Impact of baseline disease volume and prior docetaxel therapy on prostate-specific antigen-related outcomes in patients with metastatic hormone-sensitive prostate cancer treated with enzalutamide plus androgen deprivation therapy

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Disclosures

- I have the following potential conflicts of interest to report:
  - Research and consultancy: Amgen, Astellas, AstraZeneca, Bayer, BMS, Clovis, Dendreon, Ferring, Janssen, Merck, Myovant, Nymox, Pfizer, Sanofi-Genzyme, Tolmar

Introduction

- **Enzalutamide** is approved in the United States for the treatment of **metastatic CSPC (also referred to as mHSPC)** based on the **Phase 3 ARCHES study** (NCT02677896) and supported by the **Phase 3 ENZAMET trial** (NCT02446405)[1-3]
  - Both trials demonstrated **improved clinical outcomes (rPFS and OS, respectively)** with enzalutamide versus the comparator arm[2,3]
- The treatment benefit of enzalutamide plus ADT on the primary endpoint of **rPFS** in ARCHES was observed **regardless of baseline PSA level** (≤ or > median) at study entry[2,4]
  - **Improvements in other PSA-related outcomes** in the overall population were also observed[2]
  - Inclusion of patients **regardless of disease volume and prior chemotherapy** in ARCHES enables additional insights on treatment efficacy in these patient subgroups[2]

1. Astellas. Press Release 2019. Available at https://www.astellas.com/en/news/15451. Accessed April 27, 2020; 2. Armstrong AJ et al. J Clin Oncol 2019;37:2974–2986;
3. Davis ID et al. N Engl J Med 2019381:121–131; 4. Stenzl A et al. J Urol 2019;201(Supplement 4);abstract LBA-10
ADT, androgen deprivation therapy; CSPC, castration-sensitive prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival

Objective

- To further assess **PSA-related outcomes in ARCHES**, by **disease volume** (low versus high) and **prior docetaxel therapy** (with versus without) at study entry

PSA, prostate-specific antigen

ARCHES study design

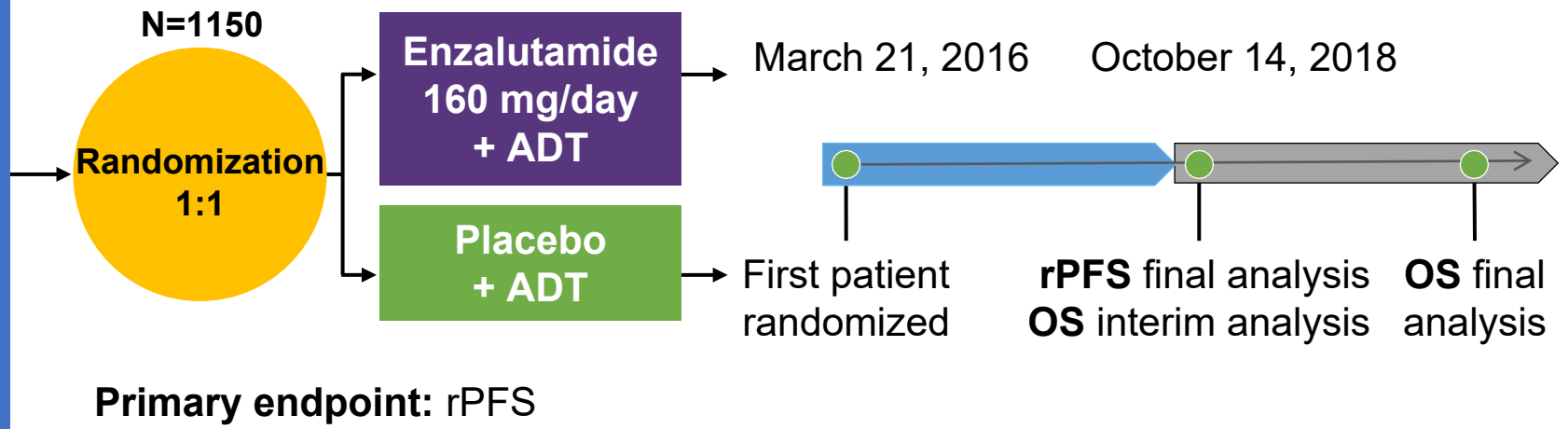
Key eligibility criteria

- **mHSPC** (confirmed by bone scan, CT, or MRI), histologically confirmed adenocarcinoma
- ECOG performance status 0–1
- Prior ADT allowed: current duration <3 months (unless prior docetaxel, then <6 months) with no radiographic disease progression or rising PSA levels prior to day 1

Stratification factors

- **Volume of disease** (low versus high*)
- **Prior docetaxel therapy** (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

*Defined, per CHAARTED criteria, as metastases involving the viscera or, in the absence of visceral lesions, ≥4 bone lesions, with ≥1 in a bony structure beyond the vertebral column and pelvic bone;
†An increase in PSA alone was not considered a study discontinuation criterion
ADT, androgen deprivation therapy; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; mHSPC, metastatic hormone-sensitive prostate cancer; MRI, magnetic resonance imaging; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival

Post hoc analyses

Analysis populations

- Overall population
- By disease volume at study entry (low versus high)
- By prior docetaxel at study entry (none versus 1–6 cycles)

Key secondary endpoint

- Time to PSA progression*

***Post hoc* endpoints**

- Time to 50% PSA reduction
- Time to undetectable PSA (<0.2 ng/mL)

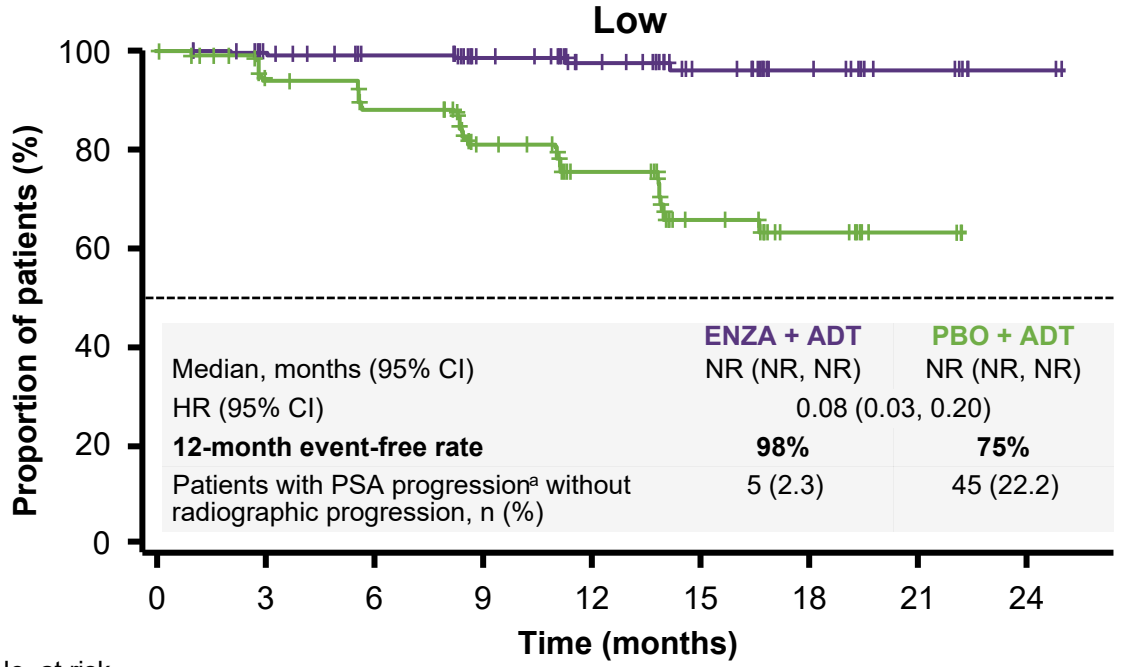
*Defined as a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir, confirmed by a second consecutive value ≥3 weeks later
PSA, prostate-specific antigen

Baseline patient characteristics (n=1150)

Characteristic	ENZA + ADT (n=574)	PBO + ADT (n=576)
Median age, years (range)	70 (46–92)	70 (42–92)
ECOG performance status 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)
Antiandrogen†	205 (36)	229 (40)
Median duration of prior ADT, months	1.6	1.6
Median PSA at study entry,‡ ng/mL (range)	5.4 (0–4823.5)	5.1 (0–19,000.0)

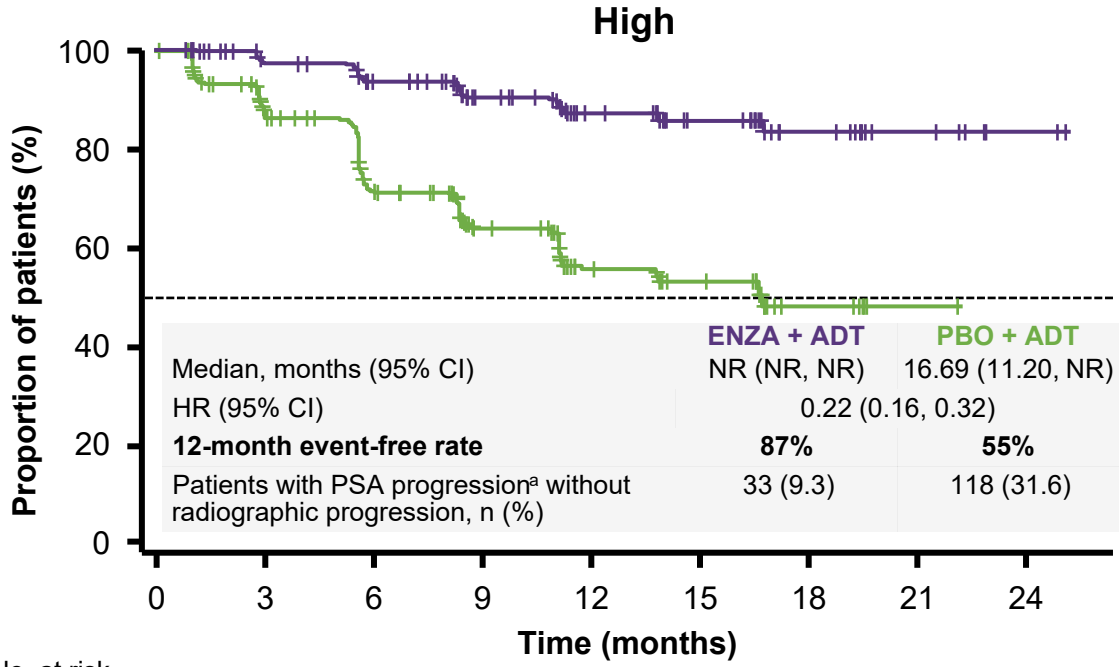
*Prior ADT <3 months was allowed (unless prior docetaxel, then <6 months), with no radiographic disease progression or rising PSA levels prior to day 1; †ENZA + ADT, n=572; PBO + ADT, n=574;
‡PSA level at initial diagnosis of prostate cancer prior to study entry was not collected
ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group; ENZA, enzalutamide; PBO, placebo; PSA, prostate-specific antigen

Time to PSA progression: disease volume



	ENZA + ADT	PBO + ADT
Median, months (95% CI)	NR (NR, NR)	NR (NR, NR)
HR (95% CI)	0.08 (0.03, 0.20)	
12-month event-free rate	**98%**	**75%**
Patients with PSA progression[a] without radiographic progression, n (%)	5 (2.3)	45 (22.2)

No. at risk									
ENZA + ADT	220	205	195	149	102	58	27	12	2
PBO + ADT	203	179	163	120	73	31	13	3	0



	ENZA + ADT	PBO + ADT
Median, months (95% CI)	NR (NR, NR)	16.69 (11.20, NR)
HR (95% CI)	0.22 (0.16, 0.32)	
12-month event-free rate	**87%**	**55%**
Patients with PSA progression[a] without radiographic progression, n (%)	33 (9.3)	118 (31.6)

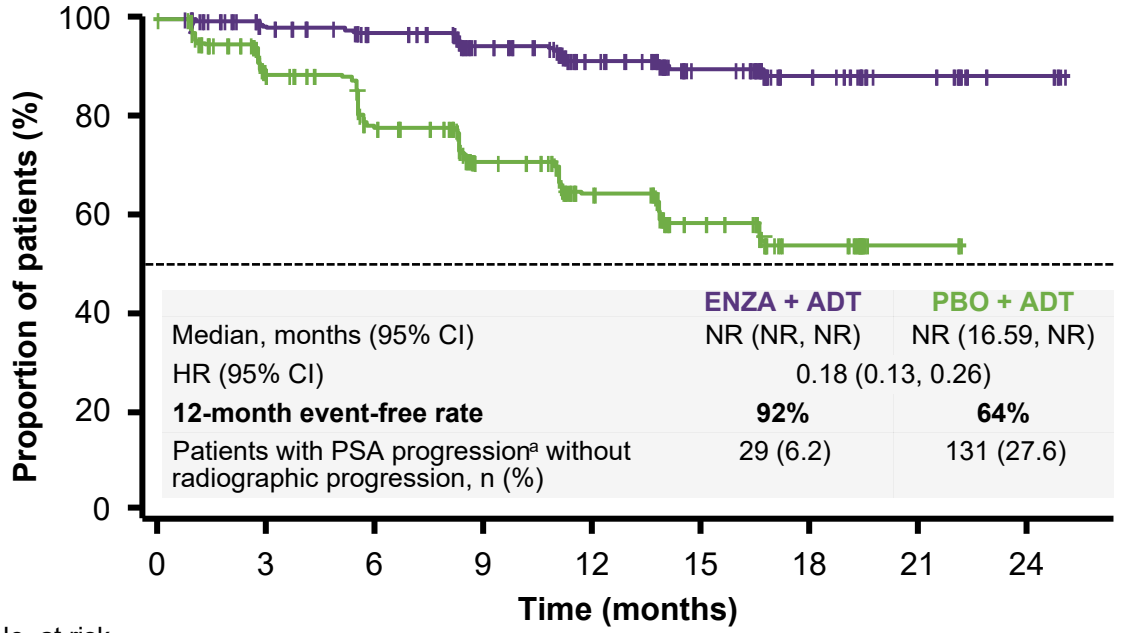
No. at risk									
ENZA + ADT	354	325	300	222	145	76	31	10	2
PBO + ADT	373	290	224	137	80	45	12	1	0

- A **reduced risk of PSA progression** with ENZA + ADT versus PBO + ADT was observed in patients with **low (92%) or high (78%) disease volume**
  - Consistent with the overall population (81% risk reduction; HR 0.19 [95% CI 0.13, 0.26][b])

PSA progression defined as a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir, confirmed by a second consecutive value ≥3 weeks later;
HR <1 favors ENZA + ADT, as it reduces the risk of PSA progression; [a]Includes patients with PSA progression earlier than radiographic progression or patients with PSA progression only;
[b]12-month event-free rate: 91% with ENZA + ADT, 63% with PBO + ADT; proportion of patients with PSA progression without radiographic progression: 38 (6.6%) with ENZA + ADT, 163 (28.3%) with PBO + ADT
ADT, androgen deprivation therapy; CI, confidence interval; ENZA, enzalutamide, HR, hazard ratio; NR, not reached; PBO, placebo; PSA, prostate-specific antigen

Time to PSA progression: prior docetaxel

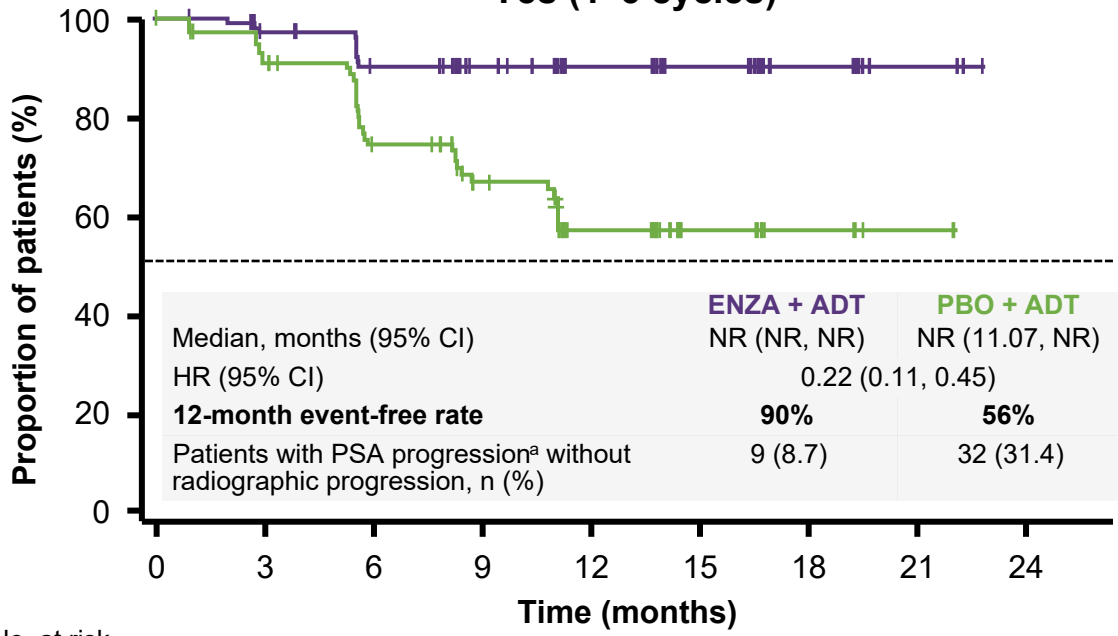
None



	ENZA + ADT	PBO + ADT
Median, months (95% CI)	NR (NR, NR)	NR (16.59, NR)
HR (95% CI)	0.18 (0.13, 0.26)	
12-month event-free rate	**92%**	**64%**
Patients with PSA progression[a] without radiographic progression, n (%)	29 (6.2)	131 (27.6)

No. at risk									
ENZA + ADT	471	434	408	308	208	114	47	19	4
PBO + ADT	474	385	323	212	134	69	22	3	0

Yes (1–6 cycles)



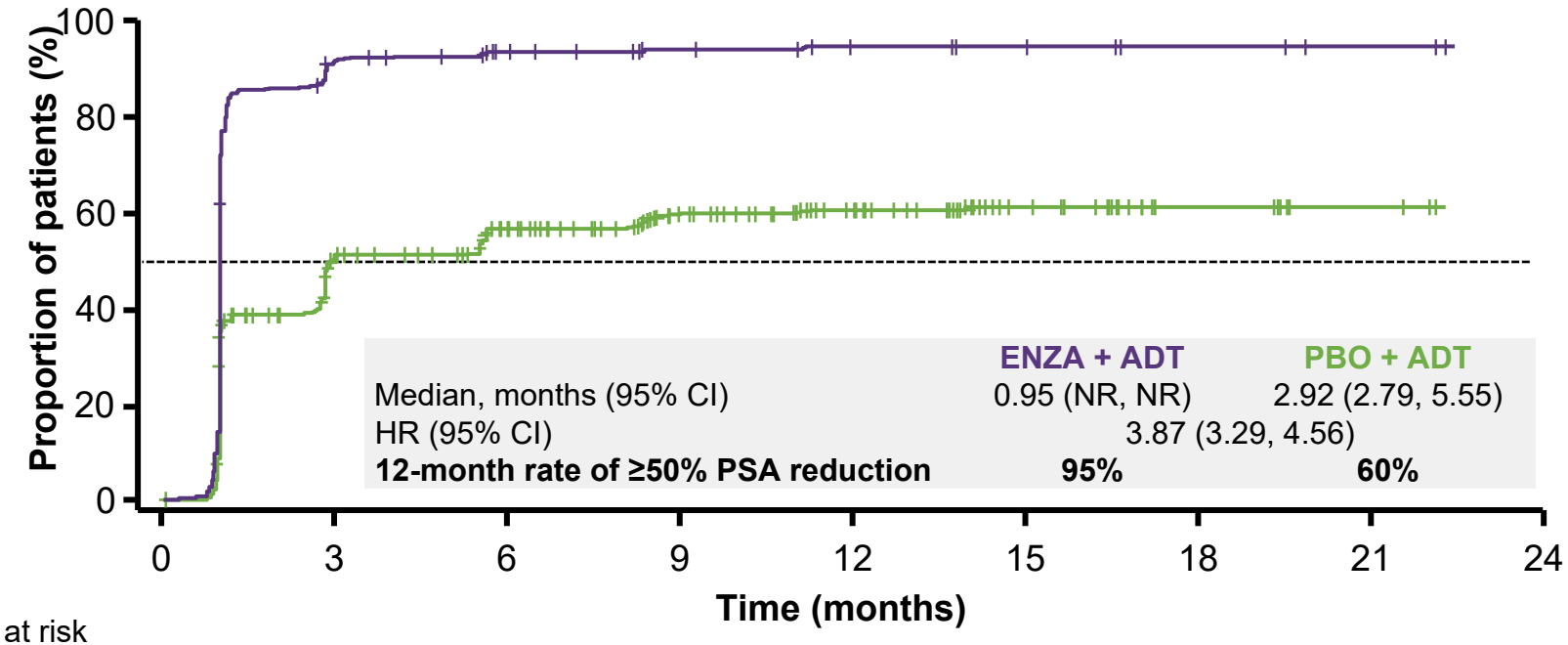
	ENZA + ADT	PBO + ADT
Median, months (95% CI)	NR (NR, NR)	NR (11.07, NR)
HR (95% CI)	0.22 (0.11, 0.45)	
12-month event-free rate	**90%**	**56%**
Patients with PSA progression[a] without radiographic progression, n (%)	9 (8.7)	32 (31.4)

No. at risk									
ENZA + ADT	103	96	87	63	39	20	11	3	0
PBO + ADT	102	84	64	45	19	7	3	1	0

- A **reduced risk of PSA progression** with ENZA + ADT versus PBO + ADT was observed in patients with **no prior docetaxel therapy (82%) or 1–6 cycles of prior docetaxel therapy (78%)**

PSA progression defined as a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir, confirmed by a second consecutive value ≥3 weeks later;
HR <1 favors ENZA + ADT, as it reduces the risk of PSA progression
ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; NR, not reached; PSA, prostate-specific antigen

Time to 50% PSA reduction: overall population

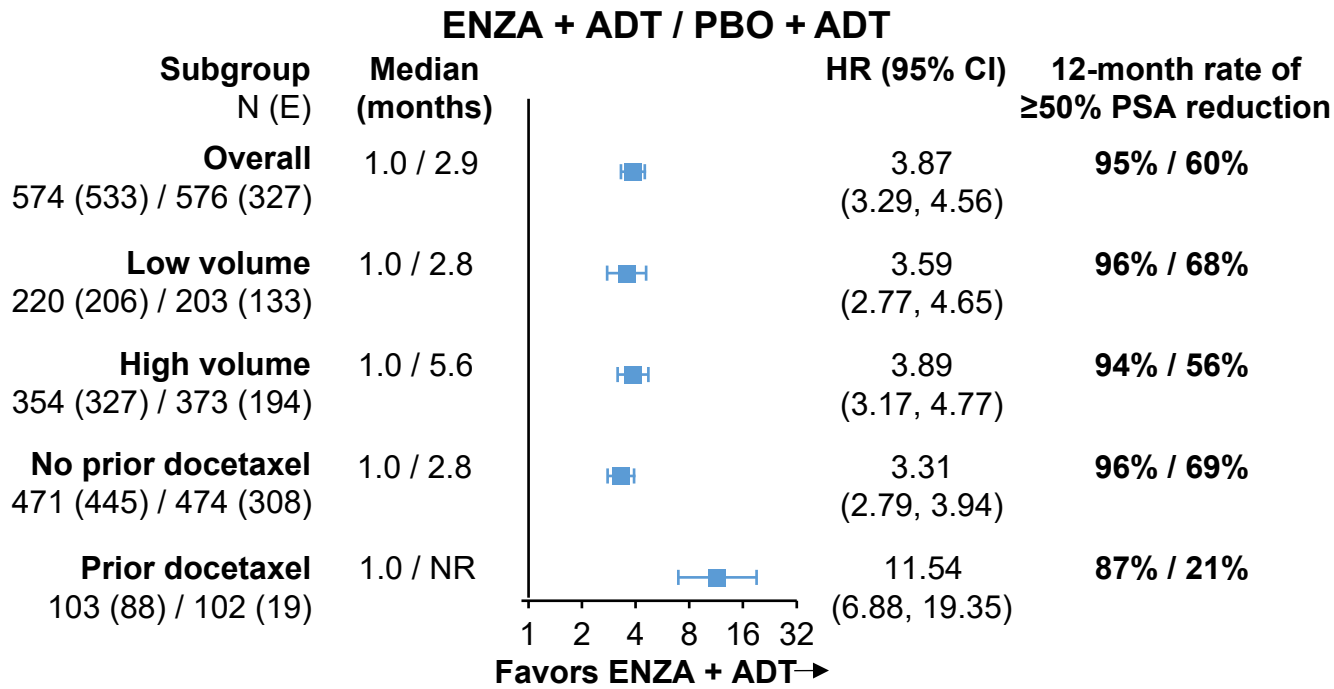


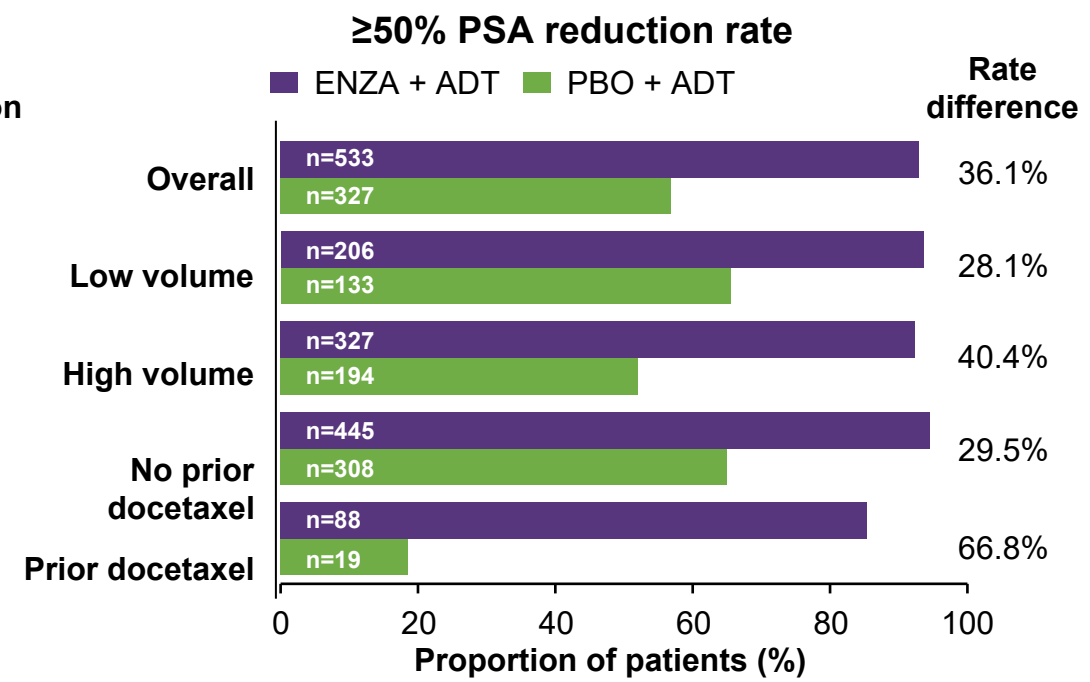
No. at risk									
ENZA + ADT	574	46	27	19	13	8	4	2	0
PBO + ADT	576	256	200	122	75	32	9	4	0

- **Median time to 50% PSA reduction** was shorter with ENZA + ADT (0.95 months) versus PBO + ADT (2.92 months) in the overall population, reflecting the **increased likelihood of 50% PSA reduction**

Time to 50% PSA reduction defined as the time from date of randomization to the date 50% PSA reduction is first observed;
HR >1 favors ENZA + ADT, as it increases the chance of PSA reduction; Unadjusted Cox HR (95% CI) 3.76 (3.20, 4.41)
ADT, androgen deprivation therapy; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; NR, not reached; PBO, placebo; PSA, prostate-specific antigen

Time to 50% PSA reduction

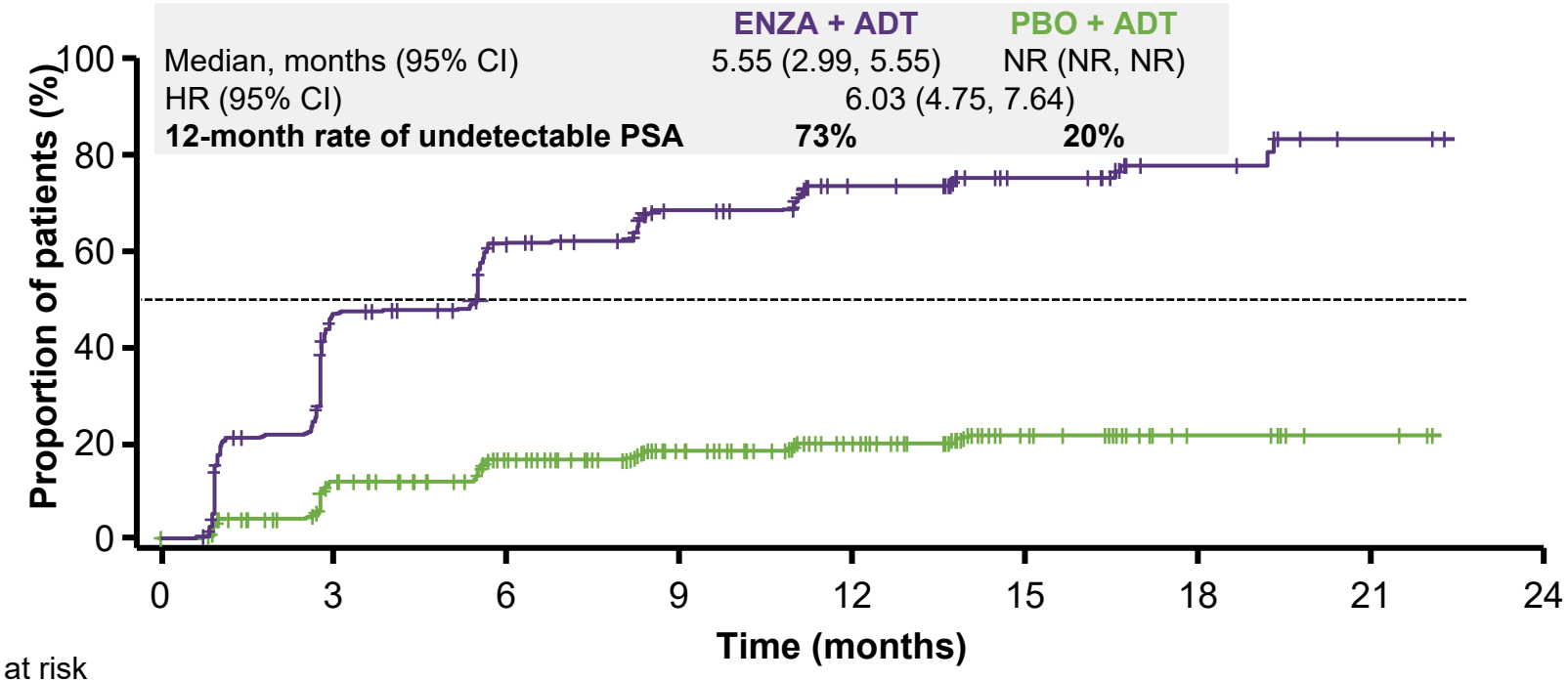




- Consistent with the overall population, **median time to 50% PSA reduction** was shorter with ENZA + ADT **regardless of disease volume or prior docetaxel**
  - ENZA + ADT: 1.0 months in all subgroups; PBO + ADT: 2.8 months–NR
- A greater proportion of patients receiving ENZA + ADT achieved **≥50% PSA reduction from baseline regardless of disease volume or prior docetaxel**
  - ENZA + ADT: 85.4–94.5%;PBO + ADT: 18.6–65.5%

Time to 50% PSA reduction defined as the time from date of randomization to the date 50% PSA reduction is first observed; HR >1 favors ENZA + ADT, as it increases the chance of PSA reduction
ADT, androgen deprivation therapy; CI, confidence interval; E, number of events; ENZA, enzalutamide; HR, hazard ratio; NR, not reached; PBO, placebo; PSA, prostate-specific antigen; RD, rate difference

Time to undetectable PSA: overall population

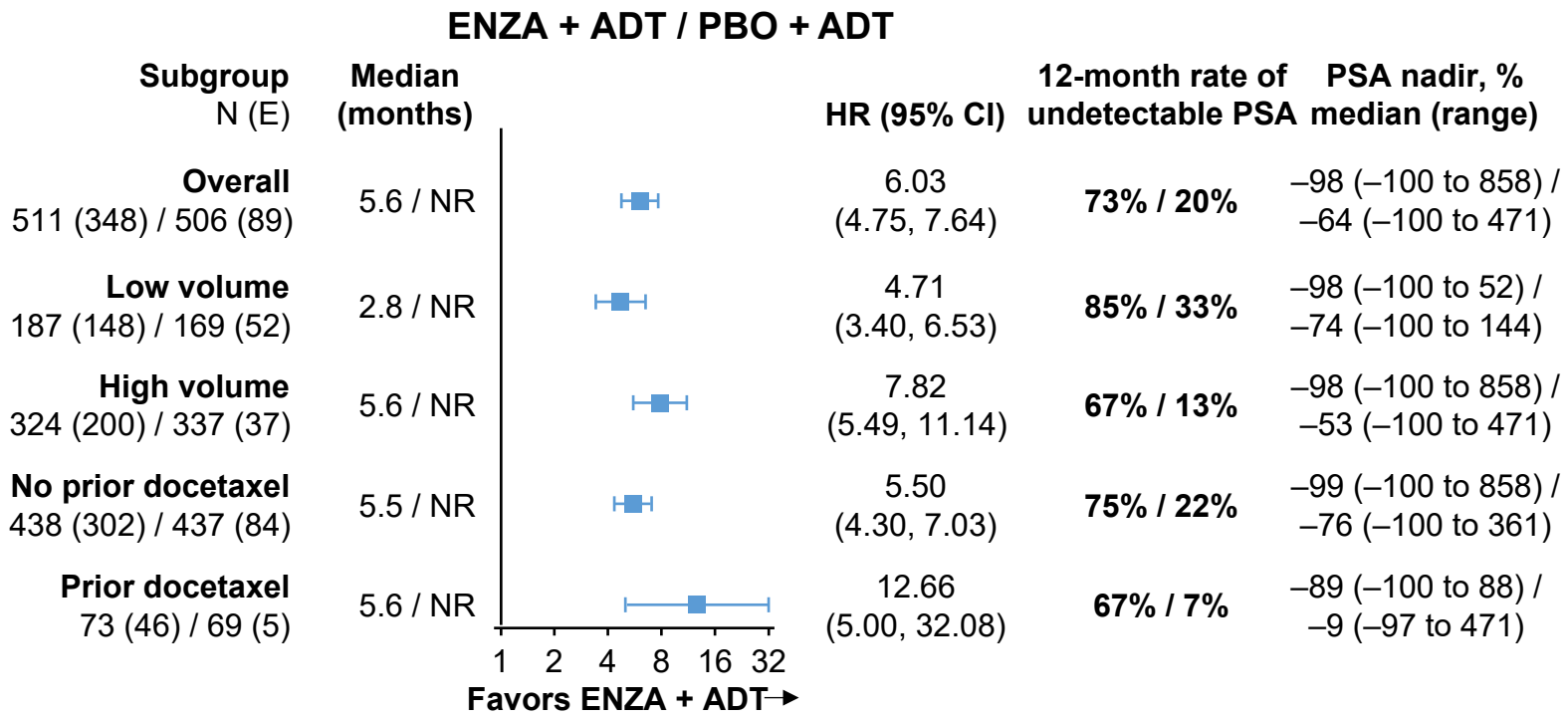


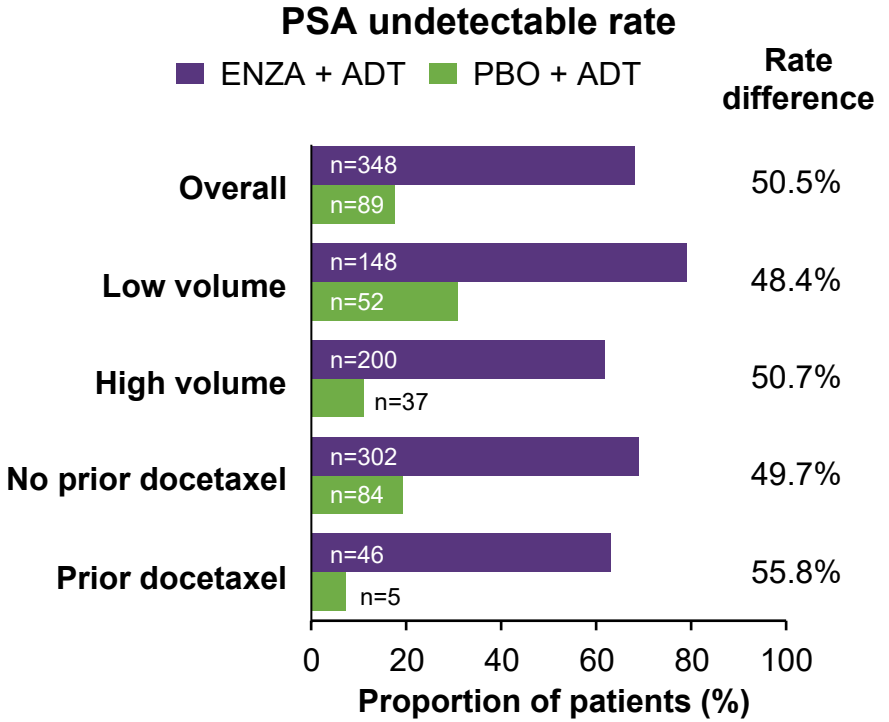
No. at risk									
ENZA + ADT	511	258	173	102	54	29	9	2	0
PBO + ADT	506	407	350	236	151	71	21	6	0

- In patients with detectable (≥0.2 ng/mL) PSA at baseline, **median time to undetectable PSA** was shorter with ENZA + ADT (5.55 months) versus PBO + ADT (NR) in the overall population

Time to undetectable PSA defined as the time from date of randomization to the date undetectable PSA is first observed;
HR >1 favors ENZA + ADT, as it increases the chance of reaching undetectable PSA levels ; Unadjusted Cox HR (95% CI) 5.88 (4.64, 7.45)
ADT, androgen deprivation therapy; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; NR, not reached; PBO, placebo; PSA, prostate-specific antigen

Time to undetectable PSA





- Consistent with the overall population, **median time to undetectable PSA** was shorter with ENZA + ADT **regardless of disease volume or prior docetaxel**
  - ENZA + ADT: 2.8–5.6 months; PBO + ADT: NR in all subgroups
- A greater proportion of patients receiving ENZA + ADT achieved **undetectable PSA regardless of disease volume or prior docetaxel**
  - ENZA + ADT: 61.7–79.1%; PBO + ADT: 7.2–30.8%

Time to undetectable PSA defined as the time from date of randomization to the date undetectable PSA is first observed;
PSA nadir is the largest maximal PSA reduction postbaseline, expressed as the percentage change from baseline ; HR >1 favors ENZA + ADT, as it increases the chance of reaching undetectable PSA levels
ADT, androgen deprivation therapy; CI, confidence interval; E, number of events; ENZA, enzalutamide; HR, hazard ratio; NR, not reached; PBO, placebo; PSA, prostate-specific antigen; RD, rate difference

Conclusions

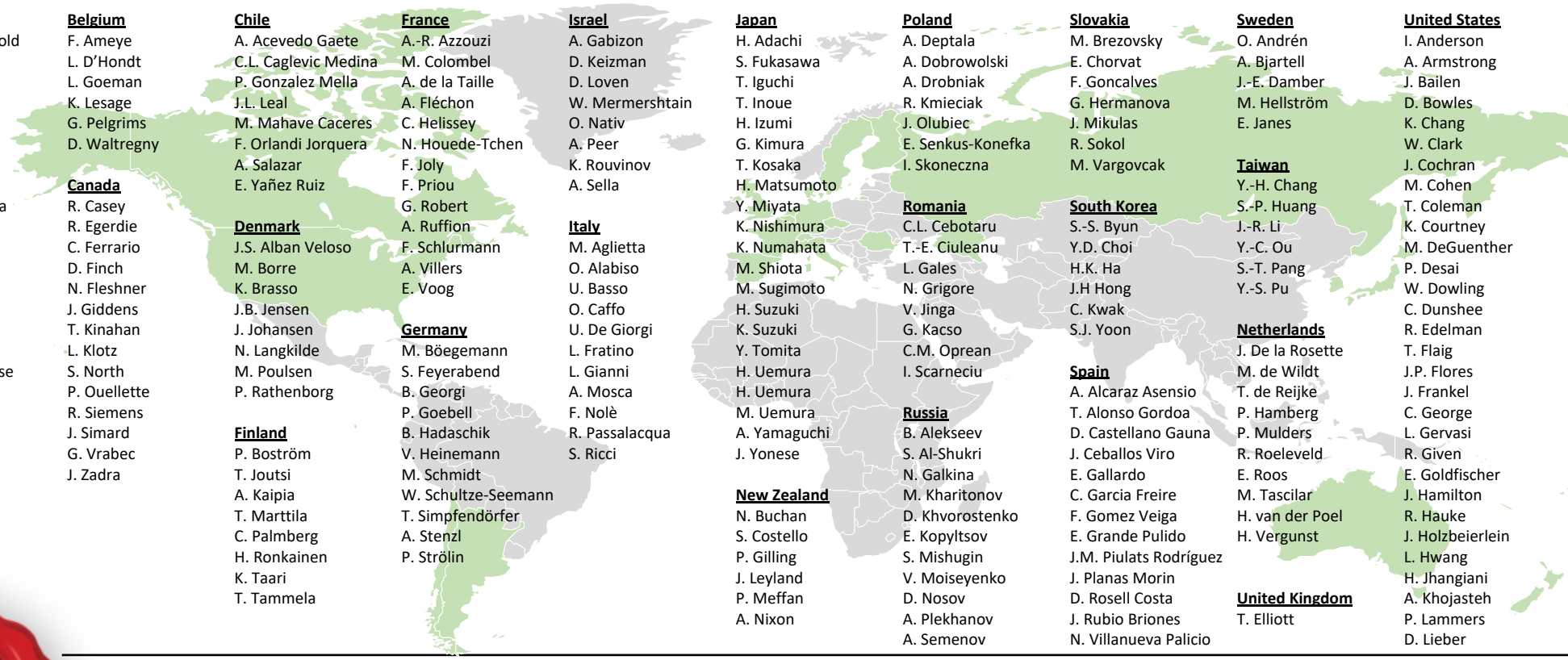
- Compared with placebo plus ADT in this *post hoc* analysis of patients with mHSPC, **enzalutamide plus ADT** resulted in:
  - **A long-term reduced risk of PSA progression**
  - **A more rapid and long-term reduction in PSA from baseline**
- The **treatment benefit** with enzalutamide plus ADT on PSA-related outcomes was observed **regardless of disease volume** (low versus high) or **prior docetaxel therapy** (with versus without) at study entry

ADT, androgen deprivation therapy; mHSPC, metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen

Acknowledgments

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

Study sites by country



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