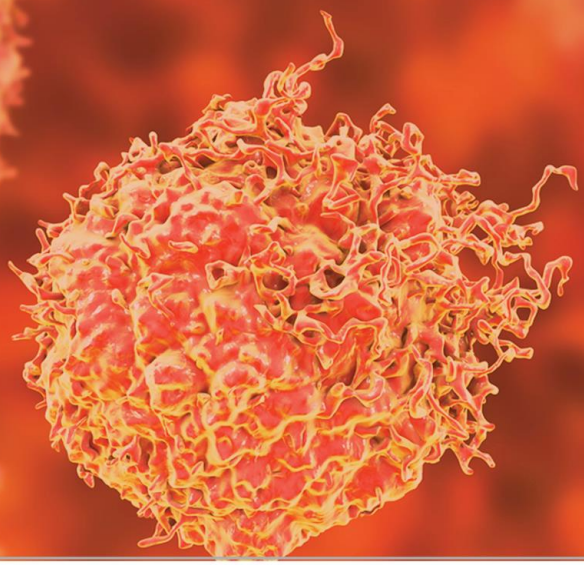
Managing Castration-sensitive PROSTATE CANCER:

How Does Your Approach Compare with the Experts?



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This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This activity is supported by an educational grant from Astellas.

AGENDA

I. **Managing Patients with Castration-Sensitive Prostate Cancer (CSPC)**
   a. Risk stratification
   b. Initial management of noncastrate advanced, recurrent, or metastatic disease
   c. Biochemical recurrence without metastatic disease
   d. Hormonal therapies for prostate cancer
   e. Clinical trial data on new hormonal therapies

II. **Treating Metastatic Disease**
   a. Guideline-recommended treatment of mCSPC
   b. When to use chemotherapy in mCSPC
   c. Defining "high-volume" and "high-risk" disease
   d. Clinical trial data on the efficacy and safety of available treatment options
      i. Abiraterone
      ii. Enzalutamide
      iii. Apalutamide
   e. Managing adverse events

III. **Personalizing the Care of Patients with CSPC**
   a. Treatment considerations in mCSPC
   b. How to personalize the selection of treatment options
   c. Real-world patterns in mCSPC
   d. Shared decision-making in clinical practice

IV. **Conclusions**

V. **Questions and Answers**

Managing Castration-sensitive Prostate Cancer: How Does Your Approach Compare with the Experts'?

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PROGRAM OVERVIEW

This live activity will cover early detection and intervention in prostate cancer.

TARGET AUDIENCE

This activity is designed to meet the educational needs urologists, medical oncologists, and other HCPs responsible for treatment decisions for patients with prostate cancer, as well as primary care providers and other members of a multi-disciplinary care team involved in the management of Adverse Events (AE's).

LEARNING OBJECTIVES

After completing the CME activity, learners should be better able to:

- Contrast the distinct mechanisms of action and clinical profiles of newer therapeutic regimens for managing CSPC in the disease's early stages and in the BCR setting
- Incorporate risk stratification approaches to inform clinical decision-making for managing patients with CSPC
- Plan strategies for diagnosing and managing AEs associated with newer therapeutic regimens for treating patients with CSPC
- Facilitate open communication and shared decision-making as part of patient-centered CSPC management

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NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in caring for patients with prostate cancer.
Credit: 1.0 ANCC Contact Hour

CNE Accreditation Statement: Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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Neil Desai, MD	Consultant/Contracted Research	Boston Scientific
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CME content review

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The reviewer of this activity has nothing to disclose.

CNE Content Review

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2. Participate in the live activity.
3. Submit the pre- and post-test and evaluation form to Med Learning Group.

You will receive your certificate as a downloadable file.

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Managing Castration-Sensitive Prostate Cancer: How Does Your Approach Compare with the Experts?

1

Disclosures

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This activity is supported by an educational grant from Astellas.

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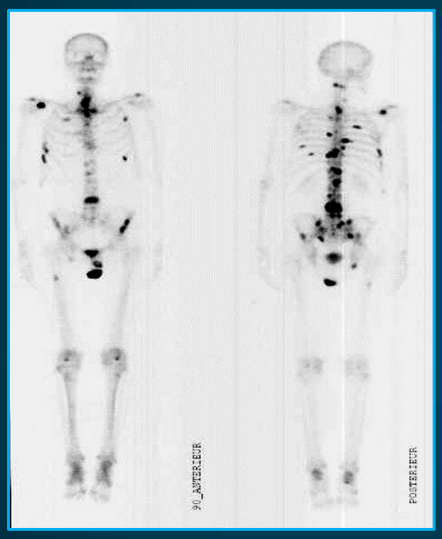
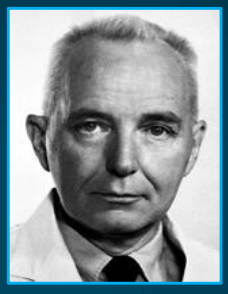
Learning Objectives

- Contrast the distinct mechanisms of action and clinical profiles of newer therapeutic regimens for the management of castration-sensitive prostate cancer (CSPC) in the early stages of disease and in the biochemical-recurrence setting
- Incorporate risk-stratification approaches to inform clinical decision-making for the management of patients with CSPC
- Plan strategies for diagnosing and managing adverse events associated with newer therapeutic regimens for the treatment of patients with CSPC
- Facilitate open communication and shared decision-making as part of patient-centered CSPC management

3

Prostate Cancer Is Hormone Dependent





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

Charles B. Huggins
Nobel lecture
December 13, 1966

Huggins CB. Nobel prize (www.nobelprize.org/uploads/2018/06/huggins-lecture.pdf) Accessed 5/13/2021.

4

Risk Stratification

- Pretreatment parameters, including clinical stage, PSA, and Gleason score, are established predictors of disease recurrence and are used in high-risk disease classifications

AUA	RTOG	NCCN
Clinical T stage of at least cT2c OR Gleason score ≥8 OR PSA ≥20 ng/mL	PSA of 20-100 ng/mL, Gleason score of ≥7, and any clinical T stage OR PSA <100 ng/mL, Gleason score of 8-10, and clinical T stage cT2c	High-risk: Clinical T stage cT3a, Gleason score of ≥8, OR PSA of ≥20 ng/mL Very high-risk: T3b or T4 disease

AUA = American Urologic Association; RTOG = Radiation Therapy Oncology Group.
McKay RR, et al. *Am Soc Clin Oncol Educ Book.* 2020;40:1-12.

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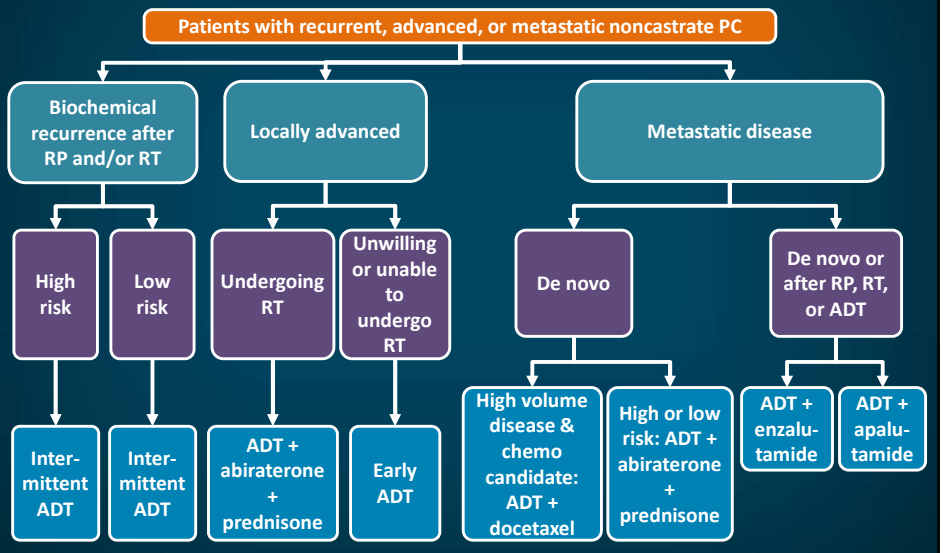
Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer



ASCO Guideline Update 2021.

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Advanced Prostate Cancer: Biochemical Recurrence Without Metastatic Disease

Prognosis

- Inform patients of risk of developing metastatic disease
- Follow patients with serial PSA measurements and clinical evaluation
- In high risk patients (eg, PSADT <12 months), perform periodic staging evaluations consisting of cross sectional imaging (CT, MRI) and technetium bone scan
- Consider novel PET-CT scans in patients with negative conventional imaging
- May use radiographic assessments based on overall PSA and PSA kinetics

Treatment

- Offer observation or clinical trial enrollment
- Do NOT routinely initiate ADT
- Consider intermittent ADT in lieu of continuous ADT if ADT is initiated in the absence of metastatic disease

Lowrance WT, et al. 2021;205:14-21.

7

Hormonal Therapies for Prostate Cancer

Drug	Monitoring parameters
Antiandrogens • Flutamide • Bicalutamide • Nilutamide	Monitor serum transaminases at baseline and monthly for 1st 4 months for all. Baseline chest x-ray and PFT at baseline for nilutamide. Periodic monitoring of CBC, EKG, echocardiograms, serum testosterone, LH, and PSA with bicalutamide.
Androgen Synthesis Inhibitor • Abiraterone	Serum transaminases should be monitored at baseline, every 2 weeks for 3 months, and then monthly. Monitor for adrenocorticoid insufficiency, hypertension, hypokalemia, and fluid retention monthly.
LH agonists • Leuprolide • Goserelin • Triptorelin	Leuprolide: Monitor serum testosterone 4 weeks after initiation, and PSA, blood glucose, and HbA1c at baseline and periodically. Goserelin: Monitor bone mineral density, serum calcium, and cholesterol/lipids.
GNRH antagonist • Degarelix • Relugolix	Monitor LFTs, serum electrolytes, and bone mineral density at baseline. Monitor serum testosterone monthly until castration and then every other month once achieved.
Androgen receptor pathway inhibitors (ARPI) • Apalutamide • Enzalutamide • Darolutamide	Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Monitor and manage patients at risk for fractures and falls and consider use of bone-targeted agents with enzalutamide and apalutamide. Lower threshold for seizures with enzalutamide and apalutamide.

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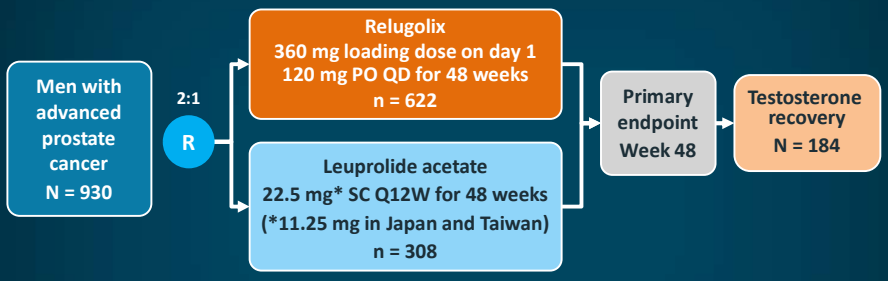
Phase 3 HERO Study Design

Multinational phase 3 randomized, open-label, parallel group study to evaluate safety and efficacy of relugolix in men with advanced prostate cancer



- **Primary endpoint:** sustained castration through 48 weeks (testosterone suppression <50 ng/dL)
- **Secondary endpoints:** noninferiority to leuprolide (noninferiority margin of –10%), castration on days 4 and 15, profound castration <20 ng/dL) on day 15, PSA response on day 15, FSH at end of week 24
- **Stratification** based on geographic region (North/South America vs Europe vs Asia-Pacific region), presence/ absence of metastatic disease, and age (≤75 vs >75 years)

PO = by mouth (orally); QD = each day; SC = subcutaneous; Q12W = every 12 weeks.

Shore ND, et al. *N Engl J Med*. 2020;382:2187-2196.

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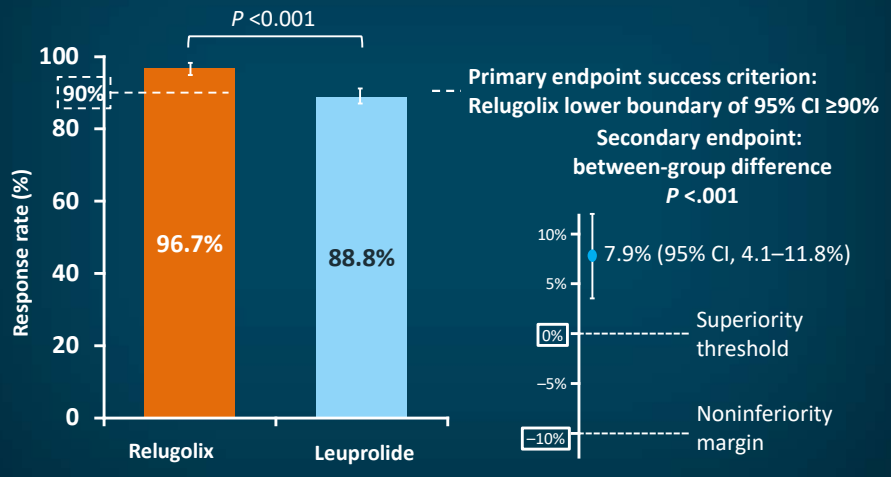
HERO: Primary Endpoint (Sustained Castration) Key Secondary Endpoint—Noninferiority to Leuprolide



Shore ND, et al. *N Engl J Med*. 2020;382:2187-2196.

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HERO: Key Secondary Endpoints

Secondary endpoints	Relugolix (n = 622)	Leuprolide (n = 308)	*P*-value
Proportion of patients with PSA response at day 15 followed with confirmation at day 29	79.4%	19.8%	<.001
Cumulative probability of testosterone suppression to <50 ng/dL on day 15	98.7%	12.0%	<.001
Cumulative probability of profound testosterone suppression to <20 ng/dL on day 15	78.4%	1.0%	<.001
Cumulative probability of testosterone suppression to <50 ng/dL on day 4	56.0%	0.0%	<.001
Mean of FSH level at end of week 24, IU/L	1.72	5.95	<.001

54% reduction in risk of major adverse cardiovascular events (MACE) noted with relugolix compared with leuprolide

IU = international unit.

Shore ND, et al. *N Engl J Med.* 2020;382:2187-2196.

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HERO: Adverse Events Reported for >10% of Patients in Either Treatment Group

	Relugolix (n = 622)	Leuprolide (n = 308)
Hot flush/flash	54.3%	51.6%
Fatigue	21.5%	18.5%
Constipation	12.2%	9.7%
Diarrhea*	12.2%	6.8%
Arthralgia	12.1%	9.1%
Hypertension	7.9%	11.7%

*Adverse events of diarrhea were grade 1 or 2 and did not result in study discontinuation.

Shore ND, et al. *N Engl J Med.* 2020;382:2187-2196.

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Metastatic CSPC

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Background

- Androgen-deprivation therapy (ADT) monotherapy for metastatic prostate cancer has been foundational, but it has been limited due to poor clinical outcomes
- Tumor burden/location/biology affect overall survival
- New standard of care for metastatic castration-sensitive prostate cancer (mCSPC) is combined therapy: ADT plus the early addition of either docetaxel or an androgen receptor-pathway inhibitor (ARPI)

National Comprehensive Cancer Network (NCCN) Prostate Cancer guidelines, v2.2021 (www.nccn.org/professionals/physician_gls/pdf/prostate.pdf). American Urological Association (AUA) 2020 guidelines (www.auanet.org/guidelines/guidelines/advanced-prostate-cancer). Accessed 5/13/2021.

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mCSPC Patients Have Numerous Presentations: ADT Has Been Foundational

- Patients present de novo (*newly diagnosed*) vs recurrent, after prior prostatectomy or radiation
- Performance status spectrum: age/conditioning varies—ranging from young and healthy to elderly and frail
- Tumor-burden spectrum: ranging from minimal to widespread disease on conventional imaging
- Varying use of adjuvant testosterone suppression with radiation, prostatectomy

mCSPC = metastatic castration-sensitive prostate cancer.

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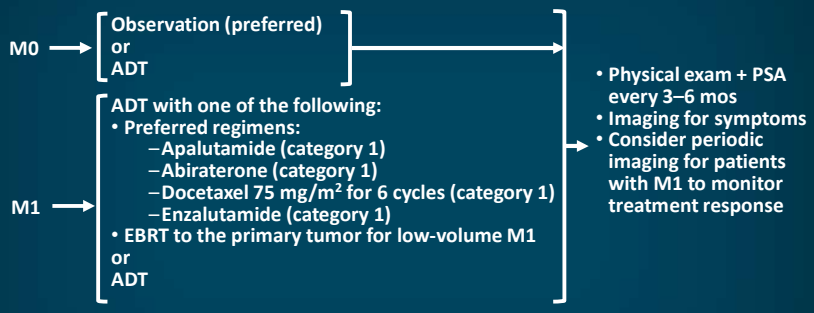
Treatment Options for CSPC in 2021

Systemic Therapy for Castration-Naïve Prostate Cancer



How to choose?

Quality of life and patient preferences must be considered!

EBRT = external-beam radiation therapy; M0 = nonmetastatic; M1 = metastatic; mo(s), month(s); PSA = prostate specific antigen.

NCCN Guidelines Prostate Cancer. Version 2.2021 (www.nccn.org/professionals/physician_gls/pdf/prostate.pdf). Accessed 5/13/2021.

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Reported RCTs in mCSPC

RCTs in High-Volume, High-Risk mCSPC

Trial	Clinical Trial Information	Comparator Arm	Control Arm	No. of Trial Participants	PFS, HR, or EP	OS, HR, or EP
Docetaxel						
CHAARTED	NCT00309985	ADT + DOC	ADT	513	0.58 (time to CRPC)	0.63
GETUG-15	NCT00104715	ADT + DOC	ADT	183	NA	0.78
STAMPEDE arm C	NCT00268476	ADT + DOC	ADT	724	NA	TBD
ARPI						
LATITUDE	NCT01715285	ADT + AAP	ADT	955	NA	0.62
STAMPEDE arm G	NCT00268476	ADT + AAP	ADT	473	0.31 (FFS)	0.54
ENZAMET	NCT02446405	ADT + ENZA (± DOC)	ADT + NSSA (± DOC)	588	0.45	0.80
ARCHES	NCT02677896	ADT + ENZA (prior DOC allowed)	ADT (prior DOC allowed)	727	0.44 (rPFS)	TBD
TITAN	NCT02489318	ADT + APA (prior DOC allowed)	ADT (prior DOC allowed)	660	0.53	0.68

RCT = randomized controlled trial; DOC = docetaxel; AAP = abiraterone acetate + prednisone; ENZA = enzalutamide; APA = apalutamide; NSAA = nonsteroidal antiandrogen; CRPC = castration-resistant prostate cancer; PFS = progression-free survival; rPFS = radiographic PFS; FFS = failure-free survival; HR = hazard ratio; EP = endpoint; NA = not available; TBD = to be determined.

VanderWeele DJ, et al. *J Clin Oncol.* 2019;37:2961-2967.

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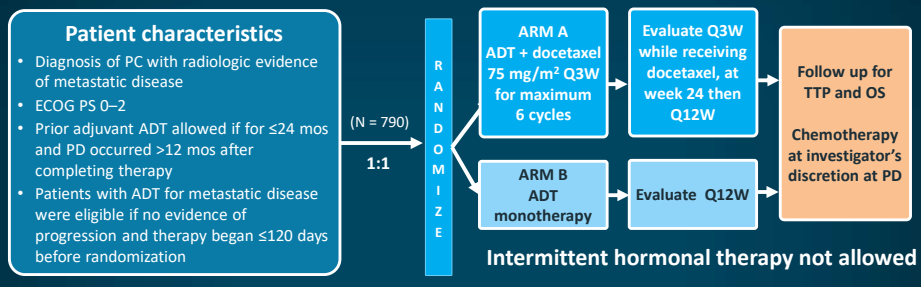
CHAARTED Study Design

Phase 3, multicenter, open-label study



- **Primary endpoint:** OS with docetaxel therapy at beginning of ADT for mCSPC vs ADT alone
- **Secondary endpoints:** decrease in PSA to <0.2 mg/mL at 12 mos, time to hormone-refractory disease, time to clinical progression, time to PSA progression, toxicity
- **Stratification** based on extent of metastasis (high volume vs low volume*), age (≥70 vs <70 years), ECOG (0–1 vs 2), CAB >30 days (yes vs no), SRE prevention (yes vs no), and prior adjuvant ADT (≤12 vs >12 mos)

***At study start only patients with high-volume disease were enrolled; study was amended to also include patients with low-volume disease.**

PC = prostate cancer; ECOG = Eastern Cooperative Oncology Group; PS = performance status; Q3W = every 3 weeks; Q12W = every 12 weeks; TTP = time to progression; OS = overall survival; PD = disease progression; CAB = combined androgen blockade; SRE = skeletal-related event.

Sweeney CJ, et al. *N Engl J Med.* 2015;373:737-746. NCT00309985 (www.clinicaltrials.gov/ct2/show/NCT00309985?term=CHAARTED&rank=1). Accessed 5/13/2021.

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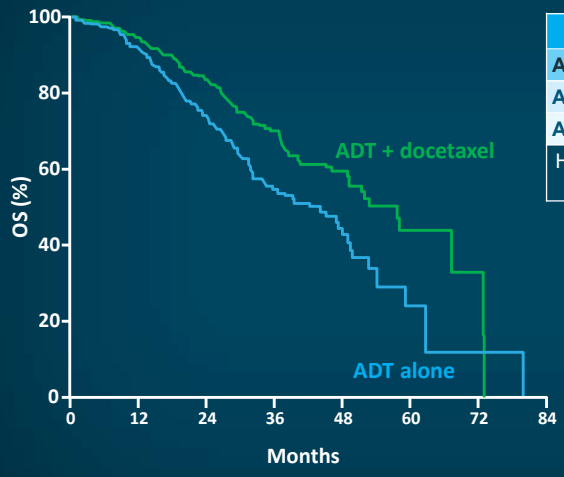
CHAARTED: Docetaxel for mCSPC



OS in All Patients	
Arms	mOS
ADT + DOC	57.6 mos
ADT	44.0 mos
HR* = 0.61 (95% CI, 0.47–0.80) *P* <.001	

mOS was 13.6 mos longer with ADT + docetaxel

*HR for death.

mOS = median OS; HR = hazard ratio; CI = confidence interval.

Sweeney CJ, et al. *N Engl J Med.* 2015;373:737-746.

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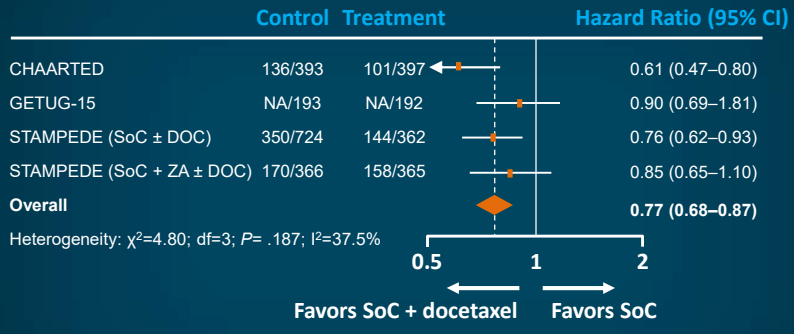
Meta-analysis of RCTs of Docetaxel in mCSPC

Overall Survival



- Results based on 2992 men/2198 events
- 9% absolute improvement in survival at 4 years

SoC = standard of care; ZA = zoledronic acid

Vale CL, et al. *Lancet Oncol.* 2016;17:243-256.

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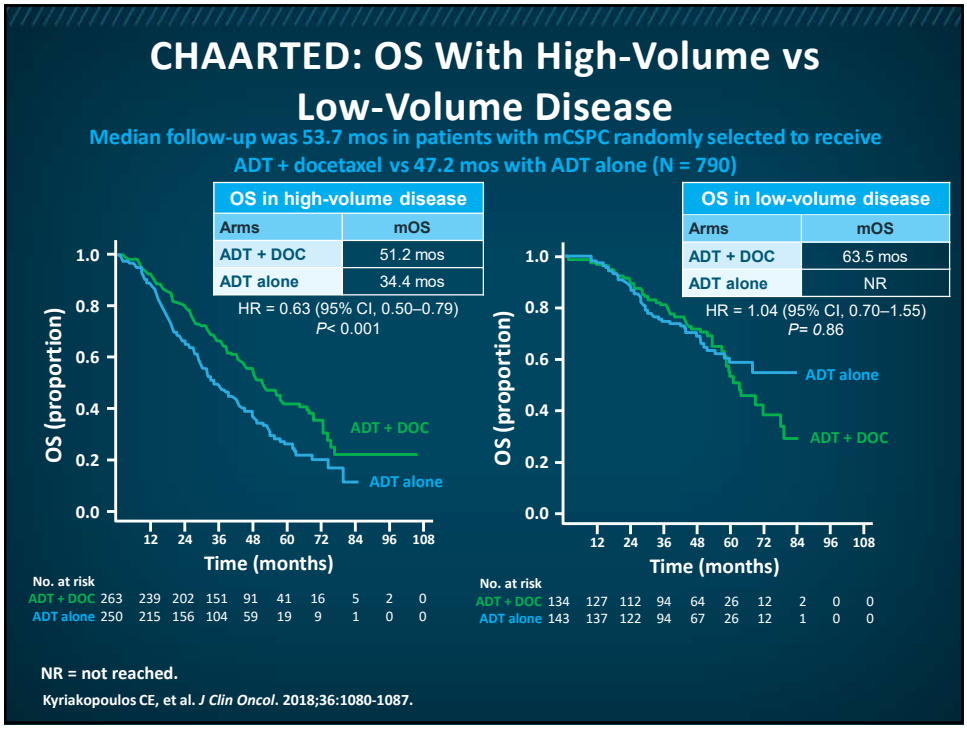
CHAARTED: OS With High-Volume vs Low-Volume Disease
Median follow-up was 53.7 mos in patients with mCSPC randomly selected to receive ADT + docetaxel vs 47.2 mos with ADT alone (N = 790)
OS in high-volume disease
Arms | mOS
ADT + DOC | 51.2 mos
ADT alone | 34.4 mos
HR = 0.63 (95% CI, 0.50–0.79)
P< 0.001
OS in low-volume disease
Arms | mOS
ADT + DOC | 63.5 mos
ADT alone | NR
HR = 1.04 (95% CI, 0.70–1.55)
P= 0.86
OS (proportion)
Time (months)
ADT + DOC
ADT alone
No. at risk
ADT + DOC 263 239 202 151 91 41 16 5 2 0
ADT alone 250 215 156 104 59 19 9 1 0 0
No. at risk
ADT + DOC 134 127 112 94 64 26 12 2 0 0
ADT alone 143 137 122 94 67 26 12 1 0 0
NR = not reached.
Kyriakopoulos CE, et al. J Clin Oncol. 2018;36:1080-1087.

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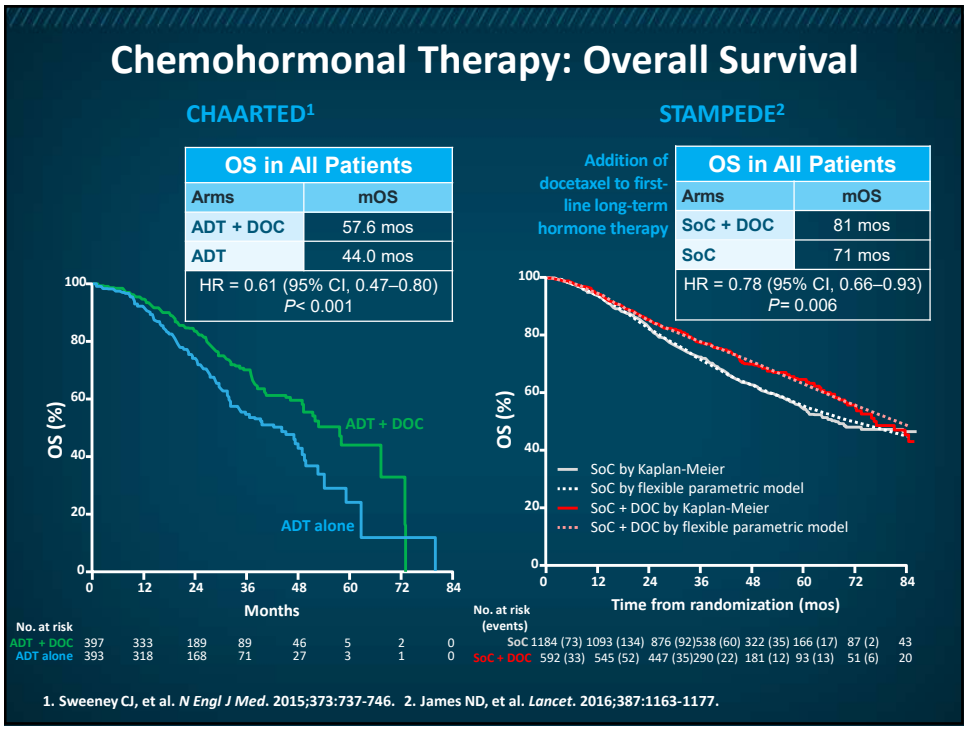
Chemohormonal Therapy: Overall Survival
CHAARTED[1]
OS in All Patients
Arms | mOS
ADT + DOC | 57.6 mos
ADT | 44.0 mos
HR = 0.61 (95% CI, 0.47–0.80)
P< 0.001
OS (%)
Months
ADT + DOC
ADT alone
No. at risk
ADT + DOC 397 333 189 89 46 5 2 0
ADT alone 393 318 168 71 27 3 1 0
STAMPEDE[2]
Addition of docetaxel to first-line long-term hormone therapy
OS in All Patients
Arms | mOS
SoC + DOC | 81 mos
SoC | 71 mos
HR = 0.78 (95% CI, 0.66–0.93)
P= 0.006
OS (%)
Time from randomization (mos)
SoC by Kaplan-Meier
SoC by flexible parametric model
SoC + DOC by Kaplan-Meier
SoC + DOC by flexible parametric model
No. at risk (events)
SoC 1184 (73) 1093 (134) 876 (92) 538 (60) 322 (35) 166 (17) 87 (2) 43
SoC + DOC 592 (33) 545 (52) 447 (35) 290 (22) 181 (12) 93 (13) 51 (6) 20
1. Sweeney CJ, et al. N Engl J Med. 2015;373:737-746. 2. James ND, et al. Lancet. 2016;387:1163-1177.

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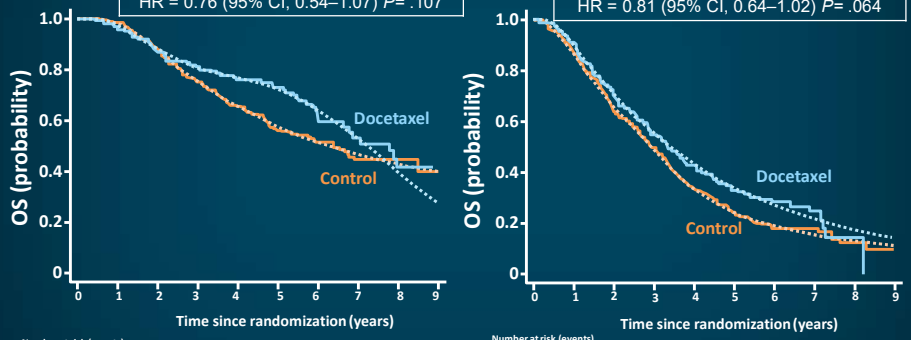
STAMPEDE: Survival Outcomes by Volume

OS in Low-Burden M1		
Arms	RMST	5-yr OS
DOC	78.8 mos	72%
Control	75.8 mos	57%
HR = 0.76 (95% CI, 0.54–1.07) *P*= .107		

OS in High-Burden M1		
Arms	RMST	5-yr OS
DOC	51.3 mos	34%
Control	44.8 mos	24%
HR = 0.81 (95% CI, 0.64–1.02) *P*= .064		



Number at risk (events)

Control	238 (4)	227 (24)	201 (29)	172 (22)	149 (20)	104 (8)	69 (7)	33 (0)	16 (1)	1
DOC	124 (5)	117 (11)	105 (7)	96 (6)	86 (3)	70 (11)	38 (3)	24 (4)	10 (1)	1

Number at risk (events)

Control	320 (40)	277 (75)	200 (43)	154 (49)	102 (29)	57 (13)	32 (0)	16 (4)	7 (1)	1
DOC	148 (13)	132 (29)	102 (23)	77 (17)	59 (13)	40 (5)	21 (2)	9 (3)	2 (1)	0

RMST = restricted mean survival time.

Clarke NW, et al. *Ann Oncol.* 2019;30:1992-2003.

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Development of Novel Hormone Therapy and Chemotherapy in mCSPC

CHAARTED (docetaxel)
First patient in 2007
ASCO 2015[1]

→ **LATITUDE** (abiraterone)
First patient in 2013
ASCO 2017[2]

→ **STAMPEDE** (abiraterone)
First patient in 2006
ESMO 2018 (arm G)[3]

→ **TITAN** (apalutamide)
First patient in 2015
ASCO 2019[4]

→ **ARASENS** (darolutamide + DOC)
First patient in 2016
Primary completion in 2021[8]

← **PEACE1** (abiraterone + DOC + RT)
First patient in 2013
Last patient in 2020[7]

← **ENZAMET** (enzalutamide)
First patient in 2014
ASCO 2019[6]

← **ARCHES** (enzalutamide)
First patient in 2016
ASCO GU 2019[5]

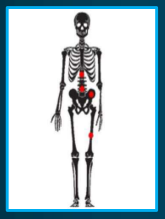
ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; GU = genitourinary; RT = radiation therapy.

1. Maughan BL, et al. *J Clin Oncol.* 2015;33(15 suppl): abstract e16079. 2. Fizazi K, et al. *J Clin Oncol.* 2017;35(18 suppl): abstract LBA3. 3. Hoyle AP, et al. *Ann Oncol.* 2018;29(suppl 8):viii722 (abstract LBA4). 4. Chi KN, et al. *J Clin Oncol.* 2019;37(15 suppl): abstract 5006. 5. Armstrong AJ, et al. *J Clin Oncol.* 2019;37(suppl 7): abstract 687. 6. Sweeney C, et al. *J Clin Oncol.* 2019;37(18 suppl): abstract LBA2. 7. NCT01957436 (https://clinicaltrials.gov/ct2/show/NCT01957436?term=NCT01957436&draw=2&rank=1). 8. NCT02799602 (https://clinicaltrials.gov/ct2/show/NCT01957436?term=NCT01957436&draw=2&rank=1). URLs accessed 5/14/2021.

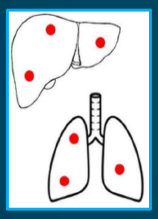
24

Definitions of "High Volume" and "High Risk"

Definition of high-volume disease (CHAARTED STUDY)[1,2]
At least one of the following criteria:

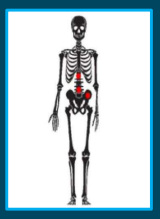


4 or more bone mets
(with at least one outside pelvis/column)

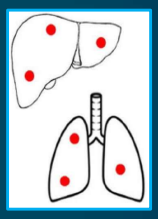


Visceral mets

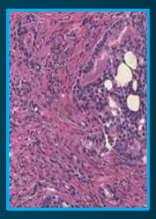
Definition of high-risk disease (LATITUDE STUDY)[1,3]
At least two of the following criteria:



3 or more bone mets



Visceral mets



Gleason score ≥8

"Low volume" is not high risk!

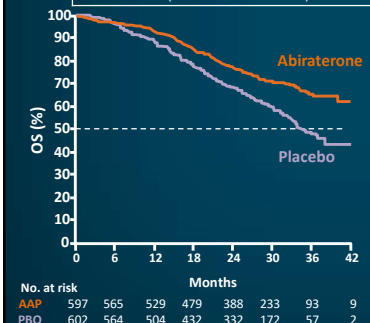
mets = metastases.

1. Iacovelli R, et al. *Crit Rev Oncol Hematol*. 2019;139:83-86. 2. Sweeney CJ, et al. *N Engl J Med*. 2015;373:737-746.
3. Fizazi K, et al. *N Engl J Med*. 2017;377:352-360.

25

LATITUDE: ADT + Abiraterone/Prednisone or PBO in Newly Diagnosed High-Risk Metastatic Hormone-Naïve Prostate Cancer

OS		
Arms	mOS	3-year OS
AAP + ADT	NR	66%
PBO + ADT	34.7 mos	49%
HR = 0.62 (95% CI, 0.51–0.76) *P* <.001		



Endpoints, median mos	AAP + ADT (n = 597)	PBO + ADT (n = 602)	HR (95% CI)	*P*-value
Primary endpoint: OS	**53.3 mos**	**36.5 mos**	**0.66 (0.56–0.78)**	**<.0001**
Secondary endpoints, time to:				
Pain progression	47.4	16.6	0.72 (0.61–0.86)	.0002
Skeletal-related event	NR	NR	0.75 (0.60–0.95)	.0181
Chemotherapy initiation	NR	57.6	0.51 (0.41–0.63)	<.0001
Subsequent PC therapy	54.9	21.2	0.45 (0.38–0.53)	<.0001
Exploratory endpoint: PFS2	53.3	30.1	0.58 (0.49–0.68)	<.0001

AAP = abiraterone acetate + prednisone; PC = prostate cancer; PFS2 = time to second disease progression.

Fizazi K, et al. *N Engl J Med*. 2017;377:352-360. Fizazi K, et al. *Lancet Oncol*. 2019;20:686-700.

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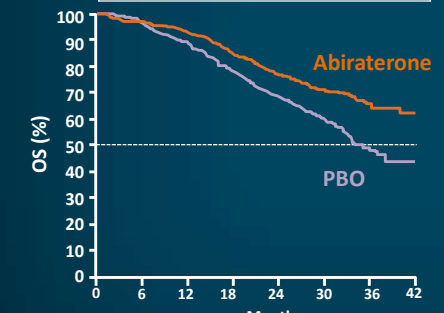
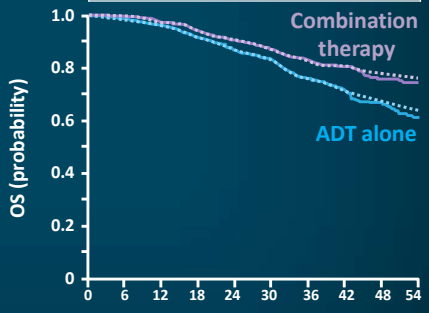
Abiraterone Acetate

LATITUDE: M1 High-Risk mCSPC[1]	
Arms	mOS
Abiraterone	NR
PBO	34.7 mos
HR = 0.62 (95% CI, 0.51–0.76), *P*< .001	

STAMPEDE: M1 and M0 mCSPC[2]	
Arms	3-year OS
Combination	83%
ADT alone	76%
HR = 0.63 (95% CI, 0.52–0.76), *P*< .001	



No. at risk								
Abiraterone	597	565	529	479	388	233	93	9
Placebo	602	564	504	432	332	172	57	2



No. of patients (deaths)						
Combination	960	917 (63)	840 (67)	541 (25)	161	
ADT alone	957	909 (88)	806 (92)	491 (36)	123	

1. Fizazi K, et al. *N Engl J Med*. 2017;377:352-360. 2. James ND, et al. *N Engl J Med*. 2017;377:338-351.

27

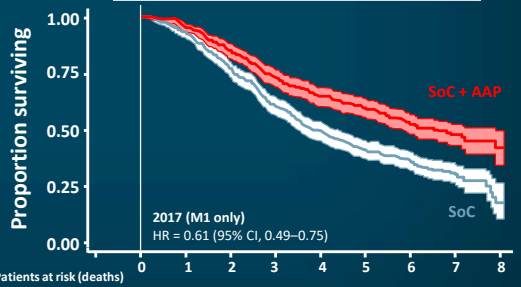
STAMPEDE: SoC + AAP vs SoC

1003 (52%) of randomized population had metastatic disease

M1 patient characteristics	SoC (n = 502)	SoC + AAP (n = 501)
Median age (range), years	67 (39–84)	67 (42–85)
Metastatic burden, %		
Low risk	44	43
High risk	46	48
Unclassified	10	9
Eligibility criteria, %		
Newly diagnosed	95	93
Relapsing	5	7
Median PSA (IQR), ng/mL	97.2 (26–358)	96.3 (29–371)

OS: SoC + AAP vs SoC

	SoC (n = 502)	SoC + AAP (n = 501)
mOS, years	3.8	6.6
Events, n	329	244
HR = 0.60 (95% CI, 0.50–0.71) *P*= .0000000003		



Patients at risk (deaths)									
SoC	502 (0)	464 (34)	380 (114)	297 (196)	241 (250)	182 (290)	100 (311)	39 (322)	2 (329)
SoC + AAP	501 (0)	474 (23)	421 (74)	357 (134)	314 (175)	284 (198)	176 (230)	56 (241)	6 (244)

IQR = interquartile range.

James ND, et al. *N Engl J Med*. 2017;377:338-351. James N, et al. *Ann Oncol*. 2020;31(suppl 4): abstract 611O.

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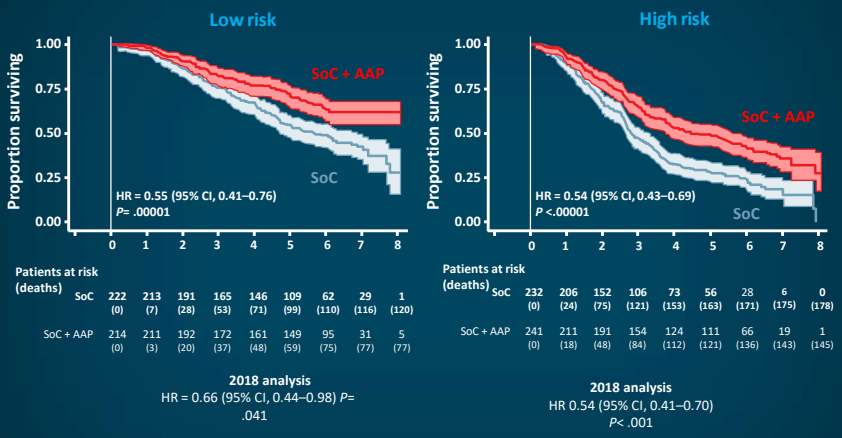
STAMPEDE: SoC + AAP vs SoC

OS by risk group, based on LATITUDE trial



2018 analysis
HR = 0.66 (95% CI, 0.44–0.98) *P*= .041

2018 analysis
HR 0.54 (95% CI, 0.41–0.70)
P< .001

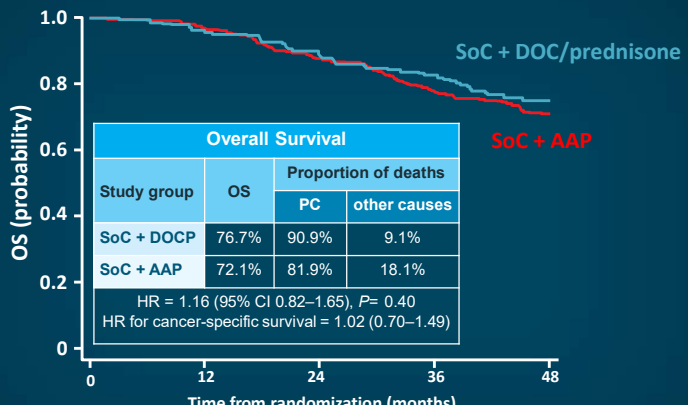
Toxicity at 4 years post-randomization was similar between treatment arms, with 16% of patients in each group reporting grade ≥3 toxicity

Hoyle AP, et al. *Eur Urol.* 2019;76:719-728. James N, et al. *Ann Oncol.* 2020;31(suppl 4): abstract 611O.

29

STAMPEDE Comparison: Overall Survival

OS: Abiraterone vs Docetaxel



Overall Survival			
Study group	OS	Proportion of deaths	
		PC	other causes
SoC + DOCP	76.7%	90.9%	9.1%
SoC + AAP	72.1%	81.9%	18.1%

HR = 1.16 (95% CI 0.82–1.65), *P*= 0.40
HR for cancer-specific survival = 1.02 (0.70–1.49)

Number of patients (events)									
SoC + DOCP	189 (1)	183 (7)	175 (5)	168 (7)	158 (7)	146 (4)	139 (10)	112 (2)	74
SoC + AAP	377 (3)	371 (9)	358 (16)	339 (17)	320 (12)	307 (24)	278 (9)	240 (12)	161

DOCP = docetaxel + prednisone.

Sydes MR, et al. Ann Oncol. 2018;29:1235-1248.

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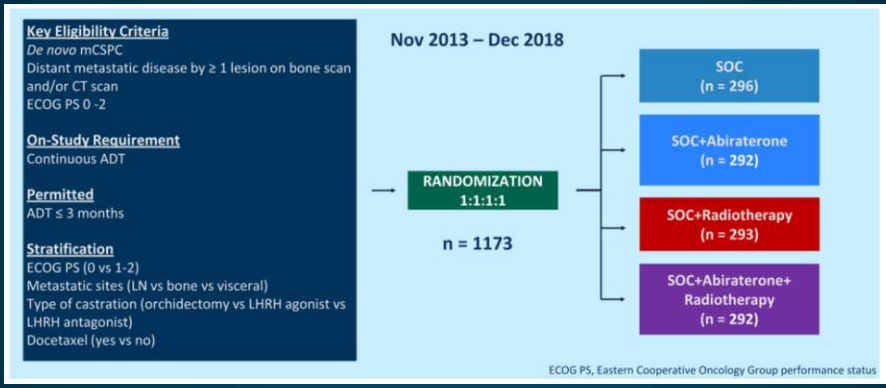
PEACE-1: Interim Results



- SOC: ADT + docetaxel after 2017, ADT +/- docetaxel before 2015
- Co-primary endpoints: rPFS and OS with 2x2 factorial design and hierarchical testing

Fizazi K, et al. ASCO 2021. Abstr 5000.

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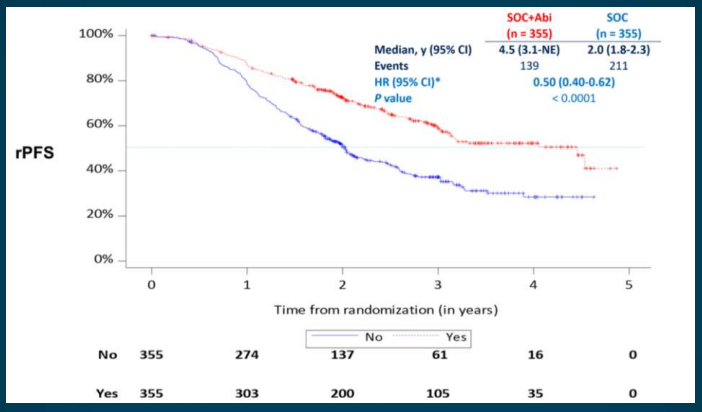
PEACE-1: Interim Results



- Median CRPC-free survival: 3.8 months with abiraterone vs 1.5 months with SOC
- No meaningful additional short-term toxicity observed

Fizazi K, et al. ASCO 2021. Abstr 5000.

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AR-Targeted Agents: Trial Design and Patient Population Overview

	ARCHES[1] (double-blind)	ENZAMET[2] (open-label)	TITAN[3] (double-blind)
Treatment	Enzalutamide + ADT (n = 574) vs PBO + ADT (n = 576)	Enzalutamide + ADT (n = 563) vs NSAA + ADT (n = 562)	Apalutamide + ADT (n = 525) vs PBO + ADT (n = 527)
Key Inclusion criteria			
Metastasis	Bone or soft tissue	Bone or soft tissue	≥1 bone lesion ± visceral/ lymph-node involvement
Prior ADT	Allowed	Allowed	Allowed
Prior docetaxel	Allowed (18%)	Not allowed	Allowed (11%)
Early concomitant docetaxel	Not allowed	Allowed (45%)	Not allowed
Duration of therapy*	median = 12.8 vs 11.6 mos	at 36 months, 62% vs 34%	median = 20.5 vs 18.3 mos

AR = androgen receptor; NSAA = nonsteroidal anti-androgen.
*first vs second treatment group listed.

1. Armstrong AJ, et al. *J Clin Oncol.* 2019;37:2974-2986. 2. Davis ID, et al. *N Engl J Med.* 2019;381:121-131.
3. Chi KN, et al *N Engl J Med.* 2019;381:13-24.

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TITAN: Apalutamide for mCSPC

Radiographic PFS

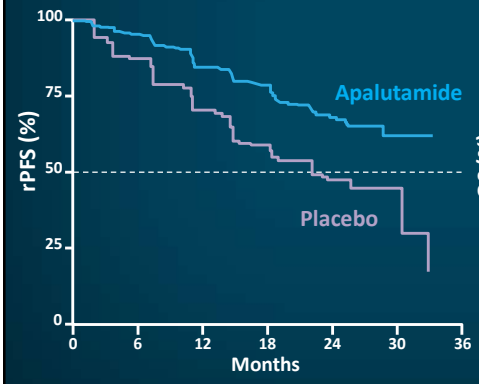
Arms	mPFS mos (95% CI)	2-yr PFS % (95% CI)
Apalutamide	NE	68.2 (62.9–72.9)
PBO	22.1 (18.5–32.9)	47.5 (42.1–52.8)

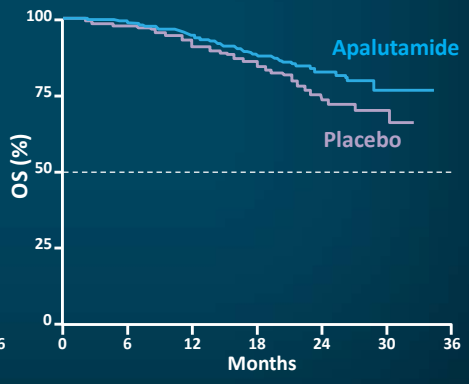
HR = 0.48 (95% CI, 0.39–0.60) *P*< .001

OS

Arms	mOS mos (95% CI)	2-yr PFS % (95% CI)
Apalutamide	NE	82.4 (78.4–85.8)
PBO	NE	73.5 (68.7–77.8)

HR = 0.67 (95% CI, 0.51–0.89) *P*= .005





NE = not estimated/estimable.

Chi KN, et al. *N Engl J Med.* 2019;381:13-24.

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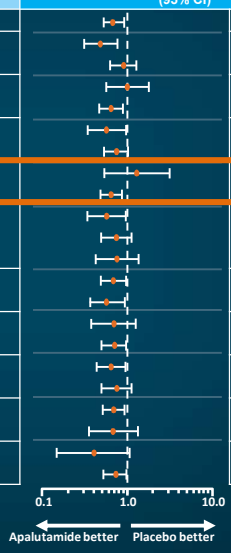
TITAN Subgroup Analyses: Overall Survival

Subgroup		Apalutamide No. of events/patients	PBO No. of events/patients	Apalutamide Median OS (mos)	PBO Median OS (mos)	HR for death (95% CI)
All patients		83/525	117/527	NE	NE	0.68 (0.51–0.90)
Bone metastasis only at baseline	Yes	28/289	53/269	NE	NE	0.47 (0.30–0.75)
	No	55/236	64/258	NE	NE	0.88 (0.61–1.26)
Visceral disease and bone metastasis at baseline	Yes	20/56	25/72	NE	26.6	0.99 (0.55–1.77)
	No	63/469	92/455	NE	NE	0.63 (0.46–0.87)
Gleason score at diagnosis	≤7	21/174	34/169	NE	NE	0.56 (0.33–0.97)
	>7	62/351	83/358	NE	NE	0.73 (0.52–1.01)
Previous docetaxel use	Yes	11/58	9/55	NE	NE	1.27 (0.52–3.09)
	No	72/467	108/472	NE	NE	0.63 (0.47–0.85)
Age	<65 yr	21/149	43/182	NE	NE	0.56 (0.33–0.94)
	65–74 yr	42/243	51/232	NE	NE	0.73 (0.48–1.10)
	≥75 yr	20/133	23/113	NE	NE	0.74 (0.41–1.35)
Baseline PSA above median	Yes	58/285	66/241	NE	NE	0.68 (0.48–0.97)
	No	25/240	51/286	NE	NE	0.56 (0.35–0.91)
Baseline LDH above ULN	Yes	18/60	25/60	NE	NE	0.68 (0.37–1.24)
	No	62/443	86/442	NE	NE	0.69 (0.49–0.95)
Baseline ALP above ULN	Yes	40/177	61/180	NE	NE	0.63 (0.42–0.93)
	No	43/346	56/345	NE	NE	0.73 (0.49–1.09)
Disease volume	High	69/325	97/335	NE	NE	0.68 (0.50–0.92)
	Low	14/200	20/192	NE	NE	0.67 (0.34–1.32)
Metastasis stage at initial diagnosis	M0	7/85	11/59	NE	NE	0.40 (0.15–1.03)
	M1	71/411	101/441	NE	NE	0.72 (0.53–0.98)



LDH = lactic acid dehydrogenase; ULN = upper limit of normal range; ALP = alkaline phosphatase.

Chi KN, et al. N Engl J Med. 2019;381:13-24.

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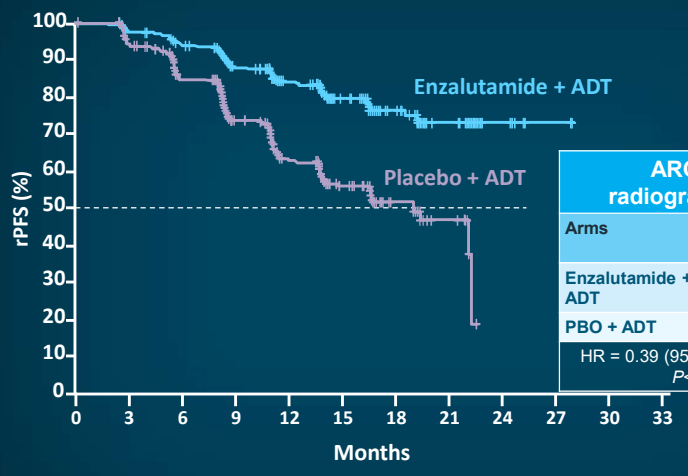
ARCHES: Enzalutamide for mCSPC



ARCHES: radiographic PFS	
Arms	mPFS, mos (95% CI)
Enzalutamide + ADT	NR (NR–NR)
PBO + ADT	19.0 (16.6–22.2)
HR = 0.39 (95% CI, 0.30–0.50), *P*< .001	

Overall survival: HR = 0.81 (95% CI, 0.53–1.25), *P*= .3361, but survival data were immature, with only 14.4 months median follow-up and 84 deaths

Armstrong AJ, et al. *J Clin Oncol*. 2019;37:2974-2986.

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ARCHES: Subgroup Analysis rPFS

Subgroup	No. patients (events)		HR (95% CI)
	Enza + ADT	PBO + ADT	
All patients	574 (91)	576 (201)	0.39 (0.30–0.50)
Age <65 years	148 (21)	152 (58)	0.29 (0.17–0.47)
Age ≥65 years	426 (70)	424 (143)	0.44 (0.33–0.58)
Geographic region—Europe	341 (55)	344 (122)	0.42 (0.31–0.58)
Gleason score at initial diagnosis <8	171 (21)	187 (47)	0.42 (0.25–0.70)
Gleason score at initial diagnosis ≥8	386 (65)	373 (151)	0.36 (0.27–0.48)
Disease localization at BL, bone only	268 (35)	245 (82)	0.33 (0.22–0.49)
Disease localization at BL, soft tissue only	51 (5)	45 (12)	0.42 (0.15–1.20)
Disease localization at BL, bone and soft tissue	217 (50)	241 (104)	0.42 (0.30–0.60)
BL PSA value at or below overall median	293 (41)	305 (96)	0.38 (0.26–0.54)
BL PSA value above overall median	279 (50)	269 (104)	0.41 (0.30–0.58)
Low volume of disease	220 (14)	203 (47)	0.25 (0.14–0.46)
High volume of disease	354 (77)	373 (154)	0.43 (0.33–0.57)
No prior docetaxel therapy	471 (70)	474 (166)	0.37 (0.28–0.49)
Prior docetaxel therapy	103 (21)	102 (35)	0.52 (0.30–0.89)
Previous use of ADT or orchiectomy	535 (88)	515 (179)	0.41 (0.32–0.53)
No previous use of ADT or orchiectomy	39 (3)	61 (22)	0.19 (0.06–0.62)

BL = baseline.

Armstrong AJ, et al. *J Clin Oncol*. 2019;37:2974-2986.

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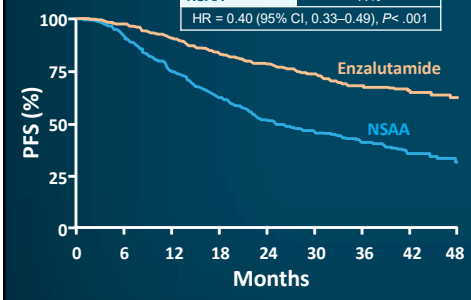
ENZAMET: Enzalutamide for mCSPC

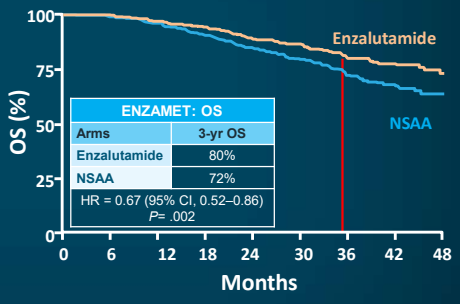
Varied inclusion criteria: high and low volume, de novo vs metachronous metastasis, concurrent docetaxel, many permutations

ENZAMET: clinical PFS	
Arms	3-yr PFS
Enzalutamide	68%
NSAA	41%
HR = 0.40 (95% CI, 0.33–0.49), *P*< .001	



OS (primary endpoint)

ENZAMET: OS	
Arms	3-yr OS
Enzalutamide	80%
NSAA	72%
HR = 0.67 (95% CI, 0.52–0.86) *P*= .002	



Davis ID, et al. *N Engl J Med*. 2019;381:121-131. Sweeney C, et al. *J Clin Oncol*. 2019;37(18 suppl): abstract LBA2.

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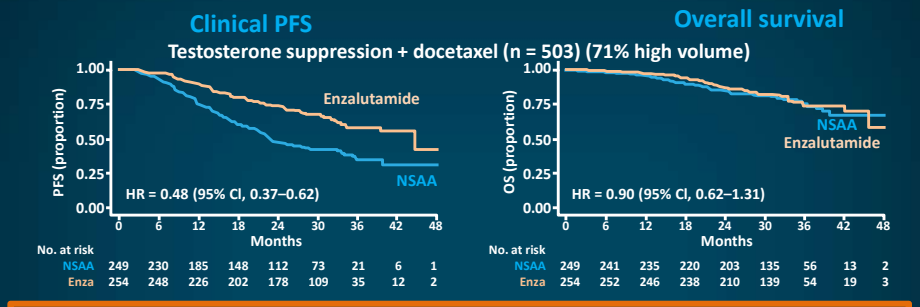
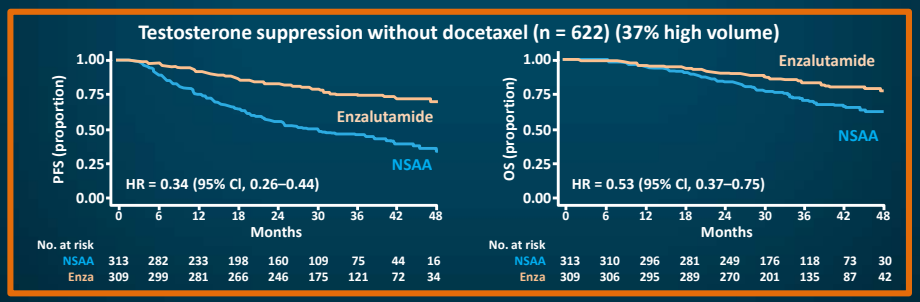
ENZAMET: Concurrent Docetaxel





Davis ID, et al. *N Engl J Med*. 2019;381:121-131. Sweeney C, et al. *J Clin Oncol.* 2019;37(18 suppl): abstract LBA2.

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Enzamet: Selected Docetaxel-Relevant Adverse Events

AE During First 6 Months	TS + NSAA + docetaxel n = 246	TS + ENZA + docetaxel n = 254	TS + NSAA, no docetaxel n = 312	TS + ENZA, no docetaxel n = 309
Neutropenic fever	32 (13%)	35 (14%)	0	1 (<1%)
Sensory neuropathy, grade 2	7 (3%)	24 (9%)	2 (<1%)	0
Sensory neuropathy, grade 3	1 (<1%)	3 (1%)	0	0
Motor neuropathy, grade 2	1 (<1%)	4 (2%)	0	0
Motor neuropathy, grade 3	0	0	0	1 (<1%)
Nail discoloration	13 (5%)	25 (10%)	0	0
Watery eyes, grade 1 or 2	15 (6%)	52 (20%)	0	0
Fatigue, grade 2	35 (14%)	52 (20%)	9 (3%)	32 (10%)

AE = adverse event; ENZA = enzalutamide; TS = testosterone suppression.

Sweeney C, et al. J Clin Oncol. 2019;37(18 suppl): abstract LBA2.

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Selected Side Effects to Consider

Agent	Route	Issues	Duration	Cost
Docetaxel	IV	Fatigue, cytopenias, diarrhea, neuropathy, hair loss	6 cycles	low
Enzalutamide	oral	Fatigue, HTN, cognitive affects	Until progression	high
Apalutamide	oral	Rash, hypothyroidism, HTN		
Darolutamide*	oral	Fatigue, HTN		
Abiraterone	oral	HTN, hypokalemia,		

How will cardio-oncology and neuro-oncology affect treatment selection and management considerations?

*Darolutamide only approved for nmCRPC.

IV = intravenous; HTN = hypertension; nmCRPC = nonmetastatic castration-resistant prostate cancer.

Shore N. ASCO 2020 educational symposium.

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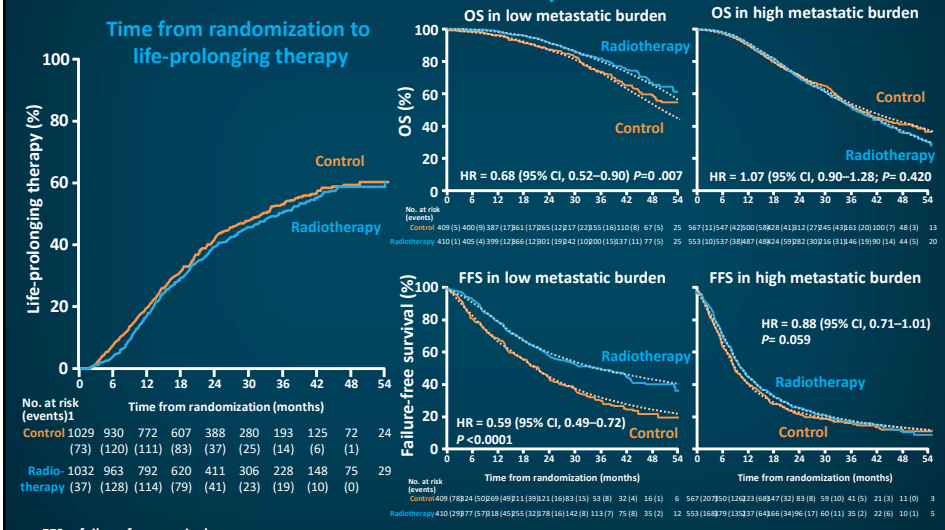
STAMPEDE: Potential Role for Primary Tumor Therapy in mCSPC

Phase 3 study



FFS = failure-free survival

Parker CC, et al. *Lancet*. 2018;392:2353-2366.

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Primary Directed Therapy in Low-Volume mCSPC?

Trial	Intervention
STAMPEDE-H[1]	Radiation to primary, **low volume**
SWOG 1802 (results pending)[2]	Radical prostatectomy

SWOG = Southwest Oncology Group.

1. Parker CC, et al. *Lancet*. 2018;392:2353-2366. 2. NCT03678025 (SWOG 1802) (https://clinicaltrials.gov/ct2/show/NCT03678025?term=SWOG+1802&cond=prostate+cancer&draw=2&rank=1). Accessed 5/17/2021.

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Ongoing Questions: Oligometastases

- Oligometastases: either 1–3 or 1–5 mets
- Different presentations: de novo or synchronous vs oligorecurrent or metachronous vs oligoprogressive
- Metastasis-directed therapy (MDT) of regional and distant recurrences after curative treatment of prostate cancer: a systematic review of the literature
  - 15 single-arm **case series**: a total of 450 patients
  - Conclusions: MDT is a promising approach for oligometastatic PC recurrence, **but the low level of evidence generated by small case series does not allow extrapolation to a standard of care**
- Issues to consider
  - How many lesions and where?
  - Has primary been treated?
  - Sensitivity and accuracy of imaging?
  - Therapy objectives: impact on OS vs delay ADT (STOMP, ORIOLE)
  - Prospective randomized phase 3 data still needed

Ost P, et al. *Eur Urol*. 2015;67:852-863. Radwan N, et al. *BMC Cancer*. 2017;17:453. Ost P, et al. *J Clin Oncol*. 2018;36:446-453.

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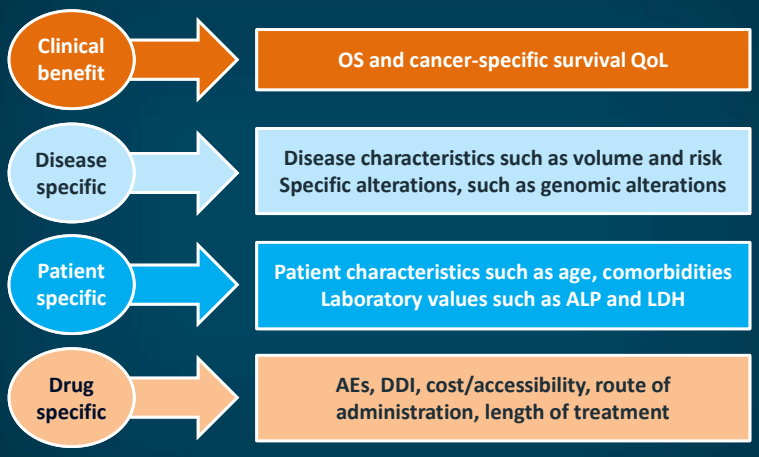
Decision-Making Factors in mCSPC



QoL = quality of life; DDI = drug-drug interaction.

Neal Shore, MD—based on personal experience. Modified from Cattrini C, et al. *Cancers* (Basel). 2019;11:1355.

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Treatment Considerations in mCSPC

- Volume of disease
  - Low-volume disease, chemotherapy less appropriate (Evidence for ARI and abiraterone)
  - High volume disease, chemotherapy appropriate (Docetaxel, ARI, or abiraterone)
- Clinical factors
  - Fitness for chemotherapy
  - Fitness for ARI – frailty, comorbidities
  - Fitness for abiraterone- blood sugar, cardiac history, liver disease
  - Prior therapy (ie, ARI in nmCRPC)
  - "Non-AR phenotype": poor PSA expressor, presence of hepatic metastases

VanderWeele DJ, et al. *J Clin Oncol*. 2019;37:2961. Neal Shore, MD—based on personal experience.

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Additional Treatment Considerations

- De novo versus recurrent disease at presentation
- Comorbidities
- Adverse effect profiles
- Patient preferences
- Duration of therapy
- Cost: financial/physical—patient-preference values
- Convenience
- COVID-19 concerns
- Availability of drugs
- Subsequent therapies

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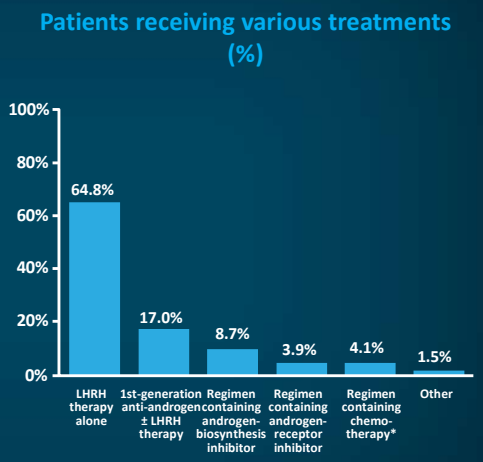
Real-World Treatment Patterns in mCSPC

- Most men with mCSPC are treated with LHRH therapy alone
- Physician-based syndicated patient record-tracking study in US capturing usage of anticancer and supportive-care agents in PC
  - Data collected online between June 2018 and June 2019
  - 156 physicians reporting on 1360 patients
- Patients with mCSPC identified with following query:
  - Prostate, stage IV, not hormone refractory, metastatic line 1 by regimen



*Excludes regimens containing androgen-biosynthesis inhibitor or androgen-receptor inhibitor

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mCSPC: How to Choose

Trial	Drug	Comparison
CHAARTED	docetaxel	ADT
STAMPEDE	abiraterone	ADT
LATITUDE	abiraterone	ADT
TITAN	apalutamide	ADT (± DOC 11%)
ENZAMET	enzalutamide	ADT (± DOC 45%)

- ADT + docetaxel or ARPI is superior to ADT alone (phase 3 trials)
  - Is docetaxel benefit in high-volume patients only?
  - ARPI benefit: high/low volume
- *Question: therapeutic choice?*
  - Tradeoffs
    - Toxicity
    - Therapy duration
    - Physical cost
    - Financial cost
- ***Is ADT alone still an option?***

Neal Shore, MD—based on personal experience.

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Sorting Through the Maze of Treatment Options mCSPC

Treatment	Trial, Publication Year	Population	Comparator	Phase; Study Size	Primary Endpoint	Treatment vs Control	Serious AEs
Abiraterone acetate with prednisone	LATITUDE 2017	mCSPC	ADT + PBO	3; 1199	OS	53.3 vs 36.5 mos, (HR = 0.66 [95% CI, 0.56–0.78], *P* <.0001)	Elevated AST Elevated ALT Hypokalemia HTN Cardiac disorder
	STAMPEDE 2017	mCSPC and locally advanced PC	ADT alone	3; 1917	OS	Est 83% vs 73% alive at 3 yrs (HR = 0.63 [95% CI, 0.52–0.76], *P* <.001)	
Enzalutamide	ENZAMET 2019	mCSPC	ADT+ nonsteroidal ART	3; 1125	OS	Est 80% vs 72% alive at 3 yrs (HR = 0.67 [95% CI, 0.52–0.86]; *P*= .002)	Fatigue Falls Seizures Ischemic heart disease
	ARCHES 2019	mCSPC, stratified by CHAARTED Criteria	ADT + PBO	3; 1150	rPFS or death	NR vs 19 mos (HR = 0.39 [95% CI, 0.3–0.5], *P* <.001)	
Apalutamide	TITAN 2019	mCSPC	ADT + PBO	3; 1052	rPFS or death	68.2% vs 47.5% at 24 mos (HR = 0.48 [95% CI 0.39–0.60], *P* <.001)	Fatigue HTN Rash Falls/fractures Hypothyroidism
					OS	82.4% vs 73.5% alive at 2 yrs (HR = 0.67 [95% CI, 0.51–0.89], *P*= .005)	
Docetaxel	CHAARTED 2015	mCSPC	ADT alone	3; 790	OS	57.6 vs 44 mos (HR = 0.61 [95% CI, 0.47–0.80], *P* <.001)	Neutropenia Hepatotoxicity Neuropathy Hypersensitivity Fatigue
	GETUG-AFU 15 2013	mCPSC	ADT alone	3; 192	OS	58.9 vs 54.2 mos (NS)	
	STAMPEDE 2017	mCSPC and locally advanced PCa	ADT alone	3, 1086	OS	49% vs 37% at 5 yrs (HR = 0.81 [95% CI, 0.69–0.95], *P*= .009)	

Est = estimated; yrs = years; NS = not significant.

Modified from Schulte B, et al. *Am Soc Clin Oncol Educ Book.* 2020;40:198-207.

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Shared Decision-Making

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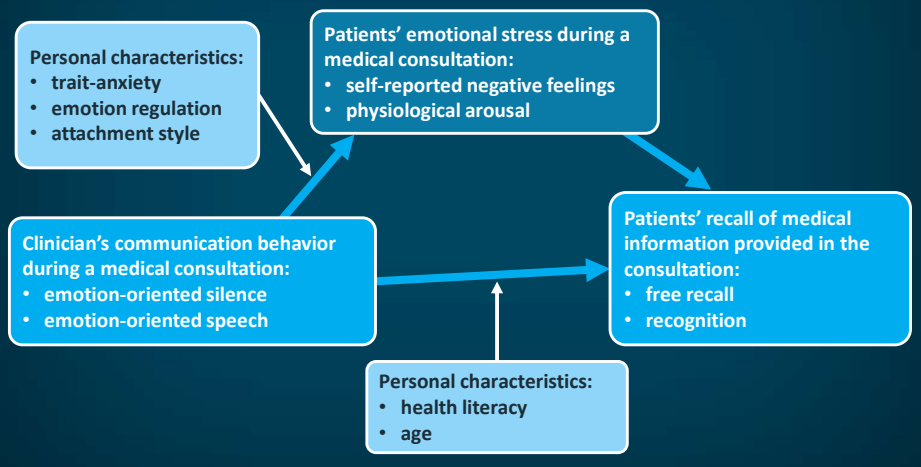
Barriers to Communication

It is suggested that patients remember only 20–60% of medical information provided by their healthcare provider



Mendendorp NM, et al. *Patient Educ Couns.*2017;100:1338-1344. Modified from Visser LNC, et al. *Patient Educ Couns.* 2019;102:43-52.

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Shared Decision-Making (SDM)

Shared decision-making involves the patient and healthcare provider working together to make a healthcare decision that is *best* for the patient, using:

- **Evidence-based information** about available options (including no intervention) and the associated risks and benefits
- The **provider's expertise** in communicating and tailoring evidence to the individual
- The **patient's *values, goals, concerns, expertise*** (of living with the condition) ***and preferences*** (including treatment burdens)

- Studies of SDM in practice have demonstrated better health outcomes, improved QoL, increased compliance with treatment regimens, and lower demand for healthcare resources

Agency for Healthcare Research and Quality (AHRQ). SHARE approach workshop curriculum (www.ahrq.gov/sites/default/files/wysiwyg/professionals/education/curriculum-tools/shareddecisionmaking/tools/tool-1/share-tool1.pdf). AHRQ. Strategy 6.I: shared decision-making (ahrq.gov/sites/default/files/wysiwyg/cahps/quality-improvement/improvement-guide/6-strategies-for-improving/communication/cahps-strategy-section-6-i.pdf). Both accessed 4/13/2020.

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5 Essential Steps of SDM: SHARE Approach

It's all about Communication!

AHRQ. SHARE approach (www.ahrq.gov/sites/default/files/publications/files/share-approach_factsheet.pdf). Assessed 4/14/2020.

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Conclusions

- Standard of care for mCSPC requires consideration of early addition of either docetaxel or ARPI (abiraterone acetate, apalutamide, enzalutamide) to ADT
- Triple therapy adds toxicity but does not appear to add an early survival benefit; data continue to mature
- ARPIs and docetaxel appear to have similar overall-survival benefits in patients with high-risk or high-volume disease
- AR-targeted agents have similar relative benefits for patients with high-risk disease and patients with low-risk or low-volume disease
- Ongoing RCTs are evaluating the efficacy and safety of combination treatments for mCSPC

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Thank You

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Managing Castration-Sensitive Prostate Cancer:
How Does Your Approach Compare with the Experts'?

Resource	Address
Lowrance WT, et al. Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline PART I. *J Urol*. 2021;205:14-21.	https://pubmed.ncbi.nlm.nih.gov/32960679/
Lowrance WT, et al. Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline PART II. *J Urol*. 2021;205:22-29.	https://pubmed.ncbi.nlm.nih.gov/32960678/
VanderWeele DJ, et al. Metastatic hormone-sensitive prostate cancer: clinical decision making in a rapidly evolving landscape of life-prolonging therapy. *J Clin Oncol.* 2019;37:2961-2967.	https://pubmed.ncbi.nlm.nih.gov/31498754/
Shore ND, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *N Engl J Med.* 2020;382:2187-2196.	https://pubmed.ncbi.nlm.nih.gov/32469183/
Sweeney CJ, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med.* 2015;373:737-746.	https://pubmed.ncbi.nlm.nih.gov/26244877/
Vale CL, et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. *Lancet Oncol.* 2016;17:243-256.	https://pubmed.ncbi.nlm.nih.gov/26718929/
Kyriakopoulos CE, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED Trial. *J Clin Oncol*. 2018;36:1080-1087.	https://pubmed.ncbi.nlm.nih.gov/29384722/
James ND, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*. 2016;387:1163-1177.	https://pubmed.ncbi.nlm.nih.gov/26719232/
Clarke NW, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. *Ann Oncol*. 2019;30:1992-2003.	https://pubmed.ncbi.nlm.nih.gov/31560068/
Fizazi K, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2017;377:352-360.	https://pubmed.ncbi.nlm.nih.gov/28578607/

Resource	Address
Fizazi K, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer. (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2019;20:686-700.	https://pubmed.ncbi.nlm.nih.gov/30987939/
Hoyle AP, et al. Abiraterone in "high-" and "low-risk" metastatic hormone-sensitive prostate cancer. *Eur Urol.* 2019;76:719-728.	https://pubmed.ncbi.nlm.nih.gov/31447077/
Sydes MR, et al. Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol. *Ann Oncol*. 2018;29:1235-1248.	https://pubmed.ncbi.nlm.nih.gov/29529169/
Armstrong AJ, et al. ARCHES: A randomized, phase iii study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol*. 2019;37:2974-2986.	https://pubmed.ncbi.nlm.nih.gov/31329516/
Davis ID, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med.* 2019;381:121-131.	https://pubmed.ncbi.nlm.nih.gov/31157964/
Chi KN, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med.* 2019;381:13-24.	https://pubmed.ncbi.nlm.nih.gov/31150574/
Parker CC, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet.* 2018;392:2353-2366.	https://pubmed.ncbi.nlm.nih.gov/30355464/
Ost P, et al. Metastasis-directed therapy of regional and distant recurrences after curative treatment of prostate cancer: a systematic review of the literature. *Eur Urol*. 2015;67:852-863.	https://pubmed.ncbi.nlm.nih.gov/25240974/
Radwan N, et al. A phase II randomized trial of Observation versus stereotactic ablative RadiatIon for OLigometastatic prostate CancEr (ORIOLE). *BMC Cancer.* 2017;17:453.	https://pubmed.ncbi.nlm.nih.gov/28662647/
Ost P, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. *J Clin Oncol.* 2018;36:446-453.	https://pubmed.ncbi.nlm.nih.gov/29240541/