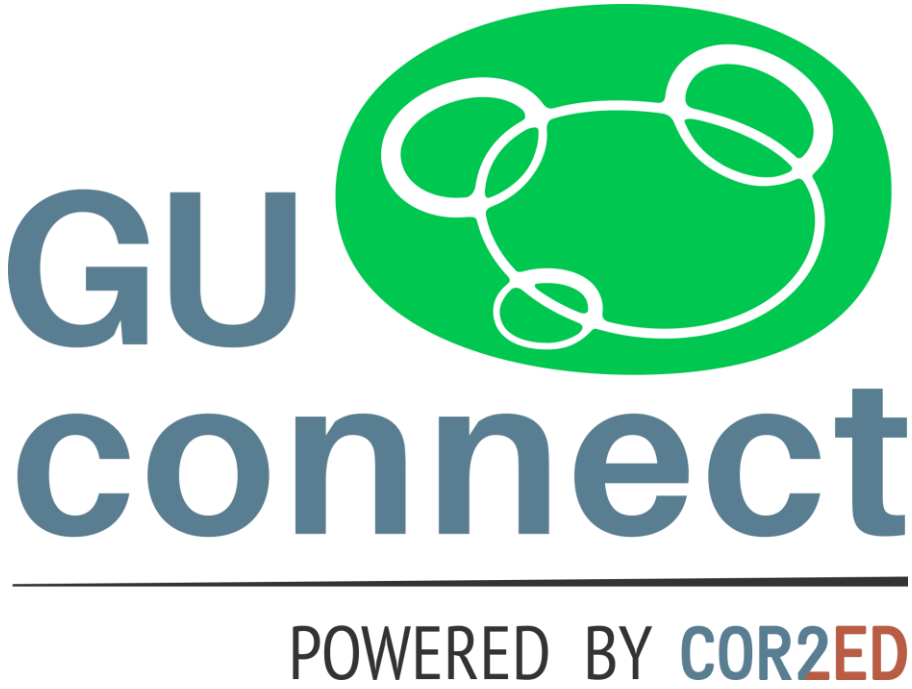
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MEETING SUMMARY
ASCO 2019, Chicago, USA

Prof. Evan Y. Yu

University of Washington School of Medicine,
Fred Hutchinson Cancer Research Center, Seattle, USA

PROSTATE CANCER UPDATE
mCSPC/mHSPC

mCSPC, metastatic castration sensitive prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer

DISCLAIMER

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This content is supported by an Independent Educational Grant from Bayer.

INTRODUCTION

- Data presented on mHSPC and new treatment options
- To date docetaxel has been given to patients with high volume disease and abiraterone to those with high/low volume disease or high/low risk patients with newly mHSPC
- ASCO 2019 saw updated data presented for the ARCHES trial and new data from the ENZAMET and TITAN trials

mHSPC, metastatic hormone sensitive prostate cancer

THE ARCHES TRIAL: PHASE III STUDY OF ADT WITH ENZALUTAMIDE OR PLACEBO IN mHSPC (PRIOR THERAPY SUBGROUP)

Armstrong, et al. ASCO 2019 Abstract #5048

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

BACKGROUND

- ARCHES investigated the effect of enzalutamide (androgen receptor inhibitor) in combination with ADT in men with mHSPC
  - Initial data presented at ASCO GU 2019[1]
- Patients with high and low volume disease were included (CHAARTED criteria) and patients with and without prior docetaxel treatment[1]
- This latest analysis presents data from pre-specified subgroups based on prior therapy

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

1. Armstrong, et al. Presented at ASCO GU 2019, Abstract Number 687; Armstrong, et al. Presented at ASCO 2019, Abstract Number 5048

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

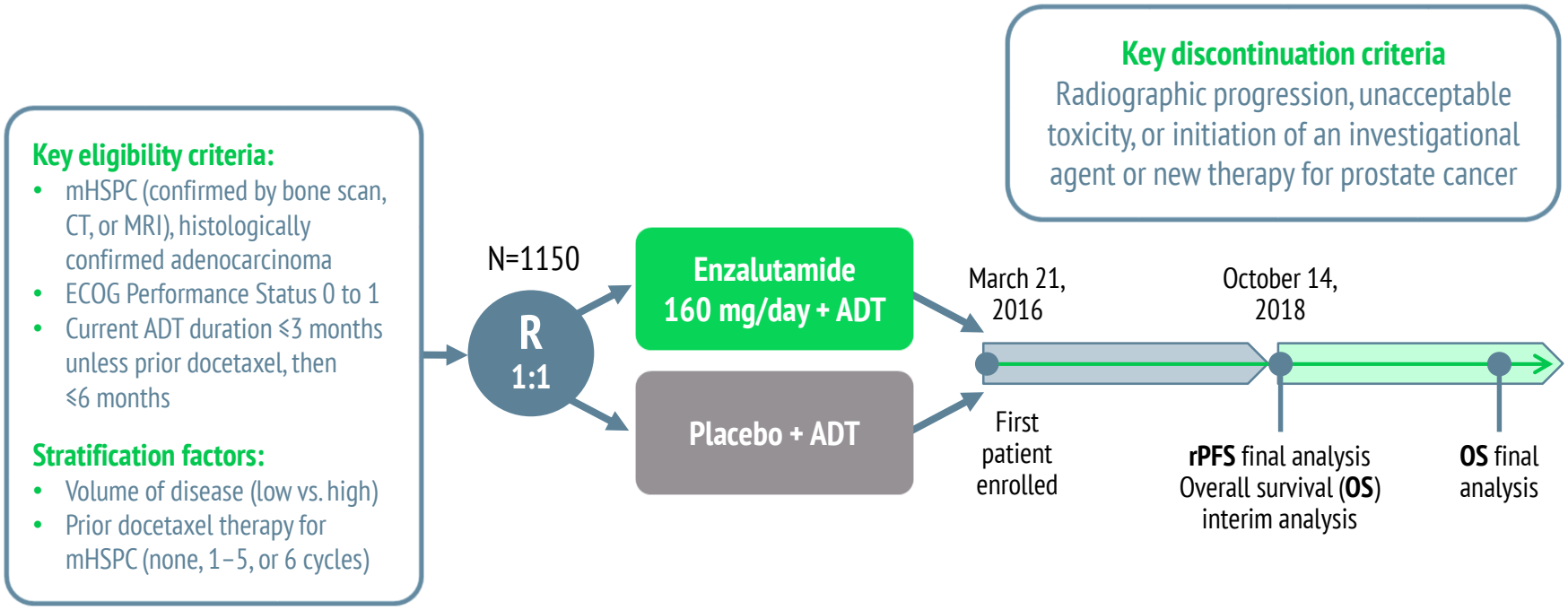
Other Secondary Endpoints

- 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; Armstrong, et al. Presented at ASCO 2019, Abstract Number 5048

ARCHES STUDY DESIGN



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

Armstrong, et al. Presented at ASCO GU 2019, Abstract Number 687; Armstrong, et al. Presented at ASCO 2019, Abstract Number 5048

ARCHES RESULTS

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- ENZA+ADT significantly improved rPFS overall and in prior treatment subgroups

Efficacy endpoint		ENZA + ADT	PBO + ADT	HR (95% CI)
rPFS: overall, n, median, months		n=574 NR	n=576 19.4	0.39* (0.30, 0.50)
	Prior docetaxel	n=103 NR	n=102 14.0	0.53 (0.31, 0.92)
	No prior docetaxel	n=471 NR	n=474 19.4	0.36 (0.27, 0.48)
	Prior ADT or orchiectomy	n=535 NR	n=515 19.4	0.41 (0.31, 0.52)
	No prior ADT or orchiectomy	n=39 NR	n=61 NR	0.20 (0.06, 0.66)
Time to initiation of new antineoplastic therapy, n, median, months		n=574 30.2	n=576 NR	0.28* (0.20, 0.40)
Objective response rate,‡ %		83.1*	63.7	–

*p<0.0001; ‡ of those with measurable disease at baseline; NR, not reached

- Grade 3-4 AEs reported in 23.6% of ENZA patients vs 24.7% PBO patients. No unexpected AEs

ADT, androgen deprivation therapy; AE, adverse event; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; PBO, placebo; rPFS, radiographic progression free survival

Armstrong, et al. Presented at ASCO 2019, Abstract Number 5048

SUMMARY

- **Enzalutamide + ADT significantly improved rPFS** compared to placebo + ADT in mHSPC patients
  - Significant improvement in rPFS was **also observed** for the enzalutamide + ADT **patients previously treated with docetaxel or ADT/orchiectomy**

- Still need to see overall survival data

- The safety profile of enzalutamide was consistent with that seen in previous trials in CRPC

ADT, androgen deprivation therapy; CRPC, castration resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer; rPFS, radiographic progression free survival

Armstrong, et al. Presented at ASCO 2019, Abstract Number 5048

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

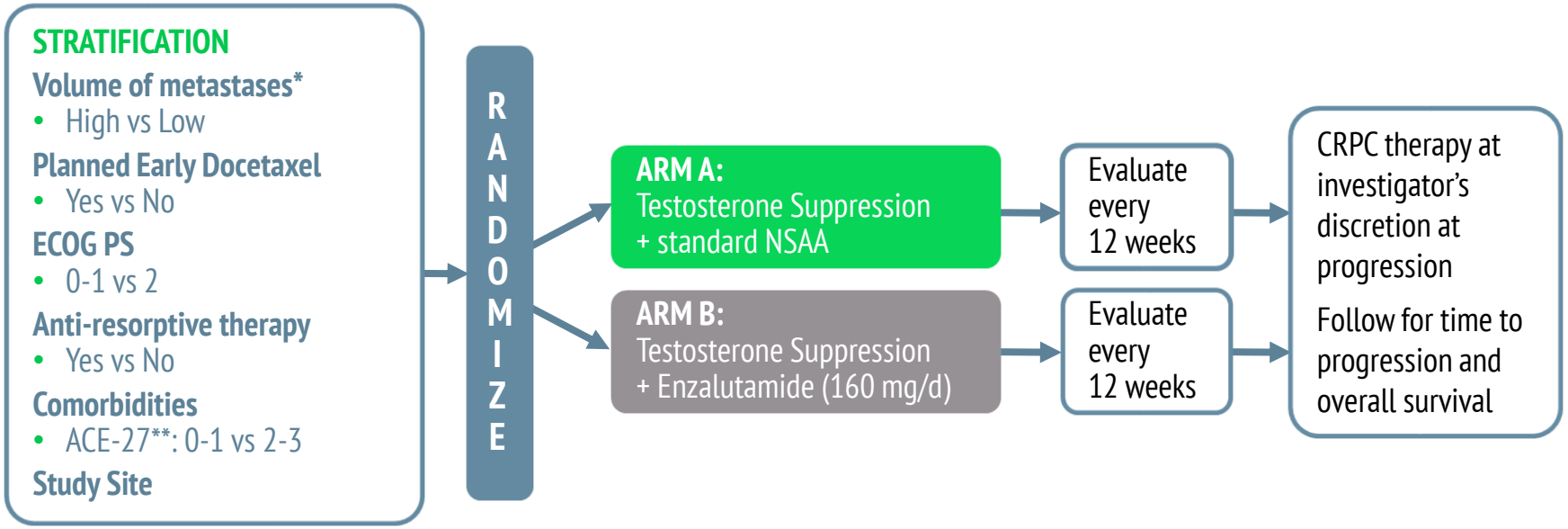
Other Secondary Endpoints

- 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

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

ENZAMET RESULTS

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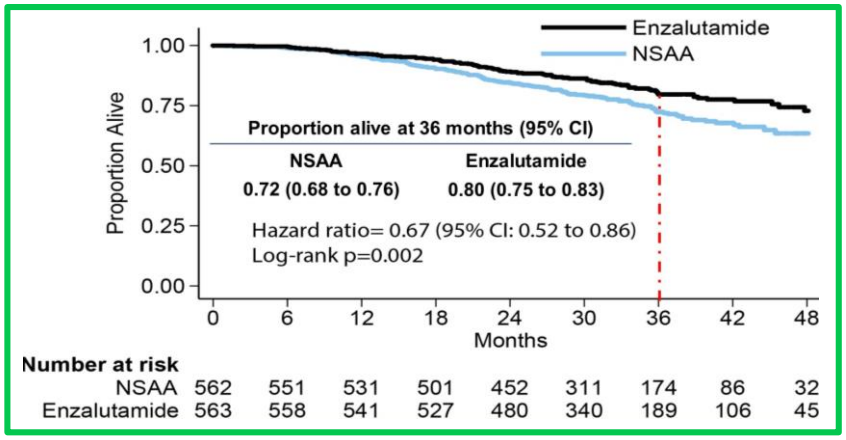
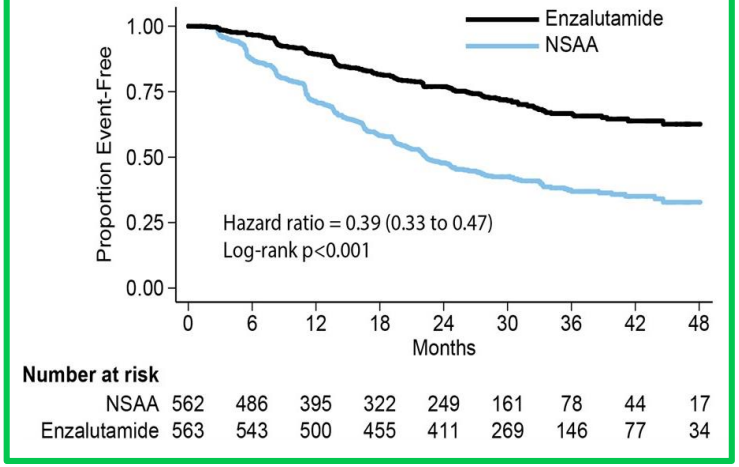
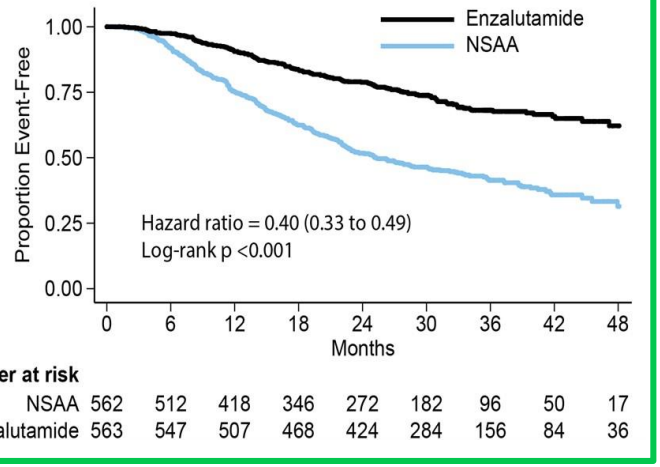
OVERALL SURVIVAL



PSA PFS



CLINICAL PFS



Median follow up of 33 months

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

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

RESULTS BY CONCURRENT DOCETAXEL THERAPY

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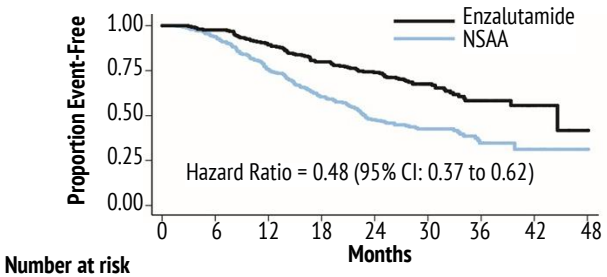
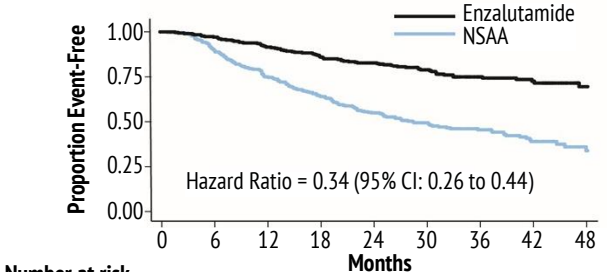
Testosterone suppression + Docetaxel N=503 (71% High Volume)

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

CLINICAL PFS

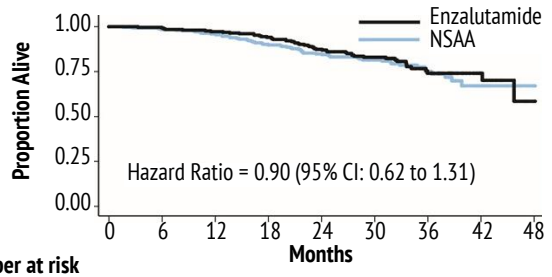


Number at risk									
NSAA	249	230	185	148	112	73	21	6	1
Enzalutamide	254	248	226	202	178	109	35	12	2

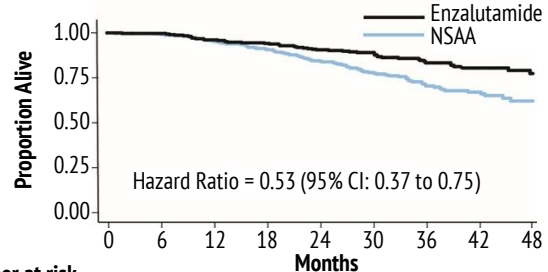


Number at risk									
NSAA	313	282	233	198	160	109	75	44	16
Enzalutamide	309	299	281	266	246	175	121	72	34

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

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

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

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)

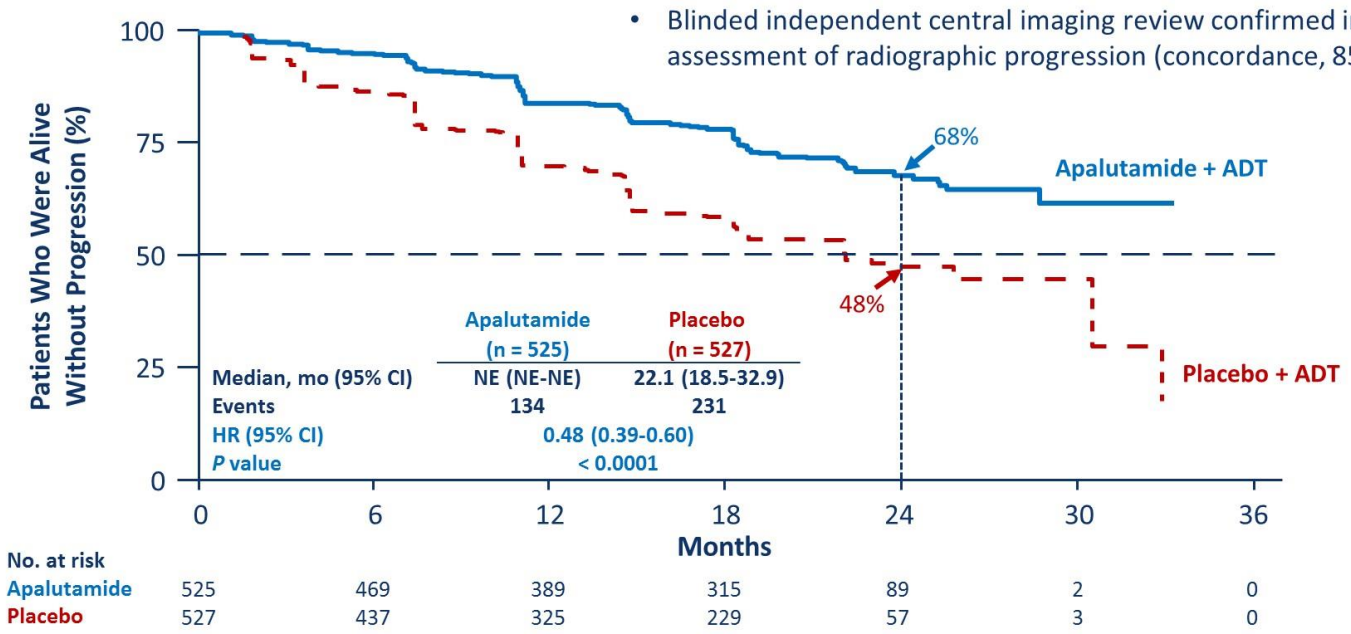
ADT, androgen deprivation therapy; ECOG, PS eastern cooperative oncology group performance status; EU, europe; mHSPC, metastatic hormone sensitive prostate cancer; NA, north america;

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

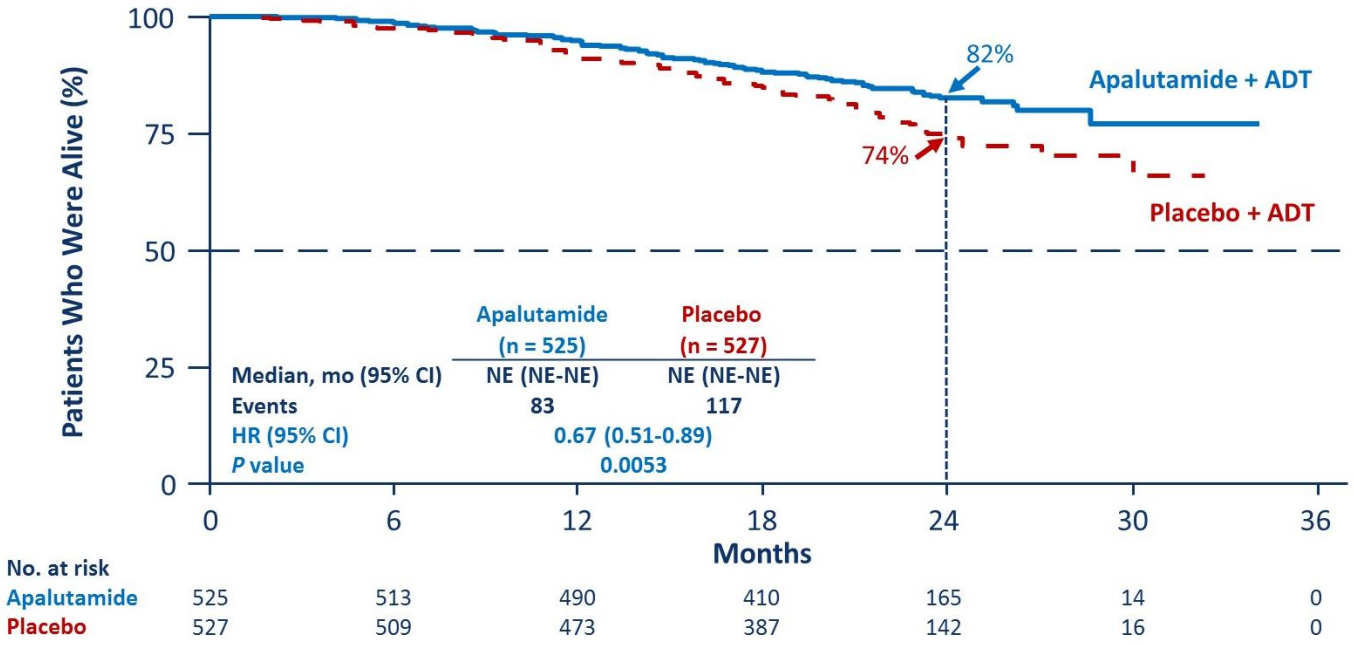
ADT, androgen deprivation therapy; CI, confidence interval; NE, not evaluable; rPFS, radiographic progression free survival

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

CONCLUSION

- **Docetaxel** continues to be a **good treatment option** for patients with **mHSPC**
- Abiraterone, enzalutamide and apalutamide are all potent androgen pathway inhibitors
- No definitive data presently available **to support** the clinical benefit of adding these treatments to chemotherapy

mHSPC, metastatic hormone sensitive prostate cancer

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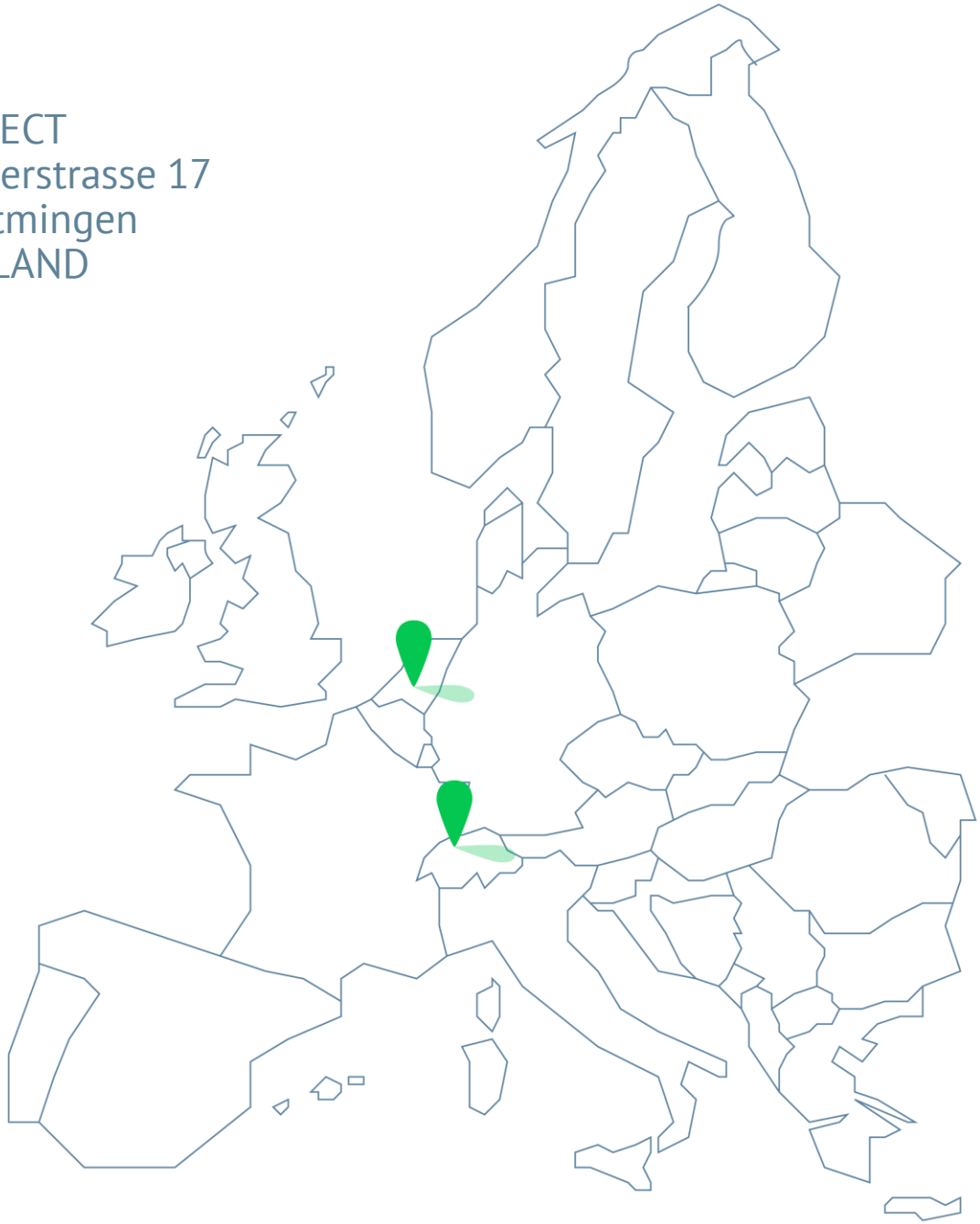

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