

## Poll Everywhere Audience Response



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## Speaker Introduction

- Megan Fonteno is currently a PGY-2 Oncology Pharmacy Resident at the University of Utah Huntsman Cancer Institute.
- She earned her PharmD from Auburn University's Harrison School of Pharmacy in Auburn, AL.
- She completed her PGY-1 Pharmacy Practice Residency at Piedmont Columbus Regional Midtown Hospital in Columbus, GA.
- Megan would love to pursue a career as a clinical oncology pharmacist after graduating from her PGY-2 program. Additionally, she would love to teach an oncology elective in the future as well.



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UTAH SOCIETY OF  
HEALTH-SYSTEM PHARMACISTS

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Megan Fonteno, PharmD  
11/6/2021

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## Deprived and Staying Alive! – with novel therapies in advanced prostate cancer

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## Disclosure

- Relevant Financial Conflicts of Interest
  - **CE Presenter, Megan Fonteno, PharmD:**
    - None
  - **CE mentor, Emma Jones, PharmD, BCOP:**
    - None
- Off-Label Uses of Medications
  - None



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## Pharmacist Questions

## Pharmacist Learning Objectives

Describe the overall impact of prostate cancer therapies on patient outcomes

Develop and/or assess an individualized treatment plan for a patient with advanced prostate cancer

Compare and contrast different prostate cancer therapies based on mechanisms of action, indicated use and side effect profile



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## Technician Questions

## Technician Learning Objectives

Discuss barriers to access of medications used in advanced prostate cancer

Select the appropriate trade name for advanced prostate cancer therapy

Explain the reasoning behind the use of androgen deprivation therapies for advanced prostate cancer



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## Prostate Cancer [PC] Background

Most common cancer in men

~250,000 new cases in 2021

1 in 8 men diagnosed in their life

60% of men >65yo have prostate cancer

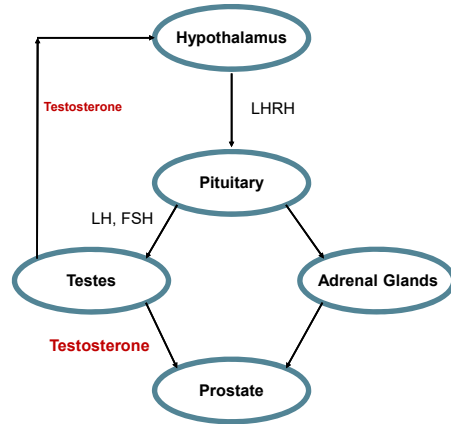
Can be local or advanced



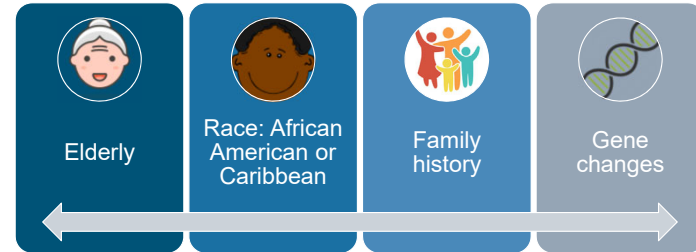
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Prostate Cancer, NCCN Guidelines, V2.2021.

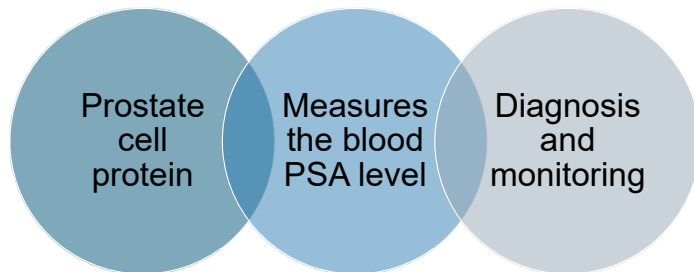
## Pathophysiology



## Risk Factors



## Prostate-Specific Antigen [PSA]



Other Diagnostic Tools:

- DRE = digital rectal exam
- Biopsy

## Response Question #1

Prostate cancer is mainly characterized by:

- A. Low testosterone
- B. Increased testosterone
- C. Stable testosterone
- D. Decrease in androgen hormones

Technician Question



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# Treatment

## Therapy Goals



Testosterone suppression



Maintain quality of life



Control disease

## Testosterone Suppression

### Definition

- Testosterone <50ng/dL

### Castration

- Medical
- Surgical



## Treatment Gold Standard

ADT = androgen deprivation therapy

ADT includes


- LHRH agonist
- LHRH antagonist

## Naïve vs Resistant Comparison

SENSITIVE	RESISTANT
"Hormone sensitive"	"Hormone resistant"
Newly diagnosed (not on ADT) or responding to therapy	Progression despite testosterone < 50ng/dL on ADT
Treatment: ADT +/- additional therapies	Treatment: ADT +/- additional therapies



## Novel Treatment Options

 ADT	Androgen biosynthesis inhibitor	Androgen receptor inhibitor	PARP inhibitors
• Relugolix	• Abiraterone	• Apalutamide	• Olaparib • Rucaparib

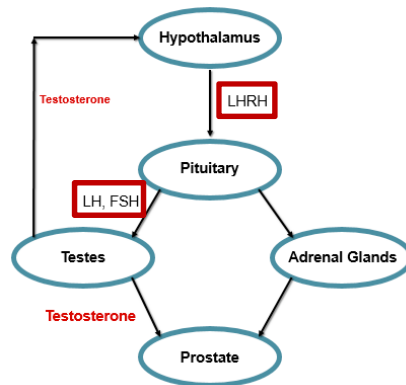
PARP = poly-ADP ribose polymerase




## Androgen Deprivation Therapy (ADT)

### LHRH Agonist:

- Leuprolide [Lupron®, Eligard®]



## Novel Treatment Options

 ADT	Androgen biosynthesis inhibitor	Androgen receptor inhibitor	PARP inhibitors
• Relugolix	• Abiraterone	• Apalutamide	• Olaparib • Rucaparib



# ★ Relugolix

Brand name: Orgovyx®

## Indication:

- Metastatic prostate cancer [sensitive AND resistant] → December 2020

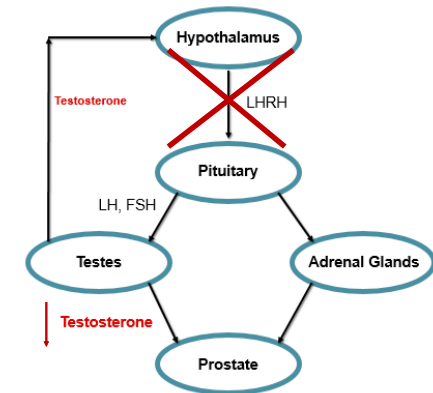
## Dosage:

- 360mg on day 1, followed by 120mg daily after
- If >7 days between doses, reinstate therapy with a 360mg load followed by 120mg daily



## Relugolix Mechanism

LHRH Antagonist



## Relugolix – Why is it so special??

**FIRST** oral LHRH receptor antagonist

Used **ALONE**

Works **FAST**



## The HERO Trial

Study Information	Relugolix*	Leuprolide	p-value
Patient Population	48weeks, 934 patients with metastatic prostate cancer • Relugolix 360mg load day 1 + 120mg daily OR • Leuprolide acetate 22.5mg SQ injection every 3-mo		
Achieve & maintain testosterone <50ng/dL	96.7%	88.8%	p<0.0001
MACE** Risk w/o history	2.9%	6.2%	p<0.001
MACE** Risk w/ history	3.6%	17.8%	p<0.001

\*\*MACE = major adverse cardiovascular event

**\*Achieved testosterone <50ng/dL as early as day 4 of therapy!!**



## Relugolix Dose Adjustments

Renal

•None

Hepatic

•None



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Orgovyx®, (relugolix) [prescribing information]

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## Relugolix Main ADRs

Hot flashes

Fatigue

Muscle/joint  
discomfort

Increased  
cholesterol

Increased  
blood  
glucose

Decreased  
bone density

Liver  
function  
problems

↓  
MACE

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Orgovyx®, (relugolix) [prescribing information]

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## Relugolix

PK/PD:

- M: primarily hepatic via CYP3A4
- E: feces 81%
- Time to castration: 4 days

Drug  
Interactions:

- P-gp inhibitors COMBINED with CYP3A4 inducers: avoid co-administration
- If co-administration unavoidable, increase relugolix to **240mg daily**

M = metabolism  
E = excretion

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Orgovyx®, (relugolix) [prescribing information]

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## Relugolix

Preparation → specialty pharmacy

- 120mg tablet

Cost

- 120mg = \$92.52
- \$2775.60/month

Storage

- Room temperature
- Dispense in original container

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Orgovyx®, (relugolix) [prescribing information]

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## Relugolix Access

### Considerations:

- Disease: indicated for all metastatic prostate cancers
- Cost → free drug available!
- Specialty pharmacy

### Non-considerations:

- Food intake
- Renal/hepatic function



## Response Question #2

Technician Question

Select the appropriate trade name for relugolix.

- A. Yonsa®
- B. Zytiga®
- C. Erleada®
- D. Orgovyx®



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## Novel Treatment Options



ADT	Androgen biosynthesis inhibitor	Androgen receptor inhibitor	PARP inhibitors
• Relugolix	• Abiraterone	• Apalutamide	• Olaparib • Rucaparib



## Abiraterone Acetate

Brand names: Yonsa®, Zytiga®

### Indications:

- High-risk metastatic castration-sensitive → approved 2018
- Metastatic castration-resistant → approved 2011
- **Fun fact: 1<sup>st</sup> novel hormonal therapy approved for metastatic PC**

### Dosing (in combo with ADT):

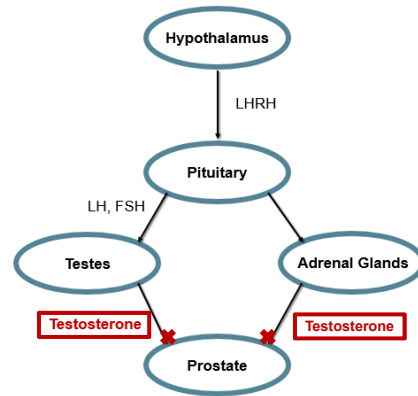
- Zytiga®: 1,000mg once daily on EMPTY stomach
- Yonsa®: 500mg daily with or without food



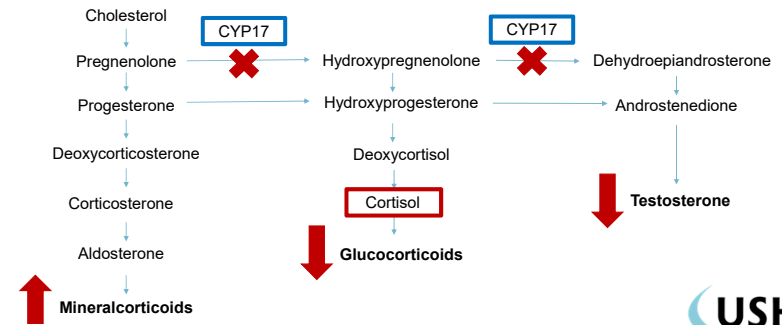


# Abiraterone Mechanism

Androgen Synthesis Inhibitor



# Abiraterone and Prednisone

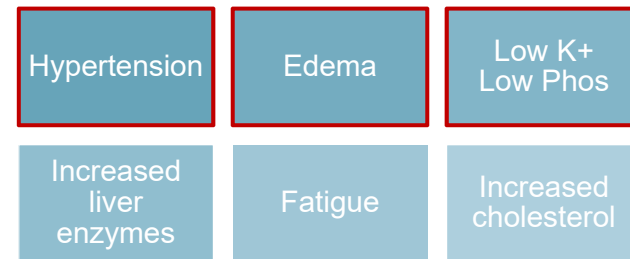


# The Latitude Trial

Study Information	Abiraterone + Prednisone	Placebo	p-value
Patient Population	1199 patients w/ newly diagnosed high-risk, metastatic, castration sensitive <ul style="list-style-type: none"> <li>• ADT + abiraterone acetate 1000mg daily + plus prednisone</li> <li>• ADT + placebos</li> </ul> Median follow-up: 30.4mo		
Overall Survival [OS] at 3 yrs	66%	49%	p<0.001
Progression-free survival	33.0mo	14.8mo	p<0.001



# Abiraterone Main ADRs



## Abiraterone Hepatic Dose Adjustments

Yonsa®

- Child-Pugh Class B: 125mg daily

Zytiga®

- Child-Pugh Class B: 250mg daily

For both:

- Child-Pugh Class C: avoid
- LFTs >5x ULN = discontinue
- Bili >3x ULN = discontinue

ULN: upper limit of normal  
LFTs: liver function tests  
Bili: total bilirubin



Yonsa, Zytiga (abiraterone acetate) [prescribing information]

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## Abiraterone

PK/PD:

- Food effect: conc. 6.5 fold higher with high fat meal
- M: active metabolite hydrolyzed via CYP3A4 and SULT2A1
- E: mostly feces

Drug Interactions:

- CYP3A4 inducers: avoid, or increase abiraterone dose
- CYP2D6 substrates: avoid or use extreme caution and reduce the CYP2D6 substrate

Conc. = concentration



Yonsa, Zytiga (abiraterone acetate) [prescribing information]

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## Abiraterone

Preparation → specialty pharmacy

- Oral tablets → 125, 250, and 500mg

Cost:

- Yonsa®: \$94.85 → \$11,382/month
- Zytiga®: \$217.74 → \$26,128/month

Storage:

- Room temperature



Yonsa, Zytiga (abiraterone acetate) [prescribing information]

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## Abiraterone Access

Considerations:

- Diagnosis
- Cost → Free drug programs available
- Specialty pharmacy
- Food intake [Zytiga® only]
- Hepatic function
- Pill burden

Non-considerations:

- Renal function



Yonsa, Zytiga (abiraterone acetate) [prescribing information]

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Pharmacist Question

### Response Question #3

Which advanced prostate cancer medication interacts with CYP2D6 substrates like metoprolol?

- A. Relugolix
- B. Apalutamide
- C. Abiraterone
- D. Rucaparib



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### Novel Treatment Options



**ADT**

- Relugolix

**Androgen biosynthesis inhibitor**

- Abiraterone

**Androgen receptor inhibitor**

- Apalutamide

**PARP inhibitors**

- Olaparib
- Rucaparib



### Apalutamide

Brand name: Erleada®

Indication:

- Metastatic castration-sensitive only → September 2019

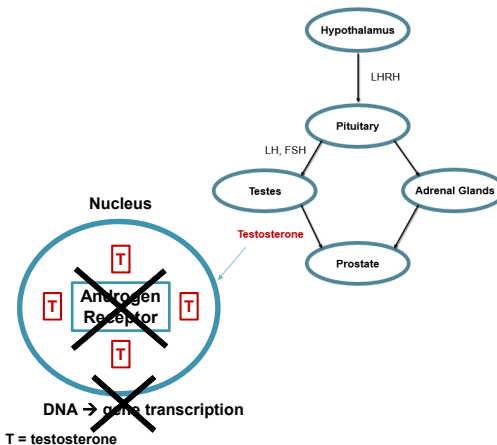
Dosing [in combo with ADT]:

- 240mg daily – no regards to food



### Apalutamide Mechanism

Androgen receptor inhibitor



## The Titan Trial

Study Information	Apalutamide	Placebo	p-value
Patient Population	525 pts with metastatic, castration-sensitive PC received: • Apalutamide 240mg daily + ADT • Placebo + ADT		
OS at 48mo	65%	52%	P<0.001
Radiographic PFS	68.2%	47.5%	p<0.001
Time to PSA progression	NE	12.9%	---

\*NE: not estimated



## Apalutamide Dose Adjustments

Renal

- None

Hepatic

- None



## Apalutamide Main ADRs

Rash	Hypertension	Hot flashes	Muscle or joint discomfort
Falls Dizziness	Fatigue	Diarrhea	Rare: seizure



## Apalutamide [Erleada®]

PK/PD

- M: hepatic primarily via CYP3A4 and CYP2C8
- E: urine and feces
- Weak GABA<sub>A</sub> inhibitor – seizures

Drug Interactions

- Substrates of CYP3A4, CYP2C19, CYP2C9, UGT, P-gp, BCRP, or OATP1B1



## Apalutamide [Erleada®]

### Preparation → specialty pharmacy

- Oral tablets: 60mg

### Cost

- 60mg: \$128.33
- \$15,399.60/month

### Storage

- Room temperature
- Protect from light and moisture



Erleada® (apalutamide) [prescribing information]

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## Apalutamide Access

### Considerations

- Diagnosis: castration **SENSITIVE** only
- Cost → free drug from available
- Specialty pharmacy
- Pill burden

### Non-considerations:

- Food intake
- Hepatic/renal function



Erleada® (apalutamide) [prescribing information]

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## Response Question #4

Which therapy decreases the risk for CV events in metastatic prostate cancer patients?

- A. Apalutamide
- B. Abiraterone
- C. Relugolix
- D. Leuprolide

### Pharmacist Question



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## Novel Treatment Options



ADT

- Relugolix

Androgen biosynthesis inhibitor

- Abiraterone

Androgen receptor inhibitor

- Apalutamide

PARP inhibitors

- Olaparib
- Rucaparib



Prostate Cancer, NCCN Guidelines, V2.2021.

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## Olaparib and Rucaparib

### Brand names:

- Olaparib [O] = Lynparza®
- Rucaparib [R] = Rubraca®

### Indications → both May 2020

- O = Metastatic castration-resistant, homologous recombination repair gene-mutated
- R = Metastatic, castration-resistant, BRCA-mutated

### Dosage:

- O = 300mg BID
- R = 600mg BID



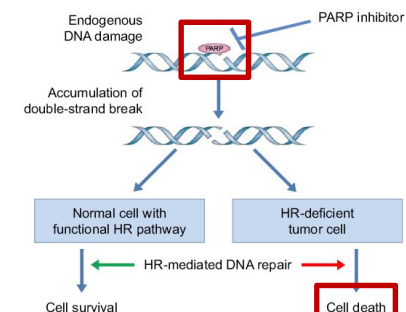
Lynparza®, (olaparib) [prescribing information]  
Rubicarab®, (rucaparib) [prescribing information]

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## PARP Inhibitor Mechanism

### Genes involved:

- BRCA1/2
- ATM
- BARD1, BRIP1
- CDK12, CHEK2
- FANCA
- NBN
- PALB2,
- RAD51/51B/51C/51D/54L



**Figure 1** Mechanism of synthetic lethality.  
**Abbreviations:** HR, homologous recombination; PARP, poly(ADP-ribose) polymerases.

Lynparza®, (olaparib) [prescribing information]  
Rubicarab®, (rucaparib) [prescribing information]

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## The PROfound Trial

Study Information	Olaparib	Enzalutamide/Abiraterone	p-value
Patient Population	387 pts with metastatic castration-resistant prostate cancer who had dx progression on new hormonal agents <ul style="list-style-type: none"> <li>• Cohort A: 245pt with ≥ 1 alteration in BRCA1/2, or ATM</li> <li>• Cohort B: 142pt with alteration in any 12 other genes</li> </ul>		
PFS	7.4mo	3.6mo	p<0.001
OS	18.5mo	15.1mo (81% crossed over)	---



N Engl J Med 2020; 382:2091-2102

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## The TRITON2 Trial – ongoing

Study Information	Rucaparib 600mg BID
Patient Population	277 pts with metastatic castration-resistant prostate cancer with homologous recombination deficiency <ul style="list-style-type: none"> <li>• Pt currently on 2<sup>nd</sup> or 3<sup>rd</sup> line therapy</li> </ul>
Objective Response Rate [ORR]	43.9% at 13.1mo
PSA Response	52.0%
Conclusions so far	<ul style="list-style-type: none"> <li>• Demonstrates promising efficacy in mCRPC and BRCA</li> <li>• No objective responses observed in ATM/CDK12 alterations</li> </ul>



\*TRITON3 trial finishing February 2022

Annals of Oncology 2020

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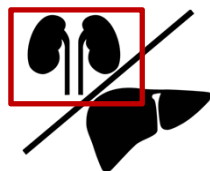
## PARP Inhibitor Dose Adjustments

### Renal

- R = none
- O = **yes\***

### Hepatic

- R = none
- O = none



#### \*Olaparib renal impairment:

- Tablets: reduced to 200mg BID when CrCl 31 – 50mL/min



Lynparzel®, (olaparib) [prescribing information]  
Rubraca®, (rucaparib) [prescribing information]

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## PARP Inhibitor ADRs

Increased liver enzymes

Nausea Vomiting

Fatigue

Decreased appetite

Rash

Constipation Diarrhea

Low platelets

Myelosuppression



Lynparzel®, (olaparib) [prescribing information]  
Rubraca®, (rucaparib) [prescribing information]

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## Olaparib

### PK/PD

- M: primarily hepatic via CYP3A4
- E: urine and feces

### Drug Interactions

- Strong or moderate CYP3A4 inhibitors: avoid
- Strong or moderate CYP3A4 inducers: avoid



Lynparzel®, (olaparib) [prescribing information]

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## Rucaparib

### PK/PD

- M: primarily hepatic via CYP2D6
- E: urine and feces

### Drug Interactions

- Substrates of CYP1A2, CYP3A4, CYP2C9, or CYP2C19



Rubraca®, (rucaparib) [prescribing information]

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## Olaparib and Rucaparib

### Preparation → specialty pharmacy

- O: oral tablets [50, 100, and 150mg]
- R: oral tablets [200, 250, 300mg]

### Cost

- O: \$144.49 → \$17,338.80/month
- R: \$173.70 → \$20,844/month

### Storage

- Room temperature
- Store in original container



Lynparzel®, (olaparib) [prescribing information]  
Rubraca®, (rucaparib) [prescribing information]

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## PARP Inhibitors Access

### Considerations:

- Diagnosis → genetic mutations
- Cost → free drug available
- Specialty pharmacy
- Renal function [olaparib only]

### Non-considerations:

- Hepatic function
- Food intake



Lynparzel®, (olaparib) [prescribing information]  
Rubraca®, (rucaparib) [prescribing information]

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## Response Question #5

### Technician Question

What is NOT considered a barrier to treatment for advanced prostate cancer?

- A. Medication cost
- B. Number of family members
- C. Pill burden
- D. Genetic mutations



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## Response Question #6

### Pharmacist Question

Patient Case: 72yo M diagnosed with metastatic castration-resistant prostate cancer, PMH: MI in October 2021, BCRA gene positive, seizures, and mild hepatic dysfunction.

Which of the following would be the best subsequent medication for our patient?

- A. Relugolix
- B. Apalutamide
- C. Abiraterone
- D. Olaparib



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## Prostate Cancer Summary

- Prostate cancer is the most common cancer in men, with elderly and AA at greater risk
- Goal of therapy: testosterone < 50ng/dL
- ADT therapy = LHRH agonists and antagonists [Relugolix]
- Discussed therapies: ADT, androgen biosynthesis inhibitor, androgen receptor inhibitor, and PARP inhibitors
- Free drugs available from manufacturers!

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## Deprived and Staying Alive! – with novel therapies in advanced prostate cancer

**CE Code: (USHP will fill in)**

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