# Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

## Prostate Cancer

**Wednesday, March 1, 2023**
**5:00 PM – 6:00 PM ET**

### Faculty

**Tanya B Dorff, MD**
**A Oliver Sartor, MD**

### Moderator

**Neil Love, MD**

RTP Year in Review 2023

# Faculty

**Tanya B Dorff, MD**
Associate Professor of Medicine
Department of Medical Oncology
and Developmental Therapeutics
Section Chief, Genitourinary Cancer Program
City of Hope National Medical Center
Los Angeles, California

**A Oliver Sartor, MD**
Laborde Professor for Cancer Research
Medical Director, Tulane Cancer Center
Associate Dean for Oncology
Tulane Medical School
New Orleans, Louisiana

**MODERATOR**
**Neil Love, MD**
Research To Practice
Miami, Florida

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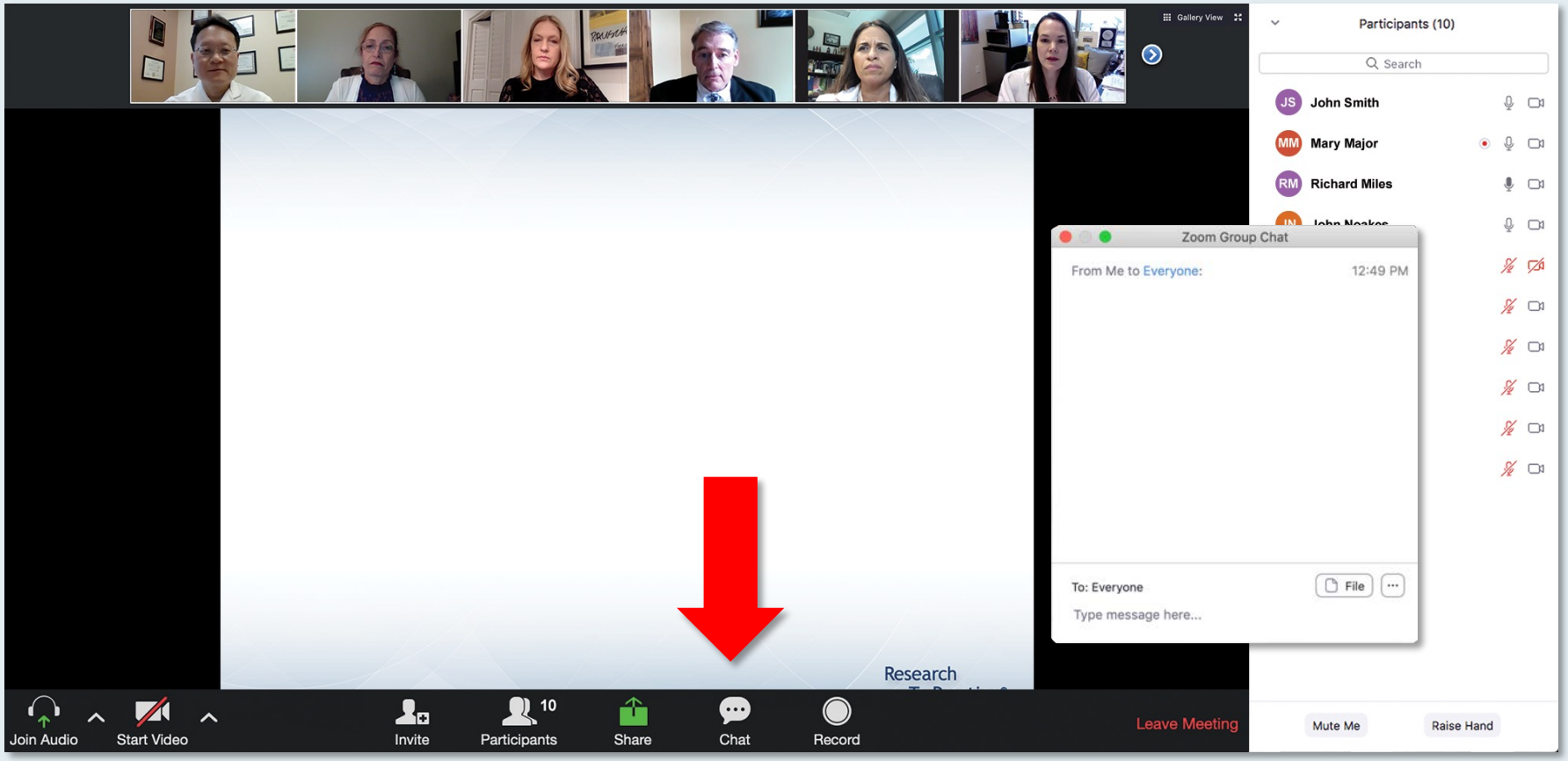


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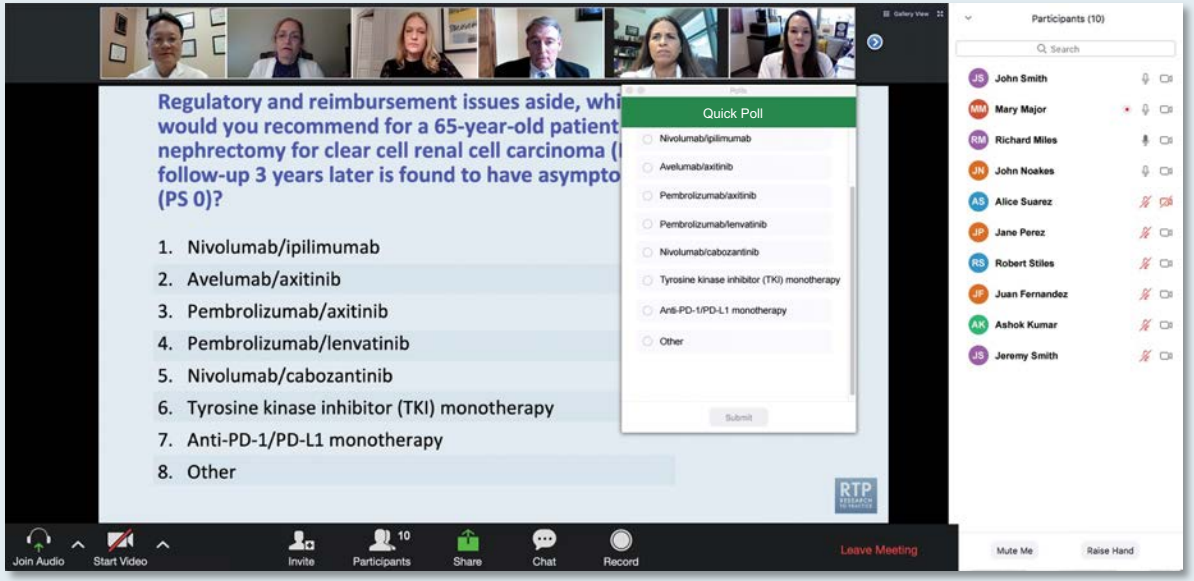


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# ONCOLOGY TODAY

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# Managing Metastatic Urothelial Bladder Cancer


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*A Multitumor CME/MOC-Accredited Live Webinar Series*

# Kidney and Bladder Cancer

**Thursday, March 2, 2023**
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## Faculty

**Matthew Milowsky, MD**

**Thomas Powles, MBBS, MRCP, MD**

## Moderator

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RTP Year in Review 2023

# *Meet The Professor*

# Optimizing the Management of ER-Positive and Triple-Negative Breast Cancer

**Tuesday, March 7, 2023**
**5:00 PM – 6:00 PM ET**

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**Sara M Tolaney, MD, MPH**

## Moderator

**Neil Love, MD**

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# Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Gastroesophageal and Hepatobiliary Cancers — A 2023 Post-ASCO GI Webcast

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## General Medical Oncologists

**Eric H Lee, MD, PhD**

**Neil Morganstein, MD**

**Swati Vishwanathan, MD**

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**Neil Love, MD**

RTP RESEARCH TO PRACTICE

# *Meet The Professor*
# Optimizing the Management of Colorectal Cancer

**Wednesday, March 22, 2023**
**5:00 PM – 6:00 PM ET**

## Faculty

**John Strickler, MD**

## Moderator

**Neil Love, MD**

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# Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Ovarian Cancer

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RTP RESEARCH TO PRACTICE

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# Dr Love — Disclosures

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Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

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# Agenda

**MODULE 1: Castration-Sensitive Prostate Cancer**

**MODULE 2: PARP Inhibitors in Castration-Resistant Disease**

**MODULE 3: Radiopharmaceuticals**

**MODULE 4: Appendix**

*Thank you for joining us!*

*CME and MOC credit information will be emailed to each participant within 5 business days.*

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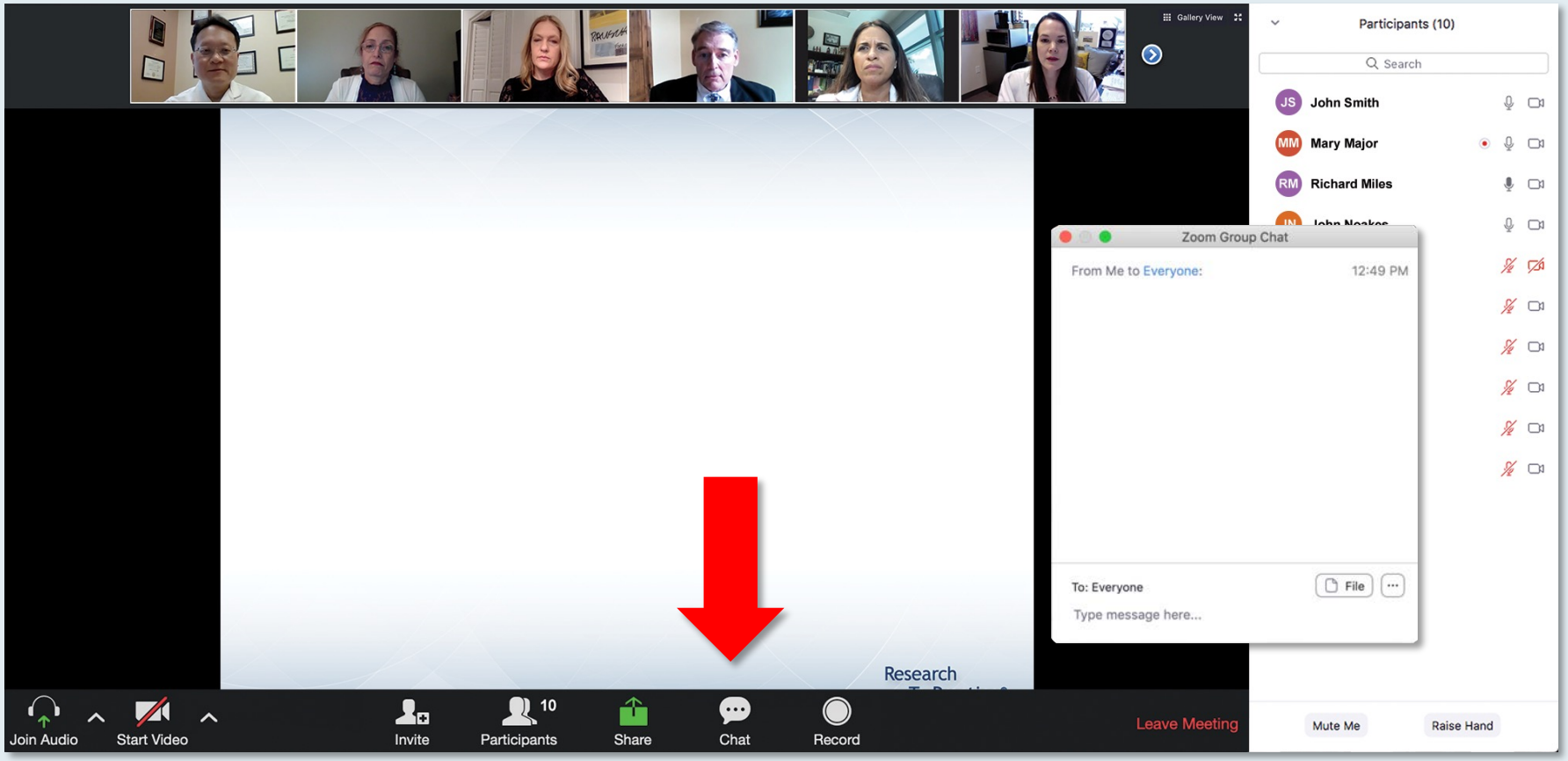


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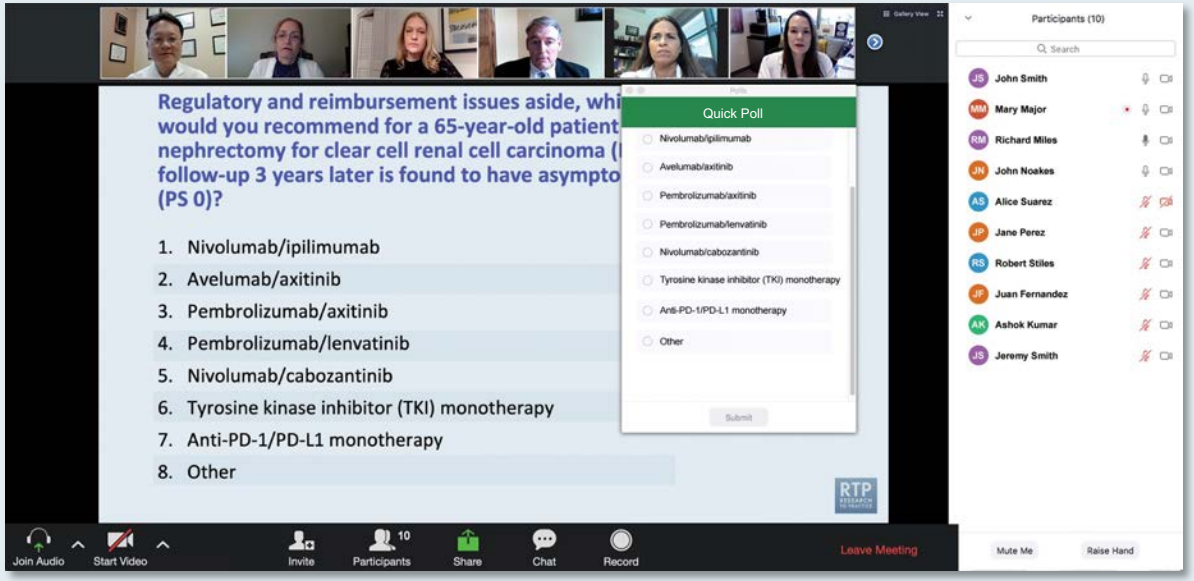


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City of Hope

# Year in Review: Optimizing use of Hormonal Therapy In Prostate Cancer

Tanya Dorff, MD
Associate Professor of Medicine
Section Chief, Genitourinary Cancer Program

# Selected Highlights in Advanced Prostate Cancer: 2022-2023

**Oliver Sartor, MD**
Laborde Professor of Cancer Research
Medical Director Tulane Cancer Center
Departments of Medicine and Urology
Assistant Dean for Oncology
Tulane Medical School
New Orleans, Louisiana

1

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# Key Data Sets

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- Aggarwal R et al. PRESTO: A phase III, open-label study of androgen annihilation in patients (pts) with high-risk biochemically relapsed prostate cancer (AFT-19). ESMO 2022;Abstract LBA63.
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- James ND et al. Abiraterone acetate plus prednisolone for metastatic patients starting hormone therapy: 5-year follow-up results from the STAMPEDE randomised trial (NCT00268476). *Int J Cancer* 2022;151(3):422-34.
- Baciarello G et al. Impact of abiraterone acetate plus prednisone in patients with castration-sensitive prostate cancer and visceral metastases over four years of follow-up: A post-hoc exploratory analysis of the LATITUDE study. *Eur J Cancer* 2022;162:56-64.

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- Davis ID et al. Updated overall survival outcomes in ENZAMET (ANZUP 1304), an international, cooperative group trial of enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC). ASCO 2022;Abstract LBA5004.
- Armstrong AJ et al. Improved survival with enzalutamide in patients with metastatic hormone-sensitive prostate cancer. *J Clin Oncol* 2022;40(15):1616-22.
- Smith MR et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med* 2022;386(12):1132-42.
- Hussain MHA et al. Efficacy and safety of darolutamide (DARO) in combination with androgen-deprivation therapy (ADT) and docetaxel (DOC) by disease volume and disease risk in the phase 3 ARASENS study. Genitourinary Cancers Symposium 2023;Abstract 15.
- Fizazi K et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): A multicentre, open-label, randomised, phase 3 study with a 2 x 2 factorial design. *Lancet* 2022;399(10336):1695-707.

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- Hussain M et al. Tumor genomic testing for >4,000 men with metastatic castration-resistant prostate cancer in the Phase III trial PROfound (olaparib). *Clin Cancer Res* 2022;28(8):1518-30.
- Matsubara N et al. Olaparib efficacy in patients with metastatic castration-resistant prostate cancer and BRCA1, BRCA2, or ATM alterations identified by testing circulating tumor DNA. *Clin Cancer Res* 2023;29(1):92-9.
- Thiery-Vuillemin A et al. Pain and health-related quality of life with olaparib versus physician's choice of next-generation hormonal drug in patients with metastatic castration-resistant prostate cancer with homologous recombination repair gene alterations (PROfound): An open-label, randomised, phase 3 trial. *Lancet Oncol* 2022;23(3):393-405.
- Bryce AH et al. Rucaparib for metastatic castration-resistant prostate cancer (mCRPC): TRITON3 interim overall survival and efficacy of rucaparib vs docetaxel or second-generation androgen pathway inhibitor therapy. Genitourinary Cancers Symposium 2023;Abstract 18.
- Smith MR et al. Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): A multicentre, open-label, phase 2 trial. *Lancet Oncol* 2022;23(3):362-73.

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## A Oliver Sartor, MD (continued)


- Clarke NW et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. *NEJM Evid* 2022;1(9).
- Saad F et al. Biomarker analysis and updated results from the Phase III PROpel trial of abiraterone (abi) and olaparib (ola) vs abi and placebo (pbo) as first-line (1L) therapy for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). ESMO 2022;Abstract 1357O.
- Clarke N et al. Final overall survival (OS) in PROpel: Abiraterone (abi) and olaparib (ola) versus abiraterone and placebo (pbo) as first-line (1L) therapy for metastatic castration-resistant prostate cancer (mCRPC). Genitourinary Cancers Symposium 2023;Abstract LBA16.
- Efstathiou E et al. Niraparib (NIRA) with abiraterone acetate and prednisone (AAP) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations: Second interim analysis (IA2) of MAGNITUDE. Genitourinary Cancers Symposium 2023;Abstract 170.

# Key Data Sets

## A Oliver Sartor, MD (continued)

- Agarwal N et al. TALAPRO-2: Phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) versus placebo (PBO) + ENZA as first-line (1L) treatment in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). Genitourinary Cancers Symposium 2023;Abstract LBA17.
- Hofman MS et al. TheraP: $^{177}$Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel — Overall survival after median follow-up of 3 years (ANZUP 1603). ASCO 2022;Abstract 5000.
- Rahbar K et al. Lutetium-$^{177}$-prostate-specific membrane antigen therapy ($^{177}$Lu-PSMA) in patients (Pts) with prior radium-223 (223Ra): Safety and effectiveness outcomes. ESMO 2022;Abstract 1392P.
- Armstrong A et al. Association between prostate-specific antigen decline and clinical outcomes in patients with metastatic castration-resistant prostate cancer in the VISION trial. ESMO 2022;Abstract 1372P.

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## A Oliver Sartor, MD (continued)


- Garje R et al. Systemic therapy update on $^{177}$Lutetium-PSMA-617 for metastatic castration-resistant prostate cancer: ASCO rapid recommendation. *J Clin Oncol* 2022;40(31):3664-6.
- Oudard S et al. Cabazitaxel every 2 weeks versus every 3 weeks in older patients with metastatic castration-resistant prostate cancer (mCRPC): The CABASTY randomized phase III trial. ESMO 2022;Abstract 1363MO.
- Petrylak DP et al. Pembrolizumab plus docetaxel for patients with metastatic castration-resistant prostate cancer (mCRPC): Randomized, double-blind, phase 3 KEYNOTE-921 study. Genitourinary Cancers Symposium 2023;Abstract 19.

# Agenda

**MODULE 1: Castration-Sensitive Prostate Cancer**

**MODULE 2: PARP Inhibitors in Castration-Resistant Disease**

**MODULE 3: Radiopharmaceuticals**

**MODULE 4: Appendix**

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**MODULE 1: Castration-Sensitive Prostate Cancer**

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**MODULE 3: Radiopharmaceuticals**

**MODULE 4: Appendix**

# Key Discussion Questions

- For castration-sensitive prostate cancer (CSPC), are clinical outcomes better with the addition of secondary hormonal treatment to androgen deprivation therapy (ADT) versus ADT alone, regardless of clinical stage?
- What is the optimal first-line treatment for metastatic CSPC?

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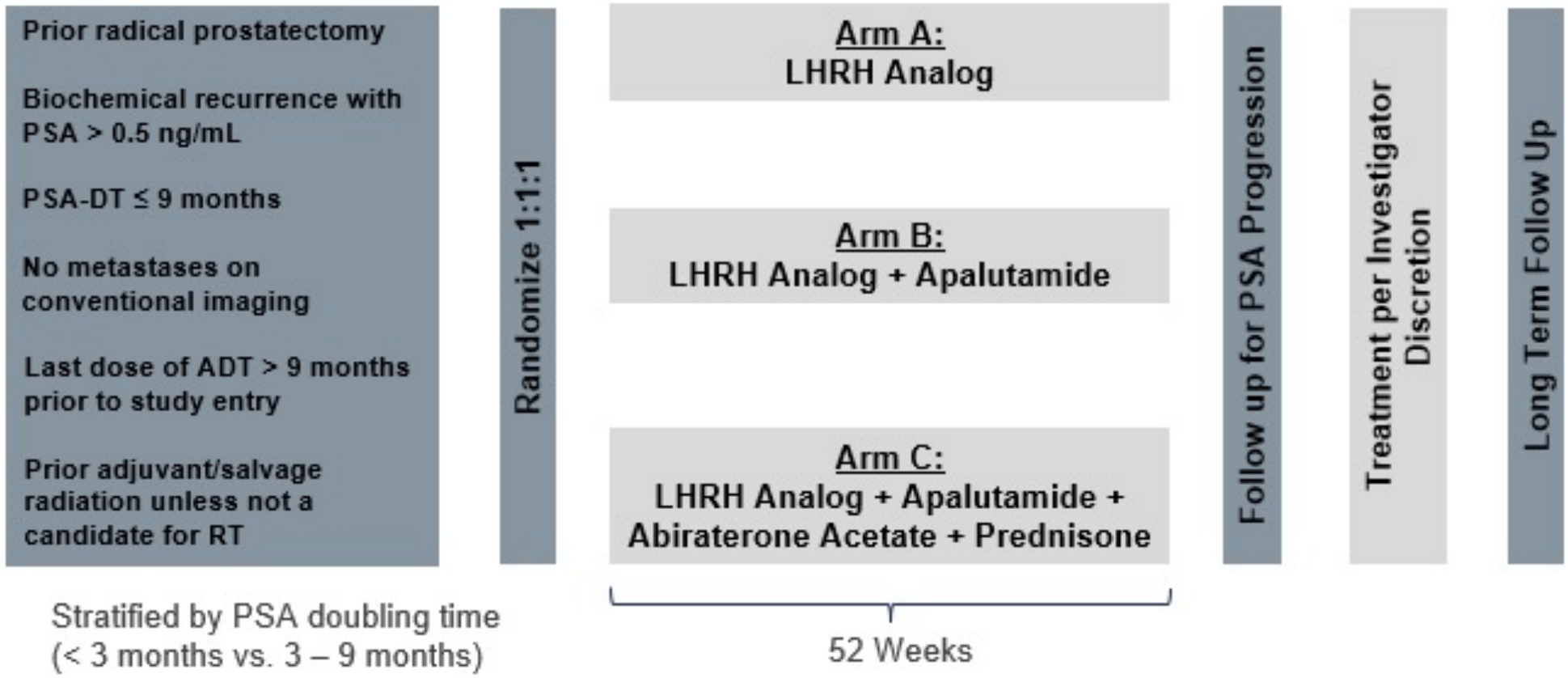
- Rush HL et al. Quality of life in men with prostate cancer randomly allocated to receive docetaxel or abiraterone in the STAMPEDE trial. *J Clin Oncol* 2022;40(8):825-36.
- James ND et al. Abiraterone acetate plus prednisolone for metastatic patients starting hormone therapy: 5-year follow-up results from the STAMPEDE randomised trial (NCT00268476). *Int J Cancer* 2022;151(3):422-34.
- Baciarello G et al. Impact of abiraterone acetate plus prednisone in patients with castration-sensitive prostate cancer and visceral metastases over four years of follow-up: A post-hoc exploratory analysis of the LATITUDE study. *Eur J Cancer* 2022;162:56-64.

# Key Data Sets

## Tanya B Dorff, MD (continued)


- Fizazi K et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): A multicentre, open-label, randomised, phase 3 study with a 2 x 2 factorial design. *Lancet* 2022;399(10336):1695-707.
- **Davis ID et al. Updated overall survival outcomes in ENZAMET (ANZUP 1304), an international, cooperative group trial of enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC). ASCO 2022;Abstract LBA5004.**
- Armstrong AJ et al. Improved survival with enzalutamide in patients with metastatic hormone-sensitive prostate cancer. *J Clin Oncol* 2022;40(15):1616-22.
- **Smith MR et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med* 2022;386(12):1132-42.**
- Hussain MHA et al. Efficacy and safety of darolutamide (DARO) in combination with androgen-deprivation therapy (ADT) and docetaxel (DOC) by disease volume and disease risk in the phase 3 ARASENS study. Genitourinary Cancers Symposium 2023;Abstract 15.

# PRESTO: intensified therapy in biochemically recurrent prostate cancer




: PSA PFS, with PSA progression defined as **nadir + 2 ng/mL during** or **> 0.2 ng/mL following treatment confirmed on repeat measurement (> 2 wks)**

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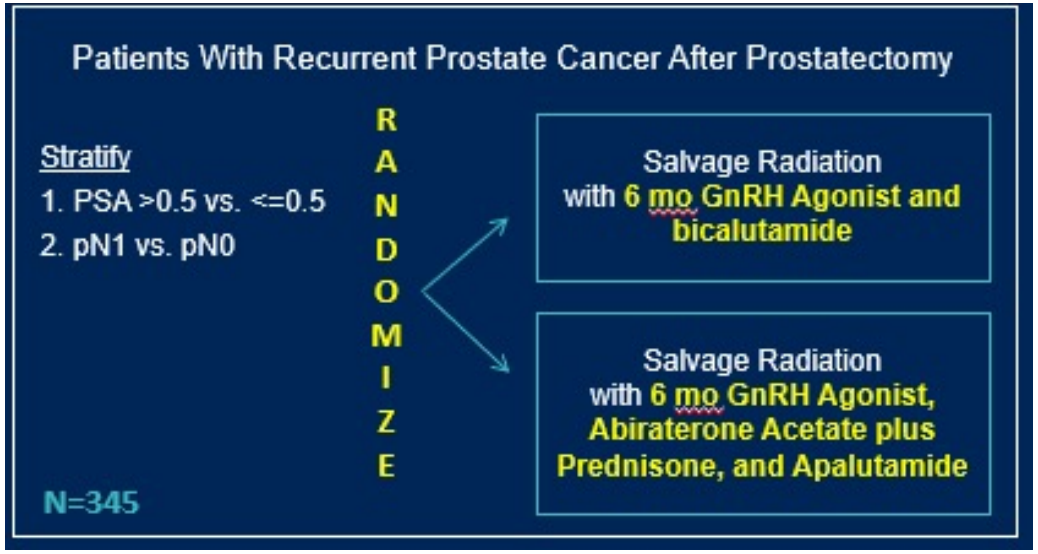
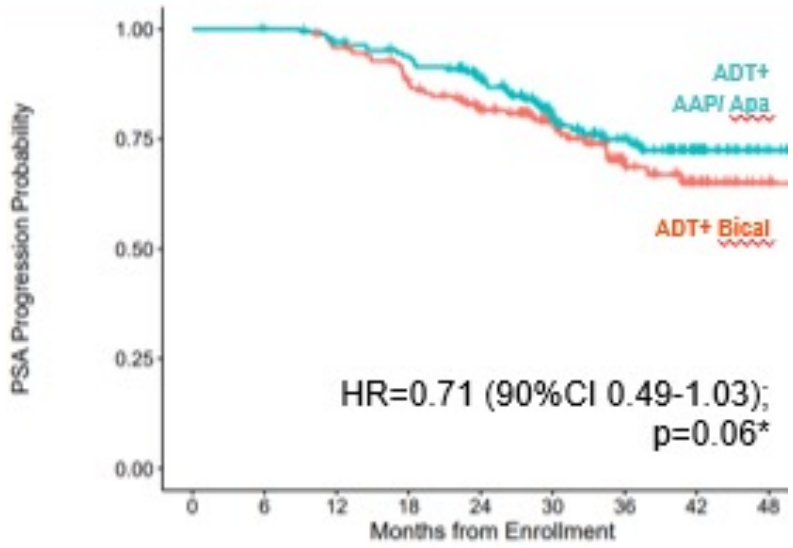
Courtesy of Tanya B Dorff, MD

Aggarwal ESMO 2022; Abstract LBA63

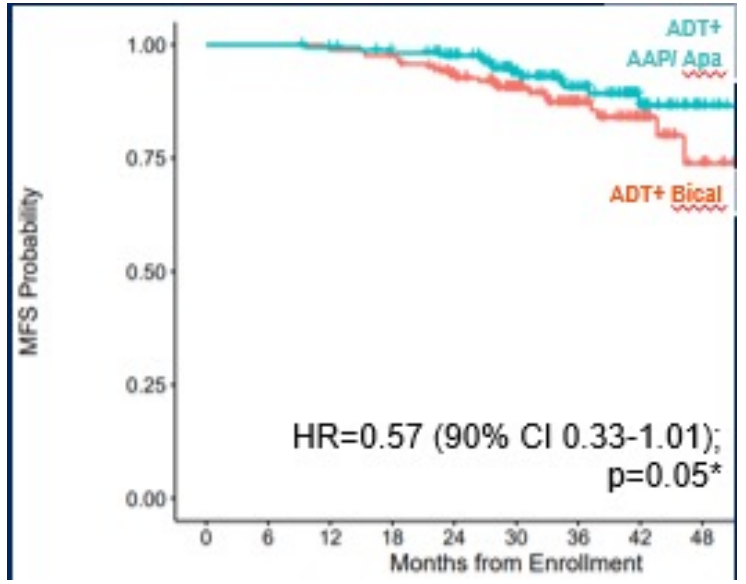
# FORMULA509: apalutamide (+ abi) with salvage XRT




PSA >0.5
3 year MFS 84.3% vs. 66.1%

<u>Absolute improvement</u>
18.2% at 3 years (NNT = 5)




Courtesy of Tanya B Dorff, MD

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Nguyen ASCO GU 2023; Abstract 303

# Toxicities with intensified therapy in FORMULA509

| | Frequency of Grade 2+ Toxicity | |
|---|---|---|
| | ADT + Bicalutamide | ADT + AAP/Apa |
| Maculopapular Rash | 0.6% | 11.5% |
| Hypertension | 13.3% | 21.8% |
| Diarrhea | 4.8% | 8.5% |
| Cardiac Disorders | 5.5% | 3.0% |
| Fatigue | 6.1% | 7.9% |

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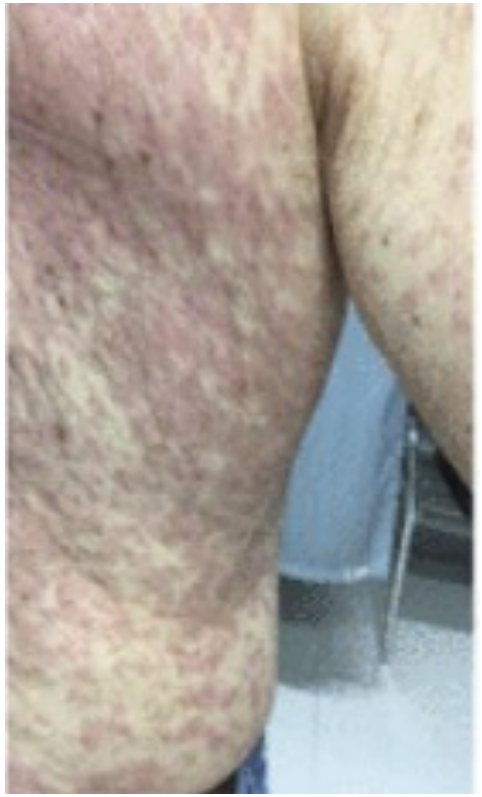
Courtesy of Tanya B Dorff, MD

Nguyen ASCO GU 2023; Abstract 303

# Dermatologic AE with apalutamide

| Clinical Presentation | No. Grade (%) | | |
|---|---|---|---|
| | 1 + 2 | 3 | Any |
| Xerosis | 23 (32.4) | 0 | 23 (32.4) |
| Maculopapular rash: | 22 (31.0) | 5 (7.0) | 27 (38.0) |
| Maculopapular rash alone | 19 (26.8) | 5 (7.0) | 21 (33.8) |
| +Xerosis | 1 (1.4) | 0 | 1 (1.4) |
| +Urticaria | 1 (1.4) | 0 | 1 (1.4) |
| +Oral lichen planus | 1 (1.4) | 0 | 1 (1.4) |
| Erythematous rash: | 6 (8.5) | 1 (1.4) | 7 (9.9) |
| Erythematous rash alone | 6 (8.5) | 0 | 6 (8.5) |
| +Xerosis | 0 | 1 (1.4) | 1 (1.4) |
| Eczematous rash: | 2 (2.8) | 1 (1.4) | 3 (4.2) |
| Eczematous rash alone | 1 (1.4) | 1 (1.4) | 2 (2.8) |
| +Xerosis | 1 (1.4) | 0 | 1 (1.4) |
| Acneiform rash | 3 (4.2) | 0 | 3 (4.2) |
| Psoriasiform rash | 1 (1.4) | 1 (1.4) | 2 (2.8) |



Pan et al. J Urol 2022

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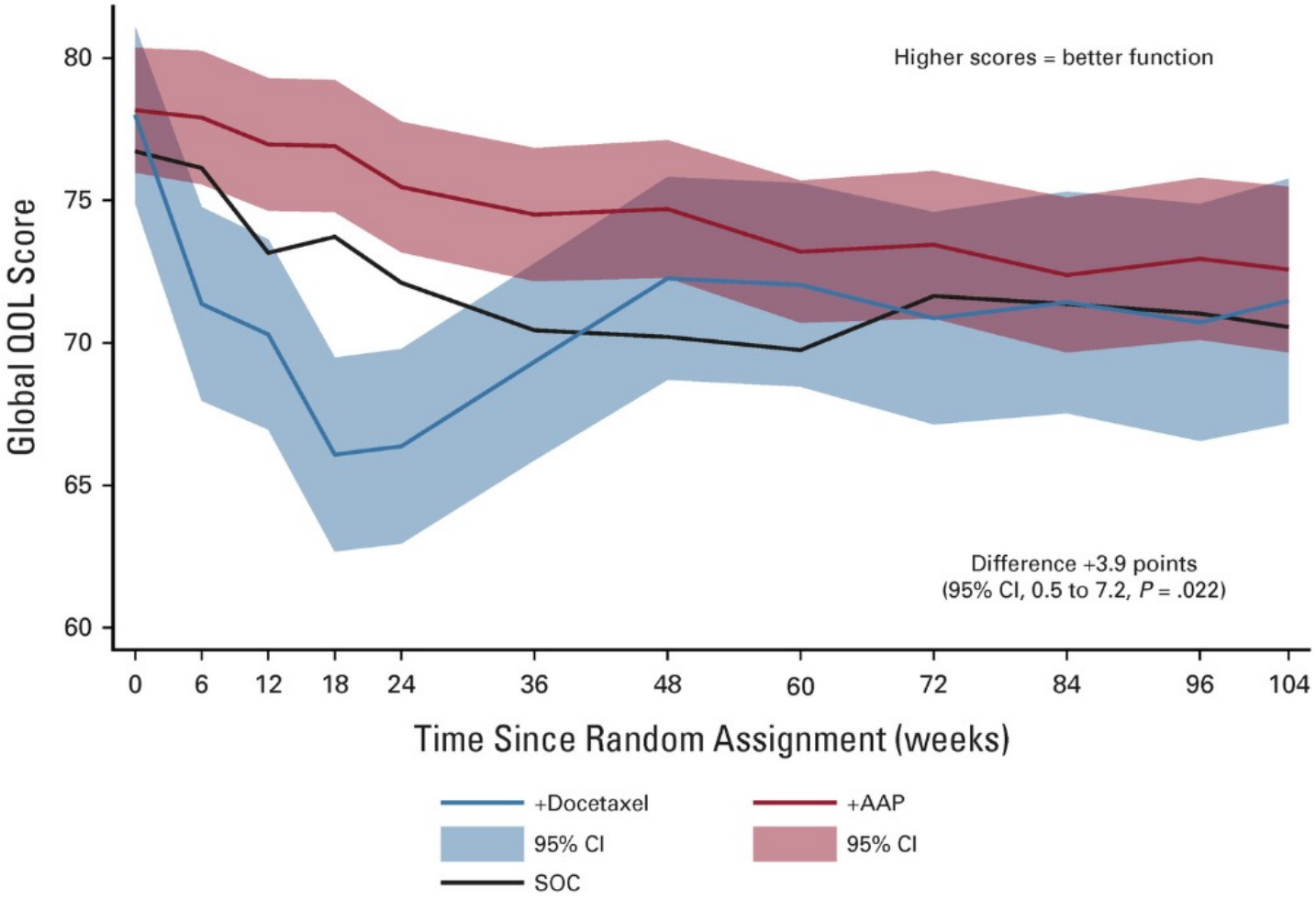
Courtesy of Tanya B Dorff, MD

# Quality of life with docetaxel or abiraterone in mHSPC (STAMPEDE)




No difference in cognitive or emotional; differences in social and physical function favored abiraterone

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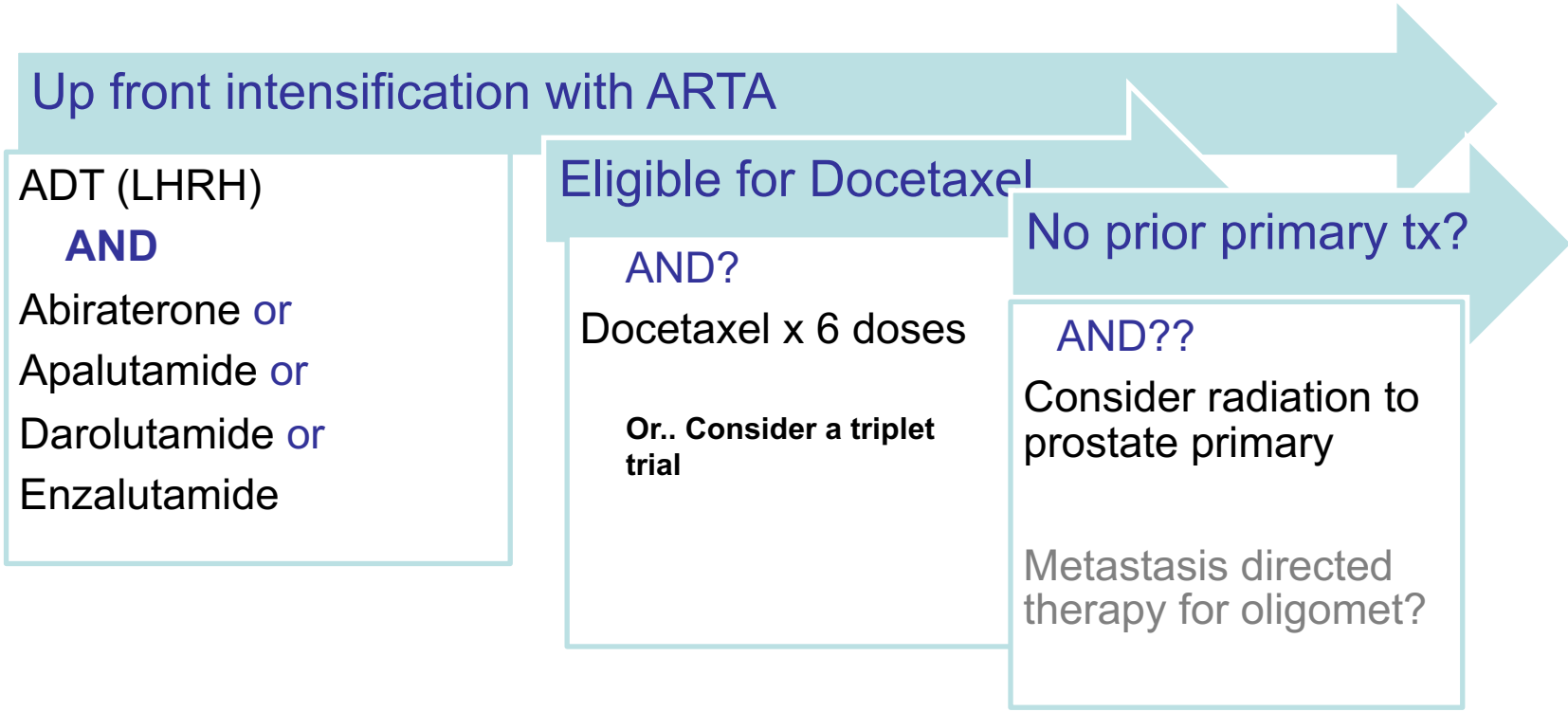
Courtesy of Tanya B Dorff, MD

Rush HL et al. J Clin Oncol 2022

# Up-front intensification: THE new paradigm in mHSPC

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Courtesy of Tanya B Dorff, MD

# Ongoing mHSPC trials with triplets

| Name/Sponsor | ARTA | 3rd agent | Design (n) |
|---|---|---|---|
| AMPLITUDE | Abiraterone | Niraparib | Randomized, HRR+ (788) |
| TALAPRO-3 | Enzalutamide | Talazoparib | Randomized HRR+ (550) |
| City of Hope PCF | Abiraterone | Talazoparib | Single arm, Unselected (70) |
| PSMAddition | Lu177-PSMA-617 | Any ARTA | Randomized, PSMA PET + (1126) |
| KEYNOTE-991 | Enzalutamide | Pembrolizumab | Randomized (1232) |
| NCT03951831 | n/a (ADT + Doce) | Cemiplimab | Single arm (20) |
| MSKCC | Abi/Enza | Atezolizumab | SBRT, Single arm (44) |
| CABIOS | Abiraterone | Cabozantinib, Nivolumab | Single arm (22) |
| CASCARA (U Minn) | Abiraterone | Cabazi + Carbo | Single arm (60) |
| Capitello-281 | Abiraterone | Capivasertib | Randomized, PTEN def (1000) |
| CYCLONE-3 | Abiraterone | Abemaciclib | Randomized, unselected (900) |

Courtesy of Tanya B Dorff, MD

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# Conclusions

- Up-front intensification in mHSPC has been a huge advance
  - Doublet (AR targeted agent) for most
  - Triplet (with docetaxel) for some (esp hi volume)
  - Future state: Biomarkers may identify populations in whom a novel triplet may be highly successful (ex: PARP, PTEN)


Courtesy of Tanya B Dorff, MD

# Agenda

**MODULE 1: Castration-Sensitive Prostate Cancer**

**MODULE 2: PARP Inhibitors in Castration-Resistant Disease**

**MODULE 3: Radiopharmaceuticals**

**MODULE 4: Appendix**

# Key Discussion Questions

- What is the ideal approach to the use of PARP inhibitors for patients with prostate cancer with and without HRR gene alterations?
- What are the short- and long-term toxicity profiles of PARP inhibitors for prostate cancer?

# Key Data Sets

## A Oliver Sartor, MD

- **Hussain M et al. Tumor genomic testing for >4,000 men with metastatic castration-resistant prostate cancer in the Phase III trial PROfound (olaparib). *Clin Cancer Res* 2022;28(8):1518-30**.
- Thiery-Vuillemin A et al. Pain and health-related quality of life with olaparib versus physician's choice of next-generation hormonal drug in patients with metastatic castration-resistant prostate cancer with homologous recombination repair gene alterations (PROfound): An open-label, randomised, phase 3 trial. *Lancet Oncol* 2022;23(3):393-405.
- Saad F et al. Biomarker analysis and updated results from the Phase III PROpel trial of abiraterone (abi) and olaparib (ola) vs abi and placebo (pbo) as first-line (1L) therapy for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). ESMO 2022;Abstract 1357O.
- **Clarke N et al. Final overall survival (OS) in PROpel: Abiraterone (abi) and olaparib (ola) versus abiraterone and placebo (pbo) as first-line (1L) therapy for metastatic castration-resistant prostate cancer (mCRPC). Genitourinary Cancers Symposium 2023;Abstract LBA16.**
- Clarke NW et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. *NEJM Evid* 2022;1(9).

# Key Data Sets

## A Oliver Sartor, MD (continued)

- Matsubara N et al. Olaparib efficacy in patients with metastatic castration-resistant prostate cancer and BRCA1, BRCA2, or ATM alterations identified by testing circulating tumor DNA. *Clin Cancer Res* 2023;29(1):92-9
- Smith MR et al. Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): A multicentre, open-label, phase 2 trial. *Lancet Oncol* 2022;23(3):362-73.
- **Efstathiou E et al. Niraparib (NIRA) with abiraterone acetate and prednisone (AAP) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations: Second interim analysis (IA2) of MAGNITUDE. Genitourinary Cancers Symposium 2023;Abstract 170.**
- **Agarwal N et al. TALAPRO-2: Phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) versus placebo (PBO) + ENZA as first-line (1L) treatment in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). Genitourinary Cancers Symposium 2023;Abstract LBA17.**

# Key Data Sets

## A Oliver Sartor, MD (continued)

- **Bryce AH et al. Rucaparib for metastatic castration-resistant prostate cancer (mCRPC): TRITON3 interim overall survival and efficacy of rucaparib vs docetaxel or second-generation androgen pathway inhibitor therapy. Genitourinary Cancers Symposium 2023;Abstract 18.**

# Clovis Oncology Files for Chapter 11 Protection and Enters into Agreement to Sell FAP-2286

## Press Release: December 12, 2022

"Clovis Oncology, Inc. (NASDAQ:CLVS) ('Clovis' or the 'Company'), a biopharmaceutical company focused on acquiring, developing, and commercializing innovative anti-cancer agents in the U.S., Europe, and additional international markets, today announced that it and certain of its subsidiaries (collectively, the 'Debtors') have voluntarily initiated a Chapter 11 proceeding in the United States Bankruptcy Court for the District of Delaware ('Bankruptcy Court') and will seek to sell their assets through a court supervised sales process.

The Debtors have filed various 'first day' motions with the Bankruptcy Court requesting customary relief that will enable them to transition into Chapter 11 without material disruption to their ordinary course operations, including seeking authority to obtain debtor-in-possession ('DIP') financing and pay employee wages and benefits.

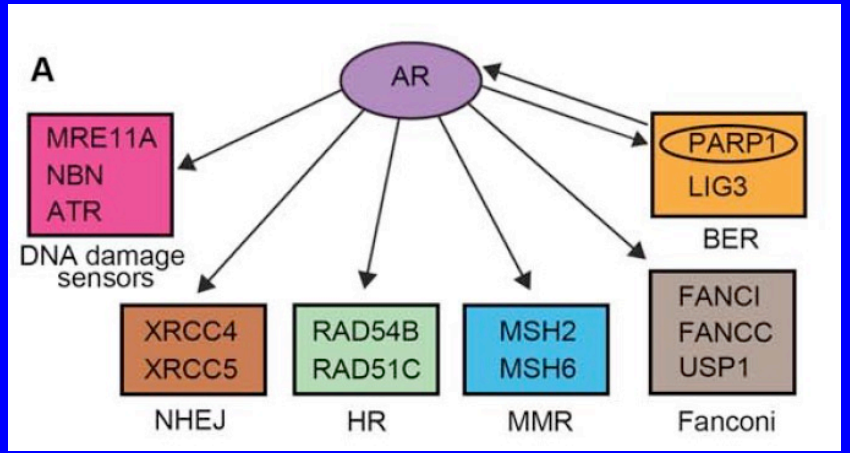
Clovis is also actively engaged in discussions with a number of interested parties with respect to a potential sale of one or more of its other assets. Any of those sales would be subject to review and approval by the Bankruptcy Court and compliance with Bankruptcy Court-approved bidding procedures."

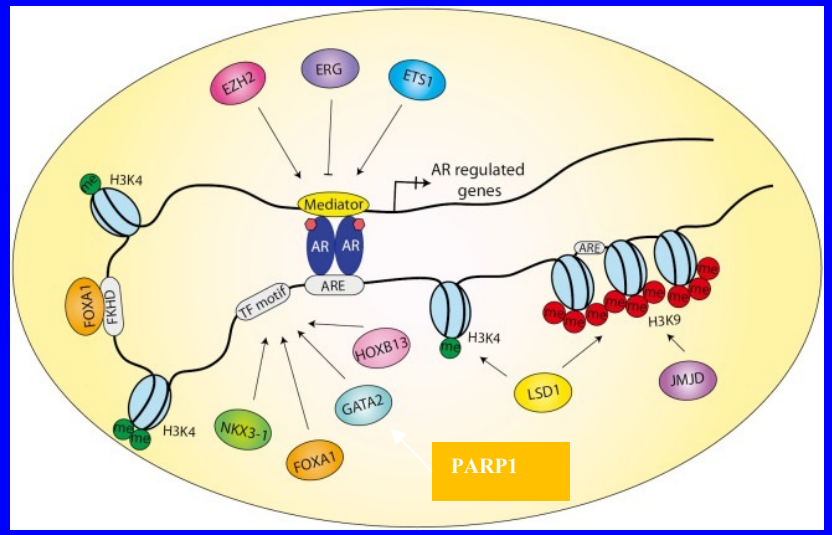
https://ir.clovisoncology.com/investors-and-news/news-releases/press-release-details/2022/Clovis-Oncology-Files-for-Chapter-11-Protection-and-Enters-into-Agreement-to-Sell-FAP-2286/default.aspx

RTP RESEARCH TO PRACTICE

# Combination PARP + AR Pathway Inhibition

- AR signaling enhances DNA damage repair
- ADT upregulated PARP-mediated repair and pre-clinical studies indicate potential synergy between ADT and PARP inhibition




JF Goodwin, et al. Cancer Discov 3:1254, 2013; WR Polkinghorn, et al. Cancer Discov 3:1245, 2013; M Asim, e al. Nat Commun 8: 374, 2017; MJ Schiewer , et al. Cancer Discov 2:1134, 2012

Courtesy of A Oliver Sartor, MD

# Summary

- Combination therapies with PARP are not FDA approved but trials are positive for rPFS
  - No OS shown yet in the overall analyses……
  - BRCA mutated subsets are substantially positive
  - How important is the primary endpoint of rPFS?
    - FDA to decide

Courtesy of A Oliver Sartor, MD

# Agenda

**MODULE 1: Castration-Sensitive Prostate Cancer**

**MODULE 2: PARP Inhibitors in Castration-Resistant Disease**

**MODULE 3: Radiopharmaceuticals**

**MODULE 4: Appendix**

# Key Discussion Questions

- What is the ideal use of $^{177}$Lu-PSMA-617 in clinical practice? To what extent has the shortage affected use?
- What are some new developments and ongoing trials with radiopharmaceuticals for prostate cancer?

# Manufacturer Halts $^{177}$Lu-PSMA-617 New Patient Starts, Struggles with Radiotherapy's Supply amid Manufacturing Expansion

## Press Release: May 5, 2022

The manufacturer today announced a temporary, voluntary suspension of production at its radioligand therapy production sites in Ivrea, Italy and Millburn, New Jersey. The company has taken this action out of an abundance of caution as it addresses potential quality issues identified in its manufacturing processes. The manufacturer is conducting a thorough review of the situation and currently expects to resolve the issues and resume some supply in the next six weeks.

As a result, the company is temporarily suspending delivery of $^{177}$Lu-PSMA-617 and other radioligand therapies in the US and elsewhere. In addition, the manufacturer is putting a temporary hold on screening and enrollment for $^{177}$Lu-PSMA-617 clinical trials globally. Quality and patient safety are our top priorities. There is currently no indication of any risk to patients from doses previously produced at these sites. Novartis has notified treatment sites to closely monitor patients who have recently been injected and asked them to report any adverse events to patient safety.

We recognize that this situation affects patients, their families and care teams. The manufacturer takes this very seriously and the company is doing everything it can to resolve this issue and resume patient doses as quickly as possible. Health authorities have been informed and will receive additional updates as they are available.

https://www.novartis.com/news/media-releases/novartis-provides-update-production-radioligand-therapy-medicines

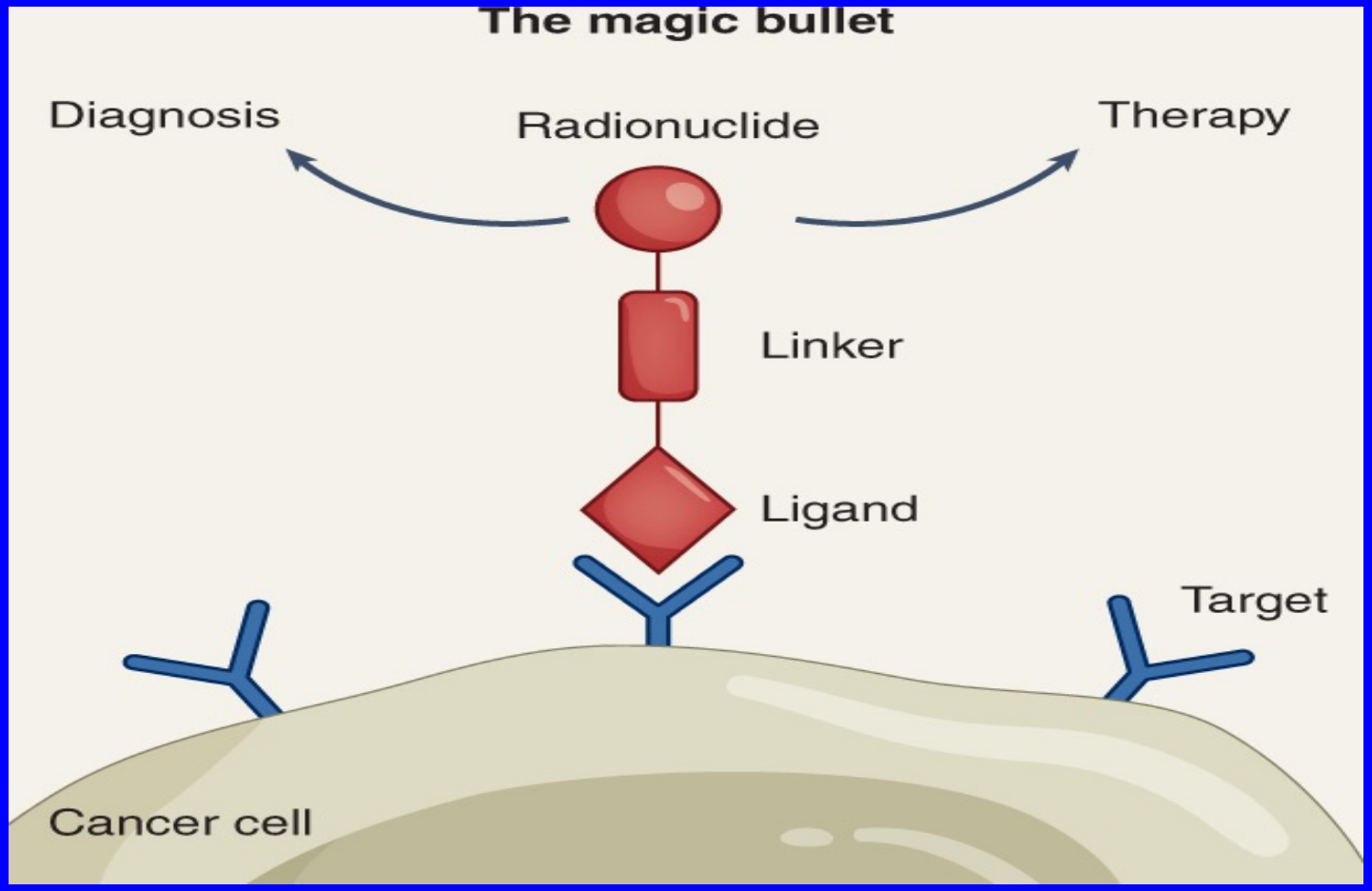
RTP RESEARCH TO PRACTICE

# Key Data Sets

## A Oliver Sartor, MD

- Hofman MS et al. TheraP: $^{177}$Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel — Overall survival after median follow-up of 3 years (ANZUP 1603). ASCO 2022;Abstract 5000.
- Rahbar K et al. Lutetium-$^{177}$-prostate-specific membrane antigen therapy ($^{177}$Lu-PSMA) in patients (Pts) with prior radium-223 (223Ra): Safety and effectiveness outcomes. ESMO 2022;Abstract 1392P.
- Armstrong A et al. Association between prostate-specific antigen decline and clinical outcomes in patients with metastatic castration-resistant prostate cancer in the VISION trial. ESMO 2022;Abstract 1372P.
- Garje R et al. Systemic therapy update on $^{177}$Lutetium-PSMA-617 for metastatic castration-resistant prostate cancer: ASCO rapid recommendation. *J Clin Oncol* 2022;40(31):3664-6.

# Theranostics:
# See it…. Treat it…..Love it!



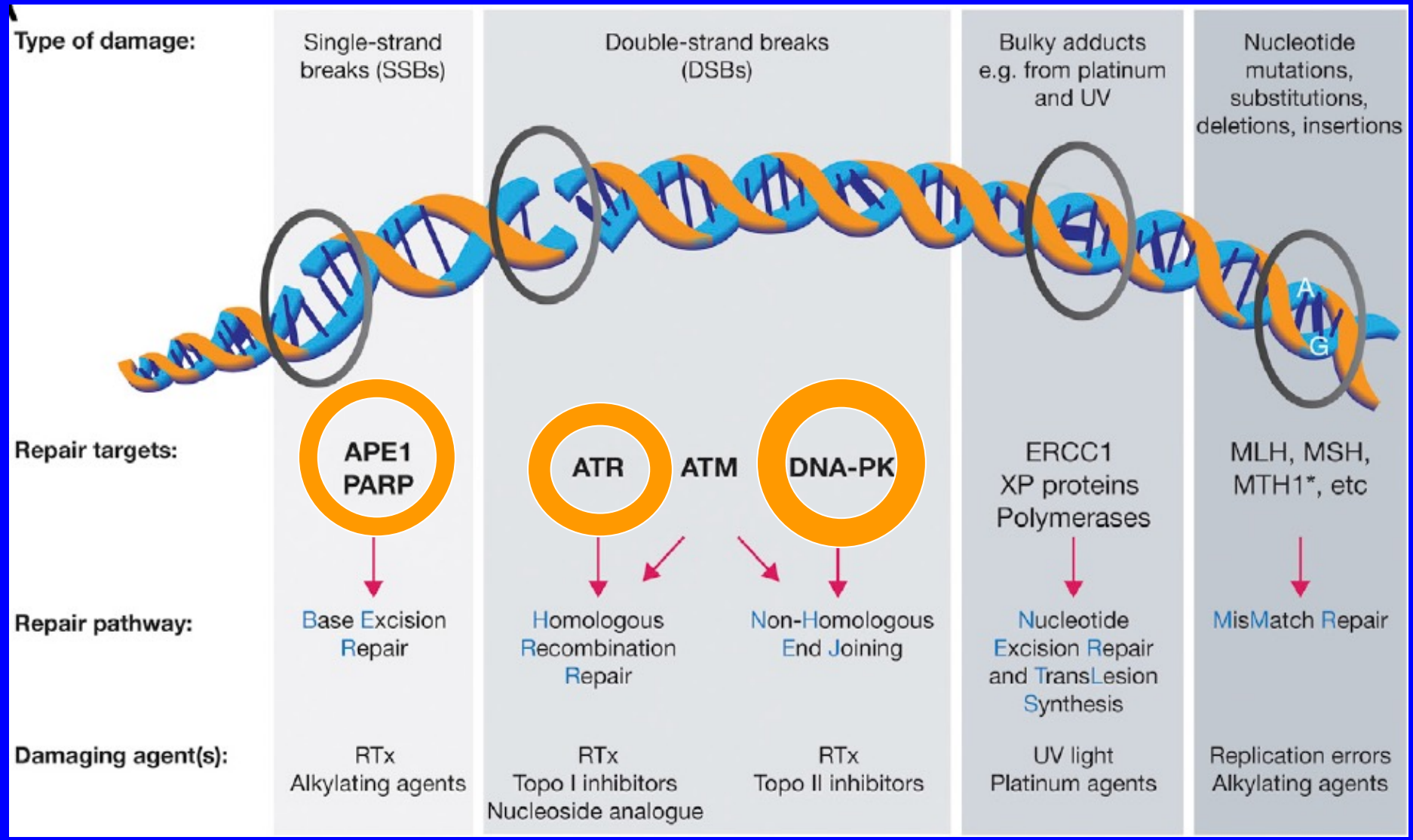

Cell surface target, a ligand, a linker, and an isotope

Courtesy of A Oliver Sartor, MD

# Synergistic opportunities with radiopharmaceuticals

Courtesy of A Oliver Sartor, MD

# Targeting DNA damage repair pathways in combination with radionuclides

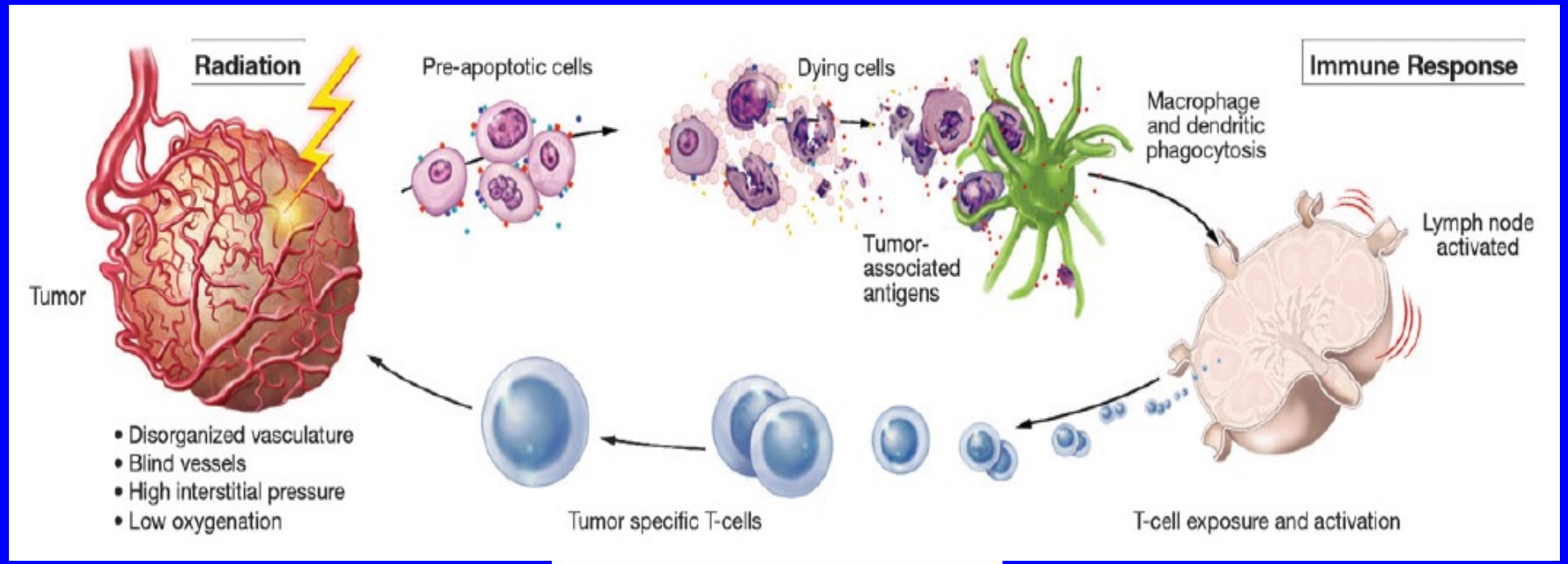



Courtesy of A Oliver Sartor, MD

O'Connor, Molecular Cell 60, November 19, 2015

# Antigen release from radiated tumor: Synergy with immunotherapies?

Kamrava et al., Molecular Biosystems: 5:1249–1372, 2009




**Systemic/local immune enhancement**

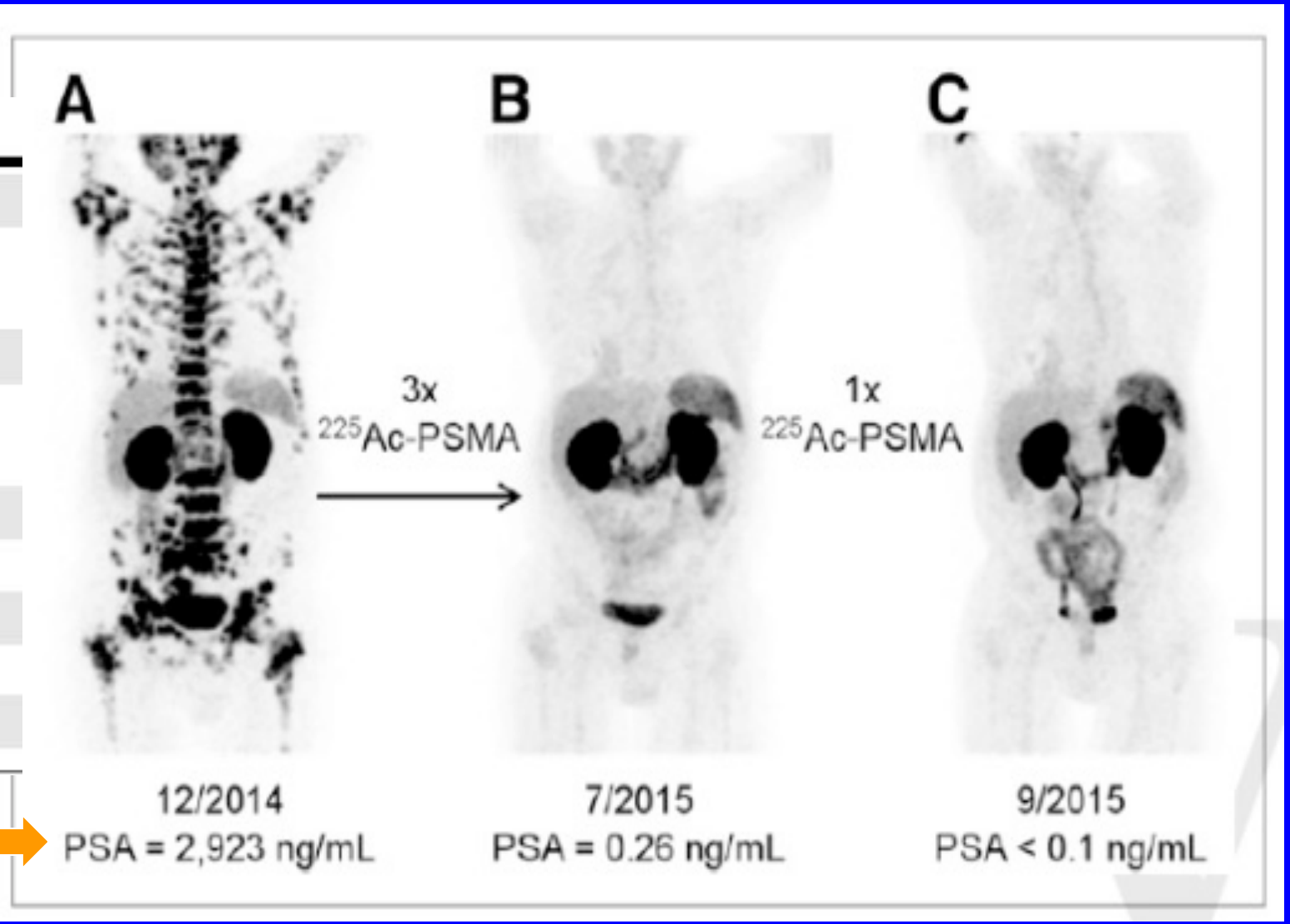
- Vaccine
- Checkpoint inhibitors
  - Anti-CTLA-4
  - Anti-PD-1
  - Anti-PD-L1
  - Anti-TIM3
- Co-stimulatory agonists
  - Anti-OX40
  - Anti-4-1BB
  - Anti-GITR
  - Anti-CD27
  - Anti-CD40
- Exogenous cytokines
  - IL-2
  - IL-7
  - IL-12
  - IL-15
  - IL-21
  - GM-CSF

Courtesy of A Oliver Sartor, MD

# Radio-conjugates: PSMA targeted alpha emitters (Actinium-225) as 9th line treatment

Kratochwil et a. J Nuc Med 57: 1-4, 2016

| Patient A |
| --- |
| Leuprorelin |
| Zoledronate |
| Docetaxel (50 cycles) |
| Carmustine/epirubicin in hyperthermia |
| Abiraterone |
| Enzalutamide |
| $^{223}$Ra (6 cycles) |
| Abiraterone reexposition |
| Estramustine |




Courtesy of A Oliver Sartor, MD

# Agenda

**MODULE 1: Castration-Sensitive Prostate Cancer**

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# Castration-Sensitive Prostate Cancer

# STAMPEDE meta-analysis in non-metastatic prostate CA

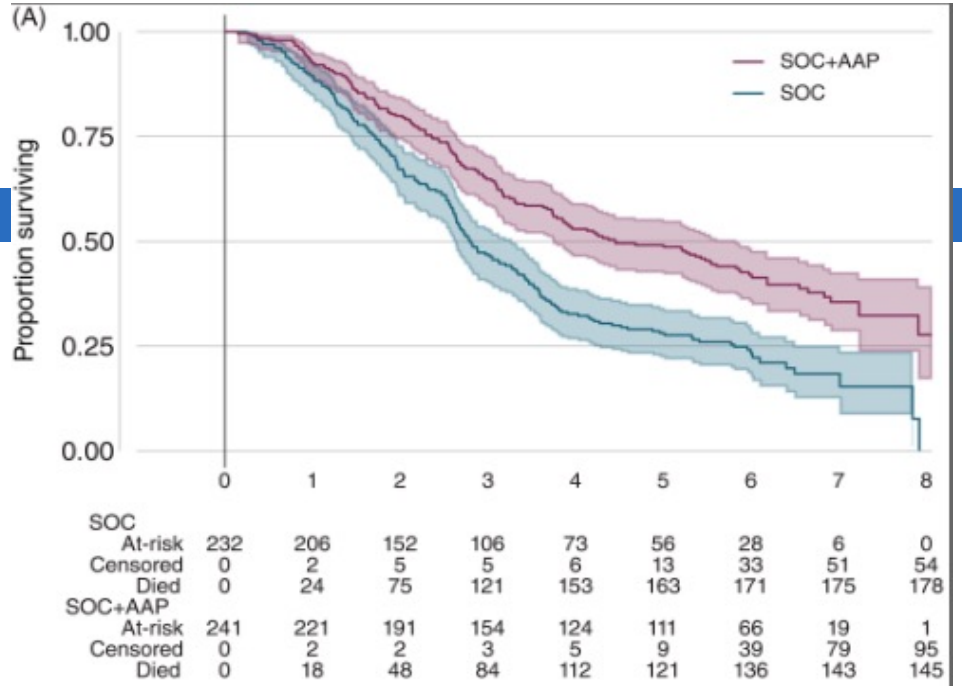
- Analyzed new data from two randomized controlled phase 3 trials from a multi-arm, multistage platform protocol to assess standard-of-care (radiation therapy plus 3 years of ADT) to standard-of-care plus abiraterone acetate plus prednisolone with or without enzalutamide for two years in the non-metastatic, high-risk M0 patient population as defined by conventional imaging
- Results showed that men with high-risk non-metastatic prostate cancer who receive ADT with combination therapy have significantly better metastases-free survival and overall survival than those who receive ADT alone
- 2 years of abiraterone and prednisolone added to ADT and, if indicated, radiotherapy is a potential new standard treatment for non-metastatic prostate cancer with high-risk features

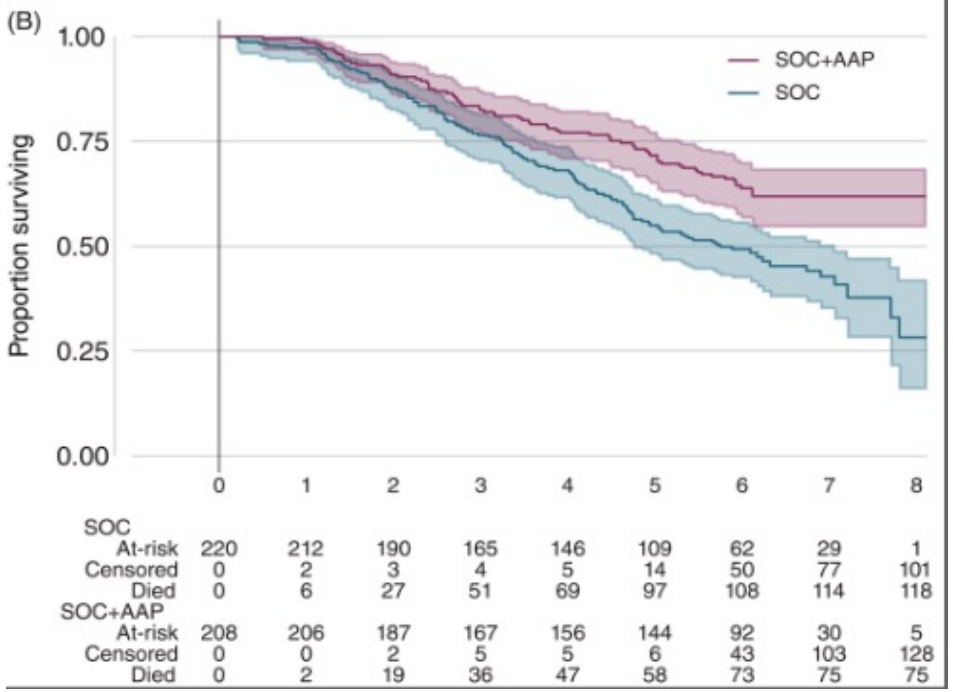

Courtesy of Tanya B Dorff, MD

Attard G et al Lancet 2022

# 5 year f/u STAMPEDE Abiraterone

- high-risk disease defined as at least two of: ≥3 bone metastases; visceral metastases; Gleason score ≥8
- A: high risk OS
- B: low risk OS



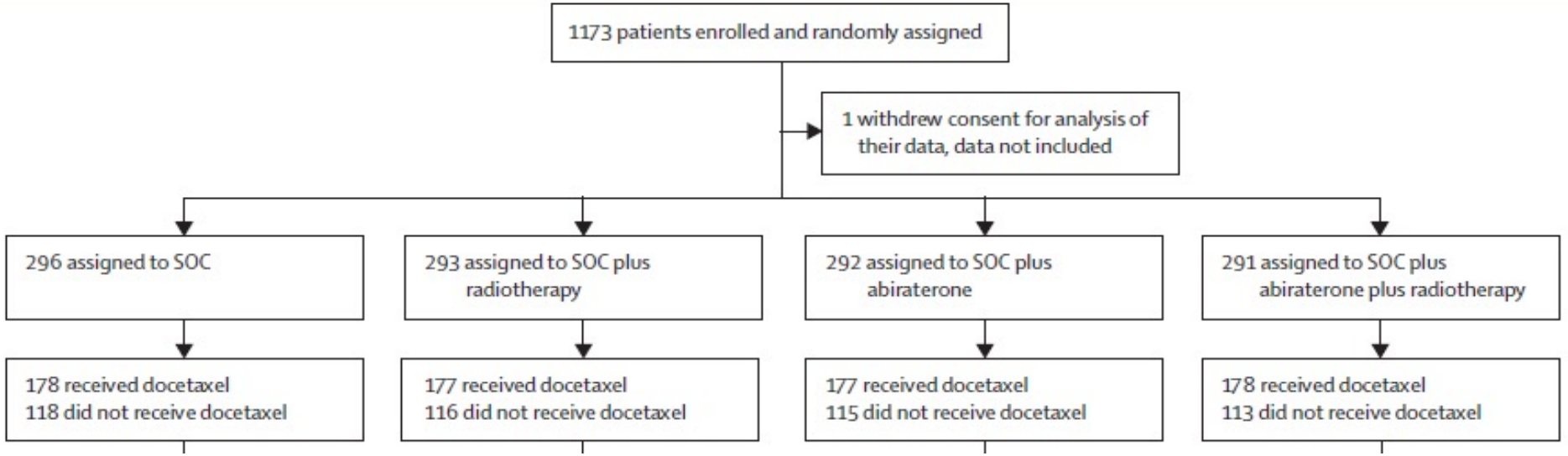




James et al. Int J Cancer 2022

City of Hope® Courtesy of Tanya B Dorff, MD

# PEACE-1: ADT +/- abiraterone +/- RT to prostate primary. AND +/- docetaxel

- Stepwise and factorial design:
  - Check for no interaction b/w abi and RT
  - Compare ADT (+/- RT) +/- abi
- Trial amended to allow doce based on evolving standard of care
  - Compare abiraterone in doce vs no doce populations

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Courtesy of Tanya B Dorff, MD

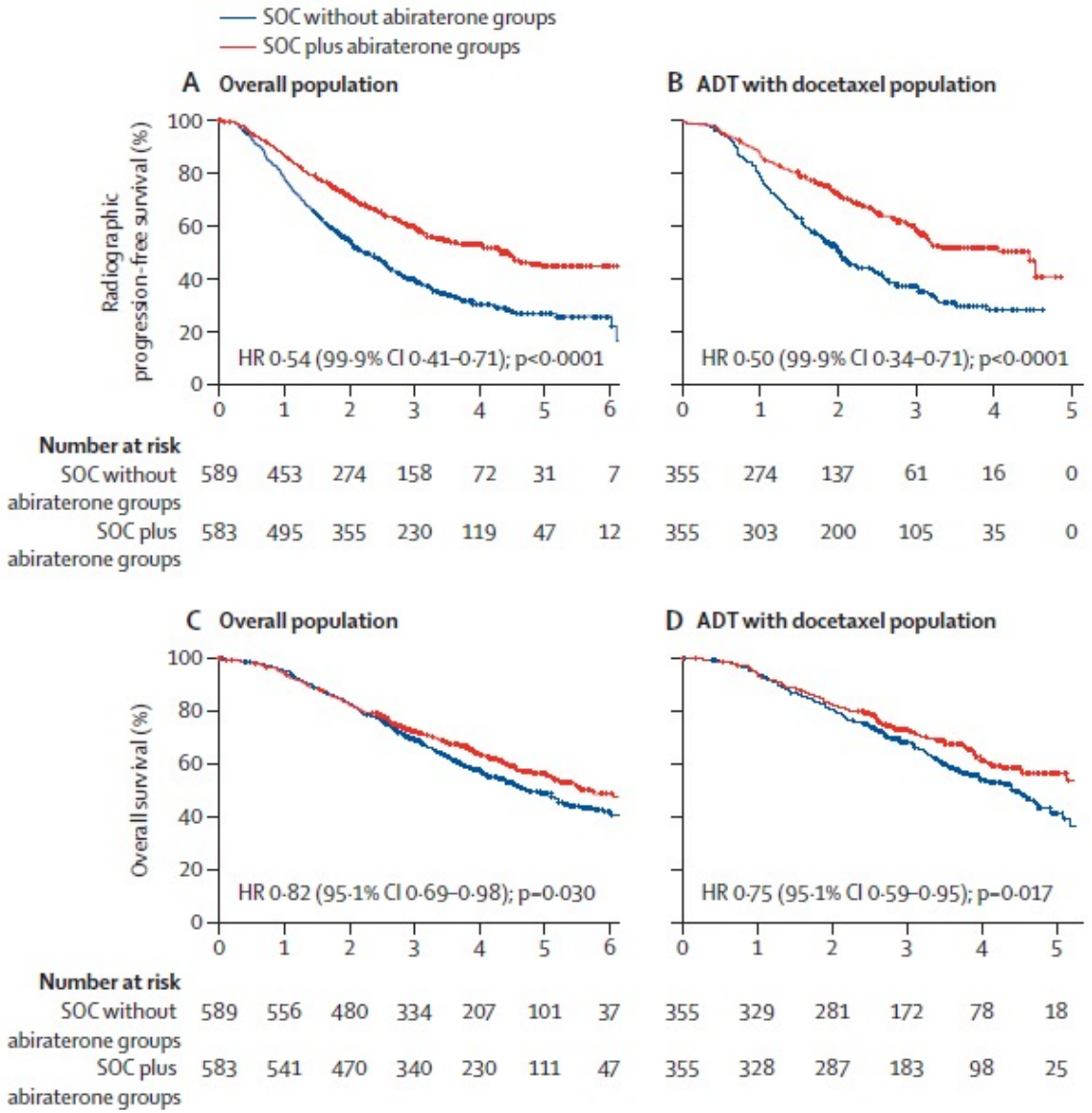
Fizazi Lancet 2022

# PEACE-1: ADT +/- abiraterone +/- RT to prostate primary. AND +/- docetaxel

No interaction between abi and RT

Overall + for abi (triple)

HR stronger for high volume (0.72; CI 0.55 – 0.95) than low volume (0.83; CI 0.50 – 1.39)




City of Hope

Courtesy of Tanya B Dorff, MD

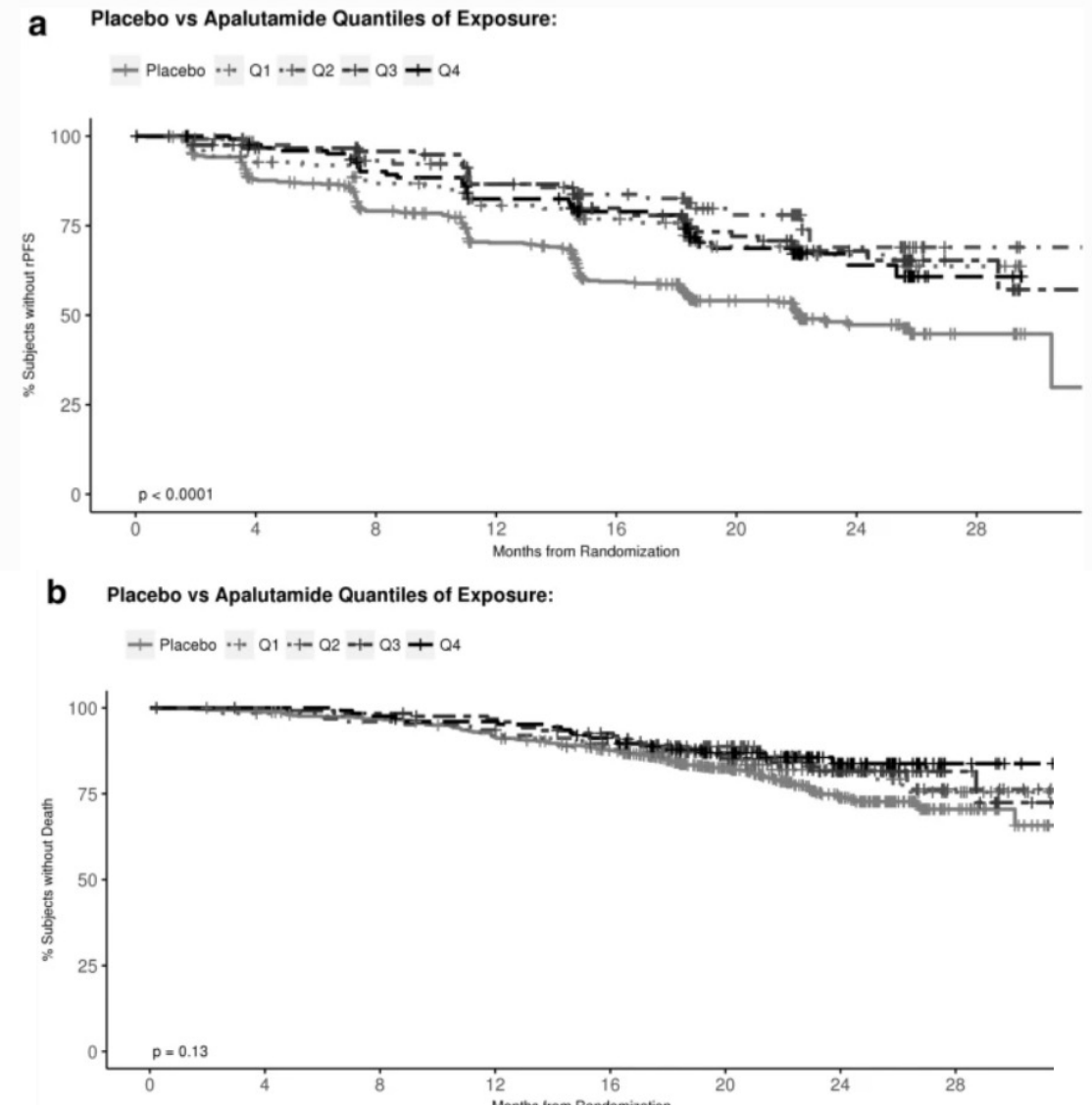
Fizazi Lancet 2022

# Exposure-response relationship apalutamide mHSPC

- Plasma levels achieve steady-state between 4-8 weeks
- AUC calculated for each patient during steady state

A: PFS

B: OS



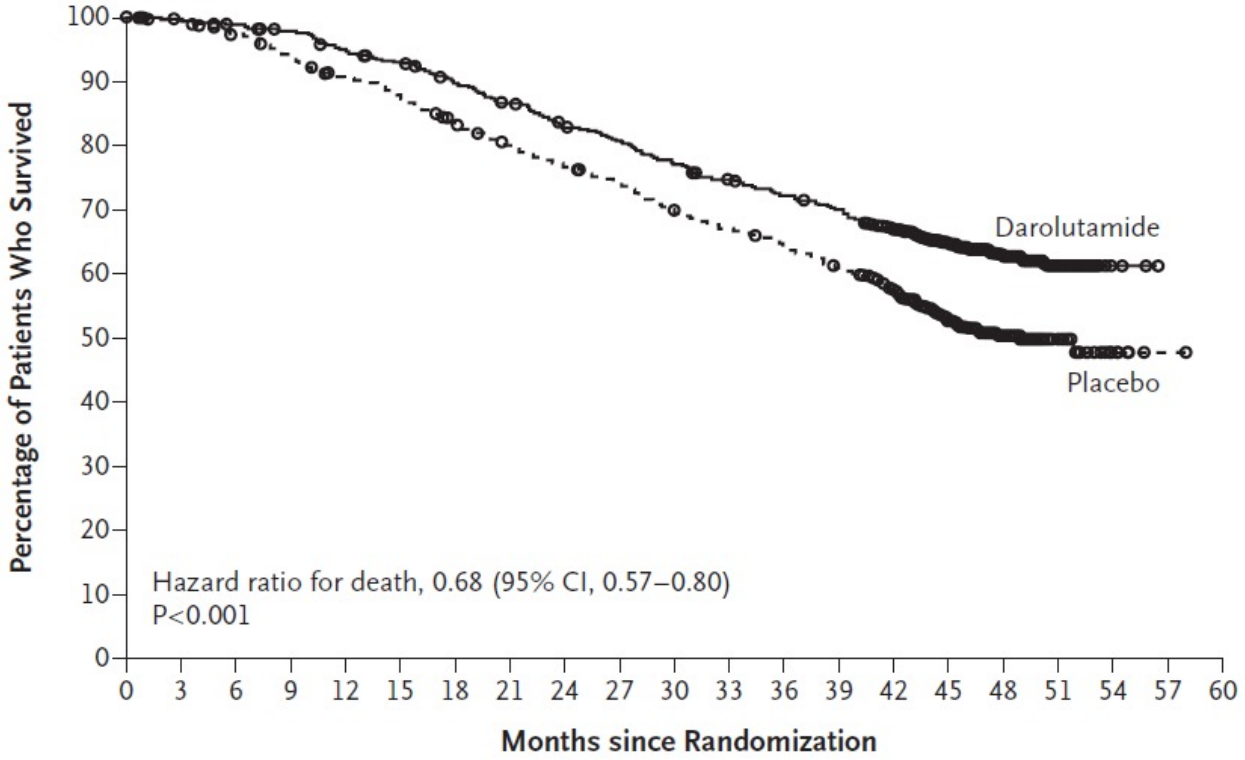

Courtesy of Tanya B Dorff, MD

City of Hope®

T'jollyn H et al Chemother Pharmacol 2022

# ARASENS: ADT + doce +/- darolutamide

- For OS the HR 0.68; 95% CI, 0.57 to 0.80; P<0.001
- Appropriate age representation:
  - 47% age 65-74
  - 16% age 75-84
- Not diverse racially
- Toxicity was acceptable:
  - Febrile neutropenia 7.8% on each arm
  - Death due to AE 4% on each arm




**No. at Risk**

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Darolutamide | 651 | 645 | 637 | 627 | 608 | 593 | 570 | 548 | 525 | 509 | 486 | 468 | 452 | 436 | 402 | 267 | 139 | 56 | 9 | 0 | 0 |
| Placebo | 654 | 646 | 630 | 607 | 580 | 565 | 535 | 510 | 488 | 470 | 441 | 424 | 402 | 383 | 340 | 218 | 107 | 37 | 6 | 1 | 0 |

City of Hope

Courtesy of Tanya B Dorff, MD

Smith MR et al. *N Engl J Med* 2022.

# PARP Inhibitors in Castration-Resistant Disease

# Improved Survival: Phase III Olaparib Trial (PROfound) in Prostate Cancer

**Sept 20, 2020**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

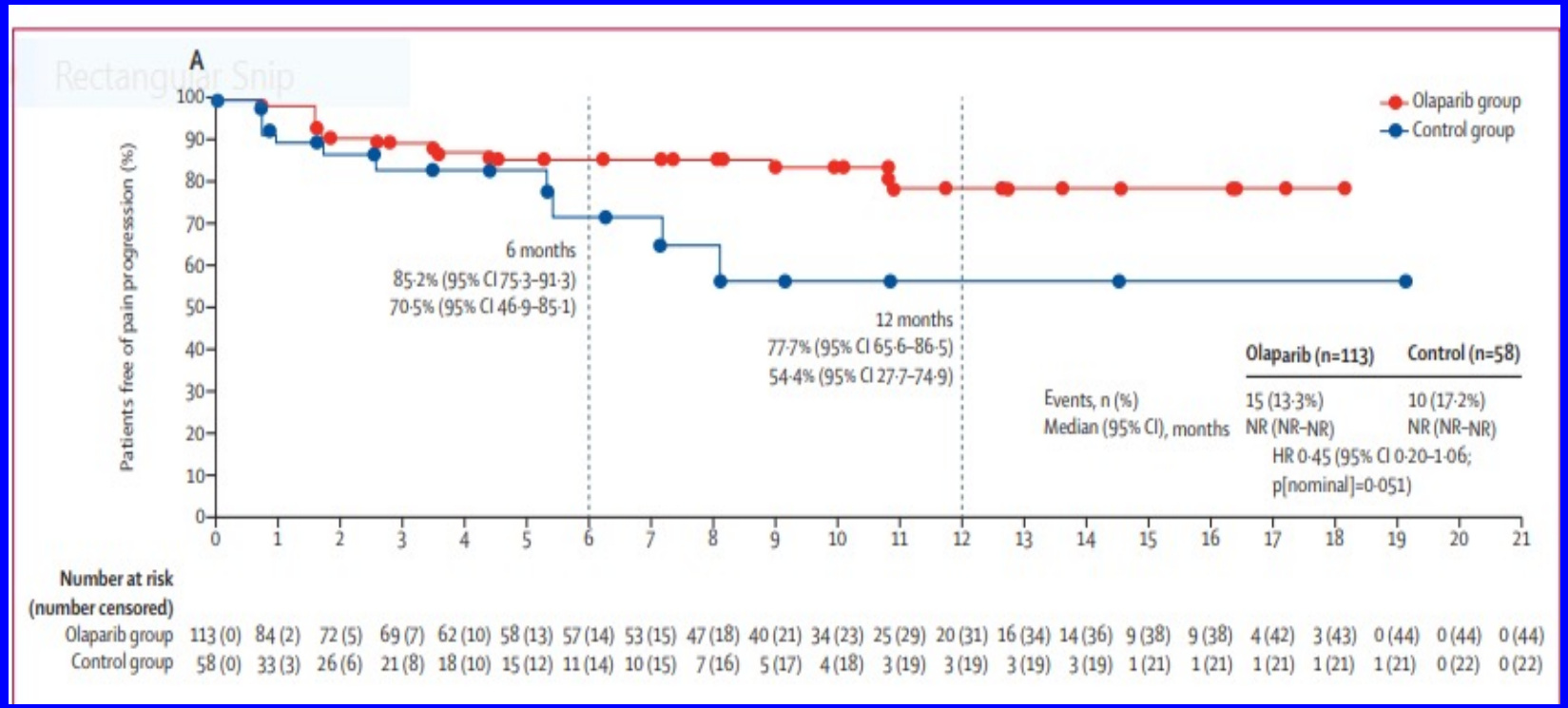
## Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer

M. Hussain, J. Mateo, K. Fizazi, F. Saad, N. Shore, S. Sandhu, K.N. Chi, O. Sartor, N. Agarwal, D. Olmos, A. Thiery-Vuillemin, P. Twardowski, G. Roubaud, M. Özgüroğlu, J. Kang, J. Burgents, C. Gresty, C. Corcoran, C.A. Adelman, and J. de Bono, for the PROfound Trial Investigators*

Courtesy of A Oliver Sartor, MD

# Pain and health-related quality of life with olaparib versus physician's choice of next-generation hormonal drug in patients with metastatic castration-resistant prostate cancer with homologous recombination repair gene alterations (PROfound): an open-label, randomised, phase 3 trial

*Antoine Thiery-Vuillemin, Johann de Bono, Maha Hussain, Guilhem Roubaud, Giuseppe Procopio, Neal Shore, Karim Fizazi, Gabriel dos Anjos, Gwenaelle Gravis, Jae Young Joung, Nobuaki Matsubara, Daniel Castellano, Arnold Degboe, Chris Gresty, Jinyu Kang, Allison Allen, Christian Poehlein, Fred Saad*

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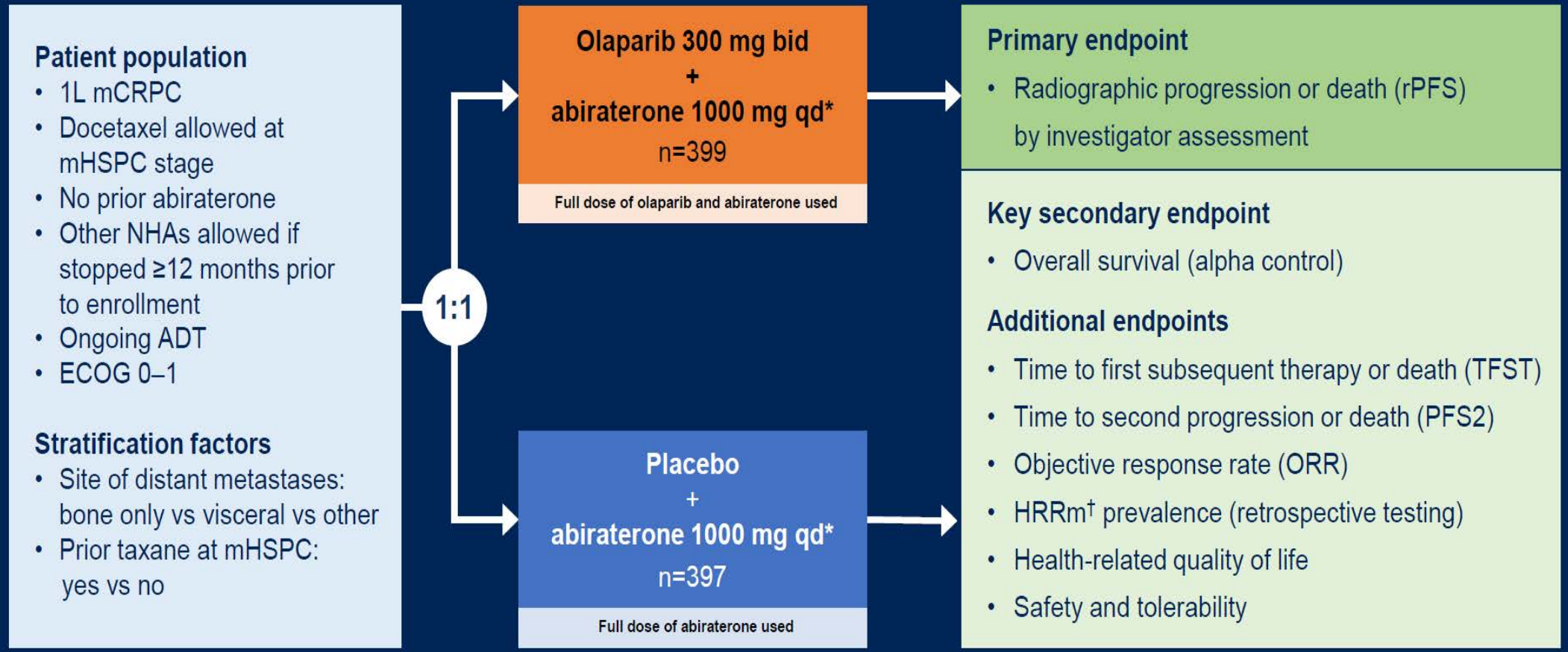
# PROpel: a global randomized double-blind phase III trial




**HRR mutations were determined <u>after randomization</u>**

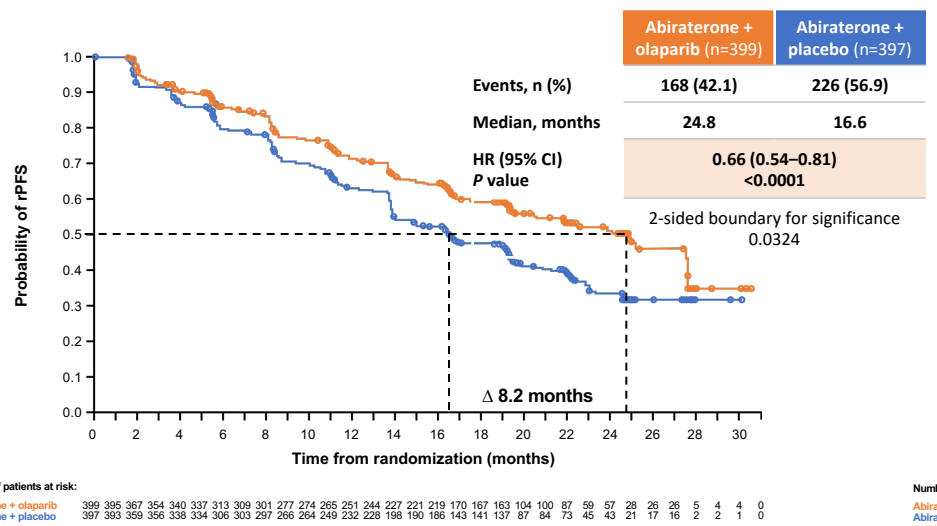
**Clarke et al. 2023**

Courtesy of A Oliver Sartor, MD

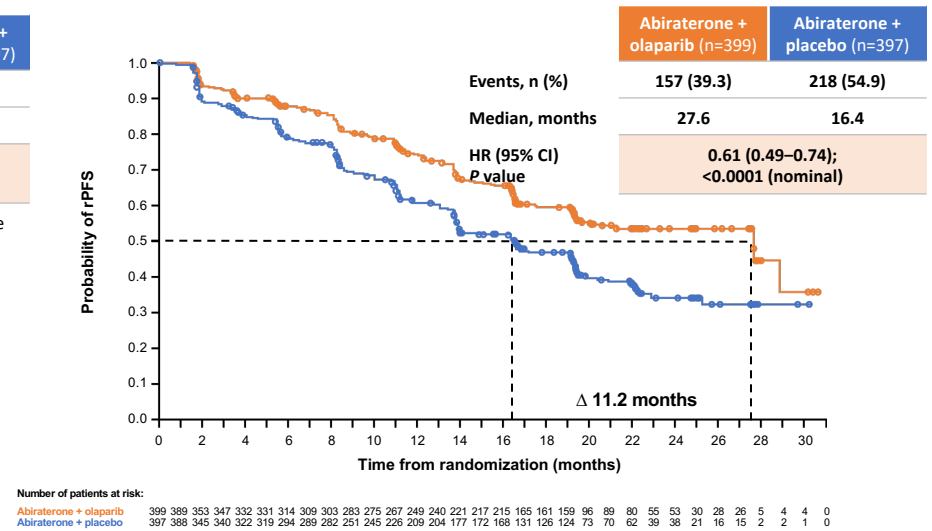
# PROpel: primary rPFS results (DCO1)[1]

Abiraterone + olaparib significantly prolonged rPFS versus abiraterone + placebo in the ITT population

**rPFS by investigator assessment (INV)**




**rPFS by blinded independent central review (BICR)**

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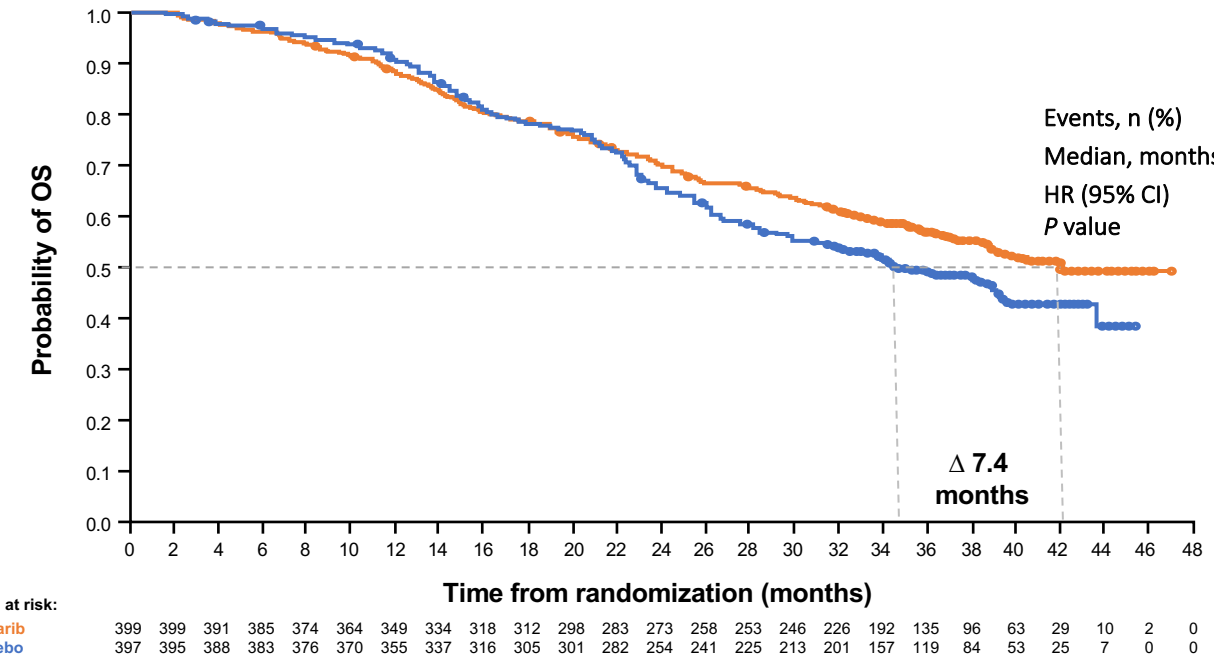
# PROpel: OS at final analysis (DCO3)

In the ITT population, median OS was >7 months longer in the abiraterone + olaparib arm




| | Abiraterone + olaparib (n=399) | Abiraterone + placebo (n=397) |
|---|---|---|
| Events, n (%) | **176 (44.1)** | **205 (51.6)** |
| Median, months | **42.1** | **34.7** |
| HR (95% CI) | 0.81 (0.67–1.00) | |
| *P* value | 0.0544 | |
| 2-sided boundary for significance | 0.0377 | |
| 47.9% maturity | | |

DCO3: 12 October 2022.
Median (range) duration of follow-up for censored patients at DCO3 was 36.6 months (8.3–47.0) in the abiraterone + olaparib arm and 36.5 months (2.9–45.3) in the abiraterone + placebo arm.

Courtesy of A Oliver Sartor, MD

# MAGNITUDE: Randomized, Double-Blind, Placebo-Controlled Study [33]

## Prospectively selected biomarker cohorts designed to test HRR BM+ and HRR BM–

**Study start: February 2019**

**Patient eligibility**
- L1 mCRPC
  - ≤4 months prior AAP allowed for mCRPC
- ECOG PS 0 or 1
- BPI-SF worst pain score ≤3

**Stratifications**
- Prior taxane-based chemo for mCSPC
- Prior ARi for nmCRPC or mCSPC
- Prior AAP for L1 mCRPC
- HRR BM+ cohort only:
  - *BRCA1/2* vs other HRR gene alterations

**Prescreening for BM status[a]**

**HRR BM+ panel:**
*ATM*
*BRCA1*
*BRCA2*
*BRIP1*
*CDK12*
*CHEK2*
*FANCA*
*HDAC2*
*PALB2*

**Allocation to cohort**

**1:1 randomization**

**HRR BM+ Planned N = 400**
- Niraparib + AAP
- Placebo + AAP

**HRR BM– Planned N = 600**
- Niraparib + AAP
- Placebo + AAP

**Primary endpoint**
- rPFS by central review

**Secondary endpoints**
- Time to cytotoxic chemotherapy
- Time to symptomatic progression
- OS

**Other prespecified endpoints**
- Time to PSA progression
- ORR
- PFS2
- Time to pain progression
- Patient-reported outcomes

**Note: Patients could request to be unblinded by the study steering committee and go on to subsequent therapy of the investigator's choice.**

Clinical data cut-off was October 8, 2021 for the final rPFS analysis.

**Patients were prospectively tested by plasma, tissue and/or saliva/whole blood. Patients negative by plasma only were required to test by tissue to confirm HRR BM– status.**

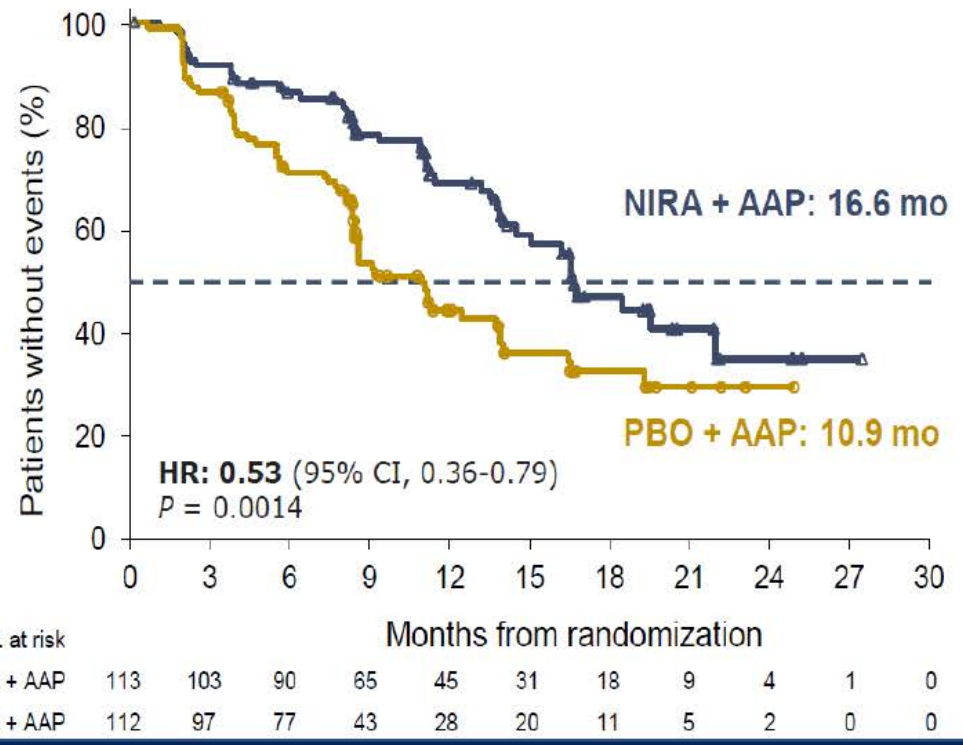
Chi et al. ASCO GU 2022

Courtesy of A Oliver Sartor, MD

# MAGNITUDE *BRCA1/2-mutated*: Primary Endpoint

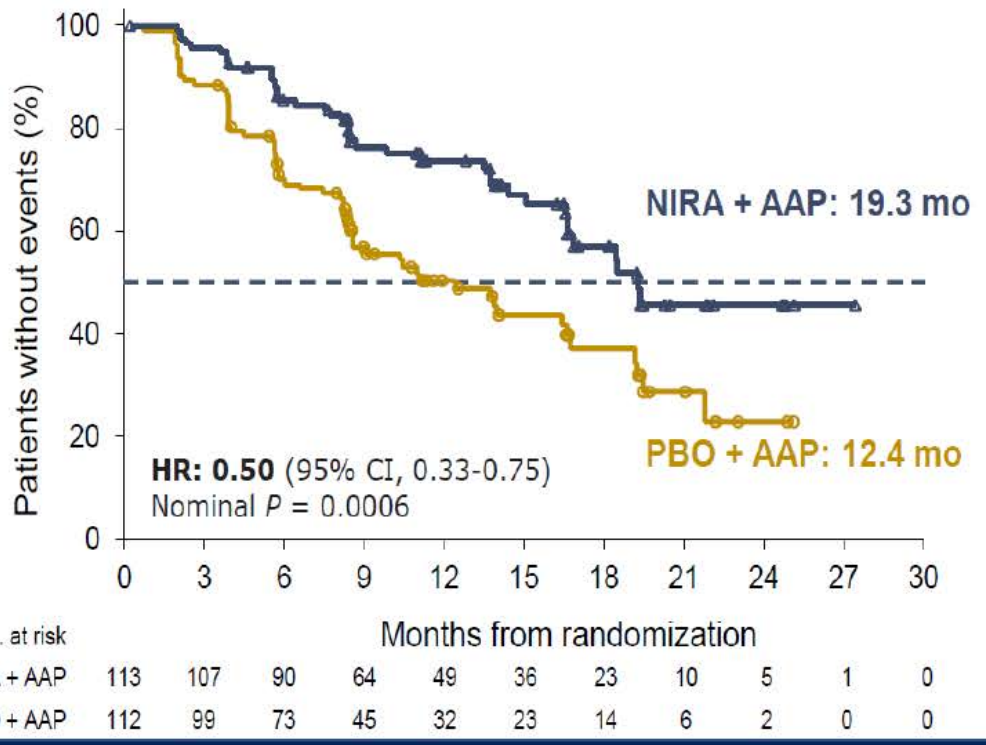
## NIRA + AAP Significantly Reduced the Risk of Progression or Death by 47%

### rPFS assessed by central review




| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NIRA + AAP | 113 | 103 | 90 | 65 | 45 | 31 | 18 | 9 | 4 | 1 | 0 |
| PBO + AAP | 112 | 97 | 77 | 43 | 28 | 20 | 11 | 5 | 2 | 0 | 0 |

### rPFS assessed by investigator



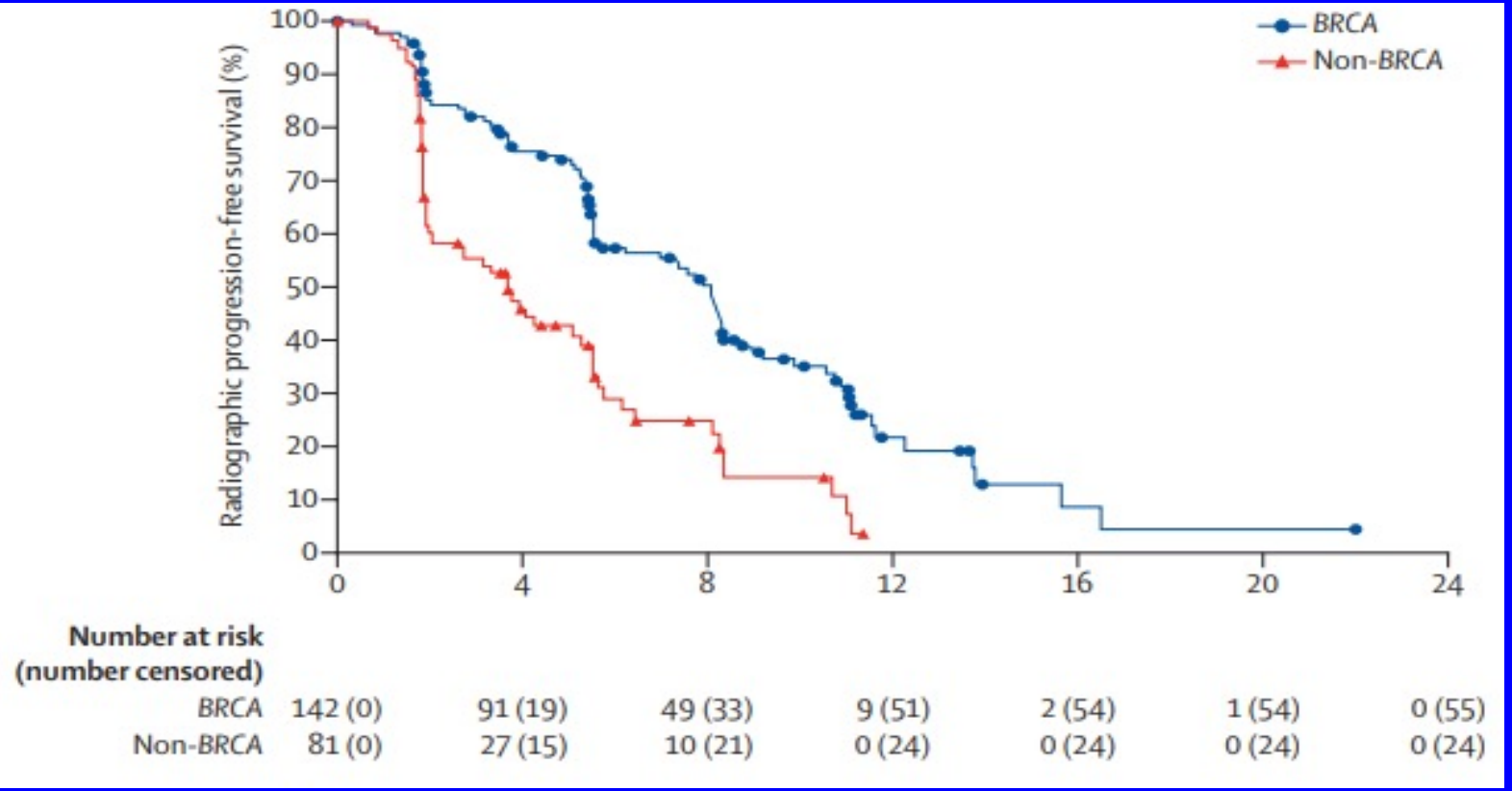

| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NIRA + AAP | 113 | 107 | 90 | 64 | 49 | 36 | 23 | 10 | 5 | 1 | 0 |
| PBO + AAP | 112 | 99 | 73 | 45 | 32 | 23 | 14 | 6 | 2 | 0 | 0 |

**Chi et al. ASCO GU 2022**

Courtesy of A Oliver Sartor, MD

# Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): a multicentre, open-label, phase 2 trial

*Matthew R Smith, Howard I Scher, Shahneen Sandhu, Eleni Efstathiou, Primo N Lara Jr, Evan Y Yu, Daniel J George, Kim N Chi, Fred Saad, Olof Ståhl, David Olmos, Daniel C Danila, Gary E Mason, Byron M Espina, Xin Zhao, Karen A Urtishak, Peter Francis, Angela Lopez-Gitlitz, Karim Fizazi, on behalf of the GALAHAD investigators**




| Number at risk (number censored) | | | | | | | |
|---|---|---|---|---|---|---|---|
| *BRCA* | 142 (0) | 91 (19) | 49 (33) | 9 (51) | 2 (54) | 1 (54) | 0 (55) |
| Non-*BRCA* | 81 (0) | 27 (15) | 10 (21) | 0 (24) | 0 (24) | 0 (24) | 0 (24) |

Courtesy of A Oliver Sartor, MD

Presentation number LBA17

ASCO® Genitourinary Cancers Symposium

# TALAPRO-2: Phase 3 study of talazoparib plus enzalutamide versus placebo plus enzalutamide as first-line treatment in patients with metastatic castration-resistant prostate cancer


Neeraj Agarwal,[1] Arun A. Azad,[2] Joan Carles,[3] Andre P. Fay,[4] Nobuaki Matsubara,[5] Daniel Heinrich,[6] Cezary Szczylik,[7] Ugo De Giorgi,[8] Jae Young Joung,[9] Peter C. Fong,[10] Eric Voog,[11] Robert J. Jones,[12] Neal D. Shore,[13] Curtis Dunshee,[14] Stefanie Zschäbitz,[15] Jan Oldenburg,[16] Xun Lin,[17] Cynthia G. Healy,[18] Nicola Di Santo,[19] Fabian Zohren,[17] Karim Fizazi[20]

*[1]Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT, USA; [2]Peter MacCallum Cancer Centre, Melbourne, Australia; [3]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [4]PUCRS School of Medicine, Porto Alegre, Brazil; [5]National Cancer Center Hospital East, Chiba, Japan; [6]Innlandet Hospital Trust, Gjøvik, Norway; [7]Department of Oncology European Health Center, Otwock, Poland, and Postgraduate Medical Education Center, Warsaw, Poland; [8]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Italy; [9]National Cancer Center, Goyang, Republic of Korea; [10]Auckland City Hospital and University of Auckland, Auckland, New Zealand; [11]Clinique Victor Hugo Centre Jean Bernard, Le Mans, France; [12]School of Cancer Sciences, University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, UK; [13]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [14]Arizona Urology Specialists, Tucson, AZ, USA; [15]National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany; [16]Akershus University Hospital (Ahus), Lørenskog, Norway; [17]Pfizer Inc., La Jolla, CA, USA; [18]Pfizer Inc., Collegeville, PA, USA; [19]Pfizer Inc., Durham, NC, USA; [20]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France*

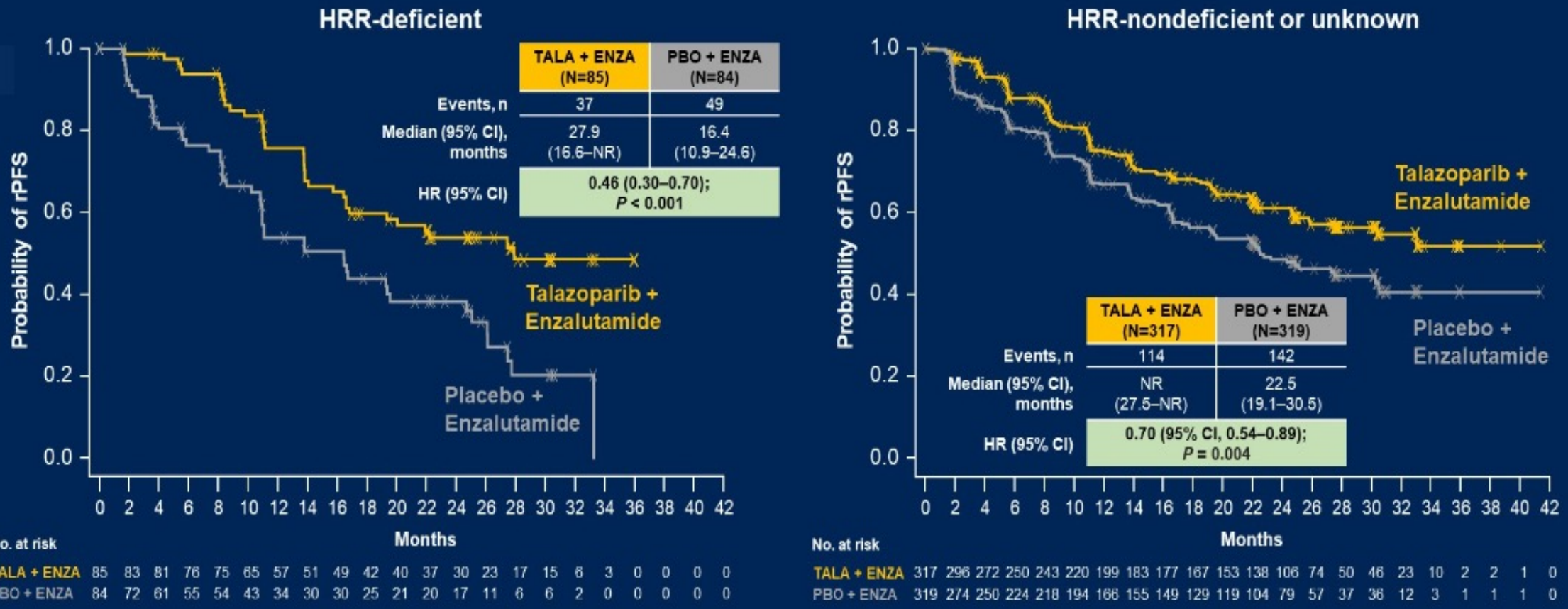


ClinicalTrials.gov identifier: NCT03395197
This study was sponsored by Pfizer Inc. Astellas Pharma Inc. provided enzalutamide


Courtesy of A Oliver Sartor, MD

# TALAPRO-2: rPFS by BICR by HRR Status

A clinically meaningful reduction in risk of progression or death was seen regardless of HRR status




HRR gene alteration status (deficient vs nondeficient or unknown) as a stratification factor.

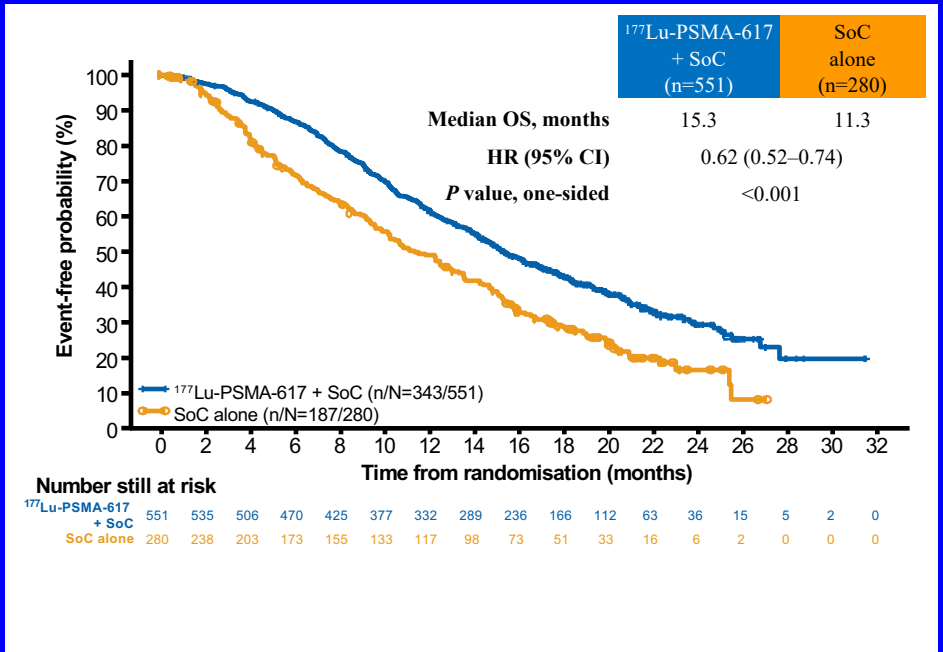
Courtesy of A Oliver Sartor, MD

# Radiopharmaceuticals

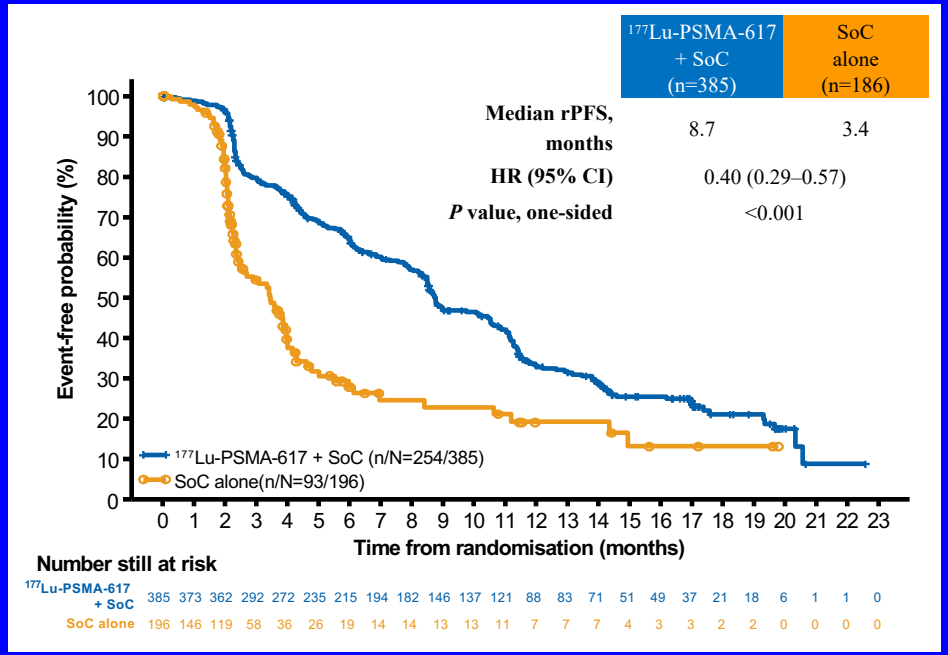
# VISION: $^{177}$Lu-PSMA-617 Phase III trial

## VISION met both primary endpoints of OS and rPFS

### OS: HR 0.62 (95% CI 0.52-0.74)




### rPFS: HR 0.40 (95% CI 0.29-57)




Note: OS positive (HR 0.63) in rPFS subset and rPFS positive (HR 0.43) in OS subset

Courtesy of A Oliver Sartor, MD

**$^{177}$Lu-PSMA-617 shows statistically significant and clinically meaningful radiographic progression-free survival benefit in patients with PSMA-positive metastatic castration-resistant prostate cancer**

Dec 05, 2022

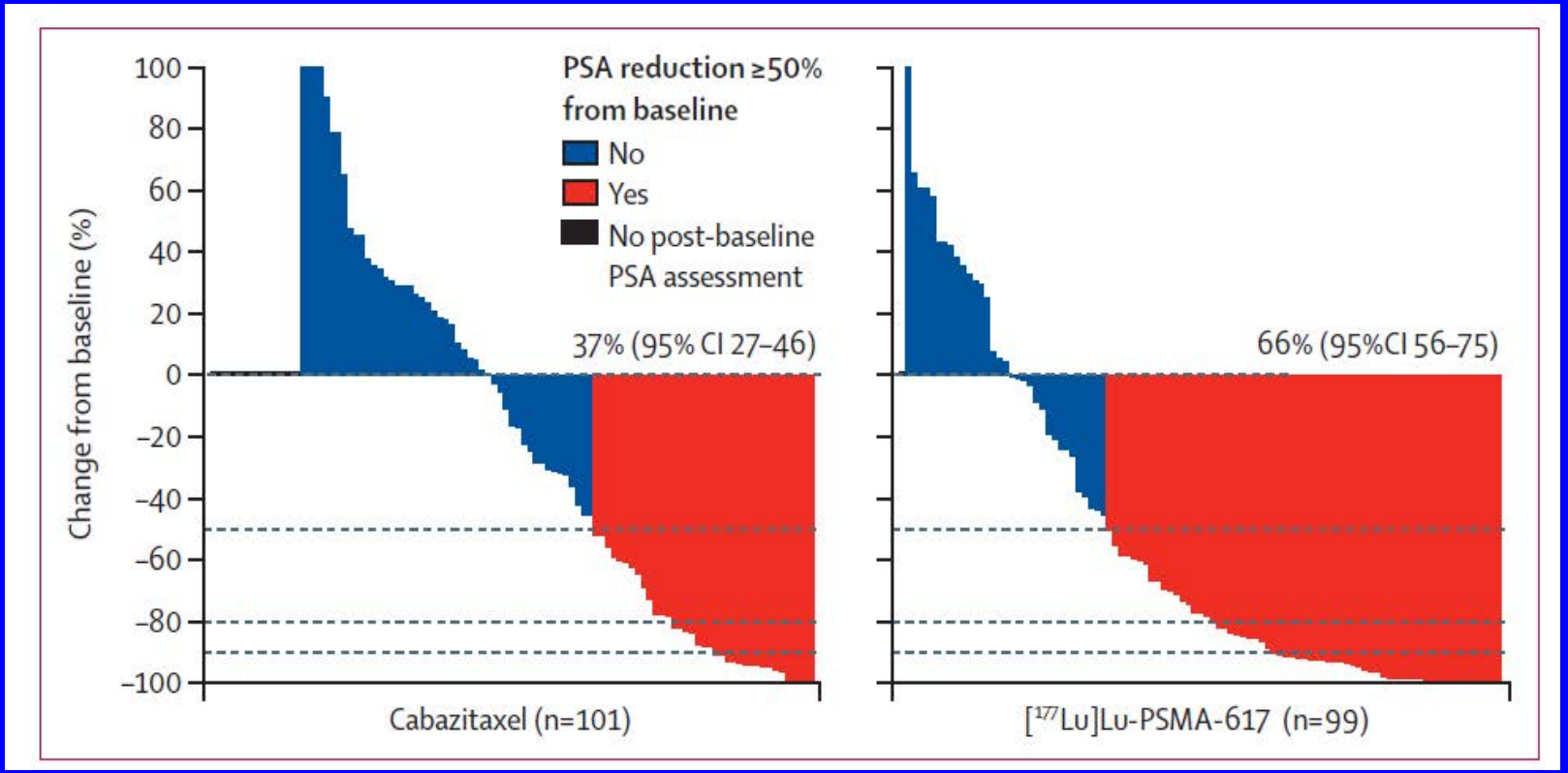
Ad hoc announcement pursuant to Art.53LR

- Phase III PSMAfore trial with $^{177}$Lu-PSMA-617 met the primary endpoint of radiographic progression-free survival for patients with PSMA-positive mCRPC who have been treated with androgen-receptor inhibitor (ARPI) therapy
- $^{177}$Lu-PSMA-617 becomes the first PSMA-targeted radioligand therapy to demonstrate clinical benefit in mCRPC patients before taxane based chemotherapy, addressing a significant unmet need

Courtesy of A Oliver Sartor, MD

# [$^{177}$Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial

*Michael S Hofman, Louise Emmett, Shahneen Sandhu, Amir Iravani, Anthony M Joshua, Jeffrey C Goh, David A Pattison, Thean Hsiang Tan, Ian D Kirkwood, Siobhan Ng, Roslyn J Francis, Craig Gedye, Natalie K Rutherford, Andrew Weickhardt , Andrew M Scott, Sze-Ting Lee, Edmond M Kwan, Arun A Azad, Shakher Ramdave, Andrew D Redfern, William Macdonald, Alex Guminski, Edward Hsiao, Wei Chua, Peter Lin, Alison Y Zhang, Margaret M McJannett, Martin R Stockler, John A Violet*, Scott G Williams, Andrew J Martin, Ian D Davis, for the TheraP Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group†*



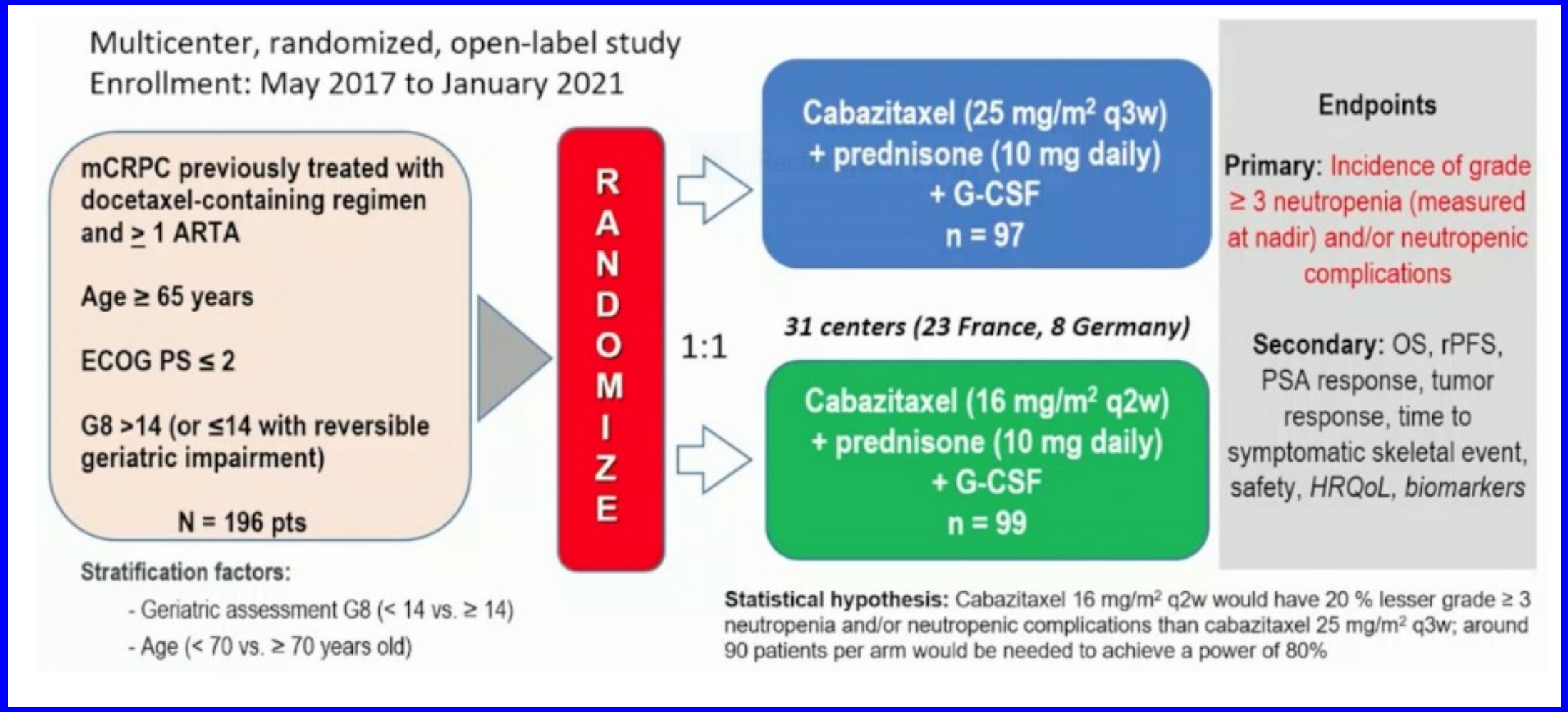

Lancet 2021; 397: 797–804

Courtesy of A Oliver Sartor, MD

# Other Therapeutic Approaches

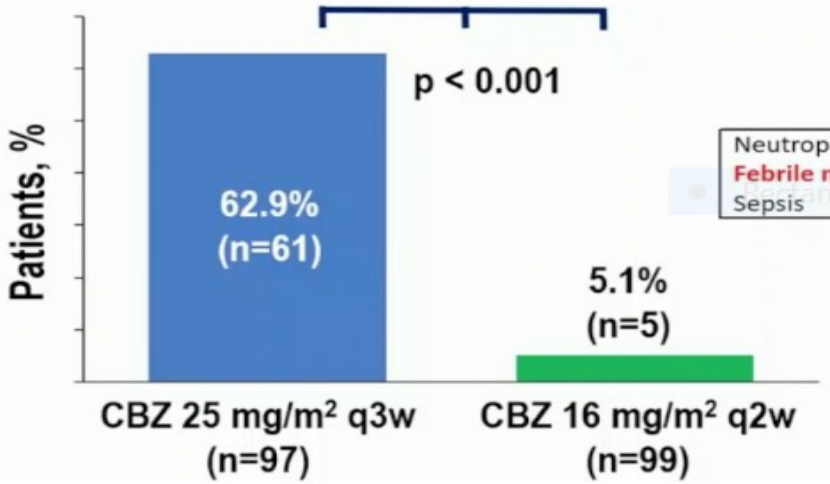
# Cabasty Trial

## Oudard et al. ESMO 2022




Courtesy of A Oliver Sartor, MD

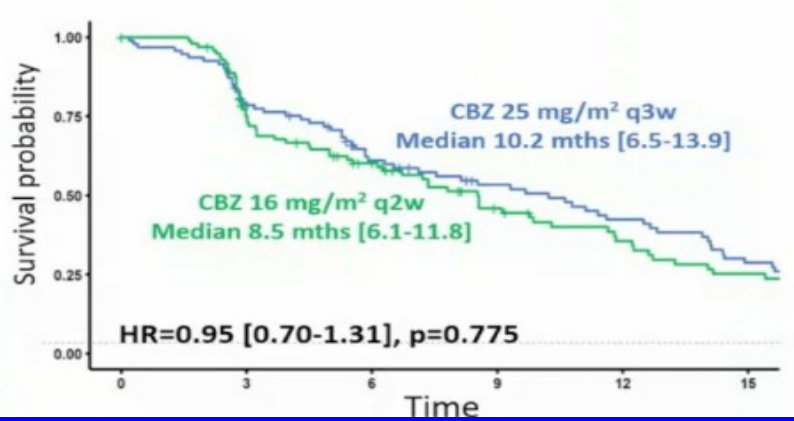
## Neutropenia grade ≥ 3 and/or neutropenic complications*



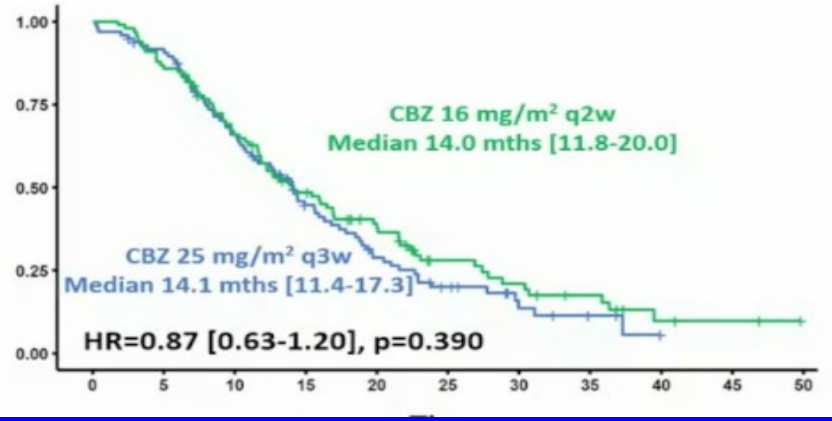

| | CBZ 25 mg/m² q3w (N = 97) | CBZ 16 mg/m² q2w (N = 99) | P value |
|---|---|---|---|
| Neutropenia grade ≥ 3 | 61 (62.9) | 2 (2.0) | |
| Febrile neutropenia | 7 (7.3) | 0 | < 0.001 |
| Sepsis | 3 (3.1) | 3 (3.0) | |

There was no difference in the secondary endpoints of radiological PFS or OS between the two

### Radiological PFS



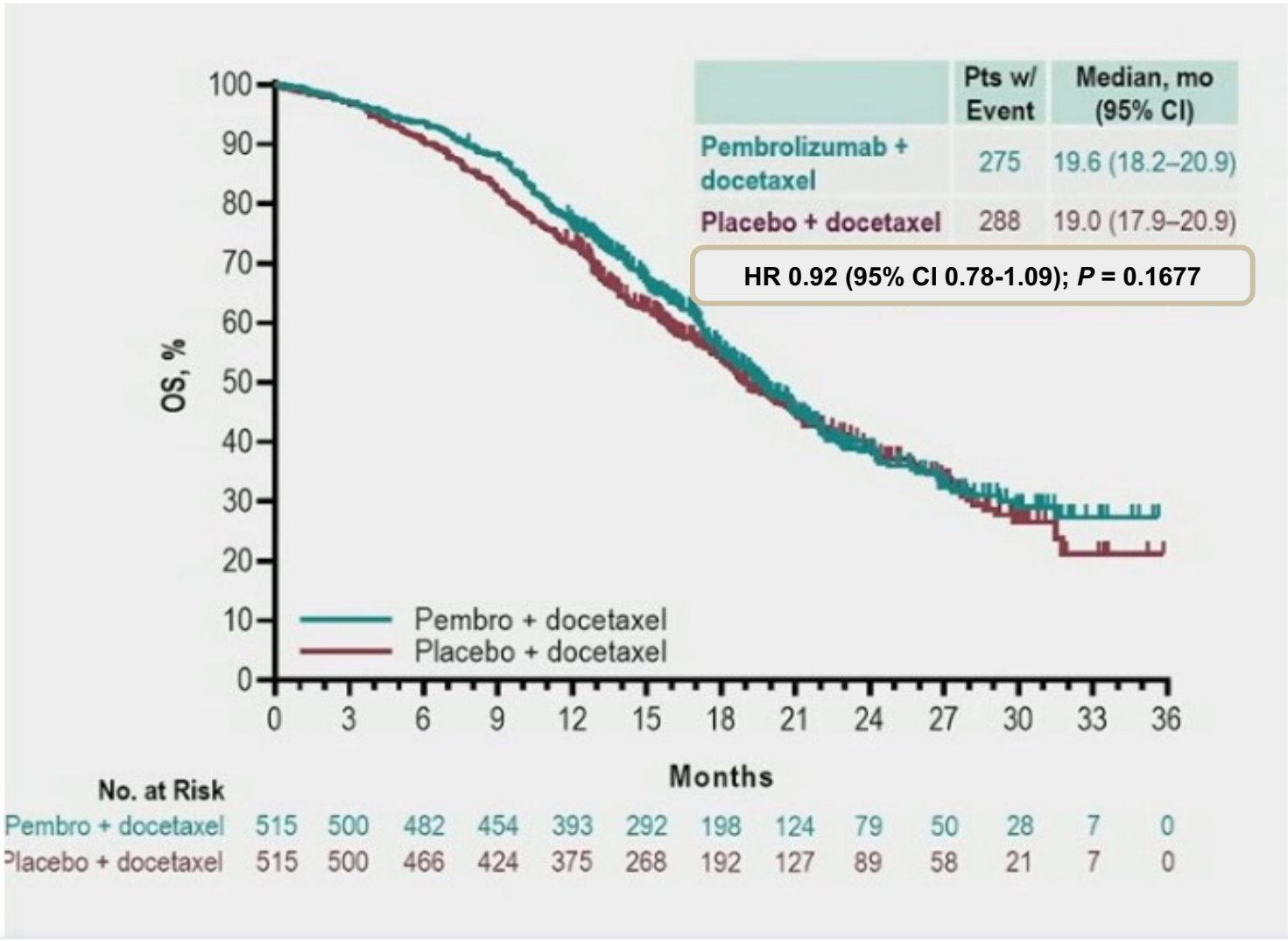

### Overall Survival




Courtesy of A Oliver Sartor, MD

# Docetaxel +/- Pembrolizumab

## Petrylak et al. ASCO GU 2023




Courtesy of A Oliver Sartor, MD

# Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

*A Multitumor CME/MOC-Accredited Live Webinar Series*

# Kidney and Bladder Cancer

**Thursday, March 2, 2023**
**5:00 PM – 6:00 PM ET**

## Faculty

**Matthew Milowsky, MD**

**Thomas Powles, MBBS, MRCP, MD**

## Moderator

**Neil Love, MD**

RTP Year in Review 2023

*Thank you for joining us!*

*Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open up to 5 minutes after the meeting ends.*

*CME and MOC credit information will be emailed to each participant within 5 business days.*

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