Please note, these are the actual video-recorded proceedings from the live CME event and may include the use of trade names and other raw, unedited content.

Weill Cornell Medicine
Englander Institute
for Precision Medicine

Weill Cornell Medicine
Meyer Cancer Center

Treatment of Hormone Sensitive Prostate Cancer

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Disclosures

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Janssen, Astellas, Sanofi, and Novartis, Bayer, Astra Zeneca

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Regulatory and reimbursement issues aside, what systemic therapy, if any, would you typically add to androgen deprivation for a 60-year-old patient presenting with Gleason 8 prostate cancer and widespread, moderately symptomatic bone metastases?

What systemic therapy, if any, would you typically add to androgen deprivation if the patient were 80 years old?

	Age 60	Age 80
 EMMANUEL S ANTONARAKIS, MD	Docetaxel or abiraterone based on patient preference	Abiraterone
 A OLIVER SARTOR, MD	Abiraterone	Abiraterone
 HOWARD I SCHER, MD	Docetaxel or abiraterone based on patient clinical status	Abiraterone
 MATTHEW R SMITH, MD, PHD	Abiraterone	Abiraterone
 CORA N STERNBERG, MD	Docetaxel	Docetaxel or abiraterone

A 60-year-old patient with Gleason 8 prostate cancer and asymptomatic liver metastases is consulting you for a second opinion after another oncologist recommends androgen deprivation in combination with docetaxel and abiraterone. How would you respond?

 EMMANUEL S ANTONARAKIS, MD	I disagree with the recommendation
 A OLIVER SARTOR, MD	I believe it is acceptable, but it is not my treatment of choice
 HOWARD I SCHER, MD	I believe it is acceptable, but it is not my treatment of choice
 MATTHEW R SMITH, MD, PHD	I disagree with the recommendation
 CORA N STERNBERG, MD	I believe it is acceptable, but it is not my treatment of choice

Regulatory and reimbursement issues aside, what systemic therapy, if any, would you typically add to androgen deprivation for a 60-year-old patient presenting with Gleason 8 prostate cancer and 3 asymptomatic rib metastases?

What systemic therapy, if any, would you typically add to androgen deprivation if the patient were 80 years old?

	Age 60	Age 80
 EMMANUEL S ANTONARAKIS, MD	Abiraterone	Abiraterone
 A OLIVER SARTOR, MD	Abiraterone	Abiraterone
 HOWARD I SCHER, MD	Apalutamide +/- abiraterone (clinical trial)	Apalutamide +/- abiraterone (clinical trial)
 MATTHEW R SMITH, MD, PHD	Abiraterone	None
 CORA N STERNBERG, MD	None initially, but add chemotherapy or abiraterone if suboptimal ADT response	None initially, but add chemotherapy or abiraterone if suboptimal ADT response

Regulatory and reimbursement issues aside, what systemic therapy, if any, would you typically add to androgen deprivation for a 60-year-old patient presenting with Gleason 8 prostate cancer and asymptomatic liver metastases?

What systemic therapy, if any, would you typically add to androgen deprivation if the patient were 80 years old?

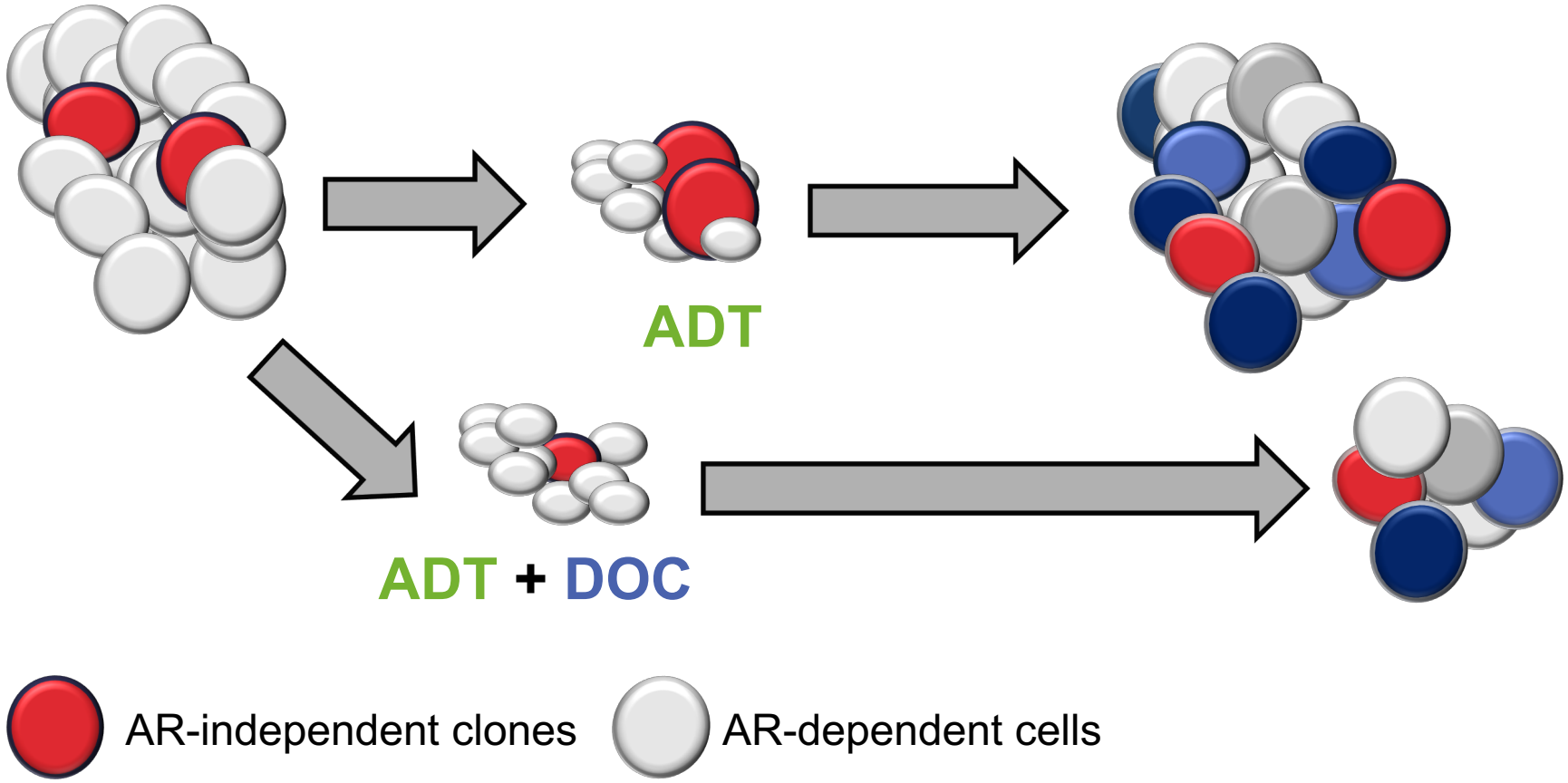
	Age 60	Age 80
 EMMANUEL S ANTONARAKIS, MD	Docetaxel or abiraterone based on patient preference	Abiraterone
 A OLIVER SARTOR, MD	Abiraterone	Abiraterone
 HOWARD I SCHER, MD	Docetaxel +/- carboplatin	Depends on functional status
 MATTHEW R SMITH, MD, PHD	Docetaxel	Abiraterone
 CORA N STERNBERG, MD	Docetaxel	Docetaxel or perhaps enzalutamide

Median OS in Advanced Prostate Cancer

1990s	• Prednisone (P) alone (mCRPC): **12.8** mo[1]
2004	• TAX327 (DOC/P - mCRPC): **18.9** mo[2]
2010	• TROPIC (DOC/P → CAB/P - mCRPC): **29.4** mo[3-4]
2011	• COU-AA-301 (DOC/P → ABI/P - mCRPC): **32.6** mo[5]
2013	• COU-AA-302 (ABI/P pre-DOC - mCRPC): **34.7** mo[6]
2014	• PREVAIL (ENZA pre-DOC - mCRPC): **35.3 mo**[7]
2015	• STAMPEDE - M1 (DOC/P + ADT - mHSPC): **60** mo[8]
2019	• STAMPEDE – M1 (ABI/P + ADT - mHSPC): NYR[9]
	• LATITUDE M1 (ABI/P + ADT - mHSPC): **53.3** mo[10,11]

1. Sartor O et al. Urology 1998;52(2):252-6; 2. Tannock IF. N Engl J Med 2004;351:1502-12; 3. De Bono JS et al. Lancet 2010;376:1147-54; 4. Sartor O. J Clin Oncol 2011;29(S15): abstract 4525 (podium presentation); 5. Fizazi K. Lancet Oncol 2012;13:983-92 (supplementary appendix); 6. Ryan CJ. Lancet Oncol 2015;16:152-60; 7. Beer TM. Eur Urol 2017;71:151-4; 8. James ND et al. Lancet 2016;387:1163-77; 9. James ND et al. N Engl J Med 2017;377(4):338-51. 10. Fizazi K et al. N Engl J Med 2017;377(4):352-60. 11. Fizazi K et al. Abst 141, GU ASCO 2019

Prostate Cancer Heterogeneity May Be Better Addressed by a Combination Strategy



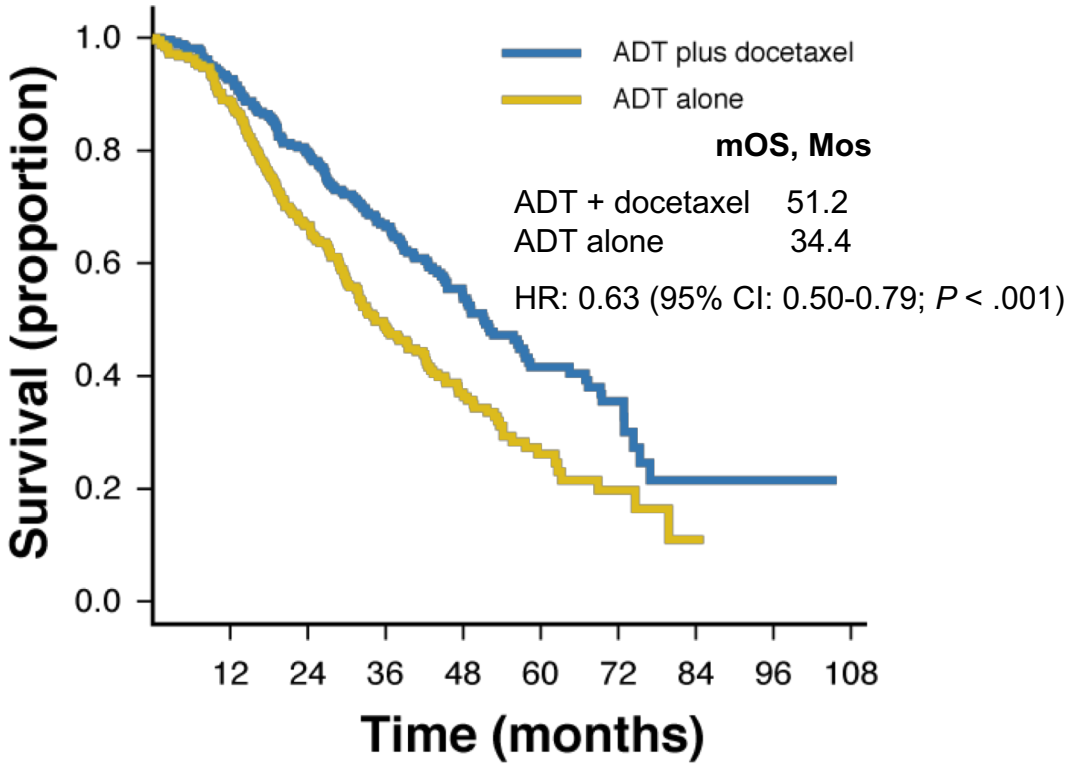
AR: androgen receptor; DOC: docetaxel (75 mg/m^2 every 3 weeks)

Sweeney C et al. J Clin Oncol 2014;32(5S):abstract LBA2 (podium presentation)

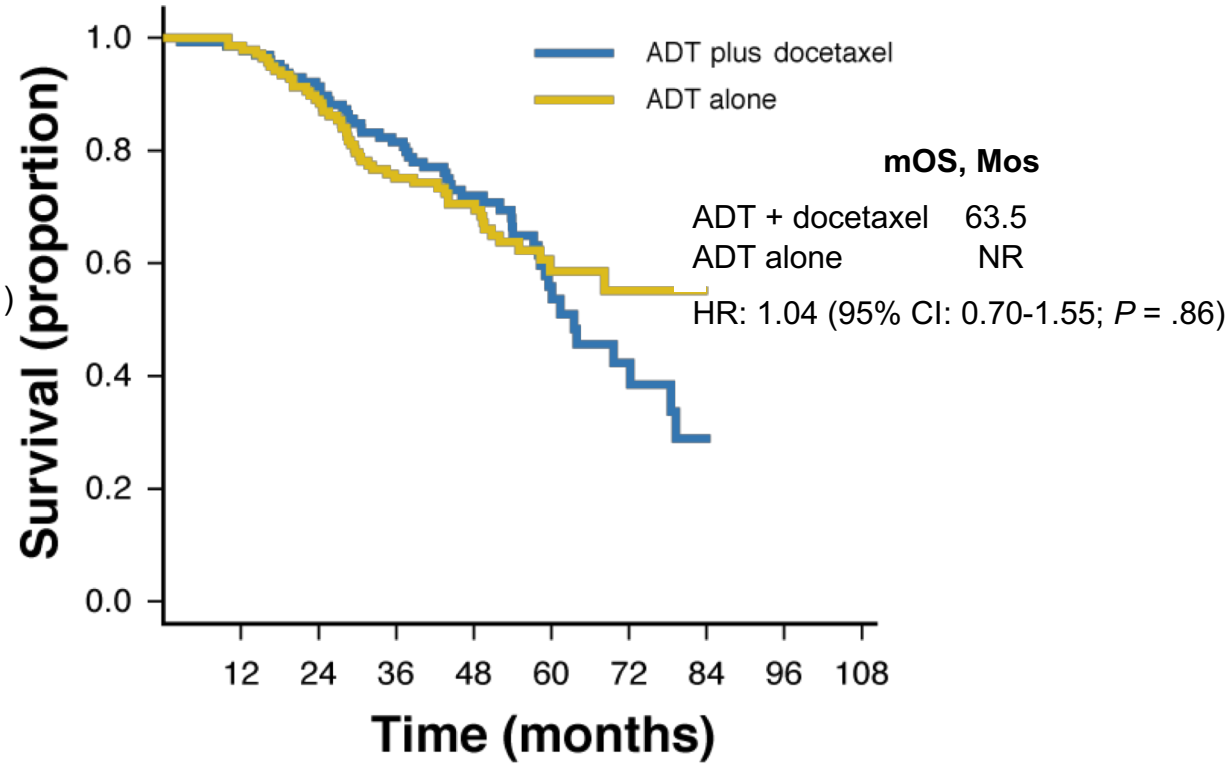
Phase III CHAARTED Trial Long-Term Follow-up: High-Volume vs Low-Volume Disease

- 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

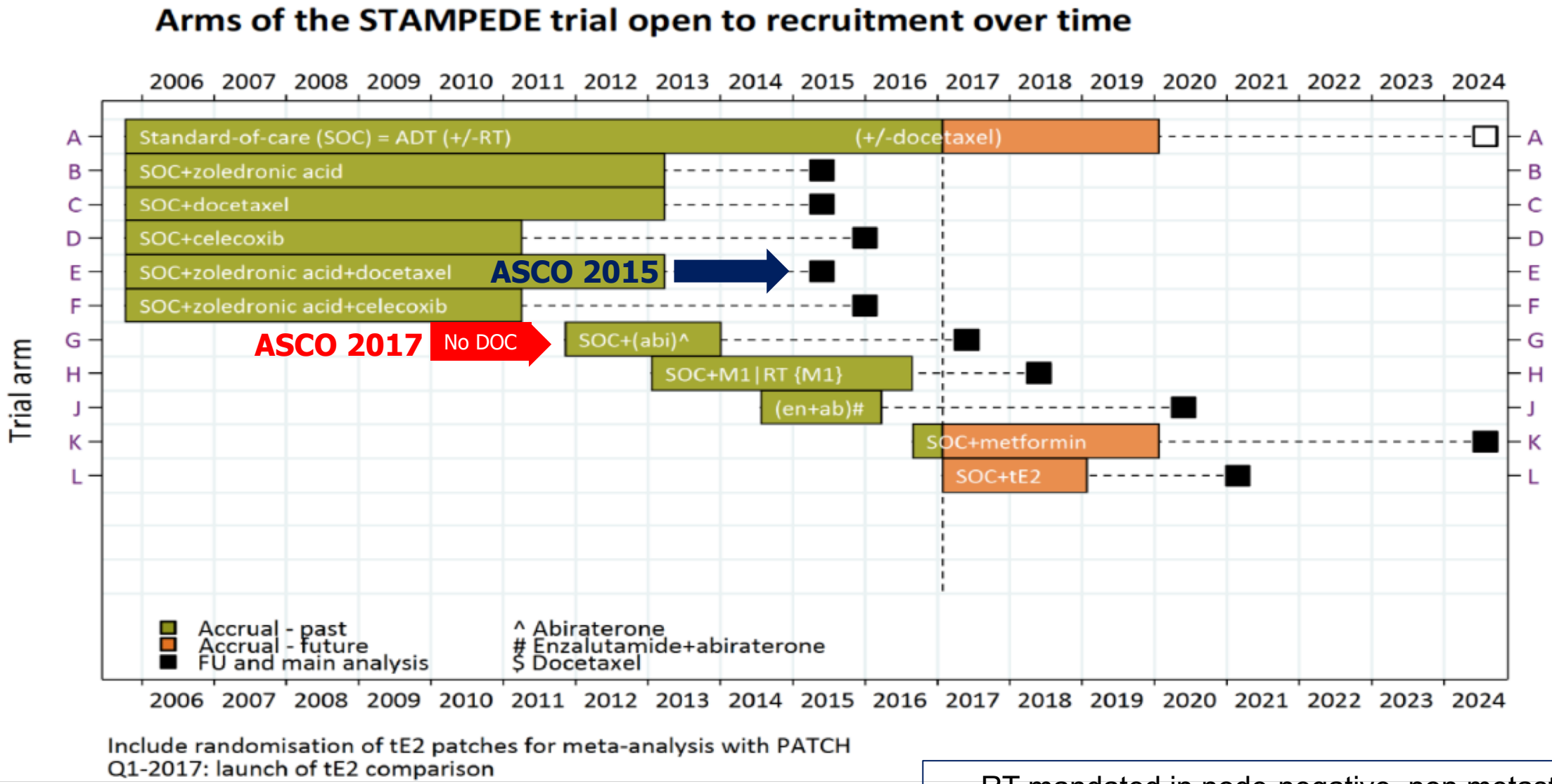


Low-Volume Disease



Kyriakopoulos CE, et al. J Clin Oncol. 2018;36:1080-1087.

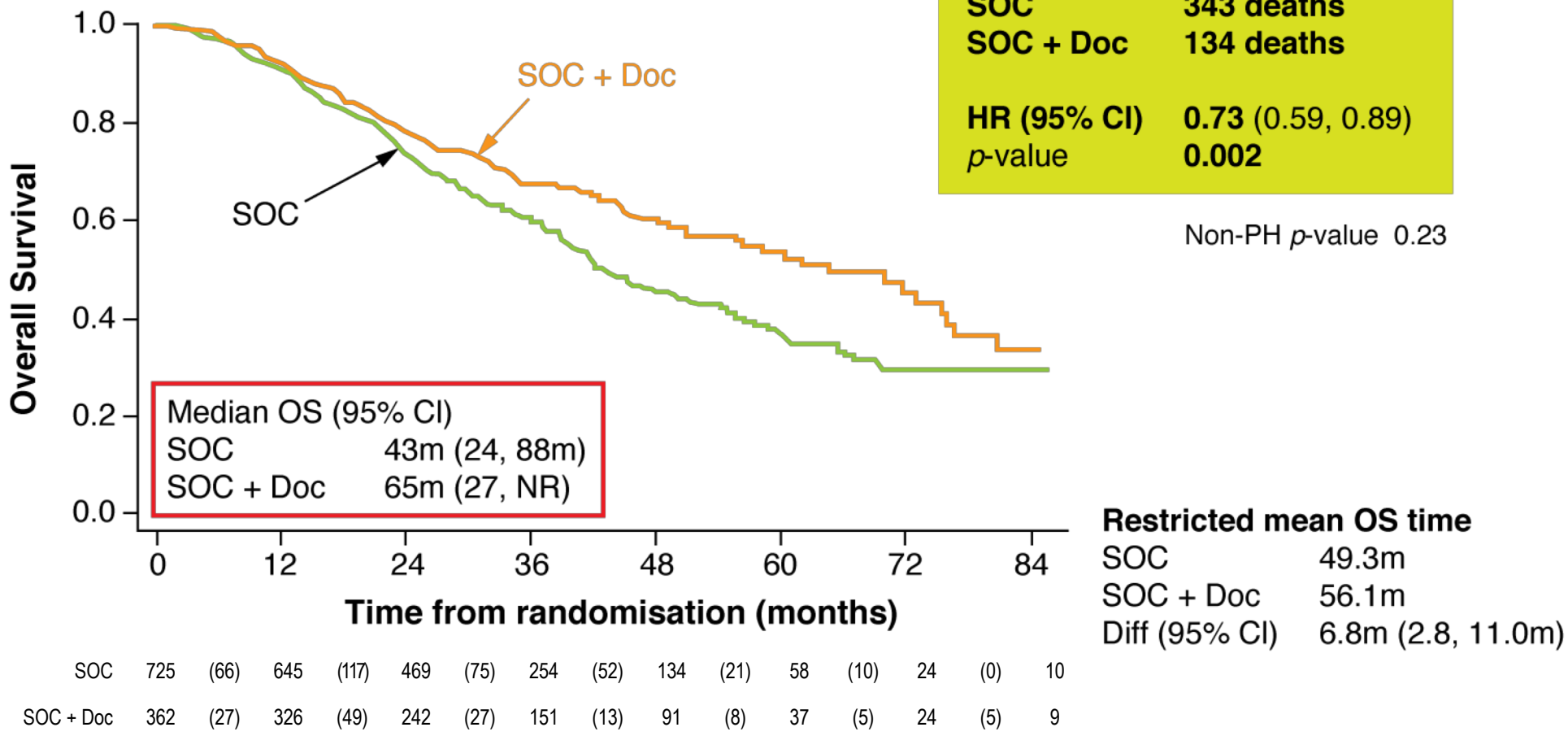
STAMPEDE Trial: a multi-arm, multi-stage design



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

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

STAMPEDE – OS in M1 Patients Docetaxel

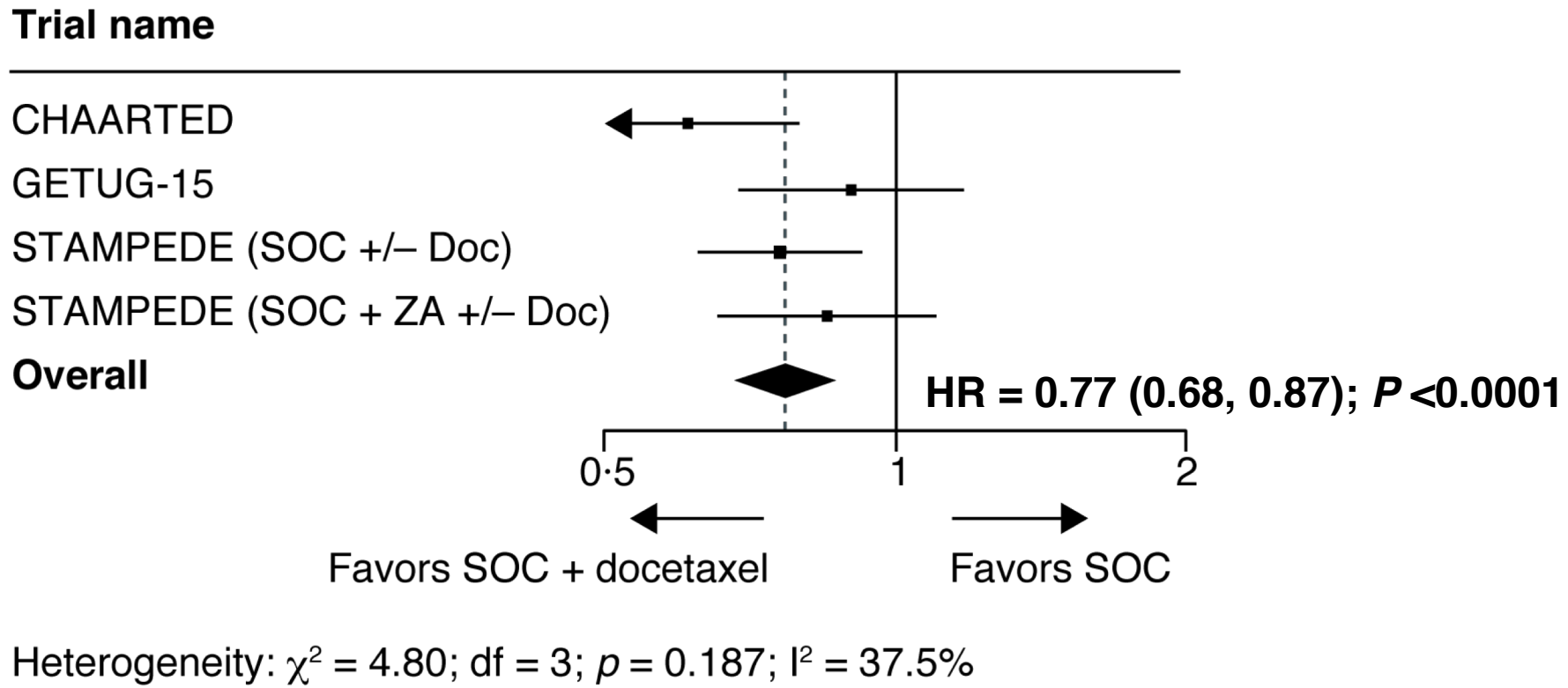


Phase III randomized trial in 2962 men with M0/M1 in 4 groups with zoledronic acid with hormone-sensitive Pca; Primary endpoint: overall survival

James, ND et al. Lancet. 2016;387:1163-77.

UPFRONT DOCETAXEL IN M1 SYSTEMATIC REVIEW AND META-ANALYSIS

- Results based on 2,993 men / 1,254 deaths

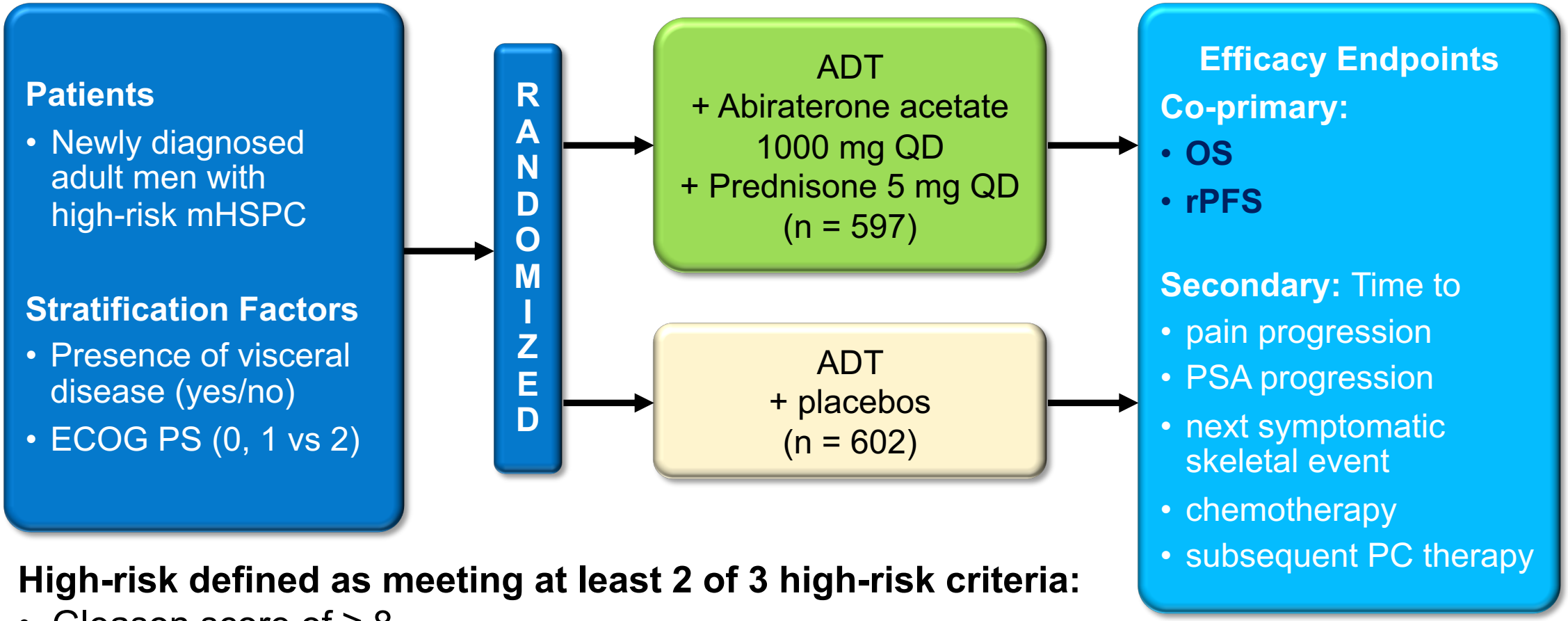


Heterogeneity: $\chi^2 = 4.80$; df = 3; $p = 0.187$; $I^2 = 37.5\%$

10% absolute improvement in survival (from 40% to 50%) at 4 years

Vale CL et al. Lancet Oncol 2016;17:243-56.

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:

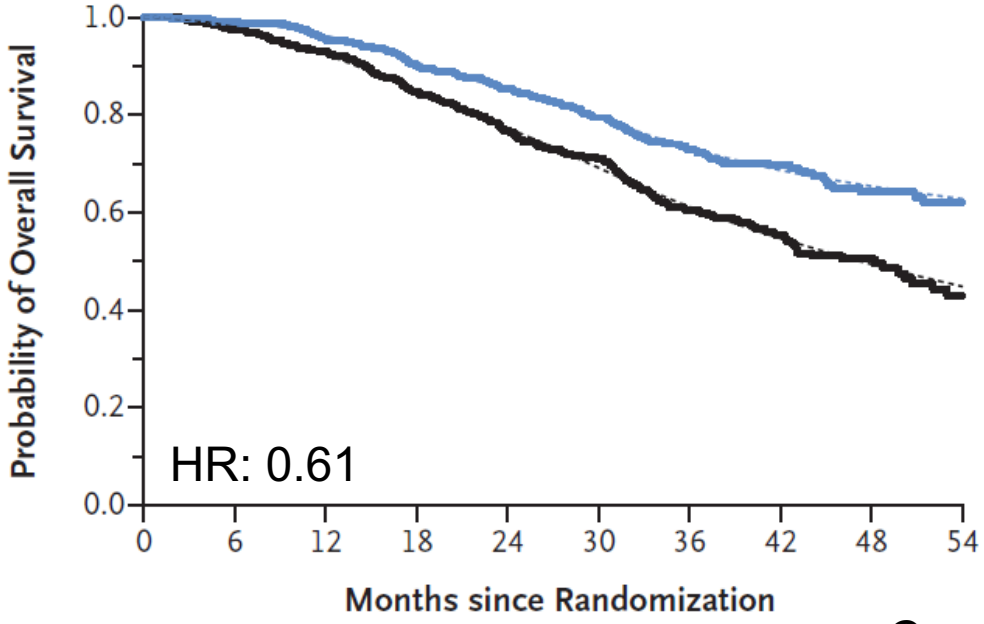
- Gleason score of ≥ 8
- Presence of ≥ 3 lesions on bone scan
- Presence of measurable visceral lesion

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

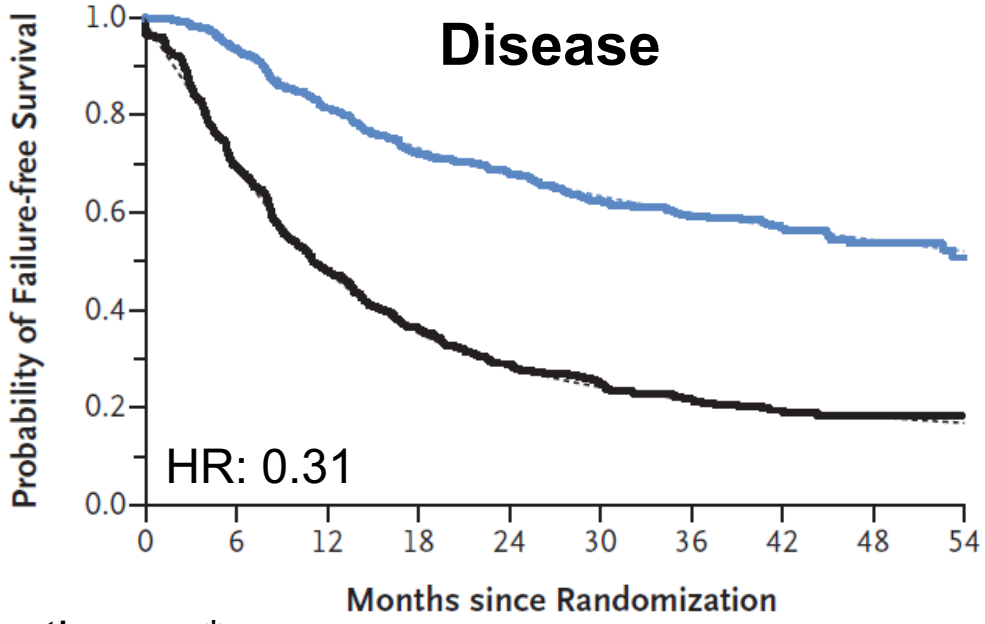
STAMPEDE: ADT + Abiraterone + Prednisolone vs ADT Alone

- Randomized, open-label, multi-arm, multistage phase II/III trial (N = 1917)

OS in Patients With Metastatic Disease



Failure-Free Survival in Patients With Metastatic Disease



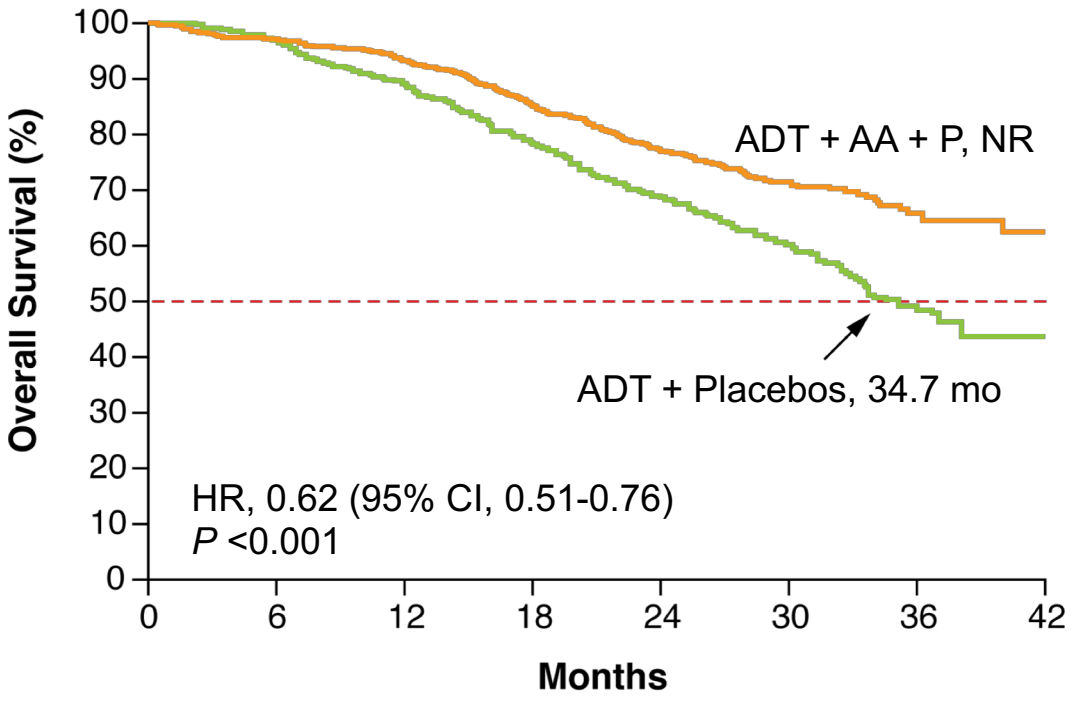
Combination therapy*
ADT alone*

* By Kaplan-Meier estimates.

James ND, et al. N Engl J Med. 2017;377:338-351. ClinicalTrials.gov. NCT00268476.

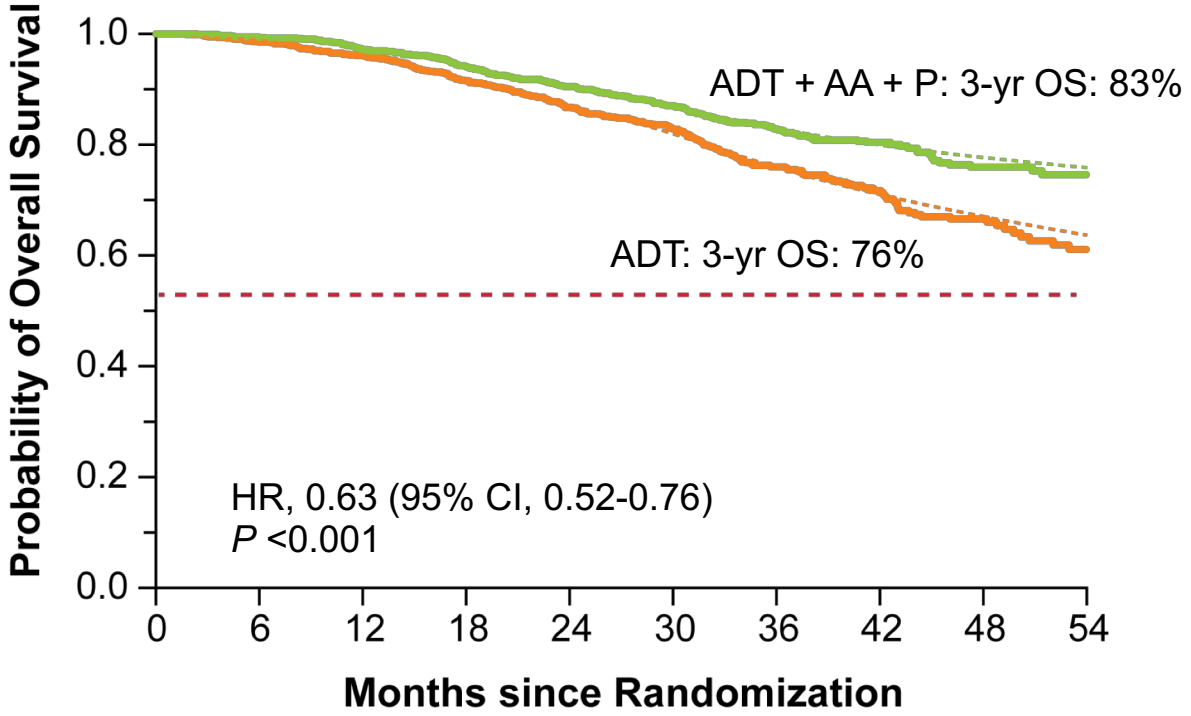
Abiraterone in mHSPC
OS is greater when abiraterone is used at diagnosis

LATITUDE M1 High Risk
38% Risk Reduction in Death



Follow up 30.4 months

STAMPEDE M1 and M0
37% Risk Reduction in Death



Follow up 40 months

Fizazi K, et al. N Engl J Med. 2017;377:352-360

James ND et al, N Engl J Med. 2017;377(4):338-351

LATITUDE: ADT + Abiraterone Acetate (AA) + Prednisone vs ADT + Placebo in Metastatic Hormone Sensitive PC (mHSPC)

Endpoints, median mo	AA + P + ADT (n = 597)	PBO + ADT (n = 602)	HR (95% CI)	*p*-value
Primary				
OS	53.3	36.5	0.7 (0.6-0.8)	<0.0001
Secondary, time to				
Pain progression	47.4	16.6	0.7 (0.6-0.9)	0.0002
Skeletal related event	NR	NR	0.8 (0.6-1.0)	0.0181
Chemotherapy initiation	NR	57.6	0.5 (0.4-0.6)	<0.0001
Subsequent PC therapy	54.9	21.2	0.5 (0.4-0.5)	<0.0001
PFS2 (randomization to progression on subsequent therapy/death)	53.3	30.1	0.6 (0.5-0.7)	<0.0001

Fizazi K et al. Genitourinary Cancers Symposium 2019; Abstract 141.

LATITUDE: ADT + Abiraterone Acetate (AA) + Prednisone vs ADT + Placebo in Metastatic Hormone Sensitive PC (mHSPC)

Grade 3/4 adverse events of special interest	ADT + AA + Prednisone (n = 597)	ADT + Placebo (n = 602)
Hypertension	21.9%	10.5%
Hypokalemia	11.7%	1.7%
Hepatotoxicity	8.9%	3.5%
Cardiac disorders	3.9%	1%
Fluid retention	0.8%	1%

Fizazi K et al. Genitourinary Cancers Symposium 2019; Abstract 141.

Phase III Ongoing Combination Therapy Trials in HSPC

Study	Identifier	Study Drugs	Pts (N)	Primary End Point	Status/Read Out
PEACE-1	NCT01957436	ADT ± DOC vs ADT + **AA** ± DOC (± local RT)	1173	PFS, OS	Recruited as of December 2018, data in 2020
STAMPEDE (Arm J)	NCT00268476	ADT ± **AA + ENZ (± Doc)**	1800	OS	Data pending
SWOG-1216	NCT01809691	ADT + **TAK-700** vs ADT + BIC	1304	OS	Recruited Est. March 2022
ENZAMET	NCT02446405	ADT + **ENZ (± Doc)** vs ADT + antiandrogen **(± Doc)**	1100	OS	Recruited in Spring 2017, data 2019 or 2020 (OS)
TITAN	NCT02489318	ADT ± **APA (ARN 509)**	1000	rPFS, OS	2019 (PFS)
ARCHES	NCT02677896	ADT ± **ENZ**	1100	rPFS (amended)	Presented at GU Cancers Symposium 2019
ARASENS	NCT02799602	ADT + DOC ± **ODM-201**	1300	OS	Data pending

Clinicaltrials.gov, Accessed January 31, 2019

PEACE-1 Phase III Trial Schema

Target Accrual: 1173 (Active, not recruiting)
Est Primary Completion: May 2019

Eligibility

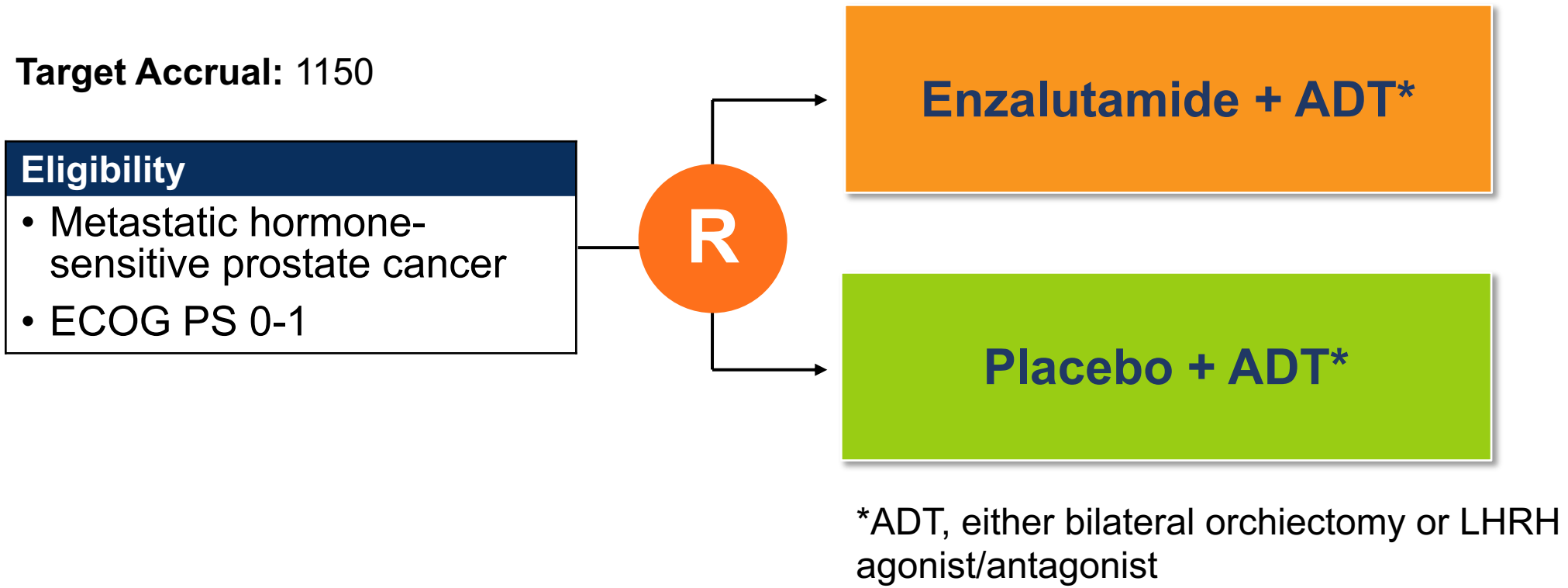
- Metastatic hormone-sensitive prostate cancer
- ECOG PS ≤ 1 (PS 2 due to bone pain accepted)

- ADT + docetaxel
- ADT + docetaxel + abiraterone + prednisone
- ADT + docetaxel + radiotherapy
- ADT + docetaxel + abiraterone + prednisone + radiotherapy

Primary endpoints: Overall and progression-free survival

Clinicaltrials.gov, January 23, 2019 (NCT01957436)

ARCHES Phase III Trial Schema



Primary endpoint: Radiographic progression-free survival

Clinicaltrials.gov, January 23, 2019 (NCT02677896)

Press Release: Dec 20, 2018
ARCHES: ADT with Enzalutamide or Placebo in mHSPC

"…the Phase 3 ARCHES trial evaluating enzalutamide plus androgen deprivation therapy (ADT) in men with metastatic hormone-sensitive prostate cancer (mHSPC) met its primary endpoint, significantly improving radiographic progression-free survival (rPFS) versus ADT alone"

https://www.prnewswire.com/news-releases/astellas-and-pfizer-announce-positive-top-line-results-from-phase-3-arches-trial-of-xtandi-enzalutamide-in-men-with-metastatic-hormone-sensitive-prostate-cancer-300769270.html

ARCHES: ADT with Enzalutamide (ENZA) or Placebo (PBO) in mHSPC

Endpoint	ENZA + ADT (n = 574)	PBO + ADT (n = 576)
Primary: rPFS, HR (95% CI)	0.39 (0.30, 0.50)	
Median (mo)	NR	19.4
Key secondary		
Time to PSA progression, HR (95% CI)	0.19 (0.13, 0.26)	
Time to initiation of new antineoplastic therapy, HR (95% CI)	0.28 (0.20, 0.40)	
PSA undetectable (<0.2 ng/mL) rate %	68.1	17.6
Objective response rate %	83.1	63.7

- 67% of patients had distant metastasis at initial diagnosis
- 63% of patients had high volume disease
- 18% of patients had prior docetaxel
- Grade 3-4 AEs: Enzalutamide (23.6%) vs placebo (24.7%)

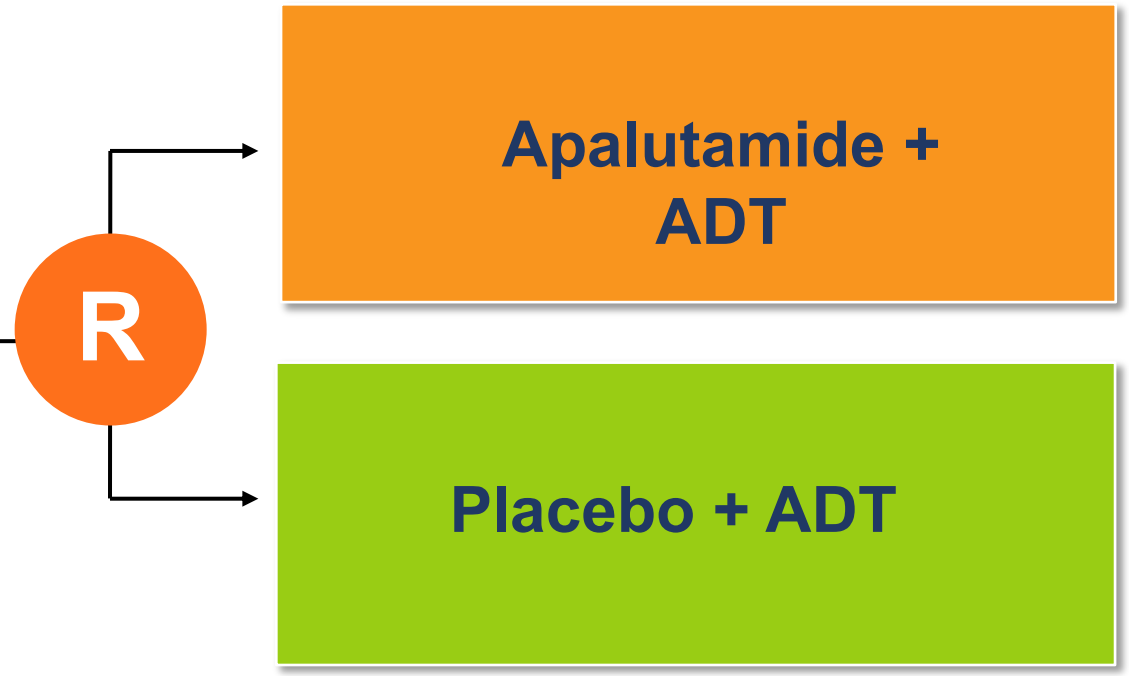
Armstrong AJ et al. Genitourinary Cancers Symposium 2019; Abstract 687.

TITAN Phase III Trial Schema

Target Accrual: 1052

Eligibility

- Metastatic hormone-sensitive prostate cancer
- 1 or more bone lesions



Primary endpoints: Radiographic progression-free survival and overall survival

Clinicaltrials.gov, February 4, 2019 (NCT02489318)

Phase III TITAN Study of Apalutamide for Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) Unblinded

Press Release – January 30, 2019

The Phase 3 TITAN study evaluating apalutamide plus ADT for pts with mHSPC has been unblinded.

The decision resulted from an IDMC recommendation coinciding with a pre-planned analysis that showed the dual primary endpoints were both achieved, significantly improving rPFS and OS.

The IDMC recommended that pts in the placebo plus ADT group be given the opportunity to cross over to treatment with apalutamide plus ADT. Pts will continue to be followed for OS and long-term safety as part of the TITAN study.

https://www.prnewswire.com/news-releases/janssen-announces-erleada-apalutamide-phase-3-titan-study-unblinded-as-dual-primary-endpoints-achieved-in-clinical-program-evaluating-treatment-of-patients-with-metastatic-castration-sensitive-prostate-cancer-300786621

A growing body of evidence that patients with mHSPC benefit from early treatment with:

- ADT plus chemotherapy
- ADT plus novel hormonal agents
- Many patients also had both of these agents