Thank you for joining us.
The program will commence momentarily.

Meet The Professors

Nurse and Physician Investigators Discuss Existing and Emerging Treatment Strategies for Patients with Prostate Cancer

Tuesday, July 28, 2020

5:00 PM – 6:00 PM ET

Faculty

Robert Dreicer, MD, MS

Victoria Sinibaldi, RN, MS, CS, CANP, BC

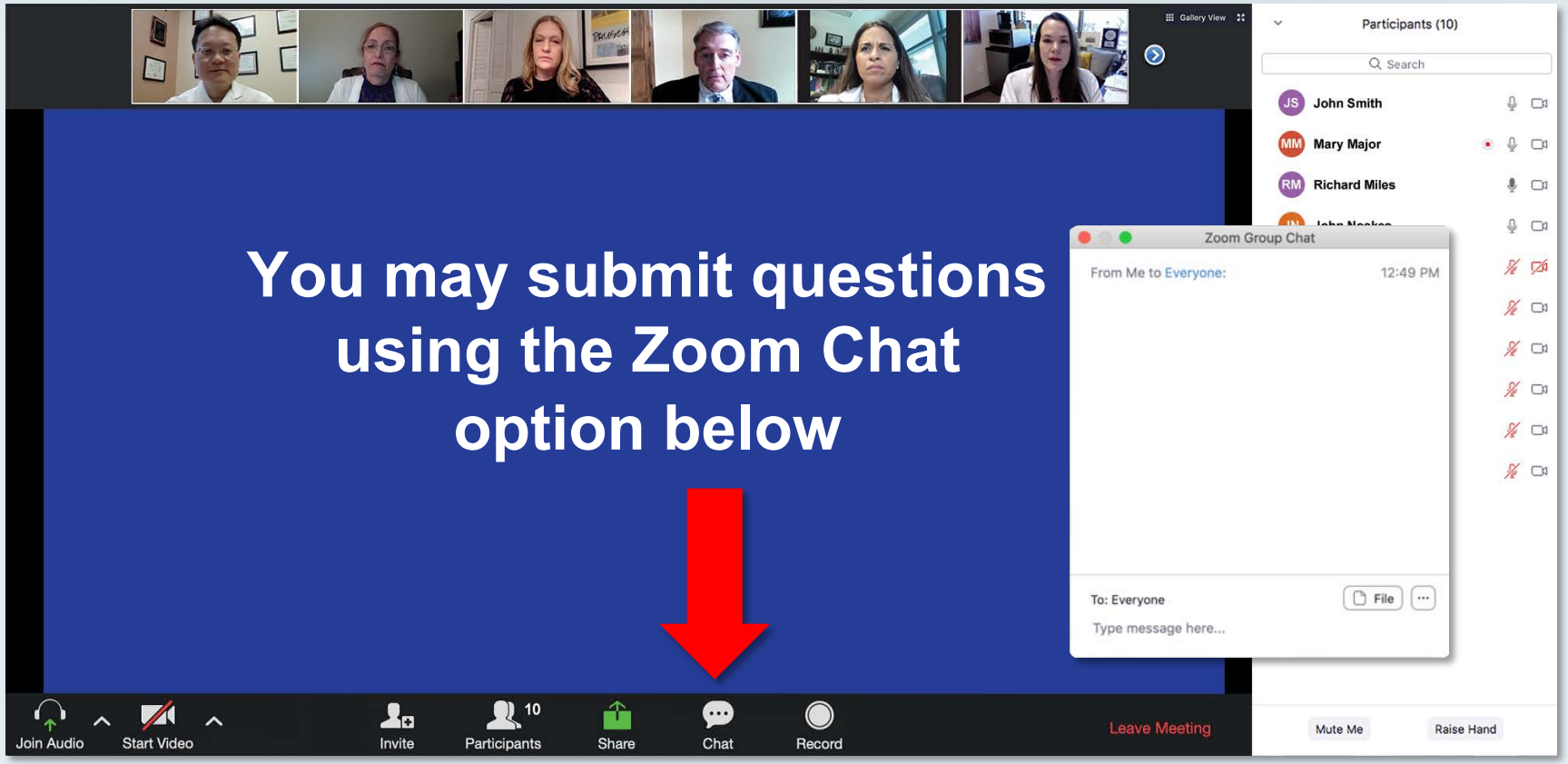
Moderator

Neil Love, MD

Jointly provided by USF Health

RTP RESEARCH TO PRACTICE

Dr Love and Faculty Encourage You to Ask Questions



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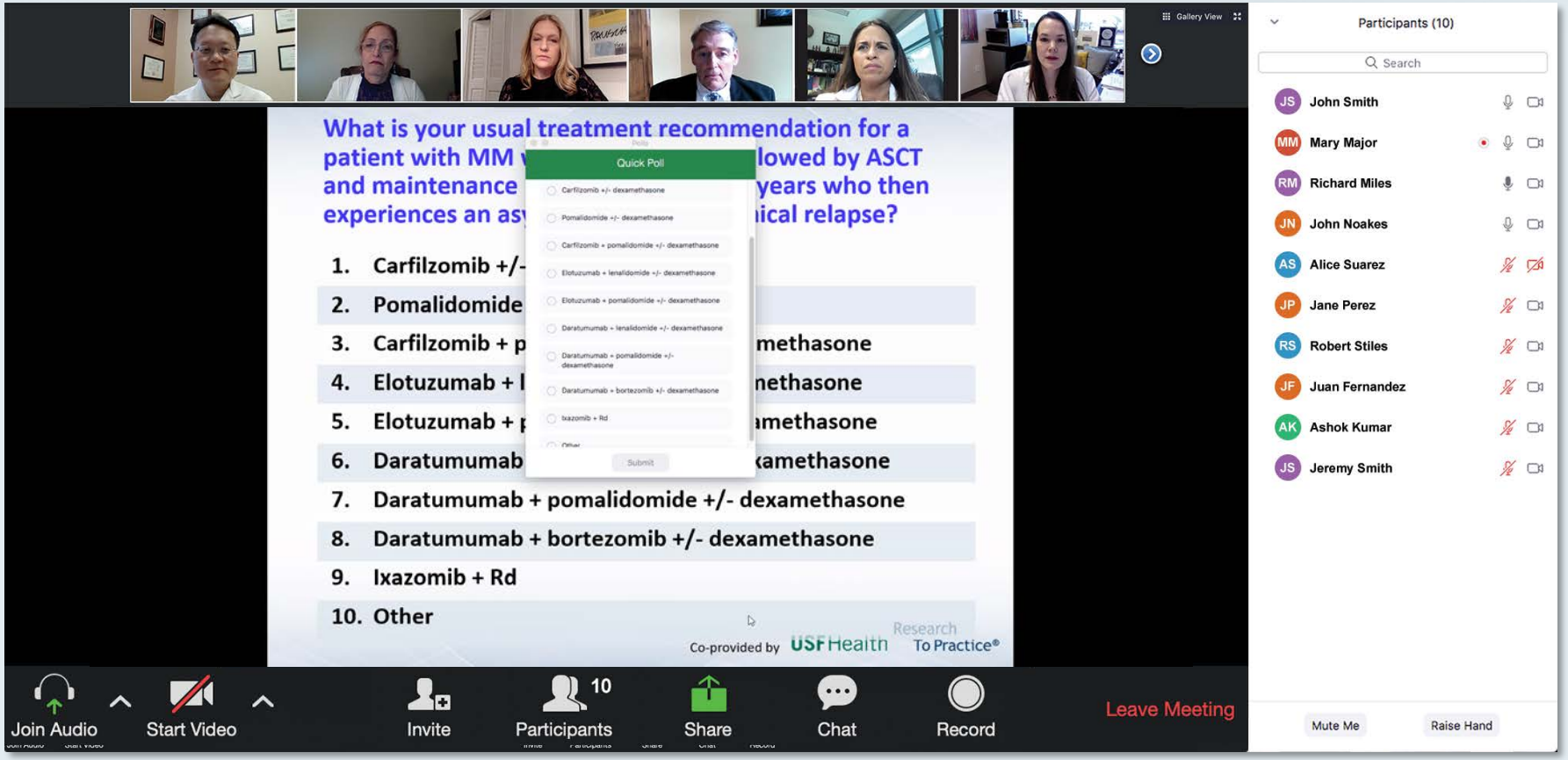
Familiarizing yourself with the Zoom interface
How to answer poll questions



When a poll question pops up, click your answer choice from the available options. Results will be shown after everyone has answered.

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Non-Faculty Disclosures

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Dr Dreicer — Disclosures

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Contracted Research	Bristol-Myers Squibb Company, Exelexis Inc, Pfizer Inc, Seattle Genetics

Ms Sinibaldi — Disclosures

No financial interests or affiliations to disclose.

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Nurse and Physician Investigators Discuss Existing and Emerging Treatment Strategies for Patients with Bladder Cancer

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Peter H O'Donnell, MD

Moderator

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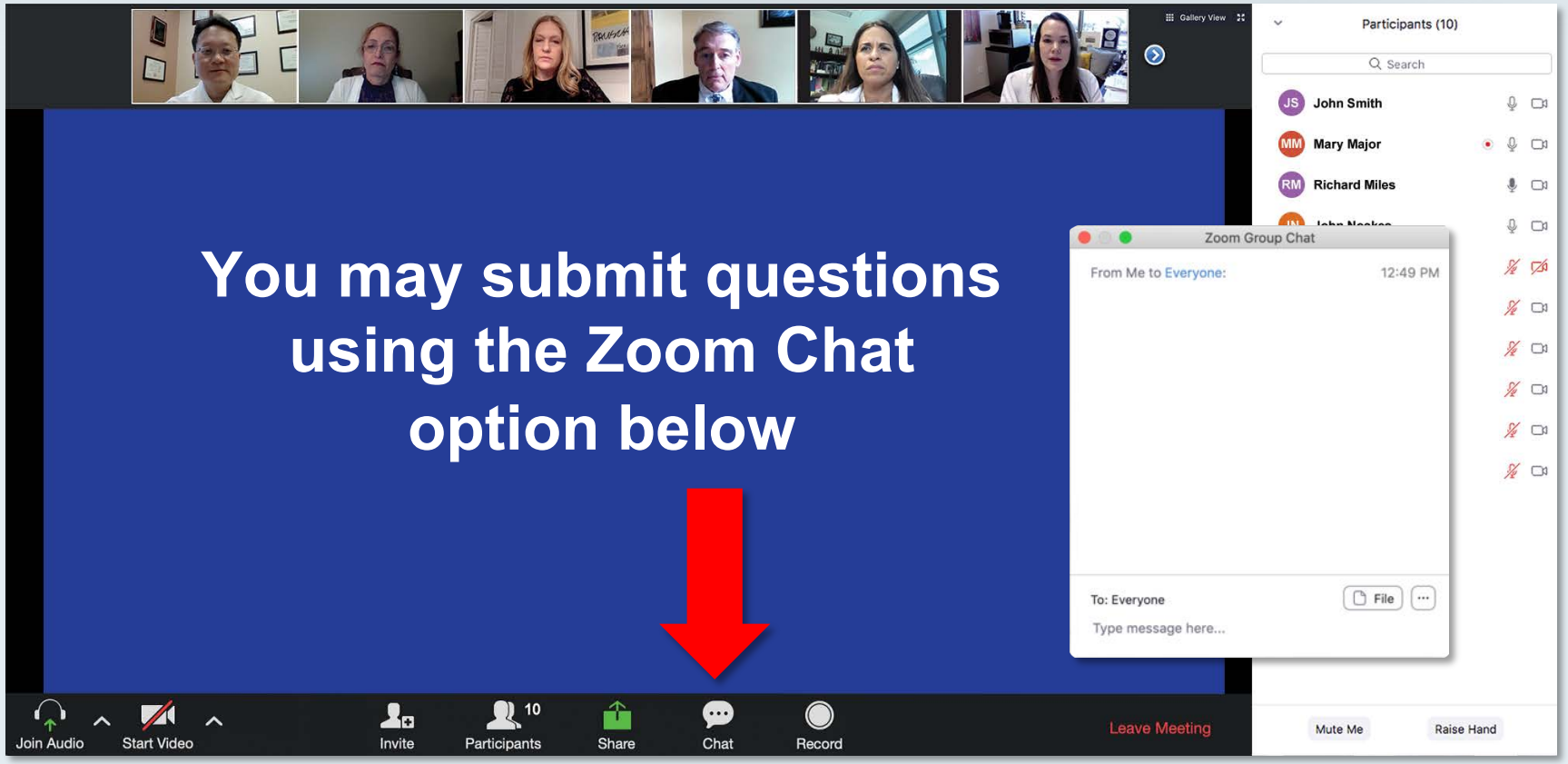

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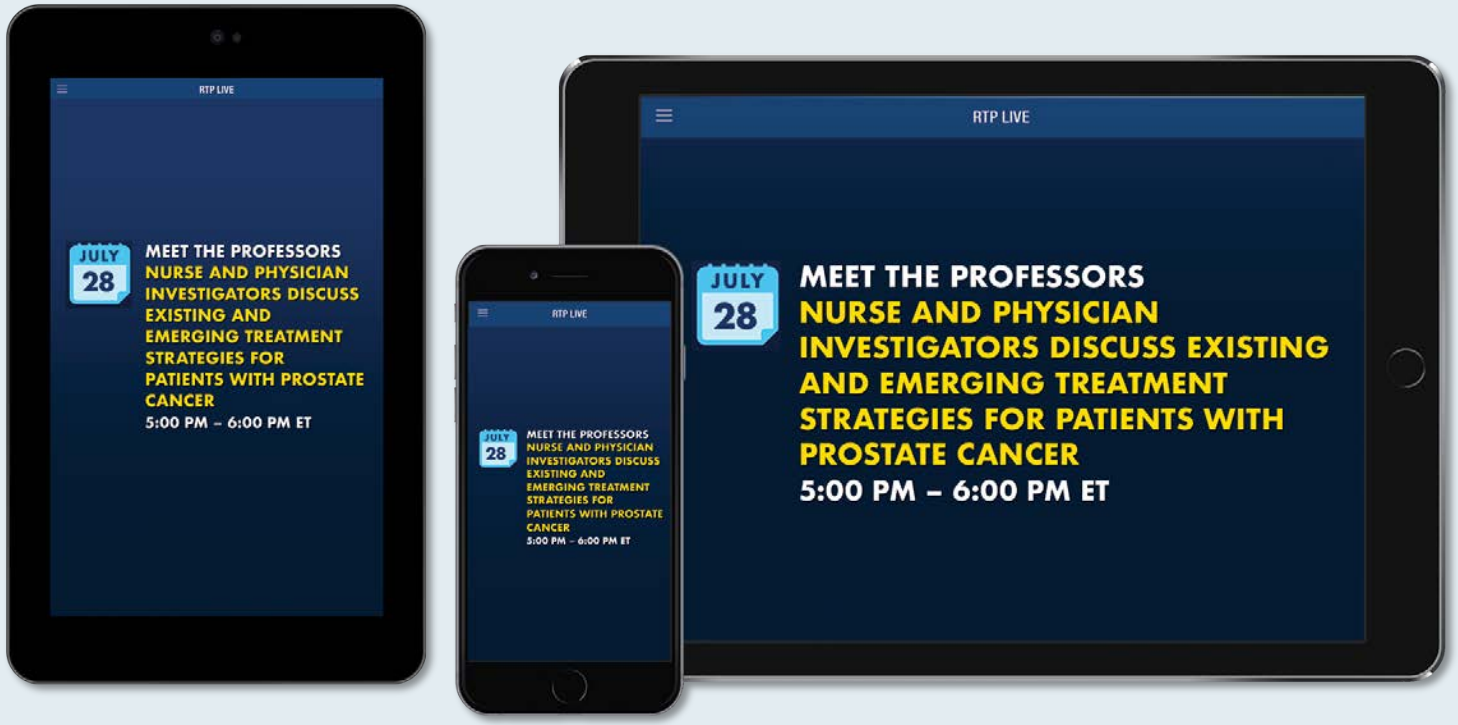

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RTP RESEARCH TO PRACTICE

Agenda

Key Decisions in Prostate Cancer and Where New Agents and Strategies Fit In

Case 1: A 60-year-old man with M0 prostate cancer (PC)

- Indications to treat
- Mechanism of action/risks and benefits of ADT
- Mechanisms of action/risks and benefits of adding a novel antiandrogen

Case 2: An 80-year-old man with hormone-sensitive metastatic PC

- Recurrent versus de novo disease; high versus low risk
- Risks and benefits of adding docetaxel, a novel antiandrogen or abiraterone

Case 3: A 73-year-old man with castration-resistant metastatic PC

- Secondary hormonal treatment versus chemotherapy (cabazitaxel)
- Mechanisms of action/risks and benefits of sipuleucel-T and radium-223
- Genetic testing and use of PARP inhibitors
- Other promising novel agents (eg, lutetium-177 PSMA radionuclide therapy)

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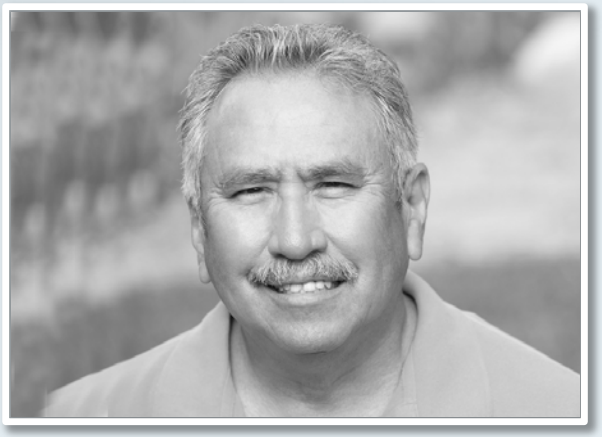
Case Presentation: A 60-year-old man with M0 prostate cancer

Special Considerations



- Recently divorced and desirous of companionship and sexual activity
- Sedentary and overweight with Type 2 diabetes on oral agents
- 2016: Radical prostatectomy for primary Gleason 7 (4 + 3) prostate cancer
- 2017: Salvage radiation therapy to pelvis; PSA undetectable; 9 months later PSA is detected

Decision 1: Treat or observe?

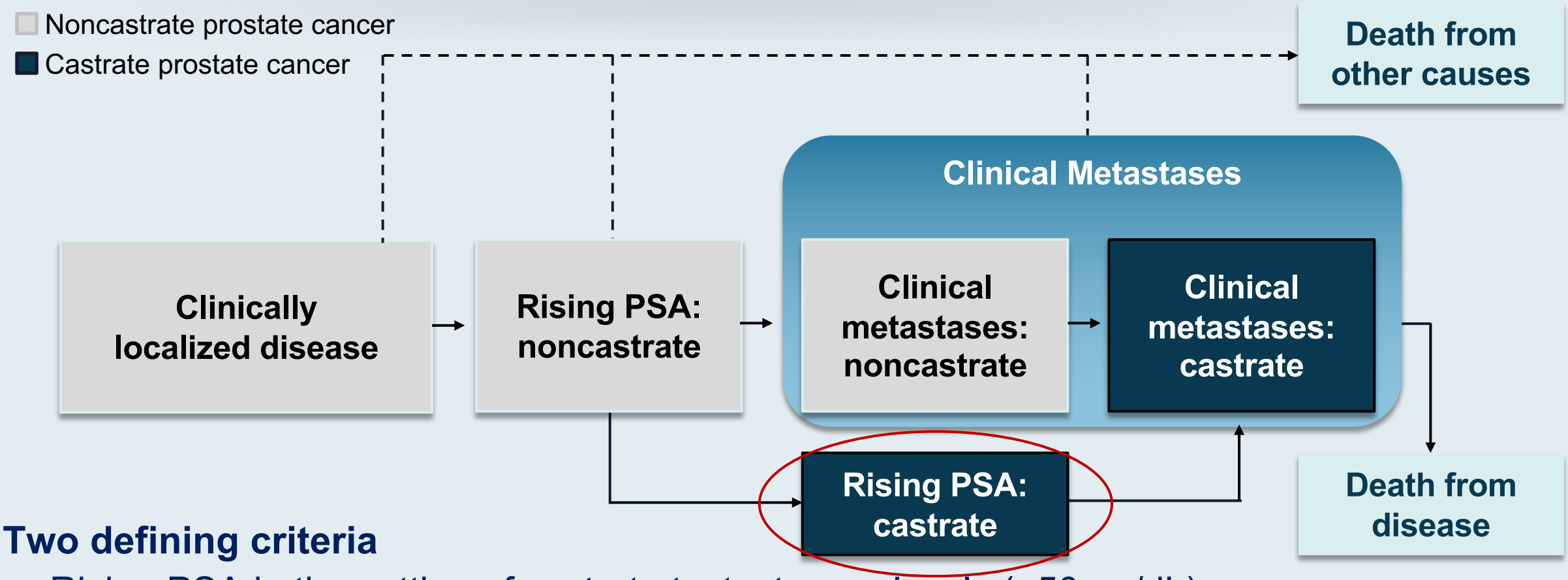
- ADT administered and PSA becomes undetectable
- 2020: PSA progression; negative workup

Decision 2: Add novel antiandrogen?

Men with M0 (PSA-only) prostate cancer (PC)…

a. Have presumed disease that is not detected clinically
b. Generally die of prostate cancer
c. Both a and b
d. Neither a nor b
e. I don’t know

Clinical Disease States Model of Prostate Cancer[1]



Two defining criteria

- Rising PSA in the setting of castrate testosterone levels (<50 ng/dL)
- No radiographically identifiable metastasis

1. Adapted from Scher HI et al. *J Clin Oncol.* 2008;26:1148-1159.

Courtesy of Matthew R Smith, MD, PhD

Definition of nmCRPC

- Patients with rising PSA despite ongoing ADT and no detectable metastases by conventional imaging (bone scan and CT or MRI)
- Most patients with nmCRPC are presumed to have occult metastatic disease not detected by conventional imaging

Courtesy of Matthew R Smith, MD, PhD

Context

- Men with nmCRPC are at significant risk for metastatic disease and prostate cancer–specific death[1]
- Metastases are a major cause of morbidity and mortality[2,3]
- Prevention of metastases represents an important unmet medical need

1. Smith MR et al. *J Clin Oncol*. 2013;31:3800-3806. 2. Scher HI et al. *PLoS One*. 2015;10;e0139440. 3. Gartrell BA et al. *Nat Rev Clin Oncol*. 2014;11:335-345.

Courtesy of Matthew R Smith, MD, PhD

Balancing the benefits/risks of treatment

- Improved survival
- Delayed progression
- Psychological benefits of receiving treatment

Benefits

Shared decision making: goals of patient

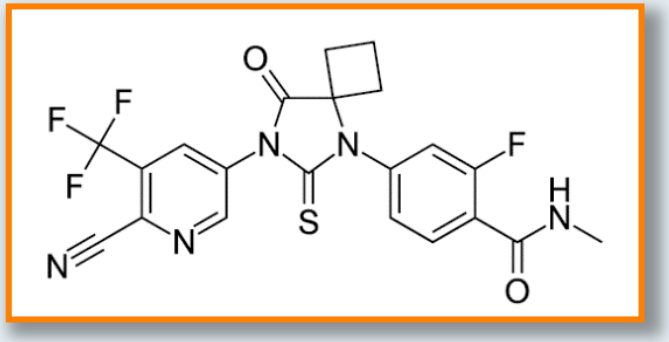
- Expense: COST $$$$... ↓ QOL
- ED and ↓ libido
- Hot flashes
- Changes in mood/ ↓cognition
- ↓ strength/ muscle mass
- Osteoporosis
- Anemia, fatigue
- Metabolic syndrome
- Cardiac risk, DM

Risks

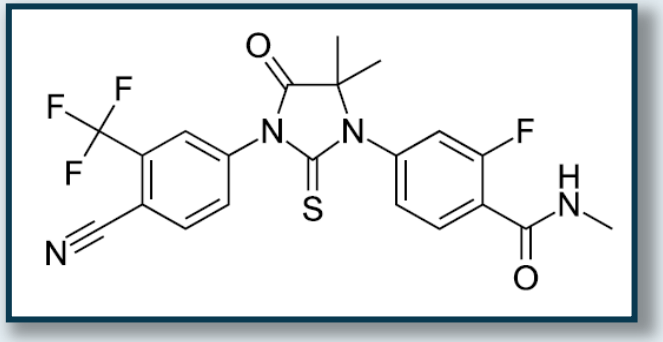
Courtesy of Victoria Sinibaldi, RN, MS, CS, CANP, BC

Next-Generation Androgen Receptor Inhibitors[1,2]

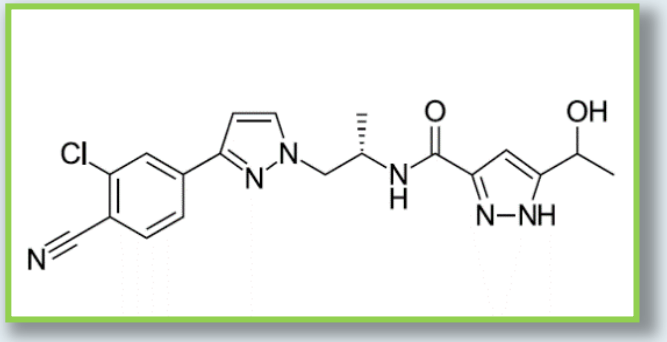
Apalutamide



Enzalutamide



Darolutamide



- Apalutamide and enzalutamide have similar structures
- Darolutamide is structurally distinct from apalutamide and enzalutamide, characterized by low blood–brain barrier penetration[1,2,] and may have improved tolerability

1. Zurth C et al. *J Clin Oncol*. 2018;36(Suppl 6):Abstract 345.
2. Sandmann S et al. American Society of Clinical Oncology 2019 Genitourinary Cancers Symposium (ASCO GU 2019). Abstract 156.

Courtesy of Matthew R Smith, MD, PhD

Oral Anti Androgens Approved For M0 Prostate Cancer – How do you choose?

- Enzalutamide
  - Cautious with patients with a history of falls and seizure
- Apalutamide
  - Risk of rash
- Darolutamide
  - Mild fatigue

*For all patients monitor CBC/diff, comprehensive metabolic panel and PSA.

Courtesy of Kara M Olivier, NP, APRN-BC

Nursing implications: oral agents

- Nurses need to be aware that there needs to be a shift in management from provider to patient
- Nurses need to become familiar with the oral agents and develop educational strategies to ensure patient understanding of medication, dosing and administration, potential side effects, symptom management, self care measures, proactive follow-up.
- Stress the import' of need to keep scheduled visits and contact the health care provider when side effects develop. If side effects are not reported, necessary adjustments will not be made and serious consequences can occur and have impact on their life and further therapy.

Courtesy of Victoria Sinibaldi, RN, MS, CS, CANP, BC

Nursing implications: oral agents (cont.')

- Nurses need to be aware of factors that affect patient compliance and reporting
- Patients are often reluctant to notify the provider because they fear that their therapy may be interrupted or dose lowered
  - Most side effects resolve with brief interruption of therapy
  - Any necessary dose reduction is simply to customize a dose that the individual needs
  - A dose reduction does not necessarily decrease the efficacy of the treatment
- Communication, education, organization, and trusting relationship are key!!

Courtesy of Victoria Sinibaldi, RN, MS, CS, CANP, BC

FDA Approval of Apalutamide[1]

Apalutamide approved on 2/14/2018

First drug approved by the FDA for nmCRPC

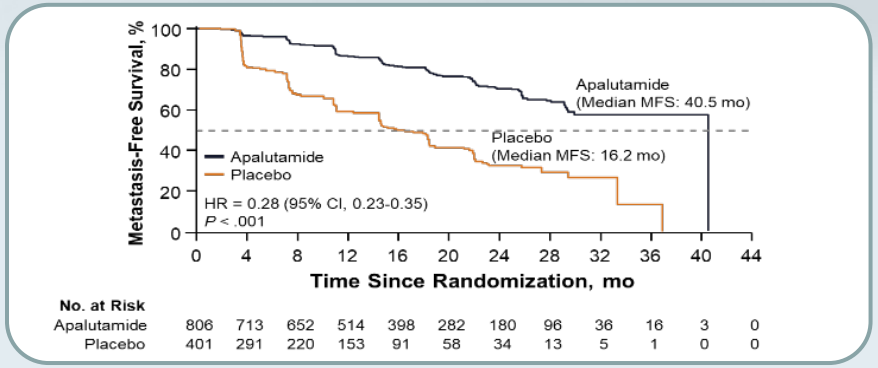
First approval based on metastasis-free survival

1. Beaver JA et al. *N Engl J Med*. 2018;378:2458-2460.

Courtesy of Matthew R Smith, MD, PhD

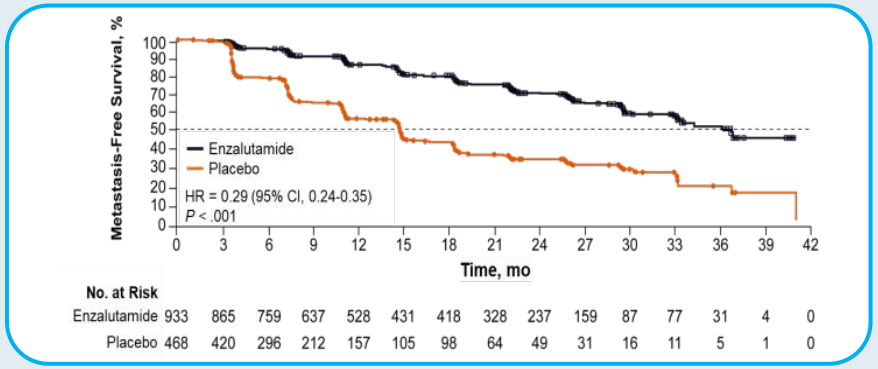
Primary Endpoint: Metastasis-Free Survival

SPARTAN[1]
Apalutamide



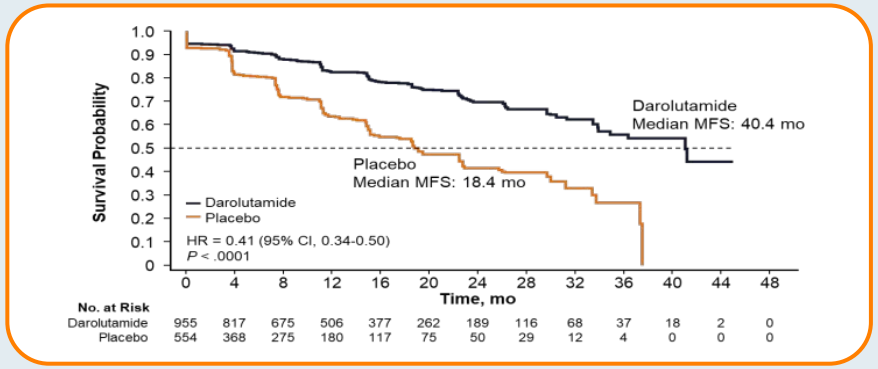
- 72% reduction of distant progression or death
- Median MFS: APA 40.5 vs PBO 16.2 months
- 24-month MFS benefit

PROSPER[2]
Enzalutamide



- 71% reduction of distant progression or death
- Median MFS: ENZA 36.6 vs PBO 14.7 months
- 22-month MFS benefit

ARAMIS[3]
Darolutamide



- 59% reduction of distant progression or death
- Median MFS: DARO 40.4 vs PBO 18.4 months
- 22-month MFS benefit

Courtesy of Matthew R Smith, MD, PhD

1. Smith MR et al. *N Engl J Med*. 2018;378:1408-1418. 2. Hussain M et al. *N Engl J Med*. 2018;378:2465-2474. 3. Fizazi K et al. *N Engl J Med*. 2019;380:1235-1246.

There is no clear difference among the 3 antiandrogens with FDA approval for the treatment of M0 PC in terms of the risk of falls and other CNS effects.

a. Agree
b. Disagree
c. I don’t know

Adverse Events of Interest

Safety[a]	SPARTAN[1]		PROSPER[2]		ARAMIS[3]	
	APA (n = 803)	PBO (n = 398)	ENZA (n = 930)	PBO (n = 465)	DARO (n = 954)	PBO (n = 554)
Any AEs, n (%)	775 (96.5)	371 (93.2)	808 (87)	360 (77)	794 (83.2)	426 (76.9)
Any serious AEs, n (%)	199 (24.8)	92 (23.1)	226 (24)	85 (18)	237 (24.8)	111 (20.0)
AEs leading to discontinuation, %	11.0	7.0	9.0	6.0	8.9	8.7
AEs leading to death, n (%)	10 (1.2)	1 (0.3)	32 (3.4)	3 (0.7)	37 (3.9)	18 (3.2)
AEs (all grades), %						
Fatigue	30.4	21.1	33.0	14.0	12.1	8.7
Hypertension	24.8	19.8	12.0	5.0	6.6	5.2
Rash	23.8	5.5	0	0	2.9	0.9
Falls	15.6	9.0	11.0	4.0	4.2	4.7
Fractures	11.7	6.5	N/A	N/A	4.2	3.6
Mental impairment disorders	5.1	3.0	5.0	2.0	0.4	0.2

[a] AE reporting every 4 weeks in SPARTAN and every 16 weeks in PROSPER and ARAMIS.

Courtesy of Matthew R Smith, MD, PhD

1. Smith MR et al. *N Engl J Med*. 2018;378:1408-1418. 2. Hussain M et al. *N Engl J Med*. 2018;378:2465-2474. 3. Fizazi K et al. *N Engl J Med*. 2019;380:1235-1246.

How does the risk of infection with and related complications of COVID-19 for men with PC who are receiving androgen deprivation therapy compare to the risk for patients with PC not receiving treatment?

a. Greater
b. Decreased
c. The same
d. I don’t know

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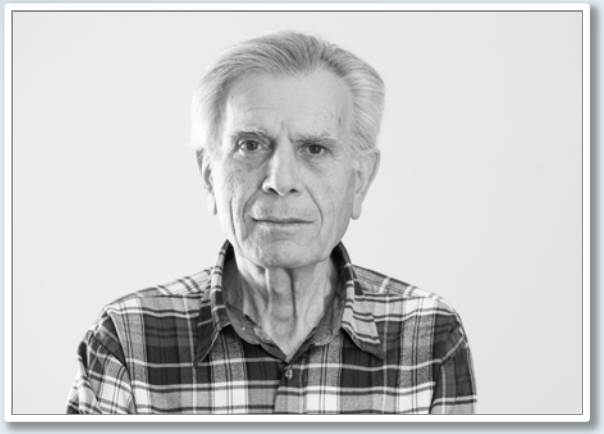
- Other promising novel agents (eg, lutetium-177 PSMA radionuclide therapy)

Case Presentation: An 80-year-old man with hormone-sensitive metastatic prostate cancer

Special Considerations

- Close with family, including 4 grandchildren
- Concerned about risk of COVID-19; also anxious his cancer care might be compromised by pandemic
- Never underwent PSA or rectal exam
- Presents with back pain and is found to have multiple bone metastases, high PSA and an enlarged prostate (biopsy: Gleason 6 [3 + 3] prostate cancer)



Decision 1: Add docetaxel, a novel antiandrogen or abiraterone to ADT?

Selected FDA Approved Drugs in Advanced Prostate Cancer

- Docetaxel: cytotoxic/taxane (fatigue, diarrhea, peripheral neuropathy, muscle cramps)
- Cabazitaxel: cytotoxic/taxane (fatigue, myelosupression)
- Abiraterone: lyase inhibitor (dramatically inhibits testosterone production) LFT abnormalities, hypertension
- Enzalutamide: androgen receptor antagonist (fatigue, cognitive issues)
- Apalutamide: androgen receptor antagonist (fatigue, cognitive issues)

Courtesy of Robert Dreicer, MD, MS

Clinical Decision-Making Hormone-Sensitive Metastatic Disease

- Patient factors
  - Performance status
  - Co-morbidities, i.e. pre-existing peripheral neuropathy
  - I hate taking pills doc etc.
- Disease factors
  - Extent of disease, volume of disease, presence/absence of visceral i.e. liver metastases
  - Non AR biology, i.e. poor psa expresser, significant neuroendocrine features
- Economic factors
  - Non viable co-pay or oral agents

Courtesy of Robert Dreicer, MD, MS

Choosing Oral Antiandrogen

- Age
- Comorbidities
  - Diabetes
  - History of seizure
  - Falls
  - Performance status
  - Concomitant medications

Courtesy of Kara M Olivier, NP, APRN-BC

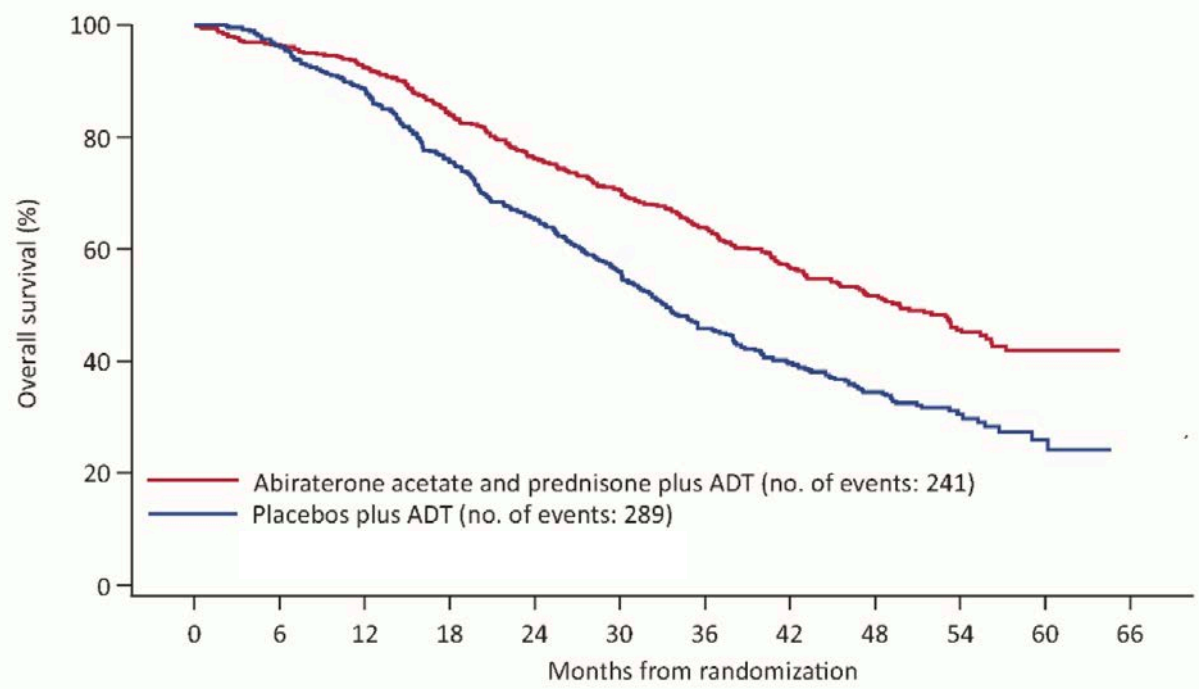
Monitoring

- Evaluation two weeks after initiating treatment with physical exam and safety laboratory monitoring
  - CBC/differential, comprehensive metabolic panel
- Based on tolerability can move to monthly follow up with serial labs and PSA
- Restaging scans within six months of initiating treatment

Courtesy of Kara M Olivier, NP, APRN-BC

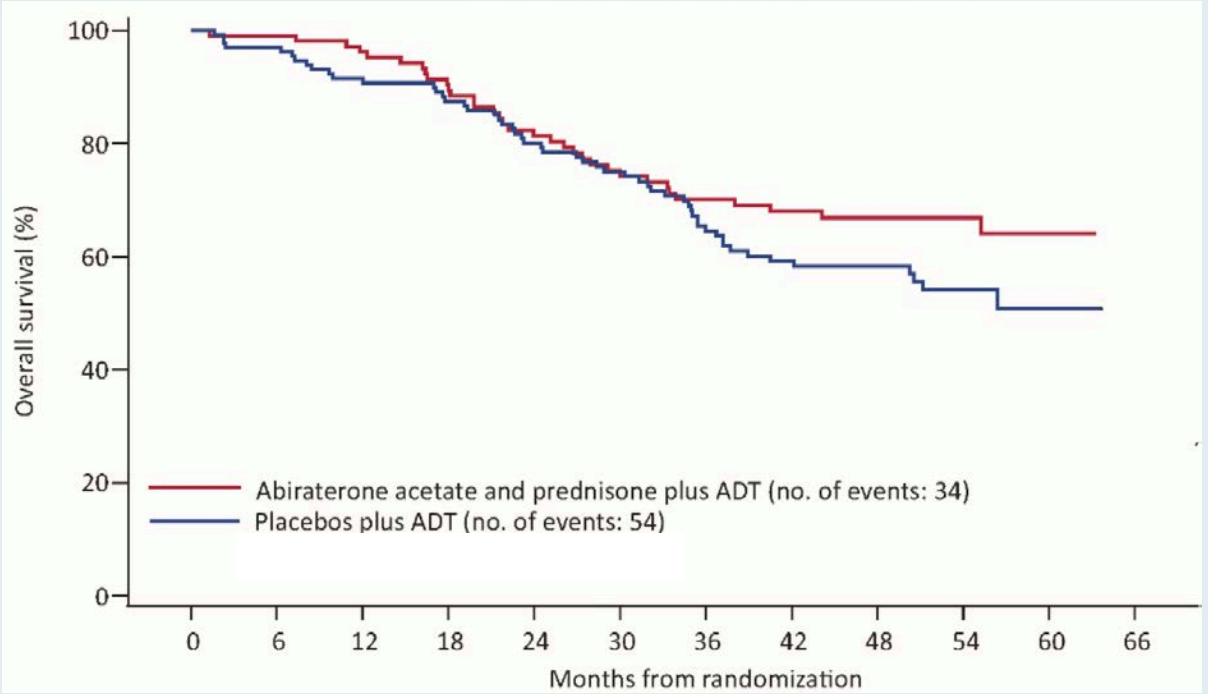
LATITUDE Final Overall Survival Analysis By Volume of Disease (CHAARTED definition*)

High-Volume Disease



	ADT + AA + P (n = 487)	ADT + Placebo (n = 468)	HR	*P*-value
mOS	49.7 mo	33.3 mo	0.62	<0.0001

Low-Volume Disease



	ADT + AA + P (n = 110)	ADT + Placebo (n = 133)	HR	*P*-value
mOS	Not reached	Not reached	0.72	0.1242

*CHAARTED definition of low vs high volume: Presence of visceral mets and/or ≥ 4 bone mets, with one outside the vertebral column or pelvis

Fizazi K et al. Lancet Oncol 2019;20:686-700. *Chi et al 2019 GU Cancers Symposium;* Abstract 141.

Summary Results for ADT + Enzalutamide (ARCHES) and Apalutamide (TITAN) in Metastatic HSPC

	ARCHES (N = 1150)		TITAN (N = 1052)	
Characteristics	• 2/3rd High Volume • 17% prior docetaxel • 25% prior RP/XRT		• 2/3rd High Volume; • 10% prior docetaxel • 17% prior RP/XRT	
	ADT + Enzalutamide (n = 574)	**ADT (n = 576)**	**ADT + Apalutamide (n = 525)**	**ADT (n = 527)**
Radiographic PFS	NR	19.0 mo	NR	22.1 mo
	HR (overall): 0.39 • HR (prior docetaxel): 0.52 • HR (high volume): 0.43 • HR (low volume): 0.25		**HR (overall): 0.48** • HR (prior docetaxel): 0.47 • HR (high volume): 0.53 • HR (low volume): 0.36	
Overall Survival	NR	NR	NR	NR
	HR: 0.81 (Immature)		**HR (overall): 0.67** • HR (prior docetaxel): 1.27 • HR (high volume): 0.68 • HR (low volume): 0.67	

NR, not reached

Armstrong AJ et al. *J Clin Oncol* 2019;[Epub ahead of print]. Chi KN et al. *N Engl J Med* 2019;381(1):13-24.

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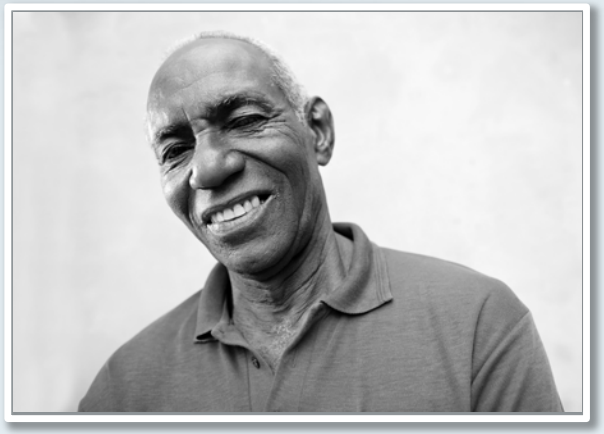
What is the usual next treatment for a man with symptomatic metastatic PC who has previously responded to and progressed on both docetaxel and enzalutamide?

a. Abiraterone
b. Cabazitaxel
c. Sipuleucel-T
d. I don’t know

Case Presentation: A 73-year-old man with castration-resistant metastatic prostate cancer

Special Considerations



- Interested in alternative, complimentary strategies, particularly supplements and diet, but is open to other approaches and is open to complementary strategies
- Lives alone and has no family; struggles with anxiety/depression about his disease and how he will manage in the future
- Compromised financial situation
- Previous history
  - Radical prostatectomy
  - PSA recurrence: Radiation therapy
  - Further progression: ADT plus docetaxel
  - Further progression: Moderate pain from widespread bone metastases

Case Presentation: A 73-year-old man with castration-resistant metastatic prostate cancer (cont)

Decision 1: Choice of systemic treatment

- Responded to enzalutamide but progressed after 9 months

Decision 2: Abiraterone versus chemotherapy

- Cabazitaxel administered with response followed by disease progression
- NGS reveals somatic BRCA mutation

Decision 3: Radium-223 versus olaparib

Metastatic Castration-Resistant Prostate Cancer (mCRPC)

- Defined: evidence of metastatic disease, with “castrate levels” of testosterone (< 50 ng/dL) with evidence of progression on imaging studies and/or rising PSA

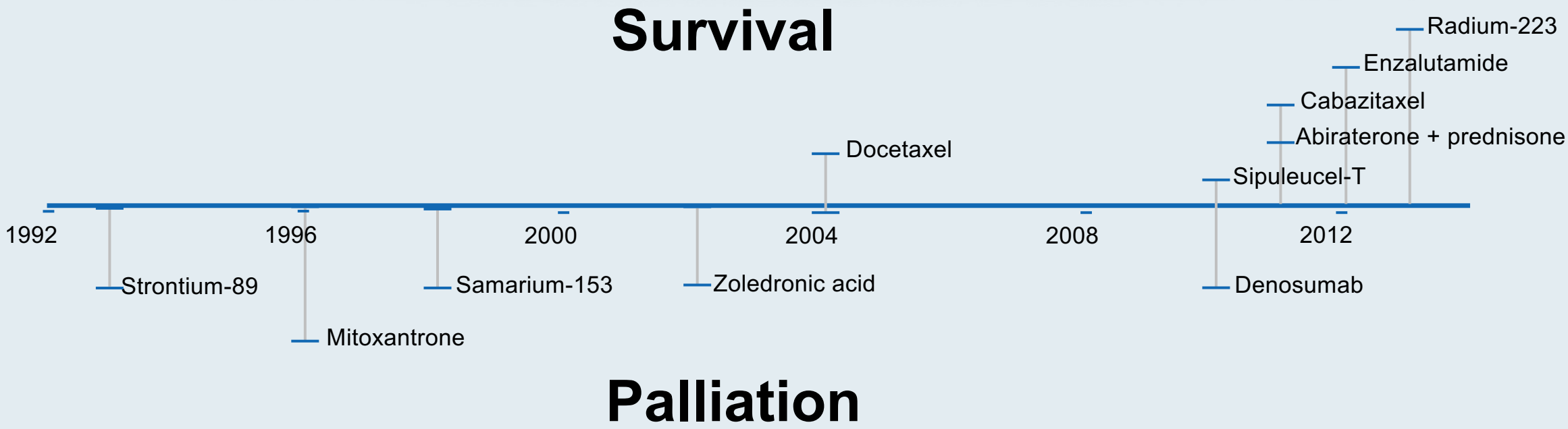
Courtesy of Robert Dreicer, MD, MS

Therapeutic Decision Making in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

- mCRPC space increasingly impacted by movement of primarily AR directed therapies early in the treatment course
  - Known resistance pathways of AR resistance limits utility of crossover of current agents
- Clinical factors
  - Symptoms yes/no
  - Biochemical or overt radiographic progression
  - Prior therapies
  - Durability of initial ADT response

Courtesy of Robert Dreicer, MD, MS

Timeline of FDA Approvals in Metastatic Castration-Resistant Prostate Cancer



Metastatic disease was defined by conventional imaging (eg, bone scan, CT scans)

Courtesy of Matthew R Smith, MD, PhD

Selected FDA Approved Drugs in Advanced Prostate Cancer

- Sipuleucel-T
  - Autologous cellular immunotherapy designed to stimulate a patient's own immune system against prostate cancer, MOA unknown
  - Minimal toxicity, apharesis required
- Radium-223
  - Radiopharmaceutical, alpha particle
  - GI toxicity, typically mild, important to remind patients re: lack of PSA activity
  - Administered by nuclear medicine or radiation oncology physicians
  - Important to monitor patients monthly as NO activity against non bone metastastic sites

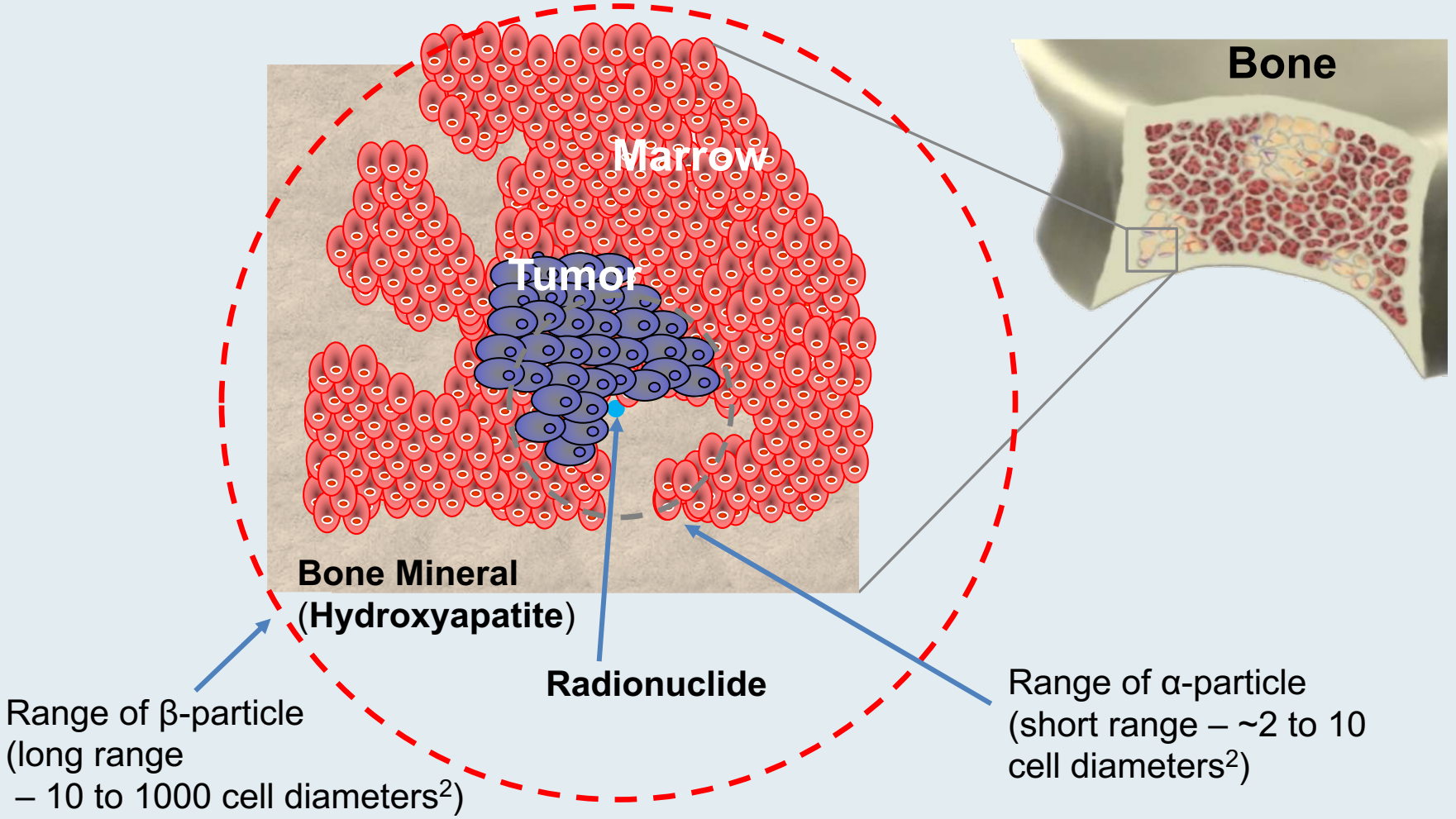
Courtesy of Robert Dreicer, MD, MS

Radium-223 has been demonstrated to…

a. Relieve pain from bone metastases
b. Extend survival
c. Both a and b
d. Neither a nor b
e. I don’t know

Range of an α-emitting Radiopharmaceutical Compared to a β-emitter

Short range of α-particles could reduce bone marrow exposure[1]



References: 1. Henriksen G, et al. *Cancer Res*. 2002;62:3120–3125. **2.** Brechbiel MW. *Dalton Trans*. 2007;43:4918-4928.

Nursing implications: Radium-223

- Rad-223 is safe and effective and targets tumor cells in the bone.
- Rad-223 -form of liquid radiation, administered IV, given every 4 weeks x6.
- Explain characteristics of RAD-223- has a short range that does limit damage to healthy cells.
- Data using this modality have shown improvement in QOL with improvement in pain, improved OS (by 3.6 months), delay in SSEs.
- Patients often focus on PSA. Point out that a decline in PSA is not an expected result of Rad-223; Patient benefits have been observed in the absence of a decreasing PSA.

Courtesy of Victoria Sinibaldi, RN, MS, CS, CANP, BC

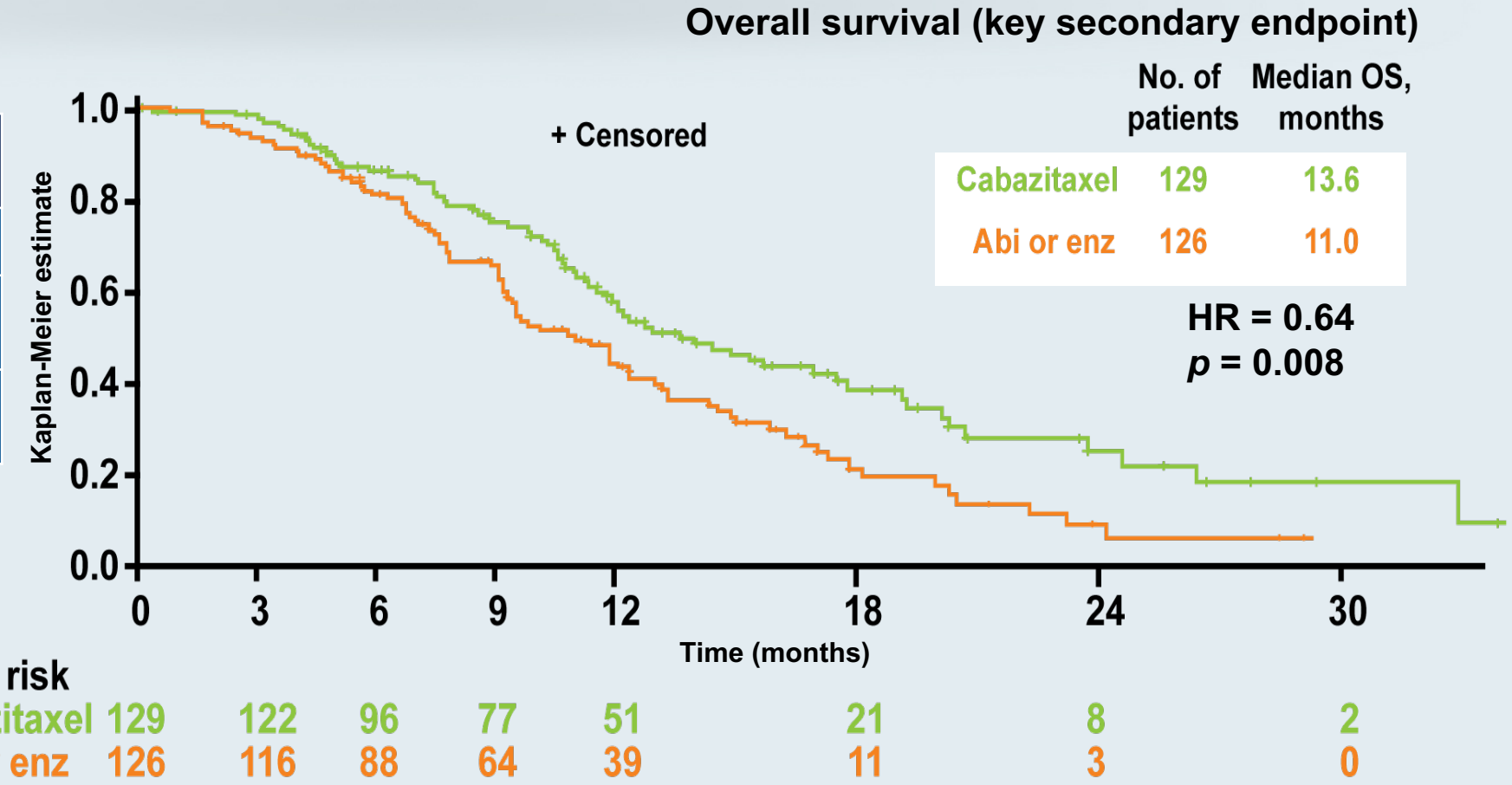
Nursing implications: Radium-223

- Fatigue
- GI: Nausea, Vomiting, Diarrhea
- Peripheral edema
- Pancytopenia: Anemia, Lymphopenia, leukopenia, thrombocytopenia, neutropenia
- Black tarry stools
- CP, Chills, Cough
- Erythema at the injection site

Courtesy of Victoria Sinibaldi, RN, MS, CS, CANP, BC

CARD: Cabazitaxel vs Abiraterone or Enzalutamide in mCRPC Previously Treated with Docetaxel and an Androgen-Signaling-Targeted Inhibitor

Summary of AEs	Cabazitaxel	Abi or Enza
Grade ≥3 AE	56.3%	52.4%
AE leading to Tx discontinuation	19.8%	8.9%
AE leading to death	5.6%	11.3%



- CARD met its primary objective: Cabazitaxel more than doubled rPFS versus abiraterone or enzalutamide

de Wit R et al; CARD Investigators. *N Engl J Med* 2019;381(26):2506-18.

Nursing Implications: Cabazitaxel chemotherapy

- Impt.' to know the results of the CARD trial: Improved benefit of use of cabazitaxel over abiraterone or enzalutamide as SOC in patients who had prior docetaxel within 12 months: improved pFS and overall survival
- Patient improvement: Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
- Dosing and administration: 20 mg/m^2 IV Q 21 days (7-10 cycles or until DLT or PD) with prednisone 10 mg by mouth
- Close monitoring for S/E imperative: **fatigue**, hypersensitivity reactions, nausea/vomiting, renal failure, **neutropenia w/wo fever**, **diarrhea**, **constipation,** hypotension, neuropathy, **hematuria**/cystitis, belching, heartburn, back pain.

Courtesy of Victoria Sinibaldi, RN, MS, CS, CANP, BC

Novel Agents for mCRPC

- Poly(ADP-ribose) polymerase (PARP) inhibitors
  - Directed at targeting cancers with defective DNA-damage repair
  - Prostate cancer, most common defects in BRCA 1, BRCA 2 and ATM genes
  - Side effects include progressive anemia, fatigue, GI side effects indigestion, nausea/vomiting, diarrhea, headaches
- PSMA (prostate specific membrane antigen) targeted therapies
  - In combination with a number of molecules: Lutetium, radioactive iodine, T cell targeting combinations

FDA approves olaparib for HRR gene-mutated metastatic castration-resistant prostate cancer

Press Release – May 19, 2020

On May 19, 2020, the Food and Drug Administration approved olaparib for adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC), who have progressed following prior treatment with enzalutamide or abiraterone.

Efficacy was investigated in PROfound (NCT02987543), an open-label, multicenter trial randomizing (2:1) 256 patients to olaparib 300 mg twice daily and 131 patients to investigator's choice of enzalutamide or abiraterone acetate. All patients received a GnRH analog or had prior bilateral orchiectomy. Patients were divided into two cohorts based on their HRR gene mutation status. Patients with mutations in either *BRCA1*, *BRCA2*, or *ATM* were randomized in Cohort A (N=245); patients with mutations among 12 other genes involved in the HRR pathway were randomized in Cohort B (N=142); those with co-mutations (Cohort A gene and a Cohort B gene) were assigned to Cohort A.

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer

FDA grants accelerated approval to rucaparib for BRCA-mutated metastatic castration-resistant prostate cancer

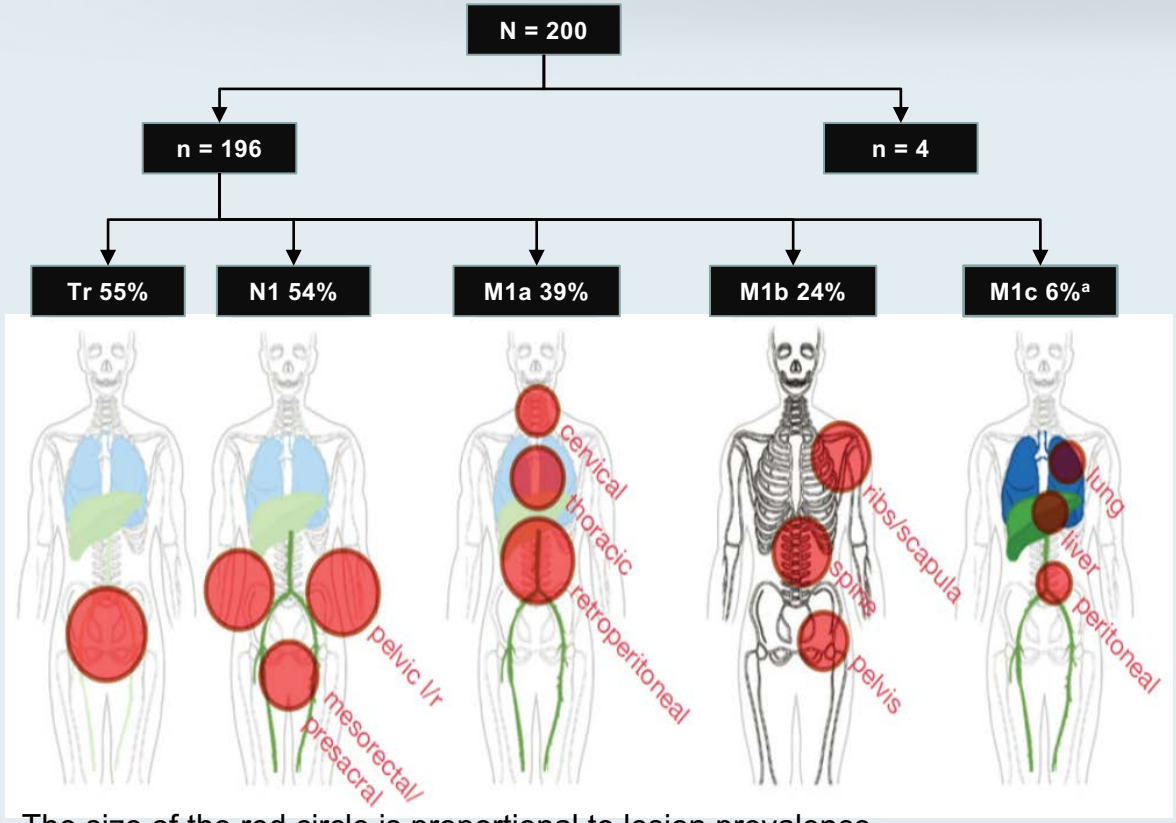
Press Release – May 15, 2020

The Food and Drug Administration granted accelerated approval to rucaparib for patients with deleterious *BRCA* mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.

Efficacy was investigated in TRITON2 (NCT02952534), an ongoing, multi-center, single arm clinical trial in 115 patients with *BRCA*-mutated (germline and/or somatic) mCRPC who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy. Patients received rucaparib 600 mg orally twice daily and concomitant GnRH analog or had prior bilateral orchiectomy.

https://www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate

PSMA-PET Results in Patients With High-Risk nmCRPC (nmCRPC, Negative Conventional Imaging, PSADT <10 mo)[1]



The size of the red circle is proportional to lesion prevalence.

PSMA-PET was positive in 196 of 200 (98%) patients; 55% of patients had any distant metastatic disease

Category Based on miTNM Stage, n (%)	All patients (N = 200)
M0	**91 (46)**
T0N0M0 (no PC lesion)	4 (2)
TrN0M0	48 (24)
T0N1M0	13 (7)
TrN1M0	26 (13)
Any M1	**109 (55)**
T0N0M1	31 (16)
T0N1M1	42 (21)
TrN0M1	9 (5)
TrN1M1	27 (14)
N/M disease extent	
Unifocal (1 lesion)	29 (15)
Oligometastatic (2-3 lesions)	28 (14)
Multiple/disseminated (≥ 4 lesions)	91 (46)

[a] Lung (n = 4), liver (n = 5), peritoneum (n = 4), connective tissue (n = 1).

1. Fendler WP et al. *Clin Cancer Res*. 2019;25:7448-7454.

Courtesy of Matthew R Smith, MD, PhD

Meet The Professors

Nurse and Physician Investigators Discuss Existing and Emerging Treatment Strategies for Patients with Bladder Cancer

Thursday, July 30, 2020

5:00 PM – 6:00 PM ET

Faculty

Anastassia Daskalova, NP
Peter H O'Donnell, MD

Moderator

Neil Love, MD

Jointly provided by USF Health

RTP RESEARCH TO PRACTICE

Thank you for joining us!

CNE (NCPD) credit information will be emailed to each participant tomorrow morning.