Sequencing therapy in prostate cancer:

UCLA State of the Art Urology 2020

Nicholas J Vogelzang MD

Vice Chair SWOG GU Committee
Comprehensive Cancer Centers of Nevada
US Oncology GU Research

Clinical Professor of Medicine
University of Nevada School of Medicine
Las Vegas, NV
Top 10 clinical advances

1. FDA approval of enzalutamide and apalutamide in metastatic hormone sensitive prostate cancer mHSPC
2. PSMA scanning is a major advance and expands pool of mHSPC
3. Oligo mHSPC management is rapidly evolving but probably requires Radiation to disease sites plus ADT. STOMP showed RT to all sites can delay need for ADT
4. Nearly all hormone sensitive metastatic patients should get 2 or more drugs (Leuprolide + 1 is the new standard)
5. FDA approval of enza, apa and darolutamide in non-metastatic CRPC
6. Abiraterone and enzalutamide are cross resistant in 90+% of cases, ARV7 identifies some resistant pts
7. Cabazitaxel is superior to 2nd line abi/enza in docetaxel resistant patients
8. PARP inhibitors will be FDA approved in 2020 and will require urologists to test for DNA mutations
9. Sip T and Radium continue to be important agents in mCRPC (African American and pain data)
10. New ARi agents are being developed but 20-30% of mCRPC lose AR thru clonal evolution so non-AR targeting is needed (pembrolizumab, cabometyx/atezo, CDK 9, etc)
In 1966, Dr. Huggins received the Nobel Prize (shared with virologist Peyton Rous) for his research on the relationship between hormones and prostate cancer. The Nobel Committee cited his "fundamental discoveries concerning the hormone dependence of normal and neoplastic cells in experimental animals and their immediate practical application to the treatment of human prostatic and breast cancer." The Committee went on to note that his work had "already given many years of an active and useful life to patients with advanced cancer over the entire civilized world--patients who would have been lost to other forms of therapy."
Charlie knew HSPC

- Hormone sensitivity (via castration/inhibition of AR) is short term
- Adrenal androgens play a role
- There were good and bad cancers
- Before he died, he told me that hormones were not the solution
- He saw the benefit of chemo in cancer

- PS the AR was discovered in Charlie’s lab, the Ben May, by Geoff Greene

Charlie did not know CRPC

- PSA/Acid Phos is a surrogate of AR action
- The AR has multiple ligands
- Prostate cancer cells produce their own ligands for AR
- Genetic variants of prostate cancer
- And many others 😊
A short History of hormone sensitive prostate ca

• Castration effective 1940, Huggins Nobel 1966
• Adrenalectomy occ effective 1950’s
• LHRH replaces castration 1971-1985 Schally Nobel 1977
• Anti-androgens (flutamide to apalutamide) improve on castration (Labrie hypothesis) esp in low vol disease
• Intra-prostatic cancer production of androgens 1993-2006
• 3 phase 3 trials document improved survival with abiraterone, enzalutamide and apalutamide
• 2.5 phase 3 trials documented improved survival with docetaxel added to LHRHa (GETUG, CHAARTED, STAMPEDE)
Androgen Receptor Overexpression is Frequent in Castration Resistant Tumors and is a Target for Therapy

Increased AR protein
AR mRNA overexpression
Increased AR DNA copy number
Increased androgen synthesis

Scher et al.
Endocrine-Related Cancer 11:2004;459
Abiraterone highly effective in early mCRPC

No prior Ketoconazole exposure (12/21)
Prior Ketoconazole exposure (5/17)
Enzalutamide highly effective in early mCRPC

Chemotherapy-Naïve (N=65)  
62% (40/65) >50% Decline

Post-Chemotherapy (N=75)  
51% (38/75) >50% Decline

Scher et al  Proc ASCOAbstract # 5011
Summary of mHSPC Rx

1. For mHSPC - ADT alone, or ADT with bicalutamide is no longer a good option (unless significant co-morbidities).
2. 2nd generation androgen axis inhibitors (abi, enza, apa) will significantly delay time to mCRPC and improve overall survival in both low and high volume disease.
3. Docetaxel also significantly delays time to mCRPC (debate about its effect in low vs high vol. and de novo disease)
4. Many oncologists start with docetaxel and add maintenance abi or enza. Merck 991 study will randomize enza after docetaxel +/- Pembrol
5. Referral to GU med Onc when? High vol/young/AA/genetic
What Determines Whether a Patient Is Castrate Refractory?

- Has an attempt been made to suppress the patient’s testosterone production through orchiectomy or hormone suppression therapy with an LHRH agonist with or without an antiandrogen (ie, ADT)?
- Is the patient’s testosterone level < 50 ng/mL?
- This state is INDEPENDENT of PSA status since PSA may not rise

If the answer to both is yes, the patient is castrate resistant
Tumor progression to CRPC is due to AR-associated signaling mechanisms

- Receptor overexpression (gene amplification and/or protein overexpression)
- AR mutations leading to receptor promiscuity or structure-function activation
- Increased AR ligand expression in surrounding tissue
- AR activation by coactivators
- Ligand-independent receptor activation via other pathways
- Ligand hypersensitivity subsequent to AR expression

Regardless of event type, the ultimate consequence is activation of the AR signaling cascade and resulting tumor growth, survival, and proliferation despite castrate androgen levels

What’s a urologist to do after castration resistance develops?

- **If mets were present at Dx and 1st line ARi (abi/enza) was used (classical mCRPC)**
  - Re-image and look to radiate oligo mets, measure T
  - If bone only use Radium 223
  - If nodal mets only use Provenge
  - Test for DNA repair germline or somatic and consider PARPi
  - Can use alternative ARi but don’t expect much
  - Refer for taxane Rx

- **If no mets at Dx (or equivocal/nodes) at Dx and 1st line ARi (abi/enza) was not used (nmCRPC)**
  - Re-image (PSMA) and look to radiate oligo mets, measure T
  - Begin, enza, apa or darolutamide
  - Test for DNA repair germline or somatic and consider PARPi as next Rx

- **If mets were present at Dx and 1st line docetaxel was used, no prior ARi (classical mCRPC)**
  - The world is your oyster, Median survival 3+ yrs
  - Re-image and look to radiate oligo mets; measure T
  - If bone only ABI/ENZA and follow with Provenge and Radium 223
  - Test for DNA repair germline or somatic and if positive consider PARPi

- **If mets were present at Dx and 1st line docetaxel and ARi was used (AR resistant mCRPC)**
  - Houston we have a problem
  - Re-image and look to radiate oligo mets
  - Provenge and Radium 223 (bone dominant)
  - Test for DNA repair germline or somatic and if positive consider PARPi
  - Cabazitaxel preferred
10 Tips for castration resistance care by urologists

1. Continue LHRHa
2. Monitor PSA rate of rise. If >12 months DT reassure patient and re-image.
3. If bone and CAP negative, consider PSMA PET
4. Test for ARV-7 if patient is ARV-7 negative 2\textsuperscript{nd} line enza or apa may work (see next slide), if positive refer for taxanes
5. Use abiraterone 1\textsuperscript{st} line, enzalutamide is more likely effective 2\textsuperscript{nd} line
6. Test for DNA repair deficiency; cell free, germline or somatic and consider PARPi
7. Continue either denosumab or zoledronic acid every 3months (not monthly) but watch for ONJ
8. Refer for/use Provenge
9. Use Radium when bone mets are dominant; always give with bone health agents (BHA), can give with abi or enza if BHA used (5% fracture rate)
10. Begin to explain that docetaxel and cabazitaxel are not evil and to be avoided
Abs 5004 - PROPHECY study

When should I recommend Abi/Enza after Enza/Abi?

- **POSTIVE**
  - ARV7 TEST
    - Patients with mCRPC after Abi/Enza
    - NO ARV7 TEST
      - Standard of care at Physician discretion
  - Docetaxel/other

- **NEGATIVE**
  - Enza/Abi/other

After Antonarakis and Scher, *European Urology*, 71 (2017); 4-7
Abs 5004 - PROPHECY study

When should I recommend Chemotherapy over Abi/Enza?

- High burden of disease with low PSA
- (High) burden of visceral metastases
- Severe symptoms
- Minimal response to primary ADT
- Consider if
  - LDH high
  - High ALP esp in conjunction with above
  - >5 CTCs by cellsearch

Slide adapted and courtesy of Dr Fred Saad
New directions for ARi in mCRPC

• Dual AR inhibition trials (abi/enza) negative
• 2\textsuperscript{nd} line ARi rarely is effective
• More reliable abiraterone formulations/ better absorption
• 1 abi/d with meal appears equivalent to 4/d on empty stomach
• Androgen receptor degrader: Arvinas
• N-terminal domain inhibitors: Essa
• More potent AR inhibitors: Tracon, Kintor
• Combine with PARP inhibitors (many DNA repair enzymes are AR responsive)
Abs 5003 - Olaparib combined with abiraterone

**Background**

Polkinghorn et al., Cancer Discovery, 2013 (3) (11) 1245-1253
Abs 5003 - Olaparib combined with abiraterone
How Androgen depletion affects PARP

Asim et al., Nature Communications, 2017 Aug 29;8(1):374
Abs 5003 - Olaparib combined with abiraterone

**Trial design**

- mCRPC
- Prior treatment with docetaxel for mCRPC
- ≤2 prior lines of chemotherapy
- No prior 2nd-generation antihormonal agents
- Candidate for abiraterone treatment

Olaparib tablets
- 300 mg bid
- + abiraterone* 1000 mg od

Randomized 1:1
Double-blind

Primary endpoint:
- Radiologic progression-free survival (RECIST 1.1; PCWG2)

Treatment until disease progression

*Prednisone/prednisolone (5 mg) was administered alongside abiraterone as indicated. bid, twice daily; CTC, circulating tumor cell; HRRm, homologous recombination repair gene mutation; mCRPC, metastatic castration-resistant prostate cancer; od, once daily; PCWG, Prostate Cancer Working Group; RECIST, Response Evaluation Criteria in Solid Tumors; RPFPS, radiologic progression-free survival.
Primary endpoint: investigator-assessed rPFS

Progression Free Survival & Overall Survival

- No difference in PFS by ETS status

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<th>Olap +abi (n=71)</th>
<th>Abi (n=71)</th>
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<tr>
<td>Median OS (95% CI):</td>
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<tr>
<td>Arm A: 30.6 m (28.4 - NR)</td>
<td>46 (65)</td>
<td>54 (76)</td>
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<td>Arm B: 32.3 m (28.4 - NR)</td>
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<tr>
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<tr>
<td>95% CI</td>
<td>0.44, 0.97; P=0.034</td>
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</table>

Abi, abiraterone; CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; olap, olaparib
New directions in mCRPC for AA men

• AA men are less sensitive to AR inhibition (Sharifi et al)
• AA men are more responsive to taxane Rx (?more than 6 doses)
• AA men may have more DNA repair mutations (PARPi and platinum sensitive)
• AA men may be more responsive to Provenge
• Specific trials of Checkpoint inhibitor trials needed
KEYNOTE-199: Pembrolizumab For Post-Docetaxel Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Johann S. de Bono, 1 Jeffrey Goh, 2 Kristlina Ojamaa, 3 Marine Gross-Goupil, 4 Josep Pluvia, 5 Charles G. Drake, 6 Christopher J. Holmes, 7 Haiyan Wu, 8 Ping Qiu, 9 Christian Poehlein, 10 Emmanuel S. Antonarakis 10

1Royal Marsden and The Institute of Cancer Research, London, UK; 2Royal Brisbane & Women’s Hospital, Herston, and University of Queensland, St. Lucia, QLD, Australia; 3East Tallinn Central Hospital, Tallinn, Estonia; 4Institut Bergonié, Bordeaux, France; 5Instituto Catalán de Oncología, Hospital Duran i Reynals, Hospital de Lleópolat, Barcelona, Spain; 6Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY, USA; 7Case Western Reserve University Hospitals Seidman Cancer Center, Cleveland, OH, USA; 8MDC China, Beijing, China; 9Merck & Co., Inc., Kenilworth, NJ, USA; 10Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA

KEYNOTE-199 Study Design

- mCRPC
- ≥1 prior targeted endocrine therapy
- ≥2 prior chemotherapy regimens, including docetaxel
- ECOG PS 0-2
- Measurable disease per RECIST v1.1

Cohort 1: PD-L1 positive
Cohort 2: PD-L1 negative
Cohort 3: PD-L1 negative
Cohort 4: RECIST-measurable disease
Cohort 5: RECIST-non-measurable disease

Treatment in all cohorts: pembrolizumab 200 mg Q3W for 35 cycles or until confirmed PD, intolerable toxicity, investigator decision, or patient withdrawal

Change From Baseline in PSA, Cohorts 1+2+3

Change From Baseline in Sum of Target Lesions, Cohorts 1+2

*Percentages are calculated out of the 193 patients who had ≥1 post-baseline PSA elevation per RECIST v1.1 by independent, central review.

Presented By Johann De Bono at 2018 ASCO Annual Meeting
**Responder 1**

- **Disease course**
  - Initial diagnosis: TXNXXM GS9 (4 + 5)
  - High-risk disease (Jul 2010)
  - Metastasized to lymph nodes (Sep 2014)
- **Prior systemic therapy**
  - Bicalutamide (Oct 2011-Sep 2014)
  - Docetaxel (Apr 2015-Oct 2015)
  - Enzalutamide (Oct 2015-Mar 2016)
- **Enrolled in KEYNOTE-199 cohort 1**
  - Age 67 years
  - First pembrolizumab: Nov 8, 2016
  - Cycle 24 of pembrolizumab: May 9, 2018
  - RECIST: 94% reduction

**Baseline**

(Oct 16, 2016)

**Current**

(May 8, 2018)

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**Responder 2**

- **Disease course**
  - Initial diagnosis: TXNXXM GS10 (5 + 5)
  - Metastasized to lymph nodes (Nov 2009)
  - Rectovaginal fistula (2012)
- **Prior systemic therapy**
  - Sunitinib (Nov 2009-Aug 2010)
  - Docetaxel (Mar 2015-Nov 2015)
  - Enzalutamide (Jan 2016-Jul 2016)
- **Enrolled in KEYNOTE-199 cohort 1**
  - Age 70 years
  - Prior pembrolizumab: Nov 8, 2016
  - Last cycle (cycle 13): Jan 13, 2017
  - Last survival follow-up: May 4, 2018
  - No radiological or biochemical evidence of disease (May 2018)

**Nov 2016 (Baseline): Bowel fistula**

**Mar 2017 (Presurgery): Bowel fistula shows responding tumor cavity**

**Jan 2018: Residual postsurgical cavity, no active disease on whole body MRI**

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**Summary and Conclusions**

- **Pembrolizumab has antitumor activity and acceptable safety in patients with mCRPC treated with docetaxel**
  - Activity observed in PD-L1–positive and PD-L1–negative cohorts
  - Activity observed in patients with RECIST-measurable disease and in those with bone-predominant disease
- **Biomarker work ongoing, but suggests that DNA repair defects may be associated with antitumor activity**
  - Low number of responses overall makes interpretation difficult
- **Further evaluation of pembrolizumab as monotherapy and as part of combination therapy is ongoing**

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*Patient was treated at the Royal Marsden in London, UK. Images courtesy of Johann de Bono.*

*Presented by Johann de Bono at 2018 ASCO Annual Meeting*
Conclusions

• The continuum from mHSPC to mCRPC may occur over years to decades but is inevitable if men live long enough. De novo and high vol mHSPC is bad
• Delaying time to mCRPC is likely by adding docetaxel or abi/enza/apa to initial ADT
• Additional drugs (i.e. 3 or 4 drugs) added to the traditional 2 drug regimens may further delay time to mCRPC. Trials awaited
• Time from mCRPC to death can be delayed with cabazitaxel, SipT, Radium and PARP inhibitors (in DNA repair deficient cancers). All such agents should be used if possible
• Agents such as platinum, checkpoint inhibitors and others may also delay time to death.
• Please refer mCRPC patients for clinical trials
Diagnostic Performance of $^{18}$F-DCFPyL-PET/CT and its Impact on Clinical Management of Patients with Biochemically Recurrent Prostate Cancer: Results from a Phase 3, Prospective, Multicenter Study (CONDOR)

Michael J. Morris*, Peter R. Carroll, Lawrence Saperstein, Frédéric Pouliot, David Josephson, Jeffrey Y.C. Wong, Austin R. Pantel, Steve Y. Cho, Kenneth Gage, Morand Piert, Andrei Iagaru, Janet H. Pollard, Vivien Wong, Jessica Donato Jensen, Nancy Stambler, Michael A. Gorin, Barry A. Siegel

Memorial Sloan Kettering Cancer Center, New York, NY; Dept. of Urology, University of California San Francisco, San Francisco, CA; Yale School of Medicine, New Haven, CT; Cancer Research Center, Centre Hospitalier Universitaire (CHU) de Québec-Université Laval, Quebec City, QC; Tower Urology, Los Angeles, CA; City of Hope, Duarte, CA; University of Pennsylvania, Philadelphia, PA; University of Wisconsin School of Medicine, Madison, WI; Moffitt Cancer Center, Tampa, FL; University of Michigan, Ann Arbor, MI; Stanford University, Stanford, CA; Carver College of Medicine - University of Iowa, Iowa City, IA; Progenics Pharmaceuticals, Inc., New York, NY; Department of Urology, Johns Hopkins University School of Medicine, Baltimore, MD; Siteman Cancer Center/Washington University, Saint Louis, MO
Background

• Previous data have suggested PSMA-PET is a superior imaging modality for prostate cancer relative to current standards

• $^{18}$F-DCFPyL is a PSMA-targeted PET radiopharmaceutical being studied to collect an evidentiary database in support of regulatory approval in the US

• CONDOR is the second of two prospective clinical trials designed in collaboration with FDA to demonstrate the diagnostic performance of $^{18}$F-DCFPyL-PET/CT
**18F-DCFPyL Clinical Development Program**

OSPREY Cohort A: Preoperative, with pathology comparator

**CONDOR**
(composite truth standard; pathology hard to secure)

OSPREY Cohort B: locally recurrent or metastatic disease to be biopsied (pathology comparator)

PCWG3 JCO 2016

Michael J. Morris, MD
$^{18}$F-DCFPyL

- Lysine-linked, urea-based small molecule
- Targets the extracellular domain of PSMA
- High specific activity
- 9 (±20%) mCi administered intravenously as bolus injection
- Imaging performed 1-2 hours following administration

Chen et al. Clin Cancer Res 2011; laboratory of Martin G. Pomper, MD, PhD
Eligibility Criteria

Select Inclusion Criteria
- Post-RP: PSA $\geq 0.2$ ng/mL or
- Post-RT or cryotherapy: PSA $\geq 2$ ng/mL above nadir
- Negative or equivocal imaging per institution’s SOC work-up (including bone scan, CT, MRI, FDG PET, $^{18}$F-fluciclovine or $^{11}$C-choline PET)

Select Exclusion Criteria
- Ongoing treatment with any systemic therapy
- Treatment with ADT within 3 months prior to Day 1

Michael J. Morris, MD
Composite Standard of Truth (SOT)

Defined either as:

1) Evaluable local histopathology findings from surgery/biopsy, or

2) Informative conventional imaging [e.g., $^{18}$F-fluciclovine PET (preferred if not performed at baseline) or choline PET; targeted MRI/CT], or

3) Confirmed PSA response (decline from baseline of ≥50%) in subjects treated with RT only (no concomitant ADT) following $^{18}$F-DCFPyL-PET/CT imaging
# Select Baseline Characteristics, N=208

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<tr>
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<tr>
<td>Patients dosed (N)</td>
<td>208</td>
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<tr>
<td>Age (years): Median (range)</td>
<td>68 (43, 91)</td>
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<tr>
<td>Months from Prostate Cancer Diagnosis: Median (range)</td>
<td>71 (3, 356)</td>
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<tr>
<td>Prior Prostate Cancer Therapies, N (%)</td>
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<td>&lt; 8</td>
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<td>55 (26.4)</td>
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<td>PSA: Median (range) ng/mL</td>
<td>0.8 (0.17, 98.45)</td>
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<td>PSA Group (N=202), N (%)</td>
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<td>&lt;2.0 ng/mL</td>
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### PSA: Median (range) ng/mL
- 0.8 (0.17, 98.45)

### PSA Group (N=202), N (%)
- <2.0 ng/mL
  - <0.5 ng/mL: 69 (34.2)
  - 0.5 to <1.0 ng/mL: 37 (18.3)
  - 1.0 to <2.0 ng/mL: 33 (16.3)
- ≥2.0 ng/mL
  - 2.0 to <5.0 ng/mL: 33 (16.3)
  - ≥5.0 ng/mL: 30 (14.9)
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**PSA:** Median (range) ng/mL  
0.8 (0.17, 98.45)

**PSA Group (N=202), N (%):**  
- <2.0 ng/mL: 139 (68.8)  
  - <0.5 ng/mL: 69 (34.2)  
  - 0.5 to <1.0 ng/mL: 37 (18.3)  
  - 1.0 to <2.0 ng/mL: 33 (16.3)  
- ≥2.0 ng/mL: 63 (31.2)  
  - 2.0 to <5.0 ng/mL: 33 (16.3)  
  - ≥5.0 ng/mL: 30 (14.9)
Detection Rate by PSA

Median values for each group of three readers provided

Michael J. Morris, MD
Change of Management

- 63.9% of evaluable subjects had a change in intended management after $^{18}$F-DCFPyL-PET/CT

  - 78.6% were attributable to positive and 21.4% to negative $^{18}$F-DCFPyL-PET/CT scans

  - Noncurative systemic therapy to salvage local therapy ($n = 43; 21.0\%$)
  - Salvage local therapy to systemic therapy ($n = 58; 28.3\%$)
  - Observation to initiating therapy ($n = 49; 23.9\%$)
  - Planned treatment to observation ($n = 9; 4.4\%$)
Efficacy Summary

• The CONDOR study has met its primary endpoint, demonstrating excellent diagnostic performance of $^{18}$F-DCFPyL-PET/CT imaging in men with biochemically relapsed prostate cancer, even at low PSA values.

• $^{18}$F-DFPyL-PET/CT is superior to standard imaging in men with BCR.

• The results yielded actionable information clinically significant information. Optimized treatment patterns need to be further defined.

• This trial, coupled with the OSPREY study, has now established the performance characteristics of $^{18}$F-DCFPyL-PET/CT in localized, BCR, and metastatic prostate cancer.

Michael J. Morris, MD
FDA grants accelerated approval to rucaparib for BRCA-mutated metastatic castration-resistant prostate cancer

On May 15, 2020, the Food and Drug Administration granted accelerated approval to rucaparib (RUBRACA, Clovis Oncology, Inc.) 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.
Phase III PROfound Study: Study Design

Key eligibility criteria:
- mCRPC with disease progression on prior NHA, eg abiraterone or enzalutamide
- Alterations in ≥1 of any qualifying gene with a direct or indirect role in HRR

Stratification factors:
- Previous taxane
- Measurable disease

Cohort A: BRCA1, BRCA2 or ATM
N=245
2:1 randomization
Open-label
- Olaparib 300 mg bid
n=162
- Physician’s choice†
n=83
Upon BICR progression, physician’s choice patients were allowed to cross over to olaparib

Cohort B: Other alterations
N=142
- Olaparib 300 mg bid
n=94
- Physician’s choice†
n=48

Primary Endpoint
- Radiographic progression-free survival (rPFS) in Cohort A (RECIST 1.1 & PCWG3 by BICR)

Key Secondary Endpoints
- rPFS in Cohorts A+B
- Confirmed radiographic objective response rate (ORR) in Cohort A
- Time to pain progression (TTPP) in Cohort A
- Overall survival (OS) in Cohort A

*An investigational Clinical Trial Assay, based on the FoundationOne® CDx next-generation sequencing test
Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and/or RAD54L in their tumor tissue
Phase III PROfound Study

Prespecified HRR-Associated Genes

- BRCA1
- BRCA2
- ATM
- BRIP1
- BARD1
- CDK12
- CHEK1
- CHEK2
- FANCL
- PALB2
- PPP2R2A
- RAD51B
- RAD51C
- RAD51D
- RAD54L

Alteration in ≥ 1 of these genes found in 28% (n = 778) of 2792 samples
PROfound: PFS by Subgroup
(Overall Population)

- **Subgroup**
  - All patients
  - Previous taxane use
    - Yes
    - No
  - Measurable disease at baseline
    - Yes
    - No
  - Metastases at baseline
    - Bone only
    - Visceral
    - Other
  - ECOG score at baseline
    - 0
    - 1
    - 2
  - Age at randomization
    - <65 yr
    - ≥65 yr
  - Region
    - Asia
    - Europe
    - North and South America
  - PSA at baseline
    - ≥Median
    - <Median
  - Gene alteration
    - BRCA1
    - BRCA2
    - ATM
    - CDK12
    - CHEK2
    - PPP2R2A
    - RAD54L

- **Hazard Ratio for Progression or Death (95% CI)**
  - All patients: 0.49 (0.38–0.63)
  - Previous taxane use:
    - Yes: 0.39 (0.29–0.53)
    - No: 0.77 (0.50–1.22)
  - Measurable disease at baseline:
    - Yes: 0.41 (0.30–0.56)
    - No: 0.64 (0.43–0.98)
  - Metastases at baseline:
    - Bone only: 0.57 (0.33–0.94)
    - Visceral: 0.42 (0.28–0.64)
    - Other: 0.57 (0.37–0.89)
  - ECOG score at baseline:
    - 0: 0.67 (0.46–1.00)
    - 1: 0.45 (0.32–0.64)
    - 2: 0.31 (0.10–1.13)
  - Age at randomization:
    - <65 yr: 0.53 (0.34–0.85)
    - ≥65 yr: 0.52 (0.39–0.70)
  - Region:
    - Asia: 0.67 (0.44–1.04)
    - Europe: 0.48 (0.33–0.71)
    - North and South America: 0.43 (0.26–0.73)
  - PSA at baseline:
    - ≥Median: 0.46 (0.33–0.65)
    - <Median: 0.65 (0.44–0.96)
  - Gene alteration:
    - ATM: 1.04 (0.61–1.87)
    - CDK12: 0.74 (0.44–1.31)
    - CHEK2: 0.87 (0.47–1.63)
    - PPP2R2A: 6.61 (1.41–26.42)
    - RAD54L: 0.33 (0.05–2.34)

- **Olaparib Better vs Control Better**
Phase III PROfound Study: Subgroup Analyses of rPFS in Cohort A
FDA approves olaparib for HRR gene-mutated metastatic castration-resistant prostate cancer

On May 19, 2020, the Food and Drug Administration approved olaparib (LYNPARZA, AstraZeneca Pharmaceuticals, LP) 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.

Today, the FDA also approved FoundationOne CDx (Foundation Medicine, Inc.) for selection of patients with mCRPC carrying HRR gene alterations and BRACAnalysis CDx test (Myriad Genetic Laboratories, Inc.) for selection of patients with mCRPC carrying germline *BRCA1/2* alterations as companion diagnostic devices for treatment with olaparib.
NCCN Guidelines: Prostate Cancer Version 2.2020

- Olaparib is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in a HRR gene (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51D, RAD54L), who have been treated with AR-directed therapy.
  - Patients with PPP2R2A mutations in the PROfound trial experienced an unfavorable risk-benefit profile. Therefore, olaparib is not recommended for patients with a PPP2R2A mutation.

- Rucaparib is a treatment option for patients with mCRPC and a pathogenic BRCA1 or BRCA2 mutation (germline and/or somatic) who have been treated with AR-directed therapy and a taxane-based chemotherapy.
  - If the patient is not fit for chemotherapy, rucaparib can be considered even if taxane-based therapy has not been given.