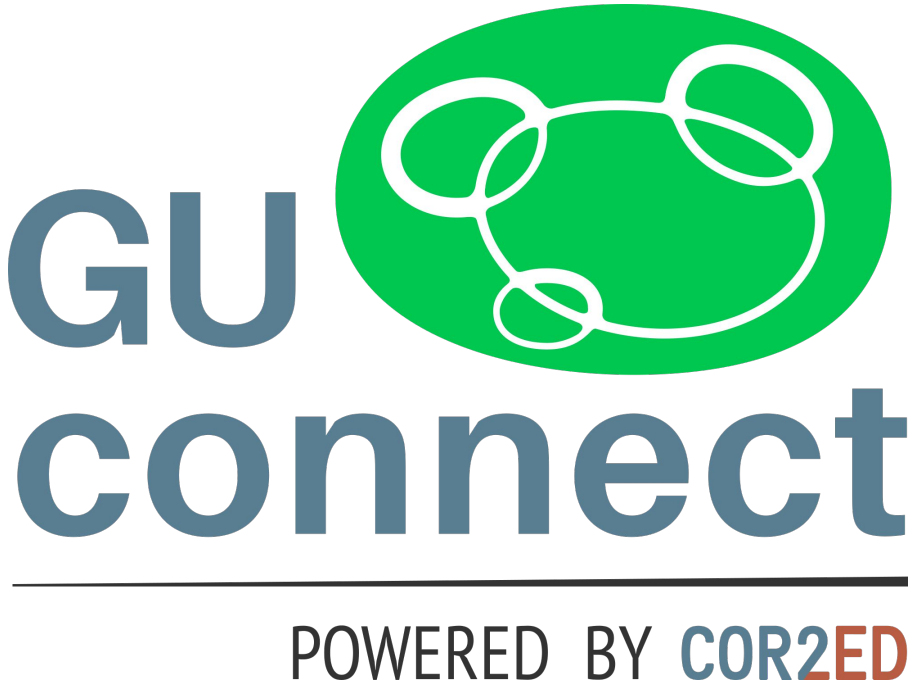

GU
connect
POWERED BY COR2ED

EXPERTS KNOWLEDGE SHARE

with

Drs. Cora Sternberg, Alicia Morgans & Gert Attard

Barcelona, Spain

Saturday September 28th

20:30-22:00

DISCLAIMER

This content is supported by an Independent Educational Grant from Bayer

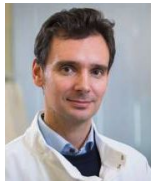
The views expressed within this programme are the personal opinions of Experts. They do not necessarily represent the views of the Experts' academic institutions or the rest of the GU CONNECT group

GU CONNECT
EXPERTS KNOWLEDGE SHARE 2019

GU connect
POWERED BY COR2ED

THE SCIENTIFIC COMMITTEE

- Dr. Cora Sternberg
- Dr. Gert Attard
- Dr. Alicia Morgans


THE DISCUSSION

Treatment sequencing for mCRPC patients within the changing landscape of mHSPC

BACKGROUND AND APPROACHES CONSIDERED

- Overview of changing landscape of mHSPC - *Dr. Sternberg*
- mCRPC treatment choices after docetaxel for mHSPC - *Dr. Attard*
- mCRPC treatment choices after abiraterone for mHSPC - *Dr. Morgans*

INTRODUCTION AND OVERVIEW

Weill Cornell Medicine
Englander Institute
for Precision Medicine

Weill Cornell Medicine
Meyer Cancer Center

THE RAPIDLY CHANGING LANDSCAPE IN HORMONE SENSITIVE PROSTATE CANCER

Cora N. Sternberg, MD, FACP

Clinical Director, Englander Institute for Precision Medicine
Weill Cornell Medicine
New York-Presbyterian, New York

DISCLOSURES

Dr. Cora Sternberg has received financial support/sponsorship for research support, consultation or speaker fees from the following companies:

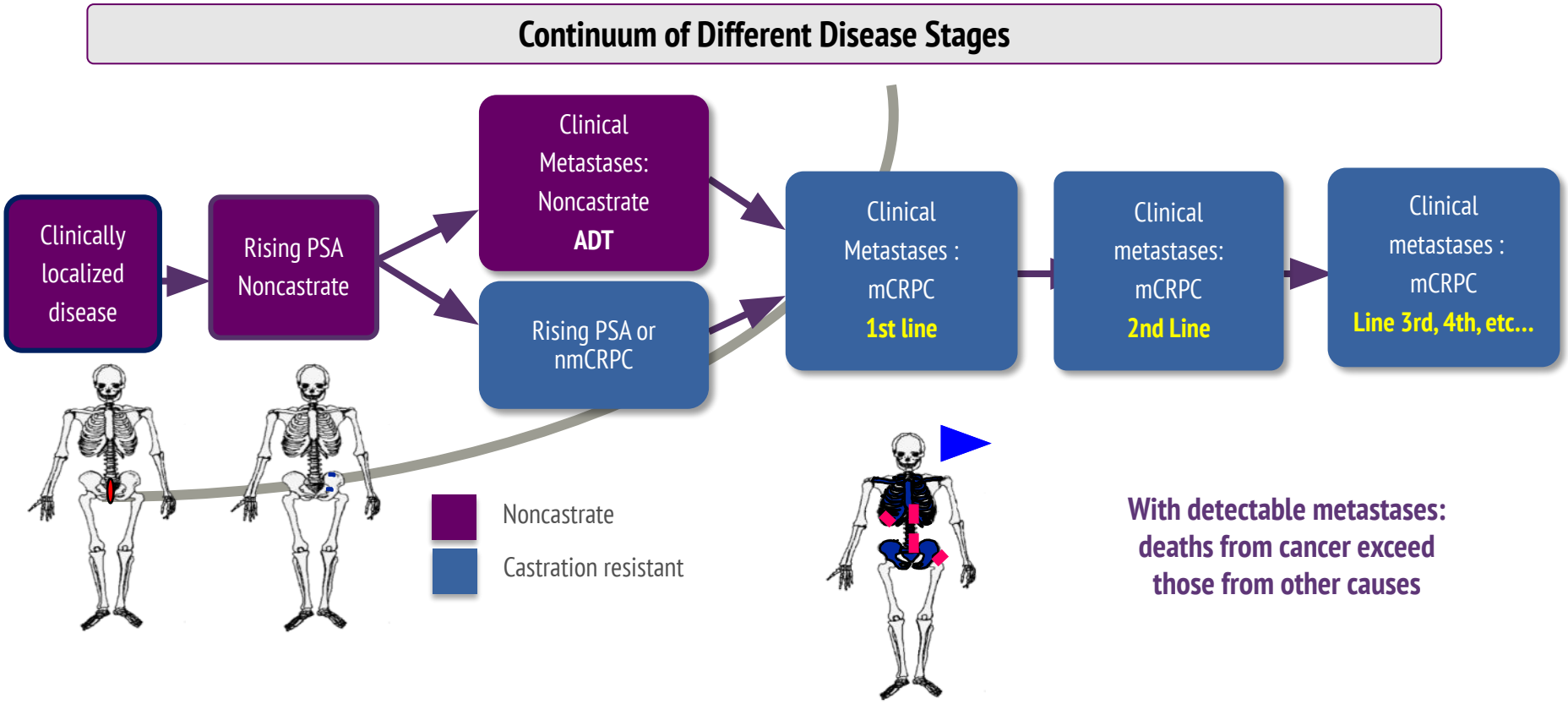
Janssen, Astellas, AstraZeneca, Bayer, Exelixis, Medivation, Roche-Genetech, Pfizer, Sanofi and Sanofi Genzyme

Please note:

The views expressed within this presentation are the personal opinions of the author. They do not necessarily represent the views of the author's academic institution or the rest of the GU CONNECT group

PROSTATE CANCER 2ND LEADING CAUSE OF CANCER

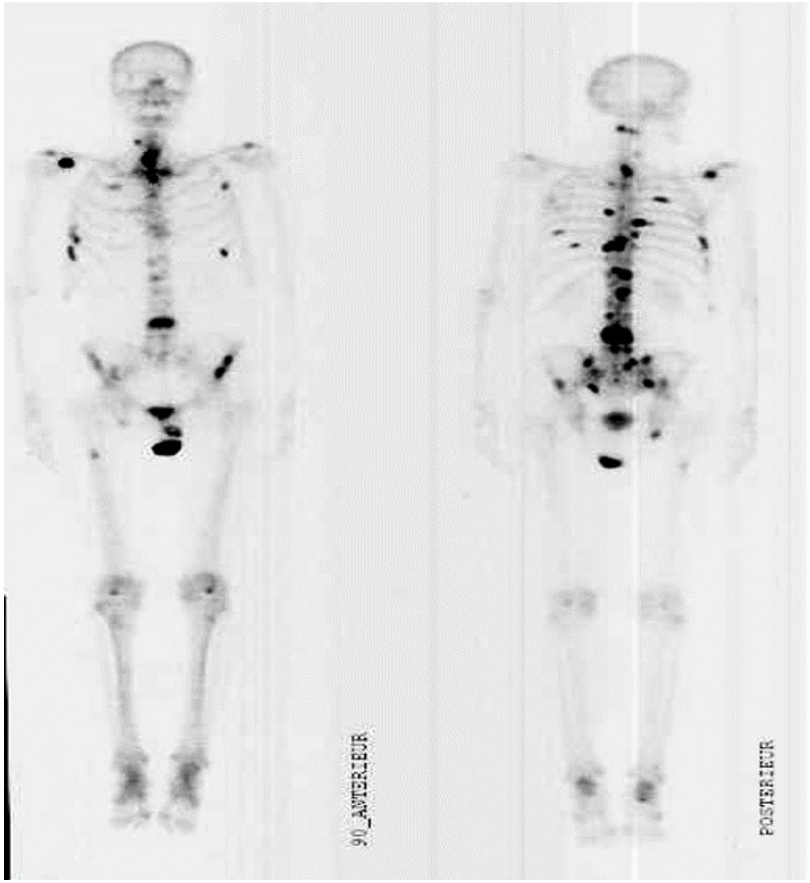
- In the US in 2018:
  - **164,690** new prostate cancer cases and **29,430** prostate cancer deaths

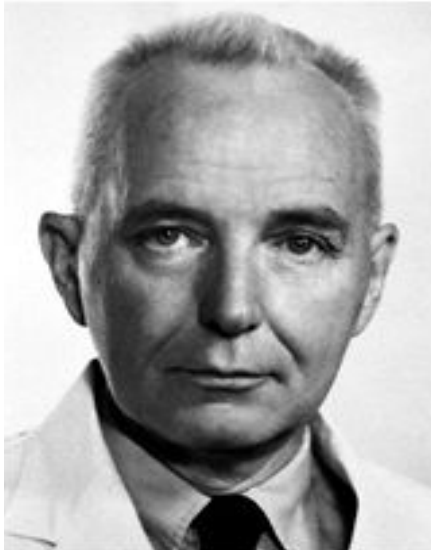


ADT, androgen deprivation therapy; mCRPC, metastatic castration resistant prostate cancer; nmCRPC, non metastatic castration resistant prostate cancer; PSA, prostate specific antigen.

Scher HI, et al. JCO 2016; 34 (12): 1402-1418; Siegel R, Miller KD, Jemal A. Cancer Statistics. 2018. CA Cancer J Clin. 2018; 68:7-30.

PROSTATE CANCER IS HORMONE DEPENDENT



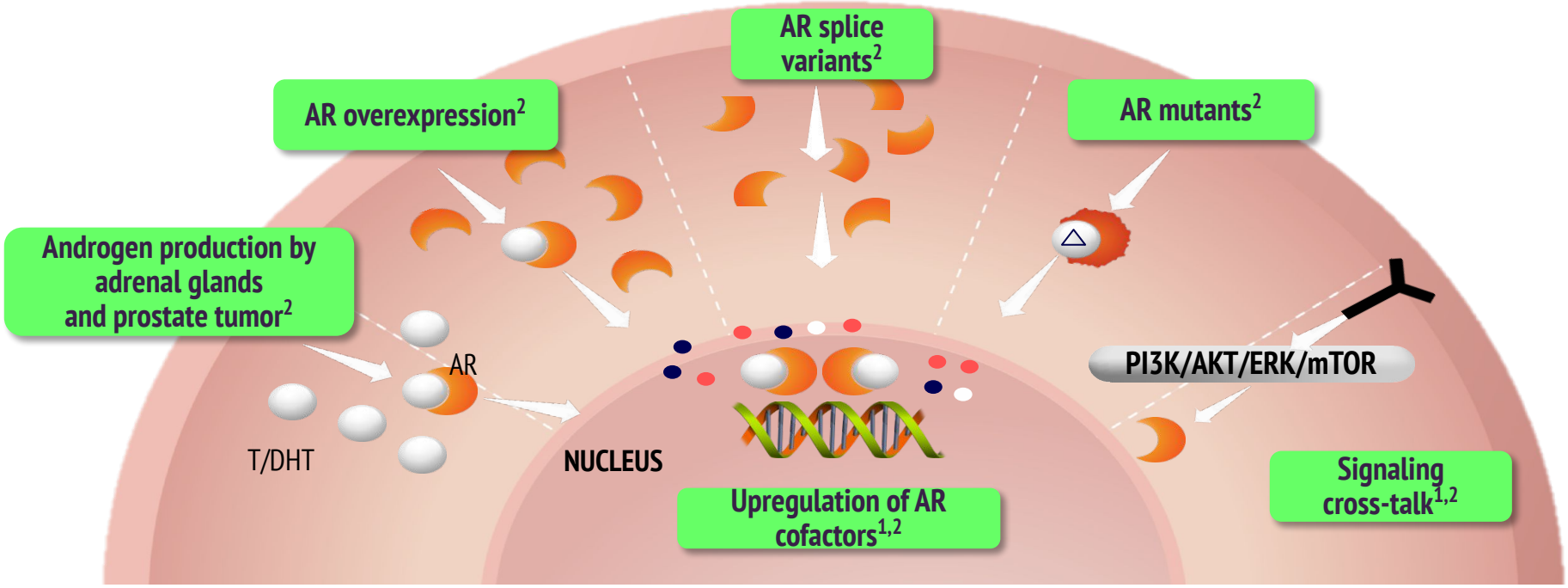


"Despite regressions of great magnitude, it is obvious that there are many failures of endocrine therapy to control the disease"

Charles B. Huggins
Nobel Lecture
December 13, 1966

http://nobelprize.org/nobel_prizes/medicine/laureates/1966/huggins-lecture.html

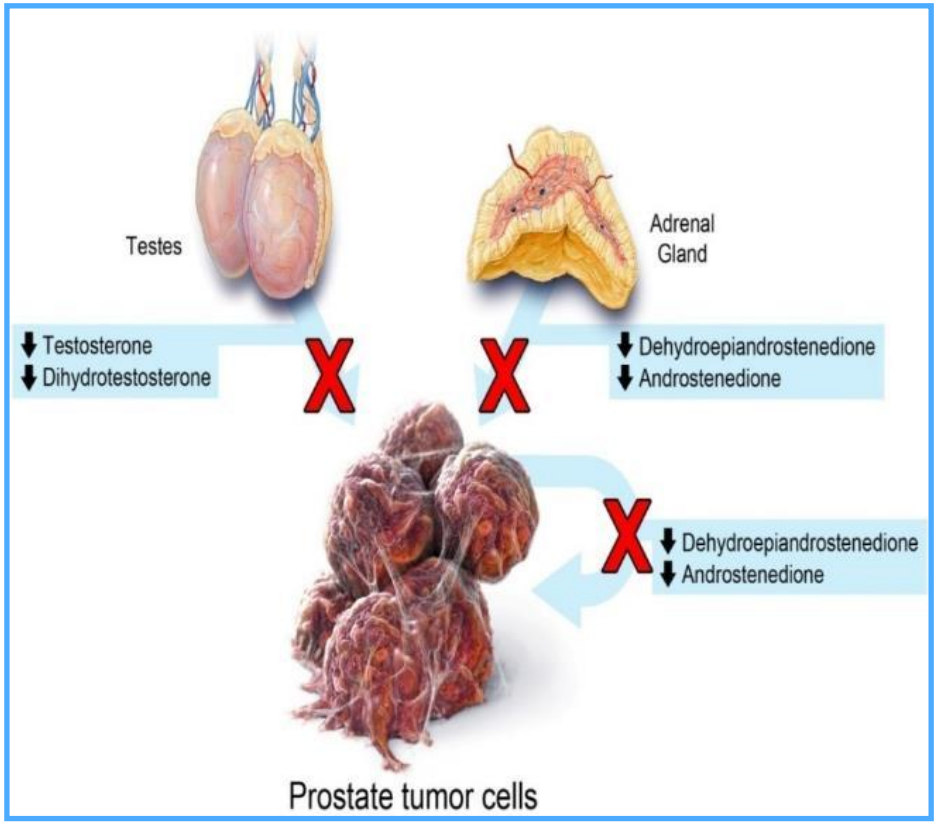
PROSTATE CANCER REMAINS DRIVEN BY ANDROGEN RECEPTOR SIGNALLING: AR ALTERATIONS SELECTED DURING THERAPY



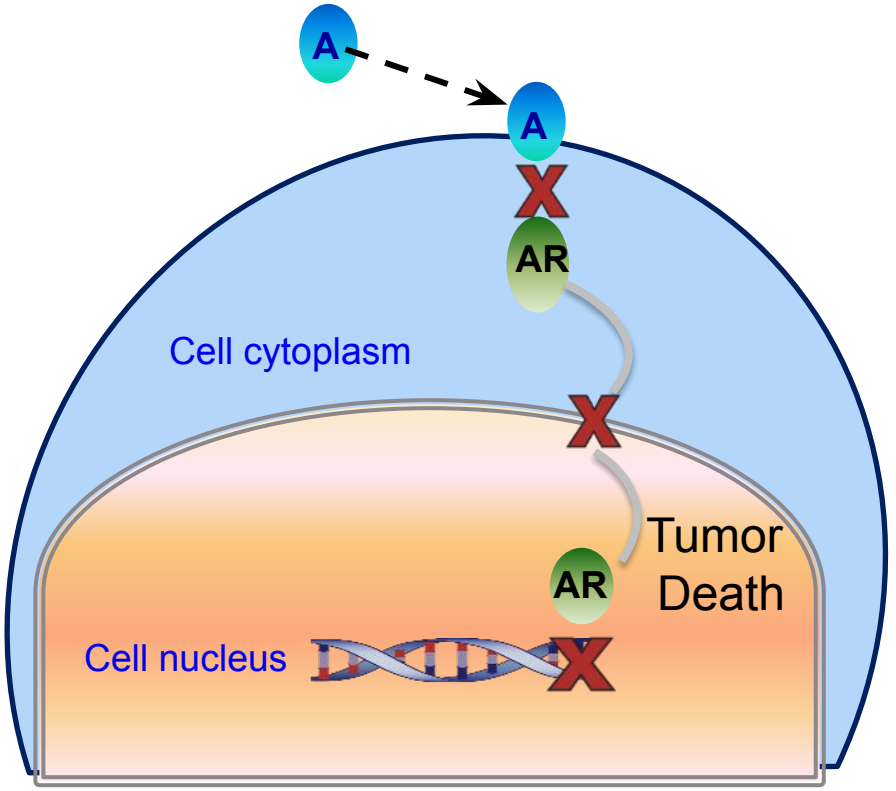
AR, androgen receptor; DHT, dihydrotestosterone; T, testosterone.

1. Heinlein CA, et al. Endocr Rev. 2004;25(2):276-308; 2. Hu R, et al. Expert Rev Endocrinol Metab. 2010;5(5):753-64.

MOA OF NOVEL HORMONAL AGENTS



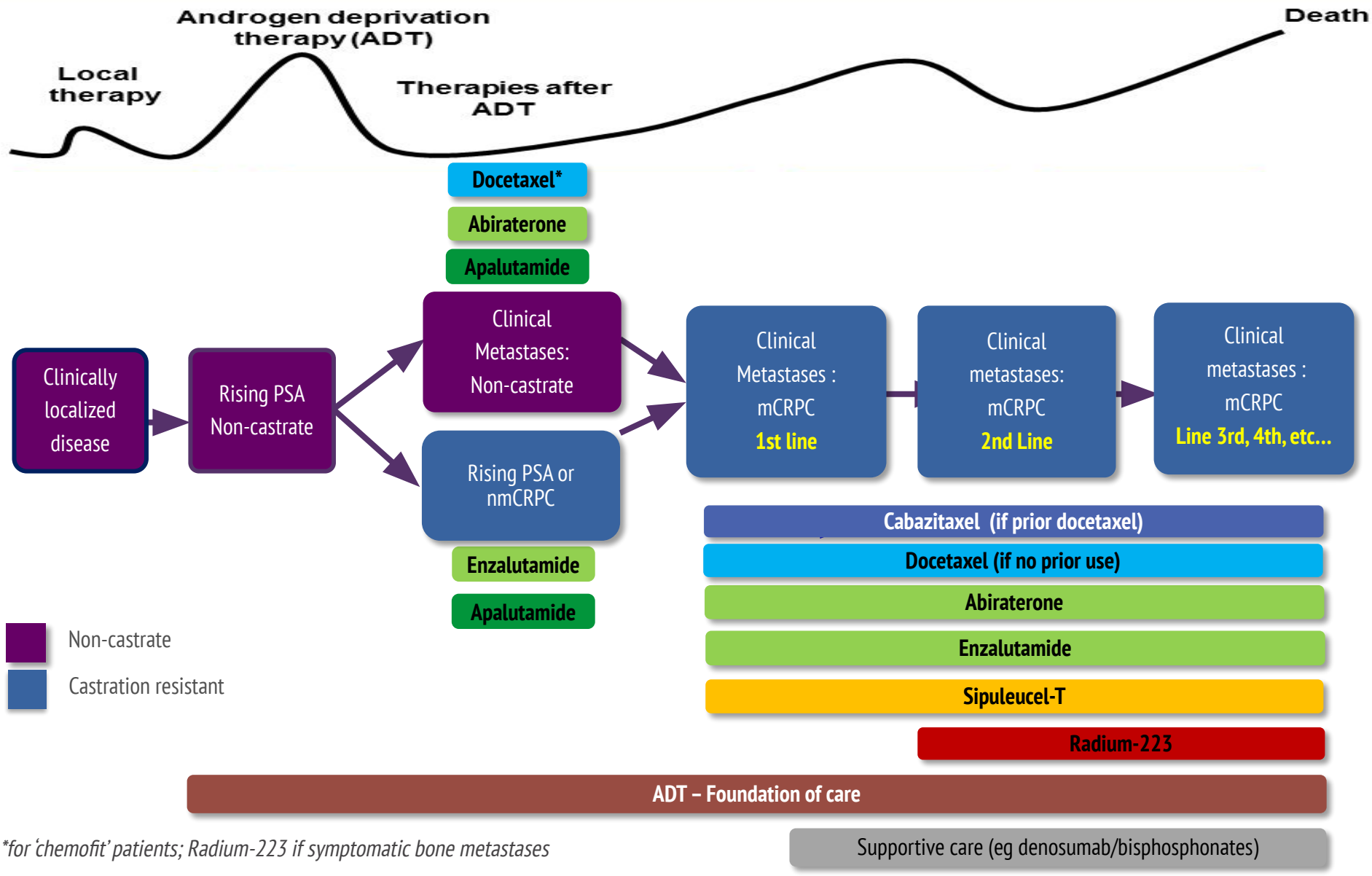
Abiraterone Inhibits Androgen Biosynthesis Through CYP17



Enzalutamide and apalutamide are AR signalling inhibitors: target multiple steps in the (AR) signalling pathway

A, androgen; AR, androgen receptor; MOA, mechanism of action.

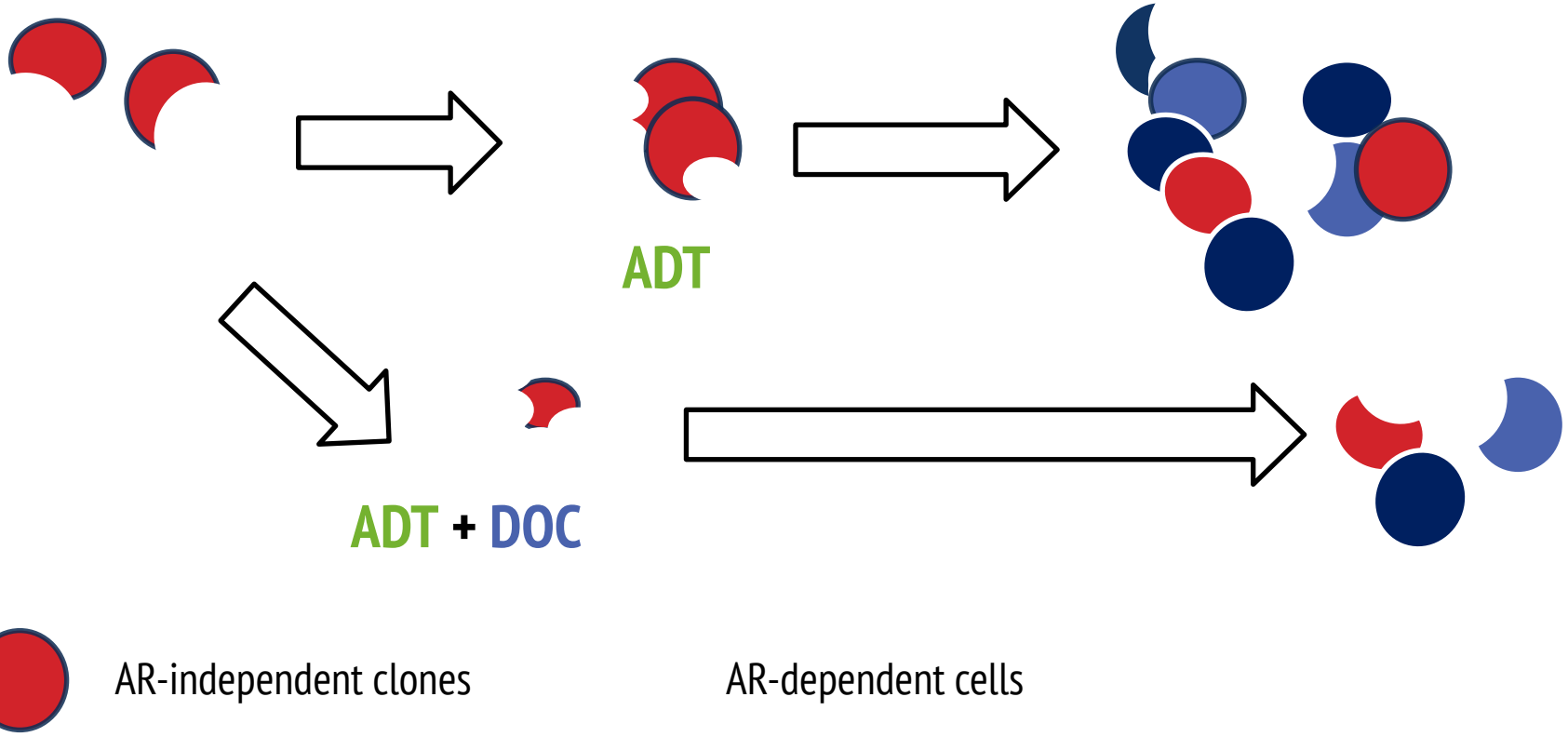
PROSTATE CANCER TREATMENT OPTIONS IN 2019



for 'chemofit' patients; Radium-223 if symptomatic bone metastases

ADT, androgen deprivation therapy; mCRPC, metastatic castration resistant prostate cancer; nmCRPC, non metastatic castration resistant prostate cancer; PSA, prostate specific antigen. Scher HI, et al. JCO 2016; 34 (12): 1402-1418

PROSTATE CANCER HETEROGENEITY MAY BE BETTER ADDRESSED BY A COMBINATION STRATEGY



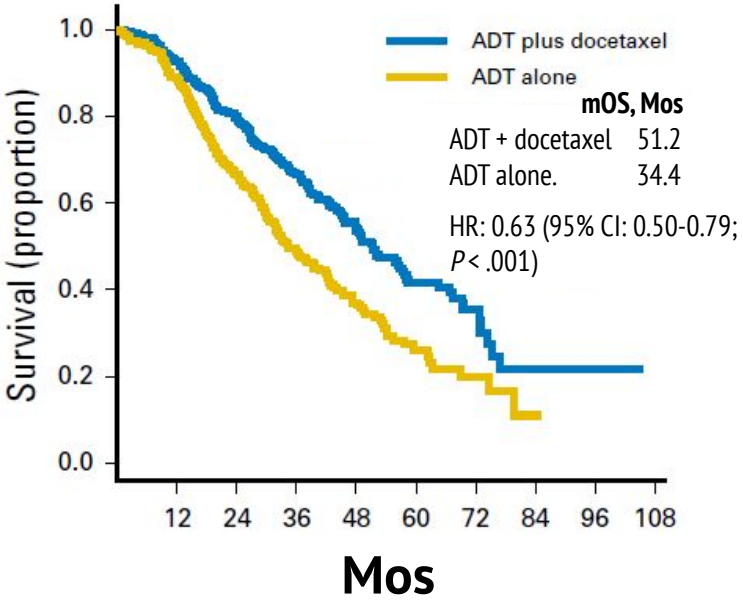
ADT, androgen deprivation therapy; AR, androgen receptor; DOC, docetaxel (75 mg/m^2 every 3 weeks).

Sweeney C, et al. J Clin Oncol. 2014;32, no.18_suppl. Abstract LBA2 (podium presentation).

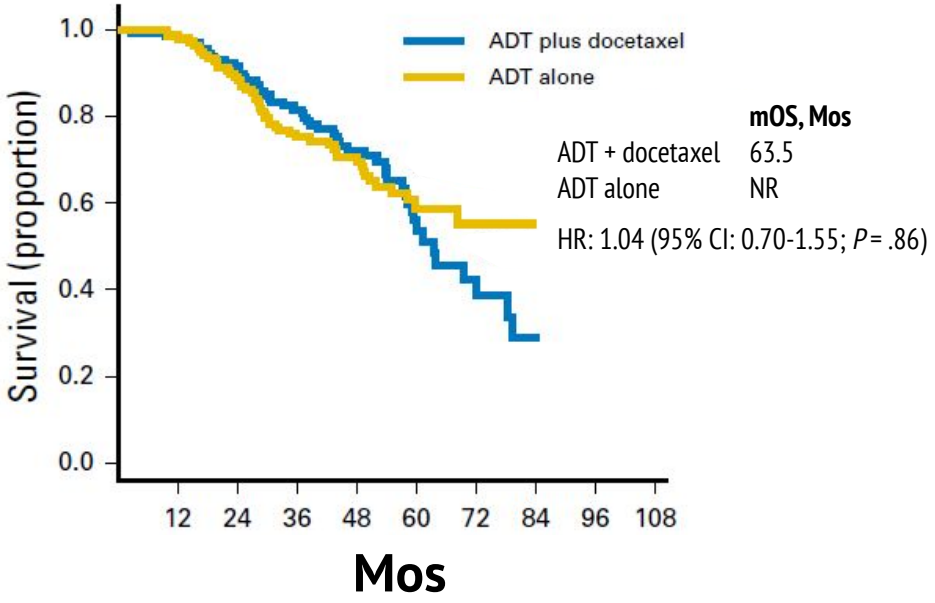
PHASE III CHAARTED TRIAL LONG-TERM FOLLOW-UP: HIGH-VOLUME VS LOW-VOLUME DISEASE

- Median follow-up of 53.7 mos in patients with metastatic hormone-sensitive prostate cancer randomized to ADT + docetaxel vs ADT alone (N=790)

High-Volume Disease



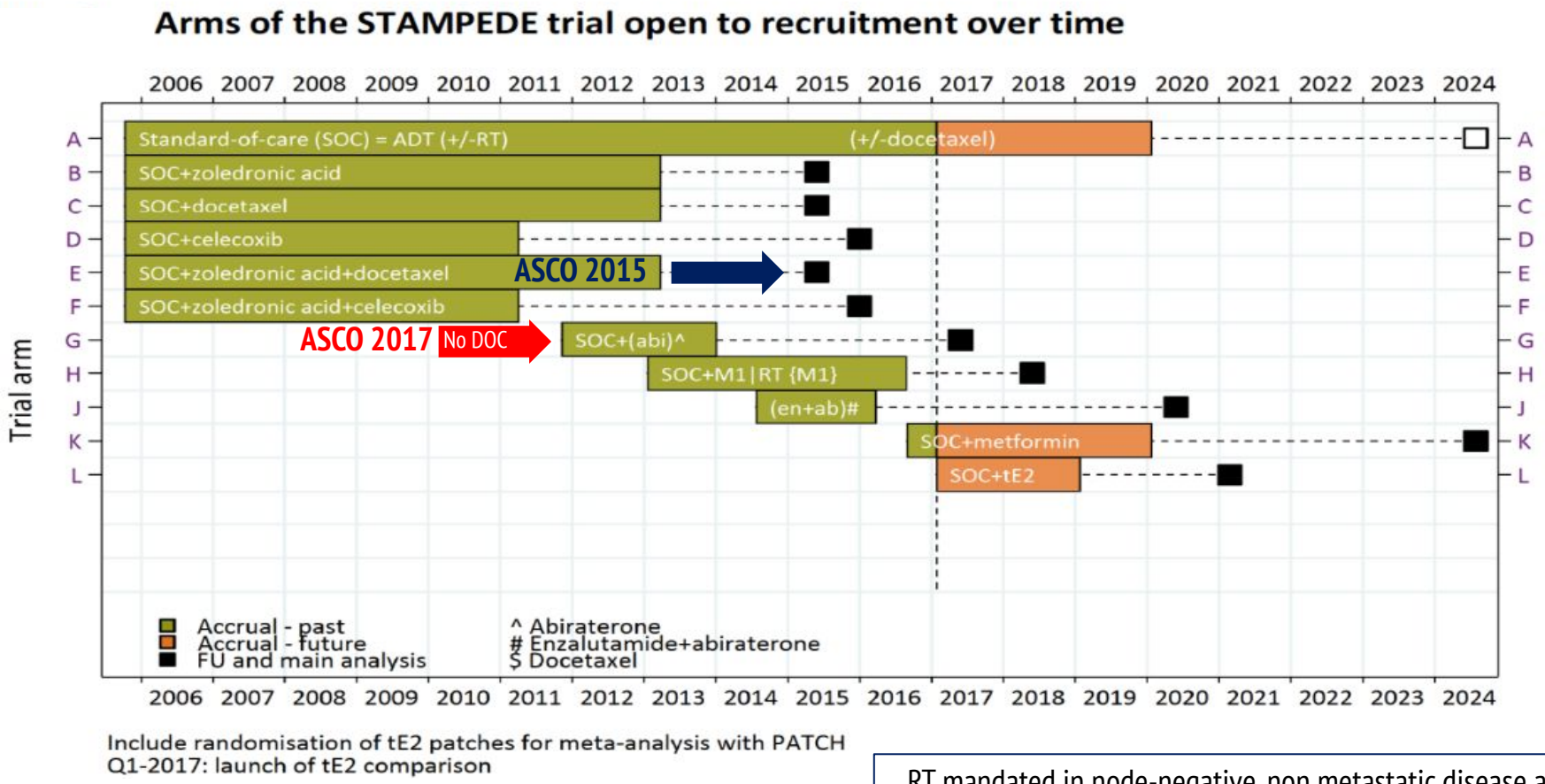
Low-Volume Disease



ADT, androgen deprivation therapy; mOS, median overall survival; Mos, months.

Kyriakopoulos CE, et al. J Clin Oncol. 2018;36:1080-87.

STAMPEDE TRIAL:
A MULTI-ARM, MULTI-STAGE DESIGN



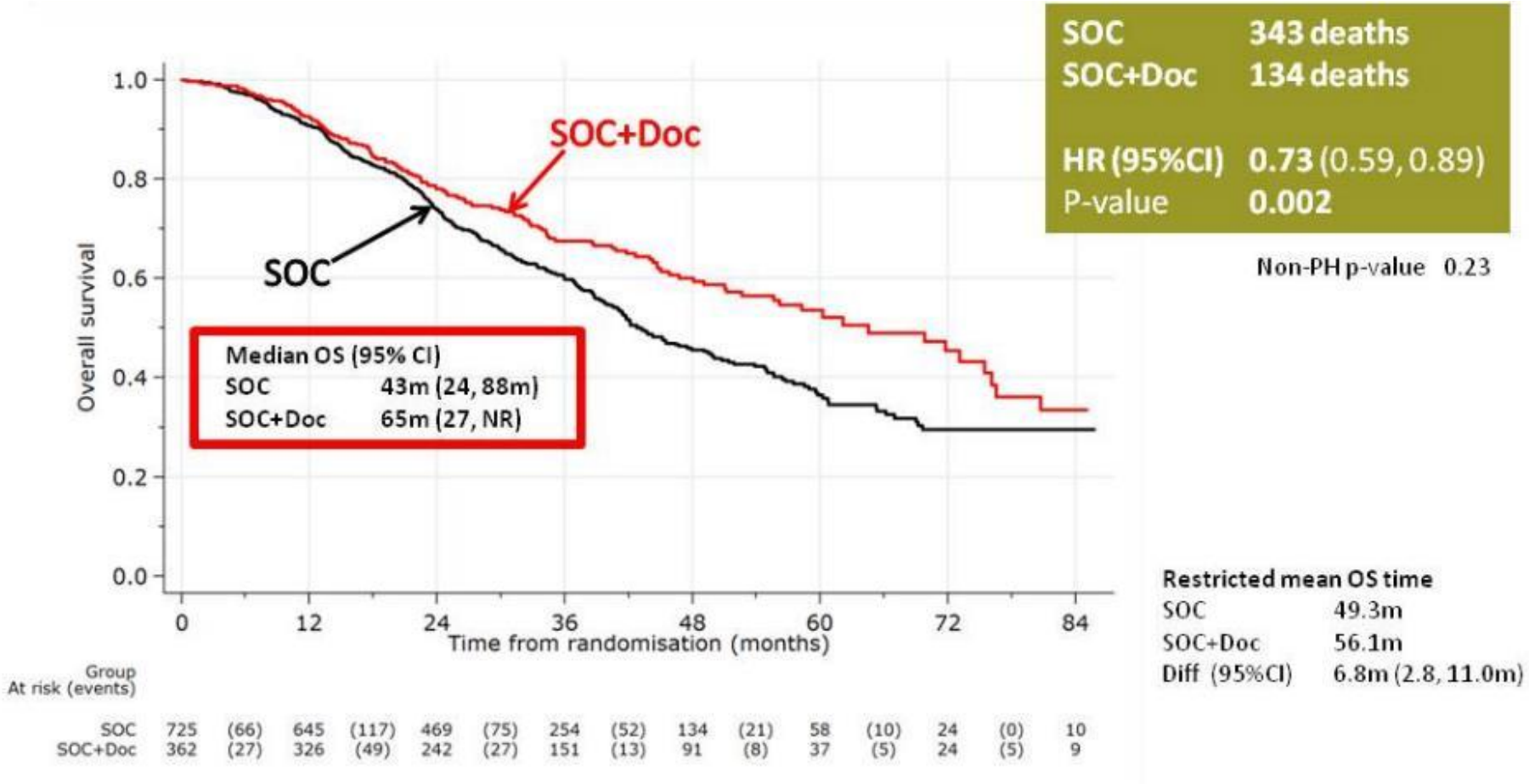
1:1 randomization AA + 5 mg prednisone vs SOC (ADT +/-RT) x 2yr

RT mandated in node-negative, non metastatic disease and encouraged in pts with positive nodes

AA, abiraterone acetate; ab, abiraterone; ADT, androgen deprivation therapy; en, enzalutamide; RT, radiotherapy; SOC, standard of care

www.stampedetrial.org

STAMPEDE – OS IN M1 PATIENTS WITH DOCETAXEL

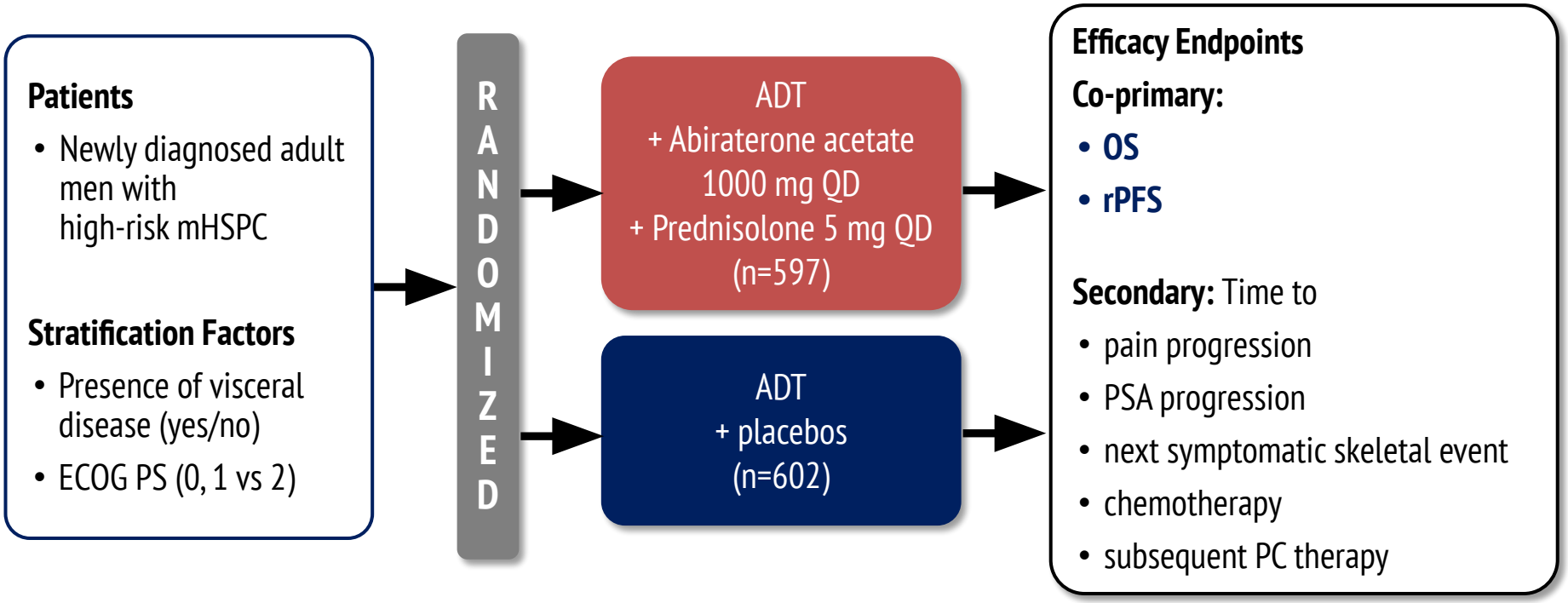


Phase III randomized trial in 2962 men with M0/M1 in 4 groups with zoledronic acid with hormone-sensitive Pca; Primary endpoint: overall survival

CI, confidence interval; DOC, docetaxel; HR, hazard ratio; M0, non metastatic; M1, metastatic; OS, overall survival; Pca, prostate cancer; SOC, standard of care

James ND, et al. ASCO 2015 Oral presentation, abstract #5001.

LATITUDE: PHASE III TRIAL OF ABIRATERONE IN NEWLY DIAGNOSED METASTATIC PROSTATE CANCER (N=1,199)



High-risk defined as meeting at least 2 of 3 high-risk criteria:

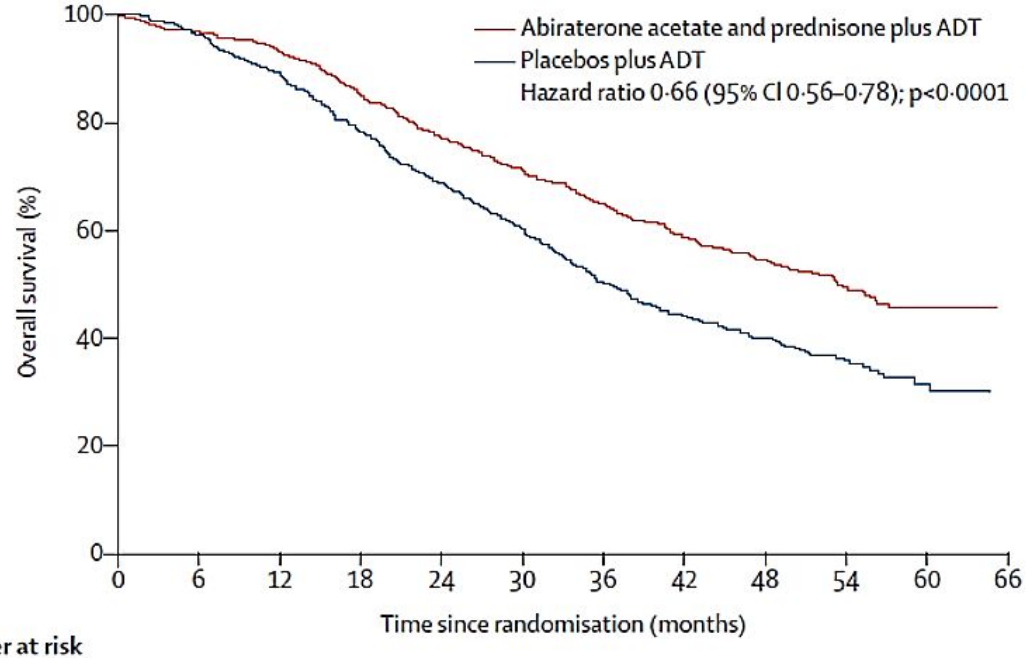
- Gleason score of ⩾8
- Presence of ⩾3 lesions on bone scan
- Presence of measurable visceral lesion

ADT, androgen deprivation therapy; ECOG PS, eastern cooperative oncology group performance status; mHSPC, metastatic hormone sensitive prostate cancer; OS, overall survival; rPFS, radiographic progression free survival; PC, prostate cancer; PSA, prostate specific antigen

Fizazi K, et al. N Engl J Med. 2017;377(4):352-60.

LATITUDE: ADT + ABIRATERONE ACETATE (AA) + PREDNISONE VS ADT + PLACEBO IN METASTATIC HORMONE SENSITIVE PC (mHSPC)

OVERALL SURVIVAL



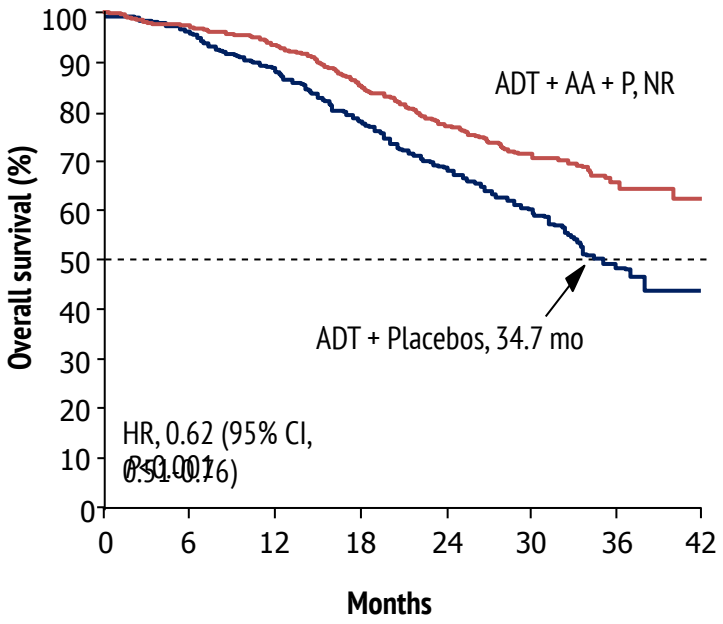
Number at risk (number censored)												
Abiraterone acetate and prednisone plus ADT	597	565 (14)	529 (28)	479 (34)	425 (42)	389 (46)	351 (50)	311 (57)	240 (106)	124 (205)	40 (282)	0 (322)
Placebos plus ADT	602	564 (17)	505 (34)	432 (47)	368 (58)	315 (37)	256 (74)	220 (79)	165 (114)	69 (197)	23 (237)	0 (259)

ADT, androgen deprivation therapy; CI, confidence interval; mHSPC, metastatic sensitive naïve prostate cancer.

Fizazi K, et al. Lancet Oncol. 2019 May;20(5):686-700.

ABIRATERONE: IN mHSPC OS IS GREATER WHEN USED AT DIAGNOSIS

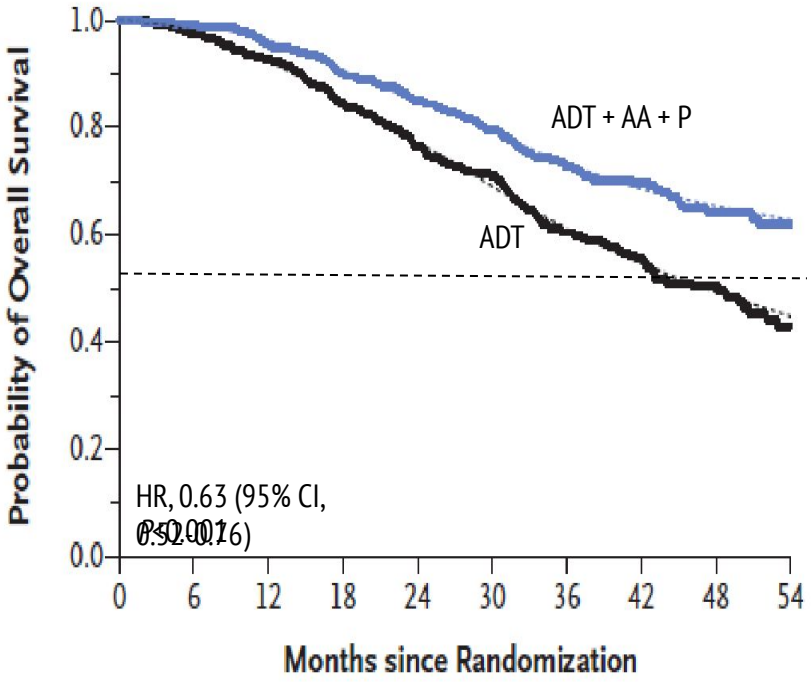
LATITUDE M1 High Risk
38% Risk Reduction in Death



Follow up 30.4 months

Fizazi K, et al. N Engl J Med. 2017;377:352-60.

STAMPEDE M1 and M0
37% Risk Reduction in Death



Follow up 40 months

James ND, et al. N Engl J Med. 2017;377:338-51.

AA, abiraterone acetate; ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; M0, non-metastatic; M1, metastatic; mHSPC, metastatic hormone sensitive prostate cancer; P, prednisolone.

mHSPC STUDIES: OVERVIEW

	Enzalutamide Studies		
	ARCHES[1]	ENZAMET[2]	TITAN[3]
Design	Randomized, double-blind, phase 3	Randomized, open-label, phase 3	Randomized, double-blind, phase 3
N	1,150	1,125	1,052
Treatment	**Enzalutamide + ADT (n=574) vs. placebo + ADT (n=576)**	**Enzalutamide+ ADT (n=563) vs. NSAA + ADT (n=562)**	**Apalutamide + ADT (n=525) vs. placebo + ADT (n=527)**
***de novo* Metastatic**	70% (Enzalutamide arm) vs. 63% (control arm)	62% (Enzalutamide arm) vs. 67% (control arm)	78% (apalutamide arm) vs. 84% (control arm)
High Volume[a]	62% (Enzalutamide arm) vs. 65% (control arm)	52% (Enzalutamide arm) vs. 53% (control arm)	62% (apalutamide arm) vs. 64% (control arm)
Docetaxel	Prior docetaxel: 18% (Enzalutamide arm) vs. 18% (control arm)	Concomitant docetaxel[b]: 45% (Enzalutamide arm) vs. 44% (control arm)	Prior docetaxel: 11% (apalutamide arm) vs. 10% (control arm)
Primary Endpoint	rPFS= HR 0.39	OS= HR 0.67	rPFS HR=0.48, OS = HR 0.67

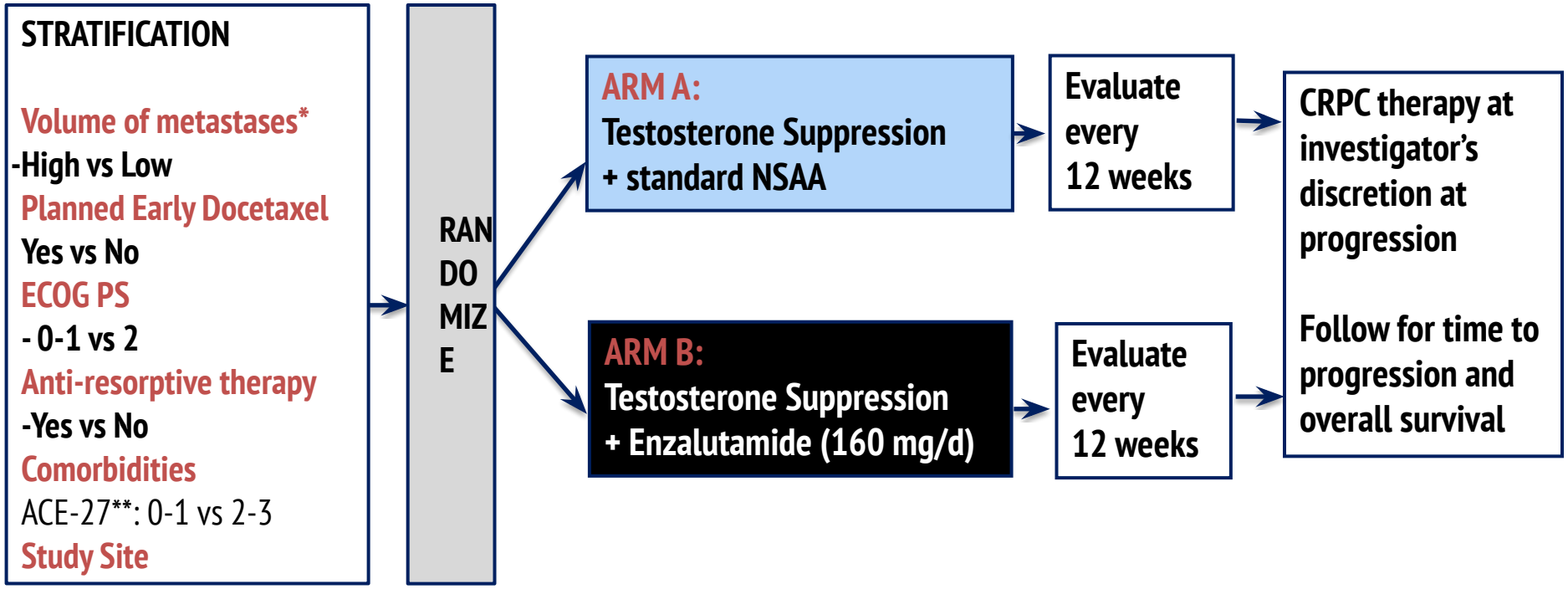
[a] High volume was defined as metastases involving the viscera or, in the absence of visceral lesions, ≥4 bone lesions, ≥1 of which must be in a bony structure beyond the vertebral column and pelvic bone in ARCHES and ENZAMET, and as visceral metastases and ≥1 bone lesion, or ≥4 bone lesions with ≥1 outside the axial skeleton in TITAN.[1-3]

[b] The early administration of docetaxel with testosterone suppression was permitted in protocol version 2 as a stratification factor before randomization, according to evidence showing improved survival with this approach.[2]

ADT, androgen deprivation therapy; HR, hazard ratio; mHSPC, metastatic hormone sensitive prostate cancer; NSAA, nonsteroidal antiandrogen; rPFS, radiographic progression free survival; OS, overall survival.

1. Armstrong A, et al, J Clin Oncol. 2019 Jul 22 [DOI: 10.1200/JCO.19.00799]; 2. Davis ID et al. N Engl J Med. 2019;381:121-31;
3. Chi KN, et al. N Engl J Med. 2019; 381:13-24.

ENZAMET TREATMENT IN mHSPC



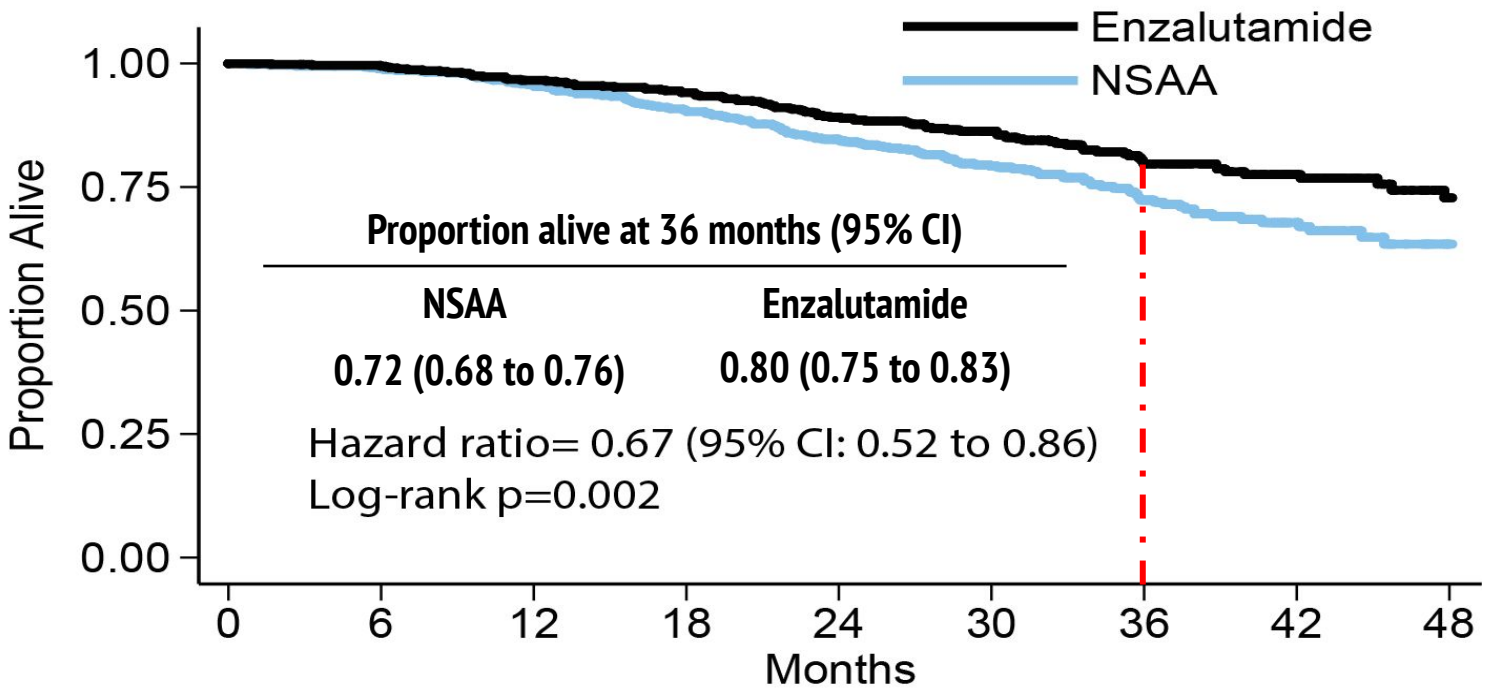
Prior to randomization testosterone suppression up to 12 weeks and 2 cycles of docetaxel was allowed; Intermittent ADT and cyproterone were not allowed; NSAA: bicalutamide; nilutamide; flutamide

*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; mHSPC, metastatic hormone sensitive prostate cancer; NSAA, nonsteroidal antiandrogen

Davis ID, et al. N Engl J Med. 2019; 381:121-31.

ENZAMET PRIMARY ENDPOINT: OVERALL SURVIVAL



Number at risk

NSAA	562	551	531	501	452	311	174	86	32
Enzalutamide	563	558	541	527	480	340	189	106	45

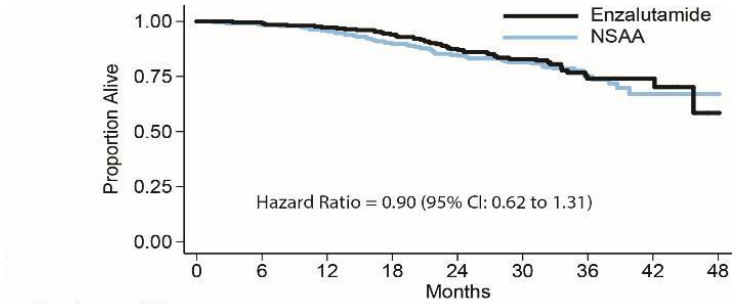
CI, confidence interval; NSAA, nonsteroidal antiandrogen; PSA, prostate specific antigen; PFS, progression free survival

Davis ID, et al. N Engl J Med. 2019; 381:121-31.

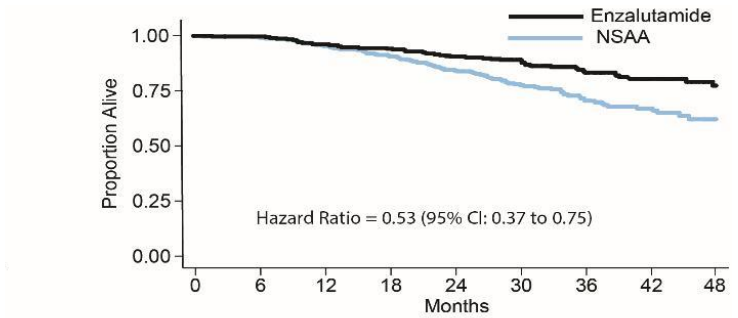
CONCURRENT DOCETAXEL: PRESPECIFIED SUBGROUP OF INTEREST (BIOLOGY AND TREATMENT IMPLICATIONS)

OVERALL SURVIVAL

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



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



CI, confidence interval; NSAA, nonsteroidal antiandrogen

Davis ID, et al. N Engl J Med. 2019; 381:121-31.

ARCHES STUDY DESIGN

Key eligibility criteria

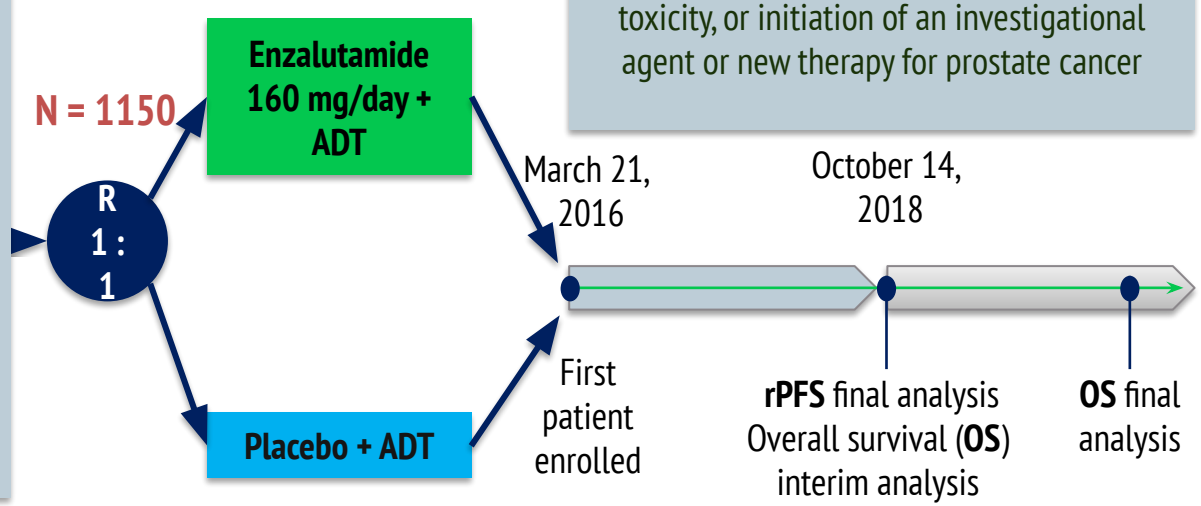
- mHSPC (confirmed by bone scan, CT, or MRI), histologically confirmed adenocarcinoma
- ECOG Performance Status 0 to 1
- Current ADT duration ≤3 months unless prior docetaxel, then ≤6 months

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



*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

Primary endpoint

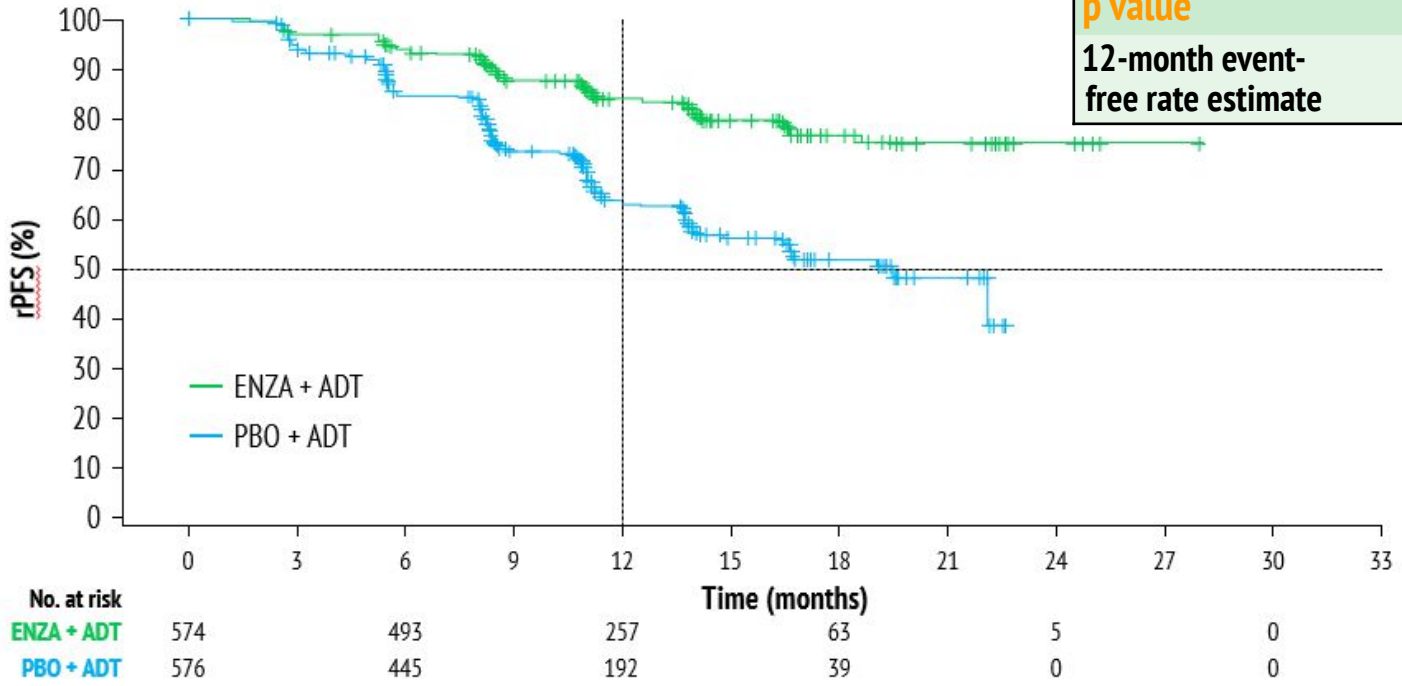
- rPFS: time from randomization to first objective evidence of radiographic progression assessed centrally, or death from any cause within 24 weeks of treatment discontinuation, whichever occurs first
  - Radiographic disease progression was defined by RECIST 1.1 criteria for soft tissue disease or by 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

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;

Armstrong A, et al, J Clin Oncol. 2019 Jul 22 [DOI: 10.1200/JCO.19.00799]

PRIMARY ENDPOINT: rPFS

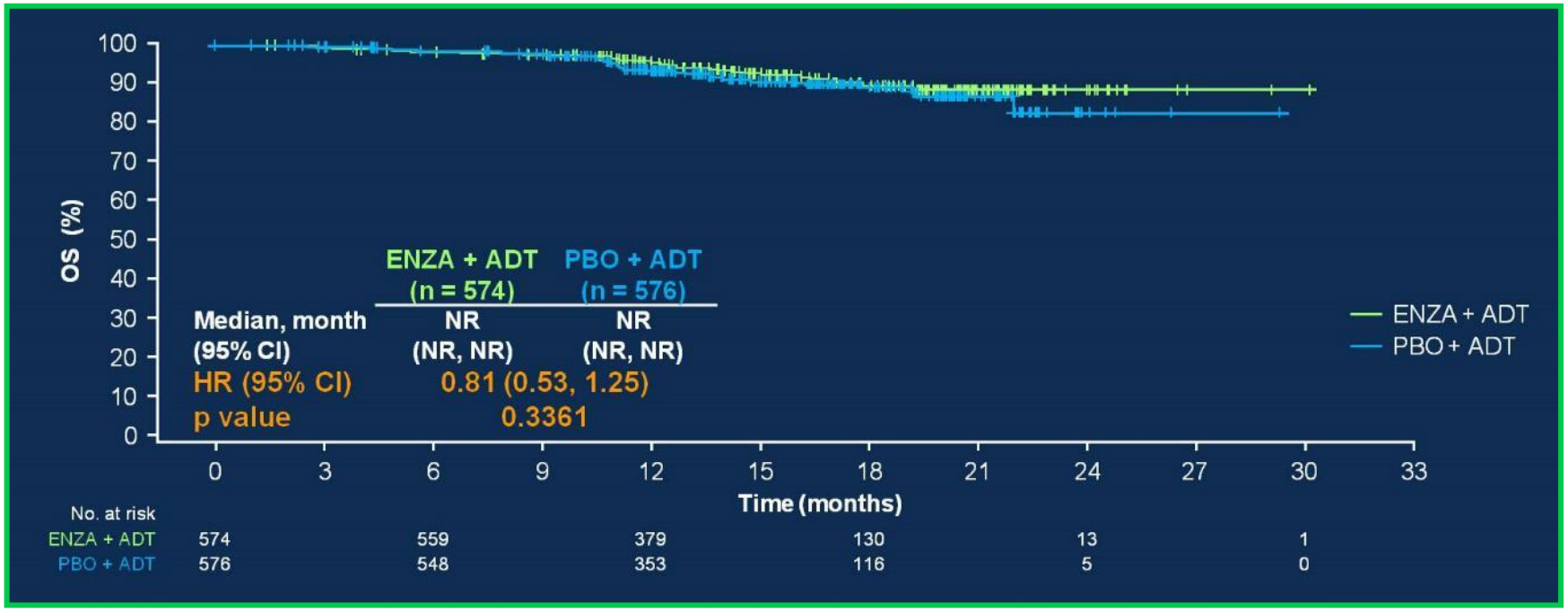
		PBO + ADT (n = 576)
Median, month (95% CI)	NR (NR, NR)	19.45 (16.59, NR)
HR (95% CI)	0.39 (0.30, 0.50)	
p value	<0.0001	
12-month event-free rate estimate	0.84	0.64



- 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

ADT, androgen deprivation therapy; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; NR, not reached; PBO, placebo; rPFS, radiographic progression free survival. Armstrong A, et al, J Clin Oncol. 2019 Jul 22 [DOI: 10.1200/JCO.19.00799]

OVERALL SURVIVAL: INTERIM ANALYSIS

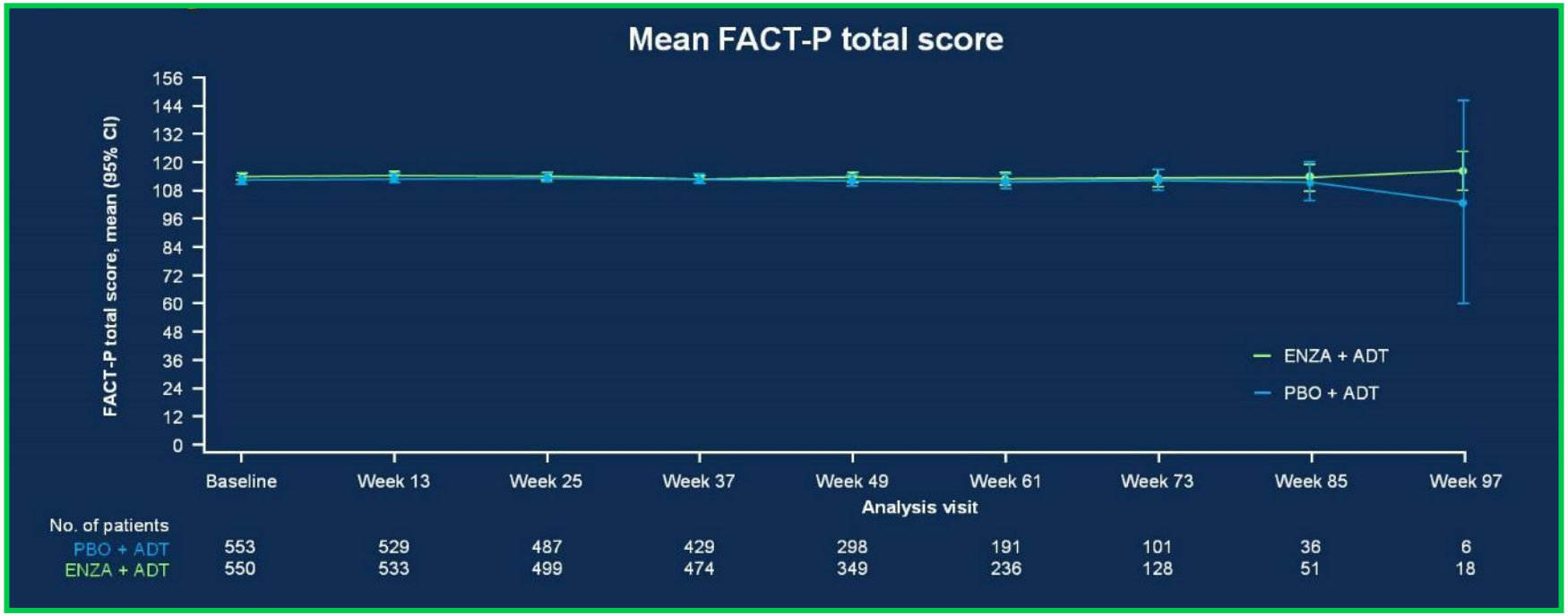


- At the time of interim analysis, OS data are not mature, with 25% of 342 events required for final analysis (enzalutamide plus ADT, 39; placebo + ADT, 45) and 19% reduction in risk of death that is not statistically significant
- Final OS analysis will be conducted with ~342 deaths at 4% significance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

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

Armstrong A, et al, J Clin Oncol. 2019 Jul 22 [DOI: 10.1200/JCO.19.00799]

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

Armstrong A, et al, J Clin Oncol. 2019 Jul 22 [DOI: 10.1200/JCO.19.00799].

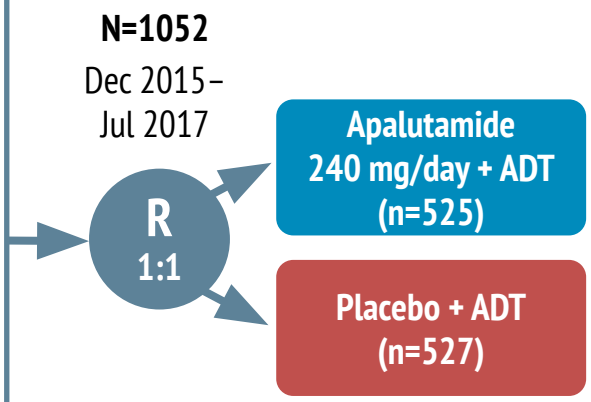
TITAN STUDY DESIGN (N=1052)

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)

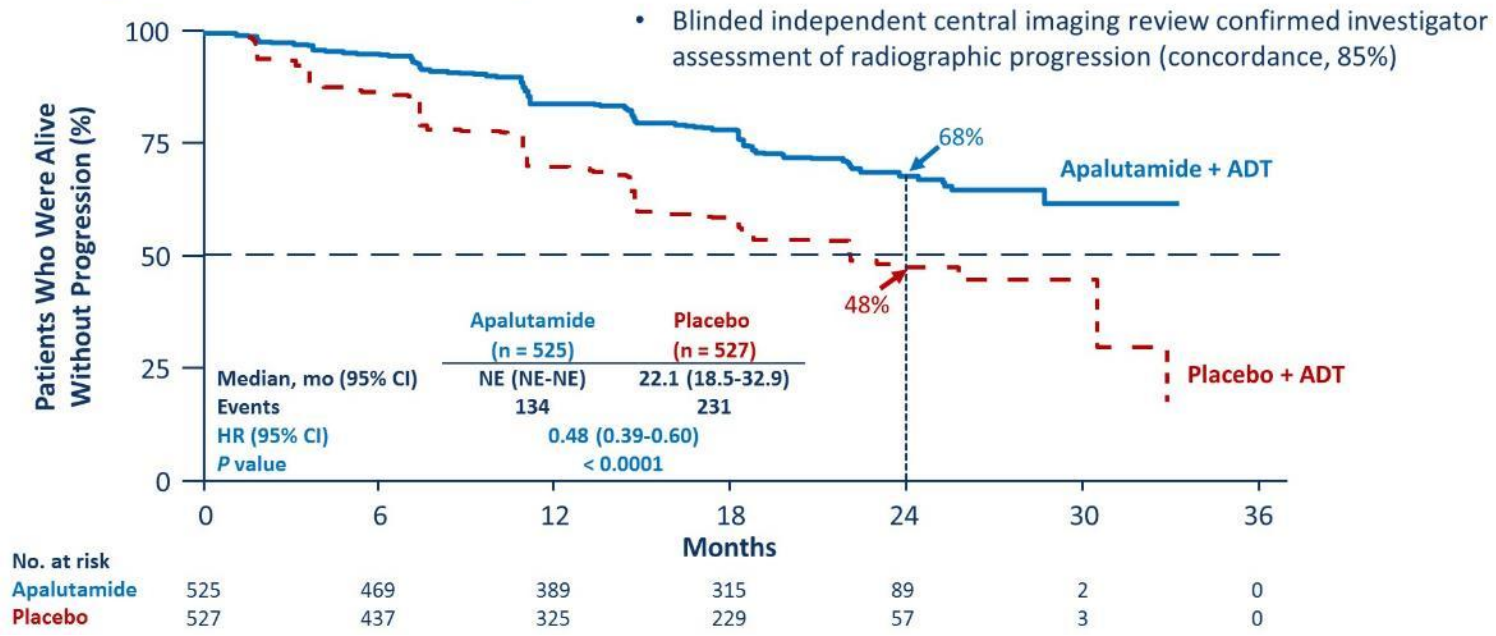


ADT, androgen deprivation therapy; ECOG, PS eastern cooperative oncology group performance status; EU, europe; mHSPC, metastatic hormone sensitive prostate cancer; NA, north america.

Chi, KN, et al. Presented at ASCO 2019, Abstract Number 5006.
Chi KN, et al. N Engl J Med. 2019 Jul 4;381(1):13-24.

TITAN: APALUTAMIDE SIGNIFICANTLY REDUCED RISK OF RADIOGRAPHIC PROGRESSION OR DEATH BY 52%

PRIMARY ENDPOINT: rPFS or DEATH



Median follow up approx. 22 months

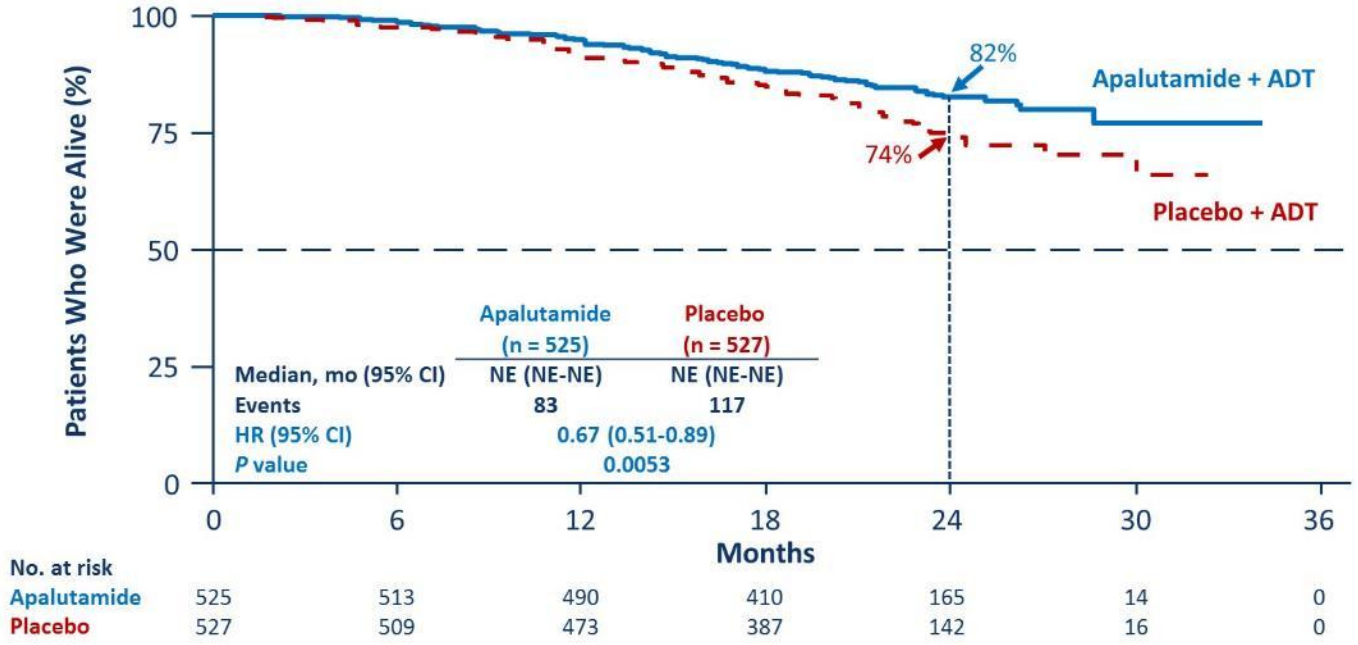
- rPFS benefit with apalutamide treatment was consistent across all subgroups

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

Chi, KN, et al. Presented at ASCO 2019, Abstract Number 5006.
Chi KN, et al. N Engl J Med. 2019 Jul 4;381(1):13-24.

TITAN: APALUTAMIDE SIGNIFICANTLY REDUCED RISK OF DEATH BY 33%

PRIMARY ENDPOINT: OVERALL SURVIVAL



Median follow up approx. 22 months

- OS benefit with apalutamide treatment was consistent across all subgroups

ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; NE, not evaluable; OS, overall survival.

Chi, KN, et al. Presented at ASCO 2019, Abstract Number 5006.
Chi KN, et al. N Engl J Med. 2019 Jul 4;381(1):13-24.

CONCLUSIONS: HSPC

- CHAARTED and LATITUDE showed **early intensive therapy with either docetaxel or abiraterone has a significant benefit in OS**

- **New generation ART's prolong OS or PFS**
  - No incremental benefit in adding in docetaxel to the ADT + ART
  - Comparable OS with improved QoL seen with abiraterone
  - Different side effects, treatment durations and costs
  - Hematologic side effects with chemotherapy but a shorter time on Rx
  - Increased cardiologic side effects for abiraterone and ART plus a longer time on Rx

- **QoL should be considered** alongside survival when choosing mHSPC Rx

- Important to consider how **early treatment choices for mHSPC impacts subsequent treatment decisions** when the patient's disease progresses

ADT, androgen deprivation therapy; ART, androgen receptor therapy; mHSPC, metastatic hormone sensitive prostate cancer; OS, overall survival; PFS, progression free survival; Rx, treatment; QoL, quality of life.

mCRPC TREATMENT CHOICES FOR MEN WHO RECEIVED DOCETAXEL AT START OF ADT

Gert Attard, MD FRCP PhD
University College London Cancer Institute
Paul O'Gorman Building
#Attardlab
www.Attardlab.Com

DISCLOSURES

Gert Attard, MD FRCP PhD

- Principal investigator for trials sponsored by Janssen, Pfizer/Astellas and Arno

- Received:-
  - Consulting fees and travel support from Janssen, Astellas, Medivation/Pfizer, Sanofi-Aventis, Ferring, Veridex, Roche/Ventana, Essa
  - Speaker's fees from Janssen, Astellas, Ferring, Ipsen, and Sanofi-Aventis
  - Grant support from Janssen, AstraZeneca, Arno

- On the Institute of Cancer Research (ICR) rewards to inventors list of abiraterone

Please note:

The views expressed within this presentation are the personal opinions of the author. They do not necessarily represent the views of the author's academic institution or the rest of the GU CONNECT group

AIMS

- mCRPC trials conducted in an era before patients received docetaxel at start of ADT
- mHSPC trials started in mid 2000s so access to mCRPC treatments has differed for patients by time of relapse, geographical (funding and regulatory) access limitations, changing views
- Selection of 1st line mCRPC is therefore driven by clinical judgement in men who received docetaxel + ADT
- ***A number of patient case studies will be reviewed and Prof. Attard will present his preferred treatment choice in these situations***

ADT, androgen deprivation therapy; mCRPC, metastatic castration resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer.

PATIENT CASE 1

- **74 year-old** presented in December 2014 with **HV M1 HSPC** and received **6 x docetaxel with ADT**. PSA decline to 0.8ng/dl. Now has **3 sequential PSA increases**, most recently 8.6 and has **2 bone mets** in ribs and one in pelvis. Treatment choices:
  - A. abiraterone (with prednisone)
  - B. enzalutamide
  - C. either A or B
  - D. docetaxel
  - E. radium-223
  - F. cabazitaxel

ADT, androgen deprivation therapy; CT, computed tomography; HSPC, hormone sensitive prostate cancer; HV, high volume; M1, metastatic; Mets, metastases; PSA, prostate specific antigen.

PATIENT CASE 1

PROF. ATTARD TREATMENT CHOICE

- **74 year-old** presented in December 2014 with **HV M1 HSPC** and received **6 x docetaxel with ADT**. PSA decline to 0.8ng/dl. Now has **3 sequential PSA increases**, most recently 8.6 and has **2 bone mets** in ribs and one in pelvis on CT scan. Treatment choices:

A. abiraterone (with prednisone)

B. enzalutamide

C. either A or B

D. docetaxel

E. radium-223

F. cabazitaxel

ADT, androgen deprivation therapy; CT, computed tomography; HSPC, hormone sensitive prostate cancer; HV, high volume; M1, metastatic; Mets, metastases; PSA, prostate specific antigen.

PATIENT CASE 2

- **64 year-old** presented in December 2017 with **M1 HSPC, PSA 1800** and received **6 x docetaxel with ADT**. PSA decline to 3.8ng/dl. Now has **2 sequential PSA increases**, most recently 24, **multiple bone mets** and a **suspected liver met**. Treatment choices:
  A. abiraterone (with prednisone)
  B. enzalutamide
  C. either A or B
  D. docetaxel
  E. radium-223
  F. cabazitaxel

ADT, androgen deprivation therapy; HSPC, hormone sensitive prostate cancer; M1, metastatic; Mets, metastases; PSA, prostate specific antigen.

PATIENT CASE 2

PROF. ATTARD TREATMENT CHOICE

- **64 year-old** presented in December 2017 with **M1 HSPC, PSA 1800** and received **6 x docetaxel with ADT**. PSA decline to 3.8ng/dl. Now has **2 sequential PSA increases**, most recently 24, **multiple bone mets** and a **suspected liver met**. Treatment choices:

  A. abiraterone (with prednisone)

  B. enzalutamide

  C. either A or B

  D. docetaxel

  E. radium-223

  F. cabazitaxel

ADT, androgen deprivation therapy; HSPC, hormone sensitive prostate cancer; M1, metastatic; Mets, metastases; PSA, prostate specific antigen.

PATIENT CASE 3

- **62 year-old** presented in October 2011 with **LV M1 HSPC** and received **6 x docetaxel with ADT** (STAMPEDE trial). PSA decline to undetectable. Now has **4 sequential PSA increases**, most recently 12, **retroperitoneal lymphadenopathy but no other mets**. Treatment choices:

  A. abiraterone (with prednisone)
  B. enzalutamide
  C. either A or B
  D. docetaxel
  E. radium-223
  F. cabazitaxel

ADT, androgen deprivation therapy; HSPC, hormone sensitive prostate cancer; LV, low volume; M1, metastatic; Mets, metastases; PSA, prostate specific antigen.

PATIENT CASE 3

PROF. ATTARD TREATMENT CHOICE

- **62 year-old** presented in October 2011 with **LV M1 HSPC** and received **6 x docetaxel with ADT** (STAMPEDE trial). PSA decline to undetectable. Now has **4 sequential PSA increases**, most recently 12, **retroperitoneal lymphadenopathy but no other mets**. Treatment choices:

  A. abiraterone (with prednisone)

  B. enzalutamide

  C. either A or B

  D. docetaxel

  E. radium-223

  F. cabazitaxel

ADT, androgen deprivation therapy; HSPC, hormone sensitive prostate cancer; LV, low volume; M1, metastatic; Mets, metastases; PSA, prostate specific antigen.

PATIENT CASE 4

- **62 year-old** presented in October 2011 with **LV M1 HSPC** and received **6 x docetaxel with ADT** (STAMPEDE trial). PSA decline to undetectable. Now has **4 sequential PSA** increases, most recently 12 and **one solitary pelvic met on PSMA-PET**. Treatment choices:
  A. abiraterone (with prednisone) or enzalutamide
  B. docetaxel
  C. radium-223
  D. cabazitaxel
  E. SBRT or similar to pelvic met and then monitor

ADT, androgen deprivation therapy; HSPC, hormone sensitive prostate cancer; LV, low volume; M1, metastatic; Mets, metastases ; PSA, prostate specific antigen; PSMA-PET, prostate-specific membrane antigen- positron emission tomography.

PATIENT CASE 4

PROF. ATTARD TREATMENT CHOICE

- **62 year-old** presented in October 2011 with **LV M1 HSPC** and received **6 x docetaxel with ADT** (STAMPEDE trial). PSA decline to undetectable. Now has **4 sequential PSA** increases, most recently 12 and **one solitary pelvic met on PSMA-PET**. Treatment choices:

A. abiraterone (with prednisone) or enzalutamide

B. docetaxel

C. radium-223

D. cabazitaxel

E. SBRT or similar to pelvic met and then monitor

ADT, androgen deprivation therapy; HSPC, hormone sensitive prostate cancer; LV, low volume; M1, metastatic; Mets, metastases ; PSA, prostate specific antigen; PSMA-PET, prostate-specific membrane antigen- positron emission tomography.

LIFE-PROLONGING TREATMENT AT mCRPC (CHAARTED)

	ADT + DOC (N=397) N (%)	ADT (N=393) N (%)
Serological progression/clinical progression	238 (59.9)	287 (73.0)
Clinical progression	180 (45.3)	228 (58.0)
Docetaxel†	54 (13.6, 23)	137^ (34.9, 48)
Other chemotherapy		
Cabazitaxel†	57 (14.4, 24)	37 (9.4, 13)
Mitoxantrone and/or platinum	29 (7.3, 12)	27 (6.9, 9)
Hormonal therapy		
Abiraterone and/or enzalutamide†	105* (26.4, 44)	104# (26.5, 36)
Antiandrogen and/or ketoconazole	80 (20.2, 34)	91 (23.2, 32)
Immunotherapy		
Sipuleucel T†	22 (5.5, 9)	19 (4.8, 7)
Radiotherapy	69 (17.4, 29)	79 (20.1, 28)
Use of agent(s) shown to prolong overall survival for mCRPC		
1 or more	150 (37.8, 63)	187 (47.6, 65)
2 or more	71 (17.9, 30)	83 (21.1, 29)

Treatment given at progression; ^10 other patients had docetaxel prior to confirmed progression; *2 pts may have had placebo on trial; †denotes agents with phase 3 data to prolong OS in mCRPC; # 9 pts may have had placebo on trial. Red text is proportion of progressors (%)

ADT, androgen deprivation therapy; DOC, docetaxel; mCRPC, metastatic castration resistant prostate cancer; OS, overall survival.

Sweeney CJ, NEJM. 2015;373:737-46 (Suppl appendix).

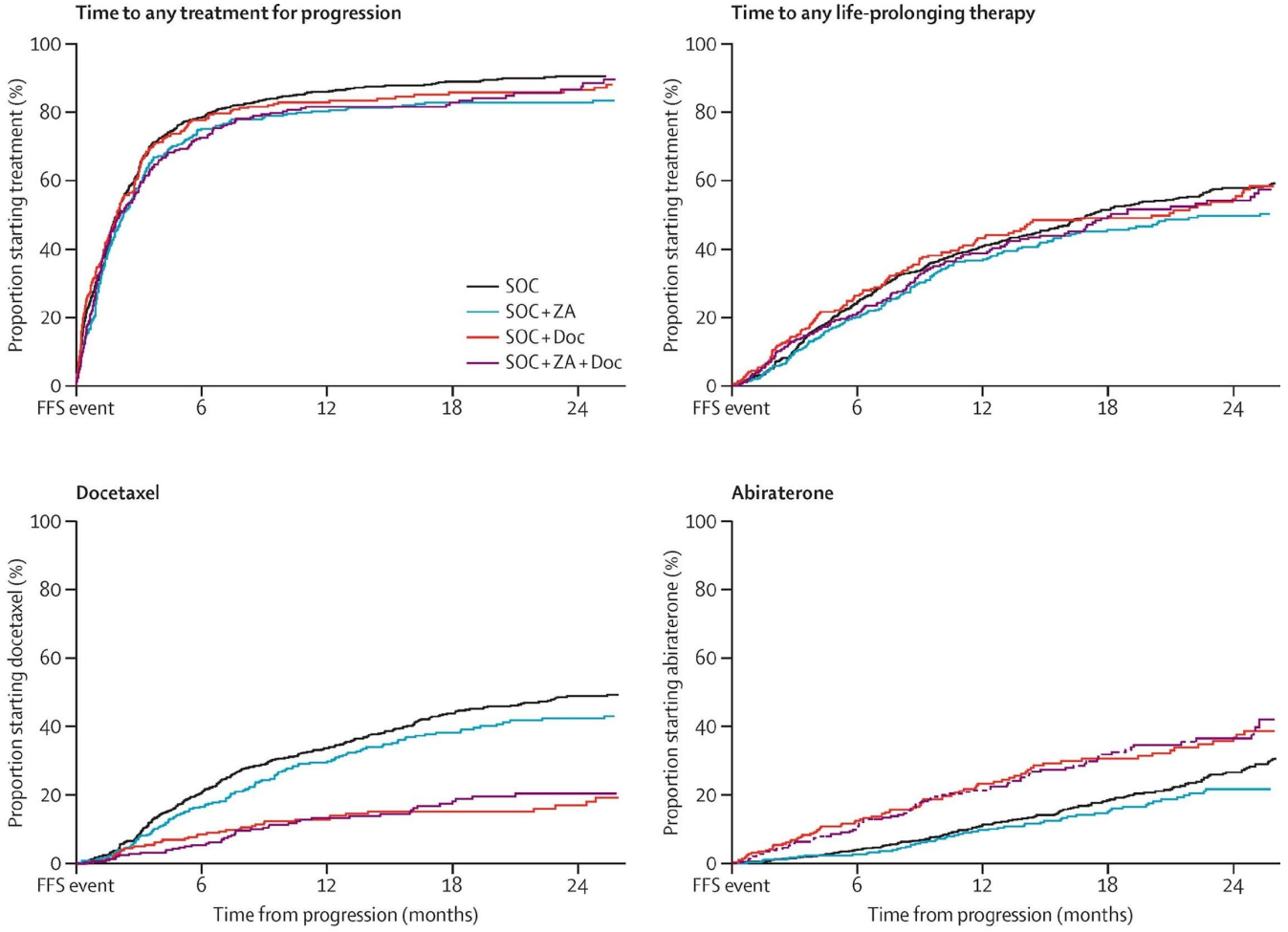
LIFE-PROLONGING TREATMENT AT mCRPC (STAMPEDE ARM A-C)

	Control		Docetaxel (Arm C)	
Randomised	724	100%	362	100%
Progression reported	641	89%	291	80%
Any SLT reported	578	80%, 90%	246	68%, 84%
Life-prolonging treatments				
Docetaxel	298	52%	49	20%
Abiraterone	196	34%	91	37%
Enzalutamide	113	20%	51	20%
Cabazitaxel	36	6%	28	11%
Radium-223	36	6%	21	9%
Other chemotherapy	23	4%	16	7%

mCRPC, metastatic castration resistant prostate cancer; SLT, second line therapy; Red text is proportion of progressors (%)

Clarke N, Annals of Oncology 2019; doi.org/10.1093/annonc/mdz396

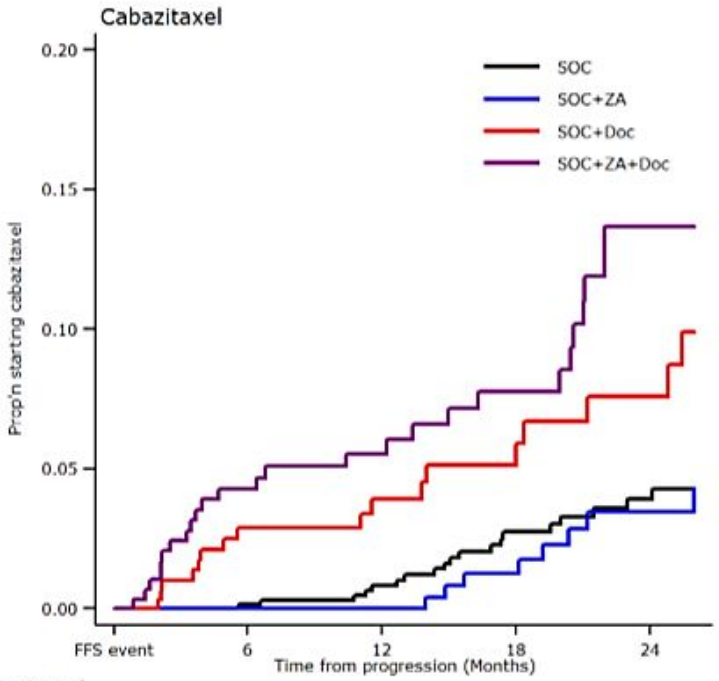
TIME TO LIFE–PROLONGING TREATMENT



DOC, docetaxel; FFS, failure-free survival; SOC, standard of care; ZA, zoledronic acid.

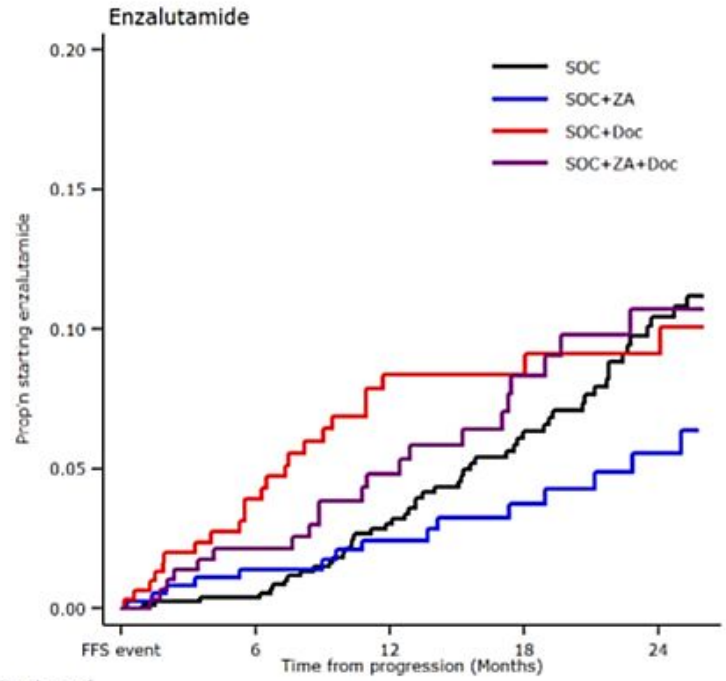
James N, Lancet. 2016;387:1163-77.

TIME TO LIFE–PROLONGING TREATMENT



Numbers of patients (events)

SOC	761	(1)	661	(4)	538	(9)	392	(4)	265
SOC+ZA	374	(0)	326	(0)	268	(3)	197	(4)	130
SOC+Doc	315	(8)	245	(2)	184	(2)	122	(3)	92
SOC+ZA+Doc	318	(12)	246	(3)	188	(4)	135	(7)	82



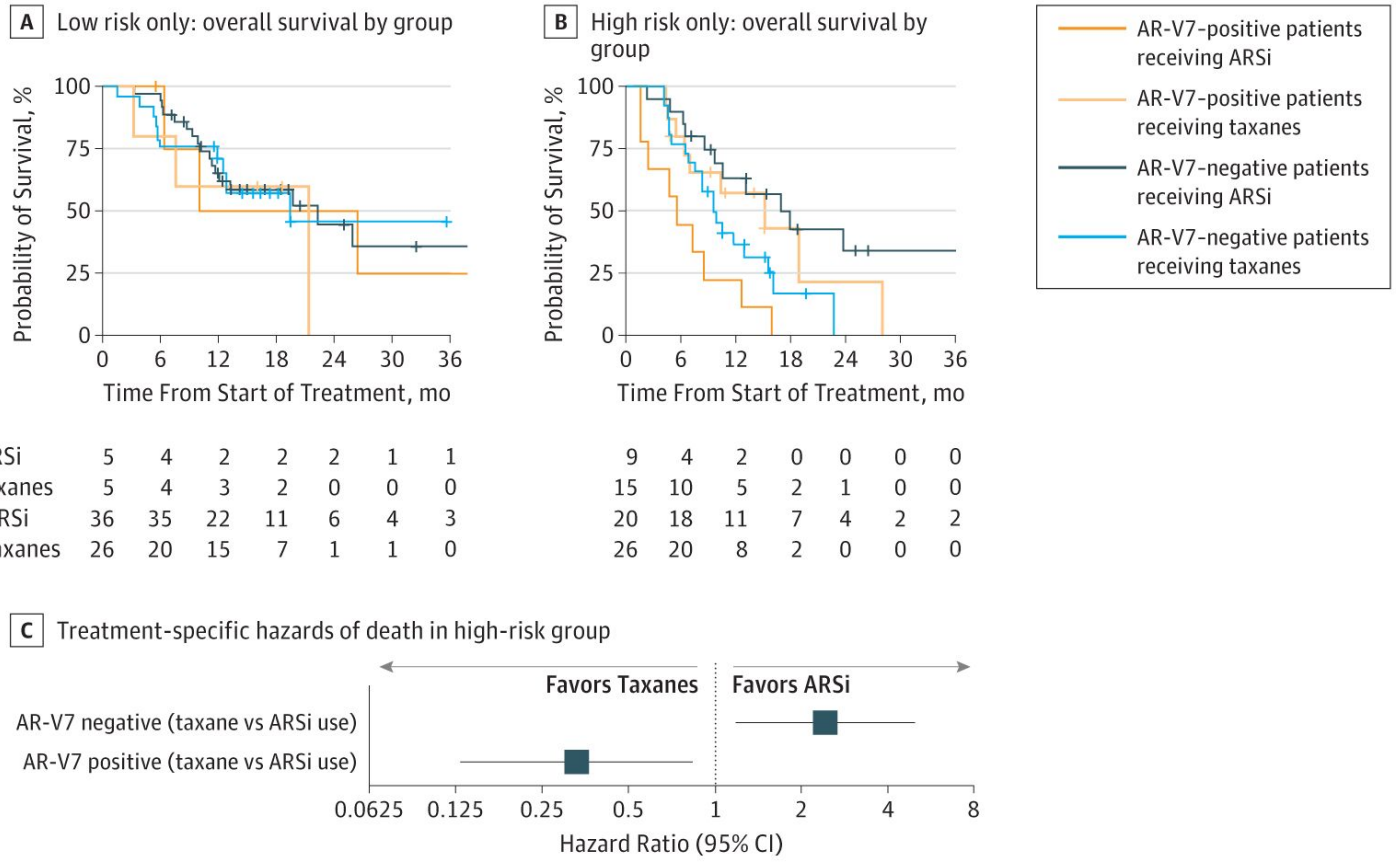
Numbers of patients (events)

SOC	761	(3)	660	(16)	531	(16)	391	(14)	256
SOC+ZA	374	(5)	321	(3)	261	(3)	193	(3)	126
SOC+Doc	315	(11)	242	(10)	178	(0)	126	(1)	95
SOC+ZA+Doc	318	(6)	250	(6)	188	(6)	138	(3)	88

DOC, docetaxel; FFS, failure-free survival; SOC, standard of care; ZA, zoledronic acid.

James N, Lancet. 2016;387:1163-77.

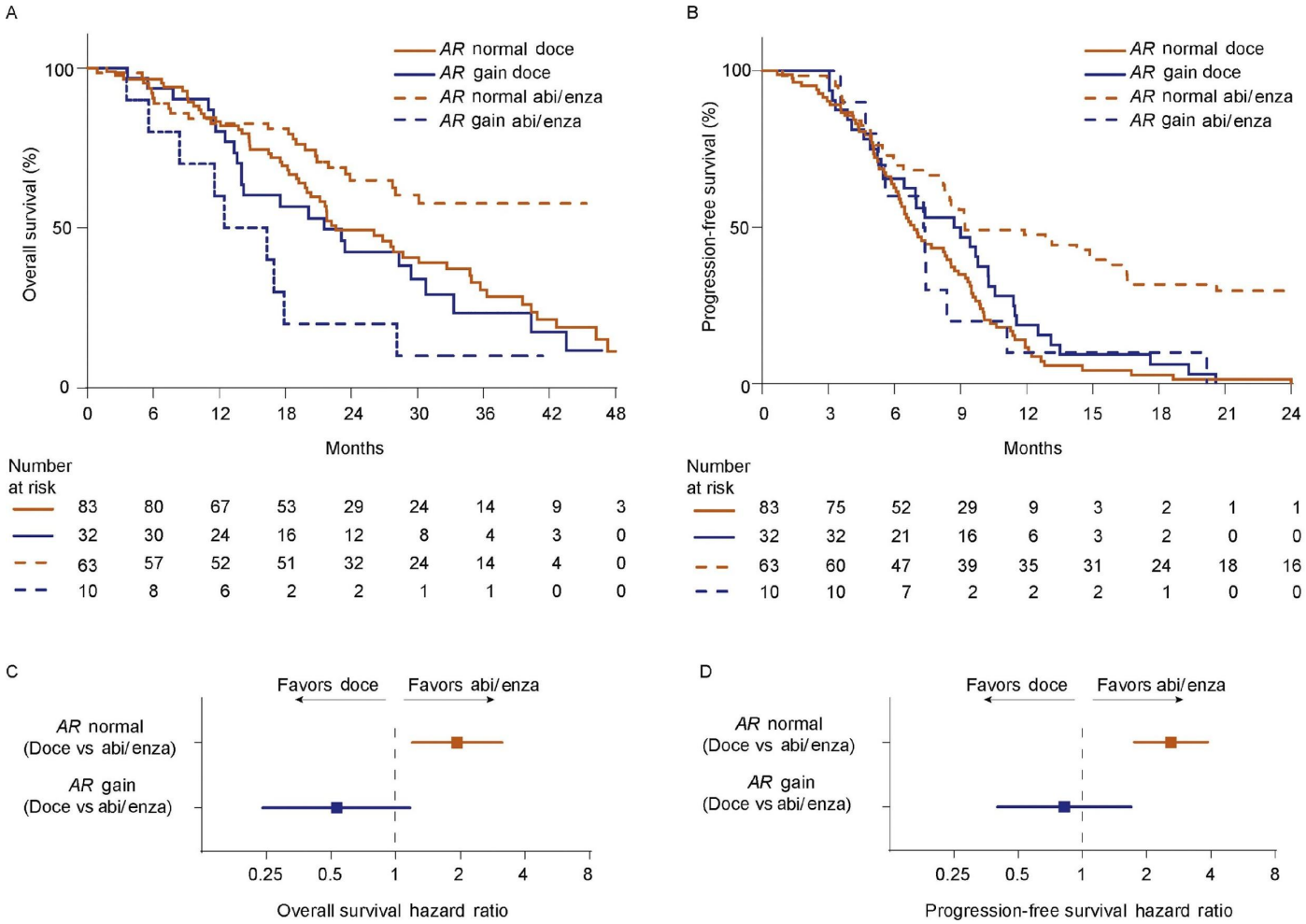
ROLE FOR BIOMARKERS FOR SELECTING PATIENTS FOR MORE TAXANES?



Abi, abiraterone; ARSI, androgen receptor signalling inhibitor; AR-V7, androgen receptor splice variant 7; CI, confidence interval; doce, docetaxel; enza, enzalutamide.

Scher H, JAMA Oncol. 2018;4(9):1179-86.

ROLE FOR BIOMARKERS FOR SELECTING PATIENTS FOR MORE TAXANES?



Abi, abiraterone; AR, androgen receptor; ARSI, androgen receptor signalling inhibitor; AR-V7, androgen receptor splice variant 7; doce, docetaxel; enza, enzalutamide.

Conteduca V, European Urology 2019;75(3):368-73.

CONCLUSION

- My treatment of choice for the majority of **men developing mCRPC after docetaxel at start of ADT is abi/enza**
- **Considerations for further taxanes** could include very **long duration of response after docetaxel or AR aberrations in blood** but these have never led me to use a taxane first
- **Radium-223** is another good option but after use of **abi/enza**
- **Other options post-abi/enza** will increase **(PARPi, platinum, immune checkpoint inhibitors)**. Many clinical trials of 1st-line mCRPC do not exclude docetaxel at start of ADT

Abi, abiraterone; ADT, androgen deprivation therapy; AR, androgen receptor; enza, enzalutamide; mCRPC, metastatic castration resistant prostate cancer; PARPi, poly ADP ribose polymerase inhibitors.

APPROACH TO mCRPC AFTER ABIRATERONE FOR mHSPC

Alicia Morgans, MD, MPH
Associate Professor of Medicine
Robert H. Lurie Comprehensive Cancer Center
Northwestern University Feinberg School of Medicine

DISCLOSURES

Alicia Morgans, MD, MPH

- Honoraria from Bayer, Janssen, Astellas, AstraZeneca, Sanofi
- Research funding from Bayer, Genentech, Seattle Genetics
- Travel funding from Sanofi

Please note:

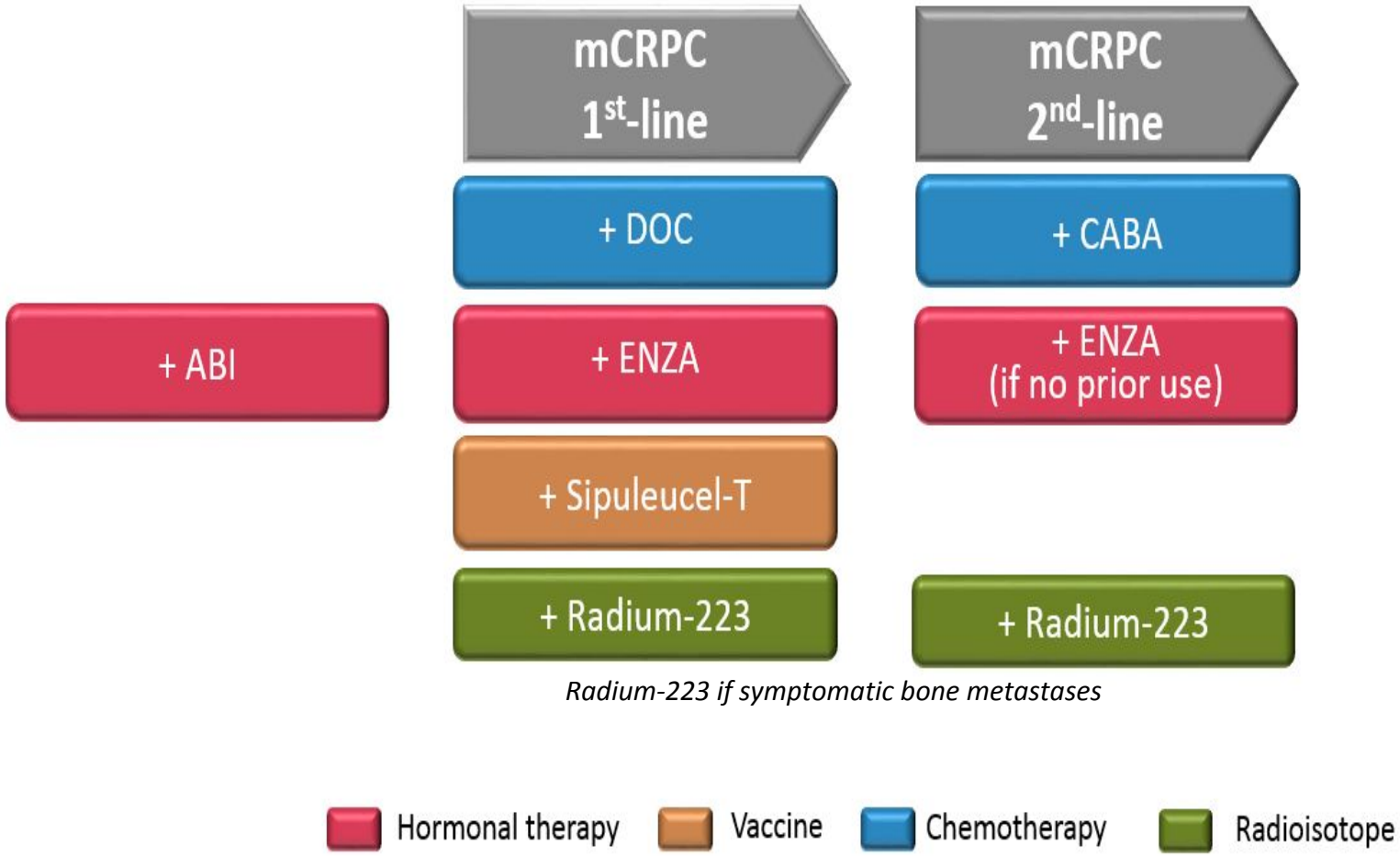
The views expressed within this presentation are the personal opinions of the author. They do not necessarily represent the views of the author's academic institution or the rest of the GU CONNECT group

OUTLINE

- Options in mCRPC after mHSPC
  - Different Mechanisms Key
  - Treatment Choice Considering Clinical and Patient Factors
- Second Line mCRPC – What's Next?
- Importance of Supportive Care
- Conclusions

mHSPC, metastatic hormone sensitive prostate cancer; mCRPC, metastatic castration resistant prostate cancer.

OPTIONS FOR TREATMENT OF mCRPC AFTER ABIRATERONE FOR mHSPC



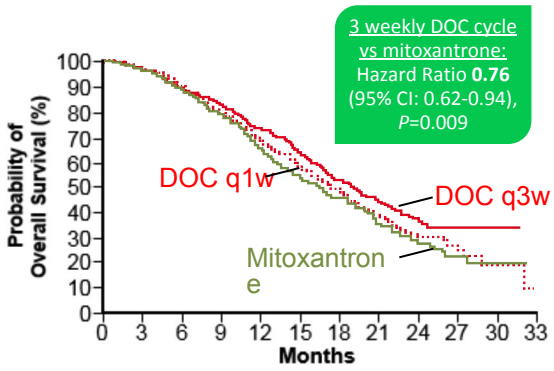
Radium-223 if symptomatic bone metastases

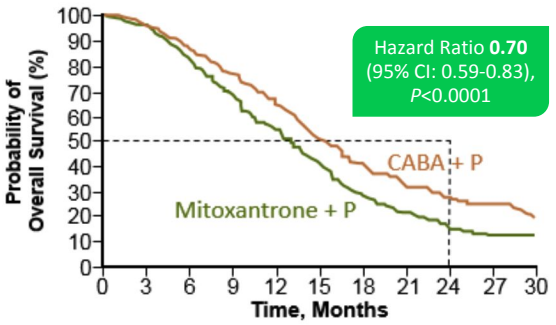
ABI, abiraterone; CABA, cabazitaxel; DOC, docetaxel; ENZA, enzalutamide; mCRPC, metastatic castration resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer.

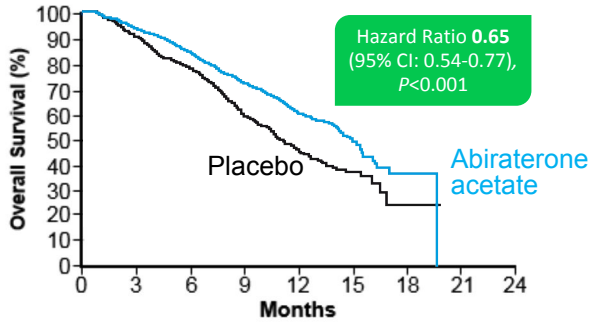
MULTIPLE TREATMENT OPTIONS FOR mCRPC

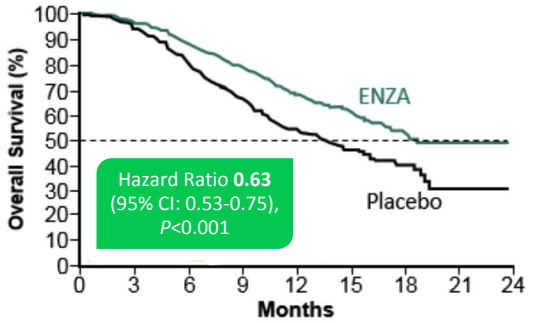
No clear recommendation for one treatment over another

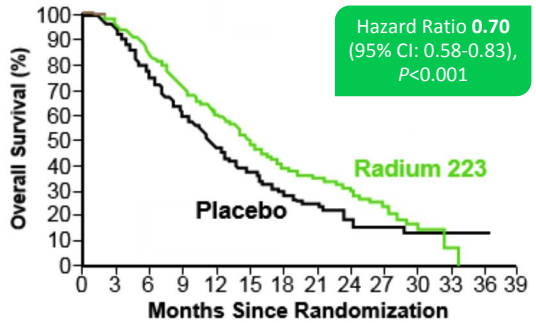
Different mechanism of action critical

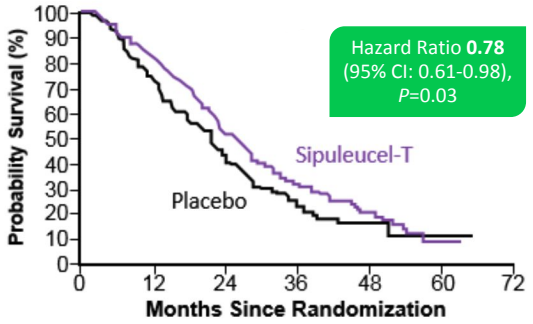












ABI, abiraterone; CABA, cabazitaxel; CI, confidence interval; DOC, docetaxel; ENZA, enzalutamide; mCRPC, metastatic castration resistant prostate cancer; q1w, once a week; q3w, every 3 weeks; P, prednisone.

Tannock IF, et al. NEJM. 2004;351:1502-12; de Bono JS, et al. Lancet. 2010;376:1147-54; de Bono JS, et al. NEJM. 2011;364:1995-2005; Scher HI, et al. NEJM. 2012;367:1187-97; Parker C, et al. NEJM. 2013;369:213-23; Kantoff PW, et al. NEJM. 2010;363:411-22.

MULTIPLE TREATMENT OPTIONS FOR mCRPC

No clear recommendation for one approach over another

NCCN Guidelines Version 4.2019
Prostate Cancer

- **Abiraterone[u] with prednisone (category 1)**
- **Docetaxel[vv,zz] (category 1)**
- **Enzalutamide[u] (category 1)**
- **Radium-223[aaa] for symptomatic bone metastases (category 1)**
- **Abiraterone[u] with methylprednisolone**
- **Clinical trial**
- **Other secondary hormone therapy[u]**

mCRPC, metastatic castration resistant prostate cancer.

Mohler JL, et al. JNCCN. 2019;17(5):479-505.

MULTIPLE TREATMENT OPTIONS FOR mCRPC

GU connect
POWERED BY CORED

6.5.11 ***Summary of evidence and guidelines for life-prolonging treatments of castrate-resistant disease***

Summary of evidence	LE
First-line treatment for metastatic castrate-resistant PCa (mCRPC) will be influenced by which treatments were used when metastatic cancer was first discovered	4
No clear-cut recommendation can be made for the most effective drug for first-line CRPC treatment (i.e. hormone therapy, chemotherapy or radium-223) as no validated predictive factors exist	3

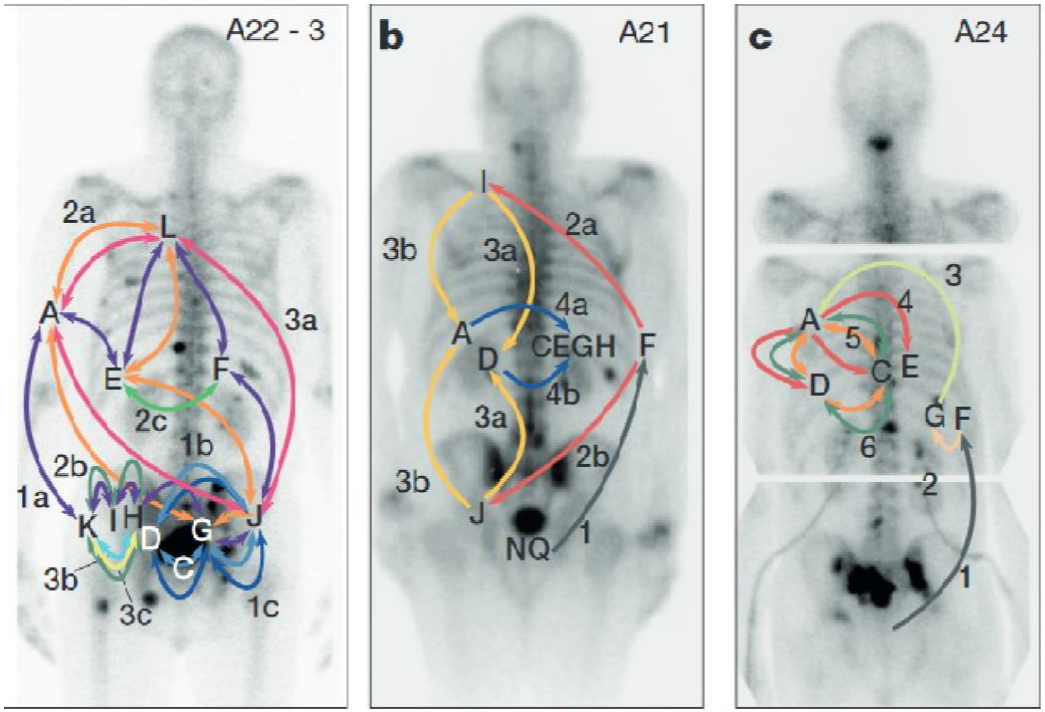
Recommendations	Strength rating
Ensure that testosterone levels are confirmed to be < 50 ng/mL, before diagnosing castration-resistant PCa (CRPC)	Strong
Do not treat patients for non-metastatic CRPC outside of a clinical trial	Strong
Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary team	Strong
Treat patients with mCRPC with life-prolonging agents Base the choice of first-line treatment on the performance status (PS), symptoms, comorbidities, location and extent of disease, patient preference, and on the previous treatment for hormone-sensitive Pca (HSPC) (alphabetical order: abiraterone, docetaxel, enzalutamide, radium-223, sipuleucel-T)	Strong

HSPC, hormone sensitive prostate cancer; mCRPC, metastatic castration resistant prostate cancer; Pca, prostate cancer; PS, performance status.

Mottet N, et al. EAU-ESTRO-ESUR-SIOG Prostate Cancer Guidelines 2018: https://uroweb.org/wp-content/uploads/Prostate-Cancer-2018-pocket.pdf.

NOVEL MECHANISM NEEDED TO TARGET RESISTANCE

- Resistance mechanisms commonly spreads through metastasis-to-metastasis seeding
- Similar resistance patterns often occur in geographic proximity (interclonal cooperativity)

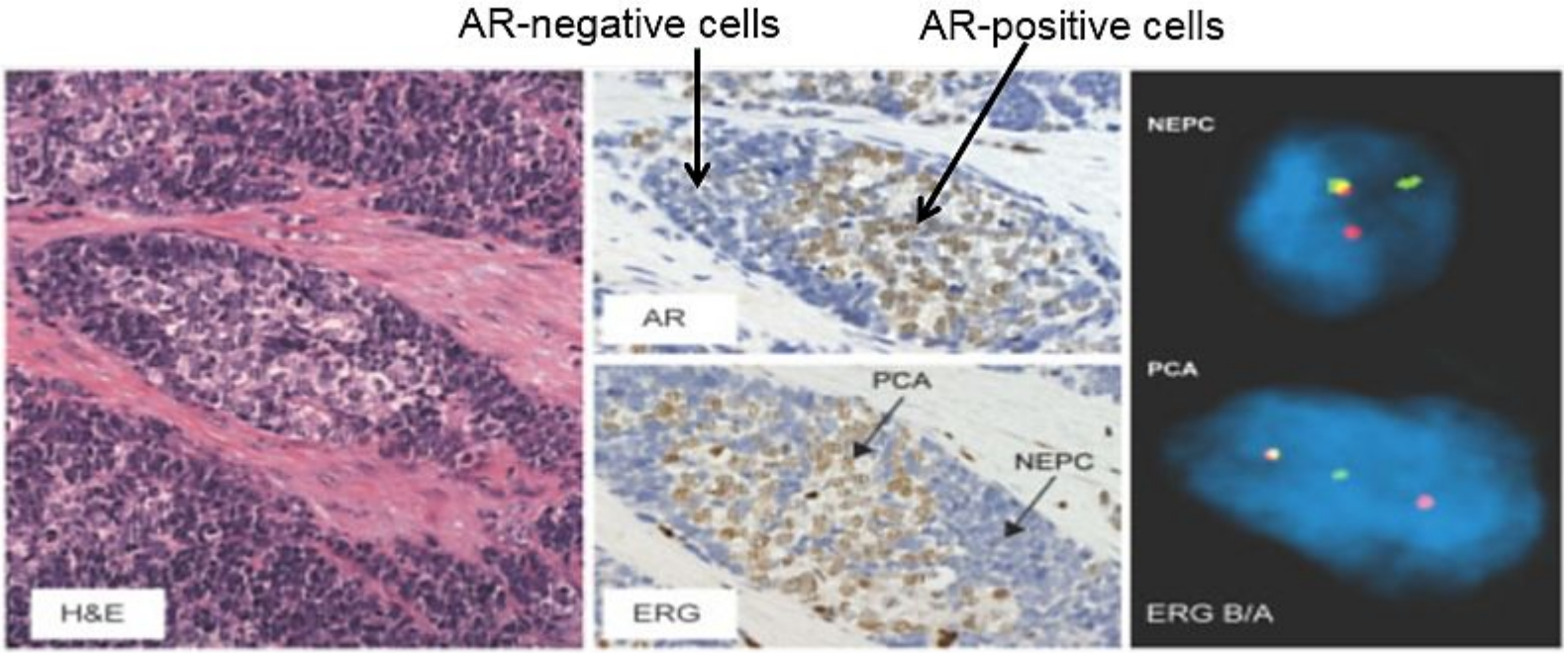


LN, lymph node

Gundem G, et al. Nature. 2015;520(7547):353-7.

NOVEL MECHANISM NEEDED TO TARGET RESISTANCE

- Resistance occurs even within the same site of disease
  - Neuroendocrine features possible adjacent to AR-positive cells



Tumor with mixed features of neuroendocrine PCa and prostate adenocarcinoma

AR, androgen receptor; ERG, E-26 transformation specific-related gene; ERG B/A, ERG break-apart; H&E, hematoxylin and eosin stain; NEPC, neuroendocrine prostate cancer; PCA, prostate adenocarcinoma.

Beltran H, et al. Cancer Discov. 2011;1(6):487-95.

BODY OF EVIDENCE SUGGESTS LIMITED BENEFIT TO SEQUENCING AR TARGETED THERAPIES

Drug	N	≥50% PSA response	Median PFS (months)	Median OS (months)
Enzalutamide → abiraterone + prednisone				
Attard G et al.[1‡]	125	2%	5.6	Not Reported
Khalaf D et al.[2]	75	4%[†]	TTPP: 1.7 months[*]	24.7
Abiraterone + prednisone → enzalutamide				
Smith MR et al.[3]	33	67%	TTPP: 2.8 months	Not Reported
Zhang T et al.[4]	9	11%	3.6	8.5
Azad AA et al.[5]	47	26%	6.6	8.6
Khalaf D et al.[2]	73	36%[†]	TTPP: 3.5 months[*]	28.8

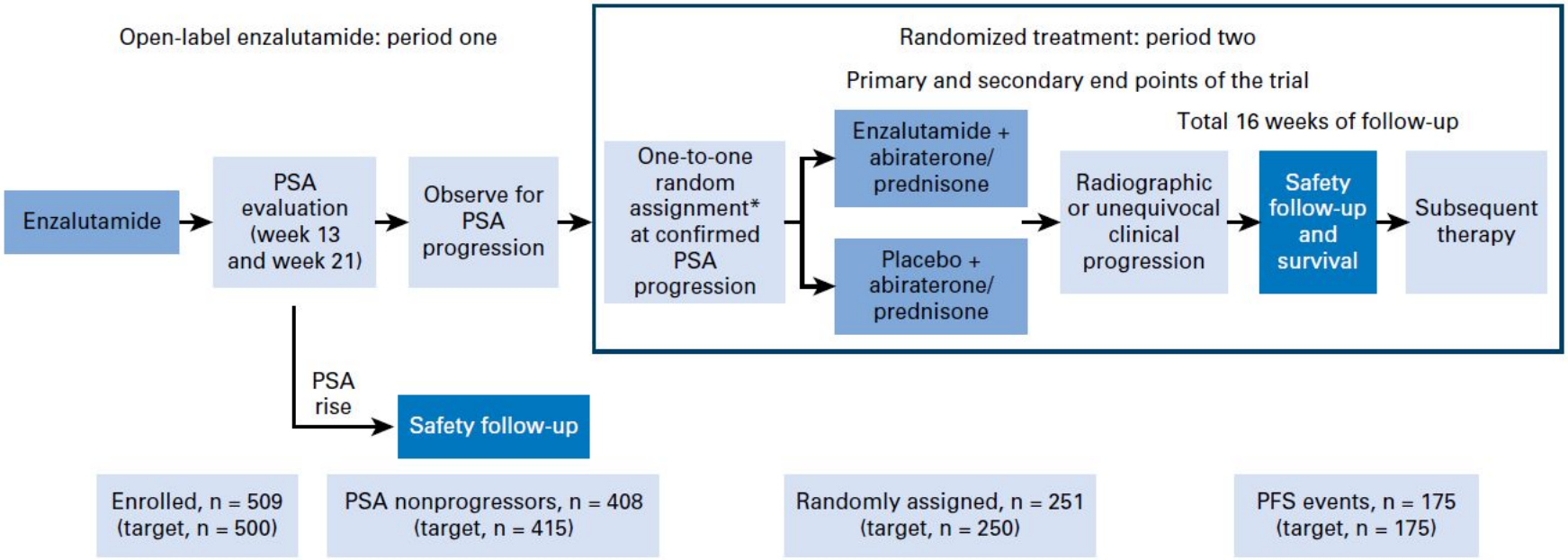
[‡]Limited benefit of using abiraterone after enzalutamide in the PLATO trial – however was not the primary aim of this trial; [†]PSA ≥ 30% decline from baseline; [*]Time to second PSA progression on second therapy

AR, androgen receptor; OS, overall survival; PFS, progression free survival; Prog, progression; PSA, prostate specific antigen; TTPP, time to PSA progression

1. Attard G, et al. JCO. 2018;36(25):2639-46; 2. Khalaf D, et al. Lancet Oncol. 2019;20:1730-39; 3. Smith MR, et al. Eur Urol. 2017;72(1):10-13; 4. Zhang T, et al. Clin Genitourin Cancer. 2015;13:392-9; 5. Azad AA, et al. Eur Urol. 2015;67:23-9.

ABIRATERONE ALONE OR IN COMBINATION WITH ENZALUTAMIDE IN mCRPC WITH RISING PROSTATE-SPECIFIC ANTIGEN DURING ENZALUTAMIDE TREATMENT (PLATO STUDY)

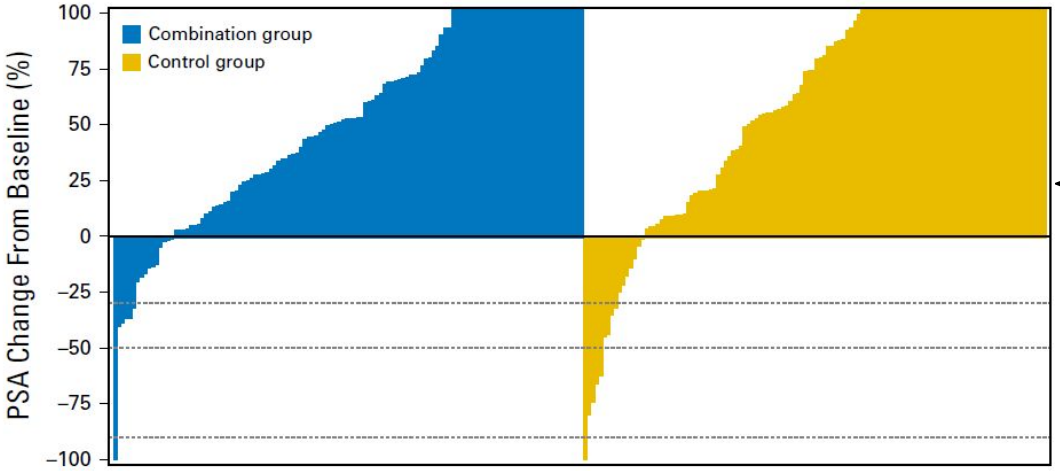
G.Attard, M. Borre, H. Gurney, Y. Loriot, C. Andersen-Daniil, R. Kalleda, T. Pham & M. Taplin on behalf of the PLATO collaborators



PFS, progression free survival; PSA, prostate specific antigen.

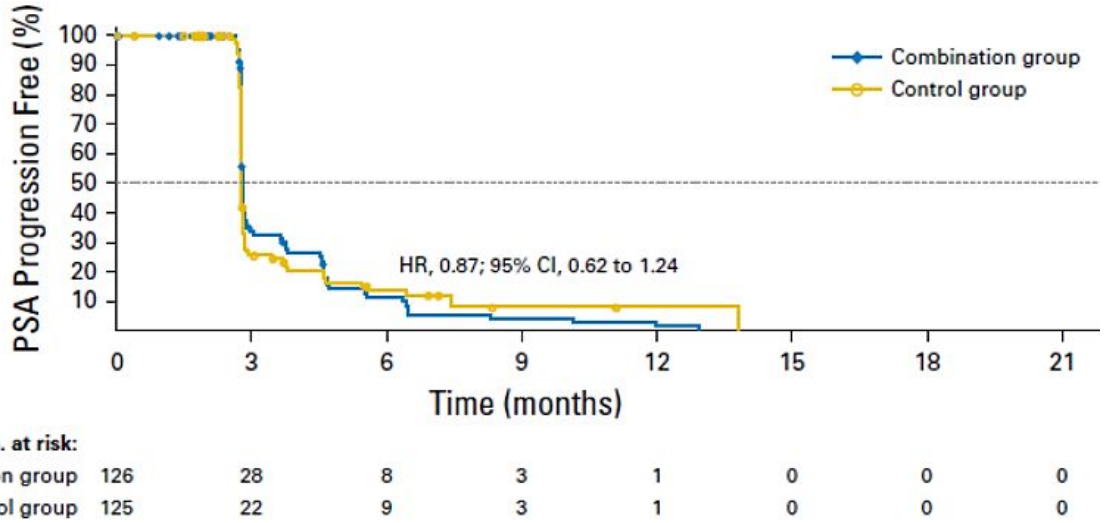
Attard G, et al. JCO. 2018;36(25):2639-48.

PLATO STUDY: PSA ENDPOINTS



Best PSA response

Time to PSA progression



No. at risk:								
Combination group	126	28	8	3	1	0	0	0
Control group	125	22	9	3	1	0	0	0

Primary endpoint of PLATO was not met therefore these endpoints are exploratory; PLATO reported limited benefit with abiraterone after enzalutamide with a low PSA response for both treatment groups

CI, confidence interval; HR, hazard ratio; PSA, prostate specific antigen.

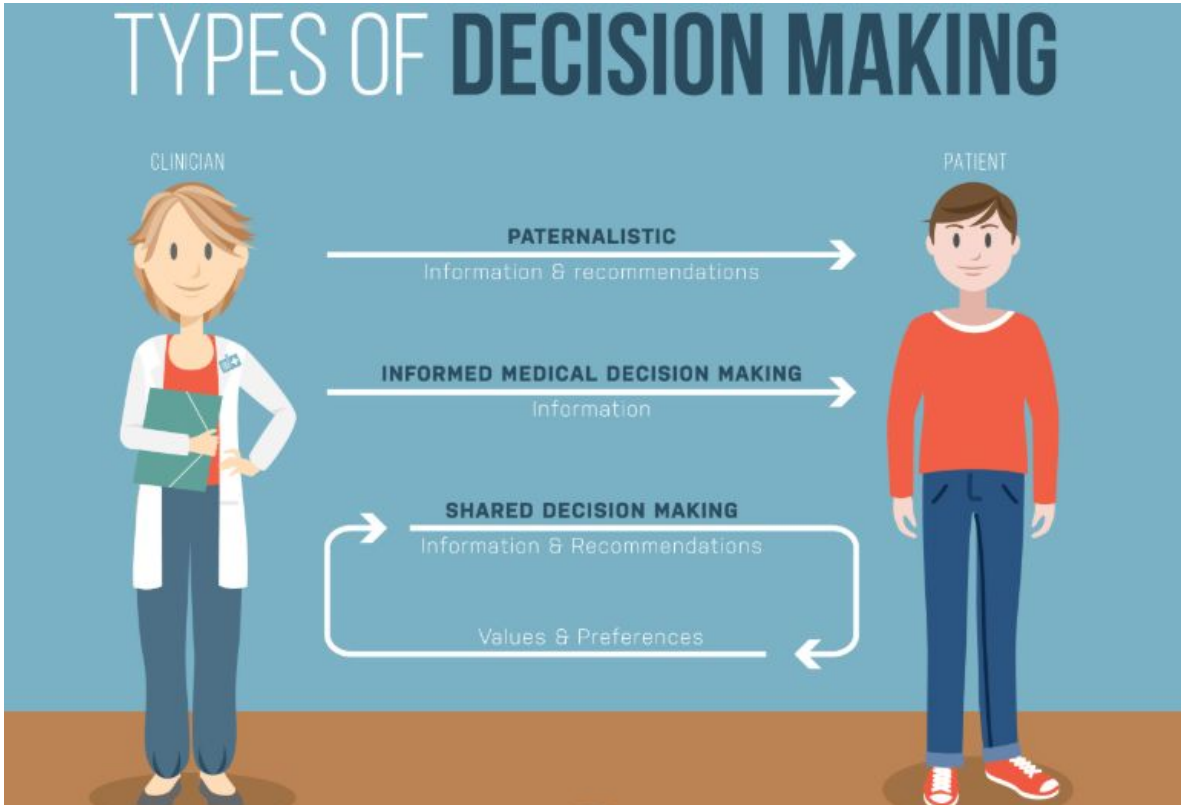
Attard G, et al. JCO. 2018;36(25):2639-46.

CLINICAL FACTORS TO SUPPORT TREATMENT CHOICE

- Prior treatments – **Novel mechanism of action preferred**
- Which options are available in my practice location?
- Are there visceral metastases? Bone only metastases?
  - Sipuleucel-T and radium not studied in men with visceral metastases
- Is the patient a candidate for chemotherapy?
  - Radium, sipuleucel-T options for non-chemotherapy candidates
- Is there small cell/neuroendocrine differentiation?
  - Platinum chemotherapy preferred
- Clinical trial options?

PATIENT FACTORS TO SUPPORT TREATMENT CHOICE

- Patient preferences should be considered in treatment decisions
- Can relate to obligations at home or work, beliefs from prior experiences, fears, insurance restrictions, etc.



https://www.therapeuticassociates.com/shared-decision-making/

PATIENT CASE

- 69 yo man with history of hypertension diagnosed with high risk mHSPC in 8/2017
  - 5 bone lesions, Gleason 8
- Treated with abiraterone per LATITUDE and STAMPEDE
- Progression of disease in 2/2019
  - PSA 45 ng/mL, multiple new bone metastases
  - No lymph node or visceral involvement
- Retired, lives with his wife

mHSPC, metastatic hormone sensitive prostate cancer; PSA, prostate specific antigen.

WHAT ARE HIS OPTIONS?

GU connect
POWERED BY CORE ED

6.5.11 ***Summary of evidence and guidelines for life-prolonging treatments of castrate-resistant disease***

Summary of evidence	LE
First-line treatment for metastatic castrate-resistant PCa (mCRPC) will be influenced by which treatments were used when metastatic cancer was first discovered	4
No clear-cut recommendation can be made for the most effective drug for first-line CRPC treatment (i.e. hormone therapy, chemotherapy or radium-223) as no validated predictive factors exist	3

Recommendations	Strength rating
Ensure that testosterone levels are confirmed to be < 50 ng/mL, before diagnosing castration-resistant PCa (CRPC)	Strong
Do not treat patients for non-metastatic CRPC outside of a clinical trial	Strong
Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary team	Strong
Treat patients with mCRPC with life-prolonging agents Base the choice of first-line treatment on the performance status (PS), symptoms, comorbidities, location and extent of disease, patient preference, and on the previous treatment for hormone-sensitive Pca (HSPC) (alphabetical order: abiraterone, docetaxel, enzalutamide, radium-223, sipuleucel-T)	Strong

HSPC, hormone sensitive prostate cancer; mCRPC, metastatic castration resistant prostate cancer; Pca, prostate cancer; PS, performance status.

Mottet N, et al. EAU-ESTRO-ESUR-SIOG Prostate Cancer Guidelines 2018: https://uroweb.org/wp-content/uploads/Prostate-Cancer-2018-pocket.pdf.

CLINICAL FACTORS TO SUPPORT TREATMENT CHOICE

- Prior treatments – **Abiraterone**
- Which options are available in my practice location? – All
- Are there visceral metastases?
- Is the patient a candidate for chemotherapy?
- Is there small cell/neuroendocrine differentiation?
- Clinical trial options?

CLINICAL FACTORS TO SUPPORT TREATMENT CHOICE

- Prior treatments – **Abiraterone**
- Which options are available in my practice location? – **All**
- Are there visceral metastases?
  - **He has bone only metastases. Using 5 mg oxycodone Q6 PRN**
- Is the patient a candidate for chemotherapy?
- Is there small cell/neuroendocrine differentiation?
- Clinical trial options?

Q6 PRN, every 6 hours as needed.

CLINICAL FACTORS TO SUPPORT TREATMENT CHOICE

- Prior treatments – **Abiraterone**
- Which options are available in my practice location? – **All**
- Are there visceral metastases?
  - **He has bone only metastases. Using 5 mg oxycodone Q6 PRN**
- Is the patient a candidate for chemotherapy?
  - **Yes, ECOG PS 1 with controlled hypertension**
- Is there small cell/neuroendocrine differentiation?
- Clinical trial options?

ECOG PS, Eastern Cooperative Oncology Group Performance Status; Q6 PRN, every 6 hours as needed.

CLINICAL FACTORS TO SUPPORT TREATMENT CHOICE

- Prior treatments – **Abiraterone**
- Which options are available in my practice location? – **All**
- Are there visceral metastases?
  - **He has bone only metastases. Using 5 mg oxycodone Q6 PRN**
- Is the patient a candidate for chemotherapy?
  - **Yes, ECOG PS 1 with controlled hypertension**
- Is there small cell/neuroendocrine differentiation?
  - **No**
- Clinical trial options?

ECOG PS, Eastern Cooperative Oncology Group Performance Status; Q6 PRN, every 6 hours as needed.

CLINICAL FACTORS TO SUPPORT TREATMENT CHOICE

- Prior treatments – **Abiraterone**
- Which options are available in my practice location? – **All**
- Are there visceral metastases?
  - **He has bone only metastases. Using 5 mg oxycodone Q6 PRN**
- Is the patient a candidate for chemotherapy?
  - **Yes, ECOG PS 1 with controlled hypertension**
- Is there small cell/neuroendocrine differentiation?
  - **No**
- Clinical trial options?
  - **No**

ECOG PS, Eastern Cooperative Oncology Group Performance Status; Q6 PRN, every 6 hours as needed.

WHAT ARE HIS OPTIONS?

GU connect
POWERED BY CORE ED

6.5.11 ***Summary of evidence and guidelines for life-prolonging treatments of castrate-resistant disease***

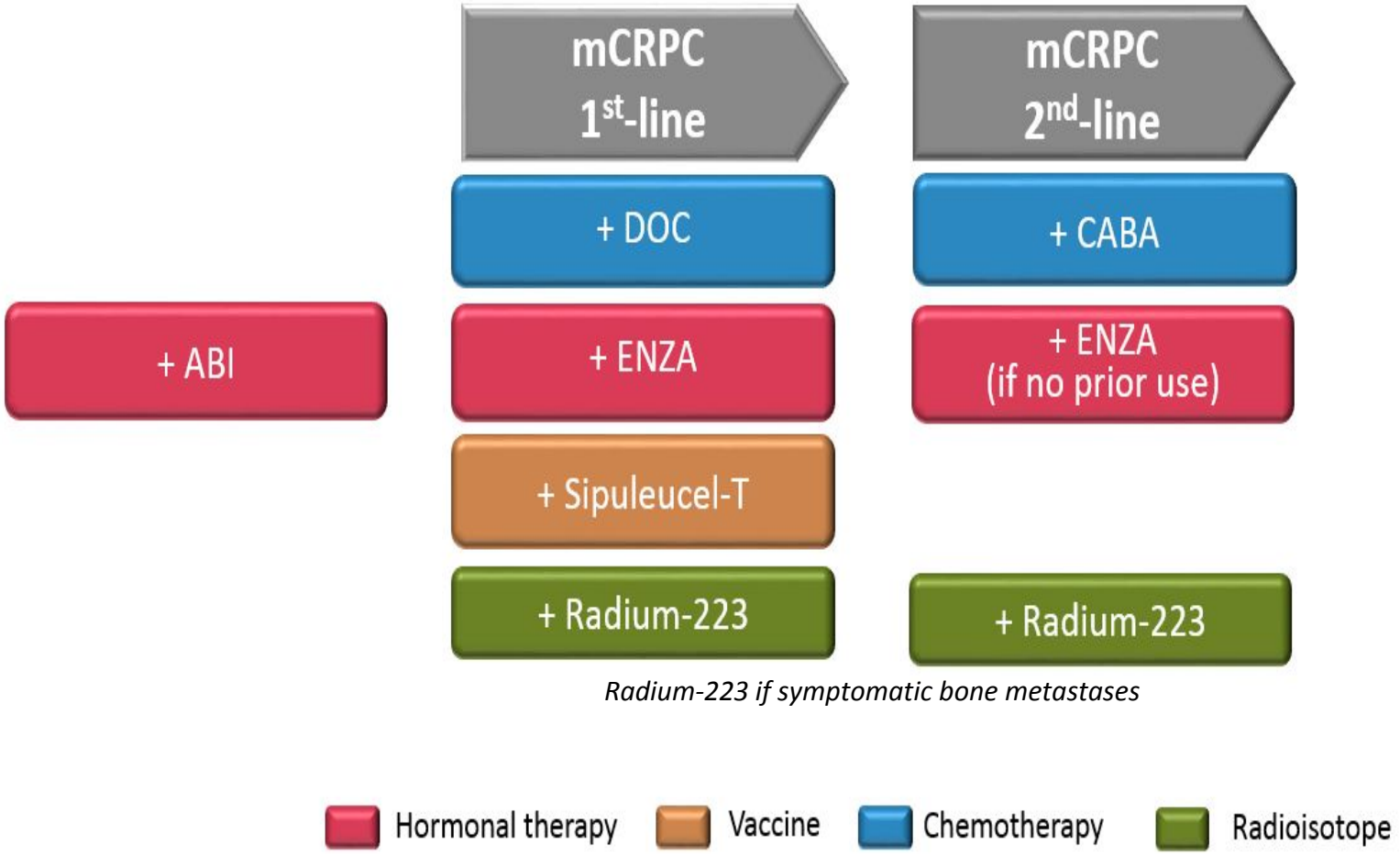
Summary of evidence	LE
First-line treatment for metastatic castrate-resistant PCa (mCRPC) will be influenced by which treatments were used when metastatic cancer was first discovered	4
No clear-cut recommendation can be made for the most effective drug for first-line CRPC treatment (i.e. hormone therapy, chemotherapy or radium-223) as no validated predictive factors exist	3

Recommendations	Strength rating
Ensure that testosterone levels are confirmed to be < 50 ng/mL, before diagnosing castration-resistant PCa (CRPC)	Strong
Do not treat patients for non-metastatic CRPC outside of a clinical trial	Strong
Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary team	Strong
Treat patients with mCRPC with life-prolonging agents Base the choice of first-line treatment on the performance status (PS), symptoms, comorbidities, location and extent of disease, patient preference, and on the previous treatment for hormone-sensitive Pca (HSPC) (alphabetical order: abiraterone, docetaxel, enzalutamide, radium-223, sipuleucel-T)	Strong

HSPC, hormone sensitive prostate cancer; mCRPC, metastatic castration resistant prostate cancer; Pca, prostate cancer; PS, performance status.

Mottet N, et al. EAU-ESTRO-ESUR-SIOG Prostate Cancer Guidelines 2018: https://uroweb.org/wp-content/uploads/Prostate-Cancer-2018-pocket.pdf.

OPTIONS FOR 2ND LINE TREATMENT OF mCRPC AFTER ABIRATERONE FOR mHSPC



ABI, abiraterone; CABA, cabazitaxel; DOC, docetaxel; ENZA, enzalutamide; mCRPC, metastatic castration resistant prostate cancer.

WHAT ARE HIS OPTIONS?

GU connect
POWERED BY COR2ED

EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer

Recommendations	Strength rating
In patients with mCRPC and progression following docetaxel chemotherapy offer further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide and radium-223	Strong
Base second-line treatment decisions of mCRPC on pre-treatment performance status, symptoms, patient preference, comorbidities and extent of disease	Strong

mCRPC, metastatic castration resistant prostate cancer.

Mottet N, et al. EAU-ESTRO-ESUR-SIOG Prostate Cancer Guidelines 2018: https://uroweb.org/wp-content/uploads/Prostate-Cancer-2018-pocket.pdf.

WHAT IS HIS PREFERENCE?

GU connect
POWERED BY COR2ED

EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer

Recommendations	Strength rating
In patients with mCRPC and progression following docetaxel chemotherapy offer further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide and radium-223	Strong
Base second-line treatment decisions of mCRPC on pre-treatment performance status, symptoms, patient preference, comorbidities and extent of disease	Strong

mCRPC, metastatic castration resistant prostate cancer.

Mottet N, et al. EAU-ESTRO-ESUR-SIOG Prostate Cancer Guidelines 2018: https://uroweb.org/wp-content/uploads/Prostate-Cancer-2018-pocket.pdf.

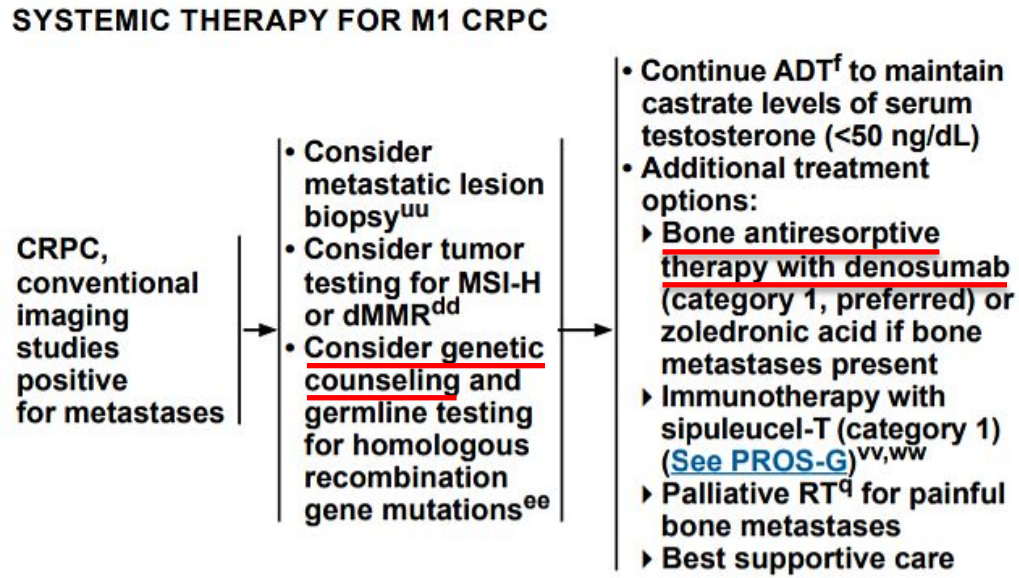
IMPORTANCE OF SUPPORTIVE CARE

6.5.13 ***Guidelines for supportive care of castrate-resistant disease***

These recommendations are in addition to appropriate systemic therapy.

Recommendations	Strength rating
Offer bone protective agents to patients with metastatic castration-resistant PCa (mCRPC) and skeletal metastases to prevent osseous complications.	Strong
Offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong

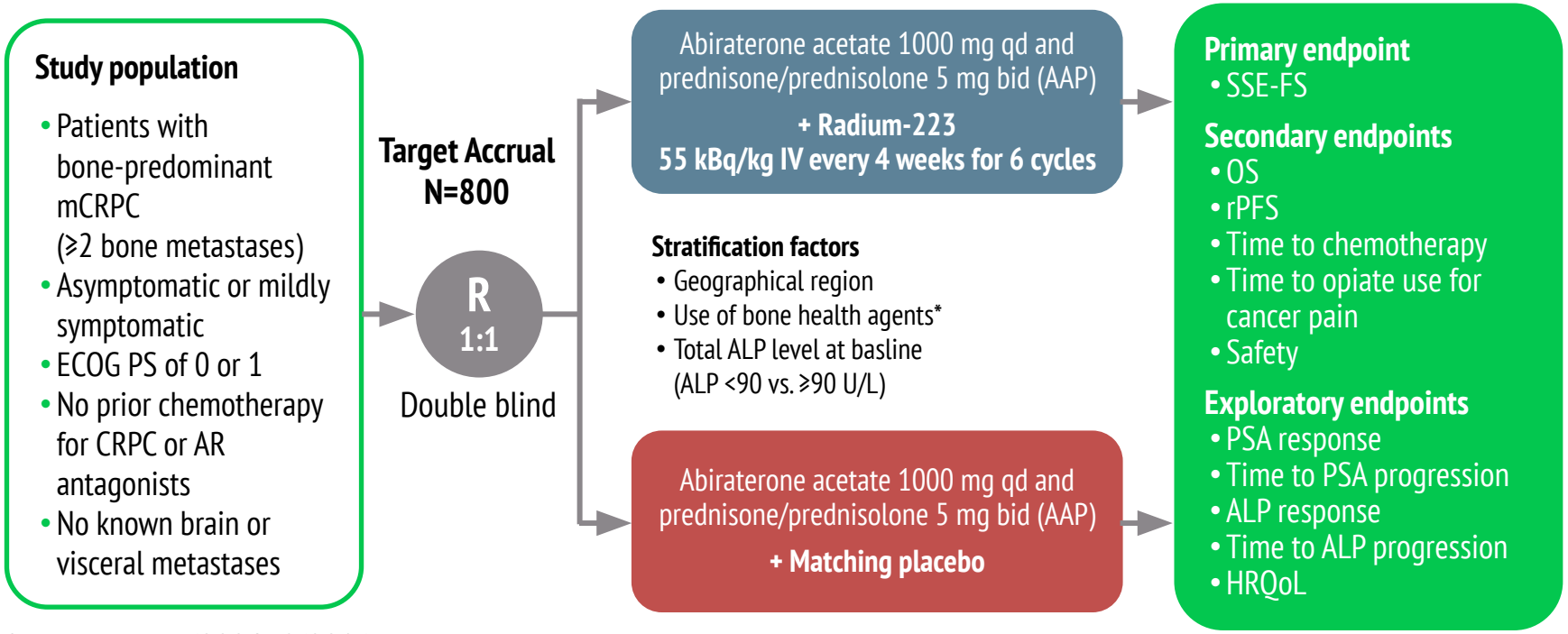
Bone health and genetic counseling are vital.



ADT, androgen deprivation therapy; dMMR, deficient mismatch repair; mCRPC, metastatic castration resistant prostate cancer; MSI-H, microsatellite instability – high; RT, radiotherapy; Pca, prostate cancer.

Mottet N, et al. EAU-ESTRO-ESUR-SIOG Prostate Cancer Guidelines 2018: https://uroweb.org/wp-content/uploads/Prostate-Cancer-2018-pocket.pdf; Mohler JL, et al. JNCCN. 2019;17(5):479-505.

ERA 223 (NCT02043678)



Accrual dates 3/2004–8/2016

389 events were required to detect a 39% increase in SSE-FS using a test with a 2-sided alpha of 0.05, 90% power and 1:1 randomisation

Bone health agents (denosumab or bisphosphonates) only permitted in patients receiving them at baseline; Initiation during study was prohibited to prevent confounding effects.

AAP, abiraterone acetate + prednisone/prednisolone; ALP, alanine phosphatase; AR, androgen receptor; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HRQoL, health related quality of life; mCRPC, metastatic castration resistant prostate cancer; OS, overall survival; PSA, prostate specific antigen; rPFS, radiographic progression free survival; SSE-FS, symptomatic skeletal event free survival.
Slide courtesy of Bertrand Tombal; Smith, M et al. The Lancet Oncology. 2019;20(3):408-19.

FRACTURES IN ERA 223

- In November 2017 the IDMC recommended unblinding in November 2017 after noting more fractures and deaths in the abiraterone acetate/prednisone (AAP) + radium 223 arm than in the AAP arm

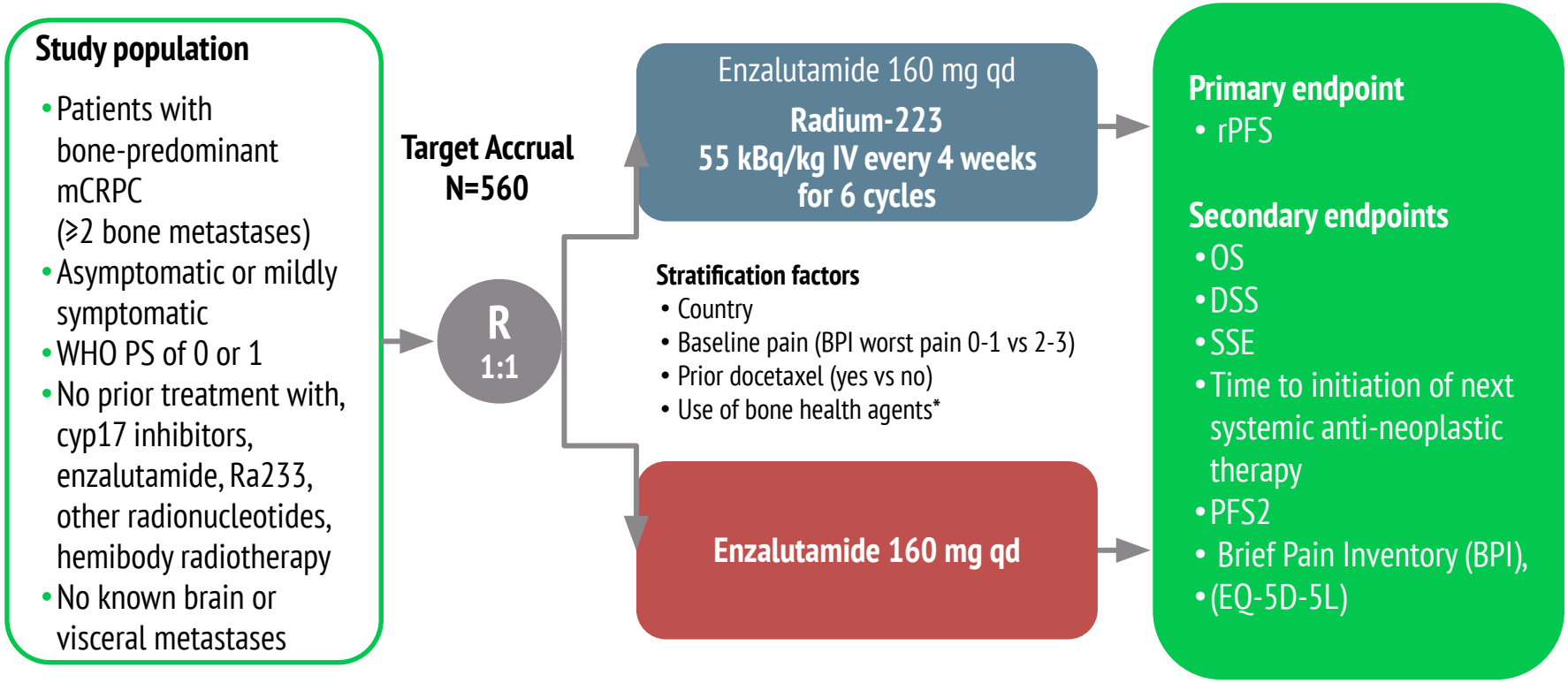
	AAP + radium 223	AAP + placebo
Patients with ≥1 fracture, n	76	23
No bone metastasis at site of fracture, n	60	17
Type of fracture, n		
Pathological	19	6
Traumatic	27	13
Osteoporotic	37	4
Indeterminate	1	0

*Independent review of fractures was based on patients with fractures and available image scans: n=80 in AAP + radium-223 group, n=27 in AAP + placebo group.

- 40% of the excess fractures in the AAP + Ra-223 occurred in the 6 first months
- 40% of the patients were receiving bone protecting agent (BPA) at entry
- In post-hoc analyses, BPA significantly impacted the rate of fracture in both arm (37% vs. 15% in Ra-223/AAP without vs. with BPA)

Smith M, et al. The Lancet Oncology. 2019;20(3):408-19.
AAP, abiraterone acetate and prednisone/prednisolone; BPA, bone protecting agents; IDMC, independent data monitoring committee;
Slide courtesy of Bertrand Tombal.

EORTC GUCG 1333 (PEACE III) ORIGINAL DESIGN



Bone health agents (denosumab or bisphosphonates) only permitted in patients receiving them at baseline; Initiation during study was prohibited to prevent confounding effects.

CYP17, cytochrome P450 17; DSS, disease specific survival; mCRPC, metastatic castration resistant prostate cancer; OS, overall survival; PFS2, progression free survival after the next line of therapy; Ra223, radium 223; rPFS, radiographic progression free survival; SSE, symptomatic skeletal event; WHO PS, world health organization performance status.
Slide courtesy of Bertrand Tombal. Tombal, B et al. JCO 2019;37:5007.

BONE FRACTURES AND CUMULATIVE INCIDENCE SAFETY POPULATION

Time point	Treatment and use of bone protecting agents			
	With exposure to BPA		Without exposure to BPA	
	Enza+Rad (N=39)	Enza (N=49)	Enza+Rad (N=37)	Enza (N=35)
	Cum Incidence (95% CI)*	Cum Incidence (95% CI)	Cum Incidence (95% CI)	Cum Incidence (95% CI)
3 months	0 (-)	0 (-)	0 (-)	5.7 (1.0-16.7)
6 months	0 (-)	0 (-)	5.6 (1.0-16.3)	8.8 (2.2-21.0)
9 months	0 (-)	0 (-)	22.6 (10.6-37.3)	8.8 (2.2-21.0)
12 months	**0 (-)**	**0 (-)**	**37.4 (21.8-53.1)**	**12.4 (3.9-26.2)**
15 months	0 (-)	0 (-)	43.6 (26.8-59.3)	16.6 (5.9-32.0)
18 months	0 (-)	0 (-)	43.6 (26.8-59.3)	16.6 (5.9-32.0)

* the one fracture in this group occurred at month 27

BPA, bone protecting agents; CI, confidence interval; Cum, cumulative; ENZA, enzalutamide; Rad, radium-223.

Slide courtesy of Bertrand Tombal; Tombal, B et al. JCO. 2019;37:5007.

CONCLUSIONS

- **Multiple choices for first line mCRPC treatment** after abiraterone for mHSPC
  - **Novel mechanism of action important**
  - Clinical factors and patient preferences guide treatment choice
- **Multiple choices for second line mCRPC** treatment
  - Novel mechanism of action remains important
  - **Consider clinical trials**
- Supportive care vital
  - Genetic counseling may broaden treatment options for patients
  - **Attention to bone health reduces morbidity and mortality**

mCRPC, metastatic castration resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer.

GU CONNECT EXPERTS KNOWLEDGE SHARE

SUMMARY

SUMMARY

- Previous trials (CHAARTED, LATITUDE and STAMPEDE) showed early intensive therapy with either docetaxel or abiraterone in mHSPC patients has a significant benefit for overall survival

- Several agents approved for mCRPC, but optimal treatment sequence remains unclear
  - None of the mCRPC trials compared the new agent to current standard of therapy
  - Treatment choice depends on prior treatment, clinical factors and patient choice
  - Treatments with different mechanisms of action preferred to avoid treatment resistance

REACH GU CONNECT VIA TWITTER, LINKEDIN, VIMEO AND EMAIL OR VISIT THE GROUP'S WEBSITE

http://www.guconnect.info

Follow us on Twitter
@guconnectinfo

Follow
GU CONNECT
on LinkedIn

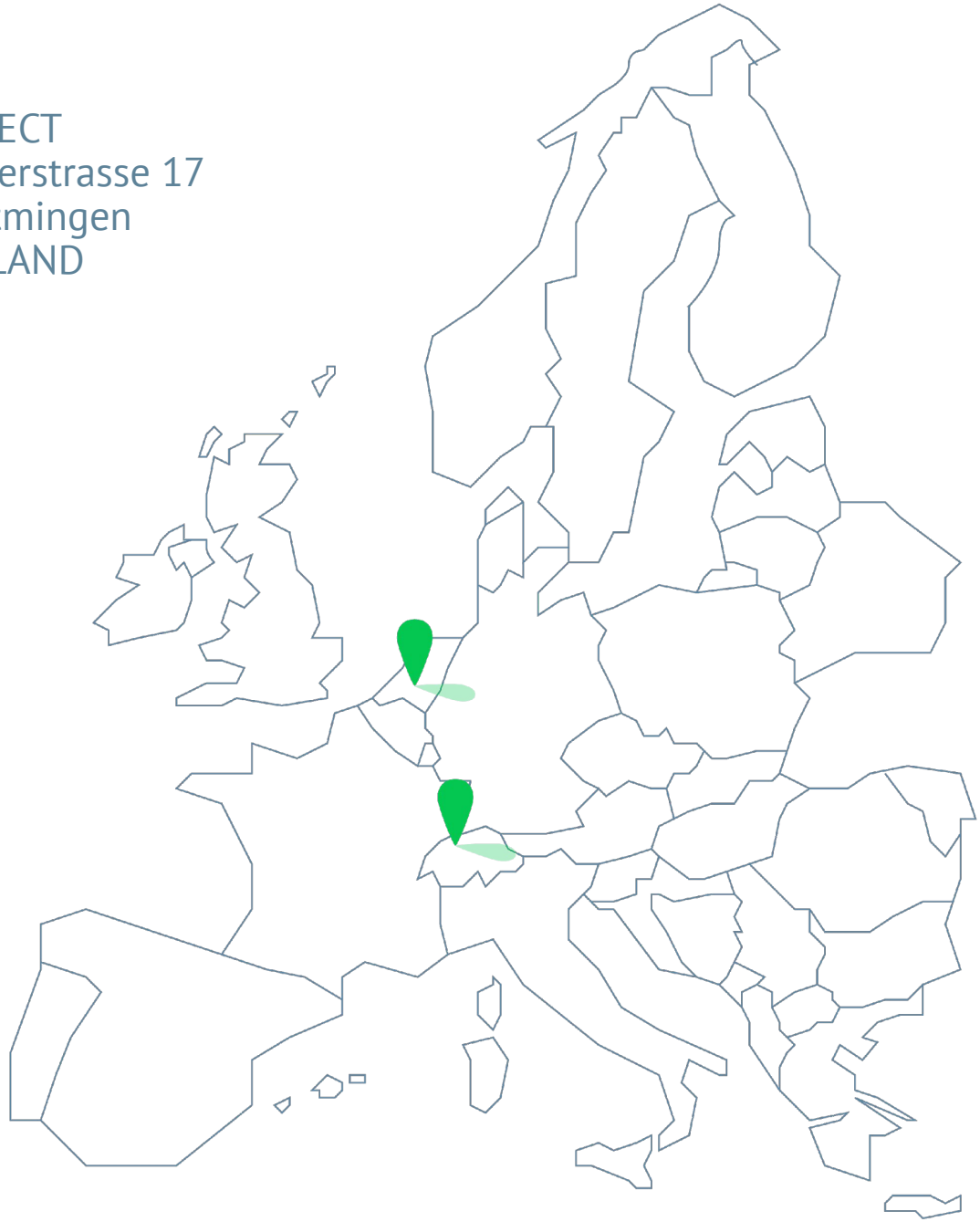
Watch us on the
Vimeo Channel
GU CONNECT

Email
elaine.wills@cor2ed.com

GU connect

POWERED BY COR2ED

GU CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND



Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.com

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com