Best of ASCO 2024

GU Cancers

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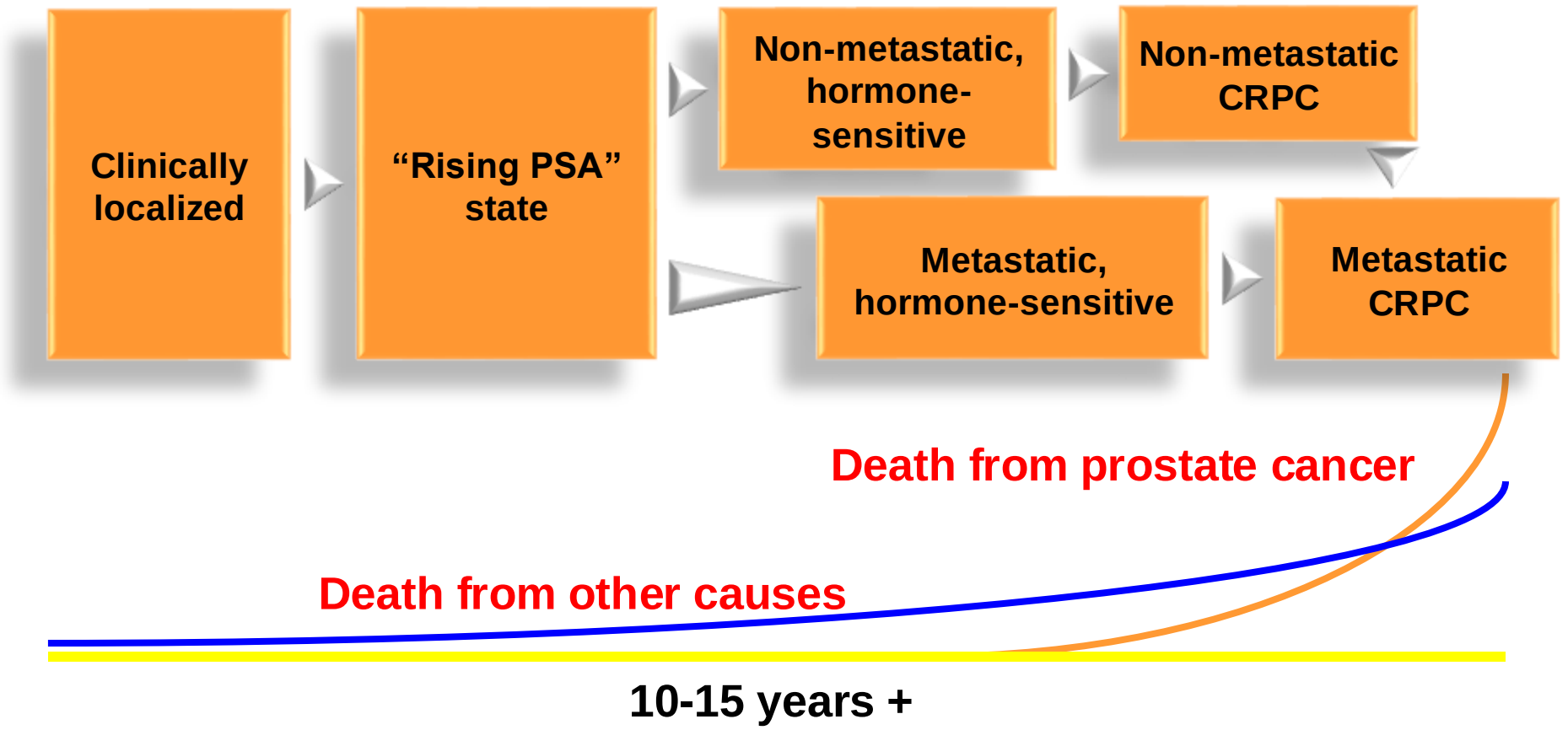
Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

Disclosures

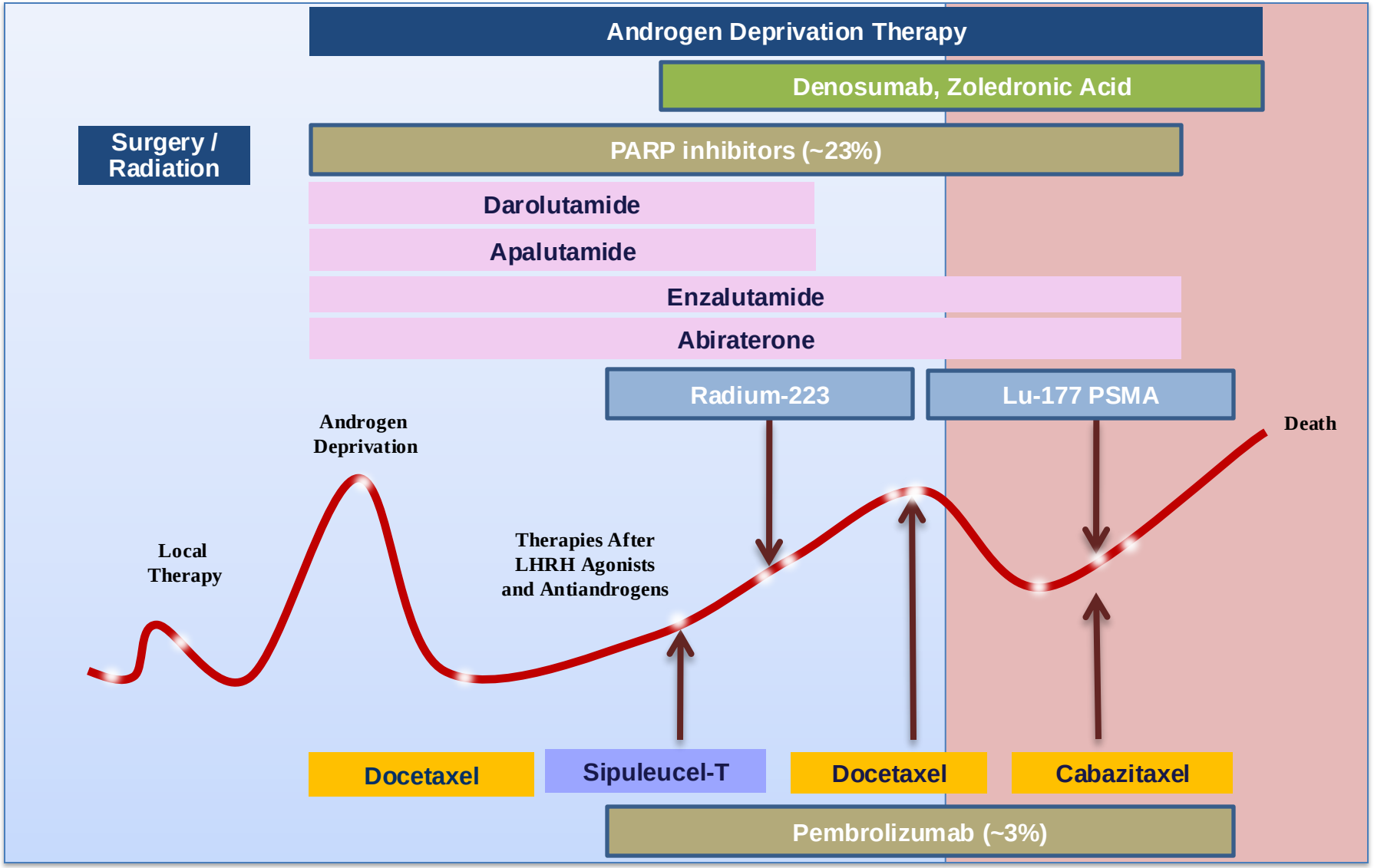
Consulting: Abbott, Astra Zeneca, Cytogen, Novartis, Sumitomo, VieCure

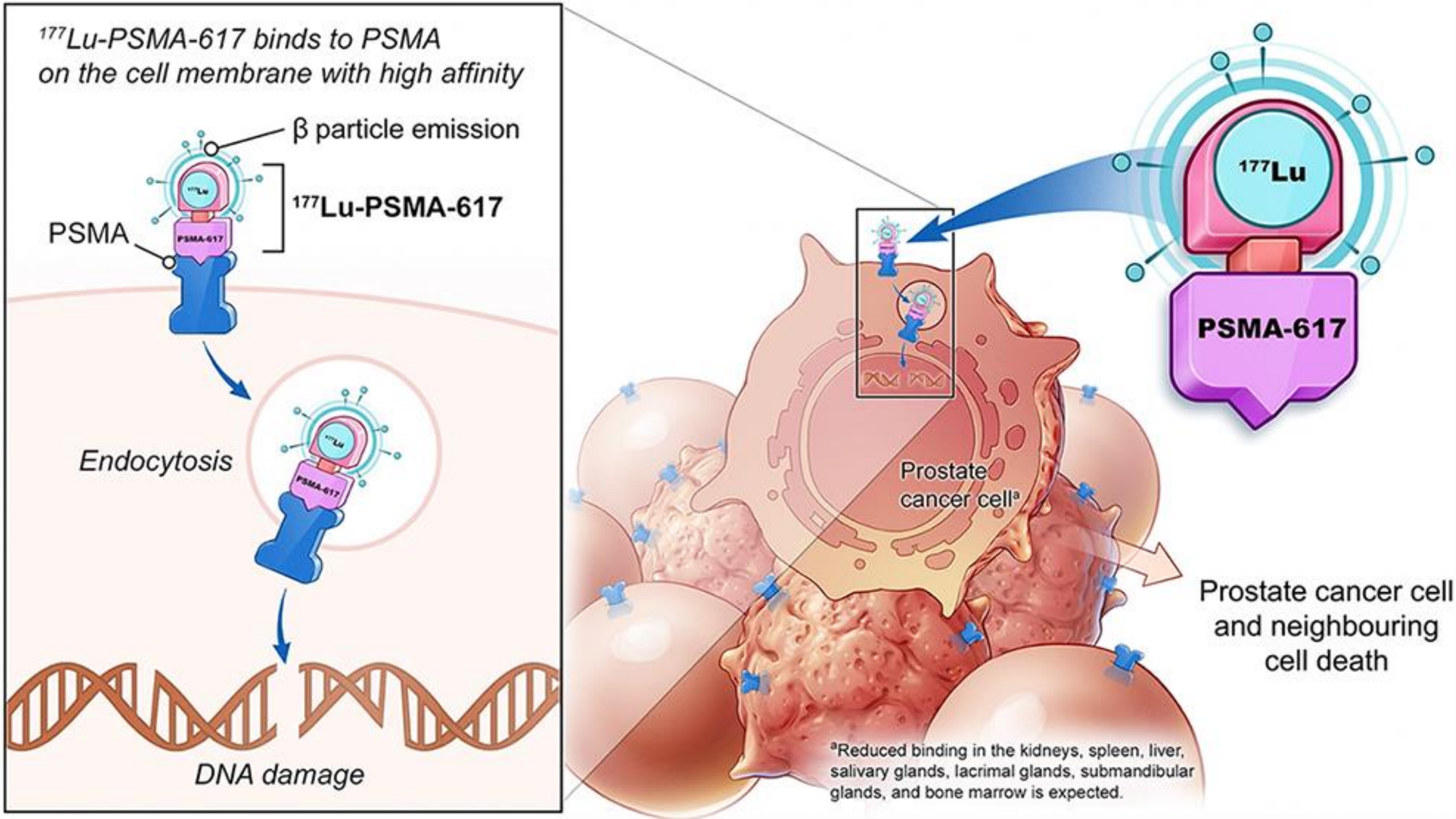
Equity: Archetype Therapeutics, GeneDx, NTx Bio, Previvor Care

Clinical States of Prostate Cancer



Treatment Landscape: 2024




177Lu-PSMA-617 binds to PSMA on the cell membrane with high affinity
β particle emission
177Lu-PSMA-617
PSMA
PSMA-617
Endocytosis
DNA damage
177Lu
PSMA-617
Prostate cancer cell[a]
Prostate cancer cell and neighbouring cell death
[a]Reduced binding in the kidneys, spleen, liver, salivary glands, lacrimal glands, submandibular glands, and bone marrow is expected.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

Sartor O, et al. *N Engl J Med*. Jun 23, 2021.

VISION: Eligible pts had ≥ 1 PSMA (+) met lesion and no sig PSMA (-) lesions

Eligible patients

- Previous treatment with both
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11

Centrally read PSMA PET imaging criteria

- ≥ 1 PSMA-positive metastatic lesion
  - Positive = ^{68}Ga uptake > liver
- No PSMA-negative metastatic lesions
  - Bone with soft tissue component ≥ 1.0 cm
  - Lymph node ≥ 2.5 cm
  - Solid organ ≥ 1.0 cm

Open-label protocol-permitted SOC ± ^{177}Lu-PSMA-617 in PSMA-positive mCRPC

Eligible patients

- Previous treatment with <u>both</u>
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
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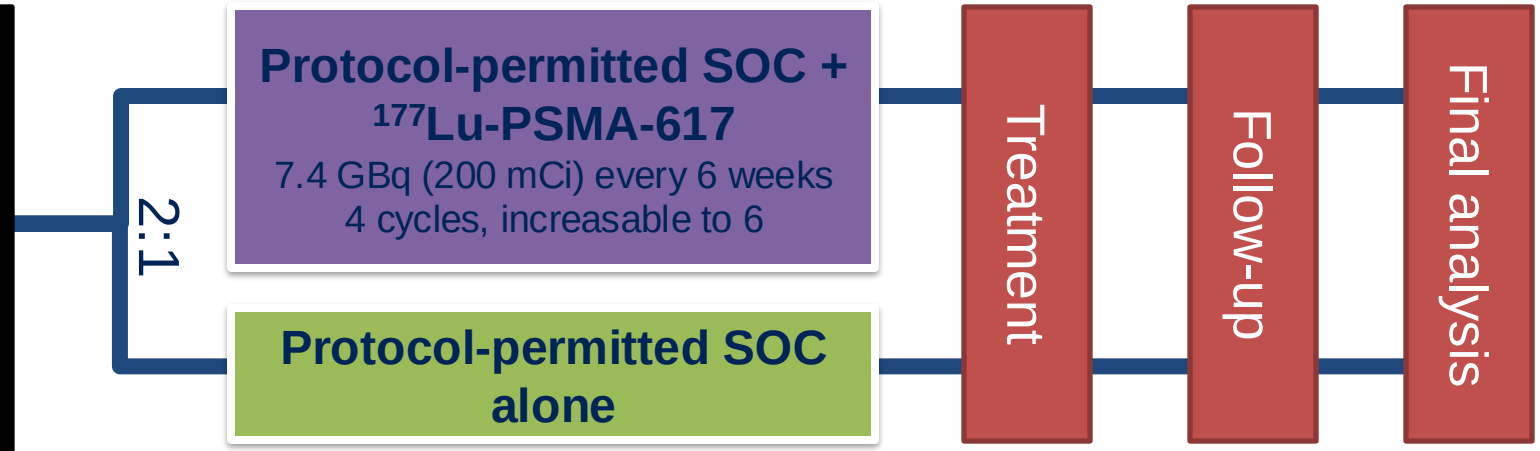
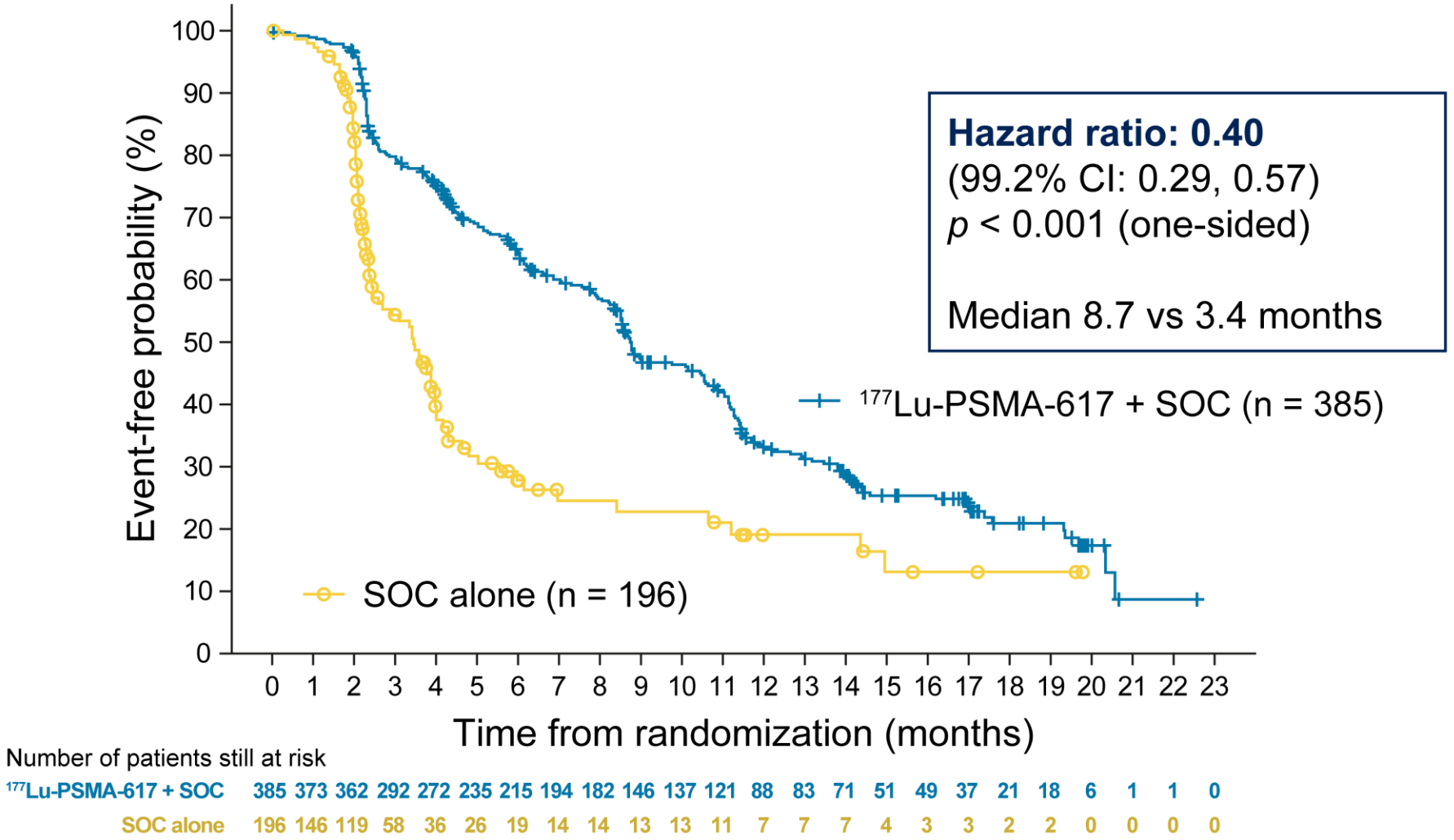


- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)

- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review

Primary endpoints: ^{177}Lu-PSMA-617 improved rPFS

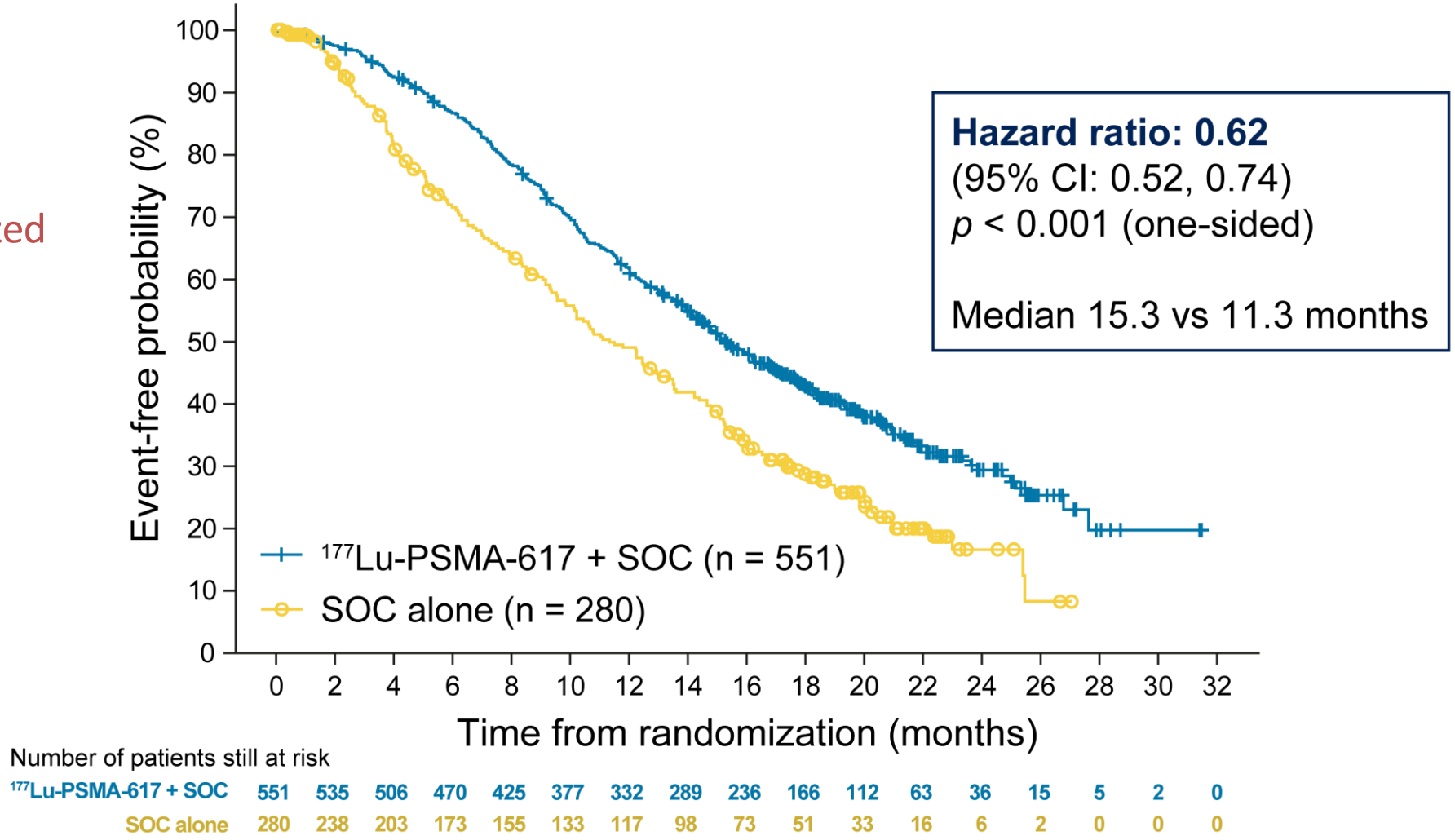
- Primary analysis
  - rPFS analysis set
  - (n = 581)



Sartor O, et al. *N Engl J Med*. Jun 23, 2021.
Morris M, et al. ASCO 2021. Abstract LBA4.

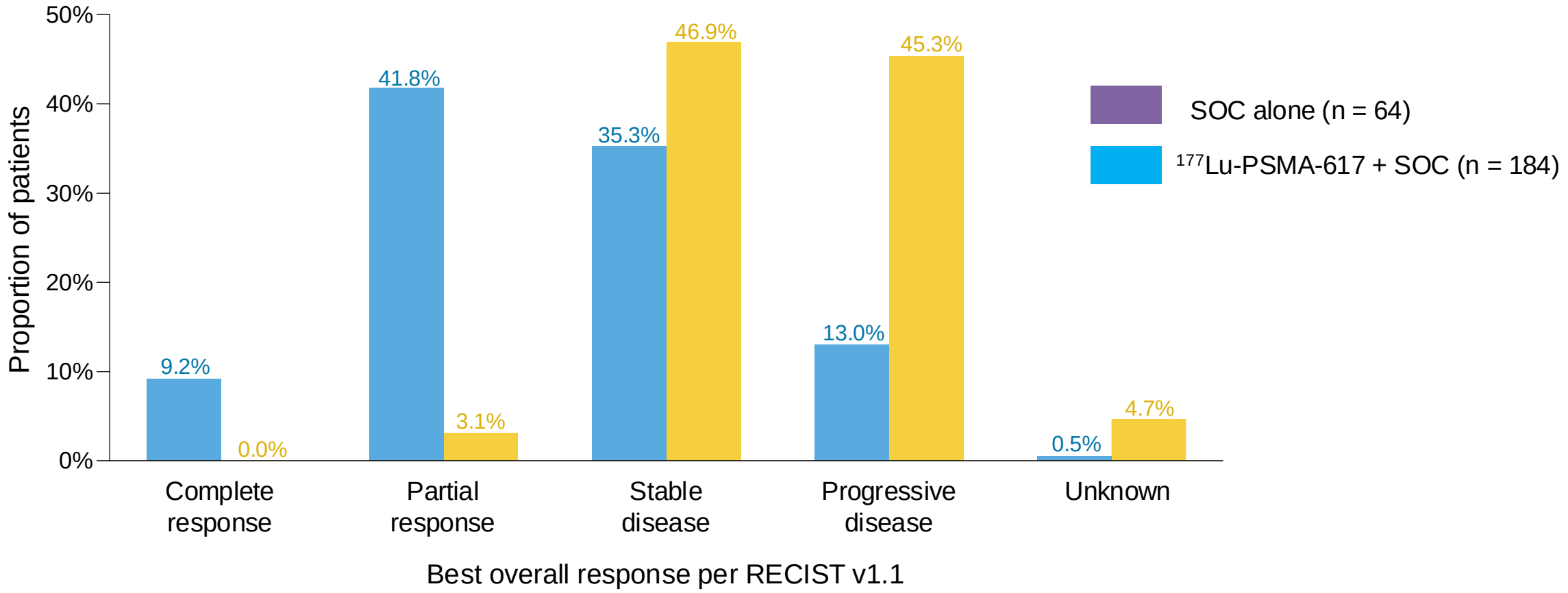
Primary endpoints: ^{177}Lu-PSMA-617 prolonged OS

- Primary analysis
  - All randomized patients
  - (N = 831)

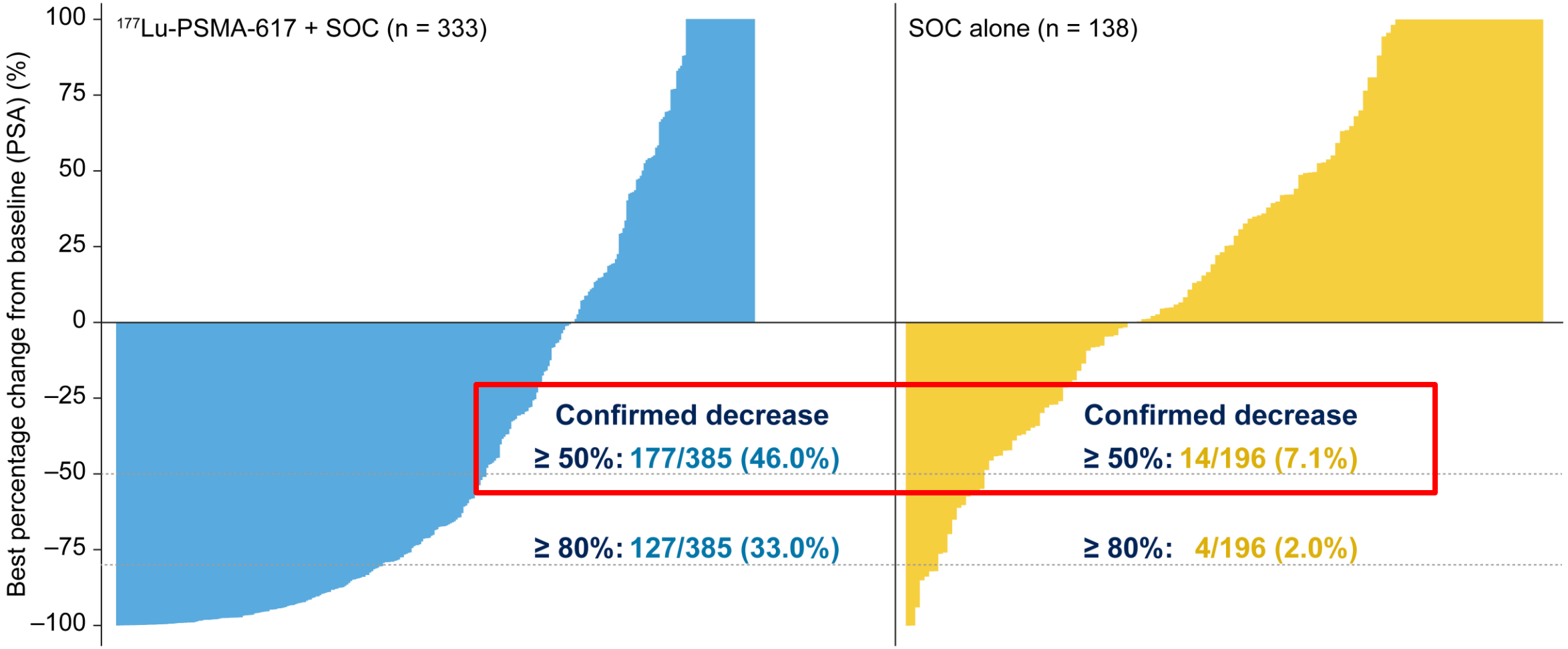


Sartor O, et al. *N Engl J Med*. Jun 23, 2021.
Morris M, et al. ASCO 2021. Abstract LBA4.

Secondary endpoint: RECIST responses favored ^{177}Lu-PSMA-617 arm in measurable dz



Secondary endpoint: PSA responses favored ^{177}Lu-PSMA-617 arm among evaluable pts



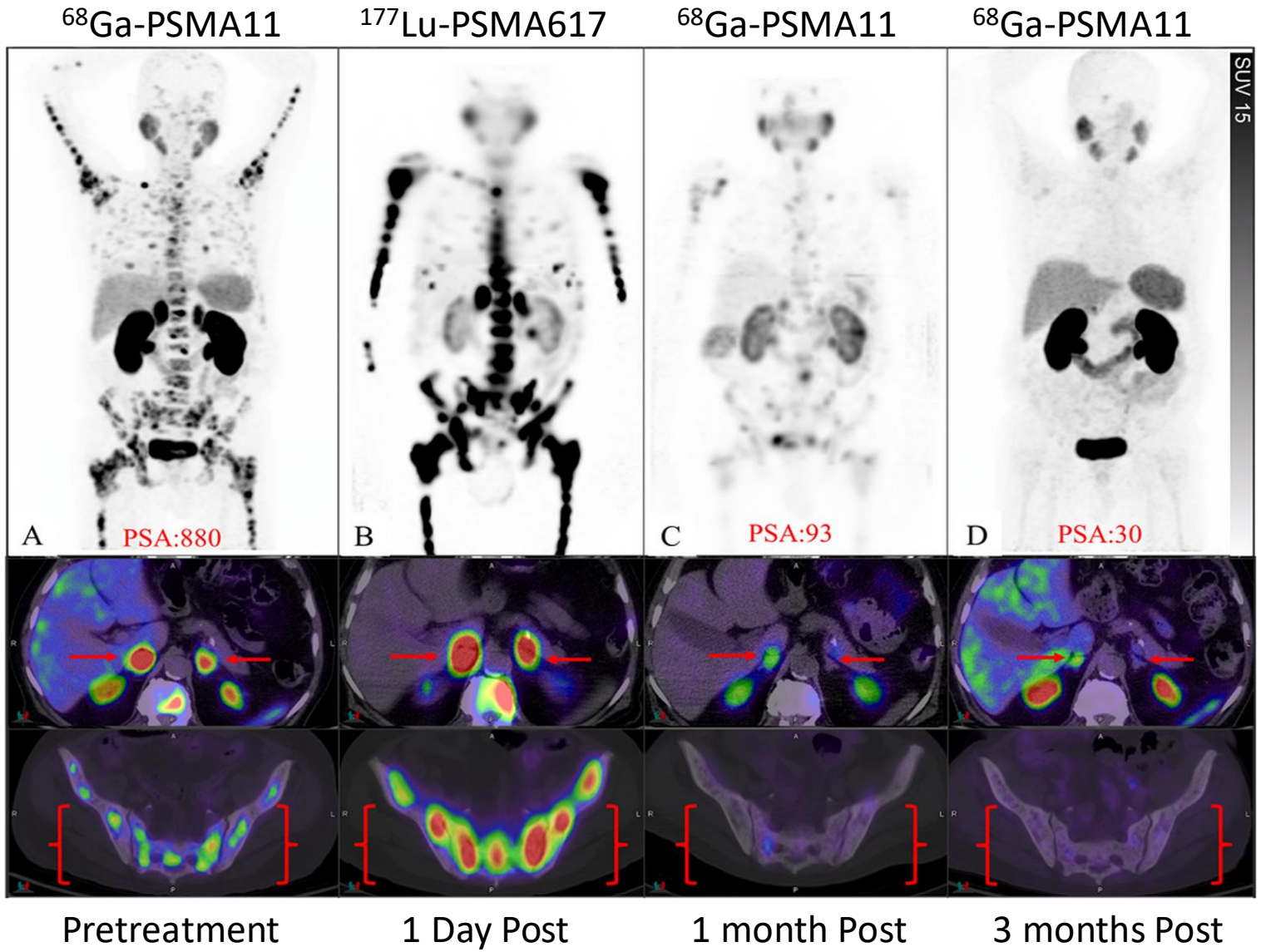
TEAE grouped as topics of interest: no unexpected or concerning safety signals

Patients, n (%)	All grades		Grade 3–5	
	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)	^{177}Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)
Fatigue	260 (49.1)	60 (29.3)	37 (7.0)	5 (2.4)
Bone marrow suppression	251 (47.4)	36 (17.6)	124 (23.4)	14 (6.8)
Leukopenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)
Lymphopenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Anemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Thrombocytopenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Dry mouth	208 (39.3)	2 (1.0)	0 (0.0)	0 (0.0)
Nausea and vomiting	208 (39.3)	35 (17.1)	8 (1.5)	1 (0.5)
Renal effects	46 (8.7)	12 (5.9)	18 (3.4)	6 (2.9)
Second primary malignancies	11 (2.1)	2 (1.0)	4 (0.8)	1 (0.5)
Intracranial hemorrhage	7 (1.3)	3 (1.5)	5 (0.9)	2 (1.0)

Conclusions: VISION Study

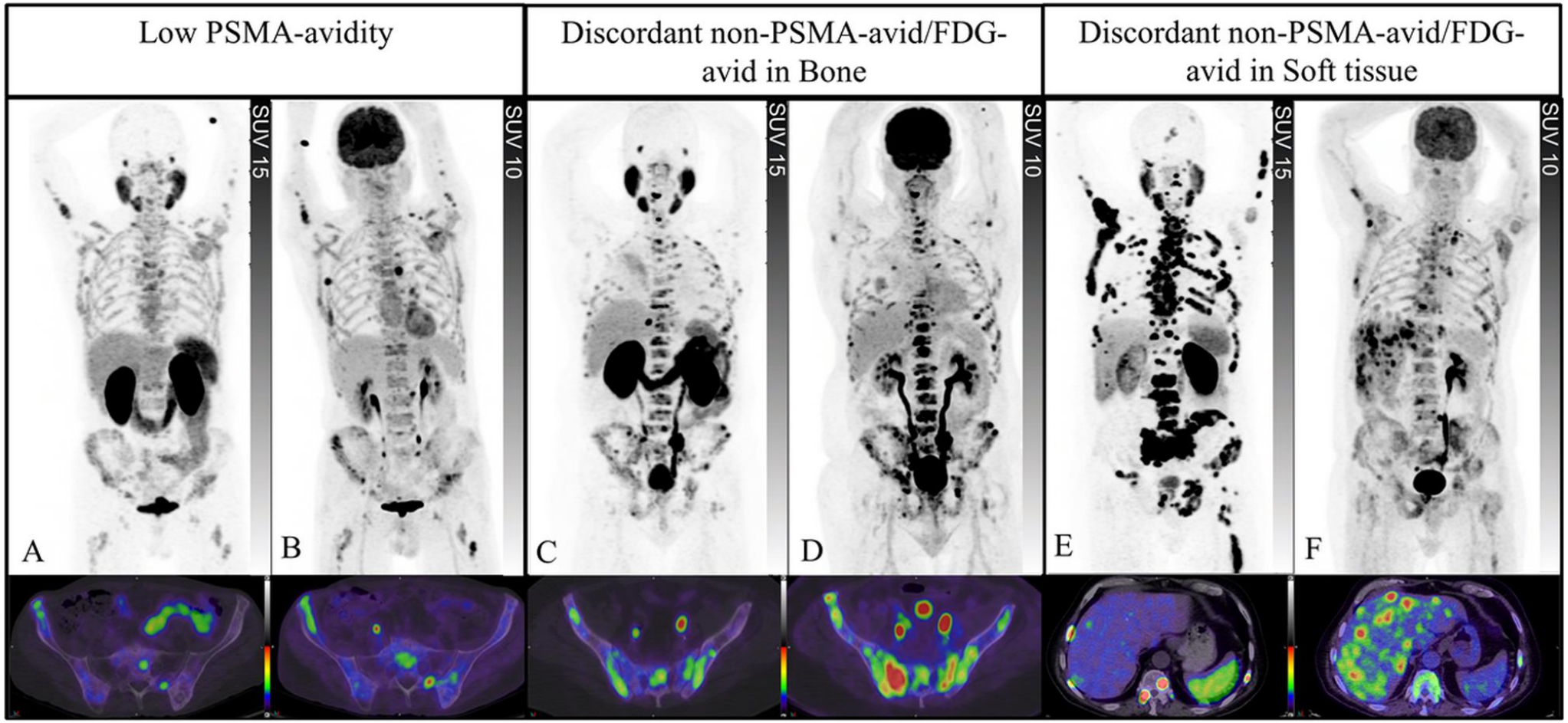
- Adding ^{177}Lu-PSMA-617 to “safely combinable” standard of care in patients with mCRPC after androgen receptor pathway inhibition and chemotherapy
  - Extended overall survival
  - Delayed radiographic disease progression
- ^{177}Lu-PSMA-617 was generally well tolerated
- ^{177}Lu-PSMA-617 is a new treatment option in patients with mCRPC post-ARPI and post-chemo

Exceptional Responder to Lu-177 PSMA



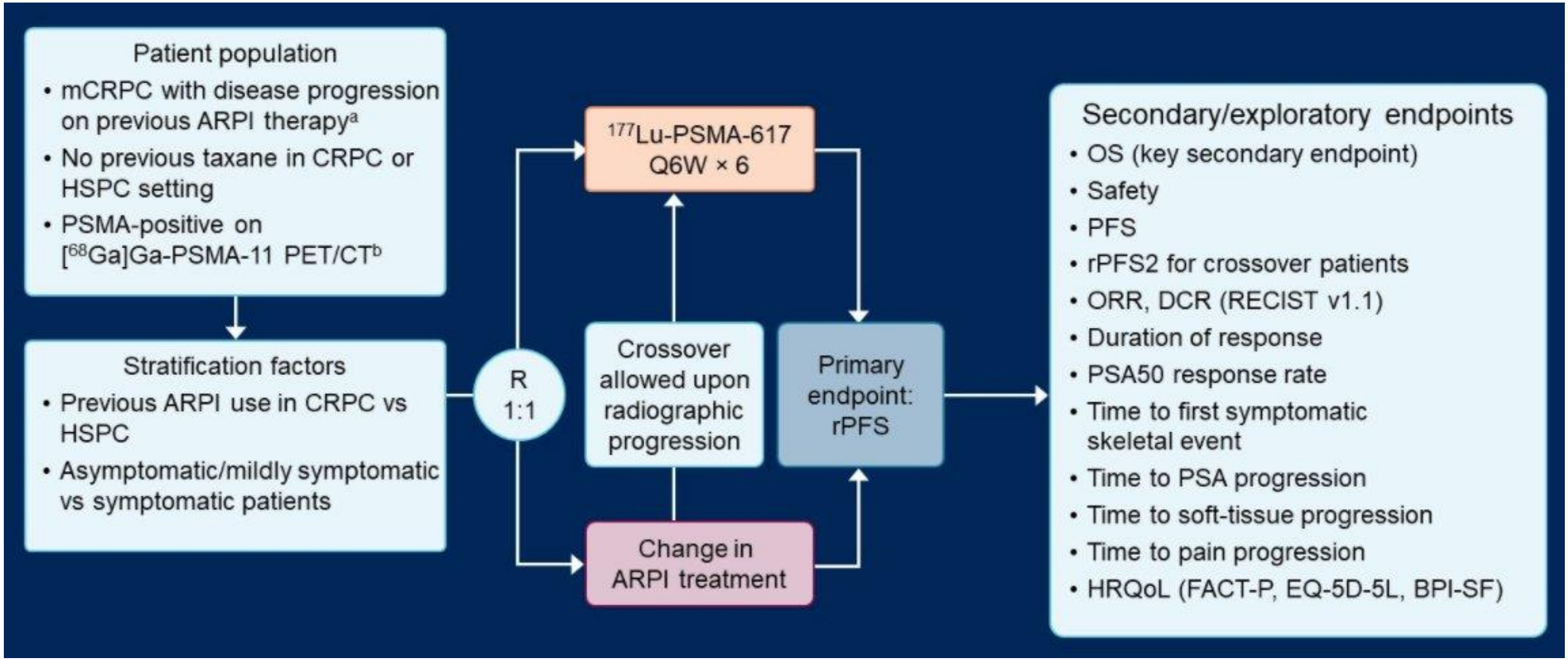
Iravani Prost Cancer Prost Dis 23, pages 38–52 (2020)

Poor Candidates for PSMA RLTs

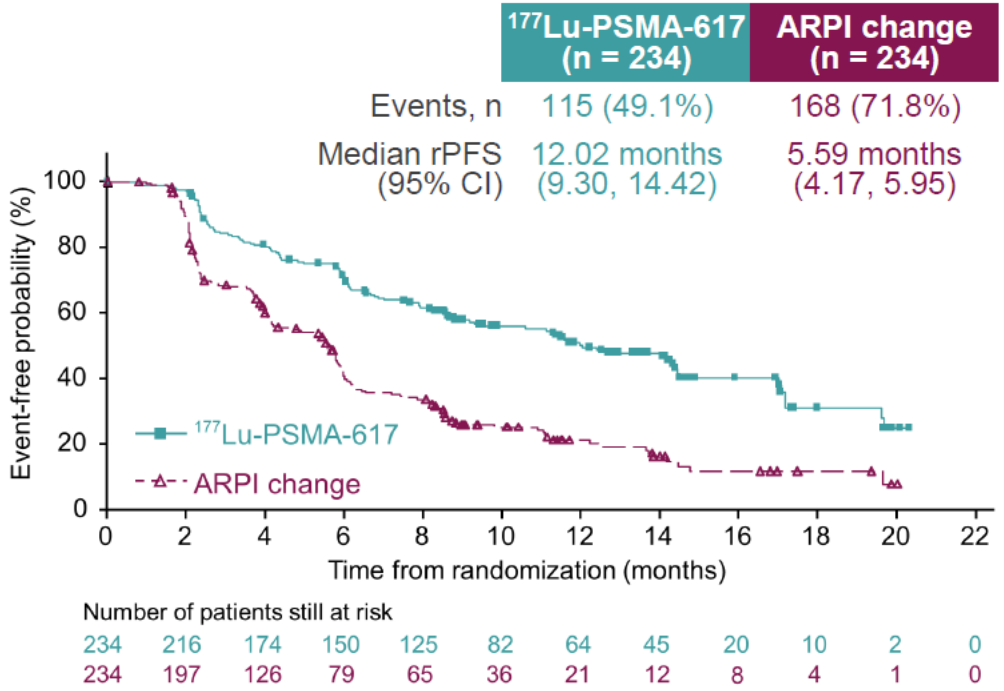


Iravani Prost Cancer Prost Dis 23, pages 38–52 (2020)

PSMAFore Trial (pre-Docetaxel mCRPC)

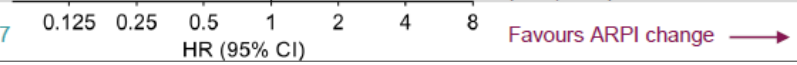


PSMAfore rPFS: Lu-177–PSMA-617 vs ARPI Change in Taxane-Naive Patients With mCRPC



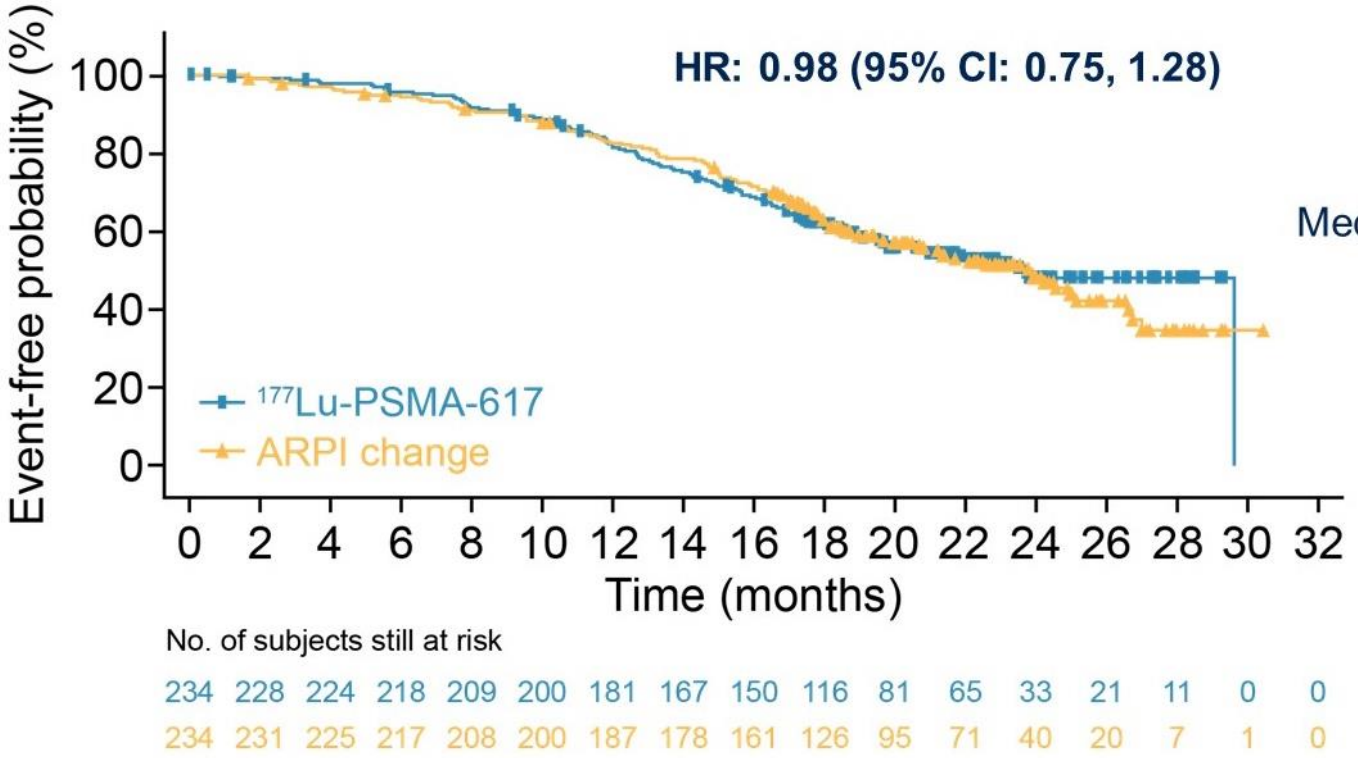
Updated rPFS in prespecified subgroups

		HR (95% CI)	Events, n/n (%) 177Lu-PSMA-617	Events, n/n (%) ARPI change
All patients		0.43 (0.33, 0.54)	155/234 (49.1)	168/234 (71.8)
Previous ARPI setting	CRPC	0.40 (0.30, 0.52)	90/190 (47.4)	139/190 (73.2)
	HSPC	0.57 (0.33, 0.98)	25/44 (56.8)	29/44 (65.9)
Symptomatology	Asymptomatic or mildly symptomatic	0.40 (0.30, 0.53)	76/165 (46.1)	124/166 (74.7)
	Symptomatic	0.51 (0.32, 0.79)	39/69 (56.5)	44/68 (64.7)
Race	White	0.41 (0.32, 0.53)	103/211 (48.8)	156/214 (72.9)
	Black or African American	0.76 (0.10, 5.51)	2/7 (28.6)	2/5 (40.0)
	Asian	NE (NE, NE)	0/1 (0.0)	0/2 (0.0)
	Other	0.43 (0.16, 1.17)	10/15 (66.7)	10/13 (76.9)
Age	< 65 years	0.46 (0.27, 0.78)	32/50 (64.0)	32/44 (72.7)
	≥ 65 years	0.38 (0.28, 0.50)	83/184 (45.1)	136/190 (71.6)
Liver metastases at baseline	Yes	0.42 (0.11, 1.61)	5/7 (71.4)	9/10 (90.0)
	No	0.43 (0.33, 0.55)	110/227 (48.5)	159/224 (71.0)
Baseline PSA level	< median	0.42 (0.29, 0.60)	44/106 (41.5)	80/122 (65.6)
	≥ median	0.40 (0.29, 0.56)	67/123 (54.5)	83/106 (78.3)
Initial Gleason score	< 6	0.55 (0.10, 3.09)	3/5 (60.0)	5/6 (83.3)
	≥ 6	0.42 (0.32, 0.54)	108/220 (49.1)	152/211 (72.0)
Baseline LDH level	≤ 260 IU/L	0.41 (0.31, 0.54)	86/177 (48.6)	139/195 (71.3)
	> 260 IU/L	0.53 (0.27, 1.07)	21/37 (56.8)	16/22 (72.7)
Region	North America	0.52 (0.29, 0.92)	20/47 (42.6)	33/52 (63.5)
	Europe	0.40 (0.31, 0.53)	95/187 (50.8)	135/182 (74.2)
Concurrent radiotherapy	Yes	1.67 (0.59, 4.74)	6/9 (66.7)	26/36 (72.2)
	No	0.40 (0.31, 0.52)	109/225 (48.4)	142/198 (71.7)
Previous ARPI	Abiraterone	0.47 (0.33, 0.66)	57/119 (47.9)	86/130 (66.2)
	Enzalutamide	0.35 (0.24, 0.52)	46/94 (48.9)	67/84 (79.8)



Sartor O, et al. ESMO 2023. Abstract LBA13.

PSMAfore OS: Lu-177–PSMA-617 vs ARPI Change in Taxane-Naive Patients With mCRPC



	177Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	104 (44.4%)	112 (47.9%)
Median, months (95% CI)	23.66 (19.75, NE)	23.85 (20.6, 26.55)

Crossover:

134/234 (57.3%) in ARPI change group
134/173 (77.5%) eligible patients

RPSFT crossover-adjusted OS analysis

- HR: 0.98 (95% CI: 0.76, 1.27)
- No difference versus the ITT analysis because RPSFT cannot adjust for crossover confounding in the context of overlapping ITT curves

Fizazi K, et al. ASCO 2024. Abstract 5003.

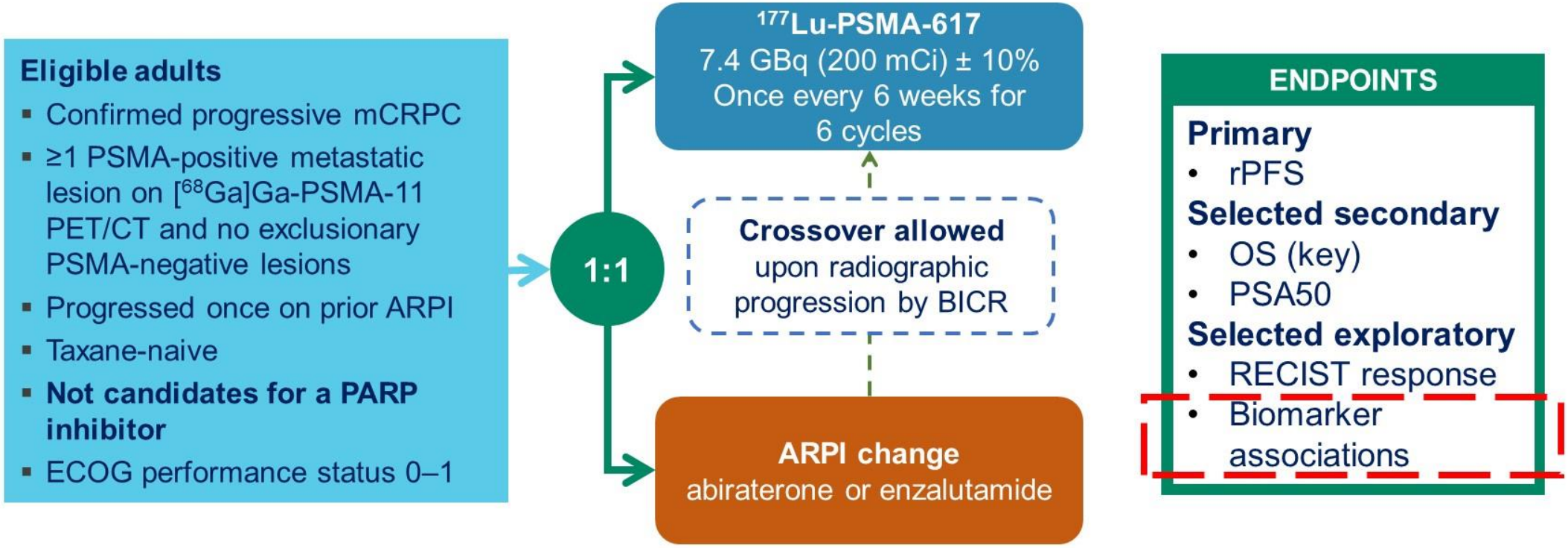
2024 ASCO® ANNUAL MEETING

Baseline ctDNA analyses and associations with outcomes in taxane-naive patients with mCRPC treated with [^{177}Lu]Lu-PSMA-617 versus change of ARPI in PSMAfore

Presenter: Johann S de Bono
The Institute of Cancer Research and The Royal Marsden Hospital, London, UK

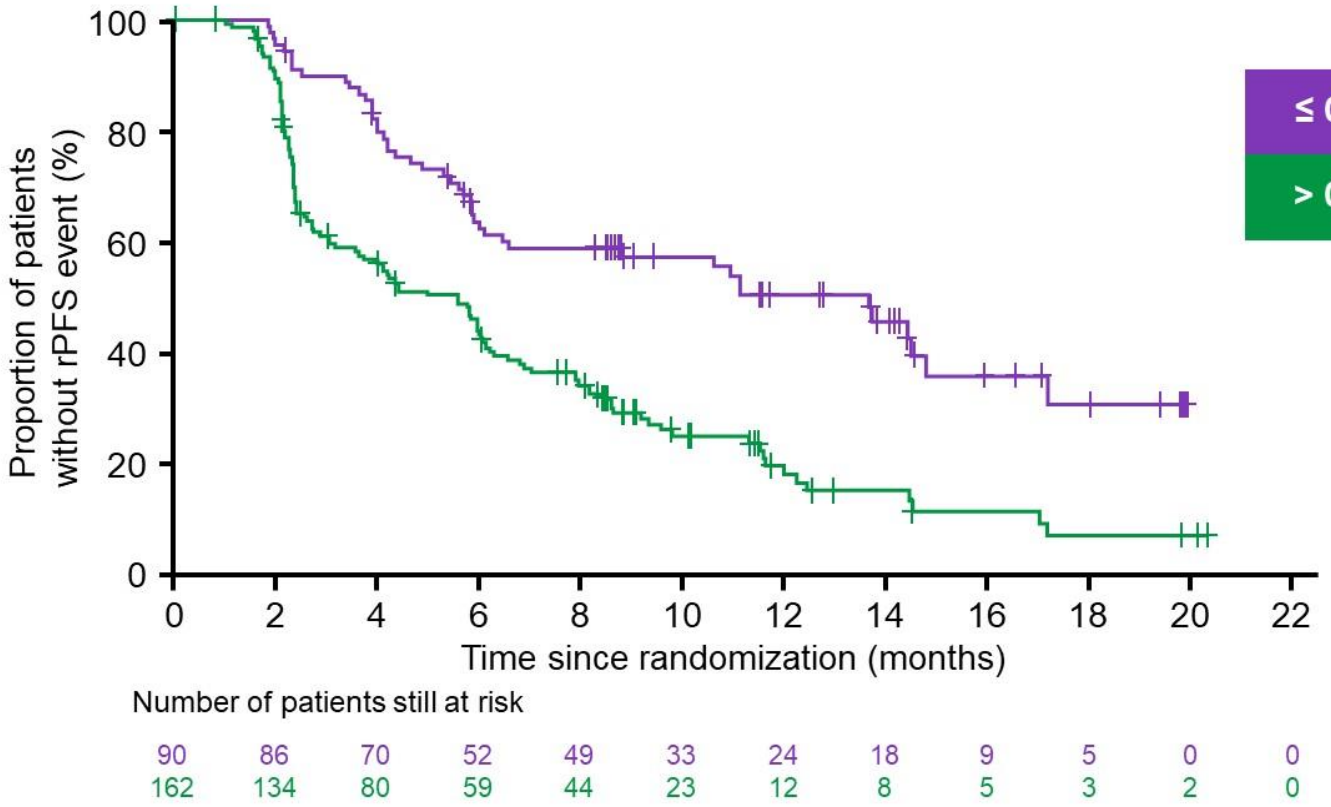
Co-authors: MJ Morris, O Sartor, XX Wei, K Fizazi, K Herrmann, JM Piulats, H Mahammedi, C Logothetis, D George, L Eldjerou, CC Wong, L Barys, N Rajagopal, T Rodosthenous and KN Chi, **on behalf of the PSMAfore investigators**

PSMAfore: a phase 3, randomized trial of ^{177}Lu-PSMA-617 versus ARPI change in taxane-naive mCRPC that met its primary endpoint



Higher baseline ctDNA fraction was associated with shorter rPFS regardless of treatment received

Analysis of overall population



	Events/patients, n/n	Median rPFS, months (95% CI)
≤ 0.5% ctDNA fraction	47/90	13.63 (6.57–17.15)
> 0.5% ctDNA fraction	116/162	2.55 (3.61–6.11)

Presence of 8q amplification, *AR* amplification or *TP53* deleterious alteration was associated with lack of tumor response

Alteration prevalence in samples with >0.5% ctDNA fraction, n/N (%)	RECIST response				PSA50			
	^{177}Lu-PSMA-617		ARPI change		^{177}Lu-PSMA-617		ARPI change	
	Non-responder	Responder	Non-responder	Responder	Non-responder	Responder	Non-responder	Responder
8q amplification	7/22 (31.8)	0/12 (0.0)	10/36 (27.8)	1/2 (50.0)	7/33 (21.2)	4/29 (13.8)	11/56 (19.6)	1/6 (16.7)
AR amplification	10/22 (45.5)	1/12 (8.3)	20/36 (63.9)	1/2 (50.0)	15/33 (45.5)	8/29 (27.6)	27/56 (48.2)	2/6 (33.3)
TP53 deleterious alteration	8/22 (36.4)	2/12 (16.7)	15/36 (41.7)	1/2 (50.0)	12/33 (36.4)	10/29 (34.5)	23/56 (41.1)	1/6 (16.7)

Conclusions

In patients with taxane-naive mCRPC:

- Higher baseline ctDNA fraction was associated with shorter rPFS across both treatment arms
- Patients receiving ^{177}Lu-PSMA-617 had longer rPFS compared with ARPI change regardless of baseline ctDNA fraction
- Early ctDNA fraction dynamics informs on rPFS and tumor response
- 8q amplification, *AR* amplification and *TP53* deleterious alteration are prognostic biomarkers that were associated with shorter rPFS and decreased tumor response in the ^{177}Lu-PSMA-617 arm

SPLASH: ^{177}Lu-PNT2002 in PSMA-positive mCRPC following progression on ARPI

SPLASH study design

Key eligibility
- Progressive mCRPC
- Progressed on previous treatment with one ARPI
- PSMA-avid PET
- ECOG performance status 0 to 1
- Taxane for CSPC allowed (>1 year prior to consent)

R 2:1

177Lu-PNT2002 6.8 GBq (±10%) Q8W for ≤4 cycles

Alternate ARPI enzalutamide or abiraterone

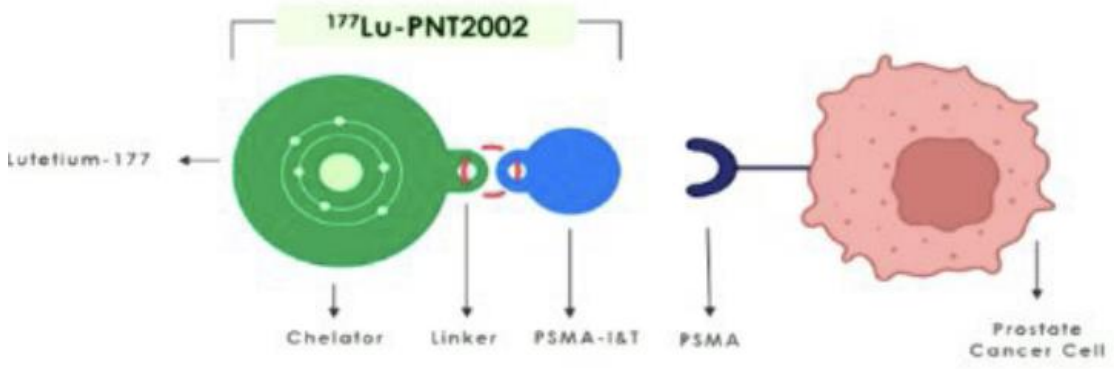
Radiographic progression

177Lu-PNT2002

Crossover

Endpoints:
- rPFS
- OS
- ORR
- Time to skeletal event
- PSA50 response
- bPFS
- HRQoL
- Safety

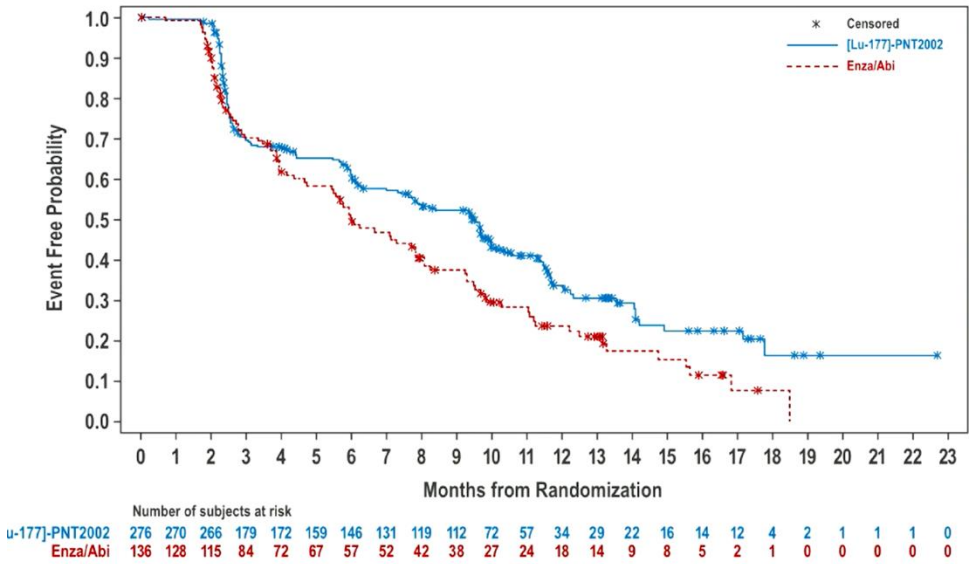
Stratification factors
- Prior taxane treatment for CSPC: Y/N
- Prior use of bisphosphonates: Y/N
- Metastatic status on prior ARPI: Y/N
- Measurable disease at study entry: Y/N



Sartor O, et al. ESMO 2024. Abstract LBA65

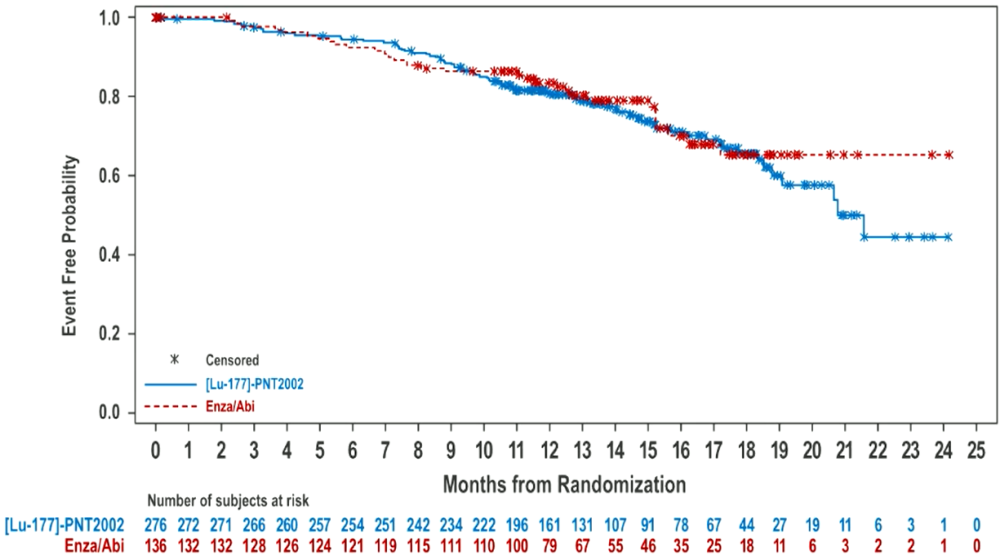
SPLASH (Phase 3): ^{177}Lu-PNT2002 in PSMA-positive mCRPC following progression on an ARPI

Primary endpoint: rPFS (primary analysis)



	^{177}Lu-PNT2002 (n=276)	Alternate ARPI (n=136)
Events, n (%)	162 (58.7)	96 (70.6)
Median follow-up, months (95% CI)	11.1 (10.1, 11.6)	12.9 (10.2, 15.9)
Median rPFS, months (95% CI)	9.5 (7.4, 10.0)	6.0 (4.7, 7.9)
HR (95% CI)	0.71 (0.55, 0.92); P=0.0088	

1st interim OS (ITT analysis)



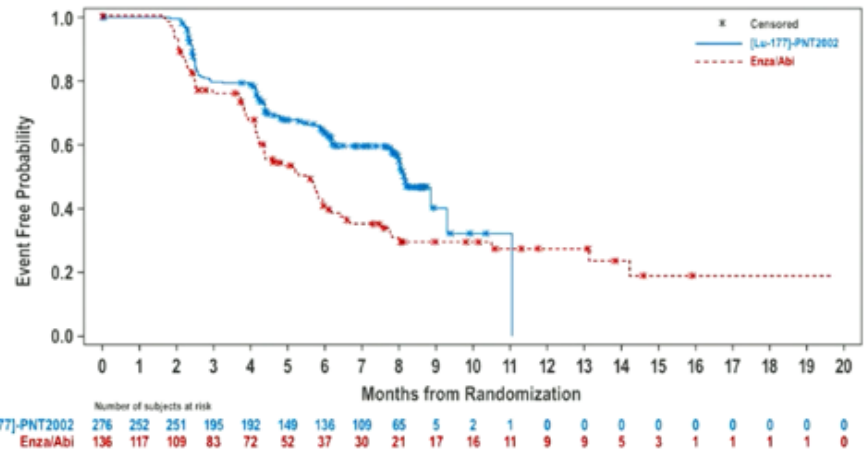
	^{177}Lu-PNT2002 (n=276)	Alternate ARPI (n=136)
Median OS, months (95% CI)	20.8 (19.1, NE)	NE (NE, NE)
HR (95% CI)	1.11 (0.73, 1.69); P=0.6154	

Data cutoff: Nov 1, 2023. ARPI, androgen receptor pathway inhibitor.

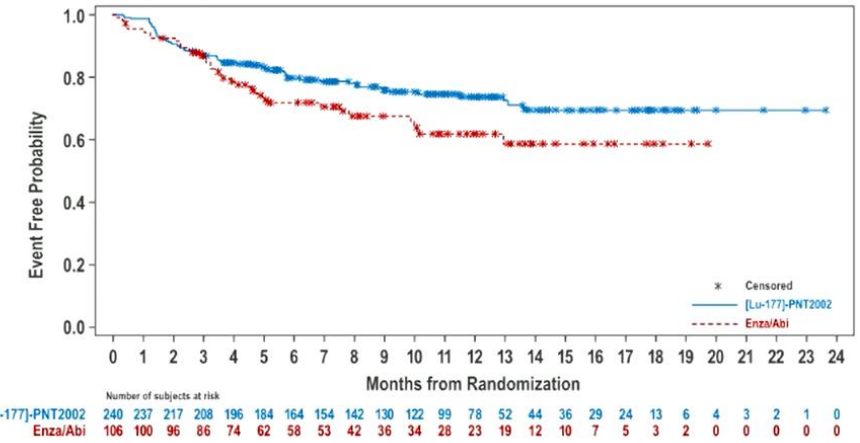
Sartor O, et al. ESMO 2024. Abstract LBA65

SPLASH (Phase 3): Secondary endpoints and safety

HRQoL deterioration (FACT-P Score)



Time to opioids use



Data cutoff: Nov 1, 2023. ARPI, androgen receptor pathway inhibitor.
Sartor O, et al. ESMO 2024. Abstract LBA65

Incidence of TEAEs

TEAE, n (%)	^{177}Lu-PNT2002 (n=269)	Alternate ARPI (n=130)
Any TEAE	267 (99.3)	123 (94.6)
TEAE of grade ≥3 Treatment-related	81 (30.1) 26 (9.7)	48 (36.9) 15 (11.5)
Serious TEAE Treatment-related	46 (17.1) 6 (2.2)	30 (23.1) 5 (3.8)
TEAE leading to death Treatment-related	5 (1.9) 0 (0.0)	5 (3.8) 0 (0.0)
Serious TEAE	46 (17.1)	30 (23.1)
TEAE leading to discontinuation	5 (1.9)	8 (6.2)
TEAE leading to reduction of study treatment	3 (1.1)	7 (5.4)

- Lu^{177}-PNT2002 shows pre-chemo activity with rPFS efficacy
- Lack of OS benefit is unsurprising given the high crossover rate
- Secondary endpoints confirm clinical value
- Favorable TEAEs vs 2nd ARPI = excellent tolerability
- Is lower dose more favorable over long term c/w Lu177-PSMA-617?

UpFrontPSMA (Phase 2): Study design

Key eligibility
- Adenocarcinoma ≤4 weeks ADT
- ≤12 weeks since diagnosis
- Metastatic CT and/or bone scan
- PSA >10ng/ml (pre ADT)

Pre-randomization
PET scans x 2
PSMA, FDG

Central imaging review
PSMA PET:
- High tumor uptake
- High volume disease

FDG PET:
- Most disease PSMA+

R 2:1

N=140

177Lu-PSMA-617, 7.5 GBq x 2 cycles (docetaxel 75 mg/m^2 x 6 cycles) (n=70)

Docetaxel (75 mg/m^2 x 6 cycles) (n=70)

Primary endpoint:
- Undetectable PSA at 48 weeks (PSA ≤0.2 ng/ml

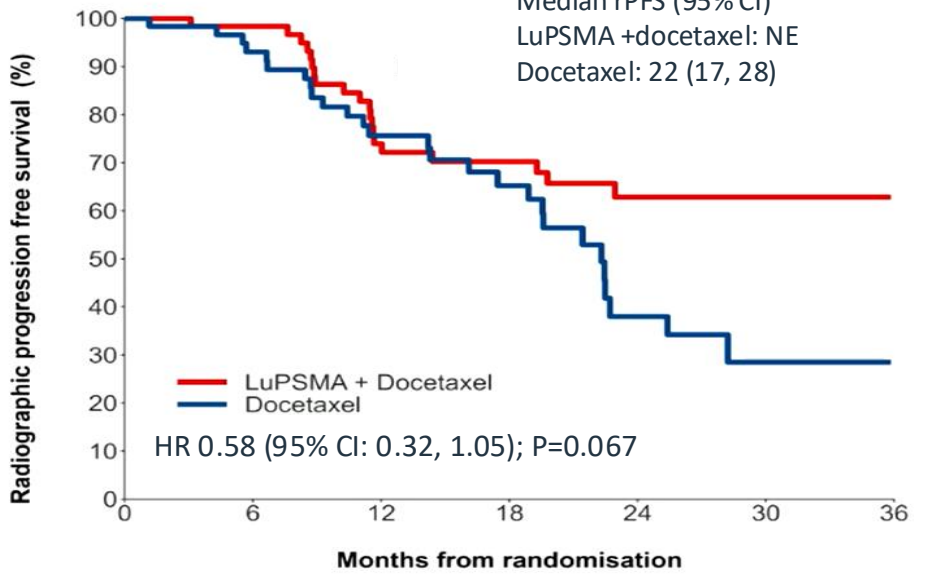
Secondary endpoints:
- PSA-PFS
- Castration-resistance
- rPFS
- OS
- QoL and pain
- Safety

Treatment	Lu-PSMA + docetaxel (n=61)	Docetaxel (n=61)
Undetectable PSA at Week 48, % (95% CI)	41 (30, 54)	16 (9, 28)
OR (95% CI)	3.88 (1.61, 9.38); P=0.002	
Undetectable PSA at any time point, % (95% CI)	51 (39, 63)	32 (22, 45)
OR (95% CI)	2.14 (1.03, 4.46); P=0.042	
Undetectable PSA at Week 12, % (95% CI)	17 (10, 29)	18 (10, 29)
OR (95% CI)	0.94 (0.37, 2.36); P=0.895	

Azad AA, et al. ESMO 2024. Abstract LBA66

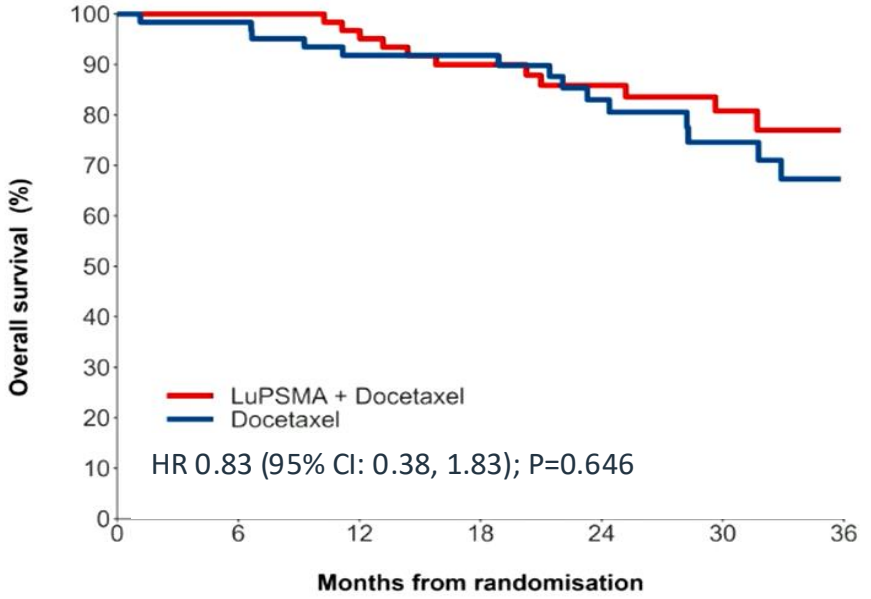
UpFrontPSMA (Phase 2): Study Design

Radiographic PFS



No. at risk (No. censored)							
LuPSMA + Docetaxel	63 (1)	59 (3)	41 (7)	31 (15)	21 (22)	14 (29)	6 (37)
Docetaxel	63 (2)	52 (7)	34 (16)	23 (23)	10 (28)	4 (32)	2 (34)

OS

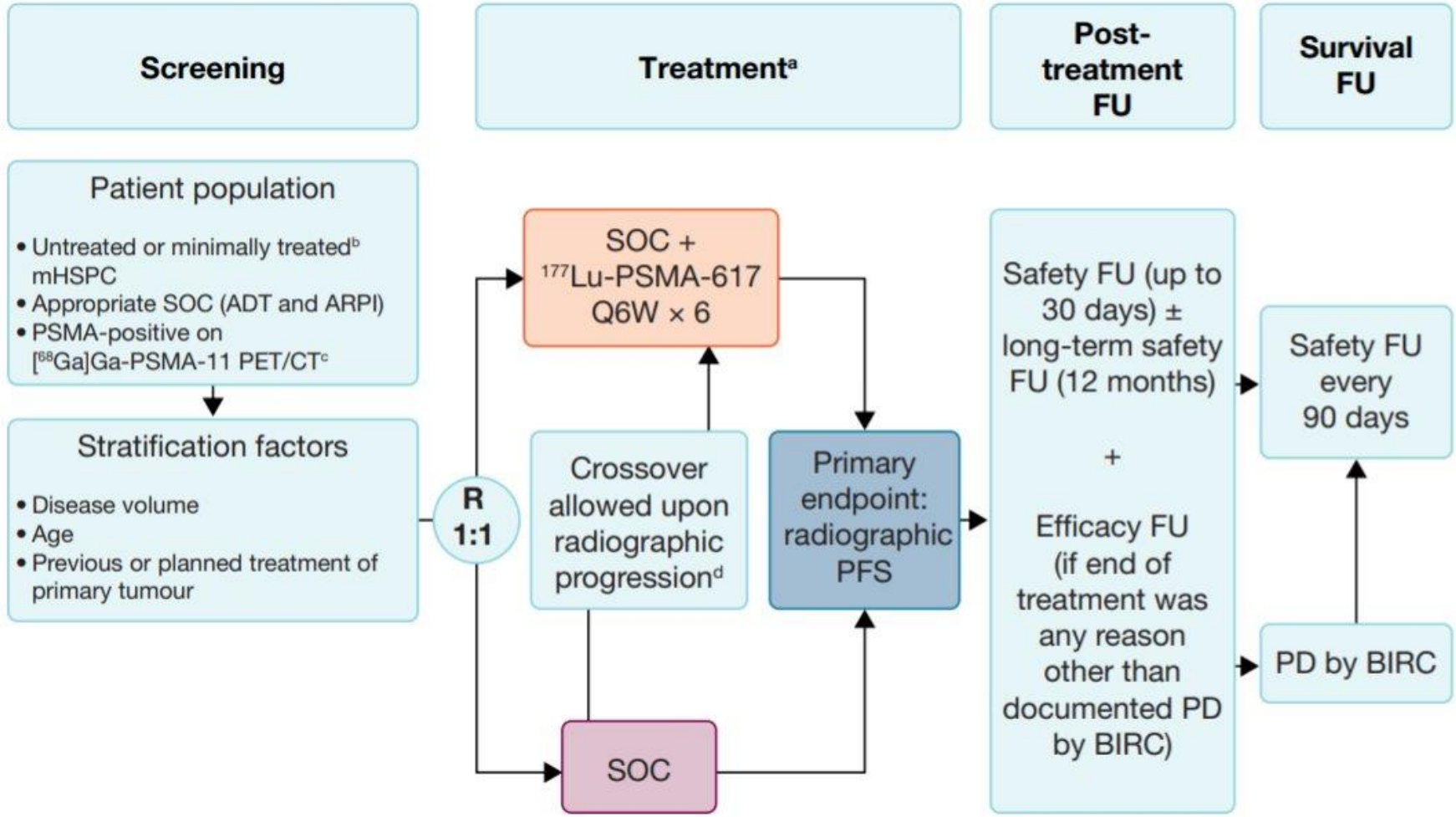


No. at risk (No. censored)							
LuPSMA + Docetaxel	63 (0)	62 (1)	59 (2)	48 (9)	39 (16)	27 (26)	14 (38)
Docetaxel	63 (0)	60 (2)	54 (4)	47 (11)	34 (20)	24 (27)	13 (36)

Azad AA, et al. ESMO 2024. Abstract LBA66

PSMAddition Trial (mHSPC)

Figure 1. Study design



Summary: RLTs in Metastatic Prostate Cancer

- Advances in prostate cancer imaging are creating new therapeutic opportunities
- PET imaging is key for patient selection for RLTs
- VISION: Lu177-PSMA therapy for mCRPC is available *post-chemotherapy* based on improved PFS, OS and tolerability
- PSMAFore/SPLASH: *Pre-chemotherapy* Lu177-PSMA therapy demonstrates PFS but not OS benefit—not yet approved
- Lu177-PSMA is being explored in earlier disease states including mHSPC, high-risk localized and other disease states
- Newer agents and isotopes (including alpha particles) will likely change the landscape of options for prostate cancer patients

2024 ASCO ANNUAL MEETING

Plain Language Summary

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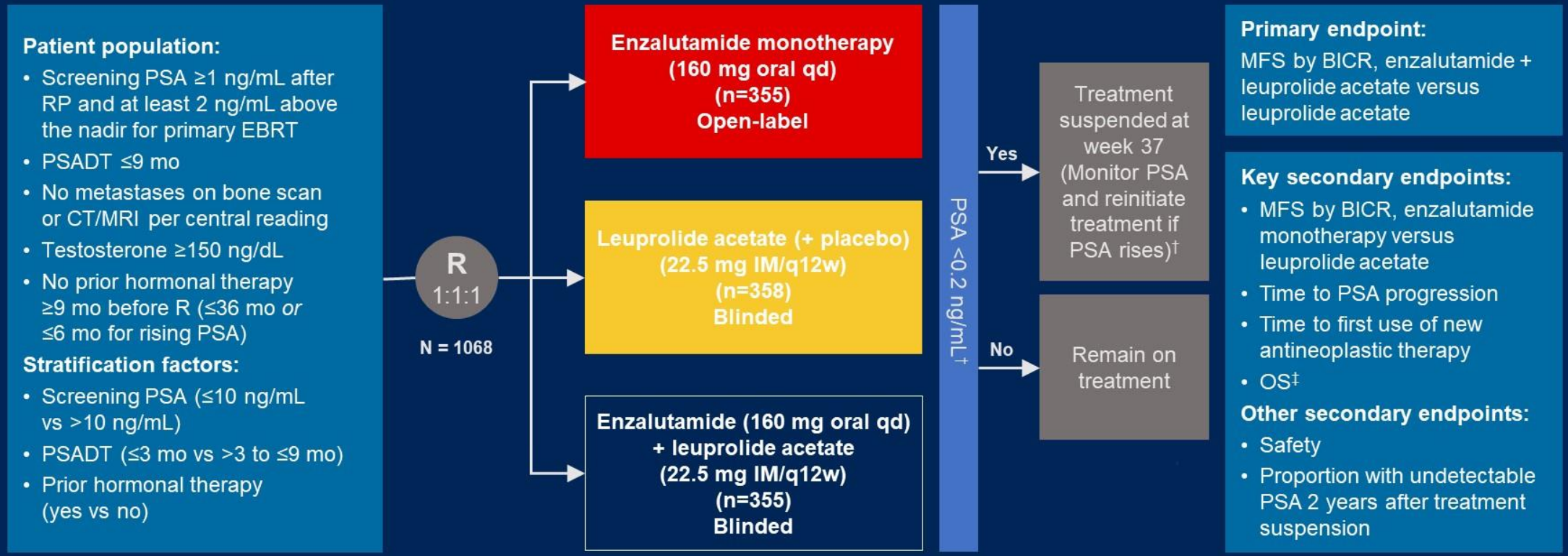
EMBARK post hoc analysis of impact of treatment suspension on health-related quality of life

Stephen J. Freedland,[1,2] Martin Gleave,[3] Ugo De Giorgi,[4] Antti Rannikko,[5] Fred Saad,[6] Miguel Ramirez-Backhaus,[7] Anchen F. Nasr,[8] Jasmina I. Ivanova,[9] Arijit Ganguli,[8] Pavol Kral,[10] Arlene L. Reisman,[9] Neal D. Shore[11]

[1]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, USA; [2]Durham VA Medical Center, Durham NC, USA; [3]Vancouver Prostate Centre, Vancouver, Canada; [4]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST), Via Piero Maroncelli, Meldola FC, Italy; [5]Department of Urology and Research Program in Systems Oncology, University of Helsinki, and Helsinki University Hospital (A.R.), Helsinki, Finland; [6]Centre Hospitalier de l'Université de Montreal, University of Montreal, Montréal, Canada; [7]Instituto Valenciano de Oncologia, Valencia, Spain; [8]Medical Affairs, Astellas Pharma Inc., Northbrook, IL, USA; [9]Pfizer Inc., New York, USA; [10]IQVIA Inc., Bratislava, Slovakia; [11]Carolina Urologic Research Center, Myrtle Beach, South Carolina, USA

EMBARK Study Design



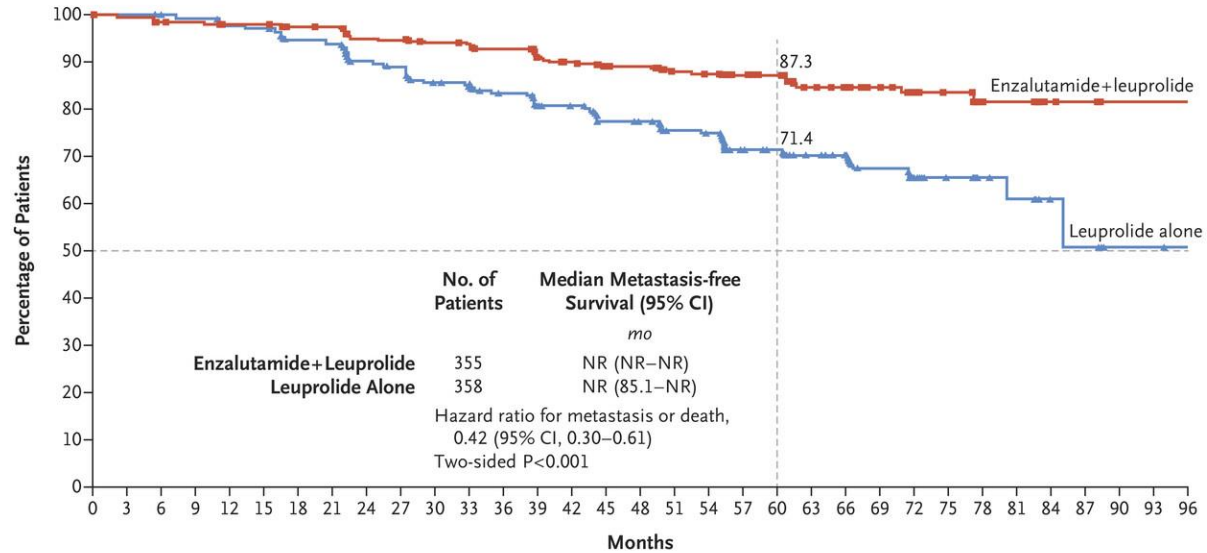
†Study treatment was suspended once if PSA was <0.2 ng/mL at week 37 and reinitiated when PSA was ≥5.0 ng/mL (without prior RP) and ≥2 ng/mL (with prior RP). ‡Primary endpoint and key secondary endpoints for enzalutamide combination and enzalutamide monotherapy are alpha-protected. P-value to determine significance for OS of combination and monotherapy treatment comparisons was dependent on outcomes of primary endpoint and key secondary endpoints.

BICR, blinded independent central review; CT, computed tomography; d, day; EBRT, external beam radiotherapy; IM, intramuscular; MFS, metastasis-free survival; mo, month; MRI, magnetic resonance imaging; OS, overall survival; PSA, prostate-specific antigen; PSADT, PSA doubling time; q, every; R, randomization; RP, radical prostatectomy; w, weeks.

Freedland SJ, et al. *N Engl J Med.* 2023;389:1453–1465.

PRESENTED BY: Neal D. Shore, MD, FACS

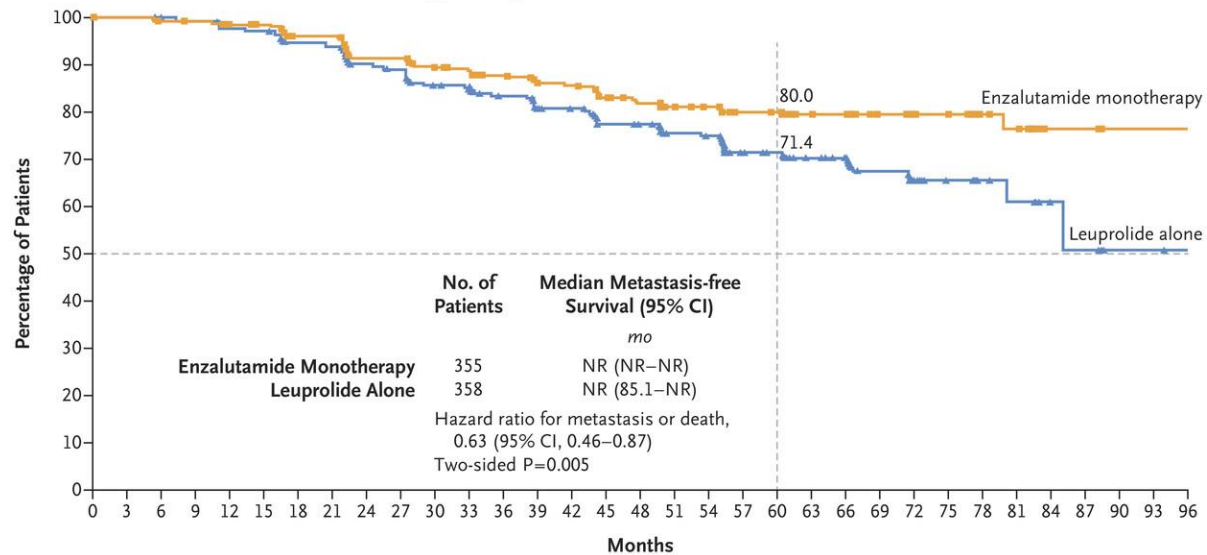
A Metastasis-free Survival with Enzalutamide plus Leuprolide vs. Leuprolide Alone



No. at Risk

Enzalutamide+ leuprolide	355	339	331	330	324	324	318	317	304	303	292	290	281	270	265	252	251	236	234	183	180	119	116	83	60	51	24	22	6	5	0	0	0
Leuprolide alone	358	344	335	334	321	320	303	301	280	276	259	256	238	226	221	205	203	185	183	141	138	93	88	66	32	27	15	13	6	5	1	1	0

B Metastasis-free Survival with Enzalutamide Monotherapy vs. Leuprolide Alone



No. at Risk

Enzalutamide monotherapy	355	350	342	341	328	326	309	309	287	287	273	269	260	248	247	235	228	211	209	172	171	109	108	76	52	49	26	24	5	5	0	0	0
Leuprolide alone	358	344	335	334	321	320	303	301	280	276	259	256	238	226	221	205	203	185	183	141	138	93	88	66	32	27	15	13	6	5	1	1	0

Background

- In the EMBARK (NCT02319837) trial, enzalutamide + leuprolide (ENZ combo) and enzalutamide monotherapy (ENZ mono) both significantly improved MFS versus placebo + leuprolide (leuprolide alone) in high-risk BCR nmHSPC[1,2]
- The FDA and the EMA recently added high-risk BCR nmHSPC as an indication for ENZ[3,4]
- ENZ with or without leuprolide is recommended by the National Comprehensive Cancer Network® (NCCN®) and EAU as a treatment option for patients with high-risk BCR nmHSPC[5,6]
- In EMBARK, treatment was suspended at week 37 if PSA <0.2 ng/mL and reinstated if PSA rose to ≥2.0 ng/mL with RP or ≥5.0 ng/mL without RP[1]

This post hoc analysis examined the HRQoL after treatment suspension

BCR: biochemical recurrence; EAU: European Association of Urology; EMA: European Medicines Agency; ENZ: enzalutamide; FDA: Food and Drug Administration; HRQoL: health-related quality of life; MFS: metastasis-free survival; nmHSPC: non-metastatic hormone-sensitive prostate cancer; PSA: prostate-specific antigen; RP: radical prostatectomy

1. Freedland SJ, et al. *N Engl J Med*. 2023;389:1453–65; 2. Freedland SJ, et al. *NEJM Evid*. 2023;2:EVIDoa2300251; 3. Astellas Pharma US, Inc.; Prescribing Information – XTANDI; 4. XTANDI EMA Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/xtandi-epar-product-information_en.pdf. (Accessed May 3, 2024); 5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.3.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed April 11 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way; 6. Cornford P, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer-2024 Update. *Eur Urol*. 2024 Apr 12:S0302-2838(24)02254-1

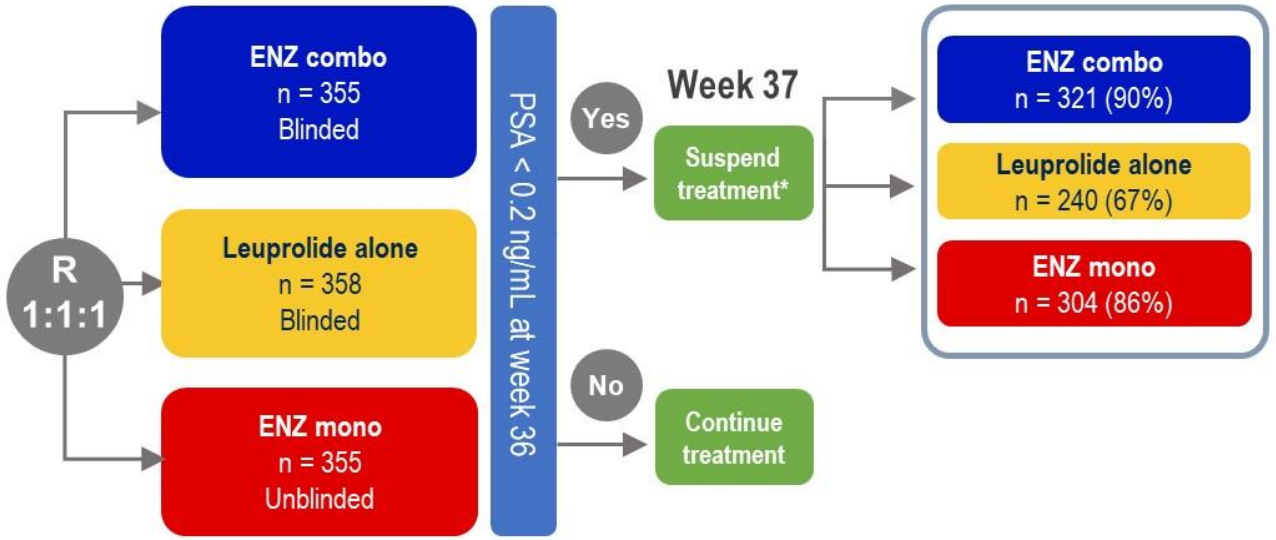
Study design

EMBARK

Phase 3 randomized study in patients with high-risk BCR nmHSPC after local therapy **(N = 1068)**

Patient population

- PSA ≥ 1 ng/mL (post-RP)
- PSA ≥ 2 ng/mL above the nadir (post-RT)
- PSADT ≤ 9 months
- T ≥ 150 ng/dL



Primary endpoint: MFS between ENZ combo vs leuprolide alone

Post hoc analysis: To examine the impact of treatment suspension on HRQoL

***Study drug treatment was suspended, but PSA levels were monitored. Treatment was reinitiated if the PSA increased to ≥2 ng/mL for patients with prior RP or to ≥5 ng/mL for patients without RP**

BCR: biochemical recurrence; ENZ combo: enzalutamide plus leuprolide; ENZ mono: enzalutamide monotherapy; HRQoL: health-related quality of life; MFS: metastasis-free survival; nmHSPC: non-metastatic hormone-sensitive prostate cancer; PSA: prostate-specific antigen; PSADT: PSA doubling time; R: randomization; RP: radical prostatectomy; RT: radiotherapy; T: testosterone

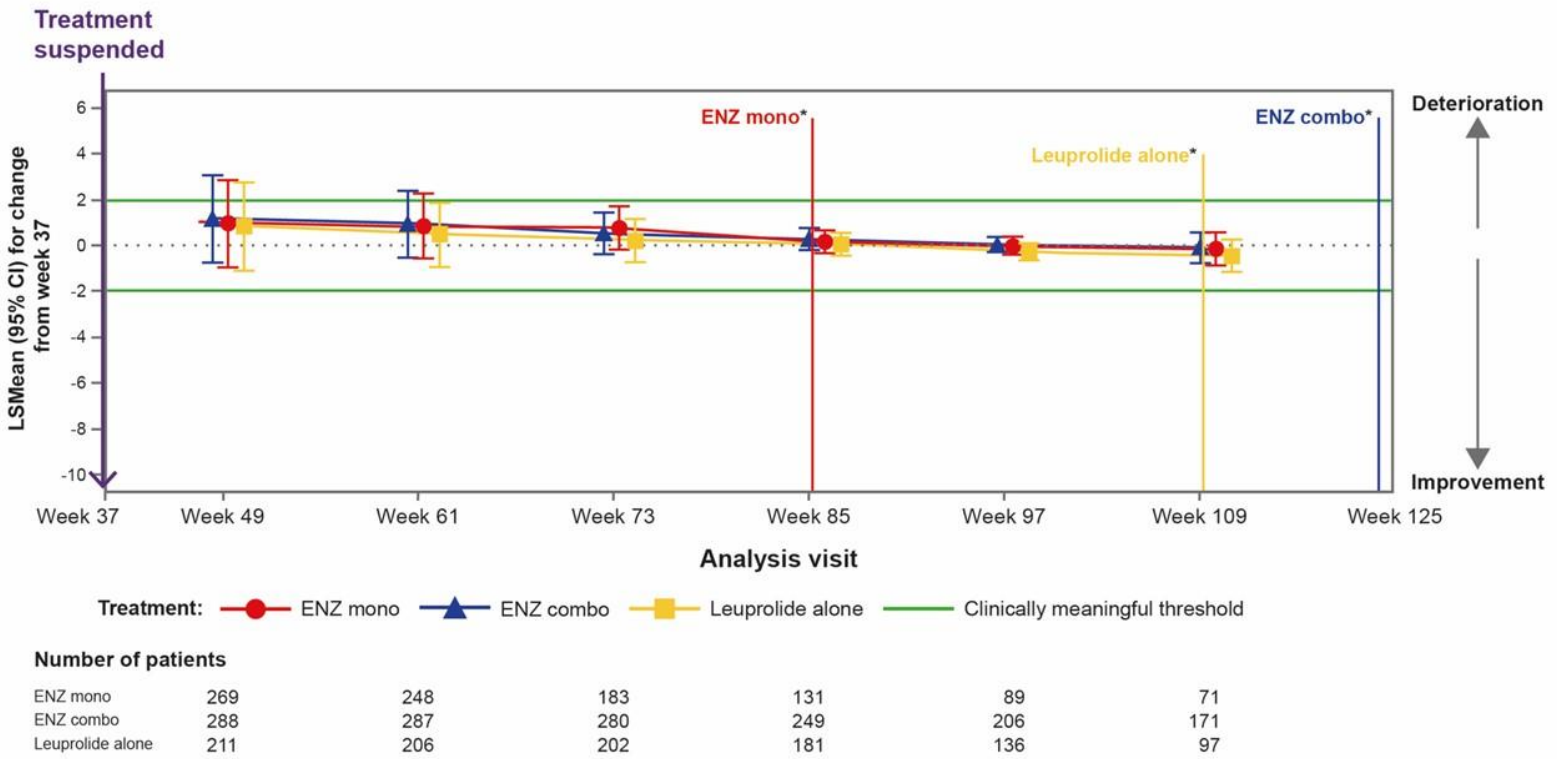
Methods

- Intention-to-treat analysis was used
- PROs assessed at baseline and every 12 weeks until disease progression
- Longitudinal change in HRQoL assessed via MMRM to evaluate change from week 37 (treatment suspension) to subsequent assessments among patients who suspended treatment at week 37, while patients remained on treatment suspension
  - For patients who reinitiated the treatment, assessments collected after reinitiating were excluded from analysis
- After week 109, the number of patients decreased considerably, and 95% CIs became very wide
  - Therefore, here we present HRQoL data through week 109

CI: confidence interval; HRQoL: health-related quality of life; MMRM: mixed model repeated measures; PRO: patient-reported outcome

Results: BPI-SF item 3 (worst pain in past 24 hours)

Instrument	PRO (range)[1]	Clinically meaningful threshold (improvement; deterioration)[1]	Interpretation[1]
BPI-SF	Item 3 (worst pain; past 24 hours) (0–10)	−2; +2	Higher score = worse pain



No meaningful changes were observed in any treatment arm after treatment suspension

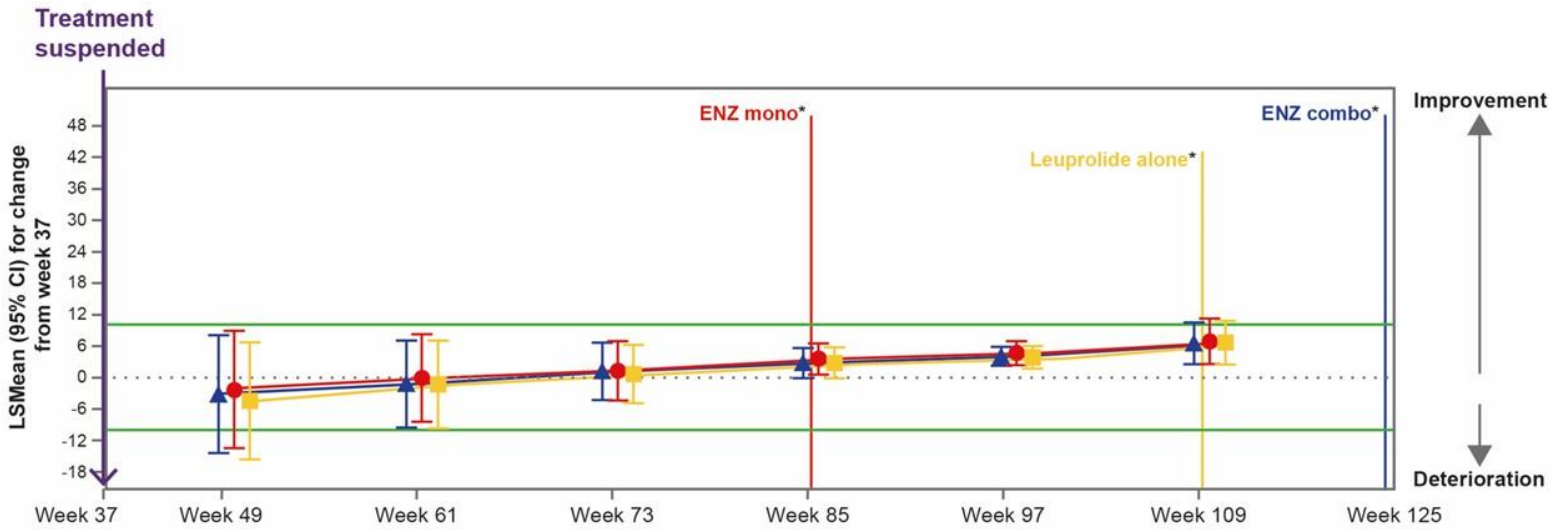
*median time of reinitiation

BPI-SF: Brief Pain Inventory–Short Form; CI: Confidence interval; ENZ combo: enzalutamide plus leuprolide; ENZ mono: enzalutamide monotherapy; LS: least squares; PRO: patient-reported outcome

1. Twycross R, et al. J Pain Symptom Manage. 1996;12:273–82.

Results: FACT-P total score

Instrument	PRO (range)[1]	Clinically meaningful threshold (improvement; deterioration)[1]	Interpretation[1]
FACT-P	Total score (0–156)	+10; −10	Higher score = better HRQoL



Number of patients

ENZ mono	271	249	183	131	89	71
ENZ combo	288	287	280	249	206	172
Leuprolide alone	211	206	202	181	136	97

No meaningful changes were observed in any treatment arm after treatment suspension

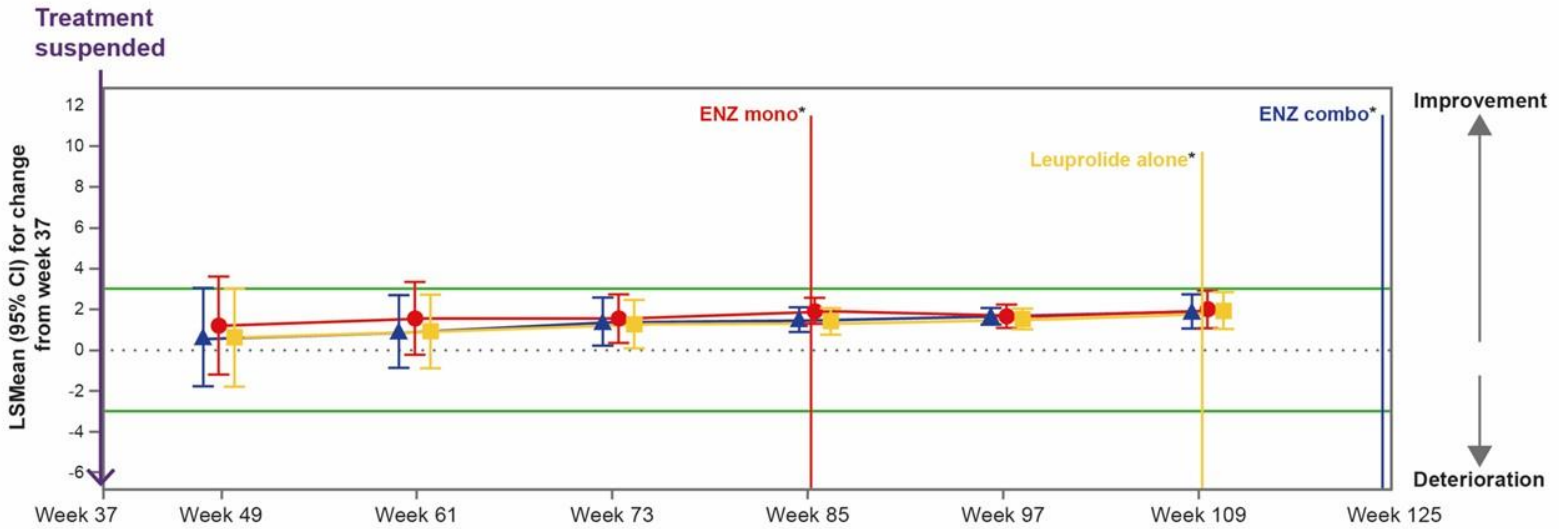
*median time of reinitiation

CI: Confidence interval; ENZ combo: enzalutamide plus leuprolide; ENZ mono: enzalutamide monotherapy; FACT-P: Functional Assessment of Cancer Therapy–Prostate; HRQoL: health-related quality of life; LS: least squares; PRO: patient-reported outcome

1. Norman GR, et al. Med Care. 2003;41:582–92.

Results: FACT-P physical well-being score

Instrument	PRO (range)[1]	Clinically meaningful threshold (improvement; deterioration)[1]	Interpretation[1]
FACT-P	Physical well-being (0–28)	+3; −3	Higher score = better HRQoL



Number of patients

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ENZ combo	288	287	280	249	206	172
Leuprolide alone	211	206	202	181	136	97

No meaningful changes were observed in any treatment arm after treatment suspension

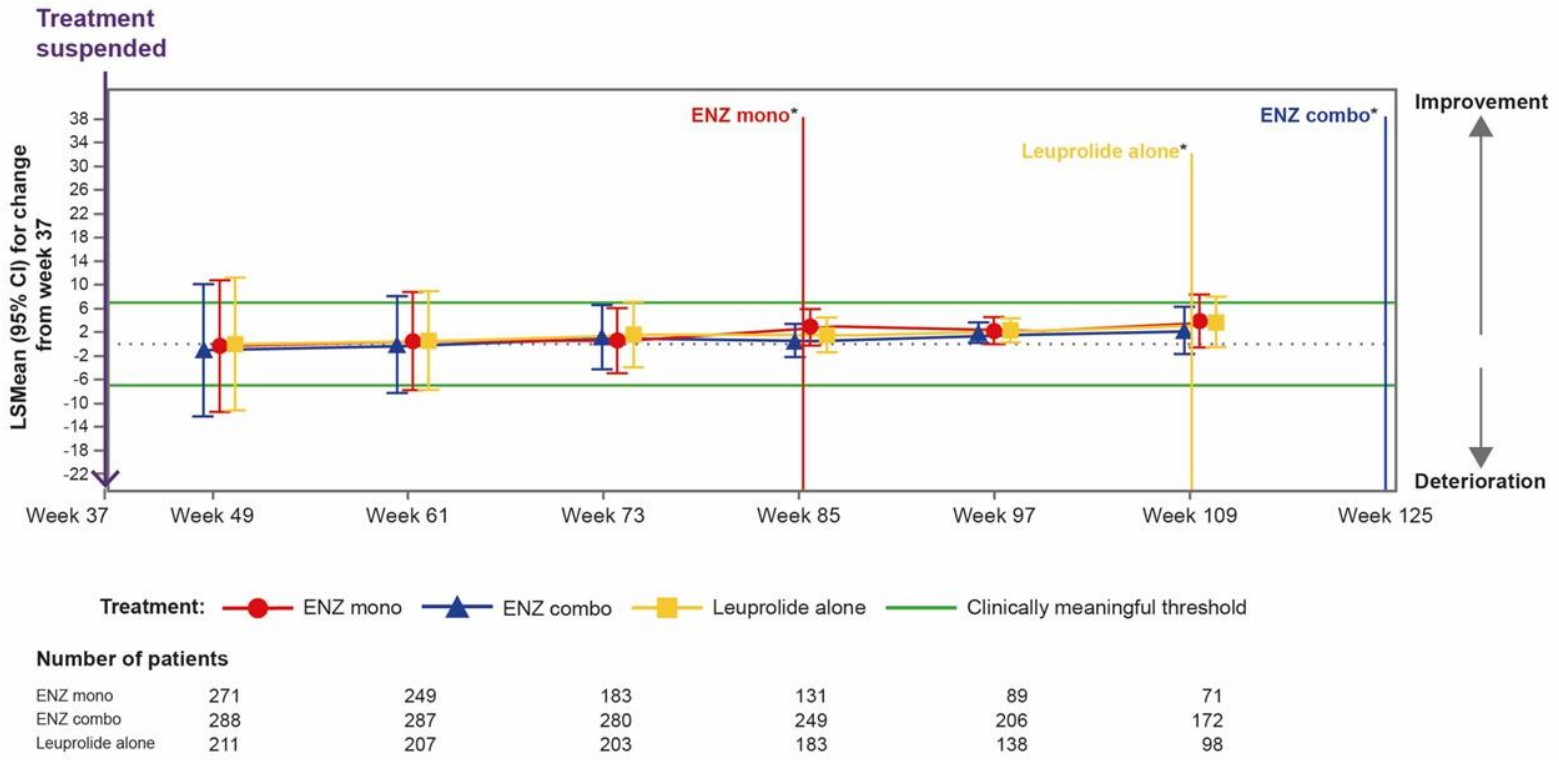
*median time of reinitiation

CI: Confidence interval; ENZ combo: enzalutamide plus leuprolide; ENZ mono: enzalutamide monotherapy; FACT-P: Functional Assessment of Cancer Therapy–Prostate; HRQoL: health-related quality of life; LS: least squares; PRO: patient-reported outcome

1. Norman GR, et al. Med Care. 2003;41:582–92.

Results: EQ-5D visual analog scale score

Instrument	PRO (range)[1]	Clinically meaningful threshold (improvement; deterioration)[1]	Interpretation[1]
EQ-5D-5L	Visual analog scale (0–100)	+7; -7	Higher score = better HRQoL



No meaningful changes were observed in any treatment arm after treatment suspension

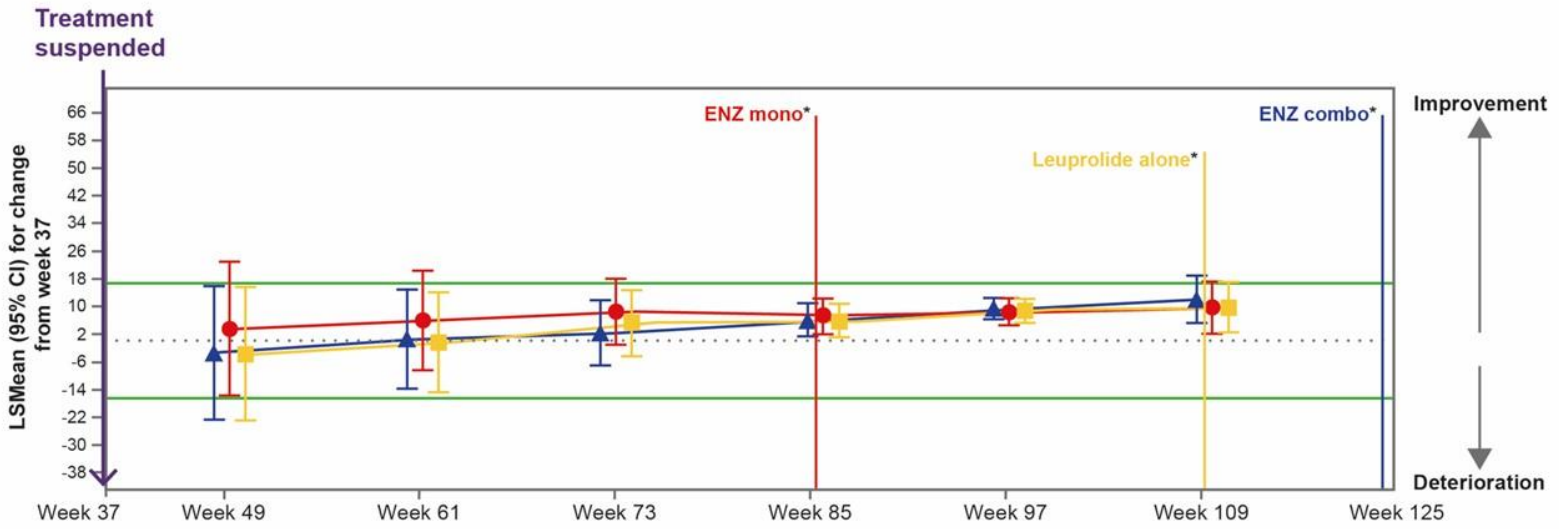
*median time of reinitiation

CI: Confidence interval; ENZ combo: enzalutamide plus leuprolide; ENZ mono: enzalutamide monotherapy; EQ-5D-5L: European Quality of Life 5-Dimensions-5 Levels; HRQoL: health-related quality of life; LS: least squares; PRO: patient-reported outcome

1. Picard et al. Health Qual Life Outcomes. 2007;5:70.

Results: QLQ-PR25 sexual activity score

Instrument	PRO (range)[1]	Clinically meaningful threshold (improvement; deterioration)[1]	Interpretation[1]
QLQ-PR25	Sexual activity (0–100)	+16.67; −16.67	Higher score = better functioning



Number of patients

ENZ mono	269	248	183	131	89	71
ENZ combo	288	287	280	249	206	171
Leuprolide alone	211	206	202	181	136	97

No meaningful changes were observed in any treatment arm after treatment suspension

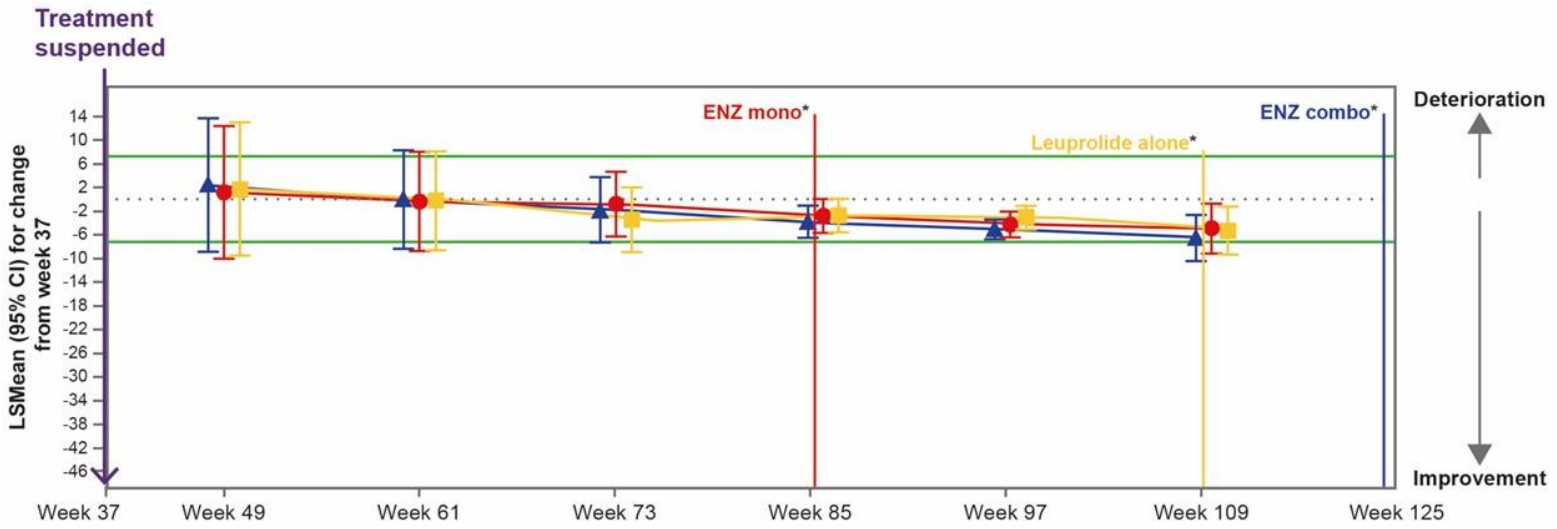
*median time of reinitiation

CI: Confidence interval; ENZ combo: enzalutamide plus leuprolide; ENZ mono: enzalutamide monotherapy; LS: least squares; PRO: patient-reported outcome; QLQ-PR25: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate 25

1. van Andel G, et al. Eur J Cancer. 2008;44:2418–24.

Results: QLQ-PR25 urinary symptoms score

Instrument	PRO (range)[1]	Clinically meaningful threshold (improvement; deterioration)[1]	Interpretation[1]
QLQ-PR25	Urinary symptoms (0–100)	−7.24; +7.24	Higher score = worse symptoms



Number of patients

ENZ mono	269	248	183	131	89	71
ENZ combo	288	287	280	249	206	171
Leuprolide alone	211	206	202	181	136	97

No meaningful changes were observed in any treatment arm after treatment suspension

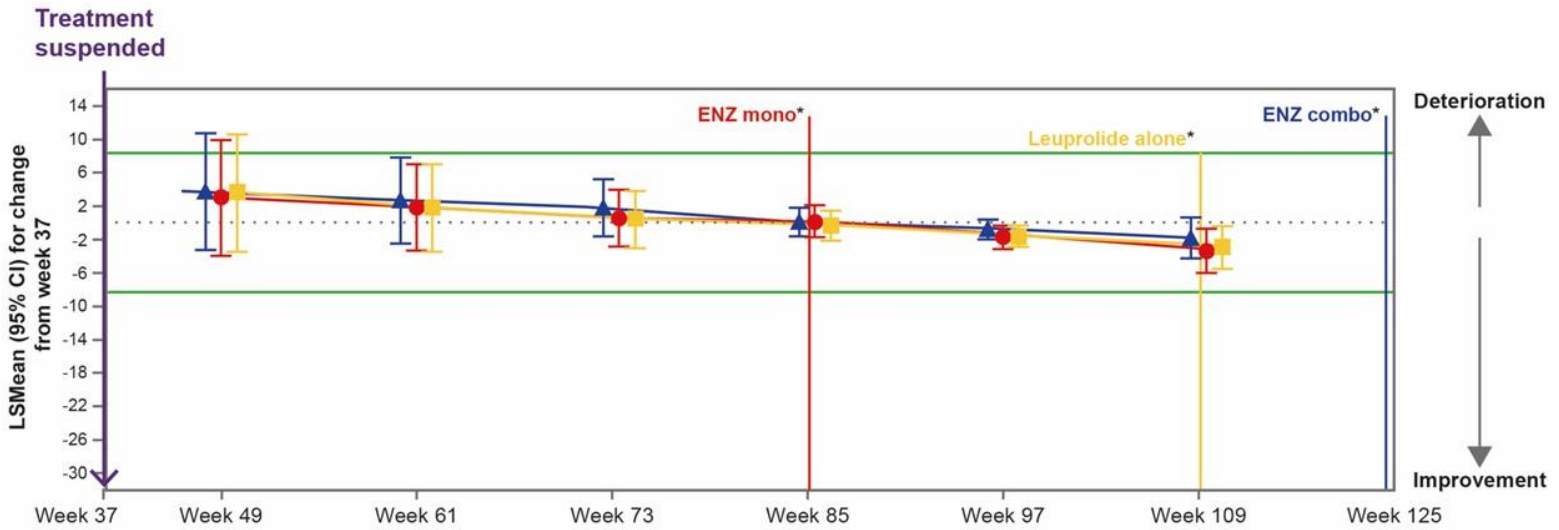
*median time of reinitiation

CI: Confidence interval; ENZ combo: enzalutamide plus leuprolide; ENZ mono: enzalutamide monotherapy; LS: least squares; PRO: patient-reported outcome; QLQ-PR25: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate 25

1. van Andel G, et al. Eur J Cancer. 2008;44:2418–24.

Results: QLQ-PR25 bowel symptoms score

Instrument	PRO (range)[1]	Clinically meaningful threshold (improvement; deterioration)[1]	Interpretation[1]
QLQ-PR25	Bowel symptoms/function (0–100)	−8.33; +8.33	Higher score = worse symptoms



Number of patients

ENZ mono	269	248	183	131	89	71
ENZ combo	288	287	280	249	206	171
Leuprolide alone	211	206	202	181	136	97

No meaningful changes were observed in any treatment arm after treatment suspension

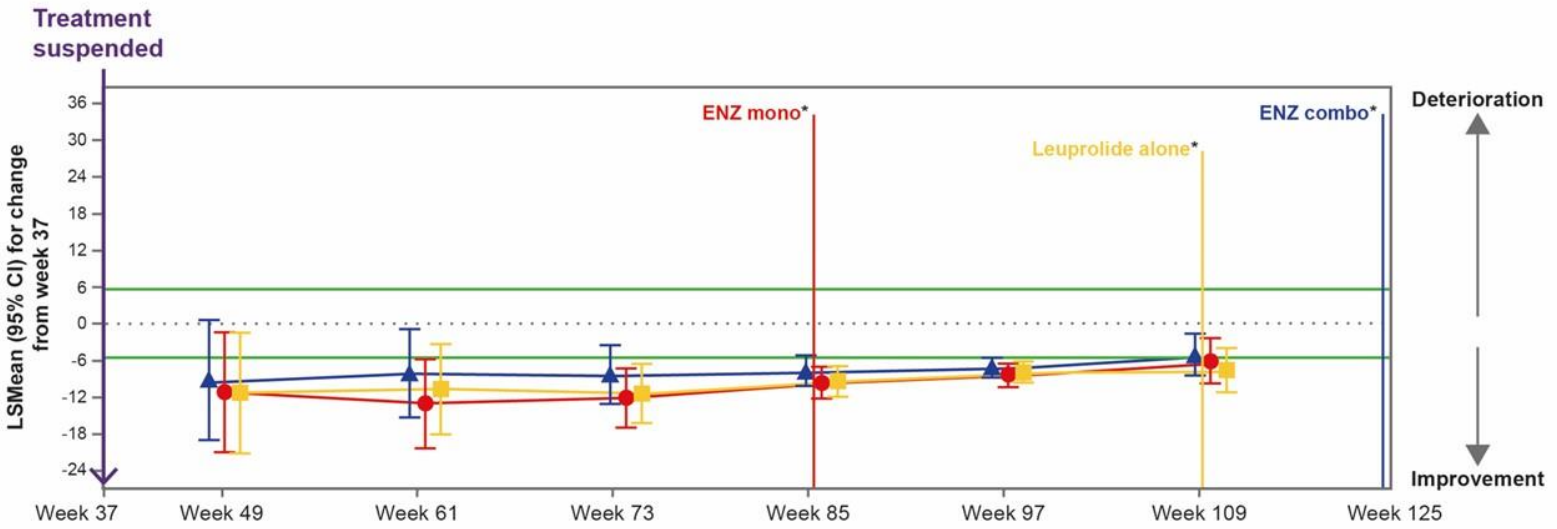
*median time of reinitiation

CI: Confidence interval; ENZ combo: enzalutamide plus leuprolide; ENZ mono: enzalutamide monotherapy; LS: least squares; PRO: patient-reported outcome; QLQ-PR25: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate 25

1. van Andel G, et al. Eur J Cancer. 2008;44:2418–24.

Results: QLQ-PR25 hormonal treatment-related symptoms

Instrument	PRO (range)[1]	Clinically meaningful threshold (improvement; deterioration)[1]	Interpretation[1]
QLQ-PR25	Hormonal treatment-related symptoms (0–100)	−5.56; +5.56	Higher score = worse symptoms



Number of patients

ENZ mono	269	248	183	131	89	71
ENZ combo	288	287	280	249	206	171
Leuprolide alone	211	206	202	181	136	97

After treatment suspension, hormonal treatment-related symptoms quickly improved but eventually began to worsen after week 97

*median time of reinitiation

CI: Confidence interval; ENZ combo: enzalutamide plus leuprolide; ENZ mono: enzalutamide monotherapy; LS: least squares; PRO: patient-reported outcome; QLQ-PR25: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate 25

1. van Andel G, et al. Eur J Cancer. 2008;44:2418–24.

Conclusion

- This post hoc analysis showed that after treatment suspension, hormonal treatment-related symptoms quickly improve in all arms, but worsen after week 97
- No clinically meaningful changes observed in other PRO domains, reflecting minimal impact of treatment on global HRQoL
- These data, along with EMBARK clinical and PRO data, show that ENZ with or without ADT, improves MFS vs. leuprolide alone, without affecting global HRQoL during treatment or after treatment suspension

Limitations:

- Patients not randomized into the treatment suspension arms
- Sample sizes decreased over time with small sample sizes beyond week 109

ADT: Androgen deprivation therapy; ENZ: enzalutamide; HRQoL: health-related qualify of life; MFS: metastasis-free survival; PRO: patient-reported outcome

2024 ASCO ANNUAL MEETING

Characterization of complete responders to nivolumab + gemcitabine-cisplatin versus gemcitabine-cisplatin alone and patients with lymph node only metastatic urothelial carcinoma from the CheckMate 901 trial

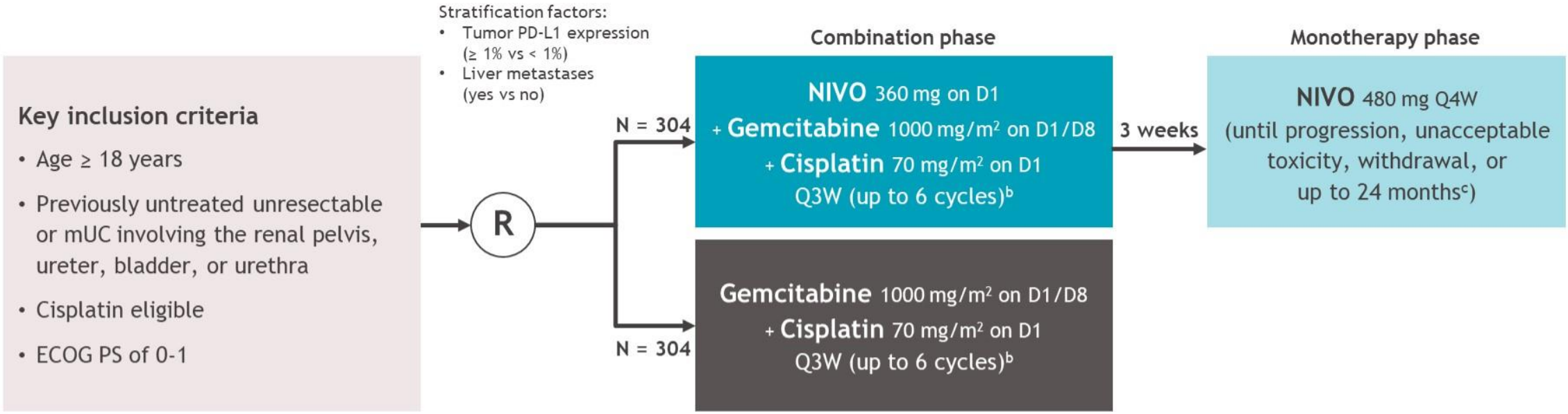
Matthew D. Galsky,[1] Guru Sonpavde,[2] Thomas Powles,[3] Melanie Claps,[4] Mauricio Burotto,[5] Michael Schenker,[6] Juan Pablo Sade,[7] Aristotelis Bamias,[8] Philippe Beuzeboc,[9] Jens Bedke,[10*] Jan Oldenburg,[11] Yüksel Ürün,[12] Dingwei Ye,[13] Begoña P. Valderrama,[14] Yoshihiko Tomita,[15] Jeiry Filian,[16] Lily Wang,[16] Daniela Purcea,[17] Michiel S. van der Heijden[18]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [2]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [3]Barts Cancer Institute, Queen Mary University of London, London, UK; [4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [5]Bradford Hill Clinical Research Center, Santiago, Chile; [6]Sf. Nectarie Oncology Center, and University of Medicine and Pharmacy, Craiova, Romania; [7]Alexander Fleming Institute, Buenos Aires, Argentina; [8]National and Kapodistrian University of Athens, ATTIKON University Hospital, Athens, Greece; [9]Hôpital Foch, Suresnes, France; [10]Eberhard Karls University Tübingen, Tübingen, Germany; [11]Akershus University Hospital (Ahus), Lørenskog, Norway; [12]Ankara University, Ankara, Turkey; [13]Fudan University Shanghai Cancer Center, Shanghai, China; [14]Hospital Universitario Virgen del Rocío, Sevilla, Spain; [15]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [16]Bristol Myers Squibb, Princeton, NJ; [17]Bristol Myers Squibb, Boudry, Switzerland; [18]Netherlands Cancer Institute, Amsterdam, the Netherlands
*Dr. Bedke is now with Eva Mayr-Stihl Cancer Center, Klinikum Stuttgart, Stuttgart, Germany

Abstract number 4509

Study design

- NIVO+GC vs GC in cisplatin-eligible patients[a]



Median (range) study follow-up:
33.6 (7.4-62.4) months

Primary endpoints: OS, PFS per BICR
Key secondary endpoints: OS and PFS per BICR by PD-L1 ≥ 1%,[d] HRQoL
Key exploratory endpoints: ORR per BICR, safety

Current analysis includes: baseline characteristics, ORR, OS, and PFS in all randomized LN only patients

[a]Further CheckMate 901 trial design details are available at https://clinicaltrials.gov/ct2/show/NCT03036098. [b]Patients who discontinued cisplatin could be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to 6 in total). [c]A maximum of 24 months from first dose of NIVO administered as part of the NIVO+GC combination. [d]PD-L1 status was defined by the percentage of positive tumor cell membrane staining in a minimum of 100 tumor cells that could be evaluated with the use of the PD-L1 IHC 28-8 pharmDx immunohistochemical assay (Dako, Santa Clara, CA).

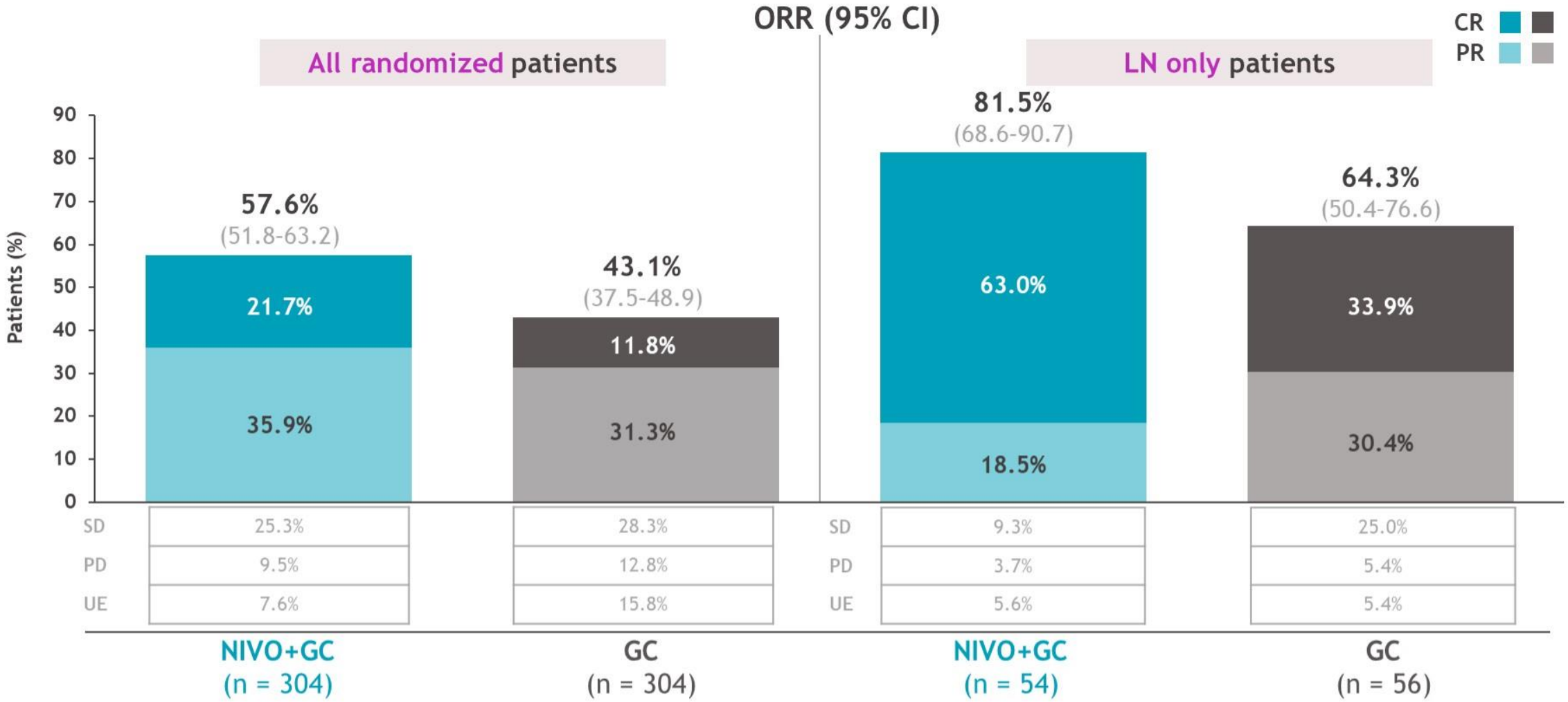
Select characteristics for all patients with complete response

	All randomized patients		Patients with CR	
	NIVO+GC (N = 304)	GC (N = 304)	NIVO+GC (N = 66)	GC (N = 36)
Median age (range), years	65.0 (32-86)	65.0 (35-85)	65.0 (33-81)	63.5 (36-80)
Male sex, n (%)	236 (78)	234 (77)	53 (80)	31 (86)
Race				
White	211 (69)	225 (74)	47 (71)	27 (75)
Black or African American	0	2 (< 1)	0	0
American Indian or Alaska Native	1 (< 1)	1 (< 1)	0	1 (3)
Asian	75 (25)	63 (21)	16 (24)	6 (17)
Other	17 (6)	13 (4)	3 (5)	2 (6)
LN only disease,[a] n (%)	54 (18)	56 (18)	34 (52)	19 (53)
Disease stage at study entry, n (%)				
Stage III	37 (12)	28 (9)	9 (14)	5 (14)
Stage IV	265 (87)	274 (90)	56 (85)	31 (86)
Not reported	2 (< 1)	2 (< 1)	1 (2)	0
PD-L1 status, n (%)				
≥ 1%	112 (37)	109 (36)	28 (42)	11 (31)
< 1%	192 (63)	195 (64)	38 (58)	25 (69)
Subsequent anticancer therapy received	108 (36)	156 (51)	23 (35)	15 (42)

- Of the 608 total patients randomized, 102 (16.8%) achieved a CR
- Approximately 50% of patients with CR had LN only mUC vs approximately 20% of all randomized patients

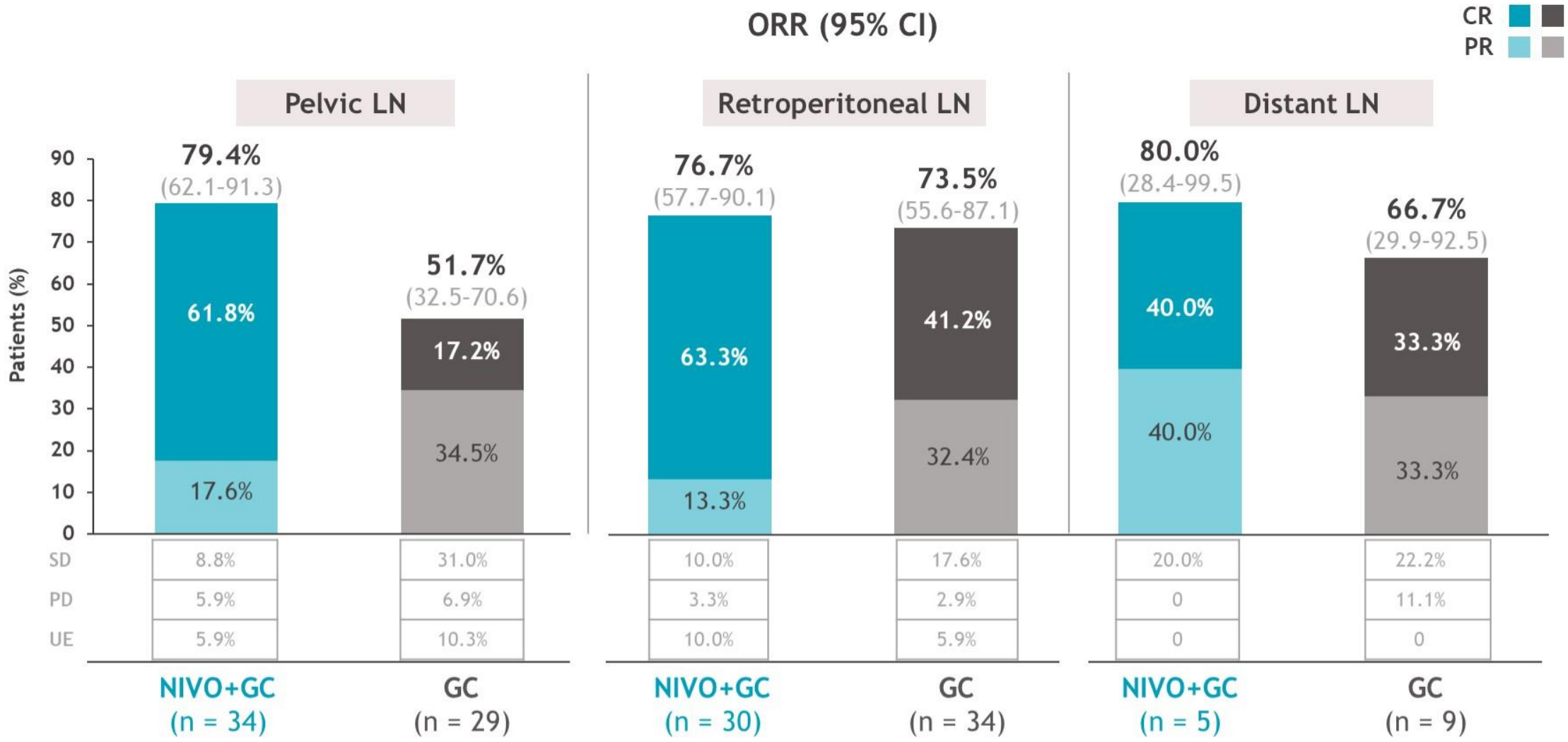
[a]LN only disease as defined per BICR. There may not be full concordance with investigator assessment.

Response per BICR



- CR rates for NIVO+GC-treated patients with LN only mUC were approximately twice that of GC-treated patients

BOR for patients with LN only mUC by LN involvement

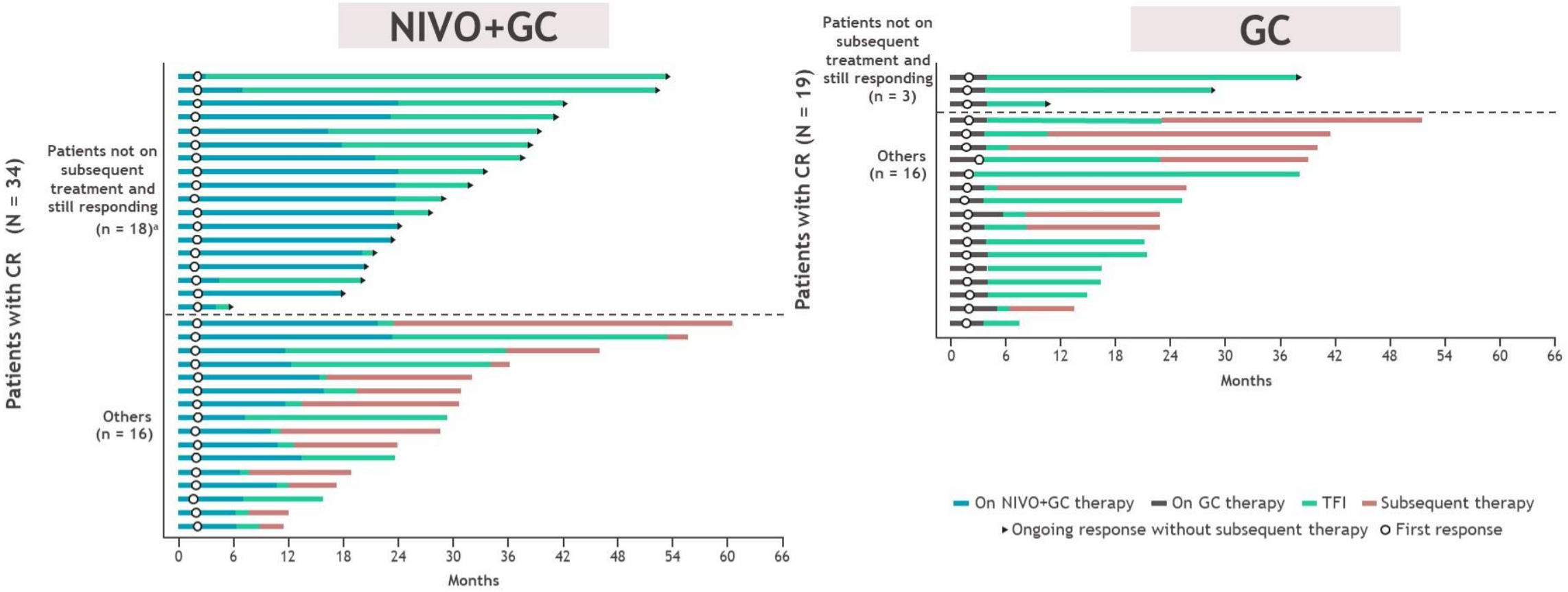


Response characteristics for LN only patients with CR

	NIVO+GC (N = 54)	GC (N = 56)
Patients with CR	n = 34	n = 19
Median time to CR (range), months	2.1 (1.8-2.2)	2.0 (1.6-3.3)
Median duration of CR (95% CI), months	NR (22.0-NE)	8.7 (6.7-15.6)
12-month CR rate (95% CI), %	70 (51-82)	32 (10-57)
24-month CR rate (95% CI), %	65 (45-79)	Not applicable (0)

- The median duration of CR was NR in the NIVO+GC group and was 8.7 months in the GC group
- The 12-month CR rate for patients treated with NIVO+GC was more than twice that of patents treated with GC

TFI and response outcomes: LN only patients achieving CR

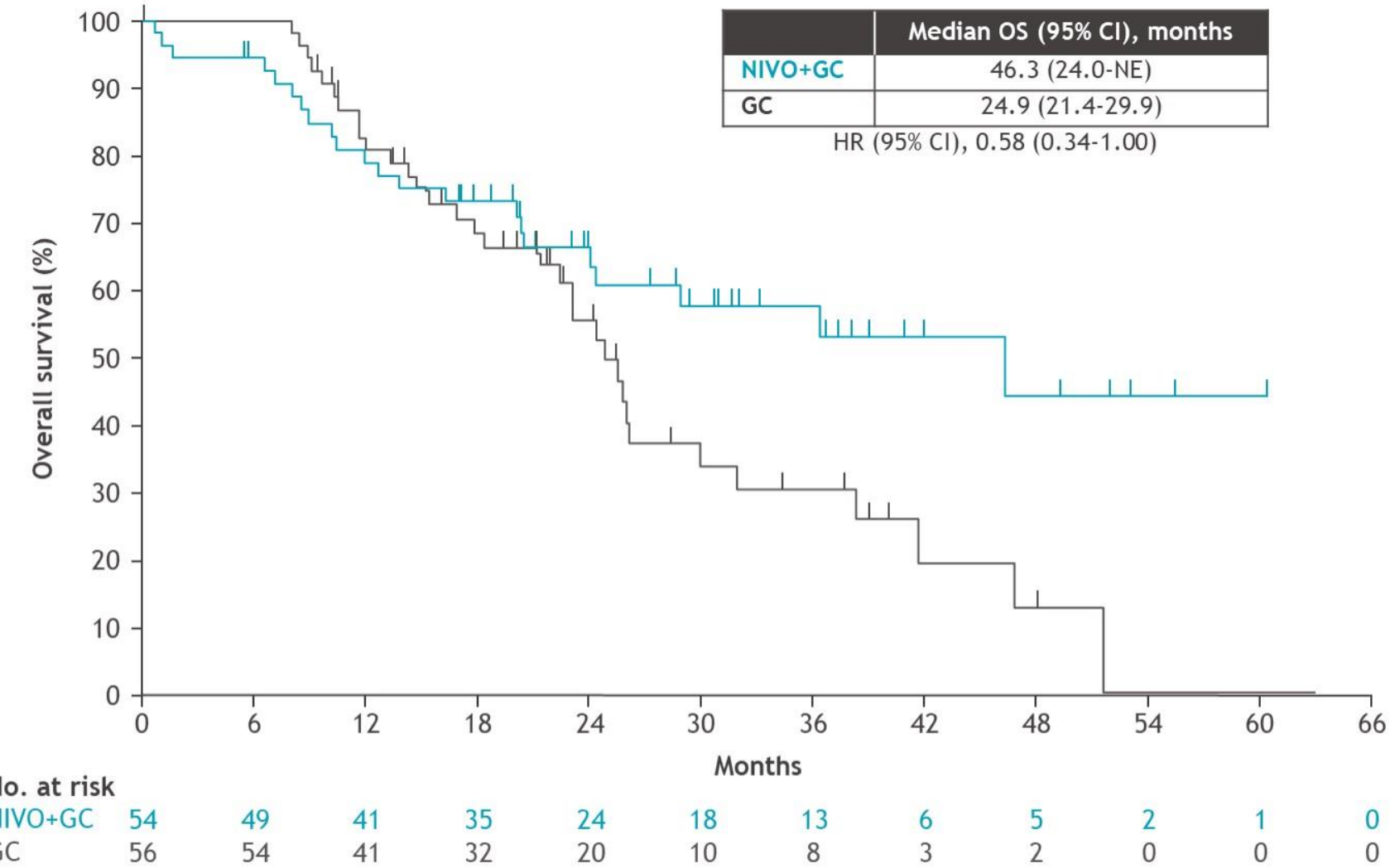


- In the NIVO+GC arm, 14 of 34 patients with CR (41%) experienced a TFI and ongoing response without subsequent therapy vs 3 of 19 patients with GC (16%)

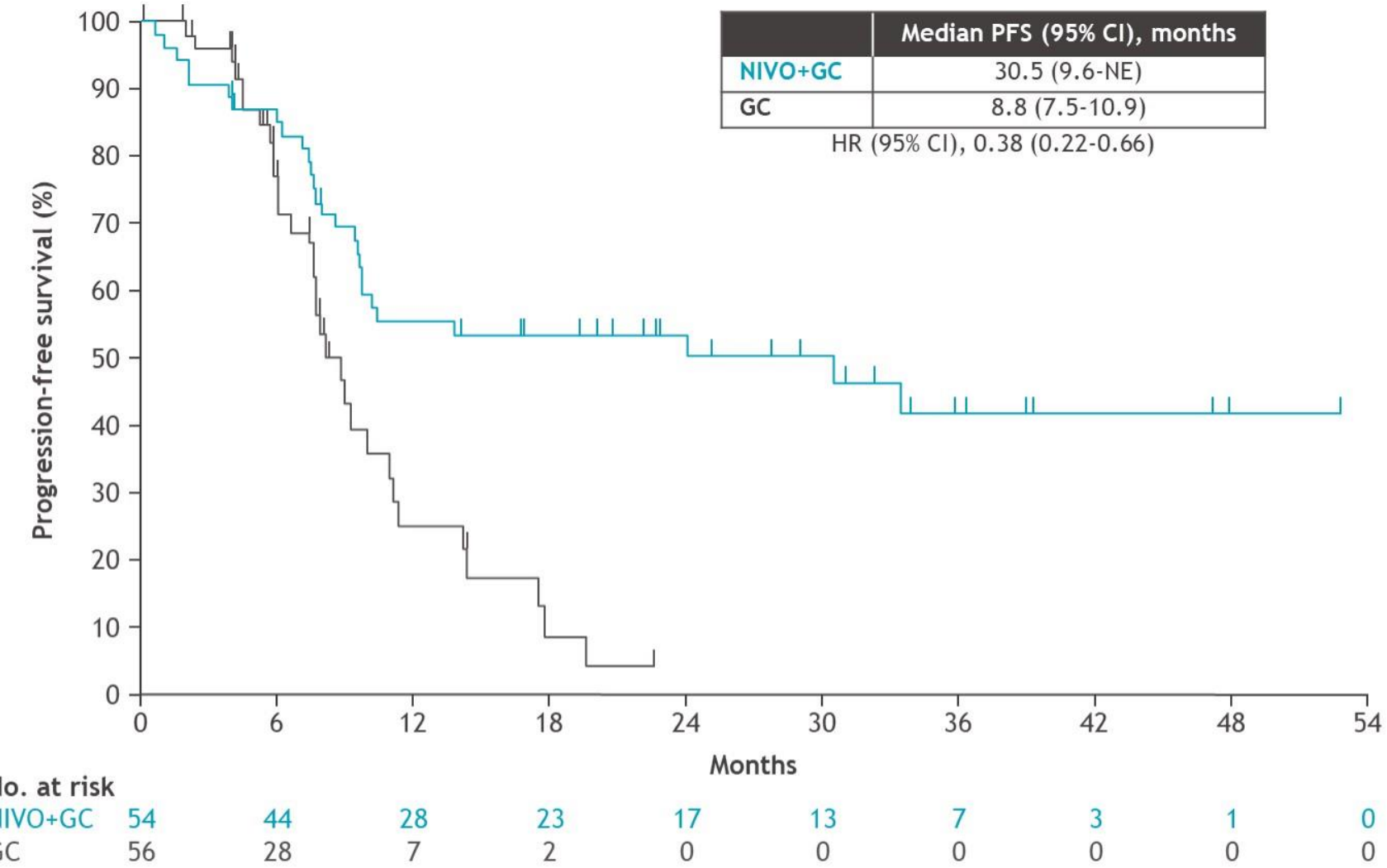
[a]Four patients in the NIVO+GC arm are still on treatment without progression.

Bar indicates OS/subsequent systemic therapy. Vertical axis origin corresponds to first treatment date. TFI is defined in patients who are off study treatment; TFI is defined as survival time from end of therapy in those who never received subsequent systemic therapy, and as time from end of therapy until subsequent systemic therapy in those who received subsequent systemic therapy (whichever occurred first).

OS: patients with LN only mUC per BICR



PFS: patients with LN only mUC per BICR



Summary

- NIVO+GC generated deep responses in CheckMate 901 with a fixed duration of therapy and with up to 2 years of treatment with NIVO
- Exploratory characterization of patients with CR identified a group of patients enriched with LN only disease
- A subset of patients with LN only mUC in the NIVO+GC arm experienced an ongoing CR off all treatment at the time of last follow-up
- In patients with LN only mUC, NIVO+GC induced durable disease control and clinically meaningful improvements in OS and PFS vs GC alone
  - ORR and CR rates were also higher with NIVO+GC vs GC alone
- These results provide additional support for NIVO plus cisplatin-based chemotherapy, which is now approved for patients with mUC in the US and Europe, and represents a standard first-line treatment option for this population

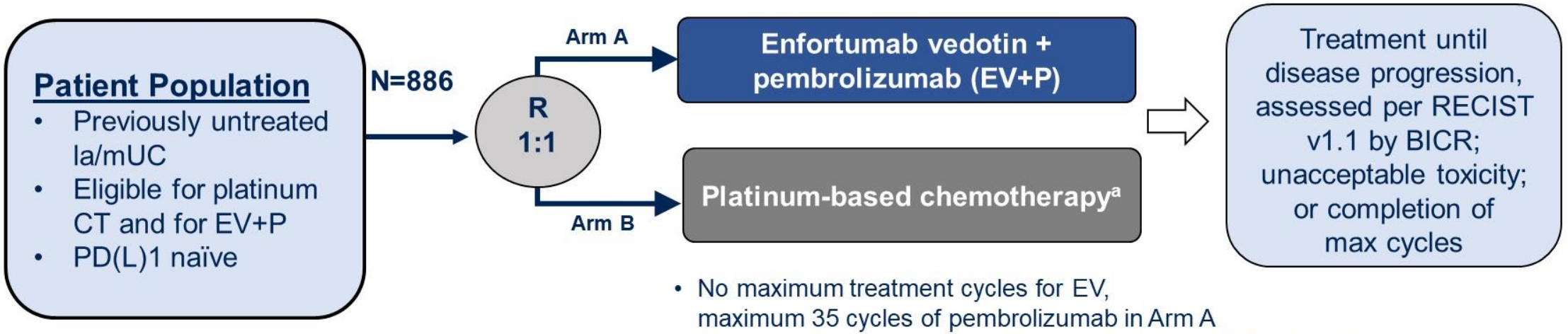
2024 ASCO® ANNUAL MEETING

Patient-Reported Outcomes (PROs) From a Randomized, Phase 3 Trial of Enfortumab Vedotin Plus Pembrolizumab (EV+P) versus Chemotherapy in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer (la/mUC)

Shilpa Gupta, Yohann Loriot, Michiel Van der Heijden, Jens Bedke, Begoña P. Valderrama, Eiji Kikuchi, Aude Fléchon, Daniel P. Petrylak, Maria De Santis, Matthew Galsky, Jae Lyun Lee, Umang Swami, Srikala S. Sridhar, Ugo De Giorgi, Phoebe Wright, Yi-Tsung Lu, Xuesong Guan, Ryan Dillon, Blanca Homet Moreno, Thomas Powles

Abstract #4502
Chicago, Illinois, June 03, 2024

EV-302 Study Design



- No maximum treatment cycles for EV, maximum 35 cycles of pembrolizumab in Arm A
- Maximum 6 cycles of gemcitabine and platinum CT in Arm B

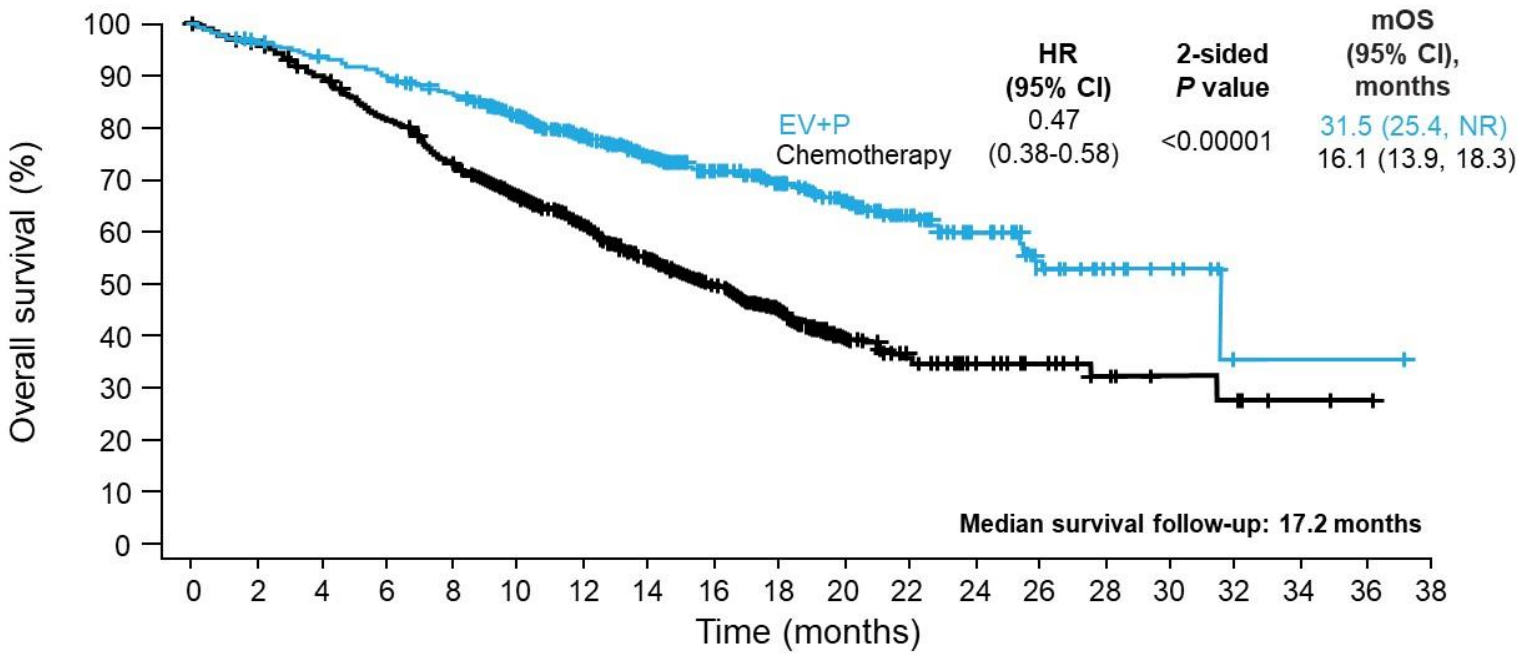
Efficacy and Safety Endpoints:
- Dual primary endpoints (PFS by BICR and OS)
- Pre-specified secondary endpoints: ORR by BICR, PFS and ORR per investigator, DOR, DCR, Safety

PRO Endpoints:
- Key secondary endpoints: Time to pain progression (TTPP), change from baseline in BPI-SF worst pain at week 26
- Other pre-specified PRO secondary endpoints were descriptive with no adjustment for multiplicity

[a]Maintenance therapy could be used following completion and/or discontinuation of platinum CT.
BICR, blinded independent central review; BPI-SF, Brief Pain Inventory-Short Form; CT, chemotherapy; DCR, disease control rate; DOR, duration of response; EV+P, enfortumab vedotin plus pembrolizumab; la/mUC, locally advanced or metastatic urothelial carcinoma; ORR, overall response rate; OS, overall survival; PD(L)1, programmed death-ligand 1; PFS, progression-free survival; PRO, patient-reported outcome; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; TTPP, time to pain progression.

EV-302 Primary Endpoints PFS and OS

- EV+P nearly doubled both PFS and OS versus CT.[1]
- Median (95% CI) PFS was 12.5 (10.4, 16.6) months in the EV+P arm and 6.3 (6.2, 6.5) months in the CT arm.
  - HR (95% CI): 0.45 (0.38, 0.54); 2-sided *P* value <0.001.



No. 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

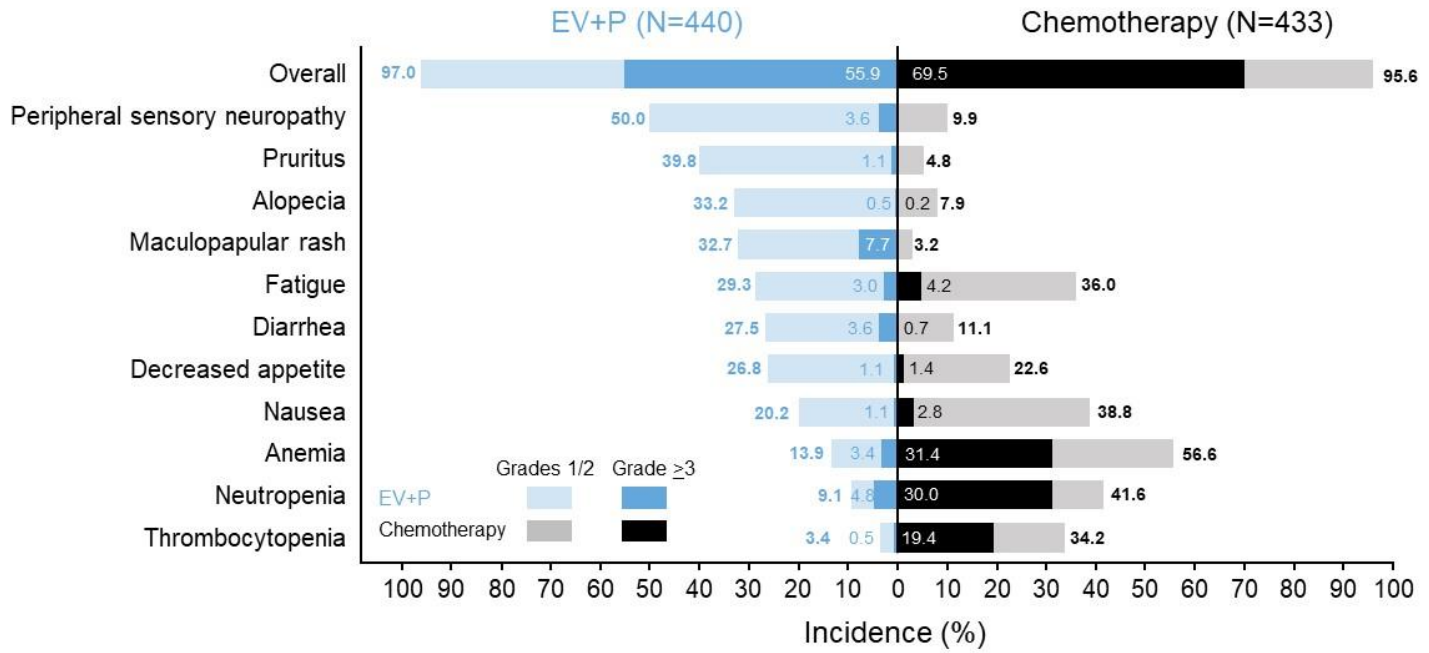
1. PADCEV® Highlights of prescribing information. https://astellas.us/docs/PADCEV_label.pdf

CT, chemotherapy; EV+P, enfortumab vedotin plus pembrolizumab; HR, hazard ratio; mOS, median overall survival; OS, overall survival; PFS, median progression-free survival; NR, not reached.

EV-302 Overall Safety Summary

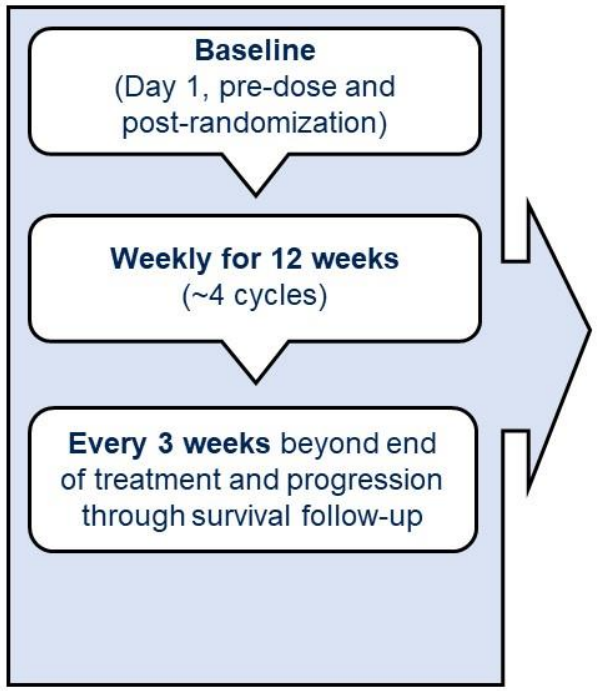
- The safety profile of EV+P was:
  - Generally manageable.
  - Consistent with previous studies.[1,2,3]
  - Distinct from the CT arm reflecting differences in treatment mechanism of action and in duration of treatment.

Treatment-related adverse events[1]



1. Powles. *N Engl J Med*. 2024;390:875-888. 2. Hoimes. *J Clin Oncol*. 2023;41:22-31. 3. O'Donnell. *J Clin Oncol*. 2023;41:4107-4117.
CT, chemotherapy; EV+P, enfortumab vedotin plus pembrolizumab.

EV-302 PRO Collection



EORTC QLQ-C30
(score range 0-100; higher score represents greater symptom burden, higher functioning, and better QoL)

Cancer-related symptoms

Appetite loss, Constipation, Diarrhea, Dyspnea, Fatigue, Insomnia, Nausea and vomiting, Pain

Function

Physical, Cognitive, Emotional, Role, Social

QoL/GHS

BPI-SF
(score range 0-10; higher score represents more pain)

Includes

Worst pain, Average pain, Least pain, Pain right now, Pain interference, Location of pain

- TTPP and mean change from baseline in worst pain (BPI-SF Question 3) at week 26 were pre-specified endpoints included in the hierarchical statistical testing plan.
- Pre-specified descriptive analyses included change from baseline and time to confirmed deterioration (TTCD).
- Patients with moderate/severe pain at baseline were a pre-specified subgroup of interest.

BPI-SF, Brief Pain Inventory-Short Form; EV+P, enfortumab vedotin plus pembrolizumab; GHS, global health status; PRO, patient-reported outcome; QoL, quality of life.

Baseline QoL and Pain Scores

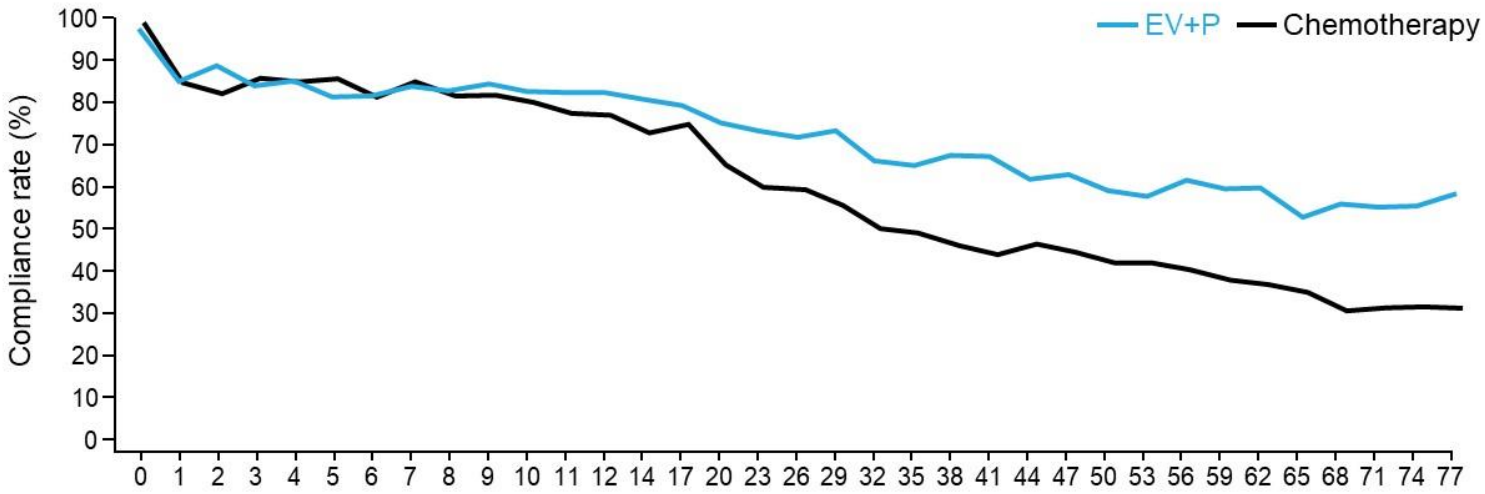
Parameter	EV+P (n=376)	Chemotherapy (n=355)
BPI-SF		
Worst pain, mean (SD)	3.1 (2.8)	3.3 (3.0)
Patients with moderate to severe pain at baseline, n (%)	128 (34)	128 (36)
EORTC QLQ-C30, mean (SD)		
GHS/QoL	62.4 (22.5)	60.3 (25.4)
Functioning scales		
Cognitive functioning	84.3 (19.6)	83.9 (19.9)
Social functioning	77.3 (27.4)	76.3 (26.3)
Emotional functioning	75.5 (20.7)	74.6 (22.0)
Physical functioning	76.5 (22.7)	72.8 (24.3)
Role functioning	75.8 (28.3)	73.2 (29.4)

- Baseline scores were balanced between treatment arms in the PRO full analysis set.[a]
- Approximately one-third of patients had moderate to severe pain (pain score of 5 or greater on a scale of 1–10) at baseline.

[a]The PRO full analysis set consisted of all randomized subjects who had received any amount of study treatment and had completed ≥1 PRO assessment at baseline.
BPI-SF, Brief Pain Inventory-Short Form; EV+P, enfortumab vedotin plus pembrolizumab; GHS, global health status; PRO; patient-reported outcome; QoL, quality of life.

PRO Compliance

- Patient compliance with PRO assessments remained >70% through week 17 in the CT arm and week 29 in the EV+P arm.
- PRO compliance rates differ between arms, in part, due to differences in visit schedules after end of protocol defined treatment.



No. of subjects with data at visit

EV+P	365	321	330	311	314	300	300	306	301	307	299	296	296	289	278	261	252	241	241	215	210	212	205	177	166	150	138	139	127	117	95	95	88	82	77
Chemotherapy	350	300	288	300	294	296	282	294	279	278	271	260	256	239	240	204	179	172	158	135	127	116	104	98	89	78	70	63	54	49	42	34	32	29	26

No. of subjects who are expected to have PRO assessments

EV+P	376	376	373	371	369	368	367	365	364	363	361	359	359	357	350	348	343	336	330	326	323	314	306	285	265	254	239	226	213	196	180	170	160	148	132
Chemotherapy	355	355	352	351	348	347	347	347	343	342	340	337	334	329	322	314	300	291	285	270	261	252	238	212	201	186	168	157	142	133	121	112	103	92	84

CT, chemotherapy; EV+P, enfortumab vedotin plus pembrolizumab; PRO, patient-reported outcome.

Time to Pain Progression (TTPP)

These data were previously presented in the primary manuscript.[1]

- TTPP was defined as the time from randomization to first pain progression:
  - Increase of ≥2 points from baseline on BPI-SF maintained for ≥2 consecutive assessments.
  - Patient reported initiation of new opioid medication.
- mTTPP (95% CI) was:
  - 14.2 (6.6, NR) months in the EV+P arm.
  - 10.0 (5.9, NR) months in the CT arm.
- No statistically significant difference observed between treatment arms.
  - HR (95% CI): 0.92 (0.72, 1.2); 2-sided *P* value 0.48.[1]

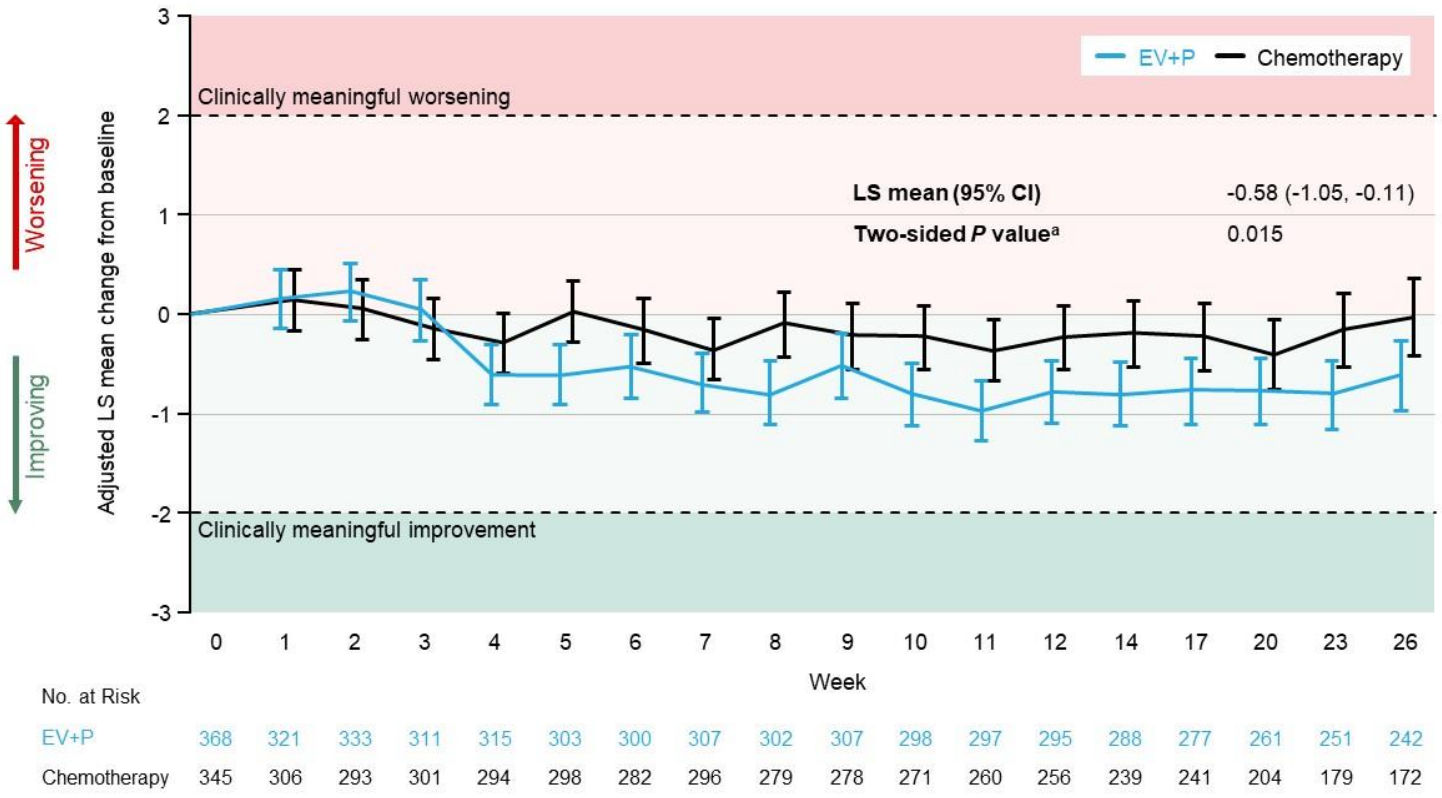
1. Powles. *N Engl J Med*. 2024;390:875-888.

BPI-SF, Brief Pain Inventory-Short Form; CT, chemotherapy; EV+P, enfortumab vedotin plus pembrolizumab; HR, hazard ratio; mTTPP, median time to pain progression; NR, not reached; PRO, patient-reported outcome.

Change in Worst Pain (BPI-SF)

"Please rate your pain from 0 (no pain) to 10 (pain as bad as you can imagine) that best describes your pain at its worst in the last 24 hours."

- Although pre-defined clinically meaningful thresholds were not met in either treatment arm:
  - Patients in the EV+P arm reported improved pain compared to baseline.
  - Larger improvements in pain were demonstrated in the EV+P arm than in the CT arm.

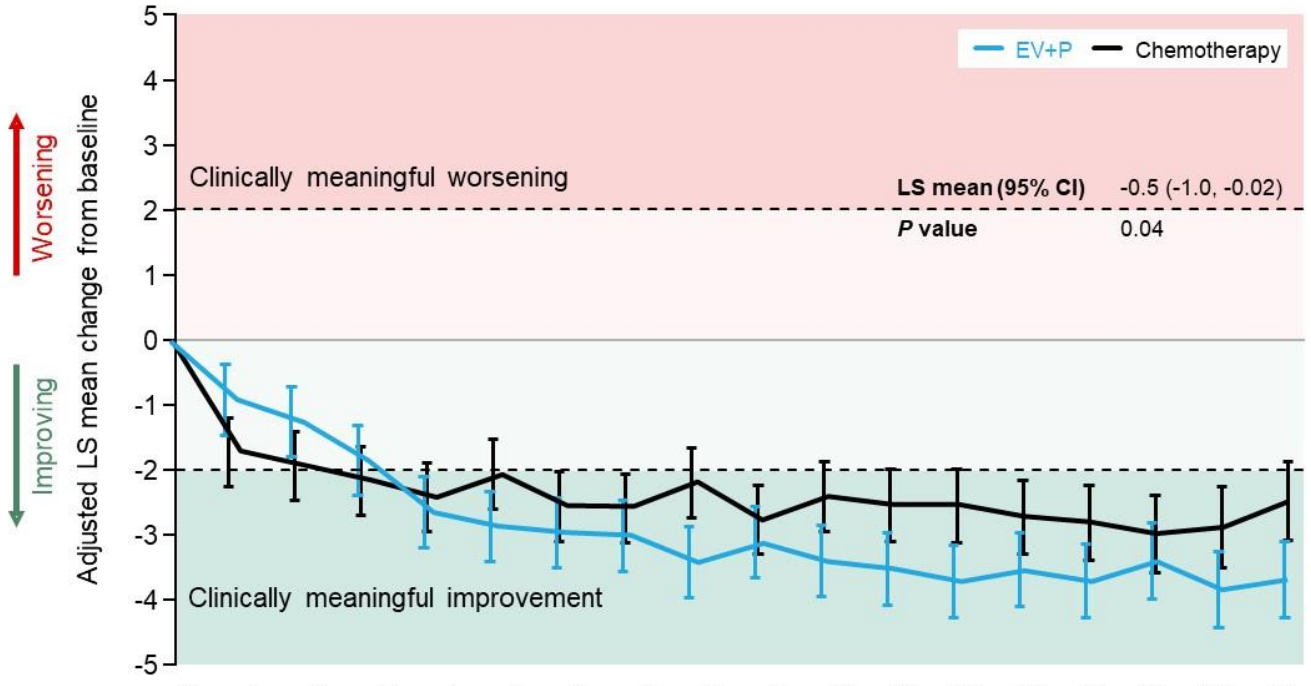


[a]Nominal *P* value.
BPI-SF, Brief Pain Inventory-Short Form; CT, chemotherapy; EV+P, enfortumab vedotin plus pembrolizumab; LS, least squares.

Change in Worst Pain (BPI-SF) in Patients With Moderate/Severe Pain at Baseline

"Please rate your pain from 0 (no pain) to 10 (pain as bad as you can imagine) that best describes your pain at its worst in the last 24 hours."

- Approximately one-third of patients had moderate to severe pain at baseline.
- Patients in both EV+P and CT treatment arms had clinically meaningful improvements in worst pain.
  - A 2-point change was considered clinically meaningful.[1]
- Greater improvements in pain were observed in the EV+P arm.



No. at Risk																	
EV+P	128	105	108	102	99	93	98	100	97	94	96	94	94	91	84	78	73	72
Chemotherapy	128	107	98	104	105	96	99	93	91	93	89	84	75	75	75	66	55	55

1. Dworkin. *J Pain.* 2008;9:105-121.

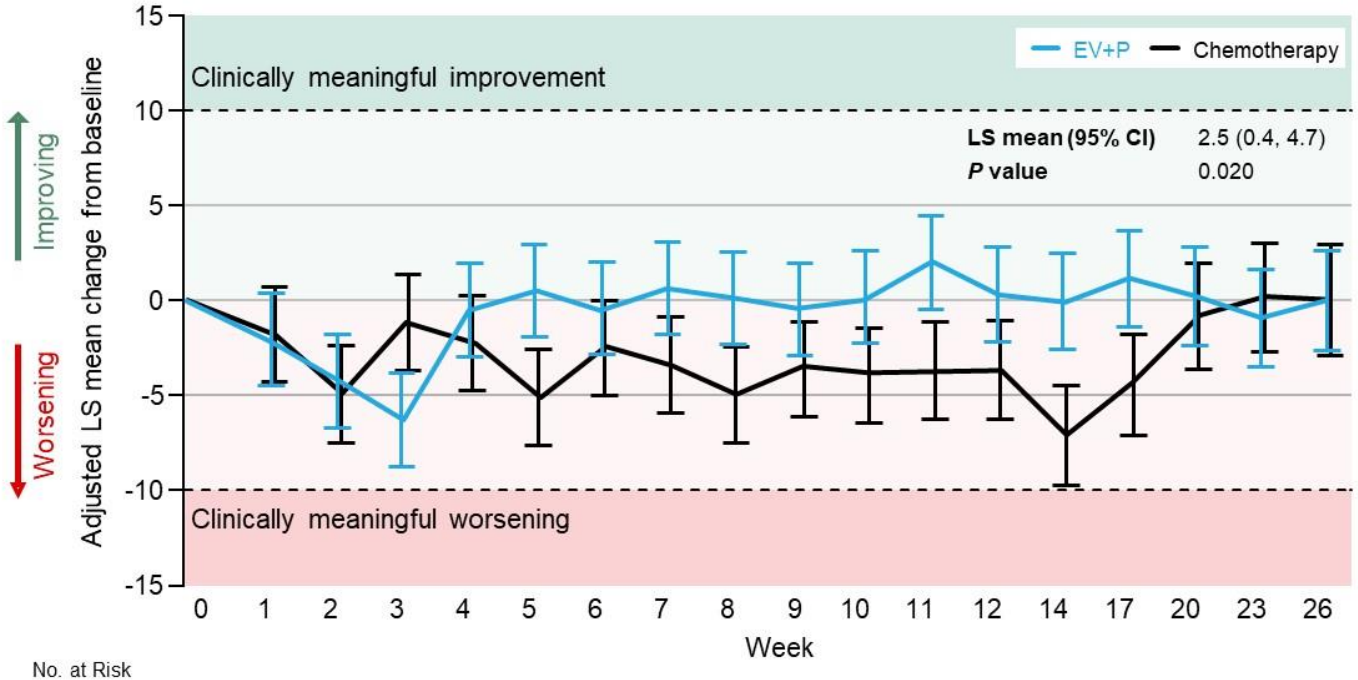
BPI-SF, Brief Pain Inventory-Short Form; CT, chemotherapy; EV+P, enfortumab vedotin plus pembrolizumab; LS, least squares.

PRESENTED BY: Shilpa Gupta, MD

Change in EORTC QLQ-C30 Global Health Status/QoL Score

"How would you rate your overall health during the past week?"
"How would you rate your overall quality of life during the past week?"

- Patients in the EV+P arm had a transient worsening in GHS/QoL score at week 3, followed by a return to baseline at week 4.
- Patients in the CT arm had a worsening from week 1 through week 17; scores returned to baseline from week 20.
- Median time to confirmed deterioration (mTTCD) was 5.9 months with EV+P and 3.2 months with CT, (HR 0.98 [95% CI: 0.79, 1.2]).



No. at Risk

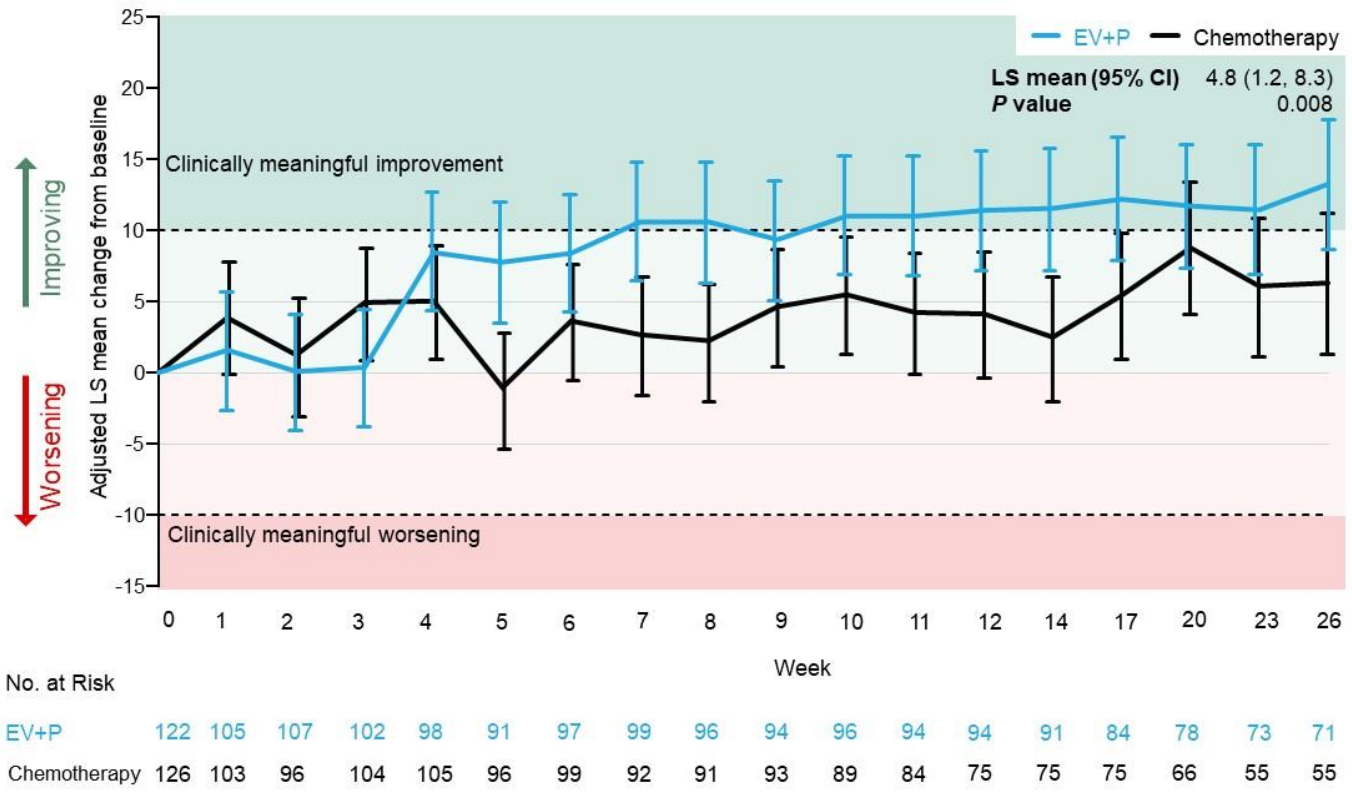
EV+P	365	321	330	311	314	300	300	306	301	307	299	296	296	289	278	261	252	241
Chemotherapy	350	300	288	300	294	296	282	294	279	278	271	260	256	239	240	204	179	172

TTCD was defined as a clinically meaningful decrease (a 10-point decrease in EORTC QLQ-C30 from baseline for two consecutive visits).
CT, chemotherapy; EV+P, enfortumab vedotin plus pembrolizumab; GHS, global health status; HR, hazard ratio; LS, least squares; QoL, quality of life.

Change in EORTC QLQ-C30 GHS/QoL Score in Patients with Moderate/Severe Pain at Baseline

"How would you rate your overall health during the past week?"
"How would you rate your overall quality of life during the past week?"

- Patients in the EV+P arm with moderate to severe pain at baseline showed a clinically meaningful improvement in EORTC QLQ-C30 GHS/QoL.
  - A 10-point change was considered clinically meaningful.[1]

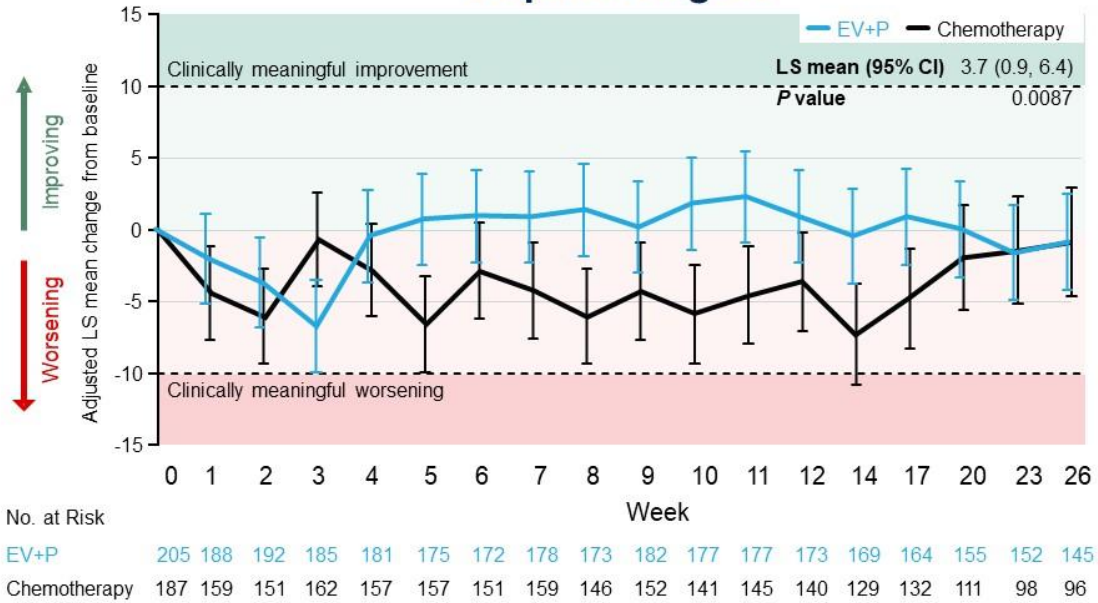


1. Cocks. *Eur J Cancer*. 2012;48:1713-1721.
EV+P, enfortumab vedotin plus pembrolizumab; GHS, global health status; LS, least squares; QoL, quality of life.

Change in EORTC QLQ-C30 Global Health Status/QoL Score by Cisplatin-Eligibility

"How would you rate your overall health during the past week?"
"How would you rate your overall quality of life during the past week?"

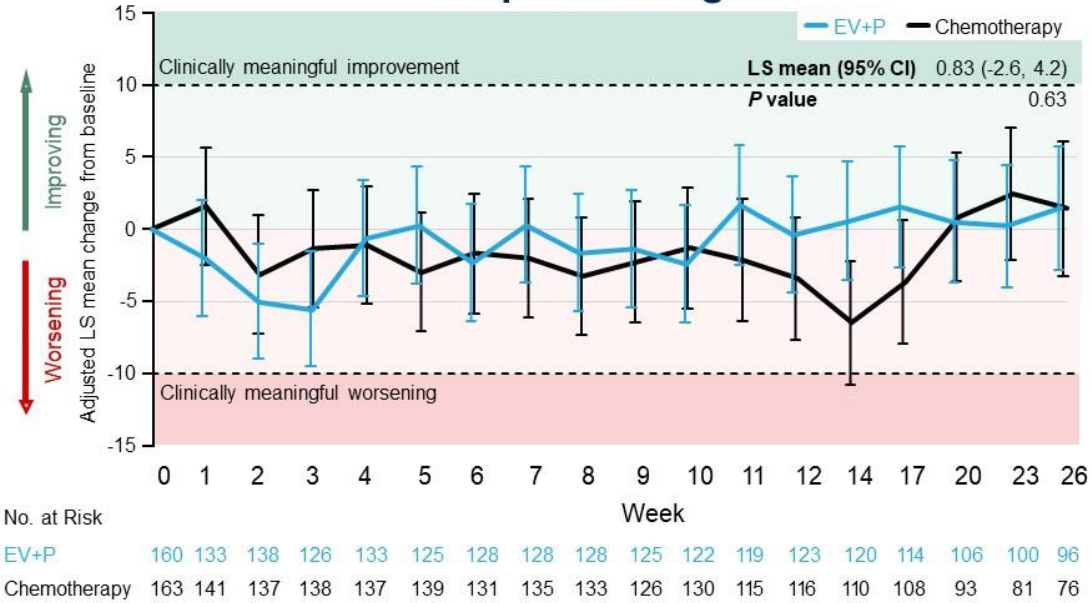
Cisplatin eligible



No. at Risk

EV+P	205	188	192	185	181	175	172	178	173	182	177	177	173	169	164	155	152	145
Chemotherapy	187	159	151	162	157	157	151	159	146	152	141	145	140	129	132	111	98	96

Cisplatin ineligible



No. at Risk

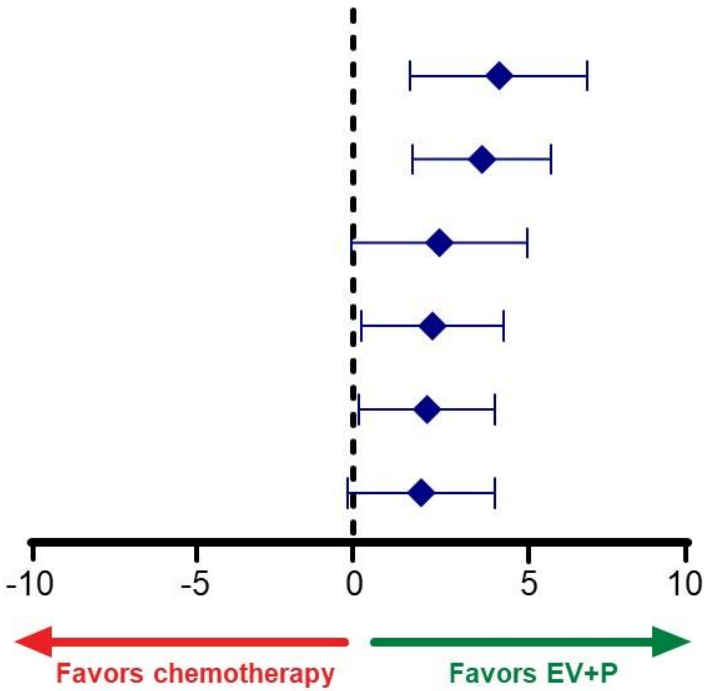
EV+P	160	133	138	126	133	125	128	128	128	125	122	119	123	120	114	106	100	96
Chemotherapy	163	141	137	138	137	139	131	135	133	126	130	115	116	110	108	93	81	76

- Both cisplatin-eligible and cisplatin-ineligible patients in the EV+P arm demonstrated a transient worsening in GHS/QoL through week 3 that returned to baseline by week 4.

EV+P, enfortumab vedotin plus pembrolizumab; GHS, global health status; QoL, quality of life.

Change in EORTC QLQ-C30 Functioning Domains

Functioning domain	EV+P LS mean (SE)	Chemotherapy LS mean (SE)	EV+P – Chemotherapy LS mean (95% CI)	*P* value
Role functioning	-5.36 (1.23)	-9.49 (1.26)	4.13 (1.47, 6.79)	0.0024
Physical functioning	-2.63 (0.96)	-6.25 (0.99)	3.62 (1.54, 5.70)	0.0007
Social functioning	-2.94 (1.22)	-5.52 (1.25)	2.57 (-0.07, 5.22)	0.0561
Global health status/QoL	-0.59 (0.99)	-3.12 (1.01)	2.54 (0.41, 4.67)	0.0197
Cognitive functioning	-0.54 (0.95)	-2.69 (0.97)	2.15 (0.10, 4.20)	0.0400
Emotional functioning	3.85 (0.97)	1.96 (0.98)	1.89 (-0.19, 3.97)	0.0750



- Patients in the EV+P arm demonstrated improved functioning across all functioning domains compared to patients in the CT arm, based on change from baseline during the first 26 weeks.

CT, chemotherapy EV+P, enfortumab vedotin plus pembrolizumab; LS, least squares; SE, standard error.

Conclusions

- Patients treated with EV+P have significantly improved PFS and OS compared with those treated with CT, without detriment to GHS/QoL, pain, or functioning.
- Patients with moderate/severe pain treated with EV+P demonstrated clinically meaningful improvements in worst pain and GHS/QoL.
- Data collection across the entire patient journey was a notable approach and was associated with differences in compliance between treatment arms.
- Findings from this study may inform design of future trials.
- PRO data presented here complement the published clinical efficacy and safety data, add the patient perspective, and support the use of EV+P for patients with la/mUC.

CT, chemotherapy; EV+P, enfortumab vedotin plus pembrolizumab; GHS, global health status; la/mUC, locally advanced or metastatic urothelial carcinoma; OS, overall survival; PFS, progression-free survival; PRO, patient reported outcome; QoL, quality of life.

2024 ASCO ANNUAL MEETING

Trastuzumab deruxtecan in patients with HER2-expressing bladder cancer: outcomes from DESTINY-PanTumor02

Piotr J Wysocki,[1] Kyung Hae Jung,[2] Do-Youn Oh,[3] Deborah Doroshow,[4] Elena Artamonova,[5] Lemonitsa Mammatas,[6] Po-Jung Su,[7] Vladimir Moiseyenko,[8] Konstantin Penkov,[9] Daniil Stroyakovskiy,[10] Jorge Bartolome,[11] Salvatore Siena,[12] Anitra Fielding,[13] Lindsey Jung[13], Flavia Michelini,[14] Soham Puvvada,[15] Vicky Makker[16,17]

[1]Jagiellonian University Medical College Hospital, Kraków, Poland; [2]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [3]Seoul National University Hospital, Seoul, Republic of Korea; [4]Icahn School of Medicine at Mount Sinai, New York, NY, US; [5]NN Blokhin National Medical Research Center of Oncology, Moscow, Russia; [6]Reinier de Graaf Gasthuis, Delft, The Netherlands; [7]Linkou Chang Gung Memorial Hospital, Taoyuan City, Taiwan; [8]Saint Petersburg Clinical Research Center of Specialized Types of Medical Care (Oncology) named after NP Napalkov, Saint Petersburg, Russia; [9]Clinical Hospital "RZHD-Medicine", Saint Petersburg, Russia; [10]Moscow City Oncology Hospital No. 62, Russia; [11]Hospital Clínico San Carlos, Madrid, Spain; [12]Università degli Studi di Milano and Niguarda Cancer Center, Milan, Italy; [13]AstraZeneca, Gaithersburg, MD, US; [14]Translational Medicine, Oncology R&D, AstraZeneca, Waltham, MA, US; [15]Oncology R&D, AstraZeneca, Cambridge, UK; [16]Memorial Sloan Kettering Cancer Center, New York, NY, US; [17]Weill Cornell Medical College, New York, NY, US

PRESENTED BY: Piotr J Wysocki, MD

Introduction

DESTINY-PanTumor02 bladder cohort

- **HER2-directed therapy** is **standard of care** in **HER2-expressing** unresectable or metastatic breast cancer, **HER2-positive** unresectable or metastatic gastric cancers, colorectal and gastroesophageal junction adenocarcinoma, and **HER2-mutant** NSCLC[1–5]
  - **Other HER2-expressing solid tumors** are associated with a **poor prognosis**, with **limited treatment options available** and many patients experiencing **disease progression** on standard therapies[6–9]
- In **DESTINY-PanTumor02**, T-DXd demonstrated **clinically meaningful** ORR, PFS, and OS in **HER2-expressing solid tumors**[10]
- In April 2024, T-DXd was granted accelerated approval in the USA for adult patients with **unresectable or metastatic HER2-positive (IHC 3+) solid tumors** that have **progressed after prior treatment** or have **no alternative treatment options**[11]
- We report further subgroup analyses from the DESTINY-PanTumor02 **bladder cancer cohort**, and characterize patients with an objective response

Bladder cancer: HER2 prevalence[12–16]

IHC 3+
4–31%

IHC 2+
5–52%

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

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PRESENTED BY: Piotr J Wysocki, MD

Methods

DESTINY-PanTumor02 bladder cohort

DESTINY-PanTumor02 is a **Phase 2, open-label, multicenter study** (NCT04482309) evaluating the efficacy and safety of **T-DXd (5.4 mg/kg IV Q3W)** in patients with **previously treated HER2-expressing solid tumors**[1]

Patient population

- **Aged ≥18 years**
- **Histologically confirmed locally advanced, unresectable, solid cancers** (excluding breast, colorectal, gastric, and NSCLC)
- Progression after **≥1 prior systemic treatment** or **without alternative treatment options**
- **Prior HER2-directed therapy allowed**
- **HER2-expressing tumors with IHC 3+/2+** (local or central testing)
  - Patients enrolled based on local HER2 IHC assessment, where available; otherwise, enrollment was based on central testing†
- **ECOG performance status: 0–1**

Endpoints*

Primary:

- Confirmed ORR

Secondary:

- DOR
- DCR
- PFS
- OS
- Safety and tolerability

Exploratory:

- Subgroup analyses by HER2 status and by biomarkers

- **Bladder**
- Endometrial
- Cervical
- Ovarian
- Other tumors‡
- Biliary tract
- Pancreatic

*Confirmed ORR determined by investigator assessment according to RECIST 1.1; DOR defined as time from date of first documented response (complete or partial), until the date of documented progression or death in the absence of disease progression; PFS defined as time from first dose until date of objective disease progression or death due to any cause, regardless of discontinuation of treatment or receipt of another cancer therapy; OS defined as time from date of first dose until death due to any cause; DCR defined as percentage of patients with a best objective response of confirmed complete response or partial response, or with stable disease for at least 11 weeks after first dose; †HER2 IHC status was assessed centrally using HER2 HercepTest (DAKO) and scored according to gastric-specific criteria[2]; ‡patients with tumors that express HER2 (IHC 3+ or 2+), excluding tumors in the tumor-specific cohorts, and breast cancer, NSCLC, gastric cancer, and colorectal cancer. DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours

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Results: patient baseline characteristics

DESTINY-PanTumor02 bladder cohort

41 patients received treatment*

- Median age (range) was **67.0 (43–85) years**
- Median prior regimens (range) was **2 (0–9)**
  - **27 (65.9%)** patients had received **≥2 prior regimens**
  - **28 (68.3%)** patients had received **prior IO therapy**
- **27 (65.9%)** patients had **PD-L1 IC ≥1%**
- **8 (19.5%)** patients had mutations detected in **FGFR1/2/3†‡**
- **6 (14.6%)** patients had mutations detected in **BRCA1/2†**
- Median (range) follow up was **12.65 (0.4–26.8) months**

The local test for enrollment and central test had a positive percentage agreement of **52.2%** for IHC 3+ and **77.8%** for IHC 2+§

HER2 status		Patients, n (%)
By enrollment test	IHC 3+	27 (65.9)
	IHC 2+	14 (34.1)
By central test¶	IHC 3+	16 (39.0)
	IHC 2+	20 (48.8)
	IHC 1+	2 (4.9)
	IHC 0	2 (4.9)
	IHC unknown	1 (2.4)

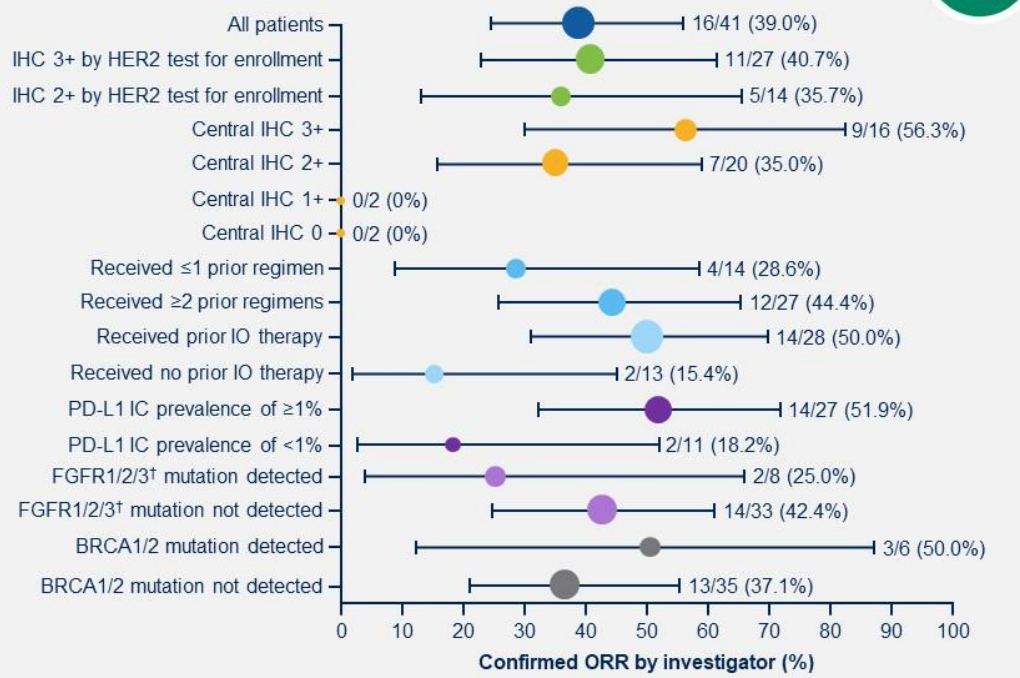
*Median number of treatment cycles (21 days) was 8.0 (range 1–34). Four patients were ongoing treatment at data cutoff (June 8, 2023); reasons for treatment discontinuation included objective disease progression (n=25), adverse event (n=4), subjective disease progression (n=2), other (n=3), patient decision (n=2), and investigator decision (n=1); †evaluated in a central laboratory; as detected by ctDNA; ‡no FGFR4 mutations were detected; §positive percentage agreement was defined as the percentage of samples classified with the same IHC score by both local and central testing; agreement was calculated excluding central IHC unknown samples; ¶patients with a central HER2 IHC status of 0/unknown were enrolled as HER2 IHC 3+/2+ by local testing, as per the eligibility criteria

BRCA1/2, breast cancer gene 1/2; ctDNA, circulating tumor DNA; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor; IC, immune cell; IHC, immunohistochemistry; IO, immuno-oncology; NA, not available; PD-L1, programmed cell death ligand 1

Results: efficacy and safety

DESTINY-PanTumor02 bladder cohort

ORR in all patients and by subgroup*



Secondary efficacy endpoints

- Median (95% CI) **DOR** was **8.7** (4.3, 11.8) **months**
- **DCR at 12 weeks** (95% CI) was **70.7%** (54.5, 83.9)
- Median (95% CI) **PFS** and **OS** were **7.0** (4.2, 9.7) and **12.8** (11.2, 15.1) **months**, respectively

Safety‡

- **Grade ≥3** drug-related TEAEs occurred in **17 (41.5%) patients**§
  - The **most common Grade ≥3** TEAEs (>5%) were **neutropenia** (14.6%), **anemia** (12.2%), and **neutrophil count decreased** (7.3%)¶
  - Drug-related TEAEs associated with **death** occurred in **1 (2.4%) patient**
- Adjudicated drug-related **ILD/pneumonitis** occurred in **4 (9.8%) patients** (Grade 1: n=1; Grade 2: n=3)

*Response determined by investigator assessment according to RECIST 1.1; †no FGFR4 mutations were detected. Patients with a central HER2 IHC status of 1+/0/unknown were enrolled as HER2 IHC 3+/2+ by local testing. Circle sizes are proportional to the number of patients in each subgroup. Prior therapy and biomarker subgroup analyses do not account for HER2 IHC status. Error bars show 95% CI; ‡median total treatment duration was 6.21 months (range 0.4–24.7); §drug-related TEAEs associated with death occurred in one patient (1.2%); ¶neutropenia and neutrophil count decrease are listed as separate terms owing to how these events were reported (adverse event or laboratory abnormality)
BRCA1/2, breast cancer susceptibility gene 1/2; CI, confidence interval; DCR, disease control rate; DOR, duration of response; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; IC, immune cell; IHC, immunohistochemistry; ILD, interstitial lung disease; IO, immuno-oncology; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumours; TEAE, treatment-emergent adverse events

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Conclusions

DESTINY-PanTumor02 bladder cohort

T-DXd demonstrated clinically meaningful benefit in heavily pretreated patients with HER2-expressing bladder tumors in DESTINY-PanTumor02

- 16/41 (39.0%) patients had a confirmed objective response by investigator
- The greatest response was seen in patients with IHC 3+ tumors (central testing)
- Durable responses were observed, with a median DOR of 8.7 months in all patients

The safety findings were consistent with the established profile for T-DXd

- Grade ≥3 drug-related TEAEs were observed in 17 (41.5%) patients
- ILD/pneumonitis remains an important identified risk; proactive monitoring, early detection, and active management are critical in preventing high-grade ILD / pneumonitis

These data support T-DXd as a recommended treatment option for pretreated patients with HER2 IHC 3+ expressing bladder cancer, and as a potential treatment option in patients with HER2 IHC 2+ expression

DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse events

2024 ASCO ANNUAL MEETING

CONQUER CANCER® THE ASCO FOUNDATION MERIT AWARD

A multi-institution analysis of outcomes with first-line systemic therapy for 102 patients with metastatic chromophobe renal cell carcinoma

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Background

- Chromophobe renal cell carcinoma (ChRCC) represents 5-10% of all renal cell carcinomas
- Given relative rarity of disease, there is limited clinical trial data to guide systemic therapy for metastatic disease

Select Trials of First-Line Systemic therapy for Patients with ChRCC

Study	Treatment	Patient number	Objective Response Rate
Monotherapy: Targeted Agents (TKI or mTORi)			
ASPEN[1]	Everolimus vs Sunitinib	16 – 10 Sunitinib, 6 Everolimus	10% Sunitinib 33% Everolimus
ESPN[2]	Everolimus vs Sunitinib	12 – 6 Sunitinib, 6 Everolimus	33% Sunitinib 17% Everolimus
Doublet Therapy: Two Targeted Agents (VEGFi/TKI + mTORi)			
Voss et al[3]	Bevacizumab + Everolimus	5	40%
Hutson et al[4]	Lenvatinib + Everolimus	9	44%
Doublet Therapy: Targeted Agent + Immunotherapy (TKI + IO)			
Lee et al[5]	Cabozantinib + Nivolumab	7	0%
KEYNOTE-B61[6]	Lenvatinib + Pembrolizumab	29	35%
Immunotherapy Alone (IO or IO + IO)			
KEYNOTE-427[7]	Pembrolizumab	21	10%
CheckMate 920[8]	Ipilimumab + Nivolumab	7	0%

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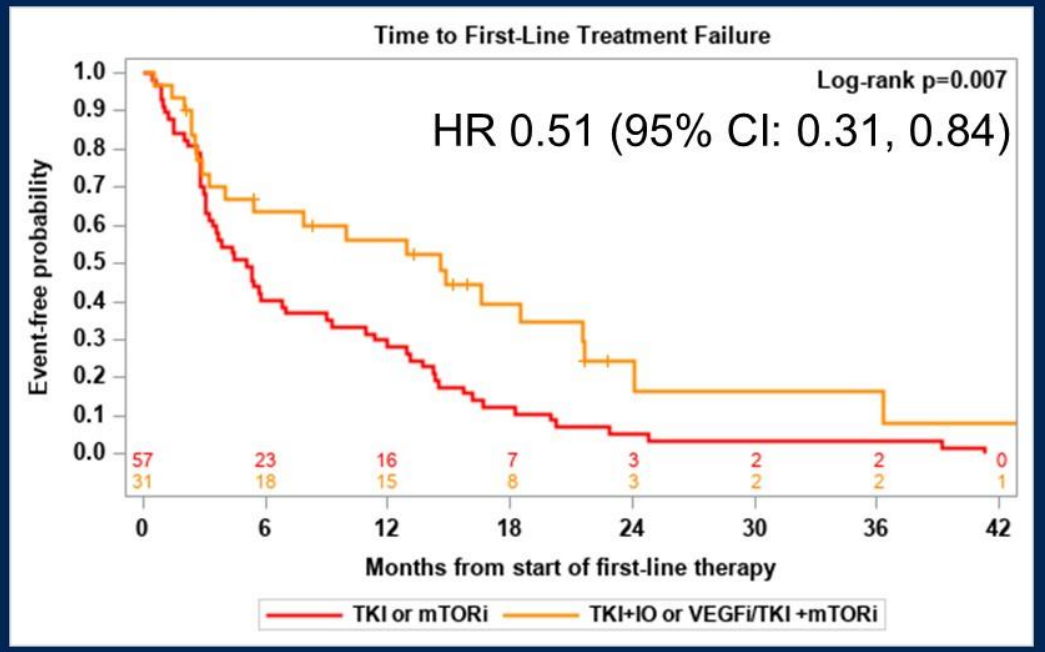
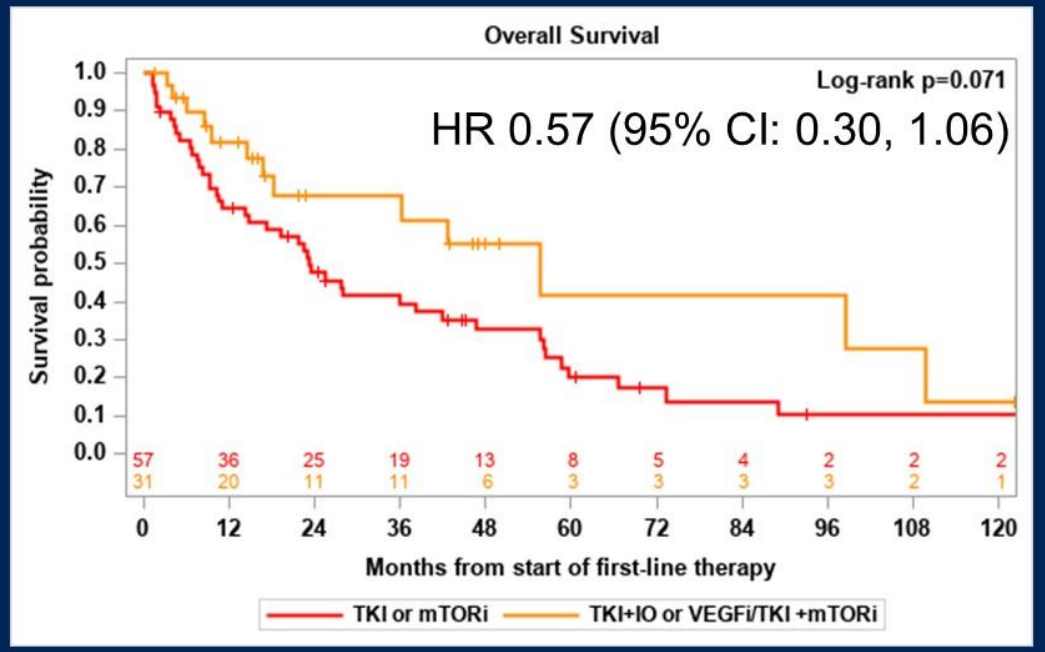
Targeted monotherapy vs doublets containing targeted therapies





	N	Median TTF, months (95% CI)	OS events	Median OS, months (95% CI)	12-month OS rate (95% CI)	Months follow-up for survivors – median (range)
TKI or mTORi Monotherapy	57	5 (3, 7)	44	23 (14, 42)	64% (50, 75)	45 (2, 156)
TKI + IO or VEGFi/TKI + mTORi Doublets	31	15 (4, 22)	13	56 (18, 110)	82% (62, 92)	16 (1, 122)

Key Takeaways

- Metastatic chromophobe renal cell carcinoma has limited prospective evidence for optimal systemic therapy selection
- Our retrospective analysis demonstrates improved clinical outcomes with doublet therapies as compared to single-agent regimens

Future Directions

- We are expanding our efforts and collaborating with additional cancer centers to increase our patient cohort and make comparisons with more contemporary regimens