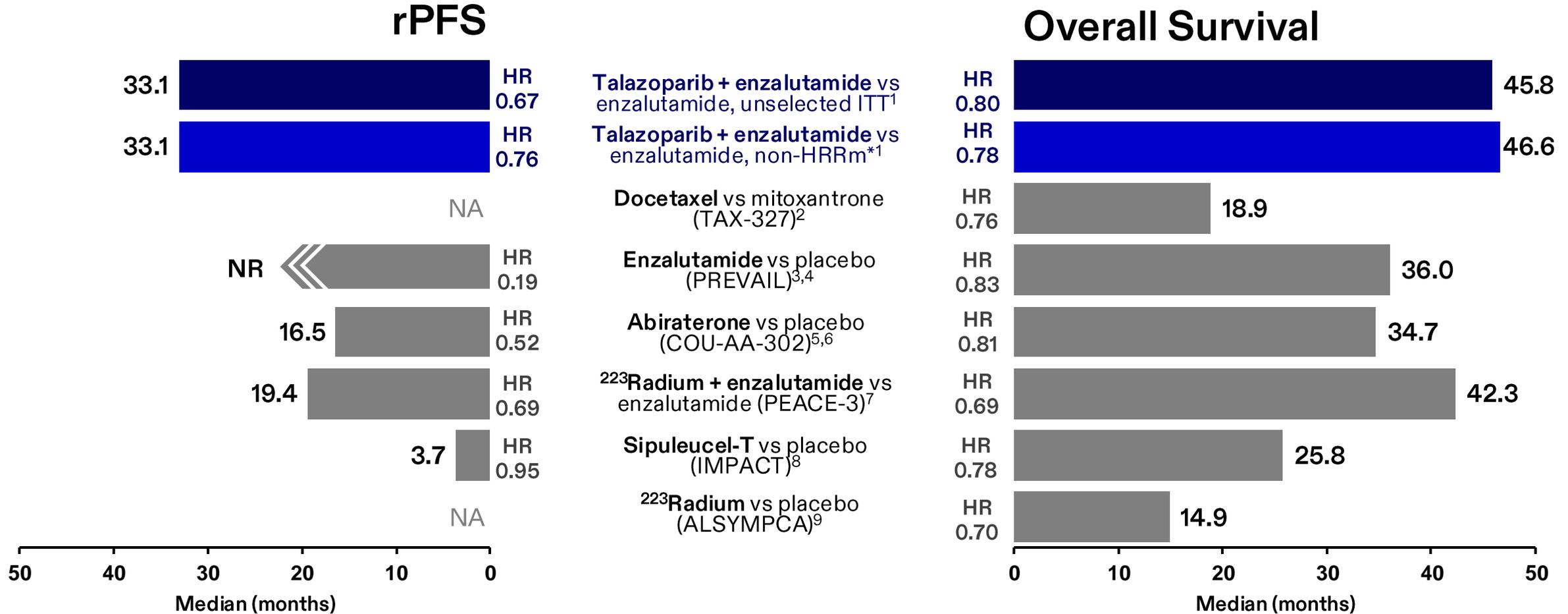
0   10   20   30   40   50
Median (months)

[a] rPFS was centrally assessed for TALAPRO-2 and investigator assessed for PROpel. All rPFS analyses shown for TALAPRO-2 are at the final OS readout, PROpel rPFS for the unselected ITT was assessed at final OS readout while non-HRR and non-BRCA rPFS results are from earlier data cuts.
[b] Negative for BRCAm by both tumor and ctDNA tests. All TALAPRO-2 results are from Cohort 1.
1. Saad et al. 2023 *Lancet Oncol* 24:1094-1108; 2. FDA ODAC Briefing Document NDA 208558/Supplement 25, 2023.
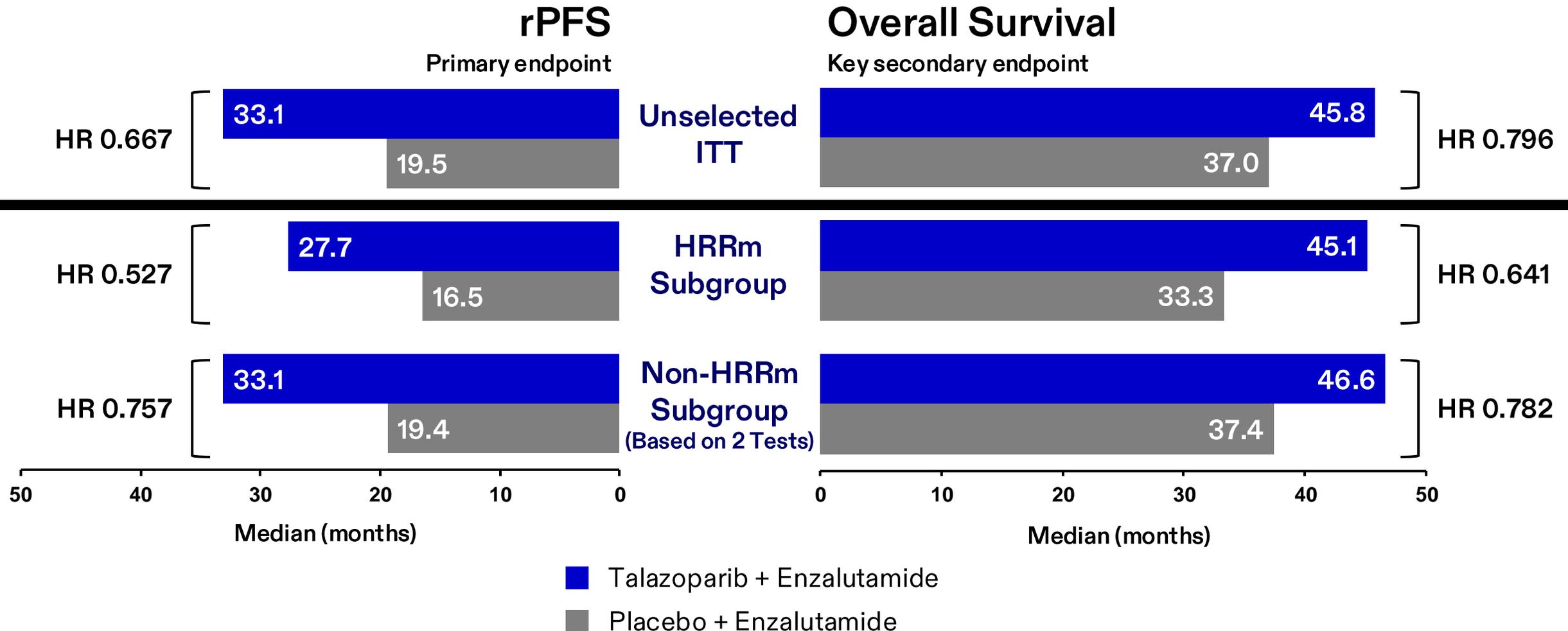
Efficacy of Current 1L Treatment Options for Unselected mCRPC

rPFS

Median (months)	HR	Treatment
33.1	HR 0.67	**Talazoparib + enzalutamide** vs enzalutamide, unselected ITT[1]
33.1	HR 0.76	**Talazoparib + enzalutamide** vs enzalutamide, non-HRRm*[1]
NA		**Docetaxel** vs mitoxantrone (TAX-327)[2]
NR	HR 0.19	**Enzalutamide** vs placebo (PREVAIL)[3,4]
16.5	HR 0.52	**Abiraterone** vs placebo (COU-AA-302)[5,6]
19.4	HR 0.69	[223]**Radium + enzalutamide** vs enzalutamide (PEACE-3)[7]
3.7	HR 0.95	**Sipuleucel-T** vs placebo (IMPACT)[8]
NA		[223]**Radium** vs placebo (ALSYMPCA)[9]

Overall Survival

HR	Median (months)
HR 0.80	45.8
HR 0.78	46.6
HR 0.76	18.9
HR 0.83	36.0
HR 0.81	34.7
HR 0.69	42.3
HR 0.78	25.8
HR 0.70	14.9

Median (months)

* Negative for HRRm by both tumor and ctDNA tests; NR=not reached; NA=not available.
1. Agarwal et al. LBA18, ASCO-GU 2025; 2. Tannock IF et al. *N Engl J Med* 2004;351:1502-1512; 3. Beer TM et al. *N Engl J Med* 2014;371:424-433; 4. Armstrong AJ et al. *European Urology* 2020;78(3):347-357; 5. Ryan JR et al. *The Lancet* 2015;16(2)152-160; 6.Rathkopf DE et al. *European Urology* 2014;66(5)815-825; 7. Gillesen et al. LBA1, ESMO 2024; 8. Kantoff PW et al. *N Engl J Med* 2010;363:411-422; 9. Parker C et al. *N Engl J Med* 2013;369:213-223.

With or Without HRRm, Patients with mCRPC Benefit from Talazoparib + Enzalutamide

rPFS
Primary endpoint

Overall Survival
Key secondary endpoint

HR 0.667 — Unselected ITT: 33.1 / 19.5 — HR 0.796: 45.8 / 37.0

HR 0.527 — HRRm Subgroup: 27.7 / 16.5 — HR 0.641: 45.1 / 33.3

HR 0.757 — Non-HRRm Subgroup (Based on 2 Tests): 33.1 / 19.4 — HR 0.782: 46.6 / 37.4

Median (months)

Median (months)

■ Talazoparib + Enzalutamide
■ Placebo + Enzalutamide

Anemia is Expected and Manageable

Anemia is the most frequently observed adverse event

- Clinical trial experience: baseline anemia and protocol requirements may have contributed to frequency of Grade 3-4 events and transfusions

- Managing anemia is common in clinical practice

- Monitor for anemia through standard CBCs, especially during first 3 months

- Managed by dose modifications per current US prescribing information

- Acceptable safety profile

Physician and Patient Benefit/Risk Discussion

Potential Benefits	Potential Risks
• Opportunity to delay progression by additional 11-14 months • Potentially delaying symptoms of progression, compared to an active therapy • Overall survival potentially extended by 9-12 months • No clinically meaningful difference in quality of life vs enzalutamide alone	• About half of the patients develop Grade 3 anemia, mostly within first 3 months • Managed by routine blood tests, dose modifications and supportive care • Potential for rare adverse events

Talazoparib + Enzalutamide is a Life-Prolonging Therapy that Should be an Option for All Patients with mCRPC

Closing Remarks

Johanna Bendell, MD

Chief Development Officer
Oncology Research and Development
Pfizer Inc.

Conclusions

- Unmet need remains in patients with non-HRRm mCRPC

- Well-documented scientific rationale for the differentiated MOA of talazoparib and enzalutamide in non-HRRm tumors

- Efficacy in the non-HRRm subgroup is clinically meaningful and reflects a true treatment effect that is unlikely due to chance alone

- Anemia is common but manageable with dose modifications and supportive care

- TALAPRO-2 demonstrated statistically significant and clinically meaningful gains in rPFS and OS in the unselected population (ITT)
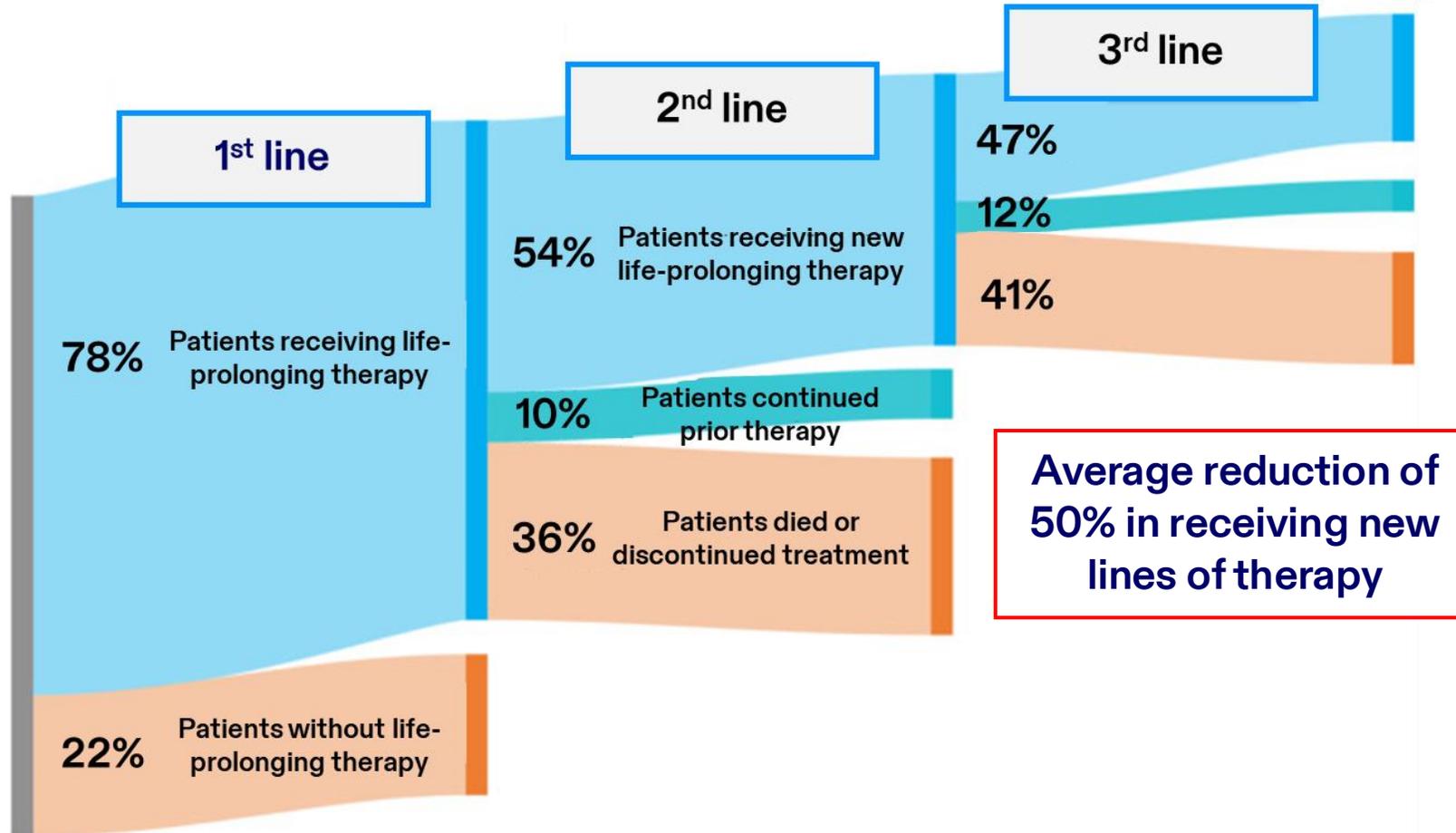
Proposed Indication: TALZENNA® (talazoparib) is indicated in combination with enzalutamide for the treatment of adult patients with mCRPC

Supporting Slides

US mCRPC Treatment Patterns[1]

mCRPC patients
(n=14,780)

1st line

2nd line

3rd line

78% Patients receiving life-prolonging therapy

22% Patients without life-prolonging therapy

54% Patients receiving new life-prolonging therapy

10% Patients continued prior therapy

36% Patients died or discontinued treatment

47%

12%

41%

Average reduction of 50% in receiving new lines of therapy

1. Adapted from Freedland S et al. Prostate Cancer Prostatic Dis. 2024 Jun;27(2):327-333

Unselected (Cohort 1)
Selected Subsequent Antineoplastic Systemic Therapies

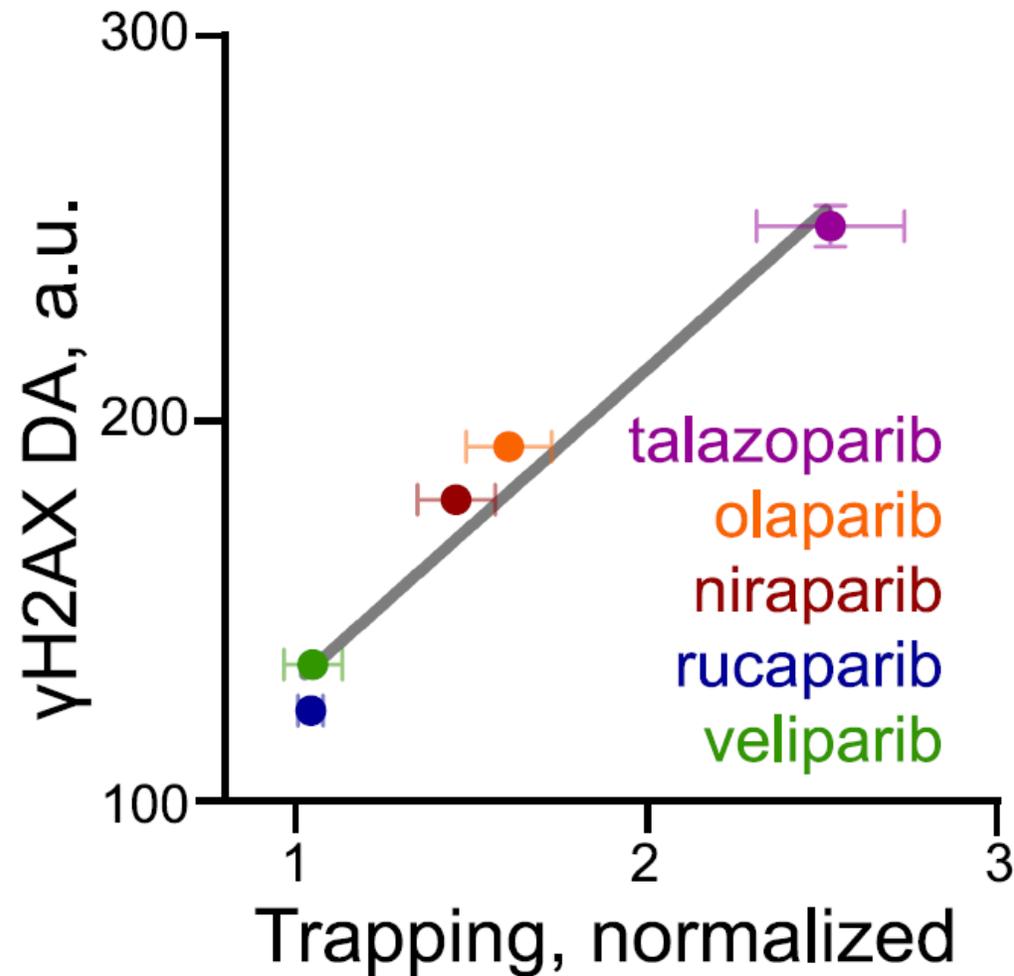| Post-Baseline Antineoplastic Therapy Use	TALA + ENZA (N=398) N (%)	PBO + ENZA (N=401) N (%)	Total (N=799) N (%)
Patients Taking any of the Selected Post-Baseline Therapy	**145 (36.4)**	**201 (50.1)**	**346 (43.3)**
Taxane-Based Therapy	102 (25.6)	149 (37.2)	251 (31.4)
Second Generation Androgen Receptor Inhibitors	22 (5.5)	25 (6.2)	47 (5.9)
Radiopharmaceuticals	36 (9.0)	44 (11.0)	80 (10.0)
Single-Agent PARP Inhibitor Therapies	6 (1.5)	15 (3.7)	21 (2.6)
Cellular Immunotherapy	1 (0.3)	1 (0.2)	2 (0.3)
Abiraterone	44 (11.1)	68 (17.0)	112 (14.0)
Other Cytotoxic Chemotherapy	5 (1.3)	19 (4.7)	24 (3.0)

Unselected (Cohort 1)
Consistent rPFS (BICR) Benefit in Non-HRRm Disease

Subgroup	N	Median (mo)	← Favors TALA + ENZA Favors PBO + ENZA →	Hazard Ratio (95% CI)	1-sided p-value
All Patients	805	33.1/19.5		0.67 (0.55, 0.81)	<0.0001
Non-HRRm "Double Negative" (FDA)	294	NR/22.4		0.68 (0.47, 0.98)	
Non-HRRm "Double Negative" (Applicant)	314	33.1/19.4		0.76 (0.55, 1.04)	0.040
Non-HRRm by Prospective Tumor Tissue and Blood	426	33.2/22.1		0.75 (0.58, 0.98)	0.0183
Non-HRRm by Prospective Plus Retrospective Plasma	547	35.8/22.8		0.77 (0.61, 0.97)	0.0140
Non-HRRm by Tumor Tissue	412	33.1/19.4		0.73 (0.56, 0.96)	0.0115
Non-HRRm by ctDNA	480	37.7/24.3		0.74 (0.57, 0.95)	0.0080

Hazard Ratio (95% CI)

0   0.5   1   1.5

Potent PARP Trapping by Talazoparib is Associated with High Accumulation of DNA DS-Break Marker GammaH2AX

Gopal AA, et al. *Cell Chem Biol*. 2024;31(7):1373-1382.e10.
ICS DA (degree of aggregation) of gH2AX IF in HT1080 cells treated with 1 μM PARPi overnight versus PARP1 trapping, with linear fit (gray line), shown are average with SEM, trapping - n = 5, DA - n≥ 536 cells, 3 biological repeats.

Unselected (Cohort 1)
Grade 1 and 2 Nausea and Decreased Appetite

Number (%) of Participants: by Preferred Term	Talazoparib + Enzalutamide (N=398)		Placebo + Enzalutamide (N=401)	
	Grade 1 N (%)	Grade 2 N (%)	Grade 1 N (%)	Grade 2 N (%)
Nausea	47 (11.8)	36 (9.0)	34 (8.5)	16 (4.0)
Decreased appetite	57 (14.3)	26 (6.5)	43 (10.7)	20 (5.0)