Highlights for clinical practice
Prostate cancer

ESMO Congress

Madrid, Spain

20-24 Oct 2023

Mirrors of medicine

ISSECAM
FORUM GU Oncology

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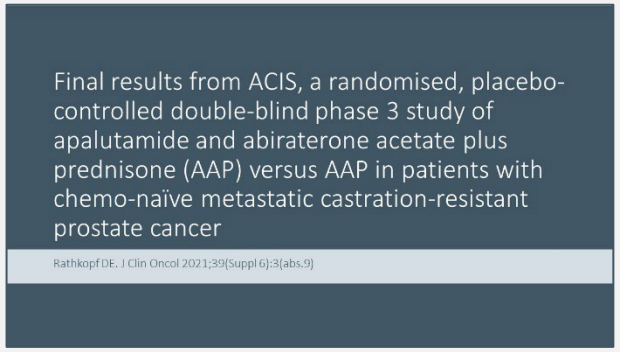
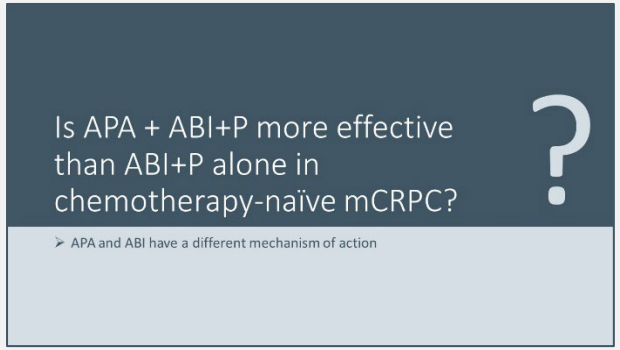
Structure of slide deck

First slide (hidden)



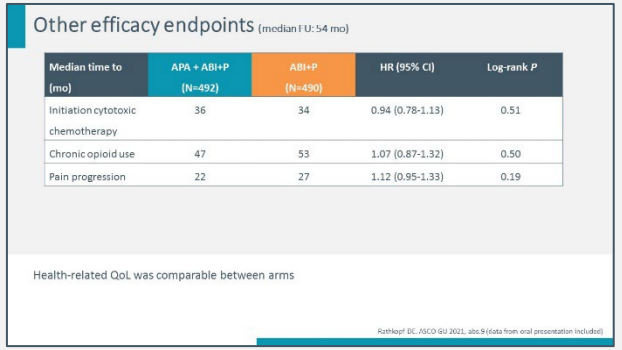
Topic (often title of the abstract) + reference
Note pages contain abstract

Second slide



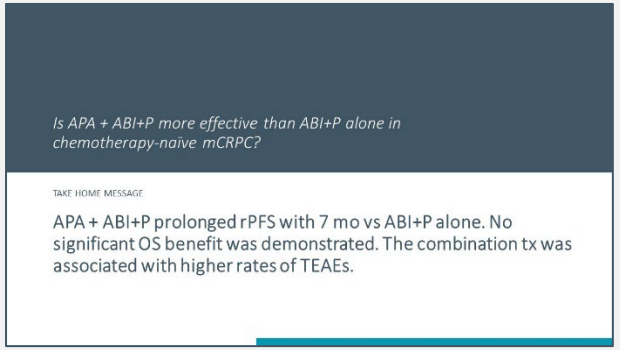
Clinical question whereon selection is based + background of the question

Following slide(s)



Description of abstract: study design + efficacy + safety data

Final slide



Repetition of clinical question + answer (take home message)

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Glossary PCa (A-N)

ABI	abiraterone
ADT	androgen deprivation therapy
AE	adverse event
ALP	alkaline phosphatase
APA	apalutamide
aRT	adjuvant radiotherapy
ARTA	androgen receptor targeted agent
BCR	biochemical recurrence
BICR	blinded independent central review
BITE	bispecific T-cell engager
BM	biomarker
BPI-SF	Brief Pain Inventory – Short Form
bPFS	biochemical progression-free survival
CABA	cabazitaxel
CAPRA-S	Cancer of the Prostate Risk Assessment post-surgical
CART	chimeric antigen receptor T-cell
chemotx	Chemotherapy
CI	confidence interval
CPS	combined positive score
CR	complete response
CRPC	castration-resistant prostate cancer
CT	computed tomography
DARO	darolutamide
DCR	disease control rate
DOC	docetaxel
DOR	duration of response
EAU	European Association of Urology
ECOG PS	Eastern Cooperative Oncology Group performance status
ENZA	enzalutamide
ESMO	European Society of Medical Oncology
EQ-5D-5L	European Quality of Life 5-Dimensions - Levels
FACT-P	Functional Assessment of Cancer Therapy - Prostate
fr	fractions
FU	follow-up
GS	Gleason score
Hb	haemoglobin
HR	hazard ratio
HRR	homologous recombination repair
HRQoL	health-related quality of life
HSPC	hormone-sensitive prostate cancer
ICS	International Continence Society
im	intramuscular
iv	intravenously
LDH	lactate dehydrogenase
LN	lymph node
Lu-PSMA	lutetium prostate-specific membrane antigen
mets	metastases
MFS	metastasis-free survival
mCRPC	metastatic castration-resistant prostate cancer
mHSPC	metastatic hormone-sensitive prostate cancer
MRI	magnetic resonance imaging
NIRA	niraparib
nmCRPC	non-metastatic castration-resistant prostate cancer
NR	not reached

Glossary PCa (O-Z)

ORR	objective/overall response rate
OS	overall survival
P	Prednisone
PARPi	poly ADP ribose polymerase inhibitor
PBO	placebo
PCa	prostate cancer
PCWG	Prostate Cancer Working Group
PD-(L)1	programmed death (ligand) 1
PEMBRO	pembrolizumab
PET	positron emission tomography
PFS	progression-free survival
po	orally
PR	partial response
PRO	patient-reported outcome
PSA	prostate-specific antigen
PSA-DT	prostate-specific antigen doubling time
PSMA	prostate-specific membrane antigen
QLQ-PR25	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
qxw	every x weeks
qd	every day
R	randomised
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RP	radical prostatectomy
rPFS	radiographic progression-free survival
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group
sdHR	subdistribution hazard ratio
SOC	standard of care
SRE	skeletal-related event
sRT	salvage radiotherapy
SSE	symptomatic skeletal event
STEAP1	six-transmembrane epithelial antigen of the prostate 1
SUVmax	maximum standardised uptake value
T	testosterone
TCE	T-cell engager
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
TTCD	time to confirmed clinically meaningful deterioration
TTFD	time to first clinically meaningful deterioration
tx	treatment
ULN	upper limit normal
UUTO	upper urinary tract obstruction
VAS	Visual Analogue Scale
WBC	white blood cells
ZA	zoledronic acid

Overview

- Primary treatment of non-metastatic PCa
- Management of recurrent PCa
- Management of metastatic hormone-sensitive prostate cancer (mHSPC)
- Management of castration-resistant prostate cancer (CRPC)

Primary treatment of non-metastatic PCa

What is the optimal timing of RT following RP?

- Initial results of the RADICALS-RT trial did not show a difference in bPFS between adjuvant RT (aRT) and salvage RT (sRT), in men with ≥1 risk factor for biochemical progression after RP, but aRT was associated with a higher risk of urinary morbidity
- A meta-analysis (ARTISTIC) suggested that aRT vs early sRT does not improve event-free survival in men with localised or locally advanced PCa

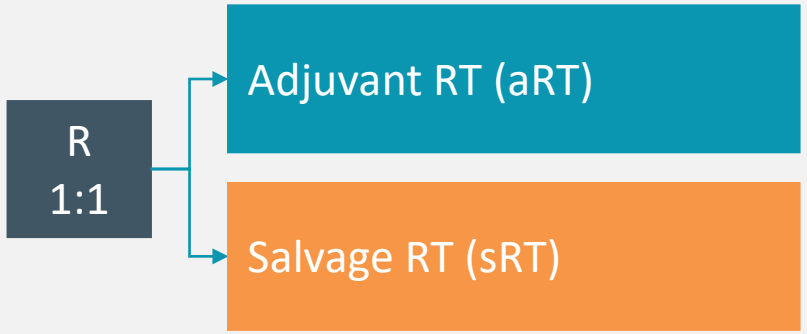
RADICALS-RT: international, multi-centre, phase III trial

(Nov 2007-Dec 2016)

Population

- Postoperative PSA ≤0.2 ng/ml
- 4-22 wk post RP
- ≥1 risk factor:
  - pT3-4
  - GS 7-10
  - Preoperative PSA ≥10 ng/ml
  - Positive margins

Design



Threshold for sRT (RT for PSA failure):
1 of:

- 2 consecutive rises & PSA >0.1 ng/ml
- 3 consecutive rises

Endpoints

Primary

- Freedom from distant metastases

Secondary

- OS
- Safety
- PROs

93% of pts treated with aRT started RT within 5 mo after RP

Current analysis: long-term FU (median FU: 8 yr)

Clarke N. ESMO 2023, abs.1764O (data from oral presentation included)

Baseline characteristics

Characteristic	aRT (N=697)	sRT (N=699)
Median age (yr)	65	65
Median PSA at diagnosis (ng/ml)	7.8	8.0
GS (%)		
<7	7	7
7 (3+4)	50	48
7 (4+3)	27	27
>7	16	17
pT stage (%)		
pT2 / pT3 / pT4	23 / 76 / 1	25 / 74 / 1
Positive surgical margins (%)	63	63
Seminal vesicle invasion (%)	19	20
CAPRA-S score (%)		
Low	8	8
Intermediate	55	55
High	37	37

Clarke N. ESMO 2023, abs.1764O (data from oral presentation included)

Efficacy (median FU: 8 yr)

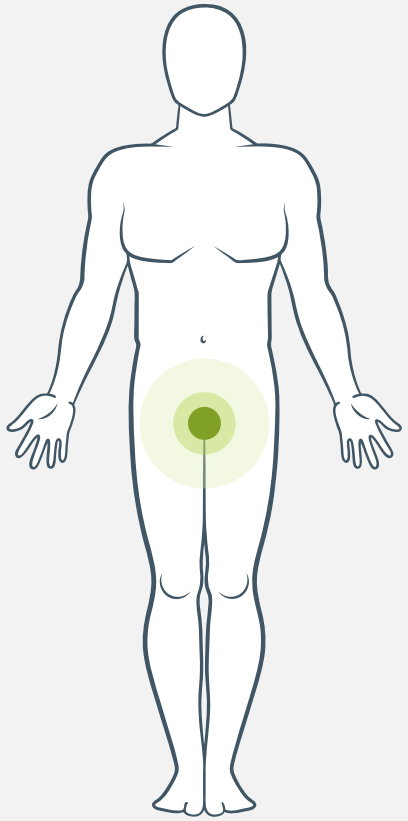
	10-year outcomes (%)		HR (95% CI)	*P*
	aRT (N=697)	sRT (N=699)		
Freedom from distant metastases	93	90	0.68 (0.43-1.07)	0.095
OS	88	87	0.98 (0.67-1.44)	0.92
Time to non-protocol hormonal tx	-	-	0.83 (0.59-1.18)	0.30
bPFS*	-	-	0.95 (0.75-1.22)	0.71

*first of: PSA ≥0.4 ng/ml following RT, PSA >2.0 ng/ml at any time, clinical progression, initiation non-protocol hormonal tx, death from PCa

39% of sRT arm started RT
Median PSA at start sRT: 0.2 ng/ml

Clarke N. ESMO 2023, abs.1764O (data from oral presentation included)

Urinary toxicity (RTOG scale)



Within 2 years

Grade ≥3 (%)	aRT	sRT
Cystitis	2	0.9
Haematuria	4	0.8
Urethral stricture	7	5

After 2 years

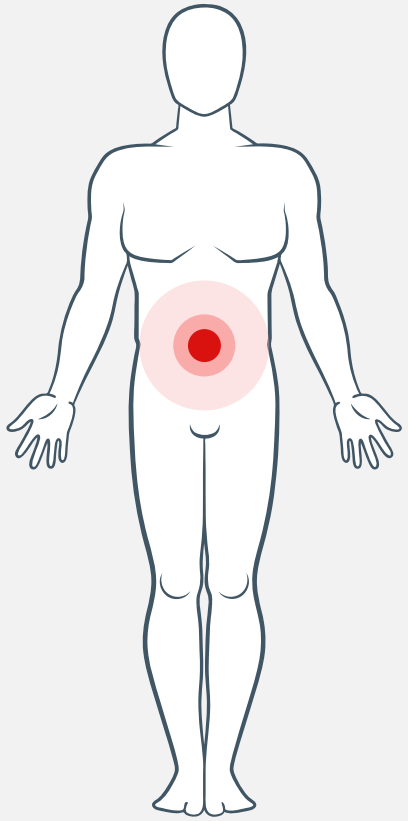
Grade ≥3 (%)	aRT	sRT
Cystitis	1	1
Haematuria	5	0.7
Urethral stricture	5	3

PROs (ICS urinary incontinence score):

- Significant difference at 1 year between both groups (*P*=0.001), in favour of sRT
- No significant differences at 5 and 10 yr

Clarke N. ESMO 2023, abs.1764O (data from oral presentation included)

Gastrointestinal toxicity (RTOG scale)



Within 2 years

Grade ≥3 (%)	aRT	sRT
Diarrhoea	2	0.6
Proctitis	1	0.4

After 2 years

Grade ≥3 (%)	aRT	sRT
Diarrhoea	0.9	0.3
Proctitis	1	0.3

PROs (Vaizey faecal incontinence score):

- Significant difference at 1 year between both groups ($P<0.001$), in favour of sRT
- No significant differences at 5 and 10 yr

Clarke N. ESMO 2023, abs.1764O (data from oral presentation included)

What is the optimal timing of RT following RP?

TAKE HOME MESSAGE

This study supports the use of early sRT for PSA failure after RP vs aRT. Early sRT might spare the majority of pts from having RT and morbidity associated with aRT, while being as effective.

Management of recurrent PCa

Is ENZA±ADT effective in pts with high-risk BCR?

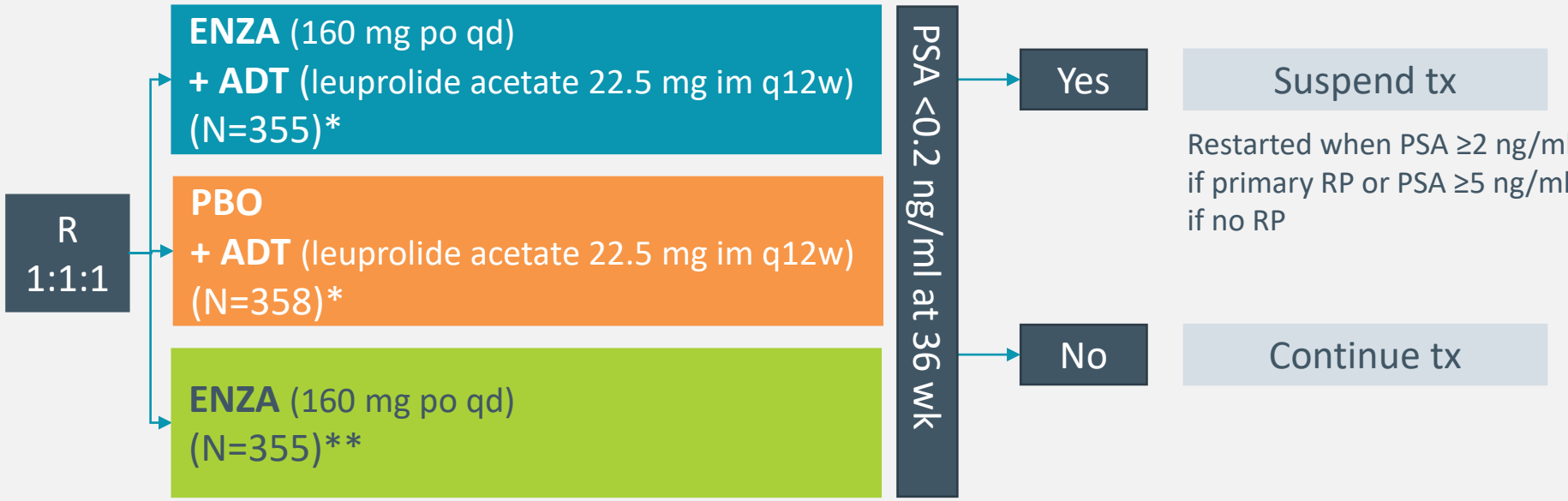
- The primary analysis of the EMBARK trial, at a median FU of 61 mo, showed a clinically meaningful improvement in MFS with ENZA+ADT vs PBO+ADT

EMBARK: international phase III trial (Jan 2015-Aug 2018)

Population

- PSA ≥1 ng/ml after RP or PSA ≥2 ng/ml above the nadir after RT
- PSA-DT ≤9 mo
- T ≥150 ng/dl
- ECOG PS 0 or 1
- M0 on conventional imaging (CT, MRI, or bone scan)

Design



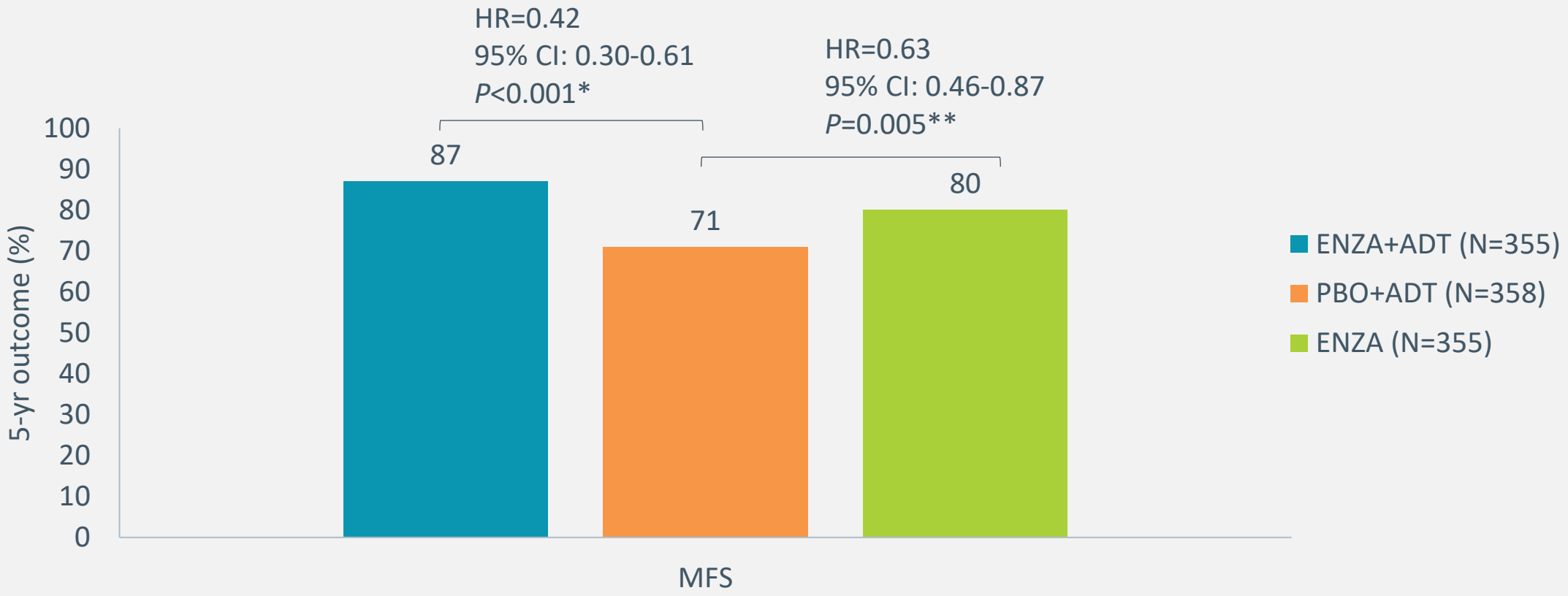
*blinded, **open-label

Primary endpoint: MFS

Secondary endpoint (current analysis): distant mets, symptomatic progression, 1st symptomatic skeletal event, resumption of any hormonal tx following tx suspension, castration resistance

De Giorgi U. ESMO 2023, abs.1777P (data from poster included); Freedland SJ. ESMO 2023, abs.1778P (data from poster included)

Metastasis-free survival (median FU: 61 mo)



*primary endpoint

**key secondary endpoint

Freedland SJ et al. N Engl J Med 2023;389:1453-65

Secondary endpoints: ENZA+ADT vs PBO+ADT

Median time to (mo)	ENZA+ADT (N=355)	PBO+ADT (N=358)	HR (95% CI)	Nominal *P*
Distant metastases	NR	NR	0.44 (0.28-0.69)	0.0002
Symptomatic progression	NR	64	0.55 (0.43-0.70)	<0.0001
Castrate resistance	NR	NR	0.09 (0.05-0.16)	<0.0001
Resumption of any hormonal tx after tx suspension*	20	17	0.69 (0.58-0.83)	<0.0001

*N=321 for ENZA+ADT and N=240 for PBO+ADT
NR: not reached; HR <1 favours ENZA+ADT

Median tx duration excluding tx suspension: 32 mo vs 35 mo

Freedland SJ. ESMO 2023, abs.1778P (data from poster included)

Secondary endpoints: ENZA vs PBO+ADT

Median time to (mo)	ENZA (N=355)	PBO+ADT (N=358)	HR (95% CI)	Nominal *P*
Distant metastases	NR	NR	0.61 (0.41-0.92)	0.017
Symptomatic progression	NR	64	0.62 (0.49-0.79)	<0.0001
Symptomatic skeletal event	NR	NR	0.42 (0.23-0.79)	0.006
Resumption of any hormonal tx after tx suspension*	11	17	1.66 (1.38-1.98)	<0.0001

*N=304 for ENZA and N=240 for PBO+ADT
NR: not reached; HR <1 favours ENZA

Median tx duration excluding tx suspension: 46 mo vs 35 mo

De Giorgi U. ESMO 2023, abs.1777P (data from poster included)

Is ENZA±ADT effective in pts with high-risk BCR?

TAKE HOME MESSAGE

Both ENZA+ADT and ENZA alone could be potential tx options for pts with high-risk BCR.

What's the impact of ENZA±ADT on HRQoL in non-metastatic HSPC pts with high-risk BCR following local tx?

- In the phase III EMBARK trial, metastasis-free survival was prolonged in pts with high-risk biochemically recurrent PCa treated with ENZA+ADT or ENZA alone vs ADT alone

EMBARK: international phase III trial (Jan 2015-Aug 2018)

Population

- PSA ≥1 ng/ml after RP or PSA ≥2 ng/ml above the nadir after RT
- PSA-DT ≤9 mo
- T ≥150 ng/dl
- ECOG PS 0 or 1
- M0 on conventional imaging (CT, MRI, or bone scan)

Design

R 1:1:1

- **ENZA** (160 mg po qd) **+ ADT** (leuprolide acetate 22.5 mg im q12w) (N=355)*
- **PBO** **+ ADT** (leuprolide acetate 22.5 mg im q12w) (N=358)*
- **ENZA** (160 mg po qd) (N=355)**

*blinded, **open-label

PSA <0.2 ng/ml at 36 wk

Wk 37

- Yes → Suspend tx
  - Restarted when PSA ≥2 ng/ml if primary RP or PSA ≥5 ng/ml if no RP
- No → Continue tx

Primary endpoint: MFS between ENZA+ADT vs PBO+ADT

Secondary endpoint (current analysis): PRO analysis (main objective BPI-SF item 3 & FACT-P total score)

Freedland SJ. ESMO 2023, abs.1766MO (data from oral presentation included)

Definitions

Time to first clinically meaningful deterioration (TTFD)

Duration of time from the date of randomisation to the date of the first clinically meaningful deterioration in PRO scores of at least one threshold unit vs the baseline score

Time to confirmed clinically meaningful deterioration (TTCD)

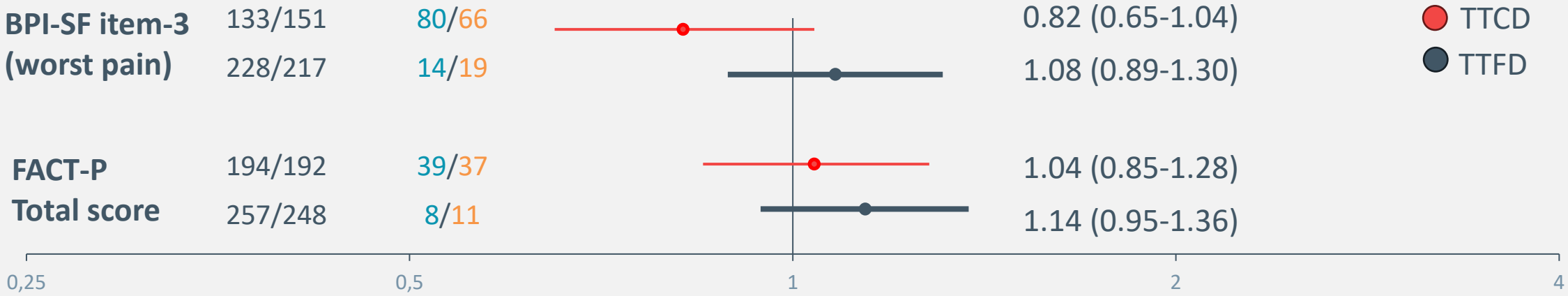
Duration of time from the date of randomisation to the date of the first clinically meaningful deterioration in PRO scores of at least one threshold unit vs the baseline score, which is confirmed at the next consecutive scheduled visit or followed by drop-out, resulting in monotone missing data

Freedland SJ. ESMO 2023, abs.1766MO (data from oral presentation included)

No differences in time to first (TTFD) and confirmed (TTCD) clinically meaningful deterioration in FACT-P total score and BPI-SF item 3

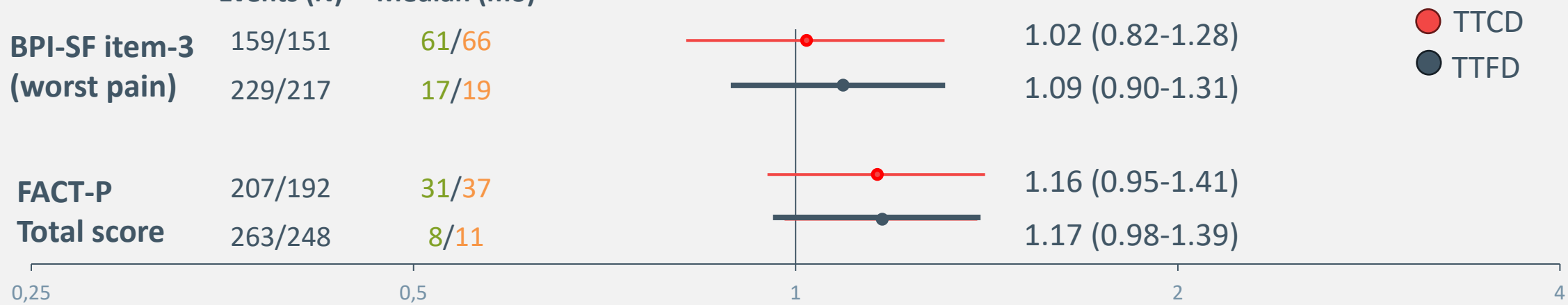
ENZA+ADT vs PBO+ADT **HR <1 favours ENZA+ADT**

	Events (N)	Median (mo)	HR (95% CI)
BPI-SF item-3 (worst pain)	133/151	80/66	0.82 (0.65-1.04)
	228/217	14/19	1.08 (0.89-1.30)
FACT-P Total score	194/192	39/37	1.04 (0.85-1.28)
	257/248	8/11	1.14 (0.95-1.36)



ENZA vs PBO+ADT **HR <1 favours ENZA**

	Events (N)	Median (mo)	HR (95% CI)
BPI-SF item-3 (worst pain)	159/151	61/66	1.02 (0.82-1.28)
	229/217	17/19	1.09 (0.90-1.31)
FACT-P Total score	207/192	31/37	1.16 (0.95-1.41)
	263/248	8/11	1.17 (0.98-1.39)



Freedland SJ. ESMO 2023, abs.1766MO (data from oral presentation included)

Outcomes in FACT-P subdomains (N=9) (time to confirmed clinically meaningful deterioration - TTCD)

Median TTCD in **PCa subscale score** significantly shorter for ENZA alone vs PBO+ADT

	Median (mo)	HR (95% CI)
ENZA vs PBO+ADT	14 vs 19	1.21 (1.01-1.45)

Median TTCD in **advanced prostate symptom score** significantly shorter for ENZA alone vs PBO+ADT

	Median (mo)	HR (95% CI)
ENZA vs PBO+ADT	36 vs 63	1.34 (1.09-1.66)

Median TTCD in **physical well-being** significantly shorter for ENZA+ADT and ENZA alone vs PBO+ADT

	Median (mo)	HR (95% CI)
ENZA+ADT vs PBO+ADT	25 vs 50	1.41 (1.15-1.72)
ENZA vs PBO+ADT	28 vs 50	1.35 (1.11-1.65)

No significant differences between groups in TTCD (or TTFD) for other FACT-P subdomains

HR <1 favours ENZA+ADT or ENZA alone

Freedland SJ. ESMO 2023, abs.1766MO (data from oral presentation included)

Outcomes in QLQ-PR25 & EQ-5D-5L (time to confirmed clinically meaningful deterioration - TTCD)

Median TTCD in **sexual activity score** significantly longer with ENZA alone vs PBO+ADT

	Median (mo)	HR (95% CI)
ENZA vs PBO+ADT	6 vs 3	0.76 (0.62-0.94)

Median TTCD in **hormonal treatment-related symptoms** significantly shorter with ENZA+ADT vs PBO+ADT

	Median (mo)	HR (95% CI)
ENZA+ADT vs PBO+ADT	2.86 vs 2.89	1.19 (1.01-1.40)

No significant differences were observed in TTCD in the EQ-5D-5L VAS score in any treatment arm

HR <1 favours ENZA+ADT or ENZA alone

Freedland SJ. ESMO 2023, abs.1766MO (data from oral presentation included)

What's the impact of ENZA±ADT on HRQoL in non-metastatic HSPC pts with high-risk BCR following local tx?

TAKE HOME MESSAGE

No significant differences were seen in clinically meaningful deterioration in the FACT-P total score and BPI-SF item 3 (worst pain in the past 24h) between ENZA+ADT, ENZA alone and PBO+ADT.

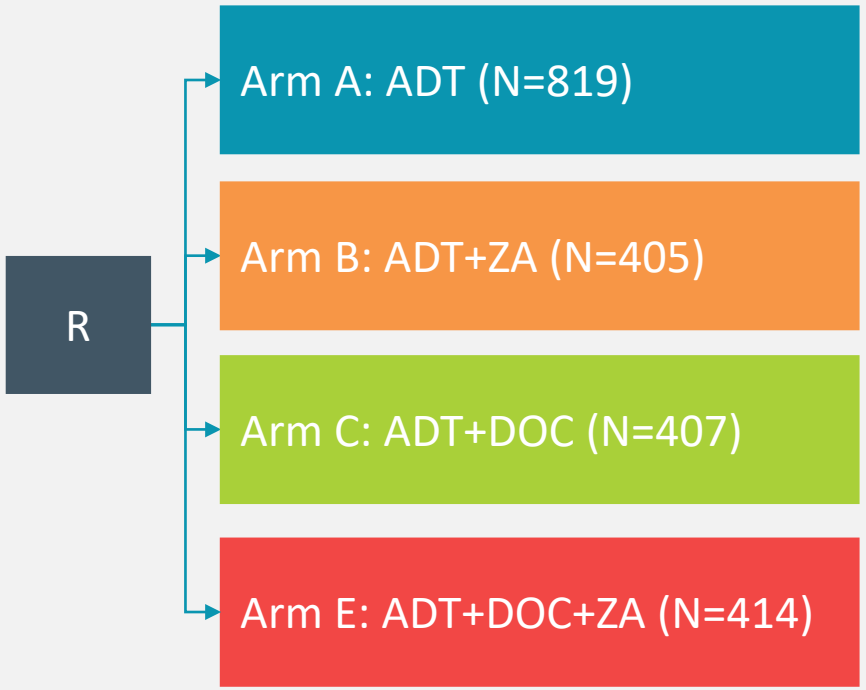
Management of metastatic hormone-sensitive prostate cancer (mHSPC)

What is the incidence of fracture-related hospitalisation in men on ADT and has adding zoledronic acid (ZA) or DOC an impact on fracture risk?

- ADT is the mainstay medical tx for men with advanced PCa
- ADT-related complications include bone loss and risk of fracture
- The EAU guidelines strongly recommend assessing bone mineral density in men starting long-term ADT, and to offer anti-resorptive therapy if needed

Analysis of pts included in STAMPEDE trial arm ABCE

Population	Design	Objectives

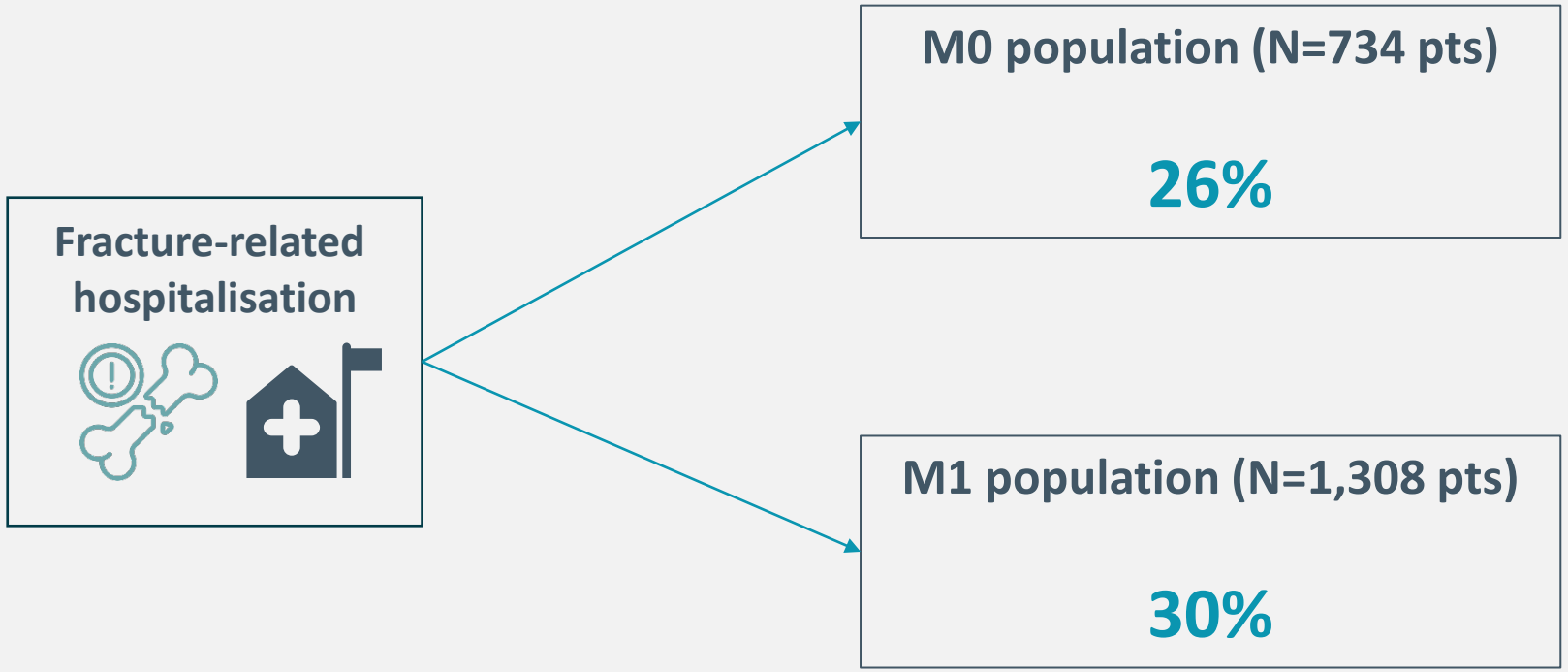
• M1
or
• M0 N+
or
• M0 with ≥2 of:
  • T3-4
  • GS 8-10
  • PSA ≥40 ng/ml
		• Quantify fracture incidence in these men using routinely collected healthcare data through Hospital Episode Statistics
		
		• Evaluate impact of adding ZA or DOC on fracture risk

Pts included in this analysis: de novo disease, UK-based, data linked to Hospital Episode Statistics

→ analysis cohort: N=2,042 pts

Jones C. ESMO 2023, abs.1768MO (data from oral presentation included)

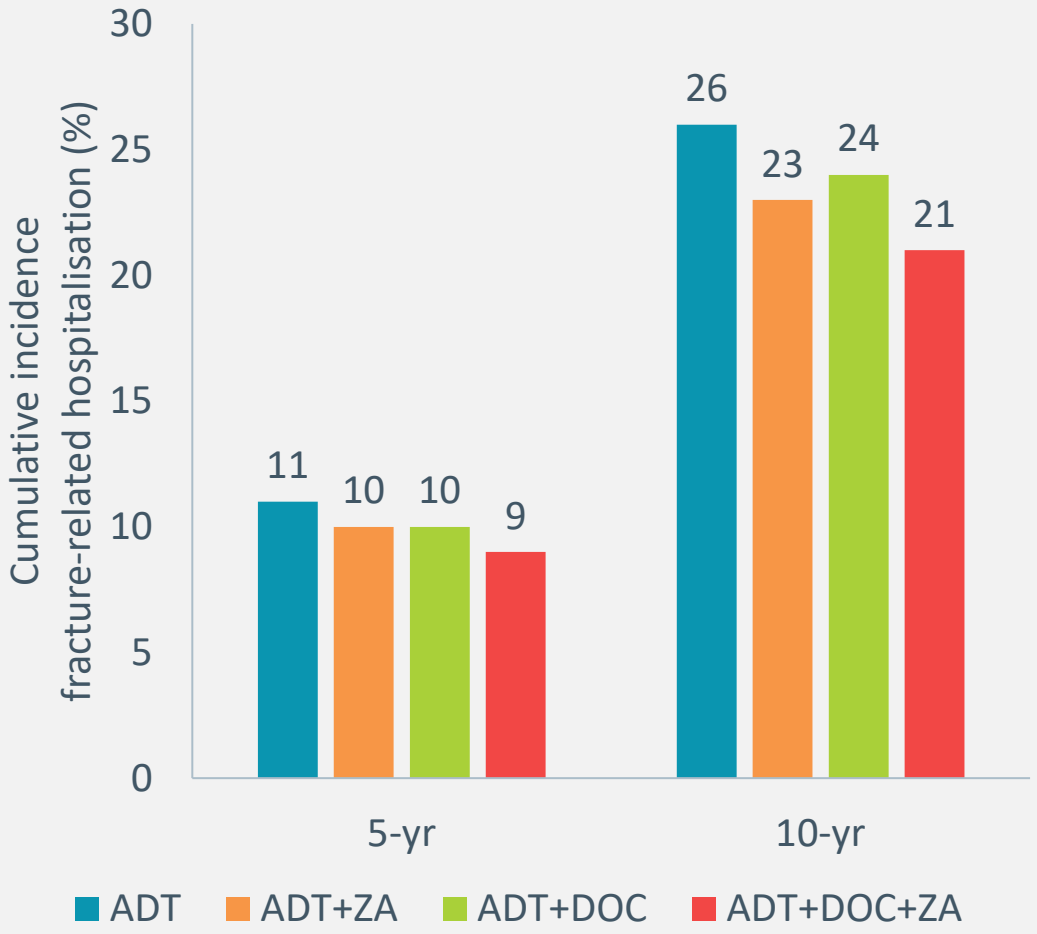
Pts with at least 1 fracture-related hospitalisation



Jones C. ESMO 2023, abs.1768MO (data from oral presentation included)

Fracture-related hospitalisations in M0 population

Cumulative incidence



Effect of treatment

Treatment	sdHR	95% CI
DOC	0.89	0.61-1.29
ZA	0.88	0.59-1.32

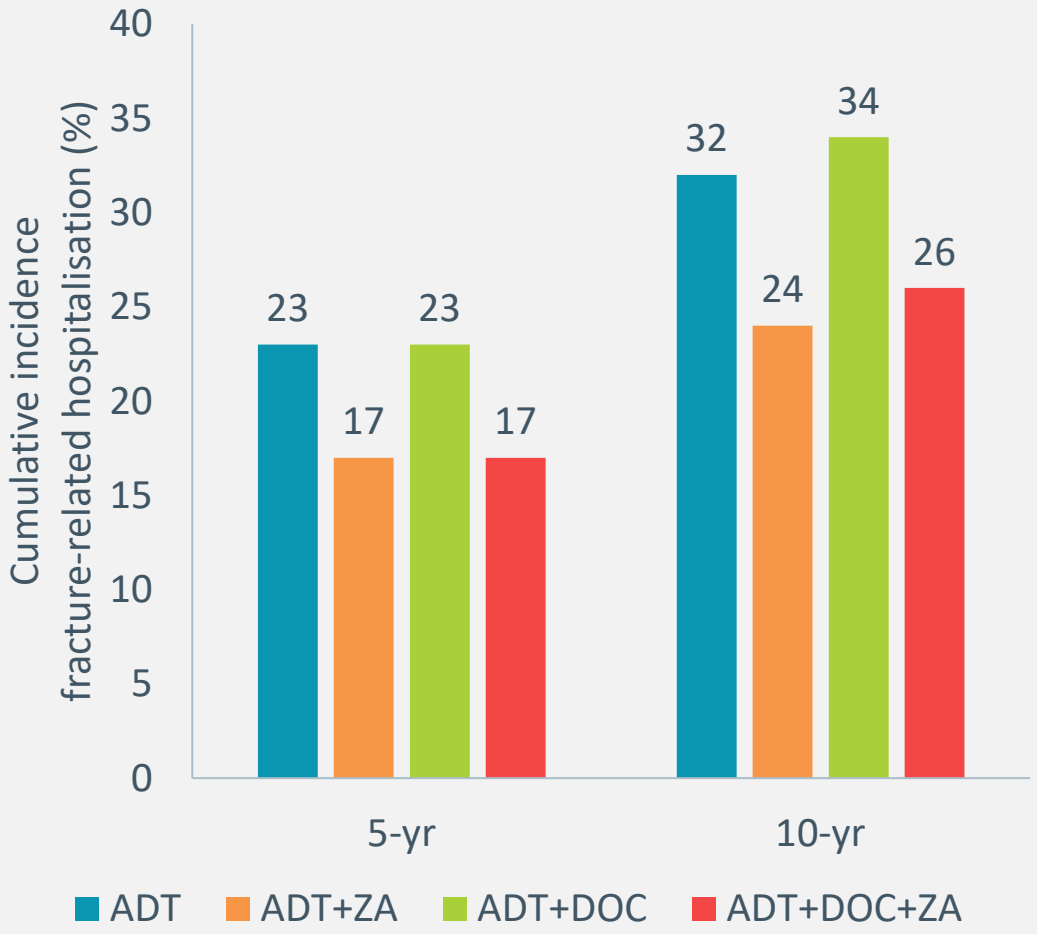
sdHR: subdistribution hazard ratio

No evidence that ZA or DOC alter the risk of fracture

Jones C. ESMO 2023, abs.1768MO (data from oral presentation included)

Fracture-related hospitalisations in M1 population

Cumulative incidence



Effect of treatment

Treatment	sdHR	95% CI
DOC	1.07	0.82-1.38
ZA	0.73	0.55-0.97

sdHR: subdistribution hazard ratio

ZA significantly reduced the risk of fracture (*P*=0.015)

No evidence that DOC alters the risk of fracture

Jones C. ESMO 2023, abs.1768MO (data from oral presentation included)

What is the incidence of fracture-related hospitalisation in men on ADT and has adding zoledronic acid (ZA) or DOC an impact on fracture risk?

TAKE HOME MESSAGE

The 5-yr cumulative incidence of fracture-related hospitalisations is 11% in M0 and 23% in M1 pts treated with ADT.

Zoledronic acid reduces the risk of fracture-related hospitalisations in M1 pts.

Does prostate RT for synchronous mHSPC reduce the use of upper urinary tract obstruction (UUTO) interventions?

- Men with advanced PCa are at risk of UUTO due to local progression
- Prostate RT+ADT is recommended for pts with low-volume (CHAARTED/M1a) synchronous mHSPC; limited data are available to show the impact of local prostate RT on local progression
- In the PEACE-1 trial, prostate RT reduced the need for interventions for obstruction in pts with low-volume disease

Analysis of pts included in STAMPEDE trial arm A and H

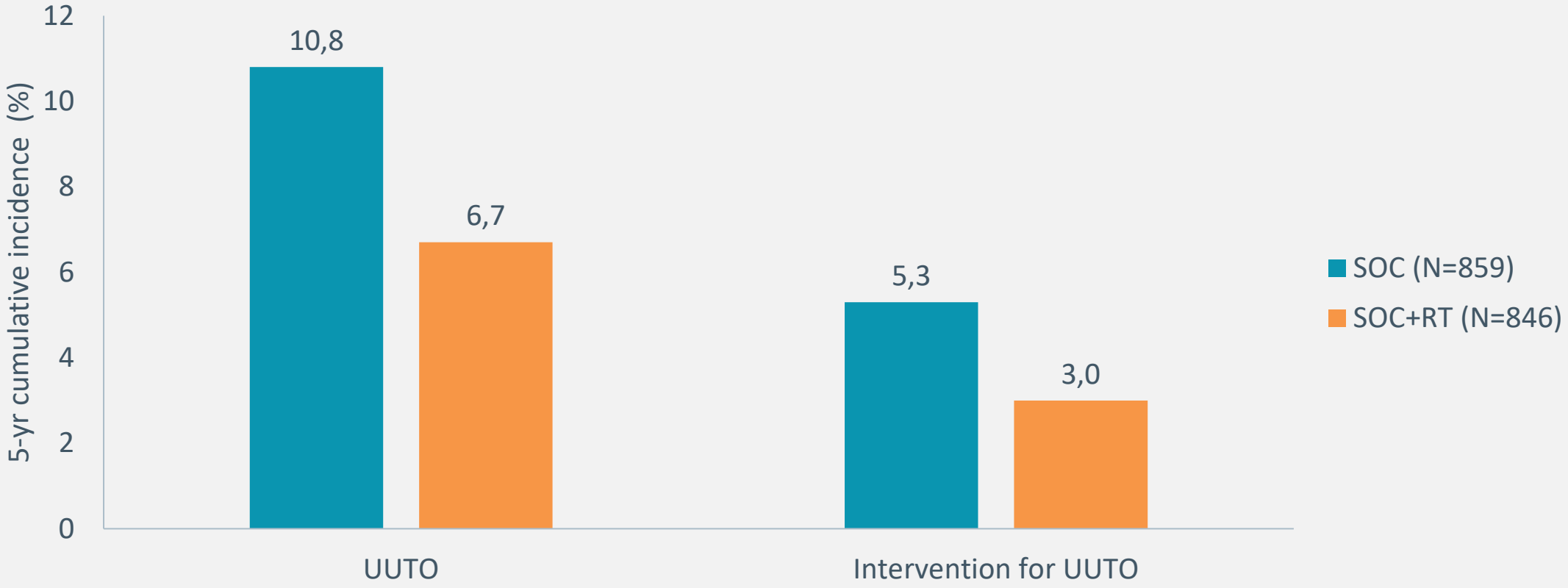
Population	Design	Objectives
• Newly presenting M1 PCa (bone scan/CT)	R → Arm A: Standard of care (N=859); Arm H: Standard of care + prostate RT (55 Gy/20fr or 36 Gy/6 fr) (N=846)	• Evaluate effect of prostate RT on risk of intervention for UUTO using routinely collected healthcare data through Hospital Episode Statistics

Pts were excluded if not based in England, data not linked to Hospital Episode Statistics, and intervention for UUTO event within 90d prior to randomisation → analysis cohort: N=1,705 out of 2,061 pts randomised to arm A and H

UUTO: upper urinary tract obstruction

Jones C. ESMO 2023, abs.1782P (data from poster included)

5-yr cumulative incidence UUTO & intervention for UUTO (median FU: 4yr)



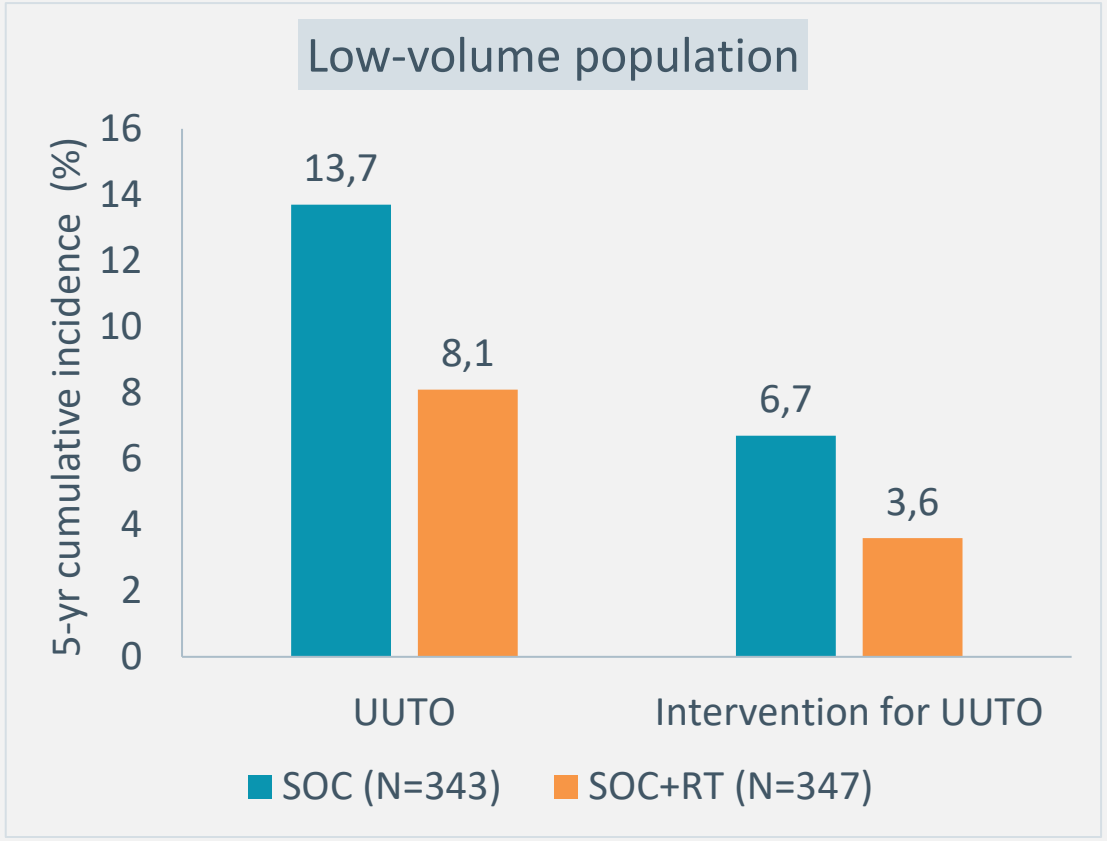
Treatment effect of primary prostate RT on incidence of intervention for UUTO:

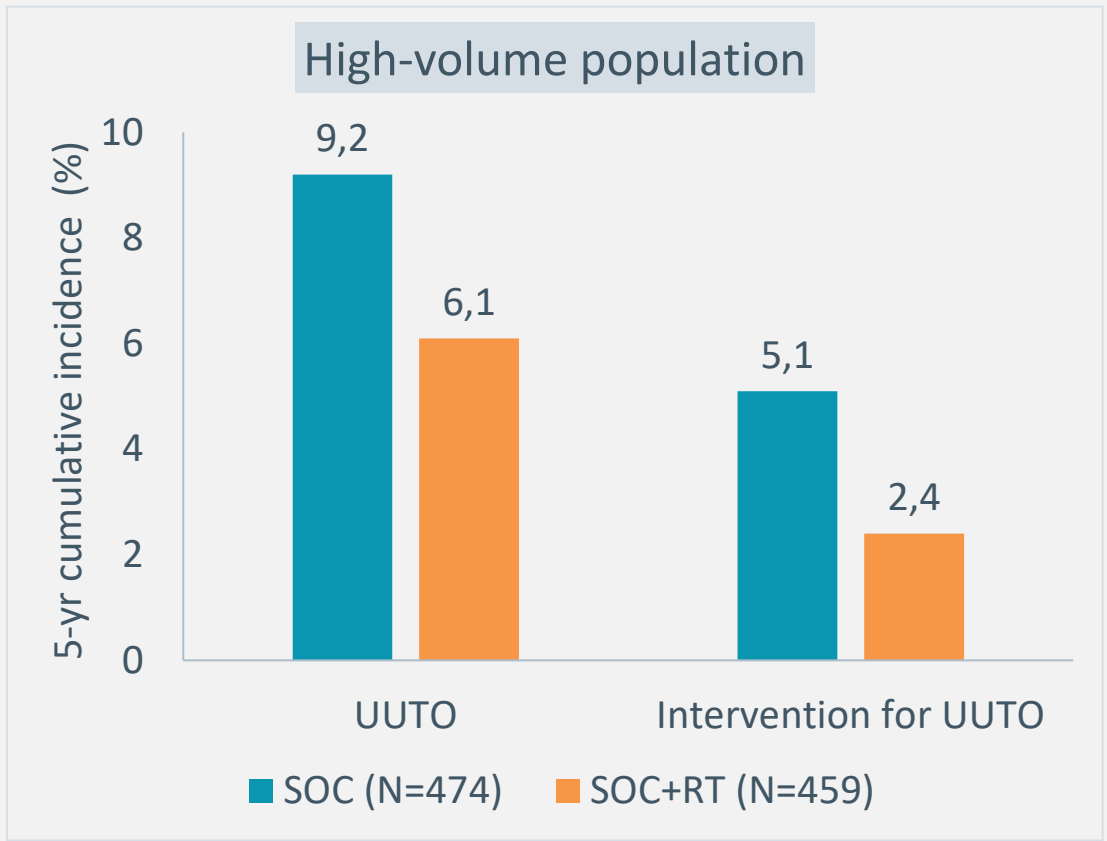
- sdHR=0.57, 95% CI: 0.35-0.91, *P*=0.017

sdHR: subdistribution hazard ratio; UUTO: upper urinary tract obstruction

Jones C. ESMO 2023, abs.1782P (data from poster included)

5-yr cumulative incidence UUTO & intervention for UUTO according to metastatic disease volume (median FU: 4yr)





Treatment effect of primary prostate RT on incidence of intervention for UUTO:

- Low-volume: sdHR=0.54, 95% CI: 0.27-1.06, *P*=0.07
- High-volume: sdHR=0.47, 95% CI: 0.23-0.96, *P*=0.03

sdHR: subdistribution hazard ratio; UUTO: upper urinary tract obstruction

Jones C. ESMO 2023, abs.1782P (data from poster included)

Does prostate RT for synchronous mHSPC reduce the use of upper urinary tract obstruction (UUTO) interventions?

TAKE HOME MESSAGE

Yes. Use of prostate RT in synchronous mHSPC significantly reduces the use of UUTO interventions.

Is PEMBRO+ENZA+ADT effective in unselected pts with mHSPC?

- PEMBRO+ENZA has shown antitumour activity in pts with metastatic PCa

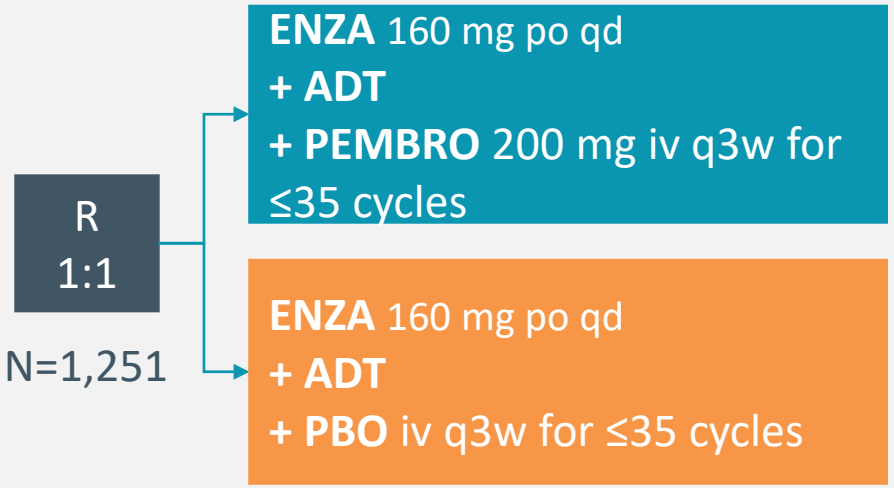
KEYNOTE-991: international, multi-centre, phase III trial

(Mar 2020-Aug 2021)

Population

- Confirmed mHSPC
- ≥2 bone lesions or visceral disease (centrally verified)
- No prior ARTA
- Prior DOC (≤6 cycles) permitted if completed ≤2mo from randomisation
- ECOG PS 0 or 1

Design



Endpoints

Primary

- rPFS (PCWG modified RECIST 1.1 by BICR)
- OS

Secondary

- Time to first subsequent tx
- Time to first symptomatic SRE
- Safety

First prespecified interim analysis

Gratzke C. ESMO 2023, abs.1772MO (data from oral presentation included)

Baseline characteristics

Characteristic	PEMBRO+ENZA+ADT (N=626)	PBO+ENZA+ADT (N=625)
Median age (yr)	68	68
ECOG PS 1 (%)	34	29
Mets at baseline (%)		
Bone	97	97
Visceral	20	19
High-volume*	63	64
Disease measurable by RECIST 1.1 (%)	40	39
Prior DOC for mHSPC (%)	10	10
PD-L1 positive (CPS ≥10) (%)	38	40

*visceral mets or ≥4 bone lesions with ≥1 beyond vertebral bodies/pelvis

Gratzke C. ESMO 2023, abs.1772MO (data from oral presentation included)

Primary endpoints (median FU: 21 mo)

Endpoint	PEMBRO+ENZA+ADT (N=626)	PBO+ENZA+ADT (N=625)	HR (95% CI)	Log-rank *P*
rPFS	Not reached	Not reached	1.20 (0.96-1.49)	0.95
OS	Not reached	Not reached	1.16 (0.88-1.53)	

- OS not formally tested per multiplicity strategy
- The study was stopped for futility at 1st prespecified interim analysis

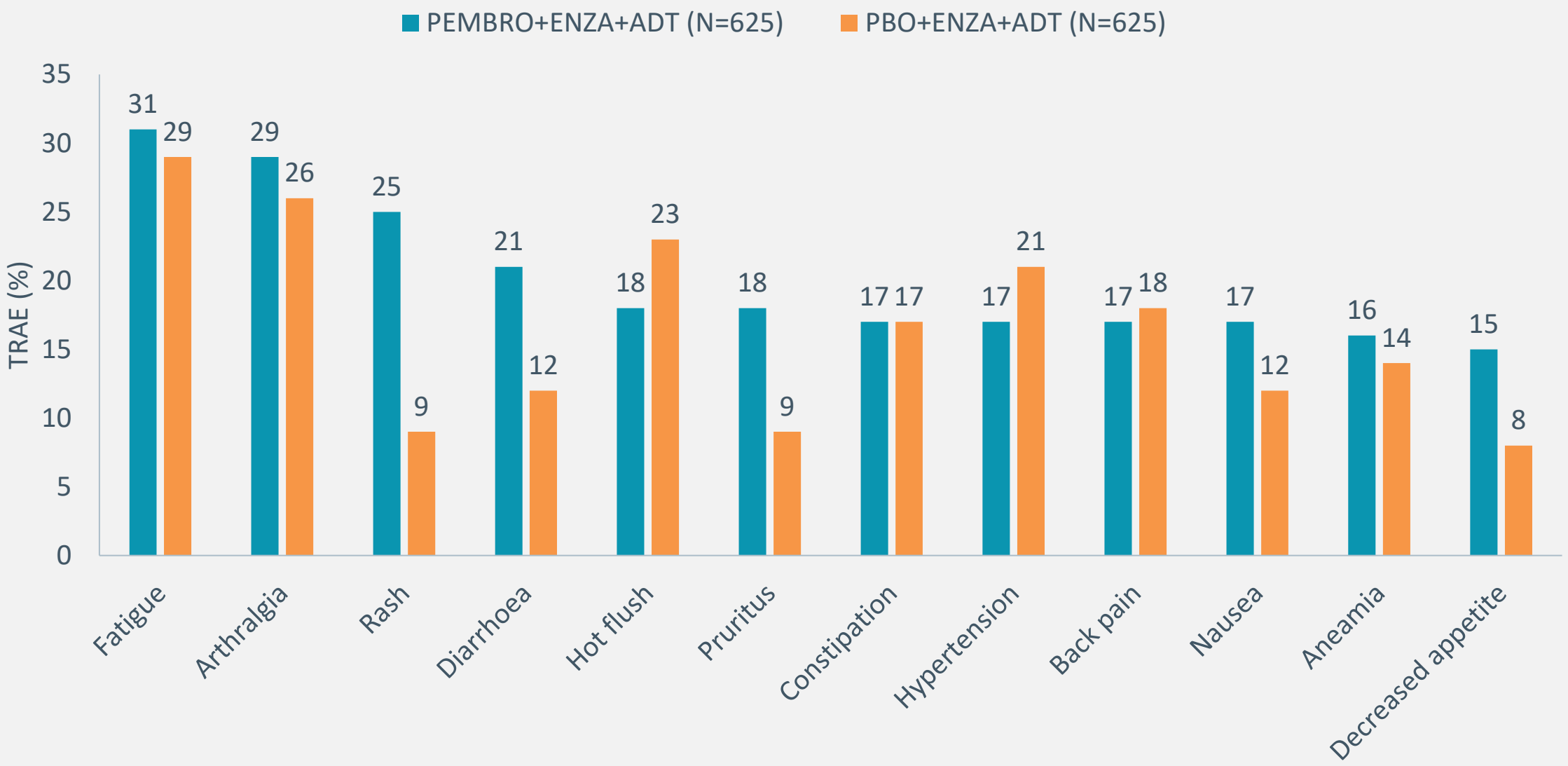
Gratzke C. ESMO 2023, abs.1772MO (data from oral presentation included)

Safety

AE (%)	PEMBRO+ENZA+ADT (N=625)	PBO+ENZA+ADT (N=625)
All-cause AE	99	95
Grade ≥3	62	38
Treatment-related AE	88	67
Grade ≥3	42	14
Immune-mediated AEs and infusion reactions	43	8
Grade ≥3	21	1

Gratzke C. ESMO 2023, abs.1772MO (data from oral presentation included)

Safety: most common all-cause AEs (≥15% of pts)



Gratzke C. ESMO 2023, abs.1772MO (data from oral presentation included)

Is PEMBRO+ENZA+ADT effective in unselected pts with mHSPC?

TAKE HOME MESSAGE

No. Adding PEMBRO to ENZA+ADT in pts with mHSPC without prior exposure to ARTA did not improve rPFS vs ENZA+ADT. More grade ≥3 TRAEs were seen in the combination arm.

Management of castration-resistant prostate cancer (CRPC)

Is PEMBRO+ENZA effective in unselected pts with chemo-naïve mCRPC?

- In a phase II study, PEMBRO had activity in mCRPC when added to ENZA. Responses were deep and durable and did not require tumour PD-L1 expression or DNA-repair defects

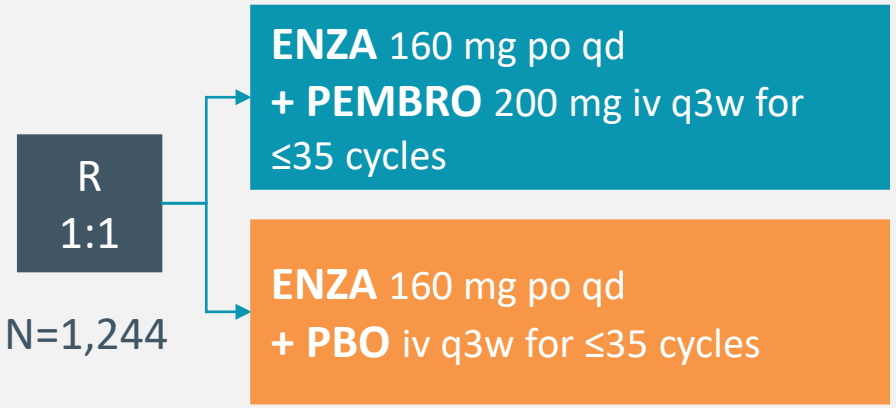
KEYNOTE-641: international, multi-centre, phase III trial

(Aug 2019-Jun 2022)

Population

- Confirmed mCRPC
- Prior ABI permitted
- No prior DOC for mCPRC (allowed for mHSPC)
- No prior ENZA, APA, or DARO
- ECOG PS 0-1

Design



Endpoints

Coprimary

- OS
- rPFS (PCWG modified RECIST 1.1 by BICR)

Secondary

- Time to first subsequent tx
- ORR
- Safety

First prespecified interim analysis after ~510 OS events and ~6 mo after enrolment completion

Graff JN. ESMO 2023, abs.1771MO (data from oral presentation included)

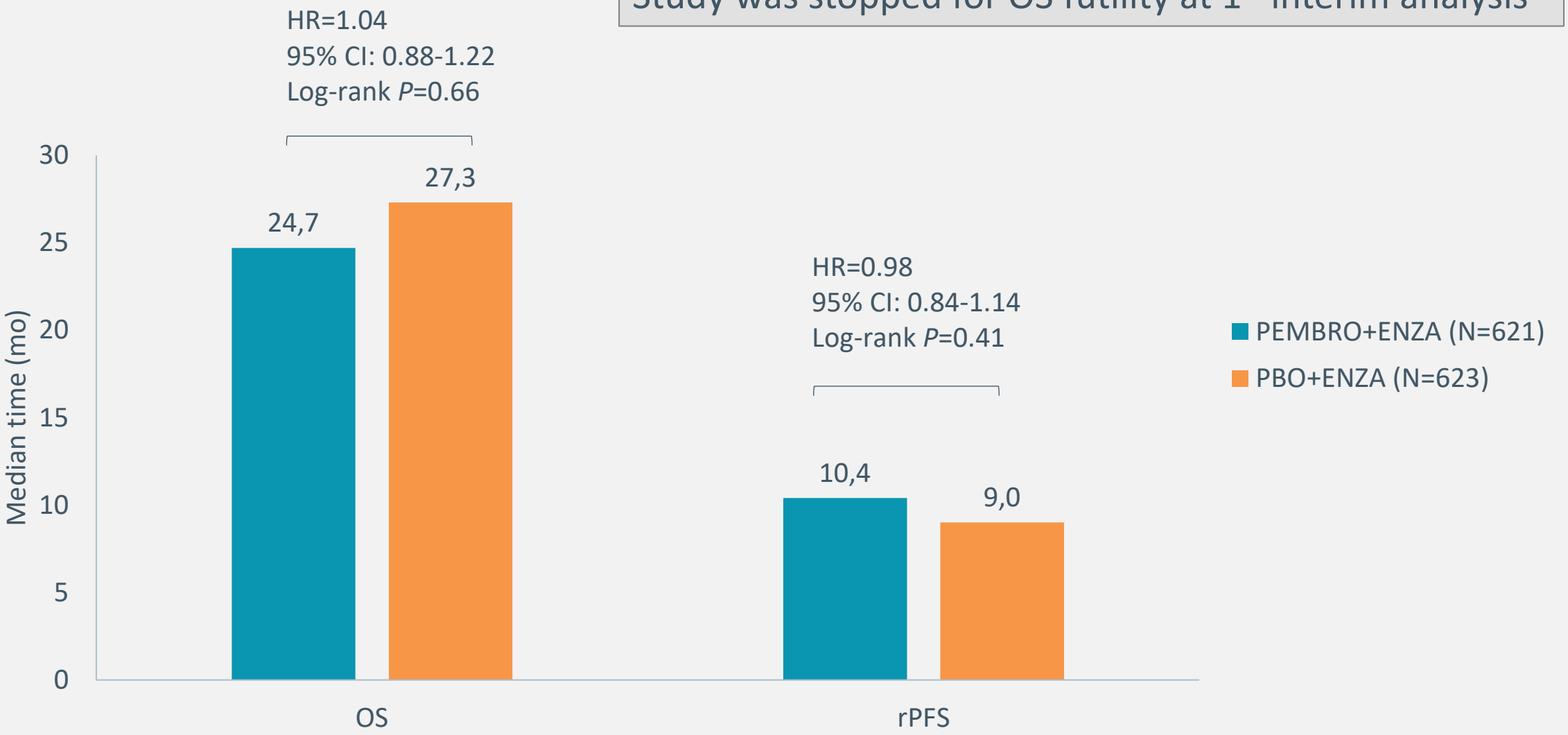
Baseline characteristics

Characteristic	PEMBRO+ENZA (N=621)	PBO+ENZA (N=623)
Median age (yr)	71	70
ECOG PS (%)		
0 / 1 / 2 / missing	58 / 41 / 0 / 1	59 / 41 / 0.2 / 0.2
Mets at baseline (%)		
Bone	86	88
Visceral	12	13
Liver	4	5
Prior ABI (%)	61	61
Prior DOC for mHSPC (%)	29	29
PD-L1 positive (CPS ≥10) (%)	27	30

Graff JN. ESMO 2023, abs.1771MO (data from oral presentation included)

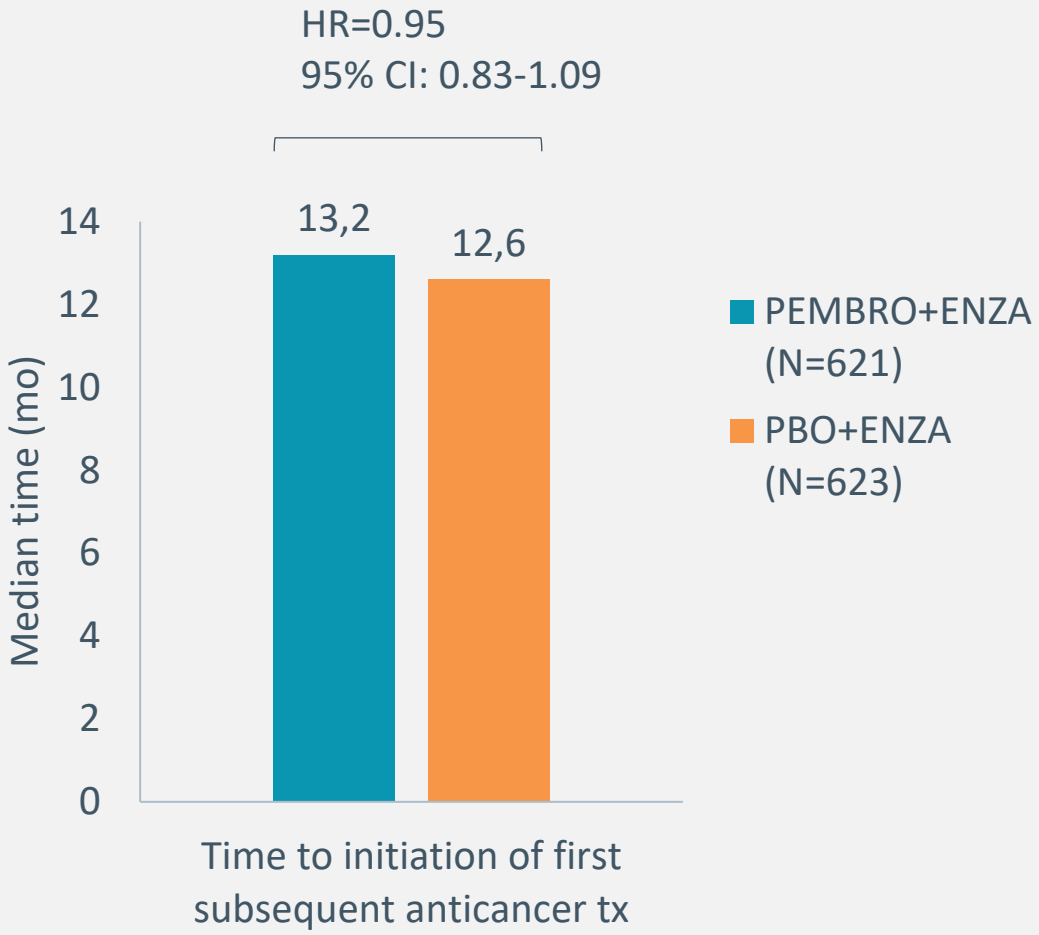
Primary endpoints (median FU: 28 mo)

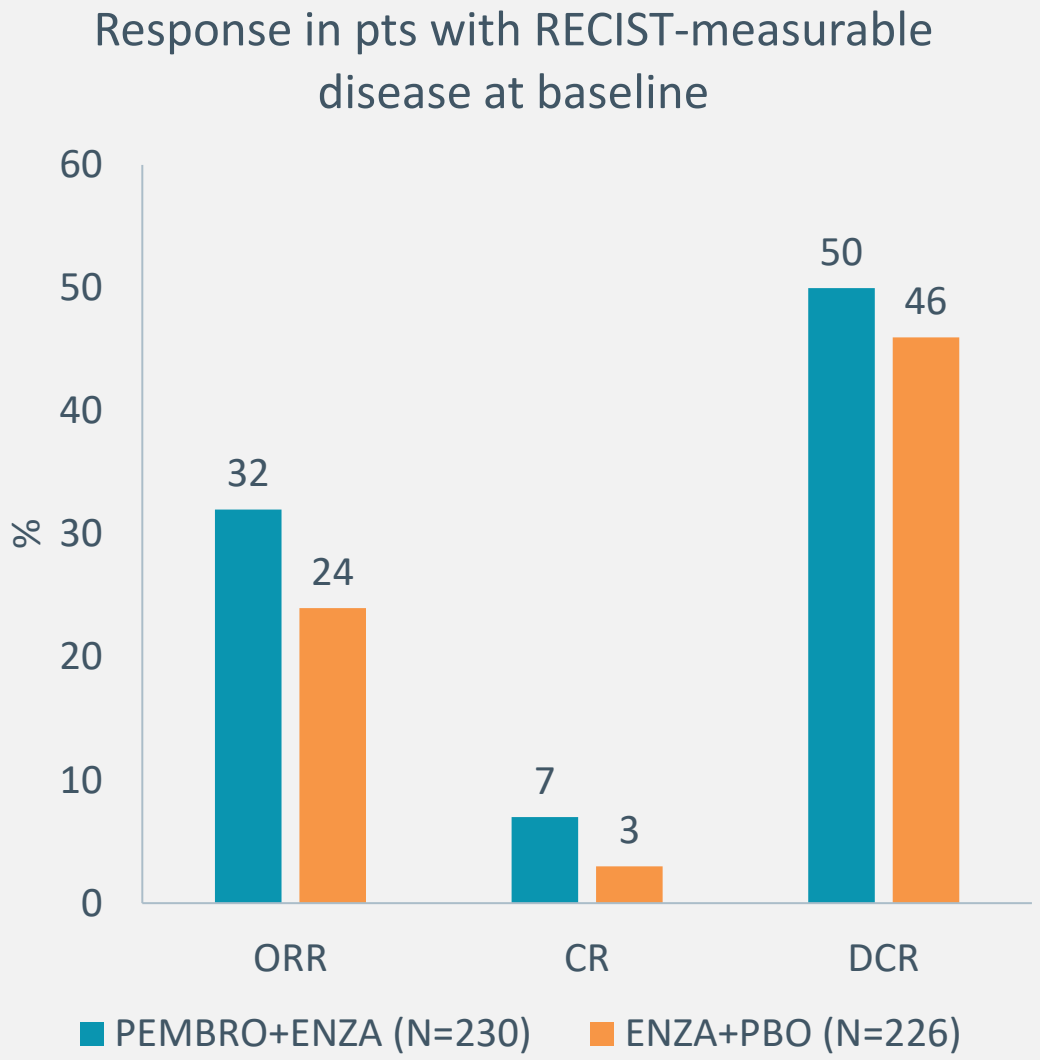
Study was stopped for OS futility at 1st interim analysis



Graff JN. ESMO 2023, abs.1771MO (data from oral presentation included)

Secondary endpoints (median FU: 28 mo)





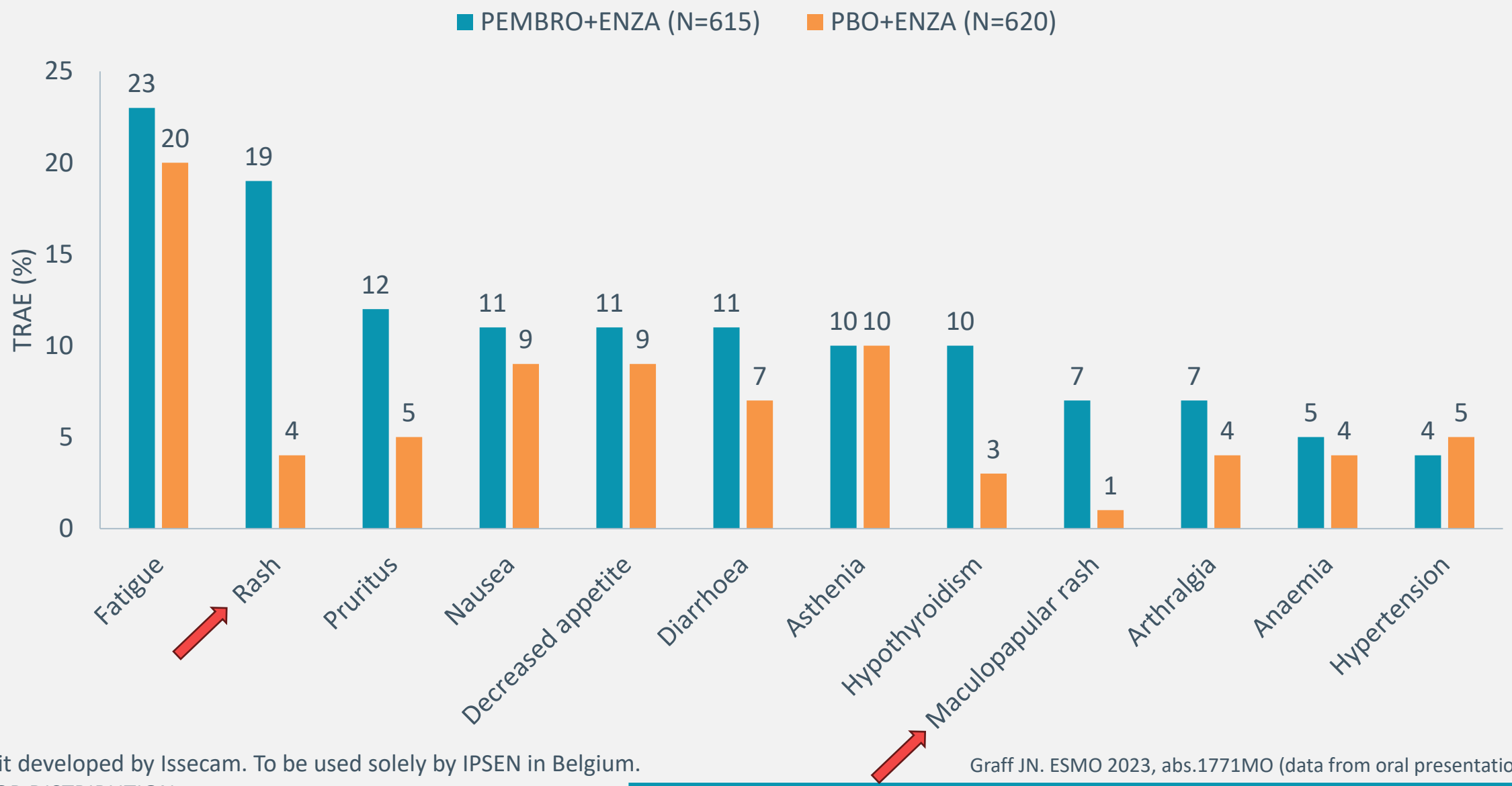
Graff JN. ESMO 2023, abs.1771MO (data from oral presentation included)

Safety

AE (%)	PEMBRO+ENZA (N=615)	PBO+ENZA (N=620)
All-cause AE	97	96
Grade ≥3	56	41
Treatment-related AE	78	62
Grade ≥3	31	11
Immune-mediated AEs and infusion reactions	31	7
Grade ≥3	15	0

Graff JN. ESMO 2023, abs.1771MO (data from oral presentation included)

Safety: most common TRAEs (≥5% of pts)



Graff JN. ESMO 2023, abs.1771MO (data from oral presentation included)

Is ENZA+PEMBRO effective in unselected pts with chemo-naïve mCRPC?

TAKE HOME MESSAGE

No. Adding PEMBRO to ENZA in pts with chemo-naïve mCRPC with or without prior ABI did not improve survival vs ENZA alone. More grade ≥3 TRAEs were seen in the combination arm.

Is immunotherapy dead for PCa?

- So far, immunotherapies have offered limited efficacy in treating mCRPC
- STEAP1 is a cell surface antigen highly expressed in PCa cells; it has low or no expression on normal tissues, making it an ideal potential therapeutic target
- BiTEs are a novel class of immunotherapy
- Xaluritamig is a BiTE designed to facilitate T-cell–mediated lysis of STEAP1-expressing cells

BiTE: bispecific T-cell engager, see next slide

Bispecific T-cell engagers

- BiTEs target both
  - a specific cancer antigen and
  - CD3

  to enhance T-cell antitumour activity

- T-cell engager (TCE) molecules represent a targeted immunotherapy approach
  - TCE binds to a tumour-associated antigen on target cells and to CD3 on T cells
  - This induces T-cell activation, cytokine induction, and T-cell–mediated tumour cell lysis

Xaluritamig, a targeted immunotherapy, is a BiTe containing

- 2 anti-STEAP1 fragment antigen–binding domains that can bind to STEAP1-expressing cells
- 1 anti-CD3 single-chain variable fragment domain that binds T-cells

From the discussion by Dr. Shahneen Sandhu

- PCa is a highly immune suppressive tumour; this is a novel strategy that might engage the immune system
- It is an « off the shelf » option as opposed to CARTs
- Cautious optimism is needed, because development of similar drugs was halted due to unacceptable toxicity and limited efficacy

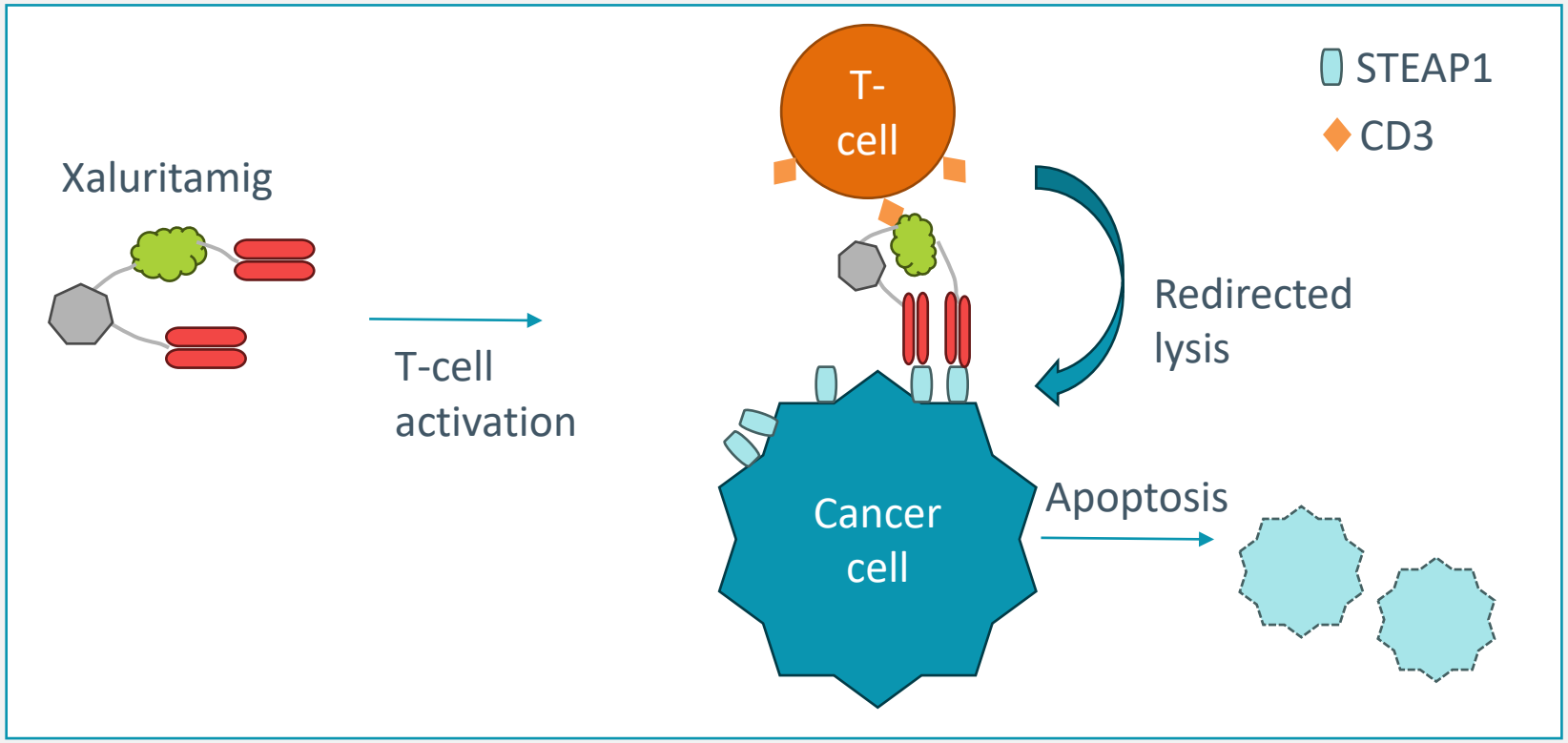
Kelly WK et al. Cancer Discov 2023;doi:10.1158/2159-8290.CD-23-0964

Kelly W. ESMO 2023, abs.1765O

Discussion of Kelly W. ESMO 2023, abs.1765O by Dr. S. Sandu

Xaluritamig: mechanism of action

- Xaluritamig, a targeted immunotherapy, is a BiTe containing
  - 2 anti-STEAP1 fragment antigen–binding domains that can bind to STEAP1-expressing cells
  - 1 anti-CD3 single-chain variable fragment domain that binds T-cells



Kelly W. ESMO 2023, abs.1765O (data from oral presentation included)

Global, first-in-human, open-label phase I trial

Population	Part 1: first-in-human Xaluritamig monotx	Endpoints
• mCRPC refractory to prior ARTA and 1-2 taxane regimens • ECOG PS 0-1 • Adequate organ function • No active autoimmune disease	Dose exploration ↓ Maximum tolerated dose Dose expansion	**Primary** • Safety & tolerability • Maximum tolerated dose **Secondary** • Pharmacokinetics • Preliminary anti-tumour activity

Kelly W. ESMO 2023, abs.1765O (data from oral presentation included)

Baseline characteristics

Characteristic	All cohorts, part 1 (N=97)
Median age (yr)	67
ECOG PS 0 / 1 (%)	46 / 54
Median number of prior tx lines (N, range)	4 (1-9)
≥5 prior tx lines (%)	28
Prior taxane (%)	85
Prior PSMA-targeting radioligand tx (%)	4
Visceral metastases (%)	53
Liver	37
Median FU (mo)	8

Kelly W. ESMO 2023, abs.1765O (data from oral presentation included)

Primary endpoints

Maximum tolerated dose: 1.5 mg iv qw (3-step: d1 0.1 mg, d8 0.3 mg, d15: 1.0 mg, d22+: 1.5 mg)

AE (%)	All cohorts (N=97)
Any TEAE	100
Grade ≥3	76
Any TRAE (to xaluritamig)	97
Grade ≥3	55
Leading to tx discontinuation	19
Leading to dose interruption	47

No grade 4-5 AEs

Most common TRAEs: cytokine release syndrome (primarily in cycle 1, low-grade and manageable), fatigue and myalgia

Kelly W. ESMO 2023, abs.1765O (data from oral presentation included)

Efficacy

Outcome	All cohorts	Low-dose cohorts	High-dose cohorts
PSA evaluable pts	N=87	N=43	N=44
PSA50 response (%)	49	40	59
PSA90 response (%)	28	19	36
RECIST 1.1 evaluable pts	N=67	N=30	N=37
ORR* (%)	24	3	41

Low-dose: target dose <0.75 mg – high-dose: target dose ≥0.75 mg
*all partial responses

Median duration of response: 9 mo

Kelly W. ESMO 2023, abs.1765O (data from oral presentation included)

Is immunotherapy dead for PCa?

TAKE HOME MESSAGE

No. These preliminary findings of xaluritamig, a targeted immunotherapy, showed encouraging responses (PSA and RECIST) in heavily pretreated, unselected mCRPC pts, supporting further development of bispecific T-cell engagers for PCa.

Is NIRA+ABI+P effective as 1st-line treatment of mCRPC pts harbouring *BRCA1/2* gene alterations?

- Pts with mCRPC and HRR gene alterations, especially *BRCA1/2* alterations, have poor outcomes
- Primary outcomes of the MAGNITUDE trial showed improved rPFS with NIRA+ABI+P vs PBO+ABI+P in patients with *BRCA+* mCRPC

MAGNITUDE: double-blind, phase III trial (study start: Feb 2019)

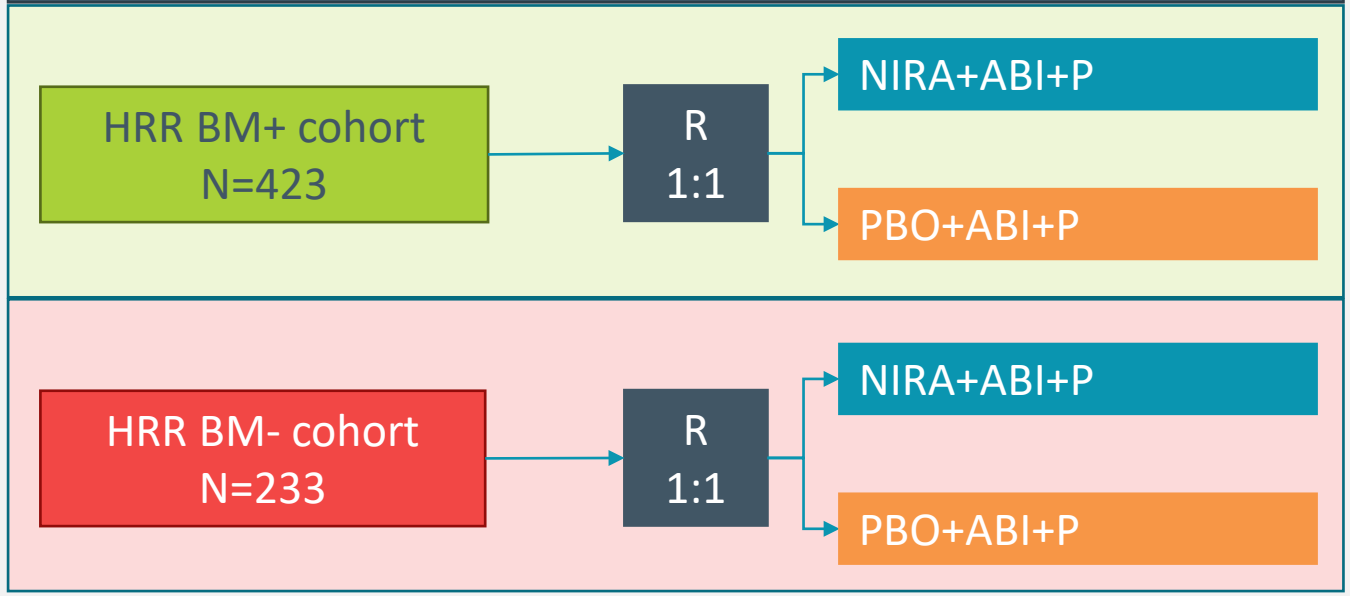
Population

- 1st-line mCRPC
- ≤4 mo prior ABI allowed for mCRPC
- ECOG PS 0-1
- BPI-SF worst pain score ≤3

Prescreening for biomarker (BM) status

- HRR BM+ panel:
  ATM, BRCA1/2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2

Design



Stratification factors: prior taxane for mHSPC, prior ARTA for nmCRPC or mHSPC, prior ABI for 1st-line mCRPC, HRR BM+ cohort: *BRCA1/2* vs other HRR gene alterations

Primary endpoint: rPFS (central review)

Key secondary endpoints: time to cytotoxic chemotherapy, time to symptomatic progression, OS, safety

Current analysis: final, pre-planned, event-driven OS analysis at median FU of 36 mo with focus on pts with *BRCA+* mCRPC

Chi KN. ESMO 2023, abs.LBA85 (data from oral presentation included)

Baseline characteristics of *BRCA+* population

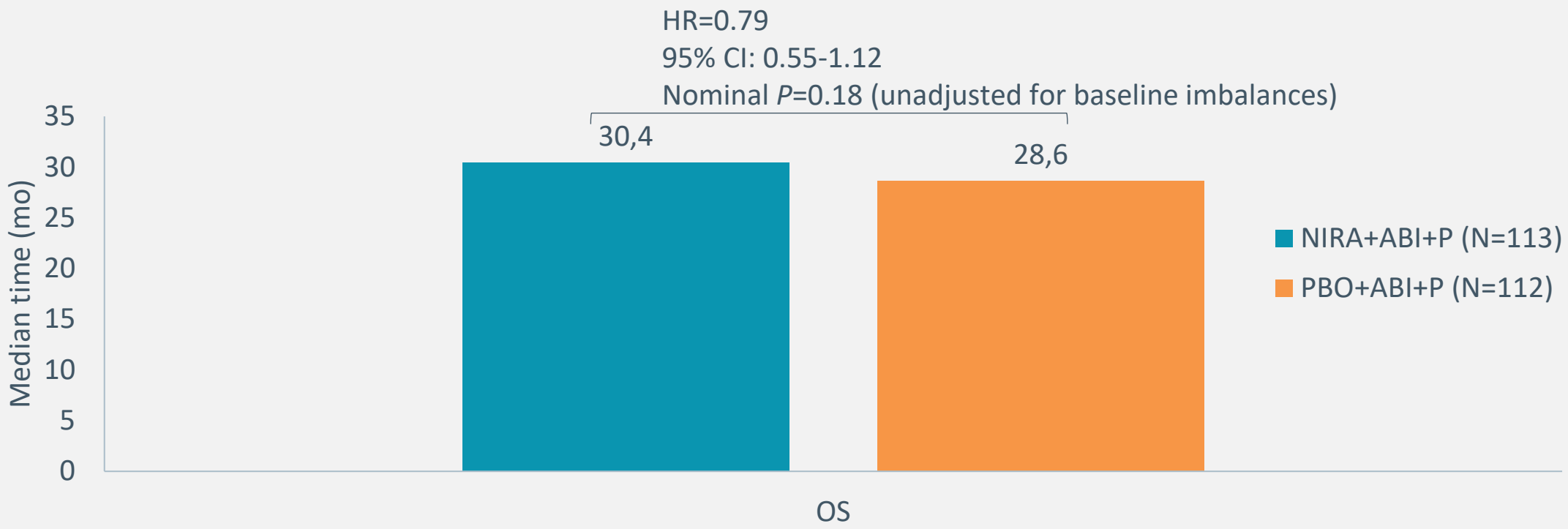
	NIRA+ABI+P (N=113)	PBO+ABI+P (N=112)
Median age (yr)	67	68
ECOG PS (%)		
0	61	71
1	39	29
Site of metastases (%)		
Bone	88	83
Visceral	23	20
Prior treatment (%)		
Taxane for nmCRPC/mHSPC	23	26
ARTA for nmCRPC/mHSPC	5	5
Prior ABI+P for 1st-line mCRPC	27	26

The PBO+ABI+P arm had more favourable characteristics, which impacted the comparison of NIRA vs PBO

Characteristics of *BRCA+* pts and the all HRR BM+ cohort were similar

Chi KN. ESMO 2023, abs.LBA85 (data from oral presentation included)

Final analysis: OS in *BRCA+* pts (median FU: 36 mo)



Preplanned multivariate analysis using prespecified prognostic factors supports OS benefit of NIRA+ABI+P vs PBO+ABI/P

- HR=0.66, 95% CI: 0.46-0.95, nominal *P*=0.02

Chi KN. ESMO 2023, abs.LBA85 (data from oral presentation included)

Subsequent life-prolonging tx in *BRCA+* pts

Subsequent tx (%)	NIRA+ABI+P (N=60)	PBO+ABI+P (N=86)
Any	70	86
PARPi	5	34
Chemotherapy	57	59
DOC	38	48
CABA	18	19
Platinum-based	15	9
Other	2	5
ARTA	20	28

Chi KN. ESMO 2023, abs.LBA85 (data from oral presentation included)

BRCA+ population: secondary endpoints

	HR	95% CI	Nominal *P*
Median time to symptomatic progression	0.56	0.37-0.85	0.01
Median time to cytotoxic chemotherapy	0.60	0.39-0.92	0.02

HR <1 favours NIRA+ABI+P

Chi KN. ESMO 2023, abs.LBA85 (data from oral presentation included)

HRR BM+ cohort: safety (median tx exposure: 20 vs 15 mo)

Overall (%)	NIRA+ABI+P (N=212)	PBO+ABI+P (N=211)
All TEAEs	100	97
Grade 3/4 TEAE	74	51
TEAE leading to discontinuation	18	8
TEAE leading to death	10	5
COVID related or suspected	5	1
Grade ≥3 TEAE of special interest (%)	**NIRA+ABI+P (N=212)**	**PBO+ABI+P (N=211)**
Anaemia	61	9
Thrombocytopenia	9	2
Neutropenia	7	2
Pulmonary embolism	3	1
Acute myeloid leukaemia	0	1

Chi KN. ESMO 2023, abs.LBA85 (data from oral presentation included)

Is NIRA+ABI effective as 1st-line treatment of mCRPC pts harbouring BRCA1/2 gene alterations?

TAKE HOME MESSAGE

The addition of NIRA to ABI+P in pts with *BRCA+* mCRPC prolonged time to symptomatic progression and time to initiation of chemotherapy and tended to improve OS.

Is it effective and safe to add Lu-PSMA to ENZA as 1st-line tx for pts with mCRPC and risk factors for early progression on ENZA?

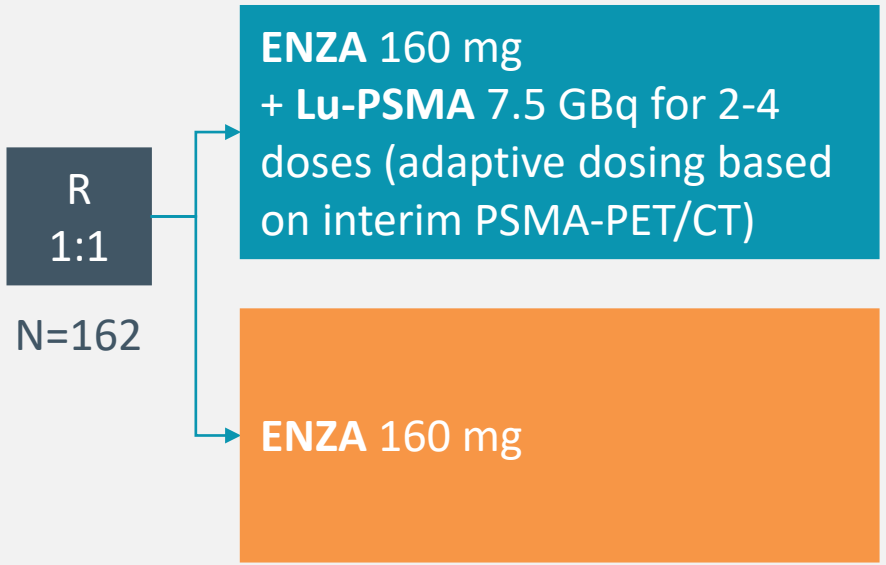
- Both ENZA and Lu-PSMA improved OS in pts with mCRPC
- Preclinical and clinical data suggest synergy for Lu-PSMA with ARTA in mCRPC

ENZA-p: Australian, multi-centre, phase II trial (interim analysis)

Population

- mCRPC with rising PSA and PSA >5 ng/ml
- No prior chemotx or ARTA for mCRPC
- ≥2 high-risk features for early ENZA failure*
- Positive 68Ga-PSMA-PET/CT**

Design



Stratification factors: study site, disease volume, DOC for mHSPC, prior ABI

Endpoints

Primary

- PSA-PFS

Secondary

- rPFS
- PSA response
- HRQoL
- AEs

*LDH ≥ULN, ALP ≥ULN, albumin <35 g/l, de novo M1 disease at diagnosis, <3 yr since initial diagnosis, >5 bone mets, visceral mets, PSA-DT <84d, pain requiring opiates >14d, prior ABI

**PSMA-PET screening criteria: SUVmax ≥15 at 1 site AND ≥10 at all measurable sites. Mismatch on diagnostic CT was not an exclusion

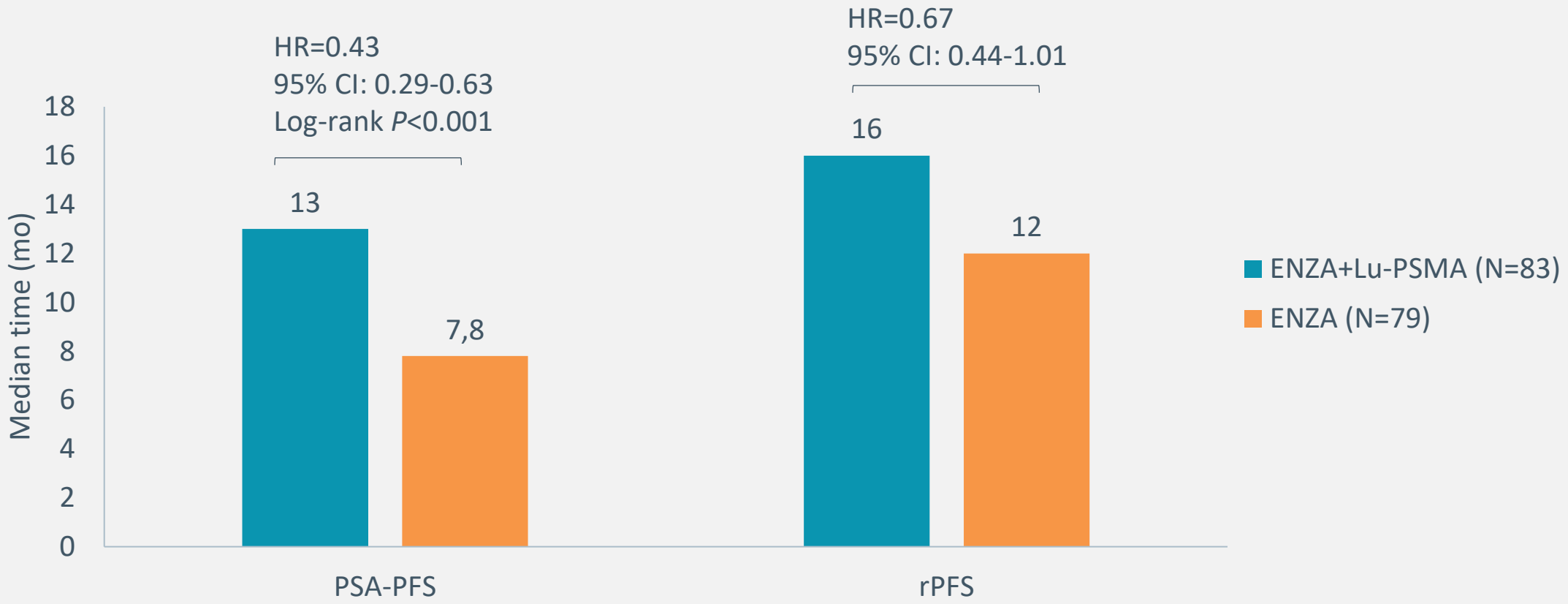
Emmett L. ESMO 2023, abs.LBA84 (data from oral presentation included)

Baseline characteristics

Characteristic	ENZA+Lu-PSMA (N=83)	ENZA (N=79)
Median age (yr)	71	71
Median PSA at enrolment (ng/ml)	39	33
>20 PSMA-avid metastases (%)	61	59
De novo M1 at diagnosis (%)	52	58
DOC for mHSPC (%)	53	56
Prior ABI (%)	14	11
Median yr since diagnosis (yr)	2.2	2.8

Emmett L. ESMO 2023, abs.LBA84 (data from oral presentation included)

Efficacy (median FU: 20 mo)



PSA50 response rate: 93% vs 68% - **PSA90 response rate**: 78% vs 37%

81% of pts in the ENZA+Lu-PSMA arm received 4 doses of Lu-PSMA

Emmett L. ESMO 2023, abs.LBA84 (data from oral presentation included)

Safety

AE (%)	ENZA+Lu-PSMA	ENZA
Any grade	95	85
Grade 3	10	4
Grade 4-5	6	4

AE (%)	ENZA+Lu-PSMA		ENZA	
	Any grade	Grade 3	Any grade	Grade 3
Fatigue	75	2	70	3
Dry mouth	40	0	10	0
Anaemia	14	4	3	0
Platelets decreased	11	1	0	0
WBC decreased	6	1	3	1

Emmett L. ESMO 2023, abs.LBA84 (data from oral presentation included)

Is it effective and safe to add Lu-PSMA to ENZA as 1st-line tx for pts with mCRPC and risk factors for early progression on ENZA?

TAKE HOME MESSAGE

Adding adaptive-dosed Lu-PSMA to ENZA as 1st-line tx for mCRPC seems safe and effective in terms of PSA-PFS and PSA response.

Is Lu-PSMA effective in pts with chemo-naïve mCRPC?

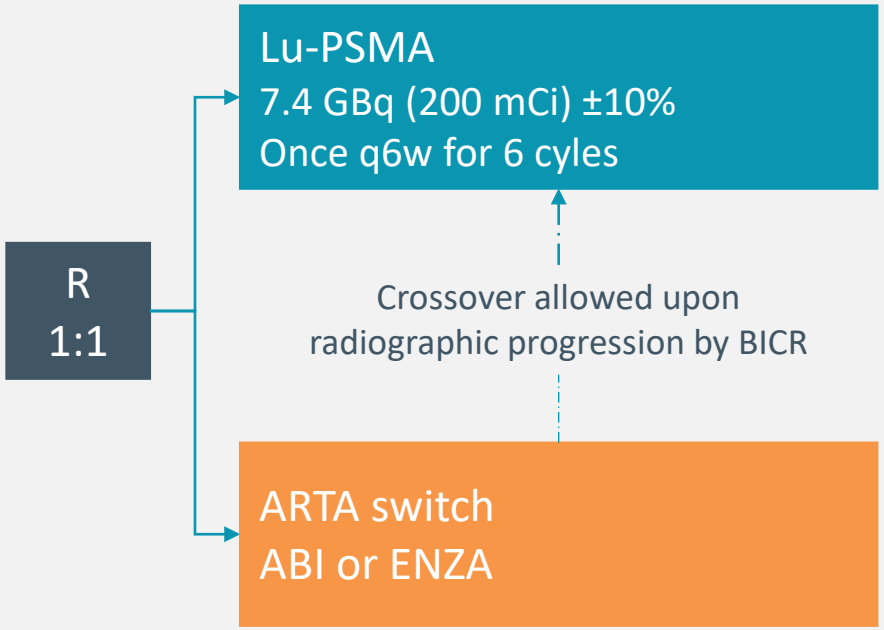
- The phase III VISION trial showed that Lu-PSMA prolonged survival in mCRPC pts who previously received an ARTA and chemotherapy and had a positive PSMA-PET/CT scan
- Based on these results, the EAU guidelines recommend Lu-PSMA in pre-treated mCRPC pts with ≥1 metastatic lesion, highly expressing PSMA on the diagnostic radiolabelled PSMA-PET/CT scan
- Also the ESMO guidelines recommend Lu-PSMA for men with mCRPC pretreated with ARTA and taxanes, if the cancer is expressing PSMA on PSMA-PET without PSMA non-expressing lesions

PSMAfore: open-label, phase III trial

Population

- Confirmed progressive mCRPC
- ≥1 PSMA-positive metastatic lesion on 68Ga-PSMA-PET/CT and no exclusionary PSMA-negative lesions
- Progressed once on prior 2nd generation ARTA
  - Candidates for switch in ARTA
- Taxane-naïve (except (neo)adjuvant >12 mo ago)
  - No candidates for PARPi
- ECOG PS 0-1

Design



Stratification factors: prior ARTA setting, BPI-SF worst pain intensity score

Endpoints

Primary

- rPFS (PCWG3 RECIST 1.1 by BICR)

Secondary

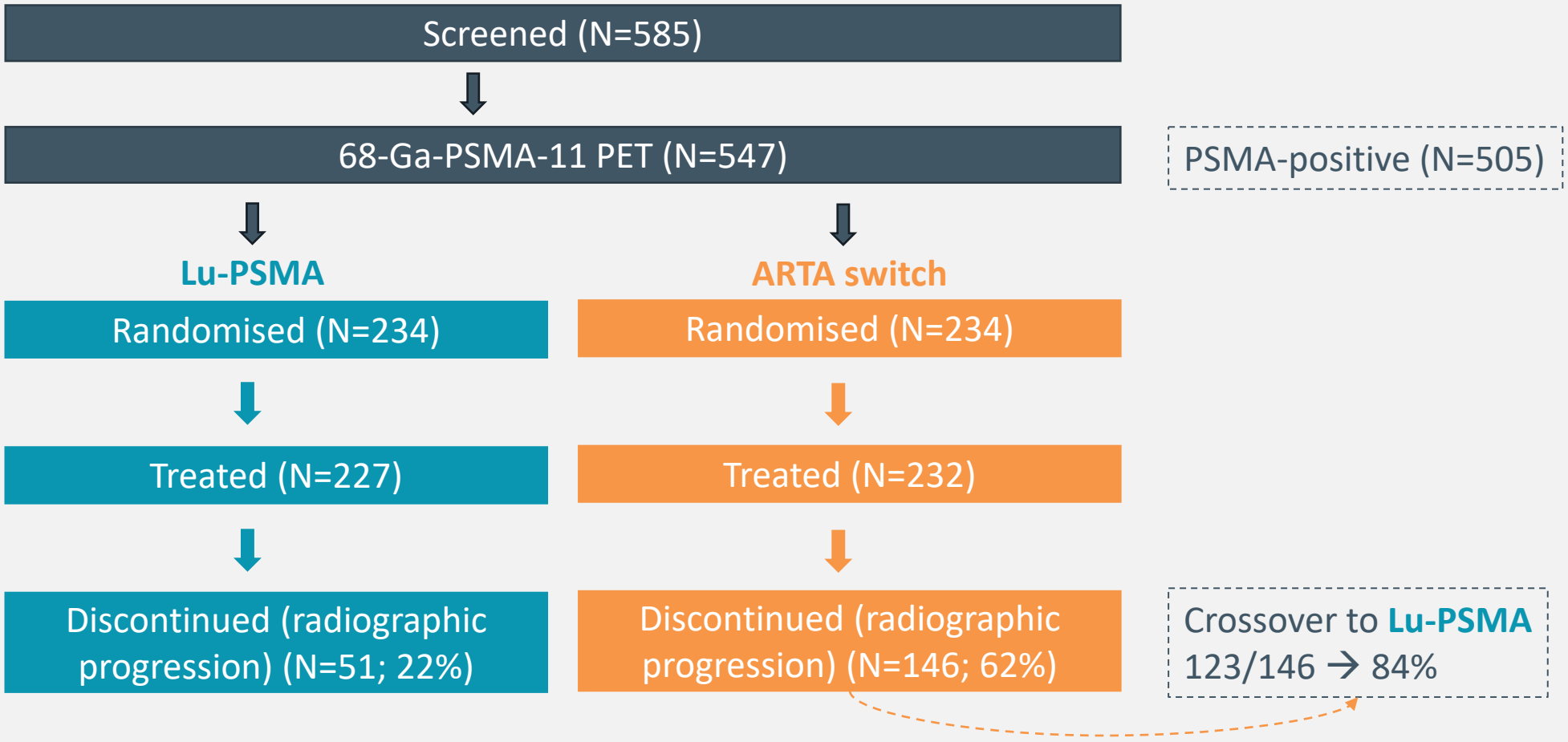
- OS*
- FACT-P
- ORR/DOR (exploratory)

*prespecified for crossover-adjusted analysis

Current analysis: rPFS at 1st interim (=primary) and 2nd interim (=updated) analysis, OS at 2nd interim analysis

Sartor O. ESMO 2023, abs.LBA13 (data from oral presentation included)

Patient disposition at 2nd interim OS analysis



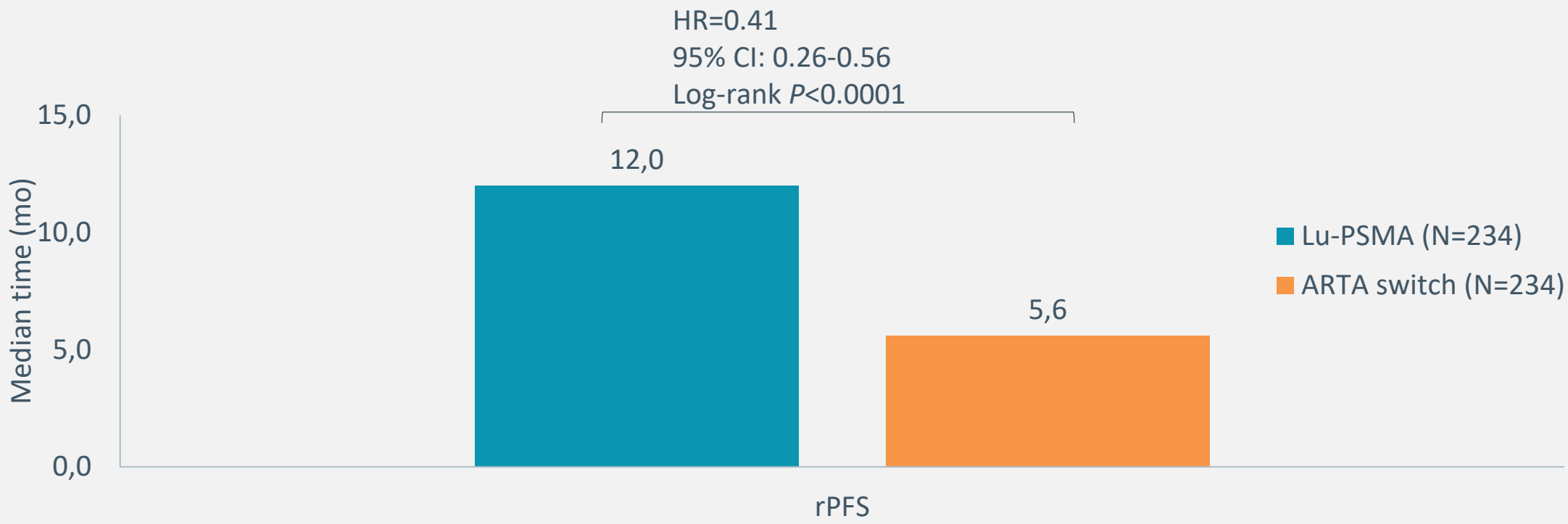
Sartor O. ESMO 2023, abs.LBA13 (data from oral presentation included)

Baseline characteristics

Characteristic	Lu-PSMA (N=234)	ARTA switch (N=234)
Median age (yr)	71	72
ECOG PS 0 / 1 (%)	62 / 37	49 / 49
Median PSA (ng/ml)	18.4	14.9
Metastatic site (%)		
Liver / LN / bone	6 / 33 / 88	3 / 32 / 87
Prior ARTA (%)		
ABI / ENZA / other	51 / 40 / 9	56 / 36 / 9
Median ALP (IU/l)	100.0	103.5
Median Hb (g/l)	128	129

Sartor O. ESMO 2023, abs.LBA13 (data from oral presentation included)

Primary endpoint: rPFS (median FU: 7 mo = primary analysis = 1st interim analysis)



rPFS at 2nd interim analysis (median FU: 16 mo)

- HR=0.43, 95% CI: 0.33-0.54

Sartor O. ESMO 2023, abs.LBA13 (data from oral presentation included)

Secondary endpoints

Outcome	Lu-PSMA	ARTA switch
Radiographic responses (measurable disease at baseline) (N=71 vs N=74)		
ORR (%)	51	15
CR (%)	21	3
Median DOR (mo)	14	10
PSA response (N=213 vs N=221)		
≥50% decrease (%)	58	20

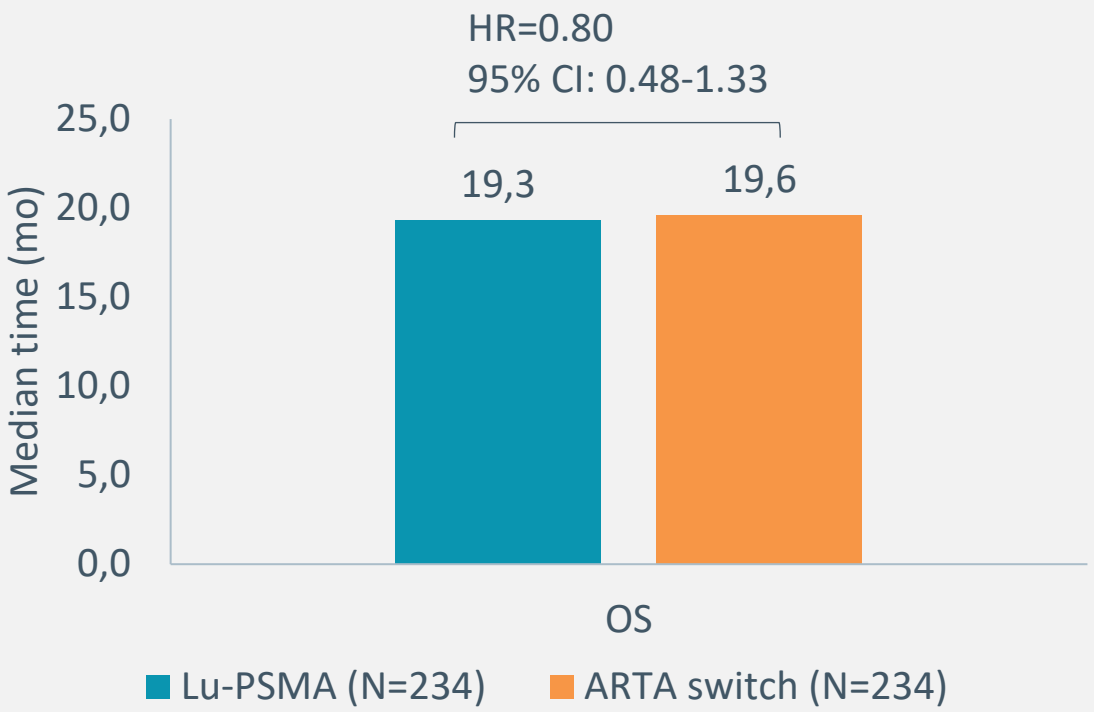
Outcome	Lu-PSMA (N=234)	ARTA switch (N=234)
Median time to SSE (mo)	NE	NE
HR (95% CI)	0.35 (0.22-0.57)	
Median time to worsening in HRQoL* (mo)	7.5	4.3
HR (95% CI)	0.59 (0.47-0.72)	
Median time worsening in pain (mo)**	5.0	3.7
HR (95% CI)	0.69 (0.56-0.85)	

*FACT-P total score, **BPI-SF pain intensity scale

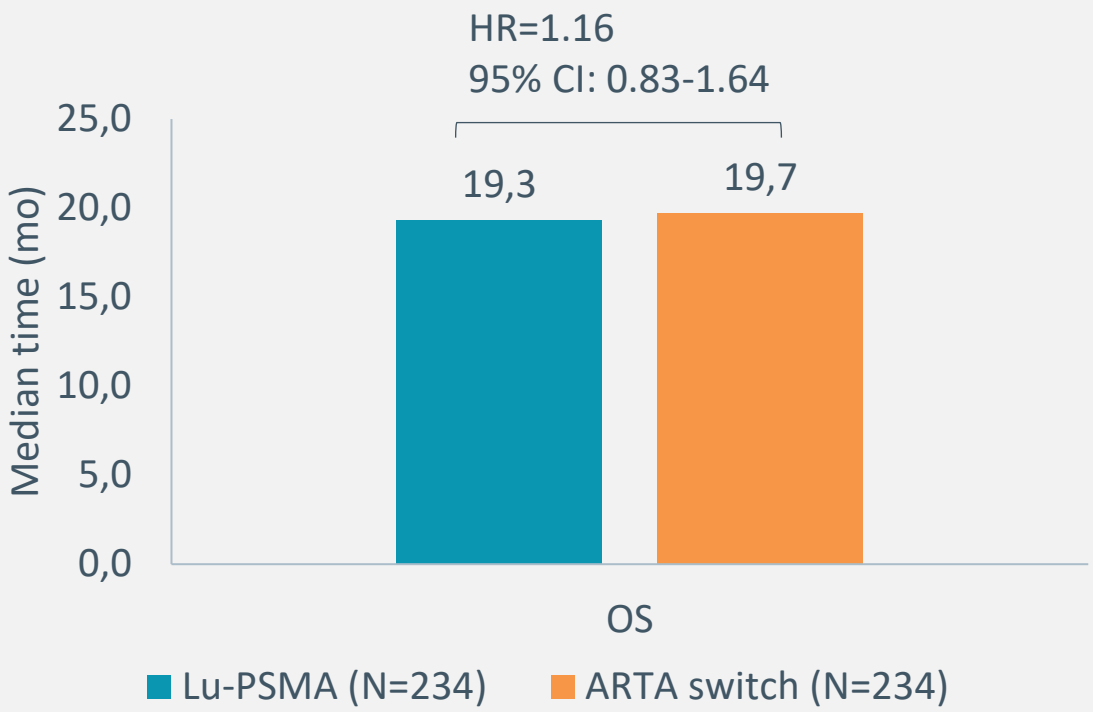
Sartor O. ESMO 2023, abs.LBA13 (data from oral presentation included)

Key secondary endpoint: OS (2nd interim analysis)

Prespecified crossover-adjusted analysis



Intent-to-treat analysis



84% of pts with radiographic progression who discontinued ARTA crossed over to Lu-PSMA at the time of the 2nd interim analysis

Median FU: 12.7 mo vs 13.1 mo

Sartor O. ESMO 2023, abs.LBA13 (data from oral presentation included)

Safety

AE (%)	Lu-PSMA (N=227)	ARTA switch (N=232)
Any	98	96
Grade 3-4	34	43
Serious AE	20	28
Treatment-related	3	2
Grade 5	2	2
Leading to dose adjustment	4	15
Leading to discontinuation	6	5

Most common grade 3-5 AE in both arms: anaemia (6% in both arms)

Sartor O. ESMO 2023, abs.LBA13 (data from oral presentation included)

Overview of Lu-PSMA data in CRPC pts, according to discussant Dr. Sweeney

	Trial	Life-prolonging, control arm	OS benefit	Median OS with Lu-PSMA	PSMA-SUVmean ≥10 "Most benefit"
Lu-PSMA after DOC and ARTA	VISION[1,2]	No	Yes	~15 mo	Yes
	THERA-P[3,4]	Yes, CABA	No	~19 mo	Yes
Lu-PSMA after ARTA	PSMAfore[5]	No, ARTA switch	No (84% cross-over)	~19 mo	Not reported (yet?)

1. Sartor O et al. N Engl J Med 2021; 2. Kuo P et al. J Nucl Med 2023; 3. Hofman MS et al. Lancet 2021; 4. Buteau JP et al. Lancet Oncol;
5. Sartor O et al. LBA13 at ESMO 2023

Is Lu-PSMA effective in pts with chemo-naïve mCRPC?

TAKE HOME MESSAGE

Lu-PSMA prolonged rPFS vs switch in ARTA in pts with chemo-naïve mCRPC who progressed on ARTA and were unwilling or unfit to receive chemotherapy.