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A Review of Prostate Cancer & Recent Updates in the Treatment of Metastatic Prostate Cancer

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OBJECTIVES

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1. Explain the background of prostate cancer
2. Outline the elements of a prostate cancer diagnosis
3. Discuss the recent updates in metastatic castration-resistant prostate cancer treatment
4. Describe the adverse effect profile of the medications recently approved for metastatic castration-resistant prostate cancer

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DISCLOSURE

No relevant financial relationships from the past 24 months have been identified for the following faculty and planners of this CE activity:

- Diana Cauley, PharmD, BCOP
- Makenna Smack, PharmD, BCOP
- Tahsin Imam, PharmD
- Daisy Doan, PharmD

Off-label agents may be discussed during this presentation.

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Background – Incidence & Risk Factors

- Incidence 2024
  - Estimated new cases: 299,010
  - About one in eight men will be diagnosed during their lifetime
- Deaths 2024
  - Estimated cases: 35,250
    - About 1 in 44 men
  - Second-leading cause of cancer death in American men

STD= sexually transmitted disease

- **Known risk factors**
  - Age (average age ~67)
  - Ethnicity
    - African American men & Caribbean men of African ancestry
  - Geography
  - Germline mutations
    - BRCA1/2, CHEK2, ATM, PALB2, HOXB13, DNA mismatch repair genes-Lynch syndrome
  - Family history
    - If 1st degree relative, twofold increased risk
- **Less clear risk factors**
  - Chemical exposure, prostate inflammation,
  - STD, vasectomy, diet, obesity, smoking

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Background - Prostate-Specific Antigen (PSA)

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- Made by cells in the prostate gland
  - Protein made by normal and cancerous cells
    - Normal, age-dependent levels (<1 to <4 ng/mL)
    - About 15% of men with level < 4 will have prostate cancer on biopsy
  - Works as an enzyme to lyse ejaculate, enhancing sperm motility
- Interpreting elevated blood PSA levels
  - 4 - 10 ng/mL: "borderline range": men have about a 25% chance of having prostate cancer
  - > 10 ng/mL: men have a greater than 50% chance of having prostate cancer
  - Percent-free PSA (%fPSA)
    - Ratio of freely circulating PSA compared to total PSA level
    - A lower result indicates a higher risk of having cancer (≤10 %)
  - PSA velocity, how fast PSA rises over time

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American Cancer Society, Early Detection, Diagnosis, and Staging: Screening Tests for Prostate Cancer. Revised 11/22/23. www.cancer.org

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Background - PSA

Factors that may raise PSA levels	Medications that may lower PSA levels
Older age	5-alpha reductase inhibitors (e.g. finasteride, dutasteride)
Benign prostatic hyperplasia (BPH)	Herbal supplements, herbal mixtures
Prostatitis (infection or inflammation)	
Ejaculation	
Urologic procedures (biopsy, cystoscopy)	
Medications that raise testosterone	

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American Cancer Society. Early Detection, Diagnosis, and Staging: Screening Tests for Prostate Cancer. Revised 11/22/23. www.cancer.org

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Background-Screening & Chemoprevention

- Screening: testing to find disease when patients have no symptoms
  - Randomized trials have not established the value of PSA screening
  - Multiple national organizations differ in their recommendations
  - Decision to screen - discussion based on family history, race, life expectancy
  - May require personalized strategies
  - Controversial
- **Chemoprevention**: no medications are recommended
- SELECT trial (selenium, vitamin E)
  - No reduction in risk with either agent; vitamin E increased risk in healthy men
- PCPT and REDUCE trials (5α-reductase inhibitors)
  - May decrease incidence by as much as 25%
  - Increased incidence of higher-grade tumors

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Andriole GL et al. J Natl Cancer Inst 2012;104:125-132. Hugosson J et al. Lancet Oncol 2010;11:725-732. Maintrana MR et al. J Adv Pract Oncol 2013;4(1):16-21. Schroder FH et al. N Engl J Med 2009;360:1320-1328. Andriole GL et al. N Engl J Med 2010;362:1192-1202. Klein E et al. JAMA 2011;306(14):1549-1556. Lippman SM et al. JAMA 2009;301(1):39-51.

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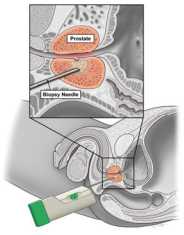
Background - Anatomy

- The prostate is an exocrine gland
  - Part of the reproductive system, makes fluid that is part of semen
  - Located in front of the rectum and under the bladder
  - Growth is commonly fueled by androgens
    - Testosterone, dihydrotestosterone



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American Cancer Society. Prostate Cancer. What is Prostate Cancer? Revised 11/22/23. www.cancer.org

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Background - Survival

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- Cure - possible when tumor is localized
- 5- year relative survival rate (United States, 2013-2019)
  - Local or regional disease: > 99%
  - Distant disease: 34%
  - All stages combined: 97%
- Large number of clinically indolent tumors
  - Estimated to range from 30-70% of men > 60 years, based on autopsy series
- Rate of tumor growth varies from very slow to moderately rapid

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National Cancer Institute. Updated 8/9/24. https://www.cancer.gov/types/prostate/hp/prostate-treatment-pdq

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QUESTION 1

What is the incidence of prostate cancer in the United States?

a. About 1 in 40 men

b. About 1 in 8 men

c. About 1 in 4 men

d. About 1 in 50 men

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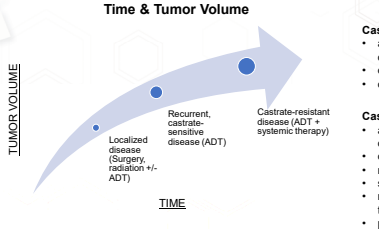
Prostate Cancer Continuum



Castration-sensitive disease
- abiraterone, enzalutamide, or apalutamide,
- docetaxel + abiraterone
- docetaxel + darolutamide

Castration-resistant disease
- apalutamide, enzalutamide, darolutamide, or abiraterone
- docetaxel, or cabazitaxel
- radium-223, or lutetium-177
- sipuleucel-T
- rucaparib, olaparib, or talazoparib
- pembrolizumab
- clinical trial

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Elements of Diagnosis

- **Symptoms**
  - Early stage often has no symptoms
  - Locally invasive to advanced disease
    - Urinary symptoms: decreased urinary stream, urgency, hesitancy, nocturia, incomplete bladder emptying
    - Impotence
    - Bone pain, pathological fractures, anemia - bone marrow involvement, cord compression
- **Digital rectal exam** (DRE)
- **Serum PSA level**
  - Elevated in prostate cancer, but also BPH and infection
- **Needle biopsy**, often transrectal
- **Imaging:** ultrasound, CT, MRI, bone scan, PET scan

BPH= benign prostatic hyperplasia

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National Cancer Institute. Updated 8/9/24. https://www.cancer.gov/types/prostate/hp/prostate-treatment-pdq

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Pathology

- Greater than 95% of prostate cancers are adenocarcinoma
  - Remaining: small cell tumors, intralobar acinar, ductal, clear cell, or mucinous carcinomas
- **Gleason scoring system**
  - Calculated based on dominant histological pattern
  - Grade 1 (well-differentiated) to grade 5 (poorly-differentiated)
  - Two most prevalent grades are added & often expressed as two components
    - e.g. Gleason score = 9 (4 + 5); minimum is 2 and maximum is 10
- **Grade groups** predict risk of recurrence after primary treatment

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Gleason ≤ 6	Gleason 3+4	Gleason 4+3	Gleason 8	Gleason 9 or 10

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National Cancer Institute. Updated 8/9/24. https://www.cancer.gov/types/prostate/hp/prostate-treatment-pdq

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Prognostic Factors

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- **Extent of the tumor**
  - TNM staging from AJCC (T=primary tumor, N=regional lymph nodes, M=distant metastasis)
- **Histologic grade of tumor**
  - Grade group 1 - 5
  - Poorly differentiated tumors – likely to metastasize before diagnosis (poorer prognosis)
- **Patient's age and comorbidities**
  - Life expectancy ≥10 years for benefit of definitive local therapy
- **PSA level**
  - Higher levels indicate higher risk of metastatic disease

AJCC= American Joint Committee on Cancer

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National Cancer Institute. Updated 8/9/24. https://www.cancer.gov/types/prostate/hp/prostate-treatment-pdq

Buyyounouski MK et al. CA Cancer J Clin 2017;67:245-253.

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Genomics


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- **Genomic Tumor Sequencing**
  - Tissue and/or blood (liquid biopsy)
- **Somatic versus germline mutations**
  - Somatic: changes within the tumor that occur after conception, not heritable
  - Germline: heritable mutation in germ cells (in egg or sperm) that is expressed in every somatic and germline cell
  - Mutations in homologous recombination repair (HRR) genes may predict benefit to PARP inhibitors
- **Timing**
  - Commonly done in the metastatic castration-resistant setting (mCRPC)
    - Increased number of copy number alterations and higher mutational burden
    - Associated with poor clinical outcomes & earlier resistance to therapies

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Rebello RJ, et al. Nature Reviews. Disease Primers 2021; 7(9):1-27.

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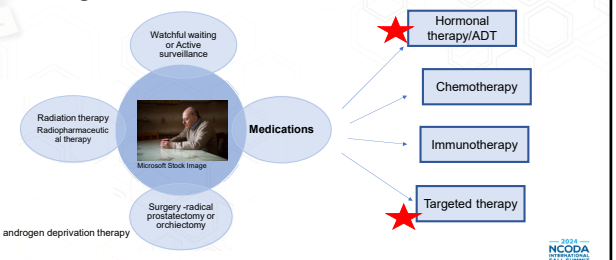
Treatment Options – At Diagnosis or Progression



ADT = androgen deprivation therapy

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Rebello RJ, et al. Nature Reviews. Disease Primers 2021; 7(9):1-27.

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Treatment Options for Metastatic CRPC

Androgen deprivation therapy (ADT)
- Is given continuously in the metastatic setting
  - Induces medical castration
  - **LHRH-agonist**
    - Leuprolide
    - Goserelin
  - **LHRH antagonist**
    - Degarelix
    - Relugolix
- Castrate levels of testosterone: < 50 ng/dL

Hormonal Therapies
- **Androgen signaling inhibitors**
  - Abiraterone acetate
  - Enzalutamide
  - Apalutamide
  - Darolutamide

Targeted therapies
- **Poly (ADP-ribose) polymerase inhibitors (PARPi)**
  - Niraparib
  - Talazoparib
  - Olaparib
  - Rucaparib

LHRH = luteinizing hormone-releasing hormone
CRPC= castrate-resistant prostate cancer

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Treatment Options for Metastatic CRPC

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To be reviewed today

LHRH = luteinizing hormone-releasing hormone
CRPC= castrate-resistant prostate cancer

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Rebello RJ, et al. Nature Reviews. Disease Primers 2021; 7(9):1-27

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Rationale for Combining PARP Inhibitor and Androgen Inhibitor

- PARPi are established in the treatment of late-stage prostate cancer (BRCA positive tumors)
- Pre-clinical evidence suggests:
  - Interplay between androgen receptor inhibition and upregulated PARP activity & downregulated HRR gene expression
  - PARP inhibition suppresses androgen receptor transcriptional activity

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Fizazi K, et al. Nature Medicine 2024; 30:257-264

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Abiraterone & Olaparib Pharmacology

	Abiraterone single agent	Olaparib single agent
FDA approved	April 2011 for mCRPC in combination with prednisone, with previous treatment with docetaxel	May 2020 mCRPC, germline or somatic HRR gene mutations and previous treatment with enzalutamide or abiraterone
Dosing & Administration	Abiraterone 1000 mg PO daily on empty stomach Prednisone 5 mg PO twice daily	300 mg PO BID, with or without food
Emetic potential	Minimal or low	Minimal or low
Interactions	Major substrate of CYP3A4, moderate inhibitor CYP2D6	Major CYP 3A4 inhibitor
MOA	Irreversibly inhibits enzyme CYP17 (17 alpha-hydroxylase/C17,20-lyase, inhibiting the formation of the testosterone precursors dehydroepiandrosterone (DHEA) and androstenedione.	Poly ADP-ribose polymerase (PARP) inhibitor, including PARP1, PARP2, PARP3, which is involved in DNA transcription, cell cycle regulation, and DNA repair. The formation of double-stranded DNA breaks can't be accurately repaired leading to cell death
30-day supply	250 mg tablets: $107 – AWP $1,665	AWP 150 mg tablets: $20,224

AWP = average wholesaler price

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UpToDate Lexidrug Standard. Olaparib & Abiraterone monograph. Updated 8/2024. Cost Plus Drug Company. www.costplusdrugs.com. updated 10/2024

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PROpel Trial

Phase III, double blind, randomized trial to assess imaging-based progression free survival (ibPFS) and overall survival (OS)

- Men ≥18 years*, with adenocarcinoma & mCRPC
- ≥1 metastatic lesion on bone scan or CT/MRI scan
- No prior systemic therapy for mCRPC except ADT, & first-generation antiandrogen
- Allowed docetaxel in localized and mCRPC setting

→ Abiraterone 1000 mg PO daily + prednisone 5mg PO BID plus

R (1:1)

- Olaparib 300 mg PO BID n=399
- or
- Matched placebo n=397

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*>19 years in South Korea

Clark NW, et al. NEJM Evid 2022;1(9). DOI: 10.1056/EVIDoa2200043

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PROpel Trial Results

	Olaparib & Abiraterone arm	Abiraterone arm	Hazard Ratio	Confidence Intervals
Median ibPFS (months)	**24.8**	**16.6**	**0.66**	95% CI, 0.54-0.81; p<0.001
-HRRm (n=226)			0.50*	
-non-HRRm (n=552)			0.76*	95% CI, 0.34-0.73 95% CI, 0.6-0.97
BRCAm subgroup (n=85/711)				
rPFS	not reached	~ 8	**0.24**	95% CI, 0.12-0.45
OS	not reached	23	**0.30**	95% CI, 0.15-0.59
PSA response (%)	79.3	69.2	**0.55**	95% CI, 0.45-0.68
-time to PSA progression (months)	not reached	12		
ORR (%)	58.4	48.1		

FDA approval based on this

ibPFS= imaging-based progression free survival. HRR= homologous recombination repair genes. HRRm= patients with any deleterious or suspected deleterious HRR gene mutation detected. BRCAm= BRCA mutation present. rPFS= radiographic progression free survival. * = aggregate.

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Clark NW, et al. NEJM Evid 2022;1(9). DOI: 10.1056/EVIDoa2200043

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PROpel Trial – Adverse Events

Adverse Event (AE)	Abiraterone & Olaparib, n=398 % (grade ≥3 %)	Abiraterone & Placebo, n=396 % (grade ≥3 %)
Anemia	46 (15.1)	16.4 (3.3)
Fatigue/asthenia	37.2 (2.3)	28.3 (1.5)
Nausea	28.1 (0.3)	12.6 (0.3)
Diarrhea	17.3 (0.8)	9.3 (0.3)
Constipation	17.3 (0)	13.9 (0.3)
Decreased appetite	14.6 (1)	5.8 (0)
Embolic and thrombotic events		
Arterial	2 (1.5)	2.5 (2)
Venous	7.3 (6.8)	3.3 (2)

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Clark NW, et al. NEJM Evid 2022;1(9). DOI: 10.1056/EVIDoa2200043

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Abiraterone & Olaparib – Adverse Effects & Clinical Pearls

- Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), 1.2%
- Pneumonitis, 0.8%
- Venous Thromboembolism, 8%
- Diabetes, reports of hypoglycemia
- Hepatotoxicity
- Hypokalemia, fluid retention, and cardiovascular adverse events
- Adrenocortical Insufficiency, stress steroids may be necessary
- Radium Ra 223 dichloride, co-administration is not recommended
- Embryo-Fetal Toxicity

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Lynparza Prescribing information. https://www.lynparzahcp.com/prostate-cancer/home.html. Accessed 9/2/24.

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Abiraterone & Olaparib - NCCN

Category 1 – for patients with mCRPC and a BRCA mutation who have not yet received a novel hormone therapy and

- *have not received prior docetaxel (category 1)*
- *have progressed on prior docetaxel (category 2A)*

Novel hormone therapies include abiraterone, enzalutamide, darolutamide, or apalutamide.
Abiraterone given as part of neoadjuvant/concomitant/adjuvant ADT with EBRT is not considered prior novel hormonal therapy

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Abiraterone & Olaparib Summary

- FDA approved the combination in May 2023 for adult patients with deleterious or suspected deleterious BRCA-mutated mCRPC as determined by an FDA-approved companion diagnostic test
  - Patients would continue their ADT
  - Can be taken with prednisone or prednisolone
- The combination has non-overlapping toxicities, and the two medications do not have significant drug-drug interactions between them
  - Monitor for myelosuppression
  - QOL was maintained in both arms
- AWP of olaparib plus lowest cost abiraterone is $20,331/month
  - Refer patients to patient access for financial support if medication copay is high

QOL = quality of life
AWP = average wholesaler price

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U.S. Food & Drug Administration. Drug Approvals and Databases. www.fda.gov. accessed 8/30/24

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QUESTION 2

Do patients continue their androgen deprivation therapy (ie: leuprolide) while on the combination of abiraterone, prednisone, and olaparib ?

a) Yes
b) No

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Abiraterone & Niraparib Pharmacology

	Abiraterone	Niraparib
FDA approved	April 2011 for mCRPC in combination with prednisone, with previous treatment with docetaxel	Ovarian, fallopian tube or primary peritoneal advanced cancer
Dosing & Administration	Abiraterone 1000 mg PO daily on empty stomach Prednisone 5 mg PO twice daily	200 – 300 mg PO once daily
Emetic potential	Minimal or low	Moderate to high
Interactions	Major substrate of CYP3A4, moderate inhibitor CYP2D6	Minor substrate of BCRP/ABCG2, PGP/ABCB1
MOA	Irreversibly inhibits enzyme CYP17 (17 alpha-hydroxylase/C17,20-lyase, inhibiting the formation of the testosterone precursors dehydroepiandrosterone (DHEA) and androstenedione.	Poly (ADP-ribose) polymerase (PARP) enzyme inhibitor, which is highly selective for PARP-1 and PARP-2. PARP enzymes detect DNA damage and promote repair, inhibiting them results in DNA damage, apoptosis and cell death.
30-day supply	250 mg tablets: $107 – AWP $11,665	AWP 200 mg tablets: $21,992
AWP	AWP combination tablet 50/500 mg or 100/500 mg: $22,500	

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UpToDate Lexidrug Standard, Niraparib & Abiraterone monograph, Updated 8/22/24

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MAGNITUDE Trial (2nd interim analysis)

Phase III, double blind, randomized trial to assess radiographic progression free survival (rPFS), time to initiation of cytotoxic chemotherapy, time to symptomatic progression, and OS

- Men ≥ 18 years, with mCRPC
- ECOG PS 0-1
- No prior systemic therapy for mCRPC except ADT & up to 4 months of abiraterone/prednisone
- Allowed apalutamide, darolutamide, enzalutamide and/or docetaxel in mCRPC or non-mCRPC
- HRR (+) gene alterations*

→ Abiraterone 1000 mg PO daily + prednisone 5mg PO BID

plus

R (1:1)

Niraparib 200 mg PO daily n=212

or

Matched placebo n=211

*HRR (-) cohort was stopped for futility in August 2020

ECOG = Eastern Cooperative Oncology Group

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Chi KN, et al. Ann Oncol 2023;34(9). DOI: 10.1016/j.annonc.2023.06.009

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MAGNITUDE Trial – Results in BRCA1/2 Subgroup

	Niraparib & Abiraterone (months) N=113	Placebo & Abiraterone (months) N=112	Hazard Ratio	95% Confidence Interval	P Value
* Median rPFS	19.5	10.9	0.55	0.29-0.78	nominal p=0.0007
Time to symptomatic progression (median)	Not evaluable	23.6	0.54	0.35-0.85),	nominal p=0.0071
Time to initiation of cytotoxic chemotherapy (median)	Not evaluable	27.3	0.56	0.35-0.90	nominal p=0.0152
Median time to PSA progression	18.4	9.2	0.48	0.33-0.70	nominal p <0.0001
OS (median)	29.3	28.6	0.88	0.58-1.34	nominal p=0.5505

* Primary endpoint. rPFS= radiographic progression free survival

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Chi KN, et al. Ann Oncol 2023;34(9). DOI: 10.1016/j.annonc.2023.06.009
Chi KN, et al. J Clin Oncol 2023;41: 3339-3351
Chen E, et al. Ann Oncol 2024;35(11):14-141

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MAGNITUTE Trial – Adverse Events

Adverse Event	Abiraterone & niraparib All grades %, n = 212	Abiraterone & niraparib (grade 3/4) %	Abiraterone & placebo All grades % n = 211	Abiraterone & placebo (grade 3) %*
Anemia	50	28.8/ 1.4	22.7	8.5
Hypertension	33	15.6/ 0	22.3	12.3
Constipation	33	0.5/ 0	15.6	0
Fatigue	29.7	3.8/ 0	19	5.2
Nausea	24.5	0.5/ 0	14.7	0.5
Thrombocytopenia	23.1	3.8/ 3.8	9.5	2.4
Dyspnea	17.9	2.4/ 0	6.6	1.9

* No grade 4 events

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Chi KN, et al. Ann Oncol 2023;34(9). DOI: 10.1016/j.annonc.2023.06.009
Chi KN, et al. J Clin Oncol 2023;41: 3339-3351

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Abiraterone & Niraparib - Adverse Effects & Clinical Pearls

- Myelodysplastic Syndrome/Acute Myelodysplastic Leukemia (MDS/AML)
- Myelosuppression
- Diabetes, reports of hypoglycemia
- Hepatotoxicity
- Hypokalemia, fluid retention, and cardiovascular adverse events
- Adrenocortical Insufficiency, stress steroids may be necessary
- Radium Ra 223 dichloride, co-administration is not recommended with abiraterone
- Posterior Reversible Encephalopathy Syndrome
- Embryo-fetal toxicity

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UpToDate Lexicog Standard, Niraparib & Abiraterone monograph. Updated 8/22/24.

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Abiraterone & Niraparib - NCCN

- Category 1 for patients with no prior docetaxel or novel hormonal therapy (NHT)
- Category 2A for patients with prior docetaxel and no prior NHT
- Category 2B for patients with no prior docetaxel and prior NHT

Novel hormone therapies include abiraterone, enzalutamide, darolutamide, or apalutamide. Abiraterone given as part of neoadjuvant/concomitant/adjuvant ADT with EBRT is not considered prior novel hormonal therapy

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Abiraterone & Niraparib - Summary

- FDA approved the combination in August 2023 for adult patients with deleterious or suspected deleterious BRCA-mutated mCRPC as determined by an FDA-approved test
  - Patients would continue their ADT
- The combination has non-overlapping toxicities
  - QOL was maintained on both arms
  - Niraparib component is associated with myelosuppression, requiring regular monitoring, patients may have red blood cell transfusion requirements
- AWP is $22,500/month; refer patients to patient access for financial support if medication copay is high

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U.S. Food & Drug Administration. Drug Approvals and Databases. www.fda.gov; accessed 8/30/24

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Enzalutamide & Talazoparib Pharmacology

	Enzalutamide	Talazoparib
FDA approved	August 2012 3 indications: CRPC, mCSPC, and nmCSPC at high risk for metastasis	October 2018 for breast cancer
Dosing & Administration	160 mg PO once daily, with or without food	0.5 – 1 mg PO once daily for breast cancer
Emetic potential	Minimal or low (<30%)	Minimal or low (<30%)
Interactions	Major substrate of CYP2C8 & CYP3A4 Inhibits: MRP2, P-glycoprotein,ABCB1 Induces: CYP2C19 (moderate), CYP2C9 (moderate), CYP3A4 (strong)	Major substrate of BCRP/ABCG2, P-glycoprotein/ABCB1
MOA	Androgen receptor signaling inhibitor. It inhibits androgen receptor nuclear translocation, DNA binding, and coactivator mobilization. This leads to cellular apoptosis.	Talazoparib is a poly (ADP-ribose) polymerase (PARP) enzyme inhibitor, including PARP1 and PARP2. It is potent, with strong catalytic inhibition & a PARP-trapping potential that is significantly greater than other PARP inhibitors. Cell death occurs due to accumulation of irreparable DNA damage. It also traps PARP-DNA complexes.
AWP (30 day supply)	$ 17,198	$21,647 (0.5 mg dose)

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mCSPC= metastatic castrate sensitive prostate cancer
nmCSPC= non-metastatic castrate sensitive prostate cancer

UpToDate LexiDrug Standard. Enzalutamide & Talazoparib monograph. Updated 8/22/24.

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TALAPRO-2 Trial

Phase III, double blind, randomized trial to assess radiographic progression-free survival (rPFS), overall survival (OS), and overall response rate (ORR).

- Men ≥ 18 years, with asymptomatic or mildly symptomatic mCRPC*
- ECOG PS 0-1
- No prior systemic therapy for mCRPC except ADT
- Allowed docetaxel and abiraterone or orteronel for CSPC
- Unselected genomics/all-comers (cohort 1) and HRR deficient (cohort 2)

*age ≥20 years in Japan

Enzalutamide 160 mg PO daily

R (1:1)

plus

Talazoparib 0.5 mg PO daily

or

Matched placebo

Cohort 1= 805 patients, 169 with gene alterations
Cohort 2 = 230 patients, all with gene alterations

Agarwal N, et al. Lancet 2023;402:291-303.

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TALAPRO-2 Trial – Results

	Enzalutamide & Talazoparib	Enzalutamide & Placebo (months)	Hazard Ratio	95% Confidence Interval	P Value
Median rPFS • all-comers in cohort 1 • HRR deficient in cohort 1 & 2 • BRCA gene alteration	 Not reached Not reached Not reached	 21.9 13.8 11	 0.63 0.45 0.20	 0.51-0.78 0.33-0.61 0.11-0.36	 p<0.0001 p<0.0001 p<0.0001
ORR (cohort 1)	62%	44%			
Time to PSA progression (cohort 1)	26.7 months	17.5	HR= 0.72	0.58-0.89	p=0.0020
OS			Data are still immature		

Cohort 1= 805 patients, 169 with gene alterations
Cohort 2 = 230 patients, all with gene alterations

Agarwal N, et al. Lancet 2023;402:291-303.
Fizazi K, et al. Nature Medicine. 2024. 30:2094-2104.

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TALAPRO-2 – Adverse Events

Adverse Event, Cohort 1	Enzalutamide & Talazoparib All grades (%) N = 398	Enzalutamide & Talazoparib Grade ≥ 3 (%)	Enzalutamide & placebo All grades (%) N = 401	Enzalutamide & placebo Grade ≥ 3 (%)
Anemia	66	46	17	4
Neutropenia	36	18	7	1
Fatigue	34	4	29	2
Thrombocytopenia	25	7	3	1
Back pain	22	3	18	1
Leukopenia	22	6	4	0
Decreased appetite	22	1	16	1
Nausea	21	<1	12	<1

Agarwal N, et al. Lancet 2023;402:291-303.

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Enzalutamide & Talazoparib – Serious AE

- Myelodysplastic syndrome/Acute myeloid leukemia (MDS/AML), <1%
- Myelosuppression
- Embryo-fetal toxicity
- Venous embolic & thrombotic events, 4%

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Pfizer professional website. Talzenna & Xtandi. https://talzennaxtandi.pfizerpro.com/. Accessed 9/2/24.
Agarwal N, et al. Lancet 2023;402:291-303.

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Enzalutamide & Talazoparib - NCCN

- Category 1 – for patients who have had no prior docetaxel or novel hormonal treatment (NHT)
- Category 2A – for patients who had prior docetaxel and no NHT
- Category 2B – for patients who have had no prior docetaxel and had prior NHT

Novel hormone therapies include abiraterone, enzalutamide, darolutamide, or apalutamide. Abiraterone given as part of neoadjuvant/concomitant/adjuvant ADT with EBRT is not considered prior novel hormonal therapy

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Enzalutamide & Talazoparib - Summary

- FDA approved the combination in June 2023 for adult patients with HRR gene-mutated mCRPC
  - Patients would continue their ADT
- The trial assessed the all-comers and HRR gene alteration subgroups
  - Talazoparib component is associated with myelosuppression, requiring regular monitoring
- AWP is $38,848 per month; refer patients to patient access for financial support if medication copay is high

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U.S. Food & Drug Administration, Drug Approvals and Databases. www.fda.gov; accessed 9/2/24

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QUESTION 3

Is one of the primary adverse effects of the combination of Talazoparib and Enzalutamide nausea and vomiting?

a) Yes
b) No

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SUMMARY

- Prostate cancer is commonly a hormonally-driven cancer that affects about 1 in 8 men in the United States each year
- Symptoms can lead patients to seek medical care and to discuss the benefits and risks of treatment if diagnosed with prostate cancer
- Recent FDA approvals of oral androgen signaling inhibitors in combination with PARP inhibitors can improve outcomes for patients with metastatic disease and HRR gene mutations
- Recognizing the AE profile of these medications allows providers to support their patients while on therapy

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QUESTION & ANSWERS

A Review of Prostate Cancer & Recent Updates in the Treatment of Metastatic Prostate Cancer

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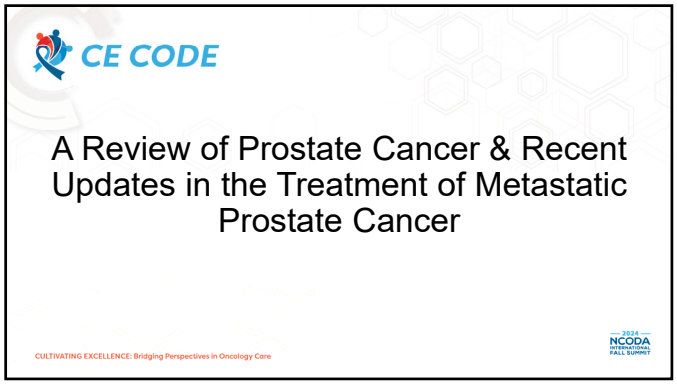
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