Phase 3 study of androgen deprivation therapy with enzalutamide (ENZA) or placebo (PBO) in metastatic hormone-sensitive prostate cancer: the ARCHES trial

Cristiano Ferrario,[1] Andrew J. Armstrong,[2] Russell Z. Szmulewitz,[3] Daniel Petrylak,[4] Arnauld Villers,[5] Arun Azad,[6,*] Antonio Alcaraz,[7] Boris Alekseev,[8] Taro Iguchi,[9] Neal D. Shore,[10] Brad Rosbrook,[11] Jennifer Sugg,[12] Benoit Baron,[13,†] Lucy Chen,[12] Arnulf Stenzl[14]

[1]Oncology Department, Jewish General Hospital and McGill University, Montreal, Quebec, Canada; [2]Duke Cancer Institute Center for Prostate and Urologic Cancers, Durham, NC; [3]The University of Chicago, Chicago, IL; [4]Yale Cancer Center, New Haven, CT; [5]University Hospital Centre, Lille University, Lille, France; [6]Monash Health, Melbourne, Victoria, Australia; [7]Hospital Clinic de Barcelona, Barcelona, Spain; [8]Hertzen Moscow Cancer Research Institute, Moscow, Russia; [9]Osaka City University Graduate School of Medicine, Osaka, Japan; [10]Carolina Urologic Research Center, Myrtle Beach, SC; [11]Pfizer Inc., San Diego, CA; [12]Astellas Pharma Inc., Northbrook, IL; [13]Astellas Pharma Inc., Leiden, the Netherlands; [14]Department of Urology, University Hospital, Eberhard Karls University, Tübingen, Germany

*Current affiliation: Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
†Current affiliation: B-value, Leiden, the Netherlands

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Presented by: Cristiano Ferrario

Potential conflict of interest disclosure

Speaker/ Chair name	Advisory boards	Speaker's bureau	Payment/ Honoraria	Grants/ Research support	Clinical trials	Investments	Patents
	AstraZeneca	Novartis	Astellas Pharma		Amgen		
	Bayer		AstraZeneca		Astellas Pharma		
	Genomic Health		Bayer		AstraZeneca		
	Merck		Merck		Bayer		
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					Roche/ Genentech		
					Sanofi		
					Zymeworks		

Background

- Androgen deprivation therapy (ADT) had been the standard of care for men with metastatic hormone-sensitive prostate cancer (mHSPC), but progression within 1–3 years to castration-resistant prostate cancer (CRPC) on ADT alone was still observed[1,2]
- Combining ADT with docetaxel, abiraterone acetate, and radiation to the prostate has been shown to delay progression to CRPC[1-6] and improve overall survival[1,3-5] in men with mHSPC
- However, the most recently published studies in mHSPC excluded men who received prior docetaxel chemotherapy[4,5]

1. Sweeney CJ et al. N Engl J Med 2015;373:737–746; 2. Gravis G et al. Lancet Oncol 2013;14:149–158; 3. James ND et al. Lancet 2016;387:1163–1177; 4. Fizazi K et al. N Engl J Med 2017;377:352–360; 5. James ND et al. N Engl J Med 2017;377:338–346; 6. Parker CC et al. Lancet 2018;392:2353–2366

Background

- Enzalutamide, a potent androgen receptor inhibitor, has demonstrated clinical benefit in men with metastatic and nonmetastatic CRPC[1-5]
- Here we report the results of the ARCHES* trial, which assessed the efficacy and safety of enzalutamide in combination with ADT in men with mHSPC
- ARCHES included patients with both low and high volume disease (CHAARTED criteria),[6] with and without prior docetaxel treatment

Hypothesis

- Enzalutamide, in combination with ADT, would prolong radiographic progression-free survival (rPFS) in men with mHSPC, compared to ADT alone

*Androgen Receptor Inhibition with CHemohormonal Therapy in Men with Metastatic Hormone-Sensitive Prostate Cancer (ARCHES)

1. Beer TM et al. N Engl J Med 2014;371:424–433; 2. Scher HI et al. N Engl J Med 2012;367:1187–1197; 3. Shore N et al. Lancet Oncol 2016;17:153–163; 4. Penson DF et al. J Clin Oncol 2016;34:2098–2106; 5. Hussain M et al. N Engl J Med 2018;378:2465–2474; 6. Sweeney CJ et al. N Engl J Med 2015;373:737–746

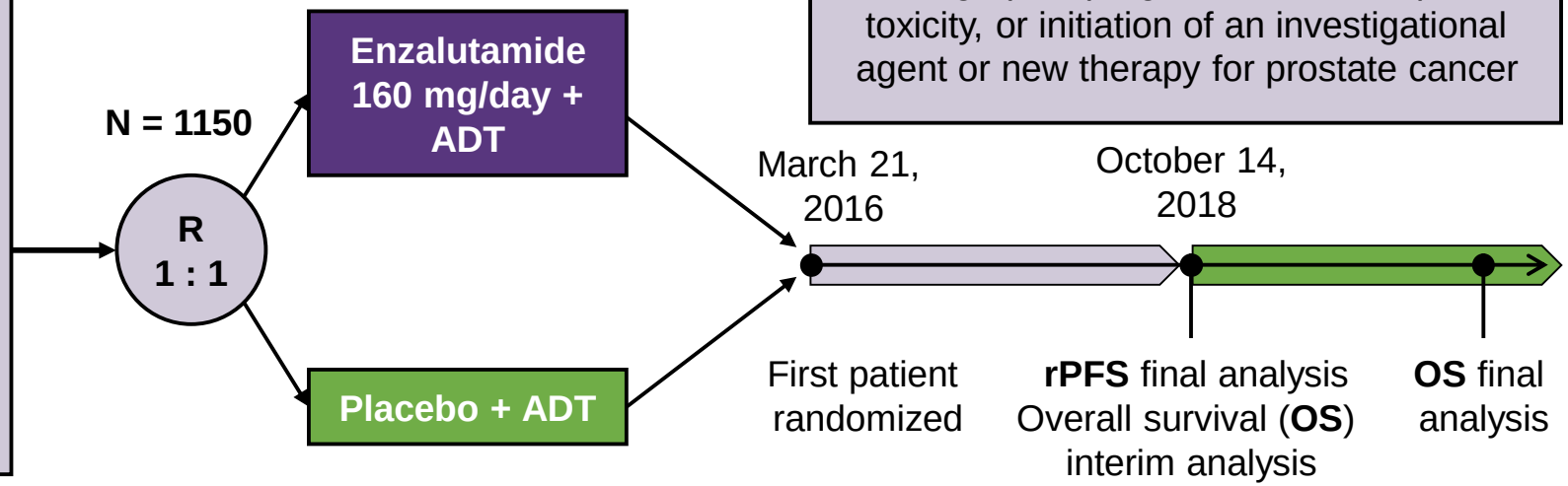
ARCHES study design

Key eligibility criteria

- mHSPC (confirmed by bone scan, CT, or MRI), histologically confirmed adenocarcinoma
- ECOG Performance Status 0 to 1
- Current ADT duration ≤3 months unless prior docetaxel, then ≤6 months

Stratification factors

- Volume of disease (low vs. high*)
- Prior docetaxel therapy for mHSPC (none, 1–5, or 6 cycles)



Key discontinuation criteria

Radiographic progression, unacceptable toxicity, or initiation of an investigational agent or new therapy for prostate cancer

Primary endpoint

- rPFS: time from randomization to first objective evidence of radiographic progression assessed centrally, or death from any cause within 24 weeks of treatment discontinuation, whichever occurs first
  - Radiographic disease progression was defined by RECIST 1.1 criteria for soft tissue disease or by appearance of ≥2 new lesions on bone scan compared to baseline (at week 13) or vs. best response on treatment (week 25 or later). New bone scan lesions observed at week 13 required confirmation of ≥2 additional new bone lesions on subsequent scans

*Defined as metastases involving the viscera or, in the absence of visceral lesions, ≥4 bone lesions, ≥1 of which must be in a bony structure beyond the vertebral column and pelvic bone

ARCHES secondary endpoints and statistical analysis plan

Key secondary endpoints

- Time to prostate-specific antigen (PSA) progression*
- Time to use of new antineoplastic therapy*
- PSA undetectable rate*
- Objective response rate*
- Time to deterioration in urinary symptoms (QLQ-PR25)*
- OS*

Other secondary endpoints

- Time to first symptomatic skeletal event
- Time to castration resistance*
- Time to deterioration of quality of life (QoL) [FACT-P]
- Time to pain progression (BPI-SF)

Safety*

*Reported in current presentation

Statistical design

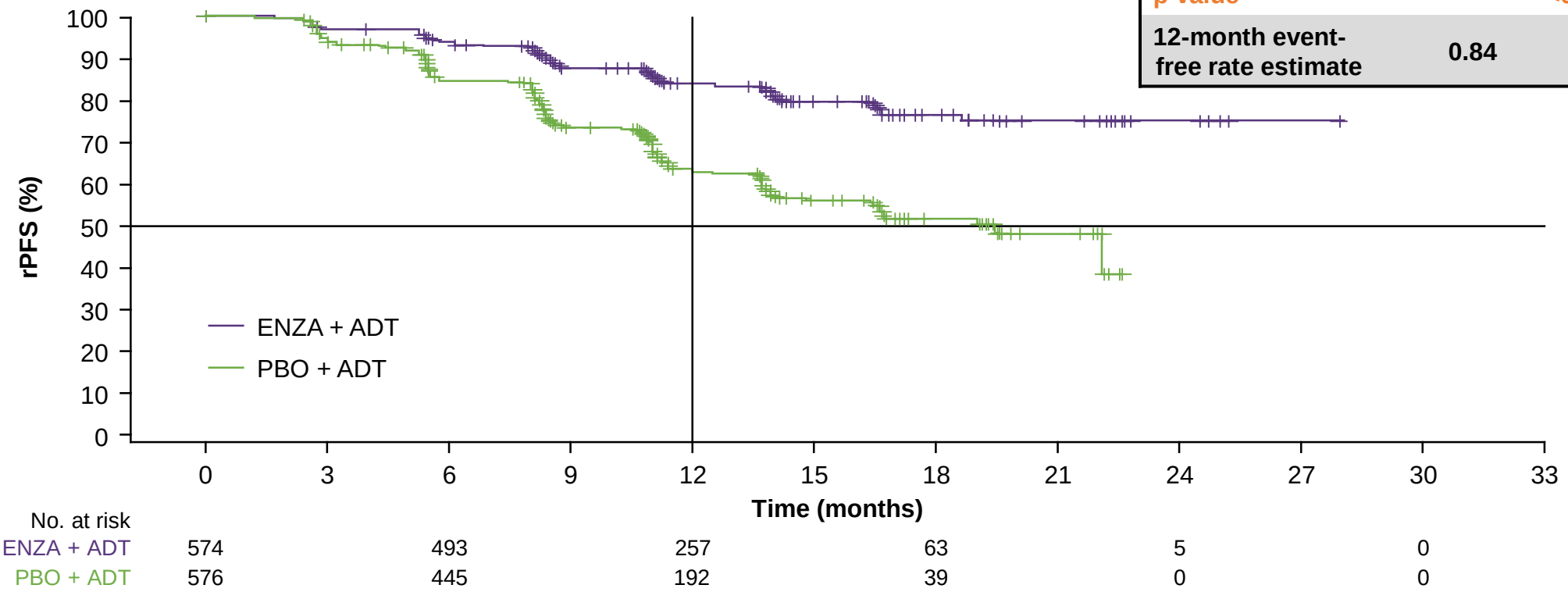
- Target of 262 progression events provided 90% power to detect a hazard ratio (HR) of 0.67, assuming a median rPFS of 20 months with placebo
- Interim analysis of OS performed at rPFS final analysis
- Final analysis of OS when ~342 deaths reported, tested at a two-sided alpha error of 0.05 only if all other five key secondary endpoint analyses, tested sequentially, are statistically significant at alpha error of ≤0.01; otherwise ≤0.04

Baseline patient characteristics (n = 1150)

Characteristic	Enzalutamide + ADT (n = 574)	Placebo + ADT (n = 576)
Median age, y (range)	70 (46–92)	70 (42–92)
Geographic region, n (%) Asia-Pacific, Europe, North America	104 (18), 341 (59), 86 (15)	113 (20), 344 (60), 77 (13)
ECOG PS 0, n (%)	448 (78)	443 (77)
High disease volume, n (%)	354 (62)	373 (65)
Gleason score ≥8 at initial diagnosis, n (%)	386 (67)	373 (65)
Localization of confirmed metastases at screening, n (%)		
Bone only	268 (47)	245 (43)
Soft tissue only	51 (9)	45 (8)
Bone and soft tissue	217 (38)	241 (42)
Distant metastasis at initial diagnosis, n (%)	402 (70)	365 (63)
Prior therapy, n (%)		
Docetaxel	103 (18)	102 (18)
ADT	535 (93)	514 (89)
Anti-androgen	205 (36)	229 (40)
Median duration of prior ADT, months	1.6	1.6
Median PSA, ng/mL	5.4	5.1

Primary endpoint: rPFS

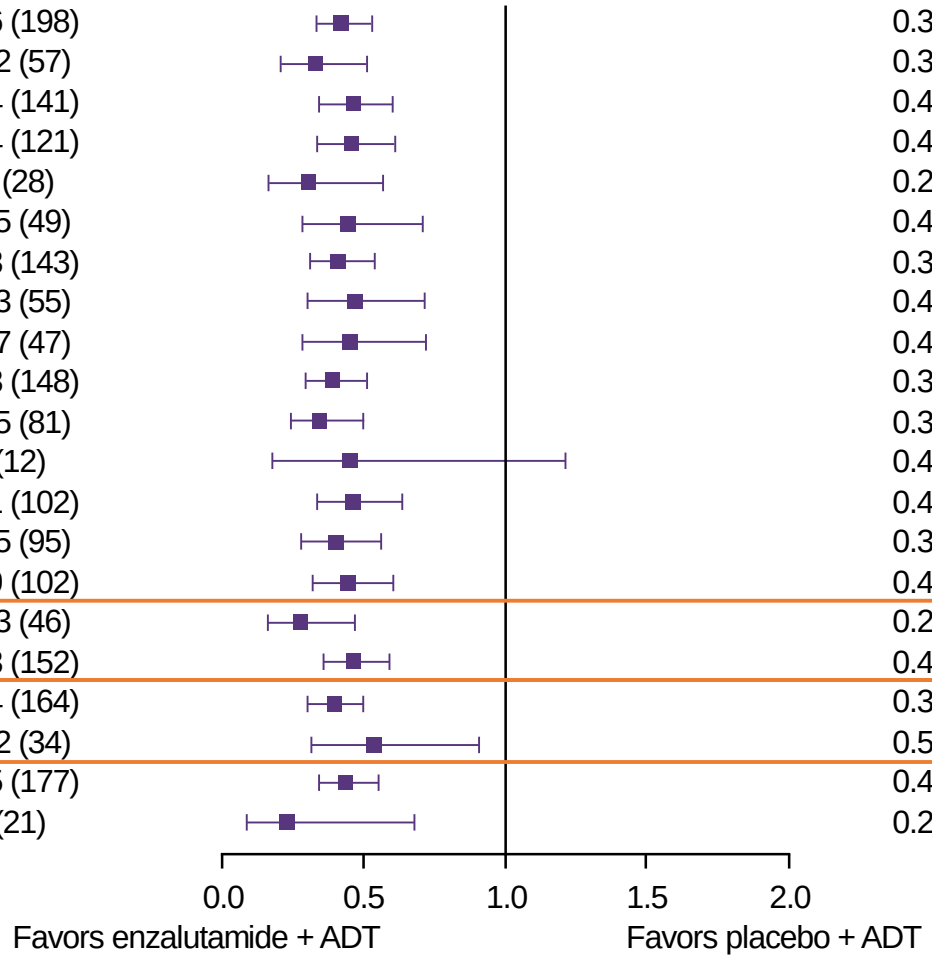
	ENZA + ADT (n = 574)	PBO + ADT (n = 576)
Median, month (95% CI)	NR (NR, NR)	19.45 (16.59, NR)
HR (95% CI)	0.39 (0.30, 0.50)	
p value	<0.0001	
12-month event-free rate estimate	0.84	0.64



- At data cut-off, there were 262 events of radiographic progression (enzalutamide + ADT, 77; placebo + ADT, 185) and 25 deaths without radiographic progression (enzalutamide + ADT, 12; placebo + ADT, 13)
- Median follow-up time is 14.4 months; median duration of therapy was 12.8 (range 0.2–26.6) months for enzalutamide + ADT and 11.6 (range 0.2–24.6) months for placebo + ADT
- As of October 14, 2018 (cut-off date), 769 patients were still on treatment, 437 (76%) for enzalutamide + ADT and 332 (58%) for placebo + ADT

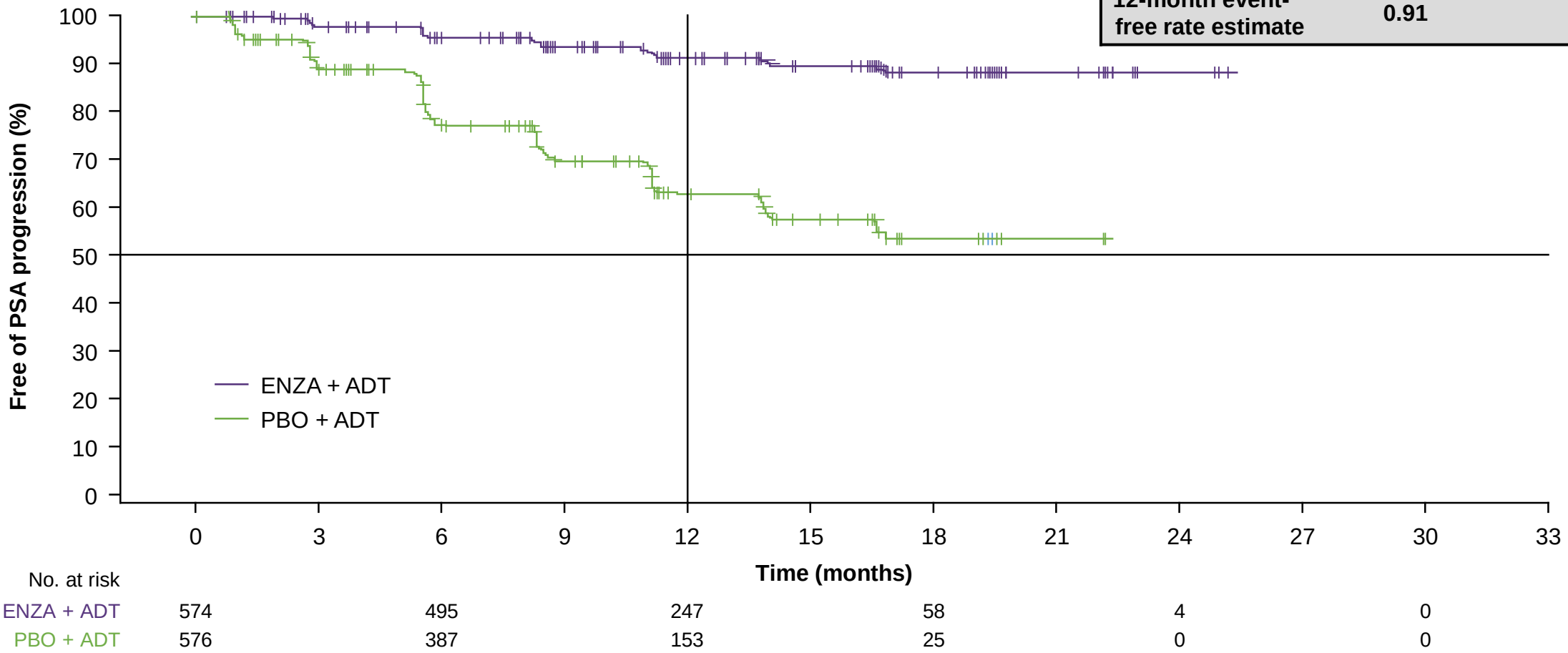
Subgroup analysis of rPFS

Subgroup	Enzalutamide + ADT / placebo + ADT N (E)	Hazard ratio (95% CI)
All patients	574 (89) / 576 (198)	0.39 (0.30, 0.50)
Age <65 years	149 (21) / 152 (57)	0.30 (0.18, 0.49)
Age ≥65 years	426 (68) / 424 (141)	0.43 (0.32, 0.58)
Geographic region – Europe	341 (55) / 344 (121)	0.43 (0.31, 0.59)
Geographic region – North America	86 (12) / 77 (28)	0.27 (0.14, 0.54)
Geographic region – rest of the world	147 (22) / 155 (49)	0.41 (0.25, 0.68)
ECOG status 0 at baseline	448 (65) / 443 (143)	0.38 (0.28, 0.51)
ECOG status 1 at baseline	125 (24) / 133 (55)	0.43 (0.27, 0.70)
Gleason score at initial diagnosis <8	171 (21) / 187 (47)	0.42 (0.25, 0.70)
Gleason score at initial diagnosis ≥8	386 (63) / 373 (148)	0.36 (0.27, 0.48)
Disease localization at baseline – bone only	268 (33) / 245 (81)	0.31 (0.21, 0.47)
Disease localization at baseline – soft tissue only	51 (5) / 45 (12)	0.42 (0.15, 1.20)
Disease localization at baseline – bone and soft tissue	217 (50) / 241 (102)	0.44 (0.31, 0.61)
Baseline PSA value at or below overall median	293 (40) / 305 (95)	0.37 (0.26, 0.54)
Baseline PSA value above overall median	279 (49) / 269 (102)	0.41 (0.29, 0.58)
Low volume of disease	220 (13) / 203 (46)	0.24 (0.13, 0.45)
High volume of disease	354 (76) / 373 (152)	0.44 (0.33, 0.57)
No prior docetaxel therapy	471 (68) / 474 (164)	0.36 (0.27, 0.48)
Prior docetaxel therapy	103 (21) / 102 (34)	0.53 (0.31, 0.92)
Previous use of ADT or orchiectomy	535 (86) / 515 (177)	0.41 (0.31, 0.52)
No previous use of ADT or orchiectomy	39 (3) / 61 (21)	0.20 (0.06, 0.66)



Time to PSA progression

	ENZA + ADT (n = 574)	PBO + ADT (n = 576)
Median, month (95% CI)	NR (NR, NR)	NR (16.59, NR)
HR (95% CI)	0.19 (0.13, 0.26)	
p value	<0.0001	
12-month event-free rate estimate	0.91	0.63



- Median time to castration resistance was not reached with enzalutamide + ADT, vs. 13.9 months for placebo + ADT (HR 0.28; 95% CI 0.22, 0.36; p<0.0001)

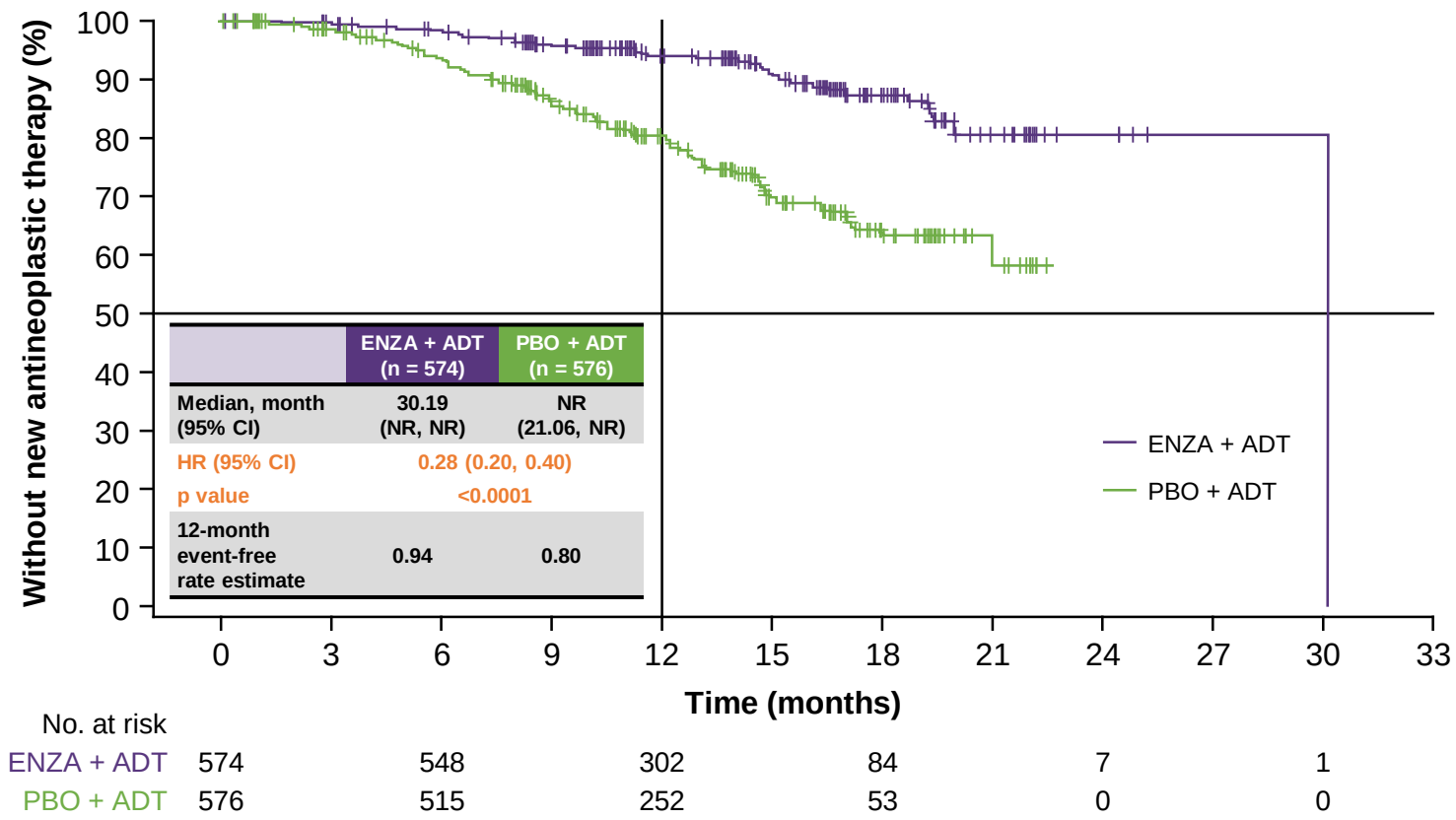
PSA undetectable rate and objective response rate

Event, n (%)	Enzalutamide + ADT	Placebo + ADT	Rate difference, % (95% CI)	p-value
PSA undetectable rate				
Detectable PSA at baseline, n	511	506		
Undetectable PSA (<0.2 ng/mL) rate, % (95% CI)	68.1 (63.9, 72.1)	17.6 (14.4, 21.2)	50.5 (45.3, 55.7)	<0.0001
Best overall response				
Measurable soft tissue disease at baseline, n	177	182		
Objective response rate,* % (95% CI)	83.1 (76.7, 88.3)	63.7 (56.3, 70.7)	19.3 (10.4, 28.2)	<0.0001
Complete response, %	36.7	23.1		
Partial response, %	46.3	40.7		

- Enzalutamide + ADT significantly increased the PSA undetectable rate and the objective response rate compared to placebo + ADT

*Complete or partial response using RECIST 1.1

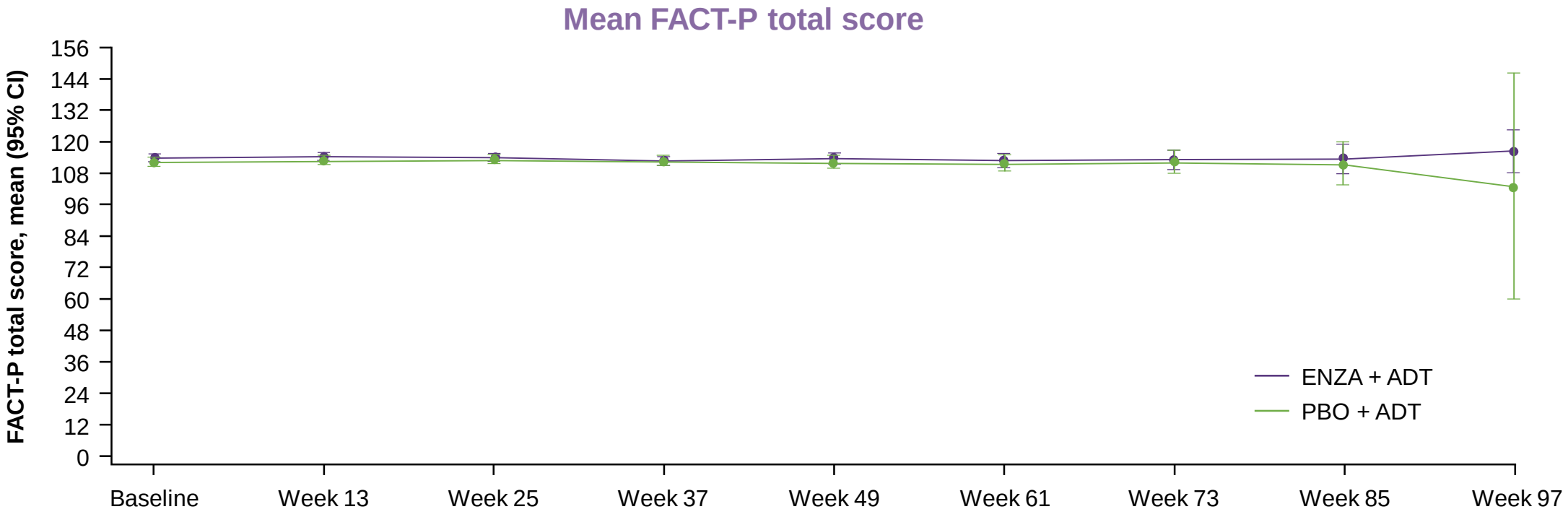
Time to initiation of new antineoplastic therapy



First new antineoplastic prostate cancer therapy	Enzalutamide + ADT	Placebo + ADT
Overall, n	46	133
Docetaxel, n (%)	11 (24)	52 (39)
Abiraterone, n (%)	13 (28)	28 (21)
Enzalutamide, n (%)	4 (9)	28 (21)
Bicalutamide, n (%)	4 (9)	12 (9)
Other, n (%)	14 (30)	15 (11)

- Enzalutamide + ADT significantly reduced the risk of starting a new antineoplastic therapy by 72% compared to placebo + ADT; median for the enzalutamide + ADT group is not a reliable estimate as it resulted from an event observed in the only remaining patient at risk at approximately 30 months, leading to the vertical drop at the end of the Kaplan-Meier curve
- Docetaxel, followed by abiraterone, was the most common first new antineoplastic prostate cancer therapy

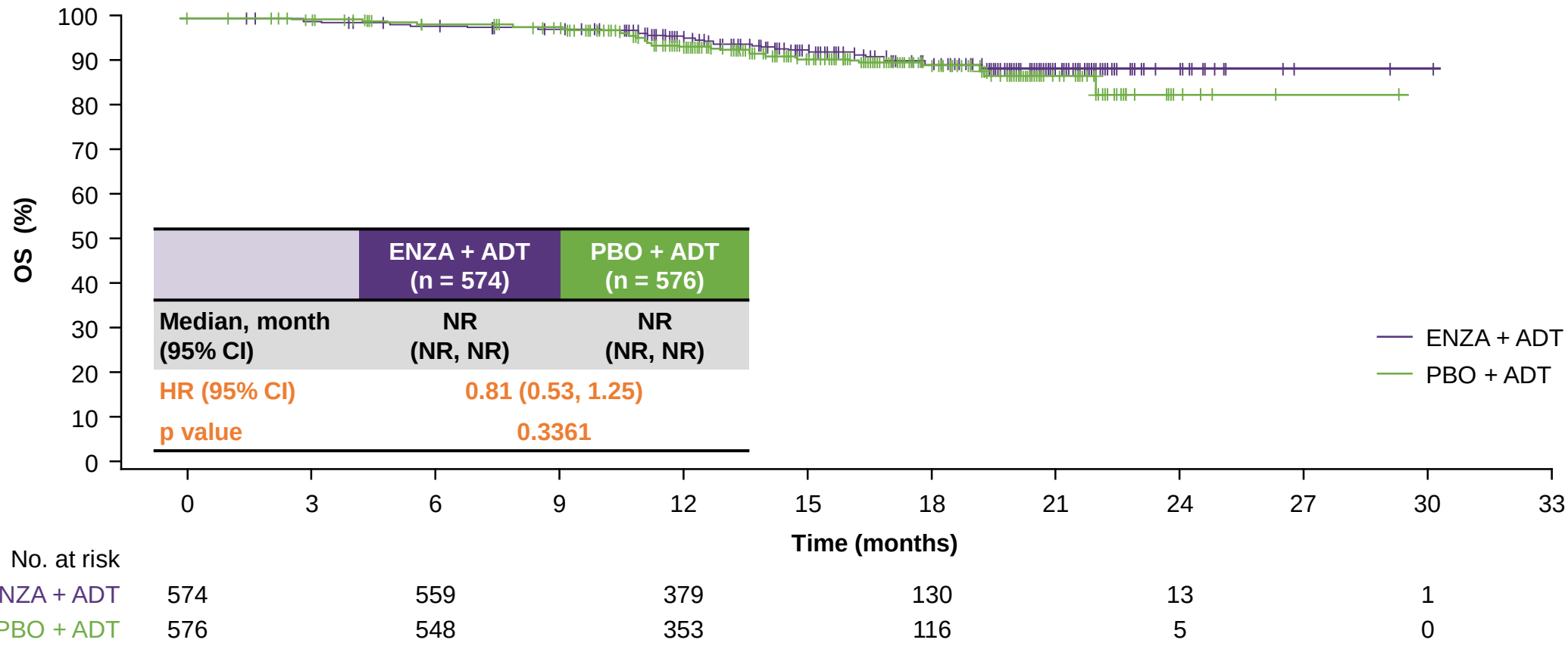
Quality of life over time



No. of patients								
PBO + ADT	553	529	487	429	298	191	101	36	6
ENZA + ADT	550	533	499	474	349	236	128	51	18

- As of data cut-off with a median follow up of 14.4 months, addition of enzalutamide to ADT did not have a significant impact on time to deterioration in urinary symptoms (HR 0.88, 95% CI 0.72, 1.08; p=0.2162) or FACT-P total score compared with placebo plus ADT

Overall survival: interim analysis (84 deaths)



No. at risk						
ENZA + ADT	574	559	379	130	13	1
PBO + ADT	576	548	353	116	5	0

- At the time of interim analysis, OS data are not mature, with 25% of 342 events required for final analysis (enzalutamide plus ADT, 39; placebo plus ADT, 45) and 19% reduction in risk of death that is not statistically significant
- Final OS analysis will be conducted with ~342 deaths at 4% significance level

Adverse events (AEs)

Event, n (%)	Enzalutamide + ADT (n = 572)		Placebo + ADT (n = 574)	
Any AE leading to treatment withdrawal	41 (7.2)		30 (5.2)	
Any AE leading to death*	14 (2.4)		10 (1.7)	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Any AE	487 (85.1)	139 (24.3)	493 (85.9)	147 (25.6)
Most common AEs (any grade) occurring in ≥5% of patients in either group†				
Hot flush	155 (27.1)	2 (0.3)	128 (22.3)	0
Fatigue	112 (19.6)	5 (0.9)	88 (15.3)	6 (1.0)
Arthralgia	70 (12.2)	2 (0.3)	61 (10.6)	4 (0.7)
Back pain	43 (7.5)	5 (0.9)	62 (10.8)	3 (0.5)
Increased weight	35 (6.1)	2 (0.3)	44 (7.7)	1 (0.2)
Hypertension	46 (8.0)	19 (3.3)	32 (5.6)	10 (1.7)
Diarrhea	34 (5.9)	0	33 (5.7)	1 (0.2)
Peripheral edema	29 (5.1)	1 (0.2)	38 (6.6)	1 (0.2)
Nausea	37 (6.5)	1 (0.2)	29 (5.1)	0
Asthenia	31 (5.4)	6 (1.0)	28 (4.9)	3 (0.5)
Constipation	28 (4.9)	0	31 (5.4)	0
Musculoskeletal pain	36 (6.3)	1 (0.2)	23 (4.0)	1 (0.2)
Dizziness	29 (5.1)	0	20 (3.5)	0

Bold: AEs (all grades) that occur >2% in enzalutamide + ADT compared with placebo + ADT
*Of the AEs leading to death, none were considered related to treatment in the enzalutamide + ADT group and one in the placebo + ADT group (general physical health deterioration); †None of the most common AEs were grade 5

AEs of special interest

Event, n (%)	Enzalutamide + ADT (n = 572)		Placebo + ADT (n = 574)	
Any AE of special interest*	324 (56.6)		291 (50.7)	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Convulsion	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)
Hypertension	49 (8.6)	19 (3.3)	36 (6.3)	12 (2.1)
Neutrophil count decreased	5 (0.9)	2 (0.3)	4 (0.7)	2 (0.3)
Cognitive / memory impairment	26 (4.5)	4 (0.7)	12 (2.1)	0
Ischemic heart disease	10 (1.7)	3 (0.5)	8 (1.4)	6 (1.0)
Other selected cardiovascular events	13 (2.3)	6 (1.0)	9 (1.6)	5 (0.9)
Posterior reversible encephalopathy syndrome	0	0	0	0
Fatigue	138 (24.1)	10 (1.7)	112 (19.5)	9 (1.6)
Fall	21 (3.7)	2 (0.3)	15 (2.6)	1 (0.2)
Fractures	37 (6.5)	6 (1.0)	24 (4.2)	6 (1.0)
Loss of consciousness	9 (1.6)	6 (1.0)	1 (0.2)	1 (0.2)
Thrombocytopenia	3 (0.5)	0	3 (0.5)	0
Musculoskeletal events	151 (26.4)	9 (1.6)	159 (27.7)	12 (2.1)
Severe cutaneous adverse reactions	0	0	1 (0.2)	0
Angioedema	7 (1.2)	1 (0.2)	1 (0.2)	0
Rash	15 (2.6)	0	9 (1.6)	0
Second primary malignancies	11 (1.9)	9 (1.6)	11 (1.9)	7 (1.2)

Bold: AEs (all grades) that occur >2% in enzalutamide + ADT compared with placebo + ADT
*Based on pre-specified combinations of preferred terms (MedDRA 21.0) related to the AE of special interest; the only AEs of special interest that were grade 5 were in the enzalutamide + ADT group (ischemic heart disease, n=1; other selected cardiovascular events, n=1)

Conclusions

- In men with mHSPC, the addition of enzalutamide to ADT significantly prolonged rPFS, with a 61% reduction in the risk of radiographic progression or death (HR 0.39; p<0.0001)
- Significant benefits in rPFS, ranging from 47–80% reduction, were seen across all pre-specified subgroups including:
  - Low and high disease volume
  - With or without prior docetaxel therapy
- Secondary endpoints (time to PSA progression, time to first use of new antineoplastic therapy, PSA undetectable rate, and objective response rate) were also significantly improved with enzalutamide + ADT compared with placebo + ADT, without significantly impacting time to deterioration in urinary symptoms and FACT-P total score

Conclusions and future directions

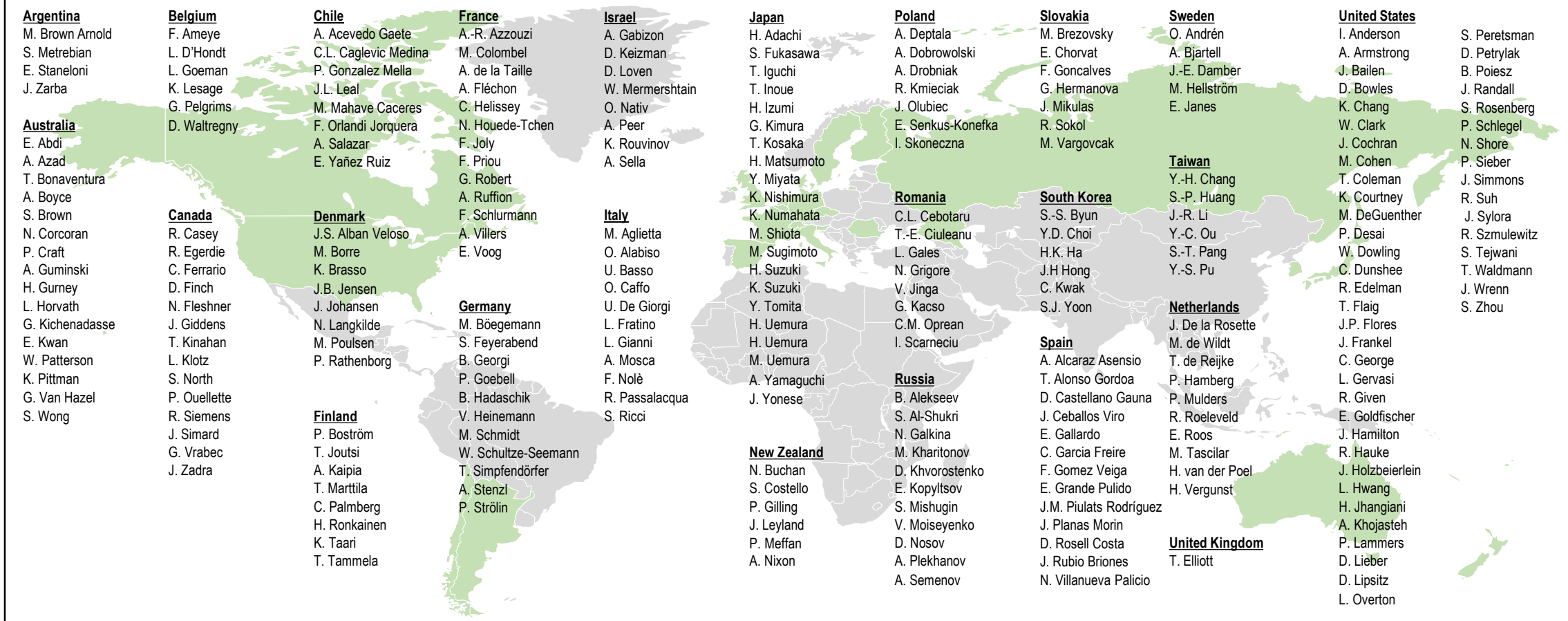
- At the time of interim OS analysis (median follow-up, 14.4 months), 93% of patients were alive; OS data are immature
- Enzalutamide + ADT was well tolerated; preliminary safety analysis appears consistent with the safety profile of enzalutamide in previous clinical trials in CRPC

- Final OS analysis will be conducted when ~342 deaths are observed
- Additional QoL outcomes are currently being analyzed
- Following unblinding at the end of the double-blind treatment period and a statistically significant positive outcome from the primary endpoint analysis, eligible patients are being offered the opportunity to be treated with enzalutamide + ADT in a pre-specified open-label extension

Acknowledgments

Thank you to our patients, their caregivers and families, ARCHES investigators, and study personnel

Study sites by country



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J. Rubio Briones
N. Villanueva Palicio

Sweden
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M. Hellström
E. Janes

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Y.-S. Pu

Netherlands
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T. de Reijke
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United States
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