Updates in Prostate Cancer

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1

Disclosures

Dr. Kesler has no relevant financial relationships with ineligible companies to disclose.

The views expressed in this presentation are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

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2

Objectives

- Review recent clinical trials and its impact on treating patients with prostate cancer
- Identify updates to the guidelines in the treatment of prostate cancer
- Discuss future horizons for the treatment of patients with prostate cancer

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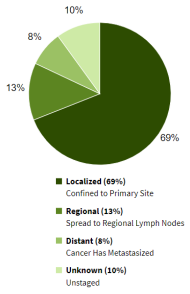
3

Prostate Cancer

- 2nd most common cancer in United States
  - Estimated 288,300 new cases in 2023
    - 29% new male cancer cases
    - Approximately 34,700 deaths
- Accounting for 14.7% of new cancer diagnoses
  - Median age 67 years old
  - 82% localized or regional disease
- 5 year relative survival rate 97%



Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 8 Registries, Nov 2021 Sub (1975-2020) – Linked To County Attributes - Time Dependent (1990-2020) Income/Rurality, 1969-2020 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2023, based on the November 2022 submission

4

Determining Initial Therapy

- Extent of disease
  - Clinically localized: Any T, N0, M0 or Any T, NX, MX
    - Risk Stratification and Staging
    - Symptomatic vs asymptomatic
  - Regional: Any T, N1, M0
  - Metastatic: Any T, Any N, M1
- Estimation of life expectancy
  - Key factor to determine primary treatment
    - Minnesota Metropolitan Life Insurance Table
    - Social Security Administration Life Insurance Table
    - WHO's Life Tables by Country
    - Memorial Sloan Kettering Male Life Expectancy
  - Adjust based on healthiest vs unhealthiest quartile
    - ± 50%

5

Risk Stratification - Localized

Very Low	Low	Intermediate	High	Very High
All of the following: • cT1c • Grade Group 1 • PSA <10ng/mL • <3 positive cores; ≤50% cancer in each • PSA density <0.15ng/mL/g	All of the following: • cT1-cT2a • Grade Group 1 • PSA <10ng/mL (does not meet criteria for very low risk)	At least 1 of the following: • cT2b-cT2c • Grade Group 2 or 3 • PSA 10-20ng/mL	Only 1 of the following: • cT3a • Grade Group 4 or 5 • PSA >20ng/mL	At least 1 of the following: • cT3b-cT4 • Primary Gleason pattern 5 • 2-3 HRF • >4 cores with Grade Group 4 or 5

Favorable	Unfavorable
All of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive	1 or more of the following • 2 or 3 IRFs • Grade Group 3 • ≥50% biopsy cores positive

6

Localized

Low Risk
- Active Surveillance
- Radical Prostatectomy (RP)
- External Beam Radiation Therapy (EBRT) or brachytherapy

Intermediate Risk
- EBRT + ADT (short term)
- RP ± PLND

High Risk
- EBRT + ADT (long term)
- RP + PLND

RP: additional therapy may be warranted if adverse features are present (positive margins; seminal vesicle invasion; extracapsular extension; or detectable PSA)

7

Advanced Disease

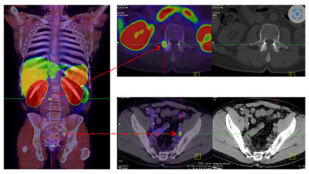
Biochemical Recurrence - PSA: >0.2 following RP or PSA nadir + 2 following RT

- M0
  - Observation
  - ADT (intermittent)
  - Salvage local therapy
- M1
  - Oligometastatic — SBRT
  - Widespread — mCSPC, mCRPC

8

Imaging

- Prostate-specific membrane antigen (PSMA) PET imaging
  - Use of a radiopharmaceuticals that binds to prostate cancer cells
  - Sensitivity and diagnostic accuracy higher compared to bone scans and conventional CT/MRI imaging
    - Increased sensitivity and specificity for micro-metastatic disease
    - Shown to change disease management in up to 64% of patients
    - Ability to change radiation treatment in 53% of patients with high- and very-high-risk PC



PSMA PET-CT Accurately Detects Prostate Cancer Spread, Trial Shows was originally published by the National Cancer Institute.

9

What is the best therapy option for his recent biochemical recurrence?

TK is a 87 year old male with prostate adenocarcinoma, low risk. He was originally diagnosed in 2018 and underwent EBRT with a PSA nadir of 0.3. He has been on active surveillance since with a recent rise in his PSA, now 4.7, PSA doubling time of 5 months. PSMA-PET negative for metastatic disease and patient is in the office today to discuss next steps. Of note, patient has a history of CAD with a recent MI and sent placement within the 2 months.

(A) Relugolix 0%

(B) Leuprolide 0%

(C) Darolutamide 0%

(D) Abiraterone/prednisone 0%

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12

HERO Trial

Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer

Multinational, randomized, open-label, phase 3
- Advanced prostate cancer
- Adenocarcinoma

R 2:1

- Relugolix 360mg x 1 followed by 120mg daily
- Leuprolide acetate 22.5mg* every 3 months

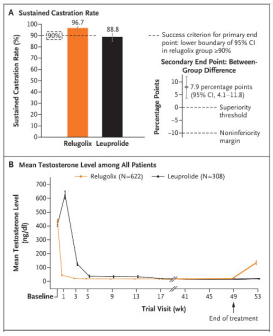
Primary Endpoint
Sustained testosterone suppression to castrate levels through 48 weeks

*11.25mg in Japan & Taiwan

N Engl J Med 2020;382:2187-96

13

HERO Trial: Results



Efficacy Endpoint	Relugolix (N=622)	Leuprolide (N=308)	95% CI
Sustained testosterone level <50ng/dL	96.7%	88.8%	94.9 – 97.9

N Engl J Med 2020;382:2187-96

14

HERO Trial: Results

Secondary Endpoints	Relugolix (N=622)	Leuprolide (N=308)	P Value
Noninferiority, %	96.7	88.8	<0.001
Probability of testosterone suppression on day 15, %	98.7	12	<0.001
PSA response at day 15, %	79.4	19.8	<0.001
Profound testosterone suppression (<20ng/dl) on day 15, %	78.4	1.0	<0.001
Mean FSH level at end of wk 24, %	1.72	5.95	<0.001

N Engl J Med 2020;382:2187-96

15

HERO Trial: Adverse Events

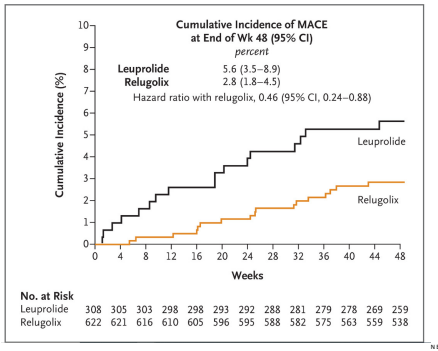
	Relugolix (N=622)	Leuprolide (N=308)
Any Adverse event – no. (%)	578 (92.9)	288 (93.5)
Serious adverse event – no. (%)	76 (12.2)	47 (15.5)
Fatal adverse event – no. (%)	7 (1.1)	9 (2.9)
MACE – no. (%) - history of MACE – no./total no. (%) + history of MACE – no./total no. (%)	18 (2.9) 15/538 (2.8) 3/84 (3.6)	19 (6.2) 11/263 (4.2) 8/45 (17.8)

Most common adverse events in both groups (>10%): hot flashes, fatigue, constipation, diarrhea, arthralgia, hypertension

N Engl J Med 2020;382:2187-96

16

HERO Trial: MACE



N Engl J Med 2020;382:2187-96

17

HERO Trial: Impact

- December 2020: FDA approved the first **oral** GnRH receptor antagonist, relugolix, for adult patients with advanced prostate cancer

LHRH Agonist	Dosing	Adverse Effects
Goserelin (Zoladex®)	3.6mg SQ every 4 weeks 10.8mg SQ every 12 weeks	Tumor flare, gynecomastia, hot flashes, erectile dysfunction, edema, injection site reaction, osteoporosis, increased CV events
Leuprolide (Lupron®, Eligard®)	7.5mg IM/SQ every month 22.5mg IM/SQ every 3 months 30mg IM/SQ every 4 months 45mg IM/SQ every 6 months	
Triptorelin	3.75mg IM every 4 weeks 11.25mg IM every 12 weeks 22.5mg IM every 24 weeks	
LHRH Antagonist	**Dosing**	**Adverse Effects**
Degarelix	240mg SQ x 1 followed by 80mg every 28 days	Injection site reactions, hot flashes, increased LFTs
Relugolix	360mg PO x 1 followed by 120mg daily	

18

Metastatic Prostate Cancer

19

Which of the following is the most appropriate treatment option?

RM is a 67 year old male with complaints of progressive swelling in his right groin area and worsening lumbar back pain who was referred to oncology after CT suspicious for metastatic cancer. PSA >2000; Adenocarcinoma of the prostate confirmed by biopsy (Gleason 5+4=9, GG5) and RM is in the office today to discuss next steps.

- Docetaxel 0%
- Docetaxel + Darolutamide 0%
- Degarelix + Darolutamide 0%
- Degarelix + Docetaxel + Darolutamide 0%

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22

ARASENS Trial

Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer

International, randomized, double-blinded, placebo-controlled phase 3 trial
- 18 years or older
- ECOG 0-1
- Metastatic prostate cancer

ADT* + docetaxel 75mg/m2 D1 every 21 days x 6 cycles

R 1:1

- Darolutamide 600mg BID
- Matched placebo

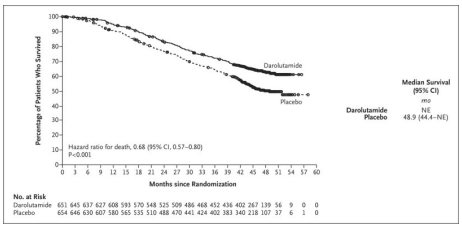
Primary endpoint: OS

N Engl J Med 2022; 386:1132-1142

23

ARASENS Trial: Results

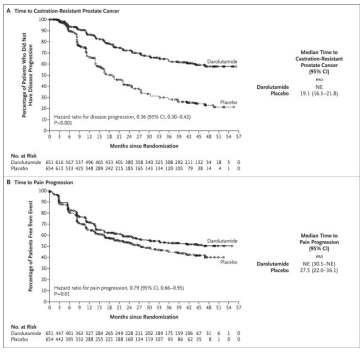
Primary end point	Darolutamide	Placebo
OS at 4 years	62.7%	50.4%



N Engl J Med 2022; 386:1132-1142

24

ARASENS Trial: Results



N Engl J Med 2022; 386:1132-1142

25

ARASENS Trial: Results

Secondary end point	Darolutamide	Placebo	P Value
Symptomatic skeletal event free survival	51.2	39.7	<0.001
Time to first SRE	NR	NR	0.02
Time to subsequent systemic therapy initiation	NR	25.3	<0.001
Time to worsening disease related symptoms	19.3	19.4	0.59
Time to opioid use for use for 7 consecutive days	NR	NR	NA

N Engl J Med 2022; 386:1132-1142

26

ARASENS Trial: Impact

- August 5, 2022: FDA approved darolutamide tablets in combination with docetaxel for adult patients with mCSPC.

M1 CSPC
ADT + one of the following: - Abiraterone (category 1) - Apalutamide (category 1) - Enzalutamide (category 1)
ADT + docetaxel + one of the following: - Abiraterone (category 1) - Darolutamide (category 1)
ADT + EBRT to primary tumor for low metastatic burden

27

What is the best treatment option for RP's metastatic CRPC?

RP is 74 year old male with PMH significant of prostate cancer, initially diagnosed in 2018. Treatment history includes EBRT, ADT with leuprolide, abiraterone, and most recently docetaxel. Patient PSA rise to 34 and disease progression confirmed by PSMA-PET.

- ADT + darolutamide 0%
- Rucaparib 0%
- Docetaxel rechallenge 0%
- Lutetium Lu-177 vipivotide tetraxetan 0%

30

VISION Trial

Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

Prospective, open-label, randomized, international, phase 3 trial
- Castrate-resistant prostate cancer
- At least 1 metastatic lesion
- Disease progression on both an ARPI and taxane regimens
- ECOG 0-2
- Life expectancy ≥ 6 months
- Adequate organ and bone marrow function

R 2:1

- Lu-PSMA-617 + standard of care*
- Standard of care*

Primary Endpoints: Imaging-based PFS and OS

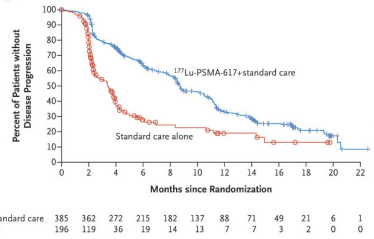
*ADT + approved hormonal therapies (abiraterone, enzalutamide), bisphosphonates, radiation therapy, denosumab, steroids

N Engl J Med 2021; 385:1091-1103

31

VISION Trial: Results

A Imaging-Based Progression-free Survival



No. at Risk

177Lu-PSMA-617+standard care	385	362	272	215	182	137	88	71	49	21	6	1
Standard care alone	196	119	36	19	14	13	7	7	3	2	0	0

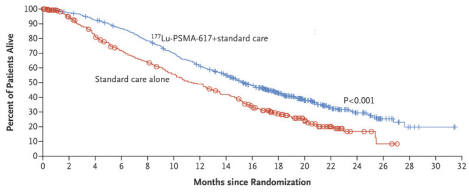
Endpoint	Lu-PSMA-617	SOC	HR	CI	P Value
Imaging-based PFS, mo	8.7	3.4	0.40	0.29 – 0.57	<0.001

N Engl J Med 2021; 385:1091-1103

32

VISION Trial: Results

B Overall Survival



No. at Risk

177Lu-PSMA-617+standard care	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
Standard care alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

Endpoint	Lu-PSMA-617 (N=551)	SOC (N=280)	HR	CI	P Value
OS, mo	15.3	11.3	0.62	0.52 – 0.74	<0.001

N Engl J Med 2021; 385:1091-1103

33

VISION Trial: Results

Secondary Endpoint	Lu-PSMA-617	SOC
Time to first symptomatic skeletal event, mo	11.5	6.8
Complete response, no. (%)	17 (9.2)	0
Partial response, no. (%)	77 (41.8)	2 (3.1)
Stable disease, no. (%)	65 (35.3)	30 (46.9)

Safety Endpoint	Lu-PSMA-617	SOC
Fatigue, no (%)	260 (49.1)	60 (29.3)
Bone marrow suppression, no (%)	251 (47.4)	36 (17.6)
Dry mouth, no (%)	208 (39.3)	2 (1.0)
Nausea ± vomiting, no (%)	208 (39.3)	35 (17.1)
Hypersensitivity, no (%)	55 (10.4)	7 (3.4)
Hepatotoxicity, no (%)	54 (10.2)	16 (7.8)

N Engl J Med 2021; 385:1091-1103

34

VISION Trial: Impact

- March 23, 2022: FDA approved Pluvicto for the treatment of adult patients with PSMA-positive metastatic-resistant prostate cancer who have been treatment with ARPI and taxane-based chemotherapy

Prior docetaxel + prior novel hormone therapy	Prior docetaxel only	Prior novel hormone only	Systemic tx naïve
• Lutetium Lu 177 vipivotide tetraxetan (category 1) **Preferred** • Cabazitaxel (category 1) • Docetaxel rechallenge	**Preferred** • Abiraterone • Cabazitaxel (category 1) • Enzalutamide	**Preferred** • Docetaxel (category 1)	**Preferred** • Abiraterone (category 1) • Docetaxel (category 1) • Enzalutamide (category 1)

35

Biomarker Testing

- Somatic mutations
  - Most common: *BRCA2* and *ATM*
  - Localized: 19%
  - Advanced/Metastatic: 23%
  - Associated with germline mutations
- Germline mutations
  - Most common: *BRCA2, CHECK2, ATM*
  - Localized: 8.9%
  - Advanced/Metastatic: 16.2%
- Testing recommendations
  - Strong family or personal history
  - Based on risk groups

36

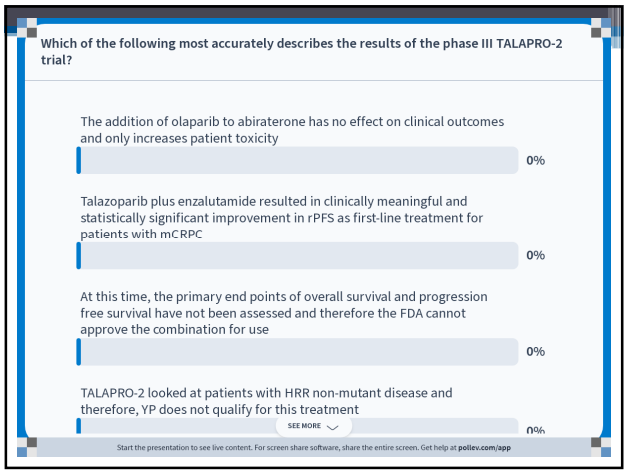
Audience Response Question

YP is a 67 year old male diagnosed with adenocarcinoma of the prostate on androgen deprivation therapy with recent progression. Workup revealed HRR mutant mCRPC. He recently heard about a new FDA approval and is asking you for information on the TALAPRO-2 trial.

Which of the following most accurately describes the results of the phase III TALAPRO-2 trial?

A. The addition of olaparib to abiraterone has no effect on clinical outcomes and only increases patient toxicity
B. Talazoparib plus enzalutamide resulted in clinically meaningful and statistically significant improvement in rPFS as first-line treatment for patients with mCRPC
C. At this time, the primary end points of overall survival and progression free survival have not been assessed and therefore the FDA cannot approve the combination for use
D. TALAPRO-2 looked at patients with HRR non-mutant disease and therefore, YP does not qualify for this treatment

37



39

TALAPRO-2 Trial

Talazoparib plub enzalutamide in men with first-line metastatic castration-resistant prostate cancer

Double-blind, randomized, placebo-controlled trial
- 18 years or older
- Receiving ADT
- mCRPC
- ECOG 0-1
- Adequate bone marrow function
- Not received previous life-prolonging therapy

R 1:1

Talazoparib 0.5mg once daily + enzalutamide 160mg once daily

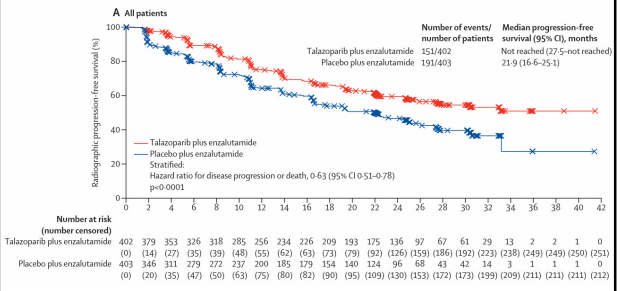
Matched placebo + enzalutamide 160mg once daily

Primary Endpoint: Radiographic PFS

Lancet 2023; 402: 291–303

40

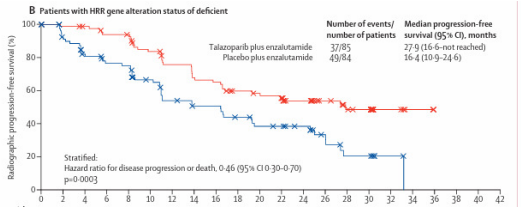
TALAPRO-2 Trial: Results



Lancet 2023; 402: 291–303

41

TALAPRO-2 Trial: Results



Lancet 2023; 402: 291–303

42

TALAPRO-2 Trial: Impact

- June 20, 2023: FDA approved talazoparib with enzalutamide for homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer.

No prior docetaxel/No prior novel hormonal therapy	Prior novel hormonal therapy/No prior docetaxel
Useful in certain circumstances • Niraparib/abiraterone for BRCA mutation (category 1) • Olaparib/abiraterone for BRCA mutation (category 1) • Radium-223 for sx bone metastases (category 1) • Sipuleucel-T (category 1) • Talazoparib/enzalutamide for HRRm (category 1)	**Useful in certain circumstances** • Cabazitaxel/carboplatin • Niraparib/abiraterone for BRCA mutation (category 2B) • Olaparib for HRRm (category 1) • Radium-223 for sx bone metastases • Sipuleucel-T • Talazoparib/enzalutamide for HRRm (category 1)

43

Future Horizons

CYCLONE Trials

- CYCLONE 1: Abemaciclib (LY2835219) in Men With Heavily Treated Metastatic Castration-Resistant Prostate Cancer
- CYCLONE 2: A Study of Abiraterone Acetate Plus Prednisone With or Without Abemaciclib (LY2835219) in Participants With Prostate Cancer
- CYCLONE 3: A Study of Abemaciclib (LY2835219) With Abiraterone in Men With Prostate Cancer That Has Spread to Other Parts of the Body and is Expected to Respond to Hormonal Treatment (Metastatic Hormone-Sensitive Prostate Cancer)

ALADDIN Trial

- Evaluation of dAroLutamide Addition to anDrogen Deprivation Therapy and radIatioN Therapy in Newly Diagnosed Prostate Cancer With Pelvic Lymph Nodes Metastases

ATLAS Trial

- An Efficacy and Safety Study of JNJ-56021927 (Apalutamide) in High-risk Prostate Cancer Subjects Receiving Primary Radiation Therapy

Clinicaltrials.gov

44

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45

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46