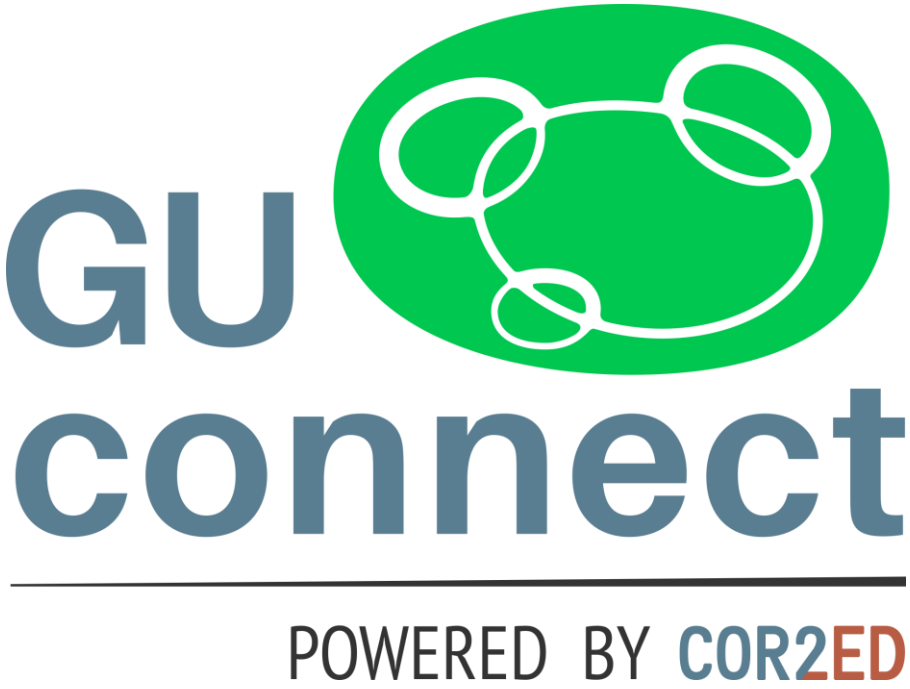
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MEETING SUMMARY
ASCO GU 2019, San Francisco, USA

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PROSTATE CANCER UPDATE

DISCLAIMER

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PHASE III STUDY OF ADT WITH ENZALUTAMIDE OR PLACEBO IN mHSPC: THE ARCHES TRIAL

Armstrong, et al. Abstract #687

ADT, Androgen Deprivation Therapy; mHSPC, metastatic Hormone Sensitive Prostate Cancer

BACKGROUND

- ADT was the standard of care for mHSPC patients but progression to CRPC in 1-3 years was observed[1,2]
- CHAARTED trial showed that ADT plus Docetaxel improved overall survival in newly diagnosed mHSPC[3]
- LATITUDE and STAMPEDE trials showed survival advantage for mHSPC patients when treated with ADT plus abiraterone and prednisone[4,5]
- The most recent trials excluded patients previously treated with docetaxel[4,5]

ADT, androgen deprivation therapy

1. Sweeney, et al. NEJM 2015;373:737-46; 2. Gravis, et al. Lancet Oncol 2013;14:149-58; 3. Sweeney, et al. NEJM 2015;373:737-46;
4. Fizazi, et al. NEJM 2017;377:352-60; 5. James, et al. NEJM 2017;377:338-46
Armstrong, et al. Presented at ASCO GU 2019, Abstract Number 687

BACKGROUND

- ARCHES investigates the effect of enzalutamide (androgen receptor inhibitor) in combination with ADT in men with mHSPC
- Patients with high and low volume disease are included (CHAARTED criteria[1]) and patients with and without prior docetaxel treatment

1. Sweeney, et al. NEJM 2015;373:737-46
Armstrong, et al. Presented at ASCO GU 2019, Abstract Number 687

ENDPOINTS

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PRIMARY: TIME TO rPFS OR DEATH (WITHIN 24 WEEKS OF TREATMENT DISCONTINUATION)

Key Secondary Endpoints

- Time to PSA progression
- Time to use of new antineoplastic therapy
- PSA undetectable rate
- ORR
- Time to deterioration in urinary symptoms
- OS

Other Secondary Endpoints

- Time to first symptomatic skeletal event
- Time to castration resistance
- Time to deterioration in QoL
- Time to pain progression
- Safety

ORR, objective response rate; OS, overall survival; PSA, prostate specific antigen; QoL, quality of life; rPFS, radiographic progression free survival

Armstrong, et al. Presented at ASCO GU 2019, Abstract Number 687

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

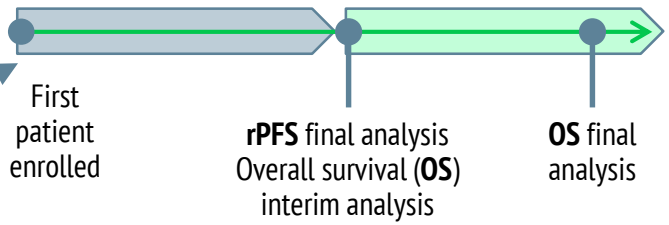
Stratification factors:
- Volume of disease (low vs. high)
- Prior docetaxel therapy for mHSPC (none, 1–5, or 6 cycles)

N=1150

R 1:1

- **Enzalutamide 160 mg/day + ADT**
- **Placebo + ADT**

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



ADT, androgen deprivation therapy; CT, computerised tomography; ECOG, eastern cooperative oncology group; mHSPC, metastatic hormone sensitive prostate cancer; MRI, magnetic resonance imaging; OS, overall survival, rPFS, radiographic progression free survival;
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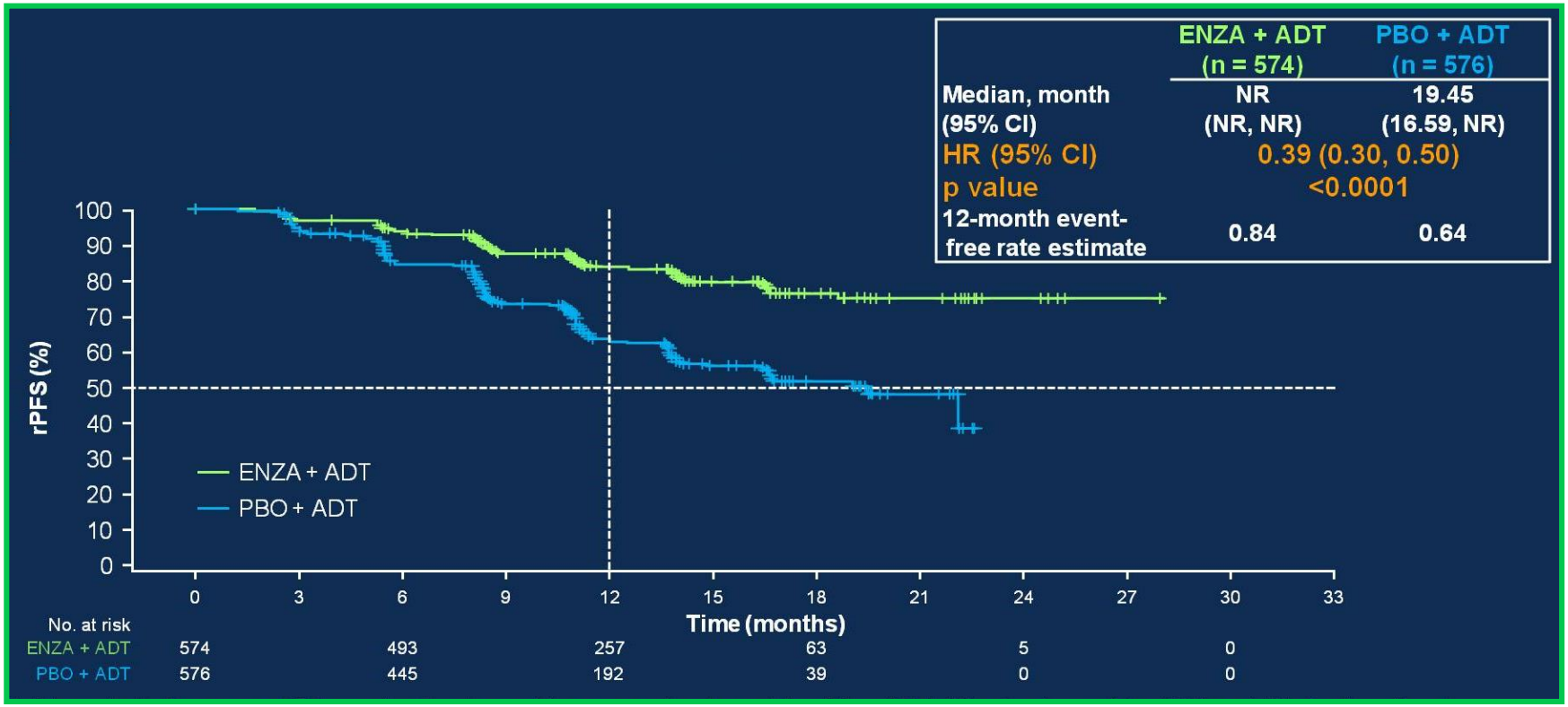
PRIMARY ENDPOINT: rPFS

- Enzalutamide plus ADT is associated with a 61% reduction in risk of rPFS or death



ADT, androgen deprivation therapy; ENZA, enzalutimde; PBO, placebo; rPFS, radiographic progression free survival

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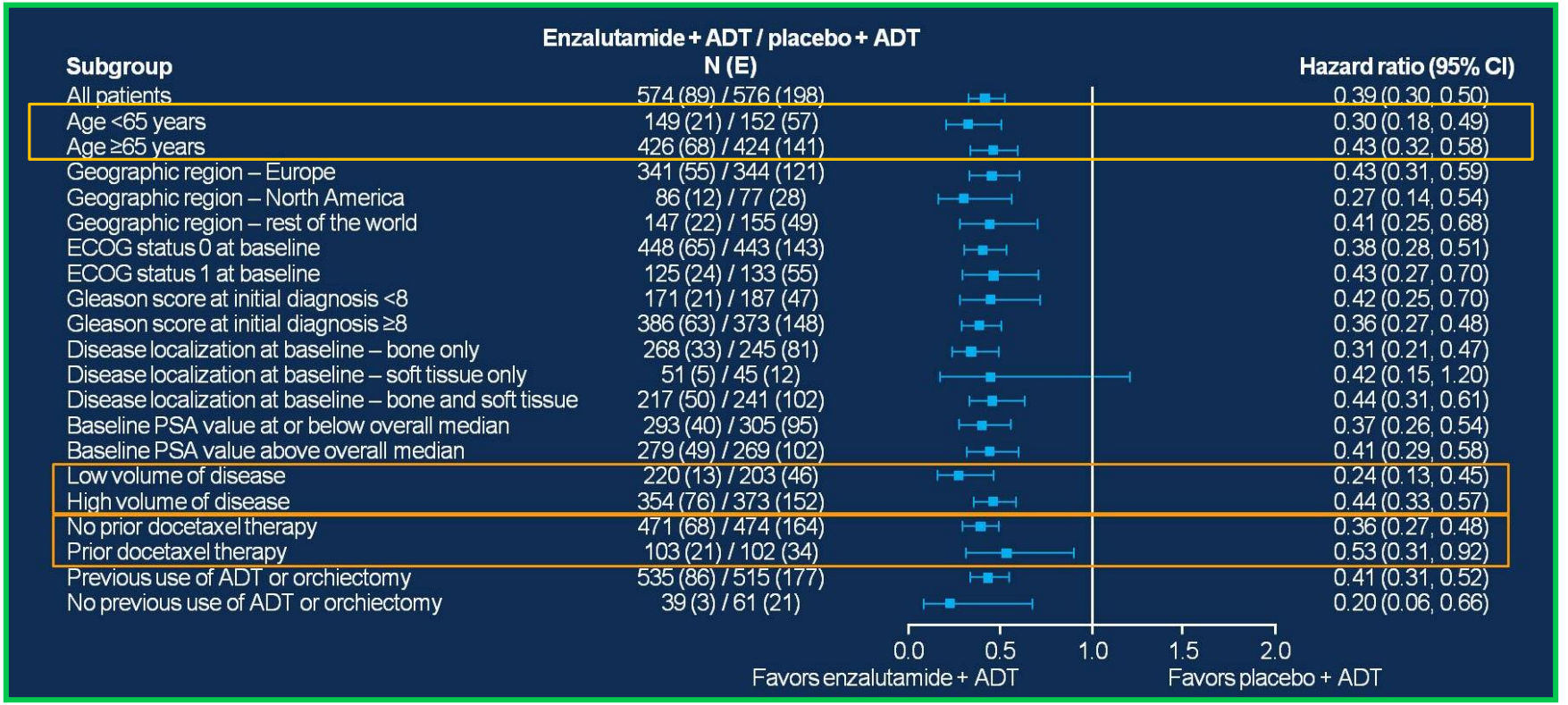
SUBGROUP ANALYSIS OF rPFS

- Excellent results observed on rPFS across all pre-specified subgroups



ADT, androgen deprivation therapy; CI, confidence interval, ECOG, eastern cooperative oncology group; PSA, prostate specific antigen; rPFS, radiographic progression free survival

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ADVERSE EVENTS (AEs)

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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

ADT, androgen deprivation therapy; AE, adverse event

Armstrong, et al. Presented at ASCO GU 2019, Abstract Number 687

AEs OF SPECIAL INTEREST

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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 pain	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)

ADT, androgen deprivation therapy; AE, adverse event

Armstrong, et al. Presented at ASCO GU 2019, Abstract Number 687

SUMMARY

- Enzalutamide added to ADT resulted in a **61% reduction in rPFS** or death in men with mHSPC (HR 0.39; p<0.0001)
- Significant reductions in rPFS were observed across **all pre-specified subgroups**, notably:
  - Low and high disease volume
  - With and without prior docetaxel therapy
  - Above and below 65 years of age
- **Overall survival data** is too early to comment on as data is **not mature** at time of analysis
- Enzalutamide +ADT **well tolerated** with safety profile consistent with that reported previously in Enzalutamide CRPC clinical trials

ADT, androgen deprivation therapy; HR, hazard ratio; mHSPC, metastatic hormone sensitive prostate cancer; rPFS, radiographic progression free survival

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ARAMIS: EFFICACY AND SAFETY OF DAROLUTAMIDE IN nmCRPC

Fizazi, et al. Abstract #140

nmCRPC, non-metastatic Castration Resistant Prostate Cancer

BACKGROUND

- nmCRPC is defined as rising PSA despite continuing ADT and no detected metastases
- nmCRPC patients are high risk for progression and cancer related mortality
- Two previously approved NSAA therapies, Enzalutamide and Apalutamide, have demonstrated improvements in MFS but have been associated with increased rates of fatigue, falls, fractures and other AE's compared to placebo[1,2]
- Darolutamide is a novel Androgen Receptor Signaling Inhibitor in development

ADT, androgen deprivation therapy; AE's, adverse events; MFS, metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; NSAA, nonsteroidal antiandrogen; PSA, prostate specific antigen

1. Hussain, et al. NEJM 2018; 378: 2465-74; 2. Smith, et al. NEJM 2018; 378:1408-18
Fizazi, et al. Presented at ASCO GU 2019. Abstract Number 140

BACKGROUND: NEXT-GENERATION ANDROGEN RECEPTOR INHIBITORS

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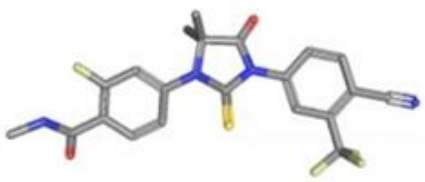
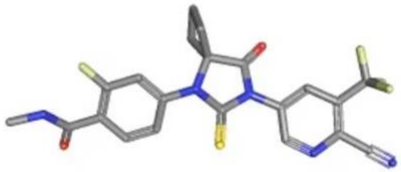
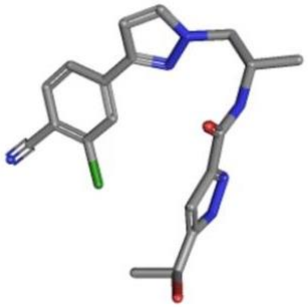
Enzalutamide



Apalutamide



Darolutamide

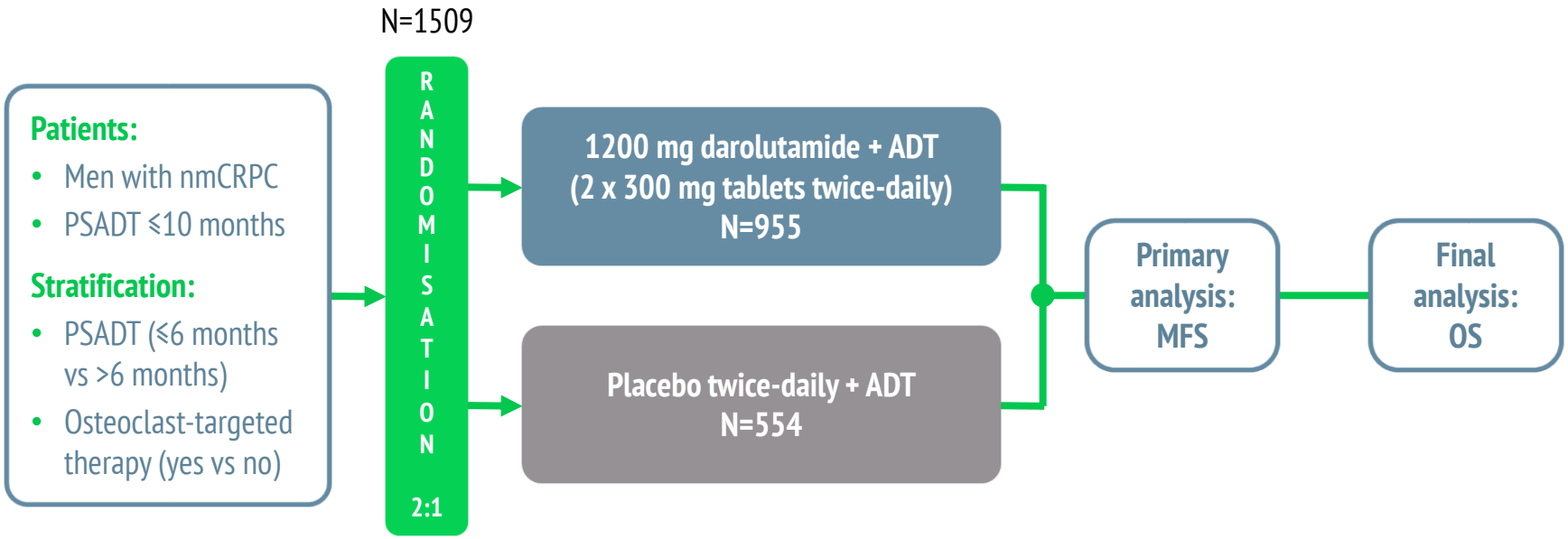


- Darolutamide is structurally distinct from apalutamide and enzalutamide, and is characterized by low blood–brain barrier penetration[1,2]
- This could result in less CNS toxicity and improved tolerability

CNS, central nervous system

1. Zurth C, et al. J Clin Oncol 2018;36:abstr 345; 2. Sandmann S, et al. ASCO GU 2019: Poster abstr 156. Images from PubChem database: https://pubchem.ncbi.nlm.nih.gov/ Fizazi, et al. Presented at ASCO GU 2019. Abstract Number 140

ARAMIS TRIAL DESIGN



ADT, androgen deprivation therapy; MFS, metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; PSADT, prostate-specific antigen doubling time

Fizazi, et al. Presented at ASCO GU 2019. Abstract Number 140; Fizazi et al. NEJM 2019, DOI:10.1056/NEJMoa1815671

ARAMIS ENDPOINTS

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Primary Endpoints

Metastasis-free survival, defined as:

- Distant metastases, or
- Death from any cause

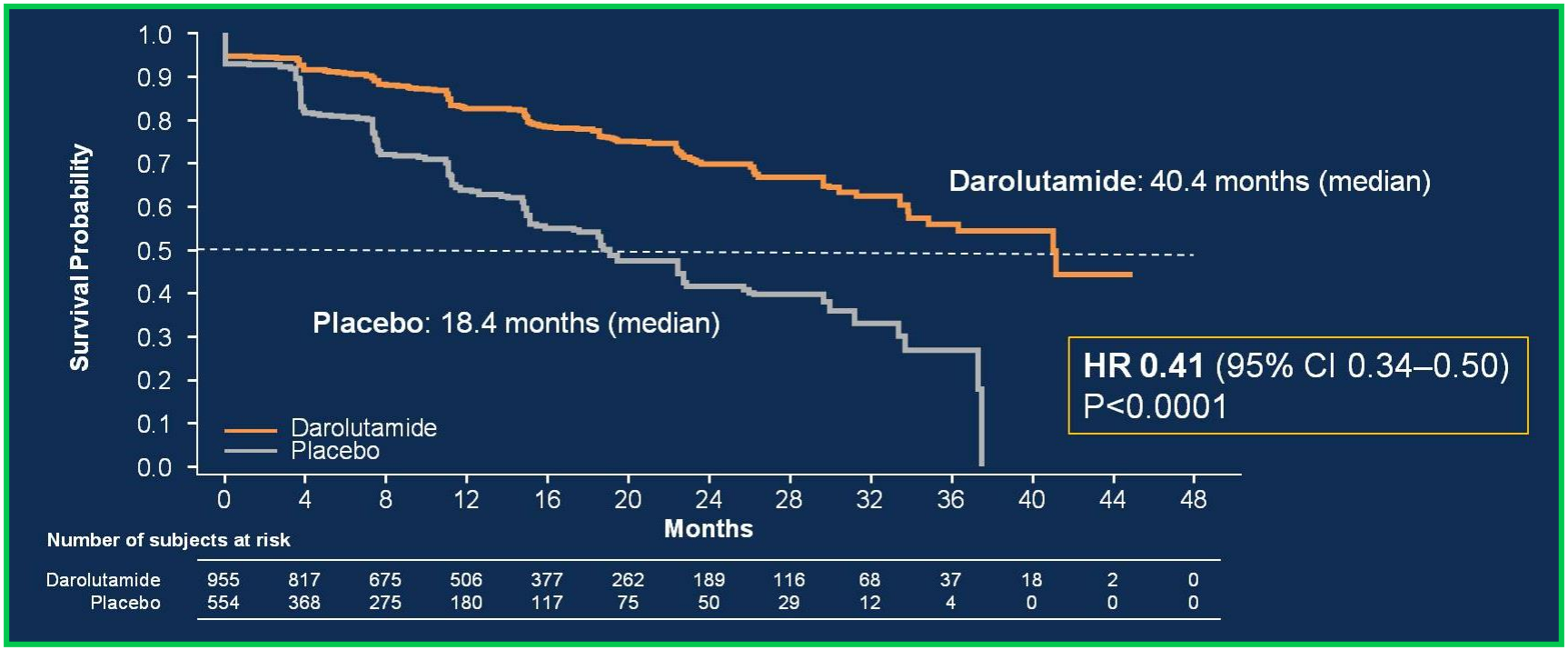
Secondary Endpoints

- Overall survival
- Time to pain progression
- Time to first chemotherapy
- Time to first skeletal event
- Safety

Fizazi, et al. Presented at ASCO GU 2019. Abstract Number 140; Fizazi et al. NEJM 2019, DOI:10.1056/NEJMoa1815671

PRIMARY ENDPOINT: METASTASIS-FREE SURVIVAL

- Darolutamide combination arm delayed MFS by 22 months (median)
- 59% risk reduction of distant metastases or death with darolutamide combination



Median follow-up time at primary analysis was 17.9 months

CI, confidence interval; HR, hazard ratio; MFS, Metastasis free survival

Fizazi, et al. Presented at ASCO GU 2019. Abstract Number 140; Fizazi et al. NEJM 2019, DOI:10.1056/NEJMoa1815671

INCIDENCE OF TEAEs

Adverse event, n (%)	Darolutamide (N=954)		Placebo (N=554)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any	794 (83.2)	236 (24.7)	426 (76.9)	108 (19.5)
Serious	237 (24.8)	151 (15.8)	111 (20)	70 (12.6)
Discontinuation	85 (8.9)	32 (3.3)	48 (8.7)	24 (4.3)
Adverse events that occurred in ≥5% of patients in either group				
Fatigue	115 (12.1)	4 (0.4)	48 (8.7)	5 (0.9)
Back pain	84 (8.8)	4 (0.4)	50 (9.0)	1 (0.2)
Arthralgia	77 (8.1)	3 (0.3)	51 (9.2)	2 (0.4)
Diarrhea	66 (6.9)	0	31 (5.6)	1 (0.2)
Hypertension	63 (6.6)	30 (3.1)	29 (5.2)	12 (2.2)
Constipation	60 (6.3)	0	34 (6.1)	0
Pain in extremity	55 (5.8)	0	18 (3.2)	1 (0.2)
Anemia	53 (5.6)	8 (0.8)	25 (4.5)	2 (0.4)
Hot flush	50 (5.2)	0	23 (4.2)	0
Nausea	48 (5.0)	2 (0.2)	32 (5.8)	0
Urinary tract infection	47 (4.9)	6 (0.6)	28 (5.1)	3 (0.5)
Urinary retention	33 (3.5)	15 (1.6)	36 (6.5)	11 (2.0)

TEAE, treatment-emergent adverse event

Fizazi, et al. Presented at ASCO GU 2019. Abstract Number 140; Fizazi et al. NEJM 2019, DOI:10.1056/NEJMoa1815671

TEAEs OF INTEREST

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Adverse event, all grades, n (%)	Darolutamide (N=954)	Placebo (N=554)
Fatigue/asthenic conditions	151 (15.8)	63 (11.4)
Dizziness (including vertigo)	43 (4.5)	22 (4.0)
Cognitive disorder	4 (0.4)	1 (0.2)
Memory impairment	5 (0.5)	7 (1.3)
Seizure (any event)	2 (0.2)	1 (0.2)
Bone fracture	40 (4.2)	20 (3.6)
Falls (including accident)	40 (4.2)	26 (4.7)
Hypertension	63 (6.6)	29 (5.2)
Coronary artery disorders	31 (3.2)	14 (2.5)
Heart failure	18 (1.9)	5 (0.9)
Rash	28 (2.9)	5 (0.9)
Weight decreased (any event)	34 (3.6)	12 (2.2)
Hypothyroidism	2 (0.2)	1 (0.2)

TEAE, treatment-emergent adverse event

Fizazi, et al. Presented at ASCO GU 2019. Abstract Number 140; Fizazi et al. NEJM 2019, DOI:10.1056/NEJMoa1815671

SUMMARY

- **Darolutamide significantly improved MFS** in men with nmCRPC
  - Median MFS 40.4 months with darolutamide vs 18.4 month with placebo
- Initial results for OS (interim analysis) showed darolutamide to be associated with a **29% reduction** on the risk of death (p=0.045)
- Darolutamide has a **consistent safety and tolerability profile:**
  - Consistent with data from early phase trials ARADES[1,2] and ARAFOR[3]
  - Rate of adverse events including rash, fatigue, cognitive impairment, falls, fractures and hypertension were well balanced between treatment groups
  - Rates of discontinuation due to AE's similar between darolutamide and placebo

AE's, adverse events; MFS, metastasis-free survival; nmCRPC, non-metastatic castration resistant prostate cancer; OS, overall survival

1. Fizazi, et al. Lancet Oncol 2014;15:975-85; 2. Fizazi, et al. Eur Urol Focus 2017;3:606-14; 3. Massard, et al. Eur Urol 2016; 69:834-40
Fizazi, et al. Presented at ASCO GU 2019. Abstract Number 140 ; Fizazi et al. NEJM 2019, DOI:10.1056/NEJMoa1815671

CONCLUSION

- Darolutamide is now **the 3rd AR Signalling Inhibitor oral drug** in development and there could potentially soon be three treatment options to discuss with patients
- ARAMIS is the third successful trial of these oral agents and adds to the **body of evidence** from the PROSPER[1] and SPARTAN[2] trials
- This is **a significant step forward** in the management of nmCRPC patients considering in December 2017 there were no new options

AR, androgen receptor; nmCRPC, non-metastatic castration resistant prostate cancer

1. Hussain, et al. NEJM 2018;378:2465-74; 2. Smith, et al. NEJM 2018;378:1408-18
Fizazi, et al. Presented at ASCO GU 2019. Abstract Number 140; Fizazi et al. NEJM 2019, DOI:10.1056/NEJMoa1815671

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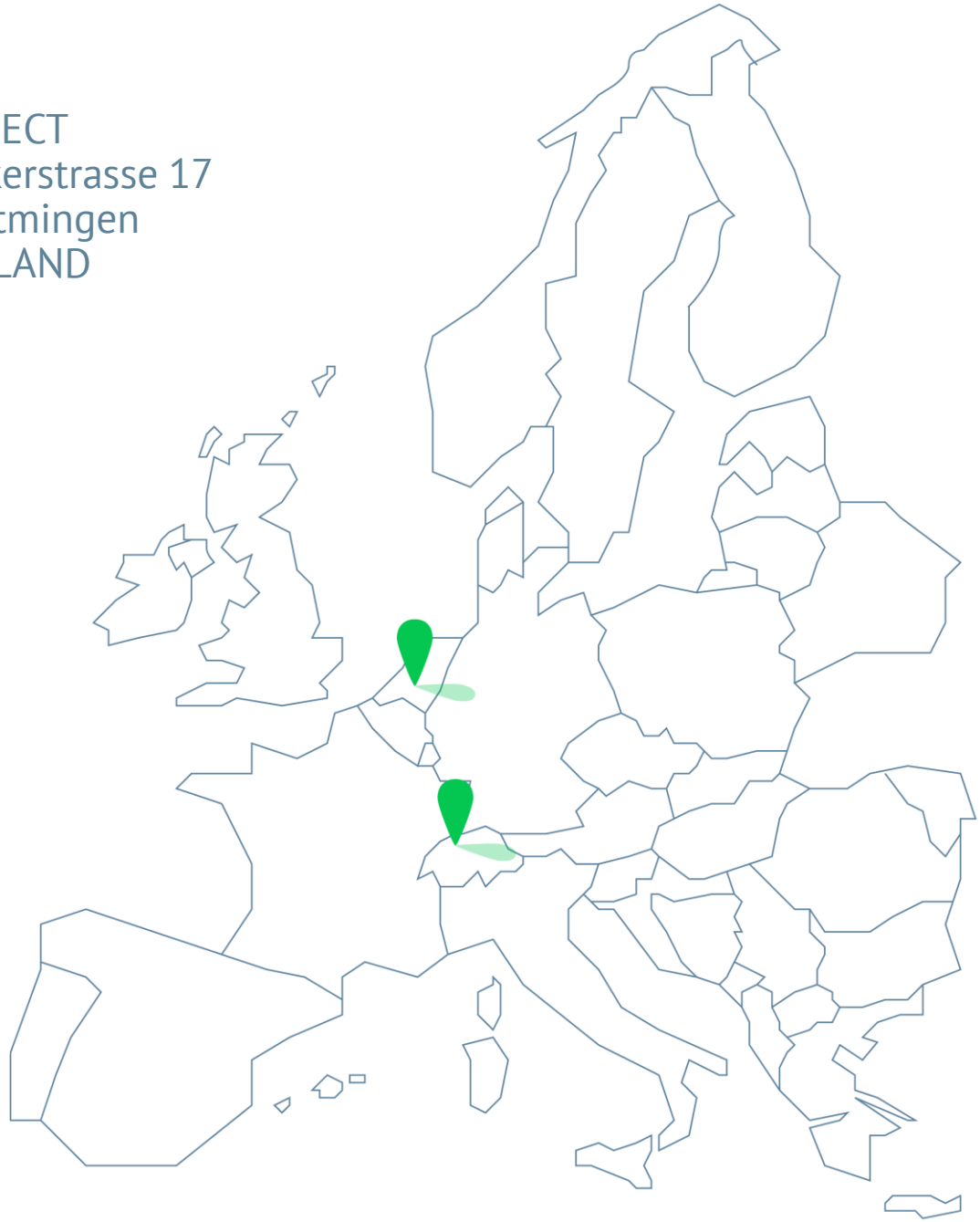

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