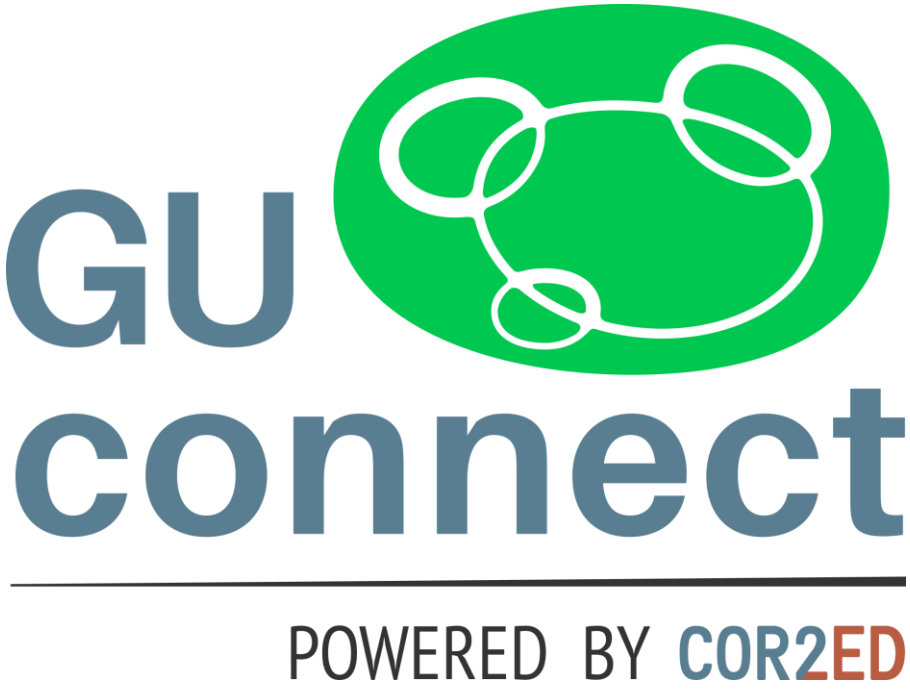
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NEW THERAPIES FOR METASTATIC HORMONE SENSITIVE PROSTATE CANCER (mHSPC)

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DISCLAIMER

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BACKGROUND

HORMONE SENSITIVE PROSTATE CANCER

- For many years, ADT was the standard of care for mHSPC patients but progression to CRPC in 1-3 years was observed

- Multiple key trials have influenced the standard of care for mHSPC patients and improved outcomes have been observed with abiraterone and chemotherapy:-

  - **CHAARTED**: ADT + docetaxel vs ADT alone

  - **LATITUDE**: ADT + abiraterone + prednisone vs ADT alone

- Treatment with systemic therapies in addition to ADT can improve survival and improve quality of life

- Data from studies investigating the next generation ARI's in mHSPC have recently reported

ADT, androgen deprivation therapy; ARI, androgen receptor inhibitor; CRPC, castration resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer; Sweeney, et al. NEJM 2015;373:737-46; Fizazi, et al. NEJM 2017;377:352-60; James, et al. NEJM 2017;377:338-51; David ID et al. NEJM 2019: DOI: 10.1056/NEJMoa1903835

ARCHES: A PHASE 3 STUDY OF ANDROGEN DEPRIVATION THERAPY WITH ENZALUTAMIDE OR PLACEBO IN METASTATIC HORMONE-SENSITIVE PROSTATE CANCER

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

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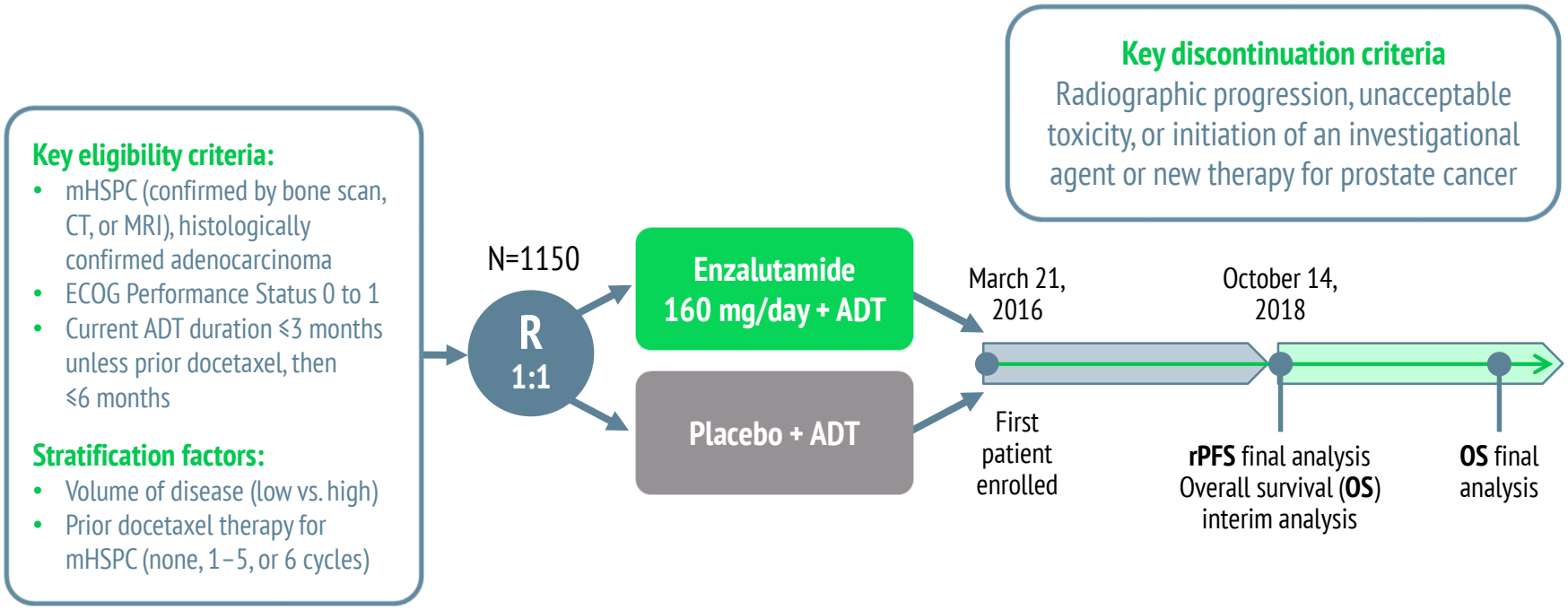
ARCHES STUDY DESIGN



ADT, androgen deprivation therapy; CT, computerised tomography; ECOG PS, eastern cooperative oncology group performance status; mHSPC, metastatic hormone sensitive prostate cancer; MRI, magnetic resonance imaging; OS, overall survival, rPFS, radiographic progression free survival;
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BASELINE PATIENT CHARACTERISTICS (N=1150)

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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 Soft tissue only Bone and soft tissue	 268 (47) 51 (9) 217 (38)	 245 (43) 45 (8) 241 (42)
Distant metastasis at initial diagnosis, n (%)	402 (70)	365 (63)
Prior therapy, n (%) Docetaxel ADT Anti-androgen	 103 (18) 535 (93) 205 (36)	 102 (18) 514 (89) 229 (40)
Median duration of prior ADT, months	1.6	1.6
Median PSA, ng/mL	5.4	5.1

ADT, androgen deprivation therapy; y, years; ECOG PS Eastern Cooperative Oncology Group performance status; PSA, prostate-specific antigen

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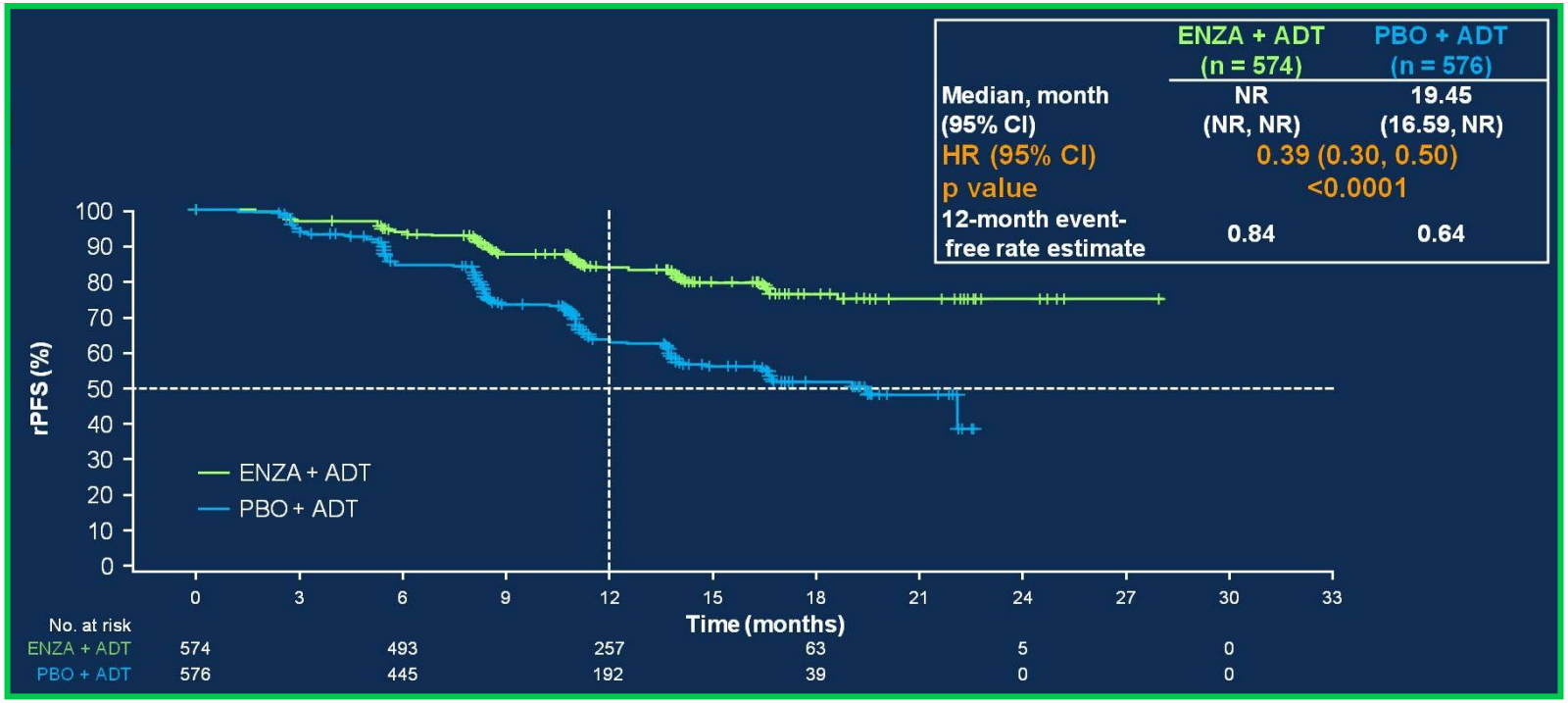
PRIMARY ENDPOINT: rPFS



- 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

ADT, androgen deprivation therapy; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; NR, not reached; PBO, placebo; rPFS, radiographic progression free survival

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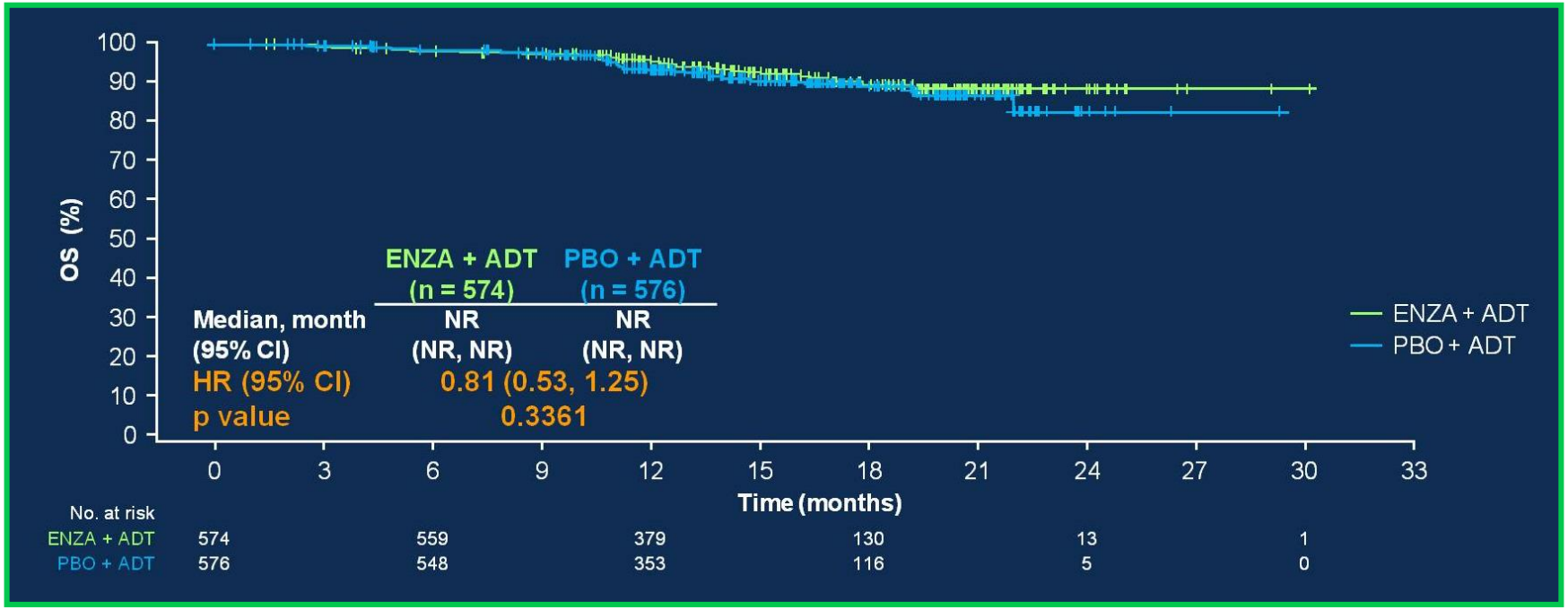
OVERALL SURVIVAL: INTERIM ANALYSIS (84 DEATHS)



- 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 + 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

ADT, androgen deprivation therapy; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; NR, not reached; OS, overall survival; PBO, placebo

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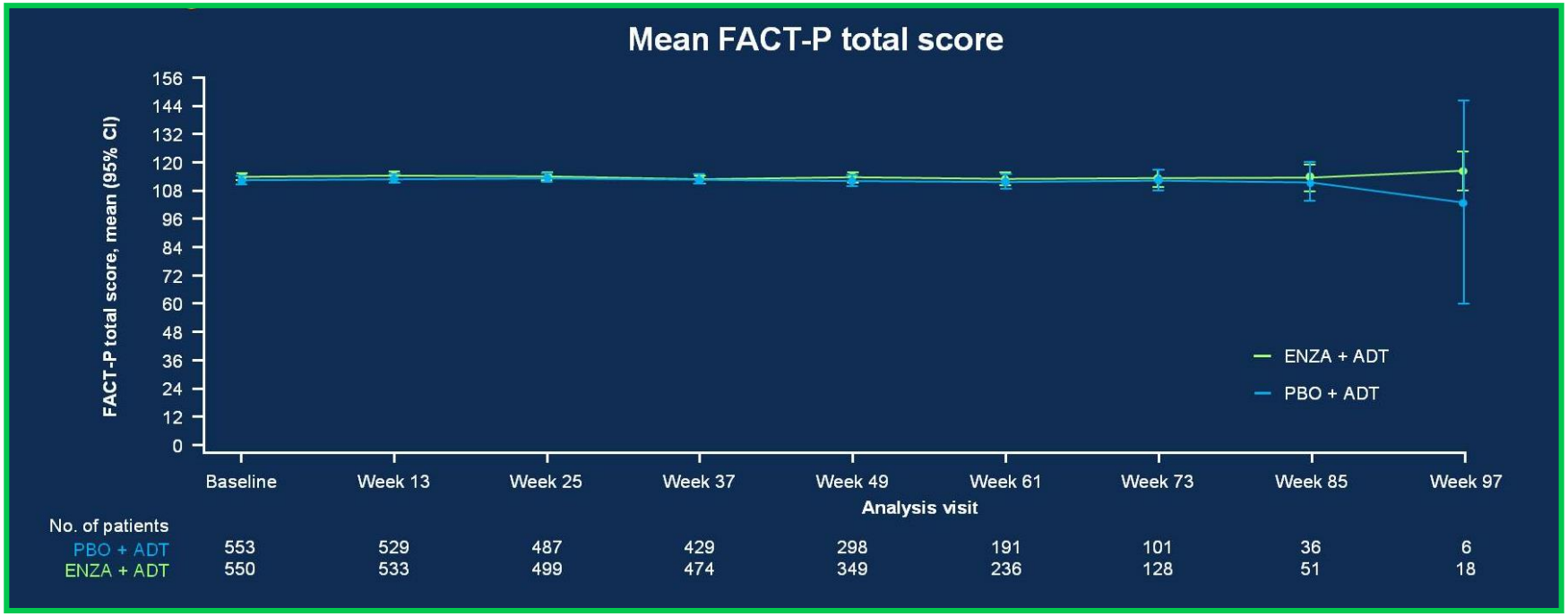
QoL OVER TIME



- 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

ADT, androgen deprivation therapy; CI, confidence interval; ENZA, enzalutamide; FACT-P, Functional Assessment of Cancer Therapy-Prostate; PBO, placebo
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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)

*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)

Bold: AEs (all grades) that occur >2% in enzalutamide + ADT compared with placebo + ADT

ADT, androgen depravation therapy; AEs, adverse events

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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
- No difference in QoL when enzalutamide was added to ADT treatment
- 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

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

THE TITAN TRIAL: PHASE III STUDY OF APALUTAMIDE AND PLACEBO IN mHSPC PATIENTS RECEIVING ADT

Chi, et al. ASCO 2019 Abstract #5006

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

BACKGROUND

- TITAN investigates the effect of apalutamide (androgen receptor inhibitor) in combination with ADT in men with mHSPC
- Direct inhibition of AR may provide more complete reduction of androgen signalling than ADT alone and thus may improve clinical outcomes

ADT, androgen deprivation therapy; AR, androgen receptor; mHSPC, metastatic hormone sensitive prostate cancer

Chi, et al. Presented at ASCO 2019, Abstract Number 5006

ENDPOINTS

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DUAL PRIMARY: OVERALL SURVIVAL AND rPFS

Key Secondary Endpoints

- Time to cytotoxic chemotherapy
- Time to pain progression
- Time to chronic opioid use
- Time to skeletal related event

Exploratory Endpoints

- Time to PSA progression
- Second progression-free survival (PFS2)
- Time to symptomatic progression

rPFS, radiographic progression free survival; PSA, prostate specific antigen

Chi, et al. Presented at ASCO 2019, Abstract Number 5006

TITAN STUDY DESIGN

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"All-comer" patient population

Key eligibility criteria:
- Hormone sensitive
- Distant metastatic disease by ≥1 lesion on bone scan
- ECOG PS 0 or 1

On-study requirement:
- Continuous ADT

Permitted:
- Prior docetaxel
- ADT ≤6 mo for mHSPC or ≤3 yr for local disease
- Local treatment completed ≥1 yr prior

Stratifications:
- Gleason score at diagnosis (≤7 vs ≥8)
- Region (NA and EU vs all other countries)
- Prior docetaxel (yes vs no)

N=1052
Dec 2015–
Jul 2017

R
1:1

Apalutamide 240 mg/day + ADT (n=525)

Placebo + ADT (n=527)

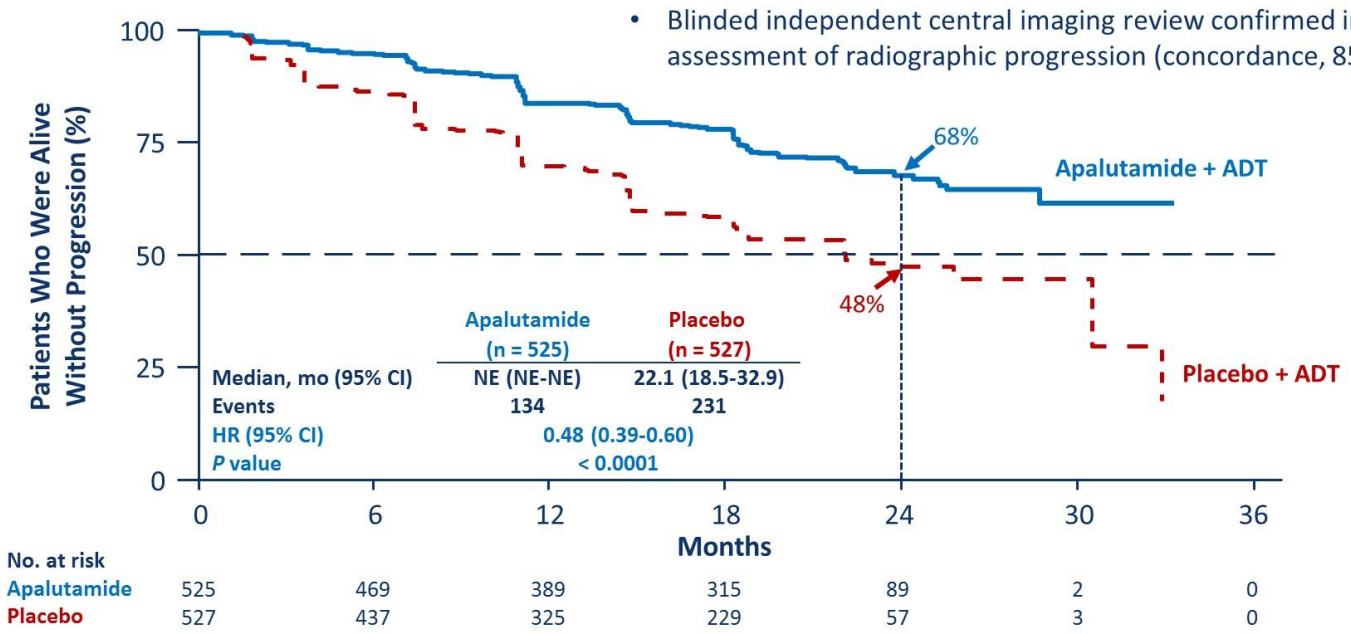
ADT, androgen deprivation therapy; ECOG, PS eastern cooperative oncology group performance status; EU, europe; mHSPC, metastatic hormone sensitive prostate cancer; NA, north america;

Chi, et al. Presented at ASCO 2019, Abstract Number 5006

TITAN RESULTS

PRIMARY ENDPOINT: rPFS

- Apalutamide significantly reduced risk of radiographic progression or death by 52%



- rPFS benefit with apalutamide treatment was consistent across all subgroups studied

Median follow up approx. 22 months

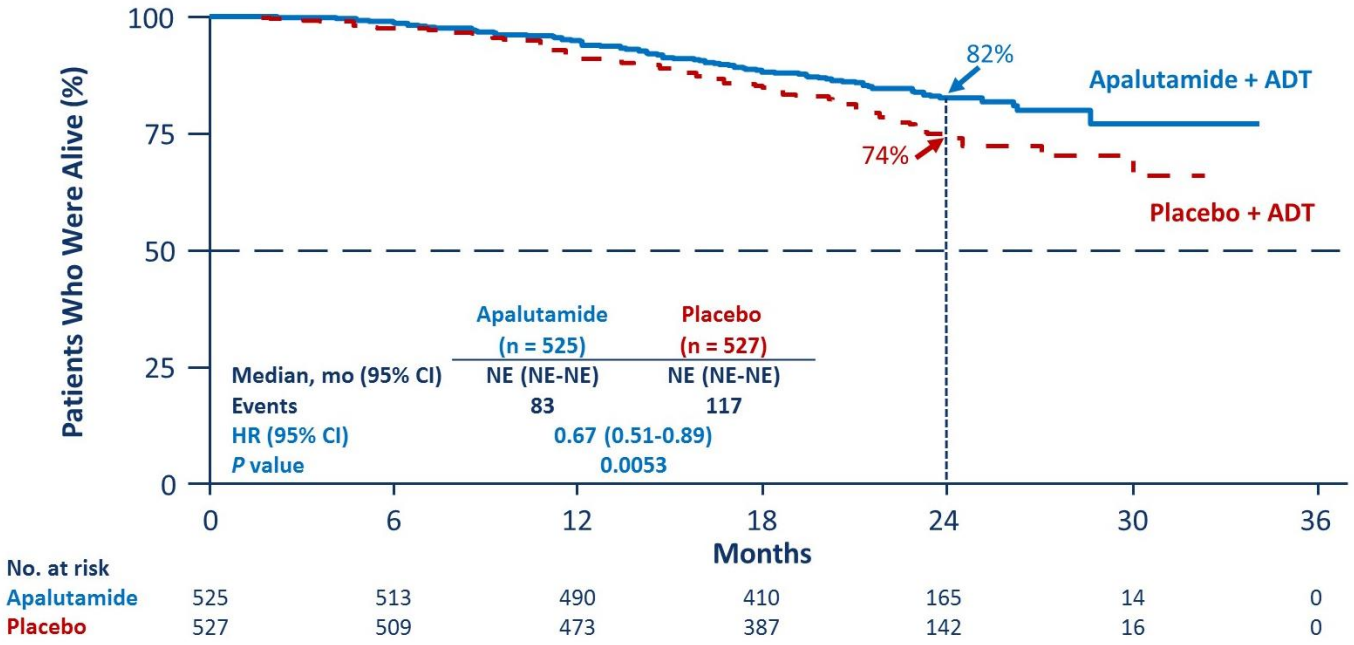
ADT, androgen deprivation therapy; CI, confidence interval; NE, not evaluable; rPFS, radiographic progression free survival

Chi, et al. Presented at ASCO 2019, Abstract Number 5006

TITAN RESULTS

PRIMARY ENDPOINT: OVERALL SURVIVAL

- Apalutamide significantly reduced risk of death by 33%



- OS benefit with apalutamide treatment was consistent across all subgroups studied

Median follow up approx. 22 months

ADT, androgen deprivation therapy; CI, confidence interval; NE, not evaluable; OS, overall survival

Chi, et al. Presented at ASCO 2019, Abstract Number 5006

SUMMARY

- Overall Survival benefit seen with apalutamide + ADT in patients with mHSPC
- All study endpoints favoured apalutamide treatment
- Subset of patients receiving docetaxel therapy was only 11%
  - too small to draw any conclusions regarding effects of docetaxel + ADT + apalutamide
- Safety profile consistent with the known side effects of apalutamide

ADT, androgen deprivation therapy; mHSPC, metastatic hormone sensitive prostate cancer
Chi, et al. Presented at ASCO 2019, Abstract Number 5006

THE ENZAMET TRIAL: PHASE III STUDY OF STANDARD OF CARE WITH OR WITHOUT ENZALUTAMIDE IN mHSPC

Sweeney, et al. ASCO 2019 Abstract #LBA2

mHSPC, metastatic Hormone Sensitive Prostate Cancer

BACKGROUND

- ENZAMET investigates whether androgen receptor inhibition with enzalutamide added to testosterone suppression:
  - Will prolong overall survival
  - Is effective as a first line therapy for mHSPC
    - With or without concurrent docetaxel therapy
  - Is more effective than a standard NSAA added to testosterone suppression

mHSPC, metastatic hormone sensitive prostate cancer; NSAA, nonsteroidal antiandrogen
Sweeney, et al. Presented at ASCO 2019, Abstract Number LBA2

ENDPOINTS

PRIMARY: OVERALL SURVIVAL

Key Secondary Endpoints

- PSA PFS
  - includes clinical progression if occurs first
- Clinical PFS
  - imaging, symptoms, signs
- Adverse events
  - CTCAE v4.03

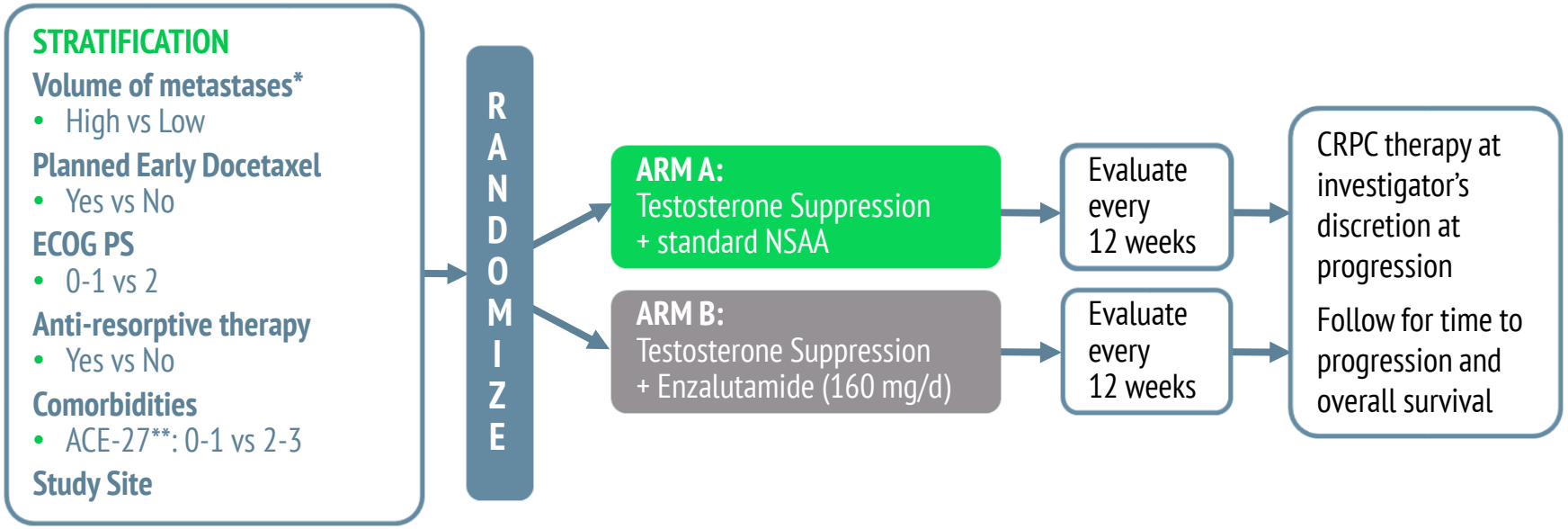
Other Secondary Endpoints

- Health related QOL
- Health outcomes relative to cost
- Translational biological studies

CTCAE, NCI common terminology criteria for adverse events; PFS, progression free survival; PSA, prostate specific antigen; QoL, quality of life

Sweeney, et al. Presented at ASCO 2019, Abstract Number LBA2

ENZAMET STUDY DESIGN



Prior to randomization testosterone suppression up to 12 weeks and 2 cycles of docetaxel was allowed; intermittent ADT and cyproterone were not allowed; NSAA: bicalutamide; nilutamide; flutamide; *High volume: visceral metastases and/or 4 or more bone metastases (at least 1 beyond pelvis and vertebral column); **Adult Co-morbidity Evaluation-27

ACE-27, adult comorbidity evaluation-27; ADT, androgen deprivation therapy; CRPC, castration resistant prostate cancer; ECOG PS, eastern cooperative oncology group performance status; NSAA, nonsteroidal antiandrogen

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ENZAMET RESULTS

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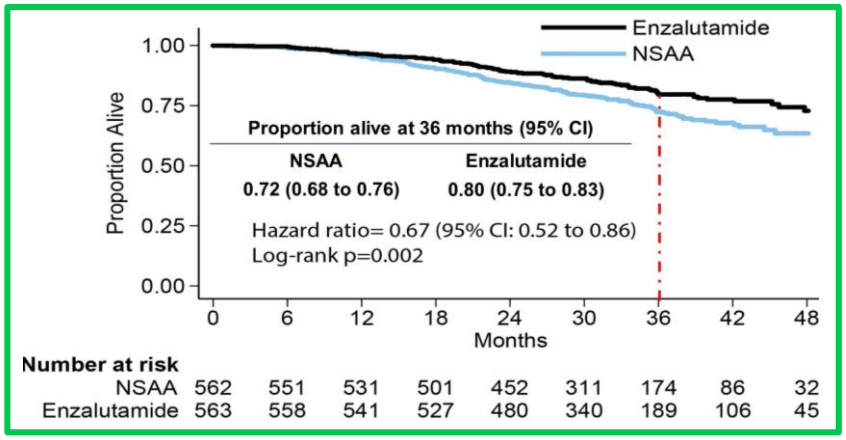
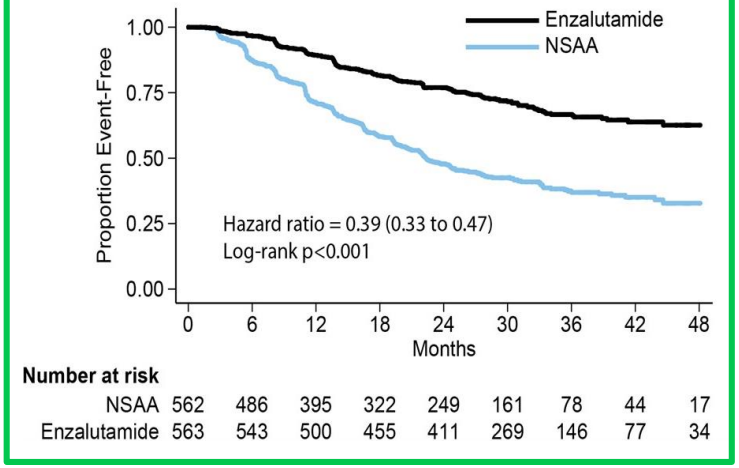
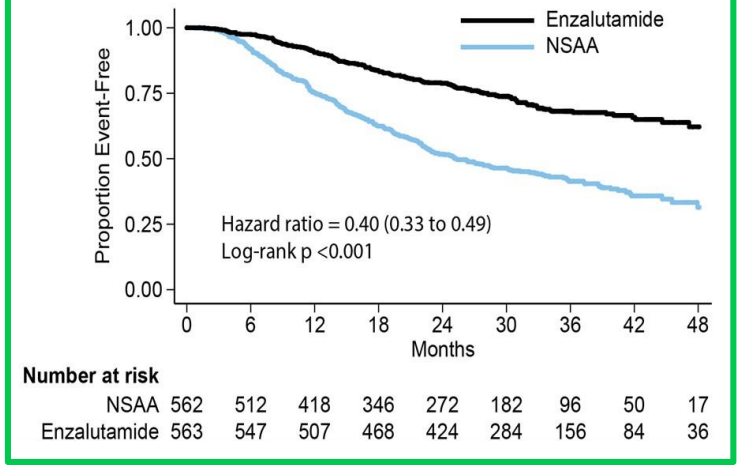
OVERALL SURVIVAL



PSA PFS



CLINICAL PFS



Median follow up of 33 months

CI, confidence interval; NSAA, nonsteroidal antiandrogen; PSA, prostate specific antigen; PFS, progression free survival

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RESULTS BY CONCURRENT DOCETAXEL THERAPY

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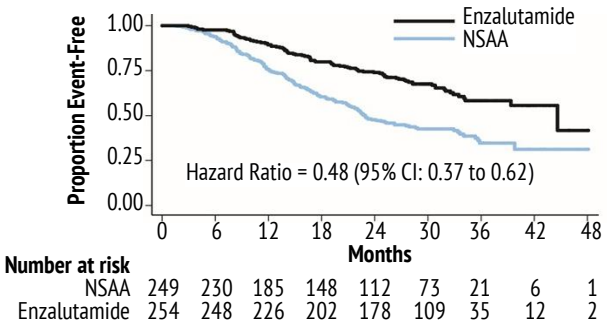
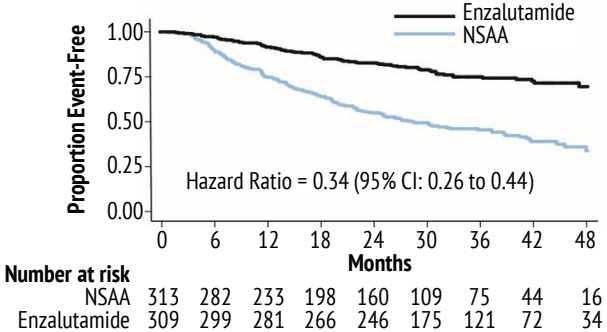
Testosterone suppression + Docetaxel N=503 (71% High Volume)

Testosterone suppression + No Docetaxel N=622 (37% High Volume)

CLINICAL PFS

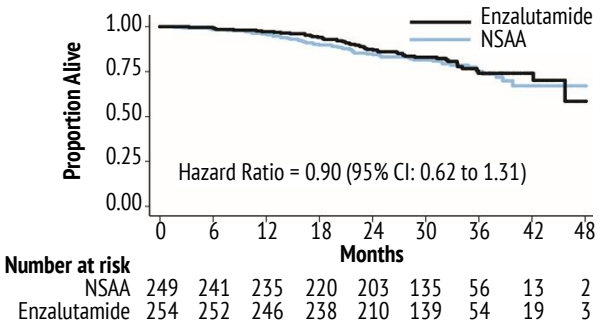


Number at risk									
NSAA	249	230	185	148	112	73	21	6	1
Enzalutamide	254	248	226	202	178	109	35	12	2

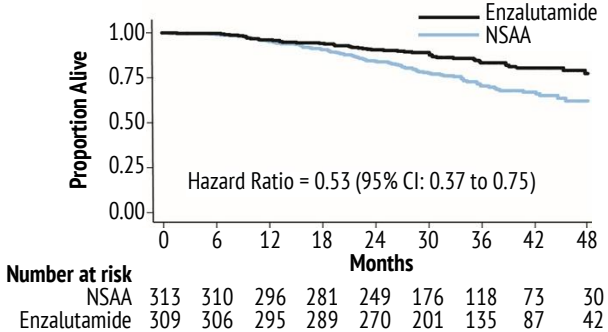


Number at risk									
NSAA	313	282	233	198	160	109	75	44	16
Enzalutamide	309	299	281	266	246	175	121	72	34

OVERALL SURVIVAL



Number at risk									
NSAA	249	241	235	220	203	135	56	13	2
Enzalutamide	254	252	246	238	210	139	54	19	3



Number at risk									
NSAA	313	310	296	281	249	176	118	73	30
Enzalutamide	309	306	295	289	270	201	135	87	42

- 45% patients in ENZA + TS treatment group and 44 % patients in TS + NSAA treatment arms received concurrent docetaxel

CI, confidence interval; ENZA, enzalutamide; NSAA, nonsteroidal antiandrogen; PFS, progression free survival; TS, testosterone suppression

Sweeney, et al. Presented at ASCO 2019, Abstract Number LBA2

SUMMARY

- Treatment with enzalutamide + TS resulted in an overall survival benefit for mHSPC patients
- Approximately 45% of patients received concurrent docetaxel treatment
- Addition of enzalutamide + TS + docetaxel appears to be no better than TS + docetaxel in terms of overall survival benefit
- More toxicity was seen with enzalutamide treatment compared to standard care
- Adding enzalutamide to docetaxel also increases adverse events
- Quality of life data not yet published

mHSPC, metastatic hormone sensitive prostate cancer; TS, testosterone suppression

Sweeney, et al. Presented at ASCO 2019, Abstract Number LBA2

CONCLUSION

- Previous trials (CHAARTED and LATITUDE) showed early intensive therapy with either docetaxel or abiraterone in mHSPC patients has a significant benefit for overall survival
- Recent data demonstrates new generation ARI's also prolong overall or progression-free survival for mHSPC patients
  - However, there appears to be no incremental clinical benefit for adding in docetaxel to the ADT + ARI combination. Might just be increasing toxicity for patients
  - Comparable overall survival with improved QoL seen with abiraterone treatment
- Different side effects and treatment durations should be considered:-
  - Haematotoxic side effects for chemotherapy but a shorter time on treatment
  - Increased cardiologic side effects for abiraterone and ARI treatment plus a longer time on treatment
- QoL should be considered alongside improvements in survival when choosing treatment for mHSPC

ADT, androgen deprivation therapy; ARI, androgen receptor inhibitor; mHSPC, metastatic hormone sensitive prostate cancer; QoL, quality of life

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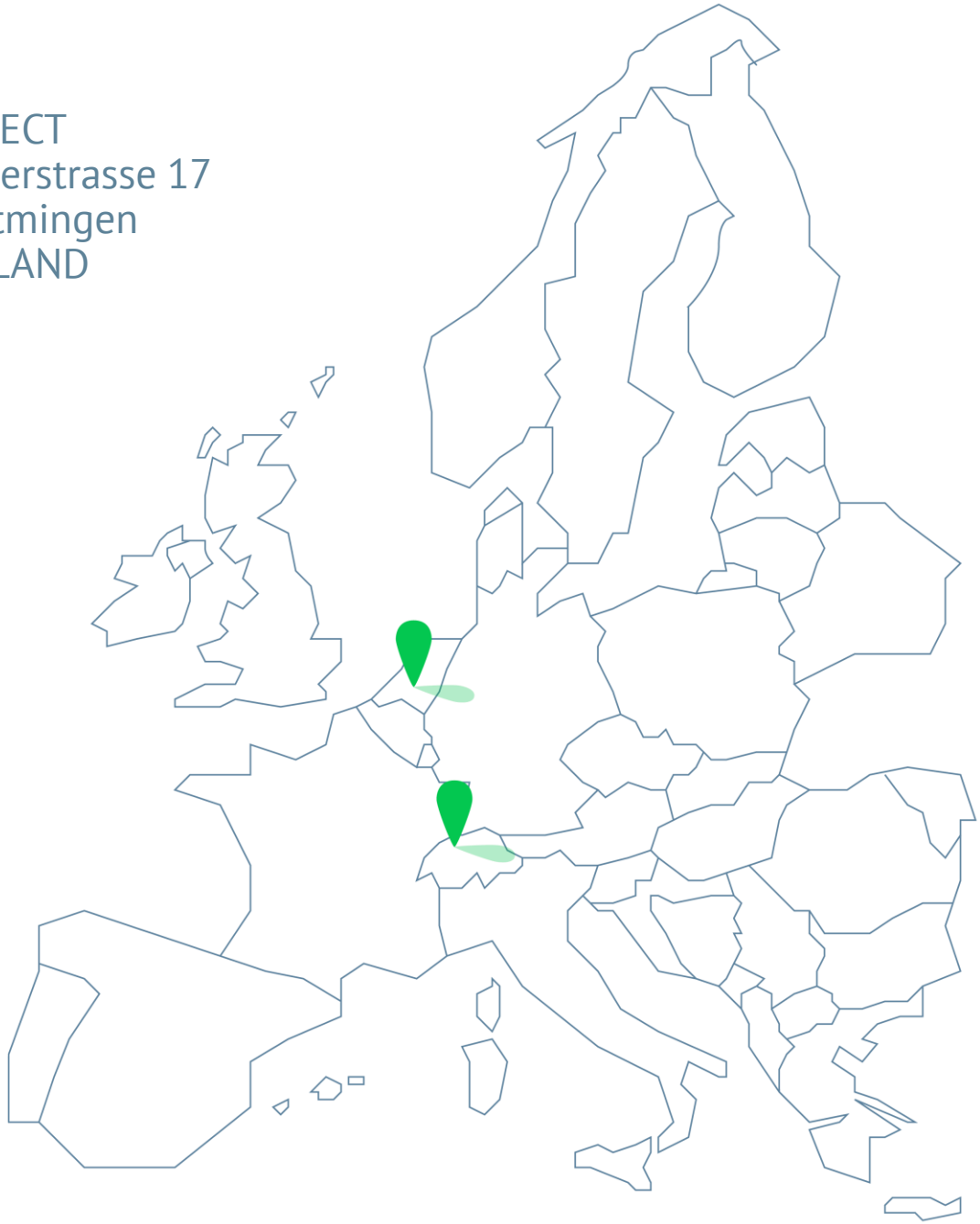

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